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Ethnopharmacological review of native traditional medicinal plants for brain disorders

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ABSTRACT

From the earliest times, herbs have been prized for their pain-relieving and healing abilities and today we still rely largely on the curative properties of plants. Over the centuries, societies around the world have developed their own traditions to make sense of medicinal plants and their uses. Some of those traditions and medicinal practices may seem strange and magical, others appear rational and sensible, but all of them are attempts to overcome illness and suffering with an aim to enhance the quality of life. Many of the thousands of plant species growing throughout the world have medicinal uses, containing active constituents that have a direct pharmacological action on the body. The brain is much complex organ of our body and hence no surprise that only a very few drugs are approved by regulatory authorities for treating multi-factorial ailments alike Alzheimer's disease. The oriental system of medicine like "Ayurveda" which is as old as 5000 years, had classified selected plants under "medhya rasayanas". In Sanskrit, "medhya" means intellect/cognition and "rasayana" means "rejuvenation". These are used both in herbal and conventional medicine and offer benefits that pharmaceutical drugs lack, helping to combat illness and support the body's efforts to regain good health and intellect. In the present article, such well known medicinal plants of Indian origin are discussed which are used in various central nervous system (CNS) disorders since ancient times. The focus of this review is an *Withania somnifera, Bacopa monniera, Centella asiatica, Convolvulus pluricaulis, Emblica officinalis* and *Ocimum sanctum* reputed for their effectiveness in CNS disorders. The other blockbuster herbal drugs of non-Indian origin like Ginkgo biloba, St. John's wort, Kava kava and Valerian are not discussed here as these herbs have already been extensively reviewed elsewhere for their effectiveness in many brain disorders. The focus of the present article is to keep abreast with the medicinal plants used in various CNS disorders.

KEY WORDS: Medicinal plants, Alzheimer's disease, Depression, Anxiety, Stress, CNS disorders.

INTRODUCTION

Today, herbal remedies are back into prominence because the efficacy of conventional medicines such as antibiotics, which once had near-universal effectiveness against serious infections, is on the wane. In *Ayurveda* (traditional Indian medicine) about 2,000 plant species are considered to have medicinal value, while the Chinese Pharmacopoeia lists over 5,700 traditional medicines, most of which are of plant origin. Ayurveda-based drug discovery uses 'reverse pharmacology', in which drug candidates are first identified based on large-scale use in the population, then validated in clinical trials. Experts say this approach can cut the time for drug discovery from 12 years to 5 years or less, and for a fraction of the usual cost (1). The history of modern psychopharmacology is short, and its current concepts are more "pharmaco-centric" than those of most other branches of modern medicine.

It was only during 1950s that the very first clinically useful psychoactive drugs were fortuitously identified or serendipitously discovered. Hereupon, meticulous clinical observations played an important role. Subsequent extensive efforts to clarify modes of action and to understand structure-activity relationships of some of these so called first generation psychotherapeutics eventually led to the sub-speciality of psychopharmacology. Thus, most current available drugs suitable for helping patients with mental health problems, are the ultimate fruits of the efforts made to properly defined, understand and improve the therapeutics potentials drugs for which clinical efficacy were already known, or by extrapolating existing knowledge on the modes of actions of known agents with clearly observable effects on mood, behaviour emotion etc. Even today most psychoactive drug discovery projects are conceived on the knowledge and experience gained by such efforts only.

Along with the development of modern neurology and technologies the situation have somewhat changed during the past decade. Several psycho-active drug discovery projects now use more refined pharmacological models conceived on the basis of our current understanding of pathological mechanisms of neurological disorders, or of diverse brain

function regulating processes essential for proper functioning of the central nervous system (CNS). It can not be ignored though that conceptual validity many of these pre-clinical screening models are not yet certain and that technologies necessary for pharmacological screening of novel agents in such models are not yet available to many researchers interested in the discovery of drugs for coping with mental health problems. Consequently, despite considerable progress in our understanding of molecular basis of CNS disorders during the past decades, therapeutic needs of a vast majority of patients with mental health problems can not yet be properly met with. In view of the situation, it is not surprising that popularity of so called herbal remedies based "alternative therapies" for mental health conditions have continued to increase during the past three decades, and during more recent years commercial interest of pharmaceutical concerns in such products have increased considerably.

All critical analysis on commercial and other information available on traditionally known CNS active herbal remedies indicate that most popular amongst such remedies are those which are clinically and pre-clinically the most well studied ones, and which are also recommended for therapeutic purposes by the health authorities of many western and other countries outside the United States. Although clinical efficacy of several such herbal extract based remedies have repeatedly been revealed by proper clinical trials conducted during the past three decades, reports of concentrated efforts to develop structurally and functionally novel psycho-therapeutics based on the acquired knowledge from herbal remedies continue to be rare. The fact that the vast majorities of currently available psycho-active drugs are not natural products or are not derived from bio-active constituents of medicinal plants seems to be a reflection of such a situation. Such is, however, not the situation in many other therapeutic areas where examples of drugs derived from secondary plant metabolites and their derivatives, or conceived on pharmacological knowledge gained from studies of herbal remedies, are abundant. In a systematic analysis published during 1997 it was assessed that 157 of 520 drugs (30%) approved by Food and Drug Administration (FDA) in the USA during 1983-94 (11 years) were natural products or their derivatives (2). This report revealed in addition, that when focused efforts are made to discover natural products for clinical use, the success level rises dramatically. Thus during the same period, 61% of anticancer agents approved were natural products or their derivatives. In the absence of targeted programs for natural products, there was no success. Thus, there were no analgesics, antidepressants, anxiolytics or other CNS active drugs derived from natural products which were approved during the 11 year time period analyzed.

Our current analysis indicates that the situation has not changed much during more recent years. Although identification of hits and leads from secondary plant metabolites continue to be a major goal of many drug discovery projects, most such efforts do not concentrate for the search of agents potentially useful for treatment of CNS-disorders. In addition, comparatively few reports on neuronal function modulating activities of herbal extracts and their active constituents that do regularly appear are, in general, not subsequently evaluated adequately in terms of their potential for identifying structurally or functionally novel CNS active drugs. The main goals of such reports continue to be the evaluation of traditionally known CNS active herbal remedies in terms of our current understanding of brain functions, or to identify their active constituents. In general, main goal of these reports have been to generate more evidence based knowledge justifying their traditionally known therapeutic uses. However, in view of the facts that clinical efficacy of several psychoactive herbal extract based remedies have been repeatedly demonstrated in properly controlled clinical trials and that their efficacy can not be easily interpreted in terms of current concepts of psychopharmacology, they deserve proper attention as readily available sources for structurally and functionally novel classes of CNS active drugs.

Withania somnifera

Withania somnifera is also called Ashwagandha in Sanskrit, belongs to the family Solanaceae, is cultivated in the soils that are unsuited for other crops and requires little care. The plant is known for its varied therapeutic uses in Ayurvedic and Unani practices in India (3). *Withania somnifera* (WS) has been held in high esteem in Ayurveda because of its rejuvenative and tonic effects that are reminiscent of Asian ginseng. Because of these similarities, Ashwagandha has been referred as Indian Ginseng. It has been traditionally used for lack of libido, fatigue, recovery from prolonged illness, mental problems and as a rasayana (rejuvenator) in Ayurveda. It is classified in modern terminology as an adaptogen (4) and some studies showed the efficacy of WS or polyherbal formulation containing WS as adoptogen (5-10). A recent report has confirmed the rejuvenating effect of WS (11, 12). In a double blind study, the growth-promoting effect of WS was studied for 60 days in 60 healthy children, age 8-12 years. The results indicate that WS may be used as growth promoter and hematinic in growing children (13). In another double-blind clinical trial of *Withania somnifera* in a group of 101 healthy males at the dosage of 3 grams daily for one year, a significant improvement of in hemoglobin, hair melanin and red blood cells was observed. Additionally, erythrocytes sedimentation rate was decreased significantly and 71.4 percent volunteers reported improvement in their sexual performance (14). Clinical investigations with the WS root extracts indicate that it exerts significant anti-aging effect in normal healthy but aged subjects (15). Its extract is used alone or in combination with other herbal drugs (8, 16-18) for the reversal of cognitive deficits associated with old age, chronic illness and behavioural disorders. The combined active principles of WS consisting of equimolar amounts of sitoindosides VII-X and withaferin A (19), were earlier shown to augment learning and memory in rats (20).

An extract from WS have shown to affect preferentially events in the cortical and basal forebrain cholinergic signal transduction cascade. The WS induced increase in cortical muscarinic acetylcholine receptor capacity might have partly explain the cognition-enhancing and memory-improving

effects of extracts from WS observed in animals and humans (18). Other studies also indicate the effectiveness of WS as anti-cholinesterase (19) and nootropic-like effect (17, 22).

The likely active principles of WS are glycowithanolides consisting of sitoindosides VII to X, and withaferin (19, 20). These active principles have shown to induce significant antistress (19) and immunomodulatory (23-29) effects. The standardized root extract find useful applications against the intracellular pathogens and in the management of immune suppressed diseases. (30) Some other studies also demonstrated the effect of some isolated constituents of WS or its extract in stress (31-34). EuMil, a polyherbal formulation consisting of standardized extracts of *Withania somnifera* (L) Dunal, *Ocimum sanctum* L, *Asparagus racemosus* Wild and *Emblica officinalis* Gaertn., is used as an anti-stress agent to attenuate the various aspects of stress related disorders. In this study, the neurochemical mechanisms underlying the anti-stress activity of EuMil were evaluated by measuring the rat brain monoamine neurotransmitter levels and tribulin activity. The amelioration of chronic stress-induced neurochemical perturbations by EuMil explains the neurochemical mechanisms underlying the observed putative anti-stress activity of the product (35). In another study by similar group it has been showed that EuMil has significant adaptogenic and anti-stress, activity, qualitatively comparable to *Panex ginseng*, against a variety of behavioural, biochemical and physiological perturbations, induced by unpredictable stress, which has been proposed to be a better indicator of clinical stress than acute stress (4). The WS glycowithanolides was investigated in experimental model of Alzheimer's disease and was found to reverse both the cognitive deficits and perturbed central cholinergic markers induces as a result of neurodegeneration produced by the neurotoxins (16, 36). Many researchers established the role of WS in neuroprotection and tardive dyskinesia (37-41). A study showed anxiolytic-antidepressant activity of WS glycowithanolides (42). The role of WS has also been implicated in the inhibition of morphine tolerance and dependence (43). It has been reported that WS contains an ingredient which has GABA-mimetic activity (44). WS has also been reported to inhibit the activity of acute phase reactants during inflammation and to induce reduction in alpha-2-macrolbumin synthesis, unlike the conventional non-steroidal anti-inflammatory drugs (45-47). Total alkaloid extract (Ashwagandholine, AG) of WS roots has been studied for its effects on the central nervous system. AG exhibited a taming effect and a mild depressant (tranquilizer) effect on the central nervous system in monkeys, cats, dogs, albino rats, and mice (48). AG also potentiated barbiturate, ethanol, and urethane- induced hypnosis in mice.

A clinical study shows that WS exerted hypoglycemic, diuretic and hypochloesterolemic effect (49). Recently, an herbal formulation containing WS showed the efficacy in diabetes mellitus (50). Few other reports also suggesting the possible role of WS in diabetes mellitus (51). It has also been shown that WS have cytoprotective properties (52). Immunomodulatory activity of WS was studied and found that it prevented myelosuppression and significantly increased the hemoglobin concentration. RBC, WBC count, platelet count and body weight in mice (29).

The glycowithanolides from WS have also shown antioxidant activity (53). A herbal formulation containing WS has also shown an anti-oxidant activity which is having natural anti-oxidant, self replicating and sustained action (35). Many other authors confirmed the antioxidant effect of WS through various experimental models (54-61). WS significantly reduced the myocardial injury and emphasize the beneficial action of WS as a cardioprotective agent (62-66). The results of a study indicated the hepatoprotective role of WS through iron induced hepatotoxicity in rats (67). WS root powder suppresses experimental gouty arthritis (68). According to a recent study leave extract of WS, as well as its major constituent withaferin A (WA), potently inhibits NFkappaB activation by preventing the tumor necrosis factor-induced activation of IkappaB kinase beta via a thioalkylation-sensitive redox mechanism (69). A glycoprotein from WS inhibited the hyaluronidase activity of cobra (*Naja naja*) and viper (*Daboia russelii*) venoms (70). There are anecdotal reports that WS may potentiate the effects of barbiturates; therefore, caution should be taken if taking WS concomitantly with this combination. WS is generally safe when taken in the prescribed dosage range (71).

Bacopa monniera

Though pharmaceutical companies continue to invest enormous resources in identifying agents that could be used to alleviate debilitating disorders and retard mental deterioration afflicting numerous people around the world, a source of potentially beneficial agents, namely phytochemicals, would appear to have significant benefits that have yet to be fully exploited (72). *Bacopa monniera* (BM) in India is locally known as Brahmi or Jalanimba (73). The name Brahmi is derived from the word ‘‘Brahma’’, the mythical ‘‘creator’’ in the Hindu pantheon. Because the brain is the centre for creative activity, any compound that improves the brain health is called Brahmi. 'Brahmi' which also means 'bringing knowledge of the Supreme Reality' and it has long been used medicinally and as an aid to meditation. In India, BM is largely treasured as a revitalizing herb that strengthens nervous function and memory.

BM has been used by Ayurvedic medical practitioners in India for almost 3000 years and is classified as a medhya rasayana, a drug used to improve memory and intellect (medhya). BM has been mentioned in several ancient Ayurvedic treatises including the Charaka Samhita (6th century AD), in which it is recommended in formulations for the management of a range of mental conditions including anxiety, poor cognition and lack of concentration and the Bhavprakash Var-Prakarana (16th century A.D.). In certain parts of India, Brahmi is believed to be an aphrodisiac; in Sri Lanka, under the name of Loonooweella, Brahmi is prescribed for fevers; in the Philippines, it is used as a diuretic (74).

The BM extracts and isolated bacosides have been extensively investigated for their neuropharmacological effects and confirmed their nootropic action or antiamnestic effect (75-88). Another study suggested that bacosides induce membrane dephosphorylation, with a concomitant increase in

protein and RNA turnover in specific brain areas (89). The other proposal is that BM enhances protein kinsae activity in the hippocampus which may also contribute to its nootropic action (90). Loss of cholinergic neuronal activity in the hippocampus is the primary feature of Alzheimer's disease (91). A team of other researcher reported that a standardized bacosides-rich extract of BM, reversed the cognitive deficits induced by intracerebroventricularly administered colchicines and injection of ibotenic acid into the nucleus basalis magnocellularis (92). In the same study, BM also reversed the depletion of acetylcholine, the reduction in choline acetylase activity and the decrease in muscarinic cholinergic receptor binding in the frontal cortex and hippocampus. Bacopa extract has shown neuroprotective effect against aluminium-induced oxidative stress in the hippocampus of rat brain (93). Aqueous extract of *Bacopa monniera* reduces nicotine-induced lipid peroxidation (LPO) and confer genoprotection in Swiss mice (94). Another study suggests that *Bacopa monniera* extract reduces amyloid levels in PSAPP mice and can be used in the therapy of Alzheimer's disease (95). A recent study has shown the protective role of bacoside A against chronic cigarette smoking induced oxidative damage in rat brain (96).

BM extract or bacosides have also shown anxiolytic effect (97, 98), antidepressant activity (99), anticonvulsive action (100-102) antioxidant activity (103-111) antistress (112, 113) and antiulcerogenic activity (114-118). Another study suggests an involvement of the GABA-ergic system in the mediation of central nervous system effects of BM (119).

Various clinical studies have also been carried out to establish the efficacy of BM in memory and attention disorders (120-127). Keeping positive results of such clinical trials, BM has been introduced in the Indian market and in other countries, alone or in combination with other phytocomplexes, and utilized in the treatment of memory and attention disorders (128). BM has been found to be well tolerated and without any untoward reaction or side effects in many regulatory pharmacological and toxicological studies (72). The LD50 of aqueous and alcoholic crude extracts of BM in rats were 1000 mg and 15 g/kg by intraperitoneal route, respectively (101). It has been reported that antiepileptic drugs, such as phenytoin, can result in cognitive impairment (129). BM reversed the phenytoin-induced cognitive impairment when administered concomitantly with phenytoin which suggests a potential corrective effect of BM extract in phenytoin-induced cognitive deficits (130). The diverse studies indicated that interactions between herbal medicines and synthetic drugs exist and can have serious consequences (131). Therefore, it is necessary to consider the possibility of BM-drug interaction.

The mechanism of action behind various reported preclinical studies indicating cognitive enhancing effect is still uncertain, as its multiple active constituents make its pharmacology complex. In light of many reports showing important activities of BM extracts or bacosides, further research is required to ascertain the findings mentioned in this review.

Centella asiatica

Centella asiatica (CA), of the Appiaceae (Umbelliferae) family, is also known as Gotu kola, Indian Pennywort, Jal Brahmi and Mandookaparni. CA has been used since ancient times as a medicinal herb. CA has also been referred into the French pharmacopoeia in 1884, in the ancient traditional Chinese Shennong Herbal some 2,000 years ago and in Indian Ayurvedic medicine some 3,000 years ago. The literature reveal that CA has been used for wound healing, better circulation, memory enhancement, sedative, anti-stress, anti-anxiety, an aphrodisiac, adaptogen cancer, immune booster, respiratory ailments, treatment of skin disorders (such as psoriasis and eczema), periodontal disease, burn and scar treatment, revitalizing connective tissue, arthritis, treatment of liver and kidneys, detoxifying the body and high blood pressure etc. However, none of these claims have been evaluated by the FDA, but research has been carried out by various research institutes and universities, which concluded that more research is needed to validate this ancient herb. CA is an outstandingly important medicinal herb that is widely used in the Orient and is becoming increasingly popular in the West.

Titrated extract of CA has along history of use in Europe as wound healing drug. Despite its long history of tradional use, Centella only appeared in the Codex in 1884 (relatively late for Western medicine) and the first dry extract was not created until 1941, three years before its triterpenoid molecules were isolated by the French scientist, P. Boiteau. The initial research, carried out from the late 1950's, demonstrated that asiaticosides was endowed with a potent wound healing and antiulcer activity (132). After that, there are many reports further supporting the efficacy of CA or its isolated triterpenes in burns and wound healing through various validated experimental approaches (133-148). The leaves of CA found application in clinical practice for dermatological disorders and in particular for improving the healing process of wound, burns, skin and vein ulcers (132). During 1980's several clinical studies showed that the Total Triterpenic fraction of *Centella asiatica* (TTFCA) (60-120 mg daily, p.o., for 30-90 days) was able to improve subjective and objective symptoms associated with primary or secondary chronic venous insufficiency of the lower limbs (132,149,150). Some recent clinical trials indicate that TTFCA may positively interfere with the various phases of venous disease: venous wall alterations, change in connective metabolism, endothelial distress and impairment of microcirculation (151-155). Various clinical studies also confirmed the effectiveness of CA or its isolated fractions in wound healing and skin disorders such as psoriasis (156-158). This multi-action CA extract is endowed with a good tolerability, no severe adverse effects were observed during these clinical trials (152). CA has also been studied for immunomodulation but in its preliminary stage (159-161). CA, its methanol and ethyl acetate extract as well as pure asiaticosides have anxiolytic properties (162).

A recent study indicates that CA extract may be useful for accelerating repair of damaged neurons (163). This study demonstrated more rapid functional recovery and increased axonal regeneration indicating that the axons grew at a faster rate. CA leaf extract have a neuronal dendritic growth stimulating property, therefore, the extract can be used for enhancing neuronal dendrites in stress and neurodegenerative

and memory disorders (164). CA has also been considered as phlebotonic supposed to treat chronic venous insufficiency (CVI), a common condition caused by inadequate blood flow through the veins, usually in the lower limbs (165). TTFCA is safe and well tolerated. Several actions of TTFCA in vascular diseases make the use of this compound very interesting in venous and arterial problems (166). Other studies also demonstrated TTFCA's role in venous hypertensive microangiopathy or CVI (167-177). A recent study showed that CA and asiaticosides have an anti-inflammatory property that is brought about by inhibition of nitric oxide (NO) and thus facilitate ulcer healing (178). Some other researchers also showed the efficacy of CA through preclinical and clinical studies for healing gastric ulcers (179-185). CA has also been investigated to demonstrate its role in periodontal therapy (186).

A recent study showed that CA by acting as a potent antioxidant exerted significant neuroprotective effect and proved efficacious in protecting rat brain against age related oxidative damage (187). Many other studies also indicated the CA's role in antioxidant mechanism (188-193). TTFCA of CA reduced the immobility time in forced swimming test and ameliorated the imbalance of amino acids therefore CA can be considered as an antidepressant (194). A clinical study suggested that CA has anxiolytic activity (195). Few studies indicate that CA has cognitive-enhancing and antioxidant properties in normal rats with an added advantage of preventing cognitive impairment (196-199).

The standardized extracts of CA and asiaticoside were well tolerated in experimental animals especially by oral route. Asiaticoside did not show any sign of toxicity up to the dose of 1 mg/kg after oral administration, whereas the toxic dose by intramuscular application to mice and rabbits was 40-50 mg/kg (132). Further, the standardized extract of CA leaves did not show any teratogenic effect in rabbits (200). Allergic contact dermatitis has been associated with topical application of *C. asiatica* (201-203). However, further testing revealed that these reactions may be due to other ingredients in the preparations (204). Another recent clinical report indicates the possibility of CA as hepatotoxic (205). Many people mistake Gotu kola for the cola nut of South America which has caffeine. Gotu does not have caffeine and has been used since prehistoric times to heal wounds and relieve leprosy.

Presently, clinical studies aimed at investigating the sedative, analgesic, antidepressive, antiviral and immunomodulatory effects that have been demonstrated experimentally, are still lacking. However, the therapeutic potential of this plant in terms of its efficacy and versatility is such that further detailed research would appear momentous (206).

Convolvulus pluricaulis

Convolvulus pluricaulis (CP) is also known as Shankhpushpi, also spelled shankapushpi, is an herb that has been used in India for hundreds of years for nervous disorders such as stress, anxiety and insomnia. It produces a feeling of peace and calm, reduces stress, anxiety and mental fatigue. Shankhpushpi is a morning-glory like perennial herb that grows on the plains of India. It has been widely used in Ayurvedic medicine to treat the nervous disorders; the same way kava-kava and valerian are prescribed by American herbalists. It is only recently that Shankhpushpi has been brought to American stores for medicinal use. Herbalists believe that Shankhpushpi calms the nerves by regulating the body's production of the stress hormones, adrenaline and cortisol (207).

In Ayurvedic medicine, it is also believed that Shankhpushpi is an anti-aging remedy called Rasayana. Even though Ayurvedic practitioners have used Shankhpushpi for centuries, there is no hard scientific evidence as to the positive effects of this herb, beside few Indian studies performed in the 1970s and '80s and most of them were published locally. In those studies, people suffering from anxiety were given Shankhpushpi for six weeks and claimed to have slept better, have more energy and better concentration. In one of these studies, published in an Indian Medical Journal in 1982, researchers gave 28 people diagnosed with anxiety 50 mg daily of an herbal formula with shankhpushpi as a primary ingredient. After six weeks of treatment, 91 percent of the patients had more energy and 60 to 70 percent could sleep and concentrate better (208). Today this herb is still a preferred method for reducing symptoms associated with anxiety, panic attacks, nervousness and insomnia. The leaves of Shankhpushpi are used in treating chronic bronchitis and asthma. The root is used for childhood fever, and the oil stimulates the growth of hair. Using the whole plant in the form of a decoction with cumin and milk is used to treat fever, debility, memory loss, syphilis and scrofula. Shankhpushpi has also been reported to have immunomodulatory effects (209). The other study indicates that CP has antiulcerogenic effect due to augmentation of mucosal defensive factors like mucin secretion, lifespan of mucosal cells and glycoprotiens rather than on the offensive factors like acid-pepsin (210).

CP shows promise as a safe, effective remedy for anxiety, but controlled human studies are needed to establish scientifically its efficacy in various CNS disorders with special emphasis on memory enhancing properties. Some investigators found that shankhpushpi has potent depressive action in mice (211).

A study has indicated CP has antiepileptic activity and researchers further investigated the CP interaction with phenytoin from both pharmacokinetic (serum levels) and pharmacodynamic (electroshock seizure prevention) aspects. They advised to avoid clinical combination of CP with phenytoin (212).

Emblica officinalis

Emblica officinalis, commonly known as Amla, is extensively found all over India, in Sri Lanka, Malaysia, China, Pakistan and Bangladesh. The fruits of the plant are used in Ayurveda as a potent rasayana (213, 214). The rasayana are used to promote health and life-span by increasing defence against disease, assisting the aging process and revitalizing the body in debilitated conditions. The clinical efficacy of the fruits of *E. officinalis* is held in high esteem in Ayurveda and Amla is referred to as a maharasayana (214). The fruits from the major constituent of chayavanprash awaleha, a polyherbal

Ayurvedic rasayana preparation described in Charaka samhita (215). This preparation is widely used in India for its preventive, curative and health restorative properties. Experimental studies conducted with the fruits indicate that they have significant effect against isoprenaline-induced myocardial injury, radiation-induced chromasomal damage and heavy metal induced liver and renal damage. Clinical studies suggest that the fruits have anabolic activity. Experimental investigations on Chyavanprash have indicated that it exhibits significant adaptogenic, anti-stress immunopotentiating and memory-facilitating effects (216). *Emblica officinalis* have been reported to have immunomodulatory properties (217) and a marketed herbal product Immuplus (containing *Emblica officnalis* as one of its ingredients) has been reported to have immunomodulatory activity through humoral and cell mediated immunity (218). The tannoid principles of *Emblica officinalis* have recently shown an antioxidant activity in chronic stress induced changes in rat brain (8). Triphala, a popular ayurvedic formulation containing *Terminalia chebula*, *Terminalia belerica* and *Emblica officinalis* prevent the noise-stress induced changes in the antioxidant as well as cell-mediated immune response in rats (219). Another study with tannoids principles of *E. officinalis* (EOT) shows that EOT exerts a prophylactive effect against neuroleptic-induced tardive dyskinesia (67). *Emblica officinalis* have been said to be effective in neurodegenerative conditions associated with aging (213) of the indirect actions, potentiation of the action of adrenaline on the blood pressure of cat, isolated frog heart and nictitating memebrane of cat and the prolongation of the hypnosis were observed (220). Amla protected effectively against tremors and clonic and tonic convulsion induced by nicotine. It also antagonised tremorine-induced tremors and other cholinergic symptoms (221). Additionally, Amla have antibacterial, anti-viral and anabolic activities (222-224). Analgesic and Anti-pyretic activity of *Emblica officinalis* Gaertn have also been reported (225). Clinical studies indicate that *Emblica officinalis* is effective in hyperchlorhydria with burning sensation in abdominal and cardiac regions and epigastric pain (226). Pepticare, a herbomineral formulation containing *Glycyrrhiza glabra*, *Emblica officinalis* and *Tinospora cordifolia* posseses anti-ulcer activity, which can be attributed to its anti-oxidant mechanism of action (227). *Emblica* fruit contains ascorbic acid (0.40%, w/w), and the Ayurvedic method of processing increases the healthy characteristics of the fruit to a higher antioxidant activity and a higher content of ascorbic acid (1.28%, w/w). It has also been found that vitamin C accounts for approximately 45–70% of the antioxidant activity (228). A recent study states that Amla churna (50, 100 and 200 mg/kg, p.o.) produced a dose-dependent improvement in memory scores of young and aged mice. Furthermore, it reversed the amnesia induced by scopolamine (0.4 mg/kg, i.p.) and diazepam (1 mg/kg, i.p.). Interestingly, brain cholinesterase activity and total cholesterol levels were reduced by Amla churna administered orally for 15 days (229).

***Ocimum anctum* -** Holi basil (*Ocimum sanctum*) popularly known in India as 'Tulsi' is worshipped every morning by most Hindus. It is perhaps the most sacred plant in India and is referred to in Ayurveda for its healing and life giving properties. There are different varieties of Tulsi that are often called Holy, but *Ocimum sanctum* is the true variety (230). It is not as leafy or bushy as most Tulsi, but is appreciated for its fragrance. Tulsi is an erect hairy annual herb, found throughout India, up to an altitude of 1,800 m in the Himalayas, cultivated also in temples and gardens.

Tulsi is useful in the treatment of variety of diseases. An ethanol extract of the leaves of *Ocimum sanctum* was screened for its effect on central nervous system. It prolonged the time of lost reflex in mice due to pentobarbital, decreased the recovery time and severity of electroshock and pentylenetetrazole induced convulsions and decreased apomorphine induced fighting time and ambulation in 'open-field' studies (230). Using a behavioural despair model involving forced swimming in rats and mice, the extracts lowered the immobility in a manner comparable to imipramine. This action was blocked by haloperidol and sulpiride, indicating a possible action involving dopaminergic neurones. In similar studies, there was a synergistic action when the extract was combined with bromocriptine, a potent D_2 -receptor agonist. Ethanol extract of leaves of *Ocimum sanctum* was screened for its anti-stressor actions against acute and chronic noise stress in albino rats by investigating the plasma corticosterone level in plasma of rats subjected to 30 min noise (100 dB) stress. Chronic exposure (4 hr daily for 30 days) to noise with same intensity reduced the hormonal level significantly. Treatment of animals with ethanol extract of *Ocimum sanctum* prevented the changes in plasma level of corticosterone induced by exposure to both acute and chronic noise stress, indicating the antistressor property of the plant against noise (230). Adaptogenic (anti-stress) activity of *O. sanctum* plant has also been reported (231). The plant enhanced the physical endurance and survival time of swimming mice, prevented stress-induced gastric ulcers in rats and protected mice and rats against hepatotoxicity induced by carbon-tetrachloride (232). It also prevented milk-induced leucocytosis in mice. Thus the plant manifested a non-specific type of protection against a variety of stress-induced biological changes. The hexobarbitone - induced hypnosis has been potentiated by *O. sanctum* (233).

The ether extract of *O. sanctum* leaves showed antibacterial activity against *Esch. Coli* and *Staph. aureus* (234). The juice of *O. sanctum* showed potent antiviral against top necrosis virus of pea (235). Tulsi is heat generative in action and very effective in curing colds, cough, sinus infections, chest congestion and other respiratory diseases (236). Tulsi had been reported to possess immunostimulant activity (237). The aqueous suspension and methanolic extract of the leaves were reported to have immunoregulatory activity and it increases cell mediated immune response. The alleged anti-asthmatic potential of *O. sanctum* leaves was also evaluated in experimental models. The results suggested the possibility of usefulness of both the drugs in non-toxic doses, in the treatment of human bronchial asthma (238). *Ocimum sanctum* has also been reported to act through humoral immunity (239).

CONCLUSION AND PERSPECTIVES

It is now becoming exceedingly apparent that available psychotherapeutics does not properly meet therapeutic demands of a vast majority of patients with mental health problems, and that herbal remedies remain to be the ultimate therapeutic hope for many such patients in the western world and elsewhere. Critical analysis of our current understanding of the most popular and most well studied CNS active medicinal plants reveal that many therapy relevant questions have not yet been properly answered for any of them. However for many (or most) of them clinically efficacy have repeatedly been demonstrated in properly controlled clinical trials. Consequently, therefore, many phyto-pharmaceutical laboratories are now concentrating their efforts to identify the active constituents and modes of actions of these herbs. Ultimate goal of most such efforts has been to obtain a patentable or better therapeutically useful or better standardized extract. However, till now, very little attention has been paid to develop structurally and/or functionally novel CNS active drugs from psychoactive medicinal plants. Available information summarized in this review strongly suggests that such a situation could be hampering more rapid progress of CNS active drug discovery projects.

Historically, extrapolation of ehtnopharmacological knowledge derived from efforts made to understand and properly define therapeutic potentials of herbal remedies has, eventually, led to the discovery of numerous currently prescribed drugs. In addition, many concepts and principles of modern medicine and pharmacology could be established also from the observations made and experiences gained by such efforts. Since therapeutic possibilities offered by a vast majority of traditionally known medicinal plants have not yet been properly explored, they are still remain to be affordable and potentially promising natural sources for obtaining structurally and functionally novel drugs and/or “hits” and “leads” suitable for drug development purposes.

It can not be ignored though, that numerous herbal remedies continue to be the only therapeutic possibilities for a vast majority of global population and that uncontrolled medicinal uses of herbal remedies in the western word have consistently increased during the past few decades. Therefore, extensive efforts to rationalize the situation continue to be major goal of many research laboratories and of almost all health authorities, around the globe.

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