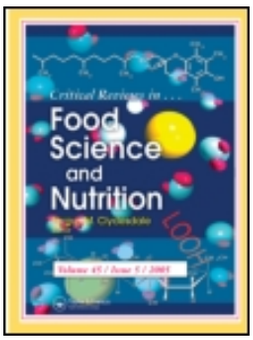

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Advance on the Flavonoid *C*-glycosides and Health Benefits

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The dietary flavonoids, especially their glycosides, are the most vital phytochemicals in diets and are of great general interest due to their diverse bioactivity. Almost all natural flavonoids exist as their O-glycoside or C-glycoside forms in plants. The dietary flavonoid C-glycosides have received less attention than their corresponding O-glycosides. This review summarizes current knowledge regarding flavonoid C-glycosides and their influence on human health. Among the flavonoid C-glycosides, flavone C-glycosides, especially vitexin, isoorientin, orientin, isovitexin and their multiglycosides are more frequently mentioned than others. Flavonoid C-monoglycosides are poorly absorbed in human beings with very few metabolites in urine and blood and are deglycosylated and degraded by human intestinal bacteria in colon. However, flavonoid C-multiglycosides are absorbed unchanged in the intestine and distributed to other tissues. Flavonoid C-glycosides showed significant antioxidant activity, anticancer and antitumor activity, hepatoprotective activity, anti-inflammatory activity, anti-diabetes activity, antiviral activity, antibacterial and antifungal activity, and other biological effects. It looks like that the C-glycosylflavonoids in most cases showed higher antioxidant and anti-diabetes potential than their corresponding O-glycosylflavonoids and aglycones. However, there is a lack of in vivo data on the biological benefits of flavonoid C-glycosides. It is necessary to investigate more on how flavonoid C-glycosides prevent and handle the diseases.

Keywords Flavonoid *C*-glycosides, biological benefits, stability, absorption

1. INTRODUCTION

Evidence from epidemiological investigations shows that the dietary flavonoids have received an increased attention due to their considerable benefits in the prevention and management of modern diseases such as cancers, diabetes, and cardiovascular diseases (Xiao et al., 2013; Cerella et al., 2014; Gechev, et al., 2014; Georgiev, 2014; Schnekenburger et al., 2014; Xiao and Högger, 2014; Xiao and Georgiev, 2015; Xiao and Högger, 2015a, b; Xiao et al., 2015). Most of the natural flavonoids are *O*-glycosides and *C*-glycosides and the most abundant flavonoid glycosides in plants are flavone and flavonol glycosides (Veitch and Grayer, 2011; Barreca et al., 2014; Xiao et al., 2014). The most reported flavonoid *O*-glycosides are 3- and 7-*O*-glycosides; however, the flavonoid *C*-glycosides are found mainly as 6- and 8-*C*-glycosides (Veitch and Grayer, 2011; Xiao et al., 2014). Among the flavonoid *C*-glycosides, flavone *C*-glycosides, especially vitexin, isoorientin, orientin, isovitexin and their multiglycosides (Figure 1) are more frequently mentioned than other flavonoids.

Several reviews on flavonoid glycosides have been published since 2011. *Flavonoids and Their Glycosides, Including Anthocyanins* by *Veitch* and *Grayer* (2011) summarized 796 new flavonoid aglycones and glycosides reported from 2007 to

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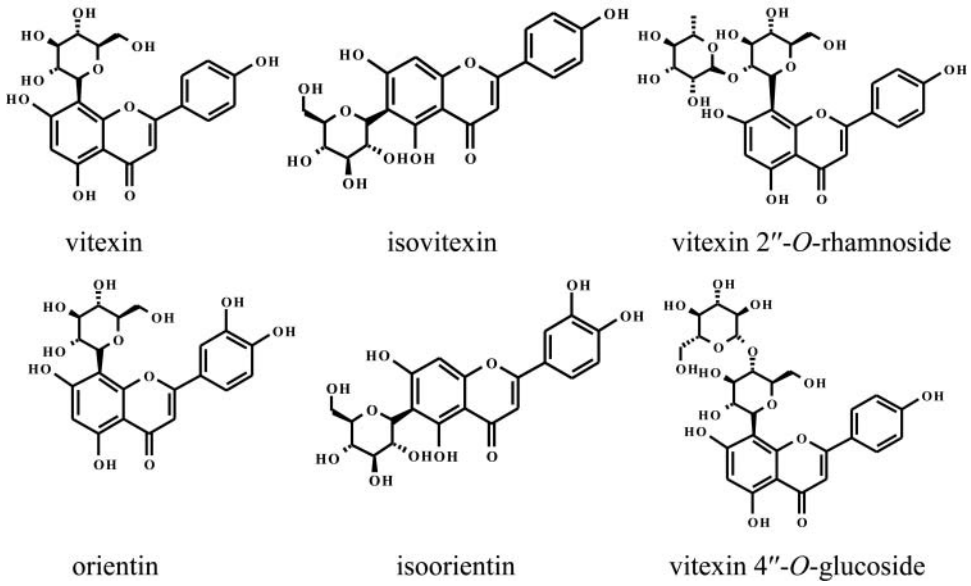


Figure 1 Chemical structures of flavonoid *C*-glycosides.

2009. Compared with the period of 2004–2006, the number of new found flavone and flavonol *O*-glycosides increased by 31% and 60%, respectively, while the number of new found flavone and flavonol *C*-glycosides decreased by 22% (Veitch and Grayer, 2011). *Advance on Biotechnology for Glycosylation of High-value Flavonoids* addressed the advances in the production and biotransformation of flavonoid glycosides by biotechnological methods (Xiao et al., 2014).

The flavonoid *C*-glycosides received much less attention than flavonoid *O*-glycosides. However, the flavonoid *C*-glycosides exhibit a wide range of benefits for human health (Choi et al., 2014a). There are almost no special reviews related to "flavonoid *C*-glycosides and their effects on human health". This review summarizes current knowledge regarding flavonoid *C*-glycosides and their biological benefits.

2. FLAVONOID C-GLYCOSIDES FROM DIETARY RESOURCES

Flavonoids are the largest group of plant phenolics, consisting of different sub-classes: flavonols, flavones, flavanonols, flavanones, flavanols, isoflavones, chalcones and anthocyanidins. Flavonoids are generally found in the form of glycosides and also in the form of aglycone which is not so common. Most of the flavonoids in foods exist primarily as *O*-glycosides in which the sugar group is linked to the aglycone by an *O*-glycosidic bond. On the other hand, *C*-glycosylated flavonoids represent a group of oxygen heterocyclic compounds widespread in a variety of plants in which the sugar group and the aglycone are linked by a *C*-glycosidic bond (Oualid and Artur, 2012). Flavonoid *C*-glycosides have received less attention compared to *O*-glycosides. However, interest in *C*-glycosides has recently increased since some studies have been published to emphasize the positive effects of *C*-glycosides on human health (Kong 2012). *C*-Glycosides are formed in microbes, plants, and insects, where they serve a diverse range of functions by acting as siderophores, antibiotics, antioxidants, attractants, and feeding deterrents (Hultin, 2005; Brazier-Hicks et al., 2009).

Flavonoids are deglycosylated to their aglycones by β-glucosidase in the small intestine (Rechner et al., 2002). Flavonoids are also exposed to *O*-methylation during transfer to small intestine (Kuhnle et al., 2000). Conjugated molecules pass to the bile and reach the colon where they are degraded by microorganisms. It is known that the biological activity of flavonoids in the body can be affected by this reaction. In order to understand the impact of flavonoid glycosides on health, these reactions and modifications should be examined thoroughly. There are published studies on *O*-glycosides and their effects on health, however, there is limited information about *C*-glycosides (Kreuz et al., 2008). Rawat et al. (2009) assumed that *C*-glycosylated flavonoids would have better therapeutic properties given their stability over aglycone or *O*-glycosylated flavonoids.

The researchers isolated the flavonoid *C*-glycosides from *Ulmus wallichiana*, plant native to India and analyzed their effects on osteoblast (bone forming cell) differentiation which is important for the treatment of osteoporosis (Rawat et al., 2009; Batool et al., 2014). Researchers started to show interest on flavonoid *C*-glycosides after the discovery of their stimulating effects on osteoblast differentiation and studies have been published on the isolation of flavonoid *C*-glycosides from different dietary sources and medicinal plants (Table 1).

In one of the first studies, the main phenolic constituent in the leaves of *Aspalathus lineari* was isolated and identified as a *C*-glycosylflavonoid, namely aspalathin by means of NMR spectroscopy (Koeppen and Roux, 1966). In another study, *C*-glycosyl

Table 1 Some important flavonoid-C-glycosides in different sources

Source	Flavonoid-*C*-glycosides	Reference
Passiflora species	Orientin, isoorientin, vitexin, isovitexin	Ulubelen et al. (1981); Zucolotto (2012); Simirgiotis et al. (2013)
Abrus mollis	Vicenin-2, schaftoside, isoschaftoside	Du et al. (2012)
Ulmus wallichiana	Naringenin 6-*C*-*β*-D-glucopyranoside, eriodictyol 6-*C*-*β*-d-glucopyranoside, kaempferol-6-*C*-*β*-d-glucopyranoside, quercetin-6-*C*-*β*-d-glucopyranoside, isoorientin	Rawat et al. (2009); Batool et al. (2014)
Aspalathus lineari	Aspalathin	Koeppen and Roux (1966)
Alternanthera philoxeroides	Alternanthin	Zhou et al. (1988)
Lupinus hartwegii	*C*-Glycosides of apigenin	Kamel (2003)
Dendrobium huoshanense	6,8-di-*C*-glycosyl flavones	Chang et al. (2010)
Sarcotheca griffithii leaves	Chrysin 6-*C*-(2″-*O*-*α*-L-rhamnopyranosyl)-*β*-D-glucopyranoside, chrysin 6-*C*-(2″-*O*-*α*-L-rhamnopyranosyl)-*β*-D-glucopyranosyl-7-*O*-*β*-D-glucopyranoside, chrysin 6-*C*-(2″-*O*-*α*-L-rhamnopyranosyl)-6′-deoxy-ribo-hexos-3-uloside, chrysin 6-C-(2″-*O*-*α*-L-rhamnopyranosyl)-*β*-L-fucopyranoside, chrysin 6-*C*-*β*-boivinopyranosyl-7-*O*-*β*-L-glucopyranoside	Muharini et al. (2014)
Dianthus L.	Orientin, isoorientin, vitexin, isovitexin	Obmann et al. (2011)
Lotus (*Nelumbo nucifera*)	Orientin, isoorientin, vitexin, isovitexin, schaftoside, isoschaftoside 6-*C*-glucosyl-8-*C*-xylosyl apigenin, 6-*C*-xylosyl-8-*C*-glucosyl apigenin, 6-*C*-glucosyl-8-*C*-pentosyl luteolin, 6-*C*-pentosyl-8-*C*-glucosyl luteolin, 6-*C*-glucosyl-8-*C*-rhamnosyl apigenin, 6-*C*-rhamnosyl-8-*C*-glucosyl apigenin	Li et al. (2014)
Fenugreek (*Trigonella foenum-graecum*) germinated seeds	Apigenin di *C*-glycosides, tri- and tetra *O*-/*C*-glycosides	Benayad et al. (2014)
Egyptian lupin (seeds)	Apigenin 6-*C*-*β*-D-glucopyranosyl-8-*C*-[*β*-D-apiofuranosyl-(1–2)]-*β*-glucopyranoside and apigenin 6-*C*-*β*-D-glucopyranosyl-8-*C*-[*α*-L-rhamnopyranosyl-(1–2)]-*β*-glucopyranoside)	Elbandy and Rho (2014)
Celtis australis L.	Isovitexin, 2″- *α* -L-rhamnopyranosyl-7-*O*-methylvitexin, cytisoside, 2″-*α*-L-rhamnopyranosylvitexin	Zehrmann et al. (2010)
Maize, wheat, rice, barley	Vitexin, isovitexin, isoorientin, saponarin, lutonarin	Harborne (1993); Harborne and Williams (2000); Brazier-Hicks et al. (2009)
Dates	Apigenin di-*C*-hexoside	Hong et al. (2006)
Kumquat (**Fortunella japonica** Swingle) juice	Acacetin 3,6-di-*C*-glucoside, vicenin-2, lucenin-2 4′-methyl ether, phloretin 3′,5′-di-*C*-glucoside, apigenin 8-*C*-neohesperidoside, acacetin 8-*C*-neohesperidoside, acacetin 6-*C*-neohesperidoside	Barreca et al. (2011b)
Citrus juice	Lucenin-2, vicenin-2, lucenin-2, 4'-methyl ether	Barreca et al. (2014)

flavonoids were identified in some members of the genus *Passiflora* (Ulubelen et al., 1981). Also, the structure of alternanthin, a flavone *C*-glycoside from *Alternanthera philoxeroides*, has been elucidated using a spectroscopic technique (Zhou et al., 1988). *C*-Glycosides of apigenin were found in *Lupinus hartwegii* (Kamel, 2003). On the other hand, a traditional Chinese medicine (*Dendrobium huoshanense*) was reported to contain four 6,8-di-*C*-glycosyl flavones which have a core of apigenin bearing pentoside (arabinoside or xyloside) and rhamnosyl-hexoside (glucoside or galactoside) substituents (Chang et al., 2010). In a study performed by Muharini et al. (2014), five new flavone *C*-glycosides, including chrysin 6-C-(2″-O-*α*-L-rhamnopyranosyl)-*β*-D-glucopyranoside, chrysin 6-C-(2″-O-*α*-L-rhamnopyranosyl)-*β*-D-glucopyranosyl-7-O-*β*-D-glucopyranoside, chrysin 6-C-(2″-O-*α*-L-rhamnopyranosyl)-6′-deoxy-ribo-hexos-3-uloside, chrysin 6-C-(2″-O-*α*-L-rhamnopyranosyl)-*β*-L-fucopyranoside, chrysin 6-C-*β*-boivinopyranosyl-7-O-*β*-L-glucopyranoside, were isolated from the leaves of *Sarcotheca griffithii* and their structures were identified by means of NMR and MS techniques (Muharini et al., 2014).

In another study, chemical composition of the extracts of leaves and fruits' pericarp of *Passiflora* species was investigated for the presence of *C*-glycosyl flavonoids. Two separate HPLC methods were developed using diode array detection

and MS. According to the results, different species and varieties showed different major constituents, but the main *C*-glycosyl flavonoids identified were orientin, isoorientin, vitexin and isovitexin (Zucolotto et al., 2012). In a recently published study, flavonoid *C*-glycosides were identified in the extract of the aerial parts of *Dianthus versicolor*, a plant used as a medicine against liver diseases in Mongolia (Obmann et al., 2011).

It has been reported that major cereal crops including maize, wheat and rice predominantly synthesize flavone *C*-glycosides, which are stable to hydrolysis and are biologically active both *in planta* and as dietary components (Harborne, 1993; Brazier-Hicks et al., 2009). Similarly, six flavone *C*-glycosides were isolated from the leaves of barley. One of the *C*-glucosides was found to be a new type of glycoside which was identified as 2′,4′,5,5′,7-penta-OH-substituted flavone linked to a 6-*C*-β-D-glucoside. Also, another flavonoid *C*-glycoside, apigenin di-*C*-hexoside, was identified in dates which are widely consumed in the Middle East (Hong et al., 2006). Micellar electrokinetic chromatography separated eight different flavonoid *C*-glycosides in *Celtis australis* L. (Zehrmann et al., 2010). Recently, two new di-*C*-glycoside flavones, apigenin 6-C-β-D-glucopyranosyl-8-C-[β-D-apiofuranosyl-(1–2)]-β-glucopyranoside and apigenin 6-C-β-D-glucopyranosyl-8-C-[α-L-rhamnopyranosyl-(1–2)]-β-glucopyranoside) have been isolated from the seeds of Egyptian lupin used as a food ingredient in the form of flour (Elbandy and Rho, 2014). A total of 25 apigenin di *C*-glycosides, tri- and tetra *O*-/*C*-glycosides were identified from fenugreek (*Trigonella foenum-graecum*) germinated seeds (Benayad et al., 2014). The germinated fenugreek seeds consisted of flavone di *C*-glycosides (32.45%), acylated flavone glycosides (30.65%), flavone tri and tetra-glycosides (23.82%) and flavonol *O*-diglycosides (11.94%).

3. STABILITY OF FLAVONOID C-GLYCOSIDES

Glycosylation is a common metabolic fate for majority of flavonoids, a process that is also known to influence their stability (Rawat et al., 2009). It has been reported that structural changes in glycosides may provide improved stability. On the other hand, it is known that patterns of glycosylation are strongly correlated with plant taxonomy and give rise to a wide range of chemical properties (Lin and Harnly, 2007). Structural differences may arise from the location of hydroxyl and methoxyl groups, the placement number, identity of saccharide moieties, and some modifications that occur as a result of metabolism including methylation, sulfonation, and glucuronidation (Davis and Brodbelt, 2004). Even though the effect of glycosylation on the stability of flavonoids has been discussed so far (Plaza et al., 2014), there is limited information on the stability of flavonoid *C*-glycosides.

It was reported that *C*-glycosylation in the A-ring decreases antioxidant activity (Mora et al., 1990), and this negative effect may result from the properties of sugar itself, rather than from the displacement of a free hydroxyl group (Heim et al., 2002). Plumb et al. (1999) have also reported that antioxidant capacities of flavonol glycosides present in tea decreased as the number of glycosidic moieties increased. Also, the total number of glycosidic moieties, the type of glycosylation (*O*- or *C*-) and the position and structure of the sugar were found to play important roles. On the other hand, *C*-glycosylated flavonoids were reported to be more stable in comparison to aglycones or *O*-glycosylated flavonoids (Rawat et al., 2009). The replacement of the oxygen atom in glycosides with carbon substituents provides carbohydrate mimetics with improved stability toward glycosidases and hydrolytic conditions. In principle, greater chemical and enzymatic stability of these *C*-glycosides is critical for their application as small molecule inhibitors of cell-surface recognition events and glycoside metabolism (Wipf et al., 2005). Besides, extraction may also affect the stability of flavonoid glycosides. Biesaga (2011) investigated the stability of flavonoid glycosides in maize by comparing four different extraction methods by LC-MS/MS.

In summary, flavonoid *C*-glycosides were found to be more stable than aglycones or flavonoid *O*-glycosides. The degradation process and stability of flavonoid *C*-glycosides were found to be affected by the type of substituents and the position of hydroxyl group. The degree of hydroxylation of flavonoids significantly influenced the stability in the order: resorcinol-type > catechol-type > pyrogallol-type, with the pyrogallol-type being highly unstable (Xiao et al., 2014). In contrast, any *O*-/*C*- glycosylation of flavonoids obviously enhanced their stability. However, the glycosylation was less important compared to the substitution pattern of the nucleus rings.

4. PHARMACOKINETICS OF FLAVONOID C-GLYCOSIDES

In most cases, flavonoid *O*-glycosides are hydrolyzed by enzymes or degraded by bacteria to their aglycones in the intestine, reduced and conjugated to form flavonoid *O*-glucuronides and *O*-sulfates in the liver (Xiao and Högger, 2013). However, flavonoid *C*-glycosides showed different pharmacokinetic behaviors compared with flavonoid *O*-glycosides (Xiao and Högger, 2014). Flavonoid *C*-monoglycosides appear to have different absorption and metabolic pathways than *C*-multiglycosides (Figure 2).

4.1. Flavonoid C-monoglycosides

It is very difficult to break the *C*-glucosyl bond of flavonoid *C*-monoglycosides by chemical and biological methods.

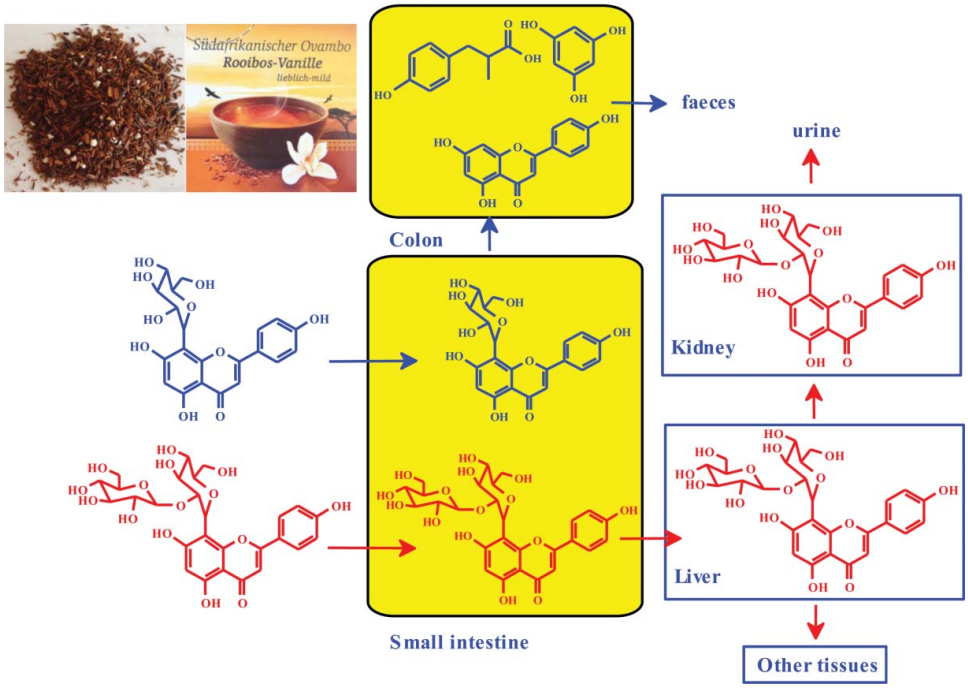


Figure 2 Absorption and metabolism of flavonoid *C*-monoglycosides (blue arrow) and *C*-multiglycosides (red arrow).

However, the intestinal bacteria can cleave the *C*-glucosyl bond in different flavonoid *C*-monoglycosides such as puerarin, homoorientin, orientin, vitexin, isovitexin, and abrusin 2″-O-*β*-D-apioside. Because *C*-1″ in the sugar is hydroxylated instead of hydrogenated, *C*-glucosyl bond-cleaving reaction is not reduction but hydrolysis. The substrates of hydrolytic enzymes in gut for the glycosyl linkage are only active for flavonoid *O*-glycosides and it is not essential to deglycosylated flavonoid *C*-monoglycosides in humans.

Flavone *C*-monoglucosides such as orientin, vitexin, homoorientin, and isovitexin were poorly absorbed in the gastrointestinal tract of rats and consequently, they reached the colon (Zhang et al., 2007) (Figure 2). No flavone *C*-glucosides were detected in the brain and liver of rats within 12 hours after administration, they were excreted with feces at 24 hours. These flavone *C*-glucosides were deglycosylated to their aglycones and degraded to form smaller metabolites such as phloroglucinol, hydrocaffeic acid, and phloretic acid. Homoorientin was converted to 6-*C*-glucosyleriodictyol, phloroglucinol, (+)-eriodictyol, 3,4-dihydroxyphenylpropionic acid, and luteolin by human intestinal bacteria (Hattori et al., 1988) (Figure 3). Puerarin was metabolized to daidzein, (3S)-equol and an intact glucose by human intestinal bacteria (Jin et al., 2008; Nakamura et al., 2011). Homoorientin and vitexin were completely metabolized to 3-(3,4-dihydroxyphenyl)propionic acid and 3-(4-hydroxyphenyl)propionic acid by intestinal bacterium *Eubacterium cellulosolvens* within 24 hours (Braune and Blaut, 2012). *E. cellulosolvens* also deglycosylated homoorientin and isovitexin to luteolin and apigenin, respectively.

Flavonoid *C*-monoglucosides, for instance eriodictyol *C*-glucoside, luteolin 6-*C*-glucoside, luteolin 8-*C*-glucoside, apigenin 8-*C*-glucoside, and apigenin 6-*C*-glucoside in rooibos tea were poorly absorbed in humans with very few metabolites found in urine and blood (Stalmach et al., 2009). 3-*O*-Methoxylaspalathin and 3-*O*-methoxylaspalathin glucuronide are the main metabolites in the urine of healthy human volunteers. The plasma level of vitexin was very low after oral administration to rats (Wang et al., 2012a).

In summary, flavonoid *C*-monoglycosides are poorly absorbed in humans with very few metabolites in urine and blood and are deglycosylated and degraded by human intestinal bacteria in colon. However, some *C*-monoglycosides for

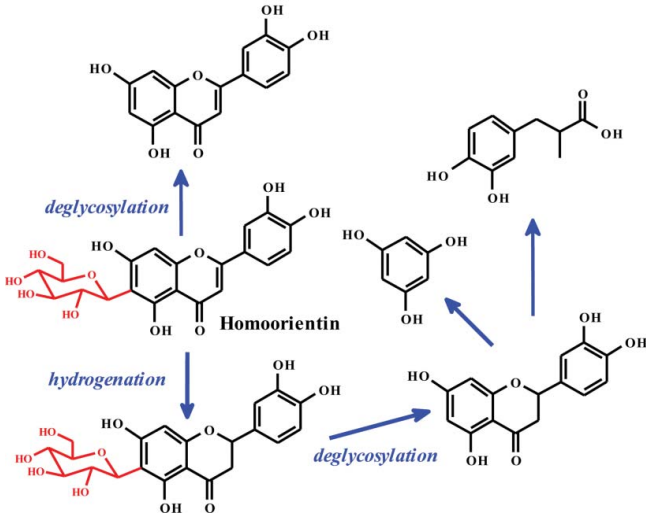


Figure 3 Biotransformation of homoorientin by human intestinal bacteria (Hattori et al., 2008).

example aspalathin are absorbed better. For example, aspalathin from an aqueous extract of green rooibos (concentration of 1.940 mg/mL) was reported to be completely transported across Caco-2 cell monolayer (Huang et al., 2008). Aspalathin was methylated and glucuronidated *in vivo* in humans (Courts and Williamson, 2009). The transcellular movement of the intact molecule across the intestinal epithelium was predominantly facilitated.

4.2. Flavonoid C-multiglycosides

Flavonoid *C*-multiglycosides are absorbed unchanged and undergo enterohepatic recirculation. In case of apigenin, both the free aglycone and its glucuronides were detected in the portal blood whereas apigenin 8-*C*-glucoside-2-*O*-xyloside was not degraded in the intestine and hardly changed in the liver, then it returned to the gut by enterohepatic recirculation (Angelino et al., 2013). Vitexin 4″-*O*-glucoside and vitexin 2″-*O*-rhamnoside, the main constituents of hawthorn leaves, showed similar pharmacokinetic profiles and were quickly absorbed into plasma with peak concentrations occurring within 0.75 h after oral administration in rats (Ma et al., 2010). Vitexin 4″-*O*-glucoside and vitexin 2″-*O*-rhamnoside were mainly distributed in liver and kidney (Figure 2). Vitexin was eliminated quickly from plasma and could not be detected at 4 h after administration in rats, however, vitexin 4″-*O*-glucoside and vitexin 2″-*O*-rhamnoside were eliminated over after 12 hours (Zhang et al., 2010). The hepatic and intestinal first-pass effects were thought to cause low bioavailability of vitexin 4″-*O*-glucoside in rats (Chen et al., 2013a, b). CYP3A might be involved in its metabolism or P-glycoprotein might reduce its absorption rate. Recently, Yin et al. compared the tissue distribution of flavone *C*-glycosides in healthy and fatty liver rats (Yin et al., 2014). Vitexin 4″-*O*-glucoside was absorbed in the stomach and then transferred to other tissues (Chen et al., 2013a, b).

The renal and biliary excretion are two main routes to eliminate vitexin 2″-*O*-rhamnoside. Vitexin 2″-*O*-rhamnoside underwent extensive first-pass metabolism after oral administration in mice, it was not absorbed and was mainly excreted in feces (An et al., 2013). The oral bioavailability of vitexin 2″-O-rhamnoside was significantly weak in rats ($p \leq 0.05$) (Liang et al., 2007), it was mainly distributed in stomach, intestine, and liver (Chen et al., 2013a, b). Moreover, the absorption rates of vitexin 2″-*O*-rhamnoside in four segments of the rat intestine were similar (Xu et al., 2008). Vitexin 2″-*O*-rhamnoside was rapidly absorbed into circulation after oral administration (120 mg/kg) in rats (T_{max}= 30.8 and $T_{1/2}$= 20.1 min) (Ying et al., 2007). The pharmacokinetics of vitexin-2″-O-rhamnoside in rats obeyed first-order kinetics (Ying et al., 2007).

However, Wang et al. (2013) found that vitexin and rhamnosylvitexin showed similar intestinal absorption and both of them were poorly absorbed in duodenum, jejunum, ileum and colon. In summary, flavonoid *C*-multiglycosides are absorbed unchanged in the intestine and then distributed to other tissues.

5. BIOLOGICAL BENEFITS OF FLAVONOID C-GLYCOSIDES

5.1. Antioxidant Activity

Sugar molecules attached *via* glycosylation play crucial biological roles in many natural products, and indeed their removal may result in loss of bioactivity (Stobiecki, 2000). Altering the structures of these sugars or the points of attachment to aglycone can enhance physiological properties (Simkhada et al., 2010). Orientin and vitexin from *Trollius chinesis* can improve the antioxidant activity in serum and tissue of mice and reduce the amount of MDA (Wang et al., 2012b). In the literature, studies on the antioxidant properties of flavonoid glycosides generally focus on *O*-glycosides (Lemmens et al., 2014). There is limited information about the antioxidant activity of flavonoid *C*-glycosides although some studies showed that the flavonoid *C*-glycosides have different biological activities, including antioxidant, antimicrobial, cytotoxic, and hepatoprotective activities (Pacifico et al., 2010) (Table 2).

Glycosylated flavonoids generally show decreased antioxidant capacity compared with the corresponding aglycones, but glycosylation also affects parameters including solubility and stability (Plaza et al., 2014). However, since the mechanism and the effect of glycosylation have not been completely enlightened, there is still a significant interest to investigate the antioxidant activity of flavonoid glycosides. Indeed, it was reported that in the future it will be of interest to apply the knowledge of flavone *C*-glucosylation in metabolic engineering experiments to generate flavone *C*-glucosides in recombinant plants and microbes in order to control the flavonoid metabolism, and for the generation of medicinally useful *C*-glycosylated phytoceuticals (Brazier-Hicks et al., 2009; Xiao et al., 2014).

In a study performed by Leong et al., flavonoid *O*- and *C*-glycosides from the leaves of *Ficus pumila* were examined for their antioxidant activity by analyzing their DPPH scavenging effects (Leong et al., 2008). According to the results, *O*-glycosides showed higher DPPH activity compared with *C*-glycosides. In another study, flavonoid *C*-glycoside extracts from pigeon pea leaves were added to blueberry juice to enhance the color and to stabilize the anthocyanins in the juice samples. The sample of juice with flavonoid *C*-glycosides showed higher DPPH radical-scavenging activity compared with the regular juice (Pan et al., 2014). On the other hand, Omar et al. detected sixteen flavone *C*-glycosides in *F. deltoidea*, a Malaysian herbal tea, including vitexin, isovitexin, and orientin (Omar et al., 2011). Luteolin and apigenin derivatives were the main flavones present, and besides them, there were

Table 2 Some activities of flavonoid C-glycosides against diseases

Activity	Example	Mechanism
Anticancer and antitumor activity	Aciculatin, 4‴-α-rhamnopyranosyl-2″-*O*-β-D-galactopyranosylvitexin, luteolin 8-*C*-β-fucopyranoside, isoorientin, alternanthin B	Inhibitory effects on inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2); inducing cell death in human cancer cells; cytotoxicity against KB cells; suppressing the MAPK signaling pathway and down-regulating nuclear AP-1 and NF-κB in breast cancer cells; inhibiting the proliferation and inducing the apoptosis of cancer cells; regulation of the NF-kappaB and c-Jun N-terminal kinase (JNK)/p38 pathways
Hepatoprotective activity	Kaempferol 8-*C*-β-galactoside, schaftoside, molinpentin 2″-*O*-rhamnoside, vicenin-2, lucenin-2, isovitexin 2″-*O*-rhamnoside, 11-*O*-galloylbergenin saponarm, cerarvensin 2″-*O*-rhamnoside, vitexin 2″-*O*-rhamnoside, isoorientin 2″-*O*-rhamnoside, bergenin, and orientin 2″-*O*-rhamnoside	Hepatoprotective effects against histopathological and histochemical damage; preventive effect on D-galactosamine-induced liver injury; hepatoprotective activity against CCl_4- and galactosamine-induced cytotoxicity; inhibition against TNF-α induced cell death in mouse hepatocytes
Antidiabetic activity	Vitexin, isovitexin, swertisin, flavocommelin, orientin, isoorientin, apigenin *C*-glycosides	α-glucosidase inhibitory effect; reducing the formation of advanced glycation endproducts (AGEs); decrease in serum glucose levels; inducing a significant increase in insulin secretion; stimulating glycogen storage
Anti-inflammatory activity	Orientin, isoorientin, kaempferol 6-*C*-glucoside, quercetin-6-*C*-glucoside, luteolin-8-*C*-glucoside	Reduction in the expression of pro-inflammatory enzymes (COX-2, iNOS) and NO levels; protecting the vascular barrier integrity by inhibiting hyperpermeability, adhesion and migration of leukocytes
Memory ameliorating activity	Spinosin	Amelioration on cholinergic blockade-induced cognitive impairment
Antiviral activity	Swertisin, isoorientin, isovitexin, swertiajaponin	Antiviral activity against respiratory syncytial virus (RSV), anti-hepatitis B virus (anti-HBV)
Antiplatelet activity	Apigenin 6,8-di-*C*-β-D-glucopyranoside, diosmetin 6,8-di-*C*-β-D-glucopyranoside, apigenin 8-*C*-β-D-glucopyranoside, apigenin 8-*C*-[α-L-arabinopyranosyl-(1→6)]-*O*-β-D-glucopyranoside, apigenin 6-*C*-[α-L-arabinopyranosyl-(1→6)]-*O*-β-D-glucopyranoside, isovitexin	Inhibition against Adenosine diphosphate (ADP) and epinephrine induced platelet aggregation
Antiaging activity	Orientin, vitexin	Ameliorating the activities of superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px)

identified isomers of schaftoside and vitexin which have not been previously reported to occur in other *Ficus* species. The potential antioxidant activity of different extracts of *Rhynchosia capitata* was also investigated by the DPPH method and flavonoid *C*-glycosides were identified by high pressure thin layer chromatography (HPTLC) technique. Luteolin 6-*C*-glucoside, luteolin 6,8-di-*C*-glucoside and apigenin 6-*C*-glucoside-8-*C*-arabinoside from pepper fruit showed strong superoxide radical and DPPH free radical scavenging potential and significantly inhibited the xanthine oxidase activity (Materska, 2015). Vitexin is a bioactive flavone glucoside in *R. capitata*. Presence of a glucose unit in *C*-8 position of vitexin was found to enhance the antioxidant potential of the compound due to the fact that *C*-8 glycosylation decreases the negative charge on the oxygen atom at the *C*-3 position (Praveena et al., 2013). Significant antioxidant and urease inhibitory activities of *Celtis africana* were reported (Perveen et al., 2011). Researchers isolated two new *C*-glycosylflavonoids: celtisides A and B from *n*-butanol-soluble fraction of *Celtis africana* which were reported for the first time in this species, together with five known *C*-glycosylflavonoids including vitexin, orientin, isoswertiajaponin, isoswertisin, and 2″-O-rhamnosyl vitexin. Devkota et al. (2013) isolated 5-*O*-acetyl-2″-α-rhamnopyranosylisovitexin, 2″-α-rhamnopyranosylisovitexin, 2″-α-rhamnopyranosylisoorientin and isoorientin. 3′-mehyl ether from the aerial parts of *Lychnis senno* Siebold et Zucc and only 2″-α-rhamnopyranosylisoorientin exhibited moderate antioxidative activity.

On the other hand, in a study performed by Huber et al. (2009), antioxidants including quercetin glycosides, butylated hydroxytoluene (BHT), and α-tocopherol were incorporated into selected polyunsaturated fatty acids (PUFA) or fish oil in aqueous emulsions and bulk oil systems. The antioxidant potential of quercetin was similar to or greater than that of quercetin glycosides in inhibiting lipid oxidation in the oil-in-water emulsion systems when oxidation was induced by heat,

light, peroxyl radical or ferrous ion. According to the results, *C*-3 glycosylation enhanced the antioxidant activity of quercetin in bulk fish oil, and the type of sugar attached to *C*-3 of quercetin influenced the effectiveness of inhibition of PUFA oxidation in the emulsion systems.

In another study, Barreca et al. (2011a) investigated the qualitative and quantitative flavonoid and furocoumarin composition of crude sour orange (*Citrus aurantium* L.) juice by using reversed-phase LC–DAD–ESI–MS–MS method, and also measured the antioxidant activity by DPPH and ABTS radicals scavenging assays. In this study, seven flavonoids (three *C*-glucosides: lucenin-2, vicenin-2 and lucenin-2, -methyl ether, two *O*-glycosides: rhoifolin-glucoside and narirutin-glucoside, two 3-hydroxy-3-methylglutaryl flavanone glycosides: melitidin and brutieridin) and a furocoumarin (epoxybergamottin) were identified for the first time in sour orange juice. Sour orange juice containing these constituents showed a high capacity of quenching DPPH and ABTS free radicals, reaching up to 48% and 75% of inhibition, respectively. In summary, the *C*-glycosylflavonoids, in most cases, showed higher antioxidant potential than the corresponding *O*-glycosylflavonoids and aglycones.

5.2. Anticancer and Antitumor Activity

One of the most potent antitumor flavone *C*-glycosides is aciculatin, which was initially purified from dichloromethane extract of a Philippines plant, *Chrysopogon aciculatis* (Carte et al., 1991). Aciculatin was reported to bind to DNA and showed cytotoxicity against KB cells (Carte et al., 1991). Some other studies showed that aciculatin is a potent anticancer agent with dual inhibitory effects on inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) (Lai et al., 2011, 2012). The mechanisms of the antitumor activity are suggested to be via the regulation of the NF-kappaB and c-Jun N-terminal kinase (JNK)/p38 pathways. It was also proved that aciculatin induces cell death in human cancer cells and HCT116 mouse xenografts due to G1 arrest followed by apoptosis (Lai et al., 2012).

Alternanthin B (Figure 4) is another flavone *C*-glycoside isolated from the aerial parts of *Alternanthera philoxeroides* together with other five compounds (Fang et al., 2007). The antitumor activity of alteranthin (Figure 4), the 3′-demethyl derivative of alternanthin B, against HeLa and L929 cells was higher than that of alternanthin B (Fang et al., 2007).

The water extract of the leaves of *Celtis occidentalis* L. exhibited the strongest activity against human hepatocellular carcinoma (HEP-G2) (ED_{50}= 18.60 μg/mL), while the ethanol extract was active against colon adenocarcinoma (COLO 205) and gastric carcinoma (NCI-N87) (ED_{50}= 24.80 and 15.80 μg/mL, respectively) (El-Alfy et al., 2011). The above cytotoxic activities were attributed to the polar constituents, especially to 4‴-α-rhamnopyranosyl-2″-*O*-β-D-galactopyranosylvitexin, a flavonoid *C*-triglycoside present in the extracts.

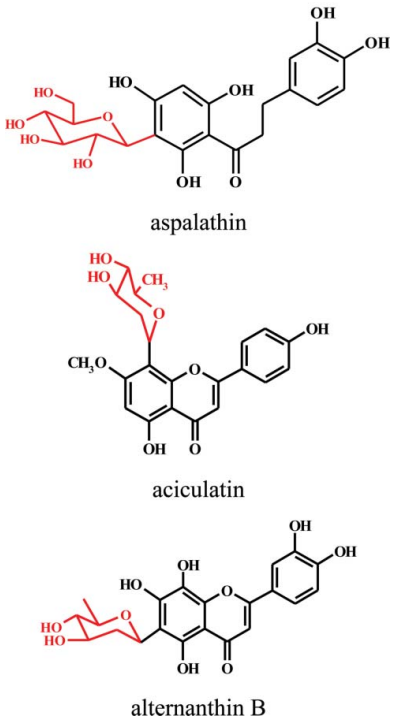


Figure 4 Chemical structures of aspalathin, aciculatin and alternanthin B.

The biological activity including anticancer activity of citrus was attributed to the presence of different flavonoids including flavone *C*-glycosides via regulation of the key enzymes involved in the cell activation and receptor binding (Manthey et al., 2001). Luteolin 8-*C*-β-fucopyranoside inhibited the secretion of TPA-induced MMP-9 and IL-8 and mRNA expression via suppressing the mitogen-activated protein kinases (MAPK) signaling pathway and down-regulating nuclear AP-1 and NF-κB in breast cancer cell line MCF-7 (Park et al., 2013). Isoorientin was reported to inhibit the proliferation and induce the apoptosis and autophagy of HepG2 cancer cells (Yuan et al., 2012, 2013, 2014). Isoorientin induced apoptosis by mitochondrial dysfunction, activating the Fas receptor-mediated apoptotic pathway and MAPK singaling pathway and inactivating the p53 and PI3K/Akt-dependent NF-κB signaling pathway. Orientin remarkably inhibited the proliferation and induced apoptosis of EC 109 cells (Zhu et al., 2012).

5.3. Hepatoprotective Activity

Flavone *C*-glycosides and the extracts rich in flavone *C*-glycosides showed significant hepatoprotective activity. *Solanum elaeagnifolium* extracts containing kaempferol 8-*C*-β-galactoside showed hepatoprotective effects against histopathological and histochemical damage induced by paracetamol in mice liver (Hawas et al., 2013). The fraction rich in apigenin *C*- and *O*-glycosides from *Dianthus versicolor* significantly stimulated the bile secretion (Obmann et al., 2010).

The extract from *Montanoa bipinnatifida* showed hepatoprotective effects on CCl_4-induced liver injury in rats (El-Toumy et al., 2011). Several flavone *C*-glycosides such as luteolin 6-*C*-apioside, luteolin 8-*C*-glucoside, apigenin 6-*C*-glucoside, apigenin 8-*C*-glucoside, apigenin 6,8-di-*C*-glucoside, luteolin 8-*C*-glucoside, luteolin 6,8-di-*C*-glucoside, luteolin 6-*C*-glucoside were identified and isolated from *M. bipinnatifida*. Wada et al. (2000) isolated a flavone *C*-glycoside from the glycosidic flavonoids-rich fraction from green tea leaves guided by the detection of a preventive effect on D-galactosamine-induced liver injury in rats. This flavone *C*-glycoside inhibited the D-galactosamine-induced increase of plasma alanine aminotransferase and asparatate aminotransferase activities in rats. Schaftoside, molinpentin 2″-*O*-rhamnoside, vicenin-2, lucenin-2, isovitexin 2″-*O*-rhamnoside, 11-*O*-galloylbergenin saponarm, cerarvensin 2″-*O*-rhamnoside, vitexin 2″-O-rhamnoside, isoorientin 2″-*O*-rhamnoside, bergenin, and orientin 2″-*O*-rhamnoside from the leaves of *Allophyllus edulis* var. *edulis* and *gracilis* obviously exhibited hepatoprotective activity against CCl_4- and galactosamine-induced cytotoxicity (Hoffmann-Bohm et al., 1992). Vitexin 7-*O*-*β*-D-glucopyranoside and 2″-*O*-*β*-D-glucopyranoside isolated from the aerial parts of *Beta vulgaris* var. *cicla* showed hepatoprotective effect in rat hepatocytes, which was similar to that of silibinin (Kim et al., 2004). Vitexin also showed inhibition against TNF-*α* induced cell death in mouse hepatocytes. Structure-activity relationships showed that flavone 8-*C*-glycosides (vitexin) seem to have hepatotoxic effects on hepatocytes, while isomeric flavone 6-*C*-glycosides (i.e. isovitexin) have hepatoprotective activity. An additional sugar moiety (rhamnosyl) attached to the *C*-bound glycosides (i.e. vitexin 2″-*O*-rhamnoside or isovitexin 2″-*O*-rhamnoside) enhanced the hepatoprotective activity. The glycosylation or methylation at the *C*-7 position of flavone 6-*C*-glycosides remarkably improved the hepatoprotective activity.

5.4. Anti-diabetic Activity

Several studies reported antidiabetic effects of flavonoid *C*-glycosides, especially vitexin and isovitexin in both *in vitro* and *in vivo* experimental models. Chen et al. isolated vitexin and isovitexin from the 70% methanol extract of the leaves of *Microcos paniculata*. Both the extract and isolated constituents (vitexin and isovitexin) showed remarkable *α*-glucosidase inhibitory effects (IC_{50} = 61.3 *μ*g/mL, 96.6 *μ*g/mL = 244 *μ*M and 115.1 *μ*g/mL = 266.2 *μ*M, respectively) in comparison with the positive control, acarbose (IC_{50} = 1007 *μ*M) (Chen et al., 2013a, b). It is noteworthy that vitexin, isovitexin and swertisin (7-O-methylapigenin-6-*C*-glucoside) isolated from other plant species (*Commelina communis, Ficus deltoidea*) were reported to inhibit *α*-glucosidase *in vitro* in different screening protocols (Choo et al., 2012; Shibano et al., 2008). Shibano et al. (2008) isolated isoquercitrin, isorhamnetin 3-*O*-rutinoside, isorhamnetin 3-*O*-*β*-D-glucoside, glucoluteolin, chrysoriol 7-*O*-*β*-D-glucoside, orientin, vitexin, isoorientin, isovitexin, swertisin, and flavocommelin from the aerial parts of *Commelina communis*. Isoquercitrin, isorhamnetin 3-*O*-rutinoside, vitexin, and swertisin had obvious inhibition against *α*-glucosidase from rat intestine. According to the IC_{50} values, the *α*-glucosidase inhibitory effects of apigenin *C*-glycosides decreased as follows: swertisin > vitexin > isovitexin ≈ flavocommelin (Shibano et al., 2008). Moreover, the *α*-glucosidase inhibitory potential of vitexin and isovitexin isolated from the leaves of *Ficus deltoidea* was confirmed in *in vivo* studies (Choo et al., 2012). In both sucrose loaded normoglycemic mice and sucrose loaded induced diabetic rats, vitexin and isovitexin considerably reduced the postprandial blood glucose levels. The doses required for a significant reduction in the postprandial blood glucose level were 1 mg/kg of vitexin or isovitexin (a dose three-fold lower than that of acarbose) in sucrose loaded normoglycemic mice and 50 mg/kg of vitexin and 20 mg/kg of isovitexin (doses ten and four-fold higher than that of acarbose) in sucrose loaded induced diabetic rats (Choo et al., 2012). Due to a hydroxyl group at the C-3′ position of the B ring, these *C*-glycosylflavones appear to have stronger *α*-glucosidase inhibitory activity than acarbose (Li et al., 2009).

Vitexin and isovitexin were also investigated for their capacity to reduce the formation of advanced glycation end-products (AGEs) and inhibit rat lens aldose reductase (RLAR), human recombinant aldose reductase (HRAR) and protein tyrosine phosphatase 1B (PTP1B). Peng et al. (2008) reported more than 85% inhibition on glucose- and methylglyoxal-induced AGEs formation for vitexin and isovitexin at 100 *μ*M, both *C*-glycosyl flavones were isolated from the mung beans (*Vigna radiata*). The inhibitory effects of vitexin and isovitexin were slightly weaker than those induced by rutin (100 *μ*M) and aminoguanidine (1 mM), well-known AGEs inhibitors. A direct methylglyoxal trapping assay showed that the anti-glycation potential of vitexin and isovitexin is more likely to be based on free radical scavenging activity than on direct trapping of reactive carbonyl species (Peng et al., 2008). Choi et al. found isovitexin to be more potent than vitexin in inhibiting RLAR (IC_{50} ‘‘= 0.49 ± 0.08 *vs*. 1.47 ± 0.08 *μ*M), HRAR (IC_{50} = 0.13 ± 0.03 *vs*. 12.07 ± 0.03 *μ*M) and AGEs (IC_{50} = 175.66 ± 3.73 *vs*. 243.54 ± 8.86 *μ*M); vitexin showed stronger PTP1B inhibitory activity than isovitexin (IC_{50} = 7.62 ± 0.21 *vs*. 17.76 ± 0.53 *μ*M) (Choi et al., 2014b). Inhibitory effects on AGEs formation have also been reported for extracts containing flavonoid *C*-glycosides (vitexin, isovitexin, isoorientin) isolated from different plant species (*Vigna radiata, Passiflora manicata*) (Peng et al., 2008; da Silva Morrone et al., 2013).

Two apigenin 6-*C*-glycosides identified as apigenin 6-*C*-*β*-fucopyranoside and apigenin 6-*C*-(2″-*O*-*α*-rhamnopyranosyl)-*β*-fucopyranoside were isolated from the leaves of *Averrhoa carambola* and tested for their effects on serum glucose levels and glycogen storage in peripheral tissues in hyperglycemic rats. Both apigenin *C*-glycosides

(50 mg/kg) caused a marked decrease in serum glucose levels at 15 min after glucose loading (19% and 32%, respectively) (Cazarolli et al., 2012). Apigenin 6-*C*-*β*-fucopyranoside (50 mg/kg) induced a significant increase in the glycogen content in soleus muscle, comparable to that of insulin (0.5 IU); a stimulatory effect on glycogen storage in the liver was also noticed. At the same dose, apigenin 6-*C*-(2″-*O*-*α*-rhamnopyranosyl)-*β*-fucopyranoside exhibited weaker effects on glycogen content in both the soleus muscle and liver. In addition, apigenin 6-*C*-*β*-fucopyranoside (1, 10, and 100 μM) stimulated ^{14}C-glucose uptake in the rat soleus muscle by activating several insulin signaling pathways such as phosphoinositide 3-kinase (PI3K), protein kinase C (PKC) and mitogen-activated protein kinase (MEK) pathways (Cazarolli et al., 2012).

Folador et al. (2010) isolated isovitexin and swertisin from the roots of *Wilbrandia ebracteata* and investigated their effects on serum glucose level, insulin secretion, glycogen content and ^{14}C-glucose uptake in the rat soleus muscle. In hyperglycemic rats, swertisin (15 mg/kg) induced a faster antihyperglycemic effect than isovitexin (same dose). Both flavonoid *C*-glycosides (15 mg/kg) induced a significant increase in insulin secretion (swertisin: 0.893 ± 0.046 ng/mL, isovitexin: 0.902 ± 0.119 ng/mL) in comparison to glipizide (10 mg/kg, 1.027 ± 0.216 ng/mL) at 60 min after treatment (Folador et al., 2010). In addition, at 15 mg/kg, they considerably stimulated glycogen accumulation in soleus muscle (swertisin: 26%, isovitexin: 27%), and glipizide (10 mg/kg) and insulin (0.05 IU) increased glycogen content by 33% and 38%, respectively. Neither swertisin nor isovitexin increased ^{14}C-glucose uptake in the rat soleus muscle (Folador et al., 2010).

Li et al. (2009) screened *α*-glucosidase inhibitors from hawthorn leaves and four flavonol/flavone glycosides were identified: quercetin a quercetin 3-*O*-glycoside and three *C*-glycosylflavones (vitexin 2″-*O*-glucoside, vitexin 2″-O-rhamnoside, and vitexin). Vitexin 2″-*O*-glucoside, vitexin 2″-*O*-rhamnoside, isovitexin, and vitexin (*C*-glycosides of apigenin) but also orientin and isoorientin (*C*-glycosides of luteolin) were screened for their *α*-glucosidase inhibitory effects. The activities, evaluated by means of IC_{50} values, varied as follows: luteolin > isoorientin > apigenin > isovitexin and orientin > vitexin (Li et al., 2009). Glycosylation of flavones at C-6 or C-8 decreased the inhibitory activity against *α*-glucosidase, although *C*-6 glycosylation had relatively less impact than *C*-8 glycosylation (Li et al., 2009). However, isovitexin, vitexin, orientin, and isoorientin showed strong *α*-glucosidase inhibitory effects.

In conclusion, studies performed so far revealed that the main mechanisms of antidiabetic activity of flavonoid *C*-glycosides are inhibition of AGEs, *α*-glucosidase, aldose reductases, and protein tyrosine phosphatase, stimulation of glycogen storage, and activation of insulin signaling (Figure 5).

5.5. *Anti-inflammatory Activity*

The anti-inflammatory potential of flavonoid *C*-glycosides has been poorly investigated. Odontuya et al. (2005) isolated isoorientin from the aerial parts of *Gentiana tenella* and *G. azurea* and studied its ability to inhibit thromboxane B_2 (TXB_2) and leukotriene B_4 (LTB_4) synthesis in rat peritoneal leukocytes. Both mediators derive from arachidonic acid *via* the cyclooxygenase (COX) and 5-lipoxygenase (5-LO) pathways, respectively and have pro-inflammatory effects. Isoorientin showed a strong inhibitory activity on TXB_2 synthesis (54.33%, 56.34%, and 66.42% inhibition at 25, 50, and 100 μg/mL, respectively) while it hardly inhibited LTB_4 synthesis (only 28.24% inhibition at 100 μg/mL). The selective inhibition on TXB_2 synthesis was attributed to the luteolin-type structure and 6-*C*-glycosylation (Odontuya et al., 2005; Venkatesha et al., 2011).

Kwon et al. (2004) screened several flavonoid *C*-glucosides (kaempferol 6-*C*-glucoside, aromadendrin-6-*C*-glucoside, taxifolin-6-*C*-glucoside, quercetin-6-*C*-glucoside, luteolin-8-*C*-glucoside or orientin) for their capacity to reduce lipopolysaccharide (LPS)-induced nitric oxide (NO) production in BV2 microglial cells. Except aromadendrin- and taxifolin 6-*C*-glucosides, all other *C*-glucosides significantly inhibited LPS-induced NO production in a concentration-dependent manner. Flavone- or flavonol-type structures and *C*-glycosylation at positions 6 or 8 appear to be important structural features for reducing NO levels. Orientin was also found to protect the vascular barrier integrity by inhibiting hyperpermeability, adhesion and migration of leukocytes, thereby endorsing its usefulness as a therapy for vascular inflammatory diseases (Lee et al., 2014).

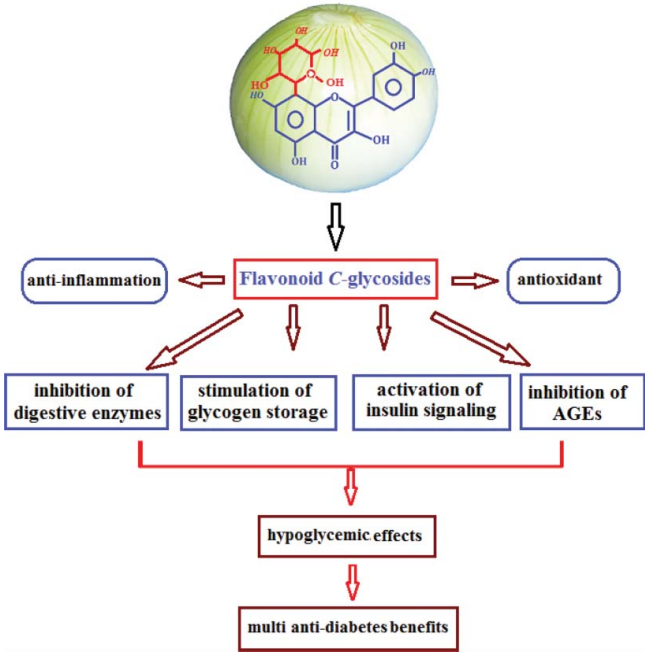


Figure 5 Diverse anti-diabetic mechanisms of flavonoid *C*-glycosides.

Aquila et al. (2009) investigated the chemical composition and the anti-inflammatory activity of a flavonoid fraction isolated from the roots of *Cayaponia tayuya* (taiuiá, tayuya). This fraction, containing a mixture of five flavonoid *C*-glycosides (vicenin-2, spinosin, isovitexin, swertisin, isoswertisin), was tested in both *in vivo* and *in vitro* experimental models. In 12-*O*-tetradecanoylphorbol 13-acetate (TPA)-induced acute ear oedema in mice, the flavonoid fraction showed a considerable anti-inflammatory activity when compared with indomethacin (66% *vs*. 89% inhibition of acute ear oedema) in similar topical dose (0.5 mg/ear). The flavonoid fraction (0.5 mg/ear, twice daily, four consecutive days) was less active in TPA-induced subchronic ear oedema producing only 37% oedema inhibition whereas dexamethasone, in lower dosage (0.025 mg/ear, once a day, four consecutive days), almost completely reduced the oedema (92%). In LPS-stimulated RAW 264.7 murine macrophages, the flavonoid fraction (22.30 μg/mL) markedly reduced the expression of cyclooxygenase-2 (COX-2) and iNOS by 65% and 97%, respectively; dexamethasone (1.8 μg/mL) exhibited almost similar inhibitory effects (76% and 95%, respectively). The flavonoid fraction showed a moderate inhibitory activity on NO production (only 42% at 33.45 μg/mL) and no effect on tumor necrosis factor-α (TNF-α) production. These results clearly indicate that the anti-inflammatory activity of the flavonoid *C*-glycosides in *Cayaponia tayuya* roots is mainly based on their ability to reduce the expression of pro-inflammatory enzymes COX-2 and iNOS (Aquila et al., 2009).

Luteolin *O*-, *C*- and *O,C*-glycosides were isolated and identified from *Cymbopogon citratus* (DC.) Stapf (Francisco et al., 2014). It was illustrated that *C*- and *O*-glycosylation of luteolin weakened the anti-inflammatory activity in lipopolysaccharide-stimulated macrophages; however, luteolin glycosides showed less cytotoxicity than that of luteolin. Zhang et al. investigated the anti-inflammatory effects of ten commercial mung bean samples (*Vigna radiata*) in relation to the total phenolic, total flavonoid, vitexin and isovitexin contents (Zhang et al., 2013). The effects of mung bean extracts, vitexin, isovitexin and a mixture of vitexin and isovitexin on the expression of pro-inflammatory cytokines (IL-1β, IL-6) and COX-2 were evaluated in LPS-stimulated RAW 264.7 mouse macrophage cells. Vitexin, isovitexin and their combination showed a significant contribution in the inhibitory effects of mung bean extracts on COX-2 mRNA expression, regarding the inhibitory effects of mung bean extracts on IL-1β and IL-6 mRNA expressions, the contribution of vitexin and isovitexin appeared to be negligible (Zhang et al., 2013).

It can be concluded that the anti-inflammatory activity of flavonoid *C*-glycosides is mainly due to a reduction in the expression of pro-inflammatory enzymes (COX-2, iNOS) and NO levels. The QSAR study on anti-inflammatory potential of flavone *C*-glycosides showed that: (1) glycosylation in ring A improved the anti-inflammatory activity, (2) methoxylation of hydroxyl groups on flavone ring reduced the anti-inflammatory activity, (3) *C*-glycosylflavones showed stronger anti-inflammatory potential than *O*-glycosylflavones, (4) the higher the polarity of the substitute on *C*-2″, the lower the anti-inflammatory is potential (Figure 6) (Wu et al., 2012).

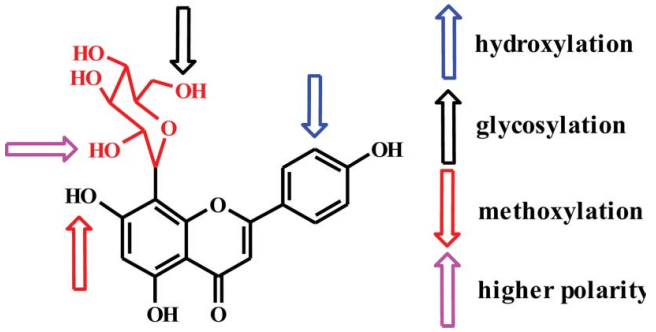


Figure 6 The potential sites of flavone *C*-glycosides affecting the anti-inflammatory potential are schematically illustrated (Wu et al., 2012). The up arrows represent increased inhibition, the down arrows represent decreased inhibition activity.

5.6. *Antipyretic Activity*

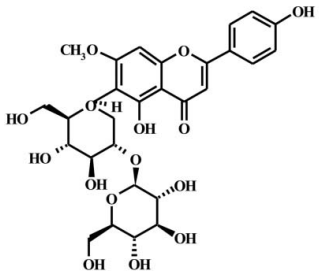
Luteolin 6-dirhamnoside isolated from *Pteranthus dichotomus* showed higher antipyretic potential in rats than the raw extract (Atta et al., 2013).

5.7. *Memory Ameliorating Activity*

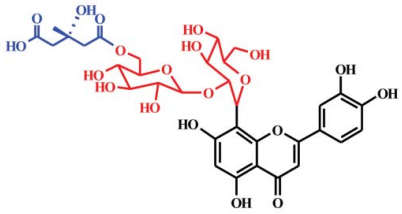
Spinosin (Figure 7) showed obvious amelioration on cholinergic blockade-induced cognitive impairment in mice (Jung et al., 2014). Spinosin significantly lengthened the prolonged latency time in the passive avoidance task, improved the percentage of spontaneous alternation in the Y-maze task, and prolonged the swimming time in target quadrant in the Morris water maze task. Wang and coworkers indicated that spinosin is a hypnotic agent and a 5-hydroxytryptamine-1A (5-HT1A) receptor antagonist (Wang et al., 2010; Wang et al., 2012c).

5.8. *Anticomplementary Activity*

Orientin, vitexin and their derivatives, 6‴-(3-hydroxy-3-methylglutaroyl)-2″-*O*-β-D-galactopyranosyl orientin, 6‴-(3-hydroxy-3-methylglutaroyl)-2″-*O*-β-D-galactopyranosyl vitexin, orientin 2″-*O*-β-D-galactopyranoside, 7-methoxyl-2″-*O*-(2‴-methylbutyryl) orientin, 7-methoxyl-2″-*O*-(3‴,4‴-dimethoxybenzoyl) vitexin, 2″-*O*-(2‴-



spinosin



6‴-(3-hydroxy-3-methylglutaroyl)-2″-*O*-β-D-galactopyranosyl orientin

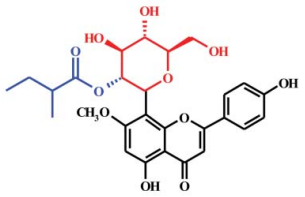
Figure 7 Chemical structures of spinosin and 6‴-(3-hydroxy-3-methylglutaroyl)-2″-*O*-*β*-D-galactopyranosyl orientin.

methylbutyryl) isoswertisin from the flowers of *Trollius chinensis* showed anticomplementary activity (Liu et al., 2013). Vitexin (IC_{50} = 3.12 mM) appeared to have a higher anticomplementary potential than that of orientin (IC_{50} = 3.36 mM), which indicated that an additional hydroxyl group in ring B weakened the bioactivity. Orientin 2″-*O*-*β*-D-galactopyranoside (IC_{50} = 4.02 mM) exhibited a lower anticomplementary activity than that of orientin, suggesting that further *O*-glycosylation reduced the activity (Liu et al., 2013). However, additional 3-hydroxy-3-methylglutaroyl attached to the C-6‴ of orientin 2″-*O*-*β*-D-galactopyranoside significantly enhanced the anticomplementary activity: 6‴-(3-hydroxy-3-methylglutaroyl)-2″-*O*-*β*-D-galactopyranosyl orientin (Figure 7) had an IC_{50} value of 0.87 mM (Liu et al., 2013).

5.9. Antiviral Activity

Cai et al. isolated four flavonoid *C*-glycosides, trollisin I, trollisin II, 2″-*O*-(2‴-methylbutanoyl) isoswertisin (Figure 8), and vitexin galactoside from the flowers of *Trollius chinensis* (Cai et al., 2006). 2″-*O*-(2‴-methylbutanoyl) isoswertisin showed cell cytotoxicity and inhibitory effects against influenza virus (type A) *in vitro*. Other three flavonoid *C*-glycosides did not exhibit significant activity.

Wang et al. (2012d) compared the *in vitro* antiviral activity against respiratory syncytial virus (RSV) of several flavone *C*-glycosides isolated from the leaves of *Lophatherum gracile*: luteolin 6-*C*-*α*-L-arabinopyranosyl-7-*O*-*β*-D-glucopyranoside, apigenin 6-*C*-*β*-D-galactopyranosiduronic acid (1→2)-*α*-L-arabinopyranoside, luteolin 6-*C*-*β*-D-galactopyranosiduronic



2″-*O*-(2‴-methylbutanoyl) isoswertisin

Figure 8 Chemical structure of 2″-*O*-(2‴-methylbutanoyl) isoswertisin.

acid (1→2)-*α*-L-arabinopyranoside, luteolin 6-*C*-*β*-D-glucopyranosiduronic acid (1→2)-*α*-L-arabinofuranoside, swertisin, orientin, lutonarin, isoorientin, isovitexin, vitexin, and swertiajaponin (Wang et al., 2012d).

Only swertisin, isoorientin, isovitexin, and swertiajaponin obviously showed anti-RSV activity. It looks like that flavone 8-*C*-monoglycosides, flavone 6-*C*-diglycosides, and flavone 6-*C*-glycosyl-7-*O*-glycosides did not exhibit any anti-RSV potential. Isovitexin (IC_{50} = 10.0 *μ*g/ml) appeared to have a higher anti-RSV activity than that of vitexin (IC_{50} >50 *μ*g/mL). Isovitexin isolated from *Swertia yunnanensis* showed anti-hepatitis B virus (anti-HBV) potential and inhibited the secretion of HBsAg and HbeAg (Cao et al., 2013).

5.10. Antileishmanial Activity

The apigenin and luteolin 5- or 7-*O*-glucosides showed similar inhibition against *Leishmania donovani* with their aglycones (Tasdemir et al., 2006). However, apigenin 8-*C*-glucoside (IC_{50}> 30 *μ*M) showed a much weaker inhibition than apigenin (IC_{50} = 1.9 *μ*M).

5.11. Antiplatelet Activity

Piccinelli et al. (2008) identified apigenin 6,8-di-*C*-*β*-D-glucopyranoside, diosmetin 6,8-di-*C*-*β*-D-glucopyranoside, apigenin 8-*C*-*β*-D-glucopyranoside, apigenin 8-*C*-[*α*-L-arabinopyranosyl-(1→6)]-*O*-*β*-D-glucopyranoside, apigenin 6-*C*-[*α*-L-arabinopyranosyl-(1→6)]-*O*-*β*-D-glucopyranoside and isovitexin in lime leaves. The extract of lime leaves showed inhibition against Adenosine diphosphate (ADP) and epinephrine induced platelet aggregation in a concentration-dependent manner. Lin et al. (1997) isolated isoorientin, isovitexin, isoorientin 6″-*O*-glucoside, isoorientin 6″-*O*-caffeate, and isovitexin 6″-*O*-glucoside from *Gentiana arisanensis*. It was found that *C*-glycosyl flavones hardly inhibited platelet aggregation and further *O*-glycosylation of *C*-glycosylflavones did not improve the antiplatelet activity.

5.12. Antibacterial and Antifungal Activity

Brango-Vanegas et al. (2014) identified isoorientin, orientin, isovitexin, and vitexin in *Cecropia pachystachya*

leaves as quorum sensing inhibitors by means of biosensors. Orientin from *Acanthopanax brachypus* showed antibacterial activity against *Staphylococcus aureus, Escherichia coli*, and *Bacillus subtilis* (Hu and Fan, 2008). Vitexin from *Alsophila spinutosa* exhibited antimicrobial activities against *Staphylococcus aureus, Escherichia coli* and *Bacillus subtilis* (Li et al., 2013).

5.13. Hypnotic Effect

Spinosin showed significant hypnotic effect (Shin et al., 1978; Wang et al., 2008). It inhibited PCPA-induced suppression of the hypnotic effect of pentobarbital, which suggests that the serotonergic system may be involved in the capacity of spinosin to potentiate the hypnotic effect of pentobarbital.

5.14. Antiaging Activity

Orientin and vitexin from flowers of *Trollius chinensis* can protect the brain of aging mice against the injury induced by D-galactose by ameliorating the activities of superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px) (Jiang et al., 2012). Vitexin significantly protected cardiovascular system against acute ischemic myocardial injury in rats by enhancing the antioxidant potential and improve energy metabolism in myocardial cells.

5.15. Angiotensin-converting Enzyme Inhibitors

Vicenin 2, carlinoside, vicenin 1, schaftoside and vicenin 3 isolated from the aerial parts of *Desmodium styracifolium* obviously inhibited against the angiotensin-converting enzyme *in vitro* (Zhang et al., 2015). Moreover, these five flavone *C*-diglycosides showed similar inhibitory potential.

5.16. Inhibition of Acrylamide Formation

The study on the structure–activity relationship of flavonoids reducing the formation of acrylamide illustrated that flavone *C*-glycosides showed greater inhibition against the formation of acrylamide than that of flavone *O*-glycosides with same aglycone structure (Zhang et al., 2014). The inhibition potential against acrylamide formation was also correlated with the trolox equivalent antioxidant capacity.

6. CONCLUSION

The flavonoids are the most important dietary polyphenols in human diets and are of great general interest due to their diverse bioactivity. The natural flavonoids almost all exist as *O*- or *C*-glycoside forms in plants. The dietary flavonoid *C*-glycosides have received less attention than their corresponding *O*-glycosides. Among the flavonoid *C*-glycosides, flavone C-glycosides, especially vitexin, isoorientin, orientin, isovitexin and their multiglycosides are more frequently mentioned than other flavonoids. Flavonoid *C*-glycosides were found to be more stable than the aglycones or flavonoid *O*-glycosides. Flavonoid *C*-multiglycosides are absorbed unchanged in the intestine and distributed to other tissues; however, flavonoid *C*-monoglycosides are poorly absorbed in humans with very few metabolites in the urine and blood and are deglycosylated and degraded by human intestinal bacteria in colon.

Most benefits ascribed to flavonoid *C*-glycosides have been deduced from *in vitro* experiments at cell level. However, due to the extensive metabolism of flavonoids during and after absorption, the form circulating in the body is different. Therefore, the metabolites of flavonoids found in plasma and tissues should be used for cell culture experiments. Since many of the flavonoids circulate in the body as metabolites and are in very low concentration, the *in vitro* cell culture experiments are not very meaningful except when tested in intestinal cells.

Flavonoid *C*-glycosides appear to have positive influences on human health, specifically antioxidant, hepatoprotective, anticancer and antidiabetic potential. The flavonoid *C*-glycosides in most cases show higher antioxidant potential than the corresponding flavonoid *O*-glycosides and aglycones. The hypoglycemic and hypolipidemic effects of dietary flavonoid *C*-glycosides on type 2 diabetes can be summarized as: inhibition of AGEs and digestive enzymes, stimulation of glycogen storage, and activation of insulin signaling.

However, there are very few data on the absorption, metabolism, and biological activities of flavonoid *C*-glycosides. It is more purposeful to understand the pharmacokinetic properties of flavonoid *C*-glycosides and to explore their bioactivities.

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CONFLICT OF INTEREST STATEMENT

There is no conflict of interest.

REFERENCES

An, Y., Zhang, C. S., Du, Y., Zhao, L., Cheng, Z. Z., Zhang, W. J., et al. (2013). Comparative excretion of vitexin-2″-O-rhamnoside in mice after oral and intravenous administration. *Afr. J. Pharm. Pharmacol.* **7**:833–837.

Angelino, D., Berhow, M., Ninfali, P. and Jeffery, E. H. (2013). Caecal absorption of vitexin-2-*O*-xyloside and its aglycone apigenin, in the rat. *Food Funct.* **4**:1339–1345.

Aquila, S., Giner, R. M., Recio, M. C., Spegazzini, E. D. and Ríos, J. L. (2009). Anti-inflammatory activity of flavonoids from *Cayaponia tayuya* roots. *J. Ethnopharmacol.* **121**:333–337.

Atta, E. M., Nassar, A. A., Hasan, N. M. and Hasan, A. R. (2013). New flavonoid glycoside and pharmacological activities of *Pteranthus dichotomus* forssk. *Rec. Nat. Prod.* **7**:69–79.

Barreca, D., Bellocco, E., Caristi, C., Leuzzi, U. and Gattuso, G. (2011a). Distribution of C- and O-glycosyl flavonoids, (3-hydroxy-3-methylglutaryl)glycosyl flavanones and furocoumarins in *Citrus aurantium* L. juice. *Food Chem.* **124**:576–582.

Barreca, D., Bellocco, E., Caristi, C., Leuzzi, U. and Gattuso, G. (2011b). Kumquat (*Fortunella japonica* Swingle) juice: Flavonoid distribution and antioxidant properties. *Food Res. Int.* **44**(7):2190–2197.

Barreca, D., Bellocco, E., Leuzzi, U. and Gattuso, G. (2014). First evidence of C- and O-glycosyl flavone in blood orange (*Citrus sinensis* (L.) Osbeck) juice and their influence on antioxidant properties. *Food Chem.* **149**:244–252.

Batool, N., Bibi, Y., Ilyas, N. (2014). Current status of *Ulmus wallichiana*: Himalayan endangered *Elm. Pure Appl. Bio.* **3**:60–65.

Benayad, Z., Gomez-Cordoves, C. and Es-Safi, N. E. (2014). Identification and quantification of flavonoid glycosides from fenugreek (*Trigonella foenum-graecum*) germinated seeds by LC-DAD-ESI/MS analysis. *J. Food Compos. Anal.* **35**:21–29.

Biesaga, M. (2011). Influence of extraction methods on stability of flavonoids. *J. Chromatogr. A* **1218**:2505–2512.

Brango-Vanegas, J., Costaa, G. M., Ortmann, C. F., Schenkel, E. P., Reginatto, F. H., Ramos, F. A., et al. (2014). Glycosylflavonoids from *Cecropia pachystachya* Trécul are quorumsensing inhibitors. *Phytomed.* **21**:670–675.

Braune, A. and Blaut, M. (2012). Intestinal bacterium *Eubacterium cellulosolvens* deglycosylates flavonoid C- and O-glucosides. *Appl. Environ. Microbiol.* **78**:8151–8153.

Brazier-Hicks, M., Evans, K. M., Gershater, M. C., Puschmann, H., Steel, P. G. and Edwards, R. (2009). The *C*-glycosylation of flavonoids in cereals. *J. Biol. Chem.* **284**:17926–17934.

Cai, S. Q., Wang, R. F., Yang, X. W., Shang, M. Y., Ma, C. M. and Shoyama, Y. (2006). Antiviral flavonoid-type *C*-glycosides from the flowers of *Trollius chinensis*. *Chem. Biodiver.* **3**:343–348.

Cao, T. W., Geng, C. A., Jiang, F. Q., Ma, Y. B., He, K., Zhou, N. J., et al. (2013). Chemical constituents of *Swertia yunnanensis* and their anti-hepatitis B virus activity. *Fitoterapia.* **89**:175–182.

Carte, K., Carr, B., DeBrosse, S., Hemling, C., MacKenzie, M. E., Offen, L., et al. (1991). Aciculatin, a novel flavone-C-glycoside with DNA binding activity from *Chrysopogon aciculatis*. *Tetrahedron.* **47**:1815–1822.

Cazarolli, L. H., Cazarolli, L. H., Kappel, V. D., Pereira, D. F., Moresco, H. H., Brighente, I. M. C., Pizzolatti, M. G., et al. (2012). Anti-hyperglycemic action of apigenin-6-C-β-fucopyranoside from *Averrhoa carambola*. *Fitoterapia.* **83**:1176–1183.

Cerella, C., Teiten, M. H., Radogna, F., Dicato, M. and Diederich, M. (2014). From nature to bedside: Pro-survival and cell death mechanisms as therapeutic targets in cancer treatment. *Biotechnol. Adv.* **32**:1111–1122.

Chang, C. C., Ku, A. F., Tseng, Y. Y., Yang, W. B., Fang, J. M. and Wong, C. H. (2010). 6,8-Di-C-glycosyl flavonoids from *Dendrobium huoshanense*. *J. Nat. Prod.* **73**:229–232.

Chen, Y. G., Li, P., Li, P., Yan, R., Zhang, X. Q., Wang, Y., et al. (2013a). α-Glucosidase inhibitory effect and simultaneous quantification of three major flavonoid glycosides in *Microctis folium*. *Molecules* **18**:4221–4232.

Chen, Y. H., Zhang, W. J., Li, D., Ai, J. J., Meng, Y. H., Ying, X. X., et al. (2013b). Hepatic and gastrointestinal first-pass effects of vitexin 4″-O-glucoside in rats. *J. Pharm. Pharmacol.* **65**:1500–1507.

Choi, J. S., Islam, M. N., Ali, M. Y., Kim, E. J., Kim, Y. M. and Jung, H. A. (2014a). Effects of C-glycosylation on anti-diabetic, anti-Alzheimer's disease and anti-inflammatory potential of apigenin. *Food Chem. Toxicol.* **64**:27–33.

Choi, J. S., Islam, N., Ali, Y., Kim, Y. M., Park, H. J., Sohn, H. S., et al. (2014b). The effects of C-glycosylation of luteolin on its antioxidant, anti-Alzheimer's disease, anti-diabetic, and anti-inflammatory activities. *Arch. Pharm. Res.* **37**:354–363.

Choo, C. Y., Sulong, N. Y., Man, F. and Wong, T. W. (2012). Vitexin and isovitexin from the leaves of *Ficus deltoidea* with *in-vivo* α-glucosidase inhibition. *J. Ethnopharmacol.* **142**:776–781.

Courts, F. L. and Williamson, G. (2009). The *C*-glycosyl flavonoid, aspalathin, is absorbed, methylated and glucuronidated intact in humans. *Mol. Nutr. Food Res.* **53**:1104–1111.

da Silva Morrone, M., de Assis, A. M., da Rocha, R. F., Gasparotto, J., Gazola, A. C. and Costa, G. M. (2013). *Passiflora manicata* (Juss.) aqueous leaf extract protects against reactive oxygen species and protein glycation *in vitro* and *ex vivo* models. *Food Chem. Toxicol.* **60**:45–51.

Davis, B. D. and Brodbelt, J. S. (2004). Determination of the glycosylation site of flavonoid monoglucosides by metal complexation and tandem mass spectrometry. *J. Am. Soc. Mass. Spectr.* **15**:1287–1299.

Devkota, H. P., Fukusako, K., Ishiguro, K. and Yahara, S. (2013). Flavone C-glycosides from Lychnis senno and their antioxidative activity. *Nat. Prod. Comm.* **8**:1413–1414.

Du, H., Wang, H., Yu, J., Liang, C., Ye, W. and Li, P. (2012). Enrichment and purification of total flavonoid *C*-glycosides from *Abrus mollis* extracts with macroporous resins. *Ind. Eng. Chem. Res.* **51**(21):7349–7354.

El-Alfy, T. S., El-Gohary, H. M. A., Sokkar, N. M., Hosny, M. and Al-Mahdy, D. A. (2011). A new flavonoid C-glycoside from *Celtis australis* L. and *Celtis occidentalis* L. leaves and potential antioxidant and cytotoxic activities. *Sci. Pharm.* **79**:963–975.

Elbandy, M. and Rho, J. R. (2014). New flavone-di-C-glycosides from the seeds of Egyptian lupin (*Lupinus termis*). *Phytochem. Lett.* **9**:127–131.

El-Toumy, S. A., Omara, E. A., Nada, S. A. and Bermejo, J. (2011). Flavone C-glycosides from *Montanoa bipinnatifida* stems and evaluation of hepatoprotective activity of extract. *J. Med. Plant Res.* **5**:1291–1296.

Fang, J. B., Jia, W., Gao, W. Y., Yao, Z., Teng, J., Zhao, A. H., et al. (2007). Antitumor constituents from *Alternanthera philoxeroides*. *J. Asian Nat. Prod. Res.* **9**:511–515.

Folador, P., Cazarolli, L. H., Gazola, A. C., Reginatto, F. H., Schenkel, E. P. and Silva, F. R. M. B. (2010). Potential insuline secretagogue effects of isovitexin and swertisin isolated from *Wilbrandia ebracteata* roots in non-diabetic rats. *Fitoterapia* **81**:1180–1187.

Francisco, V., Figueirinha, A., Costa, G., Liberal, J., Lopes, M. C., García-Rodríguez, C., et al. (2014). Chemical characterization and anti-inflammatory activity of luteolin glycosides isolated from lemongrass. *J. Funct. Foods* **10**:436–443.

Gechev, T. S., Hille, J., Woerdenbag, H. J., Benina, M., Mehterov, N., Toneva, V., et al. (2014). Natural products from resurrection plants: Potential for medical applications. *Biotechnol. Adv.* **32**:1091–1101.

Georgiev, M. I. (2014). From plants to pharmacy shelf. *Biotechnol. Adv.* **32**:1051–1052.

Harborne, J. B. (Ed.), (1993). The Flavonoids: Advances in Research Since 1986, pp. 57–93, Chapman & Hall, London.

Harborne, J. B. and Williams, C. A. (2000). Advances in flavonoid research since 1992. *Phytochem.* **55**:481–504.

Hattori, M., Shu, Y. Z., El-Sedawy, A. I., Namba, T., Kobashi, K. and Tomimori, T. (1988). Metabolism of homoorientin by human intestinal bacteria. *J. Nat. Prod.* **51**:874–878.

Hawas, U. W., Soliman, G. M., El-Kassem, A. L. T., Farrag, A. R. H., Mahmoud, K. and León, F. (2013). A new flavonoid C-glycoside from *Solanum elaeagnifolium* with hepatoprotective and curative activities against paracetamol-induced liver injury in mice. *Z. Naturforsch.* **68c**:19–28.

Heim, K. E., Tagliaferro, A. R. and Bobilya, D. J. (2002). Flavonoid antioxidants: Chemistry, metabolism and structure-activity relationships. *J. Nutr. Biochem.* **13**:572–584.

Hoffmann-Bohm, K., Lotter, H., Seligmann, O. and Wagner, H. (1992). Antihepatotoxic C-glycosylflavones from the leaves of *Allophyllus edulis* var. *edulis* and *gracilis*. *Planta Med.* **58**:544–548.

Hong, Y. J., Tomas-Barberan, F. A., Kader, A. A. and Mitchell, A. E. (2006). The flavonoid glycosides and procyanidin composition of Deglet Noor dates (*Phoenix dactylifera*). *J. Agric. Food Chem.* **54**:2405–2411.

Hu, H. B. and Fan, J. (2008). Structural identification and antibacterial activity of chemical constituents of *Acanthopanax brachypus* Harms. *Chin. Hosp. Pharm J.* **28**:1344–1347.

Huang, M., du Plessis, J., du Preez, J., Hamman, J. and Viljoen, A. (2008). Transport of aspalathin, a rooibos tea flavonoid, across the skin and intestinal epithelium. *Phytother. Res.* **22**:699–704.

Huber, G. M., Rupasinghe, H. P. V. and Shahidi, F. (2009). Inhibition of oxidation of omega-3 polyunsaturated fatty acids and fish oil by quercetin glycosides. *Food Chem.* **117**:290–295.

Hultin, P. G. (2005). Bioactive *C*-glycosides from bacterial secondary metabolism. *Curr. Top Med. Chem.* **5**:1299–1331.

Jiang, W., Qu, H. Q., Yuan, D. H., Yang, G. D., An, F. and Wang, S. H. (2012). Protection of orientin and vitexin from flowers and flower buds of *Trollius chinensis* on brain injury in aging mice induced by D-galactose. *Chin. Trad. Herb. Drug* **43**:1376–1380.

Jin, J. S., Nishihata, T., Kakiuchi, N. and Hattori, M. (2008). Biotransformation of C-glucosylisoflavone puerarin to estrogenic (3S)-equol in co- culture of two human intestinal bacteria. *Biol. Pharm. Bull.* **31**:1621–1625.

Jung, I. H., Lee, H. E., Park, S. J., Ahn, Y. J., Kwon, G., Woob, H., et al. (2014). Ameliorating effect of spinosin, a C-glycoside flavonoid, on scopolamine-induced memory impairment in mice. *Pharmacol. Biochem. Behav.* **120**:88–94.

Kamel, M. S. (2003). Flavone *C*-glycosides from *Lupinus hartwegii*. *Phytochem.* **63**:449–452.

Kim, I., Chin, Y. W., Lim, S. W., Kim, Y. C. and Kim, J. (2004). Norisoprenoids and hepatoprotective flavone glycosides from the aerial Parts of *Beta vulgaris* var. *Cicla. Arch. Pharm. Res.* **27**:600–603.

Koeppen, B. H. and Roux, D. G. (1966). *C*-Glycosylflavonoids, The chemistry of aspalathin. *Biochem. J.* **99**:604–609.

Kong, D. Y. (2012). Introduction to Natural Products Chemistry. **In**: Xu, R., Ye, Y., Zhao, W., Eds., Taylor & Francis CRC Press, NY, 2012.

Kreuz, S., Joubert, E., Waldmann, K. H. and Ternes, W. (2008). Aspalathin, a flavonoid in *Aspalathus linearis* (rooibos), is absorbed by pig intestine as a *C*-glycoside. *Nutr. Res.* **28**:690–701.

Kuhnle, G., Spencer, J. P., Schroeter, H., Shenoy, B., Debnam, E. S., Srai, S. K. S. and Hahn, U. (2000). Epicatechin and catechin are *O*-methylated and glucuronidated in the small intestine. *Biochem. Biophys. Res. Com.* **277**:507–512.

Kwon, Y. S., Kim, S. S., Sohn, S. J., Kong, P. J., Cheong, I. Y., Kim, C. M., et al. (2004). Modulation of suppressive activity of lipopolysaccharide-induced nitric oxide production by glycosidation of flavonoids. *Arch. Pharm. Res.* **27**:751–756.

Lai, C. Y., Pan, S. L., Chen, C. C. and Teng, C. M. (2011). Aciculatin, a *C*-glycosidic flavonoid, induces p53-dependent cell cycle arrest and apoptosis in HCT116 colorectal cancer cells. *FASEB J.* **25**:621–627.

Lai, C. Y., Tsai, A. C., Chen, M. C., Chang, L. H., Sun, H. L., Chang, Y. L., et al. (2012). Aciculatin induces p53-dependent apoptosis via MDM2 depletion in human cancer cells *in vitro* and *in vivo*. *PLoS ONE.* **7**:e42192.

Lee, W., Ku, S. K. and Bae, J. S. (2014). Vascular barrier protective effects of orientin and isoorientin in LPS-induced inflammation *in vitro* and *in vivo*. *Vascular.Pharmacol.* **62**:3–14.

Lemmens, K. J., van de Wier, B., Vaes, N., Ghosh, M., van Zandvoort, M. A., van der Vijgh, W. J. and Haenen, G. R. (2014). The flavonoid 7-mono-*O*-(β-hydroxyethyl)-rutoside is able to protect endothelial cells by a direct antioxidant effect. *Toxicol. in Vitro* **28**:538–543.

Leong, C. N. A., Tako, M., Hanashiro, I. and Tamaki, H. (2008). Antioxidant flavonoid glycosides from the leaves of *Ficus pumila* L. *Food Chem.* **109**:415–420.

Li, H., Song, F., Xing, J., Tsao, R., Liu, Z. and Liu, S. (2009). Screening and structural characterization of α-glucosidase inhibitors from hawthorn leaf flavonoids extract by ultrafiltration LC-DAD-MS^n and SORI-CID FTICR MS. *J. Am. Soc. Mass. Spectrom.* **20**:1496–1503.

Li, S. S., Wu, J., Chen, L. G., Du, H., Xu, Y. J., Wang, L. J., Zhang, H. J., Zheng, X. C. and Wang, L. S. (2014). Biogenesis of *C*-glycosyl flavones and profiling of flavonoid glycosides in Lotus (*Nelumbo nucifera*). *PLoS ONE.* **9**(10):e108860. doi:10.1371/journal.pone.0108860

Li, S.-H., Zhao, Q., Cheng, Y. and Liu, F. (2013). Antimicrobial activities of vitexin from *Alsophila spinutosa*. *Food Res. Develop.* **34**(14):4–6.

Liang, M. J., Xu, W., Zhang, W. D., Zhang, C., Liu, R. H., Shen, Y. H., et al. (2007). Quantitative LC/MS/MS method and *in vivo* pharmacokinetic studies of vitexin rhamnoside, a bioactive constituent on cardiovascular system from hawthorn. *Biomed. Chromatogr.* **21**:422–429.

Lin, L. Z. and Harnly, J. M. (2007). A Screening method for the identification of glycosylated flavonoids and other phenolic compounds using a standard analytical approach for all plant materials. *J. Agric. Food Chem.* **55**:1084–1096.

Lin, C. N., Kuo, S. H. and Chung, M. I. (1997). A new flavone C-glycoside and antiplatelet and vasorelaxing flavones from *Gentiana arisanensis*. *J. Nat. Prod.* **60**:851–853.

Liu, J. Y., Li, S. Y., Feng, J. Y., Sun, Y., Cai, J. N., Sun, X. F., et al. (2013). Flavone *C*-glycosides from the flowers of *Trollius chinensis* and their anticomplementary activity. *J. Asian Nat. Prod. Res.* **15**:325–331.

Ma, L. Y., Liu, R. H., Xu, X. D., Yu, M. Q., Zhang, Q. and Liu, H. L. (2010). The pharmacokinetics of C-glycosyl flavones of Hawthorn leaf flavonoids in rat after single dose oral administration. *Phytomed.* **17**:640–645.

Manthey, J. A., Guthrie, N. and Grohmann, K. (2001). Biological properties of citrus flavonoids pertaining to cancer and inflammation. *Curr. Med. Chem.* **8**:135–153.

Materska, M. (2015). Flavone C-glycosides from *Capsicum annuum* L.: Relationships between antioxidant activity and lipophilicity. *Eur. Food Res. Technol.* **240**:549–557.

Mora, A., Paya, M., Rios, J. L. and Alcaraz, M. J. (1990). Structure-activity relationships of polymethoxyflavones and other flavonoids as inhibitors of non-enzymic lipid peroxidation. *Biochem. Pharmacol.* **40**:793–797.

Muharini, R., Wray, V., Lai, D. and Proksch, P. (2014). New flavone *C*-glycosides from leaves of *Sarcotheca griffithii* (Hook F) Hallier F. *Phytochem. Lett.* **9**:26–32.

Nakamura, K., Nishihata, T., Jin, J. S., Ma, C. M., Komatsu, K., Iwashima, M. and Hattori, M. (2011). The *C*-glucosyl bond of puerarin was cleaved hydrolytically by a human intestinal bacterium strain PUE to yield its aglycone daidzein and an intact glucose. *Chem. Pharmaceut. Bull.* **59**:23–27.

Obmann, A., Tsendayush, D., Thalhammer, T., Zehl, M., Vo, T. P. N., Purevsuren, S., et al. (2010). Extracts from the Mongolian traditional medicinal plants *Dianthus versicolor* Fisch. and *Lilium pumilum* Delile stimulate bile flow in an isolated perfused rat liver model. *J. Ethnopharmacol.* **131**:555–561.

Obmann, A., Werner, I., Presser, A., Zehl, M., Swoboda, Z., Purevsuren, S. and Glasl, S. (2011). Flavonoid *C*-and *O*-glycosides from the Mongolian medicinal plant *Dianthus versicolor* Fisch. *Carbohyd. Res.* **346**:1868–1875.

Odontuya, G., Hoult, J. R. S. and Houghton, P. J. (2005). Structure-activity relationship for anti-inflammatory effect of luteolin and its derived glycosides. *Phytother. Res.* **19**:782–786.

Omar, M. H., Mullen, W. and Crozier, A. (2011). Identification of proanthocyanidin dimers and trimers, flavone *C*-glycosides, and antioxidants in *Ficus deltoidea*, a Malaysian herbal tea. *J. Agric. Food Chem.* **59**:1363–1369.

Oualid, T. and Artur, M. S. S. (2012). Advances in C-glycosylflavonoid research. *Curr. Org. Chem.* **16**:859–896.

Pacifico, S., Scognamiglio, M., D'Abrosca, B., Piccolella, S., Tsafantakis, N., Gallicchio, M. and Fiorentino, A. (2010). Spectroscopic characterization and antiproliferative activity on HepG2 human hepatoblastoma cells of flavonoid C-glycosides from *Petrorhagia velutina*. *J. Nat. Prod.* **73**:1973–1978.

Pan, Y. Z., Guan, Y., Wei, Z. F., Peng, X., Li, T. T., Qi, X. L. and Fu, Y. J. (2014). Flavonoid *C*-glycosides from pigeon pea leaves as color and anthocyanin stabilizing agent in blueberry juice. *Indust. Crops. Prod.* **58**:142–147.

Park, S. H., Kim, J. H., Lee, D. H., Kang, J. W., Song, H. H., Oh, S. R., et al. (2013). Luteolin 8-C-β-fucopyranoside inhibits invasion and suppresses TPA-induced MMP-9 and IL-8 via ERK/AP-1 and ERK/NF-kB signaling in MCF-7 breast cancer cells. *Biochimie* **95**:2082–2090.

Peng, X. F., Zheng, Z. P., Cheng, K. W., Shan, F., Ren, G. X., Chen, F., et al. (2008). Inhibitory effect of mung bean extract and its constituents vitexin

and isovitexin on the formation of advanced glycation endproducts. *Food Chem.* **106**:475–481.

Perveen, S., El-Shafae, A. M., Al-Taweel, A., Fawzy, G. A., Malik, A., Afza, N., Latif, M. and Iqbal, L. (2011). Antioxidant and urease inhibitory C-glycosylflavonoids from *Celtis africana*. *J. Asian Nat. Prod. Res.* **13**:799–804.

Piccinelli, A. L., Mesa, M. G., Armenteros, D. M., Alfonso, M. A., Arevalo, A. C., Campone, L., et al. (2008). HPLC-PDA-MS and NMR characterization of C-glycosyl flavones in a hydroalcoholic extract of *Citrus aurantifolia* leaves with antiplatelet activity. *J. Agric. Food Chem.* **56**:1574–1581.

Plaza, M., Pozzo, T., Liu, J., Ara, K. Z. G., Turner, C. and Karlsson, E. N. (2014). Substituent effects on *in vitro* antioxidizing properties, stability, and solubility in flavonoids. *J. Agric. Food Chem.* **62**:3321–3333.

Plumb, G. W., Price, K. R. and Williamson, G. (1999). Antioxidant properties of flavonol glycosides from tea. *Redox. Rep.* **4**:13–16.

Praveena, R., Sadasivam, K., Kumaresan, R., Deepha, V. and Sivakumar, R. (2013). Experimental and DFT studies on the antioxidant activity of a C-glycoside from *Rhynchosia capitata. Spectrochim.Acta A: Mol. Biomol. Spectr.* **103**:442–452.

Rawat, P., Kumar, M., Sharan, K., Chattopadhyay, N. and Maurya, R. (2009). Ulmosides A and B: Flavonoid 6-*C*-glycosides from *Ulmus wallichiana*, stimulating osteoblast differentiation assessed by alkaline phosphatase. *Bioorg. Med. Chem. Lett.* **19**:4684–4687.

Rechner, A. R., Kuhnle, G., Bremner, P., Hubbard, G. P., Moore, K. P. and Rice-Evans, C. A. (2002). The metabolic fate of dietary polyphenols in humans. *Free Rad. Biol. Med.* **33**:220–235.

Schnekenburger, M., Dicato, M. and Diederich, M. (2014). Plant-derived epigenetic modulators for cancer treatment and prevention. *Biotechnol. Adv.* **32**:1123–1132.

Shibano, M., Kakutani, K., Taniguchi, M., Yasuda, M. and Baba, K. (2008). Antioxidant constituents in the dayflower (*Commelina communis* L.) and their α-glucosidase-inhibitory activity. *J. Nat. Med.* **62**:349–353.

Shin, K.-H., Lee, C.-K., Woo, W.-S. and Kang, S.-S. (1978). Sedative action of spinosin. *Arch. Pharm. Res.* **1**:7–11.

Simirgiotis, M. J., Schmeda-Hirschmann, G., Borquez, J. and Kennelly, E. (2013). The *Passiflora tripartita* (Banana Passion) fruit: A source of bioactive flavonoid *C*-glycosides isolated by HSCCC and characterized by HPLC–DAD–ESI/MS/MS. *Molecules* **18**(2):1672–1692.

Simkhada, D., Kurumbang N. P., Lee, H. C. and Sohng, J. K. (2010). Exploration of glycosylated flavonoids from metabolically engineered *E. coli*. *Biotechnol. Biopro. Eng.* **15**:754–760.

Stalmach, A., Mullen, W., Pecorari, M., Serafini, M. and Crozier, A. (2009). Bioavailability of *C*-linked dihydrochalcone and flavanone glucosides in humans following ingestion of unfermented and fermented rooibos teas. *J. Agric. Food Chem.* **57**:7104–7111.

Stobiecki, M. (2000). Application of mass spectrometry for identification and structural studies of flavonoid glycosides. *Phytochem.* **54**:237–256.

Tasdemir, D., Kaiser, M., Brun, R., Yardley, V., Schmidt, T. J., Tosun, F., et al. (2006). Antitrypanosomal and antileishmanial activities of flavonoids and their analogues: *In vitro, in vivo*, structure-activity relationship, and quantitative structure–activity relationship studies. *Antimicrob. Agents. Chemother.* **50**:1352–1364.

Ulubelen, A., Ayyildiz, H. and Mabry, T. J. (1981). *C*-Glycosylflavonoids and other compounds from *Passiflora cyanea, P. oerstedii* and *P. menispermifolia*. *J. Nat. Prod.* **44**:368–369.

Veitch, N. C. and Grayer, R. J. (2011). Flavonoids and their glycosides, including anthocyanins. *Nat. Prod. Rep.* **28**:1626–1695.

Venkatesha, S. H., Berman, B. M. and Moudgil, K. D. (2011). Herbal medicinal products target defined biochemical and molecular mediators of inflammatory autoimmune arthritis. *Bioorg. Med. Chem.* **19**:21–29.

Wada, S., He, P., Hashimoto, I., Watanabe, N. and Sugiyama, K. (2000). Glycosidic flavonoids as rat-liver injury preventing compounds from green tea. *Biosci. Biotech. Biochem.* **64**:2262–2265.

Wang, L. E., Bai, Y. J., Shi, X. R., Cui, X. Y., Cui, S. Y., Zhang, F., et al. (2008). Spinosin, a C-glycoside flavonoid from semen *Zizhiphi Spinozae*, potentiated pentobarbital-induced sleep via the serotonergic system. *Pharmacol. Biochem. Behav.* **90**:399–403.

Wang, Y., Chen, M., Zhang, J., Zhang, X. L., Huang, X. J., Wu, X., et al. (2012d). Flavone C-glycosides from the leaves of *Lophatherum gracile* and their *in vitro* antiviral activity. *Planta Med.* **78**:46–51.

Wang, L. E., Cui, X. Y., Cui, S. Y., Cao, J. X., Zhang, J., Zhang, Y. H., et al. (2010). Potentiating effect of spinosin, a C-glycoside flavonoid of Semen *Ziziphi spinosae*, on pentobarbital-induced sleep may be related to postsynaptic 5-HT1A receptors. *Phytomed.* **17**:404–409.

Wang, Y. J., Han, C. H., Leng, A. J., Zhang, W. J., Xue, H. F., Chen, Y. H., et al. (2012a). Pharmacokinetics of vitexin in rats after intravenous and oral administration. *Afr. J. Pharm. Pharmacol.* **6**:2368–2373.

Wang, Z. B., Yuan, B., Jia, X. K. and An, F. (2012b). Investigations on antioxidation of orientin in mice and vitexin in *Trollius chinesis*. *J. Hebei. Normal. Univ.* **28**(6):72–75.

Wang, L. E., Zhang, X. Q., Yin, Y. Q. and Zhang, Y. H. (2012c). Augmentative effect of spinosin on pentobarbitalinduced loss of righting reflex in mice associated with presynaptic 5-HT1A receptor. *J. Pharm. Pharmacol.* **64**:277–282.

Wang, Y. N., Zhen, Y. L., Li, X. L., Shao, X. and Dong, L. Y. (2013). Comparative study on absorption of vitexin and rhamnosylvitexin in intestin of rat. *Anhui. Med. Pharmaceut. J.* **10**:1660–1663.

Wipf, P., Pierce, J. G. and Zhuang, N. (2005). Silver (I)-catalyzed addition of zirconocenes to glycal epoxides. A new synthesis of α-*C*-glycosides. *Org. Lett.* **7**:483–485.

Wu, X. A., Qing, F. and Du, M. Q. (2012). The QSAR study on anti-inflammatory activities of C-glycosyflavones. *Lishizhen Med. Mater. Res.* **23**:632–633.

Xiao, J. B. and Georgiev, M. I. (2015). International Symposium on Phytochemicals in Medicine and Food (ISPMF 2015): An introduction. *Food Chem.* **186**:1–5.

Xiao, J. B. and Högger, P. (2013). Metabolism of dietary flavonoids in liver microsomes. *Curr. Drug. Metab.* **14**:381–391.

Xiao, J. B. and Högger, P. (2014). Advance on the pharmacokinetics of natural bioactive polyphenols. *Curr. Drug Metab.* **15**:1–2.

Xiao, J. B. and Högger, P. (2015a). Dietary polyphenols and type 2 diabetes: Current insights and future perspectives. *Curr. Med. Chem.* **22**:23–38.

Xiao, J. B. and Högger, P. (2015b). Stability of dietary polyphenols under the cell culture condition: Avoiding erroneous conclusions. *J. Agri. Food Chem.* **63**:1547–1557.

Xiao, J. B., Kai, G. Y., Yamamoto, K. and Chen, X. Q. (2013). Advance in dietary polyphenols as α-glucosidases inhibitors: A review on structure-activity relationship aspect. *Crit. Rev. Food Sci. Nutr.* **53**:818–836.

Xiao, J. B., Muzashvili, T. S. and Georgiev, M. I. (2014). Advance on biotechnology for glycosylation of high-value flavonoids. *Biotechnol. Adv.* **32**:1145–1156.

Xiao, J. B., Ni, X. L., Kai, G. Y. and Chen, X. Q. (2015). Advance in dietary polyphenols as aldose reductases inhibitors: Structure-activity relationship aspect. *Crit. Rev. Food Sci. Nutr.* **55**:16–31.

Xu, Y. A., Fan, G. R., Gao, S. and Hong, Z. Y. (2008). Assessment of intestinal absorption of vitexin-2″-O-rhamnoside in hawthorn leaves flavonoids in rat using In situ and *in vitro* absorption models. *Drug. Develop Indust. Pharm.* **34**:164–170.

Yin, J. J., Qu, J. G., Zhang, W. J., Lu, D. R., Gao, Y. C., Ying, X. X., et al. (2014). Tissue distribution comparison between healthy and fatty liver rats after oral administration of hawthorn leaf extract. *Biomed. Chromatogr.* **28**:637–647.

Ying, X. X., Lu, X. M., Sun, X. H., Li, X. Q. and Li, F. M. (2007). Determination of vitexin-2″-O-rhamnoside in rat plasma by ultra-performance liquid chromatography electrospray ionization tandem mass spectrometry and its application to pharmacokinetic study. *Talanta* **72**:1500–1506.

Yuan, L., Wang, J., Xiao, H. F., Xiao, C. X., Wang, Y. T. and Liu, X. B. (2012). Isoorientin induces apoptosis through mitochondrial dysfunction and inhibition of PI3K/Akt signalling pathway in HepG2 cancer cells. *Toxicol. Appl. Pharmacol.* **265**:83–92.

Yuan, L., Wang, J., Xiao, H. F., Wu, W. Q., Wang, Y. T. and Liu, X. B. (2013). MAPK signaling pathways regulate mitochondrial-mediated

apoptosis induced by isoorientin in human hepatoblastoma cancer cells. *Food Chem. Toxicol.* **53**:62–68.

Yuan, L., Wei, S. P., Wang, J. and Liu, X. B. (2014). Isoorientin induces apoptosis and autophagy simultaneously by reactive oxygen species (ROS)-related p53, PI3K/Akt, JNK, and p38 signaling pathways in HepG2 cancer cells. *J. Agric. Food Chem.* **62**:5390–5400.

Zehrmann, N., Zidorn, C. and Ganzera, M. (2010). Analysis of rare flavonoid C-glycosides in *Celtis australis* L. by micellar electrokinetic chromatography. *J. Pharmaceut. Biomed. Anal.* **51**:1165–1168.

Zhang, Y., Chen, X. Y., Cheng, J., Jin, C. and Zhang, Y. (2014). The reduction effect of dietary flavone *C*- and *O*-glycosides on the formation of acrylamide and its correlation and prediction with the antioxidant activity of Maillard reaction products. *RSC Adv*. **4**:24147–24150.

Zhang, Y. Q., Luo, J. G., Han, C., Xu, J. F. and Kong, L. Y. (2015). Bioassay-guided preparative separation of angiotensin-converting enzyme inhibitory C-flavone glycosides from *Desmodium styracifolium* by recycling complexation high-speed counter-current chromatography. *J. Pharmaceut. Biomed. Anal.* **102**:276–281.

Zhang, X. W., Shang, P. P., Qin, F., Zhou, Q., Gao, B. Y., Huang, H. Q., et al. (2013). Chemical composition and antioxidative and anti-inflammatory properties of ten commercial mung bean samples. *LWT – Food Sci. Technol.* **54**:171–178.

Zhang, Y., Tie, X. W., Bao, B. L., Wu, X. Q. and Zhang, Y. (2007). Metabolism of flavone C-glucosides and p-coumaric acid from antioxidant of bamboo leaves (AOB) in rats. *Br. J. Nutr.* **97**:484–494.

Zhang, W. J., Xu, M., Yu, C. Q., Zhang, G. F. and Tang, X. (2010). Simultaneous determination of vitexin-4″-O-glucoside, vitexin-2″-O-rhamnoside, rutin and vitexin from hawthorn leaves flavonoids in rat plasma by UPLC–ESI-MS/MS. *J. Chromatogr. B* **878**:1837–1844.

Zhou, B., Blasko, G. and Cordell, G. A. (1988). Alternanthin A. C-glycosylated flavonoid from *Alternanthera philoxeroides*. *Phytochem.* **27**:3633–3636.

Zhu, D. X., An, F. and Wang, S. H. (2012). Effects of orientin from *TroHius chinensis* on cell growth and apoptosis of EC-109 cells. *Chin. Trad Patent. Med.* **34**:2055–2059.

Zucolotto, S. M., Fagundes, C., Reginatto, F. H., Ramos, F. A., Castellanos, L., Duque, C. and Schenkel, E. P. (2012). Analysis of C-glycosyl flavonoids from South American Passiflora species by HPLC-DAD and HPLC-MS. *Phytochem. Anal.* **23**:232–239.