"NEURO-NUTRACEUTICALS: FURTHER INSIGHTS INTO THEIR PROMISE FOR BRAIN HEALTH"

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Abstract

In this Special Issue on “Nutraceuticals: Molecular and Functional Insights into how Natural Products Nourish the Brain”, the editors bring together contributions from experts in nutraceutical research to provide a contemporary overview of how select chemically identified molecules from natural products can beneficially affect brain function at the molecular level. Other contributions address key emergent issues such as bioavailability, neuronal health, inflammation and the holistic benefit of multi-targeted actions that impact upon how nutraceuticals ultimately leverage the brain to function better. In terms of the benefit of nutraceuticals it is clear that some naturally occurring molecules can be advantageous to both the young and aged brain, and that they have actions that ultimately can be directed to aid either in the improvement of cognition or in the management of debilitating neurodegenerative and neuropsychiatric conditions.

Key words

Nutraceutical, traditional medicine, neurodegeneration, inflammation, development, ageing

Welcome to the second volume in this initiative "Nutraceuticals: Molecular and Functional Insights into how Natural Products Nourish the Brain". Readers are referred to the first volume published in *Neurochemistry International* 89, 1-280 (2015). The term Nutraceutical was introduced in 1989 by Dr. Stephen L. De Felice (Founder and Chairman of the Foundation for Innovation in Medicine, New Jersey, USA) from nutrition and pharmaceutical. Whilst a key aim herein was to focus on investigations of chemically identified molecules isolated from traditional medicines, a further aim was to overview the background and modern horizons of how nutraceuticals might be used to sustain brain health in daily life and during debilitating pathologies. The first volume also addressed some aspects of the limitations to the exploitation of nutraceuticals and sought to give some proper consideration to the metabolism, bioavailability and blood brain permeability of molecules that might exert beneficial actions on brain. Overall this volume engendered considerable enthusiasm amongst people interested in links between nutraceuticals and the healthy brain. Indeed the Editorial, "Neuro-nutraceuticals: The path to brain health via nourishment is not so distant", which covered broadly historical perspectives, multi-targeting, regulatory issues and highlighted key advances therein (Williams et al., 2015), has been downloaded over 900 times in 2015. The second volume contains unique insights into still more molecules and adds new perspectives to how nutraceuticals should be viewed. The editors in assembling this Special Issue, "Nutraceuticals: Molecular and Functional Insights into how Natural Products Nourish the Brain", recognized that the time was right for an overview of this expanding field. Overall, we hoped this Special Issue would provide a timely overview of this emerging field and map key future directions for neuro-nutraceutical research. The coverage provided will be of broad interest not only to academic and commercial researchers, and students, but also to the enormous numbers in the community who seek to keep their brains healthy by the use of natural products.

1. Further insights into the actions of nutraceuticals

One of the goals of this Special Issue was to document the latest advances relevant to natural products where the active principles had been identified and especially where workers in the field were attempting to describe actions at defined targets relevant to the healthy brain and crippling pathologies. Dietary intake of **creatine** continues to attract much interest - indeed its increased intake can elevate brain creatine, preserve cognitive function under stress and its consumption has thus been assessed in several adult neurodegenerative conditions since it

directly preserves mitochondrial function (Rae and Bröer, 2015). New data reported herein indicate that creatine exerts protective actions against oxidative and nitrosative stress induced in SH-SY5Y cells by L-glutamate, and appears to exert similar beneficial effects *in vivo* in brain when chronically but not acutely administered (Cunha et al.). Further, dietary creatine supplementation during pregnancy may be an effective prophylaxis that can protect the foetus from the multi-organ consequences of severe hypoxia at birth where neonatal brain injury ensues subsequent to mitochondrial energy failure and reduced ATP production (Ellery et al.). **Eugenol** (contained in *Syzygium aromaticum,* clove oil and leaves) enhanced the viability of SH-SY5Y cells by ameliorating oxidative stress in experimental hyperglycemia. Additionally, eugenol treatment of diabetic rats resulted in diminution in brain of oxidative markers and protein carbonyls in both cytosolic and mitochondrial fractions, with restoration of activities of mitochondrial complexes I, II and III (Prasad et al.). This naturally occurring polyphenol has a long history of use in Ayurvedic practices as an antiseptic, carminative and analgesic for dental problems, and thus seems worthy of consideration as an adjuvant therapeutic molecule to alleviate complications under diabetic conditions. **Curcumin**, the most abundant phenolic compound in turmeric (*Curcuma longa*), has been used extensively in Asian countries for its health-promoting effects. Its loading into lactoferrin nanoparticles provides a 3-4 fold increase in the effective concentration of curcumin achieved leading to significantly greater improvements in viability and reductions in α-synuclein relative to soluble curcumin in the neuroblastoma SK-N-SH dopaminergic cell line (Bollimpelli et al.). These findings reinforce the report in our first volume that modern drug delivery approaches improve the bioavailability and effectiveness of curcumin (Hagl et al., 2015).

2. Nutraceuticals as anti-inflammatory agents

Inflammation in neuropathologies is now a huge topic of study internationally with innate and adaptive immunity well established and cross-talk between the nervous and immune systems fully accepted. Macrophages are known to invade the brain and interface with the brain's resident inflammatory cells, microglia and astrocytes. The phenotypes of these inflammatory cells in the injured or diseased brain are the centre of great contemporary interest as they may be targets where nutraceuticals could act beneficially. We refer readers to earlier published work in the first volume where oxymatrine (Zhao et al., 2015), apocynin (Lee et al., 2015), curcumin (Kaur et al., 2015) and allyl cysteine (Colín-González et al., 2015) were all reported to have anti-inflammatory actions.

Resveratrol (found in grapes, red wine, mulberries, peanuts and various plants), a much studied stilbene, is known to dampen peripheral inflammation. Resveratrol penetrates the blood brain barrier, and Steiner et al. investigated its effects on a broad range of pro- and anti-inflammatory factors. They report that resveratrol, at concentrations found in plasma, effectively reduced pro-inflammatory cytokines in activated macrophage and microglial cell lines highlighting its broad anti-inflammatory effects and likely benefits during neuroinflammation. These new insights, when taken with findings in our first volume (Lopez et al., 2015), complement existent evidence on the neuroprotective potential of resveratrol, which is relatively well tolerated in clinical trials, and allows the brain to maintain homeostasis minimizing age-related behavioural decline (Poulose et al., 2015). Marine microorganisms also represent promising sources of metabolites with bioactivity, and Cho et al. examined the actions of **citreohybridonol** isolated from marine-derived fungal strain Toxicocladosporium sp.. Their findings suggest that citreohybridonol has anti-neuroinflammatory effects suppressing the production of pro-inflammatory mediators and cytokines, including TNF- α , IL-1 β , IL-12, IL-6, iNOS, and COX-2, in activated BV2 cells. This action focuses attention on citreohybridonol and related terpenoid derivatives for the development of anti-inflammatory treatment of pathologies where neuroinflammation has been documented.

Venigalla et al. in a timely review analyse existent findings on a select group of nutraceuticals: **curcumin, apigenin, (-) epigallocatechin-3-gallate (EGCG), docosahexaenoic acid, α-lipoic acid and resveratrol**. Importantly when considering anti-inflammatory and neuroprotective actions they delineate comprehensively the suitability of all molecules from the perspectives of pharmacokinetics, safety, mechanistic pathways and cellular studies, animal studies and human studies. The authors make the most interesting point that treatments appear more effective when initiated early in the disease and conclude that careful prospective studies are needed with these molecules in patients with mild cognitive impairment or in early stages of Alzheimer's disease. We refer readers to pertinent articles in the first volume of this Special Issue where informative and relevant background is provided on curcumin (Hagl et al., 2015; Kaur et al., 2015; Murugaiyah and Mattson, 2015), EGCG (Dutta and Mohanakumar, 2015), docosahexaenoic acid (Vauzour et al., 2015) and resveratrol (Poulose et al., 2015). **Short Chain Fatty Acids, medium Chain Fatty Acids**

(MCFA) and long Chain fatty acids (LCFA) have different functions and effects on brain, often conferring some degree of neuroprotection through a variety of mechanisms, and represent potential treatments for a wide range of neurological and psychiatric disorders (Lei et al.). Here MCFAs and LCFAs both appear more beneficial - MCFAs because they represent alternative energy sources and have anti-inflammatory actions, whereas LCFAs are highly anti-inflammatory, contribute to membrane fluidity and their levels may be linked to cognitive function. Of course, docosahexaenoic acid is the most studied and appears to be neuroprotective in various forms of brain injury, including traumatic brain injury and ischaemia. **Flavonoids** also receive attention in the context of neuroinflammation - as discussed in the first volume, flavonoids have moved from being considered purely as anti-oxidants through actions as free radical scavengers to a position where they have diverse actions, including on many signalling cascades, some of which influence cellular survival mechanisms and blood flow (Williams et al., 2015). Matias and colleagues offer a rather different focus upon the role of astrocytes as mediators of polyphenol action in brain and how these glial cells might underpin beneficial actions in brain pathologies. They identify inhibition of astrogliosis, and improved anti-oxidant response and secretion of neuroprotective soluble factors as likely key responses of these resident inflammatory cells.

3. Dietary supplements: benefits of multi-target approaches

There is frequent mention in the literature of the concept that interactions among various classes of chemicals present in foods may contribute to their potent "nutraceutical actions". Here Sinha et al. provide a very relevant demonstration of the effectiveness of a nutraceutical "cocktail". Long-term dietary supplementation of rats with a combination of **N-acetylcysteine, α-lipoic and α-tocopherol** from 18 months onwards daily till their sacrifice at 22-24 months attenuated the age-related alterations in β-amyloid metabolism. This dietary regimen remarkably prevented impairment of spatial learning and memory in aged rats. Moreover, doses employed here were chosen with reference to recommended dietary allowances. Whilst this targeted application is not exactly herbal medicine, one cannot help but be impressed with the effectiveness of this carefully chosen neuro-nutraceutical mix which harks back to the bandied expression "the whole is more than the sum of its parts" (Joseph et al., 1998). This concept is further elaborated by Solanki et al., who discuss herbal medicines and focus on the beneficial properties of **flavonoids** (e.g. fistein, quercetin, 7,8-dihydroxyflavone), especially their applications for intervention and in amelioration of injury

in various neurodegenerative diseases. As potential dietary supplements their multi-target properties may be beneficial in prevention and treatment of the age-associated neurodegenerative diseases (Williams et al., 2015). Neurobiological perspectives on some individual flavonoids can be found in the first volume of this Special Issue (Blasina et al., 2015; Dajas et al., 2015; Du and Hill, 2015; Johnston, 2015; Krasieva et al., 2015). Wadhwa et al. also contextualise the holistic, multifunctional drug/multi-target approach which may alleviate the diverse pathological consequences inflicted by the multifactorial nature of brain disorders. These authors review the actions of **Ashwagandha** (*Withania somnifera*), extensively employed in traditional medicines (Kataria et al., 2015), which enhances the body's resilience to stress.

4. Nutraceuticals and their promise

The articles in "Nutraceuticals: Molecular and Functional Insights into how Natural Products Nourish the Brain" reflect the topic's dynamic nature and the enthusiasm of authors for this rapidly expanding field. When this Special Issue was planned it was never imagined that it would grow to 39 articles across two volumes, but the number of contributors reflects the vibrancy of ongoing work across different problems, and their internationality demonstrates its global relevance to health and therapeutics. Many natural products used in traditional medicine have been known for centuries to exert beneficial actions on diverse brain functions and often the active principles have been identified, so potentially their application under appropriately regulated conditions to aid in the management of debilitating neurodegenerative and psychiatric conditions could occur in the not too distant future.

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