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REVIEW

Understanding adaptogenic activity: specificity of the pharmacological action of adaptogens and other phytochemicals

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Adaptogens are stress-response modifiers that increase an organism's nonspecific resistance to stress by increasing its ability to adapt and survive. The classical reductionist model is insufficiently complex to explain the mechanistic aspects of the physiological notion of "adaptability" and the adaptogenic activity of adaptogens. Here, I demonstrate that (1) the mechanisms of action of adaptogens are impossible to rationally describe using the reductionist concept of pharmacology, whereas the network pharmacology approach is the most suitable method; and (2) the principles of systems biology and pharmacological networks appear to be more suitable for conceptualizing adaptogen function and are applicable to any phytochemical. Molecular targets, signaling pathways, and networks common to adaptogens have been identified. They are associated with stress hormones and key mediators of the regulation of homeostasis. In this context, the mechanisms of action of adaptogens are specifically related to stress-protective activity and increased adaptability of the organism. Consequently, adaptogens exhibit polyvalent beneficial effects against chronic inflammation, atherosclerosis, neurodegenerative cognitive impairment, metabolic disorders, cancer, and other aging-related diseases. Current and potential uses of adaptogens are mainly related to stress-induced fatigue and cognitive function, mental illness, and behavioral disorders. Their prophylactic use by healthy subjects to ameliorate stress and prevent age-related diseases appears to be justified. It is very unlikely that the pharmacological activity of any phytochemical is specific and associated only with one type of receptor, particularly adaptogenic compounds, which affect key mediators of the adaptive stress response at intracellular and extracellular levels of communication.

Keywords: adaptogens; adaptability; network pharmacology; specificity

> Health is the ability to adapt to one's environment.
> –George Canguilhem, *Normal and Pathological* (1943)

Introduction

The concept of adaptogen is now more than 60 years old, and has been thoroughly reviewed in relation to physiology, pharmacology, toxicology, and potential uses in medicine and pharmacosanation.[1–14] Originally defined as substances "that increase resistance to a broad spectrum of harmful factors (stressors) of different physical, chemical, and biological natures,"[1,2] adaptogens are considered "metabolic regulators, which increase the ability of an organism to adapt to environmental factors and to avoid damage from such factors."[3] Some adaptogenic plants (Table 1) 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. However, further evidence, based on well-designed clinical trials with standardized herbal preparations, is required to support the efficacy of these traditional herbal medicines to qualify them as herbal medicinal products with well-established use in medicine. Moreover, the investigations of molecular mechanisms of action of adaptogens are required for understanding the polyvalent pharmacological activity of adaptogens. The reductionist concept of a single receptor-based view of drug action[15] would appear to be unsatisfactory for adaptogens. The orthosteric mechanism or permissive allosteric model of agonist-dependent

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Table 1. Plants cited in the literature with adaptogenic properties

Ajuga turkestanica (Regel) Briq.	*Emblica officinalis* Gaetrn.	*Piper longum* L.
Alstonia scholaris (L.) R. Br.	*Eucommia ulmoides* Oliv.	*Potentilla alba* L.
Anacyclus pyrethrum (L.) Lag.	*Evolvulus alsinoides* (L.) L.	*Ptychopetalum olacoides* Benth.
Andrographis paniculata (Burm.f.) Nees[98]	*Firmiana simplex* (L.) W.Wight	*Rhaponticum carthamoides* (Willd.) Iljin
Aralia mandshurica Rupr. & Maxim	*Gentiana pedicellata* (D.Don) Wall	*Rhodiola heterodonta* (Hook. f. & Thomson) Boriss.
Argyreia nervosa (Burm. f.) Bojer	*Glycyrrhiza glabra* L.	*Rhodiola rosea* L.
Argyreia speciosa (L. f.) Sweet	*Heteropterys aphrodisiaca* Machado	*Rostellularia diffusa* (Willd.) Nees.
Asparagus racemosus Wild	*Hippophae rhamnoides* L.	*Salvia miltiorrhiza* Bunge
Bacopa monnieri (L.) Wettst	*Holoptelea integrifolia* Planch	*Schisandra chinensis* (Turcz.) Baill.
Bergenia crassifolia (L.) Fritsch	*Hoppea dichotoma* Willd.	*Scutellaria baicalensis* Georgi
Bryonia alba L.	*Hypericum perforatum* L.	*Serratula inermis* Poir
Caesalpinia bonduc (L.) Roxb	*Lepidium peruvianum/Lepidium meyenii* Walp.	*Sida cordifolia* L.
Centella asiatica (L.) Urb.	*Ligusticum striatum* DC.	*Silene italica* (L.) Pers.
Chlorophytum borivilianum Santapau & R.R.Fern.	*Melilotus officinalis* (L.) Pall.	*Sinomenium acutum* (Thunb.) Rehder & E.H.Wilson
Chrysactinia mexicana A. Gray	*Morus alba* L.	*Solanum torvum* SW.
Cicer arietinum L.	*Mucuna pruriens* (L.) DC.	*Sutherlandia frutescens* (L.) R.Br.
Codonopsis pilosula (Franch.) Nannf.	*Nelumbo nucifera* Gaertn.	*Terminalia chebula* Retz.
Convolvulus prostratus Forssk.	*Ocimum sanctum* L.	*Tinospora cordifolia* (Willd.) Miers
Curculigo orchioides Gaertn.	*Oplopanax elatus* (Nakai) Nakai	*Trichilia catigua* A.Juss.
Curcuma longa L. Curcumin[97]	*Panax ginseng* C.A.Mey.	*Trichopus zeylanicus* Gaertn.
Dioscorea deltoidea Wall. ex Griseb.	*Panax pseudoginseng* Wall.	*Turnera diffusa* Willd. ex Schult.
Drypetes roxburghii (Wall.) Hurus.	*Pandanus odoratissimus* L.f.	*Vitis vinifera* L.
Echinopanax elatus Nakai	*Paullinia cupana* Kunth	*Withania somnifera* (L.) Dunal
Eleutherococcus senticosus (Rupr. & Maxim.) Maxim.	*Pfaffia paniculata* (Mart.) Kuntze	

Note: This table is an update from the reviews of Wagner *et al.*[2] and Panossian and Wagner.[7] It includes plants that do and do not meet the formal definition of adaptogen.

antagonism, as applied to the receptor theory of drug action, is limited by the assumption that only one receptor is involved in the pharmacological activity of adaptogens. In addition, these models do not consider the possibility that adaptogens modulate receptor expression via other mechanisms. However, adaptogens exhibit multitarget action and the shared use of a number of different receptors, including receptors for corticosteroid, mineralocorticoid, progestin, estrogen, serotonin (5-HT), *N*-methyl-D-aspartate, and nicotinic acetylcholine, receptor tyrosine kinases, and many G protein–coupled receptors.[16–38] Therefore, the possibility that numerous molecular network interactions (with feedback regulation of the neuroendocrine and immune systems) contribute to the overall pharmacological response and result in agonist-dependent antagonism is most suitable for understanding the mechanisms of action of adaptogens. Thus, the pharmacology of adaptogens is a typical example of network pharmacology.[16,39,40] Network pharmacology has the potential to provide treatments for complex diseases, chronic conditions, and syndromes, inclusive of their pathophysiologic evolution, where conventional approaches have often been disappointing.[41–48] Adaptive stress responses include several stages[49] and involve multiple molecular networks in which receptors interact with adaptogens.[16,39,40]

The aim of this review is to summarize the contemporary understanding of the specific and nonspecific mechanisms of adaptogen action and to provide a rationale for the use of adaptogens in stress- and age-related disease. Additionally, the specificity of the pharmacological action of phytochemicals is addressed.

The historical background of the adaptogen concept

Resistance to stress and survival depends on adaptability and the thresholds that determine an organism's innate tolerance to a given level of stress. The stress-induced responses of the innate and adaptive defense systems involve numerous mediators of stress signaling, including the neuroendocrine–immune complex that supports allostasis in simple and complex organisms.[50–53] Repeated mild exposure or low doses of stress result in the increased resistance of cells and organisms to subsequent stress exposure, resulting in an adaptation that favors survival.[49,50] This phenomenon of adaptation to repetitive low-level stress was first described by Hans Selye in 1936[49] using rats exposed to low temperatures, low oxygen tension, muscular exercise, adrenaline, and morphine. Several nonspecific reactions were evoked (thymus atrophy, adrenal hyperplasia, stomach ulceration, increased secretion of cortisol and catecholamines, etc.), which Selye termed the *general adaptation syndrome* (GAS).[49,50] GAS necessitates three stages. The first is the initial stress recognition or "alarm reaction" when symptoms emerge. The second stage involves the acquisition of nonspecific resistance, following which symptoms disappear. Stage 3 signals exhaustion, when the same symptoms reappear, followed by death.

Through the 1950s and 1960s, Lazarev and Brekhman suggested that certain compounds and herbal extracts, termed *adaptogens*, could prolong the duration of nonspecific resistance to stress and diminish the magnitude of the alarm phase.[1,11,12] The adaptogens were defined as nontoxic compounds with polyvalent mechanisms of action and pharmacological effects related to adaptability and survival.[1,11,12,54]

The adaptive stress response occurs in a variety of regulatory systems from the cellular level to the whole organism. At the cellular and molecular levels, intra- and extracellular signaling pathways promote upregulation of antiapoptotic proteins, neuropeptides, and antioxidant enzymes in the alarm phase.[55] Figure 1 outlines seven adaptive stress response signaling pathways that protect neurons against degeneration and promote synaptic plasticity and depicts how adaptogens influence signaling to promote neuroplasticity and decrease vulnerability to neurodegeneration. In this context, botanical adaptogens are metabolic regulators that increase survival by increasing adaptability in stress.

A characteristic feature of adaptogens is that they act as eustressors (i.e., "good stressors") and as mild stress mimetics or "stress vaccines" that induce stress-protective responses.[3,56,57] For example, Figure 2 illustrates the mild stress-mimetic effects of diglucosyl-cucurbitacin R (DCR), using measurements of corticosterone release from isolated adrenocortical cells and levels of corticosterone in the blood of rats. The inclusion of DCR lowered corticosterone release in response to restraint stress (*in vivo*), or ACTG (*in vitro*).[56,59] Similar results in other experimental models were obtained using ginsenosides[60] and *Rhodiola* extract.[57,58] These experiments clearly show a vaccination-like effect of the adaptogen with reference to protecting against subsequent stress.[3,56]

Mild (survivable) stress induces a resistance or "immunity" to subsequent, more severe stress exposure.[56,57] However, this stress-induced resistance carries no memory function, and repeated exposure to the adaptogen is required to maintain the plastic adaptive state. Another comparison could be made with repetitive physical exercise, which increases endurance and performance.[61] A state of nonspecific resistance (SNSR) could be achieved either by the gradual "training" of an organism to withstand the effects of the stress or by adaptogens that mimic the stress. The repeated administration of adaptogens and the consequent adaptogenic or stress-protective response arise in a manner analogous to repeated physical exercise that leads to prolonged SNSR and increased endurance and stamina.[61,62] The phenomenon of adaptation to stress also underpins the hormetic response, which is defined as an adaptive response characterized by a biphasic dose–response, with a low dose that is stimulatory (i.e., has a beneficial effect) and a high dose that is inhibitory (i.e., has a toxic effect).[63,64]

Pharmacology and the mechanism of action of adaptogens

The pharmacologic efficacy of adaptogens and their stress-protective effects are usually investigated by testing cognitive function and physical endurance under stressful conditions.[2,4,65] Further, the use of

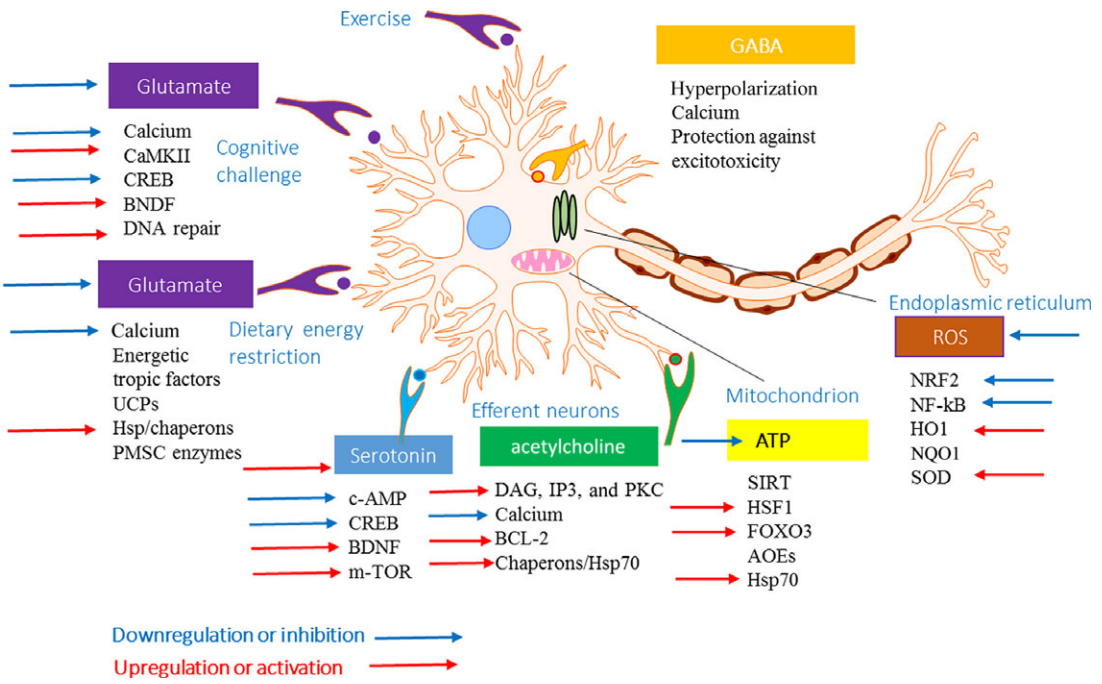

Figure 1. Adaptive stress response and effects of adaptogens. Adaptive cellular stress response signaling that mediates beneficial effects of environmental challenges (updated and adapted from Ref. 55) and adaptogens on neuroplasticity and vulnerability to neurodegeneration. A typical glutamatergic neuron in the hippocampus is depicted receiving excitatory inputs (red) from neurons activated in response to exercise, cognitive challenges, and dietary energy restriction. Examples of seven different adaptive stress response signaling pathways that protect neurons against degeneration and promote synaptic plasticity are shown. During exercise and cognitive challenges, postsynaptic receptors for glutamate, serotonin, and acetylcholine are activated to engage intracellular signaling cascades and transcription factors that induce the expression of neuroprotective proteins, including brain-derived neurotrophic factor (BDNF), mitochondrial uncoupling proteins (UCPs), and antiapoptotic proteins (e.g., BCL-2). BDNF promotes neuronal growth, in part, by activating the mammalian target of rapamycin (mTOR). Mild cellular stress resulting from reduced energy substrates and reactive oxygen species (ROS) engages adaptive stress response pathways, including those that upregulate antioxidant enzymes (AOEs) and protein chaperones. Release of GABA from interneurons in response to activity in excitatory circuits (as occurs during exercise and cognitive challenges) hyperpolarizes excitatory neurons, protecting them from Ca^{2+} overload and excitotoxicity. CaMKII, calcium/calmodulin kinase II; CREB, cyclic AMP response element–binding protein; DAG, diacylglycerol; FOXO3, forkhead box protein O3; HO1, heme oxygenase 1; HSF1, heat shock factor 1; IP3 PKC, inositol-trisphosphate 3 protein kinase C; NF-κB, nuclear factor κB; NQO1, NAD(P)H-quinone oxidoreductase 1; NRF2, nuclear regulatory factor 2.

valid and specific biomarkers related to pharmacological activity is a generally accepted practice in pharmacology.[66,67]

Which effectors are responsible for mediating adaptogenic effects, and what are their key molecular targets?

A number of human and animal studies have suggested that the stress hormones cortisol and neuropeptide Y (NPY) and several important mediators of the adaptive stress response (e.g., nitric oxide, stress-activated protein kinases, heat shock proteins (HSP70 and HSP25), and the FOXO (DAF-16) transcription factor) are key players in mediating the adaptogenic effects of plant extracts (e.g., *Rhodiola, Eleutherococcus, Schisandra*, ginseng, *Bryonia, Withania,* etc.).[57,58,66–71] These mediators orchestrate the process of stress adaptation (including aging or disease pathology), with no single contribution that can be estimated with any degree of certainty. Figures 3–5 show the hypothetical mechanisms of action of adaptogens in stress-induced fatigue, depression, and aging.

Several reviews describe the possible mechanisms of action of adaptogens on the basis of the results of *in vitro* and *ex vivo* experiments using cells of both human and animal origin.[3–9,13,67–70,72] HSP70

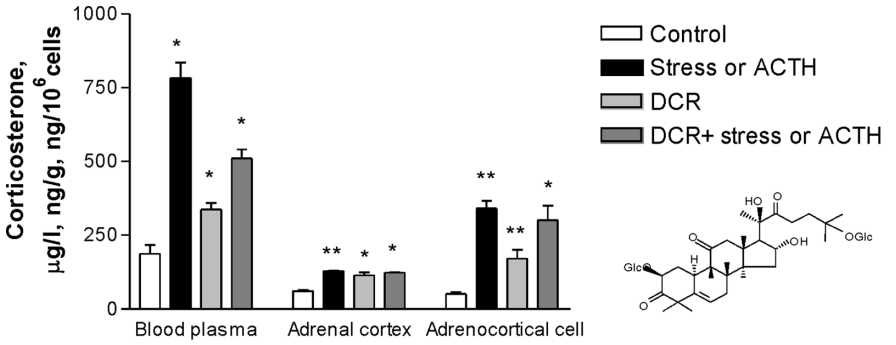

Figure 2. Corticosterone content in blood plasma (ng/mL), in adrenal cortex (μg/g), and in isolated adrenocortical cells (ng/106 cells) under stress (2.5-h immobilization) and upon the influence of ACTH (7.1×10^{-10} M) and DCR (0.1 mg/kg *in vivo* and 5×10^{-5} M *in vitro*). *, $P < 0.001$; **, $P < 0.025$. Adapted from Ref. 56.

and heat shock factor-1 (HSF1) are considered to be pharmacological targets of antiaging therapies.[73] However, chemicals used to induce HSP70 are typically cytotoxic and therefore cannot be used by the target patient population (e.g., elderly individuals) who are more susceptible to stress.[73] Fortunately, plant adaptogens have been used safely over a very wide dose range (up to 3000 mg/kg of rat body weight), even with repeated administration (over several months). The adaptogens *Rhodiola, Schisandra, Eleutherococcus*, and their combination as ADAPT-232 (with its active constituent salidroside) stimulate the expression of HSF-1 and heat shock protein 70 (HSP72) in isolated neuroglia, provoke HSP72 release from cells,[67,70] and promote the increased expression of HSP70 *in vivo*.[69,74–77] Chronic *Rhodiola rosea* use significantly ameliorated swimming-induced fatigue by promoting glycogen levels, increasing energy generated by lipogenic enzymes, and boosting defense mechanisms inclusive of HSP70 action.[75] *R. rosea* root extract significantly upregulates HSP70 mRNA and protects skeletal muscle cells against chemically induced oxidation.[77] Further, Schizandrin B pretreatment induces a time-dependent increase in HSP25 and HSP70 expression in rat heart and protects against myocardial ischemia–reperfusion injury.[74] The hepatic cytoprotective action of schizandrin B against acetaminophen-induced liver injury is also mediated, at least in part, by the induction of HSP27 and HSP70 in mice. Oral administration of schizandrin B increased HSP27 and HSP70 gene and protein expression in a time- and dose-dependent fashion.[76]

ADAPT-232–induced expression and release of HSP72 from glioma cells necessitated the action of HSF1 or NPY (Fig. 3). Thus, it has been demonstrated that HSF1 and NPY might be primary upstream molecular targets of adaptogens in neuroglia.[70] ADAPT-232 and its active constituent salidroside act on NPY expression via the upregulation of HSF-1, which lies upstream of HSP72 expression and release (Fig. 3). The most active adaptogen is ADAPT-232, which upregulates both HSP70 and NPY *in vitro*.[67] The activation of NPY by ADAPT-232 promotes HSP70 expression in neuroglia, which helps to maintain homeostasis in neuronal cells. The stimulation and release of stress-induced hormone NPY and the stress-induced chaperone HSP70 into the blood is an innate defense response to mild stress (the adaptogen), which increases tolerance and adaptation and promotes longevity. This gives rise to adaptive and stress-protective effects via various components of the central nervous, sympathetic, endocrine, immune, cardiovascular, and gastrointestinal systems. Both NPY and HSP70 are known to play important roles in the regulation of aging and in the pathogenesis of age-related disease.[78]

Rhodiola, Schisandra, Eleutherococcus, Withania, and ginseng have been shown to extend the life span and survival (when stressed) of the nematode *Caenorhabditis elegans*,[58,79,80] the fruit fly (*Drosophila melanogaster*),[81] and the yeast *Saccharomyces cerevisiae*.[82] An age-related decline in the ability to induce HSP70 was found in nervous system tissue,[83,84] in skeletal and cardiac muscle, and in the liver.[85] Inhibition of HSF1 and HSP70 expression occurs in Alzheimer's disease[86] and is associated with the accumulation of plaques of aggregated β-amyloid peptide, together with neurofibrilliary

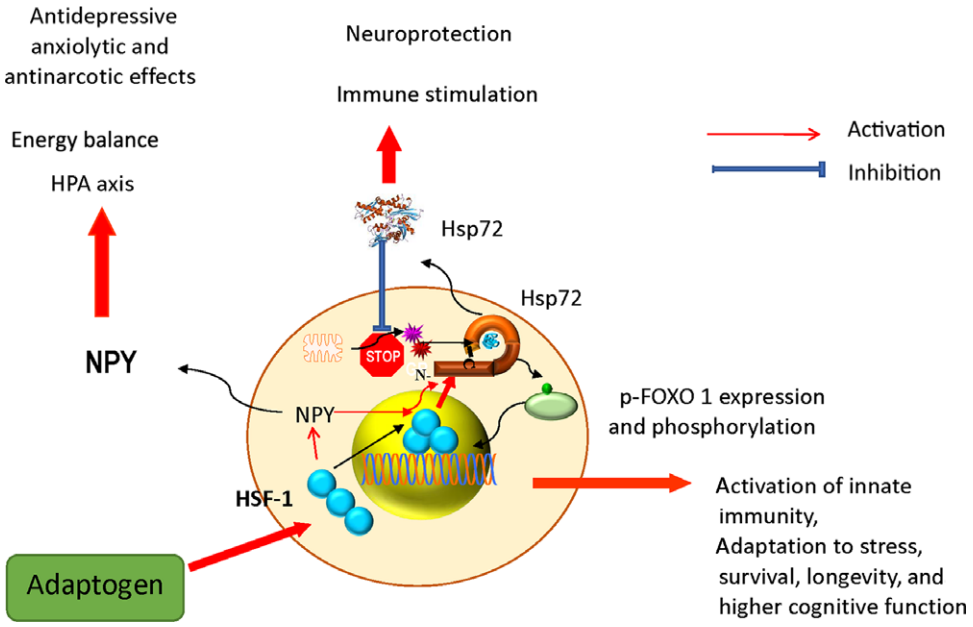

Figure 3. Hypothetical mechanism of action of adaptogens on the stress system at a cellular level. Adaptogens activate expression and release of NPY and Hsp72 via an HSF1-dependent mechanism, including the trimerization and nuclear translocation of HSF1 (blue circles). The release of HSP72 takes place via a mechanism dependent on the upregulation of NPY, which is upstream of HSP72 and other mediators of stress response involved in the effects of adaptogens. NPY is known to play an important role in the regulation of the HPA axis and energy homeostasis and secretion of HSP72, playing an important role in neuroprotection and innate immunity. HSP72 in turn inhibits the FOXO transcription factor, playing an important role in the adaptation to stress and longevity. These pathways contribute to the antifatigue effect of adaptogens, increasing attention and improving cognitive function. The activation of NPY by adaptogens initiates HSP72 expression in human neuroglia cells, which are known to maintain homeostasis of neuronal cells. Stimulation and release of these stress hormones (NPY and HSP72) into the blood circulating system is apparently an innate defense response to mild stressors (adaptogens), which increases tolerance and adaptation to stress. This gives rise to adaptive and stress-protective effects via various components of central nervous, sympathetic, endocrine, immune, cardiovascular, and gastrointestinal systems. Both NPY and HSP72 play important roles in stress, regulation of aging, and pathogenesis of age-related diseases. The antinarcotic effects of adaptogens are apparently mediated by NPY, which is known to play an essential role in the basic mechanisms of morphine tolerance and opioid dependence. For instance, morphine significantly decreases NPY levels in the hypothalamus, the striatum, and the adrenal glands. Adapted from Ref. 70.

tangles of tau protein in the brain.[84] Heat shock proteins protect liver cells from the toxic effects of alcohol, heavy metals, xenobiotics, and oxidants. Consequently, the age-related decline of HSP70 expression contributes significantly to the reduced efficacy of (detoxifying) liver function in aged individuals.[85] A 4-month study in 2-year-old rats showed that, in comparison with a control group, the ADAPT-232 group demonstrated superior liver detoxifying function, greater CNS function (memory and learning ability), no development or progression of cardiac insufficiency and hypercholesterolemia, normal protein synthesis and activity of the hormonal system, less stress sensitivity (hypodynamia-induced damage to the stomach and adrenals), no impaired apoptosis, and no spontaneous tumor promotion.[87]

It was shown that adaptogens exert protective effects against the stress-induced (heat shock, menadione-induced oxidative stress, and heavy metal–induced intoxication) death of embryos of the pond snail *Lymnaea stagnalis*.[88] However, in the developing organism, adaptogens failed to alter the expression of heat shock proteins. This may be predictable given that, in young organisms, the expression of HSP70 in stressful conditions is already maximal and will only decline with age. In comparison, chronic *R. rosea* use (and other adaptogens) significantly increases HSP70 concentration in rats and promotes their endurance in exhaustive swimming-induced fatigue.[69,79]

Exercise can induce expression of HSP70, which acts as an antiaging agent. This upregulation

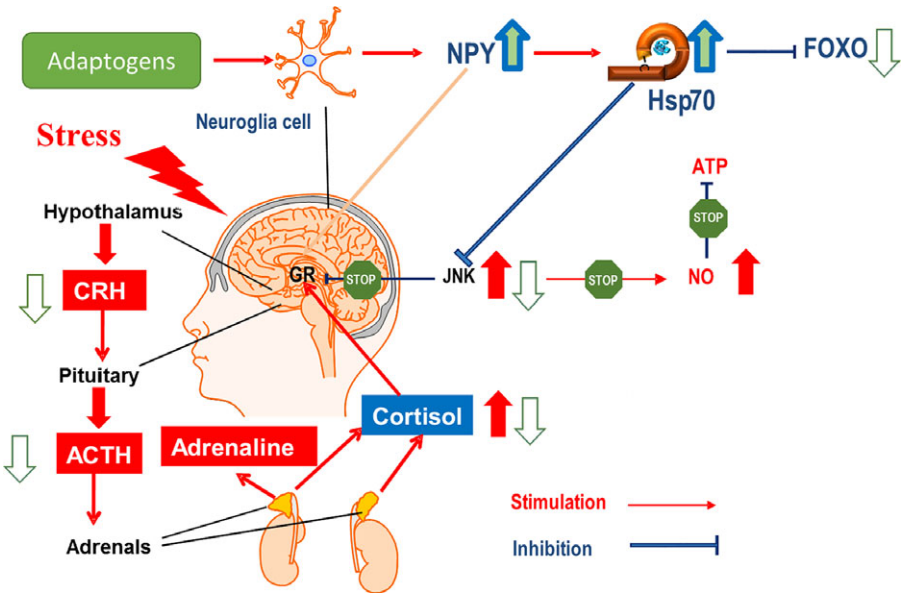

Figure 4. Hypothetical mechanism of action of adaptogens on the stress system in depression. Stress-induced release of CRH from the hypothalamus, followed by release of ACTH from the pituitary, simulates release of adrenal hormones and NPY in order to cope with the stress. Feedback regulation of overreaction is initiated by cortisol release from the adrenal cortex, followed by binding to glucocorticoid receptors (GR) in the brain. This signal stops the further release of brain hormones, and the stress-induced increase in cortisol decreases to normal levels in the circulatory system. While short and mild stress (eustress) is essential to life, severe stress can cause disease depression, which is associated with generation of active oxygen-containing molecules, including nitric oxide, which is known to inhibit ATP formation. Stress-induced signaling protein JNK was found to inhibit GR; consequently, this feedback normalization is blocked and cortisol content in blood of depressive patients is permanently high. This is associated with impaired memory, impaired ability to concentrate, fatigue, and other symptoms. Adaptogens suppress elevated JNK and cortisol in stress and stimulate the formation of HSP70, which is known to inhibit JNK. Consequently, nitric oxide levels no longer increase and ATP generation is not suppressed. Adapted from Ref. 16.

contributes to the maintenance of muscle fiber integrity and facilitates muscle regeneration and recovery. On the other hand, HSP70 expression is reduced during muscle inactivity and aging. Dysfunction of HSP70 generation may drive muscle atrophy, contractile dysfunction, and reduce regenerative capacity (associated with aging). The beneficial effects of activating the biosynthesis of HSP70 in skeletal muscle have been established in animal studies, suggesting that HSP70 is a key therapeutic target for the treatment of various conditions that negatively affect skeletal muscle mass and function.[89,90]

Thus, the strategy of therapeutic intervention in age-associated disease is directed toward the failure of specific signaling pathways that ameliorate and postpone aging by their activation of multiple genes. At the transcriptional level of regulation, there are two molecular targets that are related to complimentary longevity pathways, HSF1/HSP70 and FOXO.[73] Modulating these two pathways may delay the onset of neurodegenerative disease and other age-related pathologies, including cognitive decline, cancer, diabetes, and cardiovascular disease, owing to multigene effects.

Salidroside and extracts of *Schisandra chinensis* and *R. rosea* were found to be the most active inhibitors of stress-induced p-SAPK/p-JNK. It has been shown that oral supplements of rhodioloside, or extracts of *Eleutherococcus senticosus*, *S. chinensis*, or *R. rosea*, administered over a 7-day period to rabbits subject to restraint stress, significantly decreased their levels of stress-activated protein kinases (i.e., the phosphorylated forms of SAPK/JNK) in circulating blood.[66] This is in line with other observations in which adaptogens upregulate HSF1 and HSP70 (hypothesis; Fig. 3).

In experiments using the nematode *C. elegans*, it was shown that adaptogens induce the translocation of DAF-16 (mammalian FOXO; dFoxO

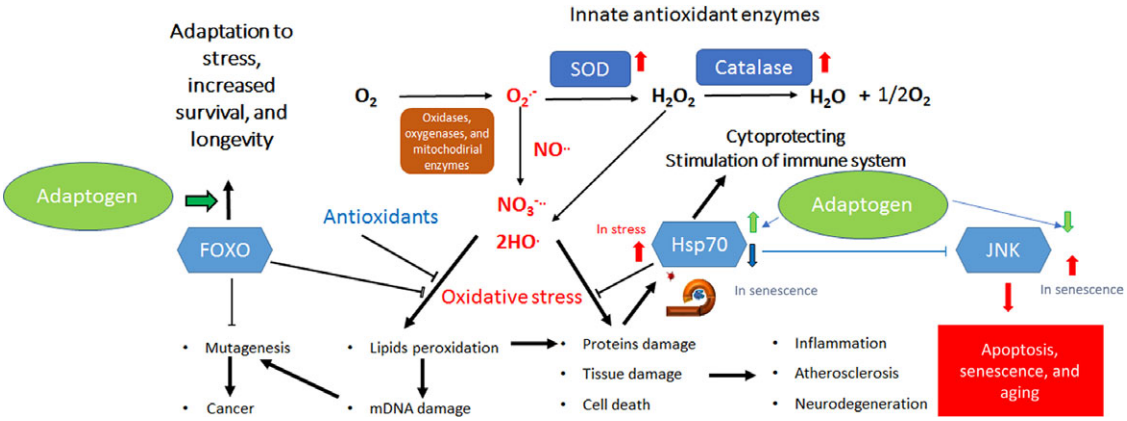

Figure 5. Hypothetical mechanism of action of adaptogens in the regulation of the innate antioxidant system and oxidative stress–induced apoptosis in aging.[9] The free radical theory of aging, known as the oxidative stress theory, postulates that the organisms living in an aerobic environment are continuously exposed to reactive oxygen species containing molecules/species (ROS, oxidative stress), which are generated as by-products of normal cellular metabolism. When the innate antioxidant system (glutathione peroxidase, superoxide dismutase, and catalase) incompletely neutralizes ROS, cumulative cellular oxidative damage to macromolecules, including lipid peroxidation and oxidation of DNA and proteins, induces irreversible functional changes leading to aging, senescence, and associated diseases. Stress-induced excising generation of ROS results in destructive interactions with many proteins that play various roles in cellular functions, including proteins that trigger two genetic programs: the program of cellular senescence and the program of cell death (apoptosis). Loss of function and progressive accumulation of damaged proteins and abnormal toxic protein aggregates are the beginning of the progression of aging-related disorders, senescence, and decreased life span. Oxidative stress can trigger two signaling pathways through activation of JNK kinase in the same cell. A balance between the pro- and antiaging JNK-mediated programs is shifted in favor of HSP70 at a young age. Despite strong oxidative stresses, a young cell can survive and divide, because stress-activated HSP70 blocks JNK-stimulated apoptosis.[9] Adaptogens (*Rhodiola, Shisandra,* and *Eleutherococcus*) upregulate HSF1 and HSP70 *in vitro* and *in vivo*, downregulate JNK *in vivo*, and inhibit apoptosis, senescence, and aging *in vivo*.[9,66,68] In turn, HSP70 directly regulates FOXO signaling in skeletal muscle. HSP70 controls FOXO/DAF-16 activity by promoting its nuclear export.[58]

in fly) from the cytoplasm into the nucleus, suggesting reprogramming that favors a stress-resistant and longevity-biased transcriptome.[58] On the basis of these data, it was suggested that adaptogens are experienced as mild stressors at concentrations that induce stress resistance and longevity.

Is there a specific target for stress response modifiers?

Specificity regarding drug action implies an ability to interact with high affinity to one or a limited number of receptors that are peculiar to a particular disease or illness. If a drug has one and only one effect in all biological systems, then it possesses specificity. However, the notion of identifying one specific interaction common to all adaptogens remains elusive for several reasons.

First, stress responses and adaptation to environmental challenge are multistep processes that involve intracellular and extracellular signaling pathways at differing levels of stress regulation (i.e., the neuroendocrine–immune complex). Consequently, the metabolic regulation of homeostasis by adaptogens at the cellular and systems levels is associated with a multitude of targets, which requires a holistic approach in relation to understanding. Adaptogens may exert a polyvalent biological activity and provoke multitarget effects at the transcriptional, proteomic, and metabolomic levels.

The reductionist method of dissecting biological systems into their constituent parts has been effective in explaining the chemical basis of numerous living processes and medicinal chemistries. However, many biologists and pharmacologists now acknowledge that this approach has its limits, especially when attempting to deduce mechanisms in complex biological systems. Further, consciousness, different states of perception, adaptation, inflammation, and aging cannot be distilled into one or even several chemical reactions that occur in the brain or other tissues that support allostasis.

The specificity of a complex biological activity does not necessarily arise from the specificity of

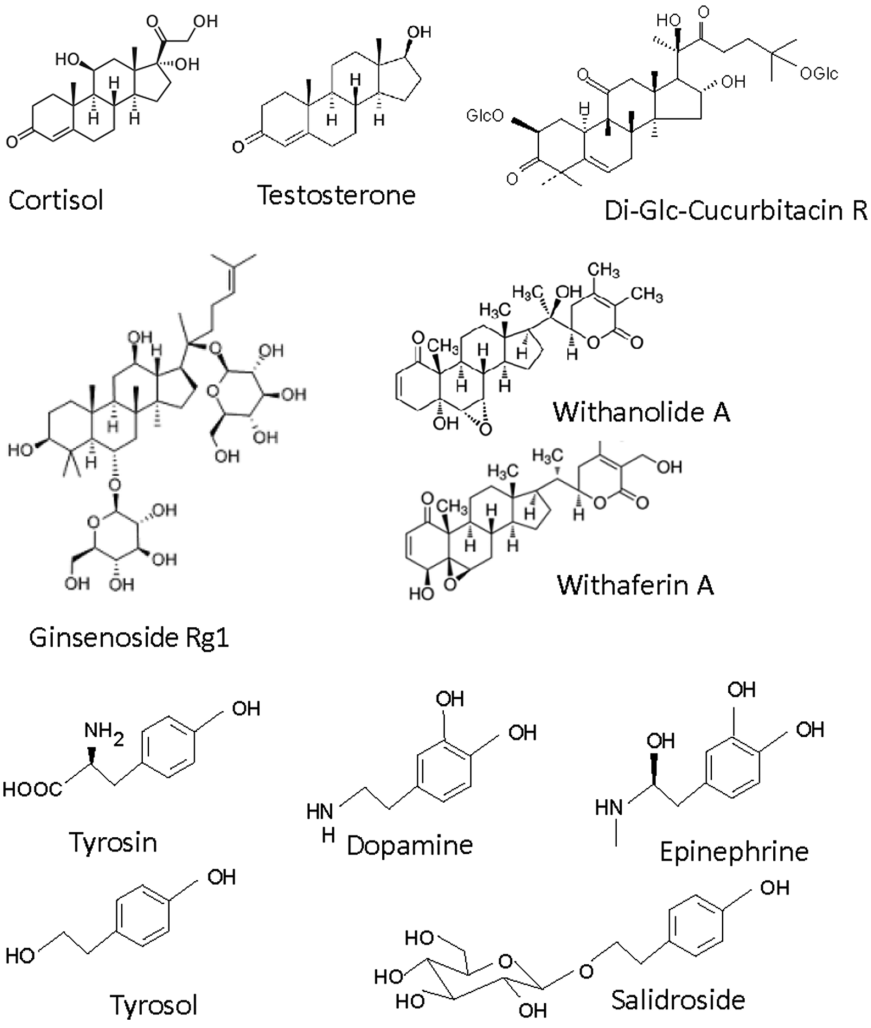

Figure 6. **Chemical structures of human hormones cortisol, testosterone, and epinephrine; neurotransmitter dopamine; its precursor tyrosine; and adaptogenic compounds of plant origin (tyrosol, salidroside, ginsenoside Rg1, withanolide A, withaferin A, and diglucoside of cucurbitacin R).**

individual molecules, as these may act in different processes. For example, genes that alter memory formation encode proteins in the cyclic adenosine monophosphate (cAMP) signaling pathway that are not specific to memory.[42] It is the particular cellular compartment and environment in which cAMP is released that allows a gene product to mediate its unique effect. Biological specificity results from the way in which these components assemble and function collectively.[94] Component interactions, as well as the environment, give rise to new features, such as network behavior,[95] which are absent when considering the isolated components.

What are the chemical structures of the principal active substances in adaptogenic plant extracts and their structure–function relationships?

Currently, no systematic studies on the structure–function activities of purified adaptogens with their targets are available. However, the principal active ingredients of plant adaptogens (as investigated thus far) can be divided into two main chemical groups (Fig. 6): (1) terpenoids, with a tetracyclic skeleton, such as cortisol and testosterone (ginsenosides, sitoindosides, cucurbitacines, and withanolides) and (2) aromatic compounds that are

structurally similar to catecholamines or tyrosine, including lignans (eleutheroside E *(E. senticosus)* and schizandrin B *(S. chinensis))*, phenylpropane derivatives (syringin *(E. senticosus)*, rosavin *(R. rosea)*), and phenylethane derivatives (salidroside *(R. rosea))*. A number of studies indicate direct interactions between ginsenosides and corticosteroid and estrogenic receptors.

Accordingly, plants containing mainly tetracylic or pentacyclic terpenoids (ginseng, *Withania, Rhaponticum, Bryonia*, etc.) are presumed to act via the hypothalamic–pituitary–adrenal (HPA) axis, while plants (e.g., *Rhodiola, Schisandra,* etc.) containing predominantly phenolic compounds (phenylpropanoids, phenylethanoids, and their dimers (lignans)) are presumed to interact with elements of the efferent sympathoadrenal system (SAS).

Interestingly, NPY contains five tyrosine residues,[91] with the same *p*-hydroxylmethylene residue as tyrosol and salidroside. Tyrosine moieties have been shown to be important for brain receptor binding, as well as for the activity of NPY.[92] We would hypothesize that the *p*-hydroxylmethylene residue of the tyrosine unit in NPY and the *p*-hydroxylethylene residues of tyrosol and salidroside could compete for receptor binding sites.[70]

Van der Waals interactions between the 4-hydroxyphenethyl residue of tyrosol (or salidroside) with the same residue in the tyrosine-rich moiety, phosphorylated by tyrosine kinases, might also provide an avenue for agonistic interactions mediated by adaptogens. Similar agonistic (or antagonistic) interactions are possible between the 3,4-dihydroxyphenethyl residues of catecholamine (dopamine, adrenaline, and noradrenaline) receptors.

The efferent SAS and HPA axis are anatomically and functionally interconnected, and during stress scenarios they can interact with each other at different levels. For example, catecholamines stimulate the HPA axis via corticotropin-releasing hormone (CRH), whereas HPA hormones act on the SAS in stress situations. The SAS provides a rapid response mechanism that primarily controls the acute response of the organism to a stressor. In addition to catecholamines, both the sympathetic and parasympathetic divisions of the autonomic nervous system secrete a variety of neuropeptides, ATP, and nitric oxide.[93] Some plants (e.g., *Eleutherococcus*) contain both types of compound, which further complicates their overall effect on the stress system.

What is the effect of the adaptogen on gene expression, and what physiological functions and diseases can adaptogens influence?

As our knowledge of cell and systems biology grows, new questions and challenges arise. One of these relates to specific indications for drug use in medicine. The one drug–one indication paradigm is ordinarily unsuitable for adaptogens, given their polyvalent mode of action and nonspecific effects on the immune, endocrine, and nervous systems.

Attempts to find commonalities[16,66,67] in the mechanistic aspects of adaptogen function have focused on their effects on upstream regulation in cellular homeostasis[16] (Fig. 7). An example would be gene expression in isolated neuroglia, which are known to play an important role in the maintenance of homeostasis in the CNS. Microarray-based, transcriptome-wide mRNA expression profiles of neuroglia after exposure to various adaptogens were analyzed, and genes specifically deregulated by adaptogens were identified.[16,39]

Common to adaptogens is deregulation of a large number of genes that encode various G protein–coupled receptors (GPCRs), including downregulation of the *HTR1A*, which encodes the serotonin GPCR, which is known to activate various biological and neurological processes that are negatively associated with anxiety, cognition, learning, memory, and mood.[16]

Furthermore, adaptogens regulate the expression of a large number of genes that encode key proteins of the G protein signaling pathways, primarily the cAMP, protein kinase A, phosphotidylinositol-4,5-bisphosphate 3-kinase/protein kinase B, phospholipase C, diacylglycerol, and the nuclear factor κB canonical signaling pathways.[16]

Other common targets of adaptogens are genes involved in the regulation of cytoplasmic and nuclear proteins that play an important role in behavioral, cognitive, and age-associated disorders. These include genes that encode the ERα estrogen receptor (ER) (2.9- to 22.6-fold downregulation), the cholesterol ester transfer protein (5.1- to 10.6-fold downregulation), heat shock protein HSP70 (3.0- to 45.0-fold upregulation), and the serpin peptidase inhibitor (neuroserpin).

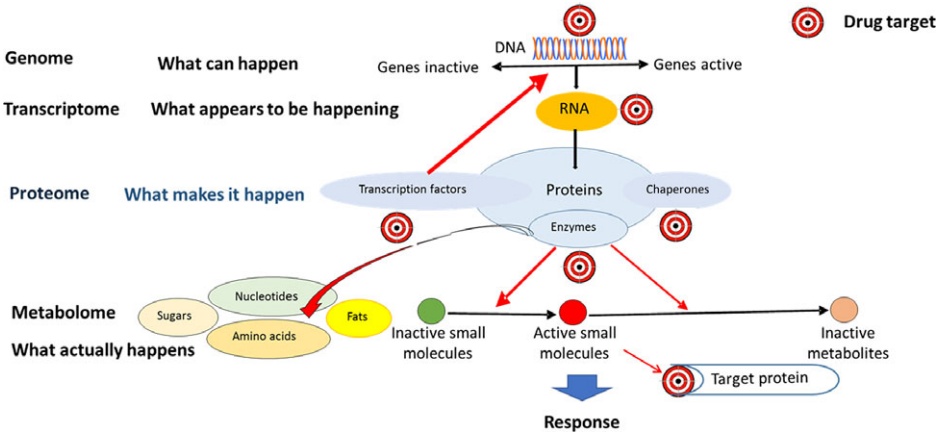

Figure 7. Flowchart showing the possible cellular molecular targets for pharmacological intervention and the cell response after an active molecule binds its receptor. Receptor binding can be activated by competitive, agonistic binding with similar/mimetic substances/drugs. The binding of active molecules (red cycle) can be inhibited by degradation of the active molecule to inactive metabolites, inhibition of the transformation (biosynthesis) of an inactive precursor (green cycle) to form an active molecule, or reversible or irreversible blockage of the active site. All of these events occur at the metabolomics and proteomics levels in cell response regulation. Theoretically, four regulation levels exist: metabolomic, proteomic, transcriptomic, and genomic. The proteomic level includes regulation of the number and activity of the receptor proteins and the biosynthesis and activity of the enzymes, chaperones, and transcription factors. The upstream levels of regulation are transcriptional and gene expression levels associated with the activation (upregulation) and inhibition (downregulation) of DNA array cascades. In some studies, gene expression in isolated neuroglia cells exposed to *Rhodiola, Eleutherococcus, Schisandra,* and *Andrographis* extracts or their active constituents was assessed by analyzing mRNA arrays. Additional downstream analyses of the mRNA microarray data were performed to predict the effects of adaptogens on cellular functions, biological processes, and pharmacological activities. These effects exclude possible interactions of adaptogens at the metabolomics level in cell response regulation during the posttranslational steps, including agonistic or antagonistic effects on receptors and effects on the allosteric regulation of enzyme activity associated with cofactor binding.[16,39,40]

Overall, many of these targets are signaling pathways and networks that are associated with chronic inflammation, atherosclerosis, neurodegenerative cognitive impairment, metabolic disorders, and cancer.[16,39,40,72] All are associated with aging (Tables S1 and S2). Diseases associated with aging that might be influenced by adaptogens are shown in Table S3 (on the basis of predictions derived from the effects of adaptogens on gene expression in neuroglia), with Table S4 listing the effects of adaptogens on several multifunctional genes involved in the regulation of age-associated disorders.

During these studies, several important observations were made. First, two or more agents working together can generate an outcome that could not be predicted from their isolated activities. Analyses of RNA microarray data from isolated neuroglia and the comparison of genes deregulated by plant extracts and their fixed herbal formulation might prove to be a useful tool/method (in humans) with which to assess the synergistic and antagonistic interactions of herbal extracts. Second, the total number of deregulated genes was fairly constant, irrespective of the number of compounds present in the extract. Even a single compound could deregulate several hundred genes (i.e., cellular effects were not additive, with a lack of correlation between the number of active compounds and the number of deregulated genes). Third, deregulated gene profiles depend on the concentration of the plant extract in cell culture, with an indication that biologic activity differs at physiologic (10^{-9} M) versus pharmacologic concentrations (10^{-6} M). Finally, the magnitude of gene deregulation is several-fold higher at physiologic concentrations, indicating selective interactions with some receptors. While the mechanisms that underpin these observations remain elusive, they may provide the basis with which to understand cellular adaptation to pharmaceutical intervention.

Do phytochemicals exhibit any specific pharmacological action?

Many plant-derived drugs with accepted uses in the treatment of certain diseases display no

specificity. For example, small doses of the highly active alkaloid morphine (an analgesic), atropine (mydriatic), pilocarpine (miotic), ephedrine (hypertensive), reserpine (hypotensive), lobeline (bronchodilator), strychnine (stimulant), berberine (antimicrobial), and vinblastine (antileukemic) interact with multiple protein targets, which results in many dose-dependent pharmacological and toxic effects.

Medicinal plants are traditionally used to treat the symptoms of several diseases. As an example, cannabis is used to provide pain relief (analgesia), stimulate the appetite, and treat the symptoms of attention deficit/hyperactivity disorder, Alzheimer's disease, anxiety, depression, arthritis, asthma, autism spectrum disorder, diabetes, epilepsy, fibromyalgia, gastrointestinal illness, glaucoma, hepatitis C/liver disease, Huntington's disease, inflammatory and autoimmune conditions, migraine, headaches, multiple sclerosis, Parkinson disease, posttraumatic stress disorder, schizophrenia, skin disorders, sleep disorders, and traumatic brain injury.

Furthermore, even purified individual compounds (e.g., curcumin, plumbagin, and salidroside) have multitarget effects and exhibit polyvalent pharmacological actions. Any pharmacological review of medicinal plants contains data on their potential effects on the immune, endocrine, or nervous systems, which is not surprising given that biologically active secondary metabolites play defense roles via the biosynthesis of a plethora of terpenoid and phenolic compounds.

In this context, it is very unlikely that there is any phytochemical that specifically interacts with high affinity to only one or two receptors exclusive to a particular disease or health condition. Occasional-specific interactions with one receptor might be observed at low dose, with a rather narrow therapeutic window for selective action.

Current and potential uses of adaptogens

The efficacy of various adaptogens in stress-induced mental illness and behavioral disorders has been reviewed.[5,6,8,13] Other applications might be associated with the regulation of the HPA axis, glucocorticoid receptors (GRs), and cortisol production. In general, corticosteroids, corticotropin-releasing factor, HSP70, and prostaglandin E2 are endogenous mediators of cellular signaling, which protect cells and whole organisms from overreacting to stimuli.

Cortisol is a stress hormone released from adrenocortical cells into the circulatory system to prevent the organism from overreaction/inflammation.[96] This is achieved by feedback-mediated downregulation of the activated HPA axis via hypothalamic GR.[98] Increased serum cortisol levels have been observed in connection with clinical depression and psychological stress involving stressors, such as hypoglycemia, illness, fever, trauma, surgery, fear, pain, physical exertion, or extremes of temperature. The HPA axis and the SAS system appear to be chronically activated in melancholic depression characterized by hyperarousal, suppression of feeding and sexual behavior, anorexia nervosa, panic anxiety, obsessive–compulsive disorder, chronic active alcoholism, alcohol and narcotic withdrawal, excessive exercise, and malnutrition. A chronically decreased basal stress-responsive activity of the stress system (CRH secretion decreased) is associated with decreased arousal, suboptimal task performance, a suppressed feeling of well-being, seasonal depression (during months with a low number of daylight hours), and depression in the postpartum period.

Adaptogens normalize chronically increased cortisol/corticosterone in the blood and saliva of humans or animals,[66,68] presumably owing to a direct interaction with GR. For example, it was shown that the ginsenoside Rg1 is a functional ligand of GR, and its direct interaction with GR ligand-binding sites has been demonstrated. Rg1 behaves as a partial agonist of GR (not an inhibitor). Interestingly, the ginsenoside Rb1 is a functional ligand of the ER, in particular, the β isoform,[19] and may also have beneficial effects in the conditions described above.

All other mediators of the effects of adaptogens (e.g., nitric oxide, JNK, SAPK, HSP70, HSP25, and FOXO (DAF16)) play roles in chronic inflammation (common to all age-related diseases), such as that seen in muscle degeneration (sarcopenia), senile dementia, Alzheimer's disease, atherosclerosis, cardiovascular disease, hypertension, osteoarthritis, type 2 diabetes, and obesity. Clearly, more randomized clinical trials of standardized botanicals are required if we are to implement these agents in medical practice for use in these specific indications.

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Conclusions

Adaptogens are stress response modifiers that nonspecifically increase an organism's resistance to various stressors, thereby promoting adaptation and survival. Adaptation to environmental challenges and aging are multistep processes that involve diverse mechanisms and interactions. Multiple molecular networks are involved that coordinate both intracellular and extracellular stress signaling. The metabolic regulation of homeostasis by adaptogens at the cellular and systems levels is associated with multiple targets. Consequently, the pharmacology of adaptogens is a typical example of network pharmacology that can be approached using the systems biology concept. The classic reductionist model that presumes a specific receptor/drug interaction is unsuitable for this scenario and insufficient when attempting to understand the mechanism of action of adaptogens. Molecular targets, signaling pathways, and networks common to adaptogens have been identified and are associated with chronic inflammation, atherosclerosis, neurodegenerative cognitive impairment, metabolic disorders, and cancer, all of which are more common with age. Current and potential uses of adaptogens in pharmacotherapy[5,6,8,13] are related to their treatment of mental diseases and behavioral disorders, stress-induced fatigue, and cognitive function. Their prophylactic use by healthy subjects to reduce the negative effects of stress and for prevention of age-related diseases is justified. Further studies are warranted if we are to understand the range of interactions between adaptogens and stress response pathways (both intracellular and extracellular) in terms of the metabolic regulation of homeostasis in stress- and age-associated disease. Further, any strict specificity of pharmacological action when using phytochemicals remains questionable.

Supporting Information

Additional supporting information may be found in the online version of this article.

Table S1. The five cellular functions most influenced (with reference to altered gene activity) by *Rhodiola, Eleutherococcus,* and *Schisandra.*

Table S2. Pathway analysis of representative microRNAs that are responsive (*in vitro*) to adaptogen therapy in isolated neuroglia.

Table S3. Age-associated diseases and the genes involved in their pathogenesis and progression that are significantly (i.e., > twofold) deregulated by all tested adaptogens in experiments with isolated neuroglia.

Table S4. The effects of adaptogens on genes involved in regulating age-associated disorders.

Competing interests

The authors declare no competing interests.

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