Dietary phenolic compound with the presence of C_2=C_3 double bond take the pre-emptive opportunities to enhance its biological effects.

Lei Chen*

School of Food Science, Fujian Agriculture and Forestry University, Fuzhou, Fujian, 350002 China

Abstract

Owing to the complexity of phenolic compounds, various experimental approaches are employed to examine the characterization of the bioactive phenolic compounds from herbs and evaluate their biological effects to human body. *In vivo* and *in vitro* studies have confirmed that phenolic compounds act a crucial role against antioxidative, antimicrobial, anti-diabetic, antitumor and anti-inflammatory effects. This manuscript gives a perspective of distinctive relationship between chemical structure of phenolic compounds and their biological effects, indicating that the presences of C_2=C_3 double bond and 3-OH group were found to significantly enhance biological effect and chemical modification of phenolic compounds may have potentials as therapeutic agents and also could be used for the prediction and improvement of food quality.

Keywords: Antioxidant, Biological effect, C_2=C_3 double bond, Flavonoid, Phenolic compounds.

Accepted on November 1, 2017

Introduction

Phenolic compounds are currently used as an important functional ingredient in foods and dietary supplements. The classification of phenolic compounds is based on the number of hydroxyl groups, which attached on benzene rings. For example, phenolic acids, flavonoids, stilbenes and lignans are familar phenolic compounds. Flavonoids, which are frequently studied, are divided into seven sub-categories including flavones, flavanones, flavonols, isoflavones, anthocyanidins, flavanols and chalcones [1]. Due to their importance in food organoleptic properties and human health, a better understanding of the relationship between their structures and biological activities are discussed, indicating chemical structure modification may have potentials as therapeutic agents and also could be used for the prediction and improvement of food quality.

C2=C3 Double Bond and 3-OH Group Increase Radical Scavenging Activity of Phenolic Compounds

For the vast majority of phenolic compounds, due to the presence of C_2=C_3 double bond, the OH-linked to the C3 position can easily undergo monoelectronic oxidation to give hydroxyl radical which unpaired electron can delocalize in C2 and in B ring. Previous studies discussed the role of the 3-OH group and C_2=C_3 double bond in biological activities of phenolic compounds. Most authors agreed on the importance of substitution with a C_2=C_3 double bond in phenolic compounds could be a signature of their high antioxidant activity [2-4]. Besides, recent investigation by Gregoris and Stevanato found that radical scavenging activities of galangin (OH at C3) and apigenin (OH at C4'), both of which have unpaired electron in different positions to B aromatic ring but differ in the position of the hydroxyl group. However, the galangin showed a much higher antioxidant activity; unlike apigenin characterized by a hydroxyl group in C4' [5]. There is a general agreement that the presence of OH groups is essential, with a preference for a catechol moiety in ring B, which, according to relative studies confers a high stability to the aroxyl radical via hydrogen bonding [6] or by expanded electron delocalization [7]. Nevertheless, naringenin that does not have the double bond C_2=C_3 showed a low antioxidant capacity, while a higher antioxidant capacity was found in kaempferol which presented the hydroxyl group at C3 and the double bond C_2=C_3 [5]. This is probably caused by the combination of the C_2=C_3 double bond with the 3-OH, which also makes flavonols and flavones better scavengers than the flavanols and flavanones. Similarly, relationships between the structures of 42 flavonoids and their antioxidant and antiradical activities were elucidated by Burda and Oleszek [8]. Among these tested compounds, only flavonols with a free hydroxyl group at the C-3 position showed a high inhibitory activity to β-carotene oxidation, meanwhile, antiradical activity was discovered to be depended on the presence of free hydroxyls at C-3 and a C_2=C_3 double bond [8]. Notwithstanding that both C3 and C4' radicals can delocalize the unpaired electron on the aromatic ring and the C_2=C_3 double bond and a substantial difference resulted in the antioxidant properties. This may be explained by the steric hindrance of the C3 hydroxyl group which gives stability to the radical, unlike C4', as previously found in case of phenol compared with 2, 6-di-iso-propylphenol (propofol) [9] as well as artepillin C, a phenolic structure with the hydroxyl group strongly obstructed [10]. It seems that the double bond C_2=C_3 is more important than the keto group in the antioxidant properties induced by the 3-OH, in fact, not reasonable resonance limit formulas are possible involving the keto group in the formation of C3 phenoxyl radical. This consideration is indirectly confirmed by Kumazawa et al., who found a low DPPH free radical scavenging activity in pinobanksin with a hydroxyl group in C3 and the keto group in C4, but not with

the double bond C_2=C_3 [11]. The binding site of hydroxyl groups to molecular structure gave a more significant influence on its antioxidant properties more than the generic number of the hydroxyl groups [12]. It is possible to state that in benzenic structures with the presence of a hydroxyl group in C3 connected with the double bond C_2=C_3 conjugated to the aromatic ring of phenolic compounds, showing a higher radical scavenging activity.

C_2=C_3 Double Bond Increases Enzyme Inhibitory Effect

High inhibitory effect against aldose reductases is attributed to the molecules with a C_2=C_3 double bond, which allows for the generation of a high p-conjugation of bond linkage of the B and C rings [13]. Moreover, isoflavones did not form H-bonds with the catalytic α-amylase residues from human saliva, which is a likely consequence of the ring B position; in isoflavones, as opposed to the other flavonoids studied, the B-ring is attached to carbon C_3 rather than C_2 of ring C [14]. Hydrogenation of the C_2=C_3 double bond for many flavonoids weakened the binding affinity for α-amylase by 2-4 orders of magnitude [15,16]. Tadera et al., reported that the inhibitory effect of apigenin with an inhibitory percentage of 21% was much stronger than naringenin (5%) against porcine pancreatic α-amylase [17]. In fact, flavonols with double bond C_2=C_3, show a planar structure being sp2, and then trigonal planar, the electronic configurations of all the carbon atoms. The oxygen atom, alone, does not change this planar configuration. Planarity of the C ring in flavonoids may have a very important role for binding interaction with proteins, as the molecules have saturated C_2=C_3 bonds (flavanones and certain others) permitting more twisting of the B ring with reference to the C ring. The molecules with near-planar structure can easily enter the hydrophobic pockets in enzymes. The missing electrons lead to weaker π-π interactions with the indole ring of Trp59 and, eventually, leading to a reduced inhibitory activity of these compounds toward human salivary α-amylase. Furthermore, flavonoids with a C_2=C_3 double bond were more effective than their corresponding homologues (comparison of flavone with flavanone, chrysin with pinocembrin, and quercetin with eriodictyol) on ethoxyresorufin O-deethylase and O-debenzylase [18]. Similar results were obtained analyzing other enzyme inhibitory effects including: angiotensin-converting enzyme [19], α-glucosidases [16], and others implicated enzymes for carcinogen activation [20]. In summary, it is clear to state that saturation of the C_2=C_3 double bond produced a decrease in enzyme inhibitions.

C2=C3 Double Bond Enhances other Biological Activity

It has been reported that reduction of the C_2=C_3 double bond results in loss of inhibitory activities on the cyclooxygenase (COX) pathway of PGE2 production [21]. In another study, a similar tendency was observed in inhibitory effects against COX-1 and COX-2 [22]. The C_2=C_3 double bond in conjugation with a 4-oxo group plays a very important role for the affinity for common human plasma proteins. In addition, the C_2=C_3 double bond also has an important role in insulin-stimulated glucose uptake in MC3T3-G2/PA6 adipose cells [23]. Flavanols, (+) - and (-)-catechin, which do not have C_2=C_3 double bond, did not affect glucose uptake. The presence of C_2=C_3 double bond in the flavones and flavonols is suggested to be critical for inhibitory activity towards protein kinases, including PI3K, PKC, myosin light chain kinase and G type casein kinase [24,25].

Taken together, current results suggested that C_2=C_3 double bond in the dietary phenolic compounds significantly enhanced various biological effects. The C_2=C_3 double bond is, therefore, an excellent choice for substitution to give the flavonoid an optimum biologic activity to allow easy applications. Understanding these and other differences will ultimately contribute to our making sense of the variable results of epidemiological studies in different populations, and allow us to make qualified statements about the impact of daily intake of phenolic enriched foods on human health.

References

1. Brenes A, Viveros A, Chamorro S, et al. Use of polyphenol-rich grape by-products in monogastric nutrition. Anim Feed Sci Technol. 2016;211:1-17.
2. Cholbi MR, Paya M, Alcaraz MJ. Inhibitory effect of phenolic compounds on CC14-induced microsomal lipid peroxidation. Experientia. 1991;47:195-99.
3. Robak J, Gryglewski RJ. Flavonoids are scavengers of superoxide anions. Biochem Pharmacol. 1987;36:317-22.
4. Ratty AK, Das NP. Effects of flavonoids on nonenzymatic lipid peroxidation: structure-activity relationship. Biochem Med Metab Biol. 1988;39:69-79.
5. Gregoris E, Stevanato R. Correlations between polyphenolic composition and antioxidant activity of Venetian propolis. Food Chem Toxicol. 2010;48:76-82.
6. Bors W, Heller W, Michel C, et al. Radical chemistry of flavonoid antioxidants. In: Emerit I, ed. Antioxidants in therapy and preventive medicine. New York: Plenum Press. 1990;165-70.
7. Bors W, Heller W, Michel C, et al. Flavonoids as antioxidants: Determination of radical-scavenging efficiencies. Methods Enzymol. 1990;186:343-54.
8. Burda S, Oleszek W. Antioxidant and antiradical activities of flavonoids. J Agric Food Chem. 2001;49:2774-79.
9. Rigobello MP, Stevanato R, Momo F, et al. Evaluation of the antioxidant properties of propofol and its nitrosoderivative. Comparison with homologue substituted phenols. Free Radical Res. 2004;38:315-21.
10. Kumazawa S, Hamasaka T, Nakayama T. Antioxidant activity of propolis of various geographic origins. Food Chem. 2004;84:329-39.
11. Heim KE, Tagliaferro AR, Bobilya DJ. Flavonoids antioxidants: chemistry, metabolism and structure-activity relationship. J Nutr Biochem 2002;13:572-84.
12. Wu WM, Lu L, Long Y, et al. Free radical scavenging and antioxidative activity of caffeic acid phenethyl ester (CAPE) and its related compounds in solution and

membranes: a structure-activity insight. Food Chem. 2007;105:107-15.

13. Xiao J, Ni X, Kai G, et al. Advance in dietary polyphenols as aldose reductases inhibitors: Structure-activity relationship aspect. Crit Rev Food Sci Nutr 2015;55:16-31.
14. Piparo EL, Scheib H, Frei N, et al. Flavonoids for controlling starch digestion: Structural requirements for inhibiting human α-amylase. J Med Chem. 2008;51:3555-61.
15. Xu W, Shao R, Xiao J. Is There Consistency between the Binding Affinity and Inhibitory Potential of Natural Polyphenols as α-amylase Inhibitors? Crit Rev Food Sci Nutr. 2016;56:1630-9.
16. Xiao J, Kai G, Yamamoto K, et al. Advance in dietary polyphenols as α-glucosidases inhibitors: a review on structure-activity relationship aspect. Crit Rev Food Sci Nutr. 2013;53:818-36.
17. Tadera K, Minami Y, Takamatsu K, et al. Inhibition of ALPHA-Glycosidase and ALPHA-Amylase by Flavonoids. J Nutr Sci Vitaminol. 2006;52(2):149-53.
18. Siess MH, Leclerc J, Canivenclavier MC, et al. Heterogenous effects of natural flavonoids on monooxygenase activities in human and rat liver microsomes. Toxicol Appl Pharmacol. 1995;130:73-78.
19. Guerrero L, Castillo J, Quiñones M, et al. Inhibition of angiotensin-converting enzyme activity by flavonoids: structure-activity relationship studies. 2012;7(11): e49493.
20. Weidmann AE. Dihydroquercetin: More than just an impurity? Eur J Pharmacol. 2012;684:19-26.
21. Landolfi R, Mower RL, Steiner M. Modification of platelet function and arachidonic acid metabolism by bioflavonoids. Biochem Pharmacol. 1984;33:1525-30.
22. Takano-Ishikawa Y, Goto M, Yamaki K. Structure–activity relations of inhibitory effects of various flavonoids on lipopolysaccharide-induced prostaglandin E 2 production in rat peritoneal macrophages: Comparison between subclasses of flavonoids. Phytomedicine. 2006;13:310-17.
23. Nomura M, Takahashi T, Nagata N, et al. Inhibitory mechanisms of flavonoids on insulin-stimulated glucose uptake in MC3T3-G2/PA6 adipose cells. Biol Pharm Bull. 2008;31:1403-09.
24. 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;53:1649-57.
25. Jinsart W, Ternai B, Polya GM. Inhibition of wheat embryo calcium-dependent protein kinase and avian myosin light chain kinase by flavonoids and related compounds. Biol Chem 1991;372:819-28.

***Correspondence to:**

Lei Chen

School of Food Science

Fujian Agriculture and Forestry University

Fuzhou, 350002

China

Tel: 86-591-83756316

Fax: 86-591-83756316

E-mail: chenlei841114@hotmail.com