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Mini Review

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Anti-stress agents from natural origin

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Abstract

An exponential rise in world population coupled with rapid industrial growth has a direct impact on environment and society thus making man easily vulnerable to stress conditions. These, in-turn, cause disturbances in the normal physiological functioning of the body by way of increased free radical generation culminating in hypertension, neurosis, immune suppression and other physical and mental disorders. Global search is on, for the development of an effective antistress drug from natural source which could effectively tone up the disturbed physiological functioning of the subjects affected by such stress problems. A number of such drugs mostly in the form of their extracts (holistic approach) or in some, as active principles isolated from them, have been evaluated for their antistress activity by a number of tests which include open field behaviour; Y-maze; Swimming endurance; effect on hexobarbitone sleeping time; stress induced ulceration; monitoring corticosterone, Ascorbic acid, MAO, SOD, SDH and neurotransmitter levels in tissues/blood and others. *Withania somnifera, Ocimum sanctum, Mikania cordata, Tinospora cordifolia, Centella asiatica, Panax ginseng, Glycerrhiza glabra, Annona muricata, Polyalthea cerasoides* and many others have been reported with encouraging results.

Keywords: Plants, Natural products as anti-stress agents.

1. Introduction

Ayurveda, an ancient system of medicine, primarily concerned with the preventive and promotive aspects of health for the well being of an individual in a society. Corroborative and tonic plants (Rasayana) are among the most ancient medicinal remedies of the folk medicines in different parts of the world. Rasayanas have been used to promote health and longevity by increasing defense against diseases, arresting disease processes and revitalizing the body against perturbed physiological situations.

Such drugs increase non-specific resistance, causes minimal disorders in the physiological functions of the organism and act only under conditions of challenge to the system [1]. The theoretical basis for the existence of a new group of medicinal substance was laid down by Lazarev [2] who phrased the concept of a state

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of non-specifically increased resistance (SNIR). The medicinal substance causing SNIR, was variously named as Adaptogens or Athenktotropic [3].

Rasayana plants are usually termed as possessing adaptogenic activity. In general, adaptogens means adapting or causing an adaptive reaction and they appear to increase the general defense power of the organism, improve physical endurance for doing work even in adverse circumstances and in difficult environment conditions. They increase tolerance to changes in environmental conditions and resistance to noxious stimuli such as exposure to cold, heat, pain and infectious organism.

For a substance to be an adaptogen [3], it should be relatively innocuous and cause minimal disorder in the physiological functions of an organism; its action should be non-specific i.e. it should increase resistance to adverse influences of many factors of physical, chemical and biological nature and should possess normalizing action irrespective of the direction of the foregoing pathological changes.

In the present review, an effort has been made to give a comprehensive coverage on a variety of experimental studies which are used to evaluate the antistress activity of some well known tonic drugs from natural origin.

Several herbal drugs have been introduced during the recent past for decreasing anxiety and stress in many emotional and physical disorders. As continuous oral administration of tranquillizers may lead to cortical synchrony, relaxation of skeletal muscles and drowziness [4], the use of adaptogenic plants have been suggested in the traditional system of medicines, for the cure of emotional disorders, depression, anxiety, melancholy, gastric ulcers rheumatism.

2. Plants, natural products as antistress agents

Withania somnifera, Ocimum sanctum, Mikania cordata, Tinospora cordifolia, Centella asiatica, either individually or in combinations, have been evaluated in a variety of experimental models which include tests to study their effects on forced swimming endurance, stress induced gastric ulcerization, stress induced autoanalgesia, tribulin output and adrenocortical activity.

It has been noted that the total methanol-water (1:1) extract of the roots of *W. somnifera* and equimolar combinations of two acetylsteryl glucosides – sitoindoside VII & VIII and withaferin-A, attenuated stress induced responses from anxiety, depression, analgesia, thermic changes, gastric ulcers, convulsions and prevented the stress induced depletion of ascorbic acid and corticosterone levels [5,6].

Similar observations have been recorded for the ethanolic extract of *O. sanctum* [7]. The anxiolytic activity of *W. somnifera* is attributed to its property of reducing stress induced augmentation in tribulin levels. In clinical trials on patients suffering from mental deficits, this drug has shown marked improvement in their state [8,9]. *Withania somnifera, Ocimum sanctum, Altingia excelsa, Diospyros perigrina, Picrorrhiza kurrora* were shown to possess antistress activity against anoxic stress, swimming endurance test, stress ulcers and on stress induced changes in ascorbic acid, corticosooterone levels and reduced audiogenic stress induced seizures [10]. *T. cordifolia, C. asiatica* and *Mikania cordata* have been effective against variety of stressors which included ulcer, milk induced leucocytosis [11,12,13].

They have been shown to be effective in stress induced changes in biogenic amines. *T. cordifolia* increased NE (Norapinephrine) DA

(Dopamine) levels and reduced 5-HT and 5-H1AA levels in the whole brain after stress suggesting it to possess antistress activity[14]. *M. cordata* root extract prevented decrease in E and NE and increment in 5-HT levels while levels of DA was further increased.

There was a marked inhibition in brain MAO and stimulation of both brain and liver SDH (Succinate dehydrogenase) activity following immbolization stress. It restored MAO activity towards normalization and facilitated stress induced changes in SDH activity [15].

A comparative evaluation of three antistress plant drugs have been conducted by fixing the calculated mean antistress units (ASU) i.e. the ED_{50} value of *O. sanctum* as 1.00, the relative potency of *O. sanctum, E. senticosus* and *P. ginseng* was found to be 1.00, 0.83 and 0.53, respectively [16]. *O. sanctum* has exhibited better safety margin and more potent antistress activity. The beneficial effects of *O. sanctum* in viral encephalitis and stress related hypertension has been observed in clinical trials [17].

Shilajit has been used in Ayurveda to prevent ageing, induce rejuvenation and to improve memory [1]. In recent studies, it has been found to possess cell stabilizing and mast cell protecting activity [18]. The antiulcerogenic activity of fulvic acid and 4$^{|}$-methoxy 6-carbomethoxy biphenyl compounds, isolated from Shilajit has been recorded in restraint stress ulcers and pylorus ligated animal models [19].

Its antiinflammatory and analgesic activity has also been recorded [20]. Recent experiments brought about the importance of processing the raw Shilajit, to eliminate free radicals and fungal toxins from it. It has been found that the processed Shilajit and its active constituents, the oxygenated dibenzo α-pyrones and fulvic acid significantly augmented learning acquisition and memory retrieval in a battery of experiments. These actions of Shilajit are postulated to be mediated by facilitating the communication between the immune and the central nervous system [21].

The observed neurochemical changes induced by Shilajit indicated a decrease in rat brain 5-HT turnover and this fact associated with an increase in dopaminergic activity explains the observed nootropic and anxiolytic effects of the drug [22].

Panax ginseng, Eleutherococcus senticosus and Acanthopanax sessiliflorum have been known for their tonic properties [23]. The active principles of *P. ginseng* have been identified to be triterpene glycosides. Apart from a number of antistress experiments reported on these plant drugs[23], their tonic properties have been recently investigated. The anti-fatigue property of *P. ginseng* was proposed to be due to its carbohydrate sparing actions during prolonged exercise.

Treatment with *Ginseng* spp. was found to alter the adrenocortical response to stress [3, 23, 24]. The adrenal cholesterol sparing action of ginseng indicates that its cellular metabolic effects are possibly related to altered glucocorticoid activity [24]. The ability of ginseng to enhance non-specific resistance of the host has been studied by evaluating its activity against experimental arbovirus infection (Semliki forest virus) in mice, wherein it was able to protect 34-40% of test animals [25].

The observed reduction in mortality of animals exposed to cold or to radial acceleration, following treatment with *Ginseng* spp. [25, 26] has been attributed to its normalizing activity on adrenal ascorbic acid levels. The chief site of action was found to be in the peripheral site of the pituitary-adrenal stress mechanisms [27].

The study to evaluate the effect of ginseng on exhaustive exercise in mice revealed that the Ginsenoside Pg I possessed anti-fatique property and that the lipophilic fractions has significantly speeded up recovery from fatigue [28], in exploratory movement, rotating rod, rectal temperature and spring board tests.

In the recent studies, a subchronic treatment with ginseng extract was found to impart antistress effect to mice, as evidenced in the higher latent period and reduction in total period of immobility in the tail suspension test [29].

This clearly improved the spatial cognitive deficit produced by scopolamine in the T-maze delayed alteration task [30]. The alcoholic extract of *P. ginseng* facilitated the ACTH and stress induced decrease in vitamin C levels and sleep time, increase in eating frequency, body weight, walking behaviour and survival time [31].

The studies on the adaptogenic properties of Siberian gingeng (*E. senticosus*) have been extensively reviewed [32] and its possible mode of action was attributed to its antioxidant effect and to the regulation of energy, nucleic acid and protein metabolism in the tissues. The antistress action of *E. elatum, E. senticosus* and *Aralia mandshurica* is attributed to the scavenging of free radical reactions and also their have antiradical properties [33].

Aralia elata root and *Schizandra chinensis* fruits were evaluated against stress induced ulcer and secretory activity. *A. elata* significantly reduced stress induced ulcer and effectively raised gastric pH, decreased gastric secretory volume and gastric acidity showing antisecretory activity too [34].

Sideritis libanotica, S. lanata, S. perfoliata, S. athoa were evaluated against swimming performance test and it showed that at higher concentration 500 mg/kg aqueous extracts of *Sideritis* species showed antistress activity [35]. *Alcea pallida* and *Tilia argentea* prolonged swimming time suggesting antistress activity in both the plant drugs [36].

Momordica grosvenori fruit extract has shown to alleviate stomach bleeding caused by immobilization stress. It inhibited lipid peroxidation induced by stress in brain, liver and kidney and protected the animals against stress induced alteration in ECG and blood pressure profiles [37].

O. sanctum, Rosa damascena, P. ginseng have attenuated stress induced increase in intestinal mobility in albino rats [38]. Ethanolic extract of *O. sanctum* prevented the changes in plasma corticosterone levels induced by exposure to both acute and chronic noise stress suggesting it to possess antistress activity against noise [39].

Carnosine, carnosic acid, carnosal, rosmanol, epirosmanol isolated from the leaves of *Rosmarinus officinalis* have inhibited lipid peroxidation, SOD anion production and have been shown to protect the biological system against oxidative stress [40]. It also reduced stress induced changes in ascorbic acid levels in brain, heart, liver and arterial blood pressure [41].

Baicalin, a flavonoid obtained from *Scutellaria baicalensis*, normalized the changes induced by stress such as blood serum levels of ACTH, insulin, 11-oxycorticosteroids, urea and glucose [42]. Cold immobilization stress induced decrease in epinephrine and norepinephrine level, increase in blood sugar and adrenal gland tyrosine hydroxylase activity which were returned back to normal levels by taurine [43]. Dihydrocucurbitacine D-diglucoside from roots of *Bryonia alba* [44] inhibited both ascorbate dependent and NADPH dependent LPO in liver microsomal preparation from animals subjected to immobilization stress. Copteproside, a total

triterpenes saponin preparation from *Climacoptera transoxana*, markedly increased endurance in cold swimming with weights [45].

Stress induced elevation in blood glucose, urea levels, lactate dehydrogenase, alkaline phosphatase levels, membrane protein clusterization, membrane fluidity and reduced membrane thickness in RBC membrane. These effects were reversed by *O. sanctum*, eugenol and *T. malabarica* suggesting their possible mode of action as antistress agents [46]. *Azardiracha indica* stimulated the gamma glutamyl transpeptidase (GGT) and nearly normalized restraint stress induced suppression of GGT in lymphoid system *viz*. the lymphocyte, spleen, thymus and macrophages [47].

Hydroalcoholic extract of roots/rhizomes of *Glycerrhiza glabra*, showed anxiolytic activity. It increased duration of occupancy of mice in open arm, increased latency to foot shock induced aggression and reduced number of fighting bouts and delayed the onset of amphetamine induced grooming, biting, sniffing and repetitive head movements [48].

The alcoholic extracts of *Annona muricata* and *Polyalthea cerasoides* showed antistress activity in albino rats by normalizing stress induced changes in brain neurotransmitters and MAO levels [49, 50, 51].

3. Overview

The plant kingdom is a virtual gold mine of new chemical compounds waiting yet to be discovered. Even today, nearly 70% population of all the developing countries put together, depend upon traditional system(s) of medicine for majority of their healthy needs. Nearly 45% of the drugs in use are either natural products or derived from natural products.

Further, plant products have traditionally provided the pharmaceutical industry, 'lead compounds' in search for newer drugs and medicines. India, a tropical country is blessed by nature with a variety of diverse florae. Therefore, in the Indian context to get newer and better antistress agents from herbal sources the search must continue, in order to provide effective, safe and cheaper drugs for public use.

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