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REVIEW

Phytocompounds in *Atriplex halimus* and their therapeutic potential: Focusing on biological properties and mechanism of action

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Abstract

Atriplex halimus is a Mediterranean xerohalophyte shrub, traditionally recognized for managing metabolic, inflammatory, and infectious disorders. Thriving under extreme conditions of soil salinity, drought, and strong solar radiation, the species has developed a stress-responsive metabolism driving a diverse and phenolic-rich phytochemistry. *Atriplex halimus* extracts have been cited to exhibit antihyperglycemic, antioxidant, anti-inflammatory, cytotoxic, antimicrobial, and other properties. These activities have been linked to enzyme inhibition (α-amylase and α-glucosidase), modulation of insulin signaling and GLUT4 translocation, regulation of redox homeostasis via the Nrf2/ARE pathway, and suppression of inflammatory mediators through NF-κB and MAPK pathways. This review summarizes botanical characteristics, ethnomedicinal applications, phytochemical composition, and the biological activities of the species, while critically addressing the conceptual and methodological limitations that constrain its therapeutic translational relevance. Within this framework, key research gaps are identified, including the need for standardized extracts, robust toxicological studies, the establishment of direct causal relationships between phytochemicals and specific pharmacological effects, as well as integrated mechanistic studies and in-depth in vivo assessments.

Keywords Medicinal plants · Halophyte · *Atriplex halimus* · Antihyperglycemic · Anti-inflammatory · Antioxidant · Antimicrobial · Antitumor · Cytotoxic · Bioactive compounds · Therapeutic potential

Abbreviations

DW	Dry weight
GA-Eq	Gallic acid equivalents
QE/g extract	Quercetin equivalents per gram of extract
GC–MS/MS	Gas Chromatography Tandem Mass Spectrometry
HPLC	High-performance liquid chromatography
TPC	Total phenolic content
CE	Catechin equivalent

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LC–MS/MS	Liquid Chromatography Tandem Mass Spectrometry
ABTS +	2,2′-Azinobis(3-ethylbenzothiazoline-6-sulfonic acid) radical cation
DPPH	2,2-Diphenyl-1-picrylhydrazyl
TAC	Total antioxidant capacity
AHHE	*Atriplex halimus* Hydroethanolic extract
AHAE	*Atriplex halimus* Aqueous extract
EO	Essential oil
ROS	Reactive oxygen species
Caco	Intestinal carcinoma
HELA	Cervical carcinoma
HEP2	Larynx carcinoma
HCT	Colon carcinoma
A549	Lung carcinoma
HepG2	Hepatocellular carcinoma
MCF-7	Breast carcinoma
PC3	Prostate carcinoma cancer cell cultures
MDA-MB-468	Human, Black, breast, adenocarcinoma
AHC	*Atriplex halimus* Chloroform extract
PCR	Polymerase Chain Reaction
AuNPs	Gold nanoparticles
MTT	3-[4,5-Dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide
MICs	Minimum inhibitory concentrations. T2D, Type 2 diabetes
SGOT	Serum glutamic oxaloacetate transaminase
SGPT	Serum glutamate-pyruvate transaminase
PAL	Alkaline phosphatase
GLUT4	Glucose Transporter Type 4
AChE	Acetylcholinesterase
IL-6	Interleukin-6
IL-1β	Interleukin-1β
TNF-α	Tumor necrosis factor-alpha
COX-2	Cyclooxygenase-2
LPS	Lipopolysaccharide
NF-kB	Nuclear factor kappaB
MAPK	Mitogen-activated protein kinase

Introduction

The global rise in metabolic, inflammatory, and degenerative disorders, together with the limitations and adverse effects frequently associated with the long-term use of conventional drugs, has generated considerable interest in herbal medicines as potentially safer and more accessible therapeutic resources. In this context, halophytic species are of particular interest, as the multiple environmental stresses they endure (high salinity, drought, and intense solar radiation) necessitate complex adaptive responses, including the synthesis of diverse bioactive secondary metabolites. Within this group, *Atriplex halimus*, commonly known as Mediterranean saltbush, has long been used in folk medicine across North Africa and the Middle East to manage glycemic imbalance, alleviate rheumatic and inflammatory symptoms and treat digestive and urinary conditions, and promote skin healing (Zennaf et al.

2022). These ethnomedicinal indications provide a useful foundation for investigating the phytochemical composition and biological activities of the species.

Consistent with its stress-driven metabolism, *Atriplex halimus* has shown a diverse phytochemistry, characterized by a high content of phenolic compounds, including phenolic acids (trans-cinnamic, gallic, ferulic, and caffeic acids), as well as flavonoids and their glycosides (kaempferol, rutin and catechin derivatives). The qualitative and quantitative composition of these phytochemicals varies with geographical origin, plant organ, extraction solvent and analytical method. Correspondingly, pharmacological investigations conducted predominantly in vitro have reported antihyperglycemic, antioxidant, anti-inflammatory, cytotoxic, antimicrobial, neuroprotective, and other activities (Walker et al. 2014; Petropoulos et al. 2018). In this regard, our analysis reports several critical gaps, the relationship between the phytochemical composition of the species and the mechanisms underlying its reported biological activities remain insufficiently clarified, with the absence of standardized extract preparations across studies, severely limiting the comparability and reproducibility of findings. Toxicological assessment has remained scarce, raising potential safety concerns when used as food or herbal preparations. This review therefore aims to critically evaluate the phytochemical profile of *Atriplex halimus* in relation to its reported biological activities, while identifying key limitations that constrain its therapeutic development.

Search strategy

A comprehensive literature search was performed in PubMed, Scopus, Web of Science, and Google Scholar between September and December 2024, screening all records containing the keyword "*Atriplex halimus*" in the title, abstract or keywords. No lower time limit, language restrictions or exclusion criteria based on publication year were applied. Reference lists of relevant articles were also examined to identify additional primary studies. All records were first assessed at the title and abstract level, and full texts were retrieved for studies that provided phytochemical characterization of *Atriplex halimus* and/or investigated its pharmacological properties in vitro, in vivo or in silico. The final collection comprises 101 publications, stricter selection criteria were subsequently applied, prioritizing studies published in indexed journals (Scopus and/or Web of Science). This led to the retention of 51 studies forming the core evidence base of this review. Additional studies published in 2025 were incorporated to complement specific sections, particularly recent advances in phytochemical profiling and biological activity, ensuring up-to-date synthesis of the available evidence.

Botanical description and taxonomy

Morphology

Commonly referred to as "Mediterranean saltbush" and, known in Morocco as "Lgtef," *Atriplex halimus* is a xerohalophytic perennial shrub characterized by specialized morphological and physiological adaptations that enable it to thrive in both arid and saline environments. These features make it exceptionally well-suited to the harsh conditions of Mediterranean climates, where extreme drought, high temperatures, and soil salinity pose significant challenges to plant survival. The species possesses a deep root system and

naturally forms a densely branched, deciduous shrub with a strong capacity to develop axillary shoots. *Atriplex halimus* ramifies from the base, typically reaching heights of up to 3 m and extending to a diameter of 3 m. Its intricately branched stems give the plant its bushy appearance, while its silvery-gray leaves are small, alternate, and succulent. Although the species is predominantly evergreen, it may shed some leaves during the hot, dry summer (Ortiz Dorda et al. 2005; Elbouzidi et al. 2022). *Atriplex halimus* exhibits considerable heteromorphism in phenotypic traits and varies in ploidy level, suggesting a range of genetic and adaptive variations that enhance its resilience and ability to occupy a wide ecological range (Ortiz Dorda et al. 2005; Sukhorukov 2012). Differences in morphological characteristics are well-documented, including variations in flowering phenology, shoot development, and leaf shedding, which highlight the significant variability within natural populations (Walker et al. 2014). The plant morphology can range from upright to compact and prostrate forms, with a strong correlation observed between plant size, shape, and combinations of height and width that reflect vegetative vigor. The size of the leaf blade shows the greatest variability, likely influenced by climatic conditions and the timing of sampling (Ortiz Dorda et al. 2005; Walker et al. 2014).

Taxonomy

Atriplex halimus L. belongs to the family *Amaranthaceae* (formerly *Chenopodiaceae*), subfamily *Chenopodioideae*, tribe *Atripliceae*, and genus *Atriplex* (Tlili et al. 2019; Cherrada et al. 2024).

Sukhorukov (2012) delineates three taxonomic units. The first unit corresponds to the nominal variety, *A. halimus* var. *halimus,* predominantly found in Southern Europe and typically characterized by broader, often ovate leaves and a relatively compact shrub habit. The second unit, *A. halimus* var. *schweinfurthii* Boiss., prevalent in the Eastern Mediterranean region and North Africa, generally exhibits narrower, more elongated leaves, a more erect growth form, and larger fruiting bracts with more pronounced ornamentation. The third unit, *A. halimus* var. *granulata* L.Chevall., reported from the vicinity of Biskra in northern Algeria, is distinguished by fruiting bracts with a more granular or tuberculate surface and certain vegetative differences compared with other varieties. Although the infraspecific taxonomy of the species has been discussed in the literature, these taxa are generally distinguished by both geographical distribution and morphological traits, and their potential differences in phytochemical composition remain largely unexplored. Further differences related to reproductive traits and fruit morphology are described in the following sections.

Inflorescence and reproductive characteristics

Atriplex halimus is classified as monoecious, with dense spike inflorescences exhibiting a tapered, compact, and paniculiform structure. Male flowers, approximately 2 mm in diameter, are located at the apex without bracts, while female flowers are positioned at the base with two bracts and a longer axis of about 10 mm. The inflorescences display a subtle greenish-brown shade during the flowering season, which spans from May to December, with variations depending on geographical location (Ortiz Dorda et al. 2005). The extended flowering period suggests a strong reproductive strategy that maximizes pollination opportunities under fluctuating climatic conditions. In a comparative study by Flores-Olvera et al. (2011) across various *Atriplex* species, *Atriplex halimus* was found to have mid-range

pollen grain dimensions, with diameters ranging from 16 to 30 µm and 54 to 72 pores per grain, although it exhibited a smaller pore diameter of 1.0 to 1.2 µm. The relatively high pore count is indicative of an efficient pollen dispersal mechanism, enhancing reproductive success in open, wind-exposed environments. Further investigations the inflorescence structure of *A. halimus*, particularly the variety *schweinfurthii*, revealed pentamerous flowers containing both male and female reproductive organs (Talamali et al. 2001). This flexibility in sex expression, as proposed by Talamali et al. (2003) is considered an adaptation to harsh environments, resulting in the manifestation of up to six distinct floral phenotypes. The removal of the gynoecium typically leads to the development of male flowers, alongside instances of hermaphroditic and pistillate flowers. Female, bracteate floral structures are induced by shorter days and reduced irradiance, suggesting a photoperiod-dependent regulatory mechanism that aligns reproductive output with seasonal resource availability. Environmental conditions have been shown to influence reproductive traits in the species, with shifts in sex expression reflecting adaptive responses to stress. In particular, variations in floral architecture and sex determination highlight the species' reproductive plasticity and its capacity to adjust reproductive investment under resource-limited conditions. This flexibility likely confers an evolutionary advantage, ensuring reproductive success across heterogeneous environments (Talamali et al. 2001, 2003). Other phenological observations indicated that *A. halimus* shows an extended reproductive cycle under Mediterranean conditions, with flowering generally occurring from May to December depending on geographical location, and fruit maturation taking place during the autumn–winter period (Ortiz Dorda et al. 2005; Walker et al. 2014).

Fruits and seeds

The fruits of *Atriplex halimus* are small, dry, and typically flattened utricles enclosing a single seed. These structures are surrounded by persistent bracteoles, whose morphology varies from kidney-shaped to nearly circular forms with entire or toothed margins. Such features are associated with effective dispersal and establishment under arid and saline conditions. Considerable intraspecific variation in fruit morphology has been reported, reflecting the influence of genetic and environmental factors on reproductive traits (Flores-Olvera et al. 2011; Sukhorukov 2012).

In addition to morphological variability, reproductive traits in *A. halimus* display considerable plasticity. The occurrence of hermaphroditic or sterile flowers, particularly in var. *schweinfurthii*, may affect seed production and, consequently, germination potential (Talamali et al. 2001).

Habitat and geographic distribution

Atriplex halimus originates from the Mediterranean region and has expanded to other environments with similar conditions, characterized by relatively high soil salinity and aridity (Ksouri et al. 2012).

The species typically thrives in regions with higher annual rainfall (> 400 mm/year), whereas the variety *schweinfurthii* grows in more arid regions with annual rainfall ranging between 100 and 400 mm (Walker et al. 2014). This historical expansion suggests a remarkable adaptability that has allowed the species to persist through fluctuating climatic conditions over millennia. *Atriplex halimus* holds significant economic and ecological value as a halophytic shrub species for land rehabilitation in arid environments, serving

critical roles in soil reinforcement and erosion control. The species' geographic distribution is extensive, spanning Macaronesia, the southern and eastern Mediterranean, and western Asia. It naturally grows in countries including Morocco, Tunisia, Syria, Lebanon, Jordan, Algeria, Libya, Turkey, Cyprus, Palestine, Greece, southern Portugal, France, southern and eastern Spain, the Canary Islands, Italy, and Malta (Ortiz Dorda et al. 2005; Walker et al. 2014). In Morocco, research has highlighted the significant and abundant presence of *A. halimus* as a wild species (Bouda et al. 2008).

Traditional uses

Ethnobotanical knowledge provides a valuable framework for guiding pharmacological investigations by identifying recurrent traditional uses, shaped by long-accumulated empirical observation.

In this context, *Atriplex halimus* has long been valued in folk medicine across North Africa and the Middle East, particularly for the management of hyperglycemia (Slama et al. 2020). Ethnobotanical studies further report that the species is used for a broad range of applications in Algeria, primarily for the treatment of digestive disorders (27%), followed by metabolic diseases, particularly diabetes (22.5%), and hydatid cysts (12%) (Zennaf et al. 2022). Additional uses include urological, dermatological, cardiovascular, dental and, respiratory conditions (Zennaf et al. 2022). According to the same study, the leaves are the most commonly used plant parts and traditional remedies are generally prepared as decoctions, infusions, or aqueous macerations for oral administration.

Overall, ethnomedicinal data provide valuable insights into the traditional uses of *A. halimus*; however, they are based on self-reported practices and lack standardization in terms of preparation methods and dosages. In addition, the concurrent use of multiple medicinal plants, which is common in traditional settings, is rarely documented, potentially confounding the attribution of therapeutic effects. Also, information regarding adverse effects and contraindications is generally absent. Despite these limitations, the consistent reporting of its use in the management of diabetes across different regions suggests a recurrent ethnopharmacological pattern rather than a mere outcome of cultural exchange, providing a strong rationale for prioritizing this activity in pharmacological research. Accordingly, the phytochemical composition of *A. halimus* has been investigated to identify the bioactive constituents that may underlie its traditional medicinal applications.

Phytochemical composition

Halophytes inhabit environments characterized by high salinity, drought, and intense solar radiation, conditions that generate considerable oxidative stress. In response to these environmental constraints, halophytic plants accumulate elevated levels of phenylpropanoid-derived secondary metabolites, particularly polyphenols such as flavonoids and phenolic acids. These compounds act as non-enzymatic antioxidants involved in reactive oxygen species (ROS) scavenging and cellular protection (Stanković et al. 2023). Consistent with this adaptive strategy, the phytochemical composition of *Atriplex halimus* exemplifies the complex stress-responsive strategies of halophytes, revealing a diverse range of secondary metabolites in which phenolic compounds predominate.

Flavonoids constitute the most extensively reported class of secondary metabolites in the species. Several studies have identified numerous flavonols and their glycosylated derivatives, including catechin, epicatechin, rutin, myricetin, kaempferol and quercetin

(Bouaziz et al. 2021; Zennaf et al. 2022). Quantitative analyses revealed that flavonoid content varies depending on plant origin and extraction method. For example, aqueous leaf extracts from Algerian populations contained catechin (717.86 µg/g DM) and rutin (360.84 µg/g DM) as major flavonoids (Zennaf et al. 2022), whereas kaempferol (~1.0 µg/g DW) was detected at trace levels in Tunisian populations (Guedri et al. 2024). Total flavonoid content also depends on extraction solvent; ethanolic leaf extracts showed higher concentrations (4.350 ± 0.023 mg QE/g extract) compared with aqueous extracts (1.995 ± 0.026 mg QE/g extract) (Benmarce et al. 2024). Additional investigations using UPLC–HR-MS revealed the presence of uncommon glycosylated derivatives of isorhamnetin and syringetin (Foletti et al. 2025), while methoxylated flavonoid glycosides derived from myricetin and quercetin were also reported (Clauser et al. 2013). More recently, structural analyses using NMR and HR-ESI–MS enabled the identification of five novel flavonol glycosides (Vitiello et al. 2025).

Phenolic acids constitute another major class of secondary metabolites identified in *A. halimus* extracts. Chromatographic analyses have reported the presence of trans-cinnamic acid, ferulic acid, caffeic acid, gallic acid, chlorogenic acid, syringic acid, p-coumaric acid and other carboxylic acids in leaf and aerial-part extracts, with significant variation depending on plant origin and extraction method (Bouaziz et al. 2021; Zennaf et al. 2022; Guedri et al. 2024). Trace levels of vanillic acid have also been detected (Bouaziz et al. 2021). Zennaf et al. 2022 reported the occurrence of p-coumaric acid (59.41 µg/g DM), protocatechuic acid (27.9 µg/g DM) and gallic acid (13.59 µg/g DM) in aqueous extracts of *A. halimus* leaves. Among these constituents, trans-cinnamic acid has been described as one of the most abundant compounds in the aerial parts of *A. halimus* according to UHPLC–MS/MS analyses (Roubi et al. 2025). Additional phenolic derivatives such as 3-hydroxy-4-methoxycinnamic acid were detected in Tunisian populations (Guedri et al. 2024). Other minor phenolic derivatives, including the glycosylated hydroquinone arbutin, were also detected using LC–MS/MS (Elbouzidi et al. 2022).

In addition to flavonoids and phenolic acids, condensed tannins and other phenolic constituents have also been reported in *A. halimus* extracts. Quantitative studies have demonstrated significant variability in total phenolic fraction depending on extraction solvent and plant origin. Moroccan leaf extracts showed total phenolic content ranging from 337.61 to 569.94 mg GAE/g DM, with the highest concentrations observed in ethanolic extracts (Benhammou et al. 2009). Condensed tannins quantified using the vanillin assay were higher in ethanolic extracts (147.26 ± 13.82 µg CE/g DM) than in aqueous extracts (75.62 ± 7.67 µg CE/g DM) (Benmarce et al. 2024).

Beyond its phenolic fraction, the essential oil of *A. halimus* was characterized by Soltani et al., (2023) using GC–MS analysis, revealing a complex phytochemical profile dominated by oxygenated sesquiterpenes and diterpenes. A total of 35 constituents representing 89.17% of the total essential oil composition were identified, with viridiflorol (40.23%) reported as the predominant compound, followed by phytol (18.24%) and germacrene D (6.94%). Other notable constituents included viridiflorene (3.23%), myristicin (3.01%), bicyclogermacrene (2.46%), p-acetanisole (1.60%), caryophyllene oxide (1.52%), and α-bisabolol oxide B (1.46%).

Complementing these findings, metabolomic analyses have indicated the presence of several fatty acids in the methanolic extract of *A. halimus*, with GC–MS profiling identifying palmitic acid (6.47%), oleic acid (5.25%), and stearic acid (4.01%) as the predominant lipid constituents (Morad et al. 2023).

Metabolomic profiling also revealed the presence of sugars and sugar alcohols including myo-inositol (5.14%), glycerol (3.43%), D-fructofuranose (2.74%), sucrose (2.24%)

and D-pinitol (1.63%). Organic acids were also detected, with citric acid accounting for approximately 4.05% of the metabolite profile. Among amino acids, alanine was the most abundant compound (1.18%) (Morad et al. 2023).

Although the phytochemical studies on *A. halimus* are characterized by considerable methodological heterogeneity and limited standardization, several phenolic constituents have been consistently identified across investigations, reflecting a stress-driven metabolic profile characteristic of halophytic species. The extreme environmental conditions under which halophytes thrive force them to produce a unique and potent chemical repertoire, which supports the significant pharmacological potential of the species and provides a plausible basis for its traditional medicinal uses, as well as for the range of biological activities reported in the literature (Fig. 1).

Toxicity and safety evaluation

The phytochemical composition of *Atriplex halimus* includes a variety of bioactive constituents. Although these metabolites are often associated with pharmacological effects,

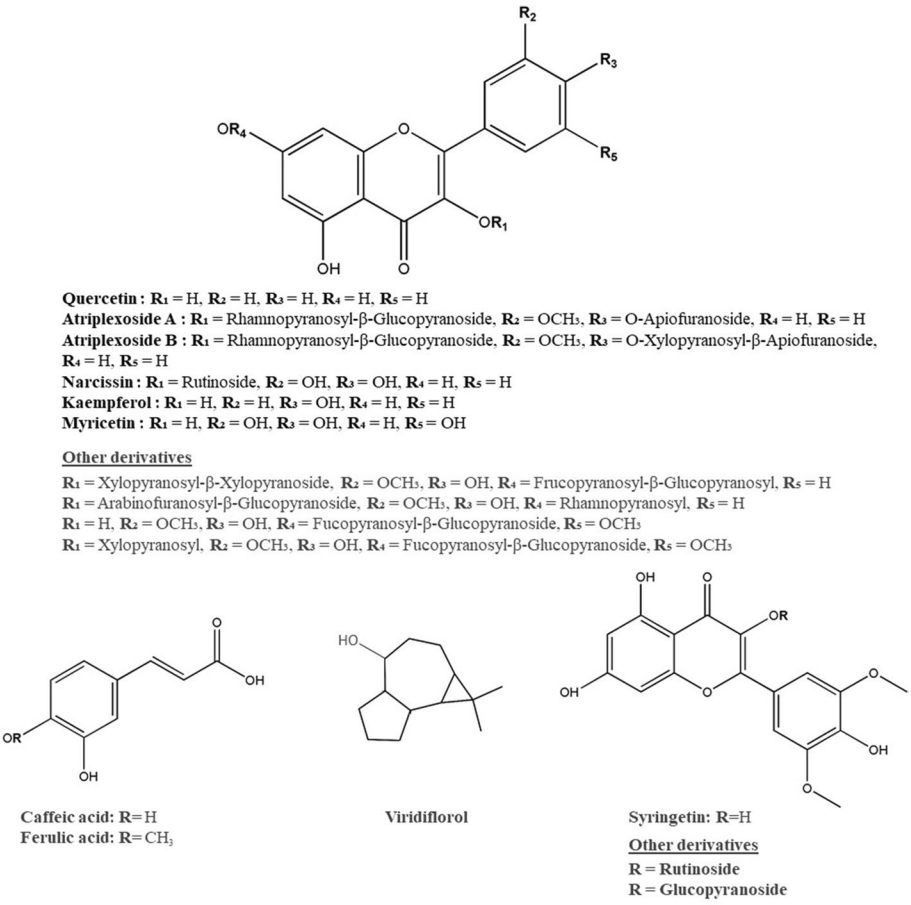


Fig. 1 Major compounds identified in *Atriplex halimus* and their chemical structures

several have been reported to exhibit dose-dependent toxicological effects. For instance, phenolic acids such as gallic acid and caffeic acid may exert pro-oxidant effects at elevated concentrations, potentially inducing oxidative stress and cytotoxicity in biological systems (Galati et al. 2002). Certain flavonoids, including quercetin and myricetin, have demonstrated cytotoxic or genotoxic effects *in vitro* at high concentrations, despite their well-known antioxidant activities at lower doses (Boots et al. 2008).

In a study investigating the *in vivo* antihyperglycemic properties of *A. halimus*, acute toxicity assessment indicated a favorable safety profile, as oral administration of aqueous leaf extracts at doses up to 5000 mg kg^{-1} body weight in rats elicited no observable adverse signs over a 48-h period (Bounouar et al. 2022). Recent investigations have provided preliminary *in vitro* evidence supporting the toxicological safety of the species' leaf extracts, with Ames test assays (24–48 h exposure) indicating no mutagenic or genotoxic effects. However, comprehensive *in vivo* and long-term toxicity studies are still lacking (Foletti et al. 2025). The species' propensity to heavy metals from the environment further complicates its toxicological profile (Bankaji et al. 2019).

The present toxicological findings remain preliminary and point to the scarcity of available data. The absence of comprehensive chronic exposure studies, coupled with potential risks associated with prolonged use, constituent interactions, and environmental contaminants, highlights the critical need for expanded investigations to establish robust safety guidelines.

Pharmacological properties

Antihyperglycemic activity

Diabetes mellitus comprises a group of metabolic disorders characterized by persistent hyperglycemia resulting from impaired insulin secretion, impaired insulin action, or both. (ElSayed et al. 2023).

Atriplex halimus has been traditionally recognized for its antihyperglycemic properties, and recent studies have begun to clarify the underlying mechanisms. *In vivo*, Studies using animal models of diabetes and obesity have demonstrated its potential to lower blood glucose levels and improve insulin sensitivity (Said et al. 2008). Direct histological evidence further demonstrated that these effects might involve improvements in the islets of Langerhans or stimulation of insulin secretion from residual beta cells, suggesting functional pancreatic recovery in streptozotocin-induced diabetic rats (Bounouar et al. 2022). Moreover, the same study reported dose-dependent decreases in liver enzyme levels, including serum glutamic oxaloacetate transaminase (SGOT), serum glutamate-pyruvate transaminase (SGPT), and alkaline phosphatase (Bounouar et al. 2022). Said et al. 2008 investigated the antihyperglycemic effects of a dry extract from *Atriplex halimus* leaves using both *in vitro* and *in vivo* approaches. Their findings revealed that when combined with other traditional medicinal plants, such as *Juglans regia* L., *Olea europaea* L., and *Urtica dioica* L., in the formulation "Glucolevel," the extract significantly inhibited glucose absorption and enhanced insulin secretion. These results support the potential use of *A. halimus* as a component of multi-herb formulations and suggest possible synergistic interactions with co-administered plant extracts. On a mechanistic basis, Guedri et al. 2024 provided further insight into the bioactive constituents of *A. halimus* extracts and their ability to inhibit key enzymes involved in carbohydrate metabolism, demonstrating a pronounced inhibitory

effect on α-amylase and a moderate effect on α-glucosidase. Although these inhibitory activities were mainly associated with the plant's rich phenolic profile, the authors suggested that they are also likely mediated by non-phenolic compounds, including terpenes, sterols, saponins, coumarins, and carotenoids. In parallel, Montaser et al. 2024 investigated the ethyl acetate fraction of *A. halimus* in a high-sugar diet–fed larvae and demonstrated that it effectively normalized elevated glucose and trehalose levels to the control level. The study attributed these effects to the fraction's high flavonoid content, as revealed by metabolomic profiling, which was associated with reduced levels of Drosophila insulin-like peptide 2 (DILP2), Drosophila insulin-like peptide 3 (DILP3), and Adipokinetic hormone (AKH), key regulators of glucose metabolism in this model organism. Complementary molecular docking analyses further showed that eriodictyol-7-O-neohesperidoside exhibited the highest binding affinity to targets involved in glucose metabolism, suggesting it as a major contributor to the observed antihyperglycemic activity.

The central proposed antihyperglycemic mechanism of *A. halimus* is suggested to involve the upregulation and increased translocation of GLUT4 (glucose transporter type 4) to the plasma membrane, which facilitates enhanced glucose uptake into muscle and adipose tissue (Kadan et al. 2013). Moreover, Zennaf et al. 2022 noted that the antihyperglycemic effect of *A. halimus* could be also attributed to the plant's chromium content, which is proposed to regulate blood glucose by potentiating insulin receptor signaling and promoting GLUT4 translocation (Fig. 2).

A recent study have demonstrated that *A. halimus* extracts exhibit significant antihyperglycemic activity through the inhibition of α-amylase and hemoglobin glycation, suggesting a role in the regulation of postprandial hyperglycemia and the prevention of glycation-related complications (Roubi et al. 2025). These effects are further supported

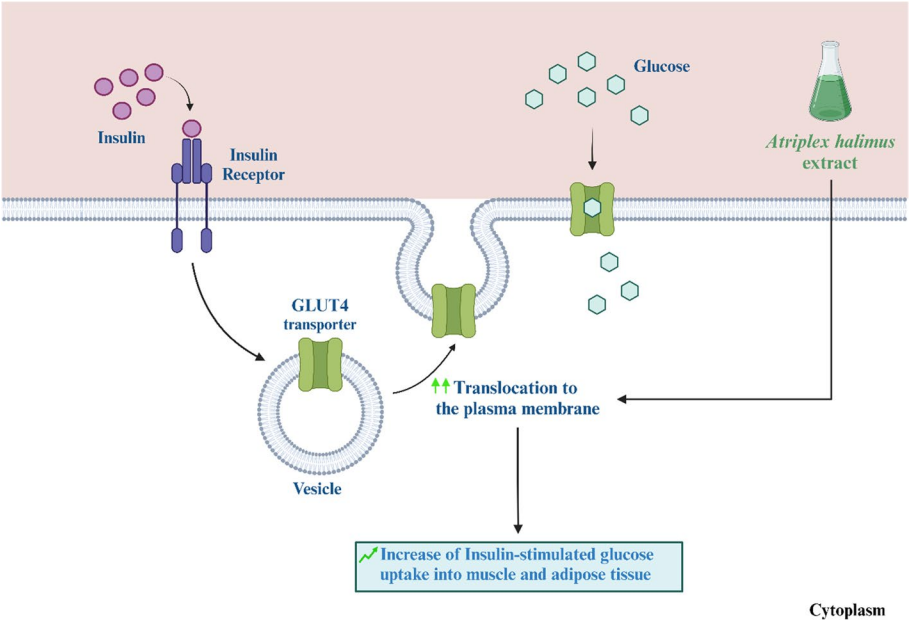


Fig. 2 Proposed antihyperglycemic mechanism of *Atriplex halimus* via modulation of insulin signaling and GLUT4 translocation, adapted from Kadan et al.2013 (created with BioRender.com)

by molecular docking analyses, indicating favorable interactions between identified phytoconstituents and enzyme active sites, thereby reinforcing the mechanistic basis of the observed bioactivity.

Although the antihyperglycemic activity of *A. halimus* is the most extensively documented, the evidence remains methodologically heterogeneous, with diverse diabetes models, varied extract types, and treatment durations ranging from acute single doses to several weeks. Mechanistic investigations examine isolated pathways rather than integrating multiple mechanisms within unified models. This variation, together with the scarcity of toxicological and comprehensive supporting data, makes it difficult to interpret the findings within a single coherent framework and therefore restricts reliable therapeutic claims.

Anti-inflammatory activity

Inflammation is a complex biological response triggered by tissue damage caused by various factors, including infections (bacterial, viral, or fungal), physical injuries, or abnormal immune reactions. The primary goal of this response is to neutralize harmful agents, clear damaged tissue components, and promote tissue repair and healing (Pedone et al. 2017). However, chronic or uncontrolled inflammation can contribute to the development of several pathological conditions, including autoimmune diseases, cardiovascular disorders, and cancer. In this context, *Atriplex halimus* has demonstrated notable anti-inflammatory properties, primarily attributed to its stress-responsive synthesis of phenolic compounds. These compounds have been shown to reduce the expression of key pro-inflammatory mediators, including interleukin-6 (IL-6), interleukin-1β (IL-1β), tumor necrosis factor-alpha (TNF-α), and cyclooxygenase-2 (COX-2), in lipopolysaccharide (LPS)-induced inflammation models. Collectively, These findings suggest the immunomodulatory potential of species (El-Aasr et al. 2016; Zennaf et al. 2022). Fatty acids identified in *A. halimus* also play a crucial role in regulating stress responses in halophytic species, while being recognized as key compounds in the prevention of chronic inflammation through the modulation of NF-κB and PPAR signaling pathways (Faustino et al. 2019). The anti-inflammatory effects of *A. halimus* methanolic extracts have also been linked to their hemostatic activity, which may be due to their ability to stabilize cell membranes and prevent hypotonic-induced hemolysis. This membrane-protective role underscores the plant's capacity to mitigate cellular damage during inflammatory processes (El-Aasr et al. 2016). The species has also shown efficacy in managing urinary tract inflammation and lithiasis (Zennaf et al. 2022).

Evidence for the anti-inflammatory effects of *A. halimus* is still limited and mainly based on studies using LPS-stimulated cells. These experiments often report decreases in cytokines such as IL-6, IL-1β and TNF-α, yet they differ in extract type and experimental conditions, making the findings difficult to integrate. Mechanistic explanations involving NF-κB or MAPK pathways remain largely speculative, since most studies infer their involvement from cytokine changes rather than from direct pathway analyses. *In vivo* inflammation models are lacking, making it unclear whether the observed activity translates to whole-organism responses. Although the available data suggest anti-inflammatory potential, more standardized extracts and rigorous mechanistic investigations are needed to substantiate these findings.

Antioxidant activity

The scientific community, including biologists and chemists, increasingly highlights the detrimental effects of uncontrolled oxidative processes triggered by reactive oxygen species (ROS) formed *in vivo*. ROS play a pivotal role in various pathological conditions and inflammatory disorders. Their accumulation initiates radical chain reactions that degrade essential biological molecules, such as lipids, proteins, and DNA, ultimately resulting in cellular and tissue damage (Finkel 2011). Given these challenges, antioxidants derived from plants have gained significant attention as potential therapeutic agents. Their ability to neutralize ROS and mitigate oxidative stress positions them as crucial components in the development of treatments and preventive strategies against oxidative damage-related diseases. *Atriplex halimus* has been identified as a promising source of bioactive flavonols and flavonoids with notable antioxidant effects. These compounds primarily function by scavenging free radicals, reducing oxidative stress, and preventing oxidative damage to biological macromolecules. In the same study, extracts of species from different regions (Biskra and Mazagran) exhibited distinct antioxidant capacities, reflecting variations in their total antioxidant capacity (TAC), reduction of $ABTS^+$, scavenging of DPPH free radicals, and inhibition of β-carotene oxidation. Remarkably, the extracts demonstrated higher antiradical activity than Trolox in these assays, a finding attributed to their high concentrations of kaempferol and quercetin, key flavonoid compounds characteristic of the genus *Atriplex* (Bylka et al. 2001).

In a recent study, the antioxidant potency of various *A. halimus* extracts was assessed using multiple techniques, including DPPH radical scavenging, $ABTS^+$ decolorization, β-carotene bleaching, TAC, and ion-chelating assays. Among the tested extracts, hydroethanolic extracts, particularly AHHE (*A. halimus* hydroethanolic extract) and AHAE (*A. halimus* aqueous extract), exhibited the highest radical-scavenging activity (Roubi et al. 2023).

In contrast, Benhammou et al. (2009) demonstrated that the ethyl acetate fraction of *A. halimus* displayed the highest potency in scavenging DPPH radicals and reducing ferric iron. This was followed by the butanolic fraction obtained from the leaves and the methanolic extract derived from the stems. Conversely, (Zennaf et al. 2022) reported only moderate antioxidant activity when compared to the reference antioxidant ascorbic acid. In their study, the decoction of *A. halimus* exhibited the highest DPPH radical scavenging activity, followed by the infusion and maceration extracts. Building on this, a more recent investigation found that ethanolic and aqueous extracts of *A. halimus* demonstrated significant antioxidant activity, with strong free-radical scavenging potential (Benmarce et al. 2024). Similarly, *Atriplex halimus* aqueous extract has been shown to mitigate oxidative stress induced by carbon tetrachloride (CCl_4) in a rat model, suggesting its potential in reducing oxidative damage *in vivo* (Slama et al. 2020). A separate study on *A. halimus* collected in Egypt identified a novel compound 5-O-methylquercetin-3-*O*-(6''-*O*-α-rhamnopyranosyl-β-glucopyranoside), which exhibited significant DPPH radical scavenging activity (Amal Kabbash et al. 2012). The essential oil of *A. halimus* also demonstrated antioxidant activity, though its potency was lower compared to standard antioxidants such as ascorbic acid and catechin (Soltani et al. 2023). Furthermore, an *in silico* receptor-ligand docking study confirmed the antioxidant potential of *A. halimus* leaf ethanolic extract, emphasizing its abundance in phenolic compounds such as gallic acid, syringic acid, and trans-ferulic acid (Elbouzidi et al. 2022). These compounds were shown to play a pivotal role in its free-radical scavenging capabilities.

Studies exploring the antioxidant activity of *A. halimus* remain relatively limited and show considerable variation in experimental approach. Extracts differ in solvent polarity, plant part, and geographic origin, all of which influence the total phenolic and flavonoid. As a result, antioxidant capacity varies widely across studies. Most investigations rely on chemical assays such as DPPH, ABTS, FRAP or β-carotene bleaching. These tests provide useful indications of radical-scavenging or reducing ability, but they measure different chemical properties and do not necessarily predict biological relevance. Only a few studies quantify major compounds such as gallic acid, ferulic acid or quercetin alongside activity measurements, making it difficult to determine whether variations in assay performance reflect true differences in phytochemical composition or methodological discrepancies. These studies collectively provide preliminary support but do not allow firm conclusions regarding pharmacological effectiveness. However, the halophytic nature of *A. halimus* characterized by stress-driven metabolic adaptations, provides a significant foundation for an in-depth exploration of the species antioxidant potential.

Cytotoxic and antitumor activity

Antioxidant and anti-inflammatory agents are recognized as key modulators in cancer prevention and therapy (Crawford 2014). In this context, the cytotoxic and antitumor potential of *Atriplex halimus* is supported by its antioxidant and anti-inflammatory effects, largely attributed to its high content of phenolic compounds (El-Aasr et al. 2016). These phytochemicals are suggested to influence signaling pathways involved in apoptosis, cell-cycle regulation, and cell proliferation, and may therefore contribute to both chemopreventive and chemotherapeutic effects (Bakrim et al. 2022).

Among the bioactive constituents investigated, viridiflorol, the predominant compound of the *A. halimus* essential oil, has gained preclinical attention owing to its promising cytotoxic and pro-apoptotic effects against breast (MCF-7), lung (A549), and brain (Daoy) tumor-derived cell lines, inducing apoptosis by over 70% within 24 h at concentrations ranging from 0.03 to 300 µM (Akiel et al. 2022; Soltani et al. 2023). Similarly, kaempferol exerts antiproliferative effects on HepG2 cells and suppresses their migration and invasion by upregulating PTEN, inhibiting miR-21, and blocking the PI3K/AKT/mTOR signaling pathway (Yang et al. 2021).

Shifting to extract-based evidence, studies indicate that leaf extracts can exert dose-dependent cytotoxic effects against several human cancer cell lines, although potency varies markedly with extraction solvent and test model. The ethanolic leaf extract showed cytotoxicity against MCF-7 and MDA-MB-231 breast cancer cells, while it did not display cytotoxicity toward normal peripheral blood mononuclear cells (PBMCs), suggesting a degree of selectivity toward tumor cells (Elbouzidi et al. 2022). More recently, Roubi et al. 2023 reported that the hydroethanolic leaf extract exhibited marked cytotoxic effects on HepG2 and MDA-MB-468 cells, whereas the aqueous leaf extract showed only moderate activity. Elbouzidi et al. 2022 suggested based on *in silico* molecular docking analyses potential interactions between several bioactive compounds in *A. halimus*, including myricetin, catechin derivatives, and chlorogenic acid, with multiple cancer-related targets, such as carbonic anhydrase isoforms, DNA topoisomerase IIα, and other enzymes involved in cellular metabolism. Additionally, nanotechnology-based formulations have also been explored. MTT assays showed that gold nanoparticles synthesized using *A. halimus* inhibited the growth of human breast cancer MCF-7 cells (Eltaweil et al. 2022).

Reports on the cytotoxic effects of *A. halimus* are encouraging; however, the evidence remains fragmented and very limited. Most studies rely on cell viability assays and selected markers of oxidative stress or apoptosis, without clarifying the underlying mechanisms across different cell lines or extract types. Further in-depth investigations are required to determine whether these activities can translate into meaningful antitumor effects. Future studies should also incorporate antiproliferative assays, such as cellular adhesion and colony formation experiments, to better evaluate long-term effects on cancer cell behavior.

Antimicrobial activity

Infectious diseases were a leading cause of illness and death worldwide at the turn of the twentieth century (Gasu et al. 2018). Over the years, however, the overuse and improper administration of antibiotics have significantly contributed to the emergence of antibiotic-resistant pathogens, affecting both humans and animals. Additionally, many antibiotics are associated with harmful side effects, creating an urgent need for alternative treatments. Medicinal plants, such as *Atriplex halimus*, represent a resource for developing safer and more effective antimicrobial agents. Accordingly, the antimicrobial properties of the species have been extensively studied, revealing a broad-spectrum of antibacterial activity. Methanolic extracts revealed variable efficacy against different bacterial strains. In more recent research, ethanol extracts of *A. halimus* demonstrated substantial inhibition of *Helicobacter pylori* growth. Methanolic extracts were found to be even more potent against this pathogen (Alkofahi et al. 2023). The essential oil of *A. halimus*, primarily composed of viridiflorol (40.23%) and phytol (18.24%), has also been linked to antimicrobial effects (Soltani et al. 2023). As is often the case with complex mixtures, attributing these effects to individual components is difficult, since both major and minor constituents may contribute and potential synergistic or antagonistic interactions between compounds should be considered. Other isolated molecules were active against Gram-negative bacteria such as *E. coli* and *Acinetobacter baumannii* and Gram-positive bacteria including *S. aureus*, *Streptococcus pyogenes* and *E. faecalis*. Several of these compounds also inhibited *Candida* species, indicating broad-spectrum antimicrobial potential (Zennaf et al. 2022). Nanotechnology has been explored as an approach to enhance the antimicrobial effects of *A. halimus* Platinum nanoparticles synthesized using *A. halimus* (At-PtNPs) showed clear antibacterial activity against *K. pneumoniae* and inhibited the growth of *E. coli*, but did not affect Gram-positive bacteria (Pedone et al. 2017; Eltaweil et al. 2022). The antibacterial effect of these nanoparticles is thought to involve alterations of the bacterial cell membrane and disruption of essential cellular processes. The selective pattern of activity observed for At-PtNPs requires further study to optimize their use and to clarify their mechanisms of action.

Other pharmacological activities

The neuroprotective effects of *Atriplex halimus* have been linked to inhibition of acetylcholinesterase (AChE). AChE is a key cholinergic enzyme that hydrolyses acetylcholine to acetic acid and choline at postsynaptic neuromuscular junctions (Fulton and Nachmansohn 1943). Inhibitors of this enzyme are widely used in the treatment of neurological disorders such as Alzheimer disease, senile dementia, ataxia and myasthenia gravis (Benhammou et al. 2009). Methanolic extracts of *A. halimus* inhibited AChE in a colorimetric assay, with IC_{50} values between 147.2 and 1536.9 µg/mL (Guedri et al. 2024). This activity is likely related to phenolic acids, flavonols and flavonoids present in the leaves, compound

classes known to inhibit AChE in other plant species (Chaowuttikul et al. 2020; Nassief et al. 2021). These findings suggest that phenolic constituents of *A. halimus* may provide neuroprotective benefits.

Conclusion and future perspectives

Alongside its impressive ecological adaptability, *Atriplex halimus* is an important medicinal halophyte with a chemically rich phytochemical profile that is not yet fully explored, as new constituents continue to be reported. The species is characterized by diverse polyphenolic constituents, including phenolic acids, flavonoids and their glycosides, together with terpenoids, fatty acids, sugars and essential-oil components such as viridiflorol and phytol, which provide a plausible basis for its reported biological activities. From a mechanistic standpoint, preclinical studies indicate that the antihyperglycemic activity is associated with inhibition of α-amylase and α-glucosidase, modulation of insulin-related signalling and increased GLUT4 translocation, while hepatoprotective-like effects have been observed in toxicant-induced liver injury. Antioxidant activity has been consistently demonstrated *in vitro* and, to a lesser extent, *in vivo*, and anti-inflammatory effects involve the downregulation of key mediators such as IL-6, IL-1β, TNF-α and COX-2 in LPS-induced models. Cytotoxic and antitumor activities are linked to ROS-mediated apoptosis, caspase-3 activation, modulation of p53, Bax and Bcl-2, and G_2/M cell-cycle arrest, with both crude extracts and individual constituents, including viridiflorol and flavonoids such as quercetin and kaempferol, contributing to these effects. Additional antimicrobial, neuroprotective and antiparasitic activities, together with emerging nanotechnology-based formulations, further broaden the pharmacological landscape of the species.

Although these findings are encouraging, the current evidence base remains predominantly preclinical and methodologically heterogeneous. Many studies rely on crude or only partially characterized extracts derived from insufficiently documented plant material, employ non-standardized extraction procedures and provide limited chemical profiling, often restricted to global phenolic or flavonoid content. Experimental designs frequently use single doses, short exposure times and a narrow panel of biochemical endpoints, while data on pharmacokinetics, toxicity, oxalate burden and metal accumulation are scarce, despite clear reasons for concern. Synergistic or antagonistic interactions among the numerous phytoconstituents are largely unexplored, and clinical data are entirely lacking. To bridge the gap from traditional use to evidence-based phytotherapeutic or nutraceutical applications, future research should prioritize standardized and chemically defined preparations, integrative mechanistic studies in disease-relevant *in vitro* and *in vivo* models, systematic safety and pharmacokinetic evaluation and, ultimately, carefully designed early-phase clinical trials. Only on this foundation will it be possible to determine whether *A. halimus* can evolve from a promising experimental resource into a safe and clinically meaningful therapeutic option.

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Declarations

Conflicts of interest The authors declare no competing interests.

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