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Biomolecules from Plants as an Adaptogen

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Received date: November 6, 2017; Accepted date: December 05, 2017; Published date: December 11, 2017

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Abstract

In present scenario, stress is a common problem which affects not only elders, but also to older and youngster. Long term stress can be detrimental and causes various diseases related to CNS, immune system, neuro-endocrine system, liver, blood, learning, memory defeat and irregular sleeping pattern. A combined approach of traditional and modern system i.e., adaptogens help to overcome the stress and stress related problems. Adaptogens are generally the plant-derived biologically active substances that help to increase the body resistance against physical, biological, emotional and environmental stressors in nonspecific manner through maintenance of internal homeostasis. Adaptogenic herbs exhibit neuro-protective, anxiolytic, anti-fatigue, nootropic, anti-depressive, and CNS stimulating activity. Non-specific action of the adaptogenic herbs decreases the targeted phenomenon and efficiency so that more study, research and clinical trials are required to find the targeted action of adaptogens. In recent years, focus has been shifted towards the adaptogens due to its safety, cost effectiveness and efficacy for maintaining and improving the quality of life. The present review focuses on the mechanism of stress induction, its relation with anxiety, depression and immune system. It also highlights the different herbal biomolecules as an adaptogens that are used in either Ayurveda or Traditional Chinese Medicine [TCM].

Keywords: Adaptogenic herbs; Adaptogens; Stress; Homeostasis, Biomolecule

Introduction

In the modern era, most of illnesses are caused by stress and stress-related disorders. Generally, stress increases the level of stress hormone known as cortisol. Cortisol is responsible for the alert and arouses response, thereby affecting sympathetic nervous system, thyroid and adrenal glands [1]. High level of cortisol affects the physiological system resulting in anxious and irritability, weight gain, bone loss and may also contribute to risk of diabetes and heart disease [2].

To overcome these problems, multiple approaches like drugs, exercise and relaxation techniques have been employed, but these methods provide mixed results and sometime often unsatisfactory results also. Further, scientist followed Ayurveda concept, an adaptogens as a novel approach to reduce stress and prevent stress-related problems [3].

Various plants have been used for hundreds of years in the Indian system of Ayurvedic medicine as an adaptogens for its medicinal properties. They are available as adaptogenic drugs which increase the body's resistance to physical, biological, emotional and environmental stressors in nonspecific manner [4]. Also, increase of attention, endurance in fatigue, reduction of stress-induced impairments and disorders related to the neuro-endocrine and immune systems to balance and maintenance of homeostasis in the body are reported [5]. Previous studies and reports revealed that adaptogens exhibit neuro-protective, anti-fatigue, anti-depressive [6], anxiolytic [7], nootropic [8] and CNS stimulating activity [9].

In this review, the plant biomolecule with their mechanism are discussed thoroughly because these molecules are available as principle

constituents which possess adaptogenic property in plants. The main focus of discussion is those biomolecules which strengthen the HPA axis and having anti-stress, antianxiety, antidepressant and immunomodulatory like activity. The mechanism by which stress is related to anxiety, depression and immune system dysfunction are also discussed briefly.

The relationship between stress and anxiety

Stress represents an interface between a certain type of stressors and specific stress response systems, such as hypothalamic-pituitary-adrenal (HPA) axis and/or catecholamines. Anxiety and fear associate a set of behavioral, cognitive, and physiological responses to nasty situations or insecurity [10]. Thus, anxiety and fear can be a part of the stress response, and a component of a potential stressor [11].

The main stress hormone system is the hypothalamic-pituitary-adrenal (HPA) axis, which activates secretion of different hormones such as cortisol [12]. In response to a stressor (such as exercise, hypoglycemia, and infection), hypothalamus synthesize corticotropin-releasing hormone (CRH), acts as secretagogue to release adrenocorticotrophic hormone (ACTH) from pituitary corticotrophs into the circulatory system, which targets the adrenal cortex and stimulates glucocorticoids synthesis and secretion. It further act to suppress immune activity and maintain and/or increase glucose in the blood, thereby prevents glucose-dependent tissue from starvation and, thus provides enough energy to maintain its alert state in stress [13].

Glucocorticoids have an ability to inhibit their own release and secretion by the negative feedback effects on CRH and ACTH secretion, and provide immediate inhibition to limit the stress response and prevent excess production of glucocorticoids [14]. The downregulation of the HPA axis is mediated mainly by three brain

regions. Firstly, stressors activate neurons containing gamma-aminobutyric acid (GABA) and inhibiting further secretion of glucocorticoids. Secondly, excessive glucocorticoid receptor (GR) in the hippocampus increase glucocorticoid level by activating GABA mediated neurons, thus diminishing HPA activity. And finally, the medial prefrontal cortex reduces HPA activation [15].

Furthermore, stress as an activator of CRH/ACTH/glucocorticoid secretion initiate secretion from the HPA axis in a circadian pattern. Thus, increased HPA axis activity is assumed to organize an organism for the upcoming increase in activity.

The relationship between stress and depression

The adaptive response to stress is characterized by activation of neural and neuroendocrine cascades mediated mainly by the sympathetic and limbic-hypothalamic-pituitary-adrenal (HPA) systems respectively. Chronic psychosocial stress has been associated with depression where increased levels of cortisol could be directly involved in the mood fluctuations, and also alter the serotonergic neurotransmission [16].

Cortisol is a vital catabolic hormone produced by the adrenal cortex and elevated plasma level is seen in psychosocial depression and an altered circadian pattern of cortisol secretion is due to the HPA axis dysfunction, which is substantiation that treatment with antidepressants leads to normalization of HPA axis activity [17].

The 5-HT system interacts with the various stress hormones on several levels, i.e., increase CRH release, decrease 5-HT turnover and increase cortisol level, may cause decrease serotonergic activity of neurons, decrease 5-HT_{1A} and 5-HT₂ receptor expression and binding. Sustained stress or sustained increase of plasma cortisol is accompanied by diminution of 5-HT turnover and reduced 5-HT release in all areas.

In depression, the 5-HT level may decrease due to altered 5-HT metabolism and downregulation of the 5-HT_{1A} receptor and, possibly, upregulation of the 5-HT_{2C} receptor. Moreover, the CRH/cortisol is hyperactive, causing or aggravating the disturbances in the 5-HT system [18].

The relationship between stress and immune system

Chronic stress is known to have numerous adverse effects on health, which are mediated through stress actions on the immune system. During short-term stress, multiple physiological systems are activated to frame the cardiovascular, musculoskeletal, and neuroendocrine systems for fight-or-flight, thus enable survival. A stressor may shape up the immune system for challenges in certain condition such as wounding or infection. Short-term stress, at the time of immune activation, augments significant subsequent immune response, thus can enhance innate and adaptive, primary and secondary immune responses [19].

Stress-induced immunosuppression may be adaptive, because this may preserve energy to deal with the abrupt demands enforced by the stressor [20]. Acute stress induced immunosuppression, such as inhibition of prostaglandin synthesis, cytokine production, or leukocyte proliferation is significantly longer. Acute stress may suppress adaptive immunity and enhance only innate immunity during energy-conservation.

Short-term stress induces an initial increase followed by a decrease in lymphocyte and monocyte numbers and an increase in neutrophils numbers, with glucocorticoids and catecholamines, major mediators of stress. Short-term stress results in a significant increase in immune response, mediated by memory and effector helper T cells at the time of primary immunization [21].

Chronic stress, suppress or deregulates immune function and decrease leukocyte mobilization from the blood to other body compartments is thought to be a suppressor of cell mediated immunity (CMI) [22]. Chronic stress has been revealed to suppress different type of immune cell such as CMI, antibody production, NK activity, leukocyte proliferation, virus-specific T cell and NK cell activity, and anti-mycobacterial activity of macrophages [23].

Basic mechanism of stress induction

The general mechanism of stress induction due to predisposing factors correlating with the stress hormone system and sympathetic nervous system has been illustrated in Figure 1.

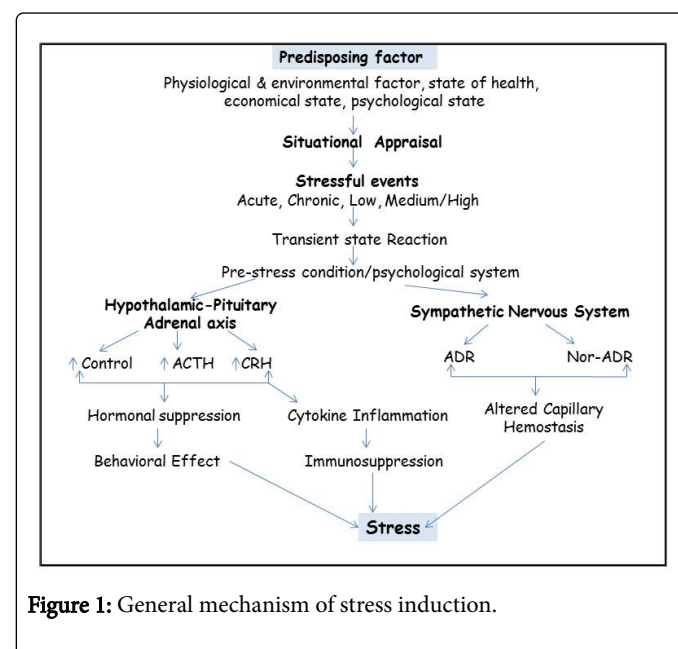


Figure 1: General mechanism of stress induction.

General mechanism of action of adaptogenic drugs

Adaptogens help to establish homeostasis especially against stress and the relief from stress is favored by various types of mechanisms directly or indirectly by maintaining the level of hormones i.e., cortisol, adrenaline, ACTH and CRH.

Adaptogen generally act on the amygdale, hypothalamus, pituitary, thyroid, adrenal. During the state of fatigue and stress, nor-adrenaline becomes imbalanced. The adaptogens activates the hormonal response to produce and release more adrenaline and nor adrenaline hormones, and help to respond more effectively and efficiently to the excess in hormones and shut down more quickly [24]. During stressful situations, the energy consumption is increased and body unable to fulfill the requirement result in enhanced generation of free radicals and the body's defense system combat against the oxidative stress [25,26]. Adaptogens support adrenal functions by allowing cells to access more energy and preventing oxidative damage [27].

Functions of adaptogen

The various function reported for adaptogens in literature are explained in Figure-2. Adaptogens boost the immune system, protect the liver by detoxification and speed up its regeneration process [28]., increase the number and activity of T-cells and natural killer cells [29]., lower the risk of cancer, improve memory, learning ability [30]., resistance to stress, reduce high cholesterol, improve blood circulation, purify the blood, strengthen the heart, inhibit platelet aggregation and control blood clotting mechanisms. It also helps in prevention of breast and prostate cancer, relieve menopause symptoms and erectile dysfunctions [31]. Further, herbs also increase natural production of growth hormone and an increase in testosterone, stabilize the blood sugar levels [32]., improve general well-being and slowing down the aging process [33]., revitalize entire body by stimulating the production of stem cells in the bone marrow [34].

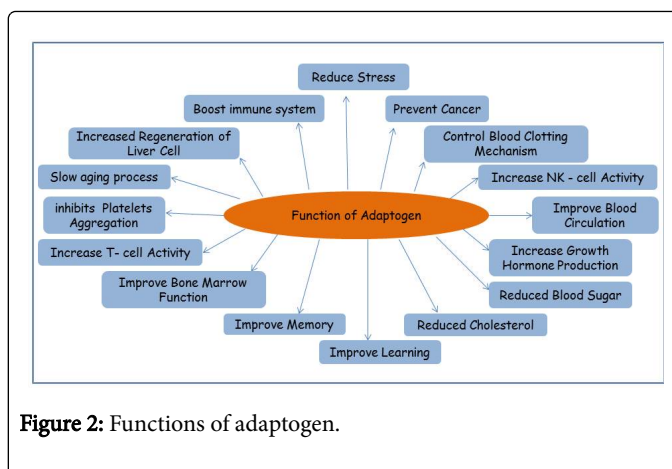


Figure 2: Functions of adaptogen.

Biomolecules from plants as an adaptogen

Most of the herbal adaptogens that are used in either Ayurveda or Traditional Chinese Medicine [TCM]. are discussed in Table 1.

SI No	Phytoconstituent	Biological effect	Tests/Models	Mechanism of action	Ref
1.	Curcumin	Adaptogenic activity Antidepressant-like effects	Chronic stress, Chronic unpredictable stress Forced swimming	Alter functional homeostasis and memory deficit and cause normalization of the hyper-activated HPA axis with subsequent decrease in corticosterone secretion. Acts on serotonergic system, which may be mediated by an interaction with 5-HT1A/1B and 5-HT2C receptors responsible for depression.	[35,36]
2.	Rutin	Anti-stress activity Anxiolytic-like activity	Forced swimming, Tail Suspension, Elevated plus-maze Elevated plus-maze, Ambulatory activity	Modulates GABA receptors and also acts as NMDA receptor antagonist. Cause inhibition of prostaglandin synthesis thereby, regulation of HPA axis activity under basal and stress conditions. Modulates GABAergic neurotransmission in the basolateral amygdala.	[37,38]
3.	Ginsenosides Rb1 and Rg1	Adaptogenic activity	Radical scavenging, Nrf2 activation, Mitochondrial dysfunction, BBB permeability	Attenuates oxidative stress and mitochondrial dysfunction, thus resulting in a reduced apoptotic cell death. The promising effects is due to activation of cytoprotective Nrf2 signaling and a mitochondrial-targeted protective action.	[39].
4.	Glycyrrhizin	Antidepressant-like activity Anti-stress activity	Forced swimming, Tail suspension, Immobilization stress Locomotor activity, Muscle co-ordination	Acts by interaction with α 1-adrenergic and D2-receptors, thereby increasing the levels of norepinephrine and dopamine in brains, and also have MAO inhibiting activity. Attenuates the HPA axis activation and free radical scavenging activity.	[40,41]
5.	Piperine	Antidepressant-like activity Antianxiety-like activity	Elevated plus-maze, Light and dark box, Social interaction, Tail suspension, Forced swimming, Open field test.	Possibly mediated through benzodiazepine-GABA receptor and increase in GABA levels and inhibition of neuronal nitric oxide synthase. Cause augmentation of the neurotransmitter synthesis or the reduction of the neurotransmitter reuptake and also mediated via the regulation of serotonergic system.	[42,43]
6.	Eugenol	Anti-stress activity	Restraint stress model	Activity is mediated through the HPA axis and BMS pathways and also changes in brain noradrenergic, serotonergic, and dopaminergic system in hippocampus, hypothalamus, prefrontal cortex, and amygdala.	[44]

7.	Andrographolide	Adaptogenic activity	Stress-induced hyperthermia, Pentobarbital-induced hypnosis	Cause upregulation of benzodiazepine site of GABA-A receptors, which involved in stress-triggered physiological responses.	[45]
8.	Ocimumosides	Anti-stress activity	Restraint stress model	Anti-stress activity by normalizing acute stress-induced hyperglycemia, corticosterone levels, creatine kinase, and adrenal hypertrophy.	[46]
9.	Astragaloside IV	Anti-stress activity	Immobilized stressors, Elevated Plus-maze	Astragaloside IV may ameliorate anxiety via serotonergic receptors and inflammation by decreasing serum levels of corticosterone, IL-6 and TNF- α .	[47]
	Astragaloside II	Immunomodulatory activity	Splenic-T-lymphocyte activation, Cyclophosphamide induced immunosuppression	Astragaloside II enhances T cell activation by regulating the activity of CD45 PTPase in primary T cells. Astragaloside II also increased IL-2 and IFN- γ secretion, upregulated of IFN- γ and T-bet in primary splenocytes, and promoted of primary CD4 + T cells.	[48]
10.	Bergenin	Immunomodulatory activity	Adjuvant-induced arthritis	Inhibits IL-2 production by CD4 + T-cells, which is regulator of immune response, stimulates the synthesis of IFN- γ in T-cells and also induces the secretion of pro-inflammatory cytokines such as TNF- α by activated macrophages. The inhibition of IL-2 is possibly responsible for reduced IFN- γ secretion by CD8 + T cells and TNF- α by macrophages and also promote IL-4 and IL-5 production.	[49]
11.	Syringin	Immunomodulatory activity	Croton oil and arachidonic acid-induced mouse ear oedema	Inhibits TNF- α production and CTLL-2 cell proliferation thus, may possess anti-allergic activity.	[50]
12.	Berberine	Antidepressant and anti-anxiety-like activity	Forced swimming, Elevated plus-maze, Locomotor activity	Acts by modulating hypothalamic Corticotrophin releasing factor and the noradrenergic system in the CNS and decrease serotonergic system activity by activating somatodendritic 5-HT _{1A} and inhibiting postsynaptic 5-HT _{1A} and 5-HT ₂ receptors.	[51,52]
13.	β -pinene	Antidepressant-like activity	Forced swimming	Acts through interaction with the serotonergic pathway through postsynaptic 5-HT _{1A} receptors and also interact with the adrenergic system through β -receptors and the dopaminergic systems through D ₁ receptors.	[53]
14.	Zeatin	Immunomodulatory activity	Thioglycollate-induced peritonitis	Modulates T lymphocyte activity via adenosine A _{2A} receptor, which induces the production of cAMP, potently inhibits the production of both TH ₁ and TH ₂ cytokines and also modulate either directly or indirectly, both humoral and cell-mediated responses.	[54]
15.	Scopoletin	Antidepressant-like activity	Forced swimming, Tail suspension, Open-field test	Interact with the 5-HT _{2A/2C} , α ₁ and α ₂ , D ₁ and D ₂ receptors systems thereby antidepressant-like effect.	[55]
16.	Ginkgolide B	Adaptogenic and anti-stress activity	in-situ hybridization of CRH and AVP mRNA	Acts at the hypothalamic level, modulate the monoaminergic inputs to the CRH synthesizing cell bodies depending upon both the nature of stress and substance.	[56]
17.	Quercetin	Anti-fatigue activity	Forced swimming	Improves endurance capability to fatigue during exhaustion and also prevent endothelial dysfunction via enhancing the activities of antioxidant enzymes and attenuating the levels of inflammatory cytokines.	[57]
18.	Gallic acid	Antidepressant-like activity	Sucrose preference test, Forced swimming	Inhibits MAO-A activity and increase levels of monoamine in brain and reduces plasma nitrite levels and reduced nitrosative stress, thus plays key role in chronic stress-induced depression.	[58]
19.	Valerenic Acid	Anti-stress activity Anxiolytic activity	Forced swimming Elevated plus-maze	Mitigate stress by decreasing the turnover of 5-HT to 5-hydroxyindoleacetic acid and NE to 3-methoxy-4-hydroxyphenylethyleneglycol sulfate in the hippocampus and amygdala. Modulates GABA-A channel and possess anxiolytic activity.	[59,60]

20.	Picracin	Immunomodulatory activity	Pro-inflammatory cytokine release, DTH response	Inhibits mitogen induced proliferation of T cells, are potent inhibitors of IL-2 release through induction of apoptosis.	[61]
21.	Esculetin	Anti-inflammatory and depressive-like activity	Tail suspension, Forced swimming, Open field test	Inhibits pro-inflammatory cytokines including interleukin-6, interleukin-1 β and tumor necrosis factor- α and also attenuated inducible nitric oxide synthase and cyclooxygenase-2 protein expression by inhibiting nuclear factor-kB pathway in hippocampus, cause upregulations of brain derived neurotrophic factor and phosphorylated tyrosine kinase B protein expression in hippocampus which provides neuroprotection.	[62]
22.	Catechin	Anxiolytic activity	Forced swimming, Elevated plus-maze	Inhibits the HPA axis-associated psychological dysfunction induced by corticosterone, and modulates hypothalamic CRF activity and the noradrenergic system within the CNS.	[63]
23.	Asiaticoside	Antidepressant-like activity	Tail suspension, Forced swimming	Regulates α 2-adrenergic receptor and increase the level of adrenalin in brain.	[64]
24.	Tumerone	Antidepressant-like activity	Forced swimming, Tail suspension, Open-field test	Increase the level of 5-HT in cortex, striatum, hippocampus, and hypothalamus, the level of NE in striatum and hippocampus, the level of 3-Methoxy-4-hydroxyphenylglycol and 3,4-dihydroxyphenylacetic acid in hypothalamus, the level of 5-Hydroxyindoleacetic acid in striatum, and the level of DA in striatum, hippocampus, and hypothalamus.	[65]
25.	Rosavin	Adaptogenic activity	Forced swimming light/dark test, Tail-flick latencies	Modulates biogenic monoamines in cerebral cortex, brain stem and hypothalamus. In cerebral cortex and brain stem, level of nor-epinephrine and dopamine decreased, while serotonin increase, due to change in monoamine level, i.e., inhibition of monoamine oxidase and catechol-o-methyltransferase.	[66]
26.	Shatavarin	Immunomodulatory Activity	Human peripheral blood lymphocytes stimulation assay	Stimulates immune cell proliferation, induce IgG, interleukin-12 and inhibit IL-6 production. It also had strong modulatory effects on Th1/Th2 cytokine profile.	[67]
27.	Salidroside	Antifatigue activity	Forced swimming	Decrease the activities of CK and CK-MB and increase the GSH-Px and SOD activities and also decrease the MDA content in liver tissue.	[68]
28.	β -sitosterol	Anxiolytic-sedative activity	Pentobarbital-induced sleeping time	Modulates GABAA receptor and producing anxiolytic effect similar to that of benzodiazepines.	[69]
29.	Ellagic Acid	Antidepressant and anti-anxiety activity	Novelty-suppressed feeding, Forced swimming, Sucrose intake test	Acts probably by interaction through adrenergic and serotonergic systems. On the other hand, cause inhibition of inducible NOS thereby acts as antidepressant.	[70]
30.	Puerarin	Antidepressant and anti-stress activity	Tail Suspension, Forced swimming	Ameliorates depression and pain via, activating ERK, CREB, and BDNF pathways, and inhibits corticotropin releasing hormone, corticosterone, adrenocorticotrophic hormone, and normalization the activity of serotonergic system thereby preventing HPA axis dysfunction.	[71,72]
31.	Chlorogenic acid	Antidepressant activity	Tail Suspension, Elevated plus-maze.	Cross blood-cerebrospinal barrier and exhibit neuroprotection and promote serotonin release through enhancing synapsin I expression.	[73]
32.	Ursolic acid	Antidepressant and Anxiolytic-like activity	Tail suspension, Forced swimming, Open field test	Action is mediated by an interaction with the dopaminergic system, through the activation of dopamine D1 and D2 receptors.	[74]
33.	Caffeic acid	Anti-depressive and anxiolytic-like activity	Elevated plus-maze, Open field test	Indirectly modulates α 1-adrenoceptor i.e., α 1A-adrenoceptor in cortical membranes and directly modulates second messenger acting through glutamate or GABAergic receptors thereby involved in the expression of its anti-depressive and/or anxiolytic-like effects.	[75,76]

34.	Sulforaphane	Antidepressant and anxiolytic-like activity	Forced swimming, Tail suspension, Chronic stress, Open field test	Normalize the stress-induced HPA axis dysfunction and have inhibitory effects on the inflammatory response to stress.	[77]
35.	Chicoric acid	Antidepressant activity Immunomodulatory activity	Forced swimming, Learned helplessness Chronic restraint stress induced altered T lymphocyte distribution	Modulates nor-adrenaline, dopamine and 5- hydroxy tryptamine in chronically stressed condition. Imparted immune-stimulation by upregulating the expression of CD28 and CD80 and downregulating CTLA-4, stimulatory effect on IL-12, IFN-gamma and IL-2 and suppress the increased IL-10 and also lower corticosterone levels, thereby showing its normalizing effect on HPA axis.	[78,79]
36.	3,4,5-trimethoxycinnamic acid	Anti-stress, anxiety and depression-like activity	Repeated cold exposure test	Augment norepinephrine in brain and also ameliorated chronic stress and induced Δ FosB protein and SC1 mRNA expression in a nucleus accumbens shell sub region.	[80,81]
37.	Rosmarinic acid	Anxiolytic-like activity	Elevated plus-maze, Step-down avoidance, Open field test	Involved in direct modulation of a second messenger through glutamate receptors, since these are directly involved in several CNS disorders, and the anxiolytic effect is seen at lower doses, without affecting the short & long-term memory retention or locomotion, exploration and motivation.	[82]
38.	Ferulic Acid	Immunomodulatory activity	Carbon clearance, Neutrophil adhesion, Serum immunoglobulins, DTH response	Acts by stimulating cell mediated immunity as well as humoral immunity by acting on B-cell and T-cell.	[83]

Table 1: Reported plant biomolecules as adaptogen.

Conclusion

Adaptogens may be considered as a novel pharmacological group of herbal preparations not only for stress-induced and stress-related problems, but also for enhancing and maintaining the quality of life when co-administered along with the standard therapy for many diseased related pathological conditions. The concept of adaptogens is sufficient to be considered in the assessment of traditional herbal medicinal products. The use of adaptogens eliminates or significantly decreases the classical signs of the prolonged stress reactions due to minimal side effects, cost-effectiveness and efficacy. The principle of an adaptogenic action needs further research and studies in the pre-clinical and clinical area to evaluate the specific molecular mechanism of action.

Conflict of Interest

The authors declare that they have no conflicts of interest to disclose.

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