ADAPTOGENIC AGENTS: A REVIEW

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SUMMARY

Adaptogens are the plant-derived biologically active substances that appear to induce a state of non-specific increase of resistance of the organism to diverse assaults that threaten internal homeostasis and improve physical endurance.[1]Supplementation with various macro and micronutrients and herbal preparations has been evaluated for their adaptogenic activity during exposure to a stressful environment.[2] Stress research in laboratory animals has assumed an important role in understanding the biological and behavioral consequences of external or internal stressors, which threaten to perturb homeostatis and may induce a number of clinical diseases when the body fails to counteract the stress situations. A variety of stress situations have been employed to investigate the consequences of stress and to evaluate antistress agents. The pharmacological assessment of adaptogens typically includes evaluation of their stimulating, tonic and stress protective effects in different screening models in which animals are challenged to acute and chronic stress conditions. Stress mediators and biochemical markers involved in mechanism ofadaptogens may be evaluated using experimental procedures.[3]

KEY WORDS: Adaptogen, Stress, Herbs

1. INTRODUCTION

An adaptogen is a herb product that is a plant derivative. Scientifically unproven, yet marketed as a supplement to increase resistance to stress, trauma, anxiety and fatigue. The term is used mainly by herbalist who also refer to adaptogens as rejuvenating herbs, tonics, rasayanas, or restoratives. One specific characteristic of adaptogen action is that its effect is believed to help the body return to a balanced state. However, there is no strict definition of the adaptogenic characteristics of a plant product, leading to a generalized usage of the term for commercial or pseudoscientific reasons.Some herbalists claim that adaptogenic herbs are distinct from other substances in their ability to balance endocrine harmones and the immune system, and that they help the body to maintain optimal homeostasis.Adaptogens are known to have side effects including increased heart rate, nausea, headaches, trouble sleeping, and restlessness. Possible effects in women may include swollen breasts and vaginal bleeding.

TABLE 1: PLANTS USED IN ADAPTOGENIC ACTIVITY

S.No	HERBAL PLANTS	COMMON NAME	PARTS USED	Reference no.
1.	*Withania somnifera*	Ashwagandha	Root	4
2.	*Panax ginseng*	Ginnsuu	Root	15
3.	*Panax ginseng*	Ginnsuu	Root	29
4.	*Caesalpinia bonduc*	Nickernuts	Seed	5
5.	*Hippophae rhamnoides*	Sea-buckthorn	Berry	6
6.	*Hippophae rhamnoides*	Seabuckthorn	Leaf	16
7.	*Garcinia kola*	Bitter kola	Seeds	7
8.	*Trichopus zeylanicus*	Arogya pacha	Leaf	8
9.	*Rhodiola imbricata*	Roseroot	Root	9
10.	*Rhodiola rosea*	Roseroot	Root, Rhizome	21
11.	*Bacopa monniera*	Brahmi	Leaf	10
12.	*Evolvulus alsinoides*	Sankhapushpi	Leaf	11
13.	*Hoppea dichotoma*	Hoppea	Root	12
14.	*Bergenia crassifolia*	Siberian Tea	Leaves	13
15.	*Butea frondosa*	Palash	Leaves	14
16.	*Panax quinquefolium*	Redberry	Root	15
17.	*Zingiber officinale*	Zingiber	Rhizome	17
18.	*Eleutherococcus senticosus*	Touch-me-not	Plant	18
19.	*Asparagus racemosus*	Shatavari	Root	19
20.	*Hypericum perforatum*	Klamath weed	Plant	20
21.	*Ptychopetalum olacoides*	Muira puama	Plant	22
22.	*Ocimum sanctum*	Tulsi	Leaves	23
23.	*Schisandra chinensis*	Bail	Plant	24
24.	*Eclipta alba*	Takasaburou	Plant	25
25.	*Azadirachta indica*	Neem	Leaves	26
26.	*Sutherlandia frutescens*	Balloon pea	Plant	27
27.	*Acanthopanax senticosus*	Touch-me-not	Plant	28

28.	*Curcuma longa*	Turmeric	Rhizome	30
29.	*Tinospora cordifolia*	Guruchi	Plant	31
30.	*Psidium guajava*	Guava	Leaf	32
31.	*Momordica charantia*	Bitter Melon	Plant	33
32.	*Sida cordifolia*	Bala	Root	34
33.	*Morus alba*	Mulberry	Root	35
34.	*Centella asiatica*	Gotu Kola	Plant	36
35.	*Camellia sinensis*	Green tea	Plant	37
36.	*Eugenia caryophyllus*	Clove	Bud	38
37.	*Tribulus terristris*	Gokshura	Plant	39
38.	*Raponticum carthamoides*	Maral root	Plant	40
39.	*Piper longum*	Long Papper	Plant	40
40.	*Terminalia chebula*	Myrobalan	Plant	40
41.	*Clitoria ternatea*	Butterfly pea	Plant	41
42.	*Ginkgo biloba*	Maidenhair tree	Rhizome	42
43.	*Heteropterys aphrodisiaca*	Brazilian plant	Plant	43
44.	*Astragalus membranaceus*	Milk-vetch	Plant	44
45.	*Curculigo orchioides*	Kali Musli	Rhizome	45
46.	*Tridax procumbens*	Coat buttons	Flower	46
47.	*Allium sativum*	Garlic	Rhizome	47

1.1. *Withania somnifera:*

(WS) Dunal is classified in Ayurveda, the ancient Hindu system of medicine, as a rasayana, a group of plant-derived drugs reputed to promote physical and mental health, augment resistance of the body against disease and diverse adverse environmental factors, revitalise the body in debilitated conditions and increase longevity. These attributes are remarkably similar to the properties ascribed to adaptogens like *Panax ginseng* (PG) in contemporary medicine. As such, the adaptogenic activity of a standardised extract of WS roots was investigated against a rat model of chronic stress (CS). The stress procedure was mild, unpredictable footshock, administered once daily for 21 days to adult male Wistar rats.[4]

1.2. *Caesalpinia bonduc*:

Caesalpinia bonduc Roxb. (Caesalpiniaceae) seed extracts were screened for adaptogenic activity using cold stress model and swim endurance model,the seed coat as well as kernel extracts showed significant antistress activity when administered orally at a dose of 300 mg/kg. The extracts

significantly increased the swim endurance time. Stress induced animals exhibited hypoglycaemia as well as depletion in serum cortisol level and increased total leukocyte count, the extracts showed a significant action in overcoming these imbalances .It was also found that extracts proved efficient in controlling the hyperlipidaemic condition due to stress.[5]

1.3. *Hippophae rhamnoides*:

The present study was carried out to investigate mechanism of adaptogenic activity of seabuckthorn dry leaves aqueous lyophilized extract, administered in rats at a dose of 100 mg/kg body weight prior to cold (5 °C)–hypoxia (428 mm Hg)–restraint (C–H–R) exposure up to fall of T_{rec} 23 °C and recovery (T_{rec} 37 °C) from C–H–R induced hypothermia. The effect of extract treatment was studied on key metabolic regulatory enzymes in blood, liver and muscle and tissue glycogen in rats on attaining T_{rec} 23 °C and post stress recovery of T_{rec} 37 °C. In control rats during C–H–R exposure on attaining T_{rec} 23 °C there was significant decrease in enzyme activities of blood hexokinase (HK), citrate synthase (CS) and glucose-6-phosphate dehydrogenase (G-6-PD), liver CS, and in muscle glycogen, and CS and G-6-PD activities. In control rats on recovery of T_{rec} 37 °C there was also a significant decrease in liver and muscle glycogen levels along with decreased enzyme activities of blood G-6-PD, liver CS, and liver and muscle G-6-PD. The results suggest that seabuckthorn extract treatment caused a trend for shifting anaerobic metabolism to aerobic during C–H–R exposure and post stress recovery.[6]

1.4. *Garcinia kola*:

Garcinia kola Heckel (family, Guttifereae) , known in commerce as 'bitter cola', is a highly valued ingredient in African traditional medicine. The plant is cultivated throughout West Africa for its edible fruit and seeds. Seeds of *G. kola* have been employed in folk medicine as rejuvenating agents and general antidotes. Bitter cola seeds have been shown to contain a complex mixture of biflavonoids, prenylated benzophenones and xanthones. Many pharmacological effects have been demonstrated for Garcinia biflavonoids, among them antiviral, anti-inflammatory, antidiabetic, bronchodilator, and antihepatotoxic properties. Other studies show that its antimicrobial activity is due to polyisoprenylated benzophenone. Some proprietary dietary supplements containing *G. kola* extractives already exist in US and African markets.Additionally, the proprietary products are discussed and evaluated as they relate to efficacy and human safety.[7]

1.5. *Trichopus zeylanicu:*

Anti-stress activity was carried out on glyco-peptido-lipid (AF) fraction from the alcoholic extract of *Trichopus zeylanicus* Gaerten and demonstrated against a battery of tests in rats and mice. AF exhibited significant anti-stress activity in dose-related manners in all the parameters studied against different models used to induce non-specific stress viz physical and chemically. The major parameters studied were immobilization induced gastric ulceration, adjuvant-induced trauma (Stress); humoral antibody synthesis in normal and immuno-suppressed mice and delayed type of hypersensitivity (DTH) reaction, chemically stress-induced alteration in

hepatic function and anti-oxidant activity.The extract of *Withania somnifera* root (a commercial preparation available locally, Dabur India ltd.) was used to compare the results. In the safety evaluation study the maximum tolerance dose (MTD) and oral LD_{50} were found to be more than 3000 mg/kg, with no signs of abnormalities or any mortality observed for 15 days period under observation after single dose of drug administration. Feeding behaviour and fecal output were normal[8].

1.6. *Rhodiola imbricate:*

To examine the dose dependent adaptogenic activity aqueous extract of *Rhodiola imbricata* root was orally administered in rats at different doses, 30 min prior to cold (5 °C)–hypoxia (428 mm Hg)–restraint (C–H–R) exposure. The maximal effective adaptogenic dose of the extract was 100 mg/kg body weight. The acute and sub-acute toxicity of the extract was also studied in rats. Sub-acute toxicity studies included administration of single oral dose of 1 g/kg and 2 g/kg of extract once daily for 14 days and maximal effective single oral dose of 100 mg/kg once daily for 30 days. At the end of each treatment period the biochemical parameters related to liver function, kidney function, lipids (triglycerides, cholesterol) and hematological parameters were estimated in serum and blood. Biochemical and hematological analysis showed no significant changes in any of the parameters examined in treated group's animal, in comparison to control animals[9].

1.7. *Bacopa monniera*:

As stress is linked to many diseases, research on an effective antistress agent (adaptogen) from plants has gained importance. We report the investigations on the adaptogenic property of a standardized extract of *Bacopa monniera* against acute (AS) and chronic stress (CS) models in rats. Panax root powder (*Panax quinquefolium*) was taken as a standard. Male SD rats, weighing 180–200 g, exposed to immobilization stress for 150 min once only for AS and for seven consecutive days in CS, were fed with *B. monniera* or Panax root powder daily for 3 days in AS and for 7 days in CS, 45 min prior to each exposure of stress. Rats were sacrificed immediately after stress, the blood was collected, and the plasma was separated out for biochemical estimation. Adrenals, spleen, and thymus were dissected for organ weight and stomach for ulcer score. AS exposure significantly increased the ulcer index, adrenal gland weight, plasma glucose, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and creatine kinase (CK) but significantly decreased the spleen weight. Pretreatment with *B. monniera* at 40 mg/kg po significantly reduced the AS-induced increase in the ulcer index, adrenal gland weight, plasma glucose, AST, and CK. A dose of 80 mg/kg po significantly reversed the AS-induced changes in adrenal gland weight, spleen weight, plasma glucose, ALT, and AST. On the basis of our result, it is concluded that the standardized extract of *B. monniera* possesses a potent adaptogenic activity.[10]

1.8. *Evolvulus alsinoides*:

Evolvulus alsinoides (EA) is well known for its memory enhancement, antiepileptic and immunomodulatory properties in the traditional Indian system of medicine, Ayurveda. In view of the increasing attention towards plants offering non-

specific resistance (adaptogens) towards stress, we have evaluated crude ethanolic extract of EA for its adaptogenic and memory enhancing properties in rodents. Adaptogenic activity was assessed in rats subjected to acute and chronic unpredictable stress. In CUS, EA at a dose of 200 mg/kg p.o. found effective in acute studies was administered 45 min prior to stress regimen for 7 days. EA reduced the stress induced perturbations similar to *Panax quinquefolium* (PQ) (100 mg/kg p.o.), a well known adaptogen.The improvement in the peripheral stress markers and scopolamine induced dementia by EA in the present study indicates the adaptogenic and anti-amnesic properties of EA.[11]

1.9. *Hoppea dichotoma*:

From the roots of *Hoppea dichotoma*, collected before flowering, two new naturally occurring glucosyloxyflavans, dichotosin and dichotosinin, have been isolated and characterized by means of comprehensive spectral analyses, chemical transformation and synthesis of the aglucone of dichotosin. This is the first report of dichotosinin from a natural source. Additionally, one known glucosyloxyflavan, diffutin, earlier reported in another Gentianaceae species (*Canscora diffusa*) also has now been isolated from this species. The glucosyloxyflavans, individually and in combination, produced varying degrees of adaptogenic (anti-stress-anti-anxiety) activity in animal models. This observation is consistent with the use of the plant extract as a nerve tonic in Ayurvedic medicine.[12]

1.10. *Bergenia crassifolia:*

The adaptogenic effect of *Bergenia crassifolia* black and fermented leaves was examined based on the forced swimming capacity and the change of biochemical parameters in mice. The treatment groups were orally administered infusions of black and fermented leaves of 3 populations of *B. crassifolia*, while the control group received distilled water for 7 days. Infusions from black leaves of *B. crassifolia* insignificantly enhanced the maximum swimming capacity of mice by increasing fat utilization, and by delaying the accumulation of plasma lactate while infusions from fermented leaves of *B. crassifolia* significantly enhanced the maximum swimming capacity of mice without change of the body weight by increasing glucose utilization and decreasing lactate level compared to the control group.[13]

1.11. *Butea frondosa:*

The plant *Butea frondosa* has been indicated in the Indian system of medicine as a plant augmenting memory and as a rejuvenator. The effect of oral administration of the aqueous and alcoholic extracts of the leaves was assessed on stress, cognitive function, and anxiety in albino rats. The antistress activity was evaluated using cold restraint induced ulcers and leukocyte count after subcutaneous injection of milk. The aqueous extract provides protection against stress-induced gastric lesions while both the alcoholic as well as the aqueous extract normalizes the white blood cell count. Effect on cognitive function was evaluated using Cook and Weidley's pole apparatus. It is concluded that the aqueous and alcoholic extract of *B. frondosa* possesses antistress and weak nootropic activity.[14]

1.12. *Panax quinquefolium:*

Ginseng is the root of the perennial herbs of *Panax quinquefolium* and *Panax ginseng* which contain a series of tetracyclic triterpenoid saponins (ginsenosides) as active ingredients. It is considered a tonic or adaptogenic that enhances physical performance (including sexual), promotes vitality and increases resistance to stress and ageing. The adaptogenic properties of ginseng are believed to be due to its effects on hypothalamic–pituitary–adrenal axis, resulting in elevated plasma corticotropin and corticosteroids levels. When used appropriately, ginseng appears to be safe. Nevertheless, documented side effects include hypertension, diarrhoea, restlessness, mastalgia and vaginal bleeding.

1.13. *Hippophae rhamnoides:*

The effects of seabuckthorn (*Hippophae rhamnoides* L., Elaeagnaceae), leaf aqueous extract were examined in rats for its adaptogenic activity and toxicity. Dose dependent adaptogenic study of extract was carried out at different doses administered orally, 30 min prior to cold (5 °C)–hypoxia (428 mmHg)–restraint (C–H–R) exposure. After sub-acute toxicity studies on 10 and 20 times doses of maximal effective dose administered for 14 days (single oral dose of 1 g/kg and 2 g/kg once daily) and maximal effective dose administered for 30 days (single oral dose of 100 mg/kg once daily), biochemical and hematological parameters were studied in the serum and blood. The maximal effective adaptogenic dose of the extract was 100 mg/kg body weight.drug treated animals in comparison to control rats. In acute toxicity study LD_{50} of the extract was observed to be >10 g/kg when given orally. These results indicate that seabuckthorn leaf aqueous extract possess potent adaptogenic activity with no toxicity even after sub-acute (30 days) maximal effective dose administration.[16]

1.14. *Zingiber officinale:*

Ethanolic extract of rhizomes of *Zingiber officinale* was investigated on anoxia stress tolerance test in Swiss mice. The animals were also subjected to acute physical stress (swimming endurance test) to gauge the anti-stress potential of the extract. Further to evaluate the anti-stress activity of *Z. officinale* in chronic stress condition, fresh Wistar rats were subjected to cold restraint stress (4° for 2 h) for 10 days. Pretreatment with the extract significantly ameliorated the stress-induced variations in these biochemical levels and blood cell counts in both acute and chronic stress models. The extract treated animals showed increase in swimming endurance time and increase in anoxia tolerance time in physical and anoxia stress models, respectively. Treatment groups also reverted back increase in liver, adrenal gland weights and atrophy of spleen caused by cold chronic stress and swimming endurance stress models. The results indicate that ethanolic extract of *Z. officinale* has significant adaptogenic activity against a variety of biochemical and physiological perturbations in different stress models.[17]

1.15. *Eleutherococcus senticosus:*

The adaptogen concept is examined from an historical, biological, chemical, pharmacological and medical perspective using a wide variety of primary and secondary literature.We attempted to

identify critically what an adaptogen supposedly does and to determine whether the word embodies in and of itself any concept(s) acceptable to western conventional (allopathic) medicine. Special attention was paid to the reported pharmacological effects of the 'adaptogen-containing plant' *Eleutherococcus senticosus* (Rupr. & Maxim.) Maxim. (Araliaceae), referred to by some as 'Siberian ginseng', and to its secondary chemical composition. We conclude that so far as specific pharmacological activities are concerned there are a number of valid arguments for equating the action of so-called adaptogens with those of medicinal agents that have activities as anti-oxidants, and/or anti-cancerogenic, immunomodulatory and hypocholesteroletic as well as hypoglycemic and choleretic action. However, 'adaptogens' and 'anti-oxidants' etc. also show significant dissimilarities and these are discussed.[18]

1.16. *Asparagus racemosus:*

It is an Ayurvedic rasayana used as an adaptogen. Adaptogenic drugs are those which are useful as anti-stress agents by promoting non-specific resistance of the body. Although, the adaptogenic effect of AR is well documented, its use in psychological disorders like depression is not scientifically evaluated. Hence, the present investigation evaluates the antidepressant effect of methanolic extract of roots of AR (MAR) standardized to saponins (62.2% w/w). Rats were given MAR in the doses of 100, 200 and 400 mg/kg daily for 7 days and then subjected to forced swim test (FST) and learned helplessness test (LH). The results show that MAR decreases immobility in FST and increases avoidance response in LH indicating antidepressant activity.[19]

1.17. *Hypericum perforatum*:

It (Hypericaceae) is a perennial herb that is commonly known as St. John's Wort. The plant has been valued for its important biological and chemical perspectives and its use in the treatment of infectious diseases has been documented in ethnobotanical reports. Most recent interest in *H. perforatum* has focused on its antidepressant effects, and only recently has its antimicrobial activity been evaluated against a number of bacterial and fungal strains. The present review gives a comprehensive summary of the ethnobotanical uses, chemical constituents and biological effects (antibacterial and antifungal) of this species. The antibacterial activity of crude extracts can be related to the use of the herb as a wound healer in ancient times. Based on the chemical and pharmacological characteristics of *H. perforatum*, we concluded that this species has beneficial therapeutic properties and has the potential for use as an effective adaptogenic herbal remedy.[20]

1.18. *Rhodiola rosea:*

The aim of this review article was to summarize accumulated information related to chemical composition, pharmacological activity, traditional and official use of *Rhodiola rosea* L. in medicine. In total approximately 140 compounds were isolated from roots and rhizome - monoterpene alcohols and their glycosides, cyanogenic glycosides, aryl glycosides, phenylethanoids, phenylpropanoids and their glycosides, flavonoids, flavonlignans, proanthocyanidins and gallic acid

derivatives. Studies on isolated organs, tissues, cells and enzymes have revealed that Rhodiola preparations exhibitadaptogenic effect including, neuroprotective, cardioprotectiv e, anti-fatigue, antidepressive, anxiolytic, nootropic, life-span increasing effects and CNS stimulating activity. A number of clinical trials demonstrate that repeated administration of R. rosea extract SHR-5 exerts an anti-fatigue effect that increases mental performance (particularly the ability to concentrate in healthy subjects), and reduces burnout in patients with fatigue syndrome. Encouraging results exist for the use of Rhodiola in mild to moderate depression, and generalized anxiety. [21]

1.19. *Ptychopetalum olacoides*:

With the recognition that high levels of sustained stress are associated with the natural course of countless illnesses, effective anti-stress agents have gained importance. Improved endurance to particularly stressful periods is one of the medicinal claims for Marapuama *(Ptychopetalum olacoides Bentham, PO),* a popular Amazonian herbal.[22]

1.20. *Ocimum sanctum*:

A methanol extract and an aqueous suspension of *Ocimum sanctum* leaves were investigated for their immunoregulatory profile to antigenic challenge of Salmonella typhosa and sheep erythrocytes by quantifying agglutinating antibodies employing the Widal agglutination and sheep erythrocyte agglutination tests and E-rosette formation in albino rats. The data of the study indicate an immunostimulation of humoral immunologie response as represented by an increase in antibody titre in both the Widal and sheep erythrocyte agglutination tests as well as by the cellular immunologic response represented by E-rosette formation and lymphocytosis. The results of the study indicate a immunostimulant capability for *Ocimum sanctum* which may be contributory in explaining the adaptogenic action of the plant.[23]

1.21. *Schisandra chinensis*:

Schisandra chinensis (Turcz.) Bail is often referred to as an example of a medicinal plant with use in modern Chinese medicine. However, *Schisandra chinensis* first gained recognition as an adaptogen in the official medicine of the USSR in the early 1960s. Pharmacological studies on animals have shown that Schizandra increases physical working capacity and affords a stress-protective effect against a broad spectrum of harmful factors including heat shock, skin burn, cooling, frostbite, immobilisation, swimming under load in an atmosphere with decreased air pressure, aseptic inflammation, irradiation, and heavy metal intoxication. The phytoadaptogen exerts an effect on the central nervous, sympathetic, endocrine, immune, respiratory, cardiovascular, gastrointestinal systems, on the development of experimental atherosclerosis, on blood sugar and acid–base balance, and on uterus myotonic activity.[24]

1.22. *Eclipta alba:*

The present study deals with the investigation of standardized and phytochemically evaluated aqueous and hydroalcoholic extracts of the plant *Eclipta alba* for sedative, muscle-relaxant, anxiolytic, nootropic and anti-stress activities.The hydrolyzed fraction of the

aqueous extract was also subjected to similar studies in rats. The findings indicated nootropic activity of the aqueous extract (300 mg/kg, p.o.) and its hydrolyzed fraction (30 mg/kg, p.o.). The effect of the extracts on stress-induced alterations was evaluated. The aqueous extract and the hydrolyzed fraction provided protection against cold restraint induced gastric ulcer formation and also normalized the white blood cell count in the milk induced leukocytosis challenge model.[25]

1.23. *Azadirachta indica:*

Azadirachta indica, a plant used widely in Ayurveda, has been reported to have anti-inflammatory, immunomodulatory and adaptogenic properties. The present study evaluates its hepatoprotective role. Fresh juice of tender leaves of *Azadirachta indica* (200 mg/kg body wt. p.o.) inhibited paracetamol (2 g/kg body wt. p.o.)-induced lipid peroxidation and prevented depletion of sulfhydryl groups in liver cells. *Azadirachta indica* pretreatment stabilized the serum levels of these enzymes. Histopathological observations of liver tissues corroborated these findings.[26]

1.24. *Sutherlandia frutescens:*

Sutherlandia frutescens (tribe Galegeae, Fabaceae), a popular plant in traditional medicine, is indigenous to South Africa, Lesotho, southern Namibia and southeastern Botswana. It is chemically, genetically and geographically extremely variable and has been divided into three subspecies and several regional forms. A second species, *Sutherlandia tomentosa*, is localized along the Cape coast. Sutherlandia is sometimes treated as part of the genus Lessertia. There are numerous vernacular names and a wide diversity of uses, including poor appetite, indigestion, stomach complaints, dysentery, colds, influenza, kidney conditions, fever, diabetes, internal cancers, uterine troubles, liver conditions, backache, rheumatoid arthritis, urinary tract infections, stress and anxiety, dropsy and heart failure. Notable is the use as a bitter tonic ("blood purifier"), anti-stress medication ('musa-pelo) and, at least since 1895, specifically as a cancer tonic (both as treatment and as prophylaxis).[27]

1.25. *Acanthopanax senticosus:*

To determine whether heat environmental stress (HES) affects the livers of rats, we investigated microarray-based expression profiling using an Affymatrix Gene Chip Rat genome 230 2.0 Array. We were also able to examine the effects of *Acanthopanax senticosus* extract (ASE) on the gene expression profile. Heat environmental stress (HES) induced changes in gene expression transcript profiles, including those related to fatty acid synthase activity, oxidoreductase activity and lipid peroxidation (LPO). We observed dramatically increased malonaldehyde (MDA) levels after HES, which indicates that HES caused LPO through the regulation of oxidative stress and LPO-related transcripts, as revealed by microarray. When ASE was orally administered to the HES group, the number of candidate validation genes as well as the MDA content decreased in comparison to rats that did not receive ASE. [28]

1.26. *Panax ginseng:*

Korean ginseng tea (KGT), prepared from the roots of *Panax ginseng*, is widely used by Korean people for antistress, antifatigue, and endurance promoting

effects. In the present study we evaluated neuroprotective/ cerebro-protective actions of KGT in stroke, using rat global and focal models of ischemia. Varied biochemical/enzymatic alterations, produced subsequent to the application of middle cerebral artery (MCAO) and bilateral carotid artery occlusion (BCAO) followed by reperfusion viz. increase in lipid peroxidation (LPO) and decrease in glutathione (GSH), glutathione reductase (GR), catalase (CAT), glutathione-S-transferase (GST), glutathione peroxidase (GPx) and superoxide dismutase (SOD), were markedly reversed and restored to near normal levels in the groups pre-treated with KGT (350 mg/kg given orally for 10 days). It is concluded that the protective action, exhibited by KGT against hypoperfusion/reperfusion induced brain injury, suggests its therapeutic potential in cerebrovascular diseases (CVD) including stroke. These findings are important because: (a) the present treatment strategies for CVD are far from adequate and (b) KGT with wide usage is known to be a safe natural product.[29]

1.27. *Curcuma longa*:

The present study was undertaken to evaluate the cardioprotective potential of *Curcuma longa* (Turmeric) in the ischemia-reperfusion (I/R) model of myocardial infarction (MI). Wistar rats were divided into three groups and received saline orally (sham, control I/R group) and *Curcuma longa* 100 mg/kg (CL-100 treated group) respectively for one month. On the 31st day, rats of the control I/R and Cl treated groups were subjected to 45 min of occlusion of the LAD coronary artery and were thereafter reperfused for 1 h. I/R resulted in significant cardiac necrosis, depression in left ventricular function, decline in antioxidant status and elevation in lipid perodixation in the control I/R group as compared to sham control. Myocardial infarction produced after I/R was significantly reduced in the Cl treated group. Cl treatment resulted in restoration of the myocardial antioxidant status and altered hemodynamic parameters as compared to control I/R. Furthermore, I/R-induced lipid peroxidation was significantly inhibited by Cl treatment. The beneficial cardioprotective effects also translated into the functional recovery of the heart. Cardioprotective effect of Cl likely results from the suppression of oxidative stress and correlates with the improved ventricular function. Histopathological examination further confirmed the protective effects of Cl on the heart.[30]

1.28.*Guduchyadi Ghrita*:

This study has been carried out to compare the Psycho-neuro-pharmacological basis for the use of Guduchyadi Ghrita and Bhringarajadi Ghrita. Guduchyadi Ghrita Rasayana consisting of Guduchi (*Tinospora cordifolia* Linn), Apamarga (*Achyrenthus aspera* Linn), Vidanga (*Embelia ribes* Burm. F.), Shankhapushpi (*Convolvulus pluricaulis* Chois), Vacha (*Acorus calamus* Linn), Haritaki (*Terminalia chebula* Retz), Kushtha (*Saussurea lappa* C.B.Clarke) and Shatavari (*Asparagus racemosus* Willd), has proven mental health promoting, memory enhancing, anti-stress, anti- depressant properties that may slow down the Aging process by counteracting stress. Bhringarajadi Rasayana consisting of Bhringaraja (*Eclipta alba* Hassk.), Krishna Tila (*Sesamum orientale* Linn.), Amalaki (*Embelica officinalis* Gaertn.), Mishri

(Sugar) with proven adaptogenic, antioxidant, free radicals scavenger, immuno-modulator properties play a major role in the management of Aging process. Both the formulations are supposed to possess CNS activity, Anti-stress, adaptogenic and other pharmacological activities. Based on this promise the test Ghrita had been studied on various experimental models such as Gross behaviour test, Anti depressant test, Anti-anxiety test and Antistress adaptogenic test on Swiss Albino Mice and Charles Foster strain albino rats of either sex.[31]

1.29. *Psidium guajava*:

Ethanolic extract of leaves of *Psidium guajava* was investigated on anoxia stress tolerance test in Swiss mice. The animals were also subjected to acute physical stress (swimming endurance test) and acute heat induced stress to gauge the antistress potential of the extract. Further to evaluate the antistress activity of *Psidium guajava* in chronic stress condition, fresh Wistar rats were subjected to cold restraint stress (4° for 2 h) for 10 days. Stimulation of hypothalamus pituitary adrenal axis in stressful condition alters plasma glucose, triglyceride, cholesterol, BUN and corticosterone levels. There is also alteration in the blood cell counts.The results indicate that ethanolic extract of *Psidium guajava* has significant adaptogenic activity against a variety of biochemical and physiological perturbations in different stress models.[32]

1.30. *Momordica charantia*:

The present study was undertaken to evaluate antistress and immunomodulatory activity of aqueous extract of *Momordica charantia (MC).* Antistress activity was evaluated by measuring the swimming time in mice and cold immobilization induced stress for 10 days in rats, using *Withania somnifera* (100mg/kg) as reference standard. Immunomodulatory activity was evaluated by carbon clearance assay and percentage adhesion of neutrophils to nylon fibers using Levamisole as reference standard. The degree of protection was determined by measuring gastric ulceration, adrenal gland and spleen weights and by measuring levels of serum glucose, AST and ALT. Swiss albino mice of either sex were divided into 4 groups such as normal control, MC lower dose (450 mg/kg, p.o), MC higher dose (900 mg/kg, p.o) and standard group, treated with standard drug Levamisole (50 mg/kg, p.o). MC increased the swimming time in mice significantly ($P<0.001$) and the results are comparable to that of standard *Withania somnifera*.[33]

1.31. *Sida cordifolia*:

Ethanol extract of roots of *Sida cordifolia* was evaluated for antistress, adaptogenic activity using cold restraint stress and swim endurance in mice. Mice pretreated with extract of *Sida cordifolia* showed significant improvement in the swim duration and reduced the elevated WBC, blood glucose and plasma cortisone.[34]

1.32. *Morus alba*:

The objective of the present study was to evaluate the adaptogenic property of the ethyl acetate-soluble fraction of methanol extract of *Morus alba* roots against a rat model of chronic stress (CS).Rats were exposed to stress procedure for 21 days. The stress procedure was mild, unpredictable footshock, administered for 1 h once daily for 21 days. Rats were administered with the ethyl acetate

soluble fraction of methanol extract of *M. alba* roots (25, 50 and 100 mg/kg p.o) 1 h before footshock for 21 days and behavioral parameters were evaluated for cognitive dysfunction and depression using elevated plus maze and despair swim test, respectively. On day 21, rats were sacrificed immediately after stress and blood was collected for biochemical estimation. The adrenal gland and spleen were dissected for organ weight and the stomach was dissected for ulcer score.CS significantly induced cognitive deficit, mental depression and hyperglycemia and increased blood corticosterone levels, gastric ulcerations and adrenal gland weight, but decreased the splenic weight.The results indicate that *M. alba* possesses significant adaptogenic activity, indicating its possible clinical utility as an antistress agent.[35]

1.33. *Centella asiatica:*

Centella asiatica (CA), a well known adaptogenic agent in Indian system of Medicine (Ayurveda), is believed to have beneficial effects in improving memory, treating anxiety and eczema. It also possesses antioxidant, cognitive enhancing and antiepileptic properties. Acute ischemia followed by reperfusion is known to bring about biochemical and histopathological alterations. In the present study the effect of *Centella asiatica* on acute cerebral reperfusion and long-term cerebral hypoperfusion in rats was investigated. Transient cerebral ischemia was induced under Ketamine anaesthesia by blocking bilateral common carotid arteries (BCCAO) for 30 min and then reperfusion was allowed for 45 min by releasing the block. Lipid peroxidation, superoxide dismutase (SOD) and brain protein were estimated, behavioral and histopathological studies were done for both acute ischemia-reperfusion and chronic hypoperfusion studies. CA treatment (100 mg/kg p.o. for 28 days) alleviated these behavioral, cognitive and histopathological changes. The results suggest that CA may be useful in cerebrovascular insufficiency conditions.[36]

1.34. *Camellia sinensis:*

The aim of this study was to study the ameliorative effects of *Ocimum sanctum* and *Camellia sinensis* on stress-induced anxiety and depression.The study was carried out using male albino rats (200 ± 50 g). The effect of *O. sanctum* and *C. sinensis* was evaluated for anxiety and depression using elevated plus maze (EPM) test, open field test (OFT), forced swim test (FST), and tail suspension test (TST).Restraint stress (3 h/day for six consecutive days) induced a significant reduction in both the percentage number of entries and time spent in open arms in EPM, and these changes were reversed with post-treatment of aqueous extract of *O. sanctum* and *C. sinensis* (100 mg/kg for 6 days). Restraint stress-induced (a) increased latency and (b) decreased ambulation and rearing were also reversed by *O. sanctum* and *C. sinensis* in OFT. A significant increase in immobility period was observed in FST and TST after restraint stress. *O. sanctum* and *C. sinensis* significantly reduced the immobility times of rats in FST and TST. *O. sanctum* and *C. sinensis* possess anxiolytic and antidepressant activities.[37]

1.35. *Eugenia caryophyllus:*

The present study was undertaken to evaluate the anti-stress effect of the hydro-alcoholic extract of clove. The anti-stress effect was evaluated on cold restraint induced gastric ulcers, sound

stress induced biochemical changes and anoxic stress induced convulsions. Clove extract was administered orally at two different doses of 100 and 200 mg/kg. Zeetress, a known anti-stress formulation (14 mg/kg p.o) was used as the standard drug. Both the doses of clove extract showed good anti-stress effect in all the tested models. The clove extract reduced the development of cold restraint induced gastric ulcers and prevented the biochemical changes induced by sound stress such as increase in plasma levels of aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, glucose, cholesterol and corticosterone. Clove extract was also effective in increasing the latency of anoxic stress induced convulsions in mice.[38]

1.36. Ayurvedic rasayanas:

Siotone (ST) is a herbal formulation comprising of *Withania somnifera, Ocimum sanctum, Asparagus racemosus, Tribulus terristris*[39] and shilajit, all of which are classified in Ayurveda as rasayanas which are reputed to promote physical and mental health, improve defence mechanisms of the body and enhance longevity. These attributes are similar to the modern concept of adaptogenic agents, which are, known to afford protection of the human physiological system against diverse stressors. The present study was undertaken to investigate the adaptogenic activity of ST against chronic unpredictable, but mild, footshock stress induced perturbations in behaviour (depression), glucose metabolism, suppressed male sexual behaviour, immunosuppression and cognitive dysfunction in CF strain albino rats. Gastric ulceration, adrenal gland and spleen weights, ascorbic acid and corticosterone concentrations of adrenal cortex, and plasma corticosterone levels, were used as the stress indices. *Panax ginseng* (PG) was used as the standard adaptogenic agent for comparison. Additionally, rat brain levels of tribulin, an endogenous endocoid postulated to be involved in stress, were also assessed in terms of endogenous monoamine oxidase (MAO) A and MAOB inhibitory activity.[39]

1.37. Rasayana herbs:

Plants from all over the world such as *Eleutherococcus senticosus, Panax ginseng, Raponticum carthamoides*[40], *Rhodiola rosea, Withania somnifera and Ocimum sanctum* have been extensively evaluated for their adaptogenic potential. However, none of them has been successfully introduced as an adaptogen in the clinic. This paper discusses some of the problems in evaluation of adaptogens which have precluded their inclusion as clinically useful drugs. We further discuss our results with six rasayana plants from Ayurveda, which were studied for their adaptogenic potential. The whole, aqueous, standardized extracts of selected plants *(Tinospora cordifolia, Asparagus racemosus, Emblica officinalis, Withania somnifera, Piper longum*[40] and *Terminalia chebula*[40]) were administered orally to experimental animals, in a dose extrapolated from the human dose, following which they were exposed to a variety of biological, physical and chemical stressors. These plants were found to offer protection against these stressors, as judged by using markers of stress responses and objective parameters for stress manifestations. Using a model of cisplatin induced alterations in gastrointestinal motility, the ability of these plants to exert a normalizing effect,

irrespective of direction of pathological change was tested. All the plants reversed the effects of cisplatin on gastric emptying, while Tinospora cordifolia and *Asparagus racemosus* also normalized cisplatin induced intestinal hypermotility. Tinospora cordifolia was also tested for its ability to modulate the changes occurring in the phagocytic activity of peritoneal macrophages after exposure of rats to either carbon tetrachloride or horse serum. It was found to normalize the phagocytic function irrespective to the direction of change, complying to the definition of an adaptogen. All the plant drugs were found to be safe in both acute and subacute toxicity studies.[40]

1.38. *Clitoria ternatea:*

Clitoria ternatea L. (CT) (Family: Fabaceae) commonly known as 'Butterfly pea', a traditional Ayurvedic medicine, has been used for centuries as a memory enhancer, nootropic, antistress, anxiolytic, antidepressant, anticonvulsant, tranquilizing and sedative agent. A wide range of secondary metabolites including triterpenoids, flavonol glycosides, anthocyanins and steroids has been isolated from *Clitoria ternatea* Linn. Its extracts possess a wide range of pharmacological activities including antimicrobial, antipyretic, anti-inflammatory, analgesic, diuretic, local anesthetic, antidiabetic, insecticidal, blood platelet aggregation-inhibiting and for use as a vascular smooth muscle relaxing properties. This plant has a long use in traditional Ayurvedic medicine for several diseases and the scientific studies has reconfirmed those with modern relevance. This review is an effort to explore the chemical constituents, pharmacological and toxicity studies of CT, which have long been in clinical use in Ayurvedic system of medicine along with a critical appraisal of its future ethnopharmacological potential in view of many recent findings of importance on this well known plant species.[41]

1.39. *Ginkgo biloba*:

Lipophilic extracts of *Ginkgo biloba* L. leaves were tested for their possible role on rodent models of depression and stress. Lipophilic extracts of Ginkgo leaves (LEG) at (50 and 100 mg/kg, p.o.) exhibited dose dependent, significant antidepressant activity in the behavioral despair test and learned helplessness rodent model of depression. The activities were comparable to that of imipramine (15 mg/kg) and EGb 761 (50 mg/kg). In the cold immobilization stress induced gastric ulcer model of stress, only the LEG showed a significant reduction in the ulcer index. GC-MS characterization of this bioactive extract was found to be rich in a group of 6-alkyl salicylates (6-AS), along with a fatty alcohol, fatty acids and cardanols. The n-heptadecenyl salicylate represented 60% of the 6-AS. Notable was the absence of dihydroxy alkylphenols which are linked to allergic reactions similar to the urushiols present in poison ivy.[42]

1.40. Heteropterys aphrodisiaca:

Literature report is lacking on pharmacological studies of the plant *Heteropterys aphrodisiaca*, endemic to the scrublands of Brazil. The present study was carried out to investigate the effects of oral dosing with extract BST0298 from this plant, on learning and on memory, in young (3–6-month-old) and aged (20–28-month-old) rats. The aged animals presented significant memory deficits in both the passive

avoidance and T-maze left/right discrimination tests. Treatment for 7 days (50 mg/kg) or 26 days (100 mg/kg) with extract BST0298 restored the memory deficits in the passive avoidance test. However, no improvement in memory was observed after acute administration of extract BST0298 (100 mg/kg) in aged rats. An improvement in learning was also observed in the left/right discrimination test in aged rats treated for 109 days with BST0298 at a dose of 50 mg/kg. These results suggest that treatment for 7 days or more with *H. aphrodisiaca* improves learning and memory deficits in aged rats.[43]

1.41. *Astragalus membranaceus:*

In this study, the haemolytic activities of *Astragalus membranaceus* saponins (AMS) and its adjuvant potentials on the cellular and humoral immune responses of ICR mice against OVA were evaluated. We determined the haemolytic activity of AMS using 0.5% rabbit red blood cell. AMS showed a slight haemolytic effect, with its haemolytic percents being 0.66% at the concentration of 500 μg/ml. Furthermore, the adjuvant potentials of AMS at three dose levels on the cellular and humoral immune responses of ICR mice against ovalbumin (OVA) were investigated. [44]

1.42. Curculigo orchioides:

The methanol extract of rhizomes of *Curculigo orchioides* Gaertn. (Amaryllidaceae) holds potential as a protective agent against cytotoxic drugs. The extract when studied on humoral and cell mediated immunity in normal, as well as cyclophosphamide-induced immunosuppressed mice produced an increase in humoral antibody (HA) titre, delayed type hypersensitivity (DTH) and levels of WBC in a dose dependent manner.[45]

1.43. *Tridax procumbens*:

The immunomodulatory properties of ethanol insoluble fraction of aqueous extract of *Tridax procumbens* Linn. (TPEIF) have been investigated. After intraperitoneal administration of TPEIF in doses of 0.25 and 0.5 g/kg body weight (BW) a significant increase in phagocytic index, leukocyte count and spleenic antibody secreting cells was noticed. Stimulation of humoral immune response was further observed with elevation in heamagglutination antibody titer. Heightened delayed type hypersensitivity reaction suggested convincing evidence for activation of cellular immune system. Protective action of herbal medicine in case of anaphylactic shock was also studied. In addition, elicitation of specific antibody titer against tetanus toxoid (TT) challenge was measured in order to explore the possible use as adjuvant along with clinical vaccination program to reduce number of non-responders. The results suggest that TPEIF influences both humoral as well as cell mediated immune system vis-a-vis assists in genesis of improved antibody response against specific clinical antigen.[46]

1.44. *Alium sativum*:

It is known as a potent spice and a medicine with broad therapeutic properties ranging from antibacterial to anticancer, and anticoagulant. One major protein has been isolated and purified, it is the 14-kDa glycoprotein. This protein has shown to have immunomodulatory effects. In this study, two sources of garlic

(freshly prepared and commercial tablet) were used. Both sources of garlic were augmented delayed type hypersensitivity (DTH) response, the optimum enhancement were detected at 20 mg/kg.[47]

2. CONCLUSION

The collections of herbal plant showing the adaptogenic activity were tabulated from the various journals and were reported above. As we can conclude that herbal plants are very rich source of substances which are responsible for increasing the adaptogenic activity.

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