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Adaptogenic Botanicals with Emphasis on *Rhodiola rosea* and *Withania somnifera*

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Authors' contributions

This work was carried out in collaboration between all authors. Authors RPM, MF and LLR performed material preparation, design and structural arrangement. The specific bibliography search and literature selection were managed by author RPM. The first draft of manuscript was created by author RPM and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

This review addresses the issue of plant adaptogens, botanical products with remarkable anti-stress effects. These actions result from its ability to increase the non-specific organism's resistance process against multiple stressors (physical, chemical or biological). They are capable of exerting a normalizing effect on the human body, being both non-toxic effects and not influencing normal organic functions. Several plants with a complex phytochemical profile meet the criteria for being adaptogens. Many of them have been used in traditional medicine as tonic-vitalizing agents for centuries to treat various health conditions. This review briefly explains the organism's stress responses against stressors and the evolution of the adaptogenic concept from a historic perspective. A rational classification of adaptogens plants is formulated although it does not cover

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the full variability of botanical adaptogens. Nevertheless, summarizing data from two of the most important plant adaptogens, golden root (*Rhodiola rosea*) and Indian ginseng (*Withania somnifera*), are described. This includes their most deserving ethnomedicinal properties, the various families of compounds that constitute their complex phytochemical profiles, pharmacological activities along with putative mechanism of action responsible for some of their multifaceted biological actions, and the multi-therapeutic and health-promoting activities obtained from the most relevant clinical trials performed to date. Additionally, several relevant and current issues regarding the safety and toxicity of both widely used adaptogens are detailed. These include potential negative drugs interactions, putative contraindications and warnings in specific physiological statuses or health conditions. Finally, despite the overlapping activities against stress and stress-related health conditions some superior therapeutic benefits are tentatively assigned both to *Withania somnifera and Rhodiola rosea* taking into account the overall evidence of efficacy from pharmacological and clinical studies.

Keywords: Adaptogens; Rhodiola rosea; Withania somnifera; stress; anxiety; fatigue; cognition; performance.

ABBREVIATIONS

SAM : *Sympathetic system*
HPA : *Hypothalamic-pituitary-adrenal axis*
R. rosea : *Rhodiola rosea*
W. somnifera : *Withania somnifera*
MAO-A : *Monoamine oxidases type A enzyme*
MAO-B : *Monoamine oxidases type B enzyme*

1. INTRODUCTION

The ability to adapt to a variable environment is a unique characteristic of living organisms. Any external or internal demand (stressor) in this environment triggers a defensive state known as “stress”, aiding the organism in reacting and adapting to events [1,2]. Stressors that elicit the stress response can be physical, chemical, or psychological in nature. Selye defined the General Adaptation Syndrome as a response that develops in the body in reaction to stress, consisting of three phases:

1) Alarm reaction: an immediate response to stress, protective and designed to be short-lived. It involves the activation of the neuroendocrine system, enhancing both the sympathetic system (SAM) and the hypothalamic-pituitary-adrenal axis (HPA). This activation promotes catabolism, rapidly providing energy and drive. The organism enters a catabolic state, and the general nonspecific resistance to stressors is elevated.

(2) Resistance: Chronic or repeated low exposure of the organism to a stressor elicits the switch from a catabolic to anabolic phase, leading to the development of stressor-specific resistance. The organism may positively adapt to stress (developing resistance to stressors and improving its adaptive capacity and health) or may show poor, detrimental adaptation, leading to the next phase.

3) Exhaustion: If stress persists or increases or poor adaptation is present, the power and duration of the organism´s resistance are overloaded, leading to disruptions in normal functions and homeostasis. A combination of factors, including energy depletion contributes to hormonal depletion, eventual exhaustion, system dysfunction, and the occurrence of disease [2].

Therefore, the ability to develop and preserve resistance to stress is crucial for coping with a wide spectrum of stressors experienced in human life. The interest in modulating stress resistance processes has led to the emergence of the science of adaptation. Research has focused on understanding the mechanisms underlying the process of adaptation, elucidating what are the key variables that guide this phenomenon [3,4]. This includes screening botanicals to modulate them, aiming to avoid insufficient, disproportionate, unnecessary or erroneous stress responses. In this review, we will briefly describe the history of the concept of adaptogens and botanical adaptogenic substances. A basic classification of adaptogens will be proposed, with a focus on two of the most widely studied botanicals: *Rhodiola rosea* (*R.*

rosea) and *Withania somnifera* (*W. somnifera*). This will include their most relevant bioactive compounds, pharmacological activities, evidence-based health properties, and safety concerns.

2. ADAPTOGENS

2.1 Adaptogen Concept

Adaptogens encompass various medicinal plants or extracts (herbal adaptogens), specific phytochemicals and some synthetic compounds (actoprotectors) that primarily protect health by non-specifically increasing resistance to stressors. They aid individuals in coping and adapting to stress. Among them, herbal adaptogens are a category of botanical medicines historically associated with herbal tonics [5,42, 43,]. Herbalists in various traditional medical systems have used them since ancient times to help mitigate the negative impact of chronic stress on health.

While the concept exists in various traditional medical systems at the clinical level and classifications, the scientific formalization of the term "adaptogen" dates back to the 1940s. The distinguished Russian scientist Lazarev [6] coined the term when he discovered the adaptogenic activity of Dibazol in a series of experiments designed to induce nonspecific resistance to stressors in humans. Lazarev defined the term “adaptogen” as any compound capable of promoting an increased state of nonspecific resistance in an organism, enabling it to counteract stressor signals and facilitate adaptation to exceptional overload [7,8].

In 1969, Russian scientists Brekhman and Dardymov refined the term and placed it within the field of phytomedicine. Their definition was based on an analysis of several preclinical studies conducted with relevant botanicals, commonly used as tonics in polyherbal formulations of traditional medical systems [9]. They specified that adaptogens must meet the following requirements:

1.An adaptogen should be harmless and minimally affect the normal physiological functions of the body.

2.An adaptogen must exhibit non-specific action, having the ability to enhance the organism's resistance to a wide range of harmful stress factors, whether physical, chemical, or biological nature.

3.An Adaptogen should exert a normalizing influence regardless of the direction of change from physiological norms caused by stressors.

4.Unlike classical stimulants, an adaptogen should have pro-excitatory effects that do not induce undesirable side effects such as low protein synthesis, restlessness, or increased energy expenditure.

In modern pharmacology and pharmacognosy, the definition of adaptogens is continually evolving with the expanding body of scientific evidence concerning their molecular mechanisms of action on various regulatory systems at the cellular, organic, and whole organism levels. Consequently, a cumulative body of contemporary research characterizes adaptogens as botanical compounds or plant extracts that enhance the adaptability, resilience, and survival of organisms to a variety of stressors [10,47,48]. This is achieved through multi-target and multi-channel actions on the neuroendocrine and immune systems, especially by modulating SAM and HPA (Fig.1). Accordingly, herbal adaptogens support the human organism's ability to respond appropriately to stressors of different origins (acting as stress response modifiers). They also enhance the capacity of physiological systems to continually adapt to changes (resilience) through multi-level dynamic modulation of mechanisms and processes throughout the body, maintaining homeostasis (allostasis) [11].

Adaptogenic herbs have proven beneficial in the treatment of various conditions, including convalescent patients after infections or other illnesses, neuro-asthenia, depressive and burn-out syndromes, or exhaustion after intensive and/or long periods of work requiring mental or physical exertion. These conditions are characterized by multiple symptoms including fatigue, weakness, irritability, headache, malaise, insomnia, poor appetite, cognitive and memory impairment, stress, depression, and anxiety [12].

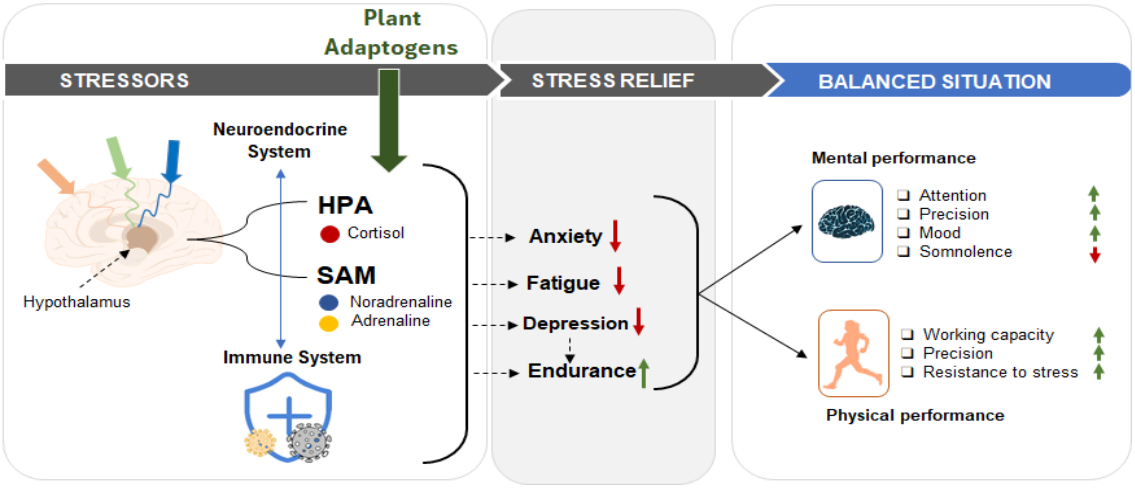

Fig. 1. Scheme showing the actions of adaptogens on stress-induced effects though multilevel modulation of neuroendocrine and immune systems

Fig. 2. Image of *Rhodiola rosea* aerial part (central picture) and slices of dried rhizomes (top right picture)

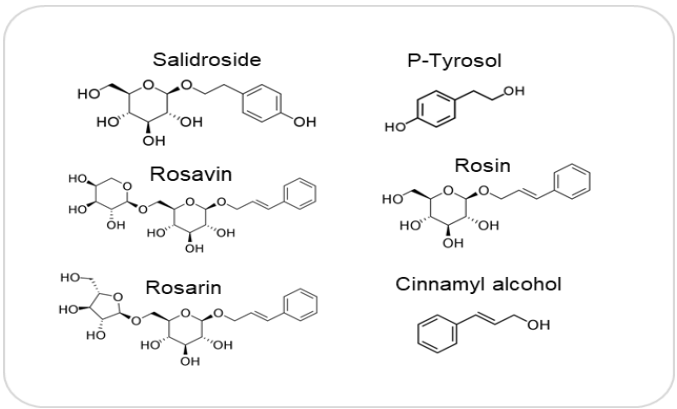

Fig. 3. Chemical structures of the key bioactive groups from *Rhodiola rosea* roots: phenylethanoids (salidroside and p-tyrosol) and phenylpropanoids (rosavin, rosin, rosarin and cinnamyl alcohol)

Fig. 4. Images of the whole plant (left) and dried roots (right) of *Withania somnifera*

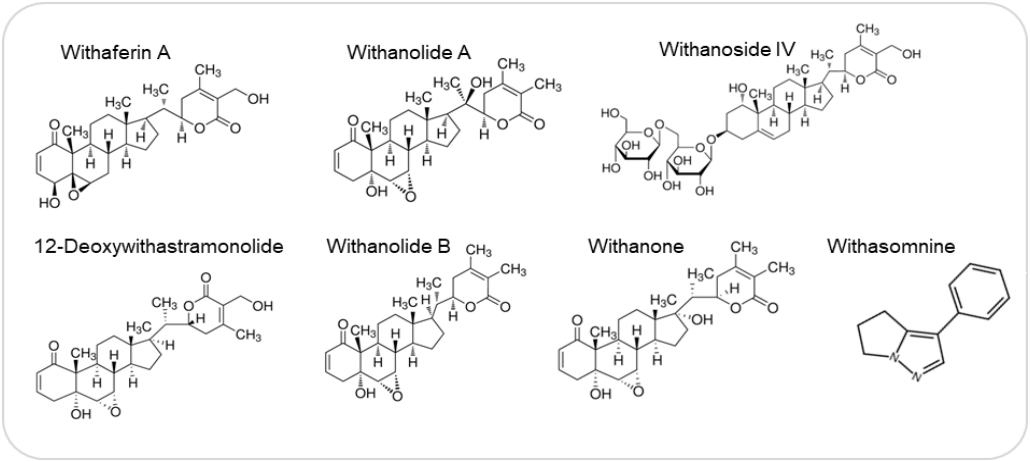

Fig. 5. Chemical structures of the main bioactives —withanosides, withanolides, and alkaloids from *Withania somnifera* root: withanoside IV, withaferin A, 12-Deoxy-withastramonolide, withanolide A, withanolide B, withanone, and withasomnine

2.2 Classification of Botanical Adaptogen

Adaptogens can be categorized into three groups: primary (or classical) adaptogens, secondary adaptogens, and adaptogen companions[13]. According to the principles of Brekhman and Dardymov (1969), the so-called "classical or primary adaptogens" include *Aralia elata* (Miq.) Seem; *Eleutherococcus senticosus* (Rupr. & Maxim.) Maxim.; *Panax ginseng* C.A. Mey; *Rhaponticum carthamoides* (Willd.) DC.; *Schisandra chinensis* (Turcz.) Baill.; *Rhodiola rosea* L.; *Oplopanax elatus* (Nakai) Nakai, *Aronia melanocarpa* (Michx.) Elliott, *Panax quinquefolious* L. and *Withania somnifera* (L.) Dunal. Notably, the first eight in the list have been extensively studied by Russian scientists since the 1940s and monographed in the State Pharmacopoeia of the Russian Federation (14th edition; included in the pharmacological group of tonic & adaptogens) [14]. Primary adaptogens have a wealth of scientific studies confirming their adaptogenic character, ensuring non-

specific action, general resistance in the organism, support of homeostasis, and a lack of adverse or toxic effects even after prolonged intake [15].

The second group is referred to as "secondary adaptogens," sharing some characteristics or qualities of traditional adaptogen definitions but not meeting all of the criteria of primary adaptogens and lacking extensive study. These adaptogens typically modulate the nervous, endocrine, and immune systems, and may enhance anabolism, but do not directly influence the HPA. Medicinal plants in this category include *Astragalus trimestris* L., *Bacopa monnieri* (L.) Wetst., *Centella asiatica* (L.) Urb., *Ocimum tenuiflorum* L., *Ptychopetalum olacoides* Benth, *Panax notoginseng* (Burkilll) F.H. Chen, *Ganoderma lucidum* (Curtis) P. Karst, *Asparagus racemosus* Willd., *Dioscorea mexicana* Scheidw., *Tinospora cordifolia* (Willd.) Miers ex Hook.f. & Thomson, *Phyllanthus emblica* L. and *Glycyrrhiza glabra* L. [15]

An additional category includes specific non-adaptogenic plants named "adaptogen companions", characterized by enhancing or synergizing the effect of primary or secondary adaptogens without directly modulating the HPA. These plants lack toxicity, exhibit increased benefits with long-term intake, supporting the ability to cope with some types of stress (notably oxidative stress & inflammation), and are typically rich in flavonoid-type nutraceutical polyphenols. Some relevant botanicals from this group include *Vaccinium myrtillus* L., *Sambucus nigra* L., *Zingiber officinale* Roscoe, *Ginkgo biloba* L., *Polygonum cuspidatum* Willd. ex Spreng., *Rosmarinus officinalis* L., *Crataegus rhipidophylla* Gand., *Cissus quadrangularis* L. [15].

2.3 *Rhodiola Rosea*

R. rosea from the Crassulaceae family (Fig.2) stands out as one of the most intensively studied medicinal plants, not only within the genus Rhodiola but also among plant-adaptogens [16]. It has been clearly recognized as a botanical adaptogen with antifatigue, antistress, and antidepressant properties. Interestingly, the current Rhodiola genus comprises 53 accepted species names [17] (wfoplantlist.org), and at least 15 of them are employed in traditional medicine in several Asian countries [16,18]. However, the majority of clinical, pharmacological and toxicological studies have been conducted on R. rosea, so whether other species confer the same medicinal properties is largely unknown [16,19]. *R. rosea* is considered a circumpolar Arctic-Alpine species originating in the southern Siberia highlands [20]. It extends to Asia (from Russia to Japan), the central mountains of Europe, Iceland, Greenland and even North America [21]. Commonly called roseroot, the plant is known by various names depending on its ethnobotanical origin, including arctic root (due to its distribution among arctic regions) and golden root, possibly in allusion to the perceived value of the root.

From an ethnobotanical point of view, *R. rosea* has been a significant traditional food source for humans and it has been used as forage for cattle. However, its roots and rhizomes are historically more prized due to its multiple beneficial health properties. *R. rosea* has been employed since ancient times in folk and traditional medical systems in the Nordic countries, Eastern Europe, Russia and Asia to address several conditions. These include increasing work productivity, promoting longevity, enhancing physical endurance, alleviating altitude sickness and treating fatigue from diverse origins, depression, gastrointestinal dysfunction, anaemia, impotence, infections and disorders of the nervous system[50-52]. These remarkable traditional medicinal properties spurred numerous formal ethnopharmacological studies, which commenced in Russia in the 1950s, especially within the context of several research programs screening natural substances from traditional medicine with potential adaptogenic properties. As a result, *R. rosea* roots were characterized as one of the primary adaptogens and a standardized liquid extract was included in the official medicine from the former USSR since 1975 [14]. It was indicated for “diminished physical and mental capabilities such as weakness, exhaustion, tiredness, convalescence, and loss of concentration”. Subsequent phytochemical research to identify *R. rosea* phytoactive compounds has led to the isolation and identification of over 120 phytochemicals from its roots and/or rhizomes [22,23]. These include phenylethanoids (p-Tyrosol and Salidroside), phenylpropanoids (cinnamyl alcohol) and their glycosides forms (rosavin, rosarin and rosin; collectively known as the “*rosavins*”) (Fig. 3), terpenes (rosaridin, rosiridol & rhodiolosides A-F), essential oils (n-decanol & geraniol), simple phenolics

(hydroxycinnamic acids, caffeic acid and chlorogenic acid) and Flavonoids (glycosides of kaempferol, herbacetin, and gossypetin). While extensive bioactivity-guided fractionation studies with *R. rosea* roots are lacking, there is a consensus among researchers that salidroside and rosavins are the major (but not the only) phytochemicals responsible for the antistress adaptogenic effects. The rosavins are specific only to *R. rosea*, whereas salidroside, even in higher concentrations, is found in other species of the *Rhodiola genus*, as well as in other plant species such as *Salix trianda* and *Olea europaea*, and in specific bacteria and yeasts [24]. Consequently, the basic chemical markers to verify the authenticity of R. rosea root preparation are represented by rosavin and by the ratio rosavin/salidroside close to 3:1 [25,26], corresponding to the natural root ratio of the compounds [16].

Pharmacopoeial standardization of products currently focuses on salidroside as well as phenylpropanoids specific to *R. rosea*, typically expressed as total rosavin. Nevertheless, other constituents of Rhodiola species have occasionally been suggested to potentially contribute to biological activities, including the aglycon of the phenylpropanoid cinnamyl alcohol [27], monoterpene glycosides such as rosaridin [28], gallic acid derivatives such as epi-gallocatechin-3-gallate [29], or lignans and some flavonoids such as rhodiosin and herbacetin [30]. From the perspective of biological activity and health effects, a summary of nearly hundreds of pharmacological studies conducted with *R. rosea* has been detailed in various comprehensive review articles. The most relevant pharmacological activities described in such research, performed on cells and rodent models include adaptogenic actions: anti-fatigue and anti-stress effects (cardio-, hepato-, and neuro-protective actions; normalization of altered neuro-endocrine activity), positive neuromodulation of SNC levels supporting improvement of cognitive functions (especially attention, learning and memory) with antidepressant and anxiolytic properties. In addition, *R. rosea* has elicited multifaceted antioxidant and anti-inflammatory activities; immunomodulatory properties aiding in viral infections and also anti-diabetic, anti-cancer, anti-hypertensive, radio-protective and anti-ageing activities [31–35] (Table 1). From a mechanistic point of view it is important to note that, although the precise receptors and/or enzymes along with its downstream intracellular mediators responsible for the pleiotropic adaptogenic and stress-protective activities of *R. rosea* are far from being completely elucidated, the possible molecular mechanism of *R. rosea* actions has been unravelled (*in vitro)* by system biology approach linked to genome-wide effect analysis [37] and (*in vivo)* by behavioural phenotyping pharmacological studies in rodents [38,39]. Briefly, preclinical research has shown that the beneficial stress-protective activities of *R. rosea* are associated with the regulation of the HPA/SAM axis by reduction of the corticotrophin-releasing factor (CRF), the enhancement of the catecholaminergic system (increasing levels of serotonin, dopamine and norepinephrine) due the inhibition of the enzymes responsible of monoamine degradation (MAO and COM-T) and the regulation of the essential signalling systems and effectors of the adaptative stress response including heat shock protein 70,72 and 16, stress-activated c-Jun *N*-terminal protein kinase 1, forkhead box O (FOXO) transcription factor DAF-16, glucocorticoid receptor, β-endorphin, nitric oxide and ATP [40].

Globally, the more than 70 human clinical trials of varying quality in methodology, design and conditions analyzed have supported most of the traditional uses of *R. rosea*. It has demonstrated that *R. rosea* preparations (root powder, dry or liquid extracts and multi-ingredient formulations) may be effective with an acceptable level of evidence against stress physical-related fatigue, low mood, anxiety and depression, and in improving physical and mental working capacity in several conditions [36,41,49]. Given the clinical adaptogenic pleiotropic actions of *R. rosea*, its preparations may have potential benefits as an adjuvant therapy improving well-being and quality of life in patients with chronic diseases [44–46] by means of stress and fatigue mitigation along with improved cognitive function, among others potential beneficial effects. (Table 1)

Based on medicinal traditional use and the background of clinical studies, the Herbal Medicinal Product Committee of the European Medicinal Agency approved its use in 2011 as an adaptogen for the "relief of symptoms of stress such as fatigue, exhaustion and sensation of weakness" in the category of Traditional Herbal Medicinal Product [53]. *R. rosea* preparation (commonly root powder or dry extracts) has been marketed in the EU for years as a food

supplement or traditional medicinal product, it is a renowned adaptogen plant utilized in the traditional medical system and eventually included in the official pharmacopoeia of Nordic & Eastern countries. After intensive research, a liquid extract was manufactured on an industrial scale and has been marketed in Russian pharmacies since 1960 without prescription and approved as a CNS stimulant and adaptogen for oral administration [14]. Despite the abundance of studies conducted to date, further research must focus on the development of preclinical studies using high-throughput technologies to identify the complex mechanism of action at the molecular and cellular levels. Additionally, the establishment of methodologically sound and well-designed large-scale clinical trials is essential to provide unequivocal evidence of efficacy and safety. Robust and comprehensive phytochemical characterization of the *R. rosea* product being tested is critical for fidelity and comparability between studies. Detailed long-term studies should be conducted to identify putative interactions and adverse effects in susceptible or vulnerable populations. Collectively, these studies would help decipher the precise mechanism of action and well define the specific doses and standardizations of *R. rosea* to optimize the various therapeutic applications.

2.3.1 *Rhodiola rosea*: Safety & toxicity Issues

Overall, considering the traditional use dating back to ancient times and the large number of clinical trials conducted to date, the use of *R. rosea* can be considered safe and generally well tolerated in individuals with various health statuses. Unlike stimulants, *R. rosea* does not induce addiction, habituation, or withdrawal symptoms. The incidence of side effects is extremely low, and when they do occur, they are mild in nature and demonstrate low clinical toxicity. However, some rare cases of mild headache, insomnia, hypersalivation, nausea, and dizziness have been reported in clinical trials. Clinical experience of reputable herbalists indicates that certain individuals, particularly those sensitive to stimulants like caffeine or those prone to high anxiety, may experience excessive energy, nervousness, agitation, or increased anxiety, especially at high doses. In such cases, a lower dose with very gradual increases or a combination with a more calming adaptogen is usually recommended. It is advisable to take *R. rosea* during the first half of the day, as it may alter sleep or cause vivid dreams if taken in the afternoon or evening, particularly during the initial weeks of use. Additionally, due to *R. rosea´s* stimulant-antidepressant action, it is not recommended for individuals with bipolar spectrum disorders who may be prone to manic states when exposed to antidepressants or stimulants [54,87,113].

Preclinical toxicological studies in rodents indicate that *R. rosea* is generally safe and even less toxic than other adaptogens, with an LD50 of 3.36 g/kg by the intraperitoneal route. The equivalent dose for a human weighing 65-75 kg would be in the range of 218-252 g. Considering that the effective administered doses of *R. rosea* are between 200 and 600 mg/day, the lethal dose in humans would be 363 to 1260 times higher than the therapeutic doses, supporting a substantial margin of safety [16].

Finally, it is important to note that concurrent use of botanical preparations and drug treatments could lead to unexpected pharmacokinetic and pharmacodynamic interactions increasing the risk of side effects/toxicity [55,56]. Some side effects potentially associated with negative drug-herb interaction between psychotropic drugs and *R. rosea* have been reported. These include, in a relatively low frequency, myalgia, altered consciousness, restless legs syndrome, headache, arthralgia, diarrhoea, nausea, jaundice, myoclonus, hypoglycemia, excessive sedation, priapism, dizziness, hypotension, hyperhidrosis, and hallucinations [57]. Consequently, concurrent administration of *R. rosea* with psychotropic medication should be done with caution, especially for drugs with a narrow therapeutic window.

2.4 *Withania somnifera*

W. somnifera belonging to the Solanaceae Family, is commonly known as Ashwagandha (Fig. 4) or Indian ginseng [58,59]. It has been a widely used medicinal plant in Ayurveda, Unani, and both indigenous Indian and African traditional medicine since very ancient times [60]. The term “Ashwagandha” originates from Sanskrit, and means “horse smell” (ashwa=horse and gandha=smell), attributing to the strong horse-like smell of the fresh root and is believed to support horse-like powder when consumed [73,76]. In Ayurveda, *W. somnifera* holds a significant position within the premium medicinal group of “rasayana” herbs, denoting its tonic

properties that provide physical and mental strength, promoting endurance and longevity [61,62].

Various pharmaceutical forms of *W. somnifera* root, such as powder, juice, paste, decoction and infusion either as single or compound formulations along with dosage, route administration and therapeutic uses, have been detailed in Ayurvedic medicinal texts since 1000 B.C. [63,79,80]. Currently, *W. somnifera* is recognized as an official drug with a detailed monograph in the official Ayurvedic pharmacopeia of India Part 1 (Volume 1). In the Ayurvedic formulary of India Part I, II and III, four different W. somnifera formulations are described, including their constituents, method of preparation, dosage and recommended therapeutic uses. From an ethnomedical perspective, ayurvedic text primarily elaborate on the use of root preparations for neurological conditions (dementia, loss of memory, insomnia and anxiety), as a tonic-restorative (children emaciation, pregnant women, senile debility or during convalescence period), rheumatism, vitiligo, constipation, goitre, bronchitis, asthma, ulcers, aphrodisiac-sterility in women, and liver tonic [63,81].

W. somnifera is listed in the American Herbal Pharmacopoeia and WHO monographs on Selected Medicinal Plants. Due to the documented and remarkable health properties of this plant in traditional medicine, intensive ethnopharmacological research has been carried out in the last decades. The phytochemical profile of *W. somnifera* has been extensively studied using classic and comprehensive metabolomic analytical techniques, resulting in the identification of nearly 140 chemical constituents belonging to several chemical classes [64] including tropane-type alkaloids [65,66], a complex group of ergostane-type steroid lactones collectively designated as Withanolides (along with their glycosylated counterparts, Withanosides & Sitoindosides) [67] (Fig. 5), glycoproteins, flavonoids, steroids, tannins, organic acids and other phenolics [68,69]. Among these, the best known are withanolides and glycol-withanolides. More than 70 individual withanolides derivatives have been reported in W. somnifera leaf and root [68,70], with higher levels found in the leaves than in the roots [71]. The major phytochemicals responsible for the biological activities are alkaloids (isopelletierine, anaferine, withanine), Withanolides (withaferin A) along with Glycosylated counterparts (sitoindoside VII, VIII, IX, X and withanosides), phenolics compounds, and glycoproteins. Not surprisingly, these rich and complex profiles of phytoactive compounds support the pleiotropic pharmacological action associated with various extract preparations and phytochemical constituents.

A large number of preclinical *in vitro* and animal studies have been conducted using various *W. somnifera* extracts or single phytochemicals to elucidate the wide spectrum of pharmacological effects based on several putative mechanisms of action [72,74]. Briefly, *W. somnifera* mixtures have demonstrated remarkable, adaptogenic and stress-relieve effects with amelioration of stress-related conditions: anxiety, depression, and insomnia [75,77]. The mechanism related to the calming and stress-relieving effects associated with *W. somnifera* adaptogenic capacity is not yet fully understood, but appears to be linked to the reduction of the cortisol, adrenaline and dehydroepiandrosterone by down-regulation of the HPA/SAM axis; stimulation of GABAergic and serotoninergic neurotransmission, mitigation of the oxidative stress and inhibition of the synthesis of proinflammatory cytokines [78,82]. In addition, neuropharmacological effects, including neuroprotective action against neurodegenerative disorders such as Alzheimer's disease, Huntington's disease, and Parkinson's disease [83] and anti-ischemic/anti-hypoxic activity have been described. Other significant pharmacological activities include anti-cancer effects, potent anti-inflammatory actions in several disease models, aphrodisiac effects, cardio-hepatoprotective activity, anti-diabetic properties and significant immunomodulatory actions [84,85]. Owing to its broad biological mechanisms of action, there is an increasing number of human trials investigating its efficacy in treating a range of physical and mental conditions as well as promoting overall health. *W. somnifera*-only preparations and extracts have demonstrated clinical efficacy, supporting a potential therapeutic role as an adaptogenic anti-stress agent and in counteracting stress-related conditions including anxiety (anxiolytics properties), insomnia (sedative and sleep-enhancing activity), fatigue (anti-tiredness action,) and depression (anti-depressant effect). In addition, trials specifically targeting depression, sleepiness and anxiety clearly indicate the anti-depressant, sedative and anxiolytic activities of *W. somnifera* in humans,

respectively [77,86,88]. Moreover, *W. somnifera* administration has demonstrated efficacy against several conditions including subclinical hypothyroidism, schizophrenia, obsessive-compulsive disorders, rheumatoid arthritis, type-2 diabetes, cognitive dysfunction, male/female infertility and low libido-sexual desire [89]. *W. somnifera* supplementation also promotes physical and Athletic performance improving outcomes related to fatigue/recovery, cardiorespiratory fitness and strength/power in healthy men and women [90]. Globally, results obtained from several clinical studies strongly suggest that *W. somnifera* has a remarkably wide range of therapeutic applications and health benefits (Table 1). Considering the quality and number of studies, the therapeutic efficacy of *W. somnifera* (in order from stronger evidence to plausible evidence) correspondent to anti-stress & anxiolytic effects [91], enhanced sexual function and pro-fertility activity [92,93], improvement of athletic performance [94] and anti-diabetic properties [95]. Nevertheless, the considerable variety in study designs, experimental methodologies, target populations, health domains and types of *W. somnifera* preparations means that additional investigation using robust methodology and appropriate trial design is mandatory to unequivocally substantiate the clinical efficacy of *W. somnifera*.

2.4.1 *Withania somnifera*: Safety & toxicity Issues

Unfortunately, no systematic clinical studies have been conducted to examine the potential acute or chronic toxicity of *W. somnifera*, either as a plant or in its various extracts. Nonetheless, a significant number of human trials and preclinical toxicity research provide plausible evidence for the safety of *W. somnifera* root preparations. Analysis of several clinical trials using *W. somnifera* root for a wide variety of conditions shows reasonable safety results with no severe side effects [96,97]. Nevertheless, a low incidence of mild to moderate, mainly transient side effects, often associated with high doses of W. somnifera extract, was observed in a few studies and case reports. These mild to moderate adverse events include cholestatic hepatitis with jaundice, blurring vision, skin rash, nocturnal cramps, hyperactivity, weight gain, dry mouth, giddiness, cough, rhinitis, vertigo, constipation, somnolence, hyperacidity, decreased appetite, gastritis, nausea, flatulence and epigastric pain/discomfort [98,99]. It is important to note that many other human trials did not report any side effects associated with root intake both in adults and children [99].

As *W. somnifera* may lower blood pressure, it must be used with caution in individuals prone to hypotension or those being treated for hypertension, due to the risk of hypotension. Additionally, since *W. somnifera* may act as an immunostimulant, it is not recommended for patients taking immunosuppressors such as azathioprine, cyclosporine, daclizumab, muromonab-CD3, tacrolimus, corticosteroids, and others, especially in patients with autoimmune diseases [100].

W. somnifera root extract has been used as a pro-fertility and aphrodisiac agent in men [101] and women [102,103]. However, men with hormone-sensitive prostate cancer or prostate hyperplasia should avoid taking *W. somnifera* preparations. According to some studies, the plant may increase testosterone production [89], which may potentially contribute to disease progression. Additionally, *W. somnifera* may be contraindicated in women planning to become pregnant or who are pregnant, as higher doses of *W. somnifera* root extract have been used as an abortifacient in traditional Ayurvedic medicine [104]. However, although a prenatal toxicity study conducted in rodents showed no evidence of maternal or fetal toxicity [105], clinical evidence is still needed to unequivocally confirm the safety of *W. somnifera* intake during such a sensitive period of life.

Several preclinical toxicity/safety studies performed in rodents have provided reasonable evidence of safety. Oral chronic or subchronic administration of both aqueous, hydroalcoholic and alcoholic extracts (3g/kg - 1 week, 2g/kg - 4 weeks 1-2 g/kg - acute) provoked neither behavioural changes, nor signs of toxicity or mortality. There are no modifications in physiological parameters, haematological or biochemical variables, nor significant pathological lesions in diverse organs. However, it is important to note that in a few studies, the oral administration of *W. somnifera* extract resulted in organic alterations including decrease in plasma cortisol level along with increases in liver and body weight (250 mg/kg - 32 weeks; aqueous extract), CNS depressant effect associated with biogenic amine neurotransmitter alteration (1g/kg - 10 days; ethanolic extract), and a significant catecholamine increase in the

heart and aorta and catecholamine decrease in the adrenal gland (200 mg/kg - 30 days; ethanolic extract). In addition, two non-toxicological studies in which mice were treated with root powder (1 g/kg - 7 days) or aqueous *W. somnifera* extract (1.4 g/kg - 20 days) resulted in the induction of anabolic activity and a significant increase in serum thyroxine (T4) levels in female mice, respectively. This last effects of *W. somnifera* extract on thyroid physiology has also been mirrored in humans, where an increase in T4 concentrations and normalization of TSH levels have been observed after administration of *W. somnifera* root to schizophrenic or subclinical hypothyroid patients [106,107]. Considering these antecedents, the use of *W. somnifera* in subjects with hyperthyroidism (even subclinical) is contraindicated, as it could promote or exacerbate the symptoms of the disease [108,109].

The risk of significant side effects due to herb-drug interactions is a possibility that should be taken into account [110,111]. The possibility of pharmacodynamic interactions between *W. somnifera* extracts and certain classes of psychotropic drugs cannot be completely excluded, as both treatments may act through similar CNS mechanisms (GABAergic and serotoninergic activities), as manifested by the clear additive effect observed in animal studies between *W. somnifera* extracts and the drugs fluoxetine [112], imipramine [112,114] and diazepam [115]. As a result, *W. somnifera* use is not recommended in individuals taking anxiolytic, sedative, or antidepressant medications due to the risk of exacerbating their effects through synergism or additivity [116,117]. In addition, *W. somnifera* may increase the somnolence in patients taking anxiolytics such as benzodiazepines [118,119].

Pharmacokinetic interactions in humans appear to be improbable because *W. somnifera* root extract or isolated phytocompounds did not show significant inhibition against several cytochrome P450 metabolizing isoenzymes from humans, rats or cell lines liver microsomes, with an IC50 in most cases greater than 100 ug/mL (extracts) or 100 µM (single compounds) [120-123].

In summary, while the overall safety of W. somnifera consumption appears favourable, growing data concerning interactions with specific medications with *W. somnifera* and potential adverse effects in susceptible individuals or those with specific health conditions or subclinical disorders highlight the importance of recognizing potential safety concerns associated with *W. somnifera* supplements. The clinical relevance of these findings hinges on factors such as the subject´s health status, the medications they are currently taking, and the specific type and dosage of the *W. somnifera* preparation. These factors collectively determine the systemic concentrations of bioactive metabolites during chronic use. To comprehensively address these pertinent issues associated with *W. somnifera* consumption, additional rigorous, long-term safety studies will be essential.

Table 1. Summary of pharmacological profile & clinical efficacy of *Rhodiola rosea* and *Withania somnifera* from *In Vitro, In Vivo* & Clinical Trials

Pharmacological effects	*Rhodiola rosea*	*Withania somnifera*
Anti-stress	+++	+++
Anti-Fatigue (Physical & Cognitive)	+++	++
Cognitive Performance	++	++
Physical Performance	++	+++
Antidepressive	++	++
Anxiolytic & Calming	+	+++
Sedative	+	+++
Cardioprotective	+++	++
Anti-atherosclerosis	+++	++
Anti-Arthritis	+	+++
Gastroprotective	+	+
Neuroprotective	++	+++
Hepatoprotective	++	++
Immunomodulatory	++	+++
Radioprotective	+++	+

Pharmacological effects	*Rhodiola rosea*	*Withania somnifera*
Hypotensive & Vasodilatatory	+	++
Anti-diabetic	+++	++
Anti-inflammatory	+++	+++
Anti-Oxidant	+++	+++
Clinical Efficacy		
Physical & Mental Fatigue	+++	++
Stress-dependent fatigue	+++	++
Physical & mental performance	++	++
Depression	+++	++
Anti-stress	+++	+++
Anxiety & Nervousness	+	+++
Immunity enhancing	+	++
Insomnia	-	+++
Anti-Arthritis	+	+++
Anti-diabetes	-	++
Male/Female Fertility	-	+++
Erectile dysfunction	-	+++
Schizophrenia	-	+

"+++" – Good evidence from several trials; "++" – Preliminary evidence from some trials; "+" - Low level of evidence; "-" - No evidences or not conclusive

3. DISCUSSION AND CONCLUSIONS

Humans are capable of adapting to dynamic challenging or unexpected environmental, physical and psychosocial stressors. The nature of stressors in modern life is extremely diverse, and, most of the time, humans can overcome these events with the aid of internal dynamic interplay processes and mechanisms (allostasis). As a result, the human body adapts to changes and psychosomatic equilibrium is preserved (homeostasis). This normal and basic "stress response" resulting in an organism's adaptive capacity to stressors is characterized by the activation of a complex physiological network directed by the neuroendocrine and immune systems, mainly the HPA and the SAM. Both are responsible for coordinating the stress response, promoting adaptation and restoring homeostasis.

While a mild to moderate level of stress is healthy, prolonged or repeated exposure to stressors can lead to overactive stress responses, where the recovery mechanism of the stress system fails to achieve balance. Several associated conditions can emerge due to this overburden, including psychological disturbances (nervousness, irritability depression, anxiety, insomnia), cardiometabolic alterations (hypertension, obesity, food cravings), and gastrointestinal dysfunctions. However, some individuals can easily adapt to changing situations, and this superior ability to cope with stress is called resilience.

Primary herbal adaptogens enhance the efficiency of the adaptive stress response to life stressors, promoting resilience while minimizing hyperreactivity, which may play a relevant role in the pathogenesis of some of the most prevalent diseases of contemporary life. The modern utilization of these ancient botanical "tonics" from traditional medicines continues to expand, and a plethora of preclinical and human trials in the last 50 years have been performed to best characterize the biological effects of primary adaptogens. Notable among them are *W. somnifera* and *R. rosea*, both of which counteract several stress-related conditions. Due to the large heterogeneity between studies and the complex polypharmacological mechanisms of action of both adaptogenic plants that are yet to be completely elucidated, it is challenging to preferentially assign one specific biological activity or therapeutic indication to *R. rosea* versus *W. somnifera*, or vice versa. However, the overall evidence clearly indicates that both *W. somnifera* and *R. rosea* are notable adaptogens with effective anti-stress activity. They ameliorate hyperreactivity HPA and SAM, counteracting stress-related manifestations such as anxiety, nervousness, irritability, insomnia and depression against various types of acute or chronic external stressors.

Nevertheless, a detailed analysis of potential mechanisms of action derived from rodent and cell culture studies may help outline the most appropriate health indications of *R. rosea* versus

W. somnifera. *R. rosea* affects the central nervous system, as evidenced by its capacity to improve symptoms of stress-induced mental and physical fatigue, depression and enhance mental and physical performance under stressful conditions. This is consistent with HPA/SAM modulation, antioxidant, anti-inflammatory activities, and central monoaminergic system up-regulation through inhibition of Monoamine oxidases type A (MAO-A) or B (MAO-B) enzymes. Not surprisingly, one officially accepted traditional use for *R. rosea* is as an "adaptogen for the temporary relief of symptoms associated with stress, such as fatigue, exhaustion and a general sensation of weakness". Likewise, *W. somnifera* has demonstrated remarkable anti-stress activity by modulating HPA/SAM and exhibiting serotonergic-dependent antidepressant effects. However, in contrast to *R. rosea*, its capacity to modulate GABAergic neurotransmission may preclude superior efficacy in combating stress-associated anxiety, nervousness and insomnia. Preclinical studies and clinical evidence provide broad support for *W. somnifera*'s ability to reduce stress, and anxiety, and improve sleep quality.

In summary, taking into account the putative neuroendocrine mechanism of action and the most robust evidence of efficacy from clinical trials, *R. rosea* may tentatively assigned as a regenerative "tonic vitalizing" adaptogen supporting stress-associated fatigue and weakness in several physical and psychological contexts, while *W. somnifera* could be considered as regenerative "tonic-nervine" counteracting stress-related anxiety and insomnia or drowsiness.

Both adaptogenic botanicals, *R. rosea* and *W. somnifera* have a long history of traditional uses and are generally regarded as safe, with no serious adverse events observed at recommended doses. Some minor side effects have been reported in clinical trials, but generally of low incidence and transitory in nature. Additionally, caution should be exercised regarding *W. somnifera* intake in pregnant or childbearing-age women, individuals with thyroid or liver dysfunction or those treated with psychotropic medication, especially in high doses or/and long-term administration.

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CONSENT

It is not applicable

ETHICAL APPROVAL

It is not applicable

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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