Frontiers in Drug, Chemistry and Clinical Research

Commentary

ISSN: 2631-5424

Flavonoid chemistry and neuroprotection

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Abstract

This short commentary is intended to highlight the relevance of flavonoids in the therapeutics against neurodegenerative disorders. In this sense, this work briefly discuss the physicochemical and biological aspects which may be involved in the biological effects of these phytocomponents against oxidative stress in brain cells. Considering that literature abundantly describes the relevance of flavonoids in neuroprotection, care must be taken regarding their true clinical effectiveness, given the lack of information regarding their pharmacokinetic profiles and adequate pharmaceutical formulation.

The basic chemistry of flavonoids

Flavonoids are polyphenolic plant secondary metabolites which are biosynthesized from a polyketide chain and a phenylpyruvic moiety which may either come from shikimate or amino-acid metabolism [1-3]. These compounds possess remarkable physicochemical behavior due to their alternating π bonds, what confers aromaticity and strong electroactivity [4]. Although the basic backbone of these compounds is widely produced in plant metabolism, polyphenols possess highly variable structure whose biosynthesis is dependent on several genetic and environmental factors [1,2]. The basic backbone of polyphenols is depicted in Figure 1 using flavanone Naringenin as example.

As previously seen in Figure 1 the alternating π bonds of flavonoids allow the inductive effect of functional groups to be transmitted through the entire molecule, a principle known in medicinal chemistry as vinylogy [5,6]. This effect turns flavonoids into highly electroactive compounds, whose oxidation or reduction is thermodynamically feasible upon small physicochemical changes in the environment [7].

The antioxidant capacity of flavonoids

Many authors discussed the biological effects of this proneness of flavonoids to undergo redox reactions. In this sense, it is acknowledged that flavonoids and other polyphenols may "sacrifice" themselves in order to safeguard biological material [8,9]. This process is the very often quoted "antioxidant activity" and is based on the antioxidant compound (i.e. flavonoid) donating electrons to the unstable species (i.e. free radicals and other reactive oxygen species - ROS). However, the organisms do often possess highly effective antioxidant capabilities of their own, in the form of reductive enzymes such as peroxidases, superoxide dismutase (SOD) and others [10]. Given the capacity to donate and accept electrons, these enzymes are also prone to be preserved by the antioxidant capacity of flavonoids, what further enhances their appeal [10]. In this context, Figure 2 showcases how flavonoids are supposed to exert their antioxidant capacity.

As showcased in Figure 2, the oxidation of flavonoids is presumed to involve reversibility, as it was supported by many electroanalytical investigations [11-14]. In this sense, it can be implied that the restitution of the catechol after the formation of the benzoquinone is thermodynamically feasible, what could explain the higher radical

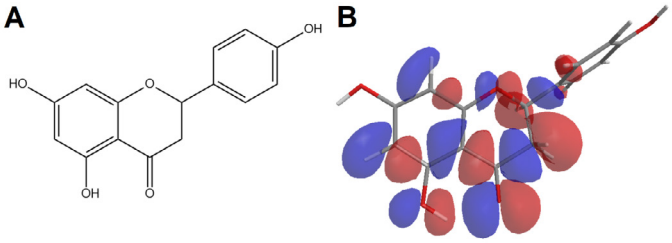

Figure 1. A. Chemical structure of flavonoid Naringenin. **B.** Graphical rendering of the first state of the highest occupied molecular orbital (HOMO n=0) according Hückel method [5]. Negative charges are colored in blue, while positive are colored red

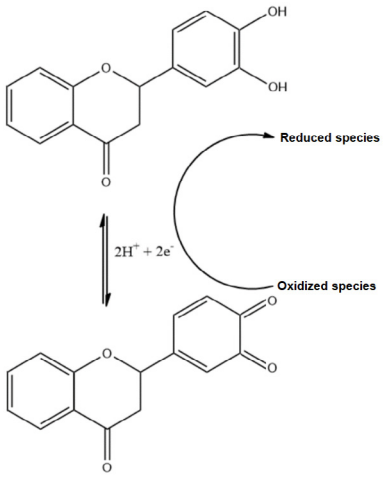

Figure 2. Proposed mechanism of a theoretical flavonoid redox reaction and its involvement in donating electrons to oxidized or unstable species and therefore reducing them

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Key words: *polyphenol pharmacokinetics, antioxidant capacity, neurodegenerative disorders, brain damage, pharmacognosy*

Received: January 05, 2020; **Accepted:** January 17, 2020; **Published:** January 22, 2020

scavenging of flavonoids in comparison to monophenols and also shed light on the biological implications of flavonoids as protective agents against oxidative stress.

Neuroprotection and antioxidant capacity

Oxidative stress is known to be involved in many neurodegenerative diseases, as free radicals such as ROS build up may lead to direct and diffuse cell damage [10,11]. There are many markers to evaluate the extent of oxidative damage, amongst them, malondialdehyde is one of the most used owing to its status as by product of lipid peroxidation [11]. Notwithstanding, peroxidases such as catalases (CAT) and reductive peptides and enzymes such as glutathione and SOD are also important biological markers to evaluate oxidative stress [11,12]. Although all cells are prone to undergo oxidative stress, those whose aerobic metabolism is remarkably high are more likely to showcase earlier the effects of this condition [15]. In this sense, oxidative stress may lead to neuronal damage, what can ultimately lead to neuron loss, being reflected as motor and cognitive impairment [11,12,16,17].

When neurodegenerative disorders are concerned, the first component in the pathogenesis of these diseases is the oxidative stress, albeit pathognomonic particularities are of upmost importance to differential diagnosis [18]. For instance, the term "neurodegenerative disorder" is considered an umbrella term, given that dementia, Alzheimer and many other diseases are based at least to some extent on neuron loss due to oxidative stress [18,19].

Regarding the available treatments, most tackle the particularities of each disease as well as support therapy, hence restitution of the lost neuronal functions is still a controversial theme. Considering that oxidative stress is intimately linked to these diseases, long-term ingestion of exogenous antioxidants such as flavonoids might provide some protection [11,12]. In this sense, many authors tackled the effects of acute and chronic exposure to flavonoid-rich formulations in several experimental models, being transition metal salts such as AlCl3 or iron intoxication often used due to the electron accepting properties of these chemicals (which enhances ROS build up given the acidity of Lewis acids) as well as their capacity to interact with enzymes involved in neuron signalling [11,12,20,21].

These investigations ultimately showcased that even acute exposure to flavonoids is beneficial to hinder neurodegeneration, however the high dose used in these experiments may turn continuous administration unpractical for life-long prophylaxis [22]. Moreover, function recovery and the extent of absorption and overall pharmacokinetics is still difficult to assess, given that the bioavailability of flavonoids and their feasibility to cross the blood-brain barrier is known to be highly variable according to the substituents in their chemical structure [23-25]. In this sense, more investigations could aid the comprehension of which pharmaceutical formulation should be optimal to properly administrate in a reproducible manner these phytocomponents in healthcare.

Conclusion

This short commentary was intended to highlight the relevance of flavonoids in the therapeutics against neurodegenerative disorders. It was observed that reports regarding the relevance of flavonoids in neuroprotection are plenty, however, care must be taken regarding their true effectiveness, given the lack of information regarding their pharmacokinetic profiles and adequate pharmaceutical formulation.

Acknowledgement

Author would like to thank CAPES, Brazil for the financial support.

Conflict of interest

Author declare that there is no conflict of interest.

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