60 Years of ADAPTOGENIC SCIENTIFIC RESEARCH

And Its Medicinal Benefits

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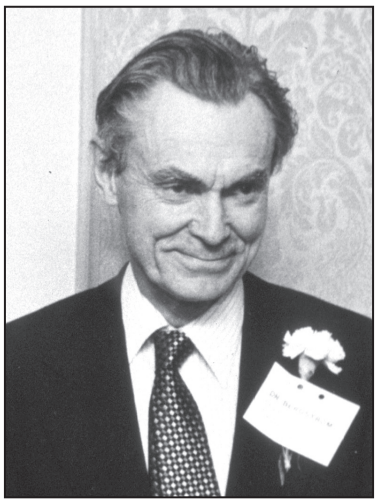
"...the traditional boundaries between various fields of science are rapidly disappearing, and what is more important science does not know any national borders. The scientists of the world are forming an invisible network with a very free flow of scientific information—freedom accepted by the countries of the world irrespective of political systems or religions...."

—Sune K. Bergström's speech at the Nobel Banquet, December 10, 1982



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Preface

The content of this book is based on recent publications in scientific journals and on our own experience in phytotherapy. Our main aim is to summarize accumulated knowledge about the adaptogens in a simplified way, to make it easy to understand for anyone regardless of educational background. That is a challenge due to the daunting complexity of living organisms and lack of knowledge of laws of life."

Cell biology is a bottomless well in complexity. However, many attempts were made to glimpse simplicity lurking within this complexity and capture this simplicity. Our book briefly introduces the adaptogenic concept based on the experience of traditional medicinal systems and recent observations from experiments on animals and studies on humans, including modern network pharmacology and systems biology approaches.

The last chapter of our book is apparently for advanced readers, despite the hope that it would be clear for anyone with a curious and thoughtful mind.

Alexander Panossian
Terry Lemerond
May 2022

INTRODUCTION

Basic Notions and Terminology, the Evolution of Adaptogens Concept: From Initial Postulates to Evidence-Based Statements and Definitions

Adaptogens constitute a therapeutic category/pharmacological group of herbal medicines or/and nutritional products (like antioxidants and vitamins), increasing ***adaptability, survival, and resilience in stress and aging***.

Term adaptogen is associated with the notions of adaptation, adaptedness, adaptability, homeostasis, stress, general adaptation syndrome, adaptive stress response, resilience, and adaptive homeostasis, where:

- ***adaptation*** is an active process of responding to challenges, which includes behavioral, physiological, structural, and genetic changes upon environmental impacts that are beyond the biologically adequate ranges (Peck and Waxman, 2018).
- ***adaptedness*** results from the adaptation process when a positive outcome, survival and reproduction, is achieved in the face of adversity. Adaptedness is a state that has a capacity for adaptation (Melnikov, 2019).
- ***adaptability*** is the ability of an organism to alter itself or its responses to the changing environment or circumstances (Canguilhem, 1943) **Figure 1**.
- ***homeostasis*** is a complex dynamic equilibrium/steady state, maintained by coordinated physiological processes in the organism (Cannon, 1926), **Figure 2.**
- ***the homeostatic range*** is a normal range of oscillation/deviation from the mean (or median) of all biological measures**, Figure 2.**
- ***adaptive homeostasis*** is the transient reversible adjustments of the homeostatic range in response to exposure to signaling molecules or events (Davies, 2016), **Figure 2.**

- ***stress*** is a state of threatened homeostasis (Cannon,1935), **Figure 3.**
- ***stress system*** is the neuroendocrine-immune complex; the adaptive stress system includes all physiological systems involved in the process of adaptation to stress (Stratakis and Chrousos, 1995) **Figure 3.**
- ***general adaptation syndrome***–non-specific reactions of organisms evoked to stress-inducing thymus atrophy, adrenal hyperplasia, stomach ulceration, increased secretion of cortisol and catecholamines, etc. (Selye, 1938, 1976), **Figure 4.**
- ***adaptive stress response*** (hormesis) biphasic dose–response to an environmental agent characterized by a low dose stimulation or beneficial effect and a high dose inhibitory or toxic effect (Calabrese and Mattson, 2007), **Figure 5.**
- ***resilience*** is the ability to maintain or quickly return to a stable physical and psychological equilibrium despite experiencing stressful events (An, 2019).

Figure 1. Upper line, from left to right: *Hans Selye, Walter Bradford Cannon, Edward Calabrese, Mark Mattson, George Canguilhem;* Bottom line: from left to right: *Nikolay Lazarev, Israel Brekhman, Norman Farnsworth,* and *Hildebert Wagner.*

Adaptability shows the ability to learn and to improve from experience. It means that all organisms on our planet, including plants, survive and stay healthy due to adaptability. That is achieved due to complex regulating interactions of numerous defenses and regulatory molecules within their organisms. The final aim is to maintain a condition, so-called ***homeostasis***, when everything is working well, harmonized, and balanced.

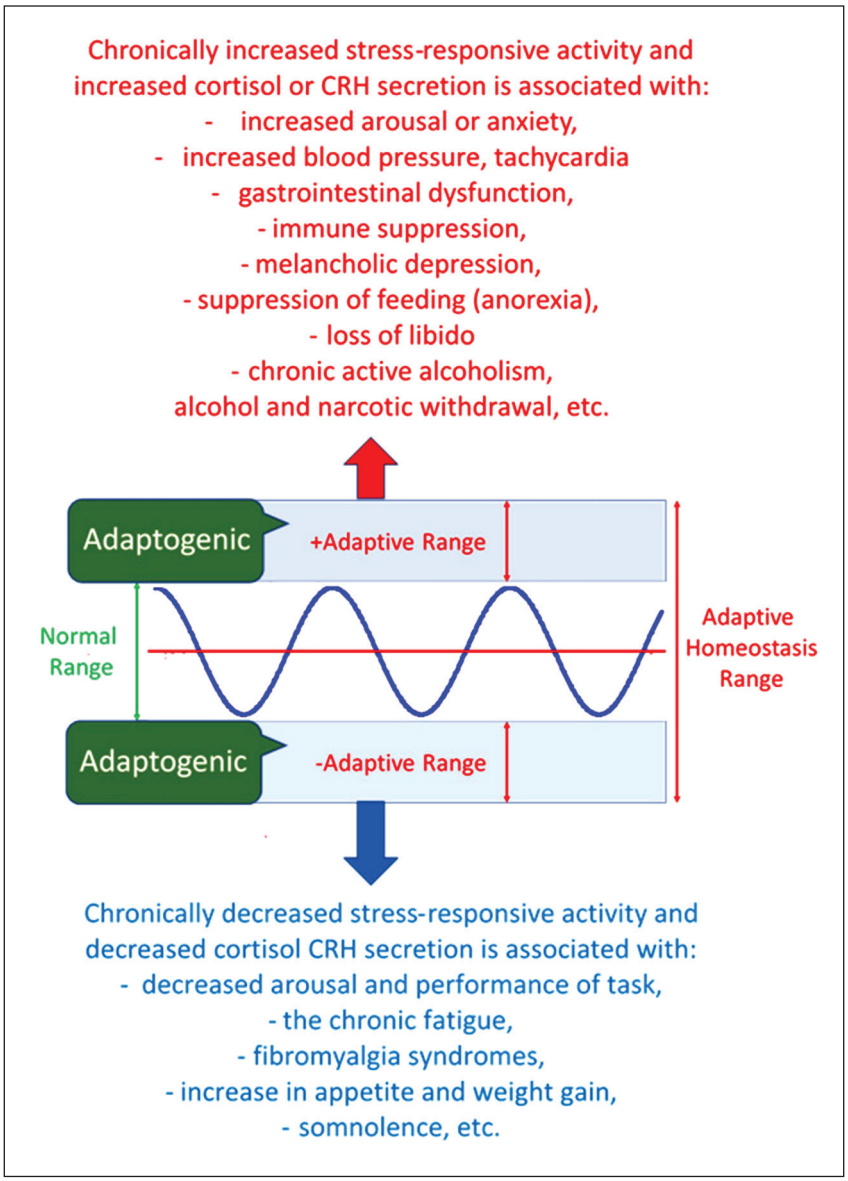


Figure 2. **Homeostasis** is the capability of an organism or cell to maintain internal balance despite changes in its conditions. Stress—is a temporary inability to maintain this steady state. **Adaptive homeostasis** is the cellular or organismal ability to adjust the homeostatic range in response to the effect of adaptogens. Adaptogens increase the homeostatic range to the level of adaptive homeostasis, activating adaptive stress response resulting in increased resilience and overall survival (Panosyan et al., 2020).

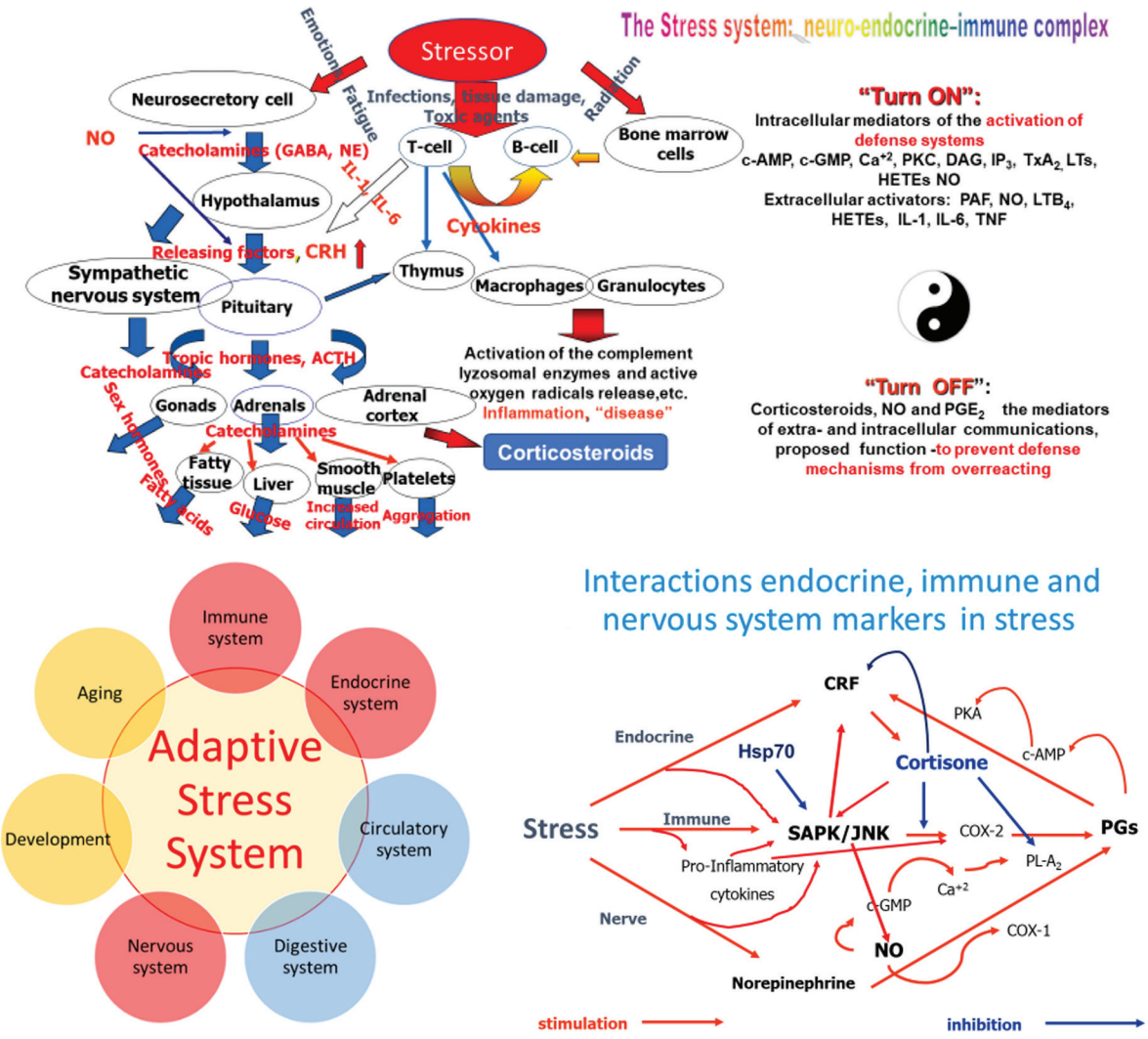


Figure 3. Stress-induced modulation of immune function by the CNS and sympathetic nervous system components and mechanisms by which inflammatory mediators may signal the central nervous system. Activating the hypothalamus-pituitary-adrenal (HPA) axis induces various effects on target tissues, including fatty tissue, liver, smooth muscle tissue, platelets, etc. Activated immunocompetent cells also interact with the endocrine system activating corticotropin-releasing factor (CRF) release and consequently corticosteroids. IL-1 and IL-6 have a direct activating effect on the hypothalamic-hypophyseal-adrenal axis. Both cytokines induce the release of CRF. Activation of the immune system causes inflammation and "disease." Intracellular mediators of the activation of defense system such as c-AMP, c-GMP, Ca^{+2}, PKC, DAG, IP3, TxA2, LTs, HETEs, NO "turn on" defense mechanisms. Corticosteroids are mediators of extra- and intracellular communications. Their function is to prevent defense mechanisms from overreacting. Corticosteroids are regulators in the activation and suppression of immune and neuroendocrine systems. Increased secretion of glucocorticoids in response to infection or injury prevents defense mechanisms from overreacting and threatening homeostasis. To do this, they "turn off" defense mechanisms, including stimulation of cytokines, nitric oxide, leukotriene B4, and PAF formation, which "turn on" the defense system.

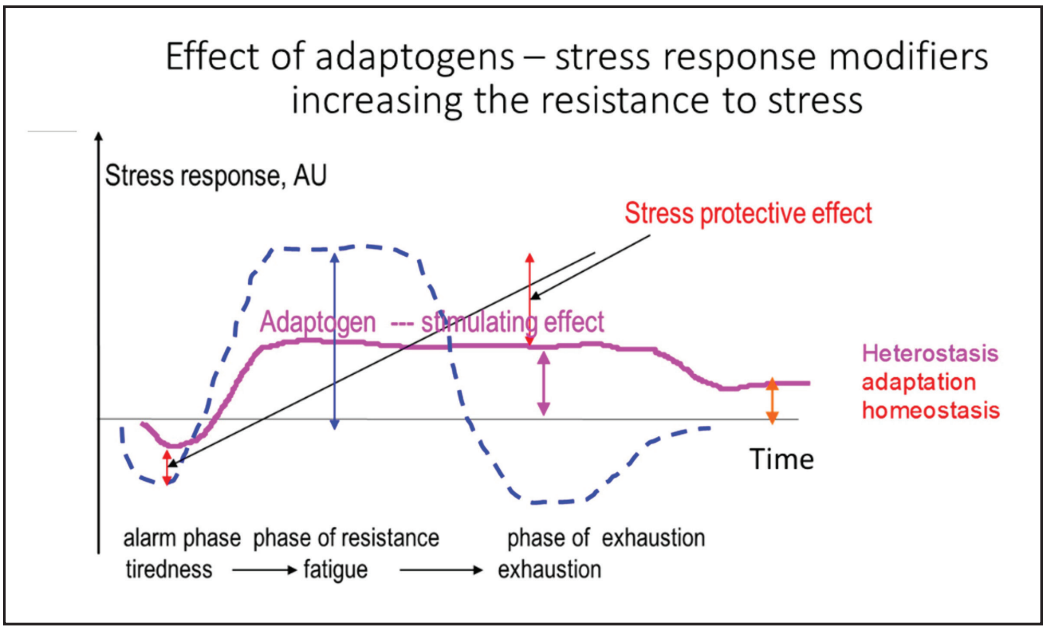


Figure 4. Stress-induced general adaptation syndrome–three-phase response including non-specific outcomes (thymus atrophy, adrenal hyperplasia, stomach ulceration, enhanced secretion of cortisol and catecholamines, etc.): (i) alarm phase, (ii) phase of non-specific resistance, and (iii) phase of exhaustion, when the same symptoms recur, followed by death. (Selye, 1938, 1976).

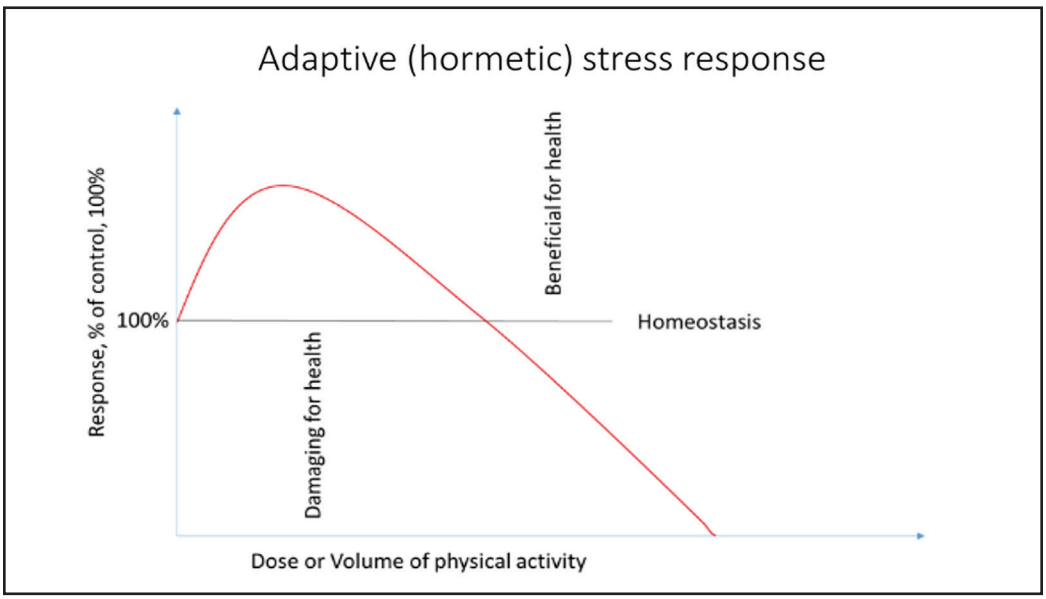


Figure 5. The phenomenon of adaptation to stress also supports so-called "hormetic response," which is defined as an adaptive response characterized by a biphasic dose-response, with a low dose that is stimulatory (i.e., has a beneficial effect), and a high dose that is inhibitory (i.e., a toxic effect).

Like other simple and higher organisms, plants have evolutionary developed ability to produce so-called plant secondary metabolites, which play a role in defense and adaptive response against various environmental challenges, so-called stressors, including physical (e.g., intense sunlight, UV, darkness, heat, cold), chemical, and biological (e.g., microorganisms, insects, and other pests). Relatively small doses, these natural compounds, adaptogens, are not toxic in humans but still induce mild cellular adaptive stress responses. As a result, adaptogens trigger the adaptive stress response in humans by stimulating organismal defense systems, resulting in overall survival due to increased resilience and adaptability to harmful environmental factors, including physical, chemical, and biological.

Adaptogen increases the resistance of an organism irrespective of the nature of the stressor. Irrespective of the nature of the stimulus (stressor), an adaptogen specifically improves adaptability, resilience, and increases survival by triggering adaptive signaling pathways of cellular and organismal defense systems (stress system—neuroendocrine-immune complex). That is a common characteristic of adaptogens. In the meantime, multitarget mechanisms of action and a wide range of pharmacological effects indicate their non-specific pharmacological activity.

Table 1 reflects the evolution of our knowledge of adaptogens synopsized in their definition initially postulated and updated evidence-based.

TABLE 1. DEFINITIONS OF ADAPTOGENS: FROM INITIAL POSTULATES TO EVIDENCE-BASED UPDATES.

Adaptogens are ***compounds*** that increase the "state of non-specific resistance" in stress (Lazarev, 1958).
Adaptogens are innocuous ***agents***, nonspecifically increasing resistance against physically, chemically, biologically, and psychologically noxious factors ("stressors"), a normalizing effect independent of the nature of pathologic state (Brekhman, 1968).
The adaptogens are nontoxic ***compounds*** with polyvalent mechanisms of action and pharmacological effects related to adaptability and survival (Farnsworth et al., 1984).
Adaptogens are ***substances*** that elicit a state of nonspecifically raised resistance in an organism, allowing them to counteract stressor signals and adapt to exceptional strain (Wagner et al., 1994).
Plant adaptogens are ***agents*** which reduce the damaging effects of various stressors due to the reduction of the reactivity of the host defense system. They adopt an organism to stress and have a curative effect in stress-induced disorders (Panossian et al., 1999).
Adaptogens are ***metabolic regulators***, which increase the ability of an organism to adapt to environmental factors and to avoid damage from such factors (Panossian et al., 1999).

Adaptogenic ***substances*** have the capacity to normalize body functions and strengthen systems compromised by stress. They have a protective effect on health against a wide variety of environmental assaults and emotional conditions (EMEA/HMPC/102655/2007).

Adaptogens comprise ***a pharmacotherapeutic group of herbal preparations*** used to: increase attention and endurance in fatigue and prevent/mitigate/reduce stress-induced impairments and disorders related to neuroendocrine and immune systems [Panossian and Wikman, 2009].

Botanical adaptogens are ***plant extracts*** or specific constituents of plant extracts, which function to increase survival in animals and humans by stimulating their adaptability to stress by inducing adaptive responses (Panossian and Amsterdam, 2017).

Adaptogens are ***stress-response modifiers*** that increase an organism's non-specific resistance to stress by increasing its ability to adapt and survive. (Panossian, 2017).

Botanical adaptogens are ***metabolic regulators*** that increase survival by increasing adaptability in stress. (Panossian, 2017).

Adaptogens are ***natural compounds*** or ***plant extracts*** that increase the adaptability and survival of living organisms to stress (Panossian, 2018).

Adaptogen—any of various natural substances used in herbal medicine to normalize and regulate the body's systems. https://www.dictionary.com/browse/adaptogen.

In brief, adaptogens are most likely effective for the prevention and treatment of stress-induced and adult-onset disorders such as:

- ✦ chronic fatigue,
- ✦ memory impairment,
- ✦ depressive state, anxiety, and sleep disturbance,
- ✦ diabetes,
- ✦ heart diseases and high blood pressure,
- ✦ chronic inflammation and autoimmune diseases,
- ✦ common cold and flu,
- ✦ infective and skin diseases,
- ✦ liver diseases,
- ✦ cancer, and more…

That can be achieved due to their ability to:

- ✦ adapt the organism to stress,
- ✦ increase resistance to infectious diseases,
- ✦ activate innate immunity and overall defense system,
- ✦ provide energy in tiredness, fatigue, and exhaustion,
- ✦ increase recovery of stress-induced damages,
- ✦ reduce the aging-associated decline of cognitive functions, immunity, and production of hormones.

Table 2 summarizes the general characteristics of adaptogens, which constitute a category of nutritional and herbal medicinal products.

TABLE 2. SUMMARY OF GENERAL CHARACTERISTICS OF ADAPTOGENS

Definition: Adaptogens are natural stress-protective compounds or plant extracts that promote the adaptability, resilience, and survival of organisms.
Chemical class: predominantly tetracyclic triterpene, phenethyl-and phenylpropanoids, lignans, etc.
Therapeutic category/pharmacological group: adaptogen.
Pharmacological activity: stress-protective, stimulating, tonic.
Mechanism of action: multitarget effect on the neuroendocrine-immune system including: • triggering of intracellular and extracellular adaptive signaling pathways that promote cell survival and organismal resilience in stress • regulation of metabolism and homeostasis via effects on expression of stress hormones (corticotropin and gonadotropin-releasing hormones, urocortin, cortisol, neuropeptide Y, heat shock proteins Hsp70) and their receptors.
Indications/health claims: stress-induced fatigue, mental and behavioral disorders, aging-associated disorders, infectious diseases.

CHAPTER 1

Adaptogenic Plants, Their Uses, Pharmacological Effects, Dosage Forms and Doses, Active Ingredients, and Contraindications

Overall, more than 100 plants were reported in the literature as adaptogenic (Table 3); however, only a few (in red color below) meet the criteria outlined in Table 2.

TABLE 3. PLANTS REPORTED IN THE LITERATURE AS ADAPTOGENIC

Acanthopanax sessiliflorum Rupr.et Maxim	*Azardirachta indica (Al, Neem),*	Curcumin from Turmeric *(Curcuma longa)*	*Heteropterys aphrodisiaca Machado*	*Mussanenda frondosa*	*Ptychopetalum olacoides* Benth.	*Solanum torvum* SW.
Aegle marmelos	*Bacopa monnieri* (L.) Wettst	*Dioscorea deltoidea* Wall. ex Griseb.	*Hibiscus cannabinus*	*Nelumbo nucifera* Gaertn.	*Pueiaria tuberosa Roxb*	*Sterculia plantanifolia L.*
Ajuga turkestanica (Regel) Briq.	*Bergenia crassifolia* (L.) Fritsch	*Diospyros peregrina gurke*	*Hippophae rhamnoides L.*	*Nigella sativa*	*Rhaponticum carthamoides* Iljin	*Sutherlandia frutescens* (L.) R.Br.
Albizzia julibrissin Durazz.	*Boerhaavia diffusa*	*Drypetes roxburghii* (Wall.) Hurus.	*Holoptelea integrifolia* Planch	*Ocimum sanctum* L.	*Rhodiola crenulaya H.Ohba*	*Terminalia chebula* Retz.
Alstonia scholaris R.Br.	*Bryonia alba* L.	*Echinopanax elatum Nakai*	*Hoppea dichotoma* Willd.	*Oplopanax elatus* (Nakai) Nakai	*Rhodiola heterodonta* Boriss.	*Tinospora cordifolia* (Willd.) Miers
Allium sativum	*Butea monosperma*	*Eleutherococcus senticosus* Maxim.	*Hypericum perforatum* L.	*Panax ginseng* C.A.Meyer.	*Rhodiola imbricata*	*Tinospora malabarica*
Anacyclus pyrethrum (L.) Lag.	*Caesalpinia bonduc* (L.) Roxb	*Eleutherococcus sessiliflorus S.Y.Hu*	*Labisia pumila*	*Panax notoginseng* (Burk.) FH Chen	*Rhodiola rosea* L.	*Tribulus terrestris*
Andrographis paniculata Nees	*Carum carvi*	*Emblica officinalis* Gaetrn.	*Lagenaria siceraria*	*Panax pseudo-ginseng* Wall.	*Rostellularia diffusa* (Willd.) Nees .	*Trichilia catigua* A.Juss.
Annona muricata	*Centella asiatica* (L.) Urb.	*Eucommia ulmoides* Oliv.	*Lepidium peruvianum/ Lepidium meyenii* Walp.	*Pandanus odoratissimus* L.f.	*Rubia cordifolia*	*Trichopus zeylanicus* Gaertn.
Aralia elata (Miq) Seem.	*Chlorophytum borivilianum* Sant&Fern	*Eugenia caryaphullus*	*Ligusticum striatum DC.*	*Paullinia cupana* Kunth	*Salvia miltiorrhiza* Bunge	*Trigonella foenom graecum*
Aralia mandshurica Rupr. & Maxim	*Chrysactinia mexicana* A. Gray	*Evolvulus alsinoides* L.	*Melilotus officinalis (L.) Pall.*	*Pfaffia paniculata* (Mart.) Kuntze	*Schisandra chinensis* (Turcz.) Baill.	*Tylophora indica*
Aralia schmidtii	*Cicer arietinum* L.	*Fagopyrum esculentum*	*Mitragyna africanus*	*Piper longum* L.	*Scutellaria baicalensis* Georgi	*Turnera diffusa* Willd. ex Schult.
Argyreia nervosa (Burm. f.) Bojer	*Cnestis ferruginea*	*Firmiana simplex* (L.) W.Wight	*Momordica charantia*	*Polyalthia cerasoids*	*Serratula inermis*	*Vitis vinifera* L.
Argyreia speciosa (L. f.) Sweet	*Codonopsis pilosula* (Franch.) Nannf.	*Gentiana pedicellata* (D.Don) Wall	*Morus alba* L.	*Potentilla alba* L.	*Sida cordifolia* L.	*Withania somnifera* (L.) Dunal
Asparagus racemosus Wild	*Convolvulus prostratus* Forssk.	*Ginkgo biloba*	*Mucuna pruriens* (L.) DC.	*Prunella vulgaris*	*Silene italica (L.) Pers.*	*Zingiber officinale*
Atragene sibirica L	*Curculigo orchioides* Gaertn.	*Glycyrrhiza glabra* L.	*Murraya koenigii(Rutaceae)*	*Psidium guajava*	*Sinomenium acutum Rehder & E.H.Wilson*	

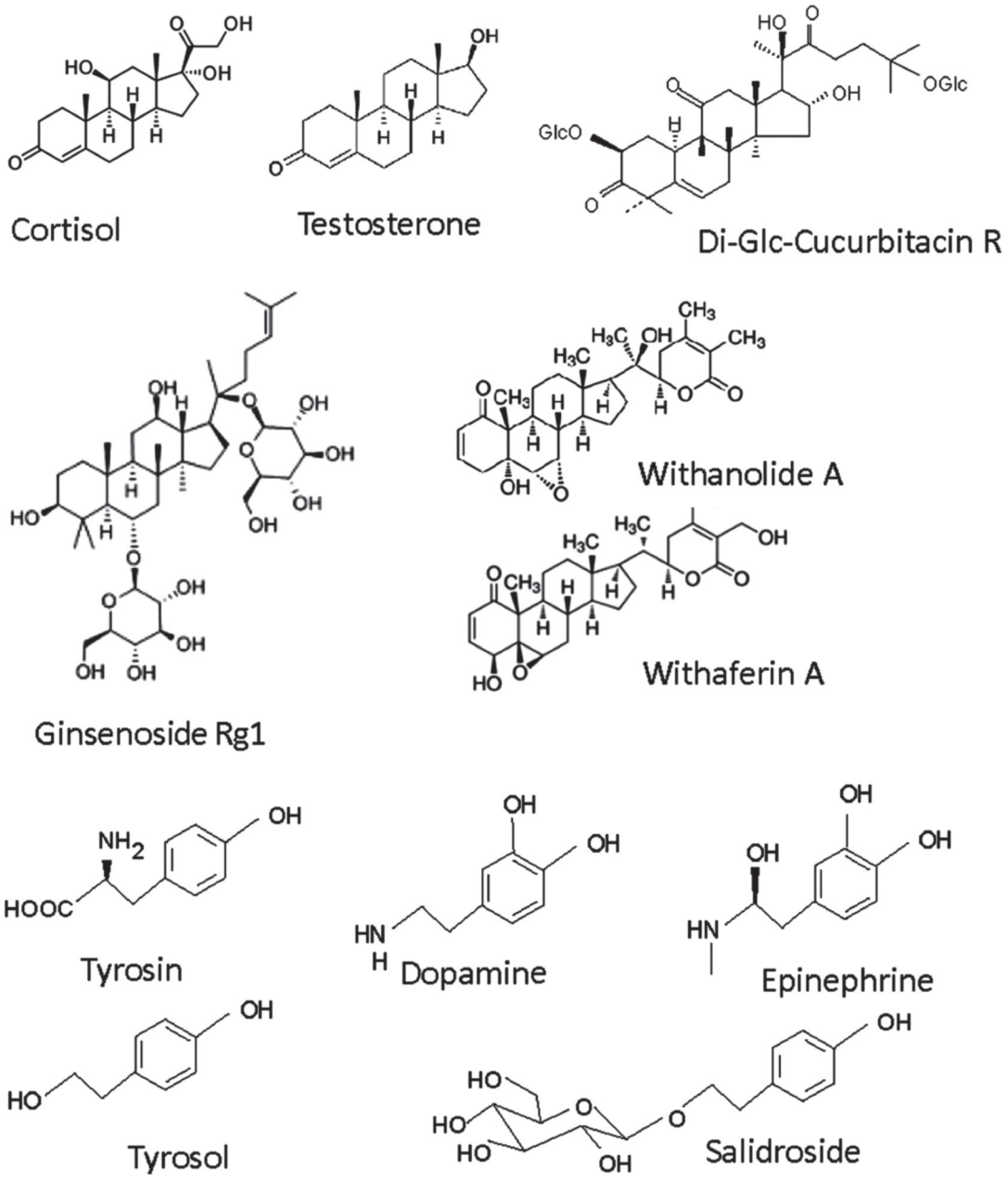


Figure 6. Chemical structures of the human hormones (cortisol, testosterone, and epinephrine); neurotransmitter dopamine; its precursor tyrosine; and adaptogens of plant origin (salidroside, tyrosol, ginsenoside Rg1, diglucoside of cucurbitacin R, withanolide A and withaferin A).

Following are the summaries of uses, pharmacological effects, contraindications, active ingredients, dosage forms, and doses of selected adaptogens.

Panax ginseng C.A. Mayer

- *Common names:* Ren Shen (white Ginseng) and Hon Shen (red Ginseng—steamed) Korean ginseng, Oriental ginseng, jenshen, shanshen, yeh-shan-seng, yuanshen, etc.
- *Parts used:* Roots (Radix et Rhizome).
- *Therapeutic category/pharmacological group:* Adaptogens, tonics.

- *Uses:*
  - *Supported by clinical data:* as a therapeutic and a prophylactic agent for enhancement of mental and physical capacities cognitive function and reduce mental fatigue in cases of mental stress, weakness, exhaustion, tiredness, and loss of concentration, and during recovery.
  - *In traditional systems of medicine:* diabetes, impotence, prevention of hepatotoxicity, arterial hypotension, neuroses, neurasthenia, asthenia of various eytiologies, gastritis, and ulcers.
  - *described in folk medicine:* liver disease, coughs, fever, tuberculosis, rheumatism, vomiting of pregnancy, hypothermia, dyspnea, and nervous disorders.
- *Pharmacological effects:* numerous effects on the nervous, cardiovascular, immune, endocrine, reproductive, detoxifying systems and skin have been detected, including antifatigue, psychomotor, antidiabetic, cytoprotective, anti-apoptotic, anti-inflammatory, antimicrobial, antiviral, immune-stimulatory, antioxidant, and anti-cancer effects.
- *Dosage forms*: crude plant material, capsules and tablets of powdered drugs, extracts, tonic drinks, wines, and lozenges.
- *Active ingredients:* A complex mixture of triterpene glycosides collectively known as ginsenosides, (not less than 1.5% calculated as ginsenoside Rg1, up to 6%).
- *Doses:* Daily dose (taken in the morning): dried root 0.5–2g by decoction; doses of other preparations should be calculated accordingly. Capsules are prescribed orally, with meals, 0.5–1 g (in terms of dry standardized ginseng extract) 2–3 times a day for 25–30 days. If necessary, repeat courses of treatment are carried out with a break of 2 weeks. Gerimax ginseng tablets: 200–400 mg (1–2 tablets) per day. Herbion Ginseng capsules: 1 capsule daily, after breakfast for 4–8 weeks. Tinctures: 30–50 drops 2–3 times a day. The daily dose for adults is 200 drops.

- As a general tonic and anti-stress drug—100 mg 2 times a day for 11 weeks.
- To increase mental performance—400 mg daily.
- To obtain a hypoglycemic effect in type 2 diabetes mellitus, as well as to increase antiviral immunity (it is possible as a supplement for vaccination)—daily, 100–200 mg.
- In case of erectile dysfunction—600 mg daily.

✦ *Overdose:* increased blood pressure, sleep disturbance.

✦ *Contraindications:* arterial hypertension, hyperexcitability, insomnia, bleeding, febrile syndrome against the background of acute infectious diseases; children's age, pregnancy, lactation period. For tincture (optional): liver cirrhosis, alcoholism, epilepsy.

✦ *Adverse events:* increased blood pressure, sleep disturbance, headache, nervousness, nausea, tachycardia, vomiting, hypoglycemia.

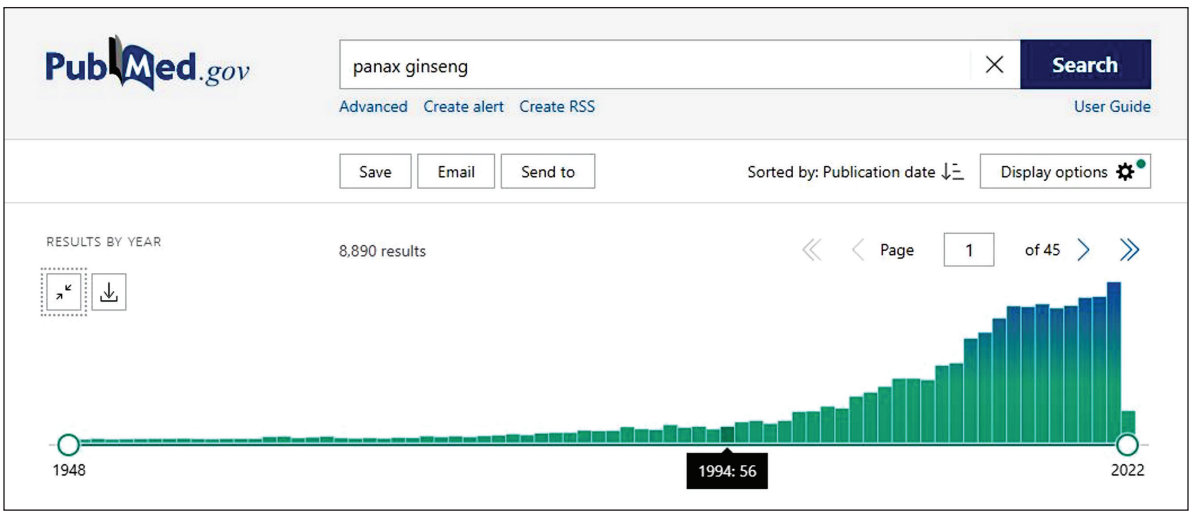


Figure 7. 7933 publications on *Panax ginseng* have been published in peer-reviewed scientific journals indexed in the NHI National Library of Medicine (USA) since 1948; each bar shows the number of publications per year. Many publications in Russian are not included.

Eleutherococcus senticosus (Rupr. and Maxim.) Maxim.

- *Common names:* Siberian Ginseng, acanthopanax, devil's bush, eleuthero, taiga root, thorny Ginseng, thorny Russian pepper bush, touch-me-not, wild pepper, etc.
- *Parts used:* roots and rhizomes (Radix et Rhizome).
- *Therapeutic category:* Adaptogenic, tonic.

- *Uses:*
  - *supported by clinical data:* As a restorative and prophylactic tonic for enhancement of mental and physical capabilities in cases of weakness, exhaustion, and tiredness, and during convalescence (after somatic and infectious diseases); arterial hypotension.
  - *In traditional systems of medicine:* Treatment of insomnia and rheumatoid arthritis.
  - *described in folk medicine:* As a carminative in the treatment of gastritis, as a diuretic, to treat impotence and to regulate blood pressure.
- *Pharmacological effects:* adaptogenic, anti-stress, antiviral, and antimicrobial activities.
- *Dosage forms*: crude plant material, capsules, and tablets of powdered drugs, extracts, tinctures, tonic drinks, teas, syrups, fluid extracts.
- *Doses:* 2–3 g powdered crude drug or equivalent preparations, total daily dose corresponding to 0.5–4 g dried root given once or in divided doses two-three times daily. Formulations include: tablets or capsules 250 mg; liquid extract (1:1, ethanol 30%–40% vol/vol) 2–3 mL; dry extracts (ethanol 28%–70% vol/vol) corresponding to 0.5–4 g dried root; dry aqueous extract (15–17:1) 90–180 mg; or tincture: 10–15 mL.
- *Active ingredients:* A complex mixture of phenylpropane derivatives of diverse structure collectively known as eleutherosides (up to 6%), including the lignans, (+)-sesamin (eleutheroside B4), (+)-syringaresinol and its monoglucoside (eleutheroside E1) and diglucoside (eleutherosides D and E); the simple phenylpropanes, syringenin and its monoglucoside (eleutheroside B); and the coumarins isofraxidin and its monoglucoside (eleutheroside B1), b-Sitosterol and daucosterol (eleutheroside A) and immunostimulant polysaccharide complex (eleutherans A–G).

- *Contraindications:* during pregnancy or lactation or by patients with hypertension grade 3 hypertension (180/90 mmHg), and in cases of allergy to plants of the Araliaceae family, arterial hypertension, hyperexcitability, acute infectious diseases, myocardial infarction, arrhythmias, insomnia, cerebrovascular pathology; children's age (up to 12 years old).
- *Adverse events:* Potentiates the effect of stimulants of the central nervous system, is an antagonist of drugs that depress the CNS (including barbiturates, anxiolytics, anti-epileptic medicines, etc.).

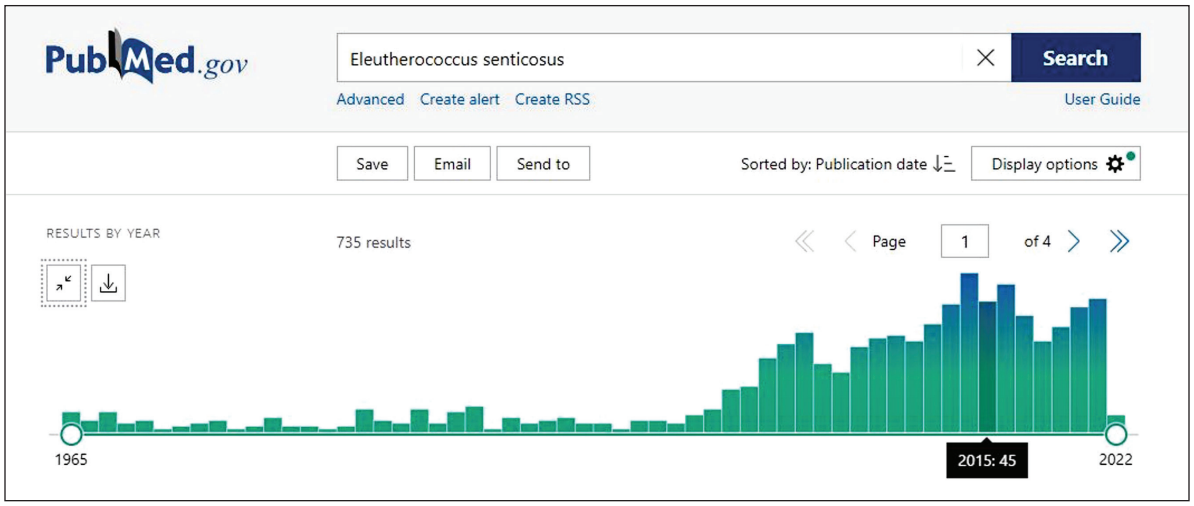


Figure 8. A total of 649 publications on *Eleutherococcus senticosus* have been published in peer-reviewed scientific journals indexed in the NHI National Library of Medicine (USA) since 1965; each bar shows the number of publications year. Many publications in Russian are not included.

Rhodiola rosea L.

- *Common names* Roseroot, Rosenroot, Golden Root, Arctic Root, Rosenwurz, Orpin Rose, etc.

- *Parts used:* rhizomes and roots (Rhizoma et radix).
- *Therapeutic category:* adaptogenic, tonic.
- *supported by clinical data:* as a prophylactic and restorative agent for enhancement of mental and physical capacities, in cases of stress (operator activity, persons working in extreme conditions: underwater work, highlands, conditions of the Arctic), weakness, exhaustion, tiredness, and loss of concentration, and during convalescence (after infectious and severe somatic diseases); alcoholism (to reduce the toxic effects of ethanol), withdrawal symptoms, drug addiction; respiratory viral infections (prevention during epidemics).
- *in traditional systems of medicine:* for relief of mental and physical symptoms of stress, such as fatigue, weakness, exhaustion, irritability, and mild anxiety; a stimulant against fatigue by patients who suffered asthenic states, and by healthy people who showed astheny during periods of high mental exertion or after intensive physical work, in cases of borderline nervous-mental diseases, neuroses, neurotic disorders, and psychopathies, psychostimulant.
- *described in folk medicine:* headaches, as astringent, to strengthen the head, to enhance the intellect, for restoration of weak nerves, to increase physical strength and endurance, resistance to cold and disease, and to promote fertility and longevity; external use for hair growth, relieve of swellings, decrease of back pain, pain in joints.
- *Pharmacological effects*:
  - clinically demonstrated—increased mental performance, antifatigue, anxiolytic, autoregressive effects.
  - non-clinical data—antifatigue, stress-protective effects, antioxidative effects, lifespan increasing effects, cardioprotective effects, effects on the vascular system, erythropoiesis-stimulating effect, effects on the nervous system, neuroprotective effects: hepatoprotective effect, anti-inflammatory, antibacterial activity, antiviral effect, effects on metabolism, effects on the endocrine system, anti-cancer effects; clinical—mental performance, fatigue, anxiety, depression.

- *Dosage forms*: crude plant material, capsules and tablets of powdered drugs, extracts, tonic drinks, wines, and lozenges.
- *Doses:* Tablets or capsules containing 144 to 200 mg (genuine drug extract ratio [DER] 1.5 to 5:1, extraction solvent ethanol 67% to 70% vol/vol): 144 to 200 mg, daily dose 2 to 4 tablets or capsules. Liquid extract (1:1, ethanol 40% vol/vol): 1 to 3 mL (5–25 drops in a quarter of a glass of water daily, 15 to 30 minutes before meals). Duration of the treatment: from 10 days to 4 months followed by a washout period of 2 weeks.
- *Active ingredients:* Phenylpropanoids (rosavin, rosin, and rosarin; the so-called rosavins), together with phenylethanol derivatives (mainly salidroside, rhodioloside). Also present are flavonoids (e. g. rodiolin), monoterpenoids (rosiridol, rosaridin), phytosterols, and phenolic acids.
- *Contraindications:* hypersensitivity, agitation, insomnia, arterial hypertension, febrile syndrome, pregnancy, childhood (up to 12 years old).
- *Adverse events:* irritability, sleep disturbances, headache.

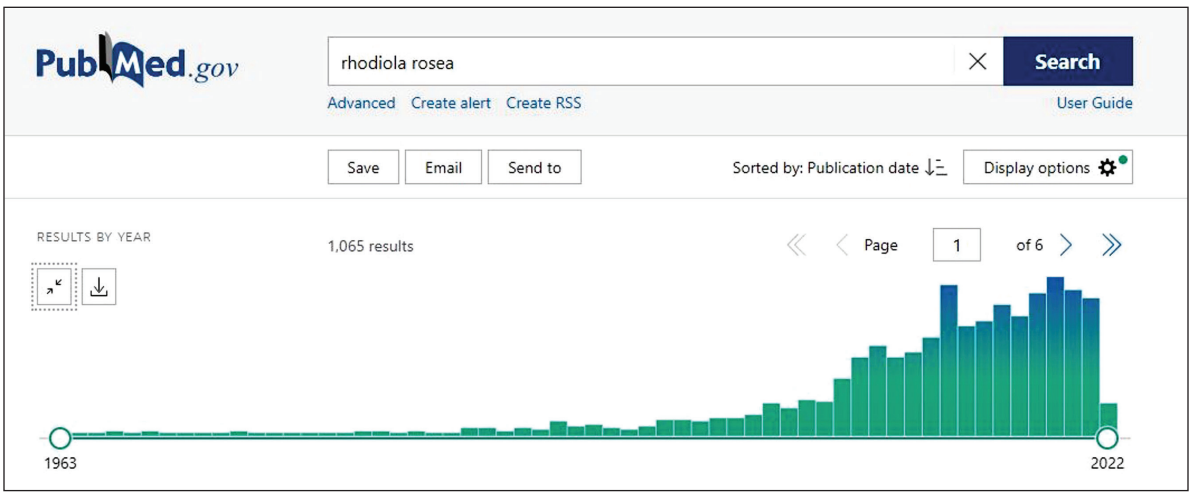


Figure 9. A total of 976 publications on *Rhodiola rosea* have been published in peer-reviewed scientific journals indexed in the NHI National Library of Medicine (USA) since 1963; each bar shows the number of publications per year. Many publications in Russian are not included.

Withania somnifera (L.) Dunal.

- *Common names:* ashwagandha, winter cherry, withania, etc.
- *Parts used:* Roots (Radix)
- *Therapeutic category:* adaptogenic, tonic, sedative.
- *Uses:*
  - *supported by clinical data:* anti-stress agent.
  - *in traditional systems of medicine:* as a general tonic to increase energy, improve overall health, and prevent disease in athletes and the elderly.
  - *described in folk medicine:* bronchitis, dyspepsia, impotence, scabies, and ulcers.

- *Pharmacological effects:* anti-stress, anti-inflammatory, anti-ischemic, antioxidant, chemopreventive, immune-stimulating, neuroprotective activities, improves memory and cognition.
- *Dosage forms*: Crude plant material, capsules, and tablets of powdered drugs, extracts, and tinctures.
- *Doses:* Daily dose of powdered crude drug: 3–6 g of the dried powdered root. Orally as an anti-stress agent: 250 mg twice daily; doses of other preparations should be calculated accordingly.
- *Active ingredients:* A complex mixture of steroidal lactones collectively known as withanolides (including withaferin A, 27-deoxywithaferin A, withanolide D, withanosides I–XI, and withasomniferols A–C) and alkaloids (not less than 0.2%).
- *Contraindications:* stomach ulcers, during pregnancy or breastfeeding.
- *Adverse events:* nausea, vomiting and diarrhea.

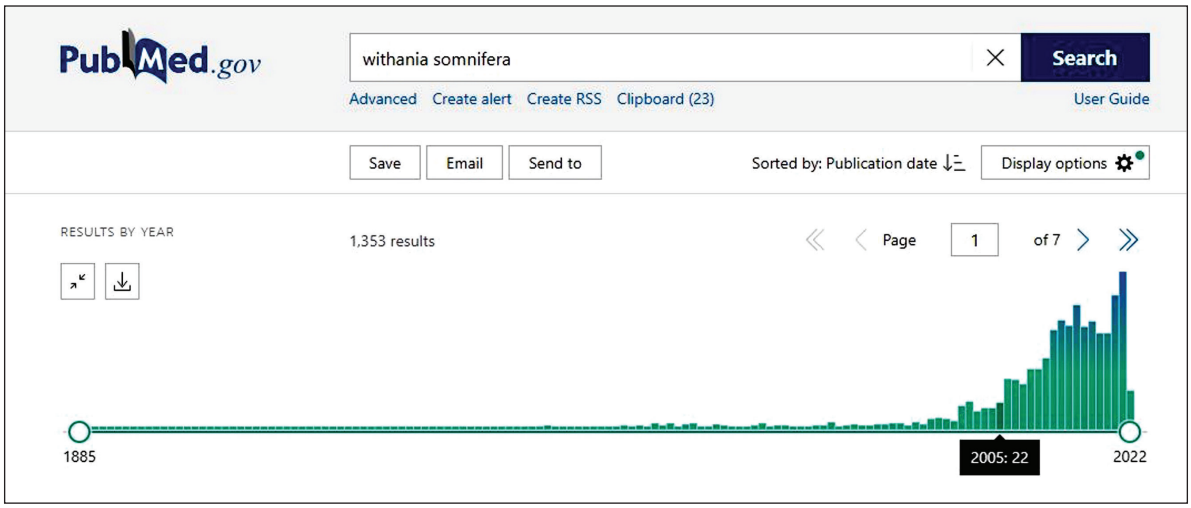


Figure 10. A total of 1201 publications on *Withania somnifera* have been published in peer-reviewed scientific journals indexed in the NHI National Library of Medicine (USA) since 1885; each bar shows the number of publications per year.

Schisandra chinensis (Turcz.) Baill.

- *Common names:* wu-wei-zi, wu-weitzu, Schisandra, limonnik, Chinesischer Limonenbaum, Chinese magnolia vine, Chinese mock-barberry, chosen-gomishi, lemonwood, etc.
- *Parts used:* dried ripe fruits (Fructus Schisandrae).
- *Therapeutic category:* Adaptogenic, tonic.
- *Uses:*
  - *supported by clinical data:* fatigue, hepatitis, gastritis, psychosis, asthenic syndrome, convalescence.
  - *in traditional systems of medicine:* as a general tonic for treating fatigue associated with illness; chronic cough and asthma, diabetes, urinary tract disorders.

  - *described in folk medicine:* As an astringent, antitussive, antidiarrhoeal, expectorant, and sedative.
- *Pharmacological effects:* anti-inflammatory, antihepatotoxic, antioxidant, antitumor, erogenic activities. CNS and metabolism.
- *Dosage forms*: crude plant material, capsules and tablets of powdered drugs, extracts, tonic drinks and tinctures.
- *Doses:* 1.5–6.0 g of dried fruits. Tablets or capsules (standardized to a minimum of 1.3% lignan) 600 to 2,000 mg per day; dry extract (DER 1.5 to 5:1, extraction solvent ethanol 67%–70% vol/vol) 144 to 400 mg; and liquid extract (1:1, ethanol 40% vol/vol) 1 to 3 mL (5–25 drops in a quarter of a glass of water 3 times a day, 15–30 minutes before meals).
- *Active ingredients:* a complex mixture, mostly of dibenzo[*a,c*]cyclooctadiene skeleton containing lignans known as schizandrins (not less than 0.4%).
- *Contraindications:* arterial hypertension, hyperexcitability, epilepsy, sleep disturbance, acute infectious diseases, chronic liver diseases, high gastric acidity or peptic ulcers, epilepsy, pregnancy, lactation, children (up to 12 years).
- *Adverse events:* allergic reactions, tachycardia, sleep disturbances, headache, increased blood pressure.

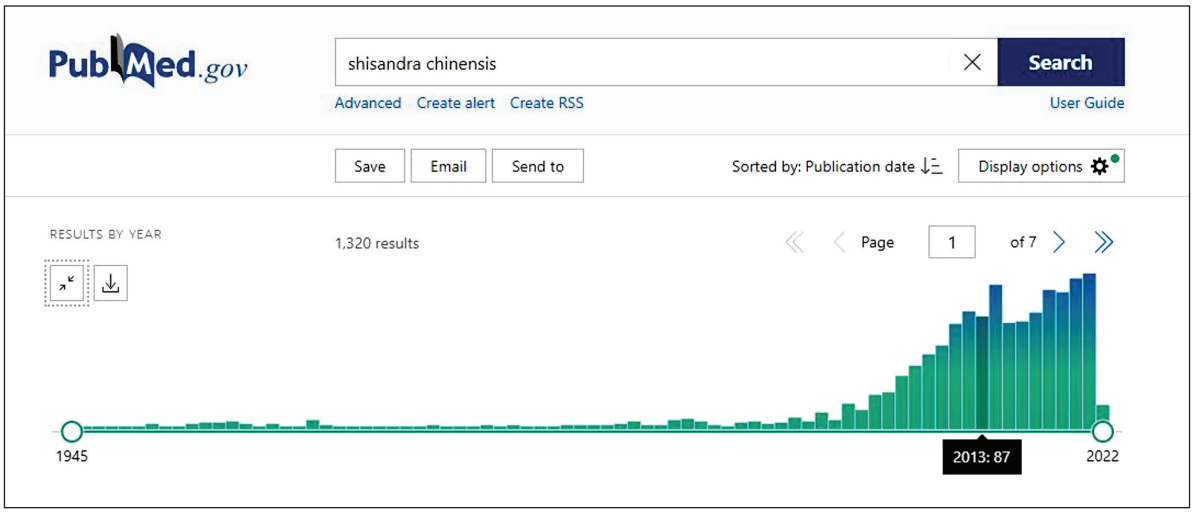


Figure 11. A total of 1192 publications on *Schisandra chinensis* have been published in peer-reviewed scientific journals indexed in the NHI National Library of Medicine (USA) since 1945; each bar shows the number of publications per year. Many publications in Russian are not included.

Andrographis paniculata (Burm. f.) Nees

- *Common names:* kalmegh, kan-jang, kariyat, khee-pang-hee, king of bitters, etc.
- *Parts used:* aerial parts (Herba Andrographidis).
- *Therapeutic category:* Adaptogenic.
- *Uses:*
  - *supported by clinical data:* prophylaxis and symptomatic treatment of upper respiratory infections, such as the common cold and uncomplicated sinusitis, bronchitis and pharyngotonsillitis, lower urinary tract infections, and acute diarrhea.
  - *in traditional systems of medicine:* bacillary dysentery, bronchitis, carbuncles, colitis, coughs, dyspepsia, fevers, hepatitis, malaria, mouth ulcers, sores, tuberculosis, and venomous snake bites.
  - *described in folk medicine:* colic, otitis media, vaginitis, pelvic inflammatory disease, chickenpox, eczema and burns.

- *Pharmacological effects:* antibacterial, anti-inflammatory, immunostimulatory, antimalarial, antivenom, antipyretic, antidiarrheal, antihepatotoxic activities.
- *Dosage forms*: crude drug, capsules, tablets and pills.
- *Doses:*
  - *for the common cold*: 1.5–3.0 g powdered crude drug three times daily, after meals and at bedtime.
  - *for diarrhea*: a decoction from 3–9 g crude drug as a single dose as needed (1, 5), or two tablets of 500 mg four times daily, after meals, and at bedtime (5).
  - *for pyrexia*: a decoction from 3 g crude drug, twice daily; doses of other preparations should be calculated accordingly.
- *Active ingredients:* a complex mixture of diterpene lactones collectively known as andrographolides (not less than 6%).
- *Contraindications:* in cases of known allergy to plants of the Acanthaceae family, pregnancy, or lactation.

- *Adverse events:* Large oral doses of Herba Andrographidis may cause gastric discomfort, vomiting, and loss of appetite. These side-effects appear to be due to the bitter taste of andrographolide. Anaphylactic reactions may occur if the crude drug extract is injected. Few cases of urticaria have been reported.

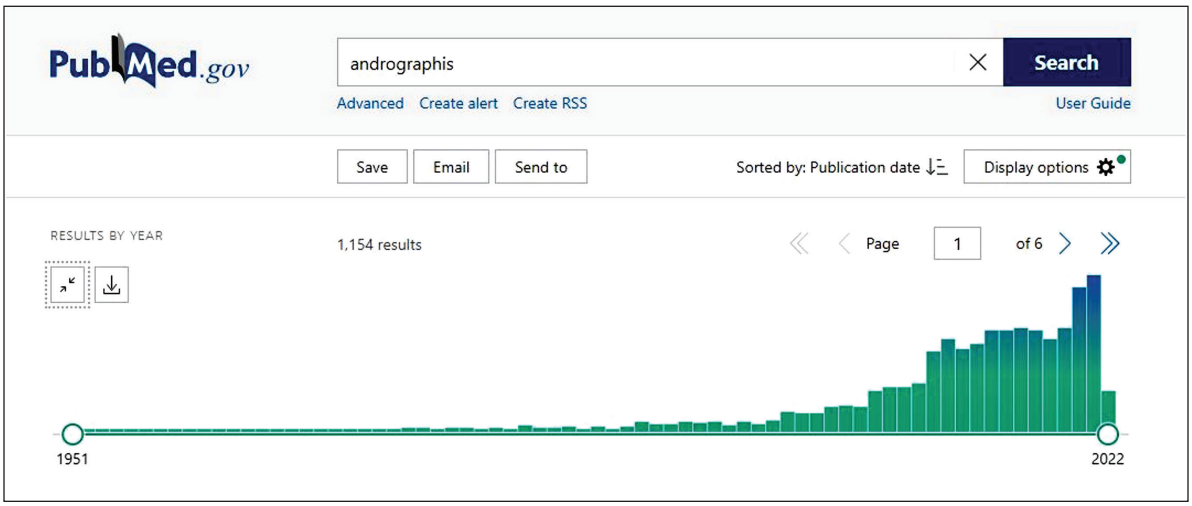


Figure 12. A total of 887 publications on *Andrographis paniculata* have been published in peer-reviewed scientific journals indexed in the NHI National Library of Medicine (USA) since 1951; each bar shows the number of publications per year.

Various dosage forms of adaptogens are used both as mono-component herbal preparations and in combination with other herbal preparations in many countries under different National regulations as:

- Herbal Medicinal Products/pharmaceuticals—quality grade is regulated by European Pharmacopoeia (European Community)
- Medicinal Natural Health Products/Pharmaceuticals—quality grade is regulated by 'Quality of Natural Health Products Guide' based on United States Pharmacopeia (USP), British Pharmacopoeia (BP), European Pharmacopoeia (PhEur), Pharmacopée française (Ph.f.), Pharmacopoeia Internationalis (Ph.I.), Japanese Pharmacopoeia (JP), and Food Chemicals Codex (FCC) (Canada)
- Medicinal Products/Medications/Pharmaceutical products—quality grade is regulated by Russian Pharmacopoeia (Russia)

- Complementary Medicines/pharmaceuticals—quality grade is regulated by British Pharmacopoeia (BP), European Pharmacopoeia (PhEur) or the United States Pharmacopeia—National Formulary (USP-NF) (Australia)
- Chinese medicines/pharmaceuticals—quality grade is regulated by Pharmacopoeia of the People's Republic of China, English edition (CPC 2015), (China)
- Japanese medicines/pharmaceuticals—quality grade is regulated by Japanese Pharmacopoeia. (CJP 2016) (Japan)
- Korean medicine/pharmaceuticals quality grade is regulated by Korean Pharmacopoeia (MFDS 2012) (South Korea)
- Dietary Supplements—quality grade is regulated by US Pharmacopoeia (USA)
- Biologically active food additives (BAA).– quality grade is regulated by National Standards (Russia)
- Food/Nutraceuticals—quality grade is regulated by USDA Standards and EFSA Standards (USA, European Community)

Pharmaceuticals are drug-containing products in dosage forms. A pharmaceutical is a chemical substance used in healthcare to cure diseases. Pharmaceuticals are regulated by Medical agencies, e.g., FDA in the USA.

A dietary supplement is a product comprising one or more ingredients that are intended to supplement one's diet by taking a pill, capsule, tablet, powder, or liquid containing nutrients either extracted from food sources or that are synthetic to increase the quantity of their consumption. Vitamins, minerals, amino acids, enzymes, botanicals (herbal medicines), and certain components or derivatives of animal foods (organ and glandular tissues) were classified as dietary supplements by the Dietary Supplement Health and Education Act of 1994.

*** A nutraceutical** is a product that may be considered a food or part of food that provides medical or health benefits in addition to its primary nutritional value, encompassing prevention and treatment of disease. In the US, "nutraceuticals" are largely unregulated. According to the Federal Food, Drug, and Cosmetic Act, they belong to the same category as the dietary supplements and food additives.

ADAPTOGENS IN STRESS-INDUCED DISORDERS

In stress or aging-related decline of vital functions, the organism uses all resources and alternative mechanisms to compensate for the rising deficit of hormones, energy, oxygen supply, and other nutrients required for functioning and survival. But as a result, we pay a high price for survival in the form of stress- and aging-induced chronic diseases. For example, a sedentary lifestyle (so-called chronic hypodynamia, e.g., when we don't move and remain seated all day long in front of a computer) is a form of chronic stress that induces a wide range of disorders and diseases. Similarly, chronic emotional stress or exposure to other stressors triggers various stress-induced conditions **(Figures 13, 14).**

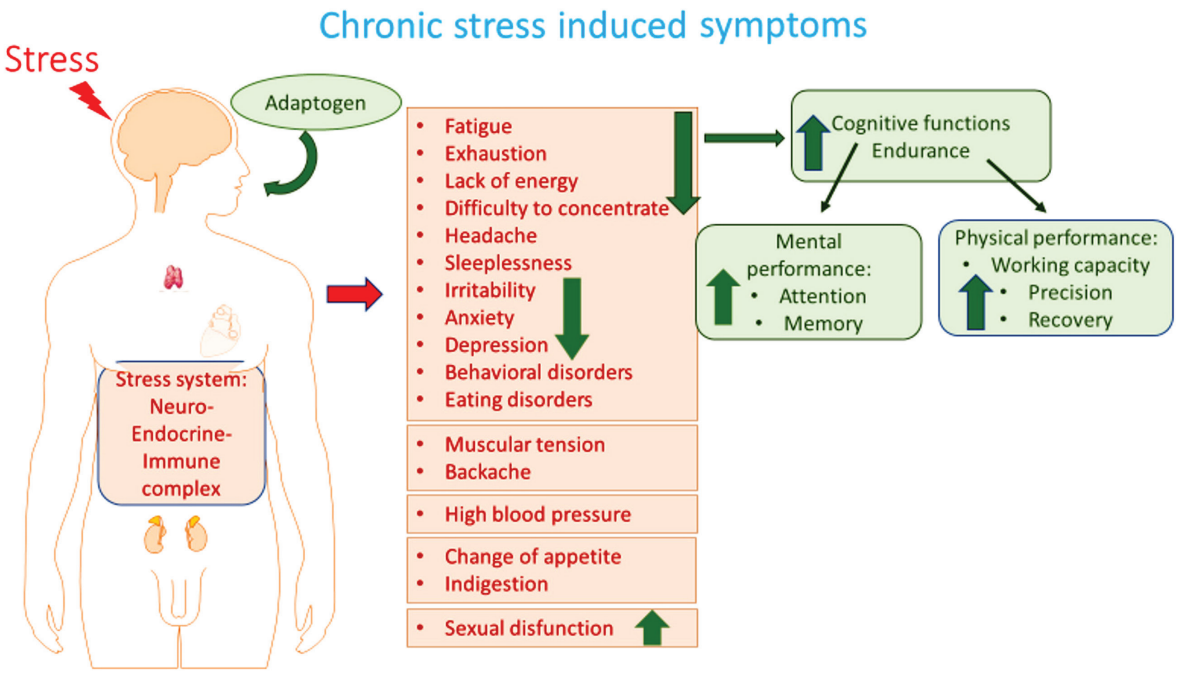


Figure 13. Effect of adaptogens on chronic stress-induced symptoms.

High susceptibility to the pathogen-induced progression of acute inflammatory response is common in subjects chronically exposed to stress and elderly people with an age-dependent increase of chronic low-grade inflammation, so-called "inflammaging," which is associated with continuous stimulation of the innate immune system and suboptimal production of hormones, and other key mediators of homeostasis during senescence.

Recent studies with adaptogens suggest that they might be helpful, not only in stress-induced mental and behavioral disorders (e.g., depression, anxiety, etc. which is significantly

increased in self-isolation during COVID-19 pandemic), but also in aging-associated disorders, including neurodegeneration, atherosclerosis, diabetes, heart diseases, and high blood pressure, chronic inflammation, osteoarthritis, etc.

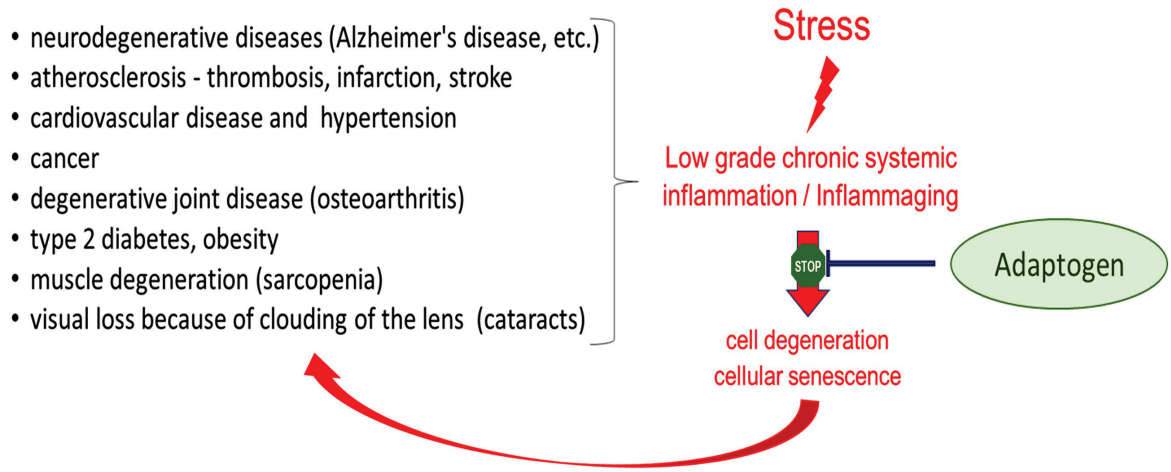


Figure 14. Age-related diseases in senescence due to decreased adaptability to stress and an ability to maintain homeostasis. Adaptogens inhibit cell degeneration and, eventually, chronic progression inflammation-induced progression of stress and aging-associated diseases.

What conclusions can be drawn?

✦ Adaptogens promote healthy aging reducing chronic inflammation (inflammaging), cell degeneration, and progression of stress and aging-associated diseases.

ADAPTOGENS FOR PREVENTION AND TREATMENT OF RESPIRATORY TRACT INFECTIOUS DISEASES

A growing body of evidence from experiments on isolated cells, experimental animals, and human subjects suggests that adaptogens might help prevent and cure infectious pulmonary diseases, including COVID-19. Furthermore, adaptogens might be effective for the relief of long-lasting symptoms of Long COVID, such as fatigue (58%), headache (44%), attention disorder (27%), hair loss (25%), and difficult breathing (dyspnea, 24%), etc.

The complexity of COVID-19 suggests a need for a choice of therapies, including antiviral agents, immunostimulants, immunosuppressants, adaptogens, and anticoagulants.

It can be achieved by multitarget pharmaceutical intervention of herbal preparations with polyvalent and pleiotropic actions on host defense systems, like adaptogens targeting multiple elements of molecular networks involved in inflammatory defense response. The clinical efficacy of some adaptogenic preparations was demonstrated in the common cold and associated uncomplicated upper respiratory infections. The clinical studies confirm their efficacy and safety, presumably due to their antiviral, anti-inflammatory, and adaptogenic activity. Further studies are required to evaluate their effectiveness in COVID-19 and other viral respiratory invidious diseases.

Pathogenesis and progression of COVID-19 is a multistep process, which requires correct therapeutic strategy on various steps of initiation of overall defense response to pathogen and its resolution, **Figure 15.**

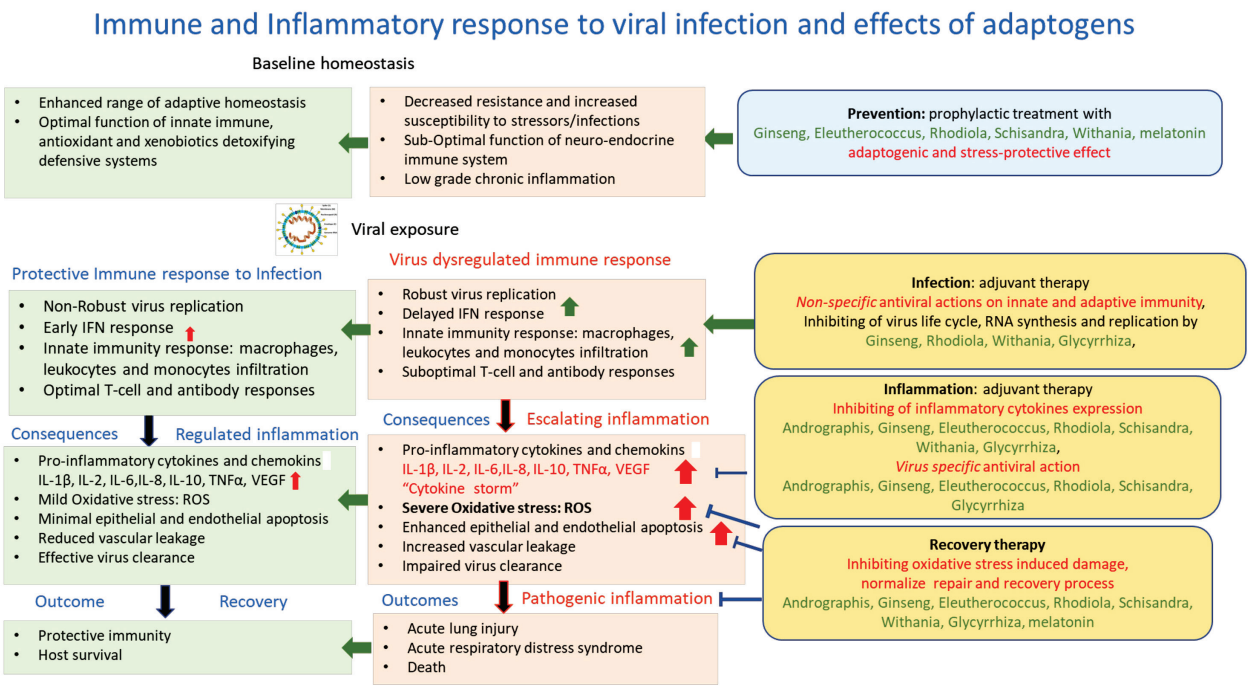


Figure 15. Schematic diagram of various phases of immune and inflammatory responses to SARS-CoV-2 infection and stages of COVID-19 progression with and without considering potential effects of adaptogenic plants on prevention, infection, inflammation, and recovery phases of viral infection.

Effective prevention or treatment of COVID-19 requires pharmaceutical adjustments of numerous innate components of the adaptive immune system, phases I-III metabolizing enzymes of detoxifying and repair systems, and the SARS-Cov-2 virus' life cycle and proliferation, **Figure 16a**. Adaptogens exerting multitarget effects on the neuroendocrine-immune system by triggering adaptive stress responses (**Figure 16a**) have a place in prevention, infection, escalating inflammation, and recovery, **Figure 15.**

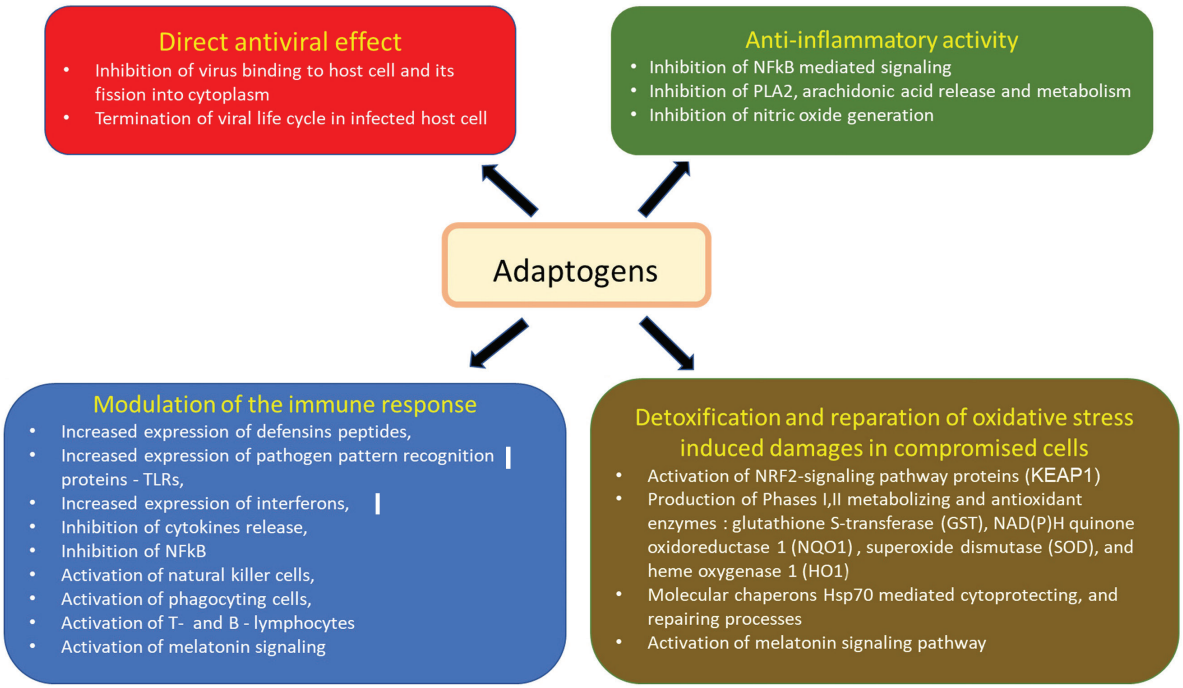


Figure 16a. Schematic diagram of reported effects of adaptogenic plants elucidated in animal and cell culture models: (i) modulatory effects on immune response (blue block), (ii) anti-inflammatory activity (green bock), (iii) detoxification and repair of oxidative stress-induced damage in compromised cells (brown block), and (iv) direct antiviral effect via infraction with viral docking or replication (red block)

Adaptogens provide baseline support through their immunomodulatory, immunostimulatory, and antioxidant effect through all four phases, combat infection through their specific and non-specific antiviral mechanisms, alleviate escalating inflammation through their anti-inflammatory effects, as well as their ability to repair oxidative stress-induced injuries in compromised cells and tissues, and address secondary disease states and comorbidities through various, infection-related activities.

For example, Red Korean ginseng was tested in mice and isolated cells infected with the influenza virus. Mice infected with a lethal dose of virus and Red Korean ginseng displayed a 100% survival rate against infection. The antiviral protective effects were observed regardless of influenza virus strains. There was also developed immunity against secondary viral infection.

It was shown that the antiviral activity of Red Korean ginseng is due to:

- its direct effect on the virus—the virus cannot enter the host cell.
- activation of innate immunity of host organisms and suppressing inflammatory "cytokine storm" (Figure 16b).

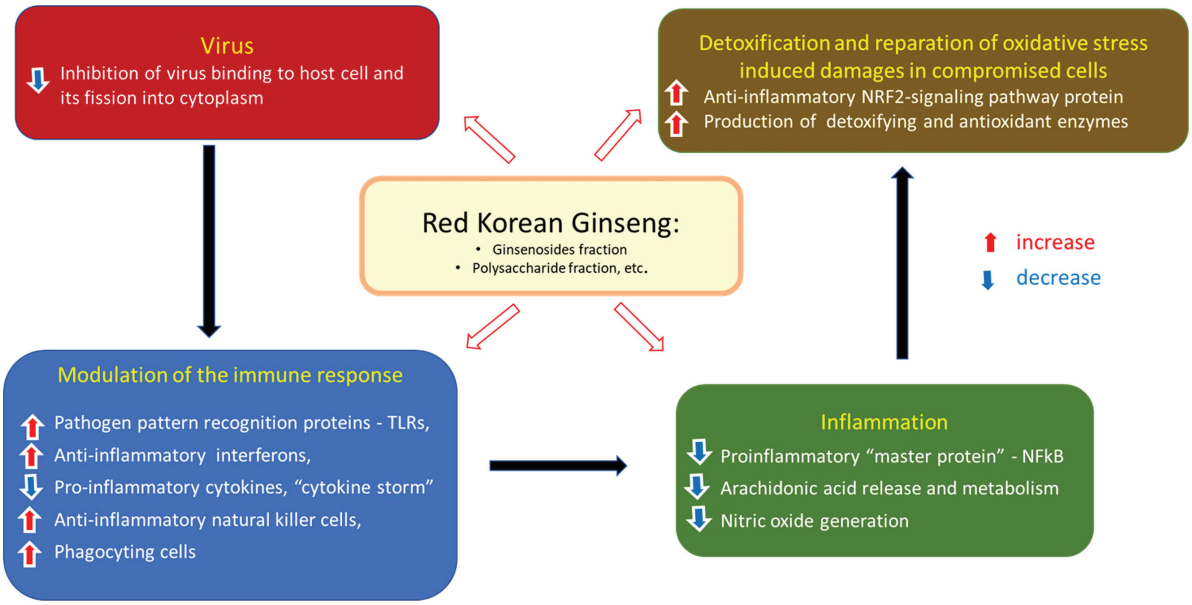


Figure 16b. Schematic diagram of reported effects of Red Ginseng: (i) direct antiviral effect via inhibition of virus binding to host cell and its fission into the cytoplasm (red block), (ii) modulatory effects on immune response (blue block), (iii) anti-inflammatory activity (green bock), and (iv) detoxification and repair of oxidative stress-induced damage in compromised cells (brown block).

As a result, Red Korean ginseng inhibits inflammation (green block) via several mechanisms:

- ✦ inhibiting proinflammatory "master protein" NFkB, which generates many proinflammatory molecules in response to virus invasion.
- ✦ inhibiting the arachidonic acid cascade (this way works for corticosteroids and many anti-inflammatory drugs, including hydroxychloroquine).
- ✦ It inhibits nitric oxide (NO), an important pro-inflammatory molecule generated after a viral infection that initiates "oxidative stress" and destroys viruses, bacteria, and healthy cells and tissues.

Furthermore, Red Ginseng can do something that antiviral drugs or vaccines cannot do: detoxify oxidative stress-induced damages in compromised cells (brown box). It is due to activation of another "master protein," Nrf2, which activates the generation of metabolic enzymes (so-called phase I, II, and Phase II transporter proteins that repair damaged proteins and remove the toxic "garbage" from the cell) and innate antioxidant system, which stops oxidative stress.

Several antiviral ingredients of Korean Red Ginseng have been identified:

- ginsenosides, particularly Rb1, interacts with viral proteins, preventing binding of virus from hosting cells and viral entry into the cytoplasm.
- polysaccharide fraction exhibits a strong antiviral effect in influenza A virus-infected mice predominantly via the effect on the immune system reducing the accumulation of proinflammatory cytokine TNF-α and nitric oxide.

One more benefit of adaptogens in COVID-19 might be their beneficial effect *during the recovery* of patients. Short-term follow-up of COVID-19 patients reveals pulmonary dysfunction, myocardial damage, and severe psychological distress. As a rule, patients with COVID-19 discharged from hospitals are considered to have entered the recovery period when they met the following criteria: (a) average body temperature for more than three days; (b) absence of respiratory tract symptoms; (c) twice negative results of consecutive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) reverse-transcriptase polymerase chain reaction assays of the sputum with a 1-day sampling interval. However, most COVID-19 patients in convalescence still had symptoms and lung inflammation after hospital discharge and recovered with time prolonged for 2–3 months. Inflammatory symptoms or abnormal clinical parameters persisting two or more weeks after COVID-19 onset that does not come back to a healthy baseline can potentially be considered long-term effects of the disease—so-called Long COVID.

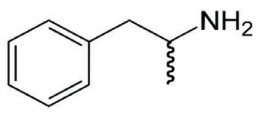
Over seven thousand clinical studies in COVID-19, including several hundred interventional trials of antiviral treatments in Long Covid-19, are currently in progress.

CHAPTER 2

Historical Background of Adaptogenic Concept

The origin of the adaptogenic concept.

The term adaptogen was implemented in the scientific literature in 1958 by toxicologist Lazarev. He assumed that adaptogens increase the organism's resistance in harmful conditions resulting in increased endurance, stamina, and performance. This postulation was based on the results of intensive studies of Ginseng and Schisandra initiated in USSR during World War II, intending to replace synthetic stimulants (used by German and British pilots, **Figure 17)** and supply the Soviet Army and Military Industry (soldiers, pilots, sailors, and civilians engaged in production of weapons and war material) with an easily available natural stimulant and tonic.



The resolution No 4654-p

of the People's Commissars Council of the USSR

"... to study Limonnik (*Schisandra chinensis*) with the purpose of finding of **tonic** substances..."

4th March 1943, Moscow

Figure 17. (a)—British pilots were provided with amphetamine. Adapted from "Turbocharging the Brain"; October 2009; *Scientific American Magazine;* by Gary Stix. (b)—Schisandra berry and the main goal of Schisandra studies formulated in the resolution No 4654-p of the People's Commissars Council of USSR, signed by A. Mikoyan in 1943.

The attention in *S. chinensis* (known as *limonnik* in Russian) arises from ethnopharmacological research by V.L. Komarov (1895) and V. Arsenyev (1903–1907) in far-eastern Siberia and northern Manchuria. The berries and seeds were revealed to have been used by Nanai hunters (a native people of far-eastern Siberia and Chinese Manchuria, also known as Goldis or Samagir) tonic; to reduce exhaustion, thirst, hunger and to improve night-time vision, **Figure 18**.

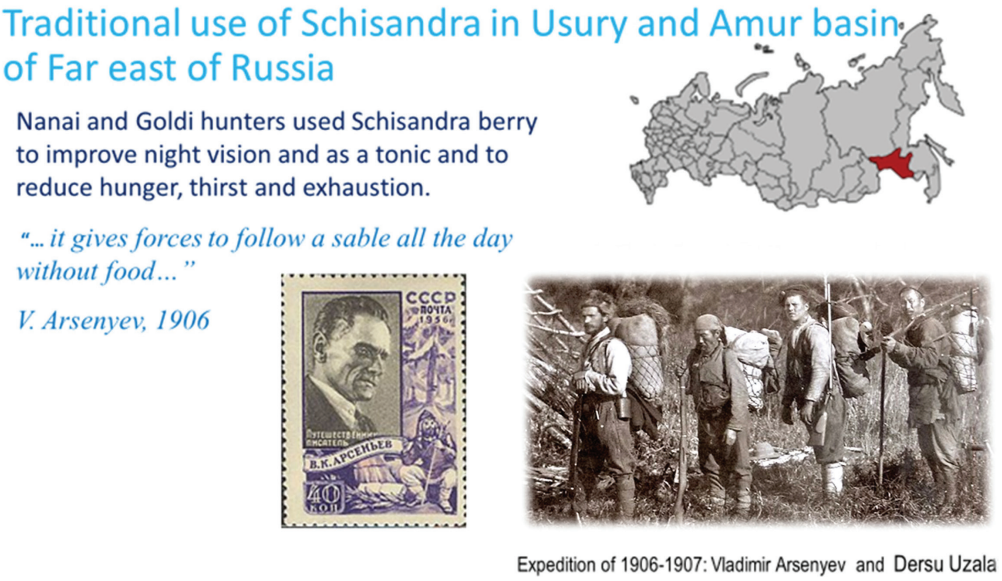


Figure 18. The Nanai hunter Dersu Uzala introduced the Schisandra berry to the Russian explorer Vladimir Arsenyev during his expedition to the Usury basin in 1902–1907.

The earliest studies on the stimulating and tonic effects of Schisandra (*Schisandra chinensis*, Schisandraceae) were published in World War II-era military journals, **Figure 19.**

In the meantime, other Soviet scientists, pharmacologists Israel Brekhman, Igor Dardimov, and Albert Saratikov have extended the research of adaptogens on "Rejuvenate and Invigorate" herbs traditionally used in China, Korea, Japan, and Siberia and Far East of USSR in a variety of pathological conditions and illnesses such as hypodynamia, anorexia, shortness of breath, palpitation, insomnia, impotence, hemorrhage, and diabetes, etc.

They screened many plants, and some of them (Table 4) were included in 1967 in official medicine of USSR as CNS busting medicinal product indicated as tonics in fatigue and general weakness during convalescence in infectious diseases, after surgeries, poisoning, heart attacks, ischemia with the purpose to speed up recovery well as to reduce adverse reactions in chemotherapy and psychiatric disorders. Adaptogens were formally approved as psychotropic drugs, CNS stimulants, and CNS busting preparations in official medicine

in USSR. An example of the adaptogenic medicinal product used in official medicine in the USSR/Russia is *Rhodiola rosea* extract, indicated in "decreased mental and physical capacities such as weakness, exhaustion, tiredness, and loss of concentration, as well as during convalescence."

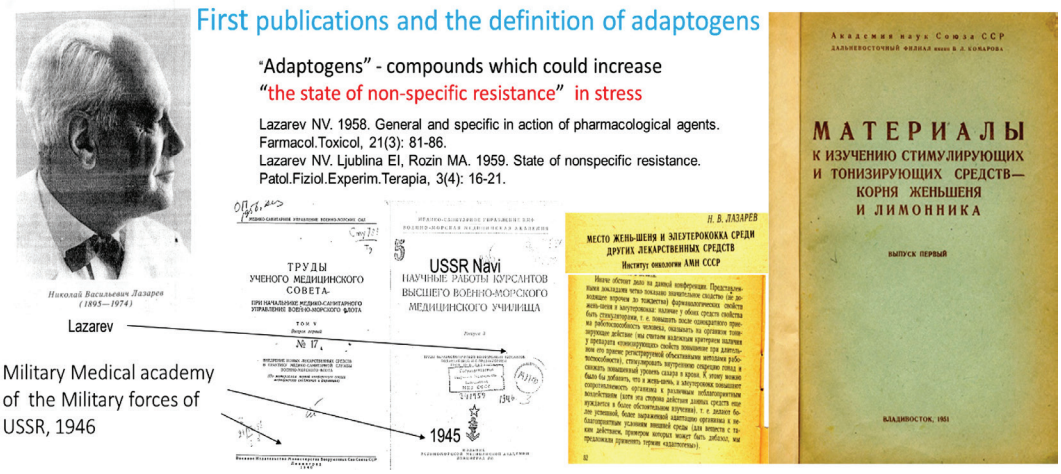


Figure 19. Title pages of scientific journals where first articles on *Shisandra chinensis* and *Panax Ginseng* were published and Editor in Chief was Nicolay Lazarev.

TABLE 4. USE OF ADAPTOGENS IN OFFICIAL MEDICINE IN THE USSR

Name of plant	Products
Aralia manshurica Rupr.et Maxim	tincture, dry extract in tablets
Echinopanax elatum Nakai	tincture
Eleutherococcus senticosis Maxim	extract
Panax ginseng C.A. Meyer	tincture, dry extract in tablets
Rhaponticum carthamoides (Willd) Iljin	tincture
Rhodiola rosea L.	extract
Schisandra chinensis (Turcz.) Bail	tincture, soft capsules

The extent of the adaptogen research carried out in USSR was enormous, with more than a thousand studies (primarily pharmacological and clinical) published in Russia up until 1982, and most of them concerned extracts or isolates prepared from Siberian Ginseng

(*Eleutherococcus senticosus)*, Schisandra *(Schisandra chinensis)*, Red Ginseng *(Panax ginseng)* and Golden Root *(Rhodiola rosea)*. Regardless of the formal indication for use as stimulants (single-dose administration) and tonics (repeated multiple administration) in official medicine in USSR, adaptogens were extensively used in:

- **sports medicine** to promote swifter recovery after heavy exercise and overstraining,
- **occupational therapy** for protection against harmful environmental factors,
- **geriatric medicine** that focuses on older adults' health care aims to promote health by preventing and curing diseases and disabilities in older adults.

These indications of use of adaptogens were of political importance in USSR, a superpower where:

- exciting Space programs associated with various stressful conditions were piloted,
- the numerous Arctic and Antarctic expeditions where people are in permanent exposure to cold stress were conducted,
- nuclear weapon industry with an extremely high risk of radiation-induced injury was developed,
- powerful Military Air Forces, Navy where chronic hypoxia, burnout syndrome, and other stresses are quite common,
- great athletes and chess players experienced physical and mental overload,
- the numerous Arctic and Antarctic expeditions where people are in permanent exposure to cold stress.

Furthermore, "Kremlin Magic Pills" and "Elixir of Youth" increasing strength, stamina, and longevity were popular among elite elderly leaders of the Communist Party of the USSR governing the country for many years.

What conclusions can be drawn?

The adaptogenic concept is traced back to:

- first definitions of adaptogens made by Soviet scientists Lazarev and Brekhman.
- Implementing herbal medicinal products in official medicine and pharmacopeia in USSR/Russia.

ETHNOPHARMACOLOGICAL BACKGROUND

Key points of the adaptogenic concept defined by Brekhman and Dardymov in1969 are in line with basic principles of Traditional Medical Systems of China, Korea, Japan, India, and Middle Asia: Ayurveda, Yunani (Unani), and Chinese.

Traditional systems are based on the holistic approach to patients and treatment.

> *"Holism is the idea that all the properties of a given system (biological, chemical, social, economic, mental, etc.) cannot be determined or explained by its parts alone. Instead, the system as a whole determines how the parts behave"*
>
> —New World Encyclopedia.
> **http://www.newworldencyclopedia.org/entry/Holism**

Western medicine considers the **generalized populations**, and "**normal"** means what is appropriate to the **majority**. On the contrary, the holistic approach considers the patient as a unique individual and "normality" as appropriate for that particular person. The patient is viewed as unique and is therefore subject to unique imbalances.

Traditional medical systems have a similar notion of "life vital energy," activating body and mind: The Qi in TCM and the Prana—in Ayurveda. A similar notion exists in various cultures, including the Greek pneuma, the Armenian oqin (ոգի), the Polynesian mana, the German od, and the Hebrew ruah. Prana is also described to as "bioplasmic energy," "subtle energy," or "life force."

In addition to herbal medicines, traditional medicinal systems, e.g., TCM and Ayurveda, also include various forms of dietary therapy, exercise, massage, meditation, and acupuncture. They are primarily used as a complementary alternative medicine approach.

Following are brief explanations of the ethnopharmacological "roots" of the adaptogenic concept.

Traditional Chinese medicine: yin-yang or Qi balance, balance determining a state of health and lifespan

Traditional Chinese Medicine (TCM) is about 5,000 years old, **Figure 20** (see next page). It means that billons of billions of people of the World's biggest population (currently about 1.7 billion Chinese live on our globe) have been treated with these herbal medicines/botanicals for centuries. It is unlikely that there were no benefits from this long-term experience with herbal medicine.

Figure 20. (a)—"Shennong's Herbal Classic" is the earliest Chinese herbal textbook, and Shennong is regarded as the founder of agriculture and medicine in China. https://plus.google.com/+shenyun/posts/b94gY8yTaS1. It was Emperor Yan, also known as Shennong, who invented ancient Chinese medicine. According to legend, Shennong's mother encountered a dragon and soon gave birth. Shennong was born with an ox's head and a human body, but this was no ordinary body—it was transparent, like crystal. Because of this, the effects of any food or herb could easily be identified upon entering his body. It is said that Shennong went into the mountains to test and record the effects of various herbs and medicinal plants. He tried hundreds of unique plants by extracting their juices with a magical whip. To counteract regularly poisoning himself, Shennong drank tea to detoxify his body. **(b)—**The symbol of Yun-Yang complementary and contradictory unity of two in one.

TCM is based on two natural laws that regulate health and longevity: *yin-yang* and the five elements, which are linked to main organs of the body, emotions, climate, seasons, and tests, Table 5:

TABLE 5. ASPECTS OF THE HOLISTIC SYSTEM OF TCM

earth	**body**	spleen	lung	kidney	liver	hearth
metal	**emotions**	reflection	grief	fear	anger	joy
water	**climates**	damp	dry	cold	windy	hot
wood	**seasons**	late summer	autumn	winter	spring	summer
fire	**tests**	sweet	pungent	salty	sour	bitter

The core of TCM is 'yin-yang theory' comprising of two complementary and contradictory natural forces of opposing polarity that interact to form a dynamic system in which the whole is dual and more significant than the assembled components. According to TCM, everything has both yin and yang aspects (for instance, a shadow cannot occur without light), which are in dynamic balance, Figure 20b:

- Yin is negative/passive/dark/female/water, while
- Yang is positive/active/bright/male/fire.

For comparison, the complementarity principle in physics postulates that a complete knowledge of electrons in atoms or light requires a description of wave and particle properties.

Yin is more substantial; however, they are always in balance.

Herbal preparations were used to maintain and restore the balance between these elements and to supply vital energy *qi,* which has both *yin* and *yang* characteristics. The treatment was based both on symptoms and patterns of imbalance.

According to TCM, the onset of diseases is due to both external (wind, cold, heat, dampness, dryness, fire) and internal causes—excessive emotional activity inducing yin/yang imbalance of seven emotions: joy, anger, anxiety, concentration, fright, grief, fear. Bacteria, viruses, and chemicals are NOT considered to be causes. If the organ is weak, it may be attacked, and therefore the weakness is the cause and must be rectified. Most people, if healthy, are not affected by external factors. Still, if the excessive emotional activity causes a severe yin/yang imbalance, blockage of qi and the impairment of vital organ function occur. Once physical damage has occurred, it will need more than emotional factors to cure it, and herbs will be used.

According to TCM theory, there is an intermediate state between health and disease—sub-health, so-called Shanghuo, characterized as "the state of increased susceptibility to stress and progression of diseases" caused by emotional stress can induce depression, insomnia, increase susceptibility to infectious diseases, promote cardiovascular disorders and cancer.

Therefore, the idea to prevent and treat stress-induced disorders caused by a yin-yang imbalance with prophylactic treatment using medicinal plants traces back to centuries (e.g., Weibing in China, Mibyeong in Korea, and Mibyou in Japan.

The state of high susceptibility to infectious diseases ("shanghuo") is due to decreased "non-specific resistance to stress" (Lazarev). Consequently, the concepts underlying preventive treatment for subhealth by adaptogens (apparently "fu zheng" in TCM for improving body resistance or strengthening vital qi) were applied in USSR under the names Medical Fitness, Farmacosanacia, and Videology.

According to TCM, the therapy of diseases must rectify harmony, restore Qi and yin/yang equilibrium. It is the quantity, quality, and balance of Qi that affect health and lifespan. Food and air affect health, so diet and breathing exercises are critical. After that, herbs are considered to treat diseases and recover vital energy, which is believed to dissipate throughout life gradually. For example, fatigue is due to Qi deficiency, and Panax Ginseng (tonic herb) activates Qi and therefore has a nourishing effect in fatigue. So, it is essential to preserve it using breathing exercise, diet, kung fu, and herbal medicine.

In Traditional Chinese Medicine, all known herbal plants were divided into inferior, middle, and superior. The highest form of medicine revered in China is the superior herbs (tonic herbs), which help heal and nurture life itself. Superior herbs possess therapeutic properties and are used as general tonics in treating disease and in recovery. The most known superior herb in TCM is Ginseng.

The therapeutic activity of Ginseng was first described in the 1st century by an unknown author. According to his records in The Shennong Bencao, Ginseng can nourish or tonify 5 vital organs of the body (the heart, kidney, spleen, lung, and liver), has sedative properties, is used for palpitations to restore a normal pulse, dispels pathogenic factors, improves visual acuity and mental activity, and enhances longevity with long-term intake. According to other ancients regards written by Hongjing Tao (AD 456–536), Ginseng can be used to relieve thirst and feelings of solidness, to enhance cognitive function, improve blood circulation, and to cure internal emotionlessness, pain in the chest or abdomen, sensations of fullness in the chest, vomiting, and diarrhea. These and other beneficial effects of Ginseng were also described in other more complete and comprehensive herbal textbooks: general weakness, spontaneous sweating, and fever, vertigo and headache, regurgitation and vomiting, alternating fever and chills, chronic diarrhea, increased urination, fatigue, externally contracted wind or hot attack, cramps, vomiting blood (hematemesis), bleeding from the rectum, bloody urinary leakage, abnormal uterine bleeding, and discomfort before or after parturition.

What conclusions can be drawn?

The adaptogenic concept is based on fundamentals, notions, and experience of TCM, such as:

- "vital energy," Qi, which has the similar meaning as adaptability or "state of non-specific resistance.
- Yin-Yang balance, a synonym of "homeostasis."

- "Shanghuo," an intermediate subhealth state between health and disease, characterized as "the state of increased susceptibility to stress and progression of diseases" actually due to decreased "non-specific resistance to stress."
- many indications for use in various conditions suggest a "non-specific" and normalizing effect of Ginseng/adaptogen on the organism.
- traditional use of Ginseng in billions of people for centuries means that it is safe, non-toxic, innocuous, and does not influence normal body functions more than required.

KAMPO—MULTICOMPONENT DRUG ADVANTAGE—SYNERGY EFFECT—GOOD STRESSORS

Kampō medicine is the Japanese adaptation of TCM that started between the 5th and 9th centuries. Since then, the Japanese have created their own unique herbal medical system based on the empirical knowledge of the effect of Kampo preparation on a particular pathological status of an individual with specified "symptom patterns" (*sho*), which is different from Western diagnoses. Each Kampo formula is indicated for individuals with the same sho, but different diseases. On the other hand, individuals with the same disease can have various *sho* and be prescribed different Kampo prescriptions. Kampo prescriptions are included in the Japanese Pharmacopoeia (JP) and regulated by the Japanese government.

The basic concept of "Hozai" was formulated in the 18th century; the philosopher Yoshimasu Todo stated that the curative and toxic effect are two phases of the same process: since an uncontrolled poisoning triggers diseases, the patient has to be healed by a positive, challenging poisoning, which initiates a regeneration process resulting in removal of both toxic procedures from the body and recovery. In this perspective, hozai and adaptogens are similar since adaptogens are eustressors (*i.e.* good stressors) acting as mild stress mimetics or stress vaccines that induce a stress-protective response, which is in line with the basics of Kampo medicine.

Kampo tradition uses fixed combinations of herbs in standardized preparations. The idea to merge two or more plants or substances in a fixed combination, which will be stronger than any ingredient alone, is entirely rational. The ingredients of new fixed combinations of herbal extracts could have different mechanisms and "targets" of action in the human organism, and therefore better effect in the combination.

Furthermore, the overall effect could be more than an additive in the combination—the ingredients can act synergistically. It means that the mixture is active, while the ingredients—are inactive. This phenomenon was observed in various experimental models with isolated cells, organisms, and social communication levels.

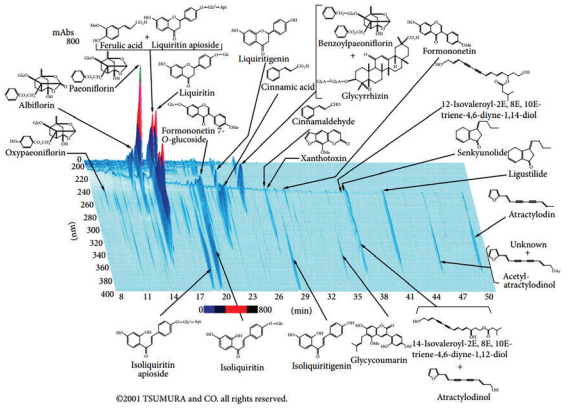
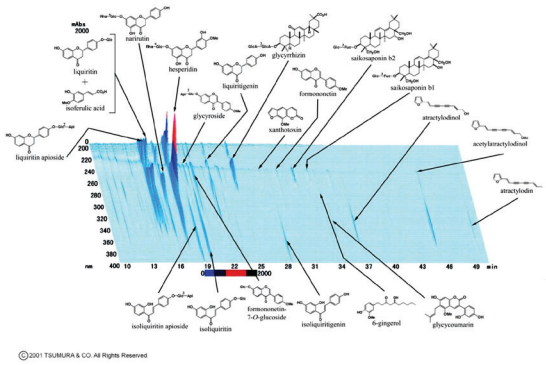
Finally, the combination can be used in a lower dose and be less toxic if any ingredients contain a toxic impurity.

A special group of Kampo prescriptions, so-called *Hozai* (support preparations, e.g., *Juzentaihoto* and *Hochuekkito*, **Table 6**), are applied in physical weakness associated with a loss of skeletal muscle mass (so-called "*cachexia*" that varies from weight loss due to malnutrition, anorexia nervosa, or anorexia due to depression or *sarcopenia*—aging-related muscle loss), as well as symptoms of degenerative diseases, typical to aging-related disorders.

Juzentaihoto is used for recovery after surgery or chronic diseases with symptoms such as exhaustion, fatigue, loss of appetite, pale face, dry skin, and anemia. In contrast, *Hochuekkito* has been used for the treatment of weak patients who have chronic respiratory diseases, tuberculosis, surgery with loss of appetite, mild fever, night sweat, palpitation, fear, restlessness, feeble voice, slurred speech, general vigor, anorexia, myasthenia gravis, chronic gastritis, atopic dermatitis and disturbance of vision. *Juzentaihoto* also inhibits tumor progression and contributes to long-term survival.

TABLE 6. RAW DRUGS AND THEIR RESPECTIVE DAILY DOSAGES (G) IN THE TWO TRADITIONAL KAMPO HOZAI PRESCRIPTIONS

Juzentaihoto (Shi-Quan-Da-Bu-Tang in Chinese, TJ-48) Tonify the Middle and Augment the Qi Decoction https://kampo.ca/herbs-formulas/formulas/juzentaihoto/	**Hochuekkito** (Bu-Zong-Yi-Qi-Tang in Chinese, TJ-41) All-Inclusive Great Tonifying Decoction https://kampo.ca/herbs-formulas/formulas/hochuekkito/
Ginseng Radix -2	Ginseng Radix -4
Astragali Radix -3	Astragali Radix -4
Glycyrrhizae Radix -2	Glycyrrhizae Radix -1
Angelicae sinensis Radix -3	Angelicae sinensis Radix -2
Atractylodis macrocephalae Rhizoma -3	Atractylodis macrocephalae Rhizoma -4
Paeoniae Radix -3	Bupleuri Radix -2
Cinnamomi Cortex -3	Jujubae Fructus -2
Ligusticum Rhizoma -3	Zingiberis Rhizoma -1
Sclerotium Poriae Cocos -3	Cimicifugae Rhizoma -1
Rehmanniae Radix preparata -3	Citri reticulatae Pericarpium -2

HPLC profile /" fingerprint"—chemical composition	HPLC profile /" fingerprint"—chemical composition
	 https://figshare.com/articles/figure/Image_1_Decline_in_Liver_Mitochondria_Metabolic_Function_Is_Restored_by_Hochuekkito_Through_Sirtuin_1_in_Aged_Mice_With_Malnutrition_pdf/19254101
Indications: for patients with the following health conditions and symptoms: • Fatigue • Poor appetite • Anemia • Cough • Pale complexion • Shortness of breath • Cold extremities • Spermatorrhea • Postpartum weakness	**Indications:** for patients with the following health conditions and symptoms: • Fatigue • Poor appetite • Spontaneous sweating • Loose stools • Frequent cold or infection • Prolapsed rectum/hemorrhage • Male infertility • Sexual dysfunction • Excessive vaginal discharge • Prolapsed uterus

What conclusions can be drawn?

The theory of "Hozai" is similar to the concept of "Adaptogen,," particularly in the context of their mode of action as eustressors (i.e., "good stressors") and as mild stress mimetics or 'stress-vaccines' that induce a stress-protective response.

Another common feature is associated with their indications in aging-related degenerative disorders and general weakness.

AYURVEDA: VITAL LIFE ENERGY (PRANA) AND BALANCE OF CNS-IMMUNE—HORMONAL SYSTEM (TRIDOSHA)

Ayurveda is a conventional medicinal system with historical origins in the Indian subcontinent. Ayurvedic treatments are varied and have grown over more than two millennia. In Ayurveda, the central notion is the "Tridosha" theory suggesting that health occurs when there is a balance between three fundamental dynamic forces "doshas" called Vata, Pitta, and Kapha, where:

- Vata—the combination of Air and Water, which is associated with the function of the nervous system. When imbalanced, it indices pain, sleeplessness, inability to concentrate and stay on task.
- Pitta—the combination of Water and Fire, which is associated with bile, digestion and metabolism.
- Kapha—the combination of Earth and Water, associated with mucous, lubrication, and the carrier of nutrients into the arterial system.

Figure 21. Dhanvantari, in the Hindu god of Ayurveda Medicine and Nagarjuna (c. 150–c. 250 CE), one of the Buddhist philosophers who invented many drugs to treat ailments.

According to Ayurvedic theory, life's vital energy, Prana, comes from the air into the brain via breathing. Prana is stayed in the brain and governs emotions, memory, and other minds' functions. Prana also rules the functioning of the heart, entering the bloodstream from where it controls all essential tissues and organs.

In Ayurveda, the plants identified as "Rasayana" are used for rejuvenating and improving the overall health of anyone undergoing this treatment. Apart from promoting good health, increasing ability to concentrate, to improve memory and mood, a significant impact of Rasayana therapy is increasing resistance to diseases. Rasayana impact is not a specific pharmacological action but rather a complex response operating through a comprehensive, holistic regulation of homeostasis regulation.

Most commonly used in Ayurveda as rejuvenating plants are:

- Aswagandha—*Withania somnifera* (L.) Dunal.
- Kalmegh—*Andrographis paniculata* (Burm. F.) Wall. Ex. Nees.
- Yasthimadhu (Licorice)—*Glycyrrhiza glabra* Linn.
- Satavari -*Asparagus racemosus* Willd.
- Tulsi (Holy basil)—*Ocimum sanctum* Linn.

Ashwagandha is used in Ayurveda to promote health and longevity, slow the aging process, revitalize the body, reduce anxiety, and generally create a sense of well-being. These traditional applications of Ashwagandha are due to a wide range of pharmacological effects observed in preclinical studies in animals and clinical study trials in humans: it has anxiolytic, hypotensive, sedative, central nervous system, immunomodulatory, analgesic, anti-inflammatory, anti-tumor, anabolic, cardiopulmonary and antioxidant effects.

Kalmegh, the "the king of bitters," is in Ayurvedic and other traditional health care systems of India, China, and many other Asian countries for numerous medicinal purposes: as an antipyretic treatment effective against a variety of infectious diseases, including urinary infection with difficult, painful urination, tonsillitis, dysentery, edema, bacillary dysentery, bronchitis, carbuncles, colitis, coughs, dyspepsia, malarial and intermittent fever, hepatitis, mouth ulcers, sores, tuberculosis, colic, otitis media, vaginitis, pelvic inflammatory disease, chickenpox, eczema. The plant is effective for carbuncles, sores, venomous snake bites, ulcers in the mouth or tongue, liver disorders, burns, and traumatic infection. The efficacy of Ashwagandha has also been supported by clinical trials to prevent and treat upper respiratory diseases, such as the common cold, uncomplicated sinusitis, bronchitis and pharyngotonsillitis, urinary tract infections, and acute diarrhea.

The root of the licorice plant (Glycyrrhiza sp.) is also a well-known "Rasayana" drug in Ayurveda mainly due to its anti-inflammatory, antiviral, and antimicrobial activity.

In Ayurveda, Satavari is used as Rasayana and acknowledged for promoting physical and mental health. The wide range of therapeutic effectiveness of Satavari as an antitussive,

antiplasmodial, anti-leishmanial, antibacterial, hepato-protective, diuretic, anti-ulcer, anti-diarrheal, antenatal tonic, cardioprotective, anti-cancerous, antiepileptic, and antidepressant plant is likely associated with its immunomodulatory and adaptogenic activity.

Modern practices derived from Ayurveda are a kind of complementary or alternative medicine.

What conclusions can be drawn?

The concept of adaptogens is in line with the fundamentals of Ayurvedic philosophy healthcare, particularly in the context of:

- ✦ regulation of the homeostasis of the stress-system (neuro-endocrine immune complex, see below).
- ✦ the state of non-specific resistance (vital life energy = prana).
- ✦ multitask (pharmacologically pleiotropic or polyvalent) effects.
- ✦ antiaging effects of adaptogens.

IMPACT OF ANCIENT GREECE, ROME, AND MEDIEVAL TRADITIONAL MEDICAL SYSTEMS OF MIDDLE ASIA— MULTITASK EFFECTS AND BENEFITS OF LOW DOSES

Greek and Roman medicine originated with Hippocrates, Aristotle, Dioscorides and Galen were also based on four elements (earth, water, air, and fire), associated with four fluids of the body (blood, phlegm, black and yellow bile that have an impact on health and temperament) as well as with heat, cold, dryness, and dampness, which were linked to herbs presumably able to restore the imbalance.

Yunani or Unani is the term for Perso-Arabic traditional medicine practiced in the Indian subcontinent and the Muslim culture in central and southern Asia. The word is derived from Arabic “Greek” and has a Hellenistic origin based on the teachings of the Greek physicians. Unani was further developed and enriched by Abu-Ali Ibn Sina (Avicenna), Amirdovlat, and other medieval doctors of philosophers, Figure 22.

Figure 22.

a. Hippocrates (460–375 BC), The Hippocratic Corpus (Latin: Corpus Hippocraticum) comprises around seventy early medical works. The Hippocratic Corpus contains textbooks, lectures, research, notes, and philosophical essays on various subjects in medicine.

b. Dioscorides (90–40 BC) wrote a five-volume book, *De Materia Medica,* a precursor to all modern pharmacopeias and one of history's most influential herbal books. The work presents about 500 plants.

c. Aelius Galenus or Claudius Galenus, 129–210, wrote five hundred books and treatises on all aspects of medical science and philosophical subjects, and his ideas were to formulate many of the scientific beliefs which dominated medical thinking for about 1,500 years. Galenical preparation—a standard medicinal preparation (as an extract or tincture) usually containing one or more active ingredients of a plant and made by a process that leaves the plant's inert and other undesirable components undisclosed.

d. Abū' Alī al-Husayn ibn 'Abd Allāh ibn Sīnā Avicena (980–1037), the author of *The Canon of Medicine,* 2 of 5 volumes describes the use of 900 drugs.

e. Amirdovlat from Amasia (1420–1496). The Armenian physician, born in Amasia and resided in Sultan Mohammed II palace in Constantinople as his physician, was concurred by Mohammed II in 1453. The author of "Benefits of Medicine" (1469), "Useless for ignoramus" (1482), where more than 3,000 herbal medicines are described in alphabetical order in six languages. Amirdovlat's "Useless for the Ignorants" is an encyclopedia of medieval Armenian pharmacology with medicaments given in five languages: Armenian, Greek, Latin, Arabic, and Persian (Basmajean K., 1926). It contains 3,500 names and synonyms of more than 1,000 medicinal plants, 250 animals, and 150 minerals.

For instance, Amirdovlat devoted great importance to herbs that had antitoxic (lavender, marigold, ironwort) and tonic properties (birthwort, bryony). Amirdovlat used bryony, the sacred herb BC, panacea for all diseases to prevent premature aging and maintain good health and vitality.

In pre-Christian times, the root of *Bryonia (*called "Loshtak" in Armenia) was even a cult object in Armenia, where it was reviewed as a "drug for all diseases." There are many references to it by the scientists of ancient Greece (Hippocrates, Dioscorides, Theophrastus), Rome (Galen, Celsius, Plinius, Columella), and Asia (Avicenna, Amirdovlat). It was mentioned in D. Jensen's thesis of 1914 (Jensen, 1914). *Bryonia* root has been used for treating a

wide variety of disorders, including bronchitis, pleurisy, asthma, lung inflammation, cough, whooping-cough, influenza, fever, tuberculosis, tonsillitis, rheumatism, gout, arthritis, sciatica, neuralgia, hypertension, cardiovascular diseases, ulcers, gastrointestinal diseases, psoriasis, abscesses, allergies, leprosy, epilepsy, lockjaw, paralysis, hysteria, madness, sleeplessness, fatigue, edema, liver diseases, cancer, impotence, and pain. It is a laxative, cathartic, lactogenic, antihelmintic, diuretic, expectorant, and abortive. It has been used as a cosmetic to remove spots, blackheads, pimples, warts, and bruises, prevent allergic reactions in the skin and avoid hair loss (eyelashes, eyebrows, head).

Bryonia extract was integrated into official medicine as a tonic and adaptogenic drug in Armenia, Russia, Ukraine, and Belorussia as an adaptogen since the 90s and the first decade of XXI. Formulations from Bryonia alba L. root extract ("Loshtak" tablets) were registered as medicines by the Russian Federation in 2002, Ukraine in 2007, Belarus in 2003, and Armenia in 1992 and 2003 as an adaptogen and tonic in asthenia, infectious diseases; for increasing of working capacity, coordination, and mental activity; preventing of stress, radiation- and chemotherapy-induced toxicity and disorders.

The efficacy and safety of the herbal preparations significantly depend on soil and altitude of growth, collection season, extraction solvents, and methods of processing of the roots. For example, fresh roots of Bryonia collected in summer containing cytotoxic cucurbitacin *I* are used in homeopathy in inflammatory conditions affecting nerves and muscles, e.g., lower back pain. In contrast, dried roots harvested in fall or early spring contain only nontoxic tetrahydro-cucurbitacin I derivatives, mainly glycosides which are safe and induce adaptogenic activity. Homeopathic preparations from Bryonia roots were also used in many respiratory diseases (acute inflammation of the lung, bronchitis, pleuritis, asthma, whooping cough, fever, and viral infections) and other chronic inflammatory conditions (e.g., gout, rheumatoid arthritis) in the USA, UK, France, Germany, Russia, and other countries.

What conclusions can be drawn?

The concept of adaptogens is based on the experience of ancient Greece, Rome, and Medieval traditional medical systems of Middle Asia, particularly regarding the multitasking effects of medicinal herbs as a "panacea" for all diseases.

EUROPEAN TRADITIONS: RATIONAL CORE OF ANTHROPOSOPHICAL MEDICINE AND HOMEOPATHY—LOW AND HIGH DOSE EFFECTS, ENHANCED THE ORGANISM'S HEALING CAPACITIES.

A holistic method to medicine, which focuses on ensuring that the conditions for health are present in a person, is in the background of anthroposophical treatment, a complementary medicine founded in the 1920s by Rudolf Steiner (**Figure 12**), who advocated for the use of *Viscum album* L. (the European white-berry mistletoe) in cancer. Anthroposophical therapies are intended to enhance the organism's healing capacities, which are associated with the adaptability concept and the concept of adaptive homeostasis.

V. album L., an obligate hemiparasite plant growing on apple, plum, pear, hawthorn, beech, willow, poplar, maple, sweetgum, oak, almond, elm, pine, spruce, juniper, and eucalyptus, exhibits immunostimulatory, anti-inflammatory, antioxidant, analgesic, anti-glycaemic, anti-hypertensive, and neuroprotective properties.

In allopathic doses, mistletoe preparations (fresh juice, tinctures, and decoctions of various parts) are used in various countries (Armenia, Russia, Ukraine, Bulgaria, the Czech Republic) to treat cough, broken bones, diarrhea, rheumatism, gout, inflammation of lymphatic glands, wounds, and ulcers, as well as hypotensive, anti-atherosclerotic, anti-osteoarthritis, analgesic, sedative, and anti-epileptic remedies. It is worth mentioning that mistletoe growing on different trees is used for various purposes. Thus, mistletoe growing on the willow is used primarily as a sedative, whereas mistletoe growing on the pear is used in cardiovascular medicine. The one growing on the hawthorn is effective as a hypotensive drug.

Meanwhile, in tiny (homeopathic) doses (0,000000001 ng per kg of body weight), the mistletoe preparations Iscador, Eurixor, Helixor, Abnoba-Viscum, and Israel standardized for the content of mistletoe lectin 1 are widely used in Europe as alternative adjuvant therapies against colon, oral, lung, pancreatic, and breast cancers. The mistletoe extracts boost immunity, delay tumor progression, improve the quality of life, and increase survival and lifespan of cancer patients by helping with coping, fatigue, sleep, exhaustion, energy, nausea, vomiting, appetite, depression, anxiety, the ability to work, and emotional and functional well-being. Mistletoe treatment also alleviates the adverse effects of chemotherapies.

Highly diluted solutions of these mistletoe preparations are typical for homeopathic preparations formulated and developed by Samuel Hahnemann in the 18th century in Germany.

The basic idea of homeopathy suggests that a substance in high doses causes the symptoms of a disease in healthy individuals would cure similar symptoms in sick patients when applied in low doses.

That is in line with the theory of hormesis, describing the process by which sublethal damage caused by small doses of a toxin would produce an exaggerated repair response in which the organism becomes more vital than it was previously.

That is in line with the basics of toxicology—pharmacology: "All things are poisons. It is only the dose which makes a thing poison" (Paracelsus, XY AM, Figure 23), as well as with notorious statement by Friedrich Wilhelm Nietzsche—"That which does not kill us makes us stronger."

Homeopathic drugs are made from substances that, in undiluted form, cause symptoms like the disease they aim to treat. These substances are repeatedly diluted, with shaking at each stage.

Homeopaths consider that this procedure:

- ✦ removes side-effects,
- ✦ "adds to their power to stimulate a response," and
- ✦ "develops the special properties of the remedy," even after multiple dilutions in so greatly diluted solutions, none of the original substance remains but affected "the structure of water matrix," which is therapeutically active.

While high-potency preparations (i.e., highly diluted) cannot be evaluated using scientific methods, lower potency (i.e., less diluted) ones may well exert relevant pharmacological and toxicological effects.

Figure 23. Founders ("Fathers") of: (a) toxicology—Paracelsus (Filippus Aureolus Theophrastus, Bombastus von Hohenheim (born in 1493), (b) homeopathy—Samuel Hahnemann (born in 1755), (c) anthroposophy—Rudolf Steiner (born in 1861).

Homeopathic remedies are generally not tested and regulated under the same laws as conventional drugs. Therefore, homeopathy has been heavily criticized for putting patients at risk by advising them to avoid conventional medical treatments. Homeopathic treatments are generally considered safe, with rare exceptions. Nevertheless, usage varies from only 2% of people in the UK and the USA using homeopathy in any one year to 15% in India, where homeopathy is now considered part of its traditional medicine.

What conclusions can be drawn?

- The same substance can exhibit dose-dependent reversal effects: in small dose activate defense systems and exhibit beneficial/curative effects. In contrast, a high dose inhibits the defense system and is harmful to the organism.
- Toxic herbs in small doses activate body defense systems, especially the immune system, to cope with cancer and other diseases associated with suppressed immunity.

CHAPTER 3

Modern Science and Scientific Evidence on the Potential Use of Adaptogenic Plants in Stress-Induced and Aging-Related Disorders

Systems Biology and Network Pharmacology of Adaptogens

Adaptation to environmental challenges and senescence are multistep processes that involve diverse mechanisms and molecular interactions. Many molecular networks are involved that harmonize intracellular and extracellular communication.

The classical reductionist model that presumes a specific receptor/drug interaction (**Figure 24**) is not suitable for understanding the molecular mechanisms of action of adaptogens associated with the physiological notion of "adaptability."

On the contrary, the systems biology and network pharmacology concepts provide ideal mechanistic tools for understanding and conceptualizing adaptogen modes and mechanisms of action (Figure 25). The effects of adaptogens on metabolic regulation of homeostasis in various cells and physiological systems are linked with multiple targets. Molecular targets of adaptogens, their networks, and signaling pathways involved in adaptive stress response have been recently identified. They are associated with chronic inflammation, atherosclerosis, neurodegenerative cognitive impairment, metabolic disorders, and cancer, more common with age.

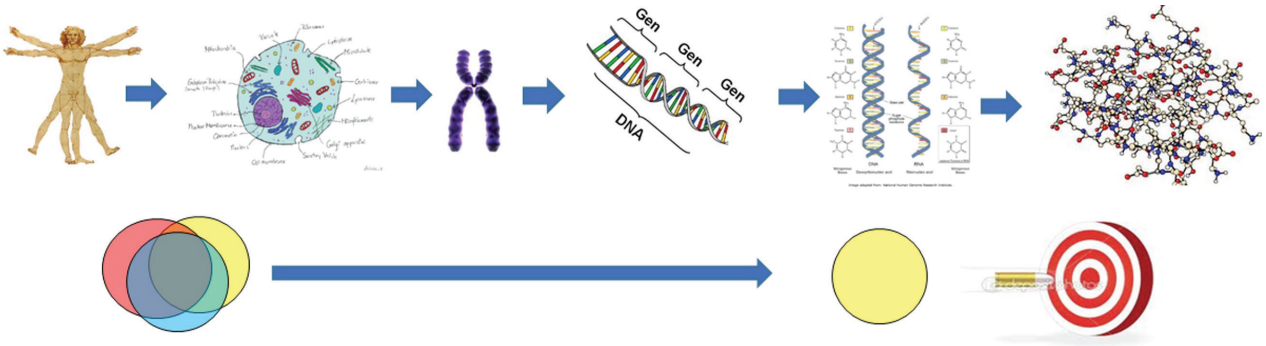


Figure 24. The reductionist methods of dissecting biological systems into their constituent parts. Bioassay-guided fractionation of herbal extracts to isolate an active principle ("magic bullet ") dominated the West for almost the last 20 centuries and was a fundamental principle in drug developing strategy in pharmaceutical science and industry. The reductionist concept of a single receptor-based (target) view of drug action would appear to be unsatisfactory for adaptogens.

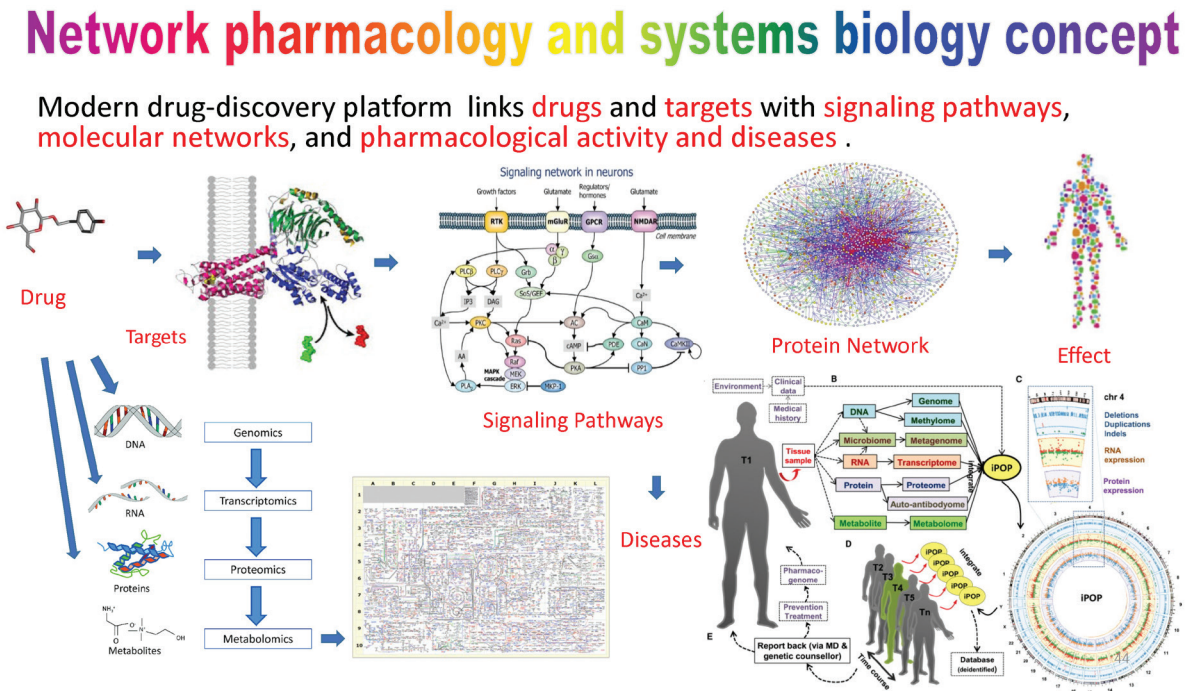
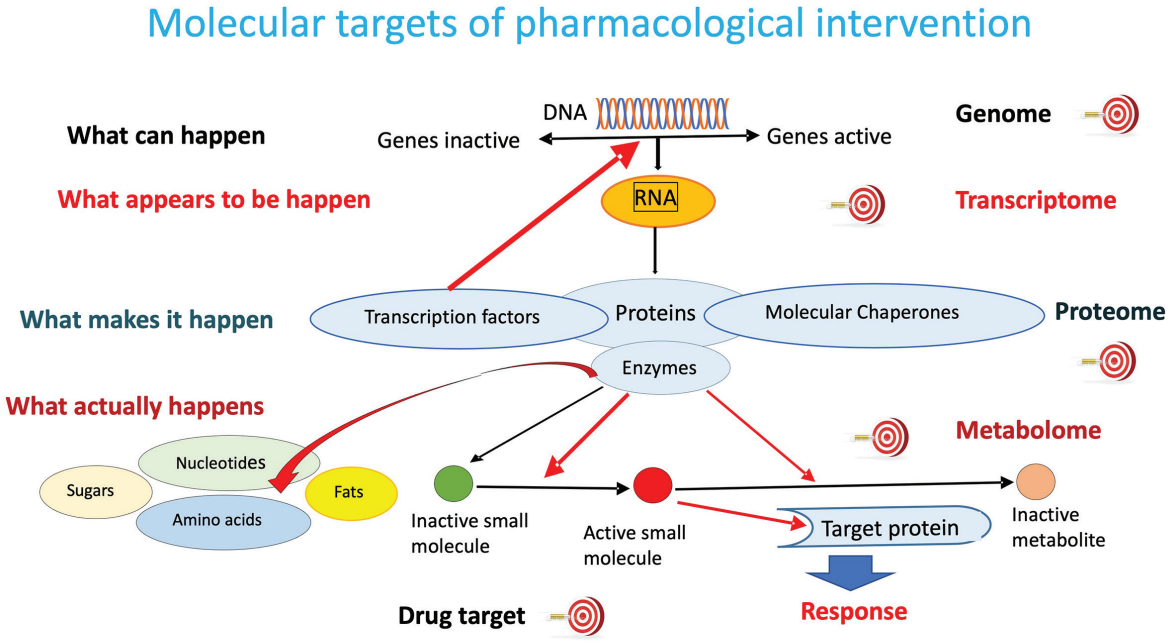


Figure 25. Molecular network-based cause-effect relationships concept. The current drug-discovery platform links drugs and targets with signaling pathways, molecular networks, and organism effects. Molecular targets of adaptogens, their networks, and signaling pathways are associated with chronic inflammation, atherosclerosis, neurodegenerative cognitive impairment, metabolic disorders, and cancer. Predicting the response of the human body to medication requires an understanding of drug–effect relationships at the organism, organ, tissue, cellular and molecular level is based on Integrative personal OMICS (DNA -genomics, RNA-transcriptomics, microbiomes, proteomics, and metabolomics) profiling and their changes in health and disease, as well as after pharmacological intervention.



Panossian A.G. 2017. Understanding adaptogenic activity: specificity of the pharmacological action of adaptogens and other phytochemicals. Ann. N.Y. Acad. Sci. 1401(1):49-64.

Figure 26. The flowchart shows four metabolic regulation levels, the possible intracellular molecular targets for pharmacological intervention, and further cell response. At least four regulation levels exist: metabolomic, proteomic, transcriptomic, and genomic. The proteomic level includes regulating the 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 using 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. 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 to form an active molecule or reversible or irreversible blockage of the active site. These events occur at the metabolomics and proteomics levels in cell response regulation. Receptor binding can be activated by competitive, agonistic binding with similar/mimetic substances/drugs.

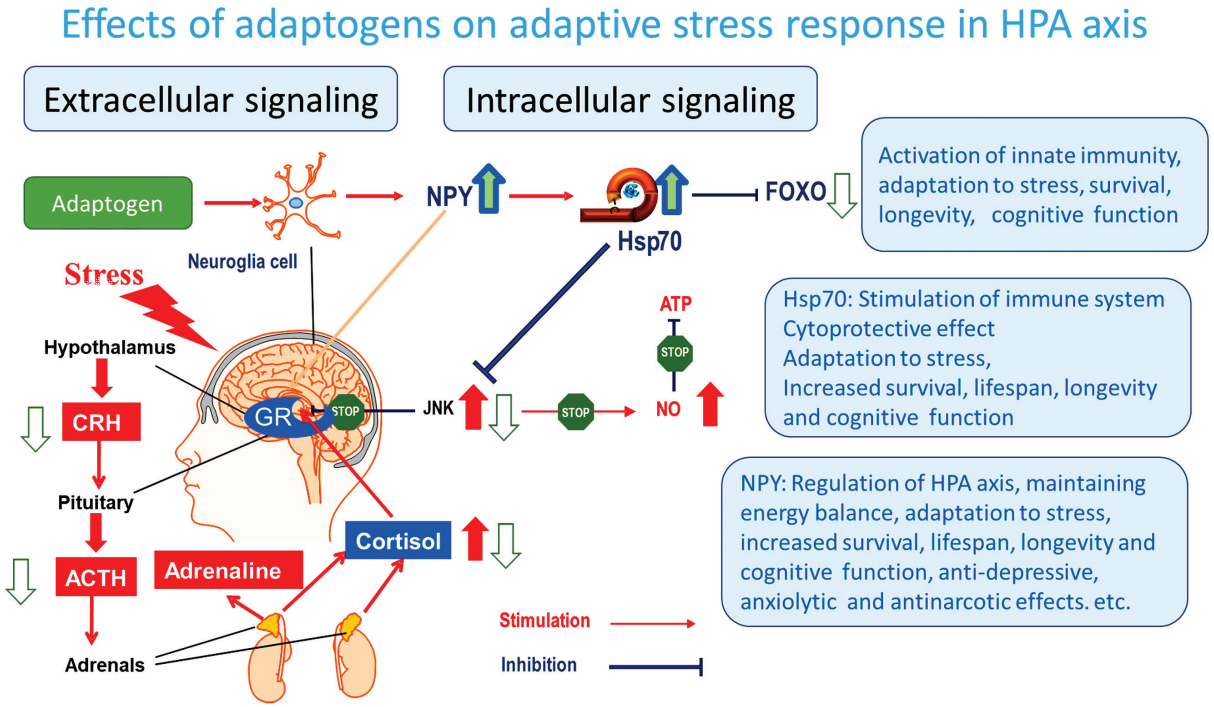


Figure 27. Hypothetical mechanism of action of adaptogens on the stress system in depression. Stress-induced release of CRH from the hypothalamus, followed by the release of ACTH from the pituitary, stimulates adrenal hormones and NPY to cope with the stress. Feedback regulation of overreaction is initiated 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 the 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 the 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. Adrenals, secreting both adaptive stress response "turn on" hormone adrenaline and 'turn off" hormone cortisol. Adrenal fatigue occurs when the adrenals' capacity to secrete enough hormones that cannot maintain homeostasis. When cortisol levels remain adequately elevated to cope with the various stresses, over time, the signs and symptoms of metabolic syndromes, such as muscle wastage, hyperglycemia, and suppresses immune or inflammatory responses, begin to appear.

ADAPTOGENS IN ADAPTIVE STRESS RESPONSE

Why are medicinal plants beneficial for human health?

One hypothesis is that plants protect themselves against microorganisms, insects, pests, fungi, viruses, and hazardous environmental changes by biosynthesis of secondary metabolites in their most exposed parts (leaves, flowers, roots). Along with so-called primary metabolites (amino acids, carbohydrates, fats/lipids, and nucleic acids), which are required for main functions (grown, cells differentiation, reproduction), plants produce so-called secondary metabolites that play a role in defense and adaptive response against various environmental stressors. Animals that rely on plants as a primary source of nutrients have evolved complex mechanisms to neutralize the potentially harmful effects of phytochemicals. These natural compounds are not toxic at relatively small doses but still induce mild cellular stress responses. One fundamental mechanism of action of secondary plant metabolites is activating the humans' adaptive cellular stress response pathways. This phenomenon has been commonly observed and has been described as an adaptive stress response or 'hormesis.' Major components of the hormetic response include various stress resistance proteins, such as heat-shock proteins (HSPs), antioxidants, and growth factors.

Plant secondary metabolites play vital roles in the defense response to microorganisms and insects. ***Some of them (adaptogens) were identified as adaptogenic plants and specifically interacted with human adaptive stress-response systems.***

Biphasic dose-effect dependence is due to the adaptive stress response. The phenomenon, known as the adaptive stress response, is a survival mechanism to environmental stress. It's not the sort of "bad stress" (distress) that we need to avoid, but a beneficial adaptive stress response (eustress) that forces the body to activate its natural resources. Depending on duration and severity, stress can have a different effect on the organism—from useful to harmful: chronic eustress (too little stress), acute stress (optimal stress) initiates helpful adaptive stress response, while when stress increases beyond a certain level—acute distress (too much stress), and chronic stress (burnout)—it leads to harmful health effects and can cause many diseases. Adaptogens act like chronic eustress, activating adaptive stress response, resilience, and overall survival in this context.

These positive stressors—exercise, severe calorie restriction, and adaptogens—certain bioactive compounds of plants, activating adaptive signaling pathways of adaptive stress system to boost the body's cellular maintenance functions into high gear, so our cells take care of themselves more efficiently than they would usually.

Another comparison could be made with repetitive physical exercise, which increases endurance and performance. A state of non-specific resistance could be achieved either by

the gradual "training" of an organism to endure 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 arises in a manner analogous to repeated physical exercise that leads to increased resistance, endurance, and stamina **Figure 28.**

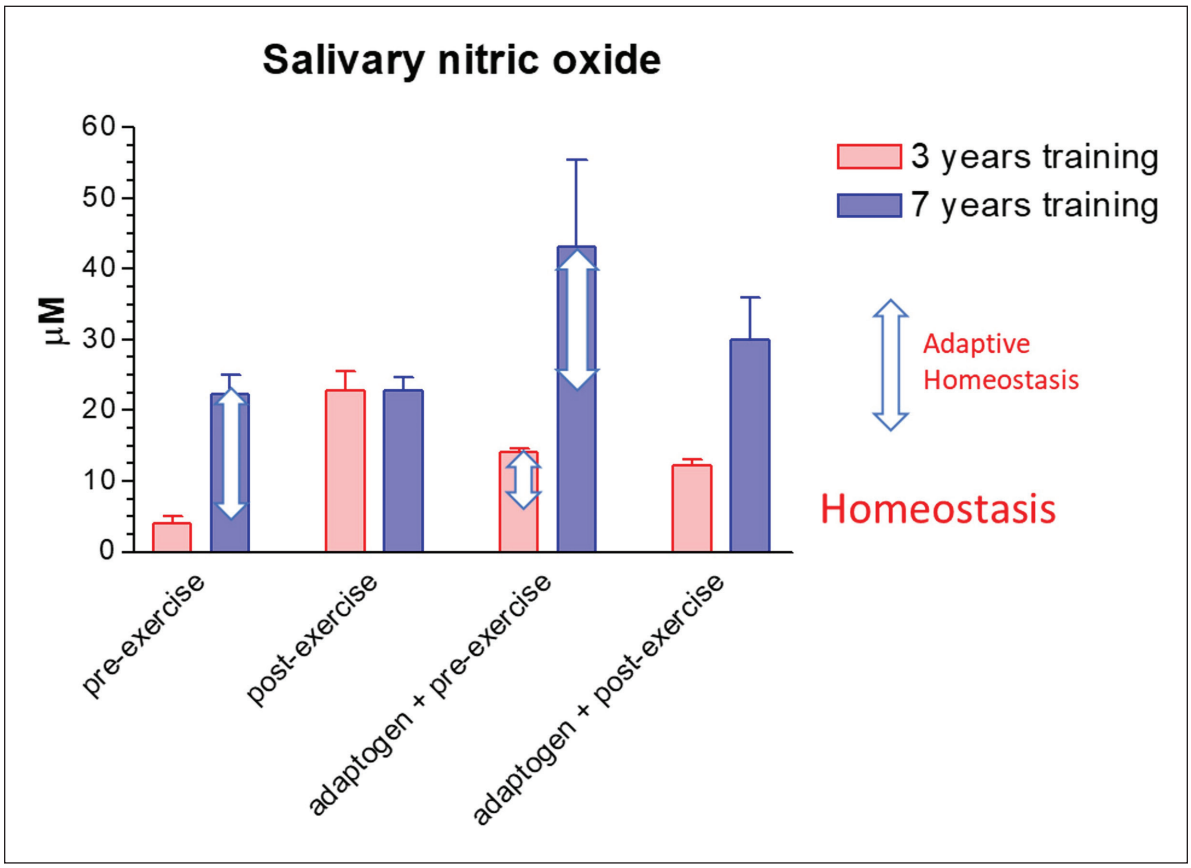


Figure 28. Adaptogens and physical exercise adjust the homeostatic range of salivary nitric oxide. Effects of physical exercise and adaptogens on the nitric oxide level in athletes' saliva.

A characteristic feature of adaptogens is that they act as mild stressors (eustressors, syn. "good stressors"), challengers inducing stress-protective effect against subsequent stress, showing a "vaccination-like" effect (mild stress mimetics) that induce stress-protective responses. Mild (survivable) stress induces a resistance or "immunity" to subsequent, more severe stress exposure. However, this stress-induced resistance carried no memory function, and repeated exposure to the adaptogen is required to maintain the "plastic" adaptive state **Figure 18**.

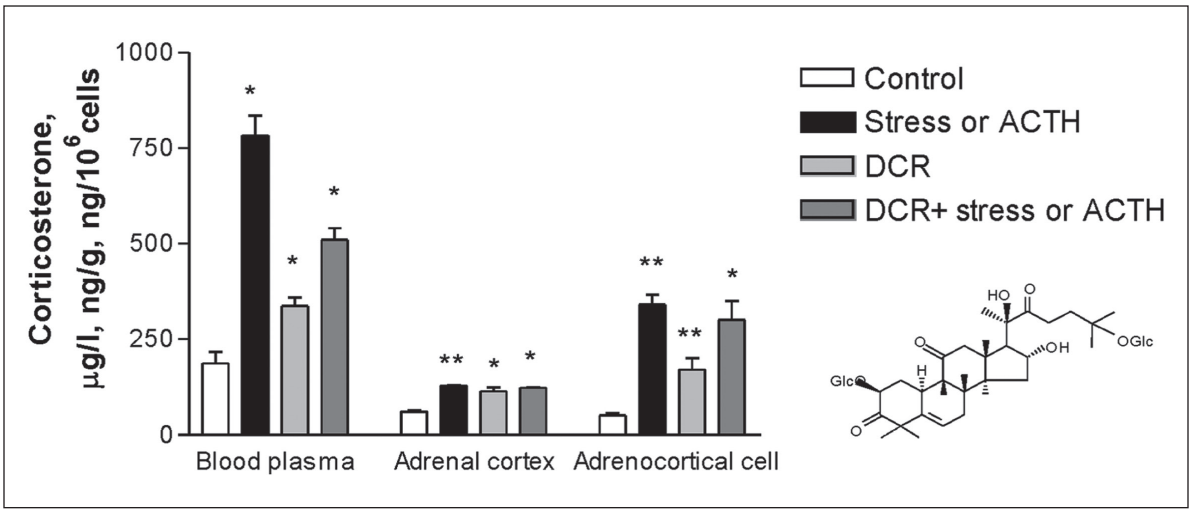


Figure 29. The mild stress mimetic effects of adaptogen DCR from *Bryonia alba* L. Corticosterone content in blood plasma (ng/mL), in the adrenal cortex (g/g), and isolated adrenocortical cells under stress (2.5-h immobilization) and upon the influence of ACTH and DCR, *- $P<0.001$; **- $P<0.025$

The adaptive stress response occurs in various regulatory systems from the cellular level to the whole organism, **Figures 28, 29**. The stress-induced responses of organismal defense systems involve numerous mediators of stress signaling, including the neuroendocrine-immune complex that supports homeostasis in simple and complex organisms.

The phenomenon of adaptation to stress also supports so-called "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., a toxic effect).

Biphasic dose-effect dependence in some in vivo and in vitro studies of Rhodiola extracts is shown in Figure 30 on the following page. The "bell shape" dose-effect relationship is typical for adaptogens with high therapeutic indices (effective dose: toxic dose ratio). Adaptogens similarly activate the body's defense systems, but at doses not harmful for humans.

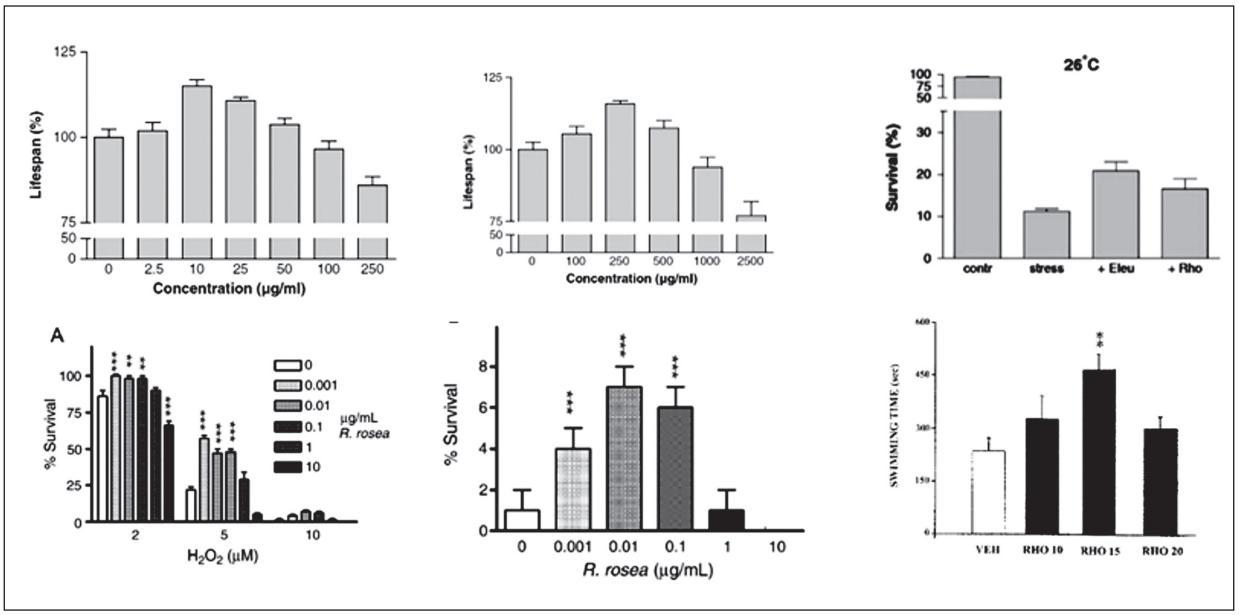


Figure 30. Reversal effect of different doses of adaptogen Rhodiola rosea extract on (a)—the lifespan of worms (Wiegand et al., 2009), (b)—swimming time to exhaustion of rats (Perfumi and Mattioli, 2007) and (c)—survival of isolated cells exposed to oxidative stress (Schriner et al., 2009).

Dose-dependent reversal effect was observed in a simple experiment where two different doses of *Withania somnifera* extract were incubated with isolated human brain cells in physiological conditions (Figures 31 and 32). In a small dose, Withania inhibits the corticotrophin-releasing hormone (CRH) signaling pathway mainly due to the downregulation expression of *CRH* gene. In contrast, Withania activates CRH signaling pathway in a higher dose due to the downregulation of some other genes regulating the expression of other genes located on the cell membranes and involved in this signaling from the membrane to the nucleus, Figure 31. It means that in a small dose, Withania is helpful in inflammatory diseases, while in a higher dose—in neurodegenerative diseases and impaired memory and other cognitive functions. A similar effect was observed in the glucocorticoid receptors signaling pathway, Figure 32, where Withania in a small dose exhibits pro-inflammatory, while in a higher dose—anti-inflammatory effects.

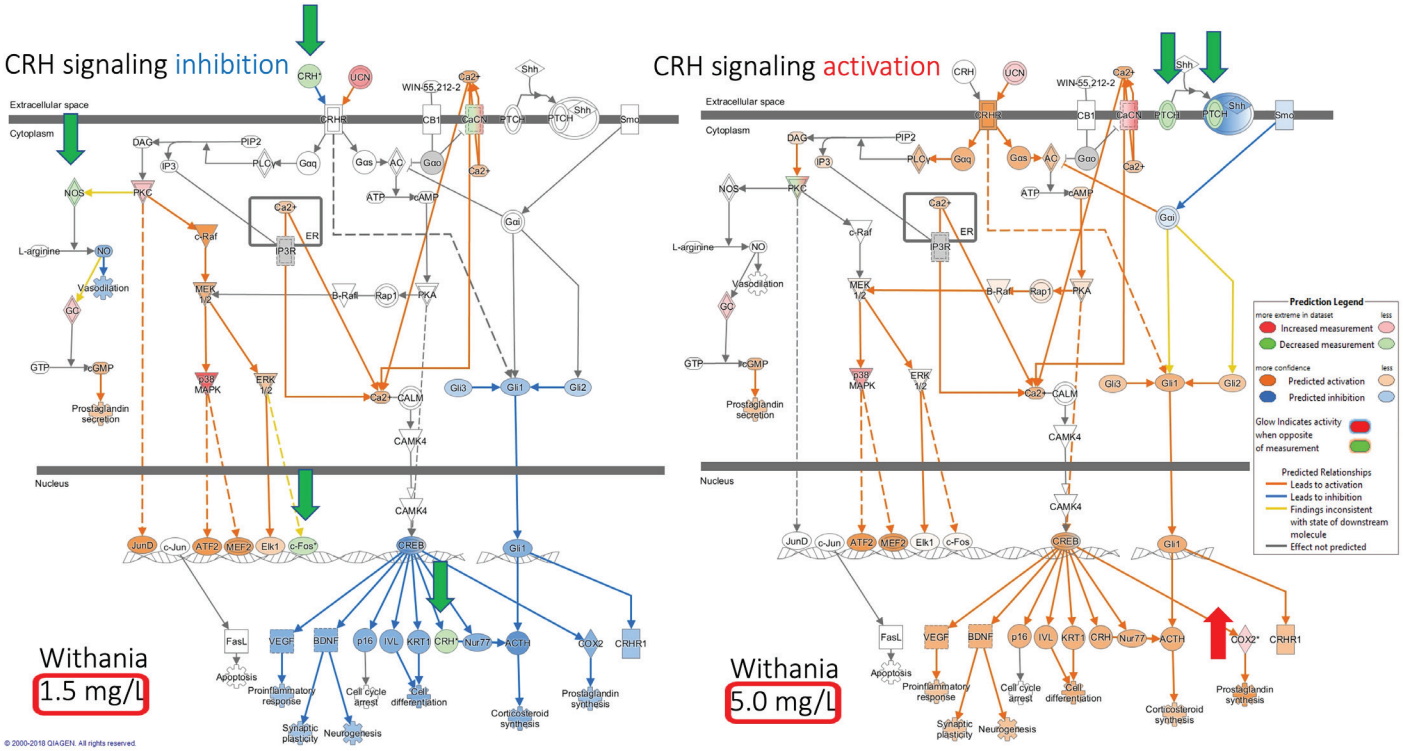


Figure 31. Reversal effect of different doses of Withania on CRH signaling pathway in isolated neuroglia cells. Proinflammatory response, corticosteroid synthesis, prostaglandin synthesis, cell differentiation, neurogenesis, synaptic plasticity, and vasodilatation, corticotropin-releasing hormone (CRH) signaling pathways which are differently regulated by Withania extract at a concentration of 1.5 mg/l (corresponding to the dose of 90 mg in humans)—(a) and 5 mg/l (corresponding to the dose of 300 mg in humans)—(b) in cultivated neuroglial cells. CRH receptors are downregulated only in a small dose of Withania, resulting in inhibition of several important downstream signaling transmitters (CREB, BNDF, COX2, NOS, and FOS) and consequently in predicted inhibition of inflammatory response, corticosteroid synthesis, prostaglandin synthesis, cell differentiation, neurogenesis, synaptic plasticity, and vasodilatation. In higher doses, we observe reversal effect—predicted activation of the inflammatory response, corticosteroid synthesis, prostaglandin synthesis, cell differentiation, neurogenesis, synaptic plasticity, and vasodilatation. It means that in a small dose, Withania is useful in inflammatory diseases, while in a higher dose—in neurodegenerative diseases and impaired memory and other cognitive functions.

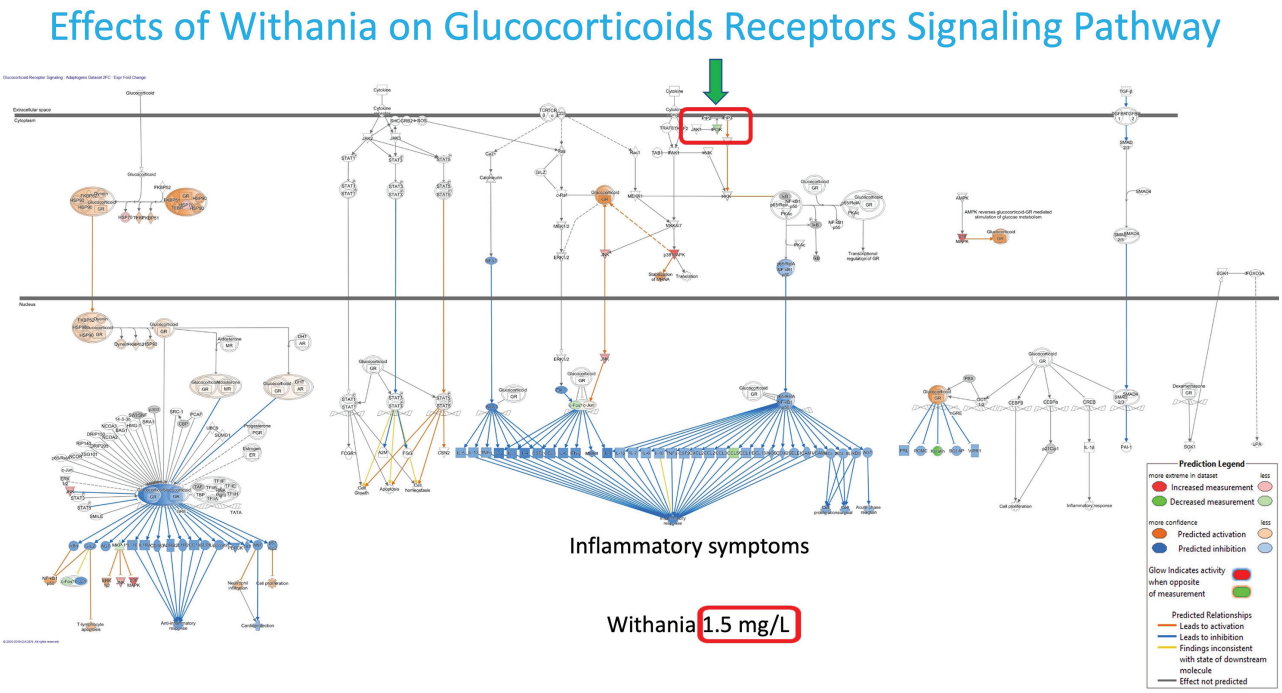


Figure 32. Reversal effect of different doses of Withania on glucocorticoid receptor signaling pathways in isolated neuroglia cells, Withania in a small dose exhibits pro-inflammatory while in a higher dose—anti-inflammatory effects.

All the functions of our body systems (cardiovascular, immune, nervous, endocrine, gastrointestinal digestive, etc.) are automatically regulated by about 30,000 genes, fragments of DNA—a very long, double-helix molecule, which is in the nucleus of every single cell. The activity of genes depends on the signals/stimulus received from numerous receptors various proteins, which are located on the outside surface of the cell membrane (Figures 33–36). The receptors very specifically trigger signals from extracellular molecules—stressors and transfer the signals to genes via many signaling cascades (***adaptive signaling pathways***), which can interact and influence each other in a complex molecular network (Figures 34–36). Collectively, this "stimulus-response" system is known as the "***adaptive stress response system***" of our body responding to environmental stress.

According to Calabrese and Matson: adaptive stress response (hormesis) involves activation of intracellular and extracellular signaling pathways and increased expression of anti-apoptotic proteins, neuropeptides, antioxidant enzymes (Figure 33), and defense response of an organism resulting in increased survival.

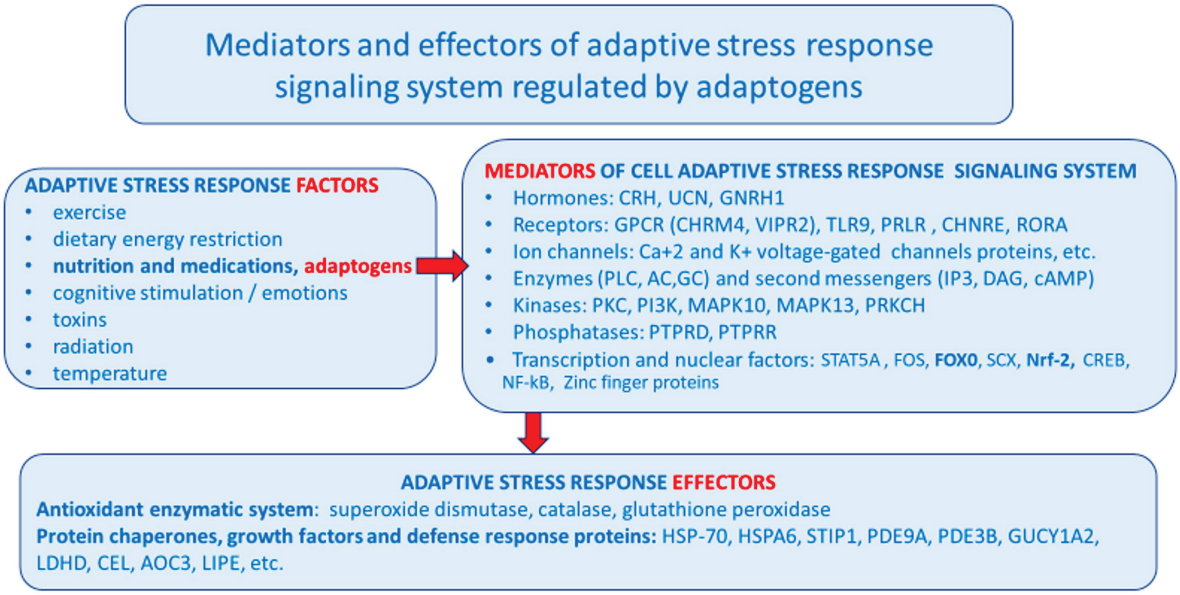


Figure 33. Adaptive stress response factors (including adaptogens), mediators, and effectors

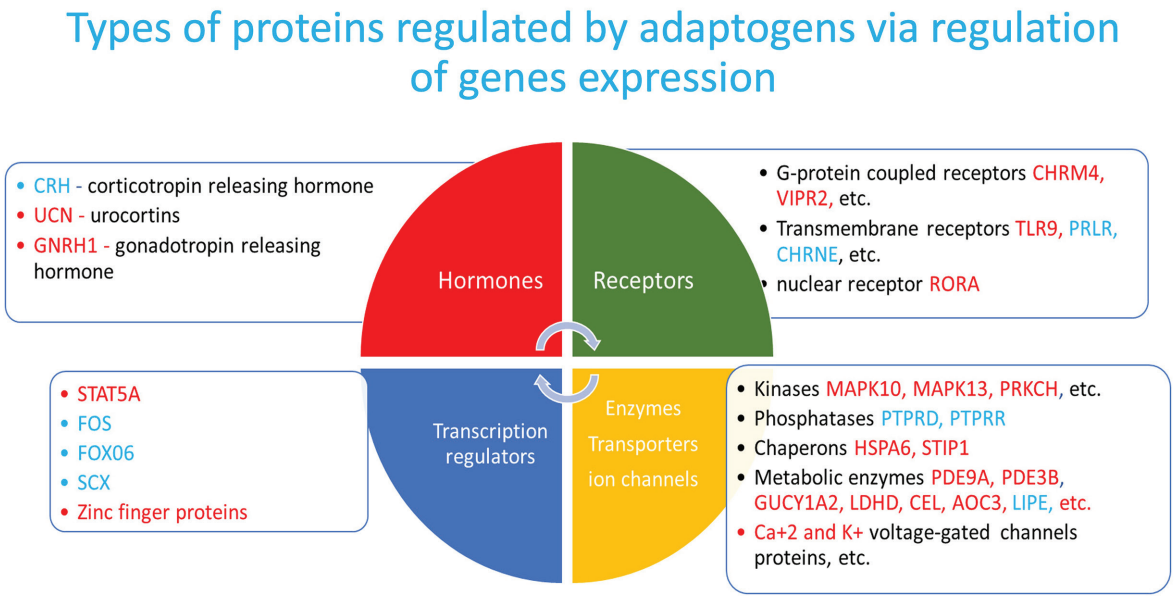


Figure 34. Types of mediators of adaptogens induced adaptive stress response

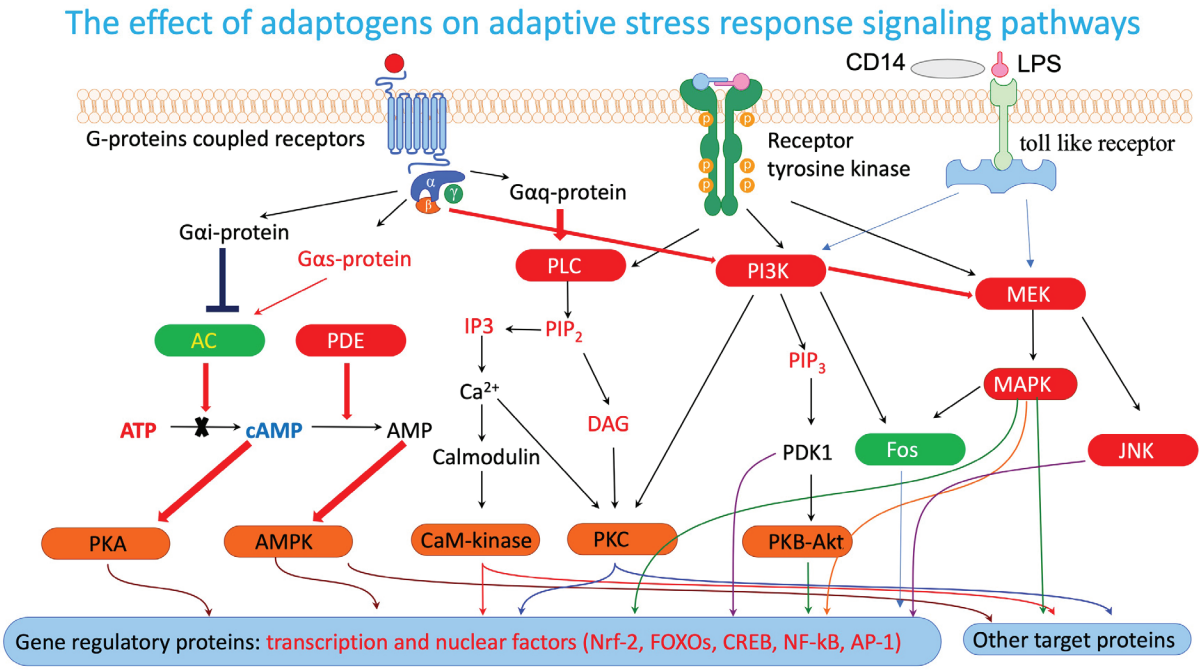
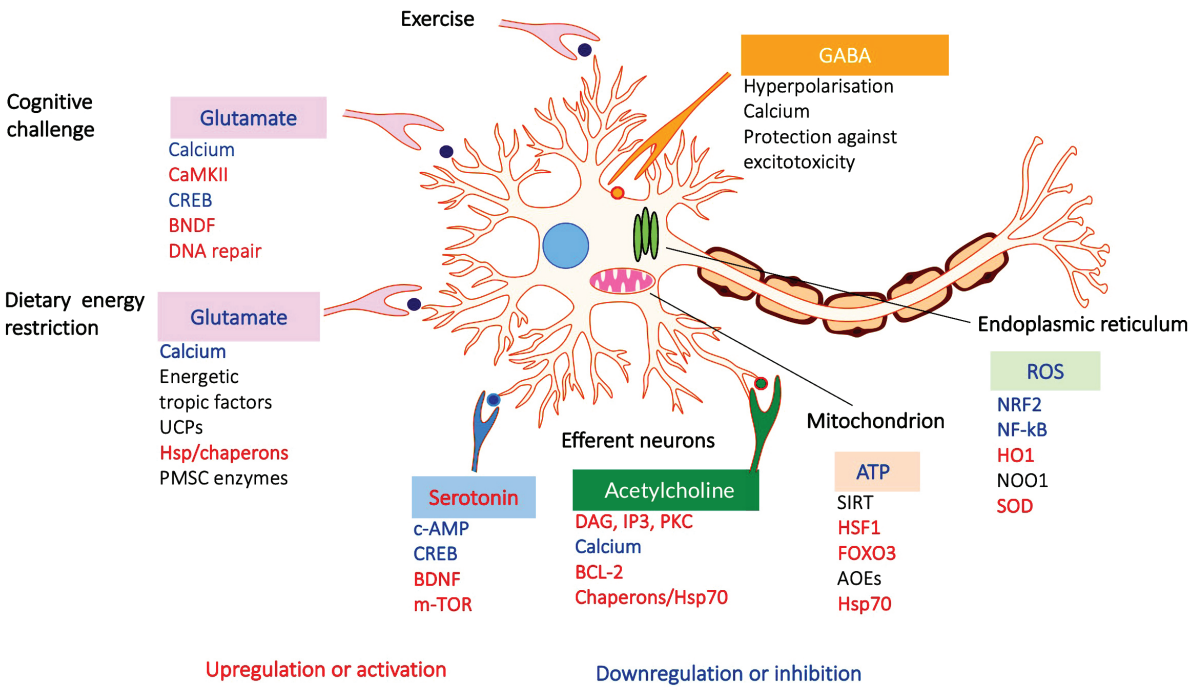


Figure 35. Effect of adaptogens on mediators of adaptogens induced adaptive stress response. FIGURE 4 Effects of adaptogens on adaptive stress response intracellular signaling pathways (updated from authors' drawings17). Activation of the PI3K/AKT/mTOR signaling pathway positively regulates cell cycle, proliferation, neural long-term potentiation (memory cognitive functions and longevity. AC, adenylate cyclase; AMPK, 5′ AMP-activated protein kinase; AP-1, activator protein 1 transcription factor; CREB, cyclic AMP response element-binding protein; DAG, diacylglycerol; Fos, Fos proto-oncogene, AP-1 transcription factor subunit; FOXOs, forkhead box proteins; IP3, inositol 1,4,5-trisphosphate; JNK, c-Jun N-terminal kinases; MaM-kinase, Ca2+/calmodulin-dependent protein kinase II; MAPK–MEK (MAPK/ERK), mitogen-activated protein kinases; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NRF2, nuclear regulatory factor 2; PDE, 3′,5′-cyclic-AMP phosphodiesterase; PI3K, phosphoinositide 3-kinase; PIP3, phosphatidylinositol (3,4,5)-trisphosphate; PIP2, phosphatidylinositol (4,5)-bisphosphate; PKA, cAMP-dependent protein kinase; PKB-Akt, serine/threonine-specific protein kinase; PKC, protein kinase C; PLC, phospholipase C.



Stranahan, A.M. &M.P.Mattson. 2012. Recruiting adaptive cellular stress responses for successful brain ageing. *Nat. Rev. Neurosci.* **13:** 209–216.

Panossian A.G. 2017. Understanding adaptogenic activity: specificity of the pharmacological action of adaptogens and other phytochemicals. Ann. N.Y. Acad. Sci. 1401(1):49–64.

Figure 36. Effects of adaptogens on adaptive stress response signaling pathways that promote synaptic plasticity and protect neurons against degeneration. Illustration of a glutamatergic neuron receiving excitatory signals from neurons activated response to intellectual tasks, exercise, and dietary energy restriction. Postsynaptic receptors for glutamate, acetylcholine, and serotonin are activated to trigger intracellular signaling pathways and transcription factors that activate the expression of neuroprotective proteins, including antiapoptotic proteins, brain-mitochondrial uncoupling proteins (UCPs), and derived neurotrophic factor (BDNF). BDNF activates neuronal growth by stimulating the mammalian target of rapamycin (mTOR). Mild cellular stress resulting from dietary energy restriction and oxidative stress (ROS) activates adaptive stress response pathways, including those that upregulate antioxidant enzymes (AOEs) and protein chaperones. CREB, cyclic AMP response element-binding protein; CaMKII, calcium/calmodulin kinase II; 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-B, nuclear factor B; NRF2, nuclear regulatory factor 2 NQO1, NAD(P)H-quinone oxidoreductase 1.

What conclusions can be drawn?

- The adaptive stress response is the body's survival mechanism to environmental stress.
- Adaptogens trigger organismal adaptive stress response signaling pathways resulting in activation of organismal defense systems to maintain homeostasis and overall survival.

ADAPTOGENS IN AGING

Life extension and healthy aging are associated with the regulation of neuroendocrine-immune and other defense mechanisms regulating homeostasis. Multiple mechanisms are underlying the cytoprotective, antioxidant, and antitoxic activities of adaptogens, including effects on:

- activation of cytoprotective chaperons heat -shock proteins (Hsp70), **Figures 36,37**
- inhibition of stress-activated pro-apoptotic protein kinase JNK, **Figures 36,37**
- activation of translocation of FOXO protein into nucleus triggering formation innate antioxidant system, survival proteins and increased longevity, **Figure 36**
- activation of Nrf2 transcription factor, a principal regulator of redox homeostasis and innate detoxifying systems, **Figure 38**
- inhibition of leukotrienes, **Figure 39**
- number of genes encoding expression of proteins involved in inflammation, atherosclerosis, neurodegeneration, cognitive functions (learning, memory, abstract thinking, planning), apoptosis, cancer, metabolic disorders, and energy metabolism, **Table 7**
- main biochemical processes most influenced, **Table 8**
- main cellular functions most affected, **Table 9**
- canonical pathways and gene targets, **Table 11.**

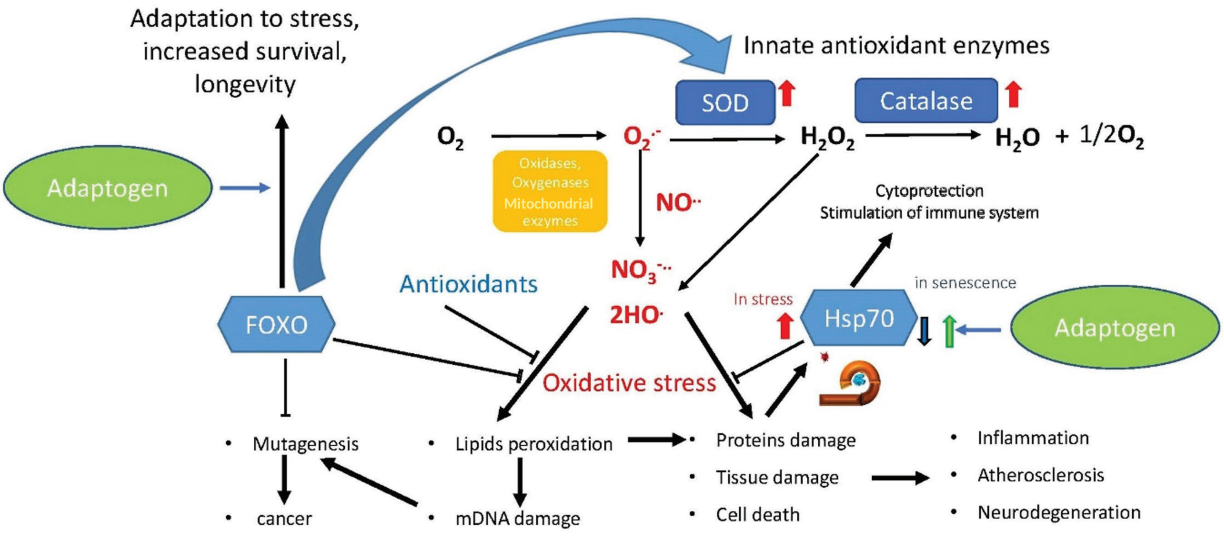


Figure 37. Hypothetical mechanism of action of adaptogens in regulating the innate antioxidant system and oxidative stress-induced apoptosis in aging. The free radical theory of aging, known as the oxidative stress theory, postulates that the organisms living in an aerobic environment are continuously 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, 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: 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 aging-related disorders, senescence, and decreased life span. Oxidative stress can trigger two signaling pathways by activating JNK kinase in the same cell. A balance between the pro-and anti-aging JNK-mediated programs is shifted in favor of HSP70 at a young age. An immature cell can survive and divide despite intense oxidative stresses because stress-activated HSP70 blocks JNK-stimulated apoptosis. Adaptogens upregulate HSF1 and HSP70 *in vitro* and *in vivo,* downregulate JNK in vivo, and inhibit apoptosis, senescence, and aging *in vivo*. In turn, HSP70 directly regulates FOXO signaling in skeletal muscle. HSP70 controls FOXO/DAF-16 activity by promoting its nuclear export.

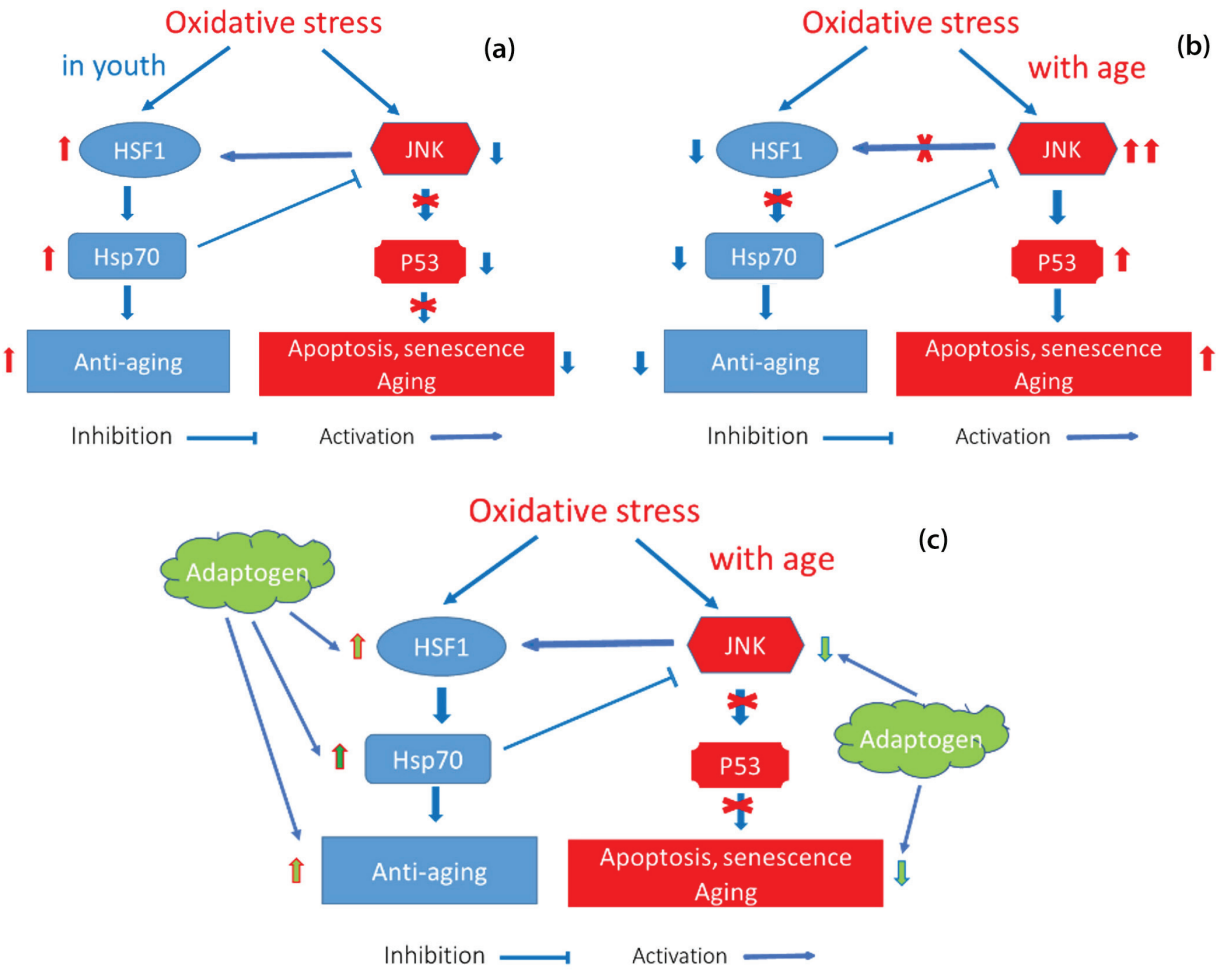


Figure 38. Effects of adaptogens on aging and anti-aging programs.

(a) When cells are exposed to oxidative stress, HSF1 initiates the production of Hsp70, which repairs damaged proteins, increases adaptability and lifespan. Oxidative stress triggers two signaling pathways through the activation of JNK kinase: the aging program by up-regulation of p-53 transcription factor and the anti-aging program, which is Hsp70-dependent. At young ages, activation of HSF1-Hsp70 inhibits JNK-mediated aging, senescence, and apoptosis pathway.

(b) With aging, induction of Hsp70 is depressed, and the balance shifts in favor of the aging and apoptosis programs. Consequently, even weak oxidative stress can induce the degeneration of neuronal cells and the progression of aging-related diseases. In aging cells, significantly reduced expression of heat shock protein Hsp70 and its precursor, heat shock transcription factor HSF1, correlates with a decreased ability to cope with stress. In most humans, the decline in the induction of Hsp70 by stress is associated with aging and age-related disease. Hsp70 does not decrease with age in some individuals who live more than 100 years. In brain cells, HSF1 and Hsp70 expression inhibition occur in Alzheimer's disease. Age-related decline of hepatic Hsp70 expression contributes to reduced liver detoxification. Attenuation of Hsp70 is associated with up-regulation of stress-activated protein kinase (JNK) dependent apoptosis and progression of cancer.

(c) Effects of adaptogens on key regulators of aging:

- Adaptogens upregulate HSF1-Hsp70 in vitro and Hsp70 *in vivo;*
- Adaptogens down-regulate JNK *in vivo;*
- Adaptogens inhibit aging, senescence, and apoptosis *in vivo.*
- Exercise can also up-regulate Hsp70 contributing to muscle fiber integrity, regeneration, and recovery.
- Conversely, Hsp70 expression is reduced during muscle inactivity and aging.
- Malfunction of HSP70 generation may drive muscle atrophy, contractile dysfunction, and reduced regeneration.

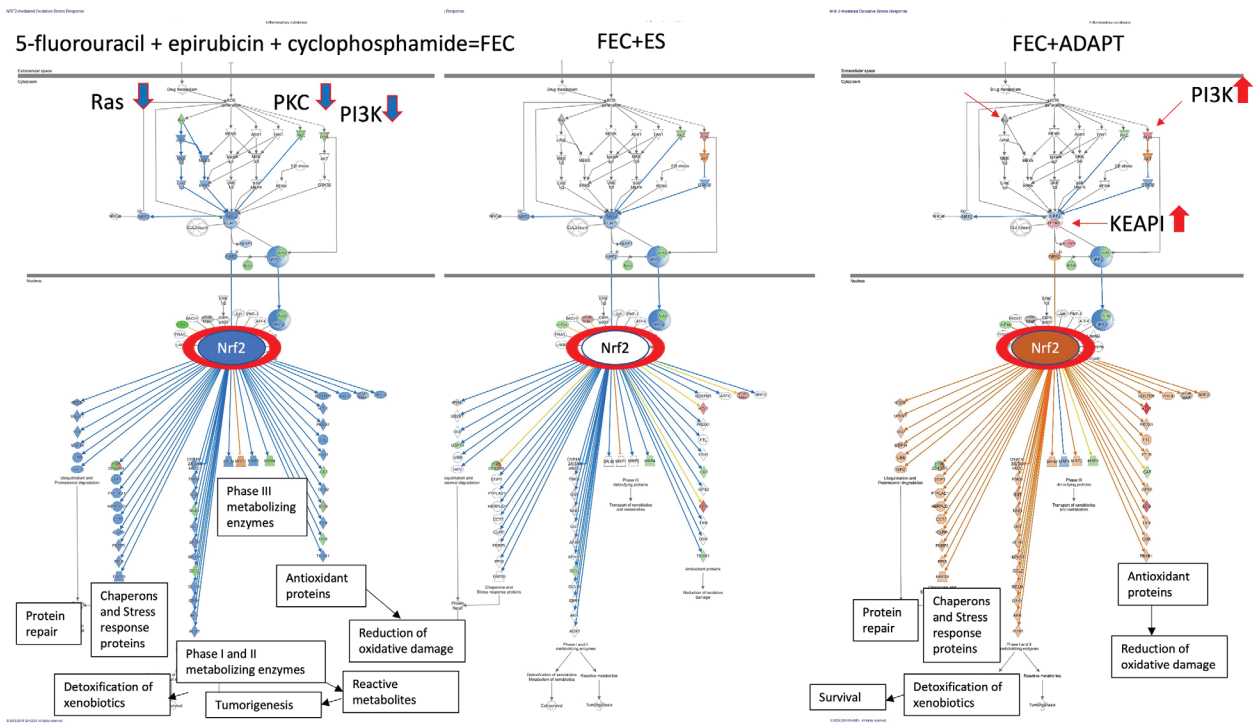


Figure 39. Adaptogens exhibit antioxidant and detoxifying effects by activating the Nrf2/ARE pathway. Nrf2 is a principal regulator of redox homeostasis typically retained in the cytoplasm by association Kelch-like ECH-associated protein-1 (Keap1). Upon exposure of cells to oxidative stress, Nrf2 is phosphorylated in response to PKC, phosphatidylinositol 3-kinase (PI3K), and MAPK pathways. After phosphorylation, this complex dissociates, and Nrf2 translocates to the nucleus, where it binds to the ARE. It triggers the expression of antioxidant and detoxifying genes, including superoxide dismutase, glutathione S-transferase, NAD(P)H quinone oxidoreductase 1, and heme oxygenase 1. Thus, activation of Nrf2 translocation or upregulation of gene expression resulting in activation of the Nrf2 signaling pathway is the key mechanism of the cellular defense response500,501 associated with the antioxidant effects of medicinal plants, and particularly of adaptogenic plants, which are useful in stress- and aging-related diseases.

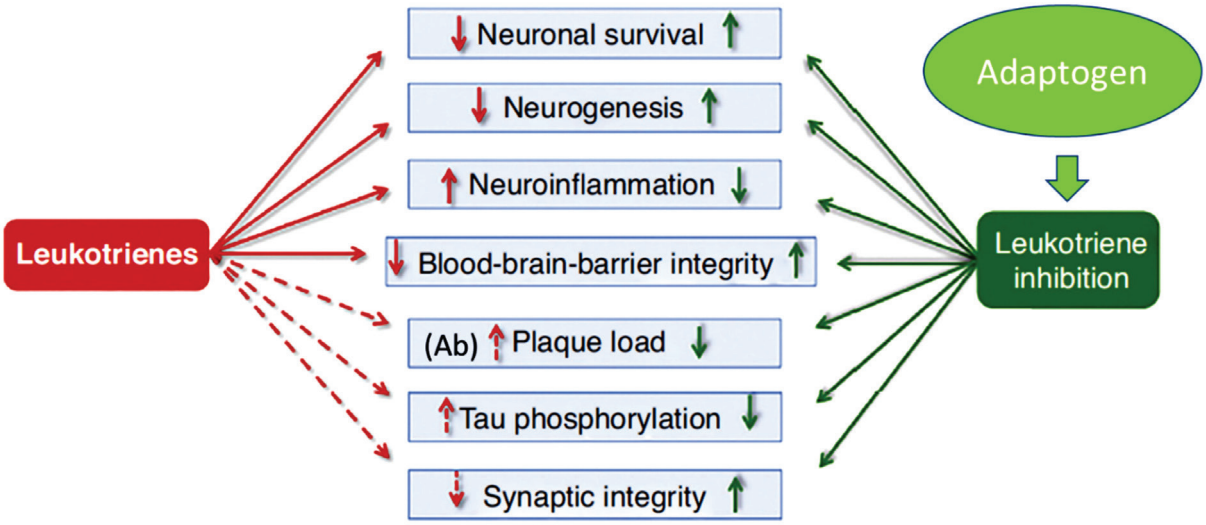


Figure 40. The pathogenesis of AD is multifactorial and not due to a single cause. Pleiotropic effects of leukotrienes in Alzheimer disease and leukotriene inhibition by adaptogens

TABLE 7.

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

Inflammation – atherosclerosis –
• Down regulation of CETP,
• Deregulation of GPCR,
Neurodegeneration – impaired cognitive functions (learning, memory, abstract thinking, planning)
• Down regulation of cAMP
• Down regulation of ESR1
• Upregulation of serpine
• Deregulation of GPCR,
Impaired apoptosis – Cancer –
• Down regulation of ESR1, OLFM
• Up regulation of IP3, PLC, DAG, PI3K, NFkB
• Deregulation of GPCR
Metabolic disorders and energy metabolism
• Down regulation of cAMP
• Inhibition of ATP metabolism

TABLE 8.

Main biochemical processes most influenced (in terms of altered gene activity) by Rhodiola, Eleutherococcus, and Schisandra.

	Genes
➢ catabolism of cyclic AMP and metabolism of cyclic GMP ➢ conversion of leukotriene A4 and lipoxin A4 ➢ oxygenation of docosahexaenoic acid ➢ synthesis of steroid and bile acid ➢ translocation, exchange and redistribution of cholesterol ester and triacylglycerol ➢ transmission of triacylglycerol and phosphatidylcholine ➢ inactivation of glucocorticoid ➢ efficacy of beta-estradiol ➢ decarboxylation of beta-alanine and L-aspartic acid ➢ deamination of cytidine ➢ removal of hypoxanthine	**AICDA, AIPL1, AKR1D1, ALOX12, APOBEC2, CETP, ESR1, GADL1, NR4A3, PDE11A, PDE3A, PDE4D, PFKFB1, SERPINA1, SLC27A2**

Panossian 2017, Ann. N.Y. Acad. Sci. 1401(1):49-64.

TABLE 9.

The most significantly affected canonical pathways and gene targets that are responsive (in-vitro) to adaptogen therapy

Canonical Pathways	Genes
tRNA Splicing	PDE3A,PDE4D,PDE11A
Protein Kinase A Signalling	PDE3A,HIST1H1T,CNGB3,PDE4D,PDE11A,PLCD4,DUSP21,TCF7L2
G-Protein Coupled Receptor Signalling	PDE3A,TAAR1,PIK3C2G,PDE4D,PDE11A,AVPR1A
Leptin Signalling in Obesity	PDE3A,PIK3C2G,PLCD4
Cardiac β-adrenergic Signalling	PPP1R1A,PDE3A,PDE4D,PDE11A
Relaxin Signalling	PDE3A,PIK3C2G,PDE4D,PDE11A
cAMP-mediated signalling	PDE3A,TAAR1,CNGB3,PDE4D,PDE11A
Salvage Pathways of Pyrimidine Nucleotides	APOBEC2,AK9,AICDA
Colorectal Cancer Metastasis Signalling	MMP8,TLR8,PIK3C2G,WNT16,TCF7L2
Inositol Pyrophosphates Biosynthesis	PPIP5K1
Airway Pathology in Chronic Obstructive Pulmonary Disease	MMP8
Axonal Guidance Signalling	NTNG1,EPHB1,RGS3,MMP8,PIK3C2G,WNT16,PLCD4
Super pathway of Inositol Phosphate Compounds	PPP1R1A,PIK3C2G,PPIP5K1,PLCD4
Sperm Motility	CNGB3,PDE4D,PLCD4
Telomere Extension by Telomerase	XRCC5
Melatonin Signalling and degradation	MTNR1A,PLCD4, UGT2A3,CYP4X1
Role of Osteoblasts, Osteoclasts and Chondrocytes in Rheumatoid Arthritis	MMP8,PIK3C2G,WNT16,TCF7L2
eNOS Signalling	PIK3C2G,CNGB3,ESR1

Panossian 2017, Ann. N.Y. Acad. Sci. 1401(1):49-64.

TABLE 10.

Main cellular functions most influenced (in terms of altered gene activity) by Rhodiola, Eleutherococcus, and Schisandra.

Cellular function	Genes
Cellular Compromise: - oxidative stress response of blood cells - degranulation of beta islet cells - damage of mitochondria - degeneration of hepatocytes - cytotoxicity of cytotoxic T cells - fragmentation of photoreceptor outer segments - degeneration of retinal cone cells	AIPL1, ALOX12, CDHR1, NGB3, GNLY, HLA-B, NCAM1, SERPINA1, ULBP3,XRCC5,
Cell Signalling	PDE3A, MUC20, PDE4D, PDE11A, ESR1, CCKBR
DNA Replication, Recombination, and Repair	PARPBP, PDE3A, APLF, PDE4D ,PDE11A, XRCC5, AICDA
Nucleic Acid Metabolism	PFKFB1,MTNR1A,PDE3A,APOBEC2,TAAR1,PDE4D,PDE11A,AIPL1,ESR1,AICDA
Lipid Metabolism	NR4A3,RGS3,SLC27A2,AKR1D1,TNXB,SERPINA1,ALOX12,ESR1,CCKBR,CETP,NCAM1

Panossian 2017, Ann. N.Y. Acad. Sci. 1401(1):49-64.

Table 11 shows age-associated diseases and the genes involved in their pathogenesis and progression that are significantly regulated by adaptogens.

TABLE 11.

Age-associated diseases and genes involved in their pathogenesis and progression that are significantly regulated by adaptogens

Category	Diseases	Genes affected by adaptogens
Organismal Injury and Abnormalities	physical disability	PDE11A,PDE3A,PDE4D - all upregulated
	degeneration of retinal cone cells - inhibition	AIPL1- down regulated,CNGB3 upregulated
	atrophy of gastric mucosa	CCKBR- down regulated
	hypoestrogenism	ESR1- down regulated
	postmenopausal vulvar atrophy	ESR1ϭ MTNR1A - down regulated,
	nociception	KCNK10, PDE11A,PDE3A,PDE4D,SCN2B - all upregulated
	cone dystrophy	CDHR1- down regulated,CNGB3 - upregulated
	pelvic organ prolapse	ESR1 - down regulated, SERPINA1 - - upregulated
Inflammatory and Pulmonary Disease	pulmonary emphysema- inhibition	PDE11A,PDE3A,PDE4D,SERPINA1- all upregulated
	bronchiectasis	PDE11A,PDE3A,PDE4D - all upregulated
	chronic bronchitis	MMP8,MTNR1A – both down regulated
	chronic obstructive pulmonary disease-inhibition	PDE11A,PDE3A,PDE4D,SERPINA1- all upregulated
Neurological and psychological Disease	non 24 hour sleep-wake disorder	MTNR1A - down regulated
	sleep-wake schedule disorder	PDE3A- upregulated
Cardiovascular Disease	ischemic cardiomyopathy	PDE11A,PDE3A,PDE4D,PPP1R1A - all upregulated
	cholesteryl ester transfer protein deficiency	CETP - down regulated
	angina pectoris	PDE11A,PDE3A,PDE4D – all upregulated
	cerebral small vessel disease	PDE3A - unregulated
Skeletal and Connective Tissue	osteochondrodysplasia	COL9A1 - down regulated, PDE4D -up regulated
Metabolic Disease	estrogen resistance	ESR1 – down regulated

Panossian 2017, Ann. N.Y. Acad. Sci. 1401(1):49-64.

Figure 41 summarizes the critical mode of action of adaptogens on the progression of aging-related diseases in senescence which is associated with decreased adaptability to stress and an ability to maintain homeostasis.

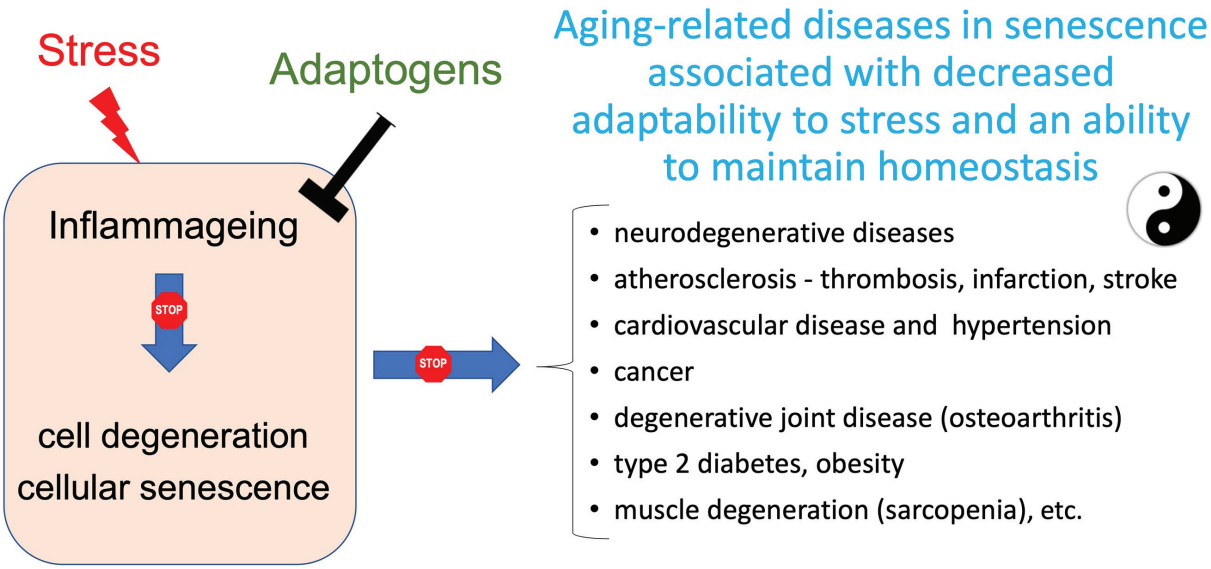


Figure 41. Mode of action of adaptogens on the progression of aging-related diseases.

The modes of the pharmacological action of adaptogens describe *functional changes* of molecules, cells, and regulatory systems on various levels of regulation of homeostasis and defensive mechanisms in the progression of diseases.

For example, hydroponically cultivated Red Ginseng root preparation HRG80^{TM} effectively prevents and mitigates the stress-induced deterioration of cognitive functions in healthy subjects and elderly patients with mild cognitive disorders. The mode of action HRG preparation related to cognitive and mood disorders is associated with its impact on brain activity, affecting various brain regions depending on the mental load during relaxation and cognitive tasks related to memory, attention, and mental performance. This ginseng preparation activates electroencephalogram (EEG) spectral powers compared to placebo. The spectral changes in the quantitative EEG induced by HRG indicated an improvement in mood and calming effects evidenced by the modulation of β2 waves, representing changes in GABA-ergic neurotransmission. HRG attenuated δ/θ waves power, which is increasing with aging. In an animal study, HRG induced higher pyramidal cells' excitability by modulation of ionotropic glutamate NMDA and Kainate receptor-mediated transmission.

The mechanisms of action of adaptogens describe the *molecular changes* and their extracellular and intracellular interactions.

Adaptogens trigger pleiotropic genes, molecular mechanisms, and cellular signaling pathways that mediate adaptive and defense responses, resulting in multitarget modes of action simultaneously and, therefore, nonspecific pharmacological activity, including aging-related diseases shown in Figure 42.

Now it is not surprising that red ginseng was traditionally used as a panacea and nowadays is known as the most intensively studied adaptogen. The scientific plant name *Panax* (derived from the Greek words *Pan*, which means "all," and axos, which means "cure"), suggests that Panax ginseng is believed to be helpful in the treatment of many diseases. Many details of rational explanation of their mysterious pleiotropic action and polyvalent pharmacological activity are still in question, though the main modes and mechanisms of action of Ginseng have been extensively studied in the last decades and elucidated to some extent due to the implementations of methods of molecular biology, network pharmacology, and systems biology concepts.

The similarity of chemical structures of ginsenosides with the stress hormone cortisol (Figure 6) suggests that their mechanism of action is associated with glucocorticoid receptors and the mode of action with the hypothalamus-pituitary-adrenal (HPA) axis—a functional part of the neuroendocrine-immune complex, collectively known as a Stress System, which regulates adaptability, survival, and resilience of organisms in stress and progression of aging-related disorders, including neurodegenerative diseases (Alzheimer's disease, Parkinson's disease, senile dementia, etc.), atherosclerosis, cardiovascular disease, metabolic diseases (type 2 diabetes, obesity, and hypertension), muscle degeneration (sarcopenia), degenerative joint disease (osteoarthritis), cancer, etc. Figure 42.

Indeed, in the earlier studies dated 1970–80, it was demonstrated that ginsenosides act as a functional ligand of glucocorticoid receptors. This finding provides a rationale for the pleiotropic pharmacological activity of Ginseng and its promising efficacy in numerous diseases associated which chronically increased (immune suppression, melancholic depression, increased arousal or anxiety, loss of libido, suppression of feeding/anorexia, gastrointestinal dysfunction, increased blood pressure, tachycardia, chronic active alcoholism, alcohol and narcotic withdrawal, etc.) and decreased (the chronic fatigue, somnolence, decreased arousal and performance of task, fibromyalgia syndromes, increase in appetite and weight gain, etc.) level of cortisol in the blood circulation system.

Furthermore, it provides a rationale for the adaptogenic concept where the critical point is maintaining adaptive homeostasis at a higher equilibrium level.

The ginsenosides act primarily on the hypothalamus and pituitary, stimulating ACTH secretion, followed by increased corticosterone biosynthesis in the adrenal cortex. On the contrary, Ginseng has an inhibitory effect on the hyperactivity of the HPA axis induced

by stresses and increased corticosterone levels associated with metabolic and psychiatric disorders, e.g., Ginsenoside Rd, inhibits corticosterone secretion in the cells and inhibits ACTH-induced corticosterone biosynthesis through down-regulation of proteins in the cAMP/PKA/ CREB signaling pathway in adrenocortical cells, Figure 42. In other words, Ginseng acts as a mild stressor ("stress vaccine"), increasing the range of adaptive homeostasis that adjusts the stress response in mental disorders and metabolic diseases. That is a typical adaptogenic activity to activate the body's defense system and metabolic rate resulting in increased resilience and survival in response to stressful factors including infections.

Further findings revealed the mechanisms and action of ginsenosides are associated with many other molecular targets except glucocorticoid receptors and multiple modes of action related to the neuroendocrine-immune complex and other regulatory systems involved in maintaining homeostasis and survival. Figure 42 shows the modes of the pharmacological action of Red Ginseng, describing functional changes of cells, physiological and regulatory systems involved in defense response at various levels of regulation of homeostasis, and the phases of progression of diseases.

Recently, multiple molecular targets of red ginseng have been identified. They are associated with chronic inflammation, atherosclerosis, neurodegenerative and cognitive impairments, metabolic disorders, and cancer, typical with age. Ginsenosides trigger pleiotropic genes, molecular mechanisms, and cellular signaling pathways that mediate adaptive and defense responses, resulting in multitarget modes of action simultaneously and, therefore, considered drugs with "nonspecific" pharmacological activity that is not justified since they specifically activate adaptive signaling pathways regulating survival, apoptosis, development, and homeostasis, Figure 42.

An example of multitarget mechanisms of action of Red Ginseng preparation HRG80 resulting in predicted antitumor activity is shown in Figure 43 (on page 76). It shows that 332 and 323 genes mediate the antitumor effect of Red Ginseng HRG80 on transcriptomic level of regulation at a concentration of 1 $\mu g/mL$ and 10 pg/mL correspondingly, Figure 43a and 43b. They could be different in different doses, and only 72 genes are the same in both dose levels, Figure 43c.

In this context, it is essential to note that blood cells and tissues are continuously exposed to varying concentrations of ginsenosides after oral administration of ginseng in daily therapeutic doses of 0.6–9.0 g. They range from maximal detected concentrations of 35 ng/mL to the limit of detection 0.5 ng/mL and less within 12–48 h after oral intake. A recent study demonstrated that ginsenoside Rg5 exhibits soft-acting effects in a wide range of physiological and sub-physiological concentrations from 1 μM to 1 aM, while at a toxic concentration of 100 μM Rg5 quite differently regulated a large number of genes. That observation aligns with the concept of homeopathic drugs, which have therapeutic efficacy in low doses while high doses are toxic.

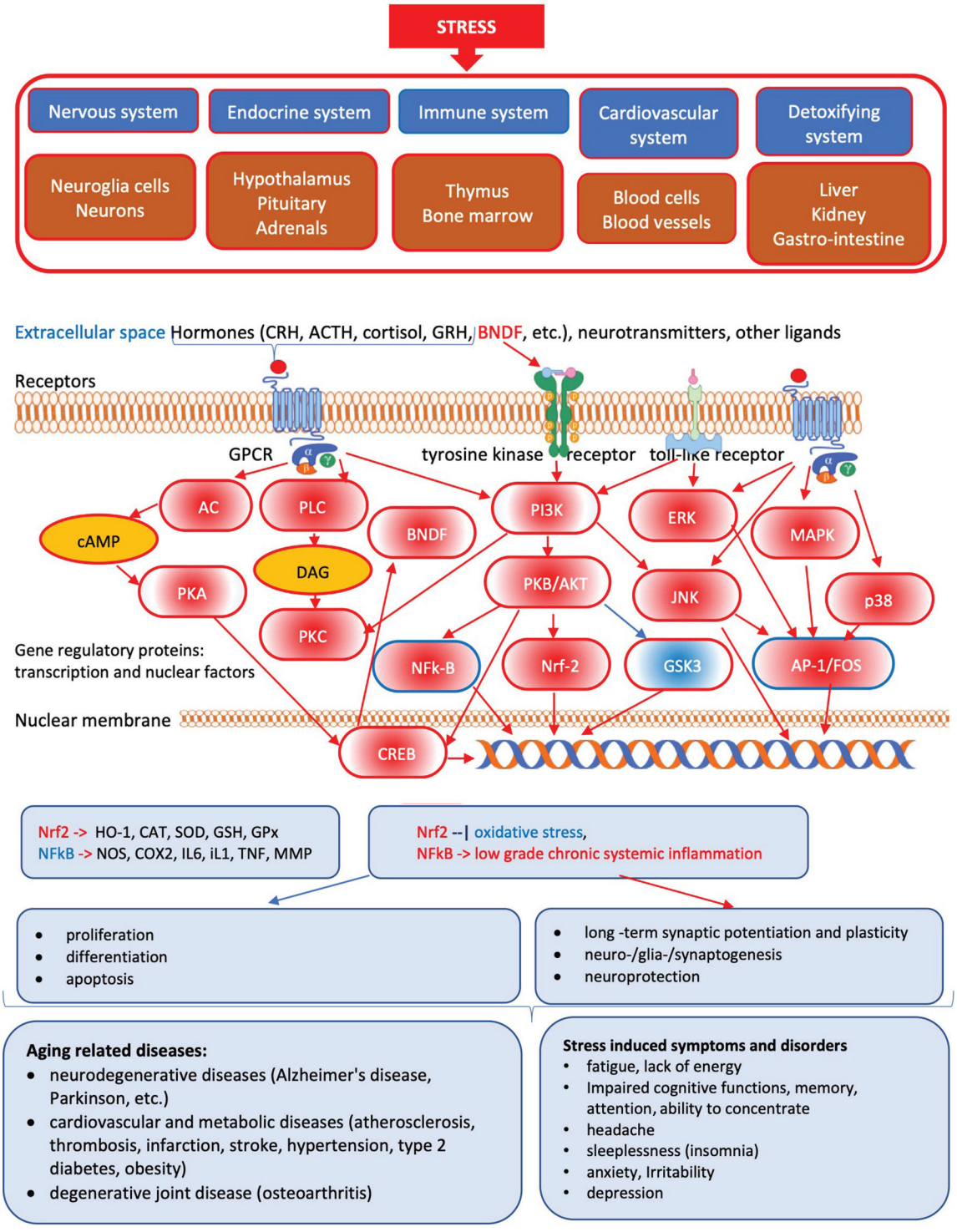

STRESS
Nervous system
Endocrine system
Immune system
Cardiovascular system
Detoxifying system
Neuroglia cells
Neurons
Hypothalamus
Pituitary
Adrenals
Thymus
Bone marrow
Blood cells
Blood vessels
Liver
Kidney
Gastro-intestine
Extracellular space Hormones (CRH, ACTH, cortisol, GRH, BNDF, etc.), neurotransmitters, other ligands
Receptors
GPCR
tyrosine kinase receptor
toll-like receptor
AC
PLC
PI3K
ERK
MAPK
cAMP
BNDF
DAG
PKB/AKT
JNK
p38
PKA
PKC
NFk-B
Nrf-2
GSK3
AP-1/FOS
Gene regulatory proteins:
transcription and nuclear factors
Nuclear membrane
CREB
Nrf2 -> HO-1, CAT, SOD, GSH, GPx
NFkB -> NOS, COX2, IL6, iL1, TNF, MMP
Nrf2 --| oxidative stress,
NFkB -> low grade chronic systemic inflammation
proliferation
differentiation
apoptosis
long -term synaptic potentiation and plasticity
neuro-/glia-/synaptogenesis
neuroprotection
Aging related diseases:
neurodegenerative diseases (Alzheimer's disease, Parkinson, etc.)
cardiovascular and metabolic diseases (atherosclerosis, thrombosis, infarction, stroke, hypertension, type 2 diabetes, obesity)
degenerative joint disease (osteoarthritis)
Stress induced symptoms and disorders
fatigue, lack of energy
Impaired cognitive functions, memory, attention, ability to concentrate
headache
sleeplessness (insomnia)
anxiety, Irritability
depression

Figure 42 (facing page)**.** The molecular mechanisms and modes of the pharmacological action of Red Ginseng. Effects of Red Ginseng and ginsenosides on key mediators of neuroendocrine immune complex, cardiovascular and detoxifying systems involved in the regulation of adaptive stress response to stressors/pathogens in stress and aging-induced diseases and disorders. CRH and ACTH induced stimulation of GPCR receptors activates cAMP-dependent protein kinase (PKA) signaling pathway in the regulation of energy balance and metabolism across multiple systems including adipose tissue (lipolysis), liver (gluconeogenesis, glucose tolerance), pancreases and gut (insulin exocytosis and sensitivity), etc. The key molecules involved in the PI3K-Akt signaling pathway are receptor tyrosine kinase (RTKs). Activation of the PI3K-Akt signaling pathway promotes cell proliferation and growth, stimulates cell cycle progression, metabolism, glycolysis, gluconeogenesis, proteins synthesis, energy storage, angiogenesis, vasodilatation, vascular remodeling, cell survival, and inhibits cell apoptosis in response to extracellular signals. Non-specific antiviral action of Ginseng is associated with activation of innate immunity by upregulation of expression of pathogen's pattern recognition receptors, specifically tall like receptors TLR mediated signaling pathways. The protein kinase C (PKC) family of protein kinase enzymes with 15 isoforms plays an essential cell-type-specific role, particularly in the immune system through phosphorylation of CARD-CC family proteins and subsequent NF-κB activation. Three stress activated MAPK signaling pathways playing important roles in cell proliferation, differentiation, survival, and death, have been implicated in the pathogenesis of many human diseases, including Alzheimer's Disease, Parkinson disease and cancer.

(1) The stress factors inducing the activation of the c-Jun N-terminal kinase (JNK)/ stress-activated protein kinase (SAPK) mediated adaptive signaling pathway are heat shock, irradiation, reactive oxygen species, cytotoxic drugs, inflammatory cytokines, hormones, growth factors, and other stresses. The activation of the JNK/MAPK10 signaling pathway promotes cell death and apoptosis via the upregulation of pro-apoptotic genes.

(2) The activation of the extracellular-signal-regulated kinase (ERK) pathway is initiated by hormones and stresses to trigger endothelial cells proliferation during angiogenesis, T cell activation, long-term potentiation in hippocampal neurons, phosphorylation of the transcription factor p53, activation of phospholipase A2 in mast cells, followed by activation of biosynthesis leukotrienes and inflammation/allergy, etc.

(3) The third major stress activated p38 signaling pathway contributes to control of inflammation, release of cytokines by macrophages and neutrophils, apoptosis, cell differentiation, and cell cycle regulation. Activation is shown in red, while the inhibition - is in blue color cycles/ellipses (effect of Ginseng/ginsenosides), arrows, and clouds. BDNF, brain-derived neurotrophic factor; cAMP, cyclic adenosine monophosphate; CREB, cAMP-responsive element-binding protein; ERK, extracellular signal-regulated kinase; GSK-3β, glycogen synthase kinase-3β; JNK; the c-Jun N-terminal kinase (JNK)/ stress-activated protein kinase (SAPK MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor-kappa B; Nrf2, nuclear factor E2-related factor 2; PI3K, phosphatidylinositol 3-kinase; PKA, protein kinase A; PKB, protein kinase B; PLC, phospholipase C.

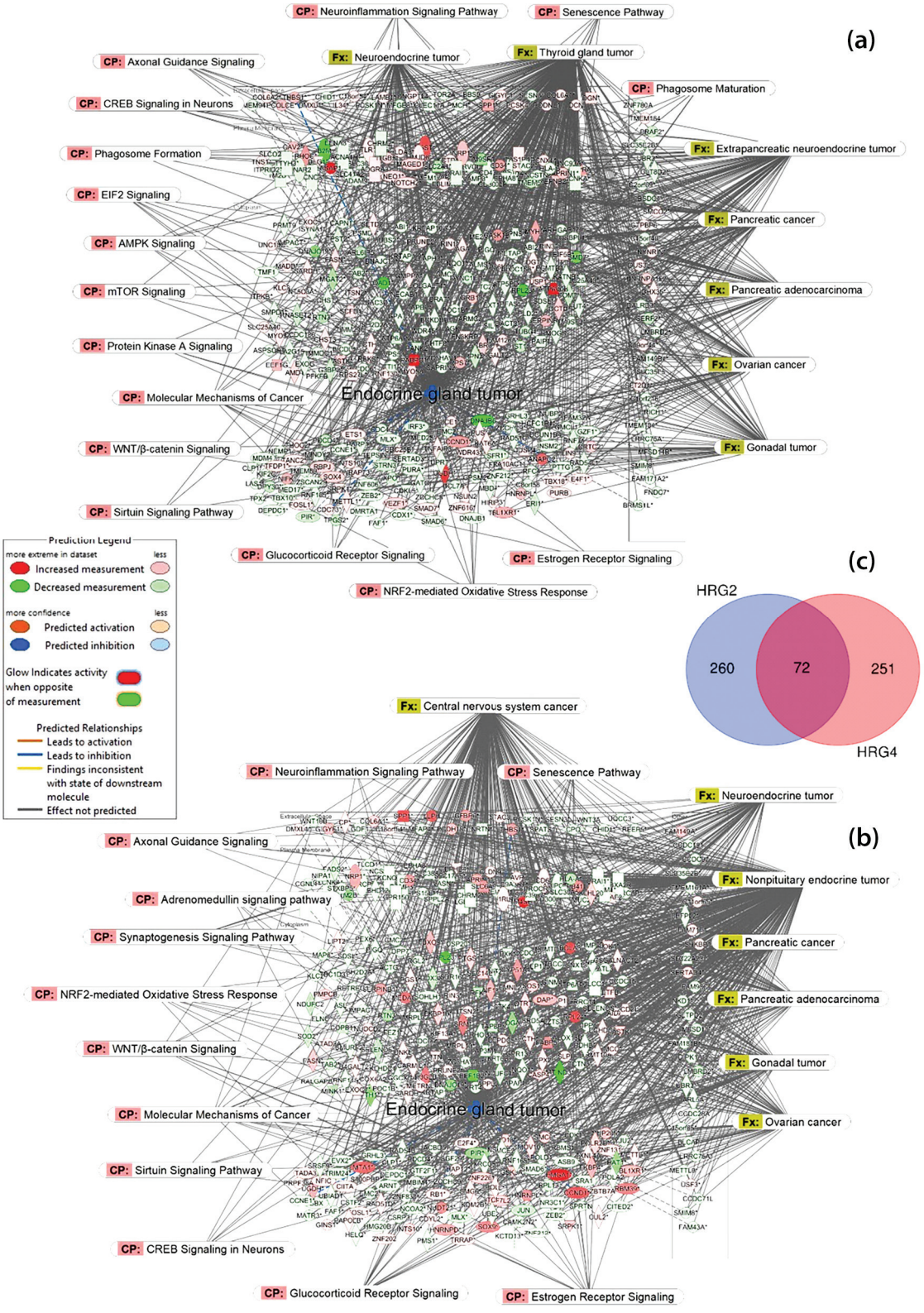

(a)
CP: Neuroinflammation Signaling Pathway
CP: Senescence Pathway
CP: Axonal Guidance Signaling
Fx: Neuroendocrine tumor
Fx: Thyroid gland tumor
CP: Phagosome Maturation
CP: CREB Signaling in Neurons
CP: Phagosome Formation
Fx: Extrapancreatic neuroendocrine tumor
CP: EIF2 Signaling
Fx: Pancreatic cancer
CP: AMPK Signaling
Fx: Pancreatic adenocarcinoma
CP: mTOR Signaling
CP: Protein Kinase A Signaling
Fx: Ovarian cancer
CP: Molecular Mechanisms of Cancer
Endocrine gland tumor
CP: WNT/β-catenin Signaling
Fx: Gonadal tumor
CP: Sirtuin Signaling Pathway
CP: Glucocorticoid Receptor Signaling
CP: Estrogen Receptor Signaling
CP: NRF2-mediated Oxidative Stress Response
Prediction Legend
more extreme in dataset
less
Increased measurement
Decreased measurement
more confidence
less
Predicted activation
Predicted inhibition
Glow Indicates activity when opposite of measurement
Predicted Relationships
Leads to activation
Leads to inhibition
Findings inconsistent with state of downstream molecule
Effect not predicted
(c)
HRG2
260
72
251
HRG4
(b)
Fx: Central nervous system cancer
CP: Neuroinflammation Signaling Pathway
CP: Senescence Pathway
Fx: Neuroendocrine tumor
CP: Axonal Guidance Signaling
Fx: Nonpituitary endocrine tumor
CP: Adrenomedullin signaling pathway
CP: Synaptogenesis Signaling Pathway
Fx: Pancreatic cancer
CP: NRF2-mediated Oxidative Stress Response
Fx: Pancreatic adenocarcinoma
CP: WNT/β-catenin Signaling
Fx: Gonadal tumor
CP: Molecular Mechanisms of Cancer
Endocrine gland tumor
Fx: Ovarian cancer
CP: Sirtuin Signaling Pathway
CP: CREB Signaling in Neurons
CP: Glucocorticoid Receptor Signaling
CP: Estrogen Receptor Signaling

Figure 43 (opposite page). Molecular network shows predicted inhibition of exocrine gland tumor by HRG80 TM at concentrations:

(a)—1 µg/ml. and

(b)—10 pg/ml. Solid red or green color nodes indicate upregulated and downregulated genes, respectively; color intensity indicates the actual log-fold changes. The tags labeled with purple display the canonical pathways related to particular genes of the network. The tags labeled with khaki show various types of tumors associated with the molecules in subnetworks.

(c)—Venn diagram showing the numbers of concentration-specific and commonly deregulated (72) genes at concentrations 1 µg/ml. and 10 pg/ml.

What conclusions can be drawn?

- Adaptogens promote healthy aging by triggering adaptive stress response signaling pathways and multiple mechanisms, reducing oxidative stress and antiaging programs associated with cells and organismal survival.

OVERVIEW OF MILESTONES OF ADAPTOGENS RESEARCH AND USE IN MEDICINE[5]

1. Use of panacea herbs in traditional medicinal systems.
2. Definition of adaptogens as stress-protective, stimulating, and tonic agents.
3. Evidence of the efficacy of adaptogens on stress-induced fatigue, cognitive functions, mental; and physical performance.
4. Evidence of the effectiveness of adaptogens in mood and behavioral disorders.
5. Evidence of efficacy of adaptogens in infectious diseases, rehabilitation, and recovery of patients.
6. Evidence on effects of adaptogens on lifespan and survival.
7. Evidence on the potential use of adaptogens in aging-related disorders.
8. Elucidation modes and putative mechanisms of action of adaptogens:
   - dose-response reversal effects of adaptogens,
   - adaptogens act as "stress vaccines" regulating stress response via the hypothalamus-pituitary—adrenals (HPA) axis, cortisol, and nitric oxide,
   - heat shock proteins and neuropeptide Y mediate the stress-protective and longevity-promoting effects of adaptogens,
   - multi-target effects on adaptive and cell survival signaling pathways associated with neuroprotective, antioxidant, antitoxic, anti-inflammatory, antiviral, antitumor activity, and metabolic regulation
9. Evidence of efficacy of adaptogens long COVID-19

References

Panossian AG, Efferth T, Shikov AN Pozharitskaya ON, Kuchta K, Mukherjee PK, Banerjee S, Heinrich M, Wu W, Guo D, Wagner H. Evolution of the adaptogenic concept from traditional use to medical systems: Pharmacology of stress- and aging-related diseases. *Med Res Rev*. 2021; 41 (1). 630–703. https://doi.org/10.1002/med.21743; https://onlinelibrary.wiley.com/journal/10981128; https://onlinelibrary.wiley.com/doi/10.1002/med.21743

Panossian A, Brendler T. The Role of Adaptogens in Prophylaxis and Treatment of Viral Respiratory Infections. *Pharmaceuticals (Basel*). 2020 Sep 8;13(9):E236; https://doi.org/10.3390/ph13090236

Panossian A.G. Understanding adaptogenic activity: specificity of the pharmacological action of adaptogens and other phytochemicals. *Ann. N.Y. Acad. Sci*. 2017, 1401(1):49–64. http://onlinelibrary.wiley.com/doi/10.1111/nyas.13399/epdf

Panossian A, Seo EJ, Efferth T. Novel molecular mechanisms for the adaptogenic effects of herbal extracts on isolated brain cells using systems biology. *Phytomedicine,* 50 (2018) 257–284. DOI information: 10.1016/j.phymed.2018.09.204; https://doi.org/10.1016/j.phymed.2018.09.204

https://www.sciencedirect.com/science/article/pii/S0944711318304835?via%3Dihub

Panossian AG. Adaptogens in Mental and Behavioral Disorders. *Psychiatr. Clin. North Am.* 2013 Mar;36(1):49–64. https://doi.org/10.1016/j.psc.2012.12.005

Amsterdam JD, Panossian AG. Rhodiola rosea L. as a putative botanical antidepressant. *Phytomedicine.* 2016, 23(7):770–83. https://doi.org/10.1016/j.phymed.2016.02.009

Panossian A., Gabrielian E., Wagner H. Plant Adaptogens II Bryonia as an Adaptogen. *Phytomedicine* 4 (1): 83–97, 1997. https://doi.org/10.1016/S0944–7113(97)80033–5

Panossian A, Wikman G, Wagner H. Plant adaptogens III. Earlier and more recent aspects and concepts on their mode of actions. *Phytomedicine*, 6 (4), 287–300, 1999. https://doi.org/10.1016/S0944–7113(99)80023–3

Panossian AG. Adaptogens. A historical Overview and Perspective. *Natural pharmacy.* Vol. 7 No.4, July August 2003, pp.1, 19–20.

Panossian AG. Adaptogens: Tonic herbs for fatigue and stress. *Alternative & Complimentary therapies.* Vol.9. No.6, pp 327–332. 2003

Panosyan A, Wagner H. Stimulating effects of adaptogens: an overview of clinical trials of adaptogens with particular reference on their efficacy at single dose administration. *Phytotherapy research*, 2005 19 (10):819–838. https://doi.org/10.1002/ptr.1751

Panossian A, Wikman G. Effect of adaptogens on the central nervous system *Arquivos Brasileiros de Fitomedicina Científica* • Vol. 2. Nr 2- Maio de 2005, pp.108–130.

Panossian A, Wikman G. Pharmacology of Schisandra chinensis Bail.: an overview of Russian research and uses in medicine. *J Ethnopharmacol*. 2008 Jul 23;118(2):183–212. https://doi.org/10.1016/j.jep.2008.04

Panossian A, Wikman G. Evidence-based efficacy of adaptogens in fatigue, and molecular mechanisms related to their stress-protective activity. *Current Clin.Pharmacol.*, 2009. 4, 198–219. DOI : 10.2174/157488409789375311. https://www.eurekaselect.com/69852/article

Panossian A, Wikman G. Effects of Adaptogens on the Central Nervous System and the Molecular Mechanisms Associated with Their Stress—Protective Activity. *Pharmaceuticals* 2010, *3*(1), 188–224; doi:10.3390/ph3010188; http://www.mdpi.com/1424–8247/3/1/188/pdf

Panossian A, Wagner H. Adaptogens. A Review of their History, Biological Activity, and Clinical Benefits. *HerbalGram*, 2011, 90: pp.52–63. http://cms.herbalgram.org/herbalgram/issue90/Feat_Adaptogens.html

Lemerond T, Panossian AG. Panax Ginseng Meyer Herbal Preparation HRG80 For Preventing And Mitigating Stress-Induced Failure Of Cognitive Functions In Healthy Subjects *J Altern Complement Integr* Med 2020, 6: 100 DOI: 10.24966/ACIM-7562/100100

https://www.heraldopenaccess.us/openaccess/panax-ginseng-meyer-herbal-preparation-hrg80-for-preventing-and-mitigating-stress-induced-failure-of-cognitive-functions-in-healthy-subjects

Panossian A, Wikman G. Evidence based efficacy and effectiveness of Rhodiola SHR-5 extract in treating stress- and age-associated disorders. Chapter 9 In the book " Rhodiola rosea" Eds. Alain Cuerrier, Kwesi Ampong-Nyarko Series: Traditional Herbal Medicines for Modern Times, CRC Press—2014, pp. 203–221.

Panossian A., Gerbarg P. Potential Use of Plant Adaptogens in Age-related Disorders. In: Complementary, Alternative, and Integrative Interventions in Mental Health and Aging. Edited by Helen Lavretsky, Martha Sajatovic, and Charles F. Reynolds III (the "Editors"). Oxford University Press—New York 2016. Pp. 197–211.

Panossian A, Amsterdam J. Adaptogens in Psychiatric Practice. Chapter 8, Pp 155–181. in the book Complementary and Integrative Treatments. Eds. PL. Gerbarg, PR. Muskin, RP. Brown, APA Publishing 2018. 425 pages.

https://www.appi.org/Complementary_and_Integrative_Treatments_in_Psychiatric_Practice

https://books.google.se/books?hl=en&lr=lang_en&id=3dQuDwAAQBAJ&oi=fnd&pg=PA135&ots=5xQNsDHXwf&sig=BayqOUMqrsDUhrFcwI7bPNAvt38&redir_esc=y#v=onepage&q&f=false

Panossian A. Discover Andrographis. Take Charge Books, Brevard, NC 2019. Pp. 1–82. ISBN: 978–0–9982658–6–5. https://www.academia.edu/40480219/DISCOVER_ANDROGRAPHIS

Panossian A., Wikman G., Kaur P., Asea A. Molecular Chaperones as Mediators of Stress Protective Effect of Plant Adaptogens. In: Heat Shock Proteins and Whole Body Physiology Asea, A.A.A., Pedersen, B.K. (Eds.), Heat Shock Proteins Vol. 5, Springer. 2010, pp. 351–364.

Panossian A. Wikman G. Efficacy of *Andrographis paniculata* in the upper respiratory tract (URT) infectious diseases and the mechanism of action. In: Evidence and rational based research on Chinese Drugs, Ed. H. Wagner and G. Ulrich Merzenich (Eds.), Springer Publ. Comp. 2012. Pp. 137–180.

Mariage PA, Hovhannisyan A, Panossian AG. Efficacy of Panax ginseng Meyer Herbal Preparation HRG80 in Preventing and Mitigating Stress-Induced Failure of Cognitive Functions in Healthy Subjects: A Pilot, Randomized, Double-Blind, Placebo-Controlled Crossover Trial. *Pharmaceuticals* (Basel). 2020;13(4):57. Published 2020 Mar 29. https://doi.org/10.3390/ph13040057

Dimpfel W, Mariage PA, Panossian AG. Effects of Red and White Ginseng Preparations on Electrical Activity of the Brain in Elderly Subjects: A Randomized, Double-Blind, Placebo-Controlled, Three-Armed Cross-Over Study. Pharmaceuticals (Basel). 2021;14(3):182. Published 2021 Feb 25. doi:10.3390/ph14030182 . https://doi.org/10.3390/ph14030182

Dimpfel W, Schombert L, Panossian AG. Panax ginseng preparations enhance long-term potentiation in rat hippocampal slices by glutamatergic NMDA and kainate receptor-mediated transmission. *J. Altern Complement Integr. Med.* 2020, 6, 106. DOI:10.24966/ACIM-7562/100106

Panossian A, Abdelfatah S, Efferth T. Network Pharmacology of Red Ginseng (Part I): Effects of Ginsenoside Rg5 at Physiological and Sub-Physiological Concentrations. *Pharmaceuticals* 2021, 14, 999. https://doi.org/10.3390/ph14100999

Panossian A, Abdelfatah S, Efferth, T. Network Pharmacology of Ginseng (Part II): The Differential Effects of Red Ginseng and Ginsenoside Rg5 in Cancer and Heart Diseases as Determined by Transcriptomics. *Pharmaceuticals* 2021, 14(10), 1010; https://doi.org/10.3390/ph14101010.

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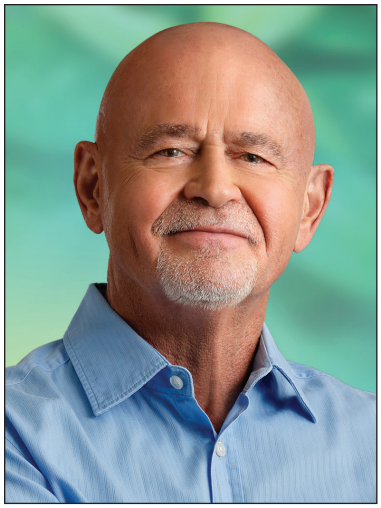
Alexander Panossian Ph.D., Dr.Sc. completed his doctorate in organic chemistry at the Yerevan State University in 1971. He obtained his scientific degrees from Moscow Institute of Bioorganic Chemistry in 1975 and Moscow Institute of Fine Chemical Technology in 1986. His professional positions include the National Academy of Sciences (Armenia) (1975–1986) and the National Institute of Health (Armenia) (1986–1993). Dr. Panossian was made a full Professor of Chemistry (Natural and Physiologically Active Compounds) in the Russian Federation, and later served as Director of the Laboratory of Quality Control of Drugs of Medical Drug Agency of the Republic of Armenia (1993–2003).

In 2003, he moved to Sweden to act as Head of Research and Development at the Swedish Herbal Institute. He has the honor of participating as a guest scientist in the Laboratory of Nobel Laureate Bengt Samuelsson at the Karolinska Institute in Stockholm (1982–1983), at Munich University (1993–1995), and at King College in London, 1996.

Dr. Panossian has written or co-authored more than 170 articles in peer-reviewed journals. His main research interest is focused on plant adaptogens—anti-stress compounds that are involved in the regulation of neuroendocrine and immune system. He is a past Editor-in-Chief of *Phytomedicine, International Journal of Phytopharmacology*, and *Phytotherapy* (Elsevier, Germany), and currently serves as Science and Research Director for EuroPharma, Inc in the United States.



Terry Lemerond is a natural health expert with over 50 years of experience. He has owned health food stores, founded dietary supplement companies, and formulated more than 400 products. A much sought-after speaker and accomplished author, Terry shares his wealth of experience and knowledge in health and nutrition through his ed-ucational programs, including the Terry Talks Nutrition website (https://www.terrytalksnutrition.com), newsletters, podcasts, webinars, and personal speaking engagements.

Terry's books include *Seven Keys to Vibrant Health* and the sequel, *Seven Keys to Unlimited Personal Achievement*, and his newest publication, *50+ Natural Health Secrets Proven to Change Your Life.* His continual dedication, energy, and zeal are part of his on-going mission to improve the health of America.