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Review Article

POTENTIAL CLINICAL BENEFITS OF ADAPTOGENS OR RESISTOGENS IN STRESS RELATED DISORDERS

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ABSTRACT

Chronic stress depresses immune functioning and increases susceptibility to disease. Some of the problems that can be induced by stress include digestive disorders, autoimmune diseases, anxiety, depression, panic attacks, memory impairment, and chronic fatigue syndrome. Adaptogens are a unique class of medicinal plants which help, restore balance of cortisol and protect the body against stress. Studies on animals and isolated neuronal cells have revealed that adaptogens exhibit neuroprotective, anti-fatigue, antidepressive, anxiolytic, nootropic and CNS stimulating activity. The use of adaptogens has also been demonstrated in sports ,post-menopausal women ,men with erectile dysfunction and in depression. The aim of this literature review is to summarize and analyze recent research conducted on Adaptogens.
Key words: Adaptogens, Stress, Resistogens

INTRODUCTION

Cortisol, is a glucocorticoid which is released from the adrenal gland under different conditions of stress. Stress stimulates the Hypothalamus which in turn stimulates the pituitary and finally the adrenal glands to release cortisol. While it is important for the body and adrenal glands to secrete more cortisol in response to stress, it is equally essential that functions of the body and cortisol levels return to normal after the stressful event. However, under current chronic high – stress culture the stress response is activated very often resulting in increased circulating levels of cortisol. These high levels of cortisol lead to problems related with health [1]. Increased cortisol levels have an effect on the physiological system including thyroid and adrenal glands This in turn results in anxiety , irritability, weight gain ,dampened thyroid function, slow wound healing ,elevated blood pressure, bone loss ,diabetes, autoimmune diseases , cold , irritable bowel , cancer , hormone imbalance , increased abdominal fat and increases risk for heart disease ,cardiovascular abnormalities memory impairment, digestive disorders, autoimmune diseases and chronic fatigue syndrome memory impairment, digestive disorders, autoimmune diseases and chronic fatigue syndrome and is also a causative factor for male infertility [2-6].As people age, they experience an increase in their baseline levels of cortisol. Independent of this, cortisol levels rise additionally late in the perimenopausal period[7]

Vasomotor symptoms including hot flashes and night sweats were found to be most severe in those with increased cortisol levels in comparison to women without increased cortisol. Further, postmenopausal women had larger increases in cortisol after a laboratory-induced psychosocial stressor compared to premenopausal women [8,9] .Elevated cortisol levels in older women have been associated with lower bone density[10] ,minor cognitive complaints[11] and risk factors for cardiovascular disease such as insulin resistance and decreased high density lipoprotein-cholesterol levels[12] (23).Sleep Deprivation, Caffeine, and Alcohol all increase cortisol levels [13,14].Studies have also suggested that elevated cortisol levels, probably seeded by stressful life events, may lower brain 5-HT function and this in turn leads to the manifestation of the depressive state [15].In chronic stress, prolonged secretion of cortisol causes muscle wastage, hyperglycemia, and suppresses immune/inflammatory responses[16, 17]

Adaptogens

Adaptogens are a unique class of medicinal plants that improve the response to stress [18] . They help the body to adapt by normalizing physiological processes in times of increased stress [19]. Adaptogens appear to exert their antistress effects by regulating homeostasis via the hypothalamic pituitary adrenal (HPA) axis and inhibiting or decreasing circulating levels of nitric oxide (NO) and cortisol. It may be proposed that adaptogens adapt (i.e. render less sensitive) an organism to a stressor by acting rather like a low molecular weight “vaccine” in inducing a mild activation of the stress system in order to cope with a more severe stress [20].It has been proposed that , adaptogens act as mild stressors or stress-mimetics and , give bring about adaptive and stress-protective effects mainly associated with the HPAaxis, a part of the stress system that also contributes to the cardiovascular, gastrointestinal immune, nervous, and endocrine systems. 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 molecular chaperons, heat shock proteins (e.g., Hsp70), stress-activated c-Jun N-terminal protein kinase (JNK1), Forkhead box O (FoxO) transcription factor, cortisol and nitric oxide (NO) [21]. Recent studies indicate that certain adaptogenic substances can activate the protective mechanisms of cells, which is associated to an increase survival rate both *in vitro* and *in vivo.*[22-25]

Use of Adaptogens

The normal pattern of one drug for one disease is not suitable for adaptogens as they can have many pharmacological effects and indications. Adaptogens exhibit pharmacological profiles, which are divergent but have common stress-protective action. Therefore, all these pharmacological effects can be combined into the groups associated with stimulating and stress protective effects in CNS and vegetative nervous systems, endocrine system and immune system, comprising by definition the parts of neuroendocrine-immune complex - stress-system.

Antitoxic activity of Adaptogens

It has been reported that adaptogens induced state of nonspecific resistance to highly toxic chemicals (e.g cyclophosphane, , phosphorus aniline, strychnine, chlorophos ,sodium nitrite, narcotics like, hexenal, chloralhydrate, benzene,acetone, sodium barbital, ether, etc.) and microbes demonstrated in many pharmacological/toxicological studies ,actually implies that they have an anti-toxic activity[27].

Adaptogens in Sports& Exercise

A recent review of published studies has shown that Adaptogens regulate the internal environment and tend to maintain the body stable, what is called as Homeostasis, and thus, achieve greater athletic performance to physical and mental stress.Some of the Adaptogens Plants; Schizandra chinensis, , Eleutherococcus senticosus , Panax ginseng and Erkang formula, have shown, in most of studies, encouraging results in improved physical performance, to be applied to sportsmen[28].

Use of Adaptogens in Post Menopause syndrome

Recent studies indicate the use of adaptogens in post menopause syndrome. "Adaptogens help cope with many facets of menopause, from increasing serotonin, to replacing estrogen, to enabling greater physical activity to assist weight control and fitness, rectify cognitive difficulties, providing a mechanism for general protein repair, and reducing cortisol and stress to improve the quality of life. Taken together, the evidence in support of the safety and efficacy of the treatment of menopausal symptoms with a program of adaptogenic herbs shows the validity of this approach among the options available to women and their health care practitioners **"**Adaptogenic plants contain phytoestrogens, like schizandrin. Phytoestrogens are natural "selective estrogen receptor modulators" due to the diphenolic rings in their structures which resemble the estrogen hormones. They bind to estrogen receptor sites on human cells, thus acting as either partial estrogen agonists or antogonists, depending on the concentrations of endogenous estrogens .The proponents of herbal medicines have formulated commercially available adaptogen containing products designed to balance cortisol, thereby reducing body fat, increasing energy, and ameliorating mood swings, thus decreasing the symptoms of declining estrogen associated with the stages of perimenopause and menopause. With stress and increased cortisol levels playing such an important role in the development of menopausal symptoms, and the clear advantage of the adaptogen option for treatment, it becomes important to look at what they do on a generalized basis[29].

Use of Adaptogens in HIV

Adaptogens are of particular importance for supporting the health of individuals with HIV, AIDS, cancer, autoimmune disorders and chronic illness. There is a permissible role for the use of both herbal medicines and allopathic drugs in the health maintenance and treatment of individuals with HIV, AIDS, cancer and chronic illness has been reported . Although some research has been conducted specifically on herbal medicine and HIV, most available data discusses the benefit plant medicine has on general immune system enhancement.Adaptogenic drugs are used to help the body cope with stress, improve resistance to infection and enhance immune system, increase physical and mental endurance, boost vitality and function, their balancing actions help maintain optimal organ function within the body and can be used in conjunction with allopathic medicine, often minimizing side effects caused by many drugs. Extensive clinical research shows that Siberian Ginseng assists the bodies' response to stress by supporting the adrenal glands and modifies the physiological response to stress, help in exhaustive states and overwork. It is a helpful to the elderly and can improve endurance and stamina in conditions of chronic disease. Animal experiments suggest that Eleutherococcus

offers many balancing actions to both hyper and hypoglycaemia and can be used for both hypertrophy and atrophy of the adrenal glands[30].

Adaptogens in cancer:

Certain adaptogenic plants like Eleutherococcus Senticosus (ES) have been reported to be used in the support of cancer patients undergoing radiation and chemotherapy ,especially in Germany. Studies have shown that ES when administered to patients, drastically reduces the side effects of radiation and chemotherapy .(e.g nausea , weakness, fatigue , dizziness and loss of appetite) . Other research with cancer patients has linked Eleutherococcus Senticosus with improved healing and recovery times ,increased weight gain and improved immune cell count .In Russia ,the administration of ES to cancer patients seemed to permit larger than normal doses of drugs utilized in chemotherapy , thus speeding up the treatment periods .Siberian Ginseng offers support in cancer therapy, helping to prevent secondary infection and improve the bodies' ability to withstand the negative side effects of drug therapies used in conventional medical treatment. Clinical studies conducted with Reishi recognize an enhanced T cell activity , increased macrophage activity , increased production of leucocytes in the bone marrow, and in addition Reishi contains anti bacterial properties to staphylococci and streptococci bacteria (opportunistic bacteria) [30-31].

Adaptogens are reported to improve the quality of life (QoL) in general, to have specific therapeutic effects in some stress-induced and stress-related diseases and to have positive impact on the QoL of patients when implemented as adjuvants in the standard therapy of several chronic diseases and pathological conditions

Use of Adaptogens in Erectile dysfunction

It has been reported that adaptogenic therapy can be promoted in erectile dysfunction[32] A paper deals compilation of informative data on Ethnobotanical plants on the basis of phytochemicals indicating their antioxidant, aphrodisiac, adaptogenic properties (3A's) and establish their correlation in order to correct sexual disability. Thus, this paper reviews the recent informative data on ethnobotanically used aphrodisiac plants having adaptogenic antioxidant potential for the management of erectile dysfunction[32].

Use of adaptogens in Adrenal Maladaptation:

Role of adaptogenscan be advocated in adrenal dysfunction as Adrenal dysfunction may be manifested by (1) an excess or inadequacy of cortisol, DHEA, ACTH and/or CRF (2) relative imbalances of these hormones and releasing factors, and (3) loss of sensitivity of the hypothalamus and pituitary to the normal inhibiting effects of these hormones.Symptoms of patients suffering from adrenal maladaptation include Fatigue Nervousness Severe PMS,Salt craving,Depression, Inability to concentrate, Carbohydrate craving, Allergies (hay fever, asthma),Anxiety, Headache,Alcohol intolerance, Muscular pain and tenderness Joint pains and tenderness (arthritis), Weakness, Poor memory Palpitation,Abdominal discomfort,Alternate diarrhea and constipation,Obesity,Poor wound healing, Glucose intolerance, Moon face,Purple striae, Loss of bone density[33]

Adaptogens in CNS Stimulatory activity , Endocrine system and Immune system

Stress protective effects of adaptogens in CNS ,vegetative nervous systems, endocrine system and immune system, consists by definition the parts of neuroendocrine-immune complex - stress-system has been studied [34]. Adaptogens *Eleutherococcus senticosus*, *Rhodiola rosea* and

Schisandra chinensis have reported Hepatoprotective ,Cardioprotective Gastroprotective, Oxidative stress/Radioprotective Anti-atherosclerosis, Vasodilatatory/hypotensive Anti-hyperglycemic Anti-inflammatory/allergy Immunotropic Antidepressive Anxiolytic activities in vitro or animal studies .[26,54] With regards to the NeuroendocrineSystem , it has been reported that the above reported adaptogens have reduced Physical fatigue, Mental fatigue(declined attention) , Stress induced chronic fatigue and Depression.Regulatory system such as Central and vegetative nervous system ,Endocrine system & Immune system have reported Stimulating effect ,Stress-mimetic and stress-protective effectsby the adaptogen *Schisandra chinensis* .[26.54]

CNS Stimulatory Effect

Apparently, stimulating (acute/single dose effect) and tonic (effect of repeated/multiple administration) effects of adaptogens are actually consequences of their stress-protective activity. CNS stimulating and tonic effects of adaptogens are well documented in numerous publications and reviewed in *Phytomedicine*

In contrast to ephedrine, fenfluramine, phentermine, prolintane which are conventional stimulants, the adaptogens are devoid of addiction, tolerance and abuse potentials, they don't impair mental function and lead to psychotic symptoms in long term use. The clinical and pharmacological activities of these are due to the differences in the mode of action. Their stimulating effect is more pronounced against a background of fatigue and stress[35-38].

Immunotropic and anti-tumor effects of adaptogens.

Adaptogen herbs are used to increase physical and mental endurance, boost vitality and helpthe body cope with stress, improve resistance to infection and enhance immune system function, their balancing actions help maintain optimal organ function within the body and canbe used in conjunction with allopathic medicine (prescription medicine), often minimizing side effects caused by many drugsImmunotropic and anti-tumor effects of plant adaptogens have been reported [39].

Active compounds: Plant constituents that are responsiblefor adaptogenic properties are classified into triterpenes ,phenylpropanes and oxylipins[40].

Triterpenes: Adaptogens are reported to be complex phenolics or tetracyclic triterpenoids/ steroids. These also include phytosterols and phytoecdysteroids, which have been reported to have adaptogenic roles in mammals and in humans. These are structurally similar to the corticosteriods which are stress hormones involved in the inactivation of the stress system and in protecting the organism from over reaction in response to stressors [43] .The active components play key roles in the HPA axis-mediated regulation of the immune and neuroendocrine systems [41-42].

Phenyl propanes: Plant adaptogens like *R. rosea*, *S. chinensis* and *E. senticosus* exhibit a stimulating effect .they are reported to contain high amounts of 28 compounds mainly phenylpropane or phenyl ethane derivatives which have a structure similar to the catecholamine, and are the mediators of the sympathoadrenal system and CNS systems. They are involved in activation of the stress system in the intial stages of stress response .Phynylpropane compound like salidroside, rosavin, rosin, rosarin and tyrosol are reported to be present in*Rhodiola rosea*[44].

Oxylipins: Oxylipins are polyunsaturated fatty acids synthesized by plants via the acetate pathway and then oxidized by the lipoxygenase pathway to produce compounds called

oxylipins 45 which are believed to play an important role in plants as signaling molecules in plant resistance against insects and pathogens. The precursor of plant oxylipins is linoleic acid. Although these physiological functions in plants are under investigation their biological roles seem to be comparable to those of the eicosanoid compounds in mammals. These compounds are involved in inflammation, infection, allergy, and exposure to xenobiotics. The polyhydroxylated oxylipins from the adaptogenic species, *Bryonia Alba*, are proposed to be responsible for its adaptogenic activity.

Administration of the amino acid tyrosine, which is a common precursor of biosynthesis of tyrosol, salidroside and catecholamines, alleviates both stress-induced depletion of brain catecholamines (norepynephrine and dopamine in the alarm phase of stress syndrome) and reduces fatigue has been reported in animals. A number of clinical studies suggest that supplementation of tyrosine might improve stress-induced (e.g., cold, noise, anxiety and fatigue) accuracy of mental performance [46,47]

Clinical Evaluation of Antistress and Stimulating Activity of Adaptogens :

Pharmacological evaluation of adaptogens includes stimulating, tonic and stress-protective activities in model animal systems under various stress conditions [48,49]. The stress protective effect of adaptogens has also been demonstrated on simple organisms as well as on isolated cells [50-53]

Mechanism of Action of Adaptogens [54]

The stress protective effect of Adaptogens is exerted by regulating homeostasis via several mechanisms of associated with the hypothalamic pituitary adrenal(HPA) axis and sympathoadrenal system (SAS)

Fig 1: Response to stress by the Hypothalamic Pituitary _ Adrenal axis (HPA axis) .In situations of chronic stress the mechanism of negative feed back in lost . Adaptogens restore the function of the axis .

Stress

↓

Hypothalamus

↓CRH (Corticotropin Releasing factor)

Anterior Pituitary gland

↓ACTH (Adrenocorticotropic Harmone)

Adrenal gland → Cortisol

Molecular mechanism . [55,56]

It has been reported that the stress protective activity of adaptogens at the molecular level was associated with the regulation of homeostasis linked with Hypothalamic pituitary-adrenal axis and the mediators involved in the regulation ofhomeostasis at c have been identified to be heat shock proteins (e.g., HSP70), stress-activated c-Jun N-terminal protein kinase 1(JNK1), such as phosphorylated stress-activated protein kinase (p-SAPK), Forkhead box O (FOXO) transcription factor DAF-16, cortisol and nitric oxide.Reviews reveal that adaptogens decrease NO, cortisol and JNK under stress and stimulate/activate the expression of Hsp70 and p-FoxO1. The stimulation of Hsp70 biosynthesis is a key point in the mechanism of action of adaptogens since the heat shock protein: increases the restoration of damaged proteins, inhibits the stress-induced

expression of NO genes . ATP is increased to normal levels in the adapted cell. Normal Glucocorticoid receptor function and normal ATP levels are associated with the anti-fatigue and anti-depressive effects of adaptogens and with normal cognitive functions like good attention, memory and learning.ATP is also required for the normal functioning of heat shock proteins (e.g., Hsp70). FoxO Forkhead protein that controls the synthesis of proteins involved in stress resistance, cell survival and longevity .Adaptogens work like a stress vaccine (stress-mimetic) by activating stress-induced self-defence mechanisms in order to adapt the cell and organism to mitigate stress-induced harmful effects. It is also believed that the key point of action of adaptogenic herbs may be due to be their upregulating and stress mimetic effects on the 'stress sensor' proteinHsp70, which plays an important role in cell survival and apoptosis. Hsp70 affects circulating levels of nitric oxide and cortisol by inhibiting expression of NO synthase II gene and interacting with glucocorticoid receptors directly and via the JNK pathway.

Summary

Adaptogens may be considered as a unique category of drugs that reduce stress-induced impairments and disorders related to the function of neuroendocrine and immune systems and also induce attention and endurance in situations of decreased performance caused by fatigue and/or weakness. It was suggested that adaptogens have not only specific therapeutic effects in some stress-induced and stress-related disorders, but may have an effect on the quality of life of patients when implemented as adjuvants in the standard therapy of many chronic diseases and pathological conditions including, , chronic obstructive pulmonary disease, post-surgery recovery ,congestive heart failure. Adaptogens may also have potential use in age related disorders, such as neurodegenerative diseases, and cardiovascular diseases. These may also help the elderly in maintaining their health status on a normal level, improve quality of life and increase longevity. The evidence in support of the safety and efficacy of the treatment of menopausal symptoms with a program of adaptogenic herbs shows the validity of this approach among the options available to women and their health care practitioners.

Current research and way forward

Today, research into adaptogens comprises the following four areas: (a) phytochemistry: isolation and structure elucidation of active constituents of adaptogenic plants; (b) biochemistry and molecular biology: mechanisms of stress protective activity of adaptogens on the molecular and cellular levels; (c) experimental and clinical pharmacology: efficacy and safety of adaptogens in stress related disorders on animals and humans; (d) pharmaceutical development of herbal preparations/products.Further studies may be required to evaluate the clinical efficacy of adaptogens and toelucidate molecular mechanisms of action of these complex herbal extracts and their active principles.

Table 1: Some of Developments and studies indicating the progress in the field of Adaptogens Similar findings have been reported by Vinod et al in their study. The present study findings are in conformity with the findings of the above study and with additional developments[57]

Name of the Medicinal plant	*Common name*	*Part*	*Model used*	*Reference*
*Abutilon Indicum (*Malvaceae)	*Atibala*	*Ethanolic extract*	*Swimming survival time and estimation of various biochemical parameters ,cold stress induced ulcer*	58
*Abutilon muticum (*Malvace)	*Karandi*	*Methanolic extract of seed*	*Swim Endurance Test*	59
Aeglemarmelos (Rutaceae)	*Bael*	*Whole plant Extract*	*Swiining endurance , Post swimming motor function test ,cold swimming endurance test*	60 .
Alstoniascholaris (Apocynaceae)	*Pulai*	*Methanolic extract of dried bark*	*Acute restraint test and alteration in biochemical parameters*	61
*Alliumsativum*Amaryllidaceae)	*Garlic*	95% ethanolic extract of bulb	*Swimming survival time and anoxia tolerance test*	62
Annonamuricata Annonaceae)	*Custard apple*	*Stem bark*	*Cold immobilization stress induced changes in brain neurotransmitters*	63
Argyreiaspeciosa(Convulvulaceae)	*Vidhara*	*Ethanol,ethyl acetate fractions of root*	*Forced swimming and chronic fatigue test*	64
Asparagusracemosus (Asparagaceae)	*Shatavari*	*Aqueous decoction of root*	*Improved the stress tolerance in chemical writhing test and swimming endurance test*	65
Bergenia crassiolia Saxifragaceae)	*Siberian tea*	*Fermented leaves*	*Forces swimming capacity , Biochemical parameters (BUN , Cholesterol, Glucose and triglycerides)*	66
Butea monosperma(Fabaceae)	*Palash Tree*	*Flower*	*Water immersion stress induced ulceration*	67
Buchanania lanzan(Anacardiaceae)	*Priyal a*	*Ethanolic extract of the leaves*	*Urinary VMA and ascorbic acid*	68
Boehavia diffusa(Nytiginacea)	*Punarnava*	*Aqueous extract of the eroot*	*E. Coli induced abdominal sepsis ,macrophage phagocytic activity and cold and forced swimming test*	69
Bacopamoniera(Scrophulariaceae)	*Brahmi*	*Standardizedextractofaerial*	*Acute and chronic immobilization stress induced variation in biochemical parameters*	70

Caesalpinia bonduc Caesalpiniaceae)	*Kantkarej,*	*Ethanolic extrac to f the seed coat*	*Swimming endurance and cold stress for biochemical estimation*	71
*Cicer arietinum*Fabaceae)	*Chickpea*			72
Carum carvi (Umbelliferae	*Caraway*	*Aqueous extract of the fruits*	*Forced swimming test*	73
*Centella Asiatica (*Apiaceae)	*Brahma manduki*	*Aqueous extract of the leaves*	*Tail Suspension Test (TST), Phenobarbitone Induced Sleeping Time in mice:*	74
Chloropytumborivillianum(Liliaceae)	*Safed musli.*	*Alcojolic and Aqueous extracts of root and leaves*	*Swim endurance, anorexic test and cold stress model*	75
Cnestisferruginea (Connaraceae)	*Senegal*	*Aqueous extract of the root*	*Anoxia tolerance test and immobilization stress induced gastric ulcers*	76
Diospyrosperegrina(Ebenaceae	*Tinduka*	*Ethyl acetate extract of the whole plant*	*Swimming performance, stress induced adrenal function test*	77
Eleutherococcu ssenticous (Araliaceae)	*Siberian Ginseng*	*Alcoholic extract of the roots*	*Swimming endurance test ,adrenal function test ,antiulcer activity*	78
Eugeniacaryaphullus (Myrtaceae)	*Clove*	*Hydro alcoholic extracts of buds*	*Cold restrain induced gastric ulcers , Anoxic stress tolerance and sound stress induced biochemical changes*	.79
Evolvulusalsinoides convolvulaceae)	*Shankhpushpi*	*Ethanolic extract of the whole plant*	*Acute immobilizing stress and biochemical estimations*	80,81
F a g o p y r u m e s c u l e n t u m Polygonaceae)	*Buckwheat*	*Whole plant*	*Swimming time and biochemical estimations*	82
Glycyrrhiza glabra Fabaceae)	*Licorice*	*Root*	*Forced swimming endurance test and chronic cold restraint stress.*	83
Ginkgo biloba (Ginkgoacae)	*Fossil Tree*	*Leaf extract*	*immobilization stress, biochemical alteration*	84
*Holoptelea integrifolia (*Ulmaceae)	*Indian Elm*	*Stem bark*	*Forced Swimming endurance stress and Cold restrain Induced ulcers*	85
Hibiscus cannabinus (Malvaceae)	*Kenaf*	*Methanolic extract of leaves*	*Anoxic stress tolerance time and Swimming endurance time*	86
H i p p o p h a e rh a m n o i d e s Elaeagnaceae)	*Sea-buckthorn*	*Aqueous leaf extract*	*Cold hypoxia induced restrain stress alterations in biochemical parameters*	87
Hypericum perforatum (Clusiaceae	*St John's wort*	*Dried leaf and stem*	*Weight variation in spleen and adrenal gland*	88
*Inula racemosa (*Asteraceae)	*Nagapala*	*Ethanolic extract of powdered roots*	*Forces swimming studies and biochemical studies*	89

*Luffa cylindrcia (*Cucurbitaceae)	*Ridge gourd*	*Ethanolic extract of the fruits*	*Anoxia tolerance test Swimming endurance* *cold restraint stress in rats.*	90
Labisiapumila Primulaceae *)*	*kacip fatimah*	Aqueous extract of leaves	*Swimming induced fatigue , hypoxia time , swimming endurance , chronic restrain stress & organ weight variation*	91.
Lagenaria siceraria (Cucurbitaceae)		*Ethanolic extract of the fruits*	*Forced swimming test , , Swimming endurance and organ weight alterations*	92
Mikania micrantha Kunth	*Bitter Vine*	*aqueous extract of roots*	*Anoxia stress tolerance and swimming endurance time*	93
*Moringa oleifera (*Moringaceae)	*Drumstick*	*Ethanolic extract of the leaves*	*Swimming endurance , cold restraint induced ulcers organ weight of adrenal glands and spleen*	94
Mitragyna africanus Rubiaceae)		*50% Methanolic extract to the stem bark*	*Pentylenetetrazol induced convulsion, Muscle Relaxant activity by Inclined Board Method*	95
*Momordica charantia (*Cucurbitaceae0	*Bitter melon*		*Swimming time , organ weight variation , Cold immobilization stress induced alterations in biochemical parameters*	96
Morus alba (Moraceae)	*White mulberry*	*Methanolic extract of the roots*	*Swim test and biochemical parameters*	97
Murraya koenigii (Rutaceae)	*Curry leaves*	*Methanol ,50% ethanol*	*Swimming endurance and forced swimming induced alterations in the e biochemical parameters*	98
Mussanenda frondosa (Rubiaceae)	*Bebina,*	*Ethanolic extract of the roots*	*Restrain Stress induced changes in the biochemical parameters*	99
Nigella sativa (Ranunculacae)	*kalonji*	*Ethanolic extract of the seeds*	*Swimming endurance test and Anoxic stress tolerance . Cold and Immobilization stress induced alterations in the biochemical parameters*	100
Ocimum santum (Lamiaceae	*Tulsi*	*70%Ethanol aqueous leaf extract*	*Swimming endurance and stressinduced ulcers*	101
Phyllanthus niruri (Phyllanthaceae)	*Tamalaki*	*Whole plant*	*Forced swimming endurance test, Cold stress model*	102
*Puinca granatum*Lythraceae)	*Anar*	*Hydroalcoholic extract of Peel and Juice*	*Forced swimming endurance test*	103
Panax-ginseng (Aralaceae)	*Five finger,*	*Root extract*	*Acute and chronic stress induced changes in the adrenal gland , Biochemical variations*	104
Polyalthia cerasoids (Allonaceae)		*Alcoholic extract of the*	*Cold immobilization stress induced*	105

		stem bark	changes	
Prunella vulgaris (Lamiaceae)	*self-heal*	*Ethanolic extract to f the leaves*	*Swimming endurance , anoxic stress induced changes*	106
Psidium guajava (Myrtaceae)	*Guava*	*Ethanolic extract of the leaves*	*Anoxic stress induced changes Swimming endurance , chronic cold restrain stress*	107
Ptychopeta lumolacoides (Olacaeae)	*Muira puama*	*Ethanolic extract to f the roots*	*Glucose and anxiety levels in mice , hypoxia time*	108
Pueiaria tuberosa (Fabaceae)	*kudzu*	*70% Ethanolic extract of the roots*	*Chronic foot shock and neurobehavioral and neuropathlogical changes*	109
Rhodio laimbricata (Crassulaceae)		*Aqueous extract of the roots*	*Cold hypoxia restrain induced changes in the kidney function .*	110
Rhodio larosea (Crassulaceae)	*Rose root*	*Hydroalcholic extract*	*Predictive behavioural test*	111
Rubia cordifolia (Rubiaceae)	*Manjistha*	*Alcoholic extract of the roots*	*Restrain stress induced ulcers and whole brain content of dopamine*	112
*Solanum xanthocarpum (*Solanaceae)	*Kantkari*	*Whole plant extract*	*Forced Swimming test and Cold Restraint stress*	113
Sida cordifolia (Malvaceae)	*bala*	*Aqueous and alcoholic extracts of root*	*Anoxia stress tolerance time in mice*	114
*Schizandra chinensis (*Schisandraceae)		*Standardized extract*	*Restrain stress induced variation in protein kinase . Measurement of Biochemical parameters cortisol and NO*	115
Trigonella foenum graceum (Leguminosae)	*Methi*	*Methanolic extract of the seeds*	*Swimming endurance time and cold stress induced changes in the biochemical parameters*	116 ,117
Tinospora cordifolia (Menispermacae)	*Guduchi*	*Aqueous alcoholic acetone and petroleum ether extract of the stem bark*	*Swimming endurance test in mice*	118 .
Tribulus terrestris (Zygophyllaceae)	*Burra gokharu*	*Ethanolic extract of the whole plant*	*Anoxic stress tolerance test , swimming endurance time ,Immobilization and cold stress induced changes in the biochemical parameters*	119
Trichopus Zeylanicus gaerth (Trichopodaceae)		*A glycol peptide lipid fraction from alcoholic extract of the whole plant*	*Swimming endurance test, and antifatigue erect*	120
Tylophora indica (Asclepiadaceae)	*Antamul*	*Aqueous extract of whole plant*	*Chronic cold restraint stress induced*	121

			biochemical changes	
Vitis vinifers (Vitaceae)	*Grapes*	*Aqueous extract of the riped seeds*	*Urinary VMA and ascorbic acid*	122
Withania somnifera(Solanaceae)	*Ashwagandha*	*Aqueous ethanol extract of root*	*Chronic stress induced hyperglycaemia,, gastric ulceratiob Corticisterone stimation ,*	123
Zingiber officinale (Zingiberaceae)	*Ginger*	Ethanolic extract of rhizomes	*Swimming endurance time , Chronic Cold restraint stress*	124

Table2: List and details of the polyherbal formulations reported to behaving antistress (adaptogenic) activity

OCTA	open label and uncontrolled clinical trial in individuals adversely affected by stress	125
Sitone(ST)	ST is a herbal formulation comprising herbs classified in Ayurveda as rasayan as, investigated against chronic unpredictable mild foot shock induced perturbations in behaviour, glucose metabolism, suppressed male sexual behaviour, immunosupression, and cognitive dysfunctions	126
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	127
Geriforte	A herbal compound drug evaluated using anoxia stress tolerance induced convulsions	128
Trasina	Polyherbal formulation evaluated using immobilization, anoxia induced stress perturnations in rodents.	129
ADAPT–232	A fixed combination of three genuine (native) extracts of *Eleuthero coccussenticocus*	130
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	131
OB–200G	The constituents of OB–200G included *Garcinia cambogia,Commiphora mukul, Zingiber officinale,Piper longum*	132
Zeetress	The contents of Zeetress are *W.Somnifera, O.Sanctum* and, *E.Officinalis* and it is evaluated by swimming endurance, stress induced gastriculcers ,levels of ascorbicacid, plasmacorticsterone	133
JawahirMohra(JM) :	Unani preparation containing a few herbal and animal ingredients investigated for antistress activity against physical swimming and subsequently motorfunction), chemical (PTZ induced defecation and urination) and metabolic stimuli	134
Ranahansa Rasayana	Was also evaluated for anti-stress activity	135
Arogh Plus	AroghPlusanAyurvedicpolyherbalformulationmanufacturedby M/s.RumiHerbals,Chennaisubjectedforadetailedrandomizedclinicaltrailcarriedoutonvolunteersunderstress	136
TriphalaMega ext	Theherbs(T.chebula,T.bellerica,E.officinalis)mixedin1:1:1w/w,evaluatedagainstforcedswimmingstressinducedexhaustion,anoxiastressinducedconvulsion	137
Trikatumega Ext	The herbal (P.nigrum,P.longum,Z.officinale)drugsmixedin1:1:1w/w,evaluatedagainstforcedswimmingstressinducedexhaustion ,anoxiastressinducedconvulsion	138
Vedic Calm	polyherbalformulationcomprisingofBacopamonnieri,Centellaasiatica,Evolvulusalsinidesandmanyotherrelatedplantsextracts,antistressactivitywasevaluatedbycoldimmobilizationinducedstress	139

CONCLUSION :

Stress is a physiological condition that is linked with various disorders of the neuroendocrine-immune system.Adaptogens were initially defined as substances that enhance the "state of nonspecific resistance" in stress. Evaluation of adaptogenic activy on animals and isolated neuronal cells have revealed that adaptogens exhibit neuroprotective, anti-fatigue, antidepressive, anxiolytic, nootropic and CNS stimulating activity. In addition, several clinical trials demonstrate that adaptogens exert an anti-fatigue effect increasing the mental work capacity against a background of stress and fatigue, particularly in mental exhaustion and enhanced attention. Indeed, recent pharmacological studies of a number of adaptogens have provided a rationale for these effects also at the molecular level. Some of the most interesting developments are studies that clearly indicate that certain adaptogenic substances can activate the protective mechanisms of cells both in vitro and in vivo.

Adaptogens can be viewed as tonics and are prescribed to enhance vitality and are indicated when stress levels are high, during convalescence after surgery or illness, or during periods of challenging or difficult life changes (events).

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