Contents lists available at ScienceDirect

Asian Pacific Journal of Tropical Disease

journal homepage:www.elsevier.com/locate/apjtd

Document heading

# A current status of adaptogens: natural remedy to stress

Pawar Vinod S*[1], Hugar Shivakumar[2]

[1] Dept of Pharmacology, SVPM's College of Pharmacy, Malegaon (Bk), Baramati 413115 (M.S), India
[2] P.G. Dept of Pharmacology, BLDEA's College of Pharmacy, Bijapur 586103, Karnataka, India

ARTICLE INFO

*Article history:*
Received 14 June 2012
Received in revised from 5 July 2012
Accepted 7 Octoberr 2012
Available online 28 October 2012

*Keywords:*
Adaptogens
allostasis
stress
HPA axis

ABSTRACT

Stress is a normal part of everyday life but it is important to be able to use tools for its management otherwise chronic stress, if left untreated, can lead to a variety of stress related illnesses including hypertension, heart disease, anxiety, depression, memory impairment and chronic fatigue syndrome. The aim of this literature review is to summarize and critically analyze research conducted on the adaptogenic herbs. The aim of this review article is to assess the level of scientific evidence presented by the adaptogens from natural origin by different screening methods and to provide a rationale at the molecular level. Strong scientific evidence is available in relation with the molecular mechanisms associated with their stress- protective activity against acute and chronic paradigms. The beneficial stress- protective effect of adaptogens is in relation with regulation of homeostasis via several mechanisms of action associated with the hypothalamic- pituitary-adrenal axis and the control of key stress mediators and biochemical markers such as nitric oxide (NO), cortisol, cholesterol, triglycerides, glucose etc. Good scientific evidence has been documented with active secondary metabolites present in adaptogens.

## 1. Introduction

Pathologic conditions related to stress have been a subject of science since 1911 when Walter Cannon applied the engineering concept of stress to a physiologic context, suggesting that emotional stimuli were capable of causing physical damage to the body. Stress and stress-related disorders are a significant cause of disease in modern times, contributing to perhaps 75% of all illnesses [1]. Stress has been postulated to be involved in the etiopathogenesis of a diverse variety of diseases ranging from psychiatric disorder such as anxiety and depression, immunosuppression, endocrine disorders including diabetes mellitus, male sexual dysfunction, cognitive dysfunctions, peptic ulcer, hypertension and ulcerative colitis [2]. Western medicine has developed multiple approaches to coping with stress, including pharmaceutical drugs, exercise, and relaxation techniques like meditation. While these methods can provide some benefits, results are mixed and often unsatisfactory. In the East, researchers have also struggled to find solutions to stress related problems [1]. The benzodiazepine anxiolytics, despite having significant antistress activity against acute models of stress, have not proved effective against chronic stress induced adverse effects on immunity, behavior, cognition, peptic ulcer and hypertension [2]. Furthermore, these drugs have adverse effects on the fetus during pregnancy and on the neonate during lactation [3]. The prevention and management of stress disorders remains a major clinical problem. An answer to this perplexing problem was first provided when Brekhman and Dardymov [4] reported that some plant derived agents could induce a state of non-specific increase of resistance to affect internal homeostasis. These agents, named adaptogens, improve the response to stress [5]. They help the body to adapt by normalizing physiological processes in times of increased stress [6]. Adaptogens can be viewed as tonics and are prescribed to enhance vitality and are indicated when stress levels are high, during convalescence after or difficult life chances (event) [6]. Adaptogens like Panax ginseng were shown to be effective in attenuating stress induced adverse effects in astronauts, soldiers and athletes in the USSR [4]. Panax ginseng, first clinically used adaptogen, has been extensively investigated experimentally and clinically for its stress-attenuating activity [7]. The processes involved in

*Corresponding author: Pawar Vinod S. Lecturer & Ph.D Scholor Dept. of Pharmacology, SVPM's College of Pharmacy, Malegaon (Bk), Baramati, Pune District. Maharashtra 413115, India
Email: vinod_pharmacology@yahoo.co.in
Mob: +919503358251
Fax: 02112254447

response to stress can help to elucidate possible mechanisms of actions of adaptogens. Therefore, it is important to examine what is currently understand about the stress response process and how this response can become dysfunctional and lead to pathological conditions.

## 2. Stress

### 2.1 An interesting stress *story*

In 1930, endocrinologist, Hans Selye a Canadian professor and leading pioneer in stress research, is internationally acknowledged as 'the father of stress' was attempting to do some research on rats to determine the effects of an ovarian extract. He would try to inject the rats, but would end up dropping them on the floor, chasing them around the room and finally injecting them with the extract. At the end of several months of this, Seyle found that the rats had peptic ulcers, greatly enlarged adrenal glands (the source of two important stress hormones) and shrunken immune tissues. He was surprised to find the same symptoms in control group [8,9,10]. He borrowed the engineering term stress to describe the phenomenon. He made two observations as
1. The body has a set of similar responses to a broad array of stressors. 2. Under certain conditions, the stressors will make you sick.

### *2.2 General adaptation syndrome and Stress response*

Hans Selye proposed the general adaptation syndrome (GAS) in 1936 that examined the actions and consequences of stressors on the healthy organism. This concept was based on Hans Selye's theory of stress and general adaptation syndrome, which was have three phases [11]: alarm phase- characterized by surprise and anxiety when a person is exposed to a new situation. During this stage the body reacts by producing epinephrine and norepinephrine. Phase of resistance -characterized by adaptation and phase of exhaustion-loss of adaptional ability also sometimes referred as adrenal maladaptation [12]. His reasoning suggested that every organism must be able to adapt to environment and social conditions that are stressful and potentially life threatening [13]. Throughout the progression of stress theories emerged the idea that the ability to maintain internal viability despite extreme or unexpressed stress events could not be produced by homeostasis alone [14]. Homeostasis regulates set points in the body such as glucose or oxygen in the blood and blood pH. When the organism is exposed to harsh or unexpected events such as sudden drop in temperature of prolonged severe temperatures, it must react and even predict these events in order to adapt and service. The process of homeostasis can only adjust set points in the body within the realm of a normal continuum.

#### *2.2.1 Allostasis*

Allostasis was first introduced by Sterling and Eye in 1988 to describe an additional process of reestablishing homeostasis, but one that responds to challenge instead of to daily ebb and flow. This theory suggests that both homeostasis and allostasis are endogenous system responsible for maintaining the internal stability of an organism. Homeostasis from Greek means "remaining stable by staying the same". Allostasis was coined similarly, from the Greek allo, which means "variable" thus "remaining stable being variable". The allostasis mechanism responds to unexpected challenges such as severe temperature drop or running to protect your child from an accident. This allostasis response to stress is traditionally known as the "fight or flight" response [14].

#### *2.2.2 Allostatic overload and pathogenesis*

Catecholamine, glucocorticoids and cytokines all respond at the first to help the body adapt when stressors activate the hypothalamic-pituitary-adrenal (HPA) axis. Short term effect of these mediators is protective and their release induces a negative feedback process on these systems. In fact, acute stress can enhance immunity while chronic stress suppresses the immune response [15]. However continued release of these mediators results in prolonged effects on target cells and this can lead to receptor desentization, tissue damage and hypo functioning or suppression of immune responses [16,17]. Chronic release of stress hormones under excessive or long term stress leads to cumulative allostatic load on the body or cost of adaptation [14]. Normally, build-in feedback system is in place that protects the organism from over secretion by turning off these mediators. The abnormal continued release mediators have been lead to pathogenic conditions [18].

### *2.3 Effect of stress on body*

The long-term effects of stress alter our ability to maintain a healthy balance and harmony. This internal shift is due to a greater demand for stress hormones, namely cortisol, which is a major contributing factor that leads to the development of chronic illnesses, and hastens the aging process. All illnesses, to some extent, are a byproduct of our inability to adapt to changes and challenges of our life. The fast pace of life in modern times contributes to an increase in the production and sustained release of the stress hormones adrenaline and cortisol. Chronic activation of these stress hormones can cause deterioration of vital organs. Research has shown a close connection between high cortisol levels and serious health problems such as obesity, diabetes, hypertension, depression and osteoporosis. One of the best and most powerful ways to lower excess cortisol levels, bring the body into a state of metabolic harmony and reduce the damaging effects of stress is to use adaptogens. Adaptogens positively change our stress response and help prevent many health problems.

## 3. Adaptogen

Dr. Nicholai Lazarev, a pioneer in the emerging fields of toxicology and preventive medicine shortly after graduating from medical school in 1928, he started working on ways to prevent the damaging effects of new industrial chemicals on humans. In 1932, Lazarev discovered that different industrial chemicals, even in mild concentrations and small dosages, can cause similar alarm reactions and that if exposure is prolonged, the body will adapt by altering its physiological response (resistance). This adaptive reaction tends to gradually disturb homeostasis, which is damaging to health. He began looking not only for substances that could improve human's general resistance to toxins, but could also correct the general adaptation reaction to all kinds of stressors, including both mental and physical stress. Lazarev's efforts again shifted, this time to finding substances that could help soldiers overcome fatigue and improve their performance on the battlefield. With the soldiers as unknowing guinea pigs for amphetamines and other stimulants, Lazarev learned that many drugs were very effective in improving performance in response to great challenges in extreme situations for very short terms. However, he realized that the stimulants were harmful when used for prolonged periods. When WWII ended, Lazarev switched his focus to natural alternatives [1]. Herbalist apply the term adaptogens to any of several plants that raise no-specific resistance towards multiple and diverse stressors (including chemical, biological and physical) in such a way that helps the patient withstand and adapt to the stress and normalizes overall physiologic function. Since ancient times, early Chinese medicine referred to these plants as "elite" or "kingly herbs" [19]. In Traditional Chinese Medicine these herbs were classified as effective for increasing physical and mental capacity, reducing fatigue, improving resistance to disease, and promoting life extension. In China, soldiers used these herbs before battle. In Siberia, hunters used the herbs before long and dangerous journeys. In 1948, Lazarev and his protege, Dr. Israel Brekhman, undertook the challenge of researching the utility and effectiveness of this group of plants that Lazarev named "adaptogens" [1]. The idea was to find ways to enhance the productivity and performance of soldier, athletes and workers without using dangerous stimulants. Much of the early research into adaptogens was done by Dr. I.I. Brekhman who, in the late 1950's studied Panax ginseng. Looking for a less expensive and more available substitute, he changed his focus to a native Russian shurb, Eleutherococcus senticosis. His first monograph of this now popular herb (Siberian Ginseng, Eleuthero) was published in 1960.

In 1969 Brekhman and Dardymov defined the general pharmacological properties of adaptogenic substances. These include [20]

(i) Adaptogens must reduce stress-induced damage, thus presenting stress-protective effects such as anti-fatigue, antiinfectious, anti-depressant and restorative activities;

(ii) adaptogens must exhibit stimulating effects, both after single and multiple administration, leading to increased working capacity and mental performance against a background of fatigue and stress;

(iii) the stimulating effect of adaptogens must be different from those of conventional CNS stimulants and anabolic that deplete the energetic and plastic resources of the organism and give rise to negative side effects such as drug withdrawal syndrome; and

(iv) adaptogens must be innocuous and must not perturb body functions from their normal levels but rather exert a normalizing influence on a pathological state, independent of the nature of that state.

### 3.1. Adaptogenic plants

According to literature survey plants reported to have adaptogenic activity are listed (Table 1)'.

### 3.2. Adaptogenic polyherbal formulations

During the stressful situations supplementation of various nutrients and single and poly-herbal preparation have been shown to increase stress tolerance [57] (Table 2).

### 3.3. Active compounds of adaptogenic species (Chemistry of plant adaptogens)

Plants synthesize thousands of primary and secondary plant compounds that have a dizzying array of chemical structures [93].

These compounds are synthesized using a relatively small number of conserved enzymatic mechanisms. This suggests that the number of metabolites exceeds the number of genes involved in their biosynthesis. For adaptogens, finding which compounds produce adaptogenic effects has been a challenging task because of the multitude of targets and activities of these plants. Adding to this challenge is that, compared to synthetic drugs that are usually concentrated, single substances, plant extracts have a complex synergistic action that has made the scientific investigation of adaptogen remedies a precipitous and tortuous affair. It appears that plant adaptogens that exhibit a stimulating single dose effect, namely, R. rosea, S. chinensis and E. senticosus, all contain relatively high amounts of phenolic 28 compounds, particularly phenylpropane or phenylethane derivatives. These compounds are structurally related to the catecholamines, and presumably play important roles in the SAS and CNS systems. In contrast, plants such *P. ginseng*, Bryonia alba, E. senticosus etc, which contain relatively large amounts of tetracyclic triterpenes that are structurally similar to corticosteroids, reveal their stress protective effects and adaptation to stressors after repeated administration for periods 1 -4 weeks. In these cases, the active components play key roles in the HPA axis-mediated regulation of the immune and neuroendocrine systems. Panossian et al (1999) and researchers before them have paved the way for identifying the primary chemical compounds thought to be responsible for adaptogenic activity. They suggest that plant compounds having adaptogenic properties fall into three diverse classes of compounds: triterpenes, phenylpropanes, and oxylipins [94]. These plant constituents originate from dissimilar biosynthetic pathways, differ markedly in their chemical structure, and involved related classes of compounds.

Tetracyclic triterpenes

Triterpenes also include phytosterols and phytoecdysteroids, both of which are thought to have adaptogenic roles in mammals and in humans [95,96]. Most adaptogen plant species contain triterpenoid saponins, in particular, Panax ginseng, Eleutherococcus senticosus and Aralia mandshurica genera of the Araliaceae family. Triterpens are structurally similar to the corticosteroids which are stress hormones involved in the inactivation of the stress system and in protecting the organism from over-reaction in response to stressors [97].

Phenylpropanes

Phenylpropane compounds in plants adaptogens (e.g., flonoids, lignans) are synthesized from tyrosine, similar to the biosynthesis of the catecholamines, norepinephrine and epinephrine, norepinephrine and epinephrine. Phynylpropane compounds particularly emphasized in Rhodiola rosea are salidroside, rosavin, rosin, rosarin and tyrosol and the lignans [98].

Oxylipins

The third group of compounds suggested by Panossian and others as having adaptogenic properties is oxylipins. These are polyunsaturated fatty acids synthesized by plants via the acetate pathway and then oxidized via the lipoxygenase pathway to produce compounds called oxylipins [99]. The precursor of plant oxylipins is linoleic acid. Oxylipins are believed to have a role in plants as signaling molecules in plant resistance against insects and pathogens. Although these physiological functions in plants are still being investigated, their biological roles seem to be comparable to those of the eicosanoid compounds in mammals. In mammals, xylipins are synthesized primarily from the precursor, arachidonic acid in the C20 fatty acid pathway. These compounds are involved in inflammation, infection, allergy, and exposure to xenobiotics. The plant oxylipins illustrated in Figure 1 have three hydroxyl (OH) groups attached. These polyhydroxylated oxylipins from the adaptogenic species, Bryonia Alba, are proposed to be responsible for its adaptogenic activity.

### 3.2 Mechanisms involved in effect of adaptogens

A typical pharmacological assessment of adaptogens includes the evaluation of stimulating, tonic and stress protective activities in animal model system, which was subjected to various stress conditions (Fig 3).

#### 3.2.1 Stress protective activity of adaptogens through HPA axis and key mediators (Endocrinology)

More recent research postulate that adaptogens work primarily by affecting the hypothalamic/ pituitary/adrenal (HPA) axis and the sympathoadrenal system (SAS)94.

Thus, adaptogens modulate response to stress (physical, environmental, or emotional) and help to regulate the interconnected endocrine, immune and nervous systems. This re-regulation of a disordered or highly stressed system is achieved by metabolic regulators such as cytokines, catecholamines, glucocorticoids, cortisol, serotonin, nitric oxide (NO), cholecystokinin, corticotrophin-releasing factor (CRF), and sex hormones. This broad array of biochemical activators helps to explain why adaptogens also have anti-inflammatory, antioxidant, anxiolytic, antidepressant, nervine, and amphoteric effects as well. Brekhman and Dardymov's list of physiological actions of adaptogens states that adaptogens help modulate system function and maintain homeostasis. So all adaptogens act as broad spectrum amphoterics to living organisms, but they rarely have a pronounced effect on only one specific organ or system.

Increased generation of oxidative free radicals (OFR) or impaired antioxidant defense mechanism have been implicated in chronic stress induced perturbed homeostasis including

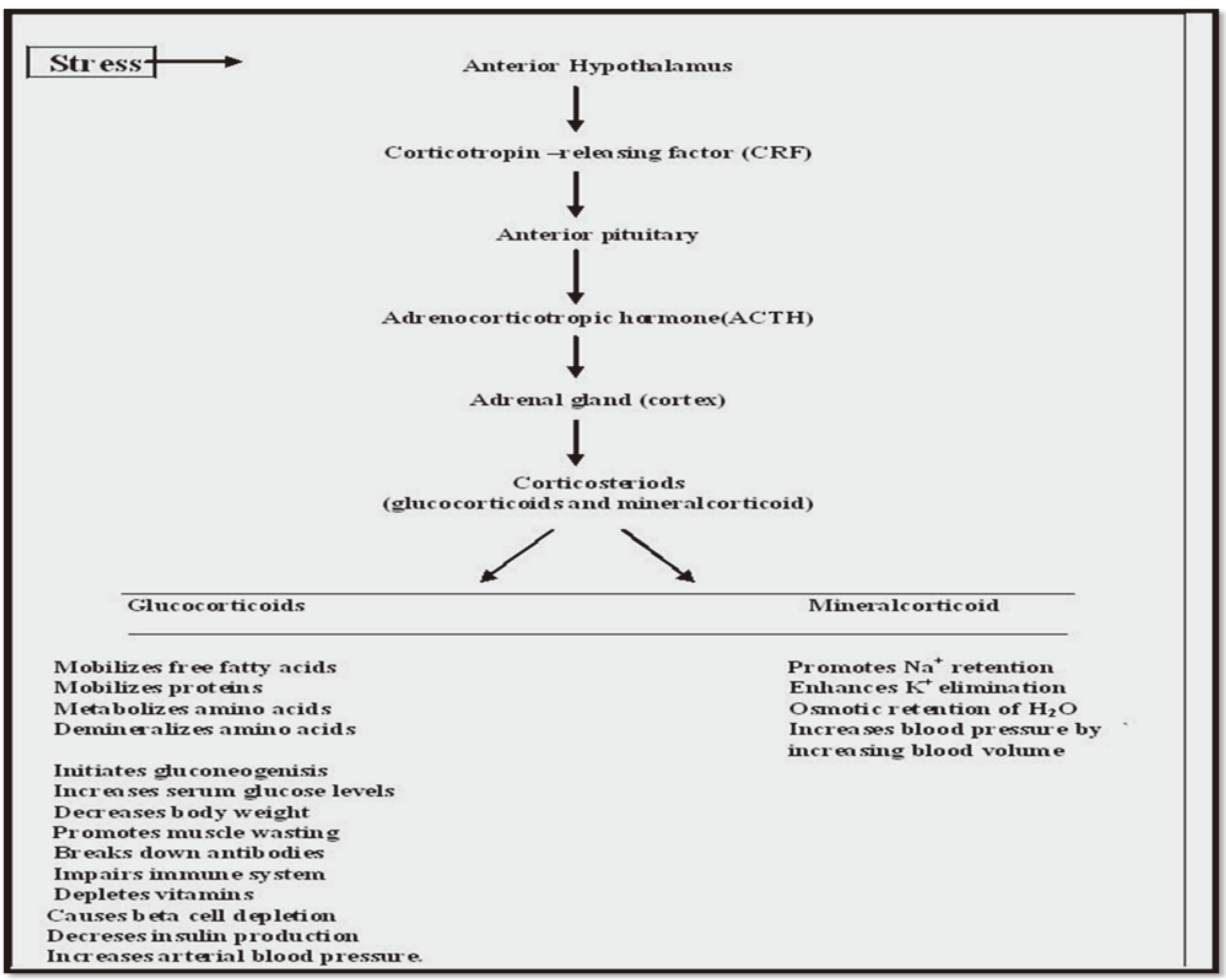


**Fig. 1.** Stress response on Hypothalamus-pituitary-adrenal (HPA) axis

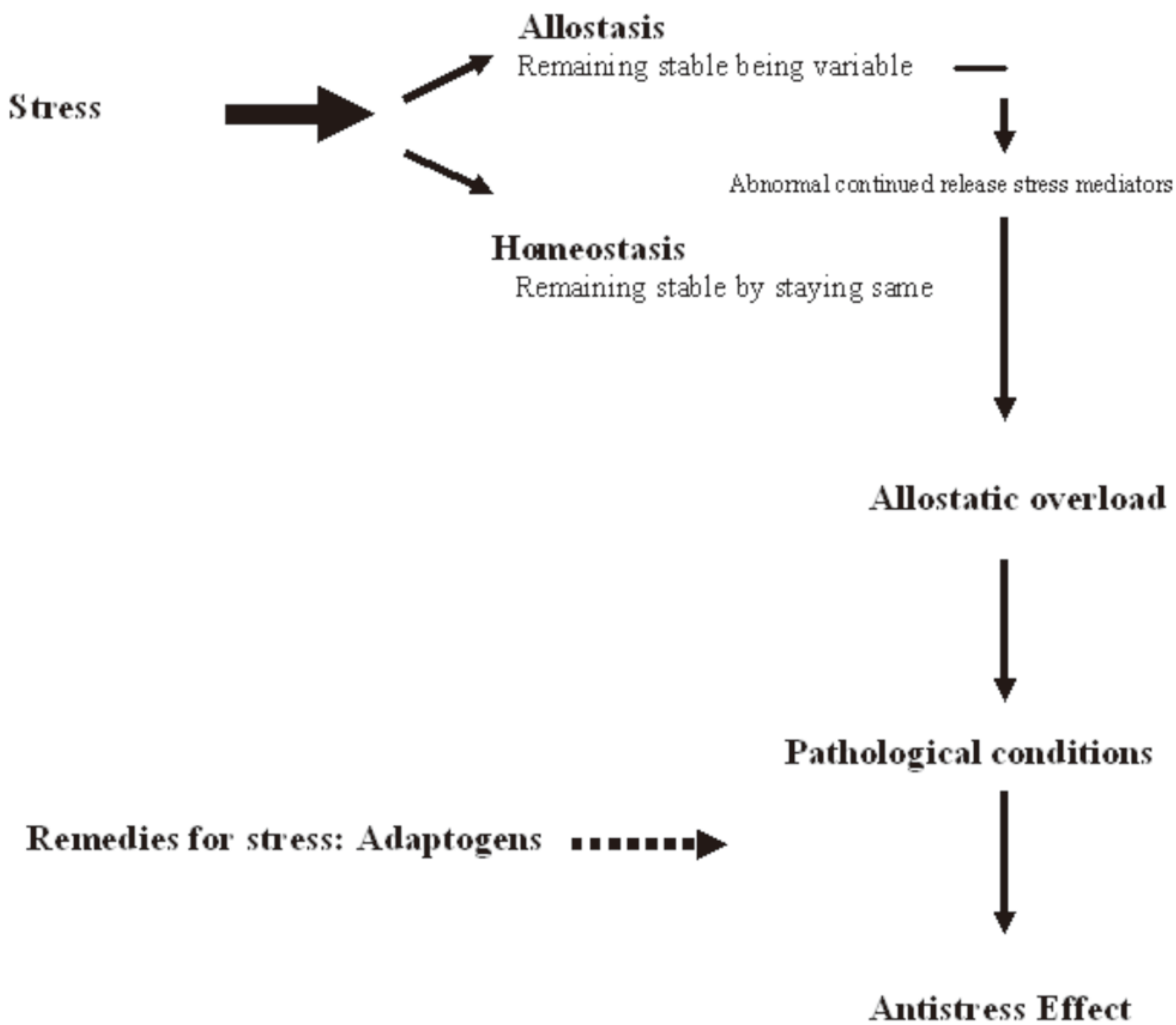


**Fig.2** The physiological response to stress

immunosuppression, inflammation, diabetes mellitus, peptic ulceration and other stress related disease [100]. One theory proposed by Dardymov and Kirkorian94 argues that adaptogens function primarily due to their antioxidant and free radical scavenging effects. While their theory is partially accurate, it is inadequate to explain the full effects of these medicinal.

### *3.2.2 CNS stimulatory effects*

The earliest studies of adaptogens were concerned primarily with demonstrating their ability to increase the mental and physical working capacity in humans [100,101,102,103] and in animals following administration of single or repeated doses [104,105]. It soon became clear, however, that there were very important differences [106] between the stimulating effects of adaptogens and those of other stimulants of the CNS and these are summarized in Table 3. Stimulants, defined as drugs that increase the activity of the sympathetic nervous system, produce a sense of euphoria and can be used to increase alertness and the ability to concentrate on mental tasks. Stimulants such as caffeine, nicotine, amphetamines and cocaine, are also used, and sometimes abused, to boost endurance and productivity. However, long-term stimulant abuse can impair mental function and lead to psychotic symptoms. Furthermore, traditional stimulants that possess addiction, tolerance and abuse potential, produce a negative effect on sleep structure, and cause rebound hypersomnolence or 'come down' effects. By definition, plant adaptogens do not exhibit such negative effects: in fact one plant adaptogen, that derived from Rhodiola rosea, has been shown significantly to regulate high altitude sleep disorders and to improve sleep quality [107]. Plant adaptogens stimulate the nervous system by mechanisms that are totally different from those of traditional stimulants, being associated rather with metabolic regulation of various elements of the stress system and modulation of stimulus-response coupling [94,108,109]

### *3.2.3 Effect on fatigue and cognitive functions*

Fatigue, also known as weariness, tiredness, exhaustion or lethargy is a common health complaint that may be generally defined as feeling of lack of energy. Physical fatigue is the inability to continue functioning at a level commensurate with normal ability. The mechanism of the anti-fatigue activity of

**Table 1**

List and details of the plants reported to have antistress (adaptogenic) activity

| Name of plant | Plant part and extract | Methods and Parameters | Ref No |
| --- | --- | --- | --- |
| *Aegle marmelos* (Rutaceae) | Standardized dried extract of whole plant | Swimming endurance time, post swimming motor function test, cold swimming endurance test and biochemical parameters | 21 |
| *Alstonia scholaris* R. Br. (Apocynaceae) | Methanoli extract of dried bark | Acute restraint stress induced alteration in biochemical parameters like corticosterone, glucose, protein, cholesterol and triglyceride level | 22 |
| *Allium sativum* (Alliceae) | 95% ethanolic extract of bulb | Swimming survival time and anoxia tolerance test | 23 |
| *Annona muricata* (Annonaceae) | Stem bark | Cold immobilization stress induced changes in brain neurotransmitters | 24 |
| *Argyreia speciosa* Burm .f (Convulvulaceae) | Ethanol, ethyl acetate fractions of root | Immobilization and swimming acute (3 days) and chronic (7 days) stress models | 25 |
| *Asparagus racemosus* | Aqueous and milk decoction of root | Forced swimming and chronic fatigue test | 26 |
| *Bacopa moniera* (Scrophulariaceae) | Standardized extract of aerial part | Acute (3 days) and chronic (7 days) immobilization stress induced variation in biochemical parameters and organs weight | 27 |
| *Bergenia crassifolia* (L) /Siberian tea (Saxifragaceae) | Fermented leaves | Forced swimming capacity and biochemical parameters (glucose, triglycerides, cholesterol, BUN) in mice | 28 |
| *Boerhaavia diffusa* (Nytiginacea) | Aqueous extract of root powder | E.coli induced abdominal sepsis, macrophage phagocytic activity in mice and cold and forced swimming stress in rat | 29 |
| *Butea monosperma* (Fabaceae) | Flower | Water soluble part of ethanolic extract of Butea monosperma on water immersion stress-induced ulceration, elevation of serotonin (5-HT) in brain and corticosterone in plasma in rats. | 30 |
| *Caesalpinia bonduc* (Caesalpiniaceae) | 95% ethanol extract of seed coat | Swimming endurance and cold stress for different biochemical parameters (glucose, triglycerides, cholesterol, BUN) | 31 |
| *Carum carvi* /caraway(Umbelliferae) | Aqueous extract of fruit materials | Forced swim stress one hour after daily treatment of Carum carvi extract. Urinary vanillylmandelic acid (VMA) and ascorbic acid were selected as non invasive biomarkers | 32 |
| *Chloropytum borivillianum* /Safed musli (Liliaceae) | Alcoholic , aqueous and successive tuber extracts of roots, leaves | Swim endurance , anorexic test and cold stress models (ulcer index, organ weight variation, BUN) | 33,34 |
| *Cnestis ferruginea*(Connaraceae) | Aqueous extract of dried root of Cnestis ferruginea whole plant | Anoxia tolerance test and immobilization stress induced gastric ulcers | 35 |
| *Diospyros peregrina gurke* (Ebenaceae) | Ethyl acetate extract of whole plant | Swimming performance, stress induced adrenal function changes and milk induced leucocytosis in mice | 36 |
| *Eleutherococcus senticous* | The 70% alcoholic extract of powdered roots of E senticosus | The methods employed for comparison of anti-stress activity were swimming endurance test, adrenal function test and tests for measuring anti-ulcer activity. | 37 |
| *Eugenia caryaphullus* /clove | Hydro alcoholic extract of buds | Cold restraint induced gastric ulcers, sound stress induced biochemical changes and anoxic stress induced convulsions | 38 |
| *Evolvulus alsinoides* (convolvulaceae) | Ethanolic extract of whole plant; bioactivity guided purification of n-BuOH soluble fraction from ethanol extract | Acute (immobilizing animals for 150min once only) and chronic unpredictable stress induced perturbations -biochemical estimations, estimation of glucose and CK, corticosterone | 39,40 |
| *Fagopyrum esculentum* (Polygonaceae) | The powdered drug (whole plant) was extracted with n-hexane, petroleum ether, ethanol and water separately. | The effect is assessed by swimming time and estimation of various biochemical parameters like glucose, cholesterol, triglycerides, cortisol and *BUN levels.* | 41 |
| *Ginkgo biloba* (Ginkgoacae) | Standardized leaf extract | Acute and chronic stress induced adrenal gland and stomach weight variation, scoring of ulcer index as well as biochemical parameters (glucose, triglycerides, cholesterol, BUN) | 42 |
| *Hibiscus cannabinus* (Malvaceae) | Methanolic extract of leaves | Swimming endurance time and anoxia stress induced convulsion in mice | 43 |
| *Hippophae rhamnoides* / seabuckthorn (Elaeagnaceae) | Aqueous lyophilized leaf extract | Cold-hypoxia-restraint (CHR) induced alteration blood malondialdehyde (MDA) levels and decrease in glutathione (GSH) and catalase (CAT) levels, biochemical and hematological parameters | 44,45 |

| | | | |
|---|---|---|---|
| *Hypericum perforatum* (Clusiaceae) | 50% ethanolic extract of dried leaves, flower & stem | Foot shock induced perturbations in behavior, suppressed male sexual behavior, cognitive dysfunction, gastric ulceration, weight variation in spleen and adrenal gland | 46 |
| *Labisia pumila* | Aqueous extract of leaves | Swimming induced fatigue, hypoxia time, swimming endurance, chronic restraint stress induced organ weight variation and alteration in ALT, lipid peroxidation, GSH | 47 |
| *Lagenaria siceraria* (Cucurbitaceae) | Ethanolic extract of shade dried, pulverized powder of fruits | Influence of forced swimming on swimming endurance, organ weights and changes is biochemical parameters in rats | 48 |
| *Mitragyna africanus* (Rubiaceae) | 50% methanolic extract of stem bark | Pentylenetetrazole induced convulsion and muscle relaxant effect | 49 |
| *Momordica charantia* | Aqueous extract of | Swimming time in mice, cold immobilization stress induced gastric ulceration, organs weight variation and levels of glucose, AST, ALT | 50 |
| *Morus alba* (Moraceae) | Methanolic extract of roots | Mild, unpredictable foot shock induced cognitive dysfunction, elevated plus maze, despair swim test and biochemical parameters, organ weight variation, ulcer index. | 51 |
| *Murraya koenigii*(Rutaceae) | Murraya koenigii extracted with Methanol, 50% ethanol and water | Weight loaded forced swimming test model used to determine the levels of serum glucose, triglyceride (TG), lactate dehydrogenase (LDH), blood urea nitrogen (BUN), muscle and liver glycogen contents and swimming endurance period were determined | 52 |
| *Mussanenda frondosa* (Rubiaceae) | Ethanolic extract of roots | In vitro antioxidant activity and restraint stress induced alteration in brain NE, DA, 5-HT, 5-HIAA levels | 53 |
| *Nigella sativa* (Ranunculacae) | Ethanolic extract of seeds | swimming endurance and anoxia tolerance time in mice, cold and Immobilization stress induced alteration in blood parameters and organ weight variation in rat | 54 |
| *Oscimum santum* (Lamiaceae) | 70% ethanol aqueous leaf extract | Swimming endurance (physical endurance), stress induced ulcers, CCl4 induced hepatotoxicity, milk induced leucocytosis | 55,56,57 |
| *Panax -ginseng* (Aralaceae) | Standardized root extract | Acute and chronic stress induced adrenal gland and stomach weight variation, scoring of ulcer index as well as biochemical parameters (glucose, triglycerides, cholesterol, BUN | 42,48 |
| *Polyalthia cerasoids* (Allonaceae) | Alcoholic extract of stem bark | Cold immobilization stress induced changes in lipid peroxidation, ascorbic acid, MAO in brain and liver, vit E levels | 24,59 |
| *Prunella vulgaris* (Lamiaceae) | Ethanolic extract of leaves | Swimming endurance, organ weights, biochemical parameters and anoxic tolerance test in mice | 60 |
| *Psidium guajava*(Myrtaceae) | Ethanolic extract of leaves | Anoxia stress tolerance, acute swimming endurance test, acute heat induced stress, chronic cold restraint stress induced stimulation of HPA, alteration in biochemical parameters, alteration in blood cell count | 61 |
| *Ptychopetalum olacoides Bentham* (Olacaeae) | Ethanolic extract of roots | Anxiety and glucose levels in mice exposed to unpredictable chronic stress , hypoxia time | 62 |
| *Pueiaria tuberosa Roxb* | 70% ethanolic extract of tuberous roots | Chronic foot shock (CS) induced physiological, neurobehavioral and neuropathological alterations in wistar rats. | 63 |
| *Rhodiola imbricata* (Crassulaceae) | Aqueous extract of roots | Cold-hypoxia-restraint (CHR) induced alteration inkidney function, lipid and hematological parameters | 64 |
| *Rhodiola rosea* (crassulaceae) | R. rosea hydroalcoholic extract | The extract was tested on antidepressant, adaptogenic, anxiolytic, nociceptive and locomotor activities at doses of 10, 15 and 20 mg/kg, using predictive behavioural tests and animal models. | 65 |
| *Rubia cordifolia* (Rubiaceae) | Alcoholic extract of roots | Restraint stress induced ulcers, whole brain content of dopamine, GABA, hydroxycorticosteroids | 66 |
| *Schizandra chinensis* | Standardized extract | Restraint stress induced variation in protein kinase, nitric oxide, cortisol, testosterone, prostaglandin E2, leukotrine B4 and thromboxane B2 were determined. | 67 |
| *Sida cordifolia* (Malvaceae) | Aqueous and alcoholic extracts of roots | Anoxia stress tolerance time in mice, Gravitational and heat stress induced changes in biochemical parameters and organ weights. | 68 |

| | | | |
|---|---|---|---|
| *Tinospora cordifolia* (Menispermacae) | Aqueous, alcohol, acetone and petroleum extract of stem | Swimming endurance test in mice | 69 |
| *Tinospora malabarica* (Menispermaceae) | Stem | Restraint stress induced altered biochemical parameters such as plasma electrolytes, metabolic substrates, enzyme activities, cell membtane dynamics using RBC and synaptosomal membranes | 55 |
| *Tribulus terrestris* (Zygophyllaceae) | Ethanolic extract of whole plant | Anoxia stress tolerance time, swimming endurance time, Immobilization and cold stress induced alteration in biochemical parameters and organ weights | 70 |
| *Trichopus Zeylanicus gaerth* (Trichopodaceae) | A glycol peptide lipid fraction from alcoholic extract whole plant | Swimming performance in mice, antifatigue effect, carrageenan induced edema in rats, swimming induced gastric ulceration, hypothermia, immobilization induced autoanalgesia, | 71 |
| *Trigonella foenom graecum* (Leguminosae) | Methanolic extract of seeds | Swimming endurance time, cold stress induced alteration in biochemical parameters and organ weights | 72,73 |
| *Tylophora indica*(Asclepiadaceae) | Aqueous extract of whole plant | Chronic cold restraint stress induced altered biochemical and physiological perturbations in rat | 74 |
| *Vitis vinifera* (Vitaceae) | Aqueous extract of riped seeds | Forced swim induced stress. Urinary VMA and ascorbic acid selected as markers | 75 |
| *Withania somnifera* (Solanaceae) | Aqueous ethanol (1:1) extract of root | Chronic stress induced hyperglycaemia, glucose intolerance, increase in plasma corticosterone, gastric ulceration, male sexual dysfunction, cognitive deficits, immunosupression and mental depression | 76 |
| *Zingiber officinale*(Zingiberaceae) | Ethanolic extract of rhizomes | Acute physical stress (swimming endurance time), chronic cold restraint stress (10 days) induced alteration in biochemical levels, alteration in blood cell count | 77 |

**Table 2**

List and details of the polyherbal formulations reported to be having antistress (adaptogenic) activity

| Polyherbal product | Brief product description and methods followed | Ref No |
|---|---|---|
| OCTA | An aqueous based liquid herbal preparation consisting of eight herbs evaluated using open label and uncontrolled clinical trial in individuals adversely affected by stress | 78 |
| Sitone (ST) | ST is a herbal formulation comprising herbs classified in Ayurveda as rasayanas, investigated against chronic unpredictable mild foot shock induced perturbations in behaviour, glucose metabolism, suppressed male sexual behaviour, immunosupression, and cognitive dysfunctions | 79 |
| AP-3000 | Polyherbal formulation containing Panax ginseng, Withania somnifera, Myristica fragrans, and Piper longum was evaluated for antistress and androgenic activity and was reported to possess significant activity associated with increased serum testosterone level | 80 |
| Geriforte | A herbal compound drug evaluated using anoxia stress tolerance induced convulsions | 81 |
| Trasina | Polyherbal formulation evaluated using immobilization, anoxia induced stress perturnations in rodents. | 82 |
| ADAPT- 232 | A fixed combination of three genuine (native) extracts of Eleutherococcus senticocus | 83 |
| AVM | AVM is a herbal formulation consisting of herbs traditionally used for centuries to promote and stimulate male health and sexual enjoyment evaluated against immobilization stress induced perturbations (biochemical and haematological parameters) in rats | 84 |
| OB-200G | The constituents of OB-200G included Garcinia cambogia, Commiphora mukul, Zingiber officinale, Piper longum, Gymnema sylvestre | 85 |
| Zeetress | The contents of Zeetress are W. Somnifera, O. Sanctum and E. Officinalis and it is evaluated by swimming endurance, stress induced gastric ulcers, levels of ascorbic acid, plasma corticsterone | 86 |
| Jawahir Mohra (JM) | Unani preparation containing a few herbal and animal ingredients investigated for antistress activity against physical (swimming and subsequently motor function), chemical (PTZ induced defecation and urination) and metabolic stimuli | 87 |
| Ranahansa Rasayana (RR) | A Sri Lankan classical compound rasayana formulation, referred in Ayurvedic Pharmacopoeia of Sri Lanka evaluated using forced swimming induced hypothermia, gastric ulcer | 88 |
| Arogh Plus | Arogh Plus an Ayurvedic polyherbal formulation manufactured by M/s. Rumi Herbals, Chennai subjected for a detailed randomized clinical trail carried out on volunteers under stress | 89 |
| Triphala Megaext | The herbs (T. chebula, T. bellerica, E. officinalis) mixed in 1:1:1 w/w, evaluated against forced swimming stress induced exhaustion, anoxia stress induced convulsion | 90 |
| Trikatu megaExt | The herbal (P. nigrum, P. longum, Z. officinale) drugs mixed in 1:1:1 w/w, evaluated against forced swimming stress induced exhaustion, anoxia stress induced convulsion | 91 |
| Vedic Calm | Vedic calm, a polyherbal formulation comprising of Bacopa monnieri, Centella asiatica, Evolvulus alsinides and many other related plants extracts, antistress activity was evaluated by cold immobilization induced stress | 92 |

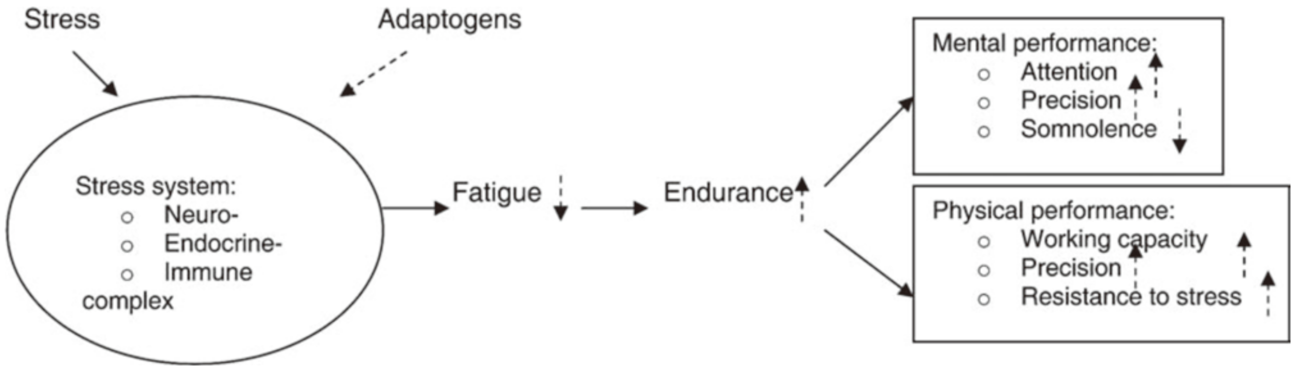


**Fig 3.** Effect of adaptogens on stress induced symptoms

adaptogens is associated with their effect on mediators of stress response especially cortisol, nitric oxide (NO), phosphorylated stress activated protein kinase and biosynthesis of ATP [110,111]. It has recently been demonstrated that activation of stress response results primarily in the increased expression of NO and cortisol. The formation of NO can strongly inhibit the production of cellular energy (ATP) in stress and fatigue [112].

**Table 3.**
The difference between adaptogens and other stimulants

| Parameters | Stimulants | Adaptogens |
|---|---|---|
| Recovery process after exhaustive physical load | Low | High |
| Energy depletion | Yes | No |
| Performance in stress | Decrease | Increase |
| Survival in stress | Decrease | Increase |
| Quality of arousal | Bad | Good |
| Insomnia | Yes | No |
| Side effects | Yes | No |
| DNA/RNA and protein synthesis | Decrease | Increase |

## 3. Conclusion

Recent pharmacological studies of some adapogens give a rationale to their effects at the molecular level. It has been shown that the beneficial stress-protective effect of adaptogens is related to the regulation of homeostasis via several mechanisms of action, which are associated with the hypothalamic-pituitary-adrenal (HPA) axis and the regulation of key mediators of the stress response, such as cortisol, corticosterone, nitric oxide(NO) etc. In summary, adaptogens may be regarded as a novel pharmacological category that:

•Reduce stress-induced impairments and disorders related to the function of stress v(neuroendocrine and immune) system.

•Iwnduce increased attention and endurance in situations of decreased performance caused by fatigue and/or sensation of weakness.

## References

[1] Ward Dean. Role of novel Russian adaptogenic compounds in restoration of adrenal function. Townsend letter for doctors and patients, Nov 2001.

[2] Elliot GR, Eisdorfer C. stress and human health. New York; Spinger Publishing; 1982.

[3] Trevor AJ, Way WL. Sedative-hypnotic drugs. Katzung BG, editor. Basic and clinical pharmacology. *New York: Lange Medical;* 2001: 364-381.

[4] Breakhman II, Dardymov IV. New substances of plant origin which increase non specific resistance. *Ann Rev Pharmacol* 1969: 419-21.

[5] Mills S, Bone K. Principles and practice of phytotherapy. UK: Churchill Livingstone.

[6] Trickey R. Women, hormones and the menstrual cycle. 2nd ed. Sydeny: 2003 Allen& Unwin.

[7] Shibata S, Tanaka O, Shoji J, Saito H. Economic and medicinal plant research. Edited by Wagner B, Hinkino H, Franswорth NR. London; Academic Press: 1985; 217.

[8] Sapolsky RM. Why zebras don't get ulcers. Freeman WHF and Co.New York. 1998.

[9] Benson H. the relaxation response. William Morrow and Co. Quill/ Harper Collins Publisher; New York. 1975 and 2000.

[10]Bill Moyers. Healing and the mind. Changing life habbits, interview with Dean Ornish. Public affairs television and David Grubin productions. Doubleday, New York.1993.

[11]Seyle H. Stress. Acta Medical Publisher: Montreal, Canada, 1950.

[12]Dilman Vladimir, Dean Ward. The neuroendocrine theory of aging and degenerative disease. The center for Bio-Gerontlogy, Pensacola, Flirida, 1992.

[13]Robyn Klein. Phylogenetic and phytochemical characteristics of plant species with adaptogenic properties. MS Thesis, Montana State University, 2004.

[14]Sterling P, Eyer J. Allostasis: A new paradigm to arousal pathology. Handbook of life stress, cognition and health. John Wiley & Sons, New York. 1988.

[15]Carrasco Gonzalo A, Van de Kar Louis D. Neuroendocrine pharmacology of stress. *European J Pharmacology* 2003; **463**: 235-275.

[16]McEwen Bruce S. mood disorders and allostasis load. *Biol Psychiatry* 2003; **54**: 200-207.

[17]McEwen Bruce S, Wingfield John C. The concept of allostasis in biology and biomedicine. *Hormones and Behavior* 2003; **43**: 2-15.

[18]Shulkin Jay. Rethinking ho,eostasis: allostatic regulation in physiology and pathophysiology. The MIT press, Cambridge. 2003.

[19]Davydov M, Krikorian AD. Eleutherococcus senticosus (Rupr & Maxim.) Maxim. (Araliaceae) as an adaptogen: a closer look. *J Ethnopharmacol.* 2000; **72**(3): 345-393.

[20]Brekhman II, Dardymov IV. New substances of plant origin which increase non-specific resistance. Ann Rev Pharmacol 1968, 8: 419-430.

[21]Duraisami R, Mohite Vijay A, Kasbe Amit J. Antistress, adaptogenic activity of standardized dried extract of Aegle marmelos against diverse stressors. *Asian J Pharmaceutical and Clinical Research* 2010; **3**(4): 1-3.

[22]Kulkarni Mrugaya P, Juvekar Archana R. Effect of Alstonia Scholaris Linn. R. Br. On stress and cognition in mice. *Indian J Expt Biol* 2008; **47**: 47-52.

[23]Roshan S, Khan Abdullah, Ali Sadath. To study the effect of Allium sativum on swimming endurance, anoxia tolerance and cold stress. *J Global Pharma Tech* 2010; **2**(7): 27-32.

[24]Padma P, Chansauria JPN, Khosa RL, Ray AK. Effect of Annova muricata and Polyalthia cerasoides on brain neurotransmitters and enzyme monoamine oxidase following cold immobilization stress. *J Nat Rem* 2001; **1**(2): 144-146.

[25]Habbu PV, Mahadevan KM, Kulkarni PV, Daulasingh C, Veerapur VP, Shastry RA. Adaptogenic and in vitro antioxidant of flavanoids and other fractions of Argyreia speciosa (Burm. f) Boj. In acute and chronic stress paradigms in rodents. *Inida J Exp Biol* 2010; **48**, January: 53-60.

[26]Garg R, Gupta VB. Adaptogenic activity of milk and aqueous decoction of Asparagus racemosus wild in acute and chronic stress paradigms in mice. *J Cell Tissue Research* 2010; **10**(2): 2281-2286.

[27]Gohil Kashmira J, Patel Jagruti A. A review on Bacopa monniera: Current research and future prospects. *International Journal of Green Pharmacy* 2010; **4** (1): 1-9.

[28]Alexander N Shikov, Olga N Pozharitskya, Marina N Makarova, Dormien Dorman HJ, Valery G Makarov, Raimo Hiltunen, Bertalan Galambost. Adaptogenic effect of black and fermented leaves of Bergenia crassiflia L in mice. *J Functional Foods* 2010; **2**: 71-76.

[29]Desai Sandhya K, Desai Soniya M, Navdeep S, Arya P, Pooja T. Antistress activity of Boerhaavia Diffusa root extract and a polyherbal formulation containing Boerhaavia Diffusa using cold restraint stress model. *INt J Pharm Pharm Sci* 2011; **3**(1): 130-132.

[30]Pal P, Bose S. Phytopharmacological and phytochemical review of Butea monosperma. *International Journal of Research in Pharmaceutical and Biomedical Sciences* 2011; **2**(3): 1374-1388.

[31]Kannur DM, Hukkeri VI, Akki KS. Adaptogenic activity of Caesalpinia bondue seed extracts in rats. *J Ethnopharmacol* 2006; **108**: 327-331.

[32]Sushruta Koppula, Spandana Rajendra Kopalli, Satyanarayana Sreemantula. Adaptogenic and nootropic activities of aqueous extract of Carum carvi linn (caraway) fruits: an experimental study in wistar rats. *Australian Journal of Medical Herbalism* 2009; **21**(3): 72-78.

[33]Gopalkrishna B, Akki KS, Patil SH, Hukkeri VI,. Preliminary phytochemical investigation and invivo antistress activity of Safed musli (Chlorophytum Borivillianum Linn.). *Indian Drugs* 2006; **43**(11): 878-880.

[34]Deore SL, Khadbadi SS. Screening of antistress properties of Chlorophytum borvilianum tumer. *Pharmacologyonline* 2009; **1**: 320-328.

[35]Ishola IO, Ashorobi RB. Antistress potential of aqueous root extract of Cnestis ferruginea. *International J Pharmacology* 2007, **3**(3): 295-298.

[36]Singh N, Nath R, Gupta ML. Pharmacological evaluation of antistress activity of Diospyos peregrina gurke. *Indian J Pharmacol* 1988; **20**: 102-108.

[37]Singh N, Verma P, Mishra N, Nath R. A comparative evaluation of some antistress agents of plant origin. *Indian J Pharmacol* 1991; **23**: 99-103.

[38]Singh Anand Kumar, Dhamanigi Sunil S, Asad Mohammed. Antistress activity of hydroalcoholic extract of Eugenia caryophyllus buds. *Indian J Pharmacol* 2009; **41**(1): 28-31.

[39]Singh Amritpal. Review of ethnomedicinal uses and pharmacology of Evlvulus alsinoides Linn. *Ethnobotanical Leaflets* 2010; **12**: 734-740.

[40]Gupta Prasoon, Akanksha, Siripurapu Kiran Babu, Ahmad Ausaf, Palit Gautam. Antistress constituents of Evolulus alsinoides: an ayurvedic crude drug. *Chem Pharm Bull* 2010; **55**(5): 771-775.

[41]Kothiyal Preeti, Ratan Parminder. Antistress effect of Fagopyrum esculentum in rats subjected to forced swimming endurance test. *Pharmacologyonline* 2011; **3**: 290-296.

[42]Deepak Rai, Gitika Bhatia, Tuhinadri Sen, Gautam Palit. Antistress effects of Ginkgo biloba and Panax ginseng: a comparative study. J *Pharmacol Sci* 2003; **93**: 458-464.

[43]Natraj GR, Nanjappaiah HM, Hugar Shivakumar. Evaluation of adaptogenic potential of Hibiscus cannabinus in acute stress induced mice. *Pharmacologyonline* 2011; **2**: 508-513.

[44]Saggu Shalini, Kumar Ratan. Effect of seabuckthorn leaf extracts on circulating energy fuels, lipid peroxidation and antioxidant parameters in rats during exposure to cold, hypoxia and restraint (C-H-R) stress and post stress recovery. *Phytomedicine* 2008; **15**: 437-446.

[45]Saggu S, Divekar HM, Gupta V, Sawhney RC, Banerjee PK, Kumar R. Adaptogenic and safety evaluation of seabuckthorn (Hippophae rhamnoides) leaf extract: A dose dependent study. *Food and Chemical Toxicology* 2007; **45**: 609-617.

[46]Vikas Kumar, Singh PN, Bhattacharya SK. Antistress activity of Indian Hypericum perforatum Linn. *Indian J Expt Biol* 2010; **39**: 344-349.

[47]Bani Sarang, Pandey Anjali, Kour Kiranjeet et al. Adaptogenic activity of Labisia pumila extract. PCT WO2010/147449 A1: 23 December 2010.

[48]Lakshmi BVS, Sudhakar M. Adaptogenic activity of Lagenaria siceraria: an experimental study using acute stress models on rats. *J Pharmacol Toxicol* 2010; 1-7.

[49]Aji BM, Effraim KD, Onyeyili PA. Antistress activity of Mitragyna africanus stembark extract. *The Sciences* 2001; **1**(3): 105-107.

[50]Sumanth Meera, Chowdary G. Antistress and immunomodulatory activity of aqueous extract of Momrdica charantia. *Pharmacog Magazine* 2009; **5**(19): 69-73.

[51]Nade Vanda S, Kawale Laxman A, Naik Rashmi A, Yadav Adhikrao V. Adaptogenic effect of Morus alba on chronic footshock induced stress in rat. *Indian J Pharmacol* 2009; **41**(6): 246-251.

[52]Saraf MN, Sonaye MM, Mengi SA. Antifatigue effect of Murraya koenigii. *Pharmacologyonline* 2011; **2**: 1025-1037

[53]Radical scavenging and antistress activity(s) of Mussaenda frondosa roots (rubiaceae). *Pharmacologyonline* 2011; **1**: 1991-1997.

[54]Roshan S, Khan Abdullah, Tazneem B, Ali Sadath. To study the effect of Nigella sative on various biochemical parameters on stress induced in rats. *International J Pharmacy and Pharmaceutical Sciences* 2010; **2**(4): 185-189.

[55]Anju. Adaptogenic and antistress activity of Ocimum sanctum in mice. Research Journal of Pharmaceutical, *Biological and Chemical Sciences* 2011; **2**(3): 670-678.

[56]Singh V, Amdekar S, Verma O. Ocimum sanctum (tulsi): Bio-pharmacological activities. WMC001046. 2011 webmedecentral.com: 1-7.

[57]Bhargava KP, Singh N. Antistress activity of Oscimum santum Indian j Med Res 1981; **73**, March: 443-451.

[58]Nocerino Emilia, Amato Marianna, Izzo Angelo A. The aphrodisiac and adaptogenic properties of ginseng. *Fitoterapia* 2000; **71**: S1-S5

[59]Padma P, Chansauria JPN, Khosa RL. Polyalthia cerasoides- a possible antistress drug. *Indian J Nat Prod* 2000; **16**(1): 20-23.

[60]Giri Mrudula, Mallikarjuna Rao P, Jayaveera KN. Evaluation of adaptogenic activity of Prunella vulgaris. *International J Pharmaceutical Sci Rev and Res* 2011; **1** May-Jun: 62-65.

[61]Lakshmi BVS, Sudhakar M. Screening of Psidium guajava leaf extracts for antistress activity in different experimental animal models. *Phcog Res* 2009; **1**(6): 359-366.

[62]Piato AL, Detanico BC, Linck VM, Herrmann AP, Nunes DS, Elisabetsky E. Antistress effect of the tonic ptychopetalum olacoides. *Phytomedicine* 2010; **17:** 248-253.

[63]Pramanik SS, Sur TK, Debnath PK, Bhattacharya D. Effect of Pueraria tuberose tuber extract on chronic foot shock stress in wistar rats. Nepal Med Coll J 2010; **12**(4): 234-238.

[64]Gupta V, Saggu S, Tulsawani RK, Sawhney RC, Kumar R. A dose dependant adptogenic and safety evaluation of Rhodiola imbricata Edgew, a high altitude rhizome. *Food and Chemical Toxicology* 2008; **46**: 1645-1652.

[65]Marina Perfumi, Laura Mattioli. Adaptogenic and central nervous system effects of single dosage of 3% rosavin and 1% salidroside Rhodiola rosea L. extract in mice. *Phytother Res* 2009; **21**(1): 37-43.

[66]Rupali A Patil, Swati C Jagdale, Sanjay B Kasture. Antihyperglycemic, antistress and nootropic activity of roots of Rubia cordifolia Linn. *Indian J Expt Biol* 2006; **44**: 987-992.

[67]Alexander Panossoan, Marin Hambardzumyan, Areg Hovhanissyan. The adaptogens Rhodiola and Schizandra modify the response to immobilization stress in rabbits by suppressing the increase of phosphorylated stress activated protein kinase, nitric oxide and cortisol. *Drug Target Insights* 2007; **1**: 39-54.

[68]Sumanth Meera, Mustafa SS. Antistress, adaptogenic activity of Sida

cordifolia roots in mice. *Indian Journal of Pharmaceutical Sciences* 2009; **71**(3): 323-324.

[69]Upadhyay Avnish K, Kumar Kaushal, Kumar Arvind, Mishra Hari S. Tinospora cordifolia (wild) Kook. F. and Thoms (Guduchi)- validation of the Ayurvedic pharmacology through experimental and clinical studies. *Int J Ayurveda Res* 2010; **1**(2): 112-121.

[70]Shivakumar H, Talha Javed, Prakash T, Nagendra Rao, Jayakumar Swamy BHM, Veerana Goud A. Adaptogenic activity ethanolic extract of Tribulus terrestris Linn. *J Nat Rem* 2006; **6**(1): 87-95.

[71]Singh B, Gupta DK, Chandan BK. Adaptogenic activity of glycopeptido-lipid fraction from the alcoholic extract of Trichopus zeylanicus gaertn. *Phytomedicine* 2001; **8**(4): 283-291.

[72]Pawar VS, Shivakumar H. Antistress activity of Trigonella foenum graecum Linn seeds using swimming endurance and cold stress in rodents. *Indian drugs* 2011; **48**(2): 56-61.

[73]Pawar Vinod S, Hugar Shivakumar. Adaptogenic activity of Trigonella foenum graecum (linn) seeds in rodents exposed to anoxia and immobilization stress. *Asian Pacific J Tropical Biomedicine* 2012: S208-S211.

[74]Kulkarni Mrugaya P, Juvekar Archana R. Effect of roots of Tylophora indica (Burm.f.) on stress and anxiety in animal models. *Internet J Pharmacol* 2010; **8**(2):

[75]Satyanarayana Sreemantula, Srinivas Nammi, Rajabhanu Kolanakonda, Sushruta Koppula, Krishna M Boini. Adaptogenic and neotropic activities of aqueous extract of Vitis vinefera: an experimental study in rat model. *BMC complementary and alternative Med* 2005; **5**: 1-11.

[76]Tiwari Shireen, Sahni YP. Antistress activity of Withania somnifera (Ashwagandha) on solar radiation induced heat stress in goats. *Indian Journal of Small Ruminants* 2012; **18**(1): 64-68.

[77]Lakshmi BVS, Sudhakar M. Attenuation of acute and chronic restraint stress induced perturbations in experimental animals by Zingiber officinale Roscoe. *Food and Chemical Toxicology* 2010; **48**: 530-535.

[78]Dugald Seely, Rana Singh. Adaptogenic potential of a Polyherbal natural health product: report on a longitudinal clinical trial. *eCAM* 2007; **4**(3): 375-380.

[79]Salil K Bhattacharya, Arunabh Bhattacharya, Amit Chakrabarti. Adaptogenic activity of Siotone, a polyherbal formulation of Ayurvedic rasayanas. *Indian J Expt Biol* 2000; **38**: 119-28

[80]Nimbakar SR, Patki VP, Patki MP. Pharmacological evaluation of antistress and androgenic activity of polyherbal formulation AP 3000, containing Panax ginseng. *Indian Drugs* 2001; **38**: 27-31.

[81]Tomar VS, Singh SP, Singh N, Kohli RP. Effect of Geriforte a herbal compound drug on anoxic stress tolerance in animals. *Indian Drugs* 1984; 233-35.

[82]Bhattacharya SK. Evaluation of adaptogenic activity of Trasina, an Ayurvedic herbal formulation, edited by Mukherjee B, Traditional medicine. Oxford and IBH Publishers; *Delhi* 1993: 320.

[83]Alexander Panossian, Georg Wilman, Punit Kaur, Alexzander Asea. Adaptogens exert a stress-protective effect by modulation of expression of molecular chaperones. *Phytomedicine* 2010; **16**: 617-622.

[84]Shaik Azmathulla, Hule Amolkumar, Naik Suresh Ramnath. Evaluation of adaptogenic activity profile of herbal preparation. *Indian J Expt Biol* 2011; **44**: 574-579.

[85]Kaur Gurupreet, Kulkarni SK. Differential effects of a polyherbal formulation OB-200G in male and female swim stress *Indian J Pharmacol* 2010; **44**(3): 281-9.

[86]Bhattacharya SK, Ghosal S. Experimental evaluation of antistress activity of an herbal formulation Zeetress. *Indian J Indigenous Med* 1994; **10**(2): 1-8.

[87]Ahmad Ghufran, Yusuf Amin KM, Khan Naeem A, Tajuddin. The antistress activity of a gem containing Unani formulation against diverse stressors. *J Ethnopharmacol* 1998; **59**: 187-193.

[88]Somarathna K Indrajith WK, Chandola HM, Ravishankar B, Pandya KN, Attanayaka AMP, Ashok BK. Evaluation of adaptogenic and antistress effexts of Ranahamsa Rasayana a Sri Lankan classical Rasayana drug on experimental anilal. *AYU* 2010; **31**(1): 88-92.

[89]Anoop Austin, Elsie CS, Thirugansambantham P. Evaluating the clinical efficacy of a polyherbal formulation Arogh Plus on stress -a randomized clinical study. *J Stress Physiol & Biochem* 2011; **7**(1): 66-78.

[90]Sonkar Rinki, Mishra RN. Adaptogenic activity of Triphala Megaext. *International J Research in Pharmaceutical and Biomedical Sciences* 2011; **2**(1): 106-109.

[91]Jain Neha, Mishra RN. Adaptogenic activity of Trikatu megaExt. *International J Research in Pharmaceutical and Biomedical Sciences* 2011; **2**(2): 570-573.

[92]McCarty R. Stress neurochemical and humoral mechanisms. Edited by Van Loon GR, Kventnansky. NY; Gordan and Breach Science Publishers: 1989; 3.

[93]Wink Michael. Biochemistry of plant secondary metabolisms. 1999 Vol 2, Sheffield Academic Press, Ltd

[94]Panossian A. Adaptogens, tonic herbs for fatigue and stress. *Alternative and Complementary Therapies* 2003; **9**(6): 327-31.

[95]Slama Karel. Ecdysteroids: insect hormones, plant defensive factors or human medicine. *Phytoparasitica* 2010; **21**(1): 3-8.

[96]Bouic Pratick JD. Sterols and sterolins: new drugs for the immune sustem. *Drug Discovery Today* 2010; **7**(14): 775-778.

[97]Munck A, Guyre PM, Holbrook NJ. Physiological functions of glucocorticoids in stress and their relation to pharmacological actions. *Endocrine Rev* 1984; **5**: 25-44.

[98]Dewick Paul M. Medicinal natural products: a biosynthetic approach. *John Wiley & sons ltd.* 2012 West Sussex.

[99]Blee Elizabeth. Phytooxylipins and plant defense reactions. *Progress in lipid Research*. 2010; **37**(1): 33-72.

[100]Maxwell SRJ. *Drugs* 2011; **49**: 347.

[101]Panossian A, Wikman G, Wagner H,. Plant Adaptogens Ш, Earlier and More Recent spects and Concepts on Their Mode of Action. *Phytomedicine* 1999: **6**(4): 287-299.

[102]Medvedev MA. Effect of Ginseng and Eleutherococcus on working parameters of radio-telegraph operators. In Materials of Studies of Ginseng and other Medicinal Plants of Far East, Brekhman II, Belikov IF, Kurentsova GE (eds), Issue 5. Primorye Publishing Press: *Vladivostok*, 1963: 237-239.

[103]Dalinger OI. Effect of Eleutherococcus extract on functional state of cardiovascular system and working capacity of skiers. In Stimulants of the Central Nervous System, Saratikov AS (ed.). Tomsk University Publishing Press: Tomsk, 1966: 106-111.

[104]Tuzov SF. Comparative characteristics of the effect of some CNS stimulants on muscular capacity on men in Stimulants of the Central Nervous System, Saratikov AS (ed.). Tomsk University Publishing Press: Tomsk, 1968: 156-161.

[105]Lebedev AA. 1971. Schizandra. Meditsina Publishing House of USSR: Tashkent.

[106]Lapajev II. 1978. Schizandra and its Curative Properties, 3rd amended andsupplemented ed. Khabarovsk Book Press: Khabarovsk.

[107]Fulder S. The drug that builds Russians. *New Scientist* 1980: **21**: 83-84.

[108]Ha Z, Zhu Y, Zhang X. The effect of Rhodiola and acetazolamide on the sleep architecture and sleep blood oxygen saturation of persons living at 5380 meters above sea level. *Chin J Tuberc Resp Dis* 2010; : 1-6.

[109]Wagner H, Norr H, Winterhoff H.. Plant adaptogens. *Phytomedicine* 2010; **1**: 63-76.

[110]Wiegant FAC, Surinova S, Ytsma E, Langelaar Makkinje M, Wikman G, Post JA.Plant adaptoges increase life span and stress resistance in C. elegans. *Biogerontology* 2010; **10**: 27-42.

[111]Abidor M, Crendal F, Grachev S, Seifulla R, Ziegenfuss T. Effect of extracts from R. rosea and R. crenulata roots on ATP content in mitochondria of skeletal muscle. *Bull Exp Biol Med* 2011; **136**: 585-587.

[112]Panossian A, Wikman G. Evidence based efficacy of adaptogens in fatigue and molecular mechanisms related to their stress protective activity. *Current Clinical Pharmacology* 2011; **4**(3): 198-219.