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Review Article

NEURO-ENDOCRINE-IMMUNE MODULATION BY AYURVEDIC *RASAYANA* DRUGS

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ABSTRACT

Ayurveda which literally means "the science of life" is the ancient Indian system of medicine. *Rasayana* is a specialized branch of Ayurveda. The drugs attributed with *Rasayana* properties are mentioned to delay the process of ageing, enhance the mental and cognitive functions and deliver freedom from a number of diseases including those caused by infectious organisms. All these activities of *Rasayana* drugs seem to be associated with neuro-endocrine-immune systems. In this study we have reviewed the growing inter-relationship between the neuro-endocrine-immune systems and stress as a neuro-endocrine-immune phenomenon. Some important Ayurvedic *Rasayana* drugs including *Aswagandha* (*Withania somnifera*), *Tulsi* (*Ocimum sanctum*), *Guduchi* (*Tinospora cordifolia*), *Shilajit* (*Asphalt*), *Brahmi* (*Bacopa monnieri*) and few others along with their pharmacological actions on the above three systems and stress as well have also been reviewed. It has been observed that most of them tend to exhibit their activities by modulating the neuro-endocrine-immune systems along with anti-stress/adaptogenic capability. The scientific inter-relationship between the three systems has been taken as the model reference. Similar actions are expected from other *Rasayana* drugs too. Therefore *Rasayana* drugs in Ayurveda can be evaluated and used as neuro-endocrine-immune modulators.

KEYWORDS: Ayurveda, *Rasayana*, Stress, *Oja*, Ageing, Glucocorticoids, Nootropic, Neuro-endocrine-immune modulation.

INTRODUCTION

Ayurveda, the Indian system of medicine was developed as an independent system of medicine during the post-Vedic era called as the "era of *Samhitas* or compendiums". The science was divided into eight different specialties including *Shalya* (general surgery), *Shalakya* (diseases of eye, ear, nose and throat), *Kaya chikitsha* (internal medicine), *Bhuta Vidya* (demnology and microbiology), *Kaumara-bhritya* (paediatrics), *Agada Tantra* (toxicology), *Rasayana Tantra* (gerontology) and *Vajikarana*s *Tantra* (aphrodisiac and virility therapy) during this period. Various texts were written on these eight branches of Ayurveda which were regarded either as *Samhitas* or as *Tantras*. Each *Samhita* had emphasized upon a particular branch of Ayurveda although other seven branches were also mentioned in accessory form. *Sushruta Samhita* emphasized on surgery, *Charaka Samhita* emphasized upon medicine while *Kahyapa Samhita* emphasized upon pediatrics. *Rasayana* is the seventh branch of Ayurveda. Among the *Samhitas* available at present, *Charaka Samhita* being a specialized text of medicine gives vivid description of *Rasayana Tantra* or gerontology followed by *Sushruta Samhita*, *Astanga Samgraha* and *Astanga Hridaya*.[1]

The term *Rasayana* when classically translated means the "rejuvenating drugs". Several properties like delaying ageing, improving mental and cognitive functions, providing freedom from several diseases including those caused by the infective organisms, promoting color and complexion of the body, restoring youthfulness, vitality, strength and stamina have been attributed to this group of drugs[2]. They tend to maintain the health of a healthy individual and are indicated in several diseases in a morbid person. The drugs covered under *Rasayana* therapy are depicted to stimulate the system of *Oja*[2], the essence of the entire body metabolism and the responsible agent for immunity, strength, stamina and luster of the body[3]. The word "*Vyadhikshamatwa*" has been used for immunity in Ayurveda. Chakrapani, a commentator on *Charak Samhita* states that the system of *Vyadhikshmatwa* antagonizes the virulence of a current disease and also protects the body to be affected by another disease. *Vyadhikshamtwa* is also regarded as *Bala* in Ayurveda[4]. Three varieties of *Bala* have been described in Ayurveda. *Sahaja Bala* or the innate immunity, *Kalaja Bala* or age related immunity and immunity due to seasons. The third variety of *Bala* is the *Yuktikruta Bala* which is the immunity conferred by diet, drugs and exercise[5]. Charaka describes that "all individuals are not equally competent in their immunity"[4]. There may be variations in the immunity depending upon the body constitution, *Doshic* predominance, body built, tissue integration, genetic factors, hereditary factors etc[4,5].

But it seems questionable to admit this fact that how a single *Rasayana* drug can be endowed with such a wide variety of body functions. This study attempts to legitimize the scientific relevance of the claims made by ancient Ayurvedic experts thousands of years ago. The study attempts to interlink the therapeutic activities of these drugs which seem to be based upon their simultaneous action on a three dimensional neuro-endocrine- immunological frame of reference. The study evaluates few single *Rasayana* entities on the basis of their classical and scientific references available especially with regards to the actions on the above three systems. The study also reviews the recent literature available on the interrelation of neuro-endocrine-immune systems.

During the last quarter of the last century and in the first quarter of the present century there has been a great deal of work in the western world regarding the psycho- neuro- endocrine- immunology which gives us ample knowledge for explaining the multiple actions of *Rasayana* drugs. This branch of medicine tries to interlink the brain and the peripheral systems in such a way that the brain can influence the immune system which in turn can send impulses to the brain by means of secreting cytokines and ultimately stimulating the hypothalamus-pituitary- adrenal (HPA) axis by the secretion of hormones and neuro-peptides[6]. The concept of stress or "general adaptation syndrome" by Professor Hans Seyle is a land mark hypothesis in this regard.[7] The derailment in the general adaptation syndrome is called as the diseases of adaptation. Anything that cause stress endangers life unless it is met by adequate adaptive response. Conversely anything that endangers life causes stress and adaptive responses. Adaptability and resistance to stress are fundamental prerequisites for life, every vital organ and their respective functions.[7] In biological sense stress is the interaction between damage and defense. In addition to damage and defense, every stressor also produces certain specific actions like anaesthetic action upon the nervous system, diuretic action on kidney, insulin action on blood sugar apart from their stressor effect.[7] Probably direct humoral impulses coming from the site of injury alerts both the nervous and the endocrine systems by activating the hypothalamus and the pituitary.[7]

Neuro-endocrine modulation of Immunity

Microbial stimulus which can be categorized under non-cognitive stimuli like bacteria, virus, spirochaetes, fungus etc are recognized by the immune system[8]. Allergens also cause stimulation of immune system[9]. On the other hand the nervous system recognizes only the cognitive stimulus like touch, pain, temperature, vision, hearing, taste etc[10]. In response to the microbial stimulation, the immune system gets activated characterized by either the innate immune response or by acquired immune response. Again the acquired immune response is characterized by the activation of the humoral immunity or the cell mediated immunity depending upon the antigenic stimuli[8]. In response to the antigenic stimulation, the immune system secretes various cytokines and peptide hormones and transmits the message to the brain by stimulating the hypothalamic neurons which ultimately modulates the immune response by activating the autonomic nervous system and the behavioral and cognitive aspects of these systems[10]. Cytokines and their receptors can be synthesized in the brain by glial cells and neuronal cells and contribute to the two main types of actions viz., modulation of neuronal excitability and local inflammatory process[11]. Receptors for cytokines like IL-1, IL-6, IL-10, TNF, have been demonstrated on the brain[11]. Receptors for various proinflammatory cytokines IL-1β, IL-6, and TNF-α and anti-inflammtory cytokines like Il-1ra (IL-1receptor antagonists) and IL-10 have been expressed on brain. It has been postulated that any pathological process in the brain has to be accompanied by and exacerbated by cytokine generation. These include traumatic brain injury, epileptic seizures, ischemia, multiple sclerosis and Alzheimers disease. Despite their unique pathological and cognitive aspects each of these conditions has a common feature of their reduced threshold to seizure. The effect of proinflammatory cytokines has been suggested to be pro-convulsant[12]. Similarly receptors for cholinergic system components like acetylcholine (Ach), choline acetyl transferase (ChAT), acetylcholinesterase (AchE) and both muscarinic and nicotinic cholinergic receptors (mAChRs and nAChRs) respectively have been expressed on B cells and T cells. Receptors for choline acetyltransferase (ChAT) have been described on the surface of T Cells, B cells, dendritic cells and macrophages. The expression of both muscarinic and nicotinic ACh receptors on lymphocytes and thymocytes has been known since early 1970s. Immune cells like B cells, T cells, dendritic cells, macrophages possess all the five isotypes of muscarinic receptors on their surface i.e., from M1 to M5. It is also postulated that the efficacy of immune activation of both T cells and B cells producing antibodies is also partially controlled by the cholinergic system.[13]

On the other hand receptors for the hormonal products like glucocorticoids, insulin, adrenalin, prolactin, testosterone, growth hormone, somatostatin, estrogens, testosterone, leptin, ghrelin, opioids etc have been displayed on the surface of the lymphoid cells and various other immune cell subsets which ensures that hormones can also influence the immune system and vice versa.[14]. It is the hormones, neuropeptides and cytokines which mediate to interlink the immune, endocrine and the nervous systems through four axes viz., hypothalamus pituitary-adrenal (HPA) axis, hypothalamus pituitary gonadal (HPG) axis, hypothalamus pituitary thyroid axis (HPT) and the hypothalamic-growth hormone axis [14].

Stimulation of both sympathetic and parasympathetic nervous system can modulate cell mediated immune response[15,16]. Dynamic exercise has the capacity to stimulate the non-specific immune response[17].

Receptors for acetylcholine (which is one of the important neurotransmitter for learning and behavior) are found on the epithelial cells of the bone marrow and the thymus[18]. Simultaneously there has been a stimulatory response of acetylcholine on the humoral immunity and the cell mediated immunity characterized by the enhanced production of antibodies from the B cells and also proliferation of the T cell count[19]. Cyclosporine and sirolimus, immunosuppressive pharmacological interventions in the treatment of graft rejection have been found to impair both cognitive and behavioral aspects in the concerned subjects as reported by various authors[20-22]. The process of adult neurogenesis is greatly influenced by the interaction between cells of the adaptive immune system and CNS-resident immune cells. It has been demonstrated that immune cells contribute to maintaining life-long hippocampal neurogenesis. Too little immune activity (as in immune deficiency syndromes) or too much immune activity (as in severe inflammatory, allergic and autoimmune diseases) can lead to impaired hippocampal neurogenesis, which could then result in hippocampal-dependent cognitive impairment[23].

Coincidentally virus induced immune-suppresion like that by the measles virus, human immunodeficiency virus (HIV), cytomegalo virus[24,25,26] is also associated with impairment of learning and processing of memory[22]. Administration of Freund's adjuvant, an immune-stimulating drug to increase the efficacy of vaccines and other immunostimulants has been found to produce improved processing of learning and memory in animals[23]. The modulation of neuronal transmissions and expression of increased learning and memory processes by the immunomodulating pharmacological interventions suggests that immune system is deeply related to the nervous system and both systems affect the activity of the other in a feedback mechanism[23,24]. The credit of this inter-relation has been given to the autonomic nervous system which has been suggested to mediate between the immune system and the central nervous systems[24].

Neuro-endocrine-immune modulation by stress

Stress or "General Adaptation Syndrome" is one of the important pathological manifestations of the neuro-endocrine-immune systems. The stimulus that produces stress is called as a stressor which can be any kind of factors like heat, cold, environmental toxins, bacterial toxins, heavy bleeding from a wound or surgery or a strong emotional reaction[25]. The general adaptation syndrome is initiated by three pathways including the alarm reaction, resistance reaction and the exhaustion reaction. The human being when exposed to stressors instantly jumps into the phase of the alarm reaction which is characterized by the stimulation of the sympathetic nervous system and the adrenal medulla producing adrenalin which produces an immediate set of responses called as the alarm reaction. The second pathway consists of the involvement of the pituitary and the adrenal cortex. The reaction is slow to start, but its effect lasts longer. The third phase is called as the exhaustion reaction and is characterized by the oxygen metabolism.[7,25,26]

Stress modulates a number of cytokines which play significant role in various immunological processes. Specifically the cytokines which take part in inflammation like IL-1, IL-6, TNF-α are modulated in an upregulated manner during stress and have been pivotal for eliciting depression and anxiety by modulating the neurochemical transmission implicated in depression and anxiety.[27] Recent evidences suggests that glucocorticoids and catecholamines, the major stress hormones inhibit the production of pro-inflammatory cytokines such as IL-12, TNF and IFN whereas they stimulate the anti-inflammatory cytokines such as IL-10, IL-4 and the transforming growth factor (TGF). On the other hand stress hormones may boost the local immune response through induction of TNF, IL-1, IL-8 and by the inhibition of TGF production in certain local response and under certain conditions. On this basis stress hormones have the potential to modulate the autoimmune disease onset and progression.[28] Psychological stress increases the pro-inflammatory cytokines such as TNF-α, IL-6, IL-1Ra, IFN-γ, and IL-10 in human individuals. Anxiety also up-regulates IFN-γ and a lower production of the negative immune-regulatory cytokines IL-10, IL-4. [29]

Cytokines like IL-1, IL-2, IL-6, IL-11, IL-12, IFN-γ TNF- α have been reported to stimulate the activities of the hypothalamus-pituitary (HP) axis thus enhancing the adreno-corticotrophin hormone (ACTH), prolactin and the growth hormones (GH). ACTH leads to the production of glucocorticoids like cortisol (hydrocortisone) and corticosterone[30,31]. This is the mechanism by which ACTH modulates the stress response. Glucocorticoids inhibit lymphocyte proliferation and also lyse the immature cells [32]. They have also been found to alter the lymphocyte kinetics, phagocytic cell function and cell mediated immunity and also the humoral immunity. Glucocorticoids suppress cell mediated immunity by inhibiting genes encoding the cytokines like IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8 and IFN-gamma and most importantly IL-2 thus preventing both CD-8 and B cell proliferation and also suppressing antibody production [33].

However the effect of stress on the above three systems is elicited in a bidirectional process with a feedback mechanism.

Concept of stress in Ayurveda

In the context of causative factors of disease Ayurveda describes three types of causes like *Prajna Paradha, Asatmendriyartha Sanjoga* and *Kala Parinama. Prajna Paradha* means a deed which is done either excessively or deficiently or in a perverted manner by body, mind, talk and other sense organs. The examples of *Prajna Paradha* are indulging in negative thoughts, abnormal meaningless insulting talks, sexual illegitimacy, abusing, scolding, anger, fear etc. Similarly *Asatmyendriyartha Sanyoga* refers to the excessive, insufficient and perverted utilization of sense organs and the functional organs. For example prolonged exposure to strong sun light, cold, winter, rain is the *Asatmyendriyartha Sanjoga* of *Sparshanendriya* (skin). Constant exposure to noise and strong sound is excessive utilization of ear (hearing sense organ). Frequently eating and eating a specific taste is excessive utilization of tongue. Sensing intense smell causes diseases of the nose. Talkativeness is also a type of excessive utilization of tongue or the *Vaak Idriya*. Similarly hard physical work, long walking, excessive sexual activities are all part of the excessive utilization of the functional organs like upper extremities, lower extremities, genitalia and the whole body and are included under the aetiology of the disease. *Kala Parinama* refers to abnormal manifestation of seasons or nature. Extreme rain, harsh winter and hard summer are all examples of perverted consequences of nature. Again no cold, no rain, no sun during their respective seasons are examples of *Kala Parinama*. All these causative factors can be included under stressors. Therefore stress is a major causative factor for causing disease. When these stressors are avoided, health intervenes [34]. Again disease is classified to be of three types. Nija or those due to endogenous causes like imbalance of *Dosha* (pathological units), *Dhatu* (body tissues) or *Mala* (excretas), those due to mental or psychological causes (*Manasika*) and those due to exogenous causes like injury, microbes, fire, poison etc (*Agantuja*). Both *Manasika* (psychiatric) and *Agantuja* (exogenous) diseases are due to stressors [34].

The following *Rasayana* drugs have been reviewed on the basis of their reported activities on the neuro-endocrine-immune systems. These drugs have been taken as model examples so that similar kind of actions can be expected from other *Rasayana* drugs thus validating their effect as neuro-endocrine-immune modulators.

***Ashwagandha* (*Withania somnifera* Linn. Dunal), Family-Solanaceae, English name-Winter cherry, Indian ginseng**

Withania somnifera (WS) is an erect, herbaceous and perennial under shrub widely distributed in the drier parts of India. The drug is considered to restore the equilibrium of deranged Kapha and Vata Doshas. It is sweet, astringent, bitter, invigorating and is a potent Rasayana with Medhya (nootropic) activity. It is indicated in Switra (vitiligo), Shotha (edema), Kshaya (debility), Apasmara (epilepsy), Unmada (insanity) and also for promoting the physical endurance (Balya). The roots of Ashwagandha are used in medicine as per Ayurveda[35, 36, 37].

Phytochemical investigations of root and leaves have shown the presence of alkaloids, flavonoids, tannins and steroidal lactones. At present 12 alkaloids, 40 withanolides and several sitoindocides (a withanolide containing a glucose molecule at C-27) are reported from aerial parts, roots and berries of WS [38]. Withanolides are a group of naturally occurring C-28 steroidal lactones. Withaferin A was the first member of withanolides isolated from WS. Withanolides are the main chemical constituents responsible for multiple biological activities of WS.[38]. Withaferin A, Withanolide D and E have been identified as active withanolides. Various physiologically active glycowithanolides named sitoindosides VII, VIII, IX, X have been also reported in the roots [39]. Presence of the amino acids like aspartic acid, glycine, glutamic acid, alamine, proline, cystin, tyrosine along with tryptophan and high contents of iron are also reported. Different chemical constituents present in Withania species are anaferine (alkaloid), anahygrine (alkaloid), beta-sitosterol, chlorogenic acid (in leaf only), cysteine (in fruits), cuscohygrine (alkaloid), pseudotropine (alkaloid), scopoletin, somniferinin (alkaloid), tropanol (alkaloid), withanine (alkaloid), withananine (alkaloid) and withanolides A-Y (steroidal lactones). [38, 39]

Ashwagandha used in several Ayurvedic formulations has now drawn the attention of immunologists worldwide. The withanolides isolated from this plant have been reported to possess simultaneous immunomodulatory, anti-stress (adaptogenic), nootropic, anti-cancerous and anti-oxidant properties.

Administration of WS root extract has enhanced various cytokines like interferon-γ (IFN-γ, 75.87pg/ml), interleukin -2 (IL-2, 14.16 pg/ml) and granulocyte macrophage colony stimulating factor (GMCSF, 49.22 pg/ml) in normal BALB/c mice. As well the drug has reversed the cyclophosphamide (CYP) induced decrease in the levels of IFN-γ (from 30 pg/ml to 74 pg/ml), IL-2 (from 4.5 to 27.5 pg/ml) and GMCSF (from 19.12 to 35.47 pg/ml). The extract also lowered the levels of TNF-α production. Administration of bone marrow cells from the donor mice treated with WS extracts increased the spleen nodular colonies in irradiated mice (8.33) compared to those treated with normal bone marrow cells (3.03). The number of these nodular colonies increased significantly when these animals were continued with WS extract treatment. The investigators substantiated the immunopotentiating and myeloprotective effect of WS as seen from enhanced cytokine production and stem cell proliferation and its differentiation [40]. The effect of Ashwagandha on the functions of macrophages obtained from mice treated with ochratoxin-A has been investigated. Treatment with WS significantly reduced the production of IL-1 and TNF-α by macrophages and ochratoxin A induced suppression of chemotactic activity of macrophages [41].

Withaferin A, a steroidal lactone from WS root inhibited Ehrlich ascites carcinoma (EAC) tumor growth and increased tumor free survival of adult Swiss albino mice in a dose dependant manner when administered intraperitonially (i.p.) after tumor cell injection with or without acute abdominal exposure to 7.5 Gy gamma irradiation[42]. In another study withaferin-A at a dose of 30 mg/kg injected intraperitoneally once daily for 5 consecutive days has significantly enhanced the spleen colony forming unit (CFUs) in 2 Gy whole body gamma irradiation animals, which had 50% less CFUs than the normal [43]. Treatment with 5 doses of WS root extract (20 mg/dose /animal, i.p) has found to enhance the total leucocyte count on the 10th day. Treatment with WS extract along with sheep red Blood cells (SRBC) produced an enhancement in the circulating antibody titre and the number of plaque forming cells (PFCs) in the spleen and the maximum number of PFCs were obtained on the 4th day. WS also reduced delayed type of hypersensitivity (DTH) reaction and an enhancement in phagocytic activity of peritoneal macrophages (76.5 pigmented cell/200 cells) when compared to the control (31.5/200) in mice. The study confirms the immunomodulatory activities of WS [44]. Aswagandha has also shown better stress tolerance by enhancing the cold water swimming performance of the experimental animals in comparison to control. The drug has been found to alter the corticosterone level in the adrenal glands of the animals [45, 46].

Disorders of cognition and memory deficit are wide spread, generally occurring in people between 50-60 years of age. The combined active principles of WS consisting of equimolar amounts of sitoindocides VII-X and withaferin-A have shown to augment learning and memory retention by altering the cholinergic markers after two weeks of treatment in a dose of 50mg/kg bw both in the frontal cortex and the hippocampus of the experimental animals. The study in models of Alzheimer's disease (pre senile disease causing memory and personality disorders) confirms the memory facilitating effect of WS validating the use of the plant as Rasayana in the treatment of cognitive function deficits including those associated with ageing [47]. One more study suggests that sitoindosides VII-X and withaferin-A derived from aqueous methanol extract from the roots of WS (cultivating variety) exhibits cognitive and memory enhancing effects by inducing the increase in acetylcholinesterase (AchE) activities in the lateral septum and globus pallidus whereas the said activity was found to be decreased in the vertical diagonal band of adult male Wistar rat brain slices. The animals were treated with an equimolar mixture of sitoindosides VII-X and withaferin A prepared from WS. These changes were accompanied by increased M1 and M2 muscarinic cholinergic receptors binding sites in a number of cortical regions. The drug induced increase in cortical muscarinic acetylcholine receptors capacity and reduced activity of AchE partly explains the cognitive enhancing and memory improving effects WS as observed in animals and humans [48].

Extension of dendrites and axons in neurons may compensate for and repair damaged neuronal circuits in the demential brain. Methanol extract of WS roots significantly increases the percentage of cells with neuritis in human neuroblastomma SK-N-SH cells. The effect of the extract was dose and time dependant. mRNA level of of dendritic markers MAP2 and PSD95 were markedly increased by treatment with the extract. The neurites extended by the extract specifically expressed MAP-2 protein. The investigators found that methanol extract of WS promoted the formation of dendrites [49].

All the above findings have been supported by clinical studies. In a study on anxiety neurosis patients, WS was observed to reduce symptoms significantly being accompanied by reduced plasma cortisol and urinary catecholamines. One month treatment with the drug has shown significant reduction in anxiety level, maladjustment, mental fatigue rate and an improvement in immediate memory span besides symptomatic relief. Another study has shown excellent improvement in mental function as observed by Hamilton-D (HAM-D) scores and electroencephalography[50].

WS when administered at a dose of 20 mg/animal i.p consecutively for 5 days prior to DMBA administration followed by twice weekly for 10 weeks has been found to reduce two stage skin carcinogenesis induced by DMBA (dimethyl benzathracine) and croton oil by significantly enhancing the anti-oxidant enzymes like glutathione (GSH), glutathione S-transferase (GST) and glutathione peroxidase (GPO) and catalase (CAT)[51].

The study reveals that WS has modulatory effects on all the three systems including the immune system by enhancing the cytokine production, total leucocyte count, PFC count, and phagocytic activity of macrophages and reducing DTH. On nervous system the action of WS has been elicited by neuroprotection (by promoting the dendrite formation) and noo-tropic action (by increased cholinergic transmission). The drug is an effective endocrine modulator ensured by the reduction of stress induced elevation of plasma cortisol. The review thus confirms the neuro-endocrine-immune modulating ability of *Ashwagandha*.

Tulsi *(Ocimum sanctum* Linn.) Family-Lamiaceae /Labiatae.) English name- Holy basil

Ocimum sanctum (OS) is a perennial aromatic, softly hairy herb or under shrub widely distributed all over India. It is a pacifier/normaliser of vitiated and deranged *Kapha, Vata Doshas* and is useful in blood disorders. It is attributed with *Katu* (pungent), *Tikta* (bitter) taste, *Lagu* (light), *Ruksha* (drying), *Tikshna* (sharp), *Ushna* (hot) properties and pungent (*Katu*) indigestion. It is good for heart (*Hrdya*), stimulates appetite (*Dipana*) and is useful in *Kustha* (skin diseases), *Mutrakrchhra* (painful micturition), diseases of blood (*Rakta* Vikara), *Parswapida* (bilateral pleurodynia), *Jwara* (fever), *Kasa* (bronchitis), *Swasa* (dyspnoea). etc. Both leaves and seeds of the plant are used for medicine. It has religious importance in Hindu culture. Whole plant is also occasionally used [52, 53].

Phytochemical investigations of OS leaves have shown the presence of glycosides, saponins and tannins. The leaves contain ascorbic acid and carotene as well. Volatile oil is the main constituent in the leaves having eugenol (70.5%) as the main component followed by methyl eugenol (20%). The essential oil contains carvacrol and sesquiterpene hydrocarbon caryophyllene, linalool, borneol, geraneol etc. Other constituents present in leaves are ursolic acid, apigenin, luteolin, isorientin, orientin, gallic acid, caffeic acid, vallinin etc [54, 55]. Seeds have yielded triglycerides and fixed oils having linoleic acid (52.23%), linolenic acid (16.63%), stearic acis, palmitic acid, oleic acid as major unsaturated fatty acids. These fatty acids are essential for human nutrition and the mixtures are used as dietary supplements [54, 55].

The holy basil or Tulsi is available almost in each and every Indian house yards. A number of reports are available on the anti-stress, immunomodulatory and anti-oxidant effect. It has been investigated that *Tulsi* is a potent immunostimulant.

A methanol extract and an aqueous suspension of OS leaves were investigated for their immune-regulatory profile to antigenic challenge of Salmonella typhosa and sheep erythrocytes by quantifying agglutinating antibodies employing the Widal agglutination and sheep erythrocytes agglutination tests and E –rosette formation in albino rats. The drugs produced immunostimulation of humoral immunologic response by increasing the antibody titer in both the Widal and sheep erythrocyte agglutination tests. The stimulation of cellular immune response was characterized by E-rosette formation and lymphocytosis. [56]

The immunomodulatory activity of *Tulsi* has also been confirmed in a double blind randomized controlled cross over trial on healthy volunteers. The drug was administered in the dose of 300 mg capsules of ethanol extract of leaves to 24 healthy volunteers on empty stomach. 22 volunteers completed the study. The drug was able to significantly increase the level of Th1 and Th2 cytokines like IFN-gamma (p=0.039) and IL-4 (p=0.001) and percentage of T helper cells (p=0.001) and NK cells (p=0.017) in the treated volunteers in post treatment period of 4 weeks in comparison to the placebo group [57].

The anti-stress activity of OS has been studied by various scientists. OS lowers the restraint stress induced cholesterol, lactate dehydrogenase (LDH) and alkaline phosphatase activity. Eugenol one of the active ingredients in OS extracts also produced similar effects besides lowering stress induced hyperglycemia. [58] Ethanol extract of OS leaves have been found to prevent the elevation of plasma corticosterone induced by exposure to both acute and chronic noise stress indicating the anti-stress property of the plant against noise stress.[59] On the other hand pretreatment of animals with ethanol extract of OS leaves for 7 days prevented the noise stress induced reduction of total acetylcholine content and increased activity of acetylcholinesterase in the albino rat cerebral cortex, corpus striatum, hypothalamus and hippocampus.[60]

The radio-protective effects of the leaf extracts of OS in combination with WR 2721 (amifostine-radioprotective drug) has been investigated in case of mice whose whole body was exposed to 4.5 Gy gamma radiation. The water extract of the drug has exhibited significant radio-protective effect [61]. The efficacy of OS crude extract when compared with steroids (dexamethasone) in the treatment of patients with acute viral encephalitis, the survival in the OS treated group was significantly higher (P<0.05) [62].

The OS has been found to be immune modulatory (by inhibiting the antigen induced histamine release from mast cells) and anti-stress (by reducing the plasma corticosterone and protecting the hippocampal neurons) agent. The nootropic action of OS can be expected from its hippocampal neuron protective action as the hippocampus plays the vital role in memory process.

***Guduchi* (*Tinospora cordifolia* (Willd.) Miers ex Hook.f. & Jhoms.), Family-Menispermaceae. English-Heart leaved moon seed**

Tinospora cordifolia (TC) is a glabrous climber with succulent corky grooved stems, branches sending down slender pendulous fleshy roots and is distributed throughout the tropical Indian subcontinent. The stem of TC is used in Ayurveda to restore balance among the vitiated and deranged *Kapha, Vata* and *Pitta Doshas* and is categorized in Ayurveda as a *Rasayana* drug. *Guduchi* is attributed with the properties like *Katu* (pungent) *Tikta* (bitter) *Rasa* (taste), *Lagu* (light) *Snigdha* (unctuous) *Guna* (properties), *Ushna Veerya* (hot in potency), *Madhura Vipaka* (sweet in digestion). It is indicated in the diseases due to the aggravation of all the three *Doshas*. It is used in *Jwara* (fever), *Vatarakta* (gout), for improving strength (*Balya*), for improving digestion and appetite, polyurea including diabetes (*Meha*), *Kasa* (bronchitis), *Pandu* (anemia), *Swasa* (dyspnoea), *Arsha* (haemorrhoides), *Kaamala* (jaundice), *Kustha* (skin diseases), Krimi (helminthes), *Vamana* (vomiting), *Mutrakrchhra* (painful micturition), *Hrdroga* (heart diseases), *Vata* (neurological diseases) etc.[63].

Chemical investigations of the stem have isolated compounds broadly classified as alkaloids (berberine, choline, magnoflorine, tinosporin, isocolumbine, palmetine etc), glycosides (furanoid diterpene glucosides, tinocordifolioside, cordioside, cordifoliosides A, B, C, D, syringing etc, lactones (tinosporone, tynosporide), steroids (β-sitosterol, δ-sitosterol, giloinsterol, makisterone A, ecdysterone), essential oil and fatty acids. The stem also contains adequate calcium, phosphorous, proteins and polysachharides. [64]

The crude aqueous extract of dry stem of TC and *Tinospora malabarica* (TM), have expressed maximum in vitro mitogenic response in splenic lymphocytes of mice. Lymphnode cells showed significant proliferation while thymus and bone marrow did not. B-lymphocytes present in mouse spleen cells showed a strong proliferative response in the presence and absence of macrophages [65]. Again it has been further demonstrated that oral administration of TC extract to mice for 15 days significantly enhanced the humoral immune response to SRBC. But the T cell response to CON-A was suppressed. The levels of Th2 cytokines IL-4, IL-10 in the supernatant of mouse spleen cells cultured with TC extracts were significantly reduced [66]. Pretreatment with TC significantly reduced the mortality in case of rats suffering from abdominal sepsis induced by caecal ligation. There was an increased peritoneal macrophage and peripheral neutrophil count associated with increased phagocytic action. [67]

The active principle syringing (TC-4) and cordial (TC-7) obtained from TC have been found to possess anti-complement, immunomodulatory activity. The compounds gave rise to a significant increase in IgG antibodies in the serum. Both humoral and cell mediated immunity were also found to be enhanced in a dose dependant manner. Macrophage activation has been reported for cordioside (TC-2) and cordiofolioside –A (TC-5) and pronounced with increasing incubation time. [68]

TC has been reported to prevent gastric damage caused by stress by altering the stress related serum cortisol level and stimulating the macrophage function[69]. TC has also been found cytotoxic to D11 and Ehrlich ascites carcinoma (EAC), but did not affect the growth of L-929 cells when administered in extract form [70]. TC has successfully reversed the hippocampal neuron degeneration induced by cyclosporine, an immunosuppressive drug. Hippocampus is a main centre for learning and memory process. Both the alcoholic and aqueous extracts have shown similar kind of activities. This cognitive enhancement is possibly due to the immune stimulation by TC and increased synthesis of acetylcholine, an important neurotransmitter in learning and memory [71].

The study suggests that TC is a potent immunomodulator (increased phagocytic action, B cell proliferation, lymph node cell proliferation, anti-complement), neuroprotective (hippocampal nerones), nootropic (increased cholinergic activity) and antistress (decreased the stress induced serum cortisol and corticosterone) agent as evidenced by the above references validating it as a neuro-endocrine-immune modulator.

***Shilajit* (Asphalt)**

Shilajit is a blackish brown powder or an exudate from high mountain rocks found in Himalayas, Nepal, Russia, Afghanistan, Mongolia and north of Chile. *Shilajeet* has been recognized as a panacea in Charak Samhita. It has been attributed with mild *Kashaya* (astringent), *Amla* (sour) *Rasa* (taste), pungent (*Katu*) in digestion (*Vipaka*) and is neither extremely hot (*Ushna*) nor extremely cold (*Sheeta*) in potency (*Veerya*). Judicious use of *Shilajit* as per classical Ayurvedic methods can eliminate all kinds of diseases if administered at right time and can prolong the ageing process. It can also enhance memory, intellect and other cognitive processes. *Charak* describes four varieties of *Shilajit* including *Swarna* (gold), *Rajata* (silver), *Tamra* (copper) and *Lauha* (iron) each being superior to the previous one in its medicinal efficacy in a respective order. *Lauha Shilajit* has been best for the *Rasayan*/ rejuvenative purpose [72].

Fulvic acid and 4'methoxine -6-carbomethoxybiphenyl (MCB) isolated from Shilajit were investigated for anti-ulcerogenic effect. The study observed that both MCB and fulvic acid have reduced the restraint stress induced ulcerogenic index in experimental animals. The drug was also investigated for its effect in memory, learning and anxiety. It has been reported that Shilajit enhanced acquisition of learning and memory in aged rats while exhibiting a marked reduction in anxiety level. These neuro-chemical effects of Shilajit have been observed to be due to a decrease in rat brain 5-hydroxytryptamine (5-HT) turn over with an increase in dopaminergic activity [73].

Shilajit has been found to affect the events in the cortical and basal forebrain cholinergic signal transduction cascade. The drug when administered in a dose of 40mg/kg in adult male Wistar rats IP daily, had given rise to reduced acetylcholinesterase staining, restricted to basal forebrain nuclei including medial septum and vertical limb of the diagonal band [48].

Shilajit activates mouse peritoneal macrophages while augmenting the fibroblast like cells in response to its treatment. It has been suggested that *Shilajit* induces initiation of macrophages to release cytokines responsible for their mobilization. It also acts as mast cell stabilizing agent and prevents the antigen induced degranulation of sensitized mast cells and this activity is due to the presence of the fulvic acid in *Shilajit*.[74]

It can be summarized that *Shilajit* possess both nootropic (by enhancing the cholinergic transmissions) and immunomodulatory (by activating the peritoneal macrophages and cytokine release) properties and anti-stress activity (by reducing the restraint stress induced ulcerogenic index).

***Mandookparni*- (*Centella asiatica* (Linn.) Urban. Syn. *Hydrocotyle asiatica* [Linn.) Urban Family-Umbelliferae. Syn-Apiaceae. English-Indian pennywort**

Mandookparni has been quoted by Charak as a potent *Medhya Rasayana* (intellect promoting) [75]. *Hydrocotyle asiatica* (HA) is sweet (*Madhura*), bitter (*Tikta*), acrid (*Kashaya*) in taste, cold (*Hima*), *Sara* (stable) and sweet (*Madhura*) indigestion. It is slender, trailing and rooting plant of the tropical area. The drug subdues the deranged *Pitta Dosha* and normalises the imbalance among the three *Doshas*, the *Vata*, *Pitta* and *Kapha*. It is a nervine tonic (*Smriti Pada*), *Ayushya* (improves life span), *Rasayana* (rejuvenates the tissues specifically the nervous tissues), *Swarya* (improves voice quality) drug in Ayurveda. It is indicated in *Kustha* (skin diseases), *Pandu* (anemia), *Meha* (polyurea including diabetes), *Kasa* (cough), *Visha* (poison), *Shotha* (inflammation), *Jwara* (fever), *Rakta Vikara* (diseases of blood). The whole plant is used in medicine. [76, 77]

HA contains diverse and complex chemical constituents which included terpenes (monoterpenes, diterpenes, sesquiterpenes, triterpenes, and tetraterpenes), phenolic compounds (flavonoids, tannins, phenyl propanoids), polyacetylene groups, alkaloids, carbohydrates, vitamins, minerals and amino acids. Triterpenes are the major constituents of HA. The triterpenes consists of asiatic acid, madecassic acid, madecassoside and asiaticoside which are the most frequent constituents identified from HA. Brahmoside, brahmic acid, brahminoside and other triterpene glycvosides are present in HA. Little amount of essential oil also found from HA. Some of the flavonoids present are quercetin and kaemferol and some phytosterols such as campesterol, sitosterol and stigmasterol are also present. [78]

The herb produces significant changes in the neurochemistry of brain showing anti-convulsant and sedative effects. The effect has been said to be induced due to increased GABAergic transmission. In an experiment the administration of *Centella asiatica* (CA) aqueous extract in a dose of 100 mg/kg and 300 mg/kg had been evaluated on the course of kindling development in the kindling induced learning deficits and oxidative stress markers in pentylenetetrazole (PTZ) kindled rats. CA in the dose of 300 mg/kg bw per oral decreased the PTZ kindled seizures and had shown improvement of learning deficits induced by PTZ kindling as evidenced by decreased seizure scores and increased latencies in passive avoidance behavior. Hydroalcoholic extract also showed protective effects against increase in intracranial electric stimulations (ICES) and chemoconvulsions induced by strychnine and PTZ on oral administration at a dose of 100 mg/kg bw and 200mg/kg bw. [79, 80]

In another study the plant drug has been observed to induce a marked protection against cold restraint stress induced ulcerisation in Charles foster rats in a dose dependant manner. The plant extract has been able to increase the brain GABA level in a dose dependant manner. [81]

Further the plant administered orally to mentally retarded children has been found to produce very significant increase in both general adaptive ability and behavioral pattern and positive effect on intelligence [82].

In an immunomodulatory study, the effect of CA was studied on cell mediated and humoral immune responses in human peripheral blood mononuclear cells (PBMCs). It was found that CA water extract significantly increased proliferation and the production of IL-2 and TNF-α. In contrast the ethanol extract of CA inhibited the human PBMC mitogenesis and the production of IL-2 and TNF-α. BALB/C mice treated with CA extracts (100mg/kg bw) showed higher responses to both primary and secondary antibodies against bovine serum albumin (BSA) when compared with non-treated group. [83]

In another experiment CA has been able to combat immunosuppressive effects of cyclophosphamide by enhancing the humoral antibody response characterized by the significant higher values of haemaglutination titre ($P<0.01$) [84].

Total triterpenes of CA were investigated for their antidepressant effect. The investigator evaluated the serum corticosterone and the contents of monoamine neurotransmitters and their metabolites in the rat cortex, hippocampus and thalamus. A significant reduction in the serum corticosterone level and increase of the contents of 5HT, noradrenalin, dopamine and their metabolites 5-HIAA, MHPG in the rat brain were observed. The investigators concluded that the anti-depressant effect of total triterpenes of CA may be involved in ameliorating the function of HPA axis and increasing the contents of monoamine neurotransmitters [85].

It was reported that treatment with *CA* fresh leaf extract at three different doses (2,4, and 6 mg/kg) administered for 2, 4, and 6 weeks enhanced learning ability and memory retention power in 2.5 months old adult Wistar rats. Spatial learning (T-maze) and passive avoidance tests were performed after the treatment period. Results were compared with those of age matched control rats. Improvement in spatial learning was significant at the dose of 6 mg/kg of extract. The enhanced memory retention was evident from passive avoidance test. [86]

The efficacy of CA in Alzheimers disease (AD) rats and its cognition enhancing activities and anti-oxidant effects have been reported. Aqueous extract of CA (100, 200 and 300 mg/kg) was administered for 21 days in streptozotocin (STZ)-induced cognitive impairment and oxidative stress in rats. Cognitive behaviors of rats treated with CA extract improved significantly. The maximum response was observed after administration of extract at the doses of 200 and 300 mg/kg which showed that CA is effective in STZ-induced cognitive impairment in rats. The reversal of the oxidative stress parameters included decreased malonaldehyde (MDA) and increased glutathione and catalase level significantly in the 200mg and 300 mg/kg bw doses only. [87]

In another experiment CA at doses of 400 and 800 mg/kg effectively reversed the anxiety and depression like behavior, amnesic behaviours, as well as the serum cortisol levels in the CUMS (chronic unpredictable mild stress) induced rat model of depression. The anti-anxiety, anti-depressant and anti-stress effect were evaluated by open field test (OFT), elevated plus maze (EPM) for anxiety, T-maze spontaneous alternation for learning and memory, serum cortisol for mild stress. Fluoxetine was used as standard anti-depressant drug for comparison. Investigators proposed the therapeutic effects of CA (at doses 400mg/kg and 800 mg/kg) are comparable with that of fluoxetine. [88]

Extracts of CA inhibited significantly gastric ulceration induced by cold and restraint stress (CRS) in Charles Foster rats. Antiulcer activity of the plant extract was comparable with the anti-ulcer effect of famotidine (H2 blocker) and sodium valproate (anti-epileptic) in a dose dependant manner. The plant extract increased the brain GABA level indicating its CNS depressant activity in a dose dependant manner. Pretreatment of bicuculline methiodide (specific GABA antagonist) at a dose of 0.5 mg/kg im reversed the antiulcerogenic activity of both plant extracts and sodium valproate. But bicuculline as such did not induce gastric ulceration in normal rats. [89]

Effect of oral and topical administration of an alcoholic extract of CA on rats dermal wound healing was studied. The extract increased cellular proliferation and collagen synthesis at the wound site as evidenced by increased DNA, protein and collagen content of the granulation tissues. Quicker and better maturation and cross linking of the collagen was observed in the extract treated rats, as indicated by high stability of acid–soluble collagen and increase in aldehyde content and tensile strength. The extract treated wounds were found to epithelialise faster and the rate of wound contraction was higher as compared to control wounds. [90]

The increased antibody producing ability, enhanced secretion of GABA and improvement in the cognitive abilities in children by HA indicates its action on nervous as well as immune systems. Its effects on the endocrine systems may be explained on the basis of its anti-stress activities.

***Yastimadhu* (*Glycyrrhiza glabra* Linn.) Family-Papilionaceae. English-Licorice root**

Glycyrrhiza glabra Linn (GG) is an under shrub or perennial herb distributed in limited areas of subtropical and warm temperature regions of the country. The shrub is found in Arab, Persian Gulf, Afghanistan and Turkey and Siberia. It is cultivated in Punjab, Andaman Nicobar islands and Miyanmar. [91, 92, 93] GG normalizes the imbalanced *Vata* and *Pitta Doshas* with homeostatic properties. It is attributed with *Madhura Rasa* (sweet taste), *Guru* (heavy) *Snigdha* (unctuous) *Guna* (properties), *Sheeta Veerya* (cold potency) and *Madhura Vipaka* (sweet in digestion). It is good for eyes (*Chakshushya*), promotes physical endurance (*Balya*), complexion (*Varnya*) and virility (*Shukrala*) and is also a *Rasayana* (rejuvenative) drug. It is also good for the hair (*Keshya*) and voice (*Swarya*). The herb is a nervine tonic (*Medhya*) and is used in sore throat (*Swarabhanga*), mouth ulcer (*Mukha Vrana*), respiratory disorders (*Swasa, Kasa*), inflammation (*Vrana Shotha*), poison (*Visha*), vomiting (*Chardi*), thirst (*Trishna*), stress (*Glani*) and emaciation (*Kshaya*). The drug has also potent anti-tussive effect. The roots and stolons are used in medicine. [92, 93]

There are many types of components isolated from GG roots. They are triterpene, saponins, flavonoids, polysachharides, pectin, simple sugars, amino acids, mineral salts, aspargins, bitters, essential oils, fat, female hormone estrogen, gums, mucilage (rhizome), proteins, resins, starches, sterols, volatile oils, tannins, glycosides and various other substances. Tritepenoid compounds accounts for the sweet taste of the licorice root. This compound represents a mixture of potassium-calcium-magnesium salts of Glycyrrhizic acid which varies between 2-25%. The yellow color is due to the flavanoid content of the root which includes liquiritin, isoliquiritin and other compounds. The isoflavones include glabridin and hispaglabridin A and B. [94]

The immunomodulatory activity of GG, aqueous extract and along with zinc was studied by a group of scientists. The parameters involved leucocyte count, spleen weight, in vivo phagocytosis (carbon clearance method), determination of cellular immune response, haemagglutination antibody titre and plaque forming cell assay using sheep red blood cells (SRBC). In addition the effect of the extract on systemic anaphylactic reaction was also measured. Both leucocyte count and phagocytic index was found to be increased significantly with treatment of aqueous licorice extract (ALE) (1.5 gm /kg) compared to control ($P<0.05$). Zinc (45mg/Kg) in combination with ALE (0.75 gm/kg) showed highly significant increase of leucocytes count and phagocyte index compared to control ($P<0.01$). Other results included increased spleen weight, enhanced foot pad thickness; increase in HA titre (when combined with zinc) and higher number of antibody secreting cells (when combined with zinc). Both dose levels of ALE and in combination with zinc showed a positive effect on anaphylaxis. [95]

Glycyrhizine (GL) was investigated for its anti-HIV action in HTLV-III/LAV in vitro. Glycyrrhizin completely inhibited the HIV induced plaque formation in MT-4 cells at a concentration of 0.6mM, the 50% inhibitory dose being the 0.15mM. GL completely inhibited the cytopathic effect of HIV induced plaque formation in MT-4 cells at a concentration of 0.6mM. GL completely inhibited the cytopathic effects of HIV and HIV specific antigen expression in MT-4 cells at a concentration of 0.3 and 0.6mM respectively. Furthermore GL inhibited giant cell formation of HIV–infected Molt-4 clone no-8 cells. GL had no direct effect on the reverse transcriptase of

HIV. [96] Glycyrhizic acid also is effective against many other DNA and RNA virus in cell culture and inactivates the Herpes simplex virus irreversibly. [97] This anti-viral activity of glycyrrhizic acid has been mediated through induction of interferon (IFN).[98]

The oral administration of the herb provides an effective treatment of peptic, duodenal and esophageal ulcers and is also useful in the treatment of oral mouth ulcers [99]. On the other hand deglycyrrhizined licorice (DGL), a soft extract with glycyrrhizin content not exceeding 3%, but containing high level of flavonoids (18.00%) has been found to exhibit a pronounced spasmolytic and anti-ulcerous actions in gastric and duodenal ulcer patients with a lack of toxicity or side effects of sodium retention.[100, 101]

The effect of oral administration of a water freeze dried extract of *Glycyrrhiza glabra* (liquorice) has been studied at doses of 100, 250, 500 mg/kg bw in rats on the plasma concentration of cortisol, adrenocorticotrophin hormone (ACTH), aldosterone, rennin and sodium (Na) and potassium (K). The investigators found that the treatment with licorice extract induced dose dependant and mostly significant decrease in the concentrations of cortisol, ACTH, aldosterone and K. There was concomitant dose dependant increase in renin and Na. The results indicated strong suppression of hypothalamus-pituitary-adrenal axis along with stimulation of the renin production by the kidney stimulating the renin-angiotensin axis [102].

Some other studies reveal GL enhances the level of urinary excretion of cortisol even upto double the quantity of pretreatment level in human subjects similar to levels seen in Cushing's syndrome patients.[103] On the contrary it also raises the serum cortisol level in Addison's disease patients where serum cortisol level is low.[104]

The anti-cancer effect of *Glycyrrhiza glabra* ethanol extract was determined by MTT assay on HeLa cell lines. The investigators found mild anti-cancer activity of GG extract on HeLa cell line having IC50 value of 31.2 microgram/ml. [105]. This study has been supported by similar investigations including anticancer activity of ethanol extract of GG on breast, colon and liver cancer cell lines. Study suggested that ethanol extract of GG has strong anti-hepatic cancer activity at 16.1 microgram/ml and anti-breast cancer activity at 100 microgram/ml while it has no activity against colon cancer cell lines at the concentration of 100 microgram/ml. The investigators also studied the anti-oxidant activity of ethanolic extract and compared it with commercial anti-oxidants like Rutin, BHT, BHA and TBHQ. Although the ethanolic extract was somewhat more efficient than the water extract, but still it was similar to BHA and BHT at 100 ppm but less efficient than TBHQ.[106] Glycyrrhetic acid, a fraction of GG inhibited the specific binding of 12–O-tetradecanoylphorbol-13-acetate (TPA) to mouse epidermal membrane fractions in a dose and time dependant manner thus working as a TPA antagonist which could be responsible for its anti-tumor potential in vivo.[107] The effect of glycyrrhizin (GL) and its aglycone glycyrrhetinic acid (GA) on the growth and differentiation of mouse melanoma (B16) cells in culture were studied. GA inhibits the growth of B16 melanoma cells, causes morphological alterations and stimulates melanogenesis. Glycyrrhizin also resulted in same changes but in 20 times more concentration than glycyrrhetinic acid. When GA was removed after 84 hours of treatment, the growth rate recovered slightly, but the doubling time was about twice that of the control. The investigators found that growth inhibition of GA is the result of inhibition of the transfer from G1 to S phase. [108]

Aqueous extracts of GG at dose levels 250 mg/kg and 500mg/kg has been able to promote the locomotor activity and spatial behavior significantly in sodium nitrite induced hypoxic rats by restoring the decreased level of brain neurotransmitters such as glutamate, dopamine and decreasing the increased level of acetylcholinesterase (AchE) activity significantly. The ethanol extract restored the antioxidant enzymes like superoxide dismutase (SOD), glutathione peroxidase (GPO), glutathione reductase (GR) and catalase (CAT) which were reduced by hypoxia and reversed the increased lipid peroxidation to almost normal level indicating the cerebroprotective effect of ethanol extract of GG which could have been mediated through its anti-oxidant activities. The cognitive deficit was also ameliorated [109].

GG and its components have also been studied for their neuroprotective effects in various neurodegenerative diseases like Alzheimer's disease, Parkinson's disease, multiple sclerosis etc through various mechanisms including anti-inflammatory pathways, anti-oxidant pathways and nurochemical modulating pathways. [110]

GG has shown a strong immunoproliferative activity on leucocyte count, spleen weight, phagocytosis, increased foot pad thickness when administered alone. When administered along with zinc, its immunoproliferative response is broadened including the increase in HA titre and higher number of antibody producing cell along with the previous parameters. Reduction of HIV induced cytopathic effect and induction of IFN-γ is also other parameters to indicate its immune-stimulating activity. Reduction of plasma cortisol, ACTH and aldosterone may possibly explain its anti-stress activity. The neuroprotective and cognition enhancing activity has been mediated partly through cholinergic action and partly through anti-oxidant activity. Therefore GG and its fractions can be concluded as neuro-endocrine-immune-modulator drugs.

Samkhapushpi (_Convolvulous pluricaulis_ Choisy.) Family-Convolvulaceae, English name-Aloe weed

Convolvulous pluricaulis (CP) is a perennial shrub which belongs to convolvulaceae family. It occurs all over India specifically in the plains of North India and Bihar. The drug is one of the important *Medhya Rasayana* in Ayurveda which promotes both intellect and memory along with other cognitive disorders. It is attributed with *Katu* (pungent) *Tikta* (bitter) *Rasa* (taste), *Snigdha* (unctuous) *Pichhila* (lubricating) *Guna* (property), *Sheeta* (cooling) *Veerya* (potency) and *Madhura* (sweet) *Vipaka* (digestion). It pacifies all the three *Doshas Vayu, Pitta* and *Kapha*. It is mentioned to be Rasayana (promoting life span), *Balya* (strength promoting), *Varnya* (complexion promoting), *Swarya* (voice promoting). It is indicated in *Apasmara* (epilepsy), *Unmada* (psychiatric diseases) and *Anidra* (insomnia) and *Bhrama* (vertigo), *Rakta Pitta* (bleeding disorders), diseases of the urinary system and diseases of the digestive system. It is also a cardiac tonic and is indicated in bronchitis (*Kasa*) and *Swarabheda* (hoarseness of voice), skin diseases (*Kustha*), fever (*Jwara*) and internal burning sensation (Daha). Three other specimen including *Evolvulus alsinoides* (convolvulaceae), *Conscora decussata* Schult (Gentianaceae), *Clitorea ternatea* (leguminosae) are also considered in the name of *Sankhapushpi* in various regions of India. Whole plant of CP is used in medicine.[111, 112]

Chemical studies of the whole plant have shown the presence of carbohydrates (D-glucose, maltose, rhamnose, sucrose, starch etc), proteins and amino acids, alkaloids (Shankhapushpine, convolamine, convoline, convolidine, convolidine, convolvine, confoline, convosine), fatty acids/volatile acids/fixed oils (volatile oils, fatty acids, fatty alcohols, hydrocarbons, myristic acid,palmitic acid and linoleic acids), phenolics/glycosides/ triterpenoids/steroids (scopoletin, β-sitosterol, ceryl alcohols, tetratriacontanoic acids, 20-oxodotriacontanol, flavonoid-kaemferol, steroids like phytosterols.[113]

Pretreatment of rats with aqueous extract (AE) of CP (150mg/kg bw) significantly reduced scopolamine induced increase in the transfer latency (TL) in elevated plus maze (EPM). Similarly in Morris water maze (MWM) administration of extract improved the impairment of spatial memory induced by scopolamine. The activity of acetylcholinesterase (AChE) was significantly reduced by the extract within the cortex and hippocampus. The extract also elevated both the level and function of glutathione reductase (GR), superoxide dismutase (SOD) and glutathione within the cortex and hippocampus whose function and quantity were reduced by scopolamine. [114]

The neuroprotective activity of chloroform and ethanol extract of CP was studied against bilateral common carotid artery (BCCA) occlusion induced cerebral ischemic reperfusion injury in Sprague dawley rats of either sex (200-250gms). Both the extracts showed neuroprotective active by decreasing the lipid peroxidation ($P<0.01$, $P<0.001$) and increasing anti-oxidant enzyme levels like SOD ($P<0.01$, $P<0.001$), CAT ($P<0.01$ and $P<0.001$), Glutathione (GSH) ($P<0.001$) and total thiol ($P<0.001$) levels in the extract treated groups as compared to control. Other parameters like measurement of cerebral infarcted area, blood brain barrier disruption, microtubule associated protein 2 (MAP2), immunohistochemical and immuno-pathological also supported the neuroprotective activity of CP. [115]

CP has been investigated clinically. At the dose of 30ml, the drug exhibited anti-anxiety effects in 30 patients. Improved mental function and relief in symptoms like nervousness, palpitation, insomnia, weakness, fatigue and dyspepsia were observed. The immediate memory span in these patients was increased.[116] The patients showed a reduction in the level of plasma cortisol and urinary catecholamines.[117] A clinical study on 980 thyrotoxicosis patients indicated that CP in the dose of 125 mg BD has tranquillising effects in addition to antithyroid property. 90-93% improvement was observed in clinical features like weakness, palpitation, nervousness and appetite where as tachycardia, tremors and easy fatiguability were found improved by 82-86%. This effect was similar to standard antithyroid drug Neomercazole with diazepam (15 mg daily + 5mg BD respectively). At the same time the thyroid function test showed a significant reduction in serum PBI levels in patients treated with CP alone or in combination with neomercazole as compared to standard drug alone. [118].

Aqueous extract of CP was evaluated in cold water forced swimming stress rat models in the doses of 100, 150, 200mg/kg bw administered through the oral route. It was found that the drug treated animals significantly restored their altered body weight, serum cortisol and lipid peroxidation level when compared to the stressed controls [119].

The study shows that CP has been effective as a neuroprotective agent in various experimental models. Clinical studies support the neuroprotective and memory enhancing activity of CP. It is also effective in ameliorating various psychiatric organic diseases like depression and anxiety neurosis. Although no direct studies are available to justify the immunomodulatory potential of CP it can be explained on the basis of the interrelationship between neuroendocrineimmune systems. The drug has shown significant cholinergic activity and cortisol reducing activity which explains its probable immune-stimulating potential. On this basis CP is found to be a neuro-endocrino-immunomodulator drug.

***Brahmi (Bacoppa monnieri* (Linn.) Pennel*.), Syn-Herpestis menniera* (Linn.) H.B.&K, Syn-*Bacopa monniera* Hayata & Matsum. Family-Scrophulariaceae. English name-Bacopa, Indian pennywort, Water hyssop**

Bacoppa monnieri (BM) belongs to the scrophulariaceae family and is a glabrous succulent creeping herb with numerous ascending branches and grows throughout India in marshy places, especially near ponds and tanks [120]. It influences all the three *Doshas* and normalizes their imbalance. It is sweet (*Madhura*), bitter (*Tikta*), acrid (*Kashaya*) in taste, cooling (*Hima*), *Sara* (stable) and sweet (*Madhura* in digestion). The drug subdues specifically the deranged *Pitta Dosha* and normalises the imbalance among all the three *Doshas, Vata, Pitta* and *Kapha*. It is a nervine tonic (*Smriti Prada*), *Ayushya* (improves life span), *Rasayana* (rejuvenates the tissues specifically the nervous tissues), improves voice quality (*Swarya*), indicated in *Kustha* (skin diseases), *Pandu* (anemia), *Meha* (polyurea), *Kasa* (cough), *Visha* (poison), *Shotha* (inflammation), *Jwara* (fever), *Rakta Vikara* (diseases of blood), *Apasmara* (epilepsy) and *Unmada* (insanity).[77]

The whole plant is used in medicine. Chemical analysis of the drug has afforded alkaloids, saponins, glycosides and phytosterols. There are 12 types of bacosides present in BM. They are Bacoside A3, bacopaside II, bacopaside I, bacopaside X, bacopasaponnins C, bacopaside N2, and the minor bacosides are bacopasaponnin F, bacoppasapponin E, bacopaside N1, bacopaside III, bacopaside IV and bacopaside V. Four cucurbitacins known in the name of bacitracin A-D, a known cytotoxic cucurbitacin E and three phernylethanoid glycosides, monnieraside I, III, were isolated from the aerial part of the plant. Two common flavonoids luteolin and apigenin have also been detected in BM. [121] The alkaloids isolated from the plant includes brahmine, nicotine and herpestine. Bacoppa monnieri also contained betulinic acid, D–mannitol, stigmastanol, beta-sitosterol and stigmasterol. Both bacoside –A and bacoside –B have been identified as the major active principles. [122]

Clinical studies have reported that BM special extract when administered to healthy volunteers daily for a period of three months in the dose of 300 mg/kg per day in two divided doses improves visual information processing, learning rate, memory consolidation, anxiety levels, working memory, spatial working memory, attention, verbal learning and cognitive processing in comparison to the placebo group with maximal effects observed after 3 months [123,124]. Additionally in AD patients, a higher dose of BM in a dose of 300mg twice daily per subject improved attention, language and comprehension following a 6 month intervention. [125]

The antistress effect of BM was studied in adult Sprague Dawley rats by administering oral doses of 20 and 40 mg /kg for 7 consecutive days. The treatment has resulted in the reduction of HSP 70 expression in all brain regions with a significant decrease in the hippocampus alone. The lower dose has decreased while the higher dose has increased the anti-oxidant enzyme SOD activity in the treated animals followed by stress in all brain regions except cerebellum and hippocampus. Activity of enzyme P-450 has been restored to almost to control level in higher dose treated animals in comparison to only stress and stress along with lower dose treated animals. On this basis the stress adaptation ability of BM is expressed in terms of modulation of Hsp-70, SOD and P-450 enzyme in the brain [126]. *Brahmi Rasayan*, a preparation consisting of BM has been found to offer protection against electroshock seizures and chemoconvulsion plus the ability to antagonise the haloperidol induced catalepsy in mice and rats. The drug prolonged the phenobarbitone induced hypnosis and produced sedation. This study suggested the CNS effects of *Brahmi Rasayana* mediated through the involvement of GABAergic system [127].

Another 3 months study in 76 healthy adults of 40-65 years old, showed an effect of Bacopa on human memory in a double blind randomized, placebo controlled study in which various memory functions were tested and level of anxiety was measured. The study examined the subjects at the baseline, after three months of trial and after 6 weeks of the completion of the trial. The results showed a significant effect of *Brahmi* on a test for the retention of new information. There was also evidence of decreased forgetfulness of newly acquired informations and the rate of learning was unaffected as observed in the follow up tests. [128]

A double blind placebo controlled trial in healthy subjects suggests that BM has shown apparently no acute effects on the cognitive functioning after two hours of drug administration at a dose of 300 mg (n=18) in comparison to placebo group (n=20)[129]. It can be proposed that BM does not induce any acute effects on cognitive parameters and it takes months for the appearance of the nootropic activity. But the activity persists even after the discontinuation of the drug.

High concentration of nitric oxide generation (NO) by activated astrocytes might be involved in variety of neurodegenerative diseases such as Alzheimer's disease, ischemia, epilepsy. After 18 hours simultaneous treatment of BM extract and S-nitroso-N acetyl-pencillamine (SNAP) to the culture of purified rat astrocytes, the extract of BM has inhibited the formation of ROS nitric oxide and also inhibited the DNA damage of cultured rat astrocytes in comparison to the control astrocytes treated only with SNAP. This effect has been observed in a dose dependant manner and the investigators suggested the role of BM in the prevention and treatment of neurodegenerative diseases. [130]

Some of the experiments indicate BM improves cognition through its anti-inflammatory effect mediated by reduced cylooxygenage-2 (COX-2) enzyme, 5-lipoxygenase (5-LOX), down regulation of TNF-α, IL-6 and nitrite production in the peripheral mononuclear cells activated by lipopolysaccharides (LPS) along with anti-inflammatory and anti-oxidant, anti-arthritic activities. [131, 132]

Long term administration of Bacopaside-1 (BS-I) reduces Amyloid β (Aβ) deposits and ameliorates cognitive impairments in a well-established strain of APP/PS1 transgenic mice via the immune-mediated clearance of Aβ. BS-I modulates the immune system by the regulation of natural killer cell-mediated cytotoxicity, Fc gamma R-mediated phagocytosis, antigen processing and presentation, hematopoietic cell lineage, chemokine signaling pathway, T cell receptor and Toll-like receptor pathway. BS -1enhance the phagocytic activity of microglia upon Aβ of the AD mice brain by exhibiting immune mediated anti-inflammatory activity upon the microglia and clearance of Aβ plaque accumulation which could be the possible mechanism of enhancement of cognitive parameters in patients of Alzheimer's disease. [133]

The adaptogenic activity of ethanol extract of BM was evaluated against acute stress model in mice. Male mice were exposed to swim endurance test and cold restraint stress (4^0C for 2 hours) after 7 days of pretreatment with BM extract in a dose of 27mg/kg p.o. Panax root powder (100 mg/kg po) was taken as a standard and the control group was administered only distilled water. Pretreatment with BM with dose of 27mg/kg p.o significantly reduced the stress induced acute increase in the adrenal gland weight, plasma cortisol, blood glucose, triglyceride and total WBC count. Panax root powder significantly reduced the stress induced increase in adrenal gland weight. [134] BME administered orally at 40 mg/kg/day for 5 weeks was able to prevent the neurotoxicity in cerebral cortex of male Wistar rat brain exposed with aluminum chloride through anti-oxidative mechanism similar to I-deprenyl. (AlCl3). [135]

In another study BME given orally at 30 mg/kg bw for 2 weeks significantly improved the memory and learning capability in intracerebro ventricular streptozotocin (ICV-STZ) induced male Wistar rats. The investigators found the therapeutic efficacy of BME on cognitive impairment and oxidative damage observed by significant reduction in LPO levels, increased GSH (glutathione) contents and upregulated anti-oxidant enzymes activity such as SOD, GST (glutathione –S transferase), CAT (catalase) and GPX (glutathione peroxidase) in the hippocampus infused by ICV-STZ model.[136]

In another study bacosides was administered in the dose of 200mg/kg BW for three months in the middle aged and aged female Wistar rat brain. Bacosides displayed significant anti-ageing property by preventing the lipofuscin aggregation in the brain cortex of middle aged and aged rats. Cholinergic neurodegeneration observed in aged rat brain cortex was mitigated by bacosides. The investigators proposed the anti-ageing effect of bacosides was mediated through prevention of lipofuscin aggregation, increased secretion of acetylcholine, increased cholinergic transmission, modulated the monoaminergic transmission and inhibited LPO in the aged rat brain. [137]

BM when given along with phenytoin (an antiepileptic drug) has been able to improve both acquisition and retention memory without affecting its anti-convulsant action in phenytoin induced cognitive deficits in epileptic mice. BM extract in the dose of 40 mg/kg for 7 days was administered along with phenytoin in the second week of the two week regimen. Phenytoin administered in a dose for 25mg/kg bw per oral for 14 days adversely affected the cognitive function in the passive avoidance task. BM provided powerful corrective effects cognitive deficits induced by phenytoin. [138]

The effect of BM alcoholic extract on cognitive function and Alzheimer's disease induced neuro-degeneration was studied in ethylcholine aziridinium ion (AF64A) induced AD animal models. BM was administered in the dose of 20, 40, 80 mg/kg bw for a period of 2 weeks before and 1 week after the administration of AF64A bilaterally. Rats were tested for spatial memory using Morris water maze test and the density of neurons and cholinergic neurons were determined by histological techniques 7 days after AF64A administration. BM extract improved the escape latency time ($p<0.01$) in Morris water maze test. Moreover the reduction of neurons and cholinergic neuron densities were also mitigated suggesting BM a powerful cognitive enhancer and neuroprotectant [139].

Adequate number of studies is available to support the neuro-endocrine-immunomodulation by *Bacopa monnieri*. The drug and its components have exhibited significant neuroprotective, nootropic and anti-stress activities both in normal and amnesic human subjects and animals.

In experimental animals it has shown strong proliferative actions on various components of the immune system like stimulation of NK cell numbers, phagocytosis, antigen processing and presentation and the cytokine production. Adaptogenic activity of BM in stress models consists of reduction in stress induced increase in adrenal weight, plasma cortisol, blood glucose, triglyceride and total WBC count. The review substantiates the neuro-endocrine-immune modulation by BM.

DISCUSSION

Rasayana concept in Ayurveda is a wonderful gift to the mankind. In the ancient days struggle for existence was an integral part of human life. To avoid social parasitism and to maintain self sustenance during old age, a robust health and strength had to be preserved. Also a disease free life in the old age was of optimum importance. Premature ageing was a frequent occurrence in the ancient days due to inadequate nutrition and challenging environment. Rasayana drugs fulfilled all the above requirements during old age by providing a robust health, delaying the process of ageing, improving life span, giving freedom from old age related diseases specifically the degenerating and infective diseases, keeping the mental and cognitive functions intact. This could be realized only with administration of a drug having concurrent neuro-endocrine-immune modulating ability.

From this review, it is evident that most of the mentioned *Rasayana* entities including WS, OS, TC, HA, GG, BM etc have clearly exhibited their action on the nervous, endocrine and immune systems. In this paper attempts have been made to accumulate and integrate the data available on their single dimensional actions on the neuro-endocrino-immune (N-E-I) axis. On the other hand the growing interrelationship between the N-E-I systems have provided us a marvelous platform to explain their N-E-I modulatory potential on the basis of their actions on either limb of the axis. For example *Tinospora cordifolia* decreases the stress induced serum cortisol, a glucocorticoid which has inhibitory effects on the cell mediated branch of the immune system, specifically the T cells. Cyclosporin, an immuno-suppressive drug indicated for selectively inhibits the T cell proliferation and production of cytokine like IL-2 and others. Cyclosporin also impairs the behavioural and cognitive functions by altering the immune system. However TC extracts have successfully reversed the immune suppression and cognitive impairment caused by cyclosporine and the stress induced elevation of serum cortisol. TC has also neuroprotective effects on the rat hippocampus, one of the main centres for learning and memory. As well it has been found to increase the cholinergic transmission. This example suggests that TC is a potent N-E-I modulator. The N-E-I modulatory actions of other Rasayana drugs can also be explained in the similar manner.

Stress or "general adaptation syndrome" itself is N-E-I phenomenon. The scientific documentation of the antistress /adaptogenic properties of most of the drugs in various stress models like the cold, immobilization, noise, swimming stress etc. greatly supplement to substantiate our claim. Our claim is further strengthened when we found that some *Rasayana* entities viz., WS, TC, *Shilajit*, GG have the ability to modulate the cytokine production. Cytokines have significant potential to alter the N-E-I axis and play a major role in stress response. The antiviral activity of GG has been mediated through the induction of IFN-γ. Probably all the *Rasayana* drugs may be studied for their actions on the cytokines. Further drugs like *Shilajit* decreases the 5-HT turn over in the brain of experimental animals which is increased in stress. All kinds of stressors initiate strong sympathetic arousal which may produce many neurological disturbances along with loss of memory and immune suppression by activating the hypothalamus-pituitary-adrenal axis. Drugs like WS, OS, TC, HA, CP, BM, etc have shown anti-stress effects and have been found to improve the memory and cognitive process. Drugs like TC, GG, HA and CP have been exclusively categorized under *Medhya Rasayana* (intellect promoting) by Charak, an authority in the field of internal medicine in Ayurveda. Besides exhibiting cognition enhancing functions, most of them have also shown immuno-modulating activities. Their anti-stress effect suggests their N-E-I modulating potential.

CONCLUSION

This study reveals the drugs mentioned under *Rasayana* in Ayurveda works in the body by modulating the neuro-endocrine-immune systems whose derangements occurs in various pathological conditions, old age and stressful situations. *Rasayanas* tend to bring them into equilibrium. The applicability of these drugs can be extended for various related disorders of all the three systems. These drugs can be useful in immune-compromised conditions like primary, (humoral, cellular, or combined immune deficiency syndrome) as well as secondary immune-deficiency states like AIDS, cancer, steroid therapy, cancer chemotherapy and also for acute and chronic persistent or latent infections (viral, bacterial) with or without chemotherapeutic agents. Similarly cognitive/ memory deficit and neurodegenerative conditions like senile dementia, Alzheimer's disease, Parkinson's disease, multiple sclerosis, cerebral ischemia, epilepsy and other secondary neurodegenerative dementia conditions deserve the application of these drugs. Drug induced dementia including dementia caused by anti-epileptic drugs, immunosuppressants, cancer chemotherapeutic agents also warrants administration of *Rasayana* drugs, specifically the *Medhya Rasayanas*. The *Rasayanas* possess overall tissue nutrient activity. The *Medhya Rasayanas* specifically have neuro-nutrient activity. Free radicals play significant role in the genesis of various diseases including cancer, cardiovascular diseases, arthritis, diabetes, oxidative hepatopathy, oxidative nephropathy, bronchial asthma etc. The study reveals that *Rasayana* drugs are good sources of natural anti-oxidants. Free radical induced diseases are also a good area for their therapeutic intervention. Stress induced diseases of mental, physical and environmental origin including gastritis, peptic ulcer, hypertension, bronchial asthma, headache, anxiety and depression etc. invite the administration of this particular group of drugs. *Rasayana* drugs will correct suo motto the stress induced secondary diseases due to their anti-stress activities and N-E-I modulating abilities.

The study reveals that a statement given around 3000 years ago still holds its optimum scientific relevance today. The properties like increasing the longevity of life (in terms of *Dirghamayu*), enhancing mental and cognitive performances (in terms of *Smriti* or memory and *Medha* or intelligence and ultimately giving freedom from different diseases (in terms of *Arogya*) including those caused by micro-organisms have been attributed to *Rasayana* drugs. These properties have been found to be elicited on the basis of their N-E-I-modulating activities. We recommend that all the future studies on *Rasayana* drugs should be conducted to establish them as N-E-I modulators. The drugs already reported to be effective on one limb of the axis should be studied for their effects on the other two limbs of the axis. We also propose that non-*Rasayana* Ayurvedic drugs exhibiting concurrent N-E-I modulating activities can be brought into therapeutic domain of *Rasayana* after careful evaluation. We conclude that *Ayurvedic Rasayana* drugs can be entrusted as Neuro-endocrine-immune modulators from natural sources.

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