ACTA SCIENTIFIC MEDICAL SCIENCES

Volume 2 Issue 8 November 2018

Review Article

Prospect of Ayurveda in Neuromedicine

Subhanil Chakraborty and Ranadhir Chakraborty*

Omics Laboratory, Department of Biotechnology, University of North Bengal, West Bengal, India

***Corresponding Author:** Ranadhir Chakraborty, Omics Laboratory, Department of Biotechnology, University of North Bengal, West Bengal, India.

Received: September 12, 2018; **Published:** October 22, 2018

Abstract

Clinical practice and research in neuromedicine severely lack the scope of exploring newer avenues of conventional drug therapy due to inadequate quantity and quality of newly developed drugs in this field. Clinical research with prospective compounds rarely addresses the potential of using Ayurveda-based natural plant-derived resources, which were found to be beneficial traditionally in diverse kinds of neurological ailments. Most promising plant products have gone through several *in-vitro* and *in-vivo* animal studies for their capability in producing desired efficacy for an indication related to the central and peripheral nervous system disorders and also towards psychological distresses without compromising the safety of the subject. However, prolonged and inferential human clinical trials utilizing the reported efficacy of promising Ayurveda-based dosing of plant extracts or products are alarmingly negligible. Scientific basis and opportunities were reviewed for hard-core scientific exploration and evaluation of genuinely prospective nature-based remedies for probable proceedings towards clinical trials and future approval for the use by neurophysicians in even most perplexing neuro-pathologies dangerously affecting the quality of life of the entire human kingdom.

Keywords: Neuromedicine; Drug Development; "Vata" Humour; Ayurveda; Neurodegenerative Diseases; Pre-clinical Studies; Human Trials; Phenome elemedicine; Evolutionary Game Theory; MATLAB

Introduction

Development of new drugs in the field of neuromedicine is severely slowed down in an intricate labyrinth of well-recognized challenges in spite the skyrocketed therapeutic need of the patients with neurological disorders. Along with common obstacles faced by drug developers like the expiration of Patents, lesser budget allocation to health-care needs, escalating rigidity in regulatory requirements for drug approval and elevating-cost of R and D; neuromedicine especially faces certain challenges mostly limited to this very field of diagnostics and therapeutics ever-trying to ameliorate CNS related disorders. Clinical programmes related to neurological ailments are inclined to be time taking, complicated and larger than other indications; consequently, these easily take nearly or even more than a decade from the initiation of clinical trials to approval with the lowest success rates in terms of benefiting end users with claimed efficacy and getting approved for therapeutic use. Only 8% of the prospective compounds undergoing Phase I clinical trials end up in shelves of drug stores. Globally, very few innovative and new CNS products were actually undergoing clinical testing and due to less opportunity of success and the heavy burden of several big- budget failures in earlier trials, most major pharmaceutical giants were withdrawn from R and D activity related to neuro disorders. It has become well recognized that there is a void in the information required for identifying valid drug targets. For researchers and clinicians of neuromedicine, identifying a diagnostic marker for early diagnosis of neurological disorders and neuropsychiatric conditions are highly challenging due to heterogenic nature of disease symptoms, the difference in patient perceptions and unavoidable need for further understanding of pathophysiology and aetiology of developing neurological disorders [1,2].

A study conducted on all CNS related products which entered Phase I clinical trials from 1990 for next 22 years has shown that only 8% of all novel entities entering clinical trials for the study period belong to the concern of neuromedicine, with fewer CNS drugs entered trial over time. The most alarming finding of the study was the reason of discontinuation of majority of the drugs

at Phase III clinical trials owing to inadequate efficacy causing CNS drugs more likely to fail than non-CNS drugs at Phase III trials giving a reason to dissuade investments from neuromedicine R and D for high likelihood of failure after a long-term course of trials [3]. Uncertainties of successful drug discovery were evident due to safety issues entangling more than half of the programmes whereas efficacy issues were faced in not less than one-third of the programmes. Further, differentiable challenges were identified in the outcome of applications in psychiatry like a correct selection of the study population, clinical efficacy and dose determination, whereas failure in reaching a primary endpoint, safety and incomplete pharmacokinetic/pharmacodynamic studies affected mostly in the field of applications in neurology [4]. In response to the challenges, the United States House of Representatives passed the 21st Century Cures Act in 2015 that would empower USFDA to approve newer drugs on the basis of surrogate measures of efficacy, including changes in imaging studies or laboratory diagnosis. Such biomarkers are currently used in trials of Alzheimer's disease and several other CNS diseases, however, impact of these biomarkers on patient health outcomes still remain doubtful [3].

Considering Alzheimer's disease as the most common type of incurable dementia, current medical science still remains incapable of offering a complete cure and newer perspective are explored for the better understanding of the disease along with a search for faster diagnosis and management protocols [5]. By the end of 2017, among the 126 Alzheimer's treatments undergoing clinical trials; only 11 natural products were being tested clinically and only one of which is on Phase III [6]. Alzheimer's Drug Discovery Foundation recognized the need of exploring combination therapies suitable for trials as most of the under-trial drugs are weighted towards Amyloid-beta and tau proteins and the need of neuroprotective functions of newer drugs were undeniable [6]. A very few treatment choices are to be had to recover the balance in degenerative cerebellar ataxias. In the present article, we would try to evaluate the potential of the nature-based reservoir of curative and neuroprotective medicinal plants with the help of ancient knowledge of Ayurveda and supported by some sort of clinical or preclinical shreds of evidence presented in form of scientific literature or trial reports.

Neuromedicine related aspects of Ayurveda

Ayurveda acknowledged more than 80 types of neuro-disorders including neuro-degenerative diseases as Vatavyadhi [7], influenced broadly by the deranged effect of "Vata" humour, identified as one major constituent of "Tridosha"; a determinant of a person's basic constitution type called as "Prakriti" and holistically approached for amelioration or cure through a variety of medicinal plant-based pharmacological or non-pharmacological means of therapy with a potential for genesis of personalized medicine [8,9]. As per Ayurveda, there are three manifestations of the 'Vata' diseases namely 'vata vriddhi' (neural hyperfunctioning), 'vata ksaya' (neural hypofunction), and 'avarana' (masked functioning). Accepting the fact that majority of 'vata' diseases are incurable, Ayurveda texts have narrated diverse treatment regimens, including 'Panchakarma' (five actions), yoga, massage and herbal medicine, that can make life easier and increase life expectancy. "Satvavajaya" or mind-control based ayurvedic psychotherapy along with yoga was employed to restore memory, intellect and fortitude of a patient [10,11]. "Marma" therapy, however, based on massage therapy to 107 vital points of the body for mild to moderate stimulation for treating diseases of nerves and brain including several types of paraplegia, hemiplegia and monoplegia [12]. Vulnerability factors were cautiously determined in Ayurveda depending upon various psycho-somatic traits for selection of correct therapy for an individual [13]. Considerable role of genopsycho-somatotyping and investigating molecular correlates among persons with different body types and their link with temperament and certain physiological characteristics were supported by some recent neuroscience studies [14]. For diverse neurological problems ranging from Epilepsy to several psycho-dermatoses, Ayurveda suggested for vast nutritional, psychological and lifestyle modifications along with other "nidan" s or therapies [15,16]. Revealing the harmony of a person's physical, emotional and spiritual levels is the fundamental principle of Ayurvedic healing as it perceives disease being the end result of the disharmonious state of one's basic constitution. The philosophy of Ayurveda advocates the principle of harmony in attaining 'sattviic' nature to overcome illness; and for the sick to inculcate a 'sattvic' mind to bring rapid healing to their body. Current studies in neurology have identified that three different states of hemispheric chemical dominance, generally termed as "Tridosha", could regulate neuro-immuno-endocrine/cellular integration differentially and therefore might be able to regulate the predisposition to several neuropsychiatric and systemic diseases [17]. For one instance, a study finding identified incidence of Parkinson's disease highest and statistically significant among people belonging to "Vata" types and suggested an Ayurvedic Constitutional Assessment Form for correctly assessing a person s constitutional type with a hope to identify vulnerable population and delaying onset of symptoms or disease progression by applying Ayurveda based therapy even as a prophylactic measure [18].

Ayurveda-based neuropharmacological approach

Healing practices for most neurological disorders in Ayurveda have broadly followed a reverse-pharmacology [8,19] based proto-

cols where individual plant parts, whole plant or a combination of plants were used as polyherbal preparations on ailing population for a prolonged period to observe the benefits or adverse effects before considering those as medicines. Based upon the observed neuromodulatory effects of certain natural herbal agents, efforts were made in consolidating details of plants which work alone or in combination for some major neurological disorders and symptoms [19]. A comprehensive list of fifty-six commonly recommended plants for treating brain disorders according to Ayurveda practice was conceived in an article that put emphasis on the popular belief that Ayurvedic drugs might produce negligible side effects and after effect in comparison with synthetic medicinal agents [20]. Psychotherapeutic effects of ten plant-extracts were demonstrated through pieces of evidence reported in primary clinical trials and animal studies and further clinical evaluations were suggested for confirmation of neuroprotective and antipsychotic activity [21]. Several major disease-specific Ayurveda remedies through uses of different medicinal plants were reviewed including Dementia [22], Parkinson's Disease [23], Epilepsy [24], Cognitive disorders in general [25], retinal degenerative diseases [26], neurodegenerative diseases [27] and Alzheimer's disease [28], where efficacies were mostly substantiated through animal studies but little or no studies were detailed for safety confirmations.

In-vitro evaluation of promising natural extracts

In-vitro safety and efficacy studies were conducted extensively for a few ayurvedic plant extracts and preparations. *Bacopa monnieri* or Brahmi was evaluated for its active chemical constituents and several *in-vitro* studies suggested its antioxidant properties and free radical scavenging action. Protective functions were exhibited by *Bacopa monnieri* after human non-immortalized fibroblasts were evaluated for the free radical-mediated toxicity and DNA damage induced by hydrogen peroxide. Reduction of oxidative stress and lipooxygenase activity was also monitored by *in-vitro* action of Brahmi. No direct genotoxicity was observed after incubating Brahmi extract with plasmid DNA pBR322 for a period of one hour at 37°C[28]. Ashwagandha or *Withania somnifera* is unsparingly used in Ayurveda for its memory boosting potential as nerve tonics. Root extracts of *Withania somnifera* was found to be neuroprotective in NGF-differentiated PC12 cells post-exposure to hydrogen peroxide and Amyloid beta induced cytotoxic effects. Aqueous extract of *Withania somnifera* inhibited lipopolysaccharide-induced microglial-mediated neuroinflammation by prevention of ROS, RNS and inflammatory cytokines release in murine BV-2 cells and also inhibited NO production in Raw 264.7 cell lines. Role of Ashwagandha in maintaining integrity of blood-brain barrier was illustrated through gelatine zymogram data, which suggested inhibition of MMP2 and MMP9, both microglial inflammatory factors responsible for degrading basal lamina and eventually disrupting blood-brain barrier [29]. Effect of Ashwagandha root extract was found to be promoting dendrite formation in human neuroblastoma cells on a dose dependent manner. Detailed *in-vitro* studies on SK-N-MC human neuronal cell lines treated simultaneously with *Withania* extract and β-amyloid, have shown neuronal growth stimulatory effects of the plant extract and also described prevention of cellular degeneration even in HIV associated neurodegenerative disorders [30]. Presence of several phenolic compounds, flavonoids and essential oils contributed to the neuroprotective actions exhibited by *Valeriana wallichii* or Tagara were tested in laboratory on mitochondrial- enriched fractions of murine brain in case of neurotoxicity when brain cells were exposed to methylmercury compounds after consumption of seafoods leading to autism spectrum disorders, Hunter Russell syndrome or Minamata disease epilepsy [31]. Four different plants belonging to three different botanical family were considered as Shankhapushpi by Ayurveda practitioners all over India. Various *in-vitro* studies were conducted to determine their neuropharmacological actions as nerve tonic and neuromodulator. Protection of cell viability in Neuro-2a a neuroblastoma cell line was exhibited by Shankhapushpi, when toxicity was induced by action of β-amyloid peptides and Ferric reducing antioxidant power (FRAP), DPPH radical-scavenging assays along with phosphomolybdenum complex methods were conducted to evaluate the total antioxidant potential and hydroxyl radical scavenging potentials of methanolic extracts of Shankhapushpi. One plant among the four tested plants, *Evolvulus alsinoides* emerged as true source Shankhapushpi, as it was found to be superior in previous actions and *in-vitro* actions exerting acetylcholine esterase and lipoxygenase enzyme inhibitory actions as well [32]. *Centella asiatica* or popularly known as Gotu Kola in western countries including USA has gained popularity as herbal dietary supplement with a potential for enhancing memory and cognitive functions. Ethanolic extracts of *Centella asiatica* was found to be increasing neurite outgrowth in SH-SY5Y human neuroblastoma cell lines by accelerating process elongation representing an interesting therapeutic alternative to speed nerve generation [33].

Animal studies supporting therapeutic effects of Ayurveda

All of the animal studies considered for review were done under ethical guidelines governed either by the country of testing or by NIH Guidelines for the Care and Use of Laboratory Animals and approved by the animal ethical committee of the Institute. In several *in-vivo* studies on the murine brain, *Bacopa monnieri* was found to reduce oxidative damage and lipid peroxidation and increase activities of important enzymes like SOD, CAT, GPx and GSH in the prefrontal cortex, striatum and also in hippocampus[28]. *Bacopa* extract has significantly shown ameliorating effects on olfactory bulbectomized mice suffering from cognitive dysfunction due to the effect of Acetylcholine Transferase enzyme and inhibition of degeneration of cholinergic neurons on a rat model of Alzheimer's disease. The positive therapeutic effect was demonstrated by Brah-

mi in the reversal of cold stress-induced hippocampal damage and phenytoin-induced memory impairment of experimental rats. Attenuating effects of Brahmi on drug-induced anterograde amnesia of rats were evaluated with positive findings in Elevated plus maze test and Morris Water Maze Task. Extract of *Bacopa monnieri* demonstrated enhancement of plasticity markers like Brain-derived neurotrophic factor in the cerebrum of Scopolamine-fed mice suggesting an improvement of brain plasticity. The decrease in the formation of amyloid fibrils, reduction in two types of amyloidogenic proteins and ROS in brain and inhibition of multiple components of beta amyloid-induced potentiation of Alzheimer's disease in C57/B16 mice were among other major findings when Brahmi extracts were used as a test therapeutic agent [28,34]. *Withania somnifera* exhibited anxiolytic and antidepressant effects in the acute sleep deprived Wistar rats along with ameliorating effects of brain impairment in ageing rats. Animal studies for five weeks involving middle-aged female rats fed with Ashwagandha extract under intermittent fasting demonstrated inhibition of pro-inflammatory cytokines and activation of microglial cells while significant reduction in expression of Iba 1, a microglia/ macrophage- specific protein suggestive of lesser occurrence of inflammatory response in both hippocampus and PC regions of brain was causing relief from anxiety [35]. Neuroprotective action of constituents of Ashwagandha root extracts on murine models of Parkinson's disease and reversal of behavioural deficit, plaque pathology, accumulation of beta-amyloid peptides and oligomers in brains of APP/PS1 transgenic mice models of Alzheimer's disease were also established [30]. Better retention of memory and recovery of cognitive functions were evident with the use of Shankhapushpi Ayurveda on scopolamine-induced amnesia models comprising male Sprague-Dawley rats through Morris Water Maze Task and performance in Cook and Wiedley's pole climbing apparatus [32]. Potential effects of *Centella asiatica* included improvement of cognitive function, learning ability, memory, performance and increased gluatathione and catalase levels while normalizing malondialdehyde levels in the murine model of Alzheimer's disease. Decreased seizure scores were reported in a dose-dependent manner and antidepressant activity of triterpene extract of *Centella asiatica* was reported in mice models using forced swimming tests [33]. *In-vivo* studies with both young and aged mice also demonstrated cognitive-enhancing effects and effect on mitochondrial and antioxidant response pathways by Gotu kola [36]. Mostly *in-vivo* studies were conducted using murine models for evaluating positive therapeutic effects of certain Ayurveda based plant extracts in case of Parkinson's disease (*Mucuna pruriens)* [37], Spinal cord injury (*Withania somnifera*) [38], Motor dysfunction in spinal cord injury (*Epimedium koreanum*) [39] and many other neuropathological conditions.

Inadequacy in number and scale of clinical trials

Several Ayurveda plants those are extensively used in perspective of neuromedicine have also undergone scarce numbers of human trials involving healthy or suffering individuals for the study of efficacies and possible determination of safety profiles. Most of the sincere and authentic human clinical trials involved only three or four plants in total, among which mainly one or two plants have undergone serious reviews. At least eight randomized, double blind, placebo controlled clinical trials were conducted on various types of subjects involving elderly people of more than 55 years of age, children with Attention deficit hyperactivity disorder, adolescents and healthy individuals for not less than twelve weeks in each trial to evaluate therapeutic claim and *in-vitro* findings of *Bacopa monnieri* using different battery of cognitive function testing with mostly positive outcomes [40,41]. A decade long research review logically tried to draw some safety remarks based on the findings of human trials [42]. However, the need of multicentric trials involving larger number of test subjects and a sincere requirement of overcoming from the state of infancy related to research with *Bacopa* that possess such huge potential in neuromedicine was undeniable [40-43]. Apart from Brahmi, very few human clinical trials were successfully conducted to establish fragments of claimed efficacy in *Mucuna pruriens* [44,45] or in some polyherbal or herbomineral Ayurvedic compositions [46-48]. *Mucuna pruriens* contains non-protein amino-acid-derived L-dopa (3,4-dihydroxy phenylalanine) in addition to hallucinogenic tryptamines, and anti-nutritional factors such as phenols and tannins. The therapeutically important component of ailment for tremor disease is the levodopa content of *Mucuna pruriens.* The endogenous accumulation of L-dopa, on a dry weight basis, in tissue-*cultured M. pruriens* plant cells was found to be in a range of 0.2 to 2.0% [49].

Conclusion

After millennia of safe and efficacious traditional use in brain and nerve disorders, with support of more than a decades old *in-vitro* and animal studies reports confirming efficacy in several indications and considerable but rigorous test-worthy safety profiles, it is quite evident that Ayurveda based plant products must pass through the gateways of stringent multicentric unbiased long term human trials in prior being used beyond doubt in the field of neuromedicine [50] and other fields of healthcare. Inclusion of more Ayurveda based medicines with proper information

of uptake, dosage and contra-indications into future clinical trials could surely expand the horizon of finding keys to cure the complex incurable ailments of our brains. Apart from studying the pharmacological activity of the active components present in the herbs, re-construction of Ayurvedic therapy in the present millennium should transcend from the existing methodology of disease detection, prognosis, treatment and follow-up to a state of exploring Ayurvedic lifestyles, regimens, and Yogic practices as a part of treatment regimen. As for example, the predictable allopathic effect of *M. pruriens* is quantifiable, but it is difficult to measure the experiences one undergoes during an effective Ayurvedic treatment of tremor disorder. Hence, the research at Phenome (evaluation as a whole; sum total of the phenotype expressed) level, going beyond genome, transcriptome and proteome studies, shall be the starting point of Ayurvedic research on neuromedicine.

Acknowledgment

Authors sincerely thank Department of Science and Technology, India as one of the authors, S.C. receives research grants through INSPIRE FELLOWSHIP vide sanction order DST/INSPIRE Fellowship/2014/IF 140766.

Conflicts of Interest

There are no conflicts of interest.

Bibliography

1. Craven R. "The risky business of drug development in neurology". *Lancet Neurology* 10 (2011): 116-117.

2. Beyer K. "Advance or stagnation in CNS drug development?" *Lancet Neurology* 9.10 (2010): 956-957.

3. Kesselheim AS., *et al*. "Two decades of new drug development for central nervous system disorders". *Nature Reviews Drug Discovery* 14.12 (2015): 815-816.

4. Butlen-Ducuing F., *et al*. "Regulatory watch: challenges in drug development for central nervous system disorders: a European Medicines Agency perspective". *Nature Reviews Drug Discovery* 15 (2016): 813-814.

5. Wang J., *et al*. "A systemic view of Alzheimer disease – insights from amyloid-β metabolism beyond the brain". *Nature Reviews Neurology* 13 (2017): 612-623.

6. Fillit H., *et al*. "Closing in on a cure: Alzheimers Clinical Trials Report (2017).

7. Patil V. "Holistic approach of Ayurveda and panchakarma in neurological disorders". *Alternative and Integrative Medicine* 6.4 (2017): 73.

8. Chakraborty S and Chakraborty R. "Genesis of Personalized Medicine: Relevance of Ayurveda in the Present Millennium". *Journal of Molecular and Genetic Medicine* 11.3 (2017): 1-3.

9. Mishra S., *et al*. "Historical perspective of Indian neurology". *Annals of Indian Academy of Neurology* 16 (2013): 468-477.

10. Behere PB., *et al*. "Ayurvedic concepts related to psychotherapy". *Indian Journal of Psychiatry* 55 (2013): 310-314.

11. Patil S and Joshi JR. "Role of Satvavajaya chikitsa in jara w.s.r. to socio – psychological problems". *Journal of Ayurveda and Holistic Medicine* 5.4 (2017): 101-105.

12. Pal PK., *et al*. "Critical analysis of Lohitaksha Marma and its applied aspect". *EJPMR* 4.12 (2017): 350-353.

13. Rizzo-Sierra CV., *et al*. "Highly Sensitive Trait and Ectomorphism: Another Link on Creativity and Psychopathology". *The Canadian Journal of Psychiatry* 56.11 (2011): 702-703.

14. Rizzo-Sierra CV. "Ayurvedic Genomics, Constitutional Psychology, and Endocrinology: The Missing Connection". *Journal of Alternative and Complementary Medicine* 17 (2011): 465-468.

15. Arya R. "Ancient Indian concepts about phenomenology, biology, and therapeutics of epilepsy". *Journal of the History of the Neurosciences* 27.1 (2017): 56-71.

16. Singh S., *et al*. "An overview of Ayurvedic and contemporary approaches to Psychodermatology". *Journal of Phytopharmacology* 3.4 (2014): 286-299.

17. Kurup RK and Kurup PA. "Hypothalamic digoxin, hemispheric chemical dominance, and the tridosha theory". *International Journal of Neurosciences* 113.5 (2003): 657-681.

18. Manyam BV and Kumar A. "Ayurvedic constitution (*Prakruti*) identifies risk factor of developing Parkinson's disease". *Journal of Alternative and Complementary Medicine* 19 (2013): 644-649.

19. Sandhya S., *et al*. "Herbs used for brain disorders". *Hygeia J D Medicine* 2 (2010): 38-45.

20. Balkrishna A and Misra LN. "Ayurvedic Plants in Brain Disorders: The Herbal Hope". *Journal of Traditional Medicine and Clinical* 6.2 (2017): 1-9.

21. Younus M., *et al*. "Value of ayurvedic medicinal plants as psychotherapeutic Agents – a review". *IJISET* 2.11 (2015): 144-148.

22. Manyam BV. "Dementia in Ayurveda". *Journal of Alternative and Complementary Medicine* 5 (1999): 81-88.

23. Gourie-Devi M., *et al*. "Treatment of Parkinson's disease in 'Ayurveda' (ancient Indian system of medicine): discussion paper". *Journal of the Royal Society of Medicine* 84.8 (1991): 491-492.

24. Ekstein D and Schachter SC. "Natural Products in Epilepsy – the Present Situation and Perspectives for the Future". *Pharmaceuticals* 3 (2010): 1426-1445.

25. Fernandes A., *et al*. "Herbal Medications to Enhance Cognition and Cognitive Ability". Recent Progress in Medicinal Plants 43 (2014): 1-11.

26. Anand A., *et al*. "Preserving neural retina through re-emerging herbal interventions". *Journal of Cell Biochemistry* 115.10 (2014): 1659-1668.

27. Kuboyama T., *et al*. "Effects of Ashwagandha (Roots of *Withania somnifera*) on Neurodegenerative Diseases". Biological and Pharmaceutical Bulletin 37.6 (2014): 892-897.

28. Chaudhari KS., *et al*. "Neurocognitive Effect of Nootropic Drug Brahmi (*Bacopa monnieri*) in Alzheimer's Disease". Annuals of Neurosciences 24.2 (2017): 111-122.

29. Gupta M and Kaur G. "Aqueous extract from the Withania somnifera leaves as a potential anti-neuroinflammatory agent: a mechanistic study". *Journal of Neuroinflammation* 13.1 (2016): 1-17.

30. Kurapati KRV., *et al*. "Ashwagandha (*Withania somnifera*) Reverses β-Amyloid$_{1-42}$ Induced Toxicity in Human Neuronal Cells: Implications in HIV-Associated Neurocognitive Disorders (HAND)". *PLoS One* 8.10 (2013): 1-15.

31. Ayyathan DM., *et al*. "Neuroprotective effect of Tagara, an Ayurvedic drug against methyl mercury induced oxidative stress using rat brain mitochondrial fractions". *BMC Complementary and Alternative Medicine* 15 (2015): 1-8.

32. Sethiya NK., *et al*. "Neuropharmacological evaluation on four traditional herbs used as nervine tonic and commonly available as *Shankhpushpi* in India". *Journal of Ayurveda and Integrative Medicine* 17 (2018): 30242-30245.

33. Soumyanath A., *et al*. "Centella asiatica accelerates nerve regeneration upon oral administration and contains multiple active fractions increasing neurite elongation in-vitro". *Journal of Pharmacy and Pharmacology* 57 (2005): 1221-1229.

34. Dhanasekaran M., *et al*. "Neuroprotective Mechanisms of Ayurvedic Antidementia Botanical. Bacopa monniera". *Phytotherapy Research* 21 (2007): 965-969.

35. Singh H., *et al*. "Intermittent fasting combined with supplementation with Ayurvedic herbs reduces anxiety in middle aged female rats by anti-inflammatory pathways". *Biogerontology* (2017): 1-14.

36. Gray NE., *et al*. "*Centella asiatica* modulates antioxidant and mitochondrial pathways and improves cognitive function in mice". *Journal of Ethnopharmacology* 180 (2016): 78-86.

37. Lieu CA., *et al*. "A Water Extract of *Mucuna pruriens* Provides Long-Term Amelioration of Parkinsonism with Reduced Risk for Dyskinesias". *Parkinsonism and Related Disorders* 16.7 (2010): 458-465.

38. Teshigawara K., *et al*. "A novel compound, denosomin, ameliorates spinal cord injury via axonal growth associated with astrocyte-secreted vimentin". *British Journal of Pharmacology* 168 (2013): 903-919.

39. Tohda C and Nagata A. "*Epimedium koreanum* Extract and Its Constituent Icariin Improve Motor Dysfunction in Spinal Cord Injury". *Evidence-Based Complementary and Alternative Medicine (*2012):1-6.

40. Pase M., *et al*. "The Cognitive-Enhancing Effects of Bacopa monneiri: A Systematic Review of Randomized, Controlled Human Clinical Trials". *Journal of Alternative and Complementary Medicine* 18.7 (2012): 647-52.

41. McPhee GM., *et al*. "Cognitive training and *Bacopa monnieri*: evidence for a combined intervention to alleviate age associated cognitive decline". *Medical Hypotheses* 95 (2016): 71-76.

42. Stough C., *et al*. "Examining the Cognitive Effects of a Special Extract of Bacopa monniera (CDRI 08: KeenMind): A Review of Ten Years of Research at Swinburne University". *Journal of Pharmacy and Pharmaceutical Sciences* 16.2 (2013): 254-258.

43. Kean JD., *et al*. "A Randomized Controlled Trial Investigating the Effects of a Special Extract of Bacopa monnieri CDRI 08) on Hyperactivity and Inattention in Male Children and Adolescents: BACHI Study Protocol (ANZCTRN12612000827831)". *Nutrients* 7.12 (2015): 9931-9945.

44. Pandit AK., *et al*. "Complementary and alternative medicine in Indian Parkinson's disease patients". *Journal of Traditional and Complementary Medicine* 6 (2016): 377-382.

45. Katzenschlager R., *et al*. "Mucuna pruriens in Parkinson's disease: a double blind clinical and pharmacological study". *Journal of Neurology, Neurosurgery, and Psychiatry* 75 (2004): 1672-1677.

46. Rastogi S. "Rehabilitative potential of Ayurveda for neurological deficits caused by traumatic spinal cord injury". *Journal of Ayurveda and Integrative Medicine* 5.1 (2014): 56-59.

47. Banerjee S. "Mentat – A Herbomineral Preparation, as an Adjuvant to Conventionally used Antipieleptic Therapy". *The Indian Practise.* 67.11 (1994): 929-937.

48. Shankar A. "Ayurveda for Neurological Disorders". *Homeopathy and Ayurvedic Medicine* 2.3 (2013) 1-2.

49. Pras N., *et al*. "*Mucuna pruriens*: Improvement of Biotechnological production of the anti-Parkinson drug L-dopa by plant cell selection". *Pharmacy World and Science* 15 (1993): 263-267.

50. Tandon M., *et al*. "Pattern of use of complementary/alternative medicine (CAM) in epileptic patients in a tertiary care hospital in India". *Pharmacoepidemiology Drug Safety* 11 (2002): 457-63.

Volume 2 Issue 8 November 2018