Flavonoids friends or foes.

Hanem M. Awad*

Regulatory Toxicology Lab, Centre of Excellence & Tanning Materials and Leather Technology Department, National research Centre, 12622, Dokki, Cairo, Egypt

Accepted on October 09, 2018

Editorial

Flavonoids, which are groups of plant bioactive compounds, are natural polyphenols and their corresponding glycosides are important constituents of fresh fruits, green vegetables, nuts, spices, seeds, tea, olive oil and red wine [1,2]. According to the chemical structures, flavonoids are classified into different subclasses including: flavonols, flavones, flavanones, flavanols, anthocyanins and isoflavones [3,4]. In plant, flavonoids are very important in protecting against oxidant damage, providing the color that attracts pollinators, and repels insects and microbes attacks. In human, flavonoids are having health benefits related to metabolic syndrome, the immune system, brain health, reducing risk of cardiovascular and photosensitivity diseases, neurodegenerative disorders, and ageing [1,2]. In addition, they are having antiviral and antibacterial properties, they also regulate gene expression and modulate some enzymatic actions [5].

In addition to their antioxidant activity, flavonoids may inhibit carcinogenesis by different mechanisms like: modulation of food-born carcinogens metabolism via inhibition and/or induction of phase I and II biotransformation enzymes; expression of various tumor-related genes including antioxidant protein genes or the tumor suppressor gene p53; abnormal proliferation suppression of early preneoplastic lesions, this suppression of cell proliferation may result from inhibition of different enzymes, including protein kinase C, tyrosine kinase, phosphatidylinositol 3-kinase [1,6-9].

Although, there is an increased interest in the use of flavonoids alone or in combination with other medicines, as food supplements and/or nutraceuticals, there is a possibility of flavonoid-drug interactions [10]. Some reported data indicated that some dietary flavonoids may have the potential to negatively interact with clinical drugs. In addition, flavonoids supplements toxicity may result from bacterial or fungal contamination or contamination with heavy metals, pesticides, and/or herbicides [11]. However, there is need for scientific support for the health benefits, identification of the active compound(s), and investigation of the possible toxicological concerns. According to Paracelsus paradigm (1493-1541), toxicity is a matter of dose; when daily consumption of these food supplements increases above a limited threshold, they may become toxic. Therefore, at higher food supplements doses, these flavonoids may become prooxidants including radicals formation instead of being radicals scavenging antioxidants [12,13].

Good antioxidant activity of these flavonoids is generally related to the presence of (1) a 3',4'-dihydroxy (=catechol) moiety; (2) the C4=O keto group; (3) a 3-hydroxyl substituent; and (4) a C2=C3 double bond [2]. Surprisingly, the flavonoids structural requirements for good antioxidant activity are the same needed for prooxidant activity; especially the presence of a two hydroxyl groups in their B ring. Flavonoids with only one hydroxyl group in their B-rings, like apigenin and naringenin, their corresponding phenoxyl radicals have high one-electron oxidation potential [14-16]. This may be the reason behind their ability to increase formation of lipid peroxidation via enzymatic and/or chemical (auto)oxidation to their corresponding semiquinone radicals, which will be able to be scavenged by glutathione (GSH) [15-17].

In case of flavonoids which have two hydroxyl groups in their B rings, because their one-electron redox potentials are not high enough, instead, these flavonoids form two-electron oxidized quinine-metabolites [18,19]. They only oxidized to semiquinones and their corresponding isomeric quinone methides but they will not be able to co-oxidize the intracellular non enzymatic molecules like GSH [14]. Instead, they will be able to form electrophilic toxic quinine-metabolites by conjugation with GSH in addition to the possibility of alkylating intracellular macromolecules like DNA and proteins [15,18-21]. Taking quercetin as an example of flavonoids which contain catechol type B ring, its corresponding carcinogenicity, prooxidant toxicity and bacterial and mammalian mutagenicity have been related to its quinone/quinone methide chemistry [1,21-41]. Therefore, the pro-oxidative toxicity of flavonoids containing catechol B rings is needed to be re-evaluated in order to confirm the risks and/or the benefits of these daily food ingredients.

Summary

Considering the high flavonoids intake as food additives and/or food supplements, and because the fact that the underlying mechanisms of action at the molecular level are still not fully understood and toxicity of flavonoids consumed in large doses remains unknown. For this reason, it is very important to more clearly understand the benefits, risks and related dosing and timing issues, in order to increase their benefits and to decrease to the lesser extent their risks. In addition, further clinical and epidemiological studies are greatly needed.

References

1. Middleton E, Kandaswami C. The impact of plant flavonoids on mammalian biology: implications for immunity, inflammation and cancer. The Flavonoids. 1993:619-652.
2. Rice-Evans CA, Miller NJ, Paganga G. Structure-antioxidant activity relationships of flavonoids and phenolic acids. Free Rad. Biol. Med. 1996;20(7):933-956.

3. Setchell KD. Soy isoflavones-benefits and risks from nature's selective estrogen receptor modulators (SERMs). J Am Coll Nutr. 2001;20(Suppl-5):354S-362S.
4. Vedavanam K, Srijayanta S, O'Reilly J, et al. Antioxidant action and potential antidiabetic properties of an isoflavonoid-containing soyabean phytochemical extract (SPE). Phytother Res. 1999;13(7):601-8.
5. Prasain JK, Barnes S. Metabolism and bioavailability of flavonoids in chemoprevention: current analytical strategies and future prospectus. Mol Pharm. 2007;4(6):846-64.
6. Deschner EE, Ruperto J, Wong G, et al. Quercetin and rutin as inhibitors of azoxymethanol-induced colonic neoplasia. Carcinogenesis. 1991;12(7):1193-6.
7. Scambia G, Ranelletti FO, Benedetti Panici P, et al. Quercetin inhibits the growth of a multidrug resistant estrogen-receptor-negative MCF-7 human breast-cancer cell line expressing type II estrogen binding sites. Cancer Chemother Pharmacol. 1991;28(4); 255-8.
8. Matter WF, Brown RF, Vlahos CJ. The inhibition of phosphatidylinositol 3-kinase by quercetin and analogs. Biochem Biophys Res Commun. 1992;186(2):624-31.
9. Avila MA, Velasco JA, Cansado J, et al. Quercetin mediates the down-regulation of mutant p53 in the human breast cancer cell line MDA-MB468. Cancer Res. 1994;54(9): 2424-8.
10. Sridar C, Goosen TC, Kent UM, et al. Silybin inactivates cytochromes P450 3A4 and 2C9 and inhibits major hepatic glucuronosyltransferases 2. Drug Metab Dispos. 2004;32(6):587-94.
11. Prasain JK, Carlson SH, Wyss JM. Flavonoids and Age Related Disease: Risk, benefits and critical Windows. Maturitas. 2010;66(2):163-171.
12. Middleton E, Kandaswami C. The impact of plant flavonoids on mammalian biology: implications for immunity, inflammation and cancer. The Flavonoids. 1993:619-652.
13. Agullo G, Gamet-Payrastre L, Manenti S, et al. Relationship between flavonoid structure and inhibition of phosphatidylinositol 3-kinase: a comparison with tyrosine kinase and protein kinase C inhibition. Biochem Pharmacol. 1997;53(11):1649-57.
14. Laughton MJ, Halliwell B, Evans PJ, et al. Antioxidant and pro-oxidant actions of the plant phenolics quercetin, gossypol and myricetin. Biochem Pharmacol. 1989;38(17): 2859-65.
15. Cao G, Sofic E, Prior RL. Antioxidant and prooxidant behavior of flavonoids: structure-activity relationships. Free Rad Biol Med. 1997; 22(5):749-60.
16. Galati G, Chan T, Wu B, et al. 1999. Glutathione-dependent generation of reactive oxygen species by the peroxidase-catalyzed redox cycling of flavonoids. Chem Res Toxicol. 1999;12(6):521-5.
17. Kameoka S, Leavitt P, Chang C, et al. 1999. Expression of antioxidant proteins in human intestinal Caco-2 cells treated with dietary flavonoids. Cancer Lett. 1999;146(2): 161-7.
18. Galati G, Moridani MY, Chan TS, et al. Peroxidative metabolism of apigenin and naringenin versus luteolin and quercetin: glutathione oxidation and conjugation. Free Rad Biol Med. 2001;30(4):370-82.
19. Sudhar PS, Armstrong DA. Redox potential of some sulphur containing radicals. J Phys Chem. 1986;90(22): 5915-7.
20. Metodiewa D, Jaiswal AK, Cenas N, et al. Quercetin may act as a cytotoxic prooxidant after its metabolic activation to semiquinone and quinoidal product. Free Rad Biol Med. 1999;26(1-2):107-16.
21. Rietjens IMCM, Awad HM, Boersma MG, et al. Structure activity relationships for the chemical behaviour and toxicity of electrophilic quinones/quinone methides. Adv Exp Med Biol. 2001:11-21.
22. Awad HM, Boersma MG, Vervoort J, et al. Peroxidase-catalysed formation of quercetin-quinone methide glutathione adducts. Arch Biochem Biophys. 2000; 378(2): 224-33.
23. Awad HM, Boersma MG, Boeren S, et al. 2001. Structure activity study on the quinone/quinone methide chemistry of flavonoids. Chem Res Toxicol. 2001;14(4):398-408.
24. Rietjens IMCM, Boersma MG, De Haan L, et al. The pro-oxidant chemistry of the natural antioxidants vitamin C, vitamin E, caretenoids and flavonoids. Environ Toxicol Pharmacol. 2002;11(3-4):321-33.
25. Boersma MG, Vervoort J, Szymusiak H, et al. Regioselectivity and reversibility of the glutathione conjugation of quercetin quinone methide. Chem Res Toxicol. 2000;13(3):185-91.
26. Brown JP. A review of the genetic effects of naturally occurring flavonoids, anthraquinones and related compounds. Mut Res. 1980;75(3):243-77.
27. MacGregor JT, Jurd L. Mutagenicity of plant flavonoids: structural requirements for mutagenic activity in Salmonella typhimurium. Mut Res. 1978;54(3):297-309.
28. Hirono I, Ueno I, Hosaka S, et al. Carcinogenicity examination of quercetin and rutin in ACI rats. Cancer Lett. 1981;13(1):15-21.
29. Hirose M. Fukushima S, Sakata T, et al. Effect of quercetin on two-stage carcinogenesis of the rat urinary bladder. Cancer Lett. 1983;21(1): 23-7.
30. Ito N, Hagiwara A, Tamano S, et al. 1989. Lack of carcinogenicity of quercetin in F334/DuCrj rats. Jpn J Cancer Res. 80, 317.
31. Stoewsand GS, Anderson JL, Boyd JN, et al. 1984. Quercetin: a mutagen, not a carcinogen in Fisher rats. J. Toxicol Environ Health. 1984;14(2-3):105-14.
32. Pamukcu AM, Yalc iner S, Hatcher JF, et al. Quercetin, a rat intestinal and bladder carcinogen present in bracken fern (Pteridium aquilinum). Cancer Res. 1980;40(10):3468-72.
33. NTP technical report (TR-409) Toxicology and carcinogenesis studies of quercetin (Cas No. 117-39-5) in F344 rats (Feed studies). NI publication No 91-3140, U.S. Department of Health and Human Services, Public Health

Service, National Toxicology program, Research Triangle Park, NC.1991.

34. Ertu¨ rk E, Hatcher JF, Pamukcu AM. Bracken ferns carcinogens and quercetin. Fed. Proc. 1985;44:2344.
35. Dunnick JK, Haily JR. Toxicity and carcinogenicity studies of quercetin, a natural component of foods. Fundam Appl Toxicol. 1992;19(3):423-31.
36. Ito N. Is quercetin carcinogenic? Jpn J Cancer Res. 1992;83(3):312-14.
37. IUPAC-IUB Joint Commission on Biochemical Nomenclature (JCBN) Nomenclature of tocopherols and related compounds Recommendations 1981. Eur. J. Biochem. 1992;123:473.
38. Zhu BT, Ezell EL, Liehr JG. Catechol-O-methyltransferase-catalyzed rapid O-methylation of mutagenic flavonoids. Metabolic inactivation as a possible reason for their lack of carcinogenicity in vivo J Biol Chem. 1994;26:292-99.
39. Williamson G, Day AJ, Plumb GW, et al. Human metabolic pathways of dietary flavonoids and cinnamates. Biochem Soc Transact. 2000;28(2):16-22.
40. Zhu BT, Liehr JG, 1996. Inhibition of catechol O-methyltransferase-catalyzed O-methylation of 2- and 4-hydroxyestradiol by quercetin. Possible role in estrogen-induced tumorigenesis. J Biol Chem. 1996;271(3):1357-63.
41. Bolton JL, Pisha E, Zhang F, et al. 1998. Role of quinoids in estrogen carcinogenesis. Chem Res Toxicol. 1998;11(10):1113-27.
42. Bolton JL, Trush MA, Penning TM, et al. Role of quinones in Toxicology. Chem. Res. Toxicol. 2000;13(3):135-60.

***Correspondence to:**

Hanem M. Awad
Regulatory Toxicology Lab
Centre of Excellence & Tanning Materials and Leather Technology Department
National research Centre
12622, Dokki, Cairo
Egypt
E-mail: hanem_awad@yahoo.com