

Dietary phenolic compound with the presence of C₂=C₃ double bond take the pre-emptive opportunities to enhance its biological effects.

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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 C₂=C₃ 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, C₂=C₃ double bond, Flavonoid, Phenolic compounds.

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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 familiar 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 C₂=C₃ 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 C₂=C₃ double bond in biological activities of phenolic compounds. Most authors agreed on the importance of substitution with a C₂=C₃ 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 C₂=C₃ 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 C₂=C₃ [5]. This is probably caused by the combination of the C₂=C₃ 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 C₂=C₃ double bond [8]. Notwithstanding that both C3 and C4' radicals can delocalize the unpaired electron on the aromatic ring and the C₂=C₃ 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 artemisinin, a phenolic structure with the hydroxyl group strongly obstructed [10]. It seems that the double bond C₂=C₃ 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 phenoxy 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

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the double bond C₂=C₃ [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 C₂=C₃ conjugated to the aromatic ring of phenolic compounds, showing a higher radical scavenging activity.

C₂=C₃ Double Bond Increases Enzyme Inhibitory Effect

High inhibitory effect against aldose reductases is attributed to the molecules with a C₂=C₃ 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 C₂=C₃ 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 C₂=C₃, 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 C₂=C₃ 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 C₂=C₃ 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 C₂=C₃ double bond produced a decrease in enzyme inhibitions.

C₂=C₃ Double Bond Enhances other Biological Activity

It has been reported that reduction of the C₂=C₃ 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 C₂=C₃ 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 C₂=C₃ 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 C₂=C₃ double bond, did not affect glucose uptake. The presence of C₂=C₃ 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 C₂=C₃ double bond in the dietary phenolic compounds significantly enhanced various biological effects. The C₂=C₃ 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.

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