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New Evidences for the Pharmaceutical Use of Flavonoid Molecules in Acute Brain Pathology

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Brain pathology is a leading cause of death all over the world. Despite intensive research aimed at developing neuroprotective treatments for brain injury, no drugs have been proved successful in advanced clinical trials.

It is known that the acute brain injury results from – among others – the combined effects of cellular energy failure, acidosis, glutamate release, intracellular calcium accumulation, lipid peroxidation, and nitric oxide neurotoxicity that disrupt essential components of the cell, resulting in death. The formation of reactive oxygen and nitrogen species is a common result of these processes in brain tissues and it can activate diverse downstream signalling pathways and transcription factors regulating expression of genes encoding a variety of pro-inflammatory proteins and inducible nitric oxide synthase. In this context, epidemiological evidences have acknowledged natural compounds with antioxidant and anti-inflammatory properties as potential neuroprotective molecules for brain pathology [1,2].

In this sense polyphenols, molecules with a broad spectrum of biological functions such as anti-oxidative, anti-bacterial, anti-tumoral, anti-viral, anti-inflammatory and cardiovascular protection activities have been identified as a group of molecules that deserve to be studied in their neuroprotective potential [3].

Flavonoids, the most important polyphenol group commonly occurring in plants, fruits, vegetables, seeds, tea and wine, are frequently components of the human diet. A substantial amount of evidence supports diverse effects of flavonoids within the brain, including the suppression of neuroinflammation, the promotion of neuronal differentiation, the protection of neurons against injury induced by neurotoxins, and the improvement in memory and learning functions [4,5]. This wide range of effects appears to involve mechanisms that could be grouped in antioxidant and non-antioxidant properties. Both mechanisms may finally converge in the modulation of common intracellular signalling pathways leading to cell survival among other beneficial effects [6,7].

Traditionally, the beneficial effects of these compounds have been attributed mainly to their antioxidant capacity, including their direct free radical scavenger and their metal chelating properties. Additionally, they show broader indirect antioxidant effects through their capacity to interact and modulate antioxidant enzyme activities and to influence antioxidant gene expression by modulation of redox sensitive transcription factors such as Nuclear Factor κB and Nrf2. These mechanisms result in the induction of genes encoding for pro-survival, detoxifying and antioxidant proteins [8,9]. As an important result of these pharmacological activities, flavonoids would re-establish the redox regulation of proteins, transcription factors and survival signalling cascades otherwise altered by oxidative stress events.

Besides their pharmacological role as potent antioxidants, flavonoids show an important additional pharmacological activity represented by their capacity to directly interact with proteins by their potential to bind to the ATP-binding sites. The enlisted properties of these compounds may finally converge in the modulation of a number of protein kinase and lipid kinase signalling cascades, such as the phosphatidylinositol 3-kinase (PI3K)/Akt, tyrosine kinase, protein kinase C (PKC) and mitogen-activated protein kinase (MAP kinase) signalling pathways [6].

The result of flavonoid central nervous system pharmacological activities would be the modulation of intracellular cascades resulting in changes of cellular function and gene expression leading to cell survival, with significant therapeutic potential against neuropathology.

Precisely, the use of flavonoids in mainly chronic studies in humans and animal dietary supplementation has shown improvements in pathology and cognitive function possibly by protecting vulnerable neurons or enhancing existing neuronal function [10,11].

In marked contrast with the beneficial effects in brain pathology observed after chronic intake, acute administration of aqueous

flavonoids has not provided consistent positive effects in brain studies.

It has been postulated that the reasons for this controversy is the high metabolization of circulating flavonoid and the difficulty of flavonoids to cross the blood–brain barrier and to enter the brain.

Drug nanosomal delivery systems for adequate and safe brain delivery are being increasingly utilized to minimize this limitation [12]. In this context, it is important to call the attention to a recent paper utilizing quercetin transported in a complex nanosome to treat the devastating effects of hypoxia in a model of perinatal asphyxia in newborn piglets [13].

The nanosomal preparation of quercetin was safe for acute intravenous administration and it was shown that it stabilized key hemodynamic parameters altered during asphyxia in newborn piglets. More interestingly, the intra venous administration of one dose of 10 mg/kg of quercetin nanosomes induced an improvement in the brain voltage as evaluated by the monitoring of cerebral function.

Although preliminary, these results show that pharmaceutical modifications of flavonoid molecules, utilizing delivering systems, could have promise for a future use of these molecules as therapeutics for acute brain disease.

Modifications of molecules such as quercetin to reduce its toxicity would likely help to obtain safer pharmacological activity.

References

1. Joseph JA, Shukitt-Hale B, Denisova NA, Bielinski D, Martin A, McEwen JJ, et al. Reversals of age-related declines in neuronal signal transduction, cognitive, and motor behavioral deficits with blueberry, spinach, or strawberry dietary supplementation. J Neurosci. 1999; 19(18):8114–8121.
2. Patil BS, Jayaprakasha JK, murthy KNC,Vikram A. Bioactive Compounds: Historical Perspectives, Opportunities,and Challenges. J Agric Food Chem. 2009; 57(18):8142–8160. doi: 10.1021/jf9000132.
3. Havsteen BH. The biochemistry and medical significance of the flavonoids. Pharmacol Ther. 2002; 96(2-3):67– 202.
4. Dajas F, Rivera F, Blasina F, Arredondo F, Echeverry C, Lafon L, et al. Cell culture protection and in vivo neuroprotective capacity of flavonoids. Neurotox Res. 2003; 5(6):425-32.
5. Macready AL, Kennedy OB, Ellis JA, William CM, Spencer JP, Butler LT. Flavonoids and cognitive function: a review of human randomized controlled trial studies and recommendations for future studies. Genes Nutr. 2009; 4(4):227–242. doi: 10.1007/s12263-009-0135-4.
6. Spencer JP. Flavonoids and brain health: multiple effects underpinned by common mechanisms. Genes Nutr. 2009; 4(4):243–250. doi: 10.1007/s12263-009-0136-3.
7. Dajas F. Life or death: neuroprotective and anticancer effects of quercetin. J Ethnopharmacol. 2012; 143(2):383-96. doi: 10.1016/j.jep.2012.07.005.
8. Nijveldt RJ, van Nood E, van Hoorn DE, Boelens PG, van Norren K, van Leeuwen PA. Flavonoids: a review of probable mechanisms of action and potential applications. Am J Clin Nutr. 2001; 74(4):418–425.
9. Arredondo F, Echeverry C, Abin-Carriquiry JA, Blasina F, Antúnez K, Jones DP, et al. After cellular internalization, quercetin causes Nrf2 nuclear translocation, increases glutathione levels, and prevents neuronal death against an oxidative insult. Free Radic Biol Med. 2010; 49(5):738–747. doi: 10.1016/j.freeradbiomed.2010.05.020.
10. Youdim KA, Joseph JA. A possible emerging role of phytochemicals in improving age-related neurological dysfunctions: a multiplicity of effects. Free Radic Biol Med. 2001; 30(6):583–594.
11. Ossola B, Kääriäinen TM, Männistö PT. The multiple faces of quercetin in neuroprotection. Expert Opin Drug Saf. 2009; 8(4):397–409. doi: 10.1517/14740330903026944.
12. Gandhi HB. Nanotechnology in Blood Brain Barrier: A Review. International Journal of Pharmaceutical and Biological Archives. 2010; 1:37–43.
13. Blasina F, Vaamonde L, Silvera F, Tedesco AC, Dajas F. Intravenous nanosomes of quercetin improve brain function and hemodynamic instability after severe hypoxia in newborn piglets. Neurochem Int. 2015; 89:149-56. doi: 10.1016/j.neuint.2015.08.007.