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Editorial: Natural products for neuroprotection and neuroregeneration

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Editorial on the Research Topic
Natural products for neuroprotection and neuroregeneration

Neuroregeneration is a fairly new concept encompassing neurogenesis, neuroplasticity and neurorestoration. Nevertheless, it is a controversial Research Topic in the field of neuroscience due to limitations of study methods hampering neurogenesis related research in adult humans. Further, neuroregeneration exceeds the concept of neurogenesis that also contitutes endogenous neuroprotection leading to neuroplasticity and neurorestoration (Enciu et al., 2011; Muresanu et al., 2012; Huang and Chen, 2015). The past decade has witnessed an intense interest in natural products that offer health-promoting effects on neurodegenerative diseases through neuroprotection and/or neuroregeneration (John et al., 2013; Phan et al., 2014; Samberkar et al., 2015; Pang et al., 2018; Chong et al., 2020; 2021; Lew et al., 2020; Subermaniam et al., 2020; Phang et al., 2021; Choy et al., 2022; Wong et al., 2022).

This Research Topic served as a networking platform to gather scientists in the field of ethnopharmacological research to share cutting-edge research and reviews related to therapeutic efficacy of natural products for the treatment of neurodegenerative diseases (Figure 1). The main objective of this Research Topic was to address the key questions with regards to molecular mechanisms in the attenuation of programmed cell death and neuroinflammation, improvement of microcirculation in the brain, and restoration of synaptic failure and altered neurogenesis, justifying their therapeutic roles.

da Silva et al. investigated the protective roles of 134 natural molecules against endoplasmic reticulum (ER) stress in *in vitro* models of MRC-5 fibroblasts and SH-SY5Y cells exposed to thapsigargin. Of these, 5-deoxykaempferol, delphinidin, fisetin, naringenin, naringin, quercetin-3-O-β-D-glucoside, sennoside B, myristic acid, and spermine appear to be potential candidates in maintaining ER homeostasis. The major cellular mechanisms include attenuation of protein aggregation and calcium overload, and activation of unfolded protein response.

For the past 3 decades, *Cannabis sativa* L. (cannabis) has been found to regulate cognitive and emotional processing. Cannabinoids represent the most studied group of

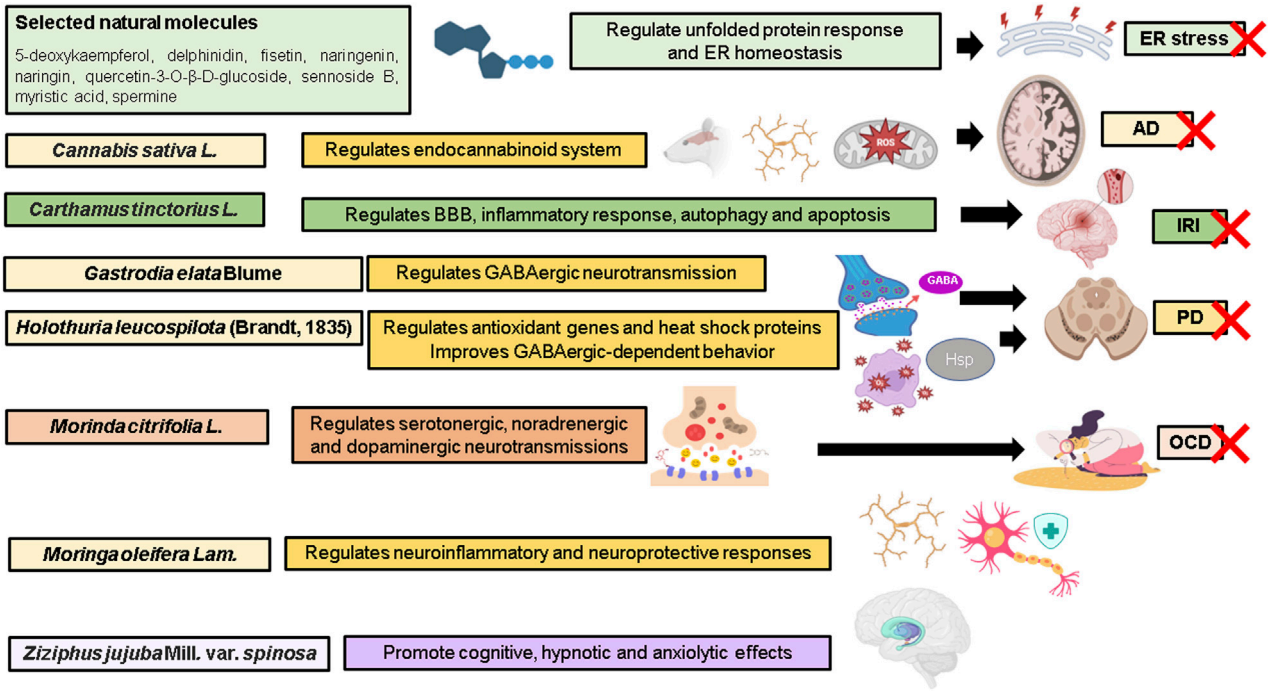

FIGURE 1
Highlights of the Research Topic. AD, Alzheimer's disease; BBB, blood brain barrier; ER, endoplasmic reticulum; GABA, gamma-aminobutyric acid; Hsp heat-shock protein; IRI, ischemia-reperfusion injury; OCD, obsessive compulsive disorder; PD, Parkinson's disease; ROS, reactive oxygen species; X, attenuate. Illustration created with BioRender.com.

compounds, mainly due to their pharmaceutical effects in humans such as psychotropic activities. Kamaruzzaman et al. presented a systematic review and meta-analysis revealing the modulatory roles of cannabinoids on endocannabinoid system in rodent models of Alzheimer's disease, leading to restoration of cognitive behavior. A total of 26 studies were included and systematically evaluated. Profound alterations were observed in the pattern of expression of cannabinoid receptor type II (CB_2) receptors and fatty acid amide hydrolase (FAAH) in the brain. These changes are linked to the inflammatory response, suggesting a crucial role for the endocannabinoid system in glial activation. The process is characterized by transformation of glial cell phenotype, upregulation and downregulation of anti-inflammatory cytokines and pro-inflammatory cytokines, respectively, glial autophagy for the clearance of aggregates, inhibition of ROS/RNS generation and lipid peroxidation, as well as modulation of synaptic plasticity.

Yu et al. presented a review on hydroxysafflor yellow A (HSYA), a major compound derived from *Carthamus tinctorius* L. (safflower). A total of 14 *in vitro* and 17 *in vivo* studies provided evidence of clinical promise, indicating saffron and HSYA are indeed safe for consumption to improve diverse clinical outcomes and therefore can be considered effective for the treatment of ischemia stroke and reperfusion injury. HSYA has been reported to inhibit excitotoxicity, oxidative stress, preserve blood-brain barrier, and regulate key pathophysiological processes such as inflammation, autophagy and apoptosis.

Lu et al. presented a review on the neuroprotective effects of bioactive components and extracts of Gastrodia elata Blume (Tianma) rhizome in preclinical models of Parkinson's disease. Of 81 bioactive compounds isolated and identified, gastrodin, vanillyl alcohol, vanillin, vanillic acid, and anisalcohol have been observed to confer neuroprotective activities targeting aggregation of α-synuclein, vulnerability of dopaminergic neurons in the substantia nigra and neuroinflammation. These compounds improved motor and cognitive functions through Nrf2-mediated antioxidant defense system regulating a battery of antioxidant and cellular protective genes, restoration of mitochondrial function, attenuation of microglial activation and oxidative stress, downregulation of c-jun N-terminal kinase (JNK)-nuclear factor-κB (NF-κB) pathway and facilitation of GABAergic neurotransmission. Additionally, Sanguanphun et al. demonstrated the neuroprotective effects of decanoic acid isolated from Holothuria leucospilota (Brandt, 1835) or black sea cucumber (HLEA-P1) in the alleviation of Parkinsonism in an *in vivo* model of *Caenorhabditis elegans* exposed to neurotoxin 6-hydroxydopamine (6-OHDA). The HLEA-P1 attenuated oxidative stress leading to suppression of aggregation of α-synuclein and intracellular deposition of lipid droplets, activated insulin/insulin-like growth factor (IGF-1) signaling (IIS) pathway and upregulated antioxidant genes and heat-shock proteins, contributing to improved GABAergic-dependent behavior.

Jeyabalan et al. demonstrated the neuroprotective potential of a standardized fruit extract of *Morinda citrifolia* L., commonly known as noni, against obsessive-compulsive disorder (OCD)-like behavioral traits in a mouse model. Oral administration of the extract suppressed nestlet shredding and marble burying without

affecting the locomotor function. Importantly, this study suggests that the attenuation of OCD-like behavior has been observed to be associated with amelioration of biogenic amines and elevation of serotonin levels and regulation of serotonergic, noradrenergic and dopaminergic neurotransmission.

Azlan et al. presented a review on Moringa oleifera Lam., popularly known as a drumstick tree or tree of life. The herbal medicine possesses neuroprotective and anti-neuroinflammatory effects by modulating the levels of NF-κB, cytokines, TNF-α, IL-1, IL-6, and nitric oxide (NO), leading to the suppression of inflammatory reaction. The therapeutic effects are associated with the abundance of phytochemicals rich in antioxidant and anti-inflammatory properties, namely, phenolic acids (gallic, chlorogenic, ferulic, and caffeic acids), flavonoids (kaempferol, myricetin, (−)- epicatechin, quercetin, isoquercitrin and astragalin), glucosinolates (GLSs) and isothiocyanates (ITCs and moringin). However, data on their pharmacokinetic properties in preclinical models are lacking. This review also discusses toxicity-related Research Topic and major safety concerns. Accumulating evidence shows that M. oleifera extracts and compounds are acceptably safe.

Kuang et al. presented a mini review on spinosin, a C-glycoside flavonoid isolated from the seeds of Ziziphus jujuba Mill. var. spinosa (red date) and demonstrated evidence in supporting the use of the compound for cognitive function, hypnosis and anxiolytic effects in preclinical models. However, there is a lack of in-depth molecular mechanisms, pharmacokinetics parameters, information content of nuclear magnetic resonance (NMR) spectra, toxicity assessment and network pharmacology to draw definitive conclusions on the effectiveness of spinosin.

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Author contributions

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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