



Plant-derived bioactive compounds as key players in the modulation of immune-related conditions

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Received: 23 October 2023 / Accepted: 7 March 2024 / Published online: 16 April 2024
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Abstract The immune system is a complex and fundamental network for organism protection. A minimal unbalance in the host defense system homeostasis can originate severe repercussions in human health. Fundamentally, immune-related diseases can arise from its compromise (immunodeficiency diseases), overactivation against itself (autoimmune diseases) or harmless substances (allergies), and failure of eliminating the harmful agent (chronic inflammation). The notable advances and achievements in the immune system diseases pathophysiology have been allowing for a dramatic improvement of the available treatments. Nevertheless, they present some drawbacks, including the inappropriate benefit/risk ratio. Therefore, there is a strong and urgent need to

develop effective therapeutic strategies. Nature is a valuable source of bioactive compounds that can be explored for the development of new drugs. Particularly, plants produce a broad spectrum of secondary metabolites that can be potential prototypes for innovative therapeutic agents. This review describes the immune system and the inflammatory response and examines the current knowledge of eight plants traditionally used as immunomodulatory medicines (*Boswellia serrata*, *Echinacea purpurea*, *Laurus nobilis*, *Lavandula angustifolia*, *Olea europaea*, *Salvia officinalis*, *Salvia rosmarinus*, and *Taraxacum officinale*). Moreover, the issues responsible for possible biologic readout inconsistencies (plant species, age, selected organ, developmental stage, growth conditions, geographical location, drying methods, storage conditions, solvent of extraction, and extraction method) will also be discussed. Furthermore, a detailed list of the chemical composition and the immunomodulatory mechanism of action of the

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s11101-024-09955-7>.

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bioactive compounds of the selected plant extracts are presented. This review also includes future perspectives and proposes potential new avenues for further investigation.

Keywords Plant extracts · Bioactive compounds · Immune system · Inflammation · Mechanism of action

Introduction

Immune-related diseases pose a huge global burden, affecting both male and female of all ages. Over the years, the incidence and prevalence of immune-related disorders have increased (Wu et al. 2023). For instance, chronic inflammatory diseases worldwide have shown a consistent yearly rise in both incidence and prevalence, with an estimated increase of 19.1% and 12.5%, respectively (Miller 2023). Moreover, a recent study demonstrated that autoimmune disorders can affect about one in ten individuals (Conrad et al. 2023). Indeed, millions of people suffer from these diseases with a serious impact on their quality of life (Vos et al. 2020). Moreover, immune-related diseases present a substantial socioeconomic challenge (Wu et al. 2023). Therefore, there is a pressing need to develop new, safe, and more effective therapies to restore immune system homeostasis and enhance the well-being of patients.

Currently, the pharmaceutical industry primarily focuses on developing new synthetic compounds and researching previously known molecules (Atanasov et al. 2015). Nonetheless, natural products continue being used for drug discovery. Indeed, several drugs derived from various natural sources, such as plants, marine organisms, and microorganisms, continue to successfully emerge (Torre and Albericio 2017; De la Torre and Albericio 2018; G. de la Torre and Albericio 2019; de la Torre and Albericio 2020, 2021, 2022, 2023). Particularly, plants have long been employed for the traditional treatment of various diseases, such as immune-related diseases. Indeed, plant-derived formulations can present promising immunomodulatory bioactivity. These formulations can, for example, influence immune cell function, modulating the production of pro-inflammatory mediators, and regulating the levels of antioxidant molecules (Alhazmi et al. 2021; Elkhawaga et al. 2023; Moudgil and Venkatesha 2023).

Thus, plant-derived formulations can help restoring immune system homeostasis and improve treatment outcomes by targeting specific dysregulated components. Furthermore, plants, presenting a rich chemical diversity of compounds, are an excellent resource for the discovery of novel, safe, and effective immunomodulatory drugs to potentially revolutionize immune-related therapeutics. Moreover, with the advances in pharmacology and pathophysiology, the integration of historical sources in the exploration of plant-based drugs can be a highly successful approach for the discovery of effective immunomodulatory agents (Ulriksen et al. 2022).

Despite the increasing focus on exploring the immunomodulatory effects of plant extracts and its isolated compounds, a comprehensive literature on its mechanism of action is required. The previous reviews provided only general discussions on the topic. Indeed, they have addressed the wide array of bioactivities associated with plant extracts and its isolated compounds (Almeida-da-Silva et al. 2022; Burlou-Nagy et al. 2022; Rufino-Palomares et al. 2022; Alesci et al. 2022; Awada et al. 2023), lacking an in-depth overview of the immune system and the inflammatory response (Gupta et al. 2021). This can pose difficulties for readers who are not familiar with these topics, particularly those who are not experts in the field. Furthermore, most of the reviews have been limited in scope, concentrating on the description of a single plant species or family (Ramos da Silva et al. 2021; Pilkington and Pilkington 2022; Batiha et al. 2023). In addition, to the best of our knowledge, none of the existing reviews offer a comprehensive and exhaustive list of the phytochemical composition of the plants under investigation. Instead, they primarily focus on the most widely recognized compounds (Burlou-Nagy et al. 2022; Rufino-Palomares et al. 2022; Awada et al. 2023; Dobros et al. 2023; Habtemariam 2023). Additionally, the existing reviews fail to approach the crucial aspects in identifying inconsistencies associated with the bioactivity of plant extracts. Although multiple reviews can offer additional insights, supporting one another, the absence of centralized and consolidated information can result in additional difficulties for the readers searching for relevant information across different sources.

Our review compiles an exhaustive, up-to-date, and critical evaluation of literature exploring several exciting and outstanding fields that will offer the

readers an integrated analysis of immunology, natural products, and drug development. This review presents an overall description of the immune system and the inflammatory response, exploring the major inflammatory signaling pathways. Examples of chronic inflammatory diseases and therapeutic options available are also provided. The role of plant-derived formulations in the pharmacological field, as well as the inconsistencies in their therapeutic effects are presented.

This review carefully examines eight plants traditionally used as immunomodulatory medicines (*Boswellia serrata*, *Echinacea purpurea*, *Laurus nobilis*, *Lavandula angustifolia*, *Olea europaea*, *Salvia officinalis*, *Salvia rosmarinus*, and *Taraxacum officinale*). It highlights their main active principle(s) and the respective mechanism of action. In addition, this review presents the most complete and comprehensive list of chemical compounds present in each selected immune-related plant ever reported to date. Those tables are complemented with additional parameters that impact the extraction process (e.g., solvent of extraction, extraction technique, and organ of the plant). It finishes with insights into future directions of further research in the field of immunomodulatory plant bioactive compounds.

Thus, this review effectively fills the gaps identified in the current literature by providing a more comprehensive and exhaustive examination of the immune-related properties of eight plants. Importantly, it goes beyond the well-known compounds, offering a more complete phytochemical composition of the plants under investigation. In summary, this review serves as a centralized and extensive resource that brings together all the pertinent and relevant data on the immune system and the selected plants.

Immune system

The immune system is in constant surveillance, recognizing and eliminating harmful stimuli that can cause diseases (Medzhitov 2008). Indeed, it has fast, specific, and effective mechanisms that are triggered by tissue injury or trauma and harmful entities (e.g., cancer cells, viruses, fungi, parasites, bacteria, allergens, and toxic compounds) (Medzhitov 2008). The immune system is highly adaptable and involves a complex and dynamic network of cells, soluble

molecules, and organized pathways. Moreover, it has different recognition and destruction mechanisms to match the several shapes, sizes, and chemical structures of harmful entities. Hence, an immune response is elicited to ensure the protection of all tissues and organs and to maintain or restore homeostasis in the body (Medzhitov 2008).

Organization of the immune system

The immune system involves innate (non-specific) and adaptive (specific) immunity (Medzhitov and Janeway 2000).

The effector mechanism of innate immunity—the first line of defense—comprises features that are encoded by genes in the germline, including anatomical barriers and cellular responses (Chaplin 2010). The main physical barriers for preventing pathogens to enter in the body are the epithelial layers of the skin, the mucosal tissues (e.g., gastrointestinal, respiratory, and urogenital tracts), and the glandular tissues (e.g., salivary, lacrimal, and mammary glands) (Turvey and Broide 2010). In addition, the secretions of these tissues (e.g., mucus and urine) wash away potential invaders and can contain enzymes (e.g., lysozyme) and peptides (e.g., defensins) with antimicrobial properties. Moreover, the acidic pH in some tissues, such as stomach and urogenital tract, is important in conferring protection against bacterial and fungal pathogens (Turvey and Broide 2010). Innate immune cells include monocytes, macrophages, neutrophils, eosinophils, mast cells, basophils, and dendritic cells (Chaplin 2010). They recognize in a fast and effectively way a wide range of pathogens after entering inside the organism, restricting and controlling their replication rate within hours (Medzhitov and Janeway 2000). The innate cells express an array of germline-encoded cellular membrane and intracellular receptors. They are defined as pattern-recognition receptors (PRRs), that immediately recognize specific conserved molecular components on the surfaces of pathogens (pathogen-associated molecular patterns, PAMPs) or endogenous molecules released from damaged cells (danger-associated molecular patterns, DAMPs) (Medzhitov and Janeway 2000; Iwasaki and Medzhitov 2010). PRRs can be categorized into secreted, transmembrane, and cytosolic classes, ensuring the recognition of PAMPs and DAMPs in both extracellular and intracellular compartments of a cell

(Iwasaki and Medzhitov 2010). PAMPs could be bacterial and viral nucleic acids and wall components, including lipopolysaccharides (LPS), carbohydrates (e.g., mannans and β -glucans), peptidoglycans, lipoteichoic acids, and surface proteins (Medzhitov 2008; Takeuchi and Akira 2010). Conversely, DAMPs are breakdown products of extracellular matrix, products of the proteolytic cascades activated by vascular and endothelial damage, or molecules released from debris cells (e.g., adenosine triphosphate—ATP, potassium ions, uric acid, high mobility group box—HMGB—1 protein, and S100 calcium-binding proteins family) (Murao et al. 2021).

The adaptive immune system provides a second and more focused set of reactive molecules and cellular components against pathogens. The adaptive immune response is slower (5 or 6 days after initial exposure) than the innate response but is more specific against the pathogen (Bonilla and Oettgen 2010). Adaptive immune cells are composed of the effectors of cellular immunity—T cells—and the antibody-producing cells—B cells—, whose receptors are not genetically encoded, but are generated by somatic recombination in each organism (Iwasaki and Medzhitov 2010; Bonilla and Oettgen 2010). The adaptive immune response is generated under the influence of signals provided by the innate immune system that can be either directly by circulating offending agents or indirectly by antigen-presenting cells (APCs) migrating to secondary lymphoid organs (Bonilla and Oettgen 2010). The antibodies (also called immunoglobulins) produced by B cells confer humoral immunity. The various subpopulations of the T cells secreting soluble cytokines confer cellular immunity (Bonilla and Oettgen 2010).

Although the innate immune system triggers the adaptive immune system, both systems communicate through cellular and molecular interactions, allowing for the protection of the organism (Medzhitov and Janeway 2000).

Cells of the immune system

The immune response involves an interconnected communication among diverse cell types that drive from hematopoietic stem cells (HSC) in the bone marrow (Fig. 1) (Mann et al. 2022). In homeostatic conditions, most HSCs are quiescent. In the presence of a stimulus (e.g., pathogen or cancer cells), HSCs

differentiate into a common myeloid-erythroid progenitor (CMP)—myeloid lineage—or a common lymphoid progenitor (CLP)—lymphoid lineage (Mann et al. 2022).

Myeloid cells are the first to respond to the invasion of a pathogen and communicate the presence of the insult to cells of the lymphoid lineage. The immune cells that arise from the myeloid lineage include granulocytes and phagocytic cells (Mann et al. 2022). Granulocytes can be classified as neutrophils, basophils, mast cells, or eosinophils, depending on the cellular morphology and the cytoplasmic characteristic granules (Chaplin 2010). Indeed, their cytoplasm is enriched in cytotoxic granules that are released after contact with different pathogens. Granulocytes present different functions. Neutrophils are implied in many types of infections and are responsible for the engulfing of the pathogen—phagocytosis (Chaplin 2010). Basophils are critical for protecting the organism against parasites, particularly helminths. Mast cells protect mucosal surfaces against pathogens. Eosinophils are key players in the defense against multicellular parasitic organisms, including worms. The group of phagocytic cells includes monocytes, macrophages, and dendritic cells, that have APCs function (Chaplin 2010). Monocytes migrate into tissues and differentiate into tissue-resident phagocytic cells, namely macrophages and dendritic cells. Depending on the nature of the activating signals, macrophages can undergo classical macrophage activation or alternative macrophage activation, yielding pro-inflammatory M1 macrophages or anti-inflammatory M2 macrophages. The first and second phenotypes participate in immune responses and tissue repair, respectively. During an immune response, M1 macrophages exhibit great phagocytic activity, improved ability to kill ingested microbes, increased secretion of inflammatory and cytotoxic mediators, and enhanced capacity to activate T cells. Dendritic cells monitor the body for signs of invasion by pathogens and capture intruding or foreign antigens, which are presented to naïve lymphocytes in the secondary lymphoid organs. All APCs express both major histocompatibility complex (MHC) class I and class II molecules, cell membrane proteins, that are essential for the activation of T cells (Chaplin 2010).

Despite the myeloid cells exhibit an unspecific immune response, the lymphoid lineage regulates a specific immune response. In this lineage,

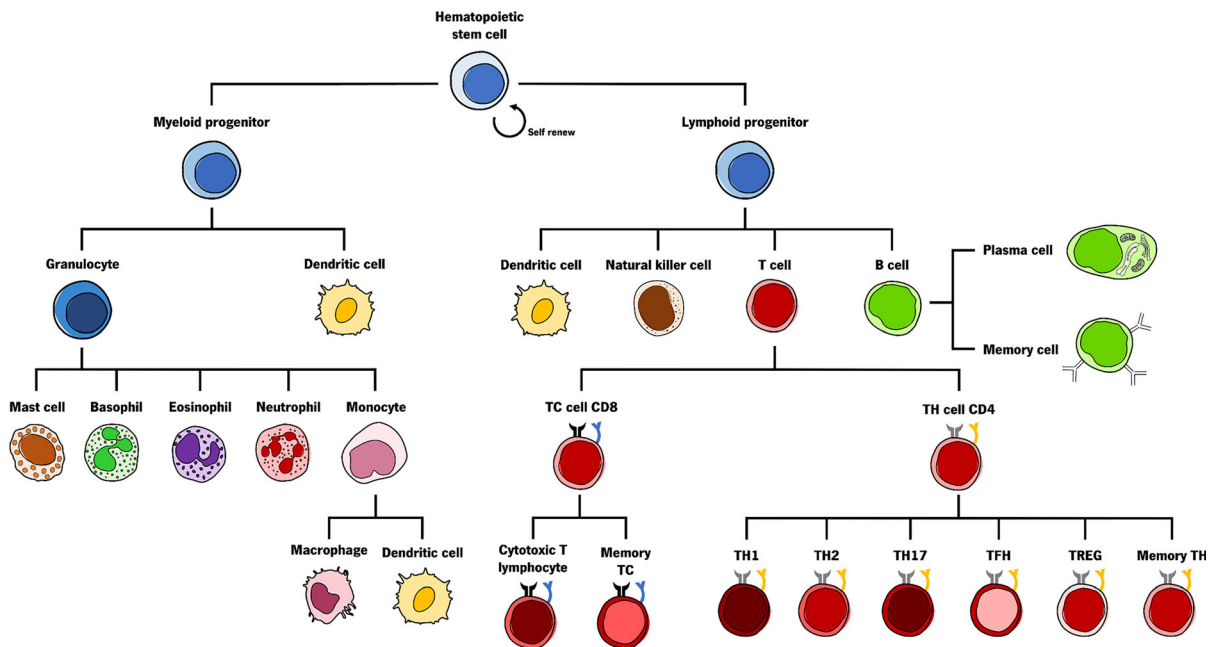


Fig. 1 Immune cell lineages. TC, T cytotoxic cells; TFH, T follicular helper cells; TH, T helper cells; TREG, regulatory T cell

lymphocytes are the main cells. According to their functional and phenotypic differences, lymphocytes can be categorized into B cells (B lymphocytes), T cells (T lymphocytes), and natural killer cells (Mann et al. 2022). B cells, matured in the bone marrow, express B-cell receptor (BCR), a membrane-bound antibody molecule that binds to processed or unprocessed antigens (Chaplin 2010). After surface antibody link to a unique antigen, they become activated. Activated B cells differentiate into effector cells—plasma cells—and secrete antibodies. T cells, matured in the thymus, express a specific antigen-binding receptor—T-cell receptor (TCR). TCR only recognizes processed pieces of antigen bound to MHC molecules (Chaplin 2010). According to the presence of glycoproteins, namely CD4 or CD8, on their surface, T cells can be classified as T helper (TH) cells and T cytotoxic (TC) cells, respectively. TH cells ($CD4^+$ T) recognize antigens in complex with MHC class II (expressed by APCs). Conversely, TC cells ($CD8^+$ T) recognize antigens in complex with MHC class I (expressed by nearly all nucleated cells of vertebrate species). When naïve $CD4^+$ T cells bind their TCR to the MHC-peptide complex, they become activated and proliferate and differentiate into a

variety of effector T cell subsets. Depending on the type of pathogen, T cell subsets can be T helper type 1 (TH1), T helper type 2 (TH2), T helper type 17 cells (TH17), T follicular helper cells (TFH), and regulatory T cell (TREG) (Chaplin 2010). TH1 and TH2 cells regulate the immune response to intracellular and extracellular pathogens, respectively. TH17 cells play an important role in cell-mediated immunity and may help the defense against fungi infections. TFH cells play an important role in humoral immunity and regulate B-cell development in germinal centers. TREG cells have the unique capacity to inhibit an immune response. Similar to naïve $CD4^+$ T cells, naïve $CD8^+$ T cells also become activated after binding their TCR to the MHC-peptide complex, and then, they proliferate and differentiate into an effector cell called cytotoxic T lymphocyte (Chaplin 2010). Natural killer cells, presenting cytotoxic granules, attack and induce cell death in a variety of abnormal cells, such as tumor cells and virus-infected cells (Chaplin 2010). They recognize these cell debris by the absence of MHC class I on their surface. Natural killer cells also express immunoglobulin-like receptors and can, therefore, bind pathogens or proteins from pathogens on the surface of infected cells.

Inflammation

Inflammation is a natural and essential protective mechanism, triggered by noxious stimuli or trauma, that aims to restore the homeostasis of the body (Medzhitov 2008; Chovatiya and Medzhitov 2014). The hallmarks, traditionally called cardinal signs, of an inflammatory response are *calor* (heat), *rubor* (redness), *tumor* (swelling), *dolor* (pain), and *functio laesa* (loss of function) (Medzhitov 2010). These signals are consequences of vascular changes and leukocyte recruitment, influx, and activation.

Some pathogens can penetrate the body through damaged anatomical barriers (e.g., wounds, abrasions, and insect bites). Once inside the human organism, the offending agent is rapidly recognized by soluble proteins and/or PRRs on the membrane surface of tissue-resident macrophages, neutrophils, dendritic cells, and mast cells (Iwasaki and Medzhitov 2010). When activated, the immune cells rapidly fight the pathogen (Medzhitov and Janeway 2000; Takeuchi and Akira 2010). The soluble phagocytosis-enhancing proteins, namely opsonins (e.g., surfactant proteins—SP—A and D, mannose-binding lectin—MBL—, L-ficolin, C-reactive protein—CRP—, and several components of complement system), that can bind to PAMPs, initiates the opsonization of the pathogen (Fig. 2A). Once bound to the surface of the pathogen, opsonins are recognized by membrane opsonin receptors on phagocytic cells, activating and enhancing the phagocytosis (Uribe-Querol and Rosales 2020). Immediately, actin polymerization is activated in phagocytic cells to perform the phagocytosis (Fig. 2B). Briefly, phagocytic cells extend their plasma membrane around the offending agent, and internalize it into phagosomes, which then fuse with lysosomes (Xu et al. 2021). The resulting phagolysosomes contain antimicrobial proteins (e.g., lactoferrin and psoriasin) and peptides (e.g., defensins and cathelicidins), low pH, acid-activated hydrolytic enzymes (e.g., lipases and proteases), and free radicals (e.g., reactive oxygen and nitrogen species—ROS/RNS), to kill and degrade the internalized offending agent (Uribe-Querol and Rosales 2017).

The recognition of the offending agent by phagocytic cells also triggers different signal-transduction pathways that activate the expression of important genes in the inflammatory process. Among the proteins encoded by these genes, there are several

inflammatory mediators that amplify the inflammatory response. Briefly, the neutrophils create a cytotoxic environment by releasing noxious chemicals from their cytoplasmic granules, including proteinases and antimicrobial proteins (Witko-Sarsat et al. 2000). Neutrophils and macrophages also initiate a massive respiratory burst, releasing high levels of ROS/RNS, as well as pro-inflammatory mediators, namely cytokines, chemokines, prostaglandins (PGs), and leukotrienes (LTs) (Nguyen et al. 2017; Gideon et al. 2019; Mosser et al. 2021; Canton et al. 2021). Histamine is released by mast cells. Some of these inflammatory mediators act on the vascular musculature to promote vasodilation, which increases blood flow and capillary permeability, to allow for the influx of leukocytes (Leick et al. 2014). The recruited leukocytes adhere to vascular endothelial cells through cell adhesion molecules (CAMs), at the site of inflammation, passing then through the walls of capillaries into the tissue space (extravasation). In the target tissue, recruited phagocytic cells are activated (Xu et al. 2021). The APCs, typically dendritic cells and macrophages, recognize and process the offending agent, and expose the pathogen-derived peptides (antigen) on the cell surface complexed with MHC class I and class II, as previously referred. Activated APCs also express high levels of costimulatory ligands (e.g., CD80 and CD86) to activate the lymphocytes. Then, they migrate through the lymphatic vessels to nearby secondary lymphoid tissues (e.g., lymph nodes and spleen) where they present the antigen to the T and B cells (Théry and Amigorena 2001).

The naïve T cells are co-stimulated by the engagement with both MHC-peptide complex by TCR (Signal 1) and costimulatory ligands (Signal 2) on APCs (Chaplin 2010). However, even with the increased functional avidity offered by coreceptors and adhesion molecules, the T cells are not fully activated. Indeed, a third set of signals, provided by local cytokines (Signal 3) are needed to completely activate the T cells (Fig. 3). Then, as previously described, activated T cells and their progeny gain unique functional abilities, becoming effector TH or TC that directly or indirectly act to clear the offending agent (Bonilla and Oettgen 2010). CD8⁺ T cells leave the secondary lymphoid tissues and migrate to sites of inflammation. Activated CD8⁺ T cells acquire the ability to induce the death of the target cell, becoming cytotoxic T lymphocyte (Bonilla and Oettgen 2010).

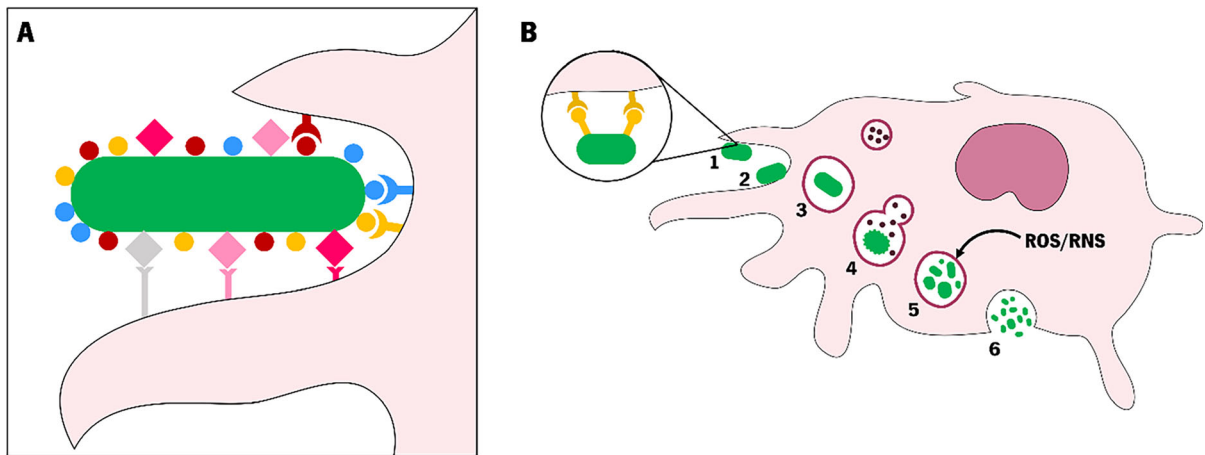


Fig. 2 Phagocytosis and intracellular destruction of invading agent (e.g., bacterium). **A** Opsonization of invading agent by different opsonin receptors on the surface of phagocytic cells. **B** Phagocytosis steps: (1) recognition and attachment: invading agent binds to phagocytic receptors present in the membrane; (2) engulfment: extension of the phagocytic membrane around the

invading agent; (3) ingestion: the invading agent is ingested, forming a phagosome. (4) fusion: phagosome fuses with a lysosome; (5) killing and degradation: the invading agent is killed and then digested by lysosomal enzymes and reactive oxygen and nitrogen species (ROS/RNS); (6) releasing: digestion products are released from the cell

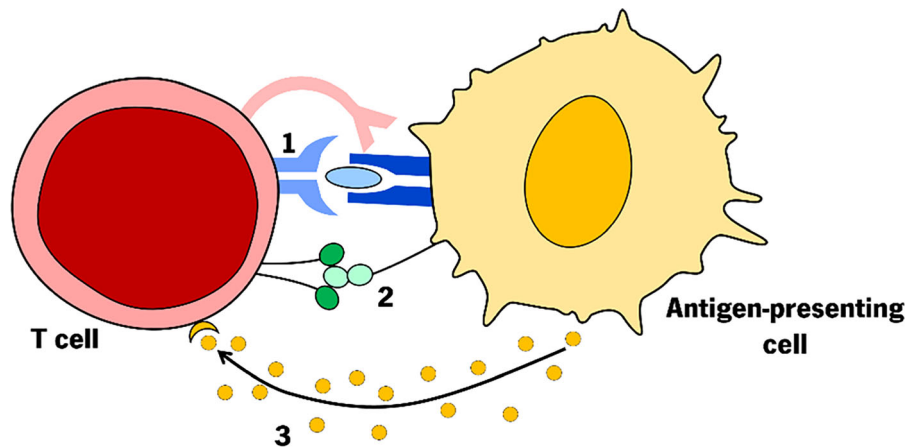


Fig. 3 Activation of naïve T cells requires three signals. (1) The T-cell receptor/major histocompatibility complex (TCR/MHC) antigen interaction, along with CD4 and CD8 co-receptors and adhesion molecules provides Signal 1. (2) Co-stimulation by a separate set of molecules, including CD28,

provides Signal 2. (3) Both Signal 1 and Signal 2 initiate a signal transduction cascade that results in activation of transcription factors and cytokines (Signal 3) that direct T-cell proliferation and differentiation

CD4⁺ T cells produce cytokines that coordinate the activity of other immune cells (B cells, macrophages, and other T cells) (Chaplin 2010). As previously referred, depending on the nature of the pathogen and its binding to specific PRRs, APCs activate different signaling pathways and induce the secretion of specific cytokines that influence the fate of the naïve CD4⁺ T cells into different subsets of cytokine-

producing phenotype (TH1, TH2, TH17, or TREG) (Saravia et al. 2019).

The naïve B cells can be directly activated by the recognition of antigen-associated APCs. Moreover, they can also be activated by two different mechanisms: T-dependent (TD) response, T-independent (TI) response (Fig. 4). The TD response is generated upon recognition of an antigen and requires the

participation of CD4⁺ T cells (Bonilla and Oettgen 2010). First, the antigen binds to the membrane immunoglobulin receptors of B cells (Fig. 4A). Some of the antigens are internalized into specialized vesicles within the B cells, processed, allocated in the antigen-binding MHC class II, and presented to CD4⁺ T cells. Then, a T cell previously activated by an antigen-bearing APC binds to the B cell through its MHC-peptide receptor and an interaction between CD40/CD80 or CD86 (on B cell) and CD40L/CD28 (on TH cell). To finalize the activation process, the bounded T cell release cytokines (e.g., IL-2 and IL-4), and other signals to the B cell. The TI response occurs directly toward multivalent or highly polymerized antigens and does not require T-cells involvement (Bonilla and Oettgen 2010). There are two subclasses of TI antigens. Type 1 TI (TI-1) antigens interact with B cells through both membrane immunoglobulin receptors and innate immune receptors (Fig. 4B). Type 2 TI (TI-2) antigens are frequently bound by complement components and crosslink both immunoglobulin and CD21 receptors on B cells (Fig. 4C).

Some of the antigen-activated B cells move into specific regions, where they differentiate into clusters of activated B cells. There, they complete their differentiation into plasma cells to secrete large amounts of antibodies (Moro-García et al. 2018). Some antigen-stimulated B cells also undergo further differentiation that results in the secretion of antibodies with altered sequences in their antigen-combining sites. This process generates B cells bearing receptors and secreting antibodies whose affinity for antigen

increases as the immune response progresses. The antibodies generated by activated B cells can protect the body against the offending agents using different mechanisms: (i) blocking receptors that offending agents use to enter into the cells; (ii) opsonizing the offending agents by binding to or recruiting phagocytic cells; (iii) initiate the complement cascade, puncturing cell membrane (Moro-García et al. 2018). The slower activity of the adaptive immune system is due to the development of the antigen specificity. An important population of both T and B cells are preserved as memory T and B cells in this primary response, ensuring a heightened reactivity to a subsequent challenge with the same antigen (Bonilla and Oettgen 2010; Chaplin 2010).

All these mechanisms result in a successful acute inflammatory response with the clearance of the invading pathogens, dead cells, and damaged tissue. This is followed by a resolution and repair phase, which is mediated mainly by M2 macrophages, restoring tissue homeostasis.

Inflammatory mediators

The inflammatory response is coordinated by several mediators that form complex regulatory networks (Medzhitov 2008). The inflammatory mediators include substances derived from plasma proteins or that are secreted by cells (Medzhitov 2008; Kumar et al. 2018). These molecules initiate and regulate inflammatory reactions and modify the functional states of tissues and organs. Inflammatory mediators act through specific receptors on target cells, generally

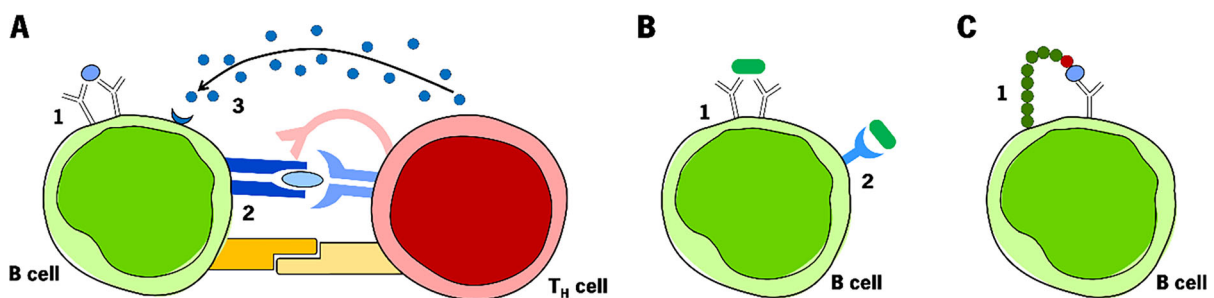


Fig. 4 B cell activation. **A** T-dependent antigens bind to the immunoglobulin receptor of B cells (1); some of the antigens are processed and presented to helper T (T_H) cells. T cells bind to the MHC-peptide antigen and deliver further activating signals to the B cell via interaction between CD40L (on T cells) and CD40 (on B cells) (2); in addition, T cells secrete activating

cytokines (e.g., IL-2 and IL-4), which are recognized by receptors on the B-cell surface (3). **B** Type 1 T-independent antigens bind to B cells through both immunoglobulin (1) and innate immune receptors (2). **C** Type 2 T-independent antigens have the ability to crosslink both the immunoglobulin receptor and CD21 receptors on B cells (1)

having multiple effects in different cell types (King 2007). Depending on the biochemical properties, the inflammatory mediators can be vasoactive amines, vasoactive peptides, fragments of complement components, eicosanoids, cytokines, chemokines, free radicals, and proteolytic enzymes (Medzhitov 2008). Table 1 presents several inflammatory mediators, as well as the main producing cells, the target cells, and the most common functions. Some of the most important inflammatory mediators will be discussed hereafter.

The two major vasoactive amines are histamine and serotonin, which are stored in the granules of mast cells, basophils, macrophages, dendritic cells, and T cells (Kumar et al. 2018). Under certain stimuli, these cells release histamine and serotonin by degranulation (Ribeiro et al. 2015). For example, they have effects on the vasculature, leading to vasodilation and thus to increase the vascular permeability (Medzhitov 2008). Vasoactive peptides promote similar events. These mediators are stored in an active form in secretory vesicles (e.g., substance P) or are generated by proteolytic cleavage of inactive precursors in the extracellular fluid (e.g., bradykinin) (Medzhitov 2008).

The complement components are synthesized by hepatocytes and by other cell types, including blood monocytes, tissue macrophages, fibroblasts, and epithelial cells of the gastrointestinal and genitourinary tracts. The complement products (e.g., C5b and C6–C9) bind to a pathogen and kill it by creating pores on its membranes. Intermediate cleavage products (e.g., C3a, C3b, C4a, and C5a) also stimulate the release of the histamine from mast cells, recruit and activate leukocytes (neutrophils, monocytes, eosinophils, and basophils), and promote phagocytosis (Medzhitov 2008; Kumar et al. 2018).

The eicosanoids comprise PGs, thromboxanes (TXs), LTs, and lipoxins (LXs) (Medzhitov 2008). PGs (e.g., PGD₂, PGE₂, PGF₂, PGI₂, and PGJ₂) and TXs (e.g., TXA₂) produced by mast cells, macrophages, and endothelial cells during a stimulus, are involved in the vascular and systemic reactions of inflammation (Ribeiro et al. 2015; Kumar et al. 2018). LTs (e.g., 5-hydroxyeicosatetraenoic acid—5-HETE—, 5-hydroperoxyeicosatetraenoic acid—5-HPETE—, LTB₄, LTC₄, LTD₄, and LTE₄) produced by leukocytes and mast cells, have prominent effects on bronchial smooth muscle, vasculature, and

leukocyte recruitment (Ribeiro et al. 2015; Kumar et al. 2018). Conversely, LXs (e.g., LXA₄ and LXB₄) are important in the resolution of inflammation, by inhibiting the recruitment of leukocytes (Kumar et al. 2018).

Cytokines are signaling molecules produced by several cell types, mainly activated lymphocytes, macrophages, and dendritic cells (Kumar et al. 2018). They can be pro-inflammatory (e.g., interleukin—IL—1, IL-2, IL-4, IL-6, IL-12, IL-17, tumor necrosis factor—TNF— α , and interferon—IFN— γ) and anti-inflammatory (e.g., IL-10 and transforming growth factor—TGF— β) cytokines. The pro-inflammatory cytokines play several roles in the inflammatory process, such as leukocyte recruitment and activation, endothelium activation, and induction of the acute-phase response. The anti-inflammatory cytokines reduce or limit the inflammation in the body. Cytokines have a pleiotropic action (induce different biological effects) and are redundant (two or more cytokines mediate similar functions). They can have synergistic (combined effect of two cytokines is greater than the additive effects of the individual cytokines) or antagonistic actions (the effect of one cytokine inhibits the effect of another). Cytokines also display a cascade induction mode (action of one cytokine-induced production of one or more additional cytokines). Chemokines (e.g., IL-8 and monocyte chemoattractant protein—MCP—1), produced by several cell types, control leukocyte extravasation and chemotaxis towards the injured tissues (Medzhitov 2008). They influence the assembly, disassembly, and contractility of cytoskeleton proteins and the expression of cell-surface adhesion molecules. Both cytokines and chemokines can act in an endocrine (act on cells some distance away from the secreting cell), paracrine (act on cells near the secreting cell), and/or autocrine (act on own cell) manner.

The activated neutrophils, macrophages, and dendritic cells produce also large amounts of ROS/RNS to that also leads to the efficient killing of the offending agent (Ribeiro et al. 2015). ROS (e.g., superoxide radical—O₂^{•−}—, hydroxyl radical—•OH—, peroxy radical—ROO•) and RNS (e.g., nitric oxide—NO— and peroxynitrite—ONOO[−]) strongly modify the chemical structure of some molecules of the offending agent (e.g., oxidation and nitration).

Proteolytic enzymes, such as matrix metalloproteinases (MMP; e.g., MMP-2, MMP-3, MMP-10,

Table 1 Principal mediators of inflammation (Mohammed 2003; O'Connor et al. 2004; Schulze-Topphoff et al. 2008; Jutel et al. 2009; Weidinger and Kozlov 2015; Merle et al.

2015; Herr et al. 2017; Yao and Narumiya 2019; Sasaki and Yokomizo 2019; Jaén et al. 2021; Liu et al. 2021)

Inflammatory mediator	Main producing cells	Target cells	Most common functions
<i>Vasoactive amines</i>			
Histamine	Mast cells	Monocytes	Vasodilation
		Basophils	Increase venular permeability
	Basophils	Dendritic cells	Enhance leukocyte rolling and firm adhesion
		T cells	Enhance leukocyte extravasation
		B cells	Immune cell maturation, activation, and differentiation
		Endothelial cells	
Serotonin	Mast cells	Mast cells	Vasodilation
	Macrophages	Macrophages	Endothelial activation
	Dendritic cells	T cells	Increase vascular permeability
	T cells	Endothelial cells	Enhance leukocyte recruitment
			Increase cytokine production
			Immune cell activation and differentiation
<i>Vasoactive peptides</i>			
Substance P	Mast cells	Mast cells	Degranulation
	Macrophages	Macrophages	Cytokine production
	Dendritic cells	Dendritic cells	Modulation of antigen presentation
	B cells	B cells	T cell activation and proliferation
	T cells	T cells	Enhancing antibody production
	Neurons	Endothelial cells	Transmission of pain signals
			Increasing vascular permeability
Bradykinin	Mast cells	Mast cells	Regulate blood pressure
	Macrophages	Macrophages	Pain
	Dendritic cells	Dendritic cells	Antigen presentation
	B cells	B cells	Cytokine and antibody production
	T cells	T cells	T and B cells activation and proliferation
	Endothelial cells	Endothelial cells	Increase vascular permeability
			Contraction of smooth muscle
<i>Complement fragments</i>			
C5a, C3a, and C4a	Monocytes	Mast cells	Chemotaxis
	Macrophages	Basophils	Histamine production
	Neutrophils	Eosinophils	Stimulate degranulation
	Dendritic cells	Neutrophils	Vasodilation
	Hepatocytes	Monocytes	Increase vascular permeability
		Natural killer cells	Recruitment and activation of leukocytes
		T cells	
C3b	Neutrophils	Neutrophils	Promote phagocytosis
	Macrophages	Macrophages	
	Dendritic cells		
	B cells		
	Hepatocytes		

Table 1 continued

Inflammatory mediator	Main producing cells	Target cells	Most common functions
C5b and C6–C9	Neutrophils Macrophages Dendritic cells Hepatocytes	Pathogen	Lysis
<i>Prostaglandins</i>			
PGE2	Mast cells	Macrophages	Pain
	Neutrophils	Dendritic cells	Fever
	Monocytes	Natural killer cells	Vasodilation
	Macrophages	T cells	Vascular hyperpermeability
	Dendritic cells	B cells	Induction of smooth muscle contraction
	B cells	Endothelial cells	Leukocyte recruitment and migration
	T cells	Neurons	Activation and differentiation of leukocytes
	Endothelial cells		Cytokine production
PGD2	Mast cells	Mast cells	Vasodilation
	Basophils	Neutrophils	Increase venules permeability
	Eosinophils	Dendritic cells	Chemoattraction
	Macrophages	B cells	Cytokine production
	T _{H2} cells	T cells	Mediation of histamine release
	Endothelial cells	Endothelial cells	Leukocyte recruitment Activation and differentiation of leukocytes
PGF2	Mast cells	Neutrophils	Vasodilation
	Neutrophils	Monocytes	Contraction of bronchial and uterine smooth muscle
	Monocytes	Macrophages	Cytokine and ROS production
	Macrophages	Dendritic cells	Modulation of antigen-presenting capacity
	T cells	T cells	Recruitment and activation of leukocytes
	Endothelial cells	Endothelial cells	
PGI2	Mast cells	Eosinophils	Vasodilation
	Macrophages	Monocytes	Platelet-aggregation inhibition
	Dendritic cells	Macrophages	Cell proliferation reduction
	T cells	Dendritic cells	Modulation of function of leukocytes
	Endothelial cells	Endothelial cells	
PGJ2	Macrophages	Macrophages	Reduction of macrophage activation
	Endothelial cells	Dendritic cells	Reduction of nitric oxide production
		B cells	Promote apoptosis
		T cells	
<i>Thromboxanes</i>			
TXA2	Mast cells	Macrophages	Platelet-aggregation promotion
	Macrophages	Dendritic cells	Vasoconstriction
	T cells	T cells	Smooth muscle contraction
	Endothelial cells	Endothelial cells	Lymphocyte proliferation Cytokine production

Table 1 continued

Inflammatory mediator	Main producing cells	Target cells	Most common functions
<i>Leukotrienes</i>			
5-HPETE	Mast cells	Mast cells	Increase intracellular Ca^{2+} levels
	Eosinophils	Eosinophils	Enhance free radical production
	Neutrophils	Neutrophils	Cytokine and chemokine production
	Monocytes	Smooth muscle cells	Induce the migration and activation of immune cells
		Endothelial cells	
5-HETE	Mast cells	Mast cells	Chemotaxis
	Eosinophils	Eosinophils	Leukocyte adhesion
	Neutrophils	Neutrophils	Enhance free radical production
	Monocytes	Smooth muscle cells	Activation and recruitment of leukocytes
	Macrophages	Endothelial cells	
LTA4	Mast cells	Neutrophils	Chemotaxis
	Eosinophils	Monocytes	Vasoconstriction
	Neutrophils	Macrophages	Recruitment of leukocytes
	Macrophages	T cells	
LTB4	Mast cells	Eosinophils	Chemotaxis
	Basophils	Neutrophils	Enhance leukocyte adhesion
	Eosinophils	Monocytes	Increase vascular permeability
	Neutrophils	Macrophages	Free radical production
	Monocytes	T cells	Release of lysosomal enzymes
	Macrophages	Endothelial cells	T cell proliferation
	Dendritic cells		
LTC4	Epithelial cells		
	Mast cells	Mast cells	Bronchospasm
	Basophils	Basophils	Microvascular vasoconstriction
	Eosinophils	Eosinophils	Increase vascular permeability
	Monocytes	Macrophages	Recruitment of leukocytes
	Macrophages		Enhance mucus secretions
LTD4	Epithelial cells		
	Mast cells	Mast cells	Vasoconstriction
	Basophils	Basophils	Bronchospasm
	Eosinophils	Eosinophils	Microvascular vasoconstriction
		T cells	Increase venules permeability
			Recruitment and activation of leukocytes
LTE4			Enhance mucus secretions
			Promotion of degranulation
	Mast cells	Eosinophils	Vasoconstriction
	Basophils	Neutrophils	Bronchospasm
	Eosinophils	Macrophages	Microvascular vasoconstrictor
	Macrophages	T cells	Increase venules permeability
		Vascular smooth muscle cells	Increase adhesion molecule expression
			Recruitment and activation of leukocytes
			Enhance mucus secretions
			Cytokine production

Table 1 continued

Inflammatory mediator	Main producing cells	Target cells	Most common functions
<i>Lipoxins</i>			
LXA4	Mast cells	Mast cells Neutrophils Monocytes Macrophages Dendritic cells T cells	Vasoconstriction antagonism Inhibition of endothelium adhesion Suppression of chemotaxis Stimulation of macrophage phagocytosis of apoptotic neutrophils Inhibit degranulation Inhibit antigen presentation Inhibit T cell proliferation Promote T _{REG} differentiation
LXB4	Mast cells Neutrophils Monocytes Macrophages	Neutrophils Monocytes Macrophages Dendritic cells	Inhibition of chemotaxis Inhibition of neutrophil adherence and activation Inhibition of cytokine production Inhibition of phagocytosis Decrease antigen-presenting capacity Promotion of apoptosis
<i>Pro-inflammatory cytokines</i>			
IL-1(α/β)	Neutrophils Monocytes Macrophages Dendritic cells T cells Endothelial cells	Natural killer B cells T cells Endothelial cells Hepatocytes Hypothalamus	Fever Induction of acute phase proteins Induction of other cytokines Promote expression of adhesion molecules
IL-2	Natural killer cells CD4 ⁺ T cells CD8 ⁺ T cells	B cells T cells Natural killer cells	Proliferation and differentiation of T cells T cell effector and memory formation TREG generation Natural killer cytotoxicity
IL-4	CD4 ⁺ T cells TH2 cells	Mast cells Macrophages B cells T cells TH2 cells	Proliferation and differentiation of TH2 cells
IL-6	Mast cells Macrophages Dendritic cells T cells TH2 cells B cells	Monocytes Macrophages Natural killer cells B cells T cells Endothelial cells Hepatocytes	Regulation of hematopoiesis Induction of acute phase response Differentiation, activation, and proliferation of leukocytes

Table 1 continued

Inflammatory mediator	Main producing cells	Target cells	Most common functions
IL-12(A/B) (p35/p40)	Macrophages	Natural killer cells	TH1 differentiation
	Dendritic cells	T cells	IFN- γ induction
	B cells	TH1 cells	Promote cytotoxicity
IL-17	CD4 ⁺ T cells	Neutrophils	Increase chemokine and cytokine production
	TH17 cells	Macrophages	Recruitment and activation of leukocytes
		Endothelial cells	
TNF- α	Neutrophils	Neutrophils	Inflammation
	Macrophages	Monocytes	Cachexia
	Monocytes	Endothelial cells	Induction of acute phase proteins
	T cells	Hepatocytes	Cytokine and chemokine production
IFN- γ			Induction of death in many types of cells
			Neutrophil activation
	Macrophages	Macrophages	Activation and differentiation of leukocytes
	Dendritic cells	Dendritic cells	Induce MHC-I and -II molecules expression
	Natural killer cells	Natural killer cells	Cytokine and chemokine production
	TH1 cells	TH1 cells	Augments natural killer cells cytotoxicity
	CD8 ⁺ cell	Endothelial cells	
	Virus-infected cells		
<i>Anti-inflammatory cytokines</i>			
IL-10	Monocytes	Macrophages	Suppression cytokines and MHC-II
	Macrophages	Dendritic cells	Inhibition of the activation and proliferation of leukocytes
	Dendritic cells	Natural killer cells	Differentiation of TREG
	TREG cells	TH1 cells	
TGF- β		TREG cells	
	Mast cells	Macrophages	Suppression B cell, T cell, and macrophages effector functions
	Macrophages	Dendritic cells	TH17 and TREG differentiation
	Dendritic cells	Natural killer cells	Tolerance promotion
	Natural killer cells	B cells	Induction of tissue repair
	B cells	T cells	
	T cells		
	T _{REG} cells		
<i>Chemokines</i>			
IL-8 (CXCL8)	Neutrophils	Neutrophils	Enhance adhesion
	Macrophages		Recruitment and activation of neutrophils
	T cells		
	Endothelial cells		
MCP-1 (CCL2)	Monocytes	Monocytes	Chemotaxis
	Macrophage	Basophils	
		Eosinophils	
		T cells	

Table 1 continued

Inflammatory mediator	Main producing cells	Target cells	Most common functions
<i>Reactive oxygen species and reactive nitrogen species</i>			
O ₂ ^{•−}	Macrophages	Pathogens	Oxidation, hydroxylation, chlorination, nitration, and S-nitrosylation of pathogen molecules
•OH	Neutrophils		
ROO•	Dendritic cells		
•NO			
ONOO [−]			
<i>Proteolytic enzymes</i>			
MMP-2	Macrophages	Components of ECM	Limit inflammation-inducing signals
	Neutrophils	Endothelial cells	Stimulate vascular permeability
	T cells		Tissue remodeling and repair
MMP-3	Macrophages	Components of ECM	Tissue remodeling
	Monocytes	Endothelial cells	Stimulate vascular permeability
	T cells		
MMP-10	Macrophages	Components of ECM	Regulate the resolution phase of acute inflammation
	T cells	Macrophages	
MMP-14	Neutrophils	Components of ECM	Generation of complement fragments
	Macrophages	Macrophages	Migration and activation of leukocytes
	Dendritic cells	Dendritic cells	Promote pro-inflammatory genes in macrophages
		T cells	
MMP-19	Neutrophils	Components of ECM	Recruitment
	Monocytes	Neutrophils	Regulate neutrophil clearance by macrophage phagocytosis
	Macrophages	Macrophages	Regulate the resolution phase of acute inflammation
	Dendritic cells		Tissue remodeling
MMP-28	Neutrophils	Components of ECM	Regulate the resolution phase of acute inflammation
	Monocytes	Macrophages	Regulation of cytokine and chemokine expression
	Macrophages		Modulation of migration and adhesion leukocytes
	T cells		

Ca²⁺, calcium ions; CCL, C–C motif chemokine ligand; CXCL, C-X-C motif chemokine ligand; ECM, extracellular matrix; IFN, interferon; IL, interleukin; LT, leukotriene; LX, lipoxin; MCP, monocyte chemoattractant protein; MMP, matrix metalloproteinase; NO, nitric oxide; O₂^{•−}, superoxide radical; •OH, hydroxyl radical; ONOO[−], peroxynitrite; PG, prostaglandin; ROO•, peroxy radical; ROS, reactive oxygen species; TGF, transforming growth factor; TH, T helper cells; TNF, tumor necrosis factor; TREG, regulatory T cell; TX, thromboxane; 5-HETE, 5-hydroxyeicosatetraenoic acid; 5-HPETE, 5-hydroperoxyeicosatetraenoic acid

MMP-14, MMP-19, and MMP-28), play an important role in tissue remodeling, in regulation of leukocyte migration and activation, as well as in controlling the cytokine and chemokine expression (Medzhitov 2008).

Inflammatory signaling pathways

If an antigen (e.g., PAMPS or DAMPS) or inflammatory mediator (e.g., cytokines or chemokines) binds to

an immune cell receptor (e.g., PPRs), there are intracellular changes at the molecular level that regulate and coordinate the inflammatory response. These series of biochemical reactions within the cell are known as intracellular signaling pathways, also called signal transduction cascades.

The immune signaling pathways result in the enhancement or inhibition of the expression of important genes involved in the inflammatory response (Medzhitov 2010). These genes encode

several inflammatory mediators, such as proteins with antimicrobial properties, chemokines, cytokines, and enzymes, that orchestrate the elimination of the offending agent and the healing of the damaged tissue.

The immune cells share common downstream inflammatory signaling pathways, including nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) (Li and Verma 2002), mitogen-activated protein kinase (MAPK) family (Arthur and Ley 2013), inflammasome activation (Guo et al. 2015), cytokine and chemokine signaling (Turner et al. 2014), cyclooxygenase (COX) and lipoxygenase (LOX) signaling (Dennis and Norris 2015), ROS/RNS mediated signaling (Conner and Grisham 1996; Mittal et al. 2014), among others.

NF- κ B signaling pathway

NF- κ B pathway is rapidly activated in response to a wide range of stimuli, including PAMPs, stress agents, mitogens, and pro-inflammatory cytokines (e.g., TNF and IL-1) (Li and Verma 2002; Liu et al. 2017). NF- κ B transcription factor family is composed of Rel (c-Rel), RelA (p65), RelB, NF- κ B1 (p50 and its precursor p105), and NF- κ B2 (p52 and its precursor p100) (Hayden and Ghosh 2008). Each member, except RelB, can form homodimers and heterodimers with each other (Li and Verma 2002). NF- κ B enhances or promotes target genes transcription of several inflammatory mediators involved in different immune responses, including pro-inflammatory cytokines (e.g., TNF- α , IL-1, and IL-6), chemokines (e.g., CCL2 and IL-8), ROS/RNS, CAMs, acute phase proteins, immunoreceptors, proteins involved in antigen presentation, stress-response proteins, and enzymes (e.g., COX-2 and inducible nitric oxide synthase—iNOS). It also participates in the regulation of the activation of inflammasome, and of the activation, differentiation, and effector functions of lymphocytes (Li and Verma 2002; Hayden and Ghosh 2008; Liu et al. 2017).

NF- κ B pathway may be activated by two distinct pathways, namely the classical (or canonical) and the alternative (or noncanonical) pathways (Fig. 5). In the classical pathway, the NF- κ B p65/p50 heterodimer is inactive in the cytosol if associated with inhibitory NF- κ B (I κ B) proteins (I κ B α , I κ B β , and I κ B ϵ) (Li and Verma 2002). Signaling through several receptors,

such PPRs (e.g., toll-like receptors—TLR—, C-type lectin receptors—CLR—, and nucleotide oligomerization domain leucine-rich repeat-containing receptors—NLR), G-protein-coupled receptors (GPCR), TNF receptor—TNFR—1, IL-1 receptor (IL-1R), TCR and BCR, recruit and activate specific intracellular adaptor proteins. This event phosphorylates the I κ B kinases (IKK) complex that consists of two kinases (IKK α and IKK β) and a regulatory subunit NF- κ B essential modulatory (NEMO) (Hayden and Ghosh 2008). Consequently, the IKK complex phosphorylates I κ B proteins, leading to its ubiquitination and proteasomal degradation, releasing NF- κ B dimers, namely p50/p65 and p50/Rel dimers (Li and Verma 2002; Hayden and Ghosh 2008; Liu et al. 2017). Free NF- κ B dimers are further activated by post-translational modifications and translocate to the nucleus where they bind to the specific site of the target genes to regulate their transcription (Hayden and Ghosh 2008). In the alternative pathway, the NF- κ B RelB/p100 complex is inactive in the cytosol. Signaling through TNFR superfamily members (e.g., lymphotoxin- β receptor—LT β R) activates the kinase NF- κ B-inducing kinase (NIK), which in turn activates the IKK α subunit that phosphorylates NF- κ B2 precursor protein p100 (Hayden and Ghosh 2008; Liu et al. 2017). Phosphorylation of the NF- κ B2 precursor protein p100 leads to its ubiquitination and proteasomal processing to NF- κ B2 p52. This creates mature NF- κ B p52/RelB complexes that translocate to the nucleus and induce the gene expression referred for the classical pathway.

MAPK signaling pathway

MAPK signaling pathway consists of the activation of three protein kinases. It initiates with the phosphorylation of MAPK kinase kinase (MPAKKK), followed by the phosphorylation and activation of MAPK kinase (MAPKK), which, in turn, activates the MAPK by dual phosphorylation (Fig. 6) (Zhang and Liu 2002; Arthur and Ley 2013). Once activated, the MAPK phosphorylates diverse substrates in the cytosol and nucleus (e.g., NF- κ B, c-Jun, ELK-1, and activator protein—AP—1), changing the protein function and gene expression of several cellular processes, such as cell growth, proliferation, differentiation, the production of pro-inflammatory cytokines

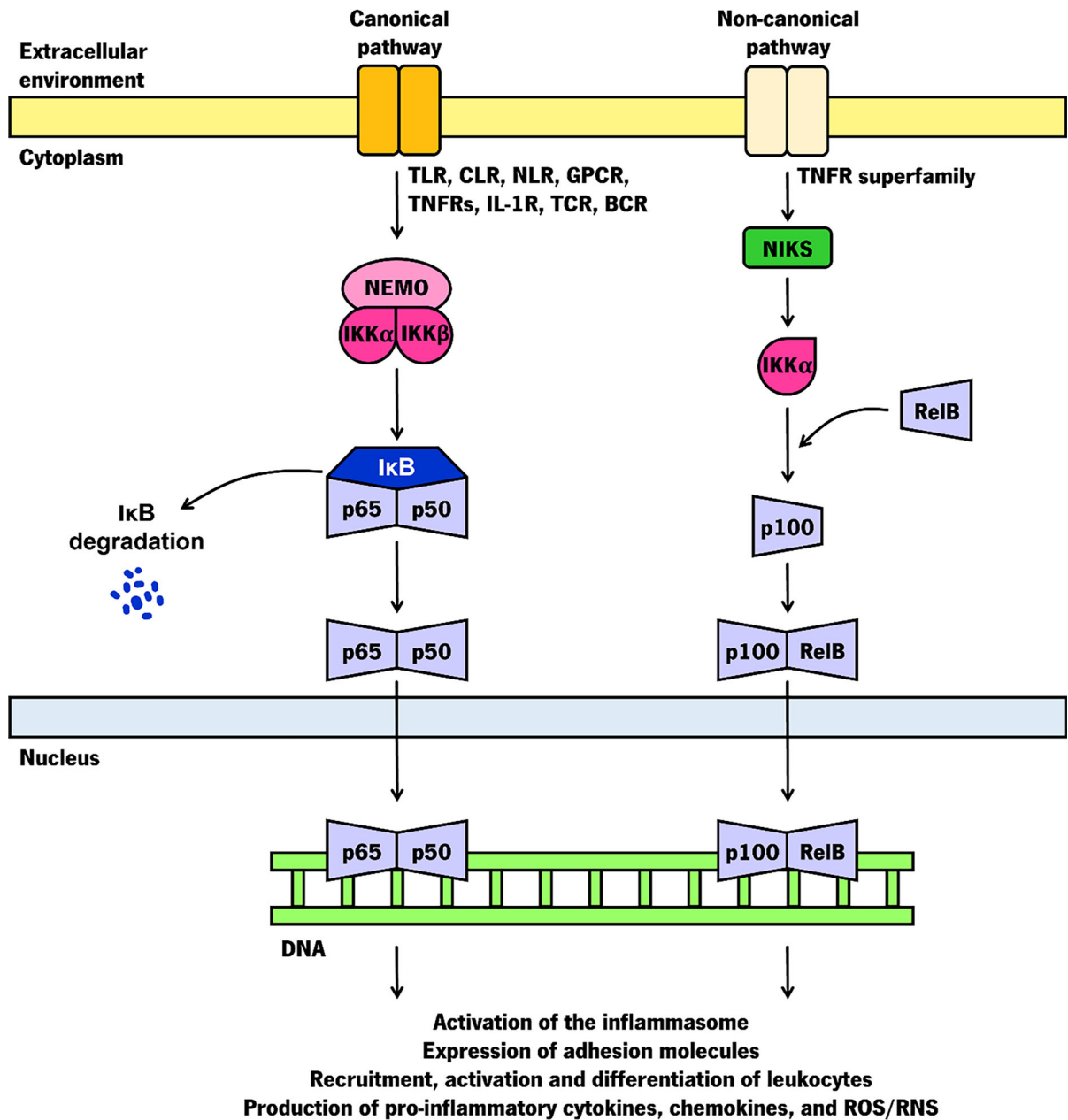


Fig. 5 NF-κB signaling pathway. BCR, B-cell receptor; CLR, C-type lectin receptor; DNA, deoxyribonucleic acid; GPCR, G-protein-coupled receptor; IKK, inhibitor of nuclear factor kappa B kinase; IL-1R, interleukin-1 receptor; IκB, inhibitor of nuclear factor kappa B; NEMO, nuclear factor kappa-light-chain-enhancer of activated B cells essential modulatory; NF-

κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NIK, nuclear factor kappa-light-chain-enhancer of activated B cells-inducing kinase; NLR, nucleotide-binding domain and leucine-rich repeat containing; RNS, reactive nitrogen species; ROS, reactive oxygen species; TCR, T-cell receptor; TLR, toll-like receptor; TNFR, tumor necrosis factor receptor;

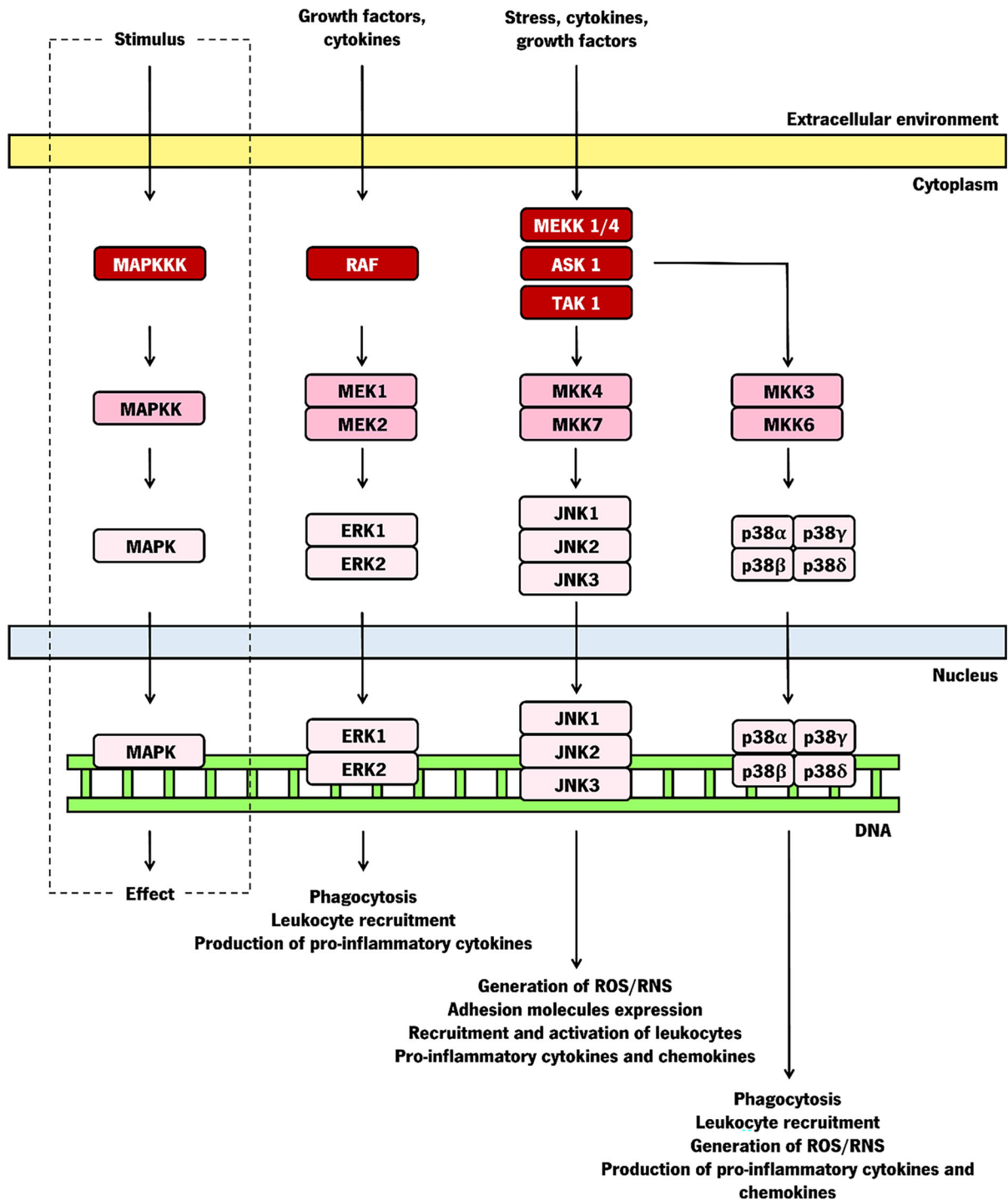


Fig. 6 MAPK signaling pathway. ASK, apoptosis signal-regulating kinase; DNA, deoxyribonucleic acid; ERK, extracellular signal-regulated kinase; JNK, C-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; MAPKK, mitogen-

activated protein kinase kinase; MAPKKK, mitogen-activated protein kinase kinase kinase; RAF, rapidly accelerated fibrosarcoma; TAK, transforming growth factor- β -activated kinase

development, cycle, survival, and death (Zhang and Liu 2002). MAPK activation also induces the production of pro-inflammatory cytokines and chemokines.

MAPK family includes extracellular signal-regulated kinase (ERK), C-Jun N-terminal kinase/stress-activated protein kinase (JNK/SAPK), and p38 kinase signaling pathways (Fig. 6) (Arthur and Ley 2013).

ERK signaling pathway

ERK1 and ERK2 are the predominant members of the ERK family (Lu and Malemud 2019). The ERK1/2 pathway is activated by growth factors (e.g., epidermal growth factor—EGF—and platelet-derived growth factor—PDGF) and cytokines (IL-1 β , IL-6, and TNF- α) through receptors tyrosine kinases (RTKs), GPCRs, integrins, and ion channels (Zarrin et al. 2021). When these receptors are bound with their ligands, the adaptor proteins recruit the MAPKKK cytoplasmic rapidly accelerated fibrosarcoma (RAF) to the cell membrane for activation (Fig. 6). Activated RAF phosphorylates the MAPKK MEK1/2, which then phosphorylates the MAPK ERK1/2. It can regulate targets in the cytosol and also translocate to the nucleus where it activates several transcription factors that induce cell growth and differentiation (Soares-Silva et al. 2016). Once inside the nucleus, ERK phosphorylates and activates a transcription factor, ELK-1, which cooperates with a second protein, serum response factor (SRF), to activate the transcription of the Fos gene. The Fos protein is also phosphorylated by ERK, and along with its partner, Jun, forms the master transcription factor, AP-1. ERK induces the production of pro-inflammatory cytokines and promotes leukocyte recruitment and phagocytosis.

JNK signaling pathway

JNK family members are constituted by JNK1, JNK2, and JNK3. The JNK pathway is activated by environmental stress (e.g., oxidative stress and DNA damage), inflammatory cytokines (e.g., TNF), and growth factors (Hammouda et al. 2020). Adaptor proteins phosphorylate and activate the MAPKKK, such as MEKK1/4, apoptosis signal-regulating kinase—ASK—1 or TGF- β -activated kinase—TAK—1, which consequently phosphorylates the MAPKK MKK4/7 (Fig. 6). Activated MKK4/7 phosphorylates the MAPK JNK1/2/3 that translocates to the nucleus

and activates several genes involved in apoptosis, inflammation, cytokine production, and metabolism (Hammouda et al. 2020). JNK stimulates the production of pro-inflammatory cytokines, chemokines, ROS/RNS, and adhesion molecules. It also participates in the recruitment and activation of leukocytes.

p38 signaling pathway

The p38 family members include p38 α , p38 β , p38 γ , and p38 δ . The p38 pathway is activated by environmental stress, growth factors, and inflammatory cytokines (e.g., TNF- α and IL-1 β) (Canovas and Nebreda 2021). Adaptor proteins phosphorylate and activate the MAPKKK, such as MEKK1/4, ASK1, or TAK1 (Fig. 6). These molecules phosphorylate the MAPKK MKK3/6. Consequently, MAPK p38 is phosphorylated and activated, which participates in the regulation of genes involved in cell apoptosis, differentiation, and cycle regulation (Arthur and Ley 2013). The p38 also stimulates the pro-inflammatory cytokine, chemokine, and ROS/RNS production and promotes leukocyte recruitment and phagocytosis.

Inflammasome activation

NLRs are a type of PRRs that can assemble in the cytosol with other proteins forming a complex inflammasome (Guo et al. 2015). The inflammasome controls the maturation and release of cytokines (Schroder and Tschopp 2010). The variety of the NLR protein-forming scaffold enables the formation of several inflammasomes, with distinct components and activation mechanism (Schroder and Tschopp 2010). The best-characterized inflammasome is the NLR family pyrin domain containing 3 (NLRP3), expressed in monocytes, macrophages, neutrophils, dendritic cells, and some lymphocytes (Schroder and Tschopp 2010; Gaffo 2014).

The NLRP3 inflammasome is activated with several PAMPs (e.g., pore-forming toxin, and fungal, bacterial, or viral pathogens) or DAMPs (e.g., ATP and nucleic acids) (Schroder and Tschopp 2010; Guo et al. 2015). However, NLRP3 must be primed before activation. The priming initiates when the NF- κ B signaling pathway is activated and the NLRP3 protein is upregulated (Fig. 7) (Guo et al. 2015). Then, NLRP3 and adaptor protein apoptosis-associated speck-like protein containing a caspase recruitment

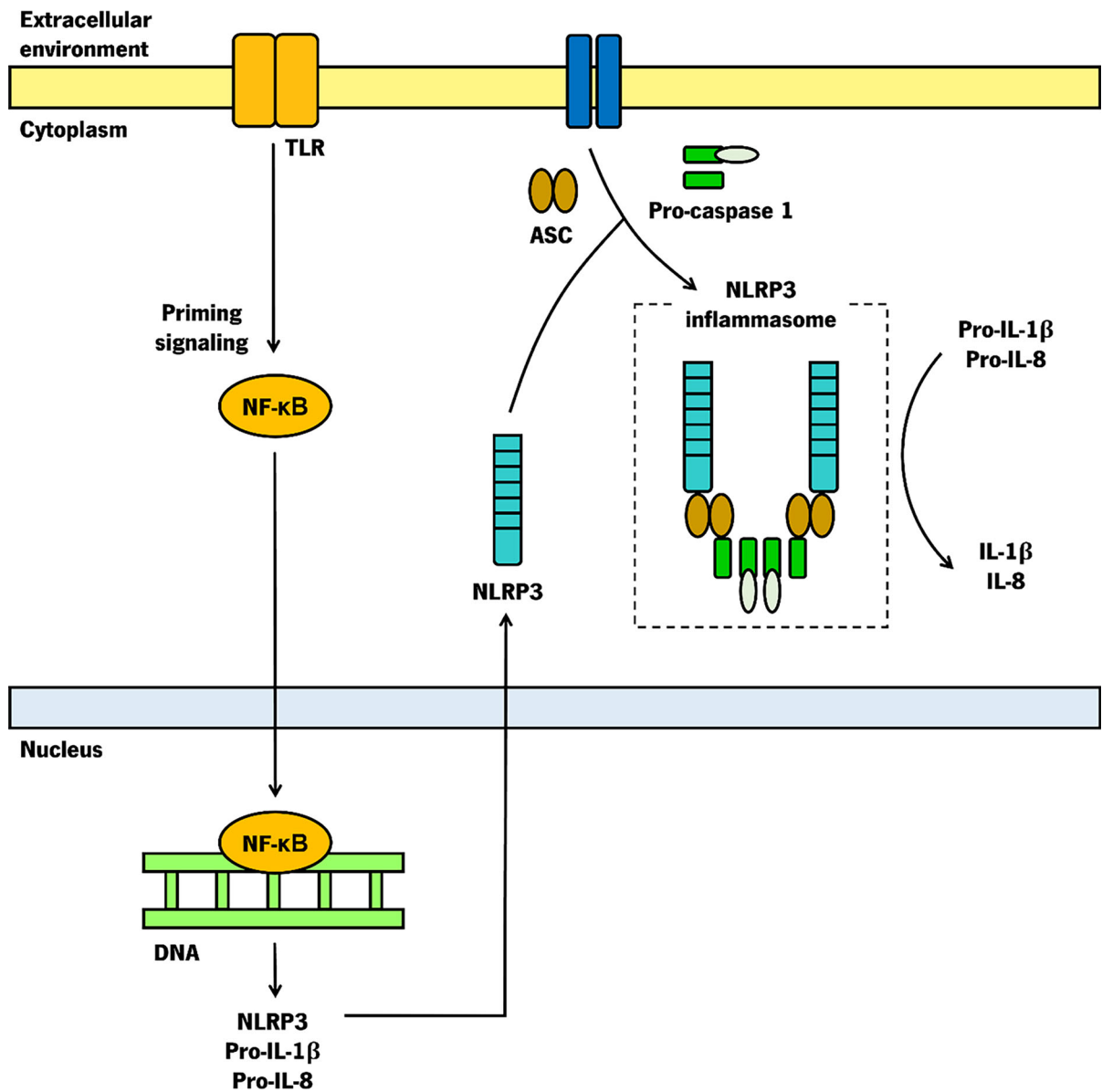


Fig. 7 NLRP3 inflammasome signaling pathway. ASC, apoptosis-associated speck-like protein containing a caspase recruitment domain; DNA, deoxyribonucleic acid; IL, interleukin; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B

cells; NLRP3, nucleotide oligomerization domain leucine-rich repeat-containing receptors family pyrin domain containing 3; TLR, toll-like receptor

domain (ASC) suffer conformational changes to assemble into an NLRP3 inflammasome. The activation of NLRP3 is related to intracellular signals, such as potassium ion efflux, ROS, and/or leakage of lysosomal contents (Guo et al. 2015). This induces oligomerization of the pro-caspase-1, ASC, and NLRP3, leading to their proximity-induced activation (Schroder and Tschopp 2010; Guo et al. 2015).

Oligomerization of pro-caspase-1 proteins induces their autoproteolytic cleavage into active caspase-1. Active caspase-1 cleaves the precursor cytokines pro-IL-1β and pro-IL-18 into mature cytokines IL-1β and IL-18, respectively (Schroder and Tschopp 2010). Active caspase-1 is also able to induce pyroptosis, an inflammatory form of cell death (Guo et al. 2015).

Cytokines signaling

Cytokines are key inflammatory molecules that allow the communication between the cells of the immune system, regulating the intensity and duration of the immune response (Turner et al. 2014). Despite there are several pro-inflammatory cytokines, the ones with a function more prominent during an inflammatory response are IL-1 β , IL-6, and TNF- α (Turner et al. 2014). Their expression is induced by the binding of PAMPs or DAMPs to the PRRs, through the activation of the inflammatory signaling pathways, resulting in a change in enzyme activity and gene expression.

IL-1 β signaling

The IL-1 β is synthesized as a precursor peptide (pro-IL-1 β) and secreted in its mature form (IL-1 β) by activated monocytes, macrophages, neutrophils, and dendritic cells (Gabay et al. 2010; Turner et al. 2014). IL-1 β is a potent pleiotropic cytokine that stimulates both local and systemic responses. IL-1 β induces the expression of adhesion molecules on endothelial cells, as well as induces the release of chemokines by stromal cells, promoting the recruitment of inflammatory cells at the site of inflammation (Gabay et al. 2010). IL-1 β also induces the release of inflammatory mediators, such as PGE2 and NO. Additionally, it promotes the differentiation of T_H cells into T_{H17} cells and the production of IL-17. Additionally, IL-1 β induces the liver to produce acute-phase proteins, which further promotes the generation of fever. IL-1 β also amplifies its production, since it induces the expression of its own genes (Weber et al. 2010).

To exert its effects, IL-1 β binds to IL-1R on the surface of several immune cells, such as monocytes, macrophages, and dendritic cells (Dinarello 2018). Then, the IL-1R accessory protein (IL-1RAcP) is recruited, forming a trimolecular signaling complex (Fig. 8) (Gabay et al. 2010; Weber et al. 2010). The complex immediately assembles with intracellular adaptor molecules, including myeloid differentiation primary response 88 (MyD88) and interleukin-1 receptor-associated kinase (IRAK). After phosphorylation, IRAK recruits TNF receptor-associated factor—TRAF—6 that activates NF- κ B and MAPK family signaling pathways and leads to the effects previously referred.

IL-6 signaling

IL-6 is a pleiotropic cytokine secreted by phagocytes, T cells, and B cells (Turner et al. 2014). IL-6 induces hematopoiesis, promotes the expansion and activation of T cells, the survival of B cells and their differentiation into antibody-secreting plasma cells, the regulation and differentiation of TH2 and TREG phenotypes, and the regulation of the acute phase response (Turner et al. 2014; Hunter and Jones 2015). IL-6 regulates the neutrophil-activating chemokines and neutrophil apoptosis, promoting and modulating the cellular adhesion molecules. IL-6 has also the ability to differentiate proinflammatory macrophages into anti-inflammatory macrophage phenotypes, promoting wound healing in the terminal step of inflammation (Schaper and Rose-John 2015).

IL-6 binds to the IL-6 receptor (IL-6R), associated with a signal transducer gp130 (Hunter and Jones 2015; Schaper and Rose-John 2015). IL-6R is restricted to neutrophils, monocytes, CD4⁺ T cells, and hepatocytes, while gp130 is expressed on all cells. The receptor subunits are associated only loosely with each other in the membrane, and the cytoplasmic region of each of the receptor subunits is associated with inactive tyrosine Janus kinases (JAKs) (Shuai and Liu 2003; Villarino et al. 2017). The binding of IL-6 to its cell-surface receptor induces dimerization of the gp130. This leads to the activation of the receptor-associated JAKs family (Fig. 9) (Shuai and Liu 2003; Hunter and Jones 2015). Consequently, the activated JAKs promotes the MAPK signaling pathway (Hunter and Jones 2015; Schaper and Rose-John 2015) or phosphorylate various specific tyrosine residues of the receptor, resulting in the creation of docking sites for the inactive transcription factor signal transducers and activators of transcription—STAT—3 (Schaper and Rose-John 2015). The inactive STAT3 is then phosphorylated by JAKs, which dimerize and change the conformation, leaving the receptor. The STAT3 dimer translocates into the nucleus, which binds specific regulatory sequences to activate or inactivate the transcription of target genes, inducing cell proliferation, differentiation, migration, apoptosis, and survival (Shuai and Liu 2003; Villarino et al. 2017).

The adamalysin proteases ADAM17 and ADAM1 in response to apoptosis or bacterial toxins cleave a site in the IL-6R that is proximal to the plasma

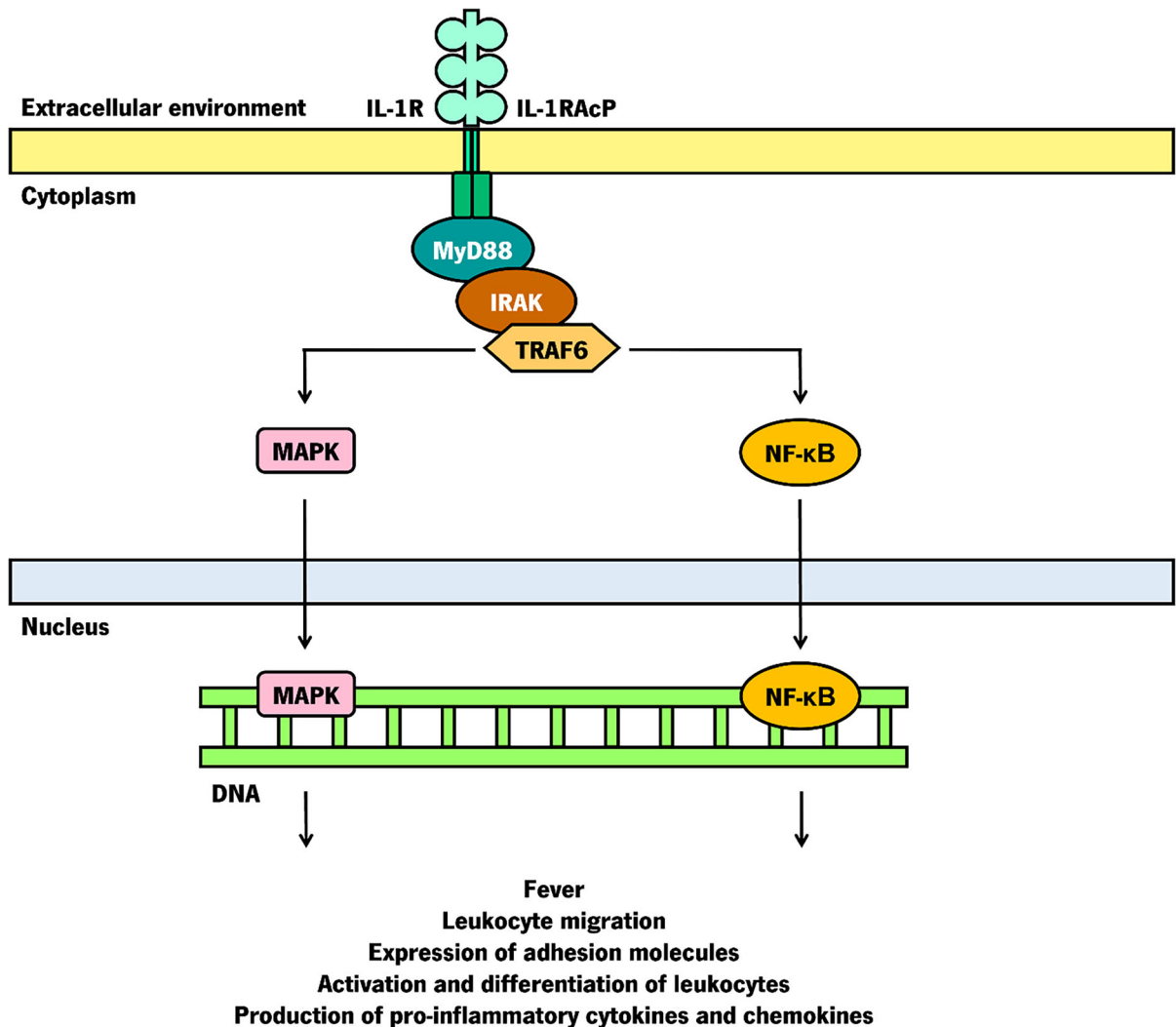


Fig. 8 IL-1 β signaling pathway. DNA, deoxyribonucleic acid; IL, interleukin; IL-1RAcP, interleukin-1 receptor 1 accessory protein; IL-1R1, interleukin-1 receptor 1; IRAK, interleukin-1 receptor-associated kinase; MAPK, mitogen-activated protein

kinase; MyD88, myeloid differentiation primary response 88; NF- κ B, nuclear factor kappa-light-chain-enhancer of activated B cells; TRAF, tumor necrosis factor receptor-associated factor

membrane of monocytes and activated T cells, resulting in the release of a soluble form of IL-6R (sIL-6R) (Hunter and Jones 2015). IL-6 can also bind to sIL-6R to form a complex that increases the circulating half-life of IL-6 and, consequently, its bioavailability (Hunter and Jones 2015; Schaper and Rose-John 2015).

TNF- α signaling

TNF- α is a central pleiotropic inflammatory mediator in the immune response, secreted by activated

macrophages, monocytes, T cells, natural killer cells, and non-immune cells, such as endothelial cells and fibroblasts (Turner et al. 2014). TNF- α induces the transcription of several genes encoding inflammation (Faustman and Davis 2013). TNF- α facilitates the proliferation of immune cell clones, stimulates differentiation and recruitment of naïve immune cells, and coordinates the destruction of immune cell clones to reduce inflammation. TNF- α also induces the production of eicosanoids (Sedger and McDermott 2014).

TNF- α is synthesized as a transmembrane precursor protein (mTNF- α) expressed on the surface of cells

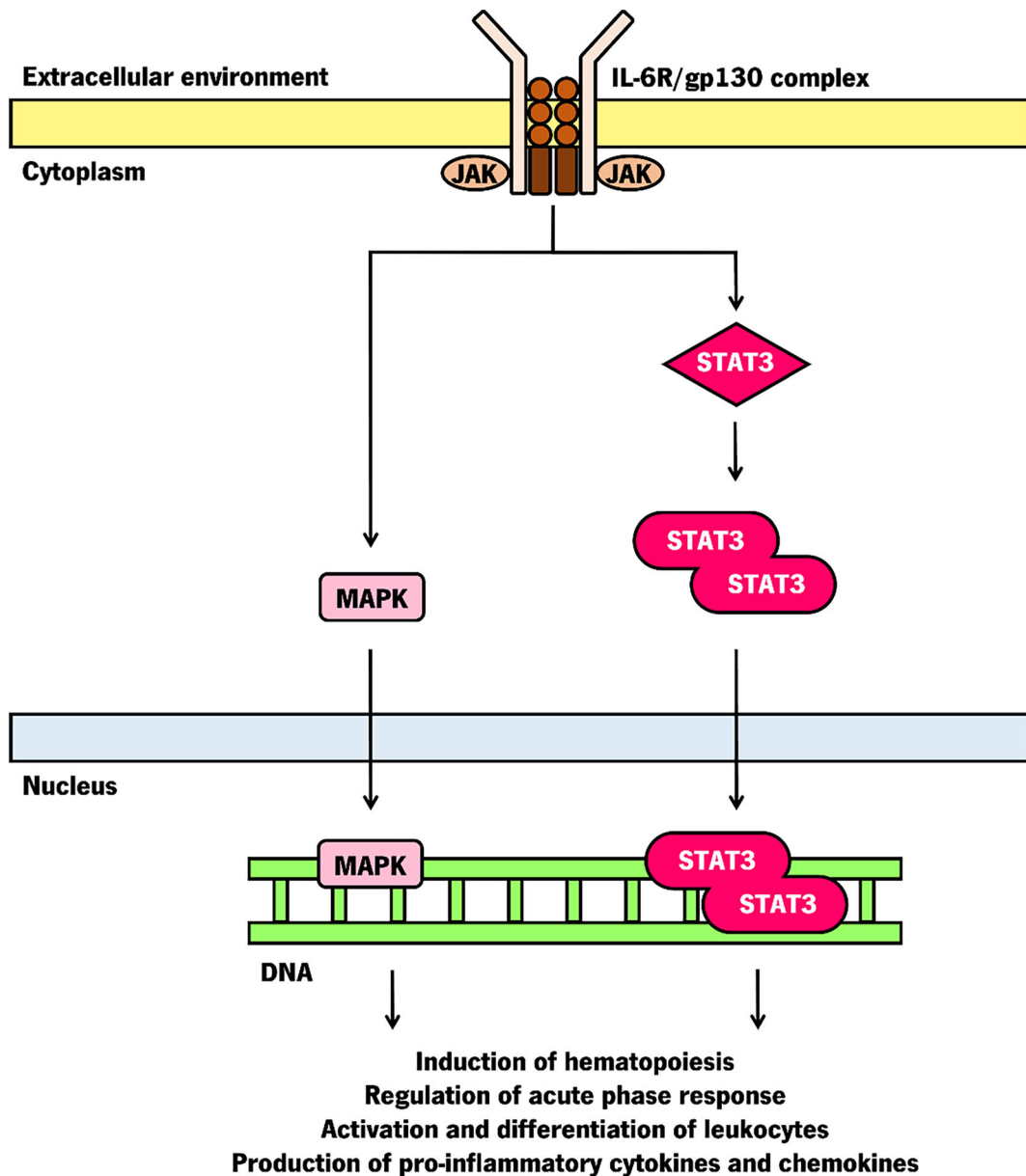


Fig. 9 IL-6 signaling pathway. DNA, deoxyribonucleic acid; IL, interleukin; IL-6R, interleukin-6 receptor; JAK, Janus kinases; MAPK, mitogen-activated protein kinase; STAT, signal transducers and activators of transcription

(Turner et al. 2014). Metalloproteinase TNF-converting enzyme (TACE) cleaves mTNF- α , releasing TNF- α in the extracellular environment. Thus, TNF- α is able to bind and activate TNFRs (Brenner et al. 2015). Signaling through TNFRs can lead to survival or cell death, as previously referred, depending on the nature of the signal and the cellular context. For both pathways, TNF- α elicits its biological effects by

binding to its receptor TNFR1 present in immune cells (Faustman and Davis 2013; Brenner et al. 2015). Binding of TNF- α to TNFR1 induces trimerization of the receptor and conformational alteration in its cytoplasmic domain (Turner et al. 2014; Brenner et al. 2015). This results in the recruitment of the TNFR1-associated death domain protein (TRADD, Fig. 10). Then, TRADD binds to receptor-interacting

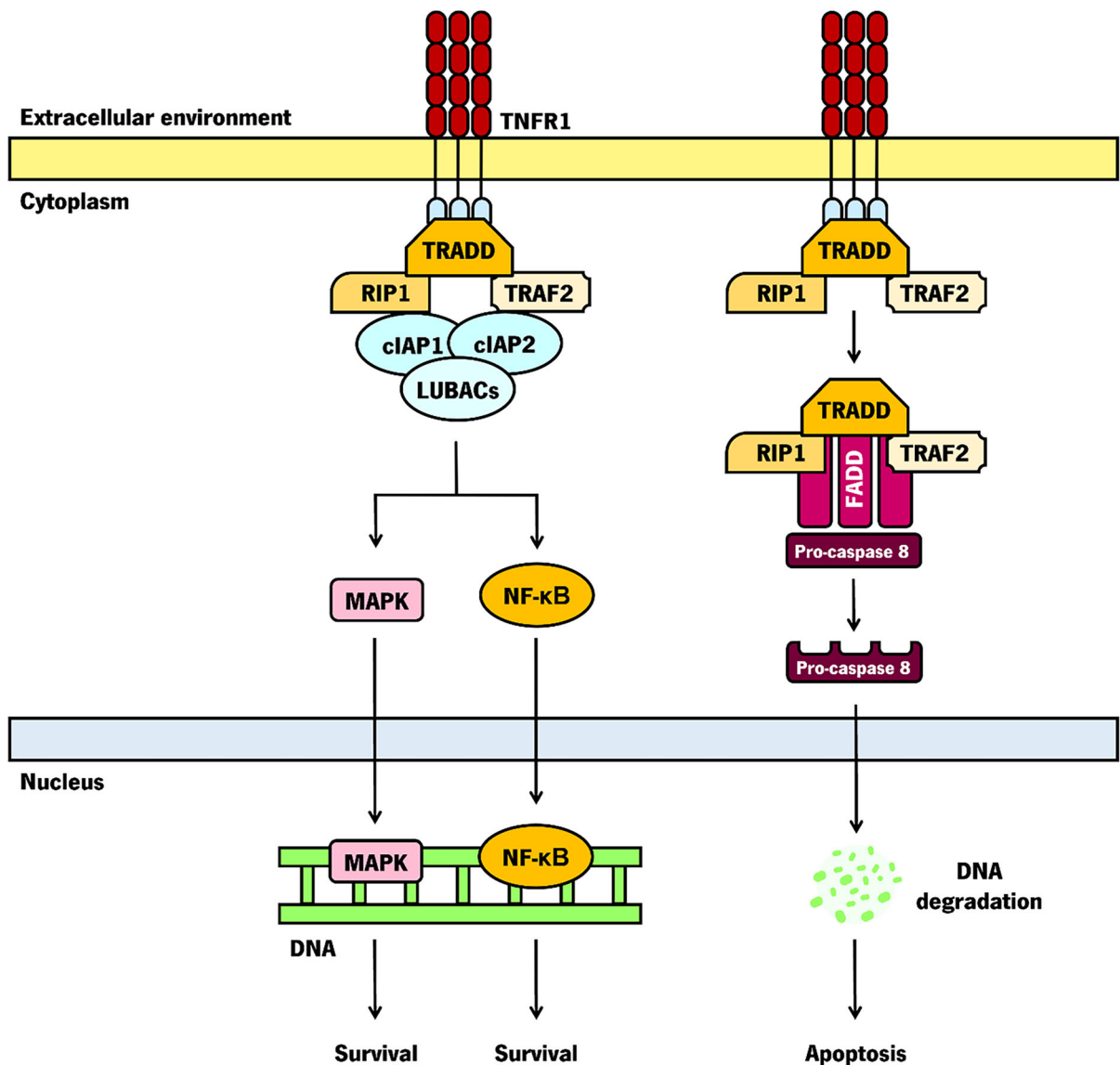


Fig. 10 TNF- α signaling pathway. cIAP, cellular inhibitor of apoptosis protein; DNA, deoxyribonucleic acid; FADD, Fas-associated death domain-containing protein; LUBAC, linear ubiquitin chain assembly complex; MAPK, mitogen-activated protein kinase; NF- κ B, nuclear factor kappa-light-chain-

enhancer of activated B cells; RIP, receptor interacting protein; TNF, tumor necrosis factor; TNFR1, tumor necrosis factor receptor 1; TRADD, tumor necrosis factor receptor 1 associated death domain protein; TRAF, tumor necrosis factor receptor-associated factor

protein—RIP—1 kinase and the TRAF2 (Turner et al. 2014; Brenner et al. 2015). The assembling of these molecules (TRADD, RIP1, and TRAF2) is known as complex I. The survival signals are generated by the binding of cellular inhibitor of apoptosis protein—cIAP—1 and cIAP2 (Brenner et al. 2015). Consequently, the proteins of the linear ubiquitin chain assembly complex (LUBAC) proteins bind to it. Then,

these molecules trigger MAPK and NF- κ B signaling pathways (Brenner et al. 2015). This results in the inhibition of the caspase-8 action, favoring the survival and proliferation of the cells. Additionally, more pro-inflammatory genes are expressed (Fig. 10). Alternatively, apoptotic signals are produced by the release of silencer of death domain (SODD) protein inside the cell. Then, the complex I dissociates from

the receptor and migrates to the cytoplasm where it binds to the adapter protein Fas-associated death domain-containing protein (FADD) (Sedger and McDermott 2014). These proteins recruit the initiator caspase, pro-caspase-8, forming complex II. Complex II activates the caspase-8 leads to cell apoptosis through DNA degradation (Fig. 10).

Chemokine signaling

Chemokines are small chemoattractants cytokines that bind to cell-surface receptors and induce the movement of leukocytes towards the site of inflammation (Turner et al. 2014). Chemokines are recognized by specific cell surface GPCRs with seven transmembrane domains (Rot and von Andrian 2004). Among the different chemokines, IL-8 is produced rapidly and abundantly in response to a variety of stimuli, including bacterial and viral pathogens, inflammatory cytokines, and other signaling molecules.

IL-8 signaling

IL-8, also known as C-X-C motif chemokine ligand—CXCL—8, is secreted by activated phagocytes and has a critical role in the recruitment and activation of myeloid cells to the site of inflammation (Turner et al. 2014). IL-8 activates the contractile system and enables leukocytes to migrate and adhere to endothelial cells (Baggiolini and Clark-Lewis 1992). IL-8 also promotes degranulation and elicits a rapid respiratory burst by activating the nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase, leading to a fast generation of $O_2^{\cdot -}$ and hydrogen peroxide (H_2O_2).

IL-8 binds with a great affinity to two GPCRs, namely CXC motif chemokine receptor—CXCR—1 and 2. This leads to their activation, with consequent dissociation of the G protein from the receptor and separation into $G\alpha$ and $G\beta\gamma$ subunits (Baggiolini and Clark-Lewis 1992; Rot and von Andrian 2004). The $G\alpha$ subunit activates the membrane-bound adenylate cyclase (AC), which generates cyclic AMP (cAMP). Consequently, cAMP activates protein kinase A (PKA), leading to the activation of the MAPK ERK1/2 signaling pathway (Turner et al. 2014). The $G\beta\gamma$ subunit activates the enzyme phosphoinositide-3 kinase (PI3K) to phosphorylate the phospholipid phosphatidyl inositol bis-phosphate (PIP2) into phosphatidylinositol-3,4,5-trisphosphate (PIP3) (Rot and

von Andrian 2004). PIP3 activates Ras-related C3 botulinum toxin substrate (Rac), which in turn activates more molecules that stimulate actin-related protein—Arp—2/3. This induces actin polymerization, responsible for the development and forward extension of the pseudopod. $G\beta\gamma$ subunit also activates a small cytoplasmic G protein, Rho, responsible for the movement of the cell through a gradient. Moreover, $G\beta\gamma$ also activates phospholipase β (PLC β) activity, which hydrolyzes PIP2, cleaving the sugar inositol trisphosphate (IP3) from the diacylglycerol (DAG) backbone (Turner et al. 2014). IP3 is released into the cytoplasm, where it interacts with specific IP3 receptors on the surface of endoplasmic reticulum vesicles, inducing the release of stored calcium ions (Ca^{2+}) into the cytoplasm, leading to the degranulation of neutrophils. DAG recruits and activates the enzyme protein kinase C (PKC), initiating a cascade that ultimately recruits TRAF6, leading to the activation of NF- κ B and MAPK signaling pathways.

Eicosanoid signaling

Eicosanoids are lipid signaling molecules produced by monocytes, macrophages, neutrophils, eosinophils, mast cells, basophils, dendritic cells, and B cells (Henderson 1994; Harizi et al. 2008; Dennis and Norris 2015). Eicosanoids arise from the oxidation of arachidonic acid (AA) present in the cells membrane. An inflammatory stimulus increases the intracellular influx of Ca^{2+} , which recruits phospholipase A2 (PLA2) enzymes, namely cytosolic PLA2 (cPLA2), to the cell membrane to release AA (Henderson 1994; Harizi et al. 2008). After, free AA is oxidized by COX and LOX, generating eicosanoids, such as PGs, TXs, LTs, and LXs (Harizi et al. 2008; Dennis and Norris 2015). Eicosanoids promote the induction of edema from postcapillary venules, mediating the leukocyte recruitment to the site of inflammation (Henderson 1994).

COX-2 signaling

COX-2 is an inducible enzyme primarily expressed in cells involved in inflammation, such as macrophages (Aoki and Narumiya 2012). COX-2, activated by several inflammatory stimuli (e.g., LPS, IL-1 β , IL-6, TNF- α), converts AA into unstable PGG2, which is further converted to PGH2. Afterward, cell-specific

prostaglandin and thromboxane synthases (e.g., PGES, PGDS, PGFS, PGIS, TBXAS1) converts PGH₂ into PGs (e.g., PGE₂, PGD₂, PGF_{2a}, PGI₂, and PGJ₂) and TXs (e.g., TXA₂), respectively (Dennis and Norris 2015). PGD₂ and PGE₂ are also metabolized to 15-deoxy-PGJ₂ and 15-keto-PGE₂, respectively. After generation, PGs and TXs are rapidly released from cells and bind to GPCRs on membranes, namely PGE receptor (e.g., EP₁, EP₂, EP₃, EP₄), PGD receptor (e.g., DP₁ and DP₂), PGF receptor (e.g., FP), PGI receptor (e.g., IP) and TXA receptor (e.g., TP) (Harizi et al. 2008; Aoki and Narumiya 2012). PGs enhance the expression of inflammation-related genes, amplifying cytokine expression (Aoki and Narumiya 2012). Particularly, PGE₂ binds to EP₁, EP₂, EP₃, and EP₄ and promotes vasodilation, vascular leakage, hyperalgesia, and fever (Dennis and Norris 2015). PGD₂ binds to DP₁ to promote mast cell maturation and vasodilation, while its binding to DP₂ promotes eosinophil recruitment. Conversely, PGE₂ also plays an anti-inflammatory role, increasing IL-10 levels and reducing TNF- α levels. TXA₂ increases platelet aggregation and promotes vasoconstriction when bound to TP.

LOX signaling

LOX enzymes, including 5-LOX, 12-LOX, and 15-LOX, generates LTs, HPETE, and HETE (Dennis and Norris 2015).

5-LOX, activated by Ca²⁺, translocates from the cytosol to the cell membrane, where it converts AA, in the presence of 5-lipoxygenase activating protein (FLAP), to 5-HPETE. 5-HPETE is further reduced to a more stable form, 5-HETE, by a peroxidase (Ribeiro et al. 2015). On the other hand, 5-HPETE can be consecutively converted into the precursor LTA₄ (Henderson 1994). LTA₄ can be synthesized into LTB₄ through the action of the cytosolic LTA₄ hydrolase in neutrophils and macrophages. LTA₄ can also be converted by LTC₄ synthase into cysteinyl leukotrienes in eosinophils, mast cells, macrophages, and endothelial cells. The LTC₄ can be metabolized extracellularly to LTD₄ by the action of transpeptidases (Ribeiro et al. 2015). LTD₄ is further converted to LTE₄. LTs exert their effects via surface receptors. LTB₄ binds to LTB₄ receptor—BLT—1 and 2, members of GPCRs, coordinating and amplifying the inflammatory response (Henderson 1994; Harizi

et al. 2008; Dennis and Norris 2015). LTB₄ promotes neutrophil chemotaxis, adhesion of neutrophils to the endothelium, neutrophil degranulation and lysosomal enzyme release, O₂^{•−} generation, pain, myelopoiesis, increase IL-6 production, and T lymphocyte proliferation. It also mediates the activation of the NF- κ B transcription factor. LTC₄, LTD₄, and LTE₄ bind to cysteinyl leukotriene receptors—CYSLT—1 and 2 and induce airway, gastrointestinal, and bronchial smooth muscle contraction (Henderson 1994; Dennis and Norris 2015). It mediates the activation of the MAPK transcription factor (Ribeiro et al. 2015). LTC₄, LTD₄, and LTE₄ also increase the venular endothelium that allows for proinflammatory cells migration to the site of inflammation, contributing to the development of edema. The leukotrienes enhance the mucous secretion in the airways and stimulate the production of IL-1 β .

LXs can be generated at mucosal surfaces via leukocyte–epithelial cell interactions and within the vascular lumen during platelet–leukocyte interactions (Ribeiro et al. 2015). LXs, including LXA₄ and LXB₄, can be produced by the conversion of LTA₄ by 5-LOX or 12-LOX (Henderson 1994; Dennis and Norris 2015). Additionally, 5-LOX and 15-LOX can metabolize AA into 15-HEPTE, which is subsequently converted into LXA₄ and LXB₄. LXs bind to G protein-coupled lipoxin A₄ receptor/formyl peptide receptor (ALX/FPR₂), playing a role in the resolution of inflammation (Chandrasekharan and Sharma-Walia 2015). LXs inhibit the immune growth of the cells, suppress cytokine synthesis, and release, and modulate the levels of immune cells to induce the resolution phase of inflammation. LXs mediate its action through the inhibition of the NF- κ B, MAPK, and STAT signaling pathways.

ROS/RNS-mediated cellular signaling

ROS and RNS, as previously described, are produced by phagocytic cells to kill the pathogen. They promote direct toxicity in the pathogen through molecule oxidation, hydroxylation, chlorination, nitration, and S-nitrosylation, along with the formation of sulfonic acids and the destruction of iron-sulfur clusters in proteins (Conner and Grisham 1996; Mittal et al. 2014). During the inflammatory response and in the presence of high concentrations of oxygen, the NADPH oxidase enzyme, present in the membrane

of the cells, generates large amounts of $O_2^{\cdot-}$ (Conner and Grisham 1996). Activated neutrophils and macrophages also secrete the enzyme myeloperoxidase (MPO), which uses the H_2O_2 , produced by dismutation of $O_2^{\cdot-}$, to oxidize chloride ions (Cl^-) into hypochlorous acid (HOCl), a powerful anti-bacterial agent (Halliwell 1991; Conner and Grisham 1996). Moreover, free radicals can interact between them, resulting in the generation of new radical species. For instance, $\cdot NO$ can react rapidly with $O_2^{\cdot-}$ producing a reactive $ONOO^-$ (Gutteridge 1994; Conner and Grisham 1996). Importantly, the decomposition of $ONOOH$ involves the intermediate generation of the highly reactive $\cdot OH$ and nitrogen dioxide ($\cdot NO_2$) radicals. Moreover, H_2O_2 has the ability to diffuse across the cell membrane, having a high capacity to form ROS in the presence of transition metals (e.g., iron and copper), also generating $\cdot OH$ (Gutteridge 1994). Additionally, $O_2^{\cdot-}$ promotes the release of redox-active iron from iron storage proteins, such as ferritin, thereby providing the catalyst for $\cdot OH$ generation (Halliwell 1991). ROS can also activate signaling pathways (NF- κB and p38 MAPK) and upregulate several genes involved in inflammation (Mittal et al. 2014). ROS promotes the synthesis of proinflammatory cytokines (e.g., IL-1 β , IL-6, and TNF- α), as well as participates in the activation of the inflammasome. Additionally, ROS controls the extravasation of leukocytes through the promotion of endothelial integrity disassembly and the expression and activation of CAMs (e.g., E-selectin, intercellular adhesion molecule—ICAM—1—, vascular cell adhesion molecule—VCAM—1). This results in the higher endothelial permeability and adhesion of leukocytes to the site of inflammation, respectively. Under an inflammatory scenario, the transcription of the iNOS gene is also activated and large amounts of $\cdot NO$ are produced by the oxidation of L-arginine to L-citrulline (Martinez and Andriantsitohaina 2009). $\cdot NO$ is a potent antimicrobial and vasodilator agent, also contributing for the elimination of the harmful agent.

Resolution of inflammation

The final event of an acute inflammatory response is its successful resolution, restoring the homeostasis of tissue (Medzhitov 2008). The resolution of inflammation is characterized by the decrease of leukocyte

infiltration, clearance of inflammatory cells, and restore of macrophages and lymphocytes to their normal pre-inflammatory phenotypes (Serhan and Savill 2005). Leukocytes have the ability to trigger a self-limiting response to acute inflammation, switching the generation of pro-inflammatory (e.g., PGE2 and PGD2) to anti-inflammatory eicosanoids (e.g., LXA4 and LXB4). As previously referred, LXs and HETES can suppress neutrophil chemotaxis, vascular dilatation, permeability, fibrosis, and pain (Nathan and Ding 2010). They also promote the phagocytosis of apoptotic neutrophils, initiating tissue remodeling (Nathan and Ding 2010). Additionally, the phagocytosis of apoptotic cells can stimulate macrophages to release anti-inflammatory mediators, such as TGF- $\beta 1$ and IL-10. These molecules are suppressors of classical pro-inflammatory macrophage activation and mediators of tissue repair (Serhan and Savill 2005; Nathan and Ding 2010). Mast cells, basophils, and TH2 cells also release IL-4 to enhance the switch of pro-inflammatory to anti-inflammatory macrophage phenotype to suppress inflammation and favor wound healing (Nathan and Ding 2010). Myeloid-derived suppressor cells, a macrophage population, have the ability to suppress T cell responses. Moreover, immune cells, such as macrophages and neutrophils, independently convert omega-3 polyunsaturated fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) to resolvins and protectins, which are anti-inflammatory lipid mediators (Serhan and Savill 2005).

Antioxidant defenses or scavenging systems are used to remove the excess of ROS and RNS to prevent cellular damage. Antioxidants are also chemical compounds obtained from food, such as α -tocopherol (vitamin E), ascorbic acid (vitamin C), flavonoids, and polyphenols (Burton et al. 1985). In addition, the induction of several antioxidant and cryoprotective genes is mainly regulated by the redox-sensitive transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2) (He et al. 2020). Under physiological conditions, Nrf2 is inactivated in the cytosol via ubiquitination by Kelch-like ECH-associated protein 1 (KEAP1). When the cell is exposed to mild oxidative stress, ROS/RNS can disrupt the Nrf2-KEAP1 complex and Nrf2 is activated (Fig. 11). Free Nrf2 translocates into the nucleus and dimerizes with specific molecules. Then, it binds to antioxidant response elements (ARE), inducing the activation of

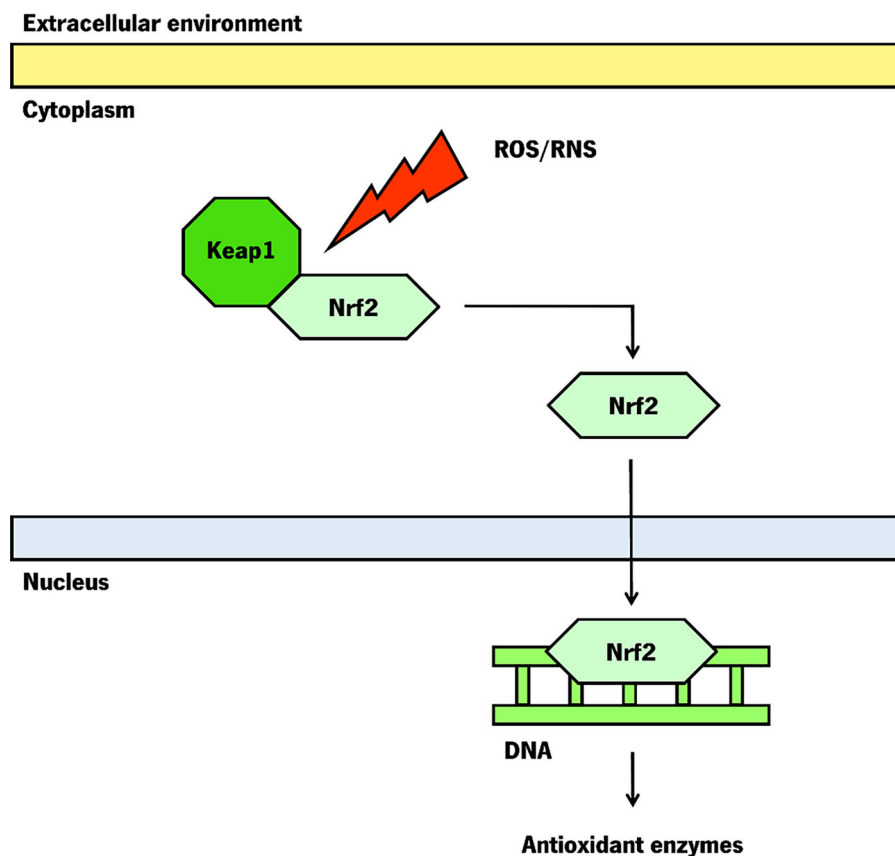


Fig. 11 Nrf2-KEAP1 signaling pathway. DNA, deoxyribonucleic acid; KEAP1, Kelch-like ECH-associated protein 1; Nrf2, nuclear factor erythroid 2-related factor 2; RNS, reactive nitrogen species; ROS, reactive oxygen species

antioxidant and cytoprotective genes, encoding quinone oxidoreductase-1 (NQO-1), glutathione peroxidase (GPx), heme oxygenase-1 (HO-1), glutathione peroxidase (GSH-Px), glutathione-S-transferase (GST), catalase (CAT), and superoxide dismutase (SOD). Therefore, the Nrf2-KEAP1 pathway confers protection against cellular oxidative stress by boosting the expression of antioxidant enzymes, being essential for the resolution of inflammation and repair of tissue damage (Nathan and Ding 2010).

Dysresolution of the immune system

The immune system response may not always lead to the expected outcomes. Indeed, if the immune systems fail to effectively eliminate the offending agent, a state of chronic inflammation can ensue. Conversely, the immune response can also be compromised, leading to

the development of immunodeficiency. Further elucidation of these events will be provided in this section.

Chronic inflammation

If the resolution phase fails, the inflammatory response can become exacerbated in magnitude and time, leading to chronic inflammation. For example, the inflammatory response can be prolonged by a failure of neutrophils to undergo apoptosis, of macrophages to clear apoptotic neutrophils, and/or by deficiency of other factors that promote ingestion of apoptotic cells by macrophages (Nathan and Ding 2010). Additionally, a failure in the suppression of T cells prolongs the expansion and activation of myeloid-derived suppressor cells. A failed phenotypic switch in macrophage and T cell populations and an inadequate production of resolution mediators also lead to the non-resolution of inflammation. Chronic inflammation can also arise in

the presence of some microorganisms, such as mycobacteria, that are difficult to eradicate, culminating in persistent infections and after prolonged exposure to potentially toxic agents (e.g., exogenous particulate silica and endogenous cholesterol). Finally, an excessive and inappropriate activation of the immune system against self-antigens (e.g., autoimmune diseases) and common environmental substances (e.g., allergic diseases) can also lead to chronic inflammation (Nakayama 2017; McInnes and Gravalles 2021).

Chronic inflammation is characterized by a long duration (weeks, months, or even a lifetime) (Oronsky et al. 2022). The hallmarks of chronic inflammation are the constant infiltration and presence of macrophages and lymphocytes, angiogenesis, tissue destruction, and fibrosis (Nathan and Ding 2010). Macrophages are the dominant cells in most chronic inflammatory reactions. Activated macrophages contribute to the prolonged inflammatory state by secreting ROS/RNS, cytokines, chemokines, and eicosanoids that activate several cells, notably T cells (Nathan and Ding 2010). An excess of ROS/RNS can be accumulated in cells and tissues, a process called oxidative and nitrosative stress (Martinez and Andriantsitohaina 2009; Mittal et al. 2014). These high amounts of ROS/RNS in the tissues alter the normal redox state within the cell environment, which can irreversibly damage several biomolecules, resulting in the loss of their function. For instance, ROS/RNS can lead to proteins unfolding and fragmentation, changing their conformation, interactions with other biological molecules, and turnover, as well as can damage the purine and pyrimidine bases of DNA, resulting in deoxyribose oxidation, strand breakage, mutations, and alterations in the encoded proteins and enzymes (Mönig et al. 1987; Aruoma et al. 1989). Moreover, ROS/RNS can induce lipid peroxidation, a free radical chain reaction, in both cellular and organellar membranes, yielding ROO[•] (Halliwell 1991). The accumulation of lipid peroxides in the membrane disrupts its function, inactivating, e.g., receptors and membrane-bound enzymes, which can culminate in its collapse. The activated T cells, as well as B cells, amplify and propagate chronic inflammation by the production of cytokines and recruitment and activation of more immune cells. These interactions strongly contribute

for the cycle—positive feedback—of chronic inflammation. Because of this dysregulated scenario, prolonged and continuous tissue damage can be translated into a chronic inflammatory disease, such as arthritic diseases (e.g., osteoarthritis and rheumatoid arthritis), autoimmune diseases (e.g., psoriasis, inflammatory bowel disease, and type 1 diabetes), neurodegenerative diseases (e.g., multiple sclerosis, Alzheimer's disease, and Parkinson's disease), hypersensitivity reactions (e.g., allergies), asthma, and cancer. Indeed, more than half of global deaths are correlated with chronic inflammatory diseases (Furman et al. 2019) and, consequently, World Health Organization ranked them as the most significant cause of death in the world nowadays (WHO (World Health Organization) 2020a, b). Moreover, its prevalence is estimated to increase persistently for the next decades (WHO (World Health Organization) 2022).

Immunodeficiency

Immunodeficiency results from the failure or absence of elements of the immune system (e.g., phagocytes, lymphocytes, and complement system) to fight against infectious diseases (Pac and Bernatowska 2016). This immunodeficiency can be either primary or secondary (acquired). The first results from an inherited genetic or developmental defect in the immune system. Examples are the Bruton disease (B-cell deficiency) (Hernandez-Trujillo et al. 2014), DiGeorge syndrome (T-cell immunodeficiency) (Lambert et al. 2018), Wiskott-Aldrich syndrome (T-cell and B-cell deficiencies) (Byrne et al. 2018), Bare leukocyte syndrome (MHC deficiency) (Aluri et al. 2018), and chronic granulomatous disease (phagocyte deficiencies) (Zhou et al. 2018). The secondary immunodeficiency occurs when the immune system is compromised by an external agent, such as a treatment or illness. The most well-known secondary immunodeficiency is the acquired immunodeficiency syndrome (AIDS), which results from infection with the human immunodeficiency virus (HIV) (Ndjoyi-Mbiguino et al. 2020). Thus, these individuals have an increased risk of opportunistic infections. Usually, these microorganisms are easily eradicated in healthy organisms, but they can cause disease and even death in those with significantly impaired immune function.

Anti-inflammatory drugs in the market

At the present time, there is no cure for chronic inflammatory diseases, being the main goals of current treatments to reduce pain and improve tissue function. Symptoms are usually treated with a combination of therapies, including, for instance, co-administration of painkillers (e.g., acetaminophen) and/or nonsteroidal anti-inflammatory drugs (NSAIDs, e.g., salicylic acid, diclofenac, and celecoxib) (Bullock et al. 2018). More potent drugs, such as corticosteroids (e.g., dexamethasone and betamethasone), conventional disease-modifying antirheumatic drugs (cDMARDs; e.g., methotrexate), biologic (b)DMARDs (e.g., TNF or IL-6 inhibitors), and targeted synthetic (ts)DMARDs (e.g., JAK inhibitors) can also be administered (Ale-taha and Smolen 2018; Oo et al. 2018). Nonetheless, these anti-inflammatory drugs can be associated with severe side effects mainly if administered for long periods (e.g., gastrointestinal, cardiovascular, blood, renal, and adrenal injuries), being their use limited (Bindu et al. 2020; Noetzlin et al. 2022). In addition, immune-suppressant agents present an increased risk for infection and/or cancer (Ben Mrid et al. 2022). Therefore, newer and safer drugs are urgently needed to efficiently treat chronic inflammatory diseases.

Nature as a source of new drugs

Nature is a broad source of bioactive compounds. In fact, the approval of natural products and their derivatives for the clinic has been increasing over the years (Cragg et al. 1997; Newman et al. 2003; Newman and Cragg 2007, 2012, 2016, 2020). From 1981 to 2019, more than half of approved drug entities (a total of 1881) are derived from natural sources (Newman and Cragg 2020). From 2019 to 2022, Food and Drug Administration (FDA) authorized 31 new drugs inspired by natural products (de la Torre and Albericio 2020, 2021, 2022, 2023). These new chemical entities include natural, semisynthetic, and synthetic natural products. The major disease areas with the highest number of drug approvals are infectious diseases (402 drugs), cancer (247 drugs), hypertension (82 drugs), antidiabetic (63 drugs), and inflammation (53 drugs) (Newman and Cragg 2020). More specifically, from the 53 approved anti-inflammatory drugs, 13 were natural product derivatives and 1 was a

synthetic drug obtained after identification of the natural product (Newman and Cragg 2020). A small number of immunostimulatory natural-derived drugs were also approved. Of the 14 immunostimulants, 8 have origin in botanical drugs (defined mixture), 3 were unaltered natural products, and 2 were natural product derivatives (Newman and Cragg 2020). Particularly, new molecular entities derived from non-mammalian natural products are mainly obtained from plants (45%), followed by bacteria (29%) and fungi (22%) (Patridge et al. 2016). These data highlight the important role of plants in drug discovery. Indeed, they present compounds with unique structural diversity. Thus, this opens several opportunities for the research of novel drugs.

Plant-derived bioactive compounds in the market

Plants synthesize several chemical compounds, known as secondary metabolites, to protect themselves against surrounding environment adversities, such as herbivores, pathogens and abiotic environmental stresses (Zaynab et al. 2018; Holopainen et al. 2018; Isah 2019; Divekar et al. 2022). Interestingly, many of those compounds have positive effects in the treatment of certain human diseases. In fact, plants have been the basis of the traditional medicine in many cultures for thousands of years to treat several conditions. Even nowadays, plants are widely used by the world population, especially in developing countries, as an important part of the primary health-care (WHO (World Health Organization) 2011). Thus, the search of plant-derived compounds as potential drugs increased, leading to the isolation of many therapeutically relevant natural products. Indeed, widely used pharmaceuticals, including analgesics, and anti-inflammatory and anti-cancers drugs, among others, arise from compounds present in plants. Table 2 comprises some of the plant-derived bioactive compounds in clinical use. The first plant-derived drug included in the clinical use was morphine, a strong analgesic isolated from the *Papaver somniferum* (Sertuerner 1817). Salicylic acid, obtained from the bark of the willow tree *Salix alba* L., was used to produce acetylsalicylic acid, known as aspirin in the market to treat inflammatory conditions (Buchner 1828). The most widely used anti-cancer drugs are also derived from plants, namely paclitaxel (*Taxus brevifolia*), as well as vincristine and vinblastine

Table 2 Examples of plant-derived bioactive compounds in clinical use (Cragg et al. 1997; Newman et al. 2003; Newman and Cragg 2007, 2012, 2016, 2020; G. de la Torre and Albericio 2019; de la Torre and Albericio 2021, 2022)

Bioactive compound	Plant specie	Therapeutical indication	Approval year
Morphine	<i>Papaver Somniferum</i>	Pain and itch	1827
Salicylic acid	<i>Salix alba</i>	Pain and itch	1899
Digoxin	<i>Digitalis lanata</i>	Cardiovascular diseases	1937
Deslanoside	<i>Digitalis lanata</i>	Cardiovascular diseases	1939
Digitoxin	<i>Digitalis purpurea</i>	Cardiovascular diseases	1948
Oxycodone	<i>Papaver somniferum</i>	Pain and itch	1950
Quinidine	<i>Cinchona succirubra</i> <i>Cinchona cordifolia</i>	Cardiovascular diseases	1950
Codeine	<i>Papaver Somniferum</i>	Pain and itch	1952
Pseudoephedrine	<i>Ephedra vulgaris</i>	Immunological diseases	1952
Methoxsalen	<i>Ammi majus</i>	Oncology	1955
Atropine	<i>Atropa belladonna</i>	Digestive diseases	1960
Vincristine	<i>Catharanthus roseus</i>	Oncology	1963
Vinblastine	<i>Catharanthus roseus</i>	Oncology	1965
Cromolyn	<i>Ammi visnaga</i>	Immunological and respiratory diseases	1966
Artemisin	<i>Artemisia annua</i>	Antiparasitic	1987
Paclitaxel	<i>Taxus brevifolia</i>	Oncology	1992
Vinorelbine	<i>Catharanthus roseus L</i>	Oncology	1994
Docetaxel	<i>Taxus baccata</i>	Oncology	1996
Galantamine	<i>Galanthus nivalis</i>	Neurological diseases	2001
Sinecatechins	<i>Camellia sinensis</i>	Infectious diseases, oncology	2006
Omacetaxine	<i>Cephalotaxus</i>	Oncology	2012
Crofelemer	<i>Croton lechleri</i>	Antidiarrheal	2012
Cannabidiol	<i>Cannabis sativa L</i>	Epilepsy	2018
Artesunate	<i>Artemisia annua</i>	Malaria	2020
Samidorphan	<i>Papaver Somniferum</i>	Schizophrenia and bipolar disorder	2021

(*Catharanthus roseus*) (Noble et al. 1958; Svoboda et al. 1961; Wani et al. 1971). All these mentioned compounds are considered the safest and most effective medicines required in a health system by the World Health Organization's List of Essential Medicines (World Health Organization 2019).

Plant-derived bioactive compounds under clinical trials

Many plant-derived compounds are currently under clinical trials for the treatment of several diseases. Besides individual chemical entities, formulations of whole plant extracts are also investigated due to the synergistic and additive effects that can arise from the different bioactive compounds. Indeed, these more

complex mixtures usually involve one or more bioactive compounds with known biological activities at high concentrations. Moreover, as several chemical compounds are present in these plant mixtures, the standardization process regarding the content of the main active principle(s) must be employed (Govindaraghavan and Sucher 2015). Therefore, it is ensured the safety, efficacy, and quality of the plant extract formulation.

For the treatment of immune system-related diseases there are several examples of plant-based drugs or formulations under clinical trials. For instance, a plant-based medication composed of concentrated extracts of *Dioscorea cirrhosa*, *Impatiens balsamina*, *Eclipta prostrata*, *Phyllanthus urinaria*, *Adenosma glutinosum*, mixed with ascorbic acid was used to

elevate T and B lymphocytes levels and decrease the damage of HIV on CD4⁺ T cells (phase 4, completed, NCT04770701). Indeed, the mixture involve compounds with complementary activities. The bioactive compound diosgenin, presented in *Dioscorea cirrhosa*, is a precursor of cortisol and when combined with ascorbic acid helps to balance the cortisol levels, reducing cell inflammation. Flavonoids present in *Impatiens balsamina* (e.g., kaempferol, quercetin, rutin, and astragalin) reduce the impact of the virus on T cells, leads to the production of antihistamine compounds, and protect the cell from inflammation. The flavonoids present in *Eclipta prostrata*, *Phyllanthus urinaria*, and *Adenosma glutinosum* also protect and increase the CD4⁺ T cell population.

Two natural oils obtained from borage and echium seed were employed in asthma treatment (phase 3, completed, NCT01560988). This formulation aimed to decrease asthma symptoms through the reduction of LTC₄ production by granulocytes. Another clinical trial analyzed the benefits of consuming ginger by individuals with asthma (early phase 1, completed, NCT03705832). Ginger blocks one of the critical inflammatory pathways in asthma, reducing the airway inflammation and relaxation of airway smooth muscle, as well as the serum levels of asthma-related inflammatory markers.

Nabiximols (trade name Sativex), an oromucosal spray formulation containing a 1:1 fixed ratio of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) derived from cloned *Cannabis sativa* L., was proposed for multiple sclerosis (completed, NCT03186664). The main active substance, THC, acts as a partial agonist of human cannabinoid receptors (CB1 and CB2) and may modulate the effects of excitatory (glutamate—GLU) and inhibitory (gamma-aminobutyric acid—GABA) neurotransmitters, leading to muscle relaxation, which in turn is responsible for spasticity improvement. In addition, the anti-inflammatory properties of the cannabinoids THC and CBD in individuals across the weight spectrum will also be assessed (recruiting, NCT04114903). The effects of nanocurcumin, the main active principle of turmeric, in multiple sclerosis was also evaluated (phase 2, completed, NCT03150966). A reduction of the number of TREG and TH17 cells, of the expression levels of their associated transcription factors, and of the secretion levels of cytokines is expected.

Inconsistences in pharmacological effects of plant-based formulations

The description in the literature of different therapeutic outcomes using “similar” plant-derived formulations occurs with some frequency. These incongruences among the published studies is intimately related to the use of formulations with different composition and purity, as well as the employment of different extraction techniques, in vitro assays, animal models, and administration routes. Indeed, the characteristics of the plant used, as well as the experimental procedure employed for the recovery of bioactive compounds demonstrate a strong impact in the biological activity. Thus, factors, such as (i) specie, (ii) age, (iii) selected organ, (iv) developmental stage, (v) growth conditions, (vi) geographical location, (vii) drying methods, (viii) storage conditions, (ix) solvent of extraction, and (x) extraction method are important in defining the final composition of the plant extract. Therefore, the extracts with the strongest bioactivity are obtained by the selection of the optimal conditions of these factors.

Plant specie

Plants are catalogued on different levels according to their morphological, histological, genetic, and molecular characteristics (Maskour et al. 2022). At the species level, the plants share certain common characteristics and are closely related genetically. However, different plant species can produce extracts with distinct compositions. For instance, Farhat et al. studied the extracts content obtained from different *Salvia* species and detected high variable composition between them (Farhat et al. 2013). In this study, the phenolic content was higher in *S. officinalis*, followed by *S. aegyptiaca*, *S. verbenaca*, and *S. argentea*. Moreover, large amounts of the bioactive compounds caffeic acid, rosmarinic acid, carnosic acid, and carnosol were found in *S. officinalis*. *S. argentea* exhibited amounts of caffeic acid and rosmarinic acid approximately four times lower. The other species presented carnosic acid and carnosol at levels around a hundred times lower. Consequently, *S. officinalis* extracts exhibited the highest antioxidant activity. Therefore, plant species can exhibit significant variations in their chemical composition, resulting in different levels of bioactivity.

Age of the plant

The biological age stage (e.g., juvenile, young, mature, and old) significantly affects the characteristics of the plant (Gatsuk et al. 1980). These characteristics are correlated with anatomical, physiological, and biochemical changes, such as the capture of nutrients, the development of the pattern of branching of the root and shoots, the form of the leaves, among others. Thus, it is not surprising that, for example, an adult plant presents different features compared to a young plant (Henn and Damschen 2021). Particularly in compounds composition, *Lavandula angustifolia* essential oils, for example, evidenced a decrease in monoterpenes and sesquiterpenes concentration in two consecutive years (the second and third year after planting) (Pistelli et al. 2017). The young leaves of *Olea europaea* also presented a high amount of secoiridoids (e.g., oleuropein, oleoside, demethyleuropein, 2''-methoxyoleuropein, ligstroside, and nuzhenide) in comparison with the aged leaves (Abaza et al. 2017). Therefore, the biological age of the plants influences its biochemical changes, leading to variations in compound composition and, consequently, potential implications in their properties and benefits.

Organ of the plant

A plant is composed of different organs, such as roots, stems, leaves, buds, flowers, and seeds (Simpson 2019). Each organ is responsible for different functions in the plant organism. Consequently, distinct chemical compositions will be observed in each of them. For instance, an aqueous extract prepared from flowers, leaves, or roots of *Echinacea purpurea* showed a particular chemical fingerprint (Vieira et al. 2022). Alkylamides were more abundant in roots extracts, while phenolic/carboxylic acids were richer in leaves extracts. Flowers extracts showed a balanced mix of both chemical compounds. These extracts exhibited the strongest anti-inflammatory activity in the reduction of IL-1 β production in LPS-stimulated macrophages, demonstrating that the mixture of compounds can be beneficial. Therefore, when specific bioactivity is required, careful consideration should be given to the selection of the appropriate plant organ.

The development stage of the plant

The plant life-cycle has cascading effects on multiple levels of its biological organization (Stucky et al. 2018). These phenological phases include processes, such as leaves emergence, flowering, fruiting, seeding, and leaves senescence, that lead to severe alterations of plant metabolites composition (Gray and Ewers 2021). For example, the concentration and composition of secondary metabolites changed significantly with the flower developmental stages (e.g., bud, full blooming, and wilting) of *E. purpurea* (Thomsen et al. 2018). The highest concentration of alkylamides in aerial parts was achieved when those parts were harvested in the wilting stage, whereas the highest concentration of caffeic acid derivatives was achieved when those parts were collected in the bud stage. Particularly, the content of the alkylamides dodeca-2E,4E,8Z,10E/Z-tetraenoic acid isobutylamide, undeca-2E,4Z-diene-8,10-dienoic acid isobutylamide, and trideca-2E,7Z-diene-10,12-dienoic acid isobutylamide in aerial parts significantly increased with the harvesting of the flowers at the development stages from bud to wilting. Conversely, the content of dodeca-2Z,4E-diene-8,10-dienoic acid isobutylamide, caffeic acid, echinacoside, and chicoric acid decreased from flower bud stage to wilting stage. It was also observed that the oleuropein levels increased within the flower maturation (from floral buds to open flowers) of the *O. europaea* (Abaza et al. 2017). The amounts of rutin, apigenin, and luteolin glucoside followed the inverse tendency. Therefore, the development stage of the plant has a strong impact on the plant composition, highlighting the importance of considering the optimal harvesting stage for desired compound profiles.

Growth conditions

To obtain a healthy growth of a plant it is required light, water, nutrients (e.g., nitrogen, phosphorus, and potassium), and an adequate soil (Sun et al. 2022). However, when the growth conditions are not ideal—stress growth conditions—the plants can adapt to the surrounding environment and switch their mechanism to an increased production of secondary metabolites (Isah 2019). Nowadays, different industrial and

pharmaceutical crops have been using this approach to increase the production of the bioactive compounds of interest in plants. For example, the salinity stress increased the production of caftaric acid, cynarin, and chicoric acid in *E. purpurea* roots (Sabra et al. 2012). The drought stress intensification also increased the amount of chicoric acid and caftaric acid in *E. purpurea* roots (Attarzadeh et al. 2020). The combination of phosphorous fertilizer with biological resources, such as mycorrhizal arbuscular fungi and/or the bacteria *Pseudomonas fluorescens*, also markedly improved the concentration of chlorogenic acid, caftaric acid, chicoric acid, cynarin, and echinacoside in *E. purpurea* roots (Attarzadeh et al. 2020). For *L. angustifolia*, it was observed that high levels of phosphorous and nitrogen strongly affected its growth and root development, respectively (Chrysargyris et al. 2016). These nutrients also led to an improvement in the synthesis of some constituents (e.g., 1,8-cineole, α -terpineol, trans-pinocarveol, camphor, borneol, myrtenal, α -bisabolol, and pinocarvone) and, therefore, enhanced antioxidant activity of the aqueous methanolic extracts. Interestingly, plant propagation also has a critical effect on secondary metabolites (Dušková et al. 2016). The total amount of essential oil recovered from *L. angustifolia* flowers was higher in cultivars propagated vegetatively than in cultivars propagated by seeds (Dušková et al. 2016). The seasonal conditions, in particular weather conditions (e.g., temperature and precipitation), are also extremely important in plant development (Hatfield and Prueger 2015). Plants also adapt to significant seasonal variations, suspending and becoming physiologically inactive, a state-denominated dormancy (Hu et al. 2022). Particularly, high or low temperatures strongly affect the metabolic process of plants. For instance, the phenolic acids, flavonoids, and tocopherols content in *Taraxacum officinale* was higher in the winter-early spring, in comparison with mid-late spring (Petropoulos et al. 2019). The phenolic acids and alkylamides content in *E. purpurea* roots also changes during seasonal conditions (early winter, early spring, late spring, summertime, and mid-autumn) (Thomsen et al. 2012). Undeca-2E,4Z-diene-8,10-diynoic acid isobutylamide, undeca-2Z,4E-diene-8,10-diynoic acid isobutylamide, undeca-2E,4Z-diene-8,10-diynoic acid 2-methylbutylamide, dodeca-2E,4E,10E-triene-8-ynoic acid isobutylamide, and trideca-2E,7Z-diene-10,12-diynoic acid isobutylamide reached the highest

concentration during summer. The highest concentration of dodeca-2E,4Z-diene-8,10-diynoic acid isobutylamide, dodeca-2Z,4E-diene-8,10-diynoic acid isobutylamide, dodeca-2E,4E-diene-8,10-diynoic acid 2-methylbutylamide, dodeca-2Z,4E-diene-8,10-diynoic acid 2-methylbutylamide, and dodeca-2E,4Z,10E-triene-8-ynoic acid 2-methylbutylamide was detected during early spring. Conversely, dodeca-2E,4E,8Z,10E/Z-tetraenoic acid isobutylamide, dodeca-2E,4E,8Z-trienoic acid isobutylamide and dodeca-2E,4E-dienoic acid isobutylamide did not have a significant change of their levels throughout the year. Considering phenolic compounds, their highest concentration was reached in spring. More particularly, echinacoside showed the highest content in early spring and both chicoric acid and caftaric acid showed the greatest amount in late spring. For *L. angustifolia*, a decrease in the average temperature resulted in a gradually reduction of the essential oil percentage (Hassiotis et al. 2014). The relative amount of linalool was negatively affected after the rainfall and several days of low temperatures, while the synthesis of the α -terpineol, borneol, lavandulyl acetate, 1,8-cineole, and terpinene-4-ol was enhanced under these environmental conditions. Indeed, the environmental factors play a crucial role in shaping the production and composition of secondary metabolites in plants. Factors, such as growth conditions, nutrient availability, propagation methods, and seasonal variations have a significant impact on the final plant extract. Understanding and effectively manipulating these factors become crucial to optimize the production of desired compounds for industrial and pharmaceutical applications.

Geographical location

The geographical location—latitude, longitude, and altitude—of plants can provide different conditions of, e.g., atmospheric pressure, precipitation, solar radiation, and soil nutrients (Daco et al. 2021). Plants can adapt to these factors by changing their genetic fingerprint, growth rate and metabolites production (Li et al. 1998). For instance, *S. officinalis* cultivated at high altitudes favored the monoterpene synthesis, while the sesquiterpene synthesis was mainly privileged at low altitudes (Ben Farhat et al. 2009). Sage extracts obtained from low altitudes demonstrated the most powerful antioxidant activity. Therefore, the geographical location of plants strongly influences

their genetic traits, growth patterns, and metabolite production, leading to distinct compositions and potential health benefits.

Drying methods

Drying is the most employed post-harvesting process to store the plants over long periods (Hazrati et al. 2021). The drying process of plant material inhibits microorganism growth and prevents certain biochemical changes in metabolites. However, the drying method (e.g., sun, shade, oven, freeze, microwave, vacuum, infrared) can alter the initial plant material composition in different ways (Nurhaslina et al. 2022). The loss of compounds can be related to their dragging to the surface of plant when water is evaporating or to degradation (e.g., oxidation and hydrolysis) (Sellami et al. 2012). Moreover, if high temperatures are used, the cell membrane integrity can be disrupted, releasing bioactive compounds, as well as some undesired enzymes (e.g., polyphenol oxidase) that can degrade the compounds of interest (Zhang et al. 2011). Nonetheless, the degradation products generated can also demonstrate potential biological activity (Zhang et al. 2012; Medicherla et al. 2016). For example, the extraction yield of essential oils was higher when aerial parts of *S. officinalis* were dried with an infrared moisture analyzer, followed by the air-drying method, oven, and microwave (Sellami et al. 2012). Indeed, the concentration of major compounds present in the fresh plant increased (e.g., 1,8-cineole, camphor, β -thujone, and viridiflor) or decreased (e.g., α -thujone and terpinen-4-ol) with the drying method. Some compounds were lost (e.g., sabinene, α -terpinene, valencene, and methyl eugenol), while others only appear when the plant was dried (e.g., β -pinene, octanal, β -caryophyllene, α -humulene and α -selinene). The same tendency was observed for the phenolic and flavonoid content in *S. officinalis* methanolic extracts (Hamrouni-Sellami et al. 2013). In this case, ferulic acid, rosmarinic acid, and carnosic acid are presenting higher amounts in dried aerial parts in comparison with fresh ones. On the other hand, caffeic acid concentration decreased and luteolin was lost in the drying method. Similarly, the increase of the temperature to dry aerial parts of *S. officinalis* significantly reduced (e.g., caffeic acid and rosmarinic acid) or enhanced (e.g., carnosol and carnosic acid) the amount of some compounds in the final extract (Hamrouni-

Sellami et al. 2013). The high drying temperature also significantly reduced the content of chicoric acid and caftaric acid in *E. purpurea* extracts (Kim et al. 2000a; Lin et al. 2011). As well, alkylamides are susceptible to degradation at high drying temperatures (Kim et al. 2000b). Thus, the specific drying method employed can significantly influence the composition of bioactive compounds, with some compounds being lost, and others generated. This highlights the importance of selecting appropriate drying methods to maintain the desired composition and quality of plant materials.

Storage conditions

Appropriate storage conditions contribute to the preservation of the plant material. Factors, such as water content, oxygen concentration, temperature, humidity, and light strongly influence the quality of the plant over time (Laher et al. 2013; Coradi et al. 2020). For example, low temperatures (10–20 °C), low relative humidity (40–60%), and dark conditions were preferred to store *E. purpurea* samples in sealed polyethylene terephthalate/aluminum foil/polyethylene or nylon/polyethylene bags, since their content of chicoric acid and caftaric acid did not change over 180 days (Lin et al. 2011). Indeed, light accelerates the loss of chicoric acid and caftaric acid in dried samples stored at 20 °C for longer than 90 days. Also, the re-uptake of moisture from air with a high relative humidity (80%) favors the chicoric acid degradation due to the enhanced enzymatic activity. The proper storage conditions are essential for preserving the quality and stability of plant materials, preventing degradation of the bioactive compounds.

Solvent of extraction

The solvent strongly influences the type of bioactive compounds recovered from the plant material (Mandal et al. 2015). The ability of different solvents to solubilize dissimilar chemical classes of molecules is determined by their polarity (Zarrinmehr et al. 2022). Polar solvents (e.g., water, methanol, and ethanol) have the ability to extract more polar compounds (e.g., alkaloids, flavonoids, glycosides, tannins, and phenolic compounds) (Bonventre 2014). Nonpolar solvents (e.g., hexane and dichloromethane) are not miscible in water and remove lipophilic compounds (e.g., fatty acids and alkanes). For example, the solid–liquid

extraction efficacy of *O. europaea* was significantly different for several solvents, namely hexane—0.9%; ethanol—4.1%; dichloromethane—6.2%; acetone—6.8%; water—5.7%; and methanol—7.2% (Borges et al. 2020). However, no correlation was obtained between the extraction yield and scavenging activity. The acetonic extracts exhibited the highest biological activity and methanolic and ethanolic extracts presented the lowest. Also, aqueous and ethanolic *S. officinalis* extracts exhibited different extraction yields, chemical composition, and anti-inflammatory activity (Vieira et al. 2020). Rosmarinic acid was found in aqueous and ethanolic extracts, while carnosol and carnosic acid were only present in ethanolic extracts. Interestingly, ethanolic extracts, with the smallest extraction yield (12.2%), were more efficient in the reduction of IL-6 production, than the aqueous extracts, with approximately twice the extraction yield (29.9%). Different chemical compositions and consequent bioactivity were also observed for *E. purpurea* aqueous and ethanolic extracts obtained from leaves (Vieira et al. 2022). Only phenolic/carboxylic acids were found in aqueous extracts, while a mixture of phenol/carboxylic acid with alkylamides was detected in ethanolic extracts. Consequently, ethanolic extracts reduced more efficiently the IL-6 production in LPS-stimulated macrophages than the aqueous extracts.

The ratio between plant material and volume of solvent also directly influences the recovery of specific chemical compounds. The extraction of dodeca-2E,4E,8Z,10E/Z-tetraenoic acid isobutylamide and dodeca-2E,4E,8E,10Z-tetraenoic acid isobutylamide from *E. purpurea* roots was more efficient with a plant to solvent ratio of 1:5 (W:V) (Spelman et al. 2009). The ratio of 1:11 (W:V) was more effective for the removal of dodeca-2E-ene-8,10-dienoic acid isobutylamide.

As demonstrated in the selected studies, the meticulous selection of solvents of extraction and the ratio between plant material and volume of solvent are crucial in the extraction process, as they strongly influence the extraction efficiency, chemical composition, and subsequent bioactivity of the resulting formulations.

Extraction method

There are different extraction methods, which can be divided into traditional and advanced techniques

(Zhang et al. 2018; Jha and Sit 2022). The traditional methods can mimic the conventional use of plant preparations (Zhang et al. 2018). Examples of traditional methods are infusion, decoction, maceration, stirring, shaking, Soxhlet apparatus, and reflux. Steam distillation and hydrodistillation by Clevenger apparatus are also employed. Other equipment are also applied to increase the efficacy of the extraction process (e.g., UltraTurrax, enamel boiler, Unger apparatus, and ball mill). Nowadays, new advanced techniques have arisen to improve the recovery of bioactive compounds and reduce, for instance, the time of extraction (Belwal et al. 2018). Examples of new advanced techniques are ultrasounds, supercritical fluid extraction, accelerated solvent extraction, and microwaves. Furthermore, the employment of temperature can improve the efficiency of the extraction by changing the physicochemical properties of the solvent (Deans et al. 2020). Nonetheless, as heat can have a significant impact on structure integrity of the bioactive compound, a balance between the level of temperature and the preservation of compound must be achieved. Methods that include an enzymatic, mechanical, or chemical pre-treatment of the plant material can also increase the concentration of some chemical compounds since they degrade the cell wall structure, releasing the intracellular content. For example, the recovery of several compounds from *L. angustifolia* was improved with its pre-treatment with cellulase (e.g., cis-linalool oxide, trans-linalool oxide, lavandulol, 1-octen-3-ol acetate, and borneol), hemicellulase (e.g., 1,8-cineole), or a mixture of both (e.g., linalool, lavandulyl acetate, α -terpinol, geranyl acetate, geraniol, and neryl acetate) (Rashed et al. 2017). The same tendency was observed in the extraction of essential oils from *L. angustifolia* (Rashed et al. 2017) and *Laurus nobilis* (Boulila et al. 2015) if preceded by an enzymatic pre-treatment. The mechanochemical pre-treatment of *L. nobilis* leaves with lithium carbonate in a ball mill also yielded comparable phenolic content to the one obtained for Soxhlet extraction (Rincón et al. 2019).

Each extraction method has its own particularities, obtaining, therefore, different chemical compounds and/or concentrations. For instance, significant differences between the oil composition of *S. officinalis* obtained by infusion (25 compounds) and hydrodistillation (60 compounds) were reported (Lima et al. 2004). More particularly, high-volatile compounds

(e.g., ocimene, camphene, and 1-octen-3-ol) were present in the extracts obtained by hydrodistillation, but not when infusion was used (Radulescu et al. 2004). In fact, hydrodistillation is based on distillation of the volatile compounds at a lower temperature than their boiling points. Conversely, infusion uses the boiling temperature to extract the compounds. In addition, the infusion is performed in an open extraction system, during which the most volatile compounds are lost due to direct volatilization and co-vaporization with water vapors. In another study, a high percentage of compounds with higher polarity (e.g., linalool) were obtained by hydrodistillation of *L. angustifolia* flowers, while increased amounts of compounds with lower polarity (e.g., linalyl acetate and neryl acetate) were observed after microwave-assisted extraction (Dănilă et al. 2018). Conversely, the main compounds of the *L. nobilis* leaves extracts were obtained using different extraction methods—steam distillation, microwave-assisted hydrodistillation, and ohmic-assisted hydrodistillation, hydrodistillation—but their amount was dramatically different (Taban et al. 2018). Microwave-assisted hydrodistillation and ohmic-assisted hydrodistillation showed high yield for oxygenated monoterpenes, whereas sesquiterpenes recovery was enhanced by hydrodistillation and steam distillation.

Given the potential variations in the obtained chemical compounds composition and their concentrations, it is imperative to thoroughly consider the selection of the extraction method for biological assays.

Plant-derived immunomodulatory compounds and their mechanism of action

A variety of preparations obtained from several species of plants have been reported to have ability to interact with immune cells, either stimulating or inhibiting their function. The immunomodulatory activity is closely related to the chemical composition of the plant extract. Various extraction methods and solvents have been used to prepare different plant extracts that can modulate both in vitro and in vivo inflammatory signaling pathways. Particularly, *Boswellia serrata*, *Echinacea purpurea*, *Laurus nobilis*, *Lavandula angustifolia*, *Olea europaea*, *Salvia officinalis*, *Salvia Rosmarinus*, and *Taraxacum officinale*

formulations have been traditionally used as immunomodulatory medicines, whose bioactivity is being under investigation. Therefore, in the next sections, the bioactive compounds present in formulations obtained from these plants, as well as their mechanism of action are reviewed and cataloged in Tables 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 and 15. Some of the more complete studies presented in these tables were selected to be discussed in detail. Furthermore, the phytochemical composition of these plants is presented, together with, when provided, the solvent of extraction, the extraction method, and the organ of the plant used in Supplementary Tables S1–S8.

Boswellia serrata

B. serrata (Burseraceae family), commonly known as Indian Frankincense, olibanum or Salai guggal, is a small branching tree native to North Africa and Asia. It is used in Ayurvedic medicine for centuries. Its oleo gum resin, collected through the exudes from an incision in the bark of the trunks, has been traditionally used as a decoction or tincture to reduce the pain and to treat asthma, rheumatoid arthritis, osteoarthritis, and inflammatory bowel disease.

B. serrata extracts (Boswe-E) are mainly constituted by monoterpenes, triterpenes, sesquiterpenes, diterpenes, monosaccharides, and fatty acids (Supplementary Table S1). The triterpene boswellic acids (e.g., β -boswellic acid, acetyl- β -boswellic acid, 11-keto- β -boswellic acid and acetyl-11-keto- β -boswellic acid) were found to be the main responsible compounds for the biological activity of the Boswe-E (Tables 3 and 4).

The anti-inflammatory activity of Boswe-E is related to (i) the inhibition of the complement system; (ii) the decrease in immune cell proliferation; (iii) the diminution of immune cells migration; (iv) the reduction of pro-inflammatory cytokines, chemokines, prostaglandins, and leukotrienes expression and production; (v) the decrease of respiratory burst and molecular oxidation levels; (vi) the reduction of antibodies production; (vii) the amelioration of edema, pain, and tissue injury; and (viii) the increase in antioxidant enzymes levels and anti-inflammatory cytokines (Ammon et al. 1993; Knaus and Wagner 1996; Sharma et al. 1996; Safayhi et al. 2000; Kimmatkar et al. 2003; Gayathri et al. 2007; Sengupta

Table 3 *Boswellia serrata* bioactive compounds, methods of their extraction, biological assays, and anti-inflammatory effects

Plant extract composition/ Isolated compound	Extraction method	Biological assay	Anti-inflammatory effects	References
β -boswellic acid	β -boswellic acid was purified from the gum resin of <i>B. serrata</i>	Isolated compound (5, 10, 50, and 100 μ M) was incubated with human serum or guinea pig serum (as the complement source) and sheep erythrocytes sensitized with rabbit anti-sheep erythrocyte antibody for 45 min, at 37 °C Human serum was mixed with rabbit erythrocytes and isolated compound (50 and 100 μ M) in the presence of veronal buffered saline containing EGTA and Mg^{2+} Human serum was incubated with isolated compound (5 μ g/ μ L) for 160 min, at 37 °C	$\downarrow$ classical pathway of the complement system $\downarrow$ alternative pathway of the complement system $\uparrow$ conversion of factor B	Knaus and Wagner (1996)
Acetyl-11-keto- β -boswellic acid, 11-keto- β -boswellic acid, and acetyl- β -boswellic acid	<i>B. serrata</i> resin extract H15 was obtained from Gufic (Bombay, India)	Ca^{2+} /calcium ionophore-stimulated polymorphonuclear leukocytes were pre-treated with extract (40 μ g/mL)	$\downarrow$ LBT4 and 5(S)-HETEproduction	Safayhi et al. (2000)
Acetyl-11-keto- β -boswellic acid	Defatted ethanolic extracts obtained from the resin of <i>B. serrata</i>	Ca^{2+} /calcium ionophore-stimulated rat polymorphonuclear leukocytes were treated with extract (15–40 μ g/mL)	$\downarrow$ LTB ₄ , 5-HETE, and 5-all-trans-isomers of 5,12-diHETE production	Ammon et al. (1993)
3-acetyl-11-keto- β -boswellic acid	Dried powdered gum resin was soaked in 80% ethanol. Then, the extraction (4–6 h) was carried under stirring, at 40 °C Dried powdered gum resin was soaked (overnight) in water, at RT	Hydrogen peroxide-stimulated THP-1 human monocytes were pre-treated overnight with aqueous ethanolic extracts (10, 20, 30, and 40 μ g dwt/mL) or aqueous extracts (50, 100, 200, 300, and 400 μ g dwt/mL)	$\downarrow$ cellular ROS production: aqueous ethanolic extracts > aqueous extracts $\uparrow$ CAT levels: aqueous ethanolic extract $\uparrow$ total reducing power	Kokkiripati et al. (2011)

Table 3 continued

Plant extract composition/ Isolated compound	Extraction method	Biological assay	Anti-inflammatory effects	References
β-phellandrene, caryophyllene oxide, β-caryophellene, ovalifoliolatin B, incensole oxide acetate, incensole, p-menth-5-ene-1,2-diol, boscartol A, boscartol C, boscartol D, boscartol F, boscartol G, boscartin C, boscartin F, β-hydroxy tirucallic acid, epoxy-cembradienediol, cembrenol, incensole acetate, olibanumol D, serratol, boscartene D, boscartene F, β-elemonic acid, atricin B, lupeolic acid, 9,11-dehydro-acetyl-β-boswellic acid, eleganene B, α/β-acetyl boswellic acid, 12-ursene-3,24-diol, β-amyrine, α-amyrine, isoflindissol lactone, dihydroxy-lupenoic acid methyl ester, acetoxo-oxo tirucalla-dien-oic acid, tirucalla-dien-oic acid, acetyl lupeolic acid, lupenone	Grounded powder oleo-gum-resin (10 g) were extracted (30 min) with dichloromethane or ethanol (100 mL) by ultrasounds, at 55 °C	LPS-stimulated human white blood cells were treated with extracts (0, 3, 6, 13, 25, and 50 μ g/mL) for 72 h	$\downarrow$ TNF- α , IL-1 β , IFN- γ , IL-6 expression	Elhaddad et al. (2023)
11-keto- β -boswellic acid and acetyl-11-keto- β -boswellic acid	Dry extract of <i>B. serrata</i> gum resin was provided by EOS, Treviso, Italy	LPS-stimulated human peripheral blood mononuclear cells and HMC-1.1 mast cell line were pre-treated with extract (0.1, 1, and 10 μg/mL) for 24 h LPS-stimulated Caco-2 intestinal epithelium cell line were pre-treated extract (1 μg/mL) for 24 h and then peripheral blood mononuclear cells were co-cultured for 1 h	$\downarrow$ IL-8 production in peripheral blood mononuclear cells $\downarrow$ IL-6 production in HMC-1.1 mast cell line $\downarrow$ leukocyte infiltration	Governa et al. (2018)

Table 3 continued

Plant extract composition/ Isolated compound	Extraction method	Biological assay	Anti-inflammatory effects	References
12-ursene-2-diketone	Dried plant resin (100 g) was sequentially extracted with hexane, dichloromethane, ethyl acetate and methanol, at RT	LPS-stimulated human peripheral blood mononuclear cells were co-treated with methanolic extract (30 µg/mL) for 1, 3, 6, 12 and 24 h LPS-stimulated murine RAW 264.7 macrophages were co-treated with methanolic extracts extract (10, 20, 30, and 50 µg/mL) for 6, 12, and 24 h	↓ lymphocyte proliferation ↓ NO production ↓ IL-6 expression ↓ TNF-α, IL-1β, IFN-γ and IL-12 expression ↓ iNOS expression ↓ COX-2 expression ↓ ERK1/2, JNK, and p38 phosphorylation ↓ c-jun and c-fos expression ↑ IL-10 and IL-4 expression	Gayathri et al. (2007)
11-keto-β-boswellic acid and <i>O</i> -acetyl-11-keto-α-boswellic acid	Gum resin (1 amount) was defatted with petrol ether (3 amounts) at 60–80 °C. Then, 1 amount of the dried residue was extracted with 3 amounts of alcohol	Multiple low-dose streptozotocin-induced diabetes in wild-type BK ^{+/+} mice was treated with extracts (150 mg/kg/BW/day, intraperitoneal) for 5 or 10 days	↓ tissue injury ↓ CD3 lymphocyte infiltration ↓ G-CSF, GM-CSF, IL-1α, IL-1β, IL-2, IL-6, IFN-γ, and TNF-α production	Shehata et al. (2011)
(α/β)-boswellic acid and keto-boswellic acids	Boswellic acid extract, obtained from Puritan Pride (Oakdale, NY), was subjected to ethanol extraction yielding an extract enriched in boswellic acids. Then, two formulations of topical application (cream and ointment) were prepared, containing 5% boswellic acids	Destabilization of the medial meniscus-induced osteoarthritis in C57BL/6 J mice was treated with extracts (10 mg/kg, twice a day, oral), cream extracts (25 mL, topical), or ointment extracts (25 mL, topical) for 12 weeks After 3 months of destabilization of the medial meniscus-induced osteoarthritis in C57BL/6 J mice, the synovium was co-treated with LPS or IL-1β and extract (140 µg/mL)	↓ tissue injury ↓ synovitis ↓ IL-1β, IL-12p40, MCP-1, RANTES, and TNF-α production ↓ MMP-3, MMP-13, ADAMTS-4, ADAMTS-5, IL-1β, TNF-α, VEGF-α, COX-2, and MCP-1 expression	Wang et al. (2014)
Boswellic acids (e.g., 3-acetyl-11-keto-β-boswellic acid)	<i>B. serrata</i> extract was obtained from the laboratory of the Vedic Apsen Fitomedicine	Acetic acid-induced colitis in Wistar rats was pre-treated with extract (34.2 mg/kg/day)	↓ tissue injury ↓ edema ↓ TBARS levels ↓ inflammatory infiltrate ↑ GPx and GSH levels	Hartmann et al. (2012)
3-acetyl-11-keto-β-boswellic	Vedica was obtained from Apsen Farmacêutica	Acetic acid-induced ulcerative colitis in Wistar rats was treated with extracts (4.2 mg/kg/day) for 48 h	↓ tissue damage ↓ edema ↓ lipid peroxidation ↓ NO production ↓ iNOS production	Hartmann et al. (2014)

Table 3 continued

Plant extract composition/ Isolated compound	Extraction method	Biological assay	Anti-inflammatory effects	References
2,7,8- trimethoxy-3-methyl-5,6-methylenedioxy-naphtho-1,4-quinine, (1S,2E,4S,6E,8R,11S,12R)-8,11-epoxy-2,6-thunbergadiene-4,12-diol, [(E,E,10S)-10,11-epoxy-3,7,11-trimethyl-2,6-dodecadiene-1-yl] acetate, benzo(h) quinolino (1'',2'':1',2') imidazo (4',5':4,5) imidazo (1,2-a) benzo-(h) quinoline, (3E)-4-(5,5-dimethyl-1-oxaspiro[2,5]oct-4-yl)-3-buten-2-one	Dried grounded oleogum resin were extracted with petroleum ether (2 L) in a percolator, at RT ($\times$ 3). Further, the residue were extracted with alcohol (2 L)	High fat/fructose and streptozotocin-induced diabetes and Alzheimer's diseases in Wistar rats were treated with extracts (200, 300, and 400 mg/kg/day, oral gavage) for 8 weeks	↓ TNF-α, IL-1β, and IL-6 production ↓ MDA levels ↑ GSH and SOD levels	Gomaa et al. (2019)
(α/β)-boswellic acid, acetyl-(α/β)-boswellic acid, keto- β -boswellic acid, 11-keto- β -boswellic acid, and acetyl-keto- β -boswellic acid	Ethanol extract isolated from gum resin was obtained from Herbosin CORPS, Meerut, U.P., India	Collagen-induced arthritis in Wistar rats was treated with extracts (100 and 200 mg/kg/BW/day, oral) for 21 days	↓ tissue injury ↓ arthritis score ↓ hind paw swelling ↓ synovial hyperplasia ↓ MPO and elastase production ↓ polymorphonuclear neutrophils infiltration and activation ↓ lipid peroxidation ↓ NO production ↓ IL-1β, IL-6, TNF-α, IFN-γ, and PGE2 production ↑ IL-10 production ↑ SOD, GSH and CAT levels	Umar et al. (2014)
(α/β)-boswellic acid, 11-keto- β -boswellic acid, 3-O-acetyl-11-keto- β -boswellic acid, and 3-O-acetyl-(α/β)-boswellic acid	Gum resin granules (100 g) were extracted with ethyl acetate (200 mL). The extract solution was fractionated	Freund's complete adjuvant-induced arthritis in albino Wistar rats was treated with extract (20 and 40 mg/kg/day, oral) for 45 days	↓ edema ↓ infiltration of leucocytes ↓ MDA levels ↑ SOD levels	Banji et al. (2022)
3-O-acetyl-11-keto- β -boswellic acid and non-volatile oils	Alfapin	Freund's complete adjuvant-induced paw inflammation in Wistar albino rats was pre-treated with extract (100 mg/kg) for 14 days	↓ edema ↓ TNF-α production	Sengupta et al. (2011)

Table 3 continued

Plant extract composition/ Isolated compound	Extraction method	Biological assay	Anti-inflammatory effects	References
Acetyl-11-keto- β -boswellic acid	Dried powdered oleo-gum resin (10 g) was soaked and gently agitated (48 h) in 96% ethanol (100 mL) or distilled water (100 mL) at 40 °C	Focal cerebral ischemia-induced Wistar rats was treated with extracts (125, 250, and 500 mg/kg, intraperitoneal) for 24 h	↓ tissue injury ↓ MDA levels ↑ GSH and SOD levels	Forouzanfar et al. (2016)
3- <i>O</i> -acetyl-11-keto- β -boswellic acid, β -boswellic acid, 3- <i>O</i> -acetyl- β -boswellic acid, and 11-keto- β -boswellic acid	Boswellin Super (BSE) FJ	Hydrogen peroxide-stimulated murine RAW 264.7 macrophages were treated with extract (2.5 and 5 μ g/mL) for 4 h LPS-stimulated murine RAW 264.7 macrophages or peripheral blood mononuclear cells were co-treated with extract (2.5 and 5 μ g/mL) for 16 or 24 h Calimycin-stimulated peripheral blood mononuclear cells were co-treated with extracts (2.5 and 5 μ g/mL) for 30 min Collagen-induced arthritis in Wistar rats was co-treated with extracts (40 and 80 mg/kg/day, oral gavage) for 21 days	↓ tissue injury ↓ edema and pain ↓ arthritic index ↑ motility ↓ synovial hyperplasia ↓ inflammatory cell infiltration ↓ C-reactive protein levels ↓ intracellular ROS production ↓ NO production ↓ MMP-9 production ↓ TNF- α , IL-6, IL-1 β , PGE2, and LTB4 production ↓ iNOS, TNF- α , IL-6, and IL-1 β expression ↓ NF- κ B p65 phosphorylation	Majeed et al. (2021)
β -boswellic acid, acetyl- β -boswellic acid, 11-keto- β -boswellic acid, and acetyl-11-keto- β -boswellic acid	Pure fractions of four of acids were isolated from <i>B. serrata</i>	Sheep red blood cells-induced delayed type hypersensitivity reaction and humoral antibody response in Swiss albino mice were treated with extracts (25, 50, 100, and 200 mg/kg, oral) for 2 days Sheep red blood cells-induced chronic reaction in Swiss albino mice was treated with extracts (25, 50, 100, and 200 mg/kg, oral) for 7 days prior to immunization and for 7 days after immunization Mice spleen cells were treated with extracts (1.95, 3.90, 7.81, 15.62, 31.25, 62.50, and 125 μ g/mL) for 6 to 7 days	↓ foot swelling ↓ delayed type hypersensitivity reaction (24 h) ↓ primary antibody production ↓ splenocytes proliferation	Sharma et al. (1996)

Table 3 continued

Plant extract composition/ Isolated compound	Extraction method	Biological assay	Anti-inflammatory effects	References
3-acetyl-11-keto- β -boswellic acid, 11-keto- β -boswellic acid, β -boswellic acid, and 3-acetyl- β -boswellic acid	Boswellin tablets	Patients with knee osteoarthritis were treated with Boswellin tablets (169.33 mg of extract contain 3-acetyl-11-keto- β -boswellic acid—53.27 mg—, 11-keto- β -boswellic acid—7.11 mg—, β -boswellic acid—20.83 mg—, and 3-acetyl- β -boswellic acid—6.06 mg), twice a day, for 30, 60, 90 and 120 days	↓ tissue injury ↑ physical function ↓ pain and stiffness ↓ C-reactive protein levels ↑ gap between the knee joints	Majeed et al. (2019)
3- <i>O</i> -acetyl-11-keto- β -boswellic acid	5-Loxin	Patients with knee osteoarthritis were treated with 5-Loxin (50 and 125 mg, twice a day), on days 7, 30, 60 and 90	↓ tissue injury ↓ pain ↑ physical ability ↑ joint stiffness ↓ MMP-3 production	Sengupta et al. (2008)
11-keto- β -boswellic acid, 3- <i>O</i> -acetyl-11-keto- β -boswellic acid, β -boswellic acid, 3- <i>O</i> -Acetyl- β -boswellic acid, α -boswellic acid, and 3- <i>O</i> -acetyl- α -boswellic acid	Wokvel	Patients with knee osteoarthritis were treated with Wokvel (333 mg/capsule, thrice a day) for 8 weeks	↓ joint pain ↓ joint swelling ↑ physical ability	Kimmatkar et al. (2003)

ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; BW, body weight; Ca^{2+} , calcium ion; CAT, catalase; CD, cluster of differentiation; COX, cyclooxygenase; GSH, glutathione; GPx, glutathione peroxidase; EGTA, ethylene glycol-bis(β -aminoethyl ether)- N,N,N',N' -tetraacetic acid; GM-CSF, granulocyte-macrophage colony-stimulating factor; G-CSF, granulocyte colony-stimulating factor; HETE, hydroxyeicosatetraenoic acid; ERK, extracellular signal-regulated kinase; IFN, interferon; IL, interleukin; iNOS, inducible nitric oxide synthase; JNK, c-Jun N-terminal kinase; LPS, liposaccharides; LT, leukotriene; MCP, monocyte chemoattractant protein; MDA, malondialdehyde; Mg^{2+} , magnesium ion; MMP, matrix metalloproteinase; MPO, myeloperoxidase; PG, prostaglandin; NF- κ B, nuclear factor kappa-light-chain-enhancer of activated B cells; NO, nitric oxide; RANTES, regulated upon activation, normal T cell expressed and secreted; ROS, reactive oxygen species; RT, room temperature; SOD, superoxide dismutase; TBARS, thiobarbituric acid reactive substances; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor

et al. 2008, 2011; Kokkiripati et al. 2011; Shehata et al. 2011; Hartmann et al. 2012, 2014; Umar et al. 2014; Wang et al. 2014; Forouzanfar et al. 2016; Governa et al. 2018; Gomaa et al. 2019; Majeed et al. 2019, 2021; Banji et al. 2022; Elhaddad et al. 2023). The details of the anti-inflammatory studies are described in Table 3. Some of the most relevant studies will be presented in more detail.

The β -boswellic acid, isolated from *B. serrata*, exhibited strong activity in the inhibition of the complement system (Knaus and Wagner 1996). The β -boswellic acid reduced the hemolytic activity of guinea pig and human serum towards antibody-coated

erythrocytes, showing its potential in the inhibition of the classical pathway of the complement system. The β -boswellic acid also demonstrated a strong activity on the inhibition of the alternative pathway of the complement. The analysis of the single complement component showed a conversion of Factor B, but no fragments of the complement compound C3 were detectable. Based on this, the authors suggested that there was an inhibition of the C3-convertase. Aqueous ethanolic and aqueous Boswe-E, prepared from gum resin, were reported to have antioxidant properties under an oxidative stress scenario (Kokkiripati et al. 2011). Both Boswe-E were capable to reduce cellular

ROS production in hydrogen peroxide-stimulated human THP-1 monocytes, thought the upregulation of cellular CAT activity and the sustaining of cellular reducing power. Curiously, the aqueous ethanolic extracts presented higher antioxidant activity than the aqueous extracts. However, the authors did not attribute this difference to the presence of 3-acetyl-11-keto- β -boswellic acid, which was higher in the first one.

Boswe-E was also proposed as a promising herbal drug for inflammatory bowel diseases (Governa et al. 2018). The pre-treatment of Boswe-E in human peripheral blood mononuclear cells (PBMCs) attenuated the production of IL-8, while the pre-treatment in LPS-stimulated HMC-1.1 mast cells significantly reduced the production of IL-6. Moreover, this extract also demonstrated a strong protective effect on the epithelial barrier by reducing immune cells infiltration. In addition, a methanolic Boswe-E, isolated from the gum resin, showed potent anti-inflammatory activity in LPS-stimulated human PBMCs (Gayathri et al. 2007). The treatment with this Boswe-E led to a high down-regulation of the TNF- α and IL-1 β production. Moreover, this extract significantly reduced the gene expression of T_H1 cytokines (IL-12 and IFN- γ) and enhanced the gene expression T_H2 cytokines (IL-10 and IL-4). In fact, the treatment with methanolic Boswe-E in LPS-stimulated PBMCs had a significant inhibitory effect on the phosphorylation of JNK and p38 in MAPK pathway. Then, a decrease in the c-jun transcription factors was observed, which could be correlated with the reduction of the production of the pro-inflammatory cytokines. A decreased in the NO production in LPS-stimulated murine RAW 264.7 macrophages was also observed, which could result from the downregulation of the iNOS gene expression. The strong anti-inflammatory activity can be intimately related with the presence of 12-ursene 2-diketone in the Boswe-E.

In another study, ethanolic Boswe-E obtained from the gum resin was purposed for the treatment of diabetes (Shehata et al. 2011). The administration of ethanolic Boswe-E in multiple low-dose streptozotocin-induced diabetic mice attenuated the inflammatory state, through the reduction of the T-lymphocyte infiltration into pancreatic islets—identified by CD3 receptors of T-cells and thymocytes—and of production of several inflammatory cytokines in the serum—G-CSF, GM-CSF, IL-1 α , IL-1 β , IL-2, IL-6, IFN- γ ,

and TNF- α . Additionally, the decrease of caspase-3 activation was observed, indicating a reduction of the tissue injury. The authors suggested two mechanisms of action for the anti-inflammatory effect of this Boswe-E. Thus, the observed activity can be due to the reduction of the production of cytokines by immune cells, or by the decrease in the releasing of NF- κ B from these cells, which further diminished its transcription action for production of cytokines. The ethanolic Boswe-E also reduced the progression of rheumatoid arthritis in collagen-induced arthritis rats (Umar et al. 2014). The oral administration of this ethanolic Boswe-E markedly decreased the articular elastase and MMP levels. Ethanolic Boswe-E also decreased the infiltration and activation of the neutrophils in the synovial tissue of the joints, reducing the joint swelling. The treatment with ethanolic Boswe-E showed a protective role mediated via its antioxidant effect through the reduction of lipid peroxidation and NO levels and the boosting of antioxidant enzymes activity (GSH, SOD, and CAT). The authors related the reduction of disease severity with the downregulation of the production of the inflammatory mediator (IL-1 β , IL-6, TNF- α , IFN- γ , and PGE2) and with the upregulation of IL-10 in the joint. Therefore, ethanolic Boswe-E reduced the cellular flux and rats' joint erosion with minimum necrotic lesions.

Oral and topical preparations of Boswe-E, enriched in boswellic acid, also showed a robust effect in the treatment of osteoarthritis (Wang et al. 2014). The both oral and topical administration of this Boswe-E in destabilization of the medial meniscus-induced osteoarthritis in C57BL/6 J mice markedly decreased the cartilage erosion, osteophyte formation, and knee synovitis. Moreover, a reduction of several inflammatory cytokines (IL-1 β , IL-12p40, MCP-1, RANTES, and TNF- α) in the synovium were observed. The authors also suggested that the presence of other undefined molecules, in addition to boswellic acid, could contribute to the therapeutic effect in the reduction of joint damage in osteoarthritis. Another study corroborated the strong efficacy of Boswe-E in the management of osteoarthritis in the knee of newly diagnosed or untreated patients (Majeed et al. 2019). The oral supplementation of Boswe-E significantly improved physical function ability by reducing joint pain, stiffness, osteophytes (spur) formation and serum levels of CRP in those patients. The authors

suggested that the major compounds (3-acetyl-11-keto- β -boswellic acid, 11-keto- β -boswellic acid, β -boswellic acid, and 3-acetyl- β -boswellic acid) acted synergistically to exert the anti-arthritic activities.

Finally, aqueous and ethanolic Boswe-E obtained from oleo gum resin showed a neuroprotective effect on ischemic cerebral injury induced by middle cerebral artery occlusion in rats (Forouzanfar et al. 2016). The treatment with aqueous and ethanolic Boswe-E significantly improved neurological deficits and decreased the tissue injury. Moreover, Boswe-E prevented the increase of MDA levels and increased the GSH content and SOD activity in the right cortical region. The authors suggested that the biological activity of Boswe-E could be attributed to the 3-acetyl-11-keto- β -boswellic acid, present in both extracts.

Some studies also reported a pro-inflammatory effect of Boswe-E (Table 4). This bioactivity is related to (i) the activation of the complement system; (ii) the activation of the immune cells; (iii) the stimulation of phagocytosis; (iv) the increase of immune cell proliferation; (v) the increment of clonal expansion of immune cells; (vi) the promotion of the pro-inflammatory cytokine, antibody, and immunoglobulin production; and (vii) the increase of respiratory burst (Sharma et al. 1996; Khajuria et al. 2007, 2008; Gupta et al. 2011). For example, a Boswe-E fraction, composed of arabinose, glucose, and galactose, was proposed as an enhancer of antigen-specific humoral and cell-mediated immune response in ovalbumin-challenged Balb/C mice (Gupta et al. 2011). The IgG1 and IgG2a antibody levels were significantly enhanced in the serum in the presence of Boswe-E fraction. Moreover, it was also observed the splenocyte proliferation and the upregulation of the cell surface marker CD4/CD8 and co-stimulatory molecules CD80/CD86. In addition, the production of IL-2 and IFN- γ in the splenic lymphocytes was induced.

Echinacea purpurea

E. purpurea (Asteraceae family), also known as the purple coneflower, is a perennial flower native to eastern and central North America. Tea, freshly pressed juice, and tinctures, containing around 60% ethanol, are traditional *E. purpurea* preparations obtained from flowers, leaves, and/or roots. They are often therapeutically employed to prevent and relief a variety of different inflammatory conditions,

including swollen gums, sore throats, skin inflammation, and gastrointestinal disorders. Additionally, Echinacea preparations have been used to prevent or treat the common cold, flu, and infections in the upper respiratory tract. *E. purpurea* preparations have also been traditionally and highly used as an immune booster during common cold or infection.

E. purpurea extracts (Echi-E) are rich in alkylamides, phenolic compounds, sesquiterpenes, monoterpenes, monosaccharides, polysaccharides, flavonoids, and fatty acids (Supplementary Table S2). Chicoric acid, caftaric acid, a mixture of alkylamides—particularly dodeca-2E,4E,8Z,10E/Z-tetraenoic acid isobutylamide—, and polysaccharides are the main responsible for the anti-inflammatory activity of Echi-E. This bioactivity of Echi-E is related to (i) the inhibition of the complement system; (ii) the decrease of intracellular calcium ion; (iii) the reduction of pro-inflammatory cytokines expression and production; (iv) the decrease of respiratory burst and molecular oxidation levels; (v) the reduction of immune cells infiltration; (vi) the reduction of the degranulation process; (vii) the decrease of clonal expansion of immune cells; (viii) the blocking of receptors on immune cells; (ix) the increase in antioxidant enzymes and anti-inflammatory cytokines levels; and (x) the amelioration of edema, pain, and tissue injury (Sasagawa et al. 2006; Wang et al. 2006; Dong et al. 2006, 2009; Cech et al. 2006; Matthias et al. 2007; McCann et al. 2007; Zhai et al. 2007, 2009; Chicca et al. 2009; Benson et al. 2010; Chen et al. 2010; Hou et al. 2010, 2020; Šutovská et al. 2015; Capek et al. 2015; Todd et al. 2015; Aarland et al. 2017; Nyalambisa et al. 2017; Gullledge et al. 2018; Abd El-Twab et al. 2019; Li et al. 2020; Zhang et al. 2020a; Jiang et al. 2021; Vieira et al. 2022, 2023; Gu et al. 2023; Dosoky et al. 2023). The details of the anti-inflammatory studies are described in Table 5. Some of the most relevant studies will be presented in more detail. For instance, an aqueous ethanolic Echi-E obtained from roots efficiently reduced the TNF- α and NO production in LPS-stimulated murine RAW 264.7 macrophages (Zhai et al. 2009). Dichloromethanolic Echi-E obtained from roots significantly reduced the production of two main proinflammatory cytokines—IL-6 and TNF- α —and ROS/RNS in LPS-stimulated primary human monocyte-derived macrophages. This Echi-E exerted their anti-inflammatory activity through the downregulation of the phosphorylation

Table 4 *Boswellia serrata* bioactive compounds, methods of their extraction, biological assays, and pro-inflammatory effects

Plant extract composition/Isolated compound	Extraction method	Biological assay	Pro-inflammatory effects	References
Arabinose, glucose and galactose	Material (0.5 kg) was extracted with methanol (3 × 1.5 L) in a percolator at RT. The dried residue (175 g) was extracted with water (1 × 700 and 1 × 200 mL). The supernatant was mixed with alcohol (1.2 L). The precipitate was collected and purified, yielding the biopolymeric fraction BOS 2000 (70 g)	Hepatitis B surface antigen-challenged BALB/c mice was treated with extract (10, 20, 40, and 80 µg) on days 0 and 15. The immunization was observed 2 weeks after the second injection	↑ anti-HBsAg antibodies production	Khajuria et al. (2007, 2008), Gupta et al. (2011)
			↑ IgG1 and IgG2a production	
		HBsAg-stimulated splenic lymphocytes of extract (10, 20, 40 and 80 µg/ml) were cultured for 3 days	↑ HBsAg-stimulated splenocyte proliferation	
		Sheep red blood cells-challenged Balb/c mice were treated with extract (1, 3, and 10 mg/kg, oral) for 14 days	↑ IFN-γ and TNF-α production	
		Concanavalin A/LPS-stimulated mice splenic lymphocytes of extract treatment were cultured for 72 h	↑ T-cell subsets: CD3 T-cell surface	
			↑ primary and secondary antibody synthesis	
		Peritoneal macrophages of extract treatment (1, 3, and 10 mg/kg) were spread with opsonized <i>Candida</i> cells for 15 min	↑ complement fixing antibody	
			↑ delayed-type hypersensitivity	
		Ovalbumin-challenged Balb/C mice were treated with extract (10, 20, 40, and 80 µg) on day 1. A challenging injection was given two weeks later	↑ splenocyte proliferation	
			↑ phagocytosis of macrophage	
			↑ NO production	
		Concanavalin A/ovalbumin-stimulated splenic lymphocytes of extract treatment were cultured for 48 h	↑ IFN-γ and TNF-α production	
			↑ CD4 and CD8 population in spleen	
			↑ IgG, IgG1, and IgG2a production	
			↑ splenocyte proliferation	
			↑ CD4 ⁺ and CD8 ⁺ T cells in the spleen cells	
			↑ CD80 and CD86 on splenic macrophages	
			↑ IL-2 and IFN-γ levels	

Table 4 continued

Plant extract composition/Isolated compound	Extraction method	Biological assay	Pro-inflammatory effects	References
β -boswellic acid, acetyl- β -boswellic acid, 11-keto- β -boswellic acid, and acetyl-11-keto- β -boswellic acid	Pure fractions of four of acids were isolated from <i>B. serrata</i>	Mouse resident peritoneal macrophages were treated with extracts (1.95, 3.90, 7.81, 15.62, 31.25, 62.50, and 125 μ g/mL). Then, the cells were challenged with heat killed and opsonized <i>Candida albicans</i> for 15 min	$\uparrow$ phagocytosis	Sharma et al. (1996)

CD, cluster of differentiation; HBsAg, hepatitis B surface antigen; IFN, interferon; Ig, immunoglobulin; IL, interleukin; LPS, liposaccharides; NO, nitric oxide; RT, room temperature; TNF, tumor necrosis factor

of p38, ERK 1/2, STAT 3, and NF- κ B signaling pathways. In addition, the downregulation of cyclooxygenase 2 expression was also observed. The authors proposed that alkylamides were the main class of compounds responsible for the this strong bioactivity of extracts. Another aqueous ethanolic Echi-E prepared from aerial parts (stems, leaves, and flowers) modulated the fate of the murine bone marrow-derived dendritic cells (BMDCs) (Benson et al. 2010). This Echi-E, primarily composed of chicoric acid and dodeca-2E,4E,8Z,10E/Z-tetraenoic acid isobutylamide, decreased the frequency and relative expression of molecules involved in antigen presentation (MHC class II) and co-stimulation (CD86 and CD54), as well as the activity of COX-2. The pre-treatment of ovalbumin-sensitized murine BMDCs with this Echi-E also reduced the frequency of dendritic cells engulfing the antigen. At this point, the APC functions of dendritic cells are compromised, and the activation of T cells, consequently, can be affected. The co-culture of ovalbumin-sensitized murine BMDCs pre-treated with extracts and T cells demonstrated that Echi-E significantly decreased the clonal expansion of CD4⁺ T cells. Therefore, alkylamides might inhibit T cell-mediated immune response by potentially affecting both innate (antigen uptake) and adaptive (CD4⁺ T cells) immunity. Other studies demonstrated that cynarin isolated from Echi-E was a strong immunosuppressive agent. It can block the CD28 receptor of human Jurkat T-cells, preventing the binding of other ligands, such as CD80 of human Raji B lymphocyte cells (Dong et al. 2006, 2009). Thus, cynarin disturbed the CD28-dependent T-cell activation and reduced the

production of IL-2 through the inhibition of the signal 2 pathway, acting as an antagonist of the CD28/CD80 interaction. The Echi-E essential oils were also recently reported to reduce the innate immunity (Dosoky et al. 2023). The pre-treatment of human neutrophils with flower essential oils—mainly composed of germacrene D, α -phellandrene, β -caryophyllene, γ -curcumene, α/β -pinene, and δ -cadinene— inhibited the intracellular Ca²⁺ mobilization and the chemotaxis. In vivo studies also demonstrated the potential of Echi-E as anti-inflammatory formulations. The treatment with an aqueous ethanolic Echi-E obtained from the whole plant in 2,4,6 trinitrobenzene sulfonic acid (TNBS)-induced acute intestinal inflammation in Sprague–Dawley rats demonstrated strong protective effects (Gu et al. 2023). This Echi-E improved the symptoms of the ulcerative colitis, as well as the integrity of intestinal epithelial barrier, and, consequently, attenuated colon injury. The production of the IL-6 and TNF- α was significantly reduced. In addition, the expression of complement factor B (CFB), CD55, TLR4, and NLRP3 were diminished. Interestingly, the Echi-E was also able to achieve therapeutic effect by inhibiting C3a/C3aR signal pathway. Furthermore, the antioxidant capacity was significantly enhanced by the increase in the expression of GSH-Px levels, resulting in the reduction of ROS production.

The administration of Echi-E prepared from flowers in ovalbumin sensitized-guinea pigs to analyze the effects on asthma treatment was also reported (Šutovská et al. 2015). The long-term treatment with Echi-E significantly decreased bronchoconstriction,

Table 5 *Echinacea purpurea* bioactive compounds, methods of their extraction, biological assays, and anti-inflammatory effects

Plant extract composition/ Isolated compound	Extraction method	Biological assay	Anti-inflammatory effects	References
Chicoric acid, chlorogenic acid, caftaric acid, and alkylamides	Fresh powdered roots and flowers were extracted with methanol (50 mL) using a goldfish extractor	H ₂ O ₂ -induced intracellular oxidation in murine RAW264.7 macrophages was pre-treated with extracts (2.5 mg/mL) overnight LPS-induced nitric oxide production in murine RAW264.7 macrophages was co-treated with extracts (0.625, 1.25, 2.5, and 5 mg/mL) for 24 h	↓ intracellular oxidation ↓ NO production	Chen et al. (2010)
Caftaric acid, chicoric acid, and alkylamides	Dried powdered roots were extracted (6 h) with different organic solvents (250 mL, 100% ethanol, 95% ethanol, chloroform, and hexane) using a Soxhlet apparatus	LPS-stimulated murine RAW 264.7 macrophages were co-treated with extracts (100, 200, and 500 µg/mL)	↓ NO production ↓ TNF-α production	Zhai et al. (2007)
Caftaric acid, chicoric acid and amides	Dried powdered roots were extracted (6 h) in a Soxhlet apparatus with 75% ethanol (250 mL)	LPS-stimulated murine RAW 264.7 macrophages were co-treated or not with extracts (10, 25, 50, 100, and 200 µg/mL) for 22 or 24 h	↓ TNF-α production ↓ NO production ↓ iNOS production	Zhai et al. (2009)
Undeca-2E/Z,4Z/E-diene-8,10-diynoic acid isobutylamide, dodeca-2E,4E-dienoic acid isobutylamide, dodeca-2Z,4E-diene-8,10-diynoic acid isobutylamide, dodeca-2E,4Z-diene-8,10-diynoic acid 2-methylbutylamide, dodeca-2E,4E,8Z-trienoic acid isobutylamide, dodeca-2E,4E,8Z,10E/Z-tetraenoic acid isobutylamide, and xanthienopyran	Dried grounded roots (1.9 kg) were macerated (7 days) with 75% ethanol (9.5 L)	LPS-stimulated murine RAW 264.7 macrophages were co-treated with extract (10, 50, and 100 µg/mL) for 10 to 18 h	↓ TNF-α production	Todd et al. (2015)
Alkylamides	Echinacea Premium Liquid	LPS-stimulated murine RAW 264.7 macrophages were pre-treated with extracts (0.2 and 2 ng/mL) for 3 or 20 h	↓ NF-κB protein expression ↓ TNF-α production	Matthias et al. (2007)

Table 5 continued

Plant extract composition/ Isolated compound	Extraction method	Biological assay	Anti-inflammatory effects	References
Dodeca-2E,4E,8Z,10E/Z-tetraenoic acid isobutylamide	Fresh whole plant was extracted in methanol (1.6 L, × 2) at RT. The dry extract was re-dissolved in water (1 L). Then, ethyl acetate was added, and this layer was chromatographed into Fractions 1–5. Fraction 3 was subsequently purified yielding dodeca-2E,4E,8Z,10Z/E-tetraenoic acid isobutylamide	LPS-stimulated murine RAW 264.7 macrophages were pre-treated isolated compound (5–100 µM) for 24 h	↓ NO production ↓ TNF-α, IL-1α, IL-1β, IL-2, IL6, IL-12p70, MCP-1, MIP-1β, and RANTES production ↓ iNOS and COX-2 production ↑ HO-1 production	Hou et al. (2010)
Malic acid, vanillic acid, protocatechuic acid, caftaric acid, chlorogenic acid, quinic acid, vanillin, caffeic acid, benzoic acid, <i>p</i> -coumaric acid, chicoric acid, rutin, quercetin, undeca-2E/Z-ene-8,10-diynoic acid isobutylamide, undeca-2E/Z,4Z/E-diene-8,10-diynoic acid isobutylamide, undeca-2E,4E-diene-8,10-diynoic acid isobutylamide, dodeca-2E-ene-8,10-diynoic acid isobutylamide, dodeca-2E,4E-dienoic acid isobutylamide, dodeca-2E,4E-dienoic acid isobutylamide isomer 1, dodeca-2E/Z,4Z/E-diene-8,10-diynoic acid isobutylamide, dodeca-2,4-diene-8,10-diynoic acid 2-methylbutylamide, dodeca-2E,4E,8Z-trienoic acid isobutylamide, dodeca-2E,4E,8Z-trienoic acid isobutylamide isomer 1 and 2, dodeca-2E,4Z,10E/Z-triene-8-ynoic acid isobutylamide, dodeca-2E/Z,4E,10Z-triene-8-ynoic acid isobutylamide, dodeca-2E/Z,4E/Z,10E/Z-triene-8-ynoic acid isobutylamide, dodeca-	Dried blended flowers, leaves, or roots (2–5 g) were extracted (30 min) with ethanol or dichloromethane using an accelerated solvent extractor (1500 psi, 40° C) Dried blended flowers, leaves, or roots (20 g) were stirred (24 h) with water (150 mL), at RT	LPS-stimulated human THP-1 macrophages were treated with extracts (12.5, 25, 50, 100, 200, and 250 µg/mL) for 22 h	↓ IL-6, IL-1β, and TNF-α production ↓ ROS/RNS/O ₂ ^{•-} production Dichloromethanolic extracts > ethanolic extracts > water extracts	Vieira et al. (2022)

Table 5 continued

Plant extract composition/ Isolated compound	Extraction method	Biological assay	Anti-inflammatory effects	References
2,4,10-triene-8-ynoic acid isobutylamide isomer 1, dodeca- 2E,4E,8Z,10E/Z- tetraenoic acid isobutylamide, dodeca- 2E,4E,8Z,10E/Z- tetraenoic acid 2-methylbutylamide, trideca-2E,7Z-diene- 10,12-diyenoic acid isobutylamide, trideca- 2E/Z,7Z-diene-10,12- diynoic acid 2-methylbutylamide, hexadeca-2E,9Z-diene- 12,14-diyenoic acid isobutylamide, pentadeca-2E,9Z-diene- 12,14-diyenoic acid isobutylamide, and pentadeca-2E,9Z-diene- 12,14-diyenoic acid 2-hydroxyisobutylamide				
Dodeca-2E,4E,8Z,10E/Z- tetraenoic acid isobutylamide, undeca- 2Z,4E-diene-8,10- diynoic acid isobutylamide, chlorogenic acid, caftaric acid, and chicoric acid	Dried leaves and flowers were macerated (7 days) in 95% ethanol solution	PHA/PMA-stimulated human Jukart T cells were treated with extracts (0.1, 1, 10, 50, 100 µg/ mL) for 24 h	↓ IL-2 production	Sasagawa et al. (2006)
Undeca-2E/Z,4Z/E-diene- 8,10-diyenoic acid isobutylamide, undeca- 2E,4Z-diene-8,10- diynoic acid 2-methylbutylamide, dodeca-2Z/E,4E/Z-diene- 8,10-diyenoic acid isobutylamide, dodeca- 2,4-diene-8,10-diyenoic acid 2-methylbutylamide, and dodeca- 2E,4E,8Z,10E/Z- tetraenoic acid isobutylamide	Fresh roots (1 g) were blended in 95% ethanol (2 mL) and macerated (7 days), at 4 °C. The solvent was removed with a hydraulic press	PHA/PMA-stimulated human Jukart T cells were treated with extracts (diluted tenfold) for 24 h	↓ IL-2 production	Cech et al. (2006)

Table 5 continued

Plant extract composition/ Isolated compound	Extraction method	Biological assay	Anti-inflammatory effects	References
Cynarin	Cynarin was purified from <i>E. purpurea</i> extracts with serial elution buffers of hexane (1 L), ethyl acetate (1 L), methanol:ethyl acetate mixture (3 L, 50:50), methanol:ethyl acetate mixture (3 L, 75:25), and methanol (3 L)	The plates were coated with anti-CD3. After 24 h, isolated compound (2–500 µg/mL) was added for 15 min, and then human Jukart T cells plus CD28 were mixed for 24 h The plates were coated with anti-CD3. After 24 h, human Jukart T-cells with isolated compound (100–1000 µg/mL) were added for 15 min, and then CD28 or human Raji B lymphocyte cells were mixed for 24 h	Block of CD28 receptor of T cells ↓ IL-2 production	Dong et al. (2006, 2009)
Alkylamides	Dried ground roots were macerated (7 days) in 75% ethanol.	Calcium ionophore-stimulated rat RBL-2H3 basophils were treated with extract (25 µg/mL) for 1 h	↓ degranulation and calcium influx	Gulledge et al. (2018)
Chicoric acid, caftaric acid, chlorogenic acid, dodeca-2E,4E,8Z,10E/Z-tetraenoic acid isobutylamide, glucitol acetate, mannitol acetate, arabinitol acetate, rhamnitol acetate, galactitol acetate, and xylitol acetate	Dried aerial parts (stems, leaves, and flowers) were macerated (7 days) in 75% ethanol (1:5, W/V)	Murine BMDCs were treated with extracts (50 and 150 µg/mL) for 48 h Ovalbumin-sensitized murine BMDCs were pre-treated with extracts (150 µg/mL) for 48 h Ovalbumin-sensitized murine BMDCs were pre-treated with extracts (150 µg/mL) for 48 h. Then, BMDCs were added to T cells at several ratios (1:1, 1:2.5, 1:10) for 4 days	↑ CD11c ⁺ frequency and relative expression ↓ clonal expansion of CD4 ⁺ T cell ↓ MHC-II and CD86 frequency and relative expression ↓ CD54 frequency ↓ frequency of antigen uptake ↓ COX-2 activity	Benson et al. (2010)
Amides and caffeic acid derivatives	Fresh diced roots (1 part) were suspended (20 min) in 50% aqueous ethanol (9 parts), at RT	Human PBMCs were treated with extracts (15 µL, diluted 1:12.5) for 24 h	↑ IL-10 production	McCann et al. (2007)

Table 5 continued

Plant extract composition/ Isolated compound	Extraction method	Biological assay	Anti-inflammatory effects	References
Malic acid, vanillic acid, protocatechuic acid, caftaric acid, chlorogenic acid, caffeic acid, benzoic acid, <i>p</i> -coumaric acid, chicoric acid, rutin, quercetin, undeca-2E/Z-ene-8,10-diyenoic acid isobutylamide, undeca-2E/Z,4Z/E-diene-8,10-diyenoic acid isobutylamide, undeca-2E,4E-diene-8,10-diyenoic acid isobutylamide, dodeca-2E-ene-8,10-diyenoic acid isobutylamide, dodeca-2E,4E-dienoic acid isobutylamide, dodeca-2E,4E-dienoic acid isobutylamide isomer 1, dodeca-2E/Z,4Z/E-diene-8,10-diyenoic acid isobutylamide, dodeca-2,4-diene-8,10-diyenoic acid 2-methylbutylamide, dodeca-2E,4E,8Z-trienoic acid isobutylamide, dodeca-2E,4E,8Z-trienoic acid isobutylamide isomer 1 and 2, dodeca-2E,4Z,10E/Z-triene-8-ynoic acid isobutylamide, dodeca-2E/Z,4E,10Z-triene-8-ynoic acid isobutylamide, dodeca-2E/Z,4E/Z,10E/Z-triene-8-ynoic acid isobutylamide, dodeca-2,4,10-triene-8-ynoic acid isobutylamide isomer 1, dodeca-2E,4E,8Z,10E/Z-tetraenoic acid isobutylamide, dodeca-2E,4E,8Z,10E/Z-tetraenoic acid 2-methylbutylamide, trideca-2E,7Z-diene-10,12-diyenoic acid isobutylamide, trideca-2E/Z,7Z-diene-10,12-diyenoic acid 2-methylbutylamide,	Dried grounded flowers or roots (2–5 g) were extracted (30 min) with ethanol or dichloromethane using an accelerated solvent extractor (1500 psi, 40 °C)	LPS-stimulated human monocyte-derived macrophages were treated with extracts (12.5, 25, 50, 100, 200, and 250 µg/mL) for 22 h	↓ IL-6 and TNF- α production ↓ ROS/RNS/O $_2^{\cdot -}$ production ↓ ERK 1/2, p38, NF- κ B p65, and STAT3 phosphorylation ↓ COX-2 expression	Vieira et al. (2023)

Table 5 continued

Plant extract composition/ Isolated compound	Extraction method	Biological assay	Anti-inflammatory effects	References
hexadeca-2E,9Z-diene- 12,14-diyenoic acid isobutylamide, pentadeca-2E,9Z-diene- 12,14-diyenoic acid isobutylamide, and pentadeca-2E,9Z-diene- 12,14-diyenoic acid 2-hydroxyisobutylamide				
Caffeic acid derivatives, flavonoids, and alkylamides (dodeca- 2E,4E,8Z,10Z-tetraenoic acid isobutylamide, dodeca-2E,4E-dienoic acid isobutylamide, undeca-2E,4Z-diene- 8,10-diyenoic acid isobutylamide, dodeca- 2E,4Z-diene-8,10- diynoic acid isobutylamide)	Echinaforce (an aqueous ethanolic extract made from fresh aerial parts and roots), aerial parts, and roots extracts were obtained from A. Vogel Bioforce AG (Switzerland) Powdered roots were percolated (12 h) with hexane	Human HL-60 CB2- positive cells were treated with extracts (10 µg/mL) LPS-stimulated human PBMCs were treated with aerial parts (9.5 µg/ mL) or roots (0.5 µg/mL) extracts for 18 h	Activation of the CB2 receptor by hexane extract ↑ [Ca ²⁺] intracellular ↓ TNF-α production ↑ IL-10 production	Chicca et al. (2009)
Chicoric acid, rutin, and alkylamides	Fresh whole plant, stems, and leaves were imbibed (30–40 days) in 70% ethanol, at RT	Human monocyte-derived immature dendritic cells were treated with extracts (1, 10, 100, and 500 µg/ mL) for 24 h	↓ MHC-II, CD32, and CD83 expression ↓ STAT 1, FASLG, B2M, IGSF6, CD34, IL1B, CD86, IL10RA, CCL22, CD1A, CCL8, CLEC1A, LILRB4, CLEC4A, CCL3, IFNA1, CDH8, CD68, ITGB1, CCR1, CCBP2 expression	Wang et al. (2006)
2-butyl furan, α-thujene, α/ β-pinene, camphene, sabinene, myrcene, α/β- phellandrene, p-cymene, limonene, bicycloelemene, β/γ/δ- elemene, α/β-cubebene, α-ylangene, α/β-copaene, β-maaliene, α-gurjunene, β-caryophyllene, trans-α- bergamotene, 5-diene-E/ Z-muurolo-3, isogermacrene D, α- humulene, allo- aromadendrene, 5-diene- E/Z-muurolo-4(14), 4-diene-Z-cadina-1(6), citronellol isobutanoate, dodecenol, 4-diene-E- cadina-1(6), γ- curcumene, germacrene D, β-selinene,	Fresh flowers were steam- distilled (3–4 h) in a Clevenger apparatus (plant material-to-water ratio: 1:6)	Human neutrophils were pre-treated with extracts (100 µg/mL) for 4 and 10 min Chemotaxis-activated human neutrophils were pre-treated with extracts (100 µg/mL) for 60 min	↓ [Ca ²⁺] intracellular ↓ neutrophil migration	Dosoky et al. (2023)

Table 5 continued

Plant extract composition/ Isolated compound	Extraction method	Biological assay	Anti-inflammatory effects	References
1-pentadecene, bicyclogermacrene, α - muurolene, $\alpha/\beta/\gamma/\delta$ - cadinene, E,E- α - farnesene, shyobunone, cubebol, isoshyobunone, zonarene, E-cadina-1,4- diene, α -elemol, $\alpha/\delta/\tau$ - cadinol, germacrene B, E-nerolidol, 1,5-epoxy salvial-4(14)-ene, germacrene D-4-ol, caryophyllene oxide, β - copaen-4- α -ol, salvial- 4(14)-en-1-one, humulene epoxide II, junenol, widdrol isomer, 1-epi-cubenol, τ - muurolol, epi- α -cadinol, epi- α -muurolol, 7-dien- 1- α -ol-eudesm-4(15), 7E- tetradecenol, epi- α - bisabolol, germacra- 4(15),5,10(14)-trien-1- α / β -ol, shyobunol, 14-oxy- α -muurolene, Z-thujopsenic acid, phytone, tricosane, pentacosane, heptacosane, nonacosane				
Uronic acid, arabinose, galactose, galacturonic acid, glucuronic acid, and glucose	Cut aerial parts were soaked (24 h) in petroleum ether at 60 °C. The defatted materials were enzymatically extracted (75 min) with 5% pectinase, at 50 °C and pH 3. The concentrated solution was applied to a cellulose column. The obtained fractions were purified by a gel filtration column to yield EPPS-3	LPS-stimulated murine RAW 264.7 macrophages were pre- treated with EPPS-3 (10, 50, and 100 μ g/mL) LPS-induced septicemia in male BALB/C mice was pre-treated with EPPS-3 (50 mg/kg, intraperitoneal administration) for 8 h	↓ tissue injury ↓ TNF- α and IL-6 expression and production ↑ IL-10 expression and production	Li et al. (2020)

Table 5 continued

Plant extract composition/ Isolated compound	Extraction method	Biological assay	Anti-inflammatory effects	References
Undeca-2E-ene-8,10-diynoic acid isobutylamide, undeca-2E,4Z-diene-8,10-diynoic acid isobutylamide, undeca-2E/Z,4Z/E-diene-8,10-diynoic acid 2-methylbutylamide, dodeca-2E-ene-8,10-diynoic acid isobutylamide, dodeca-2E-ene-8,10-diynoic acid 2-methylbutylamide, dodeca-2Z/E,4E/Z-diene-8,10-diynoic acid isobutylamide, dodeca-2E,4Z-diene-8,10-diyniic acid 2-methylbutylamide, dodeca-2E,4E,8Z,10Z-tetraenoic acid isobutylamide, dodeca-2E,4Z,8Z,10Z-tetraenoic acid isobutylamide, chlorogenic acid, sucrose, glucose, fructose saponins, anthraquinones, and flavonoids	Hydroethanolic extract prepared from roots, leaves, flowers, and seeds was obtained from certified trading houses which are subjected to trademarks	Carrageenan-induced paw inflammation in Wistar rats was treated with extracts (0.4 mL of extract/kg) for 11 days	↓ edema	Aarland et al. (2017)
Camphene, camphor, limonene, linalool, 2-hexenal, (α/β)-pinene, <i>p</i> -cymene, <i>p</i> -cymen-8-ol, α -fenchene, α -phellandrene, isomenthone, borneol, lavandulol, α -terpineol, naphthalene, estragole, (cis/trans)-carveol, carvone, thymol, (α/β)-cubebene, methyl eugenol, geranyl acetone, germacrene D, caryophyllene, caryophyllene oxide, cedrol, ledol, and α -cadinol	Dried roots (368 g) were hydrodistilled (4 h) in a Clevenger apparatus	Carrageenan-induced inflammation in Wistar rats was pre-treated with essential oils (100 and 200 mg/kg, oral) for 1, 2, 3, and 4 h Acetic acid-induced writhing in Swiss mice was pre-treated with essential oils (100 and 200 mg/kg, oral) for 20 min	↓ edema ↓ writhings	Nyalambisa et al. (2017)

Table 5 continued

Plant extract composition/ Isolated compound	Extraction method	Biological assay	Anti-inflammatory effects	References
Rhamnose, inositol, fructose, sucrose, glucose, galactose, trehalose, sorbitol, arabinose, xylitol, and fucose	Polysaccharide of <i>E. purpurea</i> was obtained from Nanjing Dasf Biotechnology Co., Ltd	LPS-induced lung injury in C57BL/6 mice was co-treated with extract (5 and 10 mg/kg) for 24 h LPS-stimulated murine RAW 264.7 macrophages were pre-treated with extract (100 µg/mL) for 25 h	↓ tissue injury ↓ wet/dry weight ratio ↓ leukocytes, eosinophils, neutrophils, lymphocytes, and macrophages infiltration ↓ MPO activity ↓ TNF-α, IL-1β, and IL-6 production ↓ TLR4, MyD88, and NF-κB p65 production ↓ IκBα and NF-κB p65 phosphorylation ↑ IκBα production	Zhang et al. (2020a)
Glucose, galactose, arabinose, galacturonic acid, and glucuronic acid	Dried aerial parts were refluxed and then extracted in water at 80 °C (× 2). The supernatant was precipitated with 80% alcohol, dried by freeze-drying, and deproteinized. Then, the polysaccharides were purified by cellulose column, yielding EPPS-3	CCl ₄ -induced hepatic injury in ICR mice was pre-treated with EPPS-3 (5, 10, and 20 mg/kg/BW, intragastric) for 5 days	↓ tissue injury ↓ inflammatory cell infiltration ↓ MDA levels ↓ JNK phosphorylation ↑ GSH-Px and SOD levels ↑ HO-1 and Nrf2 production ↓ KEAP1 production	Hou et al. (2020)
Arabinose, galactose, glucose, mannose, galacturonic acid, glucuronic acid, uronic acid, proteins, and sulfate	Dried powdered flowers were stirred (12 h) in petroleum ether. The degreased flowers (1 g) were extracted (58 min) in distilled water (28 mL) by ultrasounds, at 70 °C (× 2). The concentrated supernatant was precipitated (overnight) with absolute ethanol. The precipitate was deproteinated and decolorated, and then stepwise alcohol of 80% was added to yield EPP80. The precipitate was dialyzed for 3 days	Alcohol-induced alcoholic liver injury in Kunming mice was pre-treated with EPP80 (100, 200, and 400 mg/kg, gavage) for 21 days	↓ tissue injury ↓ MDA levels ↓ TNF-α, IL-6, and IL-1β production ↑ GSH-Px, GSH, and SOD levels ↑ Nrf2, NQO1, and HO-1 production	Jiang et al. (2021)

Table 5 continued

Plant extract composition/ Isolated compound	Extraction method	Biological assay	Anti-inflammatory effects	References
Chicoric acid	Obtained from Chengdu Purify Phytochemicals Ltd (China), isolated from <i>E. purpurea</i>	Methotrexate-induced chronic kidney disease in Wistar rats was pre-treated with chicoric acid (25 and 50 mg/kg, oral) for 15 days	↓ tissue injury ↓ inflammatory cell infiltration ↓ ROS and NO production ↓ MDA levels ↓ TNF- α production ↓ IL-1 β and NLRP3 production ↓ NF- κ B p65 phosphorylation ↑ SOD, CAT, GSH, and GPx levels ↑ Nrf2 expression and production ↑ NQO-1 and HO-1 expression	Abd El-Twab et al. (2019)
Chicoric acid and caftaric acid	Crushed dried whole plant (20 parts) was extracted (15 min) with 50% ethanol (1 part) by ultrasounds. Then, the solution was refluxed (1 h), at 70 °C	TNBS-induced acute intestinal inflammation in Sprague–Dawley rats was treated with extracts (1 and 3 g/kg, gavage), once a day, for 10 days	↓ tissue injury ↓ ROS production ↓ C3 and C3a production ↓ IL-6 and TNF- α production ↓ CD55, TLR4, CFB, and C3aR expression ↓ NLRP3 expression ↑ GSH-Px levels	Gu et al. (2023)
Uronic acid, galactose, arabinose, rhamnose residues, xylose, glucose, mannose, fucose galacturonic acid, phenols, and proteins	Dried grounded flowers were extracted (24 h) in NaOH, at RT, and then refluxed (6 h). The solution was neutralized with HCl and sequentially extracted with hexane (1:1), diethyl ether (1:1), chloroform (1:1), and chloroform:ethanol mixture (3:2). Water fraction was treated with methanol at RT and the methanolic part was used	Ovalbumin-sensitized guinea pigs were treated with the extract (50 mg/kg, oral) for 14 days	↓ bronchoconstriction ↓ hyperreactivity ↓ specific airways resistance ↓ amplitude of isomeric contraction of tracheal and pulmonary smooth muscle ↓ exhaled NO levels ↓ IL-4, IL-5 IL-13, and TNF- α production	Šutovská et al. (2015)

Table 5 continued

Plant extract composition/ Isolated compound	Extraction method	Biological assay	Anti-inflammatory effects	References
Uronic acid, galactose, <i>D</i> -galacturonic acid, <i>D</i> -arabinose, <i>D</i> -rhamnose, <i>D</i> -xylose, <i>D</i> -glucose, <i>D</i> -mannose, <i>D</i> -fucose, phenols, proteins, Rhamnogalacturonan, and arabinogalactan	Dried minced flowers (200 g) were refluxed (5 h) in hexane (2 L), at 69 °C (× 2). The plant residue was refluxed (5 h) with NaOH (2 L) at 97 °C. The supernatant was neutralized with concentrated HCl and dissolved in water (1 L). Diethyl ether (1 L) was added, and the mixture was stirred (6 h) at 34 °C. After, the water-soluble fraction was collected by separating it from the organic one (× 2). Chloroform (1 L) was added to the water extract and the mixture was refluxed (6 h) at 61 °C. The water-soluble fraction was refluxed (6 h) with a mixture of chloroform and ethanol (3:2) at 70 °C (× 2). The concentrated extract was suspended in methanol (500 mL) and stirred (24 h) at RT (× 5). The precipitate was dialyzed to yield a macromolecular substance	Citric acid-induced cough reflex in Trik strain guinea pigs was treated with the extract (50 mg/kg/BW) in time intervals of 1, 2, and 5 h Citric acid-induced contractile mediators in Trik strain guinea pigs were treated with the extract (50 mg/kg/BW) for 1 min consecutively after the short exposure (30 s)	↓ specific airway resistance ↓ number of coughs	Capek et al. (2015)

BMDCs, bone marrow-derived dendritic cells; BW, body weight; Ca^{2+} , calcium ion; CAT, catalase; CB2, cannabinoid type 2 receptor; CCBP2, chemokine-binding protein 2; CCL, chemokine C–C motif ligand; CCl_4 , carbon tetrachloride; CD, cluster of differentiation; CDH8, cadherin 8; CFB, complement factor B; CLEC1A, C-type lectin domain family 1 member A; CLEC4A, C-type lectin domain family 4 member A; COX, cyclooxygenase; ERK, extracellular signal-regulated kinase; FASLG, Fas ligand gene; GSH, glutathione; GPx, glutathione peroxidase; HCl, hydrochloric acid; HO, heme oxygenase; H_2O_2 , hydrogen peroxide; IGSF, immunoglobulin superfamily; IFN, interferon; I κ B, inhibitor of nuclear factor kappa-light-chain-enhancer of activated B cells; IL, interleukin; IL10R, Interleukin-10 receptor; iNOS, inducible nitric oxide synthase; ITGB1, integrin subunit beta 1; JNK, c-Jun N-terminal kinase; KEAP1, kelch-like enoyl-CoA hydratase-associated protein 1; LILRB4, leukocyte immunoglobulin-like receptor subfamily B member 4; LPS, liposaccharides; MCP, monocyte chemoattractant protein; MDA, malondialdehyde; MHC, major histocompatibility complex; MIP, macrophage inflammatory protein; MPO, myeloperoxidase; MyD88, myeloid differentiation primary response protein 88; NaOH, sodium hydroxide; NF- κ B, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, nucleotide-binding oligomerization domain leucine-rich repeat pyrin domain-containing protein 3; NO, nitric oxide; NQO, nicotinamide adenine dinucleotide phosphate quinone oxidoreductase; Nrf2, nuclear factor erythroid 2-related factor 2; O_2^- , superoxide anion radical; PBMCs, peripheral blood mononuclear cells; PHA, phytohaemagglutinin; PMA, phorbol 12-myristate 13-acetate; RANTES, regulated upon activation, normal T cell expressed and secreted; ROS, reactive oxygen species; RNS, reactive nitrogen species; RT, room temperature; SOD, superoxide dismutase; STAT, signal transducer and activator of transcription; TNBS, 2,4,6-trinitrobenzenesulfonic acid solution; TNF, tumor necrosis factor; TLR, toll-like receptor

Table 6 *Echinacea purpurea* bioactive compounds, methods of their extraction, biological assays, and pro-inflammatory effects

Plant extract composition/ Isolated compound	Extraction method	Biological assay	Pro-inflammatory effects	References
Caftaric acid, chicoric acid, undeca-2E/Z,4Z-diene-8,10-diynoic acid isobutylamide, dodeca-2E/Z,4Z/E-diene-8,10-diynoic acid isobutylamide, dodeca-2E,4E,8Z,10E/Z-tetraenoic acid isobutylamide, and dodeca-2E,4E-dienoic acid isobutylamide	Dried powdered dormant roots (1 g) were macerated (7 days) with 75% ethanol (5 mL). The extract was pressed using a hydraulic press	Murine RAW 264.7 macrophages were treated with aqueous ethanolic extracts (6.7 μ L in 1 mL of medium) for 24 h	$\uparrow$ TNF- α and PGE2 production	Cech et al. (2010)
Arabinose, galactose, glucose, mannose, xylose, and chicoric acid	Not described	Human TPH-1 monocytes were treated with extracts (100 μ g/mL) for 6 h	$\uparrow$ IFN- γ , TNF- α , IL-1 α , IL-1 β , IL-6, IL-8, and MIP-1 α expression	Brovelli et al. (2005)
Malic acid, vanillic acid, protocatechuic acid, caftaric acid, benzoic acid, <i>p</i> -coumaric acid, chicoric acid, undeca-2E/Z-ene-8,10-diynoic acid isobutylamide, undeca-2E/Z,4Z/E-diene-8,10-diynoic acid isobutylamide, dodeca-2E-ene-8,10-diynoic acid isobutylamide, dodeca-2E/Z,4Z/E-diene-8,10-diynoic acid isobutylamide, dodeca-2E,4E-dienoic acid isobutylamide, dodeca-2,4-diene-8,10-diynoic acid 2-methylbutylamide, dodeca-2E,4E,8Z-trienoic acid isobutylamide, dodeca-2E,4Z,10E/Z-triene-8-ynoic acid isobutylamide, dodeca-2E/Z,4E,10Z-triene-8-ynoic acid isobutylamide, dodeca-2E/Z,4E/Z,10E/Z-triene-8-ynoic acid isobutylamide, dodeca-2E,4E,8Z,10E/Z-tetraenoic acid isobutylamide, dodeca-2E,4E,8Z,10E/Z-tetraenoic acid 2-methylbutylamide, pentadeca-2E,9Z-diene-	Blended flowers, leaves, or roots (20 g) were stirred (overnight) in water (150 mL), at RT	Human THP-1 macrophages were treated with extracts (25, 50, 100, 200, and 250 μ g/mL) for 24 h	$\uparrow$ IL-6, IL-1 β , and TNF- α production: flowers > roots > leaves $\uparrow$ O ₂ ^{•−} production: leaves > flowers > roots	Vieira et al. (2022)

Table 6 continued

Plant extract composition/ Isolated compound	Extraction method	Biological assay	Pro-inflammatory effects	References
12,14-diyenoic acid isobutylamide, trideca- 2E,7Z-diene-10,12- diynoic acid isobutylamide, and trideca-2E,7Z-diene- 10,12-diyenoic acid 2-methylbutylamide				
Galactose, glucose, arabinose, mannose, rhamnose, xylose, glutamic, aspartic acid, glycine, alanine, proline, valine, threonine, serine, leucine, lysine, phenylalanine, isoleucine, arginine, tyrosine, histidine, methionine, chicoric acid, caftaric acid, and cynarin	Fresh aerial parts were grounded with spring water into a slurry and passed through a hydraulic press. Then, 20% ethanol was added to the solution overnight and the supernatant was mixed with 70% ethanol. The solid pellet was collected and re- dissolved in distilled water	PMA- and ionomycin- stimulated Low- and high-density human Jurkat E6-1 T cells were pre-treated with extracts (10, 25, 100, and 250 µg/ mL) for 24 h	↑ IL-2 and IFN-γ production in high- density culture ↓ CD25 expression in low- density culture	Fonseca et al. (2014)
Chicoric acid, caftaric acid, chlorogenic acid, and undeca-2Z,4E- diene-8,10-diyenoic acid isobutylamide	Obtained from Shandong Qilu Animal Health Co., Ltd	Murine BMDMs were treated with extracts (100 µg/mL) for 12 or 24 h Murine BMDMs were treated with extracts (100 µg/mL) for 12 h and FITC-dextran for 1 h <i>Salmonella</i> <i>entericaserovar</i> <i>Typhimurium</i> -infected murine BMDMs were pre-treated with extracts (100 µg/mL) for 24 h	↑ M1 polarization ↑ CD80, CD86, CCR7, MHC-II expression ↑ phagocytosis and bactericidal capacity ↑ NO production ↑ IL-1β, IL-6, IL-12p70, TNF-α, and IFN-γ production ↑ IL-6, TNF-α, and iNOS expression ↑ ERK, JNK, p38, and NF- κB p65 phosphorylation	Fu et al. (2017)
Hypoxanthine, chlorogenic acid, caffeic acid, chicoric acid, rutin, quercetin-3-O- rhamnosyl-(1 → 6)- galactoside, and kaempferol-3-O- rhamnosyl-(1 → 6)- galactoside	Fresh stem and leaf were imbibed (35 days) in 70% ethanol, at RT. The aqueous ethanolic extract was dried and re- suspended in water (1 L) and then successively partitioned with ethyl acetate (1 L × 3) and butanol (1 L × 3)	Murine BMDCs were treated with a butanol fraction (75 µg/mL) for 24 h Labeled murine BMDCs treated with butanol fraction (75 µg/mL) were injected in the tail vein of syngeneic BALB/c mice for 24 h	↑ cell migration and mobility ↓ macrophage capping protein ↑ CCR5 production ↑ NEMO, MMP8, CXCL5, CXCL7, CTLA4, and CD38 expression ↓ CDH10, CDH1, and PRKCE expression	Yin et al. (2010)

Table 6 continued

Plant extract composition/ Isolated compound	Extraction method	Biological assay	Pro-inflammatory effects	References
Chicoric acid, caftaric acid, dodeca-2E,4E,8Z,10E/Z tetraenoic acid isobutylamide, glucitol acetate, mannitol acetate, arabinitol acetate, rhamnitol acetate, galactitol acetate, and xylitol acetate	Dried roots were macerated (7 days) in water (1:5, W/V)	Murine BMDCs were treated with extracts (150, 450 µg/mL) for 48 h Ovalbumin-sensitized murine BMDCs were pre-treated with extracts (150 µg/mL) for 48 h Ovalbumin-sensitized murine BMDCs were pre-treated with extracts (150 µg/mL) for 48 h. Then, BMDCs were added to T cells at several ratios (1:1, 1:2.5, 1:10) for 4 days	↑ CD11c ⁺ , MHC-II, CD86 and CD54 frequency ↑ MHC-II, CD86 and CD54 relative expression ↑ TNF-α and IL-6 production ↑ clonal expansion of CD4 ⁺ T cells ↓ frequency of antigen uptake	Benson et al. (2010)
Cichoric acid, caftaric acid, chlorogenic acid, and dodeca-2E,4E,8Z,10E/Z-tetraenoic acid isobutylamide	Obtained from Shandong Qilu Animal Health Co., Ltd	BMDCs were treated with extracts (400 µg/mL) for 48 h	↑ dendritic cells maturation ↓ endocytosis ↑ CD40, CD80, CD83, CD86 expression ↑ IFN-γ and IL-12 production ↑ TLR1 and TLR2 expression ↑ JNK, p38, and NF-κB p65 phosphorylation ↓ IκBα in the cytoplasm	Li et al. (2017)
Dodeca-2E,4E-dienoic acid isobutylamide	Dried grounded roots (1.8 kg) were extracted (48 h) with hexane in a Soxhlet apparatus. The crude extract was further fractionated and dodeca-2E,4E-dienoic acid isobutylamide was purified	Human HL-60 promyelocytic CB2-positive cells were stimulated with the isolated compound (10 µM) Human whole blood was stimulated with isolated compound (5, 50, 500, and 5000 nM) for 18 h	↑ intracellular released of Ca ²⁺ in HL60 cells via the CB2 receptor ↑ IL-6 and IL-8 production, via the CB2 receptor	Raduner et al. (2006)
Caffeic acid derivatives, flavonoids, and alkylamides (dodeca-2E,4E,8Z,10Z-tetraenoic acid isobutylamide, dodeca-2E,4E-dienoic acid isobutylamide, undeca-2E,4Z-diene-8,10-dienoic acid isobutylamide, dodeca-2E,4Z-diene-8,10-dienoic acid isobutylamide)	Echinaforce (an aqueous ethanolic extract made from fresh aerial parts and roots), aerial parts, and roots extracts were obtained from A. Vogel Bioforce AG (Switzerland)	PBMCs were stimulated with Echinaforce (10, 15, 25 µg/mL) for 24 h	↑ cell cycle ↑ IL-1β, IL-6, IL-8, TNF-α, IFN-γ, and GM-CSF expression ↑ NF-κB p65, IκBα, STAT4, and NFAT expression ↑ iNOS and COX-2 expression	Gertsch et al. (2004)

Table 6 continued

Plant extract composition/ Isolated compound	Extraction method	Biological assay	Pro-inflammatory effects	References
Alkylamides and polysaccharides	Dried preparations of fresh herbs were obtained from D & F Industries	Human PBMC from either a normal individual, or a patient with CFS or AIDS were treated with extracts (0.001, 0.01, 0.1, 1, 10, and 100 µg/mL) for 4 h K562 cells (target cells, T) were mixed with PBMC (effector cells, E) at different E:T ratios (40:1, 20:1, 10:1 and 5:1) followed by the addition of extracts (0.001, 0.01, 0.1, 1, 10, and 100 µg/mL) Human HHV-6 infected-H9 T cells (target cells, T) were mixed with PBMC (effector cells, E) at different ratios (40:1, 20:1, 10:1, and 5:1), in the presence of extracts (0.001, 0.01, 0.1, 1, 10, and 100 µg/mL)	↑ function and activity of natural killer cells ↑ antibody-dependent cellular cytotoxicity	See et al. (1997)
Chicoric acid, rutin, and alkylamides	Fresh roots and flowers were imbibed (30–40 days) in 70% ethanol, at RT	Human monocyte-derived immature dendritic cells were treated with extracts (1, 10, 100, and 500 µg/mL) for 24 h	↑ CD83 expression ↑ CCL2, CCL3, CCL4, ITGAE, JUN, ICAM1, IL17R, and NFATC2 expression	Wang et al. (2006)
Hypoxanthine, caffeic acid, chlorogenic acid, chicoric acid, rutin, quercetin 3- <i>O</i> -rhamnosyl-(1 → 6)-galactoside, and kaempferol 3- <i>O</i> -rhamnosyl-(1 → 6)-galactoside	Fresh stem and leaf were imbibed in 70% ethanol, at RT. The aqueous ethanolic extract was concentrated and partitioned with ethyl acetate (1 L, × 3) and butanol (1 L, × 3)	Human monocyte-derived immature dendritic cells were treated with butanol fraction (75 µg/mL) for 4, 12, and 24 h	↑ CD83 expression ↑ gelsolin, CAPG, ACTR3, VIM, CAT, SOD2, and PRDX6 production ↑ CCL2, CCL5, TNFRSF4, JAK2, DLG1, TANK, IL-8, CXCL2, TRIM45, MMP2, and NRF1 expression	Wang et al. (2008)

Table 6 continued

Plant extract composition/ Isolated compound	Extraction method	Biological assay	Pro-inflammatory effects	References
Alkylamides, chicoric acid, and polysaccharides	Roots or aerial parts were extracted with an aqueous ethanolic solution	Sprague–Dawley rats were treated with the extracts (2000 µg/kg/day of chicoric acid, 50,000 µg/kg/day of polysaccharides, and 200 µg/kg/day of alkylamides) by oral gavage twice a day for 4 days. Alveolar macrophages were incubated with latex beads for 1 h or with LPS for 60 h. Splenocytes were incubated with PMA plus ionomycin for 60 h	↑ phagocytic activity ↑ NO and TNF- α production by alveolar macrophages ↑ TNF- α and IFN- γ production by splenocytes	Goel et al. (2002a)
Alkylamides	<i>E. purpurea</i> extracts were purified by preparative liquid chromatography, giving alkylamide fraction	Sprague–Dawley rats were treated with the extract (0.5, 4, and 12 µg/mL, oral gavage) twice a day for 4 days. Alveolar macrophages were incubated with latex beads for 1 h or with LPS for 60 h	↑ phagocytic activity ↑ NO production ↑ TNF- α production	Goel et al. (2002b)
Dodeca-2E,4E,8Z,10E/Z-tetraenoic acid isobutyl amide, alkanes, chicoric acid, caftaric acid, β -sitosterol, decanoic acid, and nonanoic acids	Content from commercial <i>E. purpurea</i> capsules (Natural Whole Herb, Idea Sphere, Inc.) was macerated (overnight) with 75% ethanol, at RT	Sprague–Dawley rats were treated with extracts (50 and 100 mg of dry weight/kg, oral gavage), once daily for 7 days. Myeloid progenitor cells of bone marrow from treated rats were cultured for 5 days, after 14 days	↑ number of myeloid progenitor cells	Ramasahayam et al. (2011)
Alkylamides, caftaric acid, chicoric acid, and β -sitosterol	Dried pulverized aerial parts were macerated (overnight) with 75% ethanol, at RT	Sprague–Dawley rats were treated with extracts (50 and 100 mg of dry weight/kg, oral gavage) once daily for 7 days. Myeloid progenitor cells of bone marrow from treated rats were cultured for 5 days, after 14 days	↑ number of myeloid progenitor cells	Ramasahayam et al. (2011)

Table 6 continued

Plant extract composition/ Isolated compound	Extraction method	Biological assay	Pro-inflammatory effects	References
Chicoric acid	Powdered aerial parts (100 g) were extracted (3 h) with 70% ethyl alcohol (800 mL), at 65–70 °C (× 3). The dry residue was dissolved in water (500 mL) and subjected to an adsorption column to purify	Murine RAW 264.7 macrophages were pre-treated with extract (200 and 400 µg/mL) for 24 h Cyclophosphamide-induced immunosuppression in BALB/c mice were treated with extracts (100 and 200 mg/kg/ BW, oral gavage), daily, from day 5 to 14	↑ NO production ↑ phagocytosis ↑ TNF-α, IL-6, and IL-1β production ↓ tissue injury ↑ spleen and thymus indices ↑ B and T lymphocyte proliferation ↑ natural killer cell activity ↑ phagocytosis ↑ TNF-α, IL-6, IL-1β, and IFN-γ production	Sudeep et al. (2023)

ACTR3, actin-related protein 3; AIDS, acquired immunodeficiency syndrome; BMDs, bone marrow-derived dendritic cells; BMDMs, bone marrow-derived macrophages; BW, body weight; Ca²⁺, calcium ion; CAPG, macrophage-capping protein; CAT, catalase; CB2, cannabinoid type 2 receptor; CCL, chemokine C–C motif ligand; CCR, C–C chemokine receptor; CD, cluster of differentiation; CDH, cadherin; CFS, chronic fatigue syndrome; COX, cyclooxygenase; CTLA4, cytotoxic T-lymphocyte associated protein 4; CXCL, C-X-C motif chemokine ligand; DLG1, discs large homolog 1; ERK, extracellular signal-regulated kinase; FITC, fluorescein isothiocyanate; GM-CSF, granulocyte–macrophage colony-stimulating factor; ICAM, intercellular adhesion molecule; IL, interleukin; IL17R, interleukin-17 receptor; IFN, interferon; iNOS, inducible nitric oxide synthase; ITGAE, integrin subunit alpha E; IκB, inhibitor of nuclear factor kappa-light-chain-enhancer of activated B cells; JAK, Janus kinase; JNK, c-Jun N-terminal kinase; LPS, liposaccharides; MHC, major histocompatibility complex; MIP, macrophage inflammatory protein; MMP, matrix metalloproteinase; NEMO, nuclear factor kappa-light-chain-enhancer of activated B cells essential modulator; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NFAT, nuclear factor of activated T cells; NFATC2, nuclear factor of activated T-cells, cytoplasmic 2; NO, nitric oxide; Nrf1, nuclear factor erythroid 2-related factor 1; O₂^{•−}, superoxide anion radical; PBMCs, peripheral blood mononuclear cells; PG, prostaglandin; PMA, phorbol 12-myristate 13-acetate; PRDX6, peroxiredoxin-6; PRKCE, protein kinase C epsilon type; RT, room temperature; SOD, superoxide dismutase; STAT, signal transducer and activator of transcription; TANK, tumor necrosis factor receptor-associated factor family member-associated nuclear factor kappa-light-chain-enhancer of activated B cells activator; TNF, tumor necrosis factor; TNFRSF4, tumor necrosis factor receptor superfamily member 4; TLR, toll-like receptor; TRIM, tripartite motif-containing protein; VIM, vimentin

basal hyperreactivity, and specific airway resistance. Echi-E significantly decreased the levels of exhaled NO and key cytokine mediating asthma (IL-4, IL-5, IL-13, and TNF-α), both in bronchoalveolar lavage fluid (BALF) and plasma. The contractile response of tracheal and pulmonary smooth muscle was also significantly lower in the presence of Echi-E. Furthermore, long-term treatment of animals with Echi-E did not change the frequency of cilia beating, maintaining its basal levels, which allowed mucociliary clearance.

The immunostimulatory activity of Echi-E is related to (i) the activation of different immune cells; (ii) the promotion of cytokine, chemokine, and prostaglandins expression and production; (iii) the stimulation of phagocytosis; (iv) the increase of respiratory burst and molecular oxidation levels; (v) the increase of immune cell and clonal

proliferation; and (vi) the stimulation of immune cells migration and mobility (See et al. 1997; Goel et al. 2002a, b; Gertsch et al. 2004; Brovelli et al. 2005; Wang et al. 2006, 2008; Raduner et al. 2006; Benson et al. 2010; Cech et al. 2010; Yin et al. 2010; Ramasahayam et al. 2011; Fonseca et al. 2014; Li et al. 2017; Fu et al. 2017; Vieira et al. 2022; Sudeep et al. 2023). The details of the pro-inflammatory studies are described in Table 6. Some of the most relevant studies will be presented in more detail.

A commercial Echi-E (chicoric acid, caftaric acid, chlorogenic acid, and undeca-2Z,4E-diene-8,10-diy-noic acid isobutylamide) exhibited the ability to modulate the polarization of BMDs (Li et al. 2017) and murine bone marrow-derived macrophages (BMDMs) (Fu et al. 2017). The CD80 and CD86 were markedly increased in both cell types. The

expression of key molecules CCR7 and MHC class II was also significantly increased in macrophages, while CD40 and CD83 were promoted in dendritic cells. Moreover, this Echi-E significantly induced the gene expression in M1 macrophages (IL-6, TNF- α , IL-12p70, and iNOS). This was validated by the increase in the production of NO and several pro-inflammatory cytokines (IL-1 β , IL-6, IL-12p70, TNF- α , IFN- γ). Echi-E also enhanced the phagocytic and bactericidal capacity of murine macrophages. These effects were obtained due to Echi-E ability to significantly activate the MAPK signaling pathway, through the phosphorylation of ERK, JNK, and p38. NF- κ B signaling pathway was also triggered with an increase of p65 protein in the nucleus, with a correspondent decrease of I κ B protein in the cytoplasm. Interestingly, the stimulation of the murine dendritic cells was promoted via the activation of the same inflammatory signaling pathways, resulting in higher production of IFN- γ and IL-12 production. A butanol fraction of Echi-E also exhibited a strong capacity to mature human monocyte-derived immature dendritic cells (Wang et al. 2006). The Echi-E fraction enhanced the expression of the CD83 and induced the gene expression of over different genes involved in various key immune modulatory activities (e.g., CCL2, CCL5, IL-8, JAK2, TANK, and CXCL2). Additionally, dendritic cells exposed to the butanol fraction of Echi-E significantly up-regulated the antioxidant defense enzymes, including manganese superoxide dismutase (MnSOD), CAT, and peroxiredoxin 6, which are essential to induce T cell activation. Moreover, cytoskeletal and actin-binding proteins were up-regulated, enabling the formation of its characteristic dendrites and veils, important for the motility and migration to lymph nodes. Other classes of proteins were also enhanced, including cell growth- or maintenance-related proteins, energy pathway-related proteins, metabolic enzymes, proteins involved in protein metabolism or degradation, ion channel/transport proteins, signal transduction, and cell communication. A bioinformatic approach hypothesized that the butanol fraction of Echi-E may activate the cAMP and PKC pathways, leading to the regulation of adenylate cyclase 8 (AC8) through a Ca²⁺ receptor calmodulin. The same Echi-E also increased the responsive genes related to cell adhesion (e.g., CDH10, ITGA6, CDH1, GJA1, and MMP8), chemokines (e.g., CXCL2 and CXCL7), and signaling

molecules (e.g., NRXN1, PKCE, and ACSS1) in murine BMDCs (Yin et al. 2010). Also, the expression of the metabolic, cytoskeleton, and singling-related proteins, led to the enhancement of mobility, migration, and adhesion of the cells in the presence of Echi-E. The maturation of dendritic cells by an aqueous Echi-E obtained from roots, mainly composed of polysaccharides, was also studied (Benson et al. 2010). Moreover, polysaccharides-enriched Echi-E have been proposed as adjuvant effectors on Jukart T cells (Fonseca et al. 2014). The pre-treatment of T cells with this Echi-E enhanced the response to PMA and ionomycin, significantly increasing the production of IL-2 and IFN- γ . The authors proposed that Echi-E could influence Ca²⁺ mobilization to increase the intensity of IL-2 production since a dose-related effect was observed when the ionomycin was used alone. Particularly, dodeca-2E,4E-dienoic acid isobutylamide, isolated from a hexane Echi-E, presented ability to bind to the human CB2 receptor, increasing the total intracellular free Ca²⁺ concentration via a CB2-mediated G-protein-coupled mechanism, leading to stimulation of PLC, in human CB2-positive promyelocytic HL60 cells (Raduner et al. 2006).

The in vivo immunostimulatory activity was recently corroborated with a standardized aqueous ethanolic Echi-E containing higher chicoric acid content (Sudeep et al. 2023). The cyclophosphamide-induced immunosuppressed BALB/c mice treated with this Echi-E significantly improved the phagocytosis, the B and T lymphocyte proliferation, and the NK cell activity. Moreover, the levels of TNF- α , IL-6, IL-1 β , and IFN- γ in the serum was observed. Consequently, the administration of Echi-E promoted the normal architecture of the thymus and spleen.

Laurus nobilis

L. nobilis (Lauraceae family), commonly known as bay, is native to the southern Mediterranean region. Its leaves have been used as a traditional medicine in the Mediterranean and Europe to treat several immunological diseases. Essential oils of bay leaves are mostly used as a topical formulation to relax contracture, to ameliorate muscle pain, joint inflammations, and rheumatism. Bay leaf oil extracts are also used to treat paronychia. Additionally, cough and bronchitis can be treated with leaves cataplasm. Infusion from the bay leaves is traditionally used to alleviate

headaches and asthma. Leaves decoctions as a compress are also used to heal skin inflammation.

L. nobilis extracts (Laur-E) are rich in sesquiterpenes, monoterpenes, flavonoids, phenolic acids, fatty acids, and megastigmanes (Supplementary Table S3). Essential oils (e.g., 1,8-cineole, sabinene, linalool, α -terpinyl acetate, α -pinene, β -elemene, camphene, and α -terpineol), lindoldhamine, magnolialide, and costunolidares were found to be the main responsible compounds for the biological activity of the Laur-E (Table 7).

The anti-inflammatory activity of Laur-E is related to (i) the inhibition of complement system; (ii) the reduction of phagocytosis; (iii) decrease of degranulation process; (iv) the reduction of pro-inflammatory cytokines expression and production; (v) the decrease of clonal expansion of immune cells; (vi) the decrease of respiratory; (vii) the increase in antioxidant enzymes levels; and (viii) the amelioration of edema, pain, and tissue injury (Kim et al. 2011; Lee et al. 2013; Pérez-Rosés et al. 2015, 2016; Osmakov et al. 2019; Brinza et al. 2021; Al-Mijalli et al. 2022; Odeh et al. 2022; Smach et al. 2024). The details of the anti-inflammatory studies are described in Table 7. Some of the most relevant studies will be presented in more detail.

The Laur-E essential oils demonstrated a strong anti-inflammatory efficacy. For example, the Laur-E essential oils significantly reduce the phagocytosis in human neutrophils Particle-stimulated human neutrophils. It also participated in the reduction of the classical pathway of the complement system (Pérez-Rosés et al. 2015). Moreover, the pre-treatment of the same Laur-E essential oils in LPS-stimulated human leukocytes resulted in the decrease of MPO activity and ROS production (Pérez-Rosés et al. 2016).

Particularly, costunolide, obtained from methanolic Laur-E, can down-regulate the early and late phase of allergic disorders, not only through the reduction of RBL-2H3 mast cells activation, but also through the decrease of subsequent IgE-amplification by the IL-5-dependent Y16 B cell proliferation (Kim et al. 2011). Magnolialide, isolated from a combined dichloromethanolic and methanolic Laur-E, had also a therapeutic potential for a type-I IgE-mediated allergic inflammatory disorder, such as asthma and atopic dermatitis (Lee et al. 2013). Magnolialide reduced the early phases of mast cell activation, through the drastic down-regulation of IgE-mediated

degranulation from RBL-2H3 mast cells. Its bioactivity was higher than cromoglycate and ketotifen, stabilizers of the mast cell traditionally used in the clinic. Moreover, the gene expression and production of IL-4 were significantly diminished. Additionally, the treatment with magnolialide significantly reduced the proliferation of the IL-5-dependent Y16 early B cells. Finally, lindoldhamine, isolated from aqueous acetic acid Laur-E, had a significant anti-inflammatory effect, through the reduction of both paw edema and thermal hyperalgesia in complete Freund's adjuvant-induced male CD-1 mice (Osmakov et al. 2019). Laur-E essential oils also demonstrated in vivo efficacy. Its administration in scopolamine-induced memory deficits in Swiss albino mice significantly reduced the tissue damage, through the reduction of MDA levels and the induction of the GSH antioxidant enzymes (Smach et al. 2024).

Lavandula angustifolia

L. angustifolia (formerly *L. officinalis* or *L. vera*), belonging to Lamiaceae family and being native to Mediterranean coast, is popularly known as lavender, English lavender or True lavender (Kivrak 2018). Its flowers and/or leaves are used in the preparation of tea, juice, tinctures, or essential oils, to treat rheumatic, kidney and gastrointestinal disorders, sinusitis, and asthma. Additionally, lavender is widely used to relieve anxiety, depression, stress, migraines, fatigue, panic attacks, and heart problems, as well as to avoid insomnia.

L. angustifolia extracts (Lava-E) are rich in monoterpenes, sesquiterpenes, flavonoids, fatty acids, phenolic acids, and monosaccharides (Supplementary Table S4). Bioactive compounds, including linalool, linalyl acetate, caryophyllene, terpineol, borneol, 1,8-cineole, pinene, and camphor are described as the major bioactive compounds in the Lava-E (Tables 8 and 9).

The anti-inflammatory activity of Lava-E is associated with (i) the reduction of pro-inflammatory cytokines and prostaglandins expression and production; (ii) the decrease in immune cell proliferation; (iii) the decrease of respiratory burst and molecular oxidation levels; (iv) the increase in antioxidant enzymes levels; and (v) the amelioration of edema, pain, and tissue injury (Hajhashemi et al. 2003; Rahmati et al. 2013; Hancianu et al. 2013; Ueno-Iio

Table 7 *Laurus nobilis* bioactive compounds, methods of their extraction, biological assays, and anti-inflammatory effects

Plant extract composition/ Isolated compound	Extraction method	Biological assay	Anti-inflammatory effects	References
(α/β)-pinene, sabinene, limonene, 1,8-cineole, <i>p</i> -cymene, (α/δ)-terpineol, (α/γ)-terpinene, terpinen-4-ol, myrtenal, trans-pinocarveol, and α -terpenyl acetate	Essential oil	Particle-stimulated human leukocytes were pre-treated with extract for 45 min Sensitized sheep erythrocytes were pre-treated with extracts for 60 min	↓ phagocytosis by human neutrophils ↓ classical pathway of the complement system	Pérez-Rosés et al. (2015)
Costunolide	Dried leaves (40 kg) were extracted with methanol (20 L $\times$ 3). The extract was partitioned between hexane and aqueous methanol (2 L). The hexane fraction was purified, yielding costunolide	IgE-sensitized rat RBL-2H3 basophilic cells were treated with isolated compound (0.32, 1.6, 8, and 40 μ M) for 20 min or 3 h and then challenged with 2,4-dinitrophenyl-bovine serum albumin IL-5-stimulated murine Y16 early B cells were treated with isolated compound (0.16, 0.8, 4, 20, 40 μ M) for 48 h	↓ release of β -hexosaminidase ↓ IL-4 expression ↓ B cell proliferation	Kim et al. (2011)
Magnolialide	Dried leaves (1.5 kg) were repeatedly extracted with dichloromethane (2L $\times$ 2) and methanol (2L $\times$ 2). The combined solutions were partitioned between n-hexane and methanol:water. Then, the aqueous methanol soluble fraction was purified, isolating magnolialide	IgE-sensitized rat RBL-2H3 basophilic cells were treated with isolated compound (0.8, 4, 20, 50, and 100 μ M) for 20 min or 3 h, then challenged with 2,4-dinitrophenyl-human serum albumin IL-5-stimulated murine Y16 early B cells were treated with isolated compound for 48 h	↓ release of β -hexosaminidase ↓ IL-4 expression and production ↓ B cell proliferation	Lee et al. (2013)
(α/β)-pinene, sabinene, limonene, 1,8-cineole, <i>p</i> -cymene, terpinen-4-ol, α -terpenyl acetate, myrtenal, trans-pinocarveol, (α/γ)-terpinene, and (α/δ)-terpineol	Essential oil	PMA-, LPS- or L-arg-stimulated human leukocytes were pre-treated with extract	↓ ROS production ↓ MPO activity	Pérez-Rosés et al. (2016)
Lindoldhamine	Dried crushed leaves (2 g) were extracted under stirring (18 h) with aqueous acetic acid containing EDTA and PMSF (80 mL), at 24 °C. After freeze-drying, lindoldhamine was purified	Complete Freund's adjuvant-induced paw inflammation and thermal hyperalgesia in CD-1 mice was treated with isolated compound (1 mg/kg, intravenous) for 2, 4, and 24 h	↓ edema ↓ thermal hyperalgesia	Osmakov et al. (2019)

Table 7 continued

Plant extract composition/ Isolated compound	Extraction method	Biological assay	Anti-inflammatory effects	References
α -thujene, camphene, myrcene, α -phellandrene, 3-carene, (α/β)-pinene, <i>p</i> -cymene, <i>D</i> -limonene, eucalyptol, (α/γ)-terpinene, sabinene, cis-sabinene hydrate, α -terpinolene, linalool, terpinen-4-ol, linalyl acetate, bornyl acetate, (α/δ)-terpineol, (α/δ)-terpinyl acetate, eugenol, and methyleugenol	Dried grounded leaves (100 g) were hydrodistilled (3 h) using a Clevenger-type apparatus	Sprague–Dawley rats were treated with extracts (1 μ L/1 g weight/day, intragastric) for 14 days	$\uparrow$ CAT and GSH levels	Odeh et al. (2022)
α -thujene, sabinene, α -pinene, <i>L</i> - β -pinene, myrcene, <i>p</i> -cymene, <i>L</i> -limonene, α -fenchene, α -terpinene, linalool, orange/rose oil, cis-limonene oxide, pinocarvone, citronellal, 1,8-cineole, <i>L</i> -(-)-menthol, terpinen-4-ol, <i>L</i> - α -terpineol, (<i>R</i>)-(+)- β -citronellol, <i>D</i> -(+)-carvone, geraniol, <i>p</i> -anisaldehyde, cinnamic aldehyde, carvacrol, piperonal, eugenol, trans-caryophyllene, cyclamen aldehyde, α -amorphene, seychellene, α -cubebene, α -curcumene, trans-caryophyllene oxide, <i>E</i> -cis- β -santalol, acetyleugenol, olivetol, methyl dihydrojasmonate	Leaves incense	Scopolamine-induced amnesia in Wistar rats was pre-treated with leaf incense for 5 min for 7 days before starting behavioral tests and continuously administered during behavioral tests for 22 days	$\downarrow$ protein carbonyl and MDA levels $\uparrow$ SOD, CAT, and GSH levels	Brinza et al. (2021)
α/β -thujene, α -pinene, camphene, eucalyptol, linalool, α -terpineol, 4-thujen-2- α -yl acetate, bornyl acetate, α -terpinyl acetate, eugenol, methyleugenol, naphthalene, β -neoclovene, isoelemicin	Dried leaves (2 kg) were hydrodistilled (3 h) using a Clevenger apparatus	Carrageenan-induced paw edema in Wistar rats were pre-treated with extracts (50 and 100 mg/kg) for 1,3, and 6 h	$\downarrow$ edema	Al-Mijalli et al. (2022)
Camphene, α/β -pinene, α -phellandrene, 3-carene, <i>p</i> -cymene, 1,8-cineole, linalool, α/β -terpinolene, α -terpinyl acetate, eugenol, eugenol methyl ether, β -caryophyllene, caryophyllene oxide	Dried leaves were hydrodistilled (3 h) using a Clevenger apparatus	Scopolamine-induced memory deficits in Swiss albino mice was treated with extracts (10 mg/kg, intraperitoneal injection) for 15 days	$\downarrow$ tissue damage $\downarrow$ MDA levels $\uparrow$ GSH levels	Smach et al. (2024)

CAT, catalase; EDTA, Ethylenediaminetetra acetic acid; GSH, glutathione; Ig, immunoglobulin; IL, interleukin; L-arg, L-arginina; LPS, liposaccharides; MDA, malondialdehyde; MPO, myeloperoxidase; PMA, phorbol 12-myristate 13-acetate; PMSF, phenylmethylsulfonyl fluoride; ROS, reactive oxygen species; SOD, superoxide dismutase; TNF, tumor necrosis factor

Table 8 *Lavandula angustifolia* bioactive compounds, methods of their extraction, biological assays, and anti-inflammatory effects

Plant extract composition/ Isolated compound	Extraction method	Biological assay	Anti-inflammatory effects	References
Gallic acid, catechin, ferulic acid, myricetin, and quercetin	Dried powdered aerial parts (50 g) were macerated (48 h) with 70% ethanol (0.5 L), at RT	Carrageenan-induced paw edema in Wistar rats was pre-treated with extracts (300 and 600 mg/kg)	↓ edema	Slighoua et al. (2022)
1-octen-3-ol, acetic acid lavandulyl ester, 3-acetoxy octene, butyl butyrate, geranyl acetate, neryl acetate, hexyl butyrate, hexyl hexanoate, 3-octanone, borneol, camphene, D-camphor, 3-carene, 1-isopropyl-3-methylbenzene, 2-(4-methylphenyl)propan-2-ol, eucalyptol, cuminaldehyde, (E,Z)-2,6-dimethylocta-2,4,6-triene, isobornyl formate, lavandulol, linalyl acetate, linalool, <i>cis</i> -linalool oxide, <i>trans</i> -linalool oxide, 4-(1-methylethyl)-2-cyclohexen-	Dried grounded inflorescences (45 g) were steamed distilled (3.5 h) in a Pyrex oil distillation apparatus with distilled water (1200 mL)	PMA-induced ear edema in BALB/c mice was treated with extracts (25, 50, and 100 mg/kg, topical) for 6 h	↓ edema ↓ COX-2 production ↓ TNF- α production ↓ NF- κ B production	Chen et al. (2020)
1-one, nerol, (E)-3,7-dimethylocta-1,3,6-triene, (3Z)-3,7-dimethylocta-1,3,6-triene, α -phellandrene, α -pinene, β -pinene, sabinene, sabinene hydrate, γ -terpinene, α -terpineol, terpinolene, α -thujene, 4-terpineol, coumarin, aromandendrene, <i>cis</i> - α -bergamotene, β -bourbonene, (+)- γ -cadinene, T-cadinol, caryophyllene, caryophyllene oxide, <i>cis</i> - β -farnesene, germacrene D, humulene, and (+)- α -santalene				

Table 8 continued

Plant extract composition/ Isolated compound	Extraction method	Biological assay	Anti-inflammatory effects	References
β -pinene, terpinolene, <i>D</i> -limonene, eucalyptol, β -ocimene, γ -terpinene, β -thujene, α -phellandrene, α -pinene, (–)-camphene, <i>o</i> -cymene, (1 <i>S</i>)-(+)3-carene, 2-carene, linalool, camphor, borneol, hexyl butyrate, α -terpineol, linalyl acetate, bornyl acetate, isobornyl acetate, benzylacetone, allo-aromadendrene, and coumarin	Dried powdered plant was extracted by steam distillation (3.5 h) in distilled water	PMA-induced ear inflammation in BALB/c mice was treated with extracts (25, 50, and 100 mg/kg) for 6 h	↓ edema ↓ ear thickness ↓ IL-6 and TNF- α production ↓ NF- κ B production	Luo et al. (2019)
Linalyl acetate, linalool, (cis/trans)- β -ocimene, β -caryophyllene, lavandulyl acetate, terpinene-4-ol, and cis- β -farnesene	Obtained from ROHTO Pharmaceutical	Ovalbumin-sensitized and -challenged BALB/c mice were treated with extract (5 and 20 μ L, inhalation) for 20 min, 5 consecutive days per week	↓ total cell number and eosinophils ↓ airway hyperresponsiveness ↓ mucous cell hyperplasia ↓ IL-5 and IL-13 production ↓ IL-4, IL-5, and Muc5b expression	Ueno-Iio et al. (2014)
1,8-cineole, (cis/trans)-linalool oxide, linalool, camphor, lavandulol, α -terpineol, linalyl acetate, lavandulyl acetate, 3-octanone, and 1-octen-3-yl acetate	Flowers were hydrodistilled (1000 mL, 3–4 h) using a Clevenger apparatus	Imiquimod cream-induced psoriasis-like skin lesions in BALB/c mice was treated with extract (2%, 5%, and 10%, daily) for 4 consecutive days	↓ tissue injury ↓ ear thickness ↓ TNF- α , IL-1 β , IL-17, and IL-22 production	Rai et al. (2020)
Linalyl acetate, linalool, β -caryophyllene, (cis/trans)- β -ocimene, lavandulyl acetate, and terpinen-4-ol	Pure lavender essential oil was obtained by Pranarom International	Spared nerve injury-induced neuropathic pain in CD1 mice was treated with extract (10 to 200 mg/kg, oral) for 30 min or 7 days	↓ paw withdrawal threshold and paw licking ↓ ERK1/2 and JNK1 phosphorylation ↓ iNOS expression	Sanna et al. (2019)

Table 8 continued

Plant extract composition/ Isolated compound	Extraction method	Biological assay	Anti-inflammatory effects	References
(Z)-3-hexanol, hexanol, tricyclene, (α/β)-pinene, camphene, octen-3-ol, 3-octanone, myrcene, (<i>o/p</i>)-cymene, (E/Z)- β -ocimene, δ -3-carene, limonene, 1,8-cineole, linalool, <i>cis</i> -linalool oxide, hexyl butyrate, octen-3-yl acetate, allo-ocimene, neoallo-ocimene, camphor, borneol, geraniol, linalyl acetate, geranial, nerol, neral, trans-carvone oxide, isobornyl acetate, lavandulyl acetate, 3-thujyl acetate, hexyl tiglate, β -phellandrene, γ -terpinene, terpinolene, terpin-4-ol, α -terpineol, α -terpinyl acetate, neryl acetate, linalool isobutyrate, geranyl acetate, hexyl n-hexanoate, β -bourbonene, β -cedrene, α -(<i>cis/trans</i>)-bergamotene, E-caryophyllene, (E/Z)- β -farnesene, (<i>ar/\gamma</i>)-curcumene, bicyclogermacrene, lavandulyl isovalerate, lavandulyl 2-methyl butyrate, δ -cadinene, <i>trans</i> -calamenene, longipinanol, dendrolasin, globulol, 1-epi-cubenol, α -muurolol, 14-hydroxy-9-epi-(E)-caryophyllene, and epi- α -bisabolol	<i>L. angustifolia</i> essential oil was obtained from Penny Price Aromatherapy, Hinckley, England	Ischemia reperfusion-induced complex regional pain syndrome type-I and complete Freund's adjuvant-induced peripheral inflammation in Swiss mice were treated with extract (100, 200, and 300 μ L/day, inhalation) for 30 min, for 5 consecutive days	$\downarrow$ mechanical hyperalgesia in both inflammatory and neuropathic phase $\uparrow$ peripheral and spinal opioid receptors $\uparrow$ peripheral and spinal CB2R	Donatello et al. (2020)
Linalool, linalyl acetate, β -ocimene, terpinen-4-ol, lavandulyl acetate, and lavandulol	Essential oil was obtained from a commercial source	Scopolamine-induced amnesia in C57BL/6 J mice was pre-treated with extract (50 and 100 mg/kg/day, intraperitoneal) for 10 days	$\downarrow$ MDA levels $\uparrow$ SOD and GPx levels	Xu et al. (2016)
Linalool, 1,8-cineole, borneol, camphor, terpinen-4-ol, linalyl acetate, α -bisabolol, α -terpineol, and (Z)- β -farnesene	Dried powdered aerial parts (dried, 500 g) were soaked in 70% aqueous ethanol (1:4) for 3 days (RT)	Pentyltetrazole-kindling induced NMRI albino mice were pre-treated with extract (200, 400, and 800 mg/kg, intraperitoneal) every second day for 24 days	$\downarrow$ NO production $\downarrow$ MDA levels $\uparrow$ SOD levels	Rahmati et al. (2013)

Table 8 continued

Plant extract composition/ Isolated compound	Extraction method	Biological assay	Anti-inflammatory effects	References
1-methoxyhexane, (E)-3-hexen-1-ol, 1-hexanol, butyl propionate, tricyclene, 3,5-dimethylphenol, camphene, (α/β)-pinene, butyl isobutyrate, octen-3-ol, 3-octanone, 1- β -myrcene, 3-octanol, butyl butanoate, (+)-3-carene, (<i>o</i> / <i>m</i> / <i>p</i>)-cymene, hexyl acetate, D-limonene, eucalyptol, (α/β)-ocimene, α -phellandrene, (α/γ)-terpinene, 5-isopropyl-2-methylbicyclo [3.1.0] hexan-2-ol, α -terpinolene, 3-methyl-2-(2-methyl-2-butenyl)-furan, linalool, 1-octen-3-yl-acetate, 3-octyl acetate, (+)-2-bornanone, hexyl isobutyrate, Isoborneol, 5-methyl-2-prop-1-en-2-ylhex-4-en-1-ol, terpinen-4-ol, 4-Isopropyl-2-cyclohexenone, α -terpineol, hexyl butanoate, (E)-2,6-dimethylocta-3,7-diene-2,6-diol, nerol, linalyl acetate, bornyl acetate, hexyl tiglate, neryl acetate, α -cubebene, geranyl acetate, 5-(1,5-dimethyl-4-hexenyl)-2-methyl-1,3-cyclohexadiene, trans-caryophyllene, trans- α -bergamotene, iso-amyl tiglate, humulene, cis-caryophyllene, (+)-cyclosativene, β -bisabolene, γ -cadinene, caryophyllene oxide, τ -cadinol, α -bisabolol, 7-methoxy-2H-1-benzopyran-2-one, nerolidyl acetate, benzyl benzoate, and 6,10,14-trimethylpentadecan-2-one	<i>L. angustifolia</i> oil was purchased from Aromarant Co. Ltd, Rottingen, Germany	Collagen-induced arthritis in chronic nicotine exposure Sprague Dawley rats was co-treated with extract (10 and 100 mg/kg, intraperitoneal) twice per week for 35 days	↓ hind paw thickness ↓ IL-6 production ↓ inflammatory status	Seo et al. (2021)

Table 8 continued

Plant extract composition/ Isolated compound	Extraction method	Biological assay	Anti-inflammatory effects	References
Linalool, linalyl acetate, lavandulyl acetate, terpinen-4-ol, camphor, and borneol	Dried flower heads were extracted by steam distillation in water	Scopolamine-induced amnesia in Wistar rats was treated with extracts (200 μ L, inhalation) for 60 min per day, for 7 continuous days	↓ MDA levels ↑ reduced GSH levels ↑ SOD, GPx, and CAT levels	Hancianu et al. (2013)
α -thujene, (α / β)-pinene, α -fenchene, camphene, δ -3-carene, 1,8-cineole, trans- β -ocimene, γ -terpinene, terpinolene, linalool, camphor, borneol, lavandulol, 4-terpineol, α -terpineol, linalyl acetate, bornyl acetate, β -caryophyllene, cis- β -farnesen, and germacrene D	Essential oils (EO): dried powdered leaves were steamed distilled (3 h) in water Hydroethanolic extract (HE): dried powdered leaves (100 g) were macerated (48 h) with 70% ethanol (500 mL) Polyphenolic extract (PE): dried leaves (100 g) was extracted successively with 90% ethanol (12 h) and 50% ethanol (12 h). The combined evaporated extracts were cleared in a separating funnel with chloroform	Formalin-induced paw writhing in Swiss mice was pre-treated with HE, PE (400, 800, and 1600 mg/kg, oral), and EO (50, 100, and 200 mg/kg, oral) Acetic acid-induced abdominal writhing in Swiss mice was pretreated with HE (400, 800, and 1600 mg/kg, oral), PE (200, 400, and 800 mg/kg, oral), and EO (100 and 200 mg/kg, oral) Carrageenan-induced paw edema in Wistar rats was pre-treated with HE (1000, 2000, and 4000 mg/kg), PE (10,000, 2000, and 4000 mg/kg), and EO (200 mg/kg) for 4 h	↓ paw licking (anti-nociceptive effect): EO > PE > HE ↓ abdominal twitches: EO > PE > HE ↓ edema by EO	Hajhashemi et al. (2003)

CAT, catalase; CB2R, cannabinoid receptor subtype 2; CD, cluster of differentiation; COX, cyclooxygenase; ERK, extracellular signal-regulated kinase; GPx, glutathione peroxidase; IL, interleukin; iNOS, inducible nitric oxide synthase; JNK, c-Jun N-terminal kinase; MDA, malondialdehyde; Muc5b, mucin-5B; NF- κ B, nuclear factor kappa-light-chain-enhancer of activated B cells; NO, nitric oxide; PMA, phorbol 12-myristate 13-acetate; RT, room temperature; SOD, superoxide dismutase; TNF, tumor necrosis factor

et al. 2014; Xu et al. 2016; Luo et al. 2019; Sanna et al. 2019; Chen et al. 2020; Donatello et al. 2020; Rai et al. 2020; Seo et al. 2021; Slighoua et al. 2022). The details of the anti-inflammatory studies are described in Table 8. Some of the most relevant studies will be presented in more detail.

A Lava-E mainly composed by essential oils was applied in PMA-induced ear inflammation in mice (Chen et al. 2020). This Lava-E efficiently reduced the ear edema, in a dose-dependent manner. Importantly, it led to better therapeutic outcomes than the clinical used anti-inflammatory drug, ibuprofen, at the same dosage. Lava-E significantly down-regulated the expression of NF- κ B transcription factor, COX-2, and TNF- α . The authors suggested that linalyl acetate, linalool, borneol and eucalyptol were responsible for the anti-inflammatory activity. Another study

corroborates the anti-inflammatory activity of Lava-E essential oils applied in PMA-induced ear inflammation in mice. A markedly reduction in ear edema and in the expression of NF- κ B were also observed, which in turn reduced the IL-6 and TNF- α levels, being again more promise than ibuprofen at the same dose (Luo et al. 2019). Three different Lava-E obtained from leaves also presented anti-nociceptive, analgesic and anti-inflammatory activities (Hajhashemi et al. 2003). In this study, hydroethanolic Lava-E, polyphenolic Lava-E and essential oils Lava-E were applied on formalin- and acetic acid-induced writhes in mice, as well as carrageenan-induced paw edema in rats. Lava-E essential oils showed to be the best anti-nociceptive, analgesic, and anti-inflammatory extract, inhibiting 90% of paw licking, 27% of abdominal twitches and 48% of paw edema, respectively. As

Table 9 *Lavandula angustifolia* bioactive compounds, methods of their extraction, biological assays, and pro-inflammatory effects

Plant extract composition/ Isolated compound	Extraction method	Biological assay	Pro-inflammatory effects	References
chPS-L1 and chPS-L2: arabinose, rhamnose, fucose, xylose, mannose, galactose, glucose, glucuronic acid, galacturonic acid, ketodeoxyoctonic acid, 2-<i>O</i>-methyl D-xylose, and 2-<i>O</i>-methyl l-fucose chPP-L: chlorogenic acid, neochlorogenic acid, vanillic acid, caffeic acid, <i>p</i>-coumaric acid, ferulic acid, ellagic acid, protocatechuic acid, cinnamic acid, gallic acid, quercetin, quercetin-3-β-glucoside, myricetin, kaempferol, naringin, naringenin, catechin, and epicatechin	Dried flowers (30 g) were mixed with water (600 mL) and boiled until the mixture volume was reduced to half ($\times 2$). The concentrated collect extracts were coagulated with 95% ethanol (4° C, overnight). The centrifuged precipitates were re-dissolved in water, purified against water (4° C, 72 h) and freeze-dried, giving origin to lavender polysaccharide complex (PSC) Lavender PSC, dissolved in water, were precipitated with 95% ethanol (24 h each, $\times 5$). After centrifugation, the polysaccharide-containing fraction (lavender PSC2) was purified in a column and two pectic fractions (chPS-L1 and chPS-L2) and one polyphenolic fraction (chPP-L) were collected. The fractions were concentrated, dialyzed, and freeze-dried	Normal porcine serum was pre-treated with chPS-L1, chPS-L2 or chPP-L Human whole blood phagocytes or isolated human neutrophils were mixed with chPS-L1, chPS-L2 or chPP-L (50 and 100 μg/mL) for 60 min Murine RAW 264.7 macrophages were treated with chPS-L1 or chPS-L2 (50 and 100 μg/mL) in the presence or not of LPS for 24 and 48 h Murine Peyer's patch cells from the small intestine of female C3H/HeJ mice treated with peptic fractions (100 μg/mL) for 6 days. The resulting culture supernatants were further added to the bone marrow cells from male ICR mice for 6 days	$\uparrow$ complement fixation activity $\uparrow$ ROS production of whole blood phagocytes and neutrophils $\uparrow$ neutrophil activity ($\uparrow$ CD18 expression and $\downarrow$ CD26L expression) $\uparrow$ iNOS production $\uparrow$ NO production $\uparrow$ bone marrow cell proliferation from Peyer's patch cells	Georgiev et al. (2017b)
Arabinose, rhamnose, fucose, xylose, mannose, galactose, glucose, glucuronic acid, and galacturonic acid	Dried flowers (30 g) were mixed with water (600 mL) and boiled until the mixture volume was reduced to half ($\times 2$). The concentrated collect extracts were coagulated with 95% ethanol (4° C, overnight). The centrifuged precipitates were re-dissolved in water, purified against water (4° C, 72 h) and freeze-dried, giving origin to lavender polysaccharide complex (PSC)	Human white blood cells were treated with PSC (100 μg/mL) for 48 h Human whole blood phagocytes were mixed with PSC (10 and 100 μg/mL) for 60 min Murine Peyer's patch cells from the small intestine of female C3H/HeJ mice treated with PSC (100 μg/mL) for 6 days. The resulting culture supernatants were further added to the bone marrow cells from ICR mice for 6 days	$\uparrow$ CD8⁺, CD25⁺, CD14, CD64, and CD3 cells $\uparrow$ CD4⁺/CD25⁺ and CD8⁺/CD25⁺ T-cell subpopulations $\uparrow$ ROS production of whole blood phagocytes $\uparrow$ bone marrow cell-proliferation and IL-6 production from Peyer's patch cells	Georgiev et al. (2017a)

CD, cluster of differentiation; IL, interleukin; iNOS, inducible nitric oxide synthase; NO, nitric oxide; ROS, reactive oxygen species

Table 10 *Olea europaea* L bioactive compounds, methods of their extraction, biological assays, and anti-inflammatory effects

Plant extract composition/ Isolated compound	Extraction method	Biological assay	Anti-inflammatory effects	References
Oleoside, hydroxytyrosol hexose isomer, secologanoside isomer, tyrosol glucoside, elenolic acid glucoside isomer, oleuropein aglycon, luteolin-diglucoside, demethyloleuropein, rutin, luteolin rutinoside, luteolin glucoside isomer, apigenin rutinoside, oleuropein glucoside isomer, chrysoeriol-7- <i>O</i> - glucoside, 2''- methoxyoleuropein isomer, oleuropein isome, oleuropein, oleuroside, Ligstroside, and luteolin	Dried crushed leaves (Arbequina, Picual and Sikitita, 0.5 g) were extracted via UltraTurrax with methanol–water (80:20, 30 mL)	LPS-stimulated murine RAW 264.7 macrophages were pre-treated with extracts (0.1 to 100 µg/ mL) for 24 h	↓ NO production	Talhaoui et al. (2016)
Quercetin, luteolin, and kaempferol	Methanolic extracts prepared from the leaves of <i>O. europaea</i> were purchased from the Plant Extract Bank in the Plant Diversity Research Center (Daejeon, Korea)	LPS-stimulated RAW264.7 murine macrophages were pre-treated with extracts (25, 50, 100, and 200 µg/ ml) for 6 or 24 h	↓ NO production ↓ COX-2 and iNOS expression and production ↓ IL-6, IL-1β, TNF-α, and PGE2 production ↓ IκBα and IKK, phosphorylation ↓ p65 and p50 nuclear translocation	Song et al. (2019)
Quercetin, kaempferol, luteolin, oleuropein isomer, secaloganoside isomer, quinic acid, hydroxytyrosol, and ligstroside	Methanolic extracts obtained from leaves were purchased in Plant Extract Bank in the Plant Diversity Research Center (Daejeon, Korea)	LPS-, Pam3CSK4- or poly (I:C)-stimulated murine RAW264.7 macrophages were pre-treated with extract (50, 100, and 200 µg/mL) for 15, 30, 60 min, 6 and 24 h	↓ IL-2, IL-6, COX-2, MMP-9, ICAM-1, TNF-α, and MCP1 production ↓ COX-2, TNF-α, IL-6 expression ↓ JNK, p38, ERK, MEK1/2, MKK7, MKK3/6, and TAK1 phosphorylation ↓ c-Fos and c-Jun nuclear production	Song et al. (2021)

Table 10 continued

Plant extract composition/ Isolated compound	Extraction method	Biological assay	Anti-inflammatory effects	References
Apigenin, apigenin-7- <i>O</i> -glucoside, hydroxytyrosol, luteolin, oleuropein, rutin, and tyrosol	Lyophilized Leaves (Ravece, 10 g) were extracted (4 h) with ethanol (100 mL), at RT	Sodium palmitate-stimulated murine RAW 264.7 macrophages or bone marrow derived macrophages were pre-treated with extract (0.1 and 0.2 mg/mL) for 30 min or 24 h	↓ IL-6, TNF-α, IL-1β, PGE₂, and NO production ↓ IL-6, TNF-α, IL-1β, iNOS, and COX-2 expression ↓ intracellular ROS production ↑ SOD2 production ↑ NRF2 nuclear translocation ↓ KEAP1 levels in cytosol ↓ iNOS⁺ cells ↓ iNOS and COX-2 production ↓ p65 NF-κB levels in nuclei ↑ IκB-α levels in cytosol ↑ ARG-1⁺, CD206⁺ cells ↑ Arg-1 and CD206 expression ↑ IL-10 expression and production	De Cicco et al. (2020)
Oleuropein, luteolin-7- <i>O</i> -glucoside, apigenin-7- <i>O</i> -glucoside, quercetin, and caffeic acid	Dried leaves were extracted with 80% ethanol	Adrenaline-, hydrogen peroxide-, L-thyroxine-induced oxidative stress in human peripheral blood leukocytes were treated with extract (0.125, 0.5, and 1 mg/mL) for 30 min	↓ oxidative DNA damaging	Cabarkapa et al. (2014), Žukovec Topalović et al. (2015)
Hydroxytyrosol and oleuropein	Dried leaves (500 g) extracted (30 min) with boiled water (5 L)	High-fat diet-induced oxidative stress in ICR mice was co-treated with extract (150 and 450 mg/kg, intragastric) for 4 weeks	↓ MDA levels ↑ SOD levels	Zhang et al. (2020b)

Table 10 continued

Plant extract composition/ Isolated compound	Extraction method	Biological assay	Anti-inflammatory effects	References
Oleoside, hydroxytyrosol hexose isomer, Secologanoside isomer, tyrosol glucoside, elenolic acid glucoside isomer, oleuropein aglycon, luteolin-diglucoside, hydroxyoleuropein, hydroxyoleuroside, rutin, luteolin rutinoside, luteolin glucoside isomer, verbascoside, apigenin rutinoside, oleuropein glucoside isomer, diosmetin rhamnoside glucoside, apigenin glucoside, chrysoeriol-7- <i>O</i> -glucoside, Hydroleuropein, hydroleuroside, oleuropein isomer, ligstroside, luteolin, quercetin, oleuropein, oleuroside methyl ether, resinoside, and apigenin	Dried crushed leaves (10 g) were extracted via UltraTurrax with aqueous methanol mixture (80:20, 200 mL, × 3)	High-fat diet-induced obesity in C57BL/6 J mice was treated with extract (1, 10, and 25 mg/kg, oral gavage) for 5 weeks	↓ TNF- α , IL-1 β , IL-6, MCP-1, JNK-1, and TLR-4 expression ↓ dendritic cells (CD11c ⁺), macrophages (CD11b ⁺ F4/80 ⁺), myeloid-derived suppressor cells (CD11b ⁺ Ly6C ⁺), T _{REG} (CD4 ⁺ Foxp3 ⁺) infiltration ↑ CD11b ⁺ Ly6C ^{low} macrophages	Veza et al. (2019)
Oleuropein, oleoside, secologanoside, oleuropein aglycone, demethyleuropein, oleuropein glucoside, 2''-methoxyoleuropein, ligstroside, hydroxytyrosol hexose, tyrosol glucoside, and elenolic acid	Dried crushed leaves (Sikitita, 0.5 g) were extracted in an UltraTurrax with aqueous methanol mixture (80:20, 30 mL)	LPS- or IL-1 β -stimulated murine RAW 264.7 macrophages and human inflammatory bowel disease-derived peripheral blood mononuclear cells were pre-treated with extract (0.1–10 μ g/mL) Dinitrobenzene sulfonic acid-induced colitis in CD1 mice was pre-treated with extract (1, 10, and 25 mg/kg/day, oral gavage) for 6 days Dextran sulfate sodium-induced colitis in C57BL/6 J mice was co-treated with extract (0.5, 1, and 10 mg/kg/day, oral) for 11 days	↓ tissue injury ↓ edema ↓ activation and migration of inflammatory cell infiltration ↓ NO production ↓ IL-1 β , IL-6, TNF- α , and IL-8 production ↓ IL-1 β , TNF- α , IL-6, IL-17, MIP-2, ICAM-1, iNOS, and COX-2 expression	Veza et al. (2017)

Table 10 continued

Plant extract composition/ Isolated compound	Extraction method	Biological assay	Anti-inflammatory effects	References
Oleuropein	Dried powdered leaves (Chemlali, 50 g) were stirred (24 h) with 40% aqueous methanol (200 mL). The dried extract (4 g) was dissolved in 40% aqueous methanol (10 mL) and fractionated with ethyl acetate (40 mL, $\times$ 3), yielding an oleuropein-rich extract	Cadmium-induced oxidative stress in mice was treated with extract (16 mg/kg/BW/day, oral gavage) for 2 weeks	↓ tissue injury ↓ leukocyte inflammatory infiltration ↓ COX-2 production ↓ TBARS levels ↑ SOD and CAT levels	Jemai et al. (2020)
Hydroxytyrosol, polyphenol, saccharide, lipid, ignition residue, and moisture	Powdered Hydroxytyrosol-20 was supplied by Eisai Food and Chemical Co., Ltd, Japan	Carrageenan-induced acute inflammation and hyperalgesia in Sprague–Dawley rats were pre-treated with extract (100, 250, and 500 mg/kg/BW, gavage) for 270 min	↓ paw swelling ↓ hyperalgesia ↓ TNF- α and IL-1 β expression	Gong et al. (2009)
Hydroxytyrosol, polyphenol, saccharide, lipid, ignition residue, and moisture	Dried leaves (100 g) were boiled (45 min) in water (250 mL)	Kaolin/carrageenan-induced arthritis in Sprague–Dawley rats was pre-treated with extract (25, 50, and 100 mg/kg/BW/day, gavage) for 5 consecutive days LPS-stimulated THP-1 monocytes were pre-treated with extract for 1 h Croton oil-induced edema in BALB/c mice was pre-treated with extract (0.5, 1.0, and 2.0 mg/ear) for 6 h	↓ synovial membrane injury ↓ paw and ear swelling ↓ periarticular soft tissue edema ↓ inflammatory cells (macrophages and lymphocytes) ↓ TNF- α production ↓ MPO activity	Gong et al. (2012)
Oleuropein, tyrosol, hydroxytyrosol, and caffeic acid	Dried powdered leaves (Sevillano, 200 g) were extracted with 80% ethyl alcohol (1 L, $\times$ 2)	Wistar rats were treated with extract (50, 100, and 200 mg/kg, intraperitoneal) and the tail-flick test and the hot-plate teste were performed Formalin-induced nociception in Wistar rats was treated with extract (1 mL/kg, intraperitoneal) and the early acute phase (0–5 min) and a late phase (15–60 min) were determined	↓ tail-flick ↓ paw withdrawal ↓ pain response	Esmaeili-Mahani et al. (2010)

Table 10 continued

Plant extract composition/ Isolated compound	Extraction method	Biological assay	Anti-inflammatory effects	References
Quinic acid, oleoside, secaloganoside isomer, hydroxytyrosol, elenolic acid, glucoside isomer, elenolic acid, diglucoside isomer, oleuropein aglycone, galocatechin, oleuropein glucoside isomer, demethyl oleuropein, luteolin diglucoside, verbascoside, luteolin glucoside isomer, hydroxy oleuropein, disomin isomer, apigenin glucoside, chryseriol glucoside, oleuropein isomer, ligstroside, luteolin, quercetin, apigenin, dihydroxypalmitic acid, and diosmetin	Ethanollic extracts obtained from leaves were acquired from Laboratory of Olive Biotechnology, Center of Biotechnology-Technopole of Borj-Cedria (Tunisia)	LPS-stimulated murine RAW264.7 macrophages were pre-treated with extract (0–200 µg/mL) for 24 h Freund's complete adjuvant-induced rheumatoid arthritis in Sprague–Dawley rats was treated with extract (100 and 200 mg/kg/day, oral) for 4 weeks	↓ tissue injury ↓ swelling and redness ↓ pain ↓ NO production ↓ PGE2 production ↓ IL-1β, iNOS, and MMP2 expression ↓ IκBα and NF-κB p65 phosphorylation ↓ AP-1 transcription factor (c-Jun and c-Fos nuclear production)	Hong et al. (2021)
Oleuropein, luteolin-7- <i>O</i> -glycoside, apigenin-7- <i>O</i> -glycoside, quercetin, caffeic acid, and tannins	Standardized dry olive leaf extract EFLA 943 was obtained from Frutarom Industry Ltd. (Wädenswil, Switzerland)	Spinal cord homogenate/ Freund's adjuvant-induced autoimmune encephalomyelitis in Dark Agouti rats was treated with extract (80 mg/kg/day = 14.4 mg/kg of oleuropein, intragastrical) for 10 days Concanavalin A-stimulated rat spinal cords and draining lymph nodes inflammatory cells were cultured for 72 h	↓ autoimmune severity ↓ activation and proliferation of draining lymph nodes ↓ spinal cords infiltrating cells ↓ IFN-γ and IL-17 production	Miljković et al. (2009)
Apigenin, oleoside, elenolic acid, glucoside isomer, hydroxytyrosol, rutin, luteolin 7- <i>O</i> -glucoside, oleuropein diglucoside isomer, oleuropein aglycone, chrysoeriol-7- <i>O</i> -glucoside, verbascoside, oleuropein, and oleuropein isomer	Dried powdered leaves (Bouricha, 200 g) were macerated (2 h) with distilled water (1 L) at 25 °C	Ovalbumin-sensitized Wistar rats were treated with extract (1 mL, oral) in days 21, 22 and 23	↓ tissue injury ↓ mucus production ↓ inflammatory cell infiltration ↓ MDA levels ↑ GSH, GPx, CAT, and SOD levels	Rouibah et al. (2019)
Oleuropein, tyrosol, hydroxytyrosol, and caffeic acid	Leaves were extracted with 80% ethanol	Acid acetic-induced colitis in Wistar rats was treated with extract (250, 500, and 750 mg/kg, oral) for 2 successive days	↓ tissue injury ↓ edema ↓ acute inflammatory cell infiltration ↓ TNF-α and IL-2 production	Fakhraei et al. (2014)

Table 10 continued

Plant extract composition/ Isolated compound	Extraction method	Biological assay	Anti-inflammatory effects	References
Tyrosol, tyrosol derivative, oleuropein, caffeic acid, rutin, luteolin derivatives, and vanillin	Dried powdered leaves (dried) were extracted (48 h) with 70% methanol at 4 °C, with mixed from time to time	HCl/ethanol-induced gastritis in Wistar albino rats was pre-treated with extract (100, 200 and 300 mg/kg/BW) for 3 h	↓ tissue injury ↓ edema ↓ inflammatory cells ↓ IL-1 β production ↓ MPO activity ↓ TNF- α , COX-2, and NF- κ B production ↓ iNOS, IL-1 β , and TNF- α expression ↓ LPO and NO levels ↑ SOD, CAT, GRd, GPx, and GSH levels ↑ SOD2, CAT, GPx, GRd, Nrf2 expression	Al-Quraishy et al. (2017)
Oleuropein	Dried pulverized leaves were stirred (12 h) with acetone. The dry extract was washed with dichloromethane-methanol mixture (98:2). The insoluble residue was subjected to a medium pressure liquid chromatography on a column, to afford pure oleuropein	Doxorubicin-induced cardiomyopathy in Wistar rats was co-treated with isolated compound (1000 and 2000 mg/kg, Intraperitoneal) at day 1, 3 and 5 and so on until day 11	↓ tissue injury ↓ edema ↓ IL-6 production ↓ MDA, nitrotyrosine, and protein carbonyl levels ↓ iNOS production	Andreadou et al. (2014)
Oleuropein, tyrosol, hydroxytyrosol, and caffeic acid	Dried powdered leaves (Sevillano, 200 g) were extracted with 80% ethyl alcohol (1 L, $\times$ 2)	Streptozotocin-induced diabetes in Wistar rats was treated with extract (300 and 500 mg/kg) for 4 weeks	↓ hyperalgesia ↓ tail-flick	Kaeidi et al. (2011)
Resveratrol, 6-hydroxycoumarin, quercetin, ferulic acid, <i>p</i> -coumaric acid, vanillic acid, quercitrin, caffeic acid, apigenin, rutin, and luteolin	Leaves were macerated with 60% alcohol	Streptozotocin-induced diabetes in fed high-fat diet Wistar rats was treated with extract (200 mg/kg and 400 mg/kg/day, oral gavage) for 10 days	↓ IL-6, IL-1, TNF- α , and IFN- γ production ↑ IL-10 production	Guex et al. (2019)
Apigenin-7-glucoside, cyanidin-3-rutinoside, rutin, dihydro- β -nuzhenide, oleuropein aglycone, luteolin-7-glucoside, hesperidin, oleuropein, glucose, oleuropein, ligustroside, caffeic acid, luteolin rutinoside, ligustroside, glucose, diosmin, verbascoside, oleanolic acid methyl ester, and oleanolic acid	Grounded leaves (Cuspidate, 1000 g) were extracted to exhaustion by percolation with 90% ethanol (15 L), at RT	Streptozotocin-induced diabetes Wistar rats was treated with extract (250 and 500 mg/kg/BW/day, gastric gavage) for 9 weeks	↓ MDA levels ↑ SOD, GPx, CAT, and GSH levels	Abdel-Kader et al. (2019), Soliman et al. (2019)

Table 10 continued

Plant extract composition/ Isolated compound	Extraction method	Biological assay	Anti-inflammatory effects	References
Oleuropein, Luteolin-7- <i>O</i> -glucoside, apigenin-7- <i>O</i> -glucoside, quercetin, caffeic acid, and tannins	Leaves (dried) were extracted with 80% ethanol	Multiple low-dose streptozotocin-induced diabetes in C57BL/6 and CBA/H were treated with extract (40 mg/kg/BW, intraperitoneal or oral), from day 5 to 21 Cyclophosphamide-accelerated diabetes in NOD/ShiLtJ mice was treated with extract (40 mg/kg/BW/day, intraperitoneal) for 2 weeks Resident peritoneal cells, pancreatic lymph nodes, and splenocytes were cultured for 48 h Concanavalin A-stimulated splenocytes, co-cultured with different density of resident peritoneal cells, were cultured for 48 h	↓ tissues injury ↓ leukocyte infiltration ↓ T cell proliferation ↓ TREG cells (CD4 ⁺ CD25 ⁺ FoxP3 ⁺) ↓ IFN- γ , IL-17, and TNF- α production ↓ NO production ↓ iNOS expression and production ↓ IFN- γ expression	Cvjetičanin et al. (2010)
Oleuropein, tyrosol, hydroxytyrosol, and caffeic acid	<i>O. europaea</i> extract (Sevillano), enriched in oleuropein, was provided by Razi Herbal Medicines Research Center (Lorestan, Iran)	Middle cerebral artery occlusion-induced neuropathy in rats was pre-treated with extracts (50, 75, and 100 mg/kg/day, gastric gavage) for 30 days	↑ glutathione levels	Rabiei et al. (2012)
Hydroxytyrosol	Dried powdered leaves (Chemlali) were stirred (24 h) with 80% aqueous methanol. The dried extract (1 g), dissolved in methanol–water mixture (4:1, 10 mL), was hydrolyzed (1 h) with HCl (5 mL), at 100 °C. The sample was diluted with water (10 mL) and the hydrophobic fraction was extracted by a separatory funnel with ethyl acetate (50 mL, $\times$ 3). The hydrolyzed extract was further purified on a column	Cholesterol-rich diet induced atherosclerosis in Wistar rats was treated with hydroxytyrosol (3 mg/kg/BW, dissolved in drinking water) for 16 weeks	↓ TBARS levels ↑ CAT and SOD levels	Jemai et al. (2008)

Table 10 continued

Plant extract composition/ Isolated compound	Extraction method	Biological assay	Anti-inflammatory effects	References
Protocatechuic acid, loganic acid, hydroxytyrosol, 3,4- dihydroxyphenylethanol glucoside, dimethyl- elenolic acid glucoside isomer, elenolic acid glucoside isomer, hydroxyloganin, elenolic acid isomer, quercetin-3- <i>O</i> -rutinoside, quercetin-3- <i>O</i> -glucoside, verbascoside, luteolin- <i>O</i> - hexoside, apigenin-7- <i>O</i> - rutinoside, diosmin, luteolin- <i>O</i> -hexoside, luteolin, apigenin, 3,4- dihydroxyphenylethanol- dihydro elenolic acid glucoside, oleacein, oleuropein, oleuropein isomer, ligustroside, 3,4- dihydroxyphenylethanol elenolic acid isomer	Water soluble olive leaf extract obtained from <i>Olea europaea</i> L. standardized in 30% of ortho-diphenols were provided by Pharmactive Biotech Products S.L. (Madrid, Spain)	Old Wistar rats were treated with extract (100 mg/ kg/day, dissolved in the drinking water) for 3 weeks	↓ IL-6 and TNF- α production ↓ iNOS and TNF- α expression ↑ GPx, GSR, SOD-1, and NOX-1 expression	González- Hedström et al. (2021)
Oleuropein, luteolin-7- <i>O</i> - glucoside, apigenine-7- <i>O</i> - glucoside, quercetin, caffeic acid, vanillin, rutin, luteolin, apigenin, and chryseriol	Dried leaves were extracted with 80% ethanol	Global ischemia-induced oxidative stress in Mongolian gerbils was pre-treated with extract (100 mg/kg, intragastric) for 80 min, 120 min, 4 h, and 24 h	↓ tissue injury ↓ MDA, NO, and O ₂ ⁻ levels ↑ SOD levels	Dekanski et al. (2011)
Oleuropein, hydroxytyrosol, verbascoside, luteolin, rutin, apigenin, quercetin, flavonoids, and kaempferol	<i>O. europaea</i> leaves extract	LPS-stimulated subjects were pre-treated with extract (1600 mg extract; 51.12 mg oleuropein and 9.67 mg hydroxytyrosol) for 24 h	↓ IL-8 production	Lockyer et al. (2015)

Table 10 continued

Plant extract composition/ Isolated compound	Extraction method	Biological assay	Anti-inflammatory effects	References
Hydroxytyrosol, polyphenol, saccharide, lipid, ignition residue, moisture	Dried leaves (100 g) were boiled (45 min) in water (250 mL)	Adult with early-stage knee osteoarthritis were treated with extract (50.1 mg/day = 10.04 mg hydroxytyrosol) for 4 weeks	↓ pain upon walking ↓ pain upon ascending/ descending stairs ↓ pain for sleeping in bed at night ↓ pain while walking on a flat surface	Takeda et al. (2013)

ARG, arginine; AP, *activator protein*; BW, body weight; CAT, catalase; CD, cluster of differentiation; COX, cyclooxygenase; DNA, deoxyribonucleic acid; ERK, extracellular signal-regulated kinase; GSH, glutathione; GSR, glutathione-disulfide reductase (glutathione reductase); GPx, glutathione peroxidase; ICAM, intercellular adhesion molecule; IFN, interferon; IκB, inhibitor of nuclear factor kappa-light-chain-enhancer of activated B cells; IL, interleukin; iNOS, inducible nitric oxide synthase; IKK, nuclear factor kappa-light-chain-enhancer of activated B cells inhibitor protein kinase; JNK, c-Jun N-terminal kinase; LPS, liposaccharides; MCP, monocyte chemoattractant protein; MDA, malondialdehyde; MIP, macrophage inflammatory protein; MKK, mitogen-activated protein kinase kinase; MMP, matrix metalloproteinase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NO, nitric oxide; NOx, nitrogen oxides; Nrf2, nuclear factor erythroid 2-related factor 2; O₂^{•−}, superoxide anion radical; Pam3Csk4, Pam3CysSerLys4; PG, prostaglandin; ROS, reactive oxygen species; RT, room temperature; SOD, superoxide dismutase; TAK, transforming growth factor-β kinase; TBARS, thiobarbituric acid reactive substances; TLR, toll-like receptor; TNF, tumor necrosis factor

these Lava-E essential oils were mainly composed by 1,8-cineole, borneol, and camphor, the authors suggested that these compounds were the principal responsible of the pharmacological activities.

Lava-E have also been applied in the treatment of asthma, a bronchial allergic inflammation (Ueno-Iio et al. 2014). A bronchial asthma-induced mice model, sensitized by ovalbumin and further challenged with nebulized ovalbumin, were treated through the inhalation of suspended essential oil components. The anti-inflammatory effect of this Lava-E were confirmed by the significant decrease of inflammatory cells accumulation, mainly eosinophils, in the bronchoalveolar fluids and in the peribronchial and perivascular tissues. The airway hyperresponsiveness and the mucous cell hyperplasia were also significantly reduced after inhalation of the essential oils. Additionally, the treatment with this Lava-E drastically decreased the levels of TH2 cytokines, IL-5, and IL-13, in bronchoalveolar fluids, reaching basal levels of the non-asthma control, as well as markedly decreased the gene expression of IL-4 and IL-5 in the lung. Moreover, Lava-E had the ability to reduce Muc5b gene expression in the lungs, but no changes were observed in Muc5ac gene expression. However, Lava-E was not able to decrease the IgE levels in serum.

A single administration of Lava-E was also tested in spared nerve injury-induced neuropathic pain in mice (Sanna et al. 2019). The treatment with Lava-E significantly down-regulated the MAPK signaling pathway, preventing the phosphorylation of the ERK1/2 and JNK1, as well as decreased the iNOS expression. The authors suggested that these effects can be related with the antinociceptive effects. Interestingly, the inhibition of p38 phosphorylation was not observed. Likewise, the treatment with Lava-E did not modify the IκBα levels, suggesting that it was unable to prevent the activation of NF-κB signaling pathway. The authors hypothesized that linalool and linalyl acetate, as major constituents of this Lava-E, had the main contribute to the molecular mechanism of the reduction of sensitivity to pain.

Finally, Lava-E showed neuroprotective activity in an Alzheimer's disease model, by enhancing the antioxidant defenses (SOD, GPx, and CAT) and decreasing the lipid peroxidation in the hippocampus and temporal cortex of scopolamine treated mice (Hancianu et al. 2013).

Some studies also reported the strengthen of the immune system by Lava-E. They can (i) induce the complement system; (ii) stimulate some immune cells; (iii) enhance the respiratory burst; (iv) promote the cytokine production; and (v) increase the clonal

expansion of immune cells (Georgiev et al. 2017a, b) (Table 9).

Lava-E pectic polysaccharides fractions, chemically characterized with predominant homogalacturonan fragments that are acetylated and highly methoxylated, activated innate and adaptive immune response (Georgiev et al. 2017b). The chPS-L1 fraction expressed a high complement fixation activity, through both classical and alternative pathways. This could be related, not only with the antibody-dependent, but also with the presence of AGII content that would interact directly with C3 component (C3b). The production of ROS by human whole blood phagocytes and neutrophils was increased in the presence of the two fractions, but chPS-L2 strongly increased the CD18 expression on neutrophils. The low molecular weight compounds and the presence of monosaccharides characteristic for RGII in chPS-L2 fraction could be the base of this immunomodulatory activity. In the presence of Lava-E pectins, murine macrophages were also activated and able to express higher levels of iNOS protein and to produce large levels of NO. Moreover, these activities contributed to the murine Peyer's patch-mediated bone marrow cell proliferation through the modulation of CD4⁺/CD25⁺ and CD8⁺/CD25⁺ T-cells and phagocytes (Georgiev et al. 2017a). Additionally, the pectic polysaccharides induced the IL-6 production from Peyer's patch cells and human white blood cells.

Olea europaea

O. europaea L. (Oleaceae), commonly known as olive tree, grows in the Mediterranean region. Since the Ancient Egypt, tea made from the dried leaves of the olive tree has been traditionally used for the treatment of different inflammatory conditions, such as diabetes, asthma, and rheumatism. Tincture of olive leaves is also used to reduce the fever.

O. europaea extracts (Olea-E) are enriched in flavonoids, iridoids, secoiridoids, monoterpenes, phenolic acids, fatty acids, sesquiterpenes, and monosaccharides (Supplementary Table S5). Oleuropein, hydroxytyrosol, tyrosol, and oleacein are reported as the most active compounds in the Olea-E (Table 10). Interestingly, olive cultivation has resulted in the development of hundreds of different cultivars within the *O. europaea* specie. These cultivars have been selectively bred over time to possess specific traits,

such as fruit size, oil content, flavor profile, disease resistance, and growth habit (Barazani et al. 2023). Some of the most widely recognized and cultivated olive cultivars include Arbequina, Picual, Frantoio, and Manzanilla. As expected, each cultivar has unique characteristics that can affect the quality of the resulting Olea-E. Therefore, in Supplementary Table S5, the cultivars used in the study are described when reported by the authors.

The anti-inflammatory activity of Olea-E is associated with (i) the reduction of pro-inflammatory cytokines, chemokines, and prostaglandins expression and production; (ii) the decrease of respiratory burst and molecular oxidation levels; (iii) the reduction of immune cells differentiation and proliferation; (iv) the diminution of infiltration of inflammatory cells; (v) preservation of genetic integrity; (vi) the increase in antioxidant enzymes and anti-inflammatory cytokines levels; and (vii) the amelioration of edema, pain, and tissue injury (Jemai et al. 2008, 2020; Gong et al. 2009, 2012; Miljković et al. 2009; Cvjetičanin et al. 2010; Esmaeili-Mahani et al. 2010; Dekanski et al. 2011; Kaeidi et al. 2011; Rabiei et al. 2012; Takeda et al. 2013; Cabarkapa et al. 2014; Andreadou et al. 2014; Fakhraei et al. 2014; Lockyer et al. 2015; Žukovec Topalović et al. 2015; Talhaoui et al. 2016; Al-Quraishy et al. 2017; Vezza et al. 2017, 2019; Abdel-Kader et al. 2019; Guex et al. 2019; Soliman et al. 2019; Song et al. 2019, 2021; Rouibah et al. 2019; De Cicco et al. 2020; Zhang et al. 2020b; González-Hedström et al. 2021; Hong et al. 2021). The details of the anti-inflammatory studies are described in Table 10. Some of the most relevant studies will be presented in more detail. For example, a methanolic Olea-E demonstrated strong anti-inflammatory activity in the presence of LPS-stimulated RAW 264.7 macrophages (Song et al. 2019). The pre-treatment of M1 macrophages with this methanolic Olea-E significantly decreased the NO and PGE2 production, through the reduction of the iNOS and COX-2 expression and production, respectively. The methanolic Olea-E also reduced the protein expression of pro-inflammatory cytokines (IL-6, IL-1 β , and TNF- α), via down-regulation of the NF- κ B p65 and p50 subunits nuclear translocation. The phosphorylation of the upstream targets—I κ B α and IKK α / β —was also observed. This methanolic Olea-E was composed by flavonoids, including quercetin, luteolin and kaempferol. The authors suggested that kaempferol was the

main phytochemical compound responsible for the bioactivity due to its high content. Another study reported an ethanolic Olea-E, obtained from leaves, with strong anti-inflammatory effects in a rat model of rheumatoid arthritis (Hong et al. 2021). The Freund's complete adjuvant-induced arthritis rats treated with Olea-E demonstrated great reduction of swelling, redness, and pain of paws. Additionally, Olea-E prevented the cartilage degeneration and reduced the tissue injury. The oleuropein and flavonoids (e.g., quercetin, apigenin, and luteolin) were proposed as the main bioactive compounds, downregulating the NF- κ B p65 signaling pathway, AP-1 transcription factor (c-Jun and c-Fos nuclear protein levels). Furthermore, the IL-1 β and iNOS gene expression were dramatically decreased. For multiple sclerosis treatment, a standardized Olea-E EFLA 943 was suggested (Miljković et al. 2009). The treatment of spinal cord homogenate/Freund's adjuvant-induced autoimmune encephalomyelitis in Dark Agouti rats with Olea-E promoted the reduction of various parameters of autoimmune severity. Indeed, it decreased the activation and proliferation of draining lymph nodes, the cells infiltration in the spinal cord, as well as their production of IFN- γ and IL-17. The authors suggested that the bioactivity was related to the polyphenolic fraction, together with the other compounds present in the mixture, including tannins and flavonoids. Olea-E were also employed for asthma treatment. The ovalbumin-sensitized Wistar rats treated with aqueous Olea-E obtained from leaves enhanced the levels of antioxidant enzymes, namely GSH, GPx, CAT, and SOD (Rouibah et al. 2019). Consequently, reduced MDA levels in the lungs were observed. Moreover, aqueous Olea-E promoted the decrease of lung injury, through the reduction of inflammatory cells infiltration and the induction of mucus production in bronchial airways. The authors attributed these anti-asthmatic effects to oleuropein, oleuropein aglycone, and hydroxytyrosol. Their ability to increase SOD, CAT, GPx, GRx, and GSH levels, strongly reduced the lipid peroxidation and the tissues injury. An aqueous methanolic Olea-E obtained from leaves was also proposed for inflammatory bowel disease treatment (Vezza et al. 2017). Dinitrobenzene sulfonic acid-induced colitis in CD1 mice and dextran sulfate sodium-induced colitis in C57BL/6 J mice pre- and co-treated, respectively, with Olea-E improved the inflammatory status of the colon and promoted the

tissue function and integrity. Olea-E reduced the expression of pro-inflammatory mediators (IL-1 β , TNF- α , IL-6, IL-17, MIP-2, iNOS, and COX-2), allowing for a decrease in inflammatory cells infiltration and edema in the mucosa. Moreover, Olea-E was able to decrease the IL-1 β , IL-6, IL-8, and TNF- α levels in LPS- or IL-1 β -stimulated PBMCs obtained from human inflammatory bowel disease. These bioactive effects can be attributed to the presence of different phenolic compounds. Particularly, the authors suggested that the oleuropein content (almost 80% of the whole extract) exerted the main anti-inflammatory activity.

Salvia officinalis

S. officinalis (Lamiaceae family), also known as garden sage, Dalmatian sage, or common sage, is cultured worldwide but mainly in the Mediterranean region. Sage tea has been traditionally used to treat mouth, throat, and bronchial inflammations, coughs, asthma, fever, aphthas, ulcers, amygdalitis, and stomach pain. Topical applications of sage preparations (tinctures) are also used after sun exposure to prevent sunburn and for the treatment of wounds.

S. officinalis extracts (Sage-E) are composed of a wide range of chemical compounds, including flavonoids, monoterpenes, sesquiterpenes, diterpenes, phenolic acids, fatty acids, triterpenes, and polysaccharides (Supplementary Table S6). Carnosol, carnosic acid, rosmarinic acid, ursolic acid, oleanolic acid, apigenin, and luteolin have been considered the main responsible for the anti-inflammatory activity of Sage-E. This bioactivity of Sage-E is associated with (i) the reduction of pro-inflammatory cytokines and prostaglandins expression and production; (ii) the decrease of respiratory burst and molecular oxidation levels; (iii) the reduction of immune cells proliferation and infiltration; (iv) the increase in antioxidant enzymes and anti-inflammatory cytokines levels; and (v) the amelioration of edema, pain, and tissue injury (Baricevic et al. 2001; Rodrigues et al. 2012; Arranz et al. 2014; Li et al. 2019a, b; Vieira et al. 2020; Jedidi et al. 2020, 2021; Brindisi et al. 2021; Ayoub et al. 2022; Silva et al. 2023). The details of the anti-inflammatory studies are described in Table 11. Some of the most relevant studies will be presented in more detail.

Table 11 *Salvia officinalis* bioactive compounds, methods of their extraction, biological assays, and anti-inflammatory effects

Plant extract composition/ Isolated compound	Extraction method	Biological assay	Anti-inflammatory effects	References
Caftaric acid, 6-O-caffeoyl-fructosyl-glucoside, caffeic acid hexoside, caffeic acid, 3-p-coumaroylquinic acid, apigenin-6,8-di-C-hexoside, salvianolic acid, luteolin-O-di-glucuronide, hydroxyluteolin-7-O-glucuronide, yunnaneic acid F, apigenin 6-C-glucose-8-C-glucose, luteolin-7-O-glucuronide, salvianolic acid B, cis/trans-rosmarinic acid, salvianolic acid K isomer, luteolin-O-hexoside isomer, luteolin-acetyl-O-glucuronide, lithospermic acid A, apigenin 6-C-pentosyl-8-C-hexoside, salvianolic acid E	Grounded dried aerial parts (2 g) were infused with boiling distilled water (200 mL) and resting (5 min) without additional heating Grounded dried aerial parts (2 g) were boiled (5 min) in boiling distilled water (200 mL) Grounded dried aerial parts (1 g) were stirred in 80% ethanol (30 mL) for 1 h, at RT ($\times 2$)	LPS-stimulated murine RAW264.7 macrophages were pre-treated with extracts (6.3–400 $\mu\text{g/mL}$) for 18 h	$\downarrow$ ·NO production	Silva et al. (2023)
Caffeic acid, luteolin-7-glucoside, luteolin-O-glucuronide, (cis/trans)-rosmarinic acid, apigenin-O-glucuronide, salvianolic acid K, nepetin, rosmanol isomer 1/2/3, luteolin, hispidulin, cirsimaritin, apigenin, genkwanin, 7-O-methylrosmanol, rosmadial, carnosol, pedalitin, 12-O-methylcarnosic acid, carnosic acid, and ursolic acid	Fresh leaves or flowers were macerated (72 h, $\times 3$) with methanol (1 L) Fresh leaves or flowers were ultrasonicated (130 W, 40 kHz, 1 h, $\times 3$) with methanol (150 mL)	LPS-stimulated murine RAW 264.7 macrophages were co-treated with extracts (1, 5, 10, 25, and 50 $\mu\text{g/mL}$) for 1, 6, or 24 h	$\downarrow$ ROS and ·NO production $\downarrow$ NF- κ B nuclear translocation $\downarrow$ TNF- α , IL-6, and IL-1 β expression	Brindisi et al. (2021)
Salofficinoid G	Dried smashed leaves (5 kg) were exhaustively extracted (2 h) under reflux with 95% ethanol ($\times 3$) The crude extract was liquid–liquid partitioned with hexane, dichloromethane, and ethyl acetate. Hexane fraction was fractionated (Fractions A–E). The Fractions B and C were purified, yielding isolated salofficinoids	LPS-stimulated murine RAW 264.7 macrophages were pre-treated with isolated compound (10, 20, and 40 μM) for 18 h	$\downarrow$ ·NO production $\downarrow$ iNOS and COX-2 production $\downarrow$ JNK phosphorylation	Li et al. (2019b)

Table 11 continued

Plant extract composition/ Isolated compound	Extraction method	Biological assay	Anti-inflammatory effects	References
Officinalin A	Dried smashed leaves (5 kg) were extracted with 95% ethanol (2 h) under reflux ($\times 3$). The crude extract was liquid–liquid partitioned with hexane, dichloromethane, and ethyl acetate. Hexane fraction was fractionated (Fractions A–F). The Fraction C was further eluted, yielding officinalin A	LPS-stimulated murine RAW 264.7 macrophages were pre-treated with isolated compound (0.63, 1.25, 2.5, 5, and 10 μ M) for 18 h	↓ NO production: ↓ p38 phosphorylation ↓ iNOS and COX-2 production	Li et al. (2019a)
Rosmarinic acid, carnosol and carnosic acid	Dried leaves (10 g) were infused (10 min) with boiling water (200 mL) Dried leaves (10 g) were macerated (7 days) with an aqueous-ethanol mixture (50:50, 100 mL), at RT Dried leaves (10 g) were extracted by Soxhlet apparatus with water, ethanol, or aqueous-ethanol mixture (50:50)	LPS-stimulated human THP-1 macrophages were treated with extracts (5, 10, 25, 75, 125, and 250 μ g/mL) for 24 h	↓ IL-6 and TNF- α production	Vieira et al. (2020)
1,8-cineole, linalool, cis-sabinol, camphor, borneol, α -terpineol, linalyl acetate, endobornyl acetate, sabinyl acetate, α -terpinenyl, E-cariophyllene, α -humulene, geranyl propionate, spathulenol, cariophyllene oxide, and viridiflorol	Dried grounded leaves (0.6 kg) were obtained by supercritical fluid extraction (30 MPa, 313 K, 50 g/min CO ₂ , 8 h), resulting in S1 and S2 extracts Dried grounded leaves (2 g) were shaken (4 h) with ethanol (100 mL) or methanol:chloroform mixture (1:1, 100 mL) at 37 °C ($\times 3$)	ox-LDL-stimulated human THP-1 macrophages were treated with extracts (10, 20, and 30 μ g/mL) for 24 h	↓ TNF- α , IL-1 β , and IL-6 expression and production ↑ IL-10 expression S1 extracts > S2 extracts > methanol-chloroformic extracts > ethanolic extracts	Arranz et al. (2014)
Ursolic acid, carnosol, rosmarinic acid, caffeic acid, oleanolic acid, kaempferol, <i>p</i> -coumaric acid, apigenin, luteolin, luteolin-7-glucoside, and apigenin-7-glucoside	Dried pulverized leaves (full bloom phase, 30 g) were successively extracted by Soxhlet apparatus with hexane, chloroform, or methanol (400 mL)	Croton oil-induced ear edema in albino Swiss mice was treated with extracts for 6 h	↓ edema chloroformic extracts > hexanolic extracts > methanolic extracts	Baricevic et al. (2001)
Carnosol, ursolic acid, oleanolic acid	Dried grounded leaves (2 kg) were percolated with 85% ethanol, at RT ($\times 2$)	Acetic acid-, formalin-, glutamate-, capsaicin- or cinnamaldehyde-induced inflammation in Swiss mice were pre-treated with extracts (10, 30, 100 mg/kg, oral)	↓ writhes ↓ edema ↓ number of total leukocytes ↓ extravasation ↓ neurogenic and inflammatory phases	Rodrigues et al. (2012)
Quinic acid, gallic acid, 1,3-di- <i>O</i> -caffeoylquinic acid,		Ethanol-induced gastric inflammation in Wistar rats	↓ tissue injury ↓ edema	

Table 11 continued

Plant extract composition/ Isolated compound	Extraction method	Biological assay	Anti-inflammatory effects	References
protocatchuic acid, <i>p</i> -coumaric acid, luteolin-7- <i>O</i> -glucoside, naringin, apigenin-7- <i>O</i> -glucoside, salviolinic acid, trans-cinnamic, quercetin, kaempherol, and cirsilineol	Dried flowers were boiled (5 min) at 100 °C in water (1:5, W/V), under stirring	was pre-treated with extracts (100 and 200 mg/kg/BW, oral) for 15 days	↓ leucocytes infiltration ↓ C-reactive protein levels ↓ MDA levels ↑ SOD, CAT, and GPx levels	Jedidi et al. (2020)
Gallic acid, coumaroyl hexose, catechin, rosmarinic acid hexoside, salvianolic acid isomer, salvianolic acid B, rosmarinic acid, and salvianolic acid A	Dried powdered leaves were boiled (5 min) at 100 °C in water (1:5, W/V), under stirring	Acetic acid-induced ulcerative colitis in Wistar rats was pre-treated with extracts (50, 100, and 200 mg/kg/BW, oral) for 10 days	↓ tissue injury ↓ edema ↓ inflammatory cell infiltration ↓ C-reactive protein levels ↓ MDA levels ↑ SOD, CAT, and GPx levels	Jedidi et al. (2021)
Apigenin- <i>O</i> -hexoside, rosmarinic acid, rosmanol, 5-hydroxy-4',6,7-trimethoxy flavanone(2,3-dihydrosalvigenin), isorhamnetin- <i>O</i> -hexoside, epirosmanol, methyl salvianolate C, carnosol, rosmadial, carnosic acid, rosmadial isomer, trihydroxy-octadecendic acid, carnosic, methyl carnosate, methyl carnosate isomer, salvianolic acid C, salvianolic acid K, rosmadial isomer, and oleanolic acid	Dried leaves (215 g) were extracted (48 h) with 95% ethanol (2 L), at 25–27 °C (× 3)	Scopolamine-induced memory impairment albino rats were treated with extracts (150 and 300 mg/Kg, oral) for 14 days	↓ tissue injury ↓ MDA levels ↑ CAT and GSH levels	Ayoub et al. (2022)

BW, body weight; CAT, catalase; COX, cyclooxygenase; CO₂, carbon dioxide; GPx, glutathione peroxidase; GSH, glutathione; IL, interleukin; iNOS, inducible nitric oxide synthase; ox-LDL, oxidized low-density lipoproteins; JNK, c-Jun N-terminal kinase; LPS, lipopolysaccharides; MDA, malondialdehyde; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NO, nitric oxide; ROS, reactive oxygen species; RT, room temperature; SOD, superoxide dismutase; TNF, tumor necrosis factor

An ethanolic Sage-E obtained from leaves inhibited the NO production in macrophages LPS-stimulated RAW 264.7 macrophages (Li et al. 2019a, b). Indeed, further fractionations revealed that C20-norabietane diterpenoid salofficinoids were responsible for the anti-inflammatory activity. All the salofficinoids also decreased the NO production in LPS-stimulated macrophages, being salofficinoid G the most potent compound (Li et al. 2019b). Additionally,

salofficinoid G significantly inhibited the phosphorylation of JNK in the MAPK signaling pathway, down-regulating the expression of iNOS and COX-2. The authors proposed that the presence of the intact C-ring, the hydroxyl at C-12, the furan-ring, and the double bond in the A-ring can increase the NO inhibitory effect. Moreover, officinalin A was also important in this bioactivity (Li et al. 2019a). Officinalin A markedly decreased the iNOS and COX-2 production,

Table 12 *Salvia officinalis* bioactive compounds, methods of their extraction, biological assays, and pro-inflammatory effects

Plant extract composition/Isolated compound	Extraction method	Biological assay	Pro-inflammatory effects	References
Apigenin-7- <i>O</i> -glucoside, homoplantagin, apigenin-acetylglucoside, rosmarinic acid, isorhamnetin-luteolin, apigenin, hispidulin, rosmanol isomer 1/2, epirosmanol, methoxycarnosol, carnosol, rosmadial, carnosic acid, methyl carnosate, betulinic acid, oleanolic acid, and ursolic acid	Dried and grounded leaves (100 g) were extracted firstly with hexane (6 h, 200 mL) and then with ethyl acetate (6 h, 200 mL), in a Soxhlet apparatus	Resident peritoneal macrophages were treated with extracts (25, 50, and 100 µg/mL) for 24 h	↑ NO production ↑ TNF-α production	Kontogianni et al. (2013)
Arabinogalactan, rhamnogalacturonan, pectin, homogalacturonan, glucuronoxylan, and xylan	Dried crushed aerial parts (480 g) were exhaustively extracted in a methanol:chloroform mixture (10:1), and the residue was successively macerated with distilled water (10 L) in the presence of 0.02% solution of natriumazid, at RT. Then, the aqueous extracts were further fractionated	Wistar rat thymocytes were treated with Fractions (3, 10, 30, 100, 300, and 1000 µg/mL)	↑ mitogenic and co-mitogenic activity	Capek et al. (2003)
Arabinose, galactose, 3- <i>O</i> -methylgalactose, glucose, mannose, xylose, fucose, rhamnose, and uronic acids	Dried crushed aerial parts (480 g) were exhaustively extracted in a methanol:chloroform mixture (10:1), and the drug residue was successively extracted (24 h) with distilled water (10 L) in the presence of 0.02% solution of natriumazid, at RT. Then, the aqueous extracts were further fractionated	Wistar rat thymocytes were treated with Fractions (1, 3, 10, 30, 100, and 300 µg/mL)	↑ mitogenic and co-mitogenic activity	Capek and Hřibálová (2004)

NO, nitric oxide; RT, room temperature; TNF, tumor necrosis factor

via downregulating the phosphorylation of p38 in the MAPK signaling pathway in LPS-stimulated RAW 264.7 macrophages. However, officinalin A did not prevent the phosphorylation of ERK and JNK. Additionally, the potential of two Sage-E obtained by supercritical extraction (S1 and S2) were investigated in the prevention of atherosclerosis with oxidized low-density lipoproteins (ox-LDL)-stimulated THP-1-derived macrophages (Arranz et al. 2014). The co-treatment with supercritical Sage-E S1 and S2 significantly decreased the production of TNF-α, IL-1β, and IL-6, which was related to the marked decrease of the gene expression of these cytokines. Particularly, the highest tested concentration of S1 led to lower amounts of TNF-α in comparison with basal conditions in non-stimulated macrophages. Moreover, S1

also exhibited higher ability to reduce IL-1β production compared to indomethacin. Supercritical extracts did not interfere in the production of IL-10, but their gene expression was significantly increased. The main compounds presented in supercritical Sage-E—camphor, borneol, and 1,8-cineole—constituted 62.4% of S1 and 48.1% of S2, indicating a potential correlation between their presence and the observed high anti-inflammatory activity.

The efficacy of Sage-E extracts was also confirmed in vivo. For instance, the pre-treatment with hydroethanolic Sage-E—mainly composed of carnosol, ursolic acid, and oleanolic acid,—in visceral inflammation and nociceptive response induced in mice exhibited anti-inflammatory and analgesic properties (Rodrigues et al. 2012). The administration of Sage-E significantly decreased the

Table 13 *Salvia rosmarinus* bioactive compounds, methods of their extraction, biological assays, and anti-inflammatory effects

Plant extract composition/ Isolated compound	Extraction method	Biological assay	Anti-inflammatory effects	References
(α/β)-pinene, α -thujene, camphene, δ -3-carene, myrcene, 1,8-cineole, γ -terpinene, <i>p</i> -cymene, camphor, linalool, bornyl acetate, β -caryophyllene, terpinen-4-ol, α -humulene, α -terpineol, and borneol	Essential oil	Human leukocytes were treated with extract for 10 min and then fluorescent particles were added for more 45 min Sensitized sheep erythrocytes were incubated with extracts for 30 min and then human pooled serum was added for 60 min	↓ phagocytosis by human neutrophils ↓ classical pathway of the complement system	Pérez-Rosés et al. (2015)
Rosmarinic acid and carnosic acid	Dried grounded leaves (5 g) was steeped (16 h) in dichloromethane-methanol mixture (1:1) (30 mL). After, the filtrated solution was extracted (30 min) with methanol (30 mL)	IgE-sensitized BMMCs, stimulated with TNP-BSA and SCF, were treated with extract (5 and 25 μ g/mL) for several timepoints (ranging from 5 min to 24 h)	↓ mast cell degranulation ↓ IL-6, IL-13, TNF, CCL1, and CCL3 expression and production ↓ CCL2 production ↓ p38 and JNK phosphorylation ↓ NF- κ B activity	Yousef et al. (2020)
Verbenone, cirsimaritin, salvigenin, carnosol, and carnosic acid	Dried powdered leaves (5 g) were obtained by supercritical fluid extraction (5000 psi, 1 mL/min CO ₂ flow rate, 30 min of static followed 90 min dynamic, 80 °C)	LPS-stimulated murine RAW 264.7 macrophages were co-treated with extract (1.56–25 μ g/mL) for 6 and 24 h	↓ lipid peroxidation ↓ TNF- α production ↓ NO production ↓ iNOS and COX-2 production ↓ I κ B- α phosphorylation ↓ p65 nuclear translocation	Kuo et al. (2011)
Carnosic acid, carnosol, and 4'-methoxytechtochrysin	Dried chopped leaves (100 g) were extracted (24 h) with 80% aqueous methanol (1 L) at RT ($\times$ 3)	LPS-stimulated murine RAW 264.7 macrophages were pre-treated with extracts (2.5, 5, and 10 μ g/mL) for 30 min or 23 h	↓ NO production ↓ PGE ₂ production ↓ iNOS protein expression ↓ p65 nuclear translocation ↓ ERK1/2 and JNK phosphorylation	Yu et al. (2013)

Table 13 continued

Plant extract composition/ Isolated compound	Extraction method	Biological assay	Anti-inflammatory effects	References
Carnosol	Leaves were extracted with hexane. Then, the dried material was redissolved in methanol and the solvent was evaporated. The residue was dissolved in hexane:ether mixture (3:1) and subjected to a preparative column to obtain carnosol	LPS-stimulated murine RAW 264.7 macrophages were co-treated with isolated compound for 24 h	↓ NO production ↓ NF-κB DNA binding activity ↓ IκBα protein phosphorylation and degradation ↓ IKK activity ↓ c-Rel, p65 and p50 protein nuclear translocation ↓ iNOS expression and production ↓ p38 and p44/42 phosphorylation	Lo et al. (2002)
(α/β)-thujene, (α/β)-pinene, camphene, sabine, 3-octanone, β-myrcene, α-phellandrene, (α/γ)-terpinene, o-cymene, limonene, 1,8-cineole, terpinolene, β-linalool, camphor, isopinocampnone, borneol, α-terpineol, α-campholenal, myrtenol, verbenone, bornyl acetate, and β-caryophyllene	Dried grounded leaves were submitted to hydrodistillation using a Clevenger apparatus	LPS-stimulated murine J774A1 macrophages were treated with extract (5, 10, 25, 50, and 100 µg/mL) for more than 24 h	↓ NO production	Borges et al. (2018)
Isorhamnetin-3-O-glucoside, homoplantagin, rosmarinic acid, luteolin-3'-O-(3''-O-acetyl)-β-D-glucuronide, luteolin-3'-O-(2''-O-acetyl)-β-D-glucuronide, isorhamnetin, diosmetin, pectolinarigenin, genkwanin, salvigenin, carnosol, rosmaridiphenol, carnosic acid, rosmadial	Dried cut aerial parts were macerated with 70% ethanol (× 3)	LPS/IFN-stimulated murine J774A.1 macrophages were pre-treated with extracts (10 µg/mL) for 6 or 24 h	↓ PGE2 production ↓ IL-6, TNF-α, PTGS2, and Nos2 expression ↓ iNOS positive cells ↓ NO and ROS production ↓ NF-κB p65 and IκB-α phosphorylation ↓ COX-2 expression	Francolino et al. (2023)
Rosmarinic acid, carnosol, and carnosic acid	Dried powdered whole residues derived from distillation (50 g) were extracted (3 h) with 80% ethanol (500 mL) and citric acid crystal (500 mg), at 50 °C	LPS-induced neuroinflammation in ICR mice was pre-treated with extracts (5.6% rosmarinic acid, 4.6% carnosol and 5.8% carnosic acid—10 and 50 mg/kg/day), for 7 days	↓ TNF-α production	Sasaki et al. (2021)

Table 13 continued

Plant extract composition/ Isolated compound	Extraction method	Biological assay	Anti-inflammatory effects	References
Quercetin and kaempherol	Dried cut aerial parts (330 g) were successive macerated (48 h) with hexane (1200 mL, $\times$ 3), at RT. The residue was re-extracted with ethanol (1200 mL, $\times$ 3)	Acetic acid- and formalin-induced nociception in Swiss Webster mice were pre-treated with extracts (10, 30, 100, and 300 mg/kg, oral) Uric acid-induced pain in Swiss Webster mice was treated with extracts (10, 30, 100, 300, and 1000 mg/kg, oral)	$\downarrow$ number of writhes $\downarrow$ paw licking time in first and second phases $\downarrow$ shaking behavior $\downarrow$ loss of functionality	González-Trujano et al. (2007)
Flavonoids, tannins, saponins and alkaloids	Dried powdered aerial parts (100 g) were prepared by decoction (15 min) in water (1 L) Dried powdered aerial parts (100 g) were macerated (48 h) in 80% ethanol (500 mL). The residue was re-macerated (24 h) and the solutions were combined	Acetic acid-induced writhing in albino mice was treated with extracts (0.64, 0.96, 1.12, and 1.68 g/kg, intraperitoneal) Morphine-dependent albino mice were treated with extracts (0.64, 0.96, 1.12, 1.68, and 2.4 g/kg)	$\downarrow$ mouse abdominal constrictions: Aqueous extracts > aqueous ethanolic extracts $\downarrow$ number of jumps: Aqueous extracts > aqueous ethanolic extracts	Hosseinzadeh and Nourbakhsh (2003)
(α/β)-pinene, terpinolene, <i>D</i> -limonene, γ -terpinene, 4-carene, (α/β)-phellandrene, camphene, cis-pinane, β -myrcene, <i>o</i> -cymene, dihydro-linalool, 1,8-cineol, linalool, (+)-2-bornanone, borneol, α -terpineol, (-)-myrtenol, carvone, safrole, longifolene, and trans- α -bergamotene	Dried powdered plant was subjected to steam distillation (3.5 h) with distilled water	PMA-induced ear inflammation in BALB/c mice was treated with extract (25, 50, and 100 mg/kg) for 6 h	$\downarrow$ edema $\downarrow$ ear thickness $\downarrow$ IL-6 and TNF- α production $\downarrow$ NF- κ B expression	Luo et al. (2019)
Carnosol, rosmarinic acid, carnosic acid, betulinic acid, oleanolic acid, and ursolic acid	Dried aerial parts (600 g) were macerated (15 days) with 96% ethanol at 25 °C	Carrageenan-induced pleurisy in Swiss mice was pre-treated with extract (50 mg/kg),	$\downarrow$ mononuclears and leukocyte number $\downarrow$ neutrophils number $\downarrow$ exudate level $\downarrow$ MPO activity $\downarrow$ NO production $\downarrow$ IL-1 β and TNF- α production	Benincá et al. (2011)

Table 13 continued

Plant extract composition/ Isolated compound	Extraction method	Biological assay	Anti-inflammatory effects	References
Carnosol and rosmarinic acid	Fresh leaves (70 g) were submitted to hydrodistillation (4 h) with water (200 mL) in a modified Clevenger-type apparatus. After, the residue was macerated with 96% ethanol (200 mL) for one week, at RT	Carrageenan-induced pleurisy in Swiss mice was pre-treated with extracts (10–100 mg/kg, intraperitoneal) for 0.5 to 4 h	↓ leukocyte migration ↓ number of neutrophils ↓ degree of exudation ↓ MPO activity ↓ NOx levels ↓ IL-17A expression and production ↑ IL-10 expression and production	da Rosa et al. (2013)
Carnosic acid, carnosol, rosmanol, methylcarnosate, rosmanol methyl ether, epirosmanol, and carnosol isomer	Methanolic extract obtained from leaves was acquired from Exotic Naturals Pvt. Ltd, Mumbai, India	LPS-stimulated murine RAW 264.7 macrophages were pre-treated with extract (5 and 10 µg/mL) for next 18 h Dextran sulphate sodium-induced ulcerative colitis in Balb/C mice was pre-treated with extract (50 and 100 mg/kg/day, oral), from 1 to day 10	↓ tissue injury ↓ infiltration of inflammatory cells ↓ MPO activity ↓ TNF-α and IL-6 production ↓ NO production ↓ COX-2 and iNOS production ↓ p38, ERK, and JNK production ↓ NF-κB p65 nuclear translocation ↓ IκBα/IκBβ ratio phosphorylation ↓ NF-κB p65-DNA binding activity	Medicherla et al. (2016)
Saponins, phenols, tannins, flavonoids, alkaloids, anthraquinones and phlorotannins	Dried powdered flowers (100 g) were boiled (2 h) in distilled water. In the next day, the supernatant was mixed with 70% ethanol (1 unit extract/5 unit alcohol) for 3 days. The supernatant was collected	Testicular torsion-induced in NMRI mice was treated with extracts (100 and 200 mg/kg/day) for 10 consecutive days	↓ tissue injury ↓ NO production ↓ MDA levels ↓ TNF-α production ↓ IL-1α, IL-1β, and IFNγ expression	Mansouri Torghabeh et al. (2022)
Rosmarinic acid	Dried powdered leaves (100 g) were steam-distilled (1 h) in a Clevenger-type apparatus in distilled water (1000 mL) The centrifuged mixture was extracted with ethyl acetate phases (× 3) and then the residue was chromatographed to give rosmarinic acid	Kunming aging mice were treated with isolated compound (50, 100, and 200 mg/kg/day, intragastric gavage) for 30 days	↓ tissue injury ↓ MDA levels ↑ SOD, CAT, and GSH-Px levels	Zhang et al. (2015)

Table 13 continued

Plant extract composition/ Isolated compound	Extraction method	Biological assay	Anti-inflammatory effects	References
Rosmarinic acid, caffeic acid, <i>p</i> -coumaric acid, chlorogenic acid, ellagic acid, ferulic acid, rosmanol, rutin, luteolin, methoxyluteolin, and nepitin	Dried leaves (7 g) were extracted with methanol (50 mL) in a Soxhlet apparatus	Carrageenin-induced paw edema in Wistar rats was pre-treated with extracts (10 and 50 mg/kg, oral) for 6 h	↓ edema	Rocha et al. (2015)
Caffeic acid hexoside, caffeic acid acetyl hexoside, caffeic acid, prolithospermic acid, lithospermic acid A isomer, yunnaneic acid F, luteolin-3- <i>O</i> -glucuronide, caffeic acid derivative, sagerinic acid isomer, acetylquercetin- <i>O</i> -rutinoside, rosmarinic acid, luteolin- <i>O</i> -glucuronide, salvianolic acid A, and acetyl luteolin- <i>O</i> -glucuronide	Dried ground leaves (20 g) were stirred (1 h) in distilled water (100 mL), at 23 °C	Freund's adjuvant-induced arthritis in Holtzman rats was pre-treated with extract (150 mg/kg/day, intragastrical) for 18 days	↓ volume paw ↓ appearance of 2° lesions in ear, front leg and tail ↓ number of recruited polymorphonuclear leukocytes ↓ weight of polipliteus lymph nodes and adrenal glands ↓ ROS and protein carbonyls levels ↓ MPO activity ↑ GSH, CAT, SOD, GPx, and GR levels	de Almeida Gonçalves et al. (2018)
Chlorogenic acid, caffeic acid, rutin, rosmarinic acid, quercetin, kaempferol, and carnolic acid	Dried leaved were extracted in a Soxhlet apparatus (1.5 h) with ethanol at 60–70 °C	Ethanol- induced acute intestinal damage in Wistar rats was pre-treated with extracts (500 and 1000 mg/kg, oral gavage) every 24 h for 3 days	↓ tissue injury ↓ tissue swelling ↓ neutrophil infiltration ↓ MPO activity ↓ MDA levels ↓ ROS/RNS production ↑ SOD, GSH and CAT levels	Amaral et al. (2013) Amaral et al. (2018)
Rosmarinic acid and carnolic acid	Dried powdered leaves (20 g) were extracted (1 h) with water (100 mL) at 23 °C Dried powdered leaves (1 g) were defatted (1 min, × 6) with tetrahydrofuran (20 mL) at 23 °C	Hypercholesterolemic-induced Wistar rats were treated with extracts (7, 14, 70 and 140 mg/kg/BW/day, oral gavage) for 4 weeks	↓ tissue injury ↓ MDA levels ↑ CAT, GPx, and SOD antioxidant enzymes levels	Afonso et al. (2013)

Table 13 continued

Plant extract composition/ Isolated compound	Extraction method	Biological assay	Anti-inflammatory effects	References
Rosmarinic acid and apigenin	Dried powdered leaves (20 g) were extracted (1 h) in distilled water (100 mL), at 23° C	Air-induced inflammation in Wistar rats was treated with extracts (100, 200, and 400 mg/kg, oral gavage). After 1 h, inflammation in the subcutaneous tissue of rats was induced with carrageenan for 4 h fMLP-induced chemotaxis or LPS-stimulated peritoneal neutrophils were treated with extracts (1, 10, 50, 100, and 500 µg/mL) for 20 min and 18 h, respectively	↓ lipid peroxidation ↓ NO production ↓ leukocytes and neutrophils migration ↓ LBT4, PGE2, IL-6 and TNF-α production ↑ SOD levels	Silva et al. (2015)
Rosmarinic acid	Dried powdered aerial parts (200 g) were successively extracted in a Soxhlet apparatus with 80% of ethanol at 68° C	Sciatic nerve chronic constriction injury- induced neuropathic pain in Wistar rats was treated with extract (100, 200, and 400 mg/kg/day, intraperitoneal), for 14 consecutive days	↓ mechanical and cold allodynia ↓ heat hyperalgesia ↓ NO production ↓ COX-2 and iNOS production ↓ IL-1β, TNF-α, and PGE2 production ↓ MMP2 production ↓ microglia and astrocytes activation ↓ TLR4 amount	Ghasemzadeh et al. (2016), Ghasemzadeh Rahbardar et al. (2017)
Carnosol	Dried powdered leaves (1 kg) were extracted (2 h) with methanol (6 L) at 60 °C. The residue was re-extracted with methanol (4 L). After concentration, distilled water (1 L) was added to the 600 mL of solution, to form a precipitate	CCl ₄ -induced acute liver injury in Sprague Dawley rats was treated with extract (200 mg/kg/day, oral) for 5 days	↓ tissue injury ↓ edema ↓ acute inflammatory cells infiltration ↓ MDA levels	Sotelo-Félix et al. (2002)
Rosmarinic acid, rosmarinic phenol, carnosol, carnosic acid, and carnosic acid methyl ester	Dried powdered leaves were stirred (3 h) in 70% ethanol (1:10, sample/solvent), at RT	High fat diet-induced oxidative stress in Gloden Syrian hamsters was treated with extracts (0.1%, 0.3% and 0.9% by weight) for 6 weeks	↓ tissue injury ↓ TNF-α and IL-1β production ↓ MDA levels ↑ SOD, CAT, and GSH-Px levels ↑ CAT, GSH-Px, Mn- SOD, and CuZn- SOD expression and production ↑ Nrf2 and HO-1 expression and production	Wang et al. (2020)

Table 13 continued

Plant extract composition/ Isolated compound	Extraction method	Biological assay	Anti-inflammatory effects	References
Tricyclene, α -thujene, (+)- α -pinene, (-)-camphene, thuja-2,4-[10]-diene, β -pinene, 3-octanone, β -myrcene, α -phellandrene, α -terpinene, m-cymene, eucalyptol, (+)-3-carene, terpinolene, linalool, (-)-camphor, isoborneol, (-)-borneol, terpinen-4-ol, L- α -terpineol, verbenone, bornyl acetate, caryophyllene, Z,Z,Z-1,5,9,9-tetramethyl-1,4,7-cycloundecatriene, caryophyllene oxide	Essential oil purchased from Poli Aromatic Pharmaceutical Technology Co. Ltd	Dinitrochlorobenzene-induced atopic dermatitis in SPF KM mice was treated with extracts (1, 2, and 4%) were applied 2 times per day	↓ tissue injury ↓ inflammatory cell infiltration ↓ mast cells number ↓ edema ↓ IL-6 and TNF- α production ↓ STAT3 and NF- κ B p65 phosphorylation	Li et al. (2023)

BMMCs, bone marrow derived mast cells; BSA, bovine serum albumin; CAT, catalase; CCL, chemokine C–C motif ligand; CCl₄, carbon tetrachloride; CO₂, carbon dioxide; COX, cyclooxygenase; CuZn-SOD, copper-zinc-superoxide dismutase; DNA, deoxyribonucleic acid; ERK, extracellular signal-regulated kinase; fMLP, N-formylmethionyl-leucyl-phenylalanine; GSH, glutathione; GSH-Px, glutathione peroxidase; HO, heme oxygenase; IFN, interferon; Ig, immunoglobulin; I κ B, inhibitor of nuclear factor- κ B; kappa-light-chain-enhancer of activated B cells; IKK, nuclear factor kappa-light-chain-enhancer of activated B cells inhibitor protein kinase; IL, interleukin; iNOS, inducible nitric oxide synthase; JNK, c-Jun N-terminal kinase; LB, leukotriene; LPS, liposaccharides; MDA, malondialdehyde; MMP, matrix metalloproteinase; Mn-SOD, manganese superoxide dismutase; MPO, myeloperoxidase; NF- κ B, nuclear factor kappa-light-chain-enhancer of activated B cells; NO, nitric oxide; Nos2, nitric oxide synthase 2; Nox, nitrogen oxides; Nrf2, nuclear factor erythroid 2-related factor 2; PG, prostaglandin; PMA, phorbol 12-myristate 13-acetate; PTGS2, prostaglandin-endoperoxide synthase 2; ROS, reactive oxygen species; RNS, reactive nitrogen species; RT, room temperature; SCF, stem cell factor; SOD, superoxide dismutase; STAT, signal transducer and activator of transcription; TLR, toll-like receptor; TNF, tumor necrosis factor

number of writhes, the number of total leukocytes, and the plasmatic extravasation in the inflamed tissue. Sage-E also promoted the inhibition of the neurogenic and inflammatory phases and nociception and decreased the edema. The authors proposed that hydroethanolic Sage-E potentially inhibits the transient receptor potential ankyrin 1 (TRPA1) and transient receptor potential cation channel subfamily V member 1 (TRPV1) pain and heat receptors. This in turn reduced the neurogenic inflammation, being the carnosol, ursolic acid, and oleanolic acid possibly responsible for the activity of the Sage-E. Moreover, ursolic acid emerged as the primary active compound of the chloroformic Sage-E in the reduction of ear edema in croton oil-induced ear edema in mice (Baricevic et al. 2001). Finally, Sage-E presented the ability to decrease oxidative stress in vivo. The administration of an ethanolic Sage-E (mainly composed of methyl carnosate, carnosic acid, carnosol, rosmanol

and salvianolic acid) in scopolamine-induced memory impairment albino rats significantly increase the CAT and GSH enzyme activity and decrease the MDA levels, and, consequently, the tissue injury was ameliorated (Ayoub et al. 2022).

Despite Sage-E have only been traditionally used for anti-inflammatory diseases, some studies show their pro-stimulatory activity. The immunostimulatory activity of Sage-E is related to (i) the increase of respiratory burst; (ii) the promotion of cytokine production; and (iii) the increment of the mitogenic and co-mitogenic cell activity (Capek et al. 2003; Capek and Hříbalová 2004; Kontogianni et al. 2013). The main active compounds associated with this activity are polysaccharides, including for example arabinogalactan, rhamnogalacturonan, pectin, homogalacturonan, glucuronoxylan, and xylan. Phenols and flavonoids also contributed to the strength of the

Table 14 *Salvia rosmarinus* bioactive compounds, methods of their extraction, biological assays, and pro-inflammatory effects

Plant extract composition/Isolated compound	Extraction method	Biological assay	Pro-inflammatory effects	References
Isorhamnetin-3-O-hexoside, homoplantagin, rosmarinic acid, hispidulin, rosmanol isomer, epirosmanol, genkwanin, methoxycarnosol, carnosol, rosmadial, rosmaridiphenol, carnosic acid, methyl carnosate, betulinic acid, oleanoic acid, and ursolic acid	Dried grounded leaves (100 g) were extracted firstly with hexane (6 h, 200 mL) and then with ethyl acetate (6 h, 200 mL), in a Soxhlet apparatus	Resident peritoneal macrophages were treated with extracts (25, 50, and 100 µg/mL) for 24 h	↑ NO production ↑ TNF-α production	Kontogianni et al. (2013)

NO, nitric oxide; TNF, tumor necrosis factor

immune system. The details of the pro-inflammatory studies are described in Table 12. Some of the most relevant studies will be presented in more detail. For instance, an ethyl acetate Sage-E had the ability to activate resident peritoneal macrophages, increasing the production of NO and TNF-α (Kontogianni et al. 2013). Moreover, different polysaccharide fractions induced rat thymocyte proliferation (Capek et al. 2003). The particular composition of each fraction contributed to the different extent of the immunostimulatory activity. In summary, potassium hydroxide-extractable polysaccharides (composed of xylan-related polysaccharides and glucuronoxylan-related polymers) exhibited the most potent immunostimulatory activity, followed by ammonium oxalate- (composed by arabinan-rich pectin component), and water-extractable polysaccharides (composed by arabinogalactans associated with a galacturonan and/or rhamnogalacturonan core). The water-extractable polysaccharides subfractions (A1–A6) also demonstrated mitogenic and co-mitogenic activity (Capek and Hřibálová 2004). The highest immunostimulatory activity was observed in the acidic subfractions A2–A4 but all subfractions were significantly more potent than the original fraction. The highest content of 3-O-methylgalactose residues in subfraction A2 and the arabinan- or arabinogalactan-rich side chains in subfractions A2–A4 could be important for the enhancement of the immunostimulatory activity. Indeed, although the polysaccharide fractions and subfractions presented similar monosaccharide composition, they considerably differ in the primary structure of their backbones, generating a

significant increase in their immunostimulatory activity.

Salvia rosmarinus

S. rosmarinus (syn. *Rosmarinus officinalis*), known as rosemary, is an evergreen shrub native from Mediterranean region that belongs to the Lamiaceae family. Rosemary tea, obtained from dried or fresh flowering tops and leaves, has been traditionally used to treat and alleviate asthma, arthritis, tonsillitis, sore throats, inflammation, headaches, ulcers, chronic bronchitis, swelling and pain.

S. rosmarinus extracts (Rosm-E) are rich in flavonoids, monoterpenes, diterpenes, sesquiterpenes, triterpenes, phenolic acids, and fatty acids (Supplementary Table S7). Rosmarinic acid, rosmanol, carnosic acid and carnosol are the main chemical compounds proposed as active principles in the Rosm-E (Tables 13 and 14).

The anti-inflammatory activity of Rosm-E is associated to (i) the inhibition of complement system; (ii) the reduction of phagocytosis; (iii) the reduction of the degranulation process; (iv) the reduction of pro-inflammatory cytokines, chemokines, prostaglandins, and leukotrienes expression and production; (v) the decrease of respiratory burst and molecular oxidation levels; (vi) the reduction of the immune cell differentiation; (vii) the reduction of immune cells infiltration; (viii) the increase in antioxidant enzymes and anti-inflammatory cytokines levels; and (ix) the amelioration of edema, pain, and tissue injury (Sotelo-Félix et al. 2002; Lo et al. 2002; Hosseinzadeh and

Table 15 *Taraxacum officinale* bioactive compounds, methods of their extraction, biological assays, and anti-inflammatory effects

Plant extract composition/ Isolated compound	Extraction method	Biological assay	Anti-inflammatory effects	References
Rutin, naringenin, chlorogenic acid, ellagic acid, gallic acid, luteolin, quercetin, ferulic acid, ascorbic acid, β -carotene, and α -tocopherol	Dried powdered leaves (1 g) were extracted with methanol (25 mL) using microwaves (irradiation-cooling-irradiation, 1 min each), Soxhlet apparatus (36 h), and maceration	LPS-stimulated RAW 264.7 macrophages were treated with extracts (10, 20, and 40 μ g/mL) for 24 h	↓ NO production: microwaves > maceration ≈ Soxhlet	Kala et al. (2017)
Luteolin and chicoric acid	Dried powdered leaves (5 g) were extracted (4 h) in methanol (50 mL), at 85 °C Dried powdered leaves (5 g) were extracted (4 h) in water (50 mL) at 100 °C, using a double boiler Both extracts were concentrated and dissolved in 10% methyl alcohol (100 mL) and ethyl acetate (100 mL). The ethyl acetate layer was concentrated	LPS-stimulated murine RAW 264.7 macrophages were pre-treated with extracts (25, 50, and 100 μ g/mL) for 20 h	↓ NO production ↓ MDA levels ↓ iNOS expression and production ↑ GSH, SOD, CAT, GPx, and GR levels ↓ DNA binding activity of NF- κ B	Park et al. (2011)
Luteolin, luteolin-7- <i>O</i> -glucoside, caffeic acid and chlorogenic acid	Flowers were extracted with 70% ethanol. Then, the extract solution was fractionated with ethyl acetate and water to produce ethyl acetate fraction and water fraction	LPS-stimulated murine RAW264.7 macrophages were pre-treated with extracts (5, 25, 50, and 100 μ g/mL) for 24 h	↓ NO production: ethyl acetate fraction > water fraction ↓ PGE2 production ↓ iNOS and COX-2 production	Hu and Kitts (2004)
Luteolin, luteolin-7-glucoside, caffeic acid, and chlorogenic acid	Freeze-dried flowers were extracted (8 h) with 70% ethanol by reflux	LPS- or AAPH-stimulated murine RAW 264.7 macrophages were co-treated with extracts (7.8, 15.6, 31.3, 62.5, 125, 250, and 500 mg/mL) for 24 h	↓ NO production ↓ ROO $\cdot$ production	Hu and Kitts (2005)
Taraxasterol	Obtained from Chengdu Fenruisi Biotechnology Co., isolated from <i>T. officinale</i>	LPS-stimulated murine RAW 264.7 macrophages were pre-treated with isolated compound (2.5, 5, and 12.5 μ g/mL) for 30 min, 18 h or 24 h	↓ iNOS and COX-2 expression and production ↓ ERK1/2 and p38 phosphorylation	Xiong et al. (2014)

Table 15 continued

Plant extract composition/ Isolated compound	Extraction method	Biological assay	Anti-inflammatory effects	References
Polysaccharides	Plant material was boiled (4 h) at 100 °C in water (tenfold volume). The freeze-dried extract was purified by column chromatography yielding TOP1 and TOP2	LPS-stimulated murine RAW264.7 macrophages were pre-treated or treated with extract (0.5, 1, 2, and 4 mg/mL) for 20 h or 4 h, respectively t-BHP-induced oxidative damage generation in murine RAW 264.7 macrophages were pre-treated with extracts (0, 0.25, 0.5, 1, and 2 mg/mL) for 4, 6, 12, and 24 h	↓ NO production: TOP2 ↓ iNOS production: TOP2 ↓ TNF- α production: TOP2 > TOP1 ↓ I κ B α and p65 phosphorylation ↑ HO-1 production ↑ Nrf2 nuclear accumulation ↑ cytoprotective potential	Park et al. (2014)
Taraxasterol	Obtained from Chengdu Fenruisi Biotechnology Co., isolated from <i>T. officinale</i>	LPS-induced endotoxic shock in Kunming mice was pre-treated with isolated compounds (2.5, 5, and 10 mg/kg/day, intragastrical) for 5 consecutively days	↑ survival rate ↓ tissue injury ↓ edema ↓ inflammatory cell influx ↓ NO production ↓ TNF- α , IFN- γ , IL-1 β , IL-6, and PGE2 production	Zhang et al. (2014)
Taraxasterol	Obtained from Chengdu Fenruisi Biotechnology Co., isolated from <i>T. officinale</i>	Ovalbumin-induced allergic asthma in BALB/c mice was treated with isolated compound (2.5, 5, and 10 mg/kg/day, oral) from day 23 to day 27	↓ total inflammatory cells and eosinophils ↓ IL-4, IL-5, and IL-13 production ↓ IgE production ↓ airway epithelial thickening ↓ degree of inflammatory cell infiltration in the peribronchial and perivascular areas ↓ mucus overproduction ↓ goblet cell hyperplasia in the airways ↓ airway hyperresponsiveness	Liu et al. (2013)

Table 15 continued

Plant extract composition/ Isolated compound	Extraction method	Biological assay	Anti-inflammatory effects	References
DRP1: glucose, galactose, and arabinose DRP2: rhamnose, glucuronic acid, glucose, galactose, and arabinose	Dried powdered roots were pre-treated (4 h) with 95% ethanol in a Soxhlet apparatus at 70 °C to remove the monosaccharides, pigments, and fats. After, the dried pre-treated residue (50 g) was immersed (4 h) with water (1200 mL) at 100 °C (× 2). The concentrated supernatant was mixed with ethanol, under stirring overnight at 4 °C. The precipitate was re-dissolved in water and Savage solution, under shaking for 30 min and then static for 30 min (× 3). The supernatants were dialyzed and freeze dried to obtain DRP. The crude DRP was re-dissolved in distilled water, and then purified by gel filtration chromatography, yielding DRP1 and DRP2	Acetaminophen-induced liver injury in ICR mice was treated with DRP1 or DRP2 (50, 100, and 200 mg/kg, thrice a day, intraperitoneal) for 2 days	↓ tissue injury ↓ MDA levels ↓ ROS production ↑ SOD, CAT, GSH, and GPx levels ↑ Nrf2, HO-1, and NQO1 production	Cai et al. (2017)
Hydroxybenzoic acid, caffeic acid, chicoric acid, feruloylquinic acid, dicaffeoylquinic acid, and dicaffeoylquinic acid isomer	Dried powdered roots (50 g) were extracted with an UltraTurrax (30 min, × 2) with 70% ethanol, at RT	Human serum albumin/d-galactosamine/LPS-induce oxidative stress in albino Wistar rats was pre-treated with extracts (50, 100, and 200 mg/kg/BW/day, gavage) for 7 days	↓ tissue injury ↓ inflammatory cells infiltrates ↓ MDA, thiols, and NOx levels	Pfingstgraf et al. (2021)
Taraxasterol	Obtained from Chengdu Fenruisi Biotechnology Co., isolated from <i>T. officinale</i>	Freund's complete adjuvant-induced adjuvant arthritis in Wistar rats was treated with isolated compound (2, 4, and 8 mg/kg/day, oral) for 28 days	↓ paw swelling ↓ arthritis index ↓ spleen and thymus index ↓ TNF- α , IL-1 β , PGE ₂ and RANKL production	Wang et al. (2016)
Luteoli and luteolin-7-O-glucoside	Dried leaves (1000 g) was extracted (4 h) with water (tenfold volume) in a double boiler with a reflux condenser	Carbon tetrachloride-induced hepatitis in Sprague–Dawley rats was pre-treated with extracts (0.5 and 2 g/kg/BW, oral) for 7 days	↓ Fas expression ↓ TNF- α expression ↓ MDA levels ↑ GSH, GSH-px, GSH-red, and SOD levels	Park et al. (2010)

Table 15 continued

Plant extract composition/ Isolated compound	Extraction method	Biological assay	Anti-inflammatory effects	References
Caffeoyl-O-hexoside, caffeoyl-tartaric acid, 3-O-caffeoylquinic acid, caffeoyl-di-hexoside, 5-O-caffeoylquinic acid, feruloyl-tartaric acid, 4-O-caffeoylquinic acid, caffeic acid, luteolin-di-O-hexoside, L-chicoric acid, meso-chicoric acid, luteolin-O-hexoside-deoxyhexoside, luteolin-7-O-glucoside, chrysoeriol-O-hexoside, di-caffeoylquinic acid, 3,5-di-caffeoylquinic acid, luteolin-4'-O-glucoside, di-caffeoylquinic acid, taraxinic acid-O-glucoside, and luteolin	Flowers (161 g) are boiled in water (0.5 L) and stored overnight. In the next day, the filtrated and squeezed solution is mixed with sucrose (0.5 kg), which is cooked for 1.5 h	Obesity-induced albino Wistar Han IGS rats were fed with normal-fat diet with extract (278.2 g/kg) in the pellets for 4 weeks	↓ MDA levels ↑ SOD levels	Majewski et al. (2021)
2,3-dihydro-3,5-dihydroxy-6-methyl-4-h-pyran-4-one, 3-hydroxy-hexanoic acid, 3-methyl-2-pentanone, hydroxy-benzene acetic acid, tetradecanoic acid, methyl ester of hexadecanoic acid, hexadecanoic acid, decanenitrile, 4-ethyl-2,6-dimethyl-4-heptanol, Hentriacontane, 2-hydroxy-1-hexadecanoic acid, tritetracontane, nonacosane, 2-octyldodecan-1-ol, eicosane, coprostan-16.beta.-ol, β -amyrin, lup-20(29)-en-3-ol, and lupeol	Dried powdered leaves, stems and roots (5 g) were extracted (3 h) with 95% methanol (100 mL) in a water bath at 37 °C. Then, the mixture was extracted (72 h) with methanol (100 mL) at RT	Acetaminophen/paracetamol-induced hepatotoxicity in Wistar rats was co-treated with extracts (300 mg/kg/BW, oral) for 7 days	↓ tissue injury ↓ MDA levels ↓ lymphocyte inflammation ↓ TNF- α and IL-6 production ↑ GSH and SOD levels	Razak et al. (2020)
Protocatechuic acid, vanillic acid, syringic acid, ferulic acid, cichoric acid, rutin, quercitrin, luteolin, apigenin	Dried powdered aerial parts (50 g) were macerated with 70% ethanol (500 mL) for 7 days, at RT	Turpentine-induced acute inflammation in Wistar albino rats was co-treated with extracts (25, 50, and 100 mg/mL, oral) every day	↓ oxidative stress ↓ MDA, thiols, and NOx levels ↓ NF- κ B expression	Epure et al. (2023)

Table 15 continued

Plant extract composition/ Isolated compound	Extraction method	Biological assay	Anti-inflammatory effects	References
Glucose, galactose, ribose, fucose, xylose, arabinose, rhamnose, mannose, glucuronic acid, and galacturonic acid	Dandelion polysaccharides were purchased from Beijing Kangruina Biotechnology Limited Liability Company (Beijing, China). Briefly, stems and roots were extracted with water, followed by alcohol precipitations. Then, the polysaccharides were purified	High-fat-diet-induced Atherosclerosis in ApoE ^{-/-} mice was daily treated with extracts (200 mg/Kg) for 8 weeks	↓ tissue injury ↓ MDA levels ↓ TNF- α , IL-6, IL-1 β , and MCP-1 expression ↑ SOD and GSH-Px levels	Zhou et al. (2023)

AAPH, 2,20-azobis (2-amidinopropane) dihydrochloride; BW, body weight; CAT, catalase; COX, cyclooxygenase; DNA, deoxyribonucleic acid; ERK, extracellular signal-regulated kinase; GSH, glutathione; GPx, glutathione peroxidase; HO, heme oxygenase; IFN, interferon; Ig, immunoglobulin; IkB, inhibitor of nuclear factor kappa-light-chain-enhancer of activated B cells; IL, interleukin; Inos, inducible nitric oxide synthase; LPS, liposaccharides; MCP, monocyte chemoattractant protein; MDA, malondialdehyde; NF-Kb, nuclear factor kappa-light-chain-enhancer of activated B cells; NO, nitric oxide; Nox, nitrogen oxides; NQO-1, quinone oxidoreductase; Nrf2, nuclear factor erythroid 2-related factor 2; PG, prostaglandin; ROO $\cdot$, peroxy radical; ROS, reactive oxygen species; RT, room temperature; SOD, superoxide dismutase; TNF, tumor necrosis factor

Nourbakhsh 2003; González-Trujano et al. 2007; Benincá et al. 2011; Kuo et al. 2011; Afonso et al. 2013; Amaral et al. 2013, 2018; Yu et al. 2013; da Rosa et al. 2013; Zhang et al. 2015; Silva et al. 2015; Pérez-Rosés et al. 2015; Rocha et al. 2015; Medicherla et al. 2016; Ghasemzadeh et al. 2016; Ghasemzadeh Rahbardar et al. 2017; de Almeida Gonçalves et al. 2018; Borges et al. 2018; Luo et al. 2019; Wang et al. 2020; Yousef et al. 2020; Sasaki et al. 2021; Mansouri Torghabeh et al. 2022; Li et al. 2023; Francolino et al. 2023). The details of the anti-inflammatory studies are described in Table 13. Some of the most relevant studies will be presented in more detail. For example, essential oils obtained from *S. rosmarinus* strongly inhibited the classical pathway of the complement system, but not the alternative pathway (Pérez-Rosés et al. 2015). These essential oils were also able to reduce the phagocytosis in human neutrophils. Besides, in vitro studies, the Rosm-E bioactivity was also validated in in vivo models. For example, methanolic Rosm-E were proposed as a protective formulation for intestinal inflammation (Medicherla et al. 2016). The administration of methanolic Rosm-E in dextran sulphate sodium-induced ulcerative colitis mice model significantly ameliorated the disease severity. The infiltration of inflammatory cells was

significantly reduced, which was corroborated by the decrease in the MPO activity. In another study, rosmarinic acid, isolated from aqueous Rosm-E, exhibited powerful antioxidant effects on aging mice (Zhang et al. 2015). The administration of this compound significantly increased the antioxidant enzymes levels (SOD, CAT, and GSH-Px) in the liver and kidney of aging mice, being the values comparable with the normal control group. Consequently, the MDA levels decreased, suggesting the prevention of lipid peroxidation by free radicals scavenging. Rosmarinic acid also reduced the tissue injury. The antioxidant activity of Rosm-E was corroborated in the following study. Arthritic rats treated with aqueous Rosm-E presented a significant decrease of the oxidative damage (de Almeida Gonçalves et al. 2018). A significant decrease in ROS and protein carbonyls levels was observed. Conversely, a markedly enhancing of the activities of GSH, CAT, GRS, SOD, and GPx was detected. Moreover, the treatment with aqueous Rosm-E also delayed and reduced the edema, the number of recruited polymorphonuclear leukocytes in the knee, and the weight of the lymph nodes and adrenal glands. Interestingly, this extract showed similar activity to the NSAID widely prescribed ibuprofen. In another study, aqueous Rosm-E

significantly decreased neutrophils migration, and the secretion of pro-inflammatory mediators (LTB₄, PGE₂, IL-6, TNF- α , and NO) in a carrageenan-induced inflammation in Wistar rats (Silva et al. 2015). Interestingly, the results were similar with the clinical prescribed indomethacin treatment. The blockade of neutrophil migration by this aqueous Rosm-E was associated with the modulation of the neutrophil chemotaxis and the inhibition of the adhesion molecules expression. Additionally, treatment with aqueous Rosm-E markedly increased SOD levels, decreasing the lipid peroxidation. Another aqueous ethanolic Rosm-E exerted potent anti-inflammatory activity in sciatic nerve chronic constriction injury-induced neuropathic pain in Wistar rats (Ghasemzadeh et al. 2016; Ghasemzadeh Rahbardar et al. 2017). The treatment with aqueous ethanolic Rosm-E significantly reduced the inflammatory response through the down-regulation of the inflammatory mediator's expression (IL-1 β , TNF- α , PGE₂, NO, iNOS, COX-2, and MMP2) and the reduction of the tissue injury.

Rosm-E also displayed strong bioactivity in allergies. The Rosm-E, obtained by steeped in dichloromethane-methanol, modulated mast cell functional responses, attenuating IgE-mediated mast cell activation (Yousef et al. 2020). The application of this Rosm-E to anti-TNP IgE-sensitized and cognate allergen-stimulated primary murine mast cells rapidly impaired the activation of MAPK and NF- κ B signaling pathways. The phosphorylation of p38 and JNK, but not ERK, was prevented. Moreover, a decrease in the NF- κ B transcriptional activity was observed. In addition, Rosm-E treatment significantly decreased the gene expression and further production and release of several pro-inflammatory cytokines and chemokines (IL-6, IL-13, TNF, CCL1, and CCL3), contributing for the resolution of late-phase of mast cell activation. Rosm-E also significantly prevented the rapid degranulation of mast cells, highlighting its capability in the reduction of the early-phase of mast cell activation.

Rosm-E have also immunostimulatory activity related to the promotion of cytokines production; and (ii) the increase of the respiratory burst (Kontogianni et al. 2013). Stimulatory study details are reported in Table 14. For example, the treatment of naïve peritoneal macrophages with ethyl acetate Rosm-E enhanced the production of NO and TNF- α (Kontogianni et al. 2013).

Taraxacum officinale

T. officinale (Asteraceae), also known as common dandelion, is native to Europe and Asia. Despite being considered a weed in many crops around world, dandelion has a long history as a traditional herbal remedy to treat skin inflammation, upper respiratory tract infections, bronchitis, pneumonia, arthritic and rheumatic conditions. Usually, the dandelion infusion is made of its dried leaves, flowers and/or roots.

T. officinale extracts (Tara-E) are composed by a wide range of chemical compounds, such as flavonoids, phenolic acids, fatty acids, triterpenes, sesquiterpenes, polysaccharides, coumarins, and diterpenes (Supplementary Table S8). The main active compounds in Tara-E are taraxasterol, luteolin, luteolin-7-glucoside, caffeic acid, and chlorogenic acid (Table 15).

The anti-inflammatory activity of Tara-E is associated with (i) the reduction of pro-inflammatory cytokines, prostaglandins, and immunoglobulins expression and production; (ii) the decrease of respiratory burst and molecular oxidation levels; (iii) the reduction of immune cells infiltration and activation; (iv) the increase in antioxidant enzymes levels; and (v) the amelioration of edema, pain, and tissue injury (Hu and Kitts 2004, 2005; Park et al. 2010, 2011, 2014; Liu et al. 2013; Xiong et al. 2014; Zhang et al. 2014; Wang et al. 2016; Cai et al. 2017; Kala et al. 2017; Razak et al. 2020; Majewski et al. 2021; Pfingstgraf et al. 2021; Epure et al. 2023; Zhou et al. 2023). The details of the anti-inflammatory studies are described in Table 15. Some of the most relevant studies will be presented in more detail. For instance, aqueous and methanolic Tara-E, obtained from leaves, ameliorated the oxidative stress and the inflammatory response in LPS-stimulated RAW 264.7 macrophages (Park et al. 2011). The pre-treatment with both extracts reduced the NO and MDA levels through the down-regulation of the iNOS expression and production. This occurred via inactivation of the NF- κ B and the upregulation of the antioxidant enzymes levels (CAT, SOD, GPx, GR, and GSH). Interestingly, the antioxidative activity of the methanolic Tara-E was significantly higher than the aqueous Tara-E, which could be related with the higher content in phenols, including luteolin and chicoric acid. Anti-inflammatory effects of polysaccharides isolated from *T. officinale* (TOP1 and TOP2) on LPS-stimulated murine

macrophages RAW 264.7 were also resorted (Park et al. 2014). The pre-treatment with TOP markedly increased HO-1 expression due to the Nrf2 nuclear accumulation, through the activation of all the MAPK (ERK, JNK, p38) and PI3K/Akt signaling pathways. Moreover, TOP enhanced the cytoprotective ability, through Nrf2-mediated HO-1 upregulation, in t-BHP-induced oxidative stress in murine macrophages. Additionally, NF- κ B and Akt signaling pathways were inhibited since the phosphorylation of I κ B α , p65 and Akt were attenuated by TOP treatment. However, they had no effect on the phosphorylation of ERK, JNK and p38. Consequently, the NO production, and iNOS and TNF- α production were reduced, however not the production of the PGE2 and COX-2. Taraxasterol was also implied in the anti-inflammatory activity. It led to the downregulation of the iNOS and COX-2 expression and production, mediated through the inhibition of ERK1/2 and p38 phosphorylation (Xiong et al. 2014). The anti-inflammatory activity of this compound was also demonstrated in vivo. Indeed, it showed a promising protective effect against Freund's complete adjuvant-induced arthritis in Wistar rats (Wang et al. 2016). The treatment with this isolated compound significantly reduced the paw swelling and arthritis index. In fact, an amelioration of the degree of synovial hyperplasia, cartilage and bone destruction, as well as the inflammatory cell infiltration into the synovium joint-space narrowing were observed. Moreover, the spleen and thymus indexes were strongly reduced, suggesting that taraxasterol may help in the recovery of the hyperfunctioning of immune organs without causing damage. Also, the serum levels of some pivotal inflammatory mediators that contribute to the clinical manifestations of rheumatoid arthritis, namely TNF- α , IL-1 β and PGE2, were significantly decreased. Therefore, taraxasterol was able to inhibit bone destruction in an animal model of rheumatoid arthritis.

Recently, a Tara-E obtained from aerial parts demonstrated its antioxidant activity in vivo (Epure et al. 2023). The treatment of turpentine-induced acute inflammation in rats with this Tara-E strongly reduced the oxidative stress, by the decrease of MDA, thiols, and nitrites/nitrates levels. Moreover, the administration of the Tara-E also reduced the expression of NF- κ B signaling pathway.

Conclusions and future perspectives

Recently, the interest in the discovery of new plant-based drugs have been re-arising as promising treatments for the health care management of immune-related diseases. In fact, several plants have high-value bioactive compounds that can interact with immune cells, enhancing or reducing the main inflammatory mediators. Thus, they can be extremely important in the biopharmaceutical and biomedical fields. Usually, the few side-effects and the low cost-effective development than the ones required for developing a new drug increase the demand in plant-based drugs for diseases where the immune system is compromised or hyperactive.

Plant extracts are a complex mixture of phytochemicals whose composition can change due to multiple variables herein discussed. Thus, incongruences between the composition of the plant extracts derived from the same plant species and, consequently, the different biological outcomes, are a well-recognized concern. Moreover, although the main bioactive compounds of plant extracts have been characterized, new entities are still arising due to the complexity of the natural mixture. Another problem in the chemical characterization of the plant extract is the various possibilities of naming a chemical compound.

The isolation and purification of a specific active principle is a major goal in the plant-based drug discovery. However, the identification of the bioactive molecules in a complex mixture could be extremely difficult. Therefore, a bio-guided fractionated method must be employed to determine the bioactive principles. Moreover, the coupling of extraction techniques with chromatographic methods could be an added-value resource in the identification and quantification of the bioactive compounds. Additionally, the advances in metabolomics and bioinformatics can help in the determination of the extract composition, molecular structure, and the mechanism of action of the main(s) bioactive molecule(s) before their corroboration with in vitro and in vivo experiments. This can reduce the time of experiment and ensures the best selection of the bioactive compounds. Additionally, if an additive or synergistic activity arise from the complex mixture of chemical compounds, the development of a standardized plant extract should be

employed. The standardization of the plant extract concentration of the active principles will certainly attenuate and/or overcome the divergence between biological activities.

The therapeutic potential of plant-based drugs can also be significantly improved. The future of plant-based drugs will be shaped by the latest advancements in cultivation practices, particularly those that enable the stimulation of a target chemical(s) compound(s) production within the plant organism. These advancements hold the potential to enhance the bioactive value of studied plants by optimizing the presence of desired bioactive molecules.

The development of a green, sustainable, and industrially scalable extraction technique is a future requirement. A faster extraction method that enables the reduction of the use of organic solvents, the decrease of the energy consumed, and the reduction of waste products must be in the basis of the plant-based drug discovery. This approach aligns with the goal of creating environmentally friendly and sustainable processes in this field.

In conclusion, phytochemicals can have huge medical, economic, and environmental impacts. Indeed, considering the urgent need of effective drugs to safely treat immune-related conditions, this is a valid strategy. The future of the plant-based immunomodulatory drugs will (re)arise from transforming low-value crops into potent and high-value formulations.

Acknowledgements We acknowledge the financial support by the FCT to the Ph.D. grant of SFV (PD/BD/135246/2017 and COVID/BD/152012/2021) and the projects PATH (PD/00169/2013), HEALTH-UNORTE (NORTE-01-0145-FEDER-000039), Associate Laboratory Project, ICVS/3B's (UIDP/50026/2020), and the “TERM RES Hub – Scientific Infrastructure for Tissue Engineering and Regenerative Medicine”, reference PINFRA/22190/2016 (Norte-01-0145-FEDER-022190), funded by FCT in cooperation with the Northern Portugal Regional Coordination and Development Commission (CCDR-N).

Funding Open access funding provided by FCT/ICCEN (b-on).

Declarations

Conflict of interest The authors declare no conflict of interest.

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