Neuroactive Botanicals

Neurological disorders have been recognized by the World Health Organization (WHO) as a significant cause of the global burden of disease worldwide, with the highest burden in low to middle-income countries, and this burden is expected to increase exponentially in the next decade [1]. Global burden of disease study has shown that mental, neurological, and substance use disorders are a significant cause of disability in the global population [2-4]. Notably, the burden of neurological diseases in low- and middle-income countries is over six times higher than in developed countries, with epilepsy being 14-fold higher, cerebrovascular disease being eight-fold higher, and migraines being six-fold higher [1, 5]. Therefore, there is a need to explore all possible interventions to help combat these diseases.

Many cultures worldwide primarily use herbs for health care needs [6] and for the treatment of conditions involving central nervous system disorders, even though conventional medical treatments have been widely adopted. Many herbs are claimed to possess anticonvulsant, antiepileptic, neuroprotective, memory-enhancing, and sedative properties; however, only some of these claims are supported by clinical data or experimental results [7]. This special issue of Current Neuropharmacology presents the state of knowledge as it relates to botanicals/herbs with neuroactive properties. It also provides proposals for additional research to better understand their efficacy and safety profiles with the hope of stimulating further research in the discovery of future medicines.

In the first review article, Choo and Shaikh examined the use of Curcuma longa (turmeric) and its constituents in the management of epileptic seizures. *C. longa* is a tropical herbaceous perennial plant of the family Zingiberaceae. Its rhizome contains curcuminoids, sesquiterpenoids, and monoterpenoids as the major constituents [8]. *C. longa* is used traditionally as a remedy for epilepsy [9]. The review determined that only non-clinical studies were available reporting the use of an aqueous extract of *C. longa* rhizome and its oil, as well as the use of its major constituents: curcumin and bisabolene sesquiterpenoids. Based on the reviewed data, the authors have suggested possible treatment parameters for epileptic seizures and hypothesized possible mechanisms of action for the bioactive constituents. The authors also propose future research to support possible drug development. The review recognizes the low bioavailability of curcumin, indicating that higher doses would be required to achieve therapeutic levels [10]. Based on studies reviewed, the most favorable route of administration would be intraperitoneal, which is not conventionally used clinically. The review also recognized that the half-life of curcumin varies significantly between animal species, but overall is short, indicating rapid metabolism, which the authors consider not necessarily a negative attribute given that metabolites may be therapeutically bioactive. Lastly, the review stated that different formulations of curcumin may incorporate compounds, like pipericine or synthetic analogues of curcumin, to help overcome bioavailability and degradation issues [11]. The authors propose the following possible mechanisms of action for neural activity: antioxidant effects, anti-inflammatory effects, improved cognition, neuroprotective effects, modulation of neurotransmitter signals, down-regulation of sodium ion channels, and downregulation of cortisone. This review has unveiled an obvious gap as no clinical studies on *C. longa* for the management of epileptic seizures are available in the public domain.

In the second review article, the authors examined how modern-day regulatory systems at the international level can create a barrier to access to traditional herbal medicines. Regulatory mechanisms are intended to protect consumers by ensuring that consumers receive safe, efficacious, and high-quality products. However, in the case of many herbal medicines, there are unintended consequences, so that in some cases, regulations may create conditions that limit opportunities for the use of traditional herbal medicinal products. This is especially the case for herbal products that are not widely recognized to have long-standing traditional uses in the global or national marketplaces. This review investigated and compared how a Southern African herbal medicine (*Mesembryanthemum tortuosum*) with potential as an anxiolytic and mild antidepressant [12, 13] has fared internationally in today’s regulatory environments. The authors argue that inadvertent regulatory favoritism combined with the inability to secure associated intellectual property due to lack of means may create economic hurdles prohibiting successful product development and introduction of botanicals from developing countries into most of the world’s health products markets.

In the third review article, the authors provide mechanistic and therapeutic insights into the neuroprotective effects of caffeic acid phenethyl ester (CAPE) in CNS disorders [14].

Botanical sources of CAPE include the bark of conifer trees and propolis from beeswax. Although relatively unexplored in human trials, CAPE has been shown to have antioxidant, anti-inflammatory, antimitogenic, and anti-cancer activities in preclinical studies. It is thought to have the potential for the treatment of neurological disorders through modulation of multiple molecular pathways and attenuation of behavioral deficits.

In the fourth review article, the authors summarize information of the phytochemistry, biological and cellular activities, and clinical trials of several plant species to provide scientific baseline information that could be used in the drug development process to find drug leads for Alzheimer’s disease (AD) and Parkinson’s disease (PD). AD and PD are complex, multifactorial age-associated diseases whose incidences are expected to increase progressively with the increasing life expectancy worldwide. These two diseases cause suffering and pain of variable kinds [15]. Amyloid β peptide (Aβ)-induced toxicity is a well-established pathway of neuronal cell death believed to play a vital role, in addition to other events, in AD progression [16]. When present in excess at the synapses, glutamate acts as a neurotoxin, causing excitotoxicity and contributing to the pathogenesis of AD and PD [17]. The few conventional drugs for the treatment of AD and PD have limited effectiveness and are associated with adverse effects. This review examined botanicals that have been used for memory disorders in traditional medicine to evaluate and determine the scientific basis, if any, for their reputed uses. The review presents a comprehensive look at plants and their constituents that have shown promise in reversing: (i) amyloid-β-related toxicity in AD models; and (ii) glutamate-induced excitotoxicity in AD and PD models.

In the fifth review article, the authors present findings on Withania somnifera (L.) Dunal (WS), also known as ashwagandha. This medicinal plant has commonly been used in Ayurvedic and other traditional Eastern medicine systems in many parts of the world [18, 19]. This review provides a detailed, comprehensive summary of studies that examined the neuropsychiatric effects of WS for the management of stress, anxiety, depression, and insomnia. The review found that WS root and leaf extracts exhibited noteworthy anti-stress and anxiolytic activities in both animal and human clinical studies; positive effects were also found in the few studies that investigated its use for treating symptoms of depression and insomnia. WS alleviated symptoms of these conditions predominately via modulation of the hypothalamic-pituitary-adrenal and sympathetic-adrenal medullary axes, as well as through the GABAergic and serotonergic pathways. Important observations were the significant variation in the quality of WS extracts used in the studies reviewed and the lack of consensus on the best extraction method and dosage regimen for neuropsychiatric applications. The authors recommended additional studies to elucidate the active constituents of WS. A few studies have demonstrated that withanolide derivatives may be responsible for WS neuropsychiatric benefits; however, there is also evidence for the presence of additional, and as of yet unidentified, active compounds [20-22]. Studies are also recommended to better design appropriate dosage regimens. Although WS generally appears safe for human use, there is a need to investigate potential herb-drug interactions involving WS because of the likelihood to be used concurrently with other medications as polypharmacy is common in aging adults [23].
In the final review article of this issue by Roe and Venkataraman, the authors examined the safety and efficacy of botanicals with nootropic effects. The world’s population continues to live longer than ever before, and many people seek ways and means to keep healthy both physically and mentally in their old age. In the wealthier developed countries, baby boomers are demanding products and services to help them stay youthful both in mind and body and with the interest of “going” natural — plant-based products have become a major interest to achieve this goal [24]. There is an increased demand for botanical dietary supplements with nootropic activities to help keep the mind active and sharp [25]. Furthermore, the authors examined data for various neuroactive botanicals targeted at improving cognitive function, stress reduction, and sleep. This review article discusses acute and long-term clinical efficacy of data, current safety profiles of these botanicals, highlights data gaps for both efficacy and safety and identifies future research needs.

Overall, the reviews in this special issue have provided an overview of some botanicals used traditionally for the treatment of neurological disorders ranging from *C. longa* rhizome for epileptic seizures to *W. somnifera* for management of stress, anxiety, depression, and insomnia. An important consideration is the overall lack of clinical studies to assess the claimed effects of these botanicals and very few animal toxicology studies. Moreover, most of the few available studies were not properly designed. Furthermore, there is a lack of information on the quality of botanical materials and extracts used; for example, in the case of WS, the authors state that there is a lack of consensus on the best extraction method and dosage regimen for neuropsychiatric applications. Finally, the case of *M. tortuosum* highlights the barriers to entering the international health product markets for lesser-known botanicals with therapeutic potential.

Future studies in this area could focus on well-designed clinical and toxicological studies to amass good quality data that would clarify the potential of these botanicals to provide new treatments for neurological disorders.

REFERENCES


