

ADAPTOGENS : STRESS-MODULATING PLANTS IN MODERN PHARMACY

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Abstract :

Adaptogens are plant remedies that promote homeostasis and increase non-specific stress resistance, a physiological condition linked to neuroendocrine-immune system issues. These herbs, which contain pharmacologically active phytonutrients like flavonoids, phytosterol, alkaloids, vitamins, lignanes, ecdysones, and triterpenoids, are used in traditional medical systems and mainstream medicine to treat stress-induced and aging-related disorders. Adaptogens are rich in a range of biologically active compounds, including flavonoids, phytosterols, alkaloids, vitamins, lignans, ecdysones, and triterpenoids, all of which are significant in medicine. These substances are widely used to improve physical stamina and manage stress. Adaptogens and immunomodulators like *Rhodiola rosea*, *Withania somnifera*, *Tinospora cordifolia*, *Bacopa monnieri*, *Emblica officinalis*, *Glycyrrhiza glabra*, *Asparagus racemosus*, *Ocimum sanctum*, and *Panax notoginseng* are known for their strong antioxidant and anti-cancer properties, owing to the diverse biologically active compounds they contain. They control important stress mediators and physiological markers, such as glucose, cortisol, nitric oxide (NO), cholesterol, and triglycerides. Scientific evidence supports the use of active secondary metabolites present in adaptogens.

Keywords : Adaptogens, HPA axis, stress, rhodiola, withania, ginseng, traditional medicine system.

1.Introduction:

Phytoadaptogens (often referred to as ‘adaptogens’) are a class of herbal medicines commonly used by herbalists – in multiple traditional medical systems – to assist in reducing the negative impact that chronic stress has on health[1]. Adaptogens are synthetic compounds (bromantane, levamisole, aphobazole, bemethyl, etc.) or plant extracts that have the ability to enhance the

body's stability against physical loads without increasing oxygen consumption[2]. The term adaptogen refers to "metabolic regulators which increase the ability of an organism to adapt to environmental stressors and prevent damage to the organism by such stressors". This definition was suggested and agreed upon at an International Conference on Adaptogens in Gothenburg, Sweden in 1996[3]. The definition of "adaptogen" was first introduced in the mid-twentieth century by the Soviet toxicologist Lazarev[4]. During World War II, many stimulants were administered to pilots and submarine crew members to increase their mental and physical performance. Early research on *Schisandrachinensis*' stimulating and tonic effects was published in Soviet Union military journals during WWII. During the period 1950-60, the idea of using herbal medicinal plants to increase stamina and survival in harmful environments was developed, and the toxicologist Lazarev introduced a new concept of "adaptogens" to describe compounds which could increase "the state of non-specific resistance" in stress[5]. Adaptogens might normalize chronically elevated cortisol/corticosterone levels, presumably through their interaction with the glucocorticoid receptors, helping to restore the balance of the HPA-axis[6]. Adaptogens have recently been defined as natural metabolic regulators that increase the ability of the organism to adapt to environmental factors and to avoid damage from such factors[7]. Almost every plant preparation that has been shown to have some beneficial effects can be classified as an adaptogen.. Because the premise of adaptogenic action requires further explanation, this term is not accepted in clinical or pharmacological terminology in the European Union and has been deemed inappropriate for marketing authorization[8]. The usage of adaptogens has grown in popularity because they are available without a prescription. For example, according to the National Institutes of Health Office of Dietary Supplements, there are currently more than 1,300 products containing *Withaniasomnifera* in the United States markets alone and by 2019, preparations derived from this plant had become the fifth most popular dietary supplement[8]. The beneficial stress-protective effect of adaptogens is related to homeostasis regulation via several mechanisms of action associated with the hypothalamic-pituitary-adrenal axis, as well as the control of key stress mediators and biochemical markers such as nitric oxide (NO), cortisol, cholesterol, triglycerides, glucose, and so on[9]. Stress is a substantial part of life, however Stress is "the nonspecific response of the body to any demand", as defined by Hans Selye, the founder of stress theory [10]. He referred to this theory as the "general adaptation syndrome,"¹ a stress model based on physiology and psychobiology. Stress

can range from short-term daily hassles to long-term unsettling conditions that can compromise an individual's health and well-being[11]. chronic stress or ongoing exposure to stressors can disrupt the balance of the HPA axis, resulting in a prolonged elevation of cortisol levels[12]. Stress may be both positive and pro-adaptive and is a part of everyone's life. Long-term exposure to stressful events or surroundings is detrimental to mental health and stands as a risk factor for numerous neuropsychiatric illnesses such as depression, mood swings, and anxiety. [13]. Stress can become chronic and function as a trigger for chronic degenerative diseases (such as type 2 diabetes, hypertension, hormonal imbalances, and obesity) if the human adaptive response fails to address it[14]. In 1948, extensive research conducted in the former Soviet Union demonstrated that adaptogens enhance physical and mental performance during periods of stress. These substances proved beneficial in treating conditions like asthenodepressive syndrome and neurasthenia, which are marked by symptoms such as fatigue, weakness, irritability, headaches, general discomfort, insomnia, lack of appetite, cognitive and memory issues, as well as stress, depression, and anxiety. [15]. Stress management calls for emotional and physical adjustments to regulate and lessen the tension brought on by stressful circumstances. Its pharmacological treatment includes antidepressants or tranquilizers (*e.g.*, benzodiazepines, sertraline)[14].the adaptogenic herb ashwagandha (*Withania somnifera*) reduced urinary tribulin in stressed animals[16]. The current four fields of adaptogen research are as follows: (a) phytochemistry: the separation and structural clarification of the active components of adaptogenic plants; (b) biochemistry and molecular biology: the mechanisms of adaptogens' stress-protective activity at the molecular and cellular levels; (c) clinical and experimental pharmacology: the effectiveness and safety of adaptogens in both human and animal stress-related disorders; and (d) pharmaceutical development of herbal preparations/products with proven medicinal uses in evidence-based medicine.[17]. The adaptogens affected many genes playing critical roles in the modulation of adaptive homeostasis, indicating their ability to modify gene expression to prevent stress-induced and aging-related disorders [18]. Adaptogens reduce the intensity and negative impact of the stress caused by mental tension, emotional difficulties, poor lifestyle habits, disease and infection, pollution and other factors[19]. Prior research has shown how certain adaptogens affect important mediators of the stress response and pathways that modulate longevity. Overall, more than 70 plants have been described as adaptogenic [20].the cross-over of herbal concepts 'tonic' and 'adaptogen'

may represent the link between traditional use and modern terminology, and provide a foundation for further examination of the historical or traditional use of adaptogens[21]. The stressful human lifestyle of the 21st century has given rise to a wide variety of lifestyle diseases like hair loss, obesity, high blood pressure and fatigue. Chronic fatigue syndrome (CFS), also referred to as Royal Free disease [22]. Adaptogens are essentially prescribed for prophylactic purposes. However, they can also be used by healthy individuals to improve their cognitive and physical performance, in which case their efficacy is questionable[23].

2. Historical background:

2.1. Traditional uses of adaptogens:

From East Asian medicine to Western herbal medicine, many civilizations and regions of the world have long used herbal medications with adaptogenic properties in the context of adaptogenic activity. [24]. The emergence of a global formalisation of traditional medicine (TM) concepts via the World Health Organisation (WHO) highlights the importance of standardisation of TM concepts[21]. Historically, the notion adaptogens (phytoadaptogens) derived from an extensive survey and screening of active substances of botanical origin during 1960–1980 in USSR [3]. A team of researchers led by Hildebert Wagner, George Wikman, and Alexander Panossian conducted extensive research on adaptogens in the 1990s and put out the following definition: Adaptogens are naturally occurring bioregulators that improve the body's capacity to adjust to external conditions and prevent harm from them. [25]. The applications of these adaptogens have been known from the ancient times but the term adaptogens was introduced by a Russian scientist Lazarev in 1947 after an adaptogenic compound namely Dibazol (2-Benzylbenzimidazol) was discovered[26]. In mountain villages of Siberia, a bouquet of roots is still given to couples prior to marriage to enhance fertility and assure the birth of healthy children. In Middle Asia, R. rosea tea was the most effective treatment for cold and flu during severe Asian winters[27]. The Araliaceae family of plants, whose roots are frequently used as medicinal parts, are more prevalent in this list. The Korean ginseng [Panaxginseng] whose roots are used for various purposes, is the best known example of adaptogen plant[25]. Adaptogenic herbs include active plant elements known as phytochemicals. Examples of phytochemicals that contribute to our wellbeing are triterpenes, phenylpropanes, oxylipins and polysaccharides[28]. Ayurveda, the world's oldest medical system and a science of life, takes a holistic approach to health and

disease, emphasizing the preservation and promotion of good health as well as disease prevention through healthy lifestyle habits[29]. The most extensively researched are *Aralia mandschurica*, *Eleutherococcussenticosus*, *Rhodiolarosea* and *Schizandrachinensis*. Of these, *Rhodiolarosea* has the most pronounced effect on mental fatigue during stress and strain[30].primarily in Russia and former USSR that preparations based on *Rhodiolarosea* rhizome and the glycoside salidroside (synonym: rhodioloside, rhodosine) have gained an established position and use within the official medicine. The use in medicine in the former USSR/Russia, goes back to a number of pharmacological and clinical investigations in the early 1960, which demonstrated primarily stimulant and anti-stress actions[31].*R. rosea* has been used for centuries in the Republic of Georgia and Siberia to enhance fertility among the people living at high altitudes in the Caucasus Mountains[32].Immunostimulating plant based studies showed that oral or intravenous administration of plant adaptogens proffers the prospect to reinstate immune competency during such immune allied alterations and immune compromised conditions[33]. *R. rosea* is a plant frequently used in traditional medicine in Eastern Europe and Asia for its "adaptogenic" qualities, meaning its ability to raise bodily resistance to physical, chemical, or biological stressors in experimental animals and people[34].

2.2.Development and Recognition in modern medicine:

Adaptogen as a new concept has become more generally recognized during the last 10 years and has recently been used as a functional term by health authorities (FDA, 1998)[35].This phenomenon of adaptation to repetitive low-level stress was first described by Hans Selye in 1936 using rats exposed to low temperatures, low oxygen tension, muscular exercise, adrenaline, and morphine[36]. The term 'adaptogen' was first used formally and scientifically In the late 1940s, Russian toxicologist N. V. Lazarev coined the term "adaptogens" in 1947, initially referring to a synthetic compound (dibazol) that was found to enhance "non-specific resistance to stress." The idea of adaptogens as herbal substances that could boost the body's "non-specific resistance" to stress was formalized in Russia between 1950 and 1960[37].Studies performed more recently, primarily in Germany and Japan , have shown a high level of consistency with the results of the Russian research[35]. Almost two decades later, the word 'adaptogen' was more explicitly defined when Brekhman and Dardymov (1969) proposed specified criteria that a chemical must meet to be classified as an adaptogen. [38].Some adaptogenic plants have been

used in traditional Chinese medicine and Ayurveda for centuries to promote physical and mental health, improve the body's defense mechanisms, and enhance longevity[36]. A review article by Brekhman (1969), one of the pioneers in plant adaptogen research, summarized almost 20 years of Russian research and made Western scientists aware of the research and the concepts[39].

3.Mechanism of action :

3.1.Physiological effects :

Adaptogens serve to establish homeostasis, especially against stress, and stress alleviation is promoted by several sorts of mechanisms directly or indirectly by maintaining the levels of hormones such as cortisol, adrenaline, ACTH, and CRH [40]. Adaptogens act as challengers and mild stressors (stress-mimetics), giving rise to adaptive and stress-protective effects mainly associated with the HPA axis[41]. Adaptogens can increase the effectiveness of adrenal gland secretion, thereby abolishing excess hormone production[42]. The mode of action of corticosteroids is known to regulate carbohydrate, lipid, protein and nucleic acid metabolism, in order to mobilize the resources of the organism under stress to increase its resistance to damaging factors[43]. Stress activates the release of CRH from the hypothalamus, which in turn triggers the release of ACTH from the pituitary, leading to the secretion of adrenal hormones and NPY to mobilize energy and manage stress. To prevent an excessive response, cortisol is released from the adrenal cortex, where it binds to glucocorticoid receptors (GR) in the brain, initiating feedback regulation. [44]. Glutamate, acetylcholine, and serotonin postsynaptic receptors activate intracellular signaling pathways and transcription factors, leading to the expression of neuroprotective proteins such as antiapoptotic proteins, brain-mitochondrial uncoupling proteins (UCPs), and BDNF[45]. The stress system is thought to play a primary role in the body's responses to repeated stress and adaptation by balancing the releases of adrenaline (the 'switch-on' hormone), corticosteroids (the feedback regulatory 'switch-off' hormones that protect an organism from overreaction), and nitric oxide (which modulates the biosynthesis and effects of many hormones)[46].

3.2.Molecular And Cellular Mechanism :

laboratory work shows at least 88 of the 3516 genes identified as being regulated by adaptogens were closely associated with adaptive stress response and adaptive stress-response signalling

pathways (ASRSPs)[47]. Adaptogens stimulate cellular and organismal defense systems, activating intracellular and extracellular signaling pathways and expression of stress-activated proteins and neuropeptides, and enhancing survival against oxidative stress[48]. In general, herbal mixes achieve their bioactivities through synergistic interactions between individual components. This synergism can be attributed to the fact that medicinal herbs contain many different phytochemicals, which may mutually influence each other's activity[49]. Adaptogens' stress-protective action is associated with the hypothalamic-pituitary-adrenal axis and the regulation of stress response mediators shared by all cells. Adaptogens function as low molecular weight "vaccines" or stress-mimetics, causing moderate activation of the stress system in order to cope with more severe stress[50]. Adaptogens have a diverse effects on cancer patients' health and well-being. First, they can modulate biological responses, modify immunological pathways, and thereby nonspecifically boost the human body's immunity. Second, adaptogens can promote bone marrow production, increase blood cell counts, and reduce infection[51]. Plant adaptogens enhance the neural system by mechanisms that are completely distinct from those of typical tonics. They are involved with metabolic regulation of several aspects of the stress system and modification of stimulus-response coupling[52]. selected adaptogenic extracts significantly attenuated FEC-induced regulation of more than 100 genes involved in the activation of neuronal death and inhibiting neurogenesis[53]. According to conventional wisdom it is reasonable to refer agents from actoprotectors' class to synthetic adaptogens and to regard their strong actoprotective effect as one of their components of adaptogenic action adaptogens of natural origin also can be referred to actoprotectors if they have potent influence on physical work capacity[54]. Adaptogens are natural plant growth regulators that help organisms adjust to changing conditions and avoid damage. adaptogens may have a direct impact on most facets of physical health and psychological state and, moreover, may indirectly improve aspects of social and environmental domains[55].

4.Common AadaptogenicPlants :

4.1.Rhodiolarosea :

Rhodiola rosea L. (Crassulaceae), commonly referred to as golden root or rose root, is a perennial herb that grows in high-altitude regions of the Arctic and mountainous areas across Europe and Asia. The roots of *R. rosea* have been traditionally used as a tonic and adaptogen in

Russia and as a hemostatic agent in Tibetan folk medicine. Various pharmacological effects of the roots of *R. rosea* have been reported, such as improvement of the memory and learning abilities, anti-stress and anticancer effects, etc [56].

4.1.1 Active compounds : *Rhodiola* rhizomes contains essential oils, fats, waxes, sterols, glycosides, organic acids (oxalic, citric, malic, gallic, succinic), phenolics including tannins and proteins[57]. A range of antioxidant compounds have been identified in *Rhodiola rosea* and acid), and flavonoids (catechins and proanthocyanidins)[58]. the rhizomes of *R. rosea*, we identified 10 components: salidroside, tyrosol, (+)-catechin, [epigallocatechin gallate](#), rosarin, rosavin, rosin, cinnamyl alcohol, rhodiosin, rhodionin[59]. Currently, more than 40 chemical compounds have been extracted from numerous *Rhodiola* plants. Among them, the main pharmacologically active ingredients are [salidroside](#) and its [aglycone tyrosol](#) [60]. The *Rhodiola rosea* extract named *Rhodiola* 5% is commercially available at Indena SpA (Milan, Italy) from the roots of *R. rosea* and standardized for 5% of rosavins, a class including rosarin (1), rosavin (2), and rosin (3), and for 1.8% of salidroside (4) [61].

4.1.2 Clinical evidence and application : *Rhodiola rosea* L. (Crassulaceae) is an [adaptogen](#) plant also known as arctic root, It is traditionally used in Eastern Europe and Asia to stimulate the nervous system[62]. *Rhodiola Rosea* extracts (RRE) stimulate the brain and increase the concentration level of [neurotransmitters](#) such as [norepinephrine](#) (NE), serotonin (5 H T) [acetylcholine](#) (Ach), and Dopamine (DA),⁶⁷ At the cortical and [brainstem](#) level it was demonstrated that sub-chronic treatment (10 days) with RRE increased the concentration of serotonin[63]. *Rhodiola rosea* is used as stimulant for the central nervous system (CNS), to enhance work performance, longevity and resistance to high altitude sickness, and to restore from fatigue and to care symptoms of asthenia subsequent to intense physical and psychological stress[64] *Rhodiola rosea* appears to relieve many of the neuropsychological symptoms reported by menopausal women, including fatigue, anxiety, depression, cognitive dysfunction, memory deterioration, impaired executive functioning, and stress intolerance[65]. *Rhodiola rosea* is a medicinal plant with numerous health advantages, including exhaustion, anti-inflammatory, anti-neoplastic, antihepatotoxic, and nerve-protective properties. It has been employed as a functional agent in Asian folkloric medicines, particularly traditional Chinese medicine, since ancient times [66] Polysaccharide is one of the key active components with antioxidant, immunological

modulation, anti-inflammatory, and anti-diabetic properties.. Furthermore, many researchers have shown that natural polysaccharides have an inhibitory effect on the proliferation of various tumor cells[67]. *R. rosea* prevents exercise-induced ATP decrease in mitochondria after exhaustive swimming[68]. *R. rosea* extracts have been reported to reduce also behavioral responses evoked by central CRF administration, such as CRF-induced anorexia *R. rosea* extract influence the expression molecular chaperones particularly Hsp70 is up-regulated by *R. rosea* extracts and is responsible for inhibition of NO synthase II gene and interaction with glucorticoid receptors[69]. *R. rosea* ingestion can improve cognitive function, reduce mental fatigue, promote free radical mitigation, and has anti-oxidative effect and neuroprotective effect, and increase endurance performance, and learning and memory[70]. The adaptogenic efficacy of RR in minimizing muscle injury during heavy exercise for athletes remains appealing. For example, report RR supplementation decreased exercise-induced inflammation and muscle damage during a 6-day period of intensified exercise in untrained subjects[71]. Modern pharmacological studies showed that *Rhodiola* has many functions such as anti-anxiety, anti-aging, anti-depressant, immune regulation, and hepatoprotection. Salidroside is nontoxic and harmless to the human body and conforms to the life philosophy of modern people, which is applied to daily chemical products such as cosmetics and detergents[72]. *Rhodiola* spp. have been developed into skincare products that exhibit effects such as delaying skin aging, moisturizing, and enhancing complexion, reducing dullness and yellowness[73]. the oligomeric proanthocyanidins from root of *Rhodiola rosea* (OPCRR) exhibited significant free radical-scavenging activities, antioxidant activities *in vivo* and lipid lowering effects[74].

4.2.Ashwagandha(withaniasomnifera):

Ashwagandha (*Withania somnifera*) commonly referred to as "Indian Ginseng" or "Winter Cherry," is a member of the Solanaceae family [75]. It is one such essential medicinal plant and has been used as an Ayurvedic rasayana since ancient culture[76]. Ashwagandha is a herb natively originated in Asia, particularly India, and found in the Middle East and parts of Africa [77].

4.2.1Active compounds : The chemical composition of ashwagandha has been extensively studied and found several groups of bioactive chemical constituents such as flavonoids, tannin, alkaloids, sitoindosides, glycosides, withanilic[78]. the phytochemical constituents such as

alkaloids, steroidal lactones, saponins, glycol-withanolides present in it [79]. Several withanolides, including withaferin A, withanolide A, withanoside IV, sitoindosides, and alkaloids, have been discovered and segregated from WS. These compounds are mainly localized in mature leaves and roots[80]. phytoconstituents of *Ashwagandha* are , withanoside I-VII, withasilolide A-F, glucosomniferanolide, withasomnilide, withasomniferanolide, withanamide A-I, somniferanolide, somniferawithanolide, somniwithanolide, somniferine, pseudo-withanine[81]. Withanolides such as Withanone (WN), Withanolide-D, and so on are naturally occurring C28 steroids, built on an ergostane skeleton functionalized at carbons 1, 22, and 26[82].

4.2.2 Clinical evidence and applications : Ashwagandha (ASH) has been used for treatment of various neurological disorders like memory and cognitive function (Medhya), anxiety (chinta), Parkinson's disease (Kampavatha), sleep disorders (Nidranasa) etc.[83] A broad spectrum of pharmacological activities, occurring at different concentrations (μg to mg), includes promoting apoptosis, inducing cytotoxicity, inhibiting cell division, and exhibiting anti-metastatic and anti-angiogenic effects. Notably, they display anti-proliferative activity against cancer cell lines associated with colon, lung, breast, pancreatic, and prostate cancers[84]. Extracts of Ashwagandha are utilized for remedies against inflammation, arthritis, diabetes, stress, asthma, and hypertension [85]. In Indian medicine, ASH is considered one of the main herbal components of geriatric tonics, and is regarded as aphrodisiac, narcotic, diuretic, anthelmintic, astringent, thermogenic, and stimulant[86]. WS root extract enhances cognitive processes and augments mental recall capacity following diabetes, amyloid β , scopolamine and foot shock stress related memory loss[87]. Ashwagandha, including its ability to cure hiccups and feminine problems. The ethnomedicinal usage of this plant indicated as per 'Ayurveda' texts as kṣaya (~pthisis), daurbalya (~weakness), vātaroga (disorders of vāta), śoṭha (~swelling), and klaibya (~impotency)[88]. Pre-clinical and clinical investigations have shown that Ashwagandha roots and extracts have adaptogenic, immunomodulatory, anxiolytic, anti-stress, anti-inflammatory, anti-bacterial, anti-aging, cardioprotective, sleep disturbance, hypothyroidism, and other properties [89]. Ashwagandha can regulate the processes of metabolism, foster homeostasis, and revitalize the body as an adaptogen.[90]. *Ashwagandha ghrita* (AG) is an

effective *ghrita* formulation beneficial for treatment of weakness, gynaecological disorders, general debility and infertility[91].

4.3.ginseng [panax ginseng]

Ginseng, a shade-requiring perennial herb with fleshy roots and green oval-shaped leaves, refers to several plant species in the *Panax* genus[92]. the *Panax* genus in the *Araliaceae* family, has been a staple in East Asian traditional medicine for thousands of years [93]. The ginseng root is the main part of ginseng used in medicine[94]. This remarkable herb has earned the title "king of herbs" and holds significant value as a traditional herbal medicine and essential raw material for healthcare products in China [95].

4.3.1Active compound : *ginseng's* various effects are exerted by multiple ingredients, making it challenging to identify active compounds and their key mechanisms[96]. Main components of *P. ginseng* are saponins, which include protopanaxadiol (PPD)- and protopanaxatriol (PPT)-type ginsenosides[97]. The ginsenosides have been characterized or isolated from the roots and rhizomes of *Panax ginseng* are helpful for us to characterize the selected ligands[98]. The percentage of various ginsenosides in ginseng total saponins were as follows: ginsenoside Ra (2.91%), ginsenoside Rb1 (18.26%), ginsenoside Rb2 (9.07%), ginsenoside Rc (9.65%), ginsenoside Rd (8.24%), ginsenoside Re (9.28%), ginsenoside Rf (3.48%), ginsenoside Rg1 (6.42%), ginsenoside Rg2 (3.63%), ginsenoside Rg3 (4.70%), ginsenoside Ro (3.82%), and other minor components.[99].

4.3.2clinical evidence and applications : Ginseng may provide anti-aging and life-extending benefits. Current pharmacological investigations have confirmed the anti-ageing properties of ginseng via processes including scavenging oxygen free radicals and controlling endocrine function and immunity[100]. the root of *Panax ginseng* has been traditionally used for the treatment of central nervous system diseases, such as learning and memory deficits, mood disorders, etc .[101]. . Ginseng is renowned for its various functions, including enhancing vitality, strengthening pulse, invigorating the spleen, and benefiting the lungs, thereby promoting body fluids, nourishing blood, soothing nerves, and enhancing wisdom[102]. *Panax ginseng* C.A. Mey (PG), a traditional Chinese medicine, has been used for thousands of years. PG generates a "Qi-invigorating" action, which serves to avoid oxidative stress and optimize energy

metabolism.[103]. Ginseng flowers have a different of therapeutic effects, involving anti-inflammatory, antioxidant, immune system modulator, and antineoplastic activity. Ginsenosides have been demonstrated thus far to be potential therapeutic agents for the management of a variety of inflammatory illnesses and have been crucial in the treatment of liver problems[104]. clinical and animal studies supports the therapeutic potential of ginseng in relieving fatigue[105]. Panax ginseng has been widely used around the world as both a medicinal treatment and a dietary supplement for various health issues. It is highly regarded in Eastern medicine for enhancing overall health, boosting vitality, and promoting longevity. Additionally, P. ginseng has a therapeutic effect on and is an attractive alternative for patients with insomnia, some of whom are reluctant to use traditional medications[106].

4.4.Holy basil :

Holy basil, also known as tulsi (*Ocimum tenuiflorum* L., synonym *O. sanctum* L.; family Lamiaceae), is an aromatic perennial herb with sacred applications in Hinduism and several defensive and medicinal properties in Ayurveda. It is widely distributed and cultivated in Tropical Asia. Various forms of holy basil were found. They are usually noticeable by leaf size, leaf color, aroma, and pubescence.[107]. *Ocimum Sanctum* (OS) often known as Holy Basil or Tulsi, has contributed essential value to herbal treatments[108]. For thousands of years, it has been used in Ayurvedic and Siddha therapy to treat infections, skin and liver disorders, and prevent snake and scorpion bites. The leaves of *O. sanctum* are the source of an essential oil which has numerous medicinal properties.[109].

4.4.1Active compounds : Basil oil is rich in valuable bioactive compounds, consisting of a diverse blend of phenylpropanoid and terpenoid derivatives. Two key compounds found in basil oil are methyl eugenol and β -caryophyllene[110]. The plant leaves include nutrients like protein, vitamins, and minerals. Basil leaves have also been claimed to be high in vitamins B and C. Basil is also rich in some valuable phytochemicals such as terpenoids, essential oils, phenols, flavonoids, and anthocyanins[111].

4.4.2Clinical evidence and applications : The plant's medicinal and curative capabilities are complemented by its culinary usage as a flavorant and aromatic, increasing its commercial worth. The rich essential oils extend modern applications that include religious, therapeutic,

gastronomic, nutritional, aromatic, and ornamental uses (Tangpao et al., 2018). Moreover, essential oils from Holy basil have insecticidal, mosquito repellent, and antileishmanial properties and are widely used as food additives and perfumes[112]. Holy basil leaves (*Ocimum tenuiflorum* L) are well-known herbs available throughout Malaysia including neighbouring countries and they are commonly used for the treatment of various diseases including diabetes mellitus[113]. Holy basil (*Ocimum sanctum*) is known as tulsi and is reported to have antibactericidal and insecticidal properties[114]. The plant has been shown to be useful against respiratory syndrome, colds, fevers, indigestion, diarrhea, headaches, bronchitis, coughs, hysteria, and many other conditions. Eugenol is an active ingredient found mostly in the herb's leaves and inflorescence, which contributes to its therapeutic potential as a pain reliever and decreases blood glucose levels in type 2 diabetics. Sacred basil has remained largely as a house hold species in India for many years[115]. *Ocimum gratissimum* is a fragrant, upright, hairy herb commonly used to relieve nasal congestion, make flavorful teas, repel mosquitoes, and treat snake bites. A review of existing literature has shown that *O. gratissimum* possesses antimicrobial properties against both gram-positive and gram-negative bacteria, antifungal effects against *Alternaria alternata* and *Alternaria tenuissima*, as well as insecticidal and repellent actions against various insect species. Several studies have shown a repellent effect on pests when the crop was intercropped with *Ocimum* specie[116] *O. sanctum* was originally described as a medicinal plant in ancient Ayurvedic literature such as Charaka Samhita, Sushruta Samhita, and Rigveda (3500-1600 BCE), and it was traditionally used to cure poisoning, impotence, and arthritis. Currently, it is mostly utilized as a nerve tonic, as *O. sanctum* has the ability to adapt an organism to stress and hence is classed as a major adaptogen. the therapeutic potential of *O. sanctum* is much broader, and it is currently being studied for its anti-cancer, antioxidant, anti-inflammatory, radiation protective, anti-microbial and anti-stress properties[117].

5.Clinical applications :

5.1.stress related disorders:

1. Anxiety and Stress Relief: Adaptogens like ashwagandha, rhodiola, and ginseng have been shown to reduce anxiety and stress levels.

2. Depression: Adaptogens like St. John's Wort, S-adenosylmethionine (SAME), and omega-3 fatty acids have been used to treat depression.

3. Attention Deficit Hyperactivity Disorder (ADHD): Adaptogens like ashwagandha, rhodiola, and ginseng may help improve focus and attention in individuals with ADHD.

5.2.Physical health :

1. Fatigue and Energy: Adaptogens like ginseng, ashwagandha, and rhodiola can help increase energy levels and reduce fatigue.

2. Sleep Disorders: Adaptogens like valerian root, melatonin, and ashwagandha can help regulate sleep patterns and improve sleep quality.

3. Exercise Performance and Recovery: Adaptogens like ashwagandha, rhodiola, and ginseng may help improve exercise performance, reduce muscle damage, and enhance recovery.

5.3.Cognitive function and performance :

1. Neuroprotection: Adaptogens like ashwagandha, rhodiola, and ginseng may help protect against neurodegenerative diseases like Alzheimer's and Parkinson's.

2. Cognitive Function: Adaptogens like ashwagandha, rhodiola, and ginseng may help improve cognitive function, including attention, memory, and executive function.

5.4.Immune system and inflammation

1. Immune System Support: Adaptogens like ashwagandha, rhodiola, and ginseng may help support immune function and reduce inflammation.

2. Anti-Inflammatory Effects: Adaptogens like turmeric, ginger, and ashwagandha have anti-inflammatory properties, which may help reduce inflammation and improve symptoms in conditions like arthritis.

5.5.Other clinical applications

1. Cardiovascular Health: Adaptogens like ashwagandha, rhodiola, and ginseng may help reduce blood pressure, improve lipid profiles, and prevent cardiovascular disease.

2. Gastrointestinal Health: Adaptogens like ashwagandha, rhodiola, and ginseng may help reduce stress-related gastrointestinal symptoms and improve gut health.

3. Menopausal Symptoms: Adaptogens like ashwagandha, rhodiola, and ginseng may help reduce menopausal symptoms like hot flashes, night sweats, and mood changes.

6.Discussion :

Adaptogens represent an interesting group of plants, which in the last few years have been receiving attention both by scientists and by consumers in general, particularly as part of contemporary stress management and health. Adaptogens are understood to possess a unique property-the ability to facilitate the body to adapt to stress, enhance resistance, and enhance homeostasis. They simply modulate the body's stress response, making it less injurious to health and wellbeing. Some of the most popular adaptogens include Ashwagandha, Rhodiola Rosea, Holy Basil, also known as Tulsi, and Ginseng. They have long been used traditionally in systems like Ayurvedic medicine and Traditional Chinese Medicine but are now being brought back into pharmacy and re-examined for potential benefits in treating chronic stress, fatigue, anxiety, and even depression. Adaptogens are thought to act by modulating the hypothalamic-pituitary-adrenal (HPA) axis, which is an important part of the body's stress response. They help to balance the body's stress system by modulating cortisol levels, the stress hormone, and thereby enhance stress resilience. They may also have antioxidant properties, support cellular repair, and improve energy metabolism, all of which can contribute to overall wellbeing under stress. Adaptogens represent very interesting topics to be considered in modern pharmacy, offering potential alternatives or adjuncts to conventional treatments against stress and its related symptoms. However, they should be regarded with balanced reasoning by science as a whole, and end consumers within society, with promise on one hand while further research is needed on the other regarding their efficacy and safety.

7.CONCLUSION :

Natural plant adaptogens are promising substances with broad effects that help alleviate stress, illness, physical weakness, anxiety, and enhance mental well-being. While the use of these adaptogens dates back to ancient times, their popularity is growing in modern society due to their healing and stress-resistance properties. These plant-based products can be consumed in the form of tea, food, or as medicine and supplements. Adaptogens represent a fascinating intersection between traditional herbal medicine and modern pharmacotherapy. As research continues to unveil their potential benefits, these plants may play an increasingly significant role in managing stress-related conditions within contemporary healthcare frameworks. The beneficial stress-protective effects of adaptogens have been shown to be linked to the regulation of homeostasis through various mechanisms, including involvement with the hypothalamic-pituitary-adrenal (HPA) axis and the modulation of key mediators of the stress response, such as molecular chaperones. While adaptogens vary subtly in their effects, we do not claim to have definitive answers regarding the best uses for each one.

8.References :

1. Gerontakos S, Casteleijn D, Wardle J. Clinician perspectives and understanding of the adaptogenic concept: A focus group study with Naturopaths and Western Herbalists. *Integrative medicine research*. 2021 Mar 1;10(1):100433.
2. Todorova V, Ivanov K, Delattre C, Nalbantova V, Karcheva-Bahchevanska D, Ivanova S. Plant adaptogens—History and future perspectives. *Nutrients*. 2021 Aug 20;13(8):2861.
3. Asea A, Kaur P, Panossian A, Wikman KG. Evaluation of molecular chaperons Hsp72 and neuropeptide Y as characteristic markers of adaptogenic activity of plant extracts. *Phytomedicine*. 2013 Nov 15;20(14):1323-9
4. Liu XX, Chen CY, Li L, Guo MM, He YF, Meng H, Dong YM, Xiao PG, Yi F. Bibliometric study of adaptogens in dermatology: pharmacophylogeny, phytochemistry, and pharmacological mechanisms. *Drug Design, Development and Therapy*. 2023 Dec 31:341-61.
5. Panossian A, Wikman G. Effects of adaptogens on the central nervous system and the molecular mechanisms associated with their stress—protective activity. *Pharmaceuticals*. 2010 Jan;3(1):188-224.

6. Boon-Niermeijer EK, Van den Berg A, Wikman G, Wiegant FA. Phyto-adaptogens protect against environmental stress-induced death of embryos from the freshwater snail *Lymnaea stagnalis*. *Phytomedicine*. 2000 Oct 1;7(5):389-99.
7. Mendes FR, Carlini EA. Brazilian plants as possible adaptogens: an ethnopharmacological survey of books edited in Brazil. *Journal of Ethnopharmacology*. 2007 Feb 12;109(3):493-500.
8. Siwek M, Woroń J, Wrzosek A, Gupało J, Chrobak AA. Harder, better, faster, stronger? Retrospective chart review of adverse events of interactions between adaptogens and antidepressant drugs. *Frontiers in Pharmacology*. 2023 Sep 27;14:1271776.
9. Pawar VS, Shivakumar H. A current status of adaptogens: natural remedy to stress. *Asian Pacific Journal of Tropical Disease*. 2012 Jan 1;2:S480-90.
10. Tóth-Mészáros A, Garmaa G, Hegyi P, Bánvölgyi A, Fenyves B, Fehérvári P, Harnos A, Gergő D, Do To UN, Csupor D. The effect of adaptogenic plants on stress: A systematic review and meta-analysis. *Journal of Functional Foods*. 2023 Sep 1;108:105695.
11. Ross SM. Resistance for strength: the role of phytomedicine adaptogens in stress management. *Holistic Nursing Practice*. 2020 Sep 1;34(5):314-7.
12. Pandit S, Srivastav AK, Sur TK, Chaudhuri S, Wang Y, Biswas TK. Effects of *Withania somnifera* Extract in Chronically Stressed Adults: A Randomized Controlled Trial. *Nutrients*. 2024 Apr 26;16(9):1293.
13. KrishnaRaju AV, Somepalli V, Thanawala S, Shah R. Efficacy and anti-inflammatory activity of Ashwagandha sustained-release formulation on depression and anxiety induced by chronic unpredictable stress: In vivo and in vitro studies. *Journal of Experimental Pharmacology*. 2023 Dec 31:291-305.
14. López-Angulo G, Díaz-Camacho SP, Heredia-Mercado B, Montes-Avila J, Delgado-Vargas F. Adaptogenic, immunomodulatory, and antioxidant activities of three *Echeveria* species (Crassulaceae). *South African Journal of Botany*. 2022 Dec 1;151:255-62.
15. Panossian AG. Adaptogens in mental and behavioral disorders. *Psychiatric Clinics*. 2013 Mar 1;36(1):49-64.
16. Abascal K, Yarnell E. Increasing vitality with adaptogens: multifaceted herbs for treating physical and mental stress. *Alternative & Complementary Therapies*. 2003 Apr 1;9(2):54-60.

17. Panossian A, Wikman G. Effects of adaptogens on the central nervous system and the molecular mechanisms associated with their stress—protective activity. *Pharmaceuticals*. 2010 Jan;3(1):188-224.
18. Panossian A, Efferth T. Network pharmacology of adaptogens in the assessment of their pleiotropic therapeutic activity. *Pharmaceuticals*. 2022 Aug 25;15(9):1051.
19. Silva LR, Valentão P, Andrade PB. Phenolic compounds in honey as health promoters. *Honey: Production, Consumption and Health Benefits*; Bondurand, G., Bosch, H., Eds. 2012:81-111.
20. Panossian A, Seo EJ, Efferth T. Novel molecular mechanisms for the adaptogenic effects of herbal extracts on isolated brain cells using systems biology. *Phytomedicine*. 2018 Nov 15;50:257-84.
21. Gerontakos S, Casteleijn D, Wardle J. Clinician perspectives and understanding of the adaptogenic concept: A focus group study with Naturopaths and Western Herbalists. *Integrative medicine research*. 2021 Mar 1;10(1):100433.
22. Semalty A, Semalty M, Panda VS, Asrani KH, Ashar HD. Herbal drugs in chronic fatigue syndrome: an overview. *Schweizerische Zeitschrift für Ganzheitsmedizin/Swiss Journal of Integrative Medicine*. 2012 May 14;24(3):155-68.
23. Mendes FR. Tonic, fortifier and aphrodisiac: adaptogens in the Brazilian folk medicine. *Revista Brasileira de Farmacognosia*. 2011;21:754-63.
24. Gerontakos S, Casteleijn D, Wardle J. Clinician perspectives and understanding of the adaptogenic concept: A focus group study with Naturopaths and Western Herbalists. *Integrative medicine research*. 2021 Mar 1;10(1):100433.
25. A preliminary review of studies on adaptogens: comparison of their bioactivity in TCM with that of ginseng-like herbs used worldwide
26. Sharma R, Sharma P, Bhardwaj R. Adaptogens: new age healing gems for physical wellbeing. *American Journal of Multidisciplinary Research & Development (AJMRD)*. 2021 Oct;3(10):26-35.
27. Brown RP, Gerbarg PL, Ramazanov Z. *Rhodiola rosea*. A phytomedicinal overview. *HerbalGram*. 2002;56:40-52.
28. Wal P, Wal A. An Overview of adaptogens with a special emphasis on *Withania* and *Rhodiola*. *Nutrition and Enhanced Sports Performance*. 2013 Jan 1:343-50.

29. Cohen MM. Tulsi-*Ocimum sanctum*: A herb for all reasons. *Journal of Ayurveda and integrative medicine*. 2014 Oct;5(4):251.
30. A double-blind, placebo-controlled pilot study of the stimulating and adaptogenic effect of *Rhodiola rosea* SHR-5 extract on the fatigue of students caused by stress during an examination period with a repeated low-dose regimen
31. *Rhodiola rosea* in stress induced fatigue - A double blind cross-over study of a standardized extract SHR-5 with a repeated low-dose regimen on the mental performance of healthy physicians during night duty
32. Gerbarg PL, Brown RP. Pause menopause with *Rhodiola rosea*, a natural selective estrogen receptor modulator. *Phytomedicine*. 2016 Jun 15;23(7):763-9.
33. Kaur P, Makanjuola VO, Arora R, Singh B, Arora S. Immunopotentiating significance of conventionally used plant adaptogens as modulators in biochemical and molecular signalling pathways in cell mediated processes. *Biomedicine & Pharmacotherapy*. 2017 Nov 1;95:1815-29.
34. Cifani C, Di B MV, Vitale G, Ruggieri V, Ciccocioppo R, Massi M. Effect of salidroside, active principle of *Rhodiola rosea* extract, on binge eating. *Physiology & Behavior*. 2010 Dec 2;101(5):555-62.
35. Panossian A, Wikman G, Wagner H. Plant adaptogens III. Earlier and more recent aspects and concepts on their mode of action. *Phytomedicine*. 1999 Oct 1;6(4):287-300.
36. Panossian A. Understanding adaptogenic activity: specificity of the pharmacological action of adaptogens and other phytochemicals. *Annals of the New York Academy of Sciences*. 2017 Aug;1401(1):49-64.
37. Panossian AG. Adaptogens: Tonic herbs for fatigue and stress. *Alternative & Complementary Therapies*. 2003 Dec 1;9(6):327-31.
38. Rege NN, Thatte UM, Dahanukar SA. Adaptogenic properties of six rasayana herbs used in Ayurvedic medicine. *Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives*. 1999 Jun;13(4):275-91.
39. Wiegant FA, Surinova S, Ytsma E, Langelaar-Makkinje M, Wikman G, Post JA. Plant adaptogens increase lifespan and stress resistance in *C. elegans*. *Biogerontology*. 2009 Feb;10:27-42.

40. Singh MK, Jain G, Das BK, Patil UK. Biomolecules from plants as an adaptogen. *Med. Aromat. Plants (Los Angeles)*. 2017;6(307).
41. Panossian A, Wikman G. Evidence-based efficacy of adaptogens in fatigue, and molecular mechanisms related to their stress-protective activity. *Current clinical pharmacology*. 2009 Sep 1;4(3):198-219.
42. Liao LY, He YF, Li L, Meng H, Dong YM, Yi F, Xiao PG. A preliminary review of studies on adaptogens: comparison of their bioactivity in TCM with that of ginseng-like herbs used worldwide. *Chinese medicine*. 2018 Dec;13:1-2.
43. Panossian A, Gabrielian E, Wagner H. On the mechanism of action of plant adaptogens with particular reference to cucurbitacin R diglucoside. *Phytomedicine*. 1999 Jul 1;6(3):147-55.
44. Panossian AG. Adaptogens in mental and behavioral disorders. *Psychiatric Clinics*. 2013 Mar 1;36(1):49-64.
45. Panossian AG, Efferth T, Shikov AN, Pozharitskaya ON, Kuchta K, Mukherjee PK, Banerjee S, Heinrich M, Wu W, Guo DA, Wagner H. Evolution of the adaptogenic concept from traditional use to medical systems: Pharmacology of stress-and aging-related diseases. *Medicinal research reviews*. 2021 Jan;41(1):630-703.
46. Panossian A, Wagner H. Stimulating effect of adaptogens: an overview with particular reference to their efficacy following single dose administration. *Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives*. 2005 Oct;19(10):819-38.
47. Gerontakos S, Casteleijn D, Wardle J. Clinician perspectives and understanding of the adaptogenic concept: A focus group study with Naturopaths and Western Herbalists. *Integrative medicine research*. 2021 Mar 1;10(1):100433.
48. Panossian A, Seo EJ, Efferth T. Novel molecular mechanisms for the adaptogenic effects of herbal extracts on isolated brain cells using systems biology. *Phytomedicine*. 2018 Nov 15;50:257-84.
49. Panossian A, Hamm R, Kadioglu O, Wikman G, Efferth T. Synergy and antagonism of active constituents of ADAPT-232 on transcriptional level of metabolic regulation of isolated neuroglial cells. *Frontiers in neuroscience*. 2013 Feb 20;7:16.

50. Panossian A, Wikman G. Effects of adaptogens on the central nervous system and the molecular mechanisms associated with their stress—protective activity. *Pharmaceuticals*. 2010 Jan;3(1):188-224.
51. Pięta E, Chrabąszcz K, Pogoda K, Suchy K, Paluszkiewicz C, Kwiatek WM. Adaptogenic activity of withaferin A on human cervical carcinoma cells using high-definition vibrational spectroscopic imaging. *Biochimica et BiophysicaActa (BBA)-Molecular Basis of Disease*. 2023 Feb 1;1869(2):166615.
52. Pawar VS, Shivakumar H. A current status of adaptogens: natural remedy to stress. *Asian Pacific Journal of Tropical Disease*. 2012 Jan 1;2:S480-90.
53. Seo EJ, Klauck SM, Efferth T, Panossian A. Adaptogens in chemobrain (Part II): Effect of plant extracts on chemotherapy-induced cytotoxicity in neuroglia cells. *Phytomedicine*. 2019 May 1;58:152743.
54. Oliynyk S, Oh S. Actoprotective effect of ginseng: improving mental and physical performance. *Journal of ginseng research*. 2013 Apr;37(2):144.
55. Narimanian M, Badalyan M, Panosyan V, Gabrielyan E, Panossian A, Wikman G, Wagner H. Impact of Chisan®(ADAPT-232) on the quality-of-life and its efficacy as an adjuvant in the treatment of acute non-specific pneumonia. *Phytomedicine*. 2005 Nov 15;12(10):723-9.
56. Ma G, Li W, Dou D, Chang X, Bai H, Satou T, Li J, Sun D, Kang T, Nikaido T, Koike K. Rhodiolosides A—E, monoterpene glycosides from *Rhodiola rosea*. *Chemical and pharmaceutical bulletin*. 2006;54(8):1229-33.
57. Panossian A, Wikman G, Sarris J. Rosenroot (*Rhodiolarosea*): traditional use, chemical composition, pharmacology and clinical efficacy. *Phytomedicine*. 2010 Jun 1;17(7):481-93.
58. Adaptogen AP. *Rhodiola rosea*: a possible plant adaptogen. *Altern Med Rev*. 2001;6(3):293-302.
59. Alperth F, Turek I, Weiss S, Vogt D, Bucar F. Qualitative and quantitative analysis of different *Rhodiola rosea* rhizome extracts by UHPLC-DAD-ESI-MSn. *Scientia Pharmaceutica*. 2019;87(2):8.
60. Feng X, Wang W, Liu F, Zhang P, Tang F, Zeng L, Tang K. Separation of active components tyrosol and salidroside from *Rhodiola rosea* crude extract by two-step

- multistage fractionation extraction. Chemical Engineering and Processing-Process Intensification. 2022 Feb 1;172:108800.
61. Masi F, Chianese G, Hofstetter RK, Cavallaro AL, Riva A, Werz O, Taglialatela-Scafati O. Phytochemical profile and anti-inflammatory activity of a commercially available *Rhodiola rosea* root extract. Fitoterapia. 2023 Apr 1;166:105439.
62. Montiel-Ruiz RM, González-Trujano ME, Deciga-Campos M. Synergistic interactions between the antinociceptive effect of *Rhodiola rosea* extract and B vitamins in the mouse formalin test. Phytomedicine. 2013 Nov 15;20(14):1280-7.
63. Concerto C, Infortuna C, Muscatello MR, Bruno A, Zoccali R, Chusid E, Aguglia E, Battaglia F. Exploring the effect of adaptogenic *Rhodiola Rosea* extract on neuroplasticity in humans. Complementary Therapies in Medicine. 2018 Dec 1;41:141-6.
64. Mannucci C, Navarra M, Calzavara E, Caputi AP, Calapai G. Serotonin involvement in *Rhodiola rosea* attenuation of nicotine withdrawal signs in rats. Phytomedicine. 2012 Sep 15;19(12):1117-24.
65. Gerbarg PL, Brown RP. Pause menopause with *Rhodiola rosea*, a natural selective estrogen receptor modulator. Phytomedicine. 2016 Jun 15;23(7):763-9.
66. Zhang Z, Liu Y, Lu M, Lyu X, Gong T, Tang B, Wang L, Zeng J, Li Y. *Rhodiola rosea* extract inhibits the biofilm formation and the expression of virulence genes of cariogenic oral pathogen *Streptococcus mutans*. Archives of oral biology. 2020 Aug 1;116:104762.
67. Wu Y, Wang Q, Liu H, Niu L, Li M, Jia Q. A heteropolysaccharide from *Rhodiola rosea* L.: preparation, purification and anti-tumor activities in H22-bearing mice. Food Science and Human Wellness. 2023 Mar 1;12(2):536-45.
68. Hung SK, Perry R, Ernst E. The effectiveness and efficacy of *Rhodiola rosea* L.: a systematic review of randomized clinical trials. Phytomedicine. 2011 Feb 15;18(4):235-44.
69. Cifani C, Di B MV, Vitale G, Ruggieri V, Ciccocioppo R, Massi M. Effect of salidroside, active principle of *Rhodiola rosea* extract, on binge eating. Physiology & Behavior. 2010 Dec 2;101(5):555-62.
70. Qu ZQ, Zhou Y, Zeng YS, Li Y, Chung P. Pretreatment with *Rhodiola rosea* extract reduces cognitive impairment induced by intracerebroventricular streptozotocin in rats:

- implication of anti-oxidative and neuroprotective effects. Biomedical and environmental sciences. 2009 Aug 1;22(4):318-26.
71. Shanely RA, Nieman DC, Zwetsloot KA, Knab AM, Imagita H, Luo B, Davis B, Zubeldia JM. Evaluation of *Rhodiola rosea* supplementation on skeletal muscle damage and inflammation in runners following a competitive marathon. Brain, behavior, and immunity. 2014 Jul 1;39:204-10.
 72. Feng X, Wang W, Liu F, Zhang P, Tang F, Zeng L, Tang K. Separation of active components tyrosol and salidroside from *Rhodiola rosea* crude extract by two-step multistage fractionation extraction. Chemical Engineering and Processing-Process Intensification. 2022 Feb 1;172:108800.
 73. Liu J, Zang E, Tian Y, Li X, Xin T, Zeng L, Xu L, Xiao P. Applications and challenges of DNA barcoding in rapid radiation groups: *Rhodiola* (Crassulaceae) as a case study. Chinese Herbal Medicines. 2024 Aug 8.
 74. Zhou Q, Han X, Li R, Zhao W, Bai B, Yan C, Dong X. Anti-atherosclerosis of oligomeric proanthocyanidins from *Rhodiola rosea* on rat model via hypolipemic, antioxidant, anti-inflammatory activities together with regulation of endothelial function. Phytomedicine. 2018 Dec 1;51:171-80.
 75. Kalaivani P, Siva R, Gayathri V, Langade D. Mutagenicity and safety evaluation of Ashwagandha (*Withaniasomnifera*) root aqueous extract in different models. Toxicology Reports. 2024 Jun 1;12:41-7.
 76. Kalaivani P, Siva R, Gayathri V, Langade D. Ninety-day repeated dose toxicity of Ashwagandha (*Withaniasomnifera*) root extract in Wistar rats. Toxicology Reports. 2023 Dec 1;11:189-98.
 77. Abdelwahed MT, Hegazy MA, Mohamed EH. A validated green UPLC method for the quantification of synthetic pharmaceutical adulterants in the extract of the aphrodisiac herbal plant ashwagandha (*Withaniasomnifera*) and in spiked human plasma. Sustainable Chemistry and Pharmacy. 2023 Dec 1;36:101297.
 78. Nile SH, Nile A, Gansukh E, Baskar V, Kai G. Subcritical water extraction of withanosides and withanolides from ashwagandha (*Withaniasomnifera* L) and their biological activities. Food and Chemical Toxicology. 2019 Oct 1;132:110659.

79. Langade D, Dawane J, Dhande P. Sub-acute toxicity of Ashwagandha (*Withaniasomnifera*) root extract in wistar rats. *Toxicology Reports*. 2023 Dec 1;11:389-95.
80. Kim SK, Venkatesan J, Rathi P, Antony B. Pharmacokinetics and bioequivalence of *Withaniasomnifera* (Ashwagandha) extracts—A double blind, crossover study in healthy adults. *Heliyon*. 2023 Dec 1;9(12).
81. Gurav S, Wanjari M, Bhole R, Raut N, Prasad S, Saoji S, Chikhale R, Khanal P, Pant A, Ayyanar M, Gurav N. Ethnological validation of Ashwagandha (*Withaniasomnifera* L. Dunal) ghrita as ‘VajikaranaRasayana’: In-silico, in-vitro and in-vivo approach. *Journal of Ethnopharmacology*. 2023 Mar 25;304:116064.
82. Singh, S.K., Valicherla, G.R., Bikkasani, A.K., Cheruvu, S.H., Hossain, Z., Taneja, I., Ahmad, H., Raju, K.S., Sangwan, N.S., Singh, S.K. and Dwivedi, A.K., 2021. Elucidation of plasma protein binding, blood partitioning, permeability, CYP phenotyping and CYP inhibition studies of Withanone using validated UPLC method: An active constituent of neuroprotective herb Ashwagandha. *Journal of Ethnopharmacology*, 270, p.113819.
83. Murthy MN, Shyamala BV. Ashwagandha-*Withaniasomnifera* (L.) Dunal as a multipotent neuroprotective remedy for genetically induced motor dysfunction and cellular toxicity in human neurodegenerative disease models of *Drosophila*. *Journal of Ethnopharmacology*. 2024 Jan 10;318:116897.
84. Dadge SD, Tiwari N, Husain A, Verma S, Agarwal A, Garg R, Rath SK, Shanker K, Gayen JR. Simultaneous estimation of five biomarkers of neuroprotective herb Ashwagandha NMITLI-118R AF1 in rat plasma and brain using LC-ESI-MS/MS: application to its pharmacokinetic and stability studies. *Journal of Chromatography B*. 2023 Aug 1;1228:123834.
85. Siddiqui S, Ahmed N, Goswami M, Chakrabarty A, Chowdhury G. DNA damage by Withanone as a potential cause of liver toxicity observed for herbal products of *Withaniasomnifera* (Ashwagandha). *Current Research in Toxicology*. 2021 Jan 1;2:72-81.
86. Khalil, H.M., Eliwa, H.A., El-Shiekh, R.A., Al-Mokaddem, A.K., Hassan, M., Tawfek, A.M. and El-Maadawy, W.H., 2021. Ashwagandha (*Withaniasomnifera*) root extract attenuates hepatic and cognitive deficits in thioacetamide-induced rat model of hepatic

- encephalopathy via induction of Nrf2/HO-1 and mitigation of NF- κ B/MAPK signaling pathways. *Journal of Ethnopharmacology*, 277, p.114141.
87. Baitharu I, Jain V, Deep SN, Hota KB, Hota SK, Prasad D, Ilavazhagan G. Withaniasomnifera root extract ameliorates hypobaric hypoxia induced memory impairment in rats. *Journal of ethnopharmacology*. 2013 Jan 30;145(2):431-41.
 88. Vaidya VG, Naik NN, Ganu G, Parmar V, Jagtap S, Saste G, Bhatt A, Mulay V, Girme A, Modi SJ, Hingorani L. Clinical pharmacokinetic evaluation of Withaniasomnifera (L.) Dunal root extract in healthy human volunteers: A non-randomized, single dose study utilizing UHPLC-MS/MS analysis. *Journal of Ethnopharmacology*. 2024 Mar 25;322:117603.
 89. Vaidya VG, Gothwad A, Ganu G, Girme A, Modi SJ, Hingorani L. Clinical safety and tolerability evaluation of Withaniasomnifera (L.) Dunal (Ashwagandha) root extract in healthy human volunteers. *Journal of Ayurveda and Integrative Medicine*. 2024 Jan 1;15(1):100859.
 90. Verma N, Gupta SK, Tiwari S, Mishra AK. Safety of ashwagandha root extract: a randomized, placebo-controlled, study in healthy volunteers. *Complementary therapies in medicine*. 2021 Mar 1;57:102642.
 91. Gurav NS, Gurav SS, Sakharwade SN. Studies on AshwagandhaGhrita with reference to murchana process and storage conditions. *Journal of Ayurveda and Integrative Medicine*. 2020 Jul 1;11(3):243-9.
 92. Pang Y, Jiang Y, Li G, Wang H. Species identification of Panax ginseng throughout the entire industrial chain: From the ginseng field to highly processed products. *Food Control*. 2025 Jan 1;167:110824.
 93. Pang Y, Tian X, Wang D, Wang H. Species authentication of Panax ginseng CA Mey. and ginseng extracts using mitochondrial nad2 intron 4 region. *Journal of Applied Research on Medicinal and Aromatic Plants*. 2024 May 1;41:100554.
 94. Jiang Y, Liu C, He G, Zhang Y, Liu M, Zhang K, Liu M, Wang A, Zhang M, Wang Y, Zhao M. Regulation of ginseng adventitious root growth in Panax ginseng by the miR156-targeted PgSPL24-09 transcription factors. *Plant Physiology and Biochemistry*. 2024 Oct 1;215:109026.

95. Sathya S, Zhang J, Feng H, Jing P, Lan Y, Cao X, Liu Q. Comparison of chemical components and quality evaluation of *Panax ginseng* and its processed products from different habitats in Northeastern China. *Biocatalysis and Agricultural Biotechnology*. 2024 Oct 1;61:103375.
96. Kim YW, Bak SB, Song YR, Kim CE, Lee WY. Systematic exploration of therapeutic effects and key mechanisms of *Panax ginseng* using network-based approaches. *Journal of Ginseng Research*. 2024 Jul 1;48(4):373-83.
97. Jang J, He Z, Huang L, Hwang JY, Kim MY, Cho JY. Upregulation of NK cell activity, cytokine expression, and NF- κ B pathway by ginsenoside concentrates from *Panax ginseng* berries in healthy mice and macrophage cell lines. *Journal of Ethnopharmacology*. 2024 Dec 5;335:118681.
98. Wang HP, Lin ZZ, Yin Q, Du J. Screening of GLP-1r agonists from natural products using affinity ultrafiltration screening coupled with UPLC-ESI-Orbitrap-MS technology: a case study of *Panax ginseng*. *Journal of Asian Natural Products Research*. 2024 Jul 19:1-3.
99. Ginseng and ginsenoside Rg3, a newly identified active ingredient of ginseng, modulate Ca²⁺ channel currents in rat sensory neurons
100. Liu J, Ma R, Fu B, Yang P, Zhang L, Zhang C, Chen Y, Sun L. Phytosterols in mountain cultivated ginseng, as master healthy ageing dietary supplement, activates steroid signaling in ageing *Drosophila melanogaster*. *Experimental Gerontology*. 2024 Oct 1;195:112554.
101. Wang GL, He ZM, Zhu HY, Gao YG, Zhao Y, Yang H, Zhang LX. Involvement of serotonergic, noradrenergic and dopaminergic systems in the antidepressant-like effect of ginsenoside Rb1, a major active ingredient of *Panax ginseng* CA Meyer. *Journal of Ethnopharmacology*. 2017 May 23;204:118-24.
102. Li Y, Wu Y, Li H, Wang M, Gao Y, Pei S, Liu S, Liu Z, Liu Z, Men L. UPLC-QTOF-MS based metabolomics unravels the modulatory effect of ginseng water extracts on rats with Qi-deficiency. *Journal of Pharmaceutical and Biomedical Analysis*. 2024 May 15;242:116019.
103. Zhao Y, Cui Y, Ni W, Yu S, Pan D, Liu S, Jia Z, Gao Y, Zhao D, Liu M, Wang S. Ginseng total saponin improves red blood cell oxidative stress injury by regulating

- tyrosine phosphorylation and glycolysis in red blood cells. *Phytomedicine*. 2024 May 28;155785.
104. Jin M, Xing Y, Qi X, Cui CB. Ameliorative actions of ginseng flower alcoholic extract, on drug-induced hepatotoxicity: A focus on PI3K/AKT/mTOR signaling modulation and intestinal microbiome homeostasis. *Journal of Functional Foods*. 2024 Nov 1;122:106482.
 105. Sun Z, Zeng Z, Chen LX, Xu JD, Zhou J, Kong M, Shen H, Mao Q, Wu CY, Long F, Zhou SS. Integrated anti-fatigue effects of polysaccharides and small molecules coexisting in water extracts of ginseng: Gut microbiota-mediated mechanisms. *Journal of Ethnopharmacology*. 2025 Jan 30;337:118958
 106. Lin H, Xu Y, Xiong H, Wang L, Shi Y, Wang D, Wang Z, Ren J, Wang S. Mechanism of action of Panax ginseng alcohol extract based on orexin-mediated autophagy in the treatment of sleep and cognition in aged sleep-deprived rats. *Journal of Ethnopharmacology*. 2025 Jan 30;337:118907.
 107. Wongpraneekul A, Havananda T, Luengwilai K. Variation in aroma level of holy basil (*Ocimum tenuiflorum* L.) leaves is related to volatile composition, but not trichome characteristics. *Journal of Applied Research on Medicinal and Aromatic Plants*. 2022 Mar 1;27:100347.
 108. Memon J, Shabbir T, Ishrat M, Aslam H, Khowaja AA, Leemani MJ. Caries affected disinfection using Phycocyanin activated by PDT, Holy Basil, and Ti-sapphire laser on adhesive bond strength, microleakage, and bond failure. *Photodiagnosis and Photodynamic Therapy*. 2023 Sep 1;43:103691.
 109. Shimizu T, Torres MP, Chakraborty S, Soucek JJ, Rachagani S, Kaur S, Macha M, Ganti AK, Hauke RJ, Batra SK. Holy Basil leaf extract decreases tumorigenicity and metastasis of aggressive human pancreatic cancer cells in vitro and in vivo: potential role in therapy. *Cancer letters*. 2013 Aug 19;336(2):270-80.
 110. Khan MM, Quasar N, Afreen R. Nanotized form of indole acetic acid improve biochemical activities, the ultrastructure of glandular trichomes and essential oil production in *Ocimum tenuiflorum* L. *Industrial Crops and Products*. 2023 Mar 1;193:116117.

111. Bakhtiar Z, Mirjalili MH. How to cook sweet basil (*Ocimum basilicum* L.) leaves to obtain the highest nutrient bioaccessibility and bioactive compounds?. *International Journal of Gastronomy and Food Science*. 2024 Jun 1;36:100915.
112. Deng X, Shi B, Ye Z, Huang M, Chen R, Cai Y, Kuang Z, Sun X, Bian G, Deng Z, Liu T. Systematic identification of *Ocimum sanctum* sesquiterpenoid synthases and (-)-eremophilene overproduction in engineered yeast. *Metabolic engineering*. 2022 Jan 1;69:122-33.
113. Khattak MM, Mohd-Shukri NA, Mahmood T, Ahmed M, Azmi SN, Alam M, Sarian MN, Ahmed QU. Antidiabetic activity evaluation of polyherbal formulation in type 2 diabetes mellitus patients. *Journal of King Saud University-Science*. 2024 Jan 1;36(1):103010.
114. Sharma H, Mendiratta SK, Agrawal RK, Gurunathan K, Kumar S, Singh TP. Use of various essential oils as bio preservatives and their effect on the quality of vacuum packaged fresh chicken sausages under frozen conditions. *LWT-Food Science and Technology*. 2017 Aug 1;81:118-27.
115. Smitha GR, Basak BB, Thondaiman V, Saha A. Nutrient management through organics, bio-fertilizers and crop residues improves growth, yield and quality of sacred basil (*Ocimum sanctum* Linn). *Industrial Crops and Products*. 2019 Feb 1;128:599-606.
116. Ogendo JO, Kostyukovsky M, Ravid U, Matasyoh JC, Deng AL, Omolo EO, Kariuki ST, Shaaya E. Bioactivity of *Ocimum gratissimum* L. oil and two of its constituents against five insect pests attacking stored food products. *Journal of Stored Products Research*. 2008 Jan 1;44(4):328-34.
117. Pavela R, Kaffková K, Smékalová K, Vrchotová N, Bednář J, Tříška J. Biomass yield potential of tulsi (*Ocimum sanctum* L.) in European conditions. *Industrial Crops and Products*. 2023 Apr 1;194:116365.