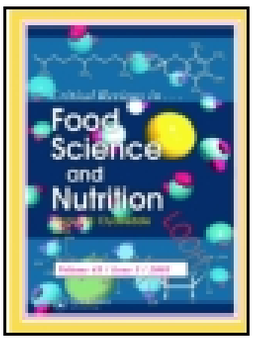

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Dietary flavonoid aglycones and their glycosides: Which show better biological significance?

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ABSTRACT

The dietary flavonoids, especially their glycosides, are the most vital phytochemicals in diets and are of great general interest due to their diverse bioactivity. The natural flavonoids almost all exist as their *O*-glycoside or *C*-glycoside forms in plants. In this review, we summarized the existing knowledge on the different biological benefits and pharmacokinetic behaviors between flavonoid aglycones and their glycosides. Due to various conclusions from different flavonoid types and health/disease conditions, it is very difficult to draw general or universally applicable comments regarding the impact of glycosylation on the biological benefits of flavonoids. It seems as though *O*-glycosylation generally reduces the bioactivity of these compounds - this has been observed for diverse properties including antioxidant activity, antidiabetes activity, anti-inflammation activity, antibacterial, antifungal activity, antitumor activity, anticoagulant activity, antiplatelet activity, antidegranulating activity, antitrypanosomal activity, influenza virus neuraminidase inhibition, aldehyde oxidase inhibition, immunomodulatory, and antitubercular activity. However, *O*-glycosylation can enhance certain types of biological benefits including anti-HIV activity, tyrosinase inhibition, antirotavirus activity, antistress activity, antiobesity activity, anticholinesterase potential, antiadipogenic activity, and antiallergic activity. However, there is a lack of data for most flavonoids, and their structures vary widely. There is also a profound lack of data on the impact of *C*-glycosylation on flavonoid biological benefits, although it has been demonstrated that in at least some cases *C*-glycosylation has positive effects on properties that may be useful in human healthcare such as antioxidant and antidiabetes activity. Furthermore, there is a lack of in vivo data that would make it possible to make broad generalizations concerning the influence of glycosylation on the benefits of flavonoids for human health. It is possible that the effects of glycosylation on flavonoid bioactivity in vitro may differ from that seen in vivo. With in vivo (oral) treatment, flavonoid glycosides showed similar or even higher antidiabetes, anti-inflammatory, antidegranulating, antistress, and antiallergic activity than their flavonoid aglycones. Flavonoid glycosides keep higher plasma levels and have a longer mean residence time than those of aglycones. We should pay more attention to in vivo benefits of flavonoid glycosides, especially *C*-glycosides.

KEYWORDS

Flavonoids; aglycones; glycosides; biological benefits; glycosylation

1. Introduction

Scientists have brought an interesting trend in pharmaceutical development since the begin of 21st century: return to nature as a source of potential drugs (Cerella et al., 2014; Choi et al., 2014a; Gechev et al., 2014; Georgiev, 2014; Pan et al., 2014; Plaza et al., 2014; Schnekenburger et al., 2014; Yuan et al., 2014). Among various nature-origin phytochemicals, flavonoids have received an increased attention due to their considerable biological benefits. Evidence based on epidemiological and nutritional data has showed that the natural flavonoids play an important role in preventing and managing of modern diseases such as cancers (Delmas and Xiao, 2012; Deng et al., 2013), diabetes (Kim et al., 2011a, 2011b; Xiao et al., 2013a, 2013b; Xiao, 2015; Xiao and Högger, 2015a), HIV (Kim et al., 1998; Olivero-Verbel and Pacheco-Londoño, 2002; Andrae-Marobela et al., 2013), inflammation (Johnson et al., 2013), influenza (Liu et al., 2008), and obesity (Panickar, 2013). The term "flavonoids" is composed of a large number of small molecules with similar structures (Fig. 1), namely a benzene ring (A) linked with a pyrone ring (C), which in the 2 or 3 position takes a phenyl ring (B) as a substitute. Most of the flavonoids can be classified to several groups such as isoflavonoids, flavanoids, flavones and anthocyanidins. Natural flavonoids, especially their glycosides, are the most abundant polyphenols in food and over 15,000 flavonoids have been separated and identified from plants (Veitch and Grayer, 2011; Wang et al., 2012a; Xiao et al., 2011a, 2011b, 2011c, 2011d; Xiao and Kai, 2012a; Carazzone et al., 2013; Li and Hagerman, 2013; Wahajuddin et al., 2013) (Fig. 1).

Several important reviews on natural flavonoids have been published since 2008. *Recent Advances in Polyphenol Research* edited by Daayf and Lattanzio (2008) addressed the

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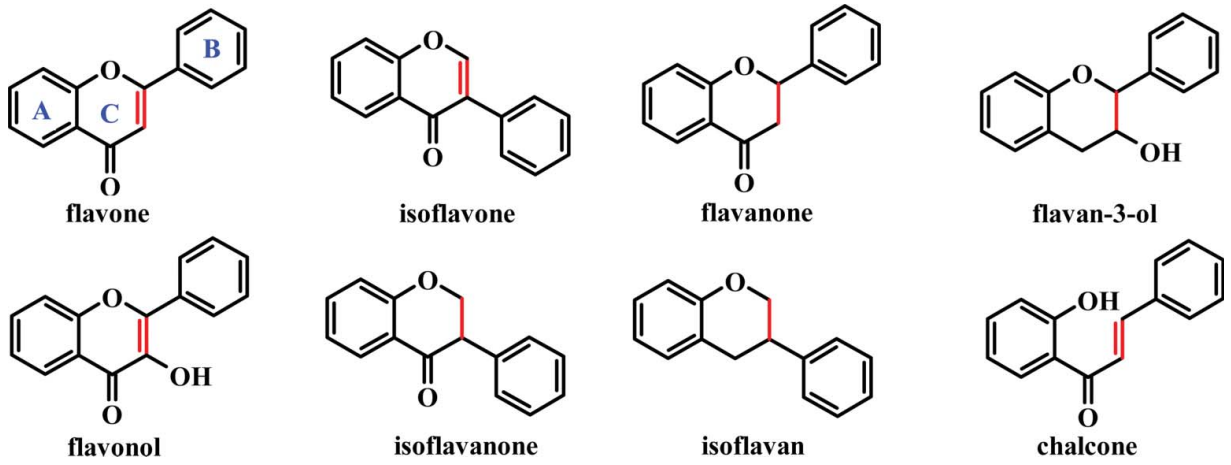


Figure 1. Skeletons and ring designations of flavonoids.

flavonoid-protein interaction, flavonoid biosynthesis in plants, advances in anthocyanins research and chemical synthesis of flavonoids. *Flavonoids: Biosynthesis, Biological Effects and Dietary Sources* (2009) by Keller (2009) summarized the progress in the benefits of dietary flavonoids. *Plant Flavonoids-Biosynthesis, Transport and Involvement in Stress Responses* by Petrussa et al. (2013) summarized the synthesis of flavonoids, their import and export in plant cell compartments, and the response to stress. Recent advances of citrus flavonoids on the regulation of the lipid metabolism and neuroprotection were presented by *Citrus Flavonoids and Lipid Metabolism* (Assini et al., 2013) and *Neuroprotective Effects of Citrus Flavonoids* by Hwang et al. (2012). Illustrations of flavonoids as acetylcholinesterase (AChE) inhibitors can be found in *Flavonoids as Acetylcholinesterase Inhibitors* by Uriarte-Pueyo and Calvo (2011). Progress in anti-inflammation and antibacterial properties of flavonoids has been evaluated by *Gonzalez et al.* (2011) and Cushnie and Lamb (2011). *Bioavailability of Dietary Flavonoids and Phenolic Compounds* by Crozier et al. (2010) reviewed recent human studies on the bioavailability of dietary flavonoids.

The dietary flavonoids in nature almost all are accumulated in the stems, flowers, leaves and fruits of plants and exist as their glycosides, such as glucoside, galactoside, rhamnoside, arabinoside, and rutinoside (Veitch and Grayer, 2011; Kong 2012; Oualid and Artur, 2012). The most abundant flavonoid glycosides in plants are flavone *O*/*C*-glycosides and flavonol *O*-glycosides. Several state-of-the-art technologies including LC-MS/MS and NMR-based metabolomics platform have been used to investigate the different glycosylation pattern of flavonoids (Kachlicki et al., 2008; Li et al., 2009b; Agnolet et al., 2010). The glycosides of chalcones, dihydrochalcones, aurones, and flavanones appear less frequently. The flavonoid glycosides are found mainly as their 3 or 7 *O*-glycosides, although the 5, 8 and 4′ *O*-glycosides were also reported in some cases. In fruits, such as apple and berries, anthocyanidin *O*-glycosides, flavonol *O*-glycosides, and flavone *O*-glycosides frequently occur at the *C*-3 position. *Flavonoids and Their Glycosides, Including Anthocyanins* by Veitch and Grayer (2011) described 796 new naturally occurring flavonois aglycones and glycosides reported in 2007–2009, which provided the sources, identification, bioactivity, biosynthesis, and ecological significance of flavonoids (Veitch and Grayer, 2011). Recently, we summarized the existing knowledge on the production and biotransformation of flavonoid glycosides using biotechnology (Xiao et al., 2014). The glycosylation of flavonoid aglycone-based biological approaches are of great general interest due to the accumulation of novel compounds with high stereo- and regio-selectivity under mild conditions. This review summarizes current knowledge regarding the influence of the glycosylation of flavonoids on their biological benefits, as well as the different pharmacokinetic behaviors between flavonoid aglycones and their glycosides. The natural flavonoids are considered as important function food in the prevention and therapy of chronic diseases. Current review is intended to support the development of health food.

2. Influence of the glycosylation of flavonoids on their pharmacokinetic behaviors

In the past 20 years, the absorption and metabolism of dietary flavonoids have been widely studied. The detailed mechanisms of absorption and metabolism of flavonoids are explained in Fig. 2. However, it is still not clear which form is actually absorbed: aglycone ord glycoside. It is illustrated that the sugar moieties attached to flavonoid aglycones influenced the absorption, distribution, and metabolism to a certain degree. For example, quercetin 3-*O*-glucoside and quercetin 4′-*O*-glucoside are both rapidly absorbed in humans, irrespective of the position of sugar moiety. After absorption, flavonoids are bound to albumin and transported to the liver via the portal vein (Mikkelson et al., 2006; D'Archivio et al., 2007; Courts and Williamson, 2009; Xiao and Kai, 2012a; Xiao and Högger, 2014).

If a flavonoid glycoside is not absorbed in the small intestine, it can be metabolized by the colonic microflora into its aglycone in the large intestine. After absorption, flavonoid glycosides are metabolized by phase II enzymes in small intestine and then in liver. Deglycosylation of flavonoid glycosides to its aglycone is considered to be the first stage of metabolism. Flavonoids and their derivatives then may undergo hydroxylation, methylation, and reduction in the liver (Xiao and Högger, 2013). Then the aglycones are sulfated or glucuronidated to form flavonoid meatbolites, which appears to be the typical metabolic pathway for the flavonoids in the liver.

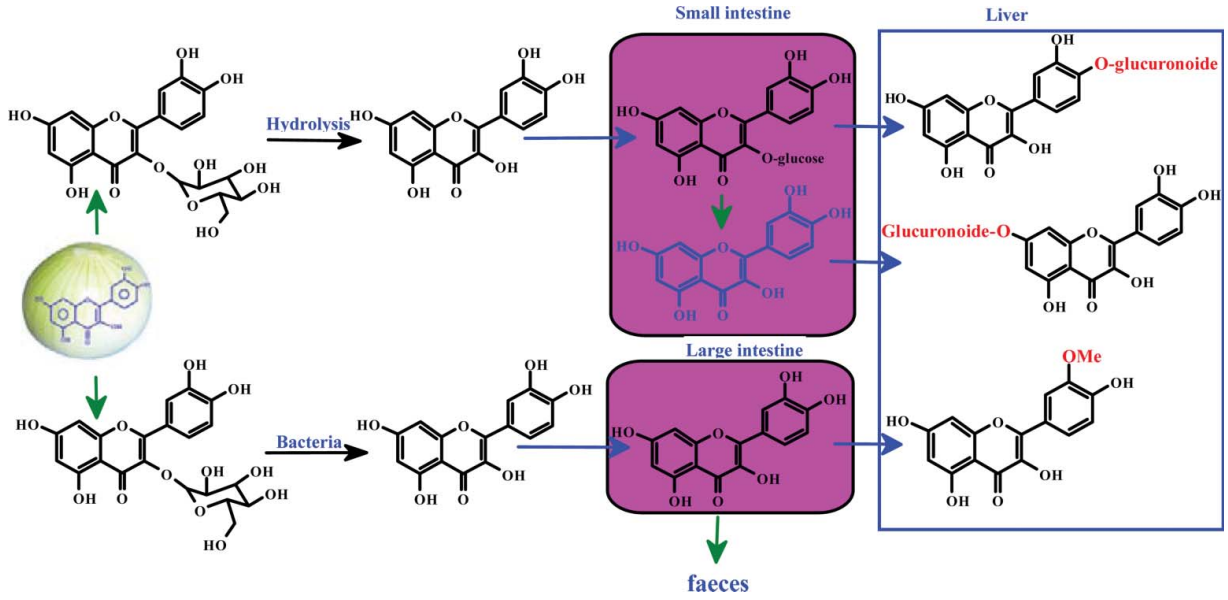


Figure 2. Absorption and metabolism of dietary flavonoids.

2.1. Absorption in the intestine

The flavonoid glycosides are commonly hydrolyzed to their aglycones to produce effects in vivo (Walle et al., 2005). Deglycosylation by small intestinal epithelial cell β-glucosidases is a critical step in the absorption and metabolism of flavonoid glycosides (Walle et al., 2005). Flavonoid glycosides in general are absorbed as their aglycones after hydrolyzing along the digestive tract. Flavonoid glycosides with high solubility and low permeability belong to Class III compounds according to the biopharmaceutics classification system (van de Waterbeemd, 1998). The absorption of flavonoid glycosides mainly depends on their permeability. However, the flavonoid glycosides are too water-soluble to diffuse across the cellular membrane. Thus, the absorption of flavonoid glycosides requires hydrolyzing their sugar group (Kottra and Daniel 2007; Chen et al., 2011). The flavonoid aglycones are more hydrophobic and can be easily absorbed by the epithelial cells through passive diffusion. The colonic microflora is considered to be a key hydrolase source for hydrolysis of flavonoid glycosides (Bokkenheuser et al., 1987; Hur et al., 2000). Human intestinal microflora mainly consists of a diversity of about more than 400 bacterial species (Lee et al., 2011). There are several hydrolases such as α-arabinofuranosidase, α-fucosidase, β-fucosidase, β-glucosidase, β-glucuronidase, and α-rhamnosidase contributing to hydrolyze flavonoid glycosides (Bokkenheuser et al., 1987). Furthermore, flavonoid glycosides can be converted to their aglycones after incubating with feces (Simons et al., 2005; Hanske et al., 2009) and there are many other enzymatic systems in the human intestine, which also can transform flavonoid glycosides into smaller molecules (Kim et al., 1998; Braune et al., 2001). The absorption and metabolism of flavonoid glycosides by human bacteria are relatively complicate and many metabolites from bacteria also can be absorbed into human circulation and subsequently undergo host metabolism (Crespy et al., 2001; Sesink et al., 2001; Heinonen et al., 2004). It is still unclear where bacterial enzymes exert metabolisms on flavonoids. To some extent, glycosides are like pro-drugs, which dramatically improve the solubility of aglycones by linking with sugar moieties. Crespy and others (2001) compared the absorption and metabolism of quercetin/quercetin 3-*O*-glucoside and phloretin/phloridzin (phloretin 2′-*O*-glucoside) in rats. Regardless of the aglycone or glucoside, only conjugated forms occurred. The hydrolysis of glucosides was a prerequisite step before their conjugation by intestinal enzymes and their transport towards the mucosal and serosal sides (Crespy et al., 2001; Sesink et al., 2001; Heinonen et al., 2004). Quercetin glucuronides but not glucosides are present in human plasma after consumption of quercetin 3-*O*-glucoside or quercetin 4′-*O*-glucoside (Crespy et al., 2001; Sesink et al., 2001; Heinonen et al., 2004).

Thus, the flavonoid glycosides can reach to high levels in the intestine, and a subsequent high concentration gradient of aglycone will occur once the sugars are removed by bacteria. It was found that baicalein, rather than baicalin, could pass through the intestinal epithelium efficiently (Liu and Jiang, 2006; Zhang et al., 2007). The flavonoid aglycones can easily permeate through the monolayer from the apical (lumen) to the basolateral (blood) side due to their high lipophilicity and low molecular weight. However, flavonoid glycosides showed limited permeability possibly due to higher hydrophilicity and larger molecular weight (Zhang et al., 2005; Dai et al., 2008). Akao and others (2004) found that baicalein was extensively metabolized to baicalin in the intestinal mucosal cells and baicalin was excreted into the intestinal lumen by multidrug resistance associate protein. Baicalin itself cannot be absorbed directly across the intestine and it is first hydrolyzed into its aglycone by intestinal bacteria (Akao et al., 2000; Zhang et al., 2013). The involvement of enzymes in GI tract such as β-glycosidase or lactase phlorizin hydrolase in the hydrolysis of baicalin has also been reported (Day et al., 2000, 2003). Relative absorption in vivo was significantly higher in mice fed with aglycone-rich diets than that of mice fed with glycosides-rich diets (Hostetler et al., 2012).

Angelino and others (2013) compared the absorption of apigenin and its glycoside, apigenin 8-*C*-glucoside-2-*O*-xyloside

into portal blood by using a rat model. Apigenin was found to be its aglycone and glucuronides in portal blood. However, apigenin 8-*C*-glucoside-2-*O*-xyloside was hardly changed. The liver received unchanged apigenin 8-*C*-glucoside-2-*O*-xyloside; then it was returned to the gut by enterohepatic recirculation. It was illustrated that apigenin *C*-glycoside is absorbed unchanged and undergoes enterohepatic recirculation instead of hydrolysis to its monoglycoside, reduction, and conjugation to form apigenin O-glucuronides (Angelino et al., 2013).

2.2. Binding to plasma proteins

The interaction between plasma proteins and various dietary flavonoids has been reviewed in detail (Xiao and Kai, 2012a) and the hydrophobic interaction is the most important driving force (Maiti et al., 2006). Our group has simply discussed the influence of glycosylation of flavonoids on the binding affinities for BSA (Xiao et al., 2009). Glycosylation of flavonoids can reduce the binding constants for BSA by 1–3-fold of magnitude depending on the conjugation site and the class of sugar (Xiao et al., 2009). Dangles and others (1999) measured the binding affinites of the quercetin–BSA complex, which illustrated the the binding constants of rutin–BSA complex and isoquercitrin–BSA complex were 11.97 and 7.10-folds lower than that of the quercetin–BSA complex. The presence of a sugar moiety at the C-3 position of quercetin obviously weakens the the quercetin–BSA affinity (Dangles et al., 1999; Bi et al., 2004). Quercetin also appears a much higher HSA binding percentage than that of rutin (Diniz et al., 2008).

As shown in Fig. 3, the glycosylation of flavonoids significantly decreased the binding constants for HSA (Xiao et al., 2011a). The binding constant of quercetin for HSA was about 478.6-time higher than that of rutin. The glucopyranosylation of genistein to genistin lowered the binding constant by 44.67 times. Puerarin (daidzein 8-*C*-glucoside) showed a

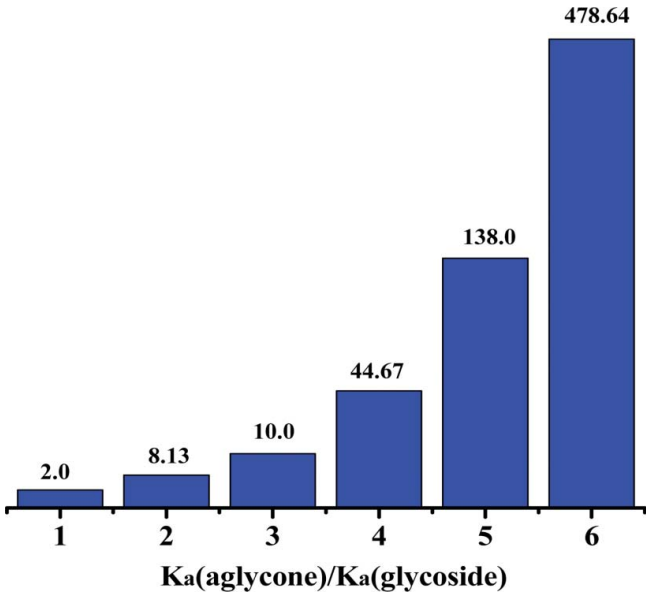


Figure 3. Glycosylation decreases the affinity of the flavonoids for HSA (Xiao et al., 2009). 1, K_a(baicalein)/K_a(baicalin); 2, K_a(kaempferol)/K_a(kaempferitrin); 3, K_a(naringenin)/K_a(naringin); 4, K_a(genistein)/K_a(sophoricoside); 5, K_a(daidzein)/K_a(puerarin); 6, K_a(quercetin)/K_a(rutin).

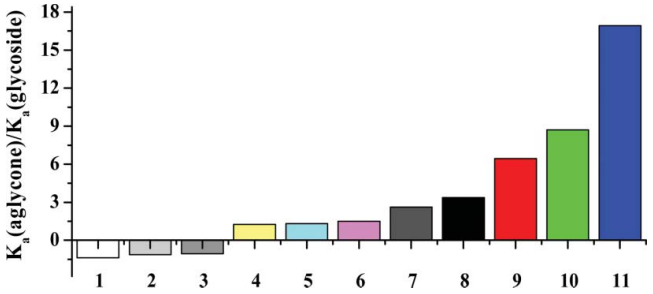


Figure 4. The glycosylation of flavonoids decreased or little affected the affinity of the polyphenols for HPP (Xie et al., 2012). 1, K_a(rutin)/K_a(quercetin); 2. K_a(narirutin)/K_a(naringenin); 3, K_a(kaempferitrin)/K_a(kaempferol); 4. K_a(genistein)/K_a(sophoricoside); 5, K_a(quercetin)/ K_a(quercitrin); 6, K_a(naringenin)/K_a(naringin); 7, K_a(daidzein)/K_a(puerarin); 8, K_a(baicalein)/ K_a(baicalin); 9, K_a(daidzein)/K_a(daidzin); 10, K_a(genistein)/K_a(genistin); 11, K_a(hesperitin)/ K_a(hesperitin 7-O-rutinoside).

138-time lower binding constant for HSA than that of its aglycone, daidzein (Xiao et al., 2011a).

The influence of glycosylation of flavonoids on the affinities for bovine hemoglobin (bHB) was also further investigated (Xiao et al., 2011e). It was found that the glycosylation of flavonoids decreased the affinity for bHB by 1 order of magnitude. The binding constant of genistin for bHB was 8.91-fold lower than that of genistein, but the affinity of kaempferitrin for bHB is approximately 1.02-fold higher than that of kaempferol. The affinities of rutin, puerarin (daidzein 8-*C*-glycoside), naringin, and baicalin for bHB were about 7.24, 2.45, 2.40, and 2.34 times higher than that of quercetin, daidzein, narigenin, and baicalein, respectively.

The impact of glycosylation of dietary flavonoids on the binding affinities for the plasma proteins from type II diabetes (TPP) and plasma proteins from healthy human (HPP) was explored (Xiao et al., 2011f, 2011g; Xie et al., 2012). The levels of glycated proteins in TPP (40%) are much higher than that of HPP (16%) (Cao et al., 2015). The sugar moieties are in 3, 7, or 4′ positions of flavonoids. As shown in Fig. 4 and 5, the glycosylation of flavonoids slightly decreased or little affected the affinities for HPP and TPP less than 1 order of magnitude (Figs. 4 and 5). For example, the affinity of quercetin for HPP was similar to that of rutin and quercetin. The affinities of baicalein and daidzein for TPP were similar to that of baicalin and puerarin, respectively (Xiao et al., 2011f).

Martini and others (2008) determined the affinity indexes and thermodynamic equilibrium constants of flavonol-BSA sysytem

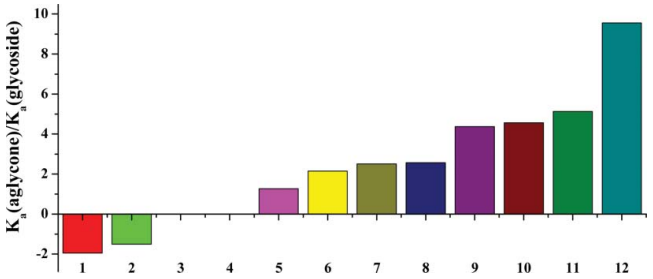


Figure 5. The glycosylation of flavonoids decreased or little affected the affinity of polyphenols for TPP (Xiao et al., 2011g). 1, K_a(Kaempferitrin)/K_a(kaempferol); 2, K_a(quercetin)/K_a(quercitrin); 3, K_a(baicalein)/K_a(baicalin); 4, K_a(daidzein)/K_a(puerarin); 5, K_a(genistein)/K_a(sophoricoside); 6, K_a(daidzein)/K_a(daidzin); 7, K_a(quercetin)/ K_a(rutin); 8, K_a(resveratrol)/K_a(polydatin); 9, K_a(naringenin)/K_a(naringin); 10, K_a (naringenin)/K_a(narirutin); 11, K_a(genistein)/K_a(genistin); 12, K_a(hesperitin)/K_a(hesperitin 7-O-rutinoside).

by means of NMR methodology. It suggested that quercetin exhibits stronger interaction with BSA than its glycosylated derivative, quercetin 3-*O*-β-D-glucopyranoside. The glycosylation of flavonoids decreased the binding affinity for proteins may be due to the greater molecular size and polarity and the nonplanar structure (Xiao et al., 2011g; Xiao and Kai, 2012a).

The above results provided direct evidence that the flavonoid aglycones are more easily bound to plasma proteins than their glycosides (Walle, 2004; Dufour and Dangles 2005).

2.3. Metabolism in liver microsomes

In mammals, dietary flavonoids are observed in urine or in bile as glucuronide, methylated or sulfate forms. Cytochrome P450 enzymes in the liver mainly metabolize drugs prior to excretion. Both phase I (oxidative) and phase II (conjugative) biotransformations in the liver represent a variety of reactions (Xiao and Högger, 2013). Flavonoid glycosides generate their respective aglycones by intestinal enzymes and/or the intestinal microflora (Xin et al., 2011; Li et al., 2012). Both microbial and mammalian biotransformation of flavonoid glycosides can modulate their biological function (Grimm et al., 2004). The sulfation and glucuronidation of flavonoid glycosides are particularly key to improve the molecular weight and solubility (Williamson et al., 2011; Wu et al., 2011).

Xing (2005) compared the metabolites from baicalein and baicalin in rat liver microsomes. The main metabolites were identified as baicalin, baicalein 7-*O*-glucuronide, and baicalein 6,7-di-*O*-glycopyranuronoside and Baicalein and baicalin show similar metabolic pathways (Xing, 2005) (Fig. 6). Wong et al. (2009) reviewed the relationships between flavonoid structural properties and their glucuronidation potential for the past two decades. Enzymes of the UGT1 and UGT2 families are the most efficient on using UDP-glucuronic acid as the glycosyl donor. UGT1A and UGT2B contribute significantly on phase II metabolism and glucuronidate a wide range of endogenous and exogenous substances including flavonoids. The major metabolites in human plasma after intake of onions are quercetin 3-*O*-glucuronide, isorhamnetin 3-*O*-glucuronide, and quercetin3′-*O*-sulfate with very limited quercetin (Day et al., 2001; Mullen et al., 2006). Glycosylation at C-7 of flavonoids reduces the chances for glucuronidation in vivo (Wong et al., 2009). Thus, flavonoid glycosides are always poor in the in vitro UGT selectivity assays. In addition, the type of glycosides also can influence its glucuronidation by UGTs (Chen et al., 2008). After uptake of scutellarein 7-*O*-glucuronide, the major metabolite formed in human urine was scutellarein 6-*O*-glucuronide, followed by scutellarein 4′-*O*-glucuronide. The parent flavonoid (7-*O*-glucuronide) was only found as a minor metabolite (Chen et al., 2006). It is very interesting to find that the glucuronidation rate by β-glucuronidase depends on the position of conjugation (Lu et al., 2003).

2.4. Pharmacokinetics properties

Puerarin 7-*O*-glucoside shows higher plasma concentration and has a longer mean residence time in the blood than puerarin (Jiang et al., 2008). Puerarin 7-*O*-glucoside appears as a significantly higher area under the plasma concentration time curve (AUC_t) and area under the time concentration curve (AUC_i) than those of puerarin. After oral administration of pure baicalin, wogonoside was detected in plasma in addition to baicalin, and wogonoside exhibited a similar plasma level with baicalin. The same result was observed after oral administration of extract to rats. It suggested that baicalin might be converted to wogonoside (Zhang et al., 2013).

Several groups checked the bioavailability of quercetin glycosides in rats (Makino et al., 2009; Duenas et al., 2013). Quercetin, quercetin 3-*O*-rutinoside, quercetin 3-*O*-glucoside, quercetin 3-*O*-maltoside, quercetin 3-*O*-gentiobioside, α-monoglucosyl rutin, α-oligoglucosyl rutin, and enzymatically modified isoquercitrin (α-oligoglucosyl isoquercitrin) were orally administered to rats. Quercetin 3-*O*-maltoside, quercetin 3-*O*-glucoside, and α-oligoglucosyl isoquercitrin showed significantly higher C_{max}, AUC_{0-12} and bioavailability than those of quercetin (Makino et al., 2009; Duenas et al., 2013). However, quercetin 3-*O*-gentiobioside and quercetin 3-*O*-rutinoside exhibited significantly lower C_{max}, AUC_{0-12}, and bioavailability

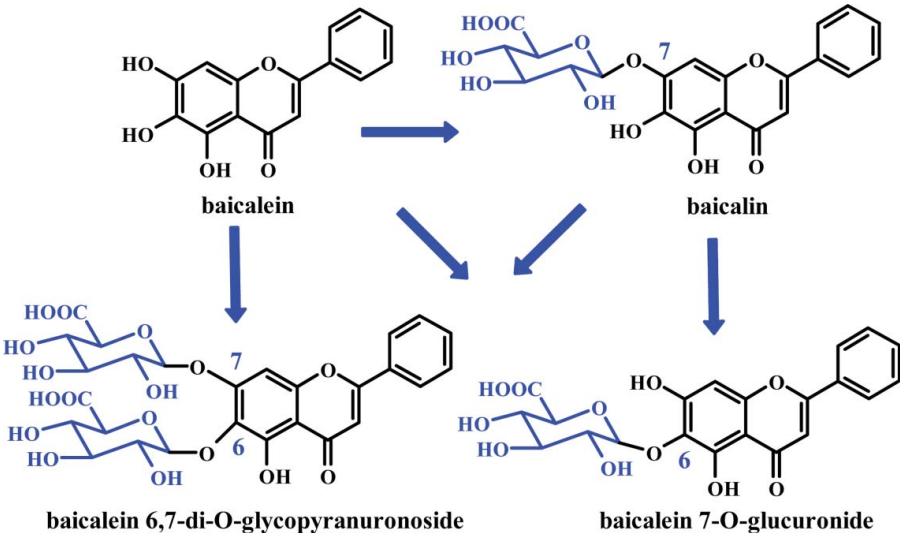


Figure 6. Microsomal metabolites of baicalein and baicalin in vitro (Xing, 2005).

than those of quercetin. Elongation of the α-linkage of the glucose moiety in quercetin 3-*O*-glucoside enhances its bioavailability.

In summary, flavonoid glycosides maintain higher levels in plasma and have longer mean residence time in the blood than those of aglycones.

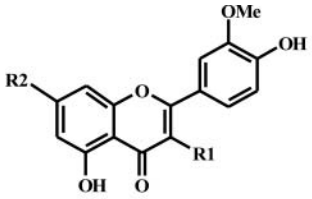
3. Impact of the glycosylation of flavonoids on their antioxidant potential

The cardiovascular protective potential of natural flavonoids relate to their capacities for inhibiting the chelate of redox-active metals, lipid peroxidation, and attenuating other processes involving reactive oxygen species (ROS). The structure-activity relationships of natural flavonoids as antioxidants were comprehensively studied. The antioxidant activity of natural flavonoids depends on the number and location of the hydroxyl moieties, the presence of 2,3-double bond in conjugation with a 4-oxo function in ring C, 3- and 5-hydroxy groups, 3,5,7-trihydroxy, ortho-catechol group (3′,4′-OH), and the glycosylation model (*C*-glycosides or *O*-glycosides) and position.

3.1. O-glycosylation

Rice-Evans and coworkers (1996) compared $ABTS^{+}$ scavenging potential of flavonoids by the Trolox equivalent antioxidant capacity (TEAC) assay. Cai and others (2006) evaluated the structure–radical scavenging activity relationships of flavonols, flavones, flavanones, and isoflavones from the traditional Chinese medicines by ABTS assay and DPPH assay and the results were expressed in terms of TEAC (mM). Quercetin and kaempferol appears higher antioxidant potential than its glycosides, such as quercetin 3-*O*-glucoside, quercetin 3-*O*-rutinoside, quercetin 3-*O*-rhamnoside, and quercetin 3-*O*-glucoside-7-*O*-rhamnoside, kaempferol 3-*O*-glucoside. Natural flavones (apigenin, baicalein, luteolin) showed higher TEAC than their 7-*O*-glycosides (apigenin 7-*O*-glucoside, baicalin, and luteolin 7-*O*-glucoside). Shafek and others (2012) reported the DPPH free radical scavenging potential of two new kaempferol 3-*O*-glycosides (kaempferol 3-*O*-β-D–glucopyranosyl (1→2) β-D-xylopyranoside, kaempferol 3-*O*-α-L-arabinopyranosyl (1→2) β-D-galactopyranoside) from *Solenostemma argel.* These two kaempferol 3-*O*-glycosides showed weaker DPPH free radical scavenging potential than that of kaempferol.

Om and others (2008) established the quantitative QSAR of 35 flavonoids based on the DPPH free radical scavenging potential by means of Genetic Algorithm-Multiple Linear Regression (GA-MLR) technique. Quercetin shows similar DPPH free radical scavenging potential with its poly-glycosides (rutin and quercetin 3-*O*-glucoside-7-*O*-rhamnoside) (Sarkar et al., 2012). Wang and others (2012b) isolates quercetin and its glycosides from *Halimodendron halodendron*. In view of the IC_{50} values in the DPPH assay, the radical scavenging activities of these flavonols were determined in this order: quercetin (0.024 μM) > 3,3'-di-O-methylquercetin (0.436 μM) >3,3'-di-*O*-methylquercetin 7-*O*-β-D-glucopyranoside (0.440 μM) > isorhamentin 3-*O*-β-D-rutinoside (0.842 μM). It illustrated that the glycosylation of flavonol on both OCH_3 and OH groups reduced the DPPH free radical scavenging potential (Rice-Evans et al., 1996; Cai et al., 2006; Om et al., 2008; De Martino et al., 2012; Sarkar et al., 2012; Wang et al., 2012b).



3,3'-di-*O*-methylquercetin R_1=*O*CH_3, R_2=OH

3,3'-di-*O*-methylquercetin-7-O-β-D-glucopyranoside R_1=*O*CH_3, R*2*=*O*-β-D-glc

isorhamentin 3-*O*-β-D-rutinoside R1=*O*-β-D-rutinose, R2=OH

Okoth and others (2013) isolated lanneaflavonol, dihydrolanneaflavonol, myricetin 3-*O*-α-rhamnopyranoside (myricitrin), and myricetin 3-*O*-α-arabinofuranoside (betmidin) from the roots of *Lannea alata*. Myricetin 3-*O*-α-rhamnopyranoside and myricetin 3-*O*-α-arabinofuranoside showed stronger DPPH free radical scavenging potential than that of myricetin, which is contrary to above reports that blocking the 3-OH group with a glycoside reduces activity.

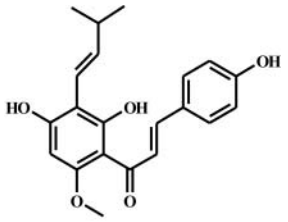
Naringenin showed higher antioxidant potential and hydroxyl/superoxide radical scavenger capacity than those of naringin (Cavia-Saiz et al., 2010). The glycosylation of naringenin attenuated the inhibition against xanthine oxidase and the naringenin looks like have stronger chelating action with metallic ions than that of its glycoside. Moreover, naringenin exhibits a more significant protective effect against oxidative damage to lipids (Cavia-Saiz et al., 2010). Ren and others (2013a) isolated five flavone glycosides (2″-*O*-α-L-rhamnosy1–6-*C*-3″deoxyglucosyl-3′-methoxyluteolin, ax-5′-methane -3′-methoxymaysin, ax-4″-OH-3′-methoxymaysin, 6,4′-dihydroxy-3′-methoxyflavone 7-*O*-glucoside, and 7,4′-dihydroxy-3′-methoxyflavone 2″-*O*-α-L-rhamnosyl-6-*C*-fucoside) from corn silk and investigated their antioxidative activity. Most of these flavone glycosides showed a strong DPPH free radical, superoxide radical, and hydroxyl radical scavenging potential. Especially, 4′-dihydroxy-3′-methoxyflavone 7-*O*-glucoside appears to have significantly higher antioxidant activity than rutin. Phloretin 2′-*O*-glucoside and phloretin 2′,4′-di-*O*-β-D-

glucopyranoside showed lower DPPH free radical and ABTS radical scavenging potential than that of phloretin (Wang et al., 2013). The DPPH free radical scavenging activity was decreased upon glycosylation of isorhamnetin (EC_{50} = 5.7 μg/mL) to its 3-*O*-glucoside (EC_{50} = 159.20 μg/mL) and 3-*O*-rutinoside (EC_{50} = 87.19 μg/mL) (Mishra et al., 2003; Majo et al., 2005; Liu et al., 2009; Kim et al., 2011a).

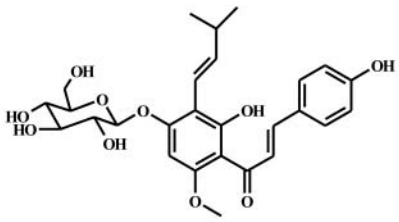
Peroxynitrite is a cytotoxic intermediate yielded by the reaction between a superoxide anion radical and NO. Choi and others (2002) investigated the structure–scavenging activity relationship of flavonoids against peroxynitrite. The glycosylation of flavonols (kaempferol and quercetin) obviously reduced the peroxynitrite scavenging potential. The inhibitory activities were determined as quercetin > quercetin 3-*O*-galactoside > quercetin 3-*O*-rutinoside> quercetin 3-*O*-glucoside > quercetin 3-*O*-arabinofuranoside and kaempferol >> kaempferol 3-*O*-glucoside ≈ kaempferol 7-*O*-glucoside.

Burda and Oleszek (2001) compared the antioxidant activity of flavonoids characterized by the potential to inhibit heat-induced oxidation in a β-carotene-linoleic acid-model system. The glycosylation of flavonols (kaempferol and quercetin) obviously reduced the peroxynitrite scavenging potential. The β-D-glucoside isolated from *Coronopus didymus* (Mishra et al., 2003). However, the glycoside is more effective to inhibit enzymatically produced superoxide anion by xanthine/xanthine oxidase system than the aglycone. Majo and others (2005) elucidated the antioxidant or pro-oxidant behaviors of flavanones using the crocin bleaching inhibition assay. The antiradical activity of the aglycones (hesperetin and naringenin) and their corresponding neohesperidosides (neohesperidin and naringin) and rutinosides (hesperidin and harirutin) were compared. The *O*-glycosylation at the C-7 position reduced the radical scavenging potential of flavanones, which may be caused by the steric effect and the ability to delocalize electrons (Majo et al., 2005).

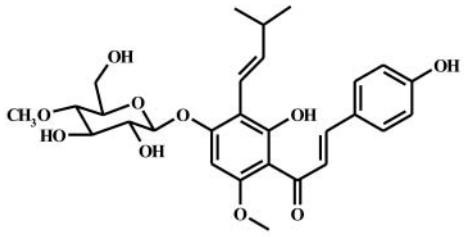
Xanthohumol isolated from hops was regioselectively glycosylated at the C-4′ position by selected to xanthohumol 4′-*O*-β-D-glucopyranoside and xanthohumol 4′-*O*-β-D-(4‴-*O*-methyl)-glucopyranoside (Tronina et al., 2013). Compared to xanthohumol (IC_{50} = 1.98 μM), xanthohumol 4′-*O*-β-D-glucopyranoside (IC_{50} = 0.77 μM) showed stronger DPPH radical scavenging potential. However, xanthohumol 4′-*O*-β-D-(4‴-*O*-methyl)-glucopyranoside (IC_{50} = 9.06 μM) appears to have significantly weak DPPH radical scavenging potential.



Xanthohumol



xanthohumol 4′-*O*-β-D-glucopyranoside



xanthohumol 4′-*O*-β-D-(4‴-*O*-methyl)- glucopyranoside

inhibitory activities were determined as laricytrin (28.5%)> laricytrin 3′-*O*-glucoside (26.2%) > larycitrin 3,3′-*O*-diglucoside (1.1%) > laricyrin 3,7,3′-*O*-triglucoside (-6.2%) and quercetin (63.6%) > quercetin 3-*O*-glucoside-7-*O*-rhamnoside (-6.2%) > rutin (-10.2%). The inhibitory potential of flavonol monoglycoside is stronger than that of flavonol diglycoside and triglycoside. Yang and others (2009) investigated the structure-activity relationship of flavonoids against lard oil oxidation. Apigenin and genistein showed similar inhibitory potential against lard oil oxidation with camellianin A (apigenin 5-*O*-[rham-6-*O*-acetyl-glucoside) and sophoricoside (genistein 4′-*O*-glucoside), respectively.

Chrysoeriol showed much better protective effect on inhibit lipid peroxidation than its glycoside, chrysoeriol 6-*O*-acetyl-4′-

In summary, as shown in Table 1 and Fig. 7, the *O*-glycosylation of flavonoids decreased their antioxidant potential in in vitro assays, such as DPPH free radical, ABST radical, superoxide radical and hydroxyl radical scavenging assay, inhibition of lard oil oxidation, and so on. However, as for cellular antioxidant capacity, the conclusion may be different. For example, quercetin displayed weaker antioxidant activity than its glycosides, while the cellular antioxidant capacity of quercetin and hyperin was stronger than that of isoquercitrin and quercitrin, indicating that the higher cell-membrane permeability of quercetin and hyperin than isoquercitrin and quercitrin was due to the different hydrophobicity and the specific membrane receptor for galactose (Choi et al., 2012). Lin and others (2011) investigated the free radical scavenging activity in HepG2 cells of flavonoids from

Table 1. Effect of the glycosylation of flavonoids on their antioxidant potential.

Biological benefits	Flavonoids	Glycosylation		Impact	Ref.
		Type	Local		
DPPH radical scavenging	Xanthohumol 4′-O-β-D-glucopyranoside	O-	4′	↑	Tronina et al. (2013)
	Xanthohumol 4′-O-β-D-(4′′′-O-methyl)-glucopyranoside	O-	4′	↓	Tronina et al. (2013)
	Phloridzin (phloretin 2′-*O*-glucoside), phloretin 2′,4′-di-*O*-β-D-glucopyranoside, avicularin	O-	2′,4′	↓	Wang et al. (2013)
	Myricetin 3-*O*-α-rhamnopyranoside, myricetin 3-*O*-α-arabinofuranoside	O-	3	↑	Okoth et al. (2013)
	Rutin	O-	3	↓	De Martino et al. (2012)
	Hesperetin 7-*O*-rutinoside	O-	7	↓	De Martino et al. (2012); Seyoum et al. (2006)
	3,3′-di-*O*-methylquercetin 7-*O*-β-D-glucopyranoside	O-	7	↓	Wang et al. (2012b)
	Isorhamentin 3-*O*-β-D-rutinoside	O-	3	↓	Wang et al. (2012b)
	Rutin, quercetin 3-*O*-glucose-7-*O*-rhamnoside, isoquercitrin, hyperoside	O-	3,7	↔	Sarkar et al. (2012); Seyoum et al. (2006)
	Quercetin 3,5-di-*O*-glucoside, kaempferol 3,5-di-*O*-glucoside, kaempferol 3-*O*-[2′′-(4′′′-acetylrhamnosyl) (1→2)- 6′′-glucosyl] glucoside,	O-	3,5	↓	Seyoum et al. (2006)
	Kaempferol 3-*O*-β-D–-glucopyranosyl (1→2) β-D-xylopyranoside	O-	3	↓	Shafek et al. (2012)
	Kaempferol 3-*O*-α-L-arabinopyranosyl (1→2) β-D-galactopyranoside				
	Isorhamnetin 3-*O*-glucoside, isorhamnetin 3-*O*-rutinoside	O-	3	↓	Majo et al. (2005)
	Chrysoeriol 6-*C*-β-boivinopyranosyl-7-*O*-β-glucopyranoside	C-	6	↑	Oh et al. (2013)
	Isoorientin	C-	8	↑	Choi et al. (2014b)
Trolox equivalent antioxidant capacity (mM)	Quercetin 3-*O*-glucoside, quercetin 3-*O*-rutinoside, quercetin 3-*O*-rhamnoside, quercetin 3-*O*-glucoside-7-*O*-rhamnoside, kaempferol 3-*O*-glucoside	O-	3	↓	Cai et al. (2006)
	Apigenin 7-*O*-glucoside, baicalin, luteolin 7-*O*-glucoside, naringin, hesperidin, genistin, daidzin	O-	7	↓	Cai et al. (2006)
	Vitexin	C-	8	↑	Cai et al. (2006)
	Apigenin 6,8-*C*-diglucoside, luteolin 6,8-*C*-diglucoside, luteolin 8-*C*-glucoside, apigenin 8-*C*-glucoside	C-	6,8	↑	Omar et al. (2011)
Inhibition of lipids oxidation	Naringin	O-	7	↓	Cavia-Saiz et al. (2010)
	Quercetin 3-*O*-glucoside, quercetin 3-*O*-galactoside, quercetin 3-*O*-rhamnoside, quercetin 3-*O*-rutinoside	O-	3	↓	Huber et al. (2009)
ABST radical scavenging	Phloridzin (phloretin 2′-O-glucose), phloretin 2′,4′-di-*O*-β-D-glucopyranoside, avicularin	O-	2′,4′	↓	Wang et al. (2013)
Peroxynitrite scavenging	Isoorientin	C-		↑	Choi et al. (2014b)
	Laricytrin 3′-*O*-glucoside, larycitrin 3,3′-*O*-diglucoside, laricyrin 3,7,3′-*O*-triglucoside, quercetin, quercetin, rutin	O-	3,7,3′	↓	Burda and Oleszek (2001)
Inhibition of xanthine oxidase	Naringin	O-	7	↓	Cavia-Saiz et al. (2010)
	Chrysoeriol 6-*O*-acetyl-4′-β-D-glucoside	O-	6	↑	Mishra et al. (2003)
Inhibition of ROS production in Hep G2 cells	Astragalin, isoquercitrin, kaempferol 3-*O*-rutinoside, rutin, quercetin 3-*O*-{α-L-rhamnopyranosyl-(1→6)[α -L-rhamnopyranosyl(1→2)]}-β-D-galactopyranoside	O-	3	↑	Lin et al. (2011)
Superoxide radical scavenging	Myricitrin, myricetin 3-*O*-(2′′-*O*-galloyl)-α-L-rhamnopyranoside, and myricetin 3-*O*-(2′′-*O*-galloyl)-β-D-galactopyranoside	O-	3	↑	Kim et al. (2013)
	Hyperoside, quercitrin	O-	3	↓	Mao et al. (2011)
	Quercetin 3-*O*-β-D-glucopyranoside-(3′→O-3′′′)-quercetin-3-*O*-β-D-galactopyranoside	O-	3	↑	Mao et al. (2011)
	Chrysoeriol 6-*C*-β-boivinopyranosyl-7-*O*-β-glucopyranoside	C-	6	↑	Oh et al. (2013)
	Naringin	O-	7	↓	Cavia-Saiz et al. (2010)

Hemerocallis fulva flowers. Astragalin, isoquercitrin, kaempferol 3-*O*-rutinoside, rutin, quercetin 3-*O*-{α-L-rhamnopyranosyl-(1→6)[α-L-rhamnopyranosyl(1→2)]}-β-D- galactopyranoside showed higher inhibition against ROS production in Hep G2 cells than that of their aglycones, kaempferol, and quercetin. However, the related data are not sufficient to make a uniform conclusion on the influence of *O*-glycosylation of flavonoids on their cellular antioxidant potential.

Lespade and Bercion (2012) theoretically investigated the influence of sugar substitution on the antioxidant properties of flavonoids. The sugar substitution significantly alters the Mulliken charges on the oxygen atoms of the hydroxyls. The substitution of the hydrogen atom by a sugar on C-3 position leads to slightly better antioxidant abilities, but the higher antioxidant properties are obtained with one hydroxyl group. The nature of the substituent at the C-3 position seems to be very important for the antioxidant properties. It indicated that the electrophilicity of the hydroxyl group does not lead to better antioxidant ability.

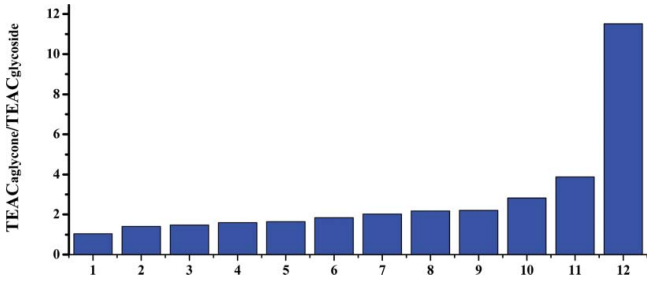
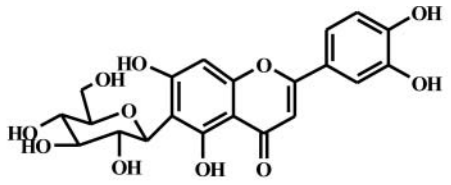


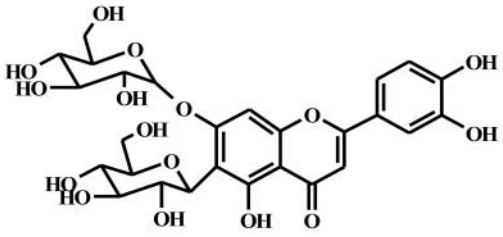
Figure 7. O-Glycosylation of flavonoids decreased their antioxidant potential base TEAC assay. 1. apigenin/apigenin 7-O-glucoside, 2. daidzein/daidzein 7-O-glucoside, 3. luteolin/luteolin 7-O-glucoside, 4. genistein/genistein 7-O-glucoside, 5. baicalein/baicalein 7-O-glucuronide, 6. quercetin/quercetin 3-O-glucoside, 7. quercetin/quercetin 3-O-rhamnoside, 8. quercetin/quercetin 3-O-rutinoside, 9. naringenin/naringenin 7-O-rutinoside, 10, 1uercetin/1uercetin 3-O-glucoside-7- O-rhamnoside, 11. hesperetin/hesperetin 7-O-rutinoside, 12. kaempferol/kaempferol 3-O-glucoside (Rice-Evans et al., 1996; Burda and Oleszek, 2001; Mishra et al., 2003; Majo et al., 2005; Cai et al., 2006; Om et al., 2008; Liu et al., 2009; Kim et al., 2011a; Sarkar et al., 2012 Wang et al., 2012; Okoth et al., 2013; Tronina et al., 2013).

3.2. C-glycosylation

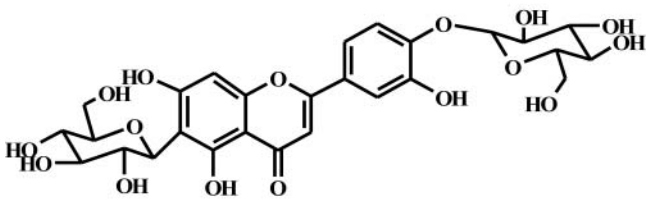
Hoyweghen and others (2010) checked the antioxidant capacity of *C*-glycosyl luteolin, namely farobin A, farobin B and luteolin 6-*C*-glucopyranoside isolated from *Fargesia robusta* var. Pingwu using TEAC and ORAC assays. It was found the antioxidant activity in the TEAC assay was lowered when more glycosides was added to luteolin 6-*C*-glucopyranoside. The 7-*O*-glycosilation of luteolin 6-*C*-glucopyranoside showed stronger activity than that of 4′-*O*-glycosilation.



luteolin 6-*C*-glucopyranoside



farobin A



farobin B

Huber and others (2009) evluated the inhibition of oxidation of omega-3 polyunsaturated fatty acids and fish oil by quercetin and its glycosides. The antioxidant potential of quercetin was similar to or greater than quercetin glycosides for the inhibition of lipid oxidation in the oil-in-water emulsion systems when oxidation was induced by heat, light, peroxyl radical or ferrous ion. In bulk fish oil, *C*-3 glycosylation enhanced the antioxidant activity of quercetin. As shown in Table 1 and Fig. 7, flavonoids aglycones showed more potent radical scavenging potential than their corresponding *O*-glycosides. The *O*-glycosylation of flavonoids aglycones weakens TEAC. However, the *C*-glycosylation of apigenin enhances TEAC about 2.51 times. Apigenin 8-*C*-glucoside and apigenin 7-*O*-glucoside appear higher DPPH free radical scavenging potential than that of apigenin (Cai et al., 2006). Omar and others (2011) studied the antioxidant potential of flavone *C*-glycosides identified from *Ficus deltoidea*. The antioxidant potential (Trolox equivalent, μM) was determined as apigenin 6,8-*C*-diglucoside (76 μM) > luteolin 6,8-*C*-diglucoside (15 μM) > luteolin 8-*C*-glucoside (9.0 μM) > apigenin 8-*C*-glucoside (0 μM). It illustrated that the *C*-glycosylation of flavones enhances their antioxidant potential.

Praveena and others (2013) investigated the radical scavenging activity of flavone *C*-glycoside from *Rhynchosia capitata* aerial and discovered the mechanism responsible for vitexin showing higher radical scavenging activity than apigenin. Optimization of structure for radical species was carried out by removing H-atom from the C-5, C-7, and C-4′ positions, respectively. In vitexin, the most stable radical order was found to be 4′-OH > 7-OH > 5-OH. It is observed that the bond dissociation enthalpies of apigenin radicals are slightly higher than vitexin, which may be due to the presence of glucose at the C-8 position which is responsible for the charge changes on the oxygen atoms of the hydroxyl groups. Being a *C*-glycoside, the stability of glucose is higher than that of the *O*-glycosides. The *C*-8 glycosylation decreases the negative charge on the oxygen atom at the C-3 position and lead to better antioxidant potency of vitexin compared to apigenin. Oh and others (2013) isolated chrysoeriol 6-*C*-β-boivinopyranosyl-7-*O*-β-glucopyranoside and chrysoeriol from the silk of *Zea mays* Linn. Chrysoeriol show lower DPPH free radical and superoxide anion scavenging potential than its 6-*C*-glycoside.

In summary, the *C*-glycosylation of flavonoids in most cases increased the antioxidant potential of flavonoid aglycones. In summary, the C-glycosylation of flavonoids in most cases increased the antioxidant potential of flavonoid aglycones (Xiao et al., 2016).

3.3. Deglycosylation

Flavonoid glycosides in orange (*Citrus sinensis*) and lime (*Citrus latifolia*) juices were de-glycosylated with commercial rhamnosidases (hesperidinase and naringinase) and β-D-glucosidase (da Silva et al., 2013). The antioxidant activity (DPPH and FRAP assay) of treated juices was higher than that of untreated juices. After incubation with hesperidinase for 4 h, 60% of the hesperidin was converted

into hesperetin in the orange juice. The antioxidant potentials of the glycosylated standards were also improved by the enzyme treatment. De Araújo and others (2013) evaluated the antioxidant and antiproliferative potentials of rutin deglycosylated with hesperidinase and naringinase. Rutin was predominantly bioconverted into quercetin 3-*O*-glucoside, which showed higher DPPH free radical scavenging potential than that of rutin.

Puerarin was transglycosylated to transglycosylated puerarins when reacted with β-CD catalyzed by maltogenic amylase from archaeon Thermofilum pendens. Although the antixoidant potential of transglycosylated puerarins is weaker than that of puerarin, the transglycosylated puerarins still fully maintained their antioxidant activity, assessed by a radical scavenging test and a reducing power assay (Li et al., 2011).

In summary, the deglycosylation of flavonoid glycosides enhanced their antioxidant activity.

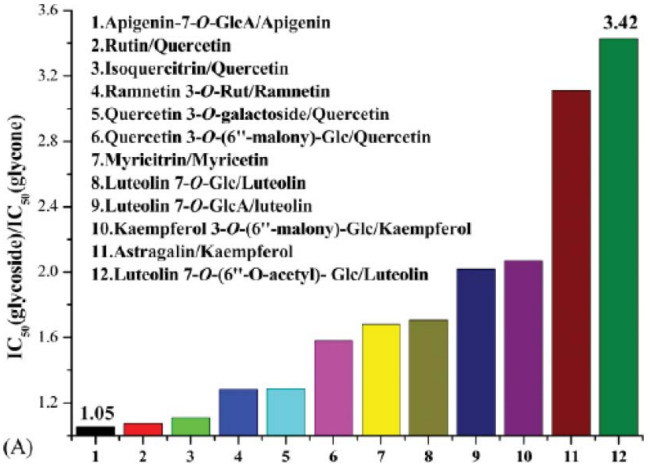


Figure 8. Effects of glycosylation on the inhibition of AGEs formation (Xie and Chen, 2013).

4. Influence of the glycosylation of flavonoids on their antidiabetes activity

4.1. Advanced glcation end products inhibitors

Advanced glcation end products (AGEs) are known as a complex and heterogeneous group of compounds that have been associated with infiammation, renal failure, aging, and especially diabetes. The properties of polyphenols as AGEs formation inhibitors have attracted great interest among researchers. Xie and Chen (2013) reviewed the antiglycation activities of polyphenols and focus on the relationship between the AGE formation inhibitory activities of polyphenols and their chemical structures.

Matsuda and coworkers (2003) compared the inhibitory effects of several flavonoid glycosides on AGE. As they found, luteolin 7-*O*-glycosides showed lower inhibitory potential against AGEs formation than that of luteolin, and the decreasing degree depended on the types of glycosyl groups (Matsuda et al., 2003). Jang and others (2010) evaluated the different glycosides of luteolin and found that β-D-glucopyranosyl only slightly decreased the activity while (6″-*O*-acetyl)-β-D-glucopyranosyl dramatically reduced the activity. On the other hand, it illustrated that the 8-*C*-glucosides of luteolin enhanced the inhibitory effect on AGEs formation than its aglycone (Matsuda et al., 2003; Jung et al., 2007).

Kim and others (2004) isolated and identified three flavonol glycosides from the extract of *Eucommia ulmoides* leaves and found that all of them exhibit glycation inhibitory activity and two quercetin glycosides show different activity. In another study, among the several flavonoid glycosides isolated from *Thuja orientalis*, quercetrin (quercetin 3-*O*-rhamnoside) was the only one with obvious inhibitory effects on AGEs formation, while the quercetin 3-*O*-glucoside (isoquercetin) and other flavonol glycosides such as kaempferin hardly inhibited AGEs formation (Lee et al., 2009).

Hesperidin and hesperetin were chirally separated and the inhibitory effects of a 1: 1 mixture of (2S)- and (2R)-hesperidin, (2S)-hesperidin, (2R)-hesperidin, 1:1 mixture of (S)-and (R)-hesperetin, (S)-hesperetin, (R)-hesperetin, and monoglucosyl hesperidin [1:1 mixture of (2S)-glucosyl hesperidin and (2R)-glucosyl hesperidin] on protein glycation reaction were investigated (Li et al., 2012). It demonstrated that hesperidin and its derivatives possessed relatively strong activity against the formation of AGEs and (S)-hesperetin possessed the highest.

The inhibition of AGEs formation potential of quercetin and its glycosides have been widely studied. It was found that isoquercetrin ($IC_{50} = 106\ \mu M$) showed weaker activity than quercetrin ($IC_{50} = 64\ \mu M$) (Matsuda et al., 2003; Shimoda et al., 2011), but a new flavonoid, 2″,4″-*O*-diacetylquercitrin along with six known flavonoids were isolated from the aerial parts of *Melastoma sanguineunz* (Lee et al., 2013a). Their inhibitory effects on advanced AGE formation in vitro were examined. Of the tested compounds, 2″, 4″-*O*-diacetylquercitrin showed the strongest inhibition against AGE.

It suggested that the *O*-glycosylation of flavonoids tends to decrease the inhibitory potential against AGE formation and *C*-glycosylation enhanced it. As shown in Fig. 8, the ratio of IC_{50} values of flavonoids glycosides and their corresponding aglycones ranges from 1.05 to 3.42.

4.2. α-amylase inhibitors

Human α-amylases are have been widely researched for clinical chemistry purposes and for drug design to treat some diseases, specially diabetes and hyperlipidemia (Xiao et al., 2011d). The inhibitory effects of polyphenols for α-amylases have been widely reported (Xiao et al., 2013a). Kim and others (2000) compared the inhibitory potential of fiavonoid glycosides on α-amylase (EC 3.2.1.1). Baicalin, pectolinarin, and linarin (5 mg/mL) hardly inhibited α-amylase. The inhibitory percentage of luteolin was found to be similar with that of luteolin 7-*O*-glucoside. The monoglycosides (quercitrin and hyperin) of quercetin are stronger than their polyglycoside form (rutin) as α-amylase inhibitors (Kim et al., 2000).

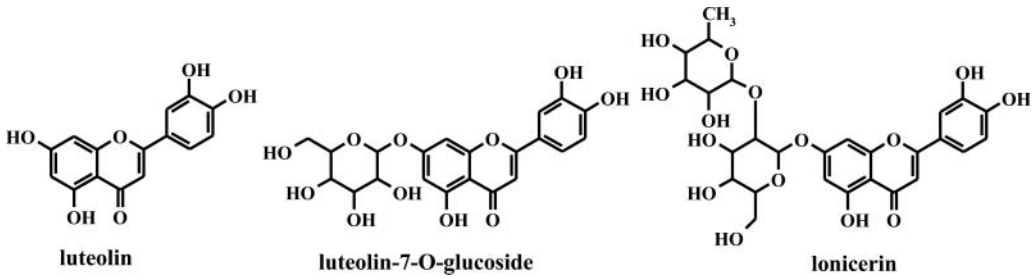
Ye and others (2010) also reported that the inhibitory potential of quercetin was much stronger than rutin against human pancreatic α-amylase. Wang and others (2010) isolated quercetin and its glycosides from guava leaves and compared their α-amylase inhibitory activity. It suggested that α-amylase inhibitory activity of quercetin was better than that of its glycosides. Komaki et al. separated and identified luteolin 7-*O*-β-glucoside and luteolin 4′-*O*-β-glucoside as α-amylase inhibitors (Komaki et al., 2003). Luteolin 7-*O*-β-glucoside and luteolin 4′-*O*-β-glucoside showed much weaker inhibition against α-amylase than that of luteolin (Kim et al., 2000). Ye et al. (2010) investigated α-amylase inhibitory activity of common constituents from traditional Chinese medicine used for diabetes mellitus, which indicated that the inhibitory effect of kaempferol is much higher than its glycoside forms.

Yang and others (2012) isolated okanin, a chalcone, and its glycosides, okanin 4-methyl ether-3′-*O*-β-D-glucoside, and okanin 4′-glc from *Bidens bipinnata* and found that okanin glycosides obviously exhibited weaker inhibition against α-amylase than that of okanin. Acacetin 7-O-α-L-rhamopyranoside showed stronger inhibitory effect on α-glucosidase and α-amylase than that of acacetin 7-*O*-β-D-glucopyranoside (Luyen et al., 2013).

In summary, the glycosylation of fiavonoids decreased the inhibitory effect against α-amylase depending on the conjugation position and the class of sugar moiety. The decreasing inhibitory potential after glycosylation may be due to the increasing molecular size and polarity, and transfer to the nonplanar structure. However, recently, an exception was reported by Manaharan and others (2012). They isolated flavonoids from *Syzygium aqueum* leaves and found that myricetin 3-*O*-rhamnoside (EC_{50} = 1.9 μM) showed stronger inhibition against α-amylase than that of myricetin (EC_{50} = 17 μM) (Manaharan et al., 2012).

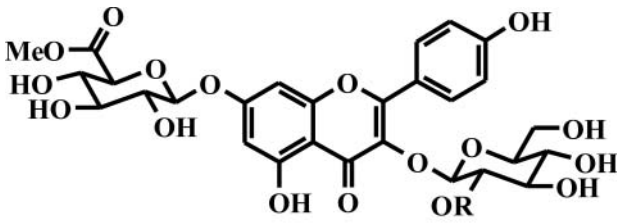
4.3. α-glucosidase inhibitors

α-Glucosidase is the most important enzyme in carbohydrate digestion. Inhibition of α-glucosidase will prevent excess glucose absorption at the small intestine. The inhibitory effects of dietary polyphenols for α-glucosidases have attracted great interest among researchers (Xiao et al., 2013b). Kim and coworkers (2000) compared the inhibitory effects of several flavonoid glycosides on α-glucosidase. Baicalin, pectolinarin, hesperidin, rutin, isorhamnetin 3-*O*-rutinoside, hyperin, and linarin (5 mg/mL) hardly inhibited α-glucosidase. The inhibitory percentages of luteolin and its glycosides were determined as: luteolin > luteolin 7-*O*-glucoside > lonicerin. It revealed that the monoglycosides of flavonoids are stronger than the polyglycoside forms. For example, the monoglycoside (luteolin 7-*O*-glucoside) of luteolin is stronger than its polyglycoside form (lonicerin) and querctrin is stronger than rutin as α-glucosidase inhibitors (Kim et al., 2000).



Wang and coworkers (2010) isolated quercetin and its glycosides, guaijaverin, avicularin, and hyperin from guava (*Psidium guajava* Linn.) leaves and compared their α-glucosidase inhibitory potential. The IC_{50} values against α-glucosidase of quercetin, guaijaverin, avicularin, and hyperin against rat intestinal sucrase were 3.5, 6.2, 6.5, and 7.5 mM, respectively. Li and coworkers (2009a) compared the effects of quercetin, isoquercetin, and rutin as α-glucosidase inhibitors by fluorescence spectroscopy and enzymatic kinetics. The sequence of binding constants (K_a) was quercetin > isoquercetin > rutin, and the number of binding sites was one. The IC_{50} values of quercetin, isoquercetin, and rutin against α-glucosidase were 0.017, 0.185, and 0.196 mM, respectively. It illustrated that the glycosylation of quercetin obviously weakened its inhibition against α-glucosidase. Fan and coworkers (2010) found that quercetin 3-*O*-β-D-galactopyranoside showed significantly more active than quercetin 3-*O*-arabinopyranoside.

Yoshida and others (2008) isolated flavonol caffeoylglycosides from *Spiraea cantoniensis* flower. Quercetin 3-O-(6-O-caffeoyl)-β-galactoside (IC_{50} = 0.085 mM) showed stronger inhibition effect on maltase than that of kaempferol 3-O-(6-O-caffeoyl)-β-galactoside (IC_{50} = 0.35 mM) from *Spiraea cantoniensis* flower. However, the inhibitory activity against maltase (IC_{50} > 1 mM) of both quercetin and kaempferol was apparently lower than that of the quercetin 3-O-(6-O-caffeoyl)-β-galactoside and kaempferol 3-O-(6-O-caffeoyl)-β-galactoside. Phuwapraisirisan and others (2009) identified two new flavonol glycosides, corchoruside A and B, from the leaves of *Corchorus olitorius*. Corchoruside A inhibited α-glucosidase activity with an IC_{50} value of 0.18 mM, which is threefold more active than that of corchoruside B (IC_{50} = 0.72 mM). This result confirmed that the caffeoyl moiety is critical in blocking enzyme function. The substitution of the sugar moiety in flavonol glycosides by a phenolic acid, in particular, caffeic acid, could thus enhance their glucosidase inhibitory activity.



corchoruside A R=caffeoyl
corchoruside B R=H

Li and others (2009b) screened α-glucosidase inhibitors from hawthorn leaf and four flavonol/flavone glycosides were identified as quercetin 3-*O*-rha-(1–4)-glc-rha and *C*-glycosylflavones (vitexin 2″-*O*-glucoside, vitexin 2″-*O*-rhamnoside, and vitexin). Vitexin 2″-*O*-glucoside, vitexin 2″-*O*-rhamnoside, isovitexin, and vitexin are *C*-glycosides of apigenin. Orientin and isoorientin are *C*-glycosides of luteolin. The inhibitory percentages of these flavone glycosides were determined as: apigenin > vitexin > isovitexin and luteolin > isoorientin > orientin (Li et al., 2009b). Glycosylation at *C*-6 or *C*-8 of flavones decreased the inhibitory activity of flavones against α-glucosidase, although the *C*-6 glycosylation had relatively less impact than the *C*-8 glycosylation (Li et al., 2009b). However, isovitexin, vitexin, orientin, and isoorientin also showed strong inhibitory activity similar to apigenin and luteolin.

Shibano and others (2008) isolated and identified 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*. In these glucosides, isoquercitrin, isorhamnetine 3-*O*-rutinoside, vitexin, and swertisin have obvious inhibition against α-glucosidase from rat intestine. The inhibitory percentages of apigenin glycosides were determined as: swertisin > vitexin > isovitexin≈ flavocommelin.

Kawabata and coworkers (2003) separated several apigenin glycosides as α-glucosidase inhibitors from *Origanum majorana* leaves. The glycosylation at the C-7 position of flavones significantly decreased the inhibitory activity of flavones against α-glucosidase, although the C-6 glycosylation had relatively less impact than the C-8 glycosylation. The IC_{50} values were determined as 6-hydroxyapigenin 7-*O*-β-D-glucopyranoside (>500 μM), 6-hydroxyluteolin 7-*O*-β-D-glucopyranoside (300 μM), 6-hydroxyapigenin 7-*O*-(6-*O*-feruloyl)-β-D-glucopyranoside (>500 μM), and 6-hydroxyluteolin 7-*O*-(6-*O*-feruloyl)-β-D-glucopyranoside (>500 μM). However, the IC_{50} value of 6-hydroxyapigenin was 32 μM.

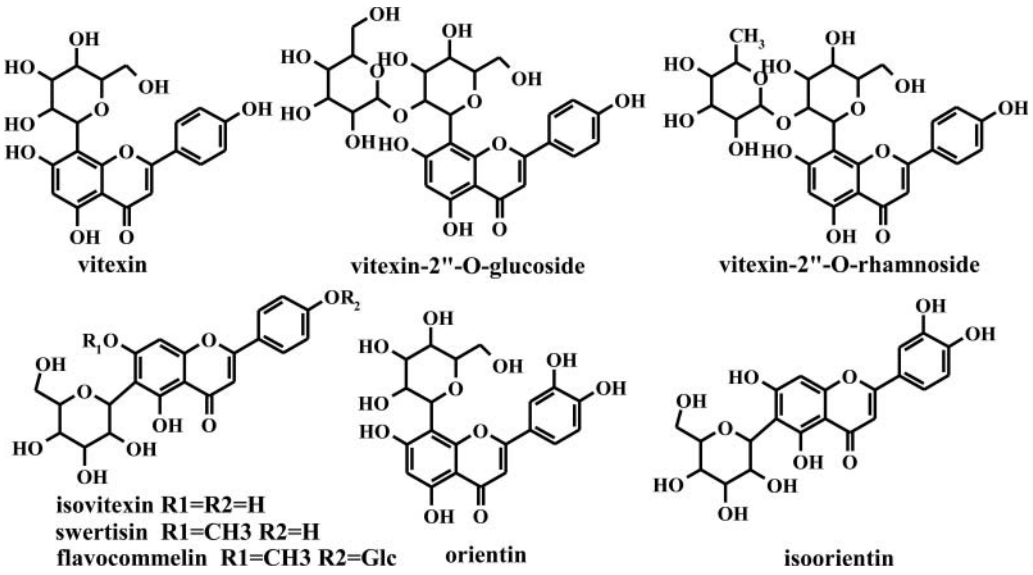
Ren and others (2013b) isolated pinocembrin and its glycosides from *Litchi chinensis* Sonn seeds and investigated their inhibition against α-glucosidase. Pinocembrin showed stronger inhibition against α-glucosidase than that of its glycosides, (2S)-pinocembrin 7-*O*-(6″-*O*-α-L-arabinosyl-β-D-glucopyranoside), pinocembrin 7-*O*-glucoside, pinocembrin 7-*O*-[(6″-*O*-β-D-glucopyranoside)-β-D-glucopyranoside], and pinocembrin 7-*O*-[(2″,6″-di-*O*-α-L-rhamnopyranosyl)-β-D-glucopyranoside]. The inhibitory activity against α-glucosidase was determined as pinocembrin > pinocembrin monoglucoside > pinocembrin diglycoside > pinocembrin triglycoside. It concluded that the more glycosylation and the larger the molecular structure, the weaker the inhibitory activity against α-glucosidase.

Chen and others (2013) investigated the α-glucosidase inhibitory effects of vitexin (IC_{50} = 244.0 μM) and isovitexin (IC_{50} = 266.2 μM), which showed similar activity against α-glucosidase. Luyen et al. (2013) isolated acacetin 7-*O*-β-D-glucopyranoside and acacetin 7-O-α-L-rhamopyranoside from *Chrysanthemum morifolium* flowers. Acacetin 7-O-α-L-rhamopyranoside showed stronger inhibitory effect on α-glucosidase than that of acacetin 7-O-β-D-glucopyranoside.

Shen and others (2012) investigated the effects of *Citrus* flavonoids (hesperidin, naringin, neohesperidin, and nobiletin) on amylase catalyzed starch digestion, and pancreatic α-amylase and α-glucosidase activities. It found that all *Citrus* flavonoids significantly inhibited amylase-catalyzed starch digestion. Moreover, naringin and neohesperidin mainly inhibited amylose digestion, whereas hesperidin and nobiletin inhibited both amylose and amylopectin digestion. However, these flavonoid gycosides showed very weak inhibitory potential against pancreas α-amylase and α-glucosidase (Shen et al., 2012).

Manaharan and others (2012) isolated myricetin 3-*O*-rhamnoside and europetin 3-*O*-rhamnoside from the ethanolic leaf extracts of *Syzygium aqueum*. Myricetin 3-*O*-rhamnoside and europetin 3-*O*-rhamnoside showed higher inhibitory potential against α-amylase than that of myricetin and quercetin. Myricetin 3-*O*-rhamnoside with an additional glucose moiety at the C-3 position was found to be 10 times more effective than its myricetin analog. Europetin 3-Orhamnoside, an analog of myricetin but with an additional methyl group at position C-7 was also seven times more effective than its myricetin analog.

Islam and others (2013) isolated quercetin and its 3-*O*-glucoside, hyperoside, from *Artemisia capillaris*. Hyperoside appears to have a significantly lower inhibiton against α-glucosidase than that of quercetin. Moradi-Afrapoli and others (2012) isolated and identified quercetin, myricetin and their 3-*O*-glycosides, quercetin 3-*O*-β-D-galactopyranoside, quercetin 3-*O*-α-L-arabinofuranoside (avicularin), quercetin 3-*O*-α-L-(3″,5″-diacetyl-arabinofuranoside), quercetin 3-*O*-α-L-(3″-acetylarabinofuranoside), myricetin 3-*O*-α-L-(3″,5″-diacetyl-arabinofuranoside), myricetin 3-*O*-β-D-galactopyranoside, myricetin 3-*O*-α-L-rhamnopyranoside (myricitrin), and myricetin 3-*O*-α-L-arabinofuranoside from aerial parts of *Polygonum hyrcanicum*. All quercetin, myricetin and their 3-*O*-glycosides showed significant α-glucosidase inhibitory activities. The *O*-glycosylation of quercetin and myricetin at the C-3 position slightly weakened the α-glucosidase inhibitory activities.



In summary, as shown in Fig. 9, the glycosylation of flavonoids lowered the inhibition against α-glucosidase depending on the conjugation position and the class of sugar moieties. The decreased inhibitory effect against α-glucosidase after glycosylation may due to the increasing molecular size and polarity, and the non-planar structure. After a hydroxyl moiety is substituted by a glycoside, the steric hindrance may happen, which weakens the binding interaction between flavonoids and α-glucosidase.

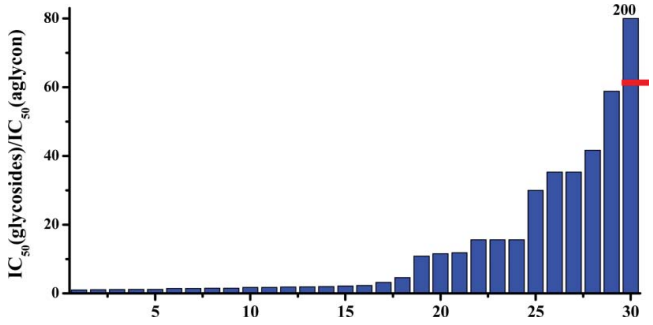


Figure 9. Glycosylation of flavonoids decreased the inhibitory effect on α-glucosidase depending on the conjugation site and the class of sugar moiety. 1. Iriflophenone 2-O-a-L-rhamnopyranoside/ iriflophenone, 2. isovitexin/apigenin, 3. aquilarisinin/iriflophenone, 4. vitexin/apigenin, 5. iriflophenone 3-C-β-D-glucoside/ iriflophenone, 6. quercetin 3-O-α-L-(3′′-acetylarabinofuranoside) /quercetin, 7. myricetin 3-O-β-D-galactopyranoside/myricetin, 8. quercetin 3-O-α-L- (3′′,5′′-diacetyl-arabinofuranoside)/quercetin, 9. isoorientin/luteolin, 10. guaijaverin/quercetin, 11. orientin/luteolin, 12. avicularin/quercetin, 13. quercetin 3-O-β-D-galactopyranoside/isoquercetin, 14. Iriflophenone 3,5-C-β-D-diglucopyranoside/ iriflophenone, 15. hyperin/quercetin, 16. avicularin/quercetin, 17. myricetin 3-O-α-L-arabinofuranoside/myricetin, 18. myricetin 3-O-α-L-(3′′,5′′-diacetyl-arabinofuranoside)/myricetin, 19. isoquercetin/quercetin, 20. rutin/isoquercetin, 21. quercetin 3-O-rhamnopyranoside/quercetin, 22. 6-hydroxyapigenin 7-O-β-D-glucopyranoside/6-hydroxyapigenin, 23. 6-hydroxyapigenin 7-O-(6-O-feruloyl)-β-D- glucopyranoside/6-hydroxyapigenin, 24. 6-hydroxyluteolin 7-O-(6-O-feruloyl)-β-D-glucopyranoside/6-hydroxyapigenin, 25. 3′,4′-dihydroxybaicalein 7-O-β-D-Glc/ 3′,4′- dihydroxybaicalein, 26. puerarin/daidzein, 27. dadzin/daidzein, 28. 4′-hydroxybaicalein 7-O-β-D-Glc/4′-hydroxybaicalein, 29. formononetin 7-O-glucoside/formononetin, 30. genistin/ genistein (Kim et al., 2000; Kawabata et al., 2003; Shibano et al., 2008; Yoshida et al., 2008; Li et al., 2009a, 2009b; Manaharan et al., 2012; Moradi-Afrapoli et al., 2012; Phuwapraisirisan et al., 2009; Wang et al., 2010; Shen et al., 2012; Chen et al., 2013; Islam et al., 2013; Luyen et al., 2013; Ren et al., 2013b).

Recently, Michael and others (2013) isolated diosmetin 7-*O*-β-L-arabinofuranosyl, diosmetin 7-*O*-β-D-apiofuranoside and diosmetin 7-*O*-β-D-apiofuranoside from the acetone extract of date fruits epicarp and assessed their biological activity on alloxan diabetic rats in vivo. These diosmetin glycosides also shows remarkable therapy effect on alloxan diabetic rats.

4.4. Aldose reductases inhibitors

Aldose reductase (AR) is the first enzyme of the polyol pathway that reduces excess D-glucose into D-sorbitol. Aldose reductase in eyes, kidney, muscle, and brain can cause accumulation of sorbitol in the presence of diabetes mellitus (Brownlee, 2001). The polyol pathway seems to play an important role in the development of degenerative complications of diabetes. The aldose reductase inhibitors (ARIs) seem to offer the possibility of preventing or arresting the progression of these long-term diabetic complications, despite high blood glucose levels and with no risk of hypoglycaemia, since they have no effect on plasma glucose (Xiao et al., 2015). The inhibitory potency of flavones (apigenin and luteolin)/isoflavones (genistein and daidzein) and their 7-glycosylated compounds have been widely studied as ARIs (Fig. 10) (Shin et al., 1995; Yoshikawa et al., 1999; Matsuda et al., 2002; Jung et al., 2004; Liu et al., 2007; Park et al., 2007; Park et al., 2010; Jung et al., 2011). The glycosides usually are β-D-glucopyranosyl, β-D-glucopyranosiduronic acid, α-L-rhamnopyranosyl, neohesperodosyl or rutinose. As shown in Figure 10, the glycosylation on the 7 position of flavones significantly decreased the inhibition against AR by 1.16 to 216.7 times (Shin et al., 1995; Yoshikawa et al., 1999; Matsuda et al., 2002; Jung et al., 2004; Liu et al., 2007; Park et al., 2007; Park et al., 2010; Jung et al., 2011).

The inhibitory percentages of luteolin and its glycosides were determined as: luteolin > luteolin 7-*O*-neohesperodoside (lonicerin) > luteolin 7-*O*-rutinoside > luteolin 7-*O*-β-D-glucopyranoside > luteolin 7-*O*-glucopyranosiduronic acid (Jung et al., 2004, 2011; Yoshikawa et al., 1999; Xie et al., 2005). The inhibition of apigenin and its glycosides were determined as: apigenin > apigenin 7-O-rutinoside ≈ apigenin 7-*O*-β-D-

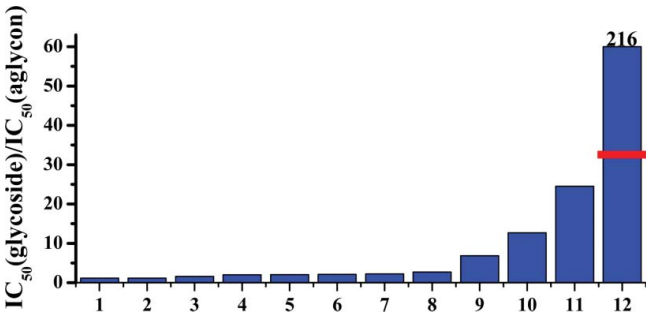


Figure 10. The 7-O-glycosylation of flavonoids significantly decreased the inhibition against aldose reductase. 1. luteolin 7-O-Neo/luteolin, 2. genistin/genistein, 3. baicalin/baicalein, 4. apigenin 7-O-Glc/apigenin, 5. luteolin 7-O-Rut/luteolin, 6. apigenin 7-O-Rut/apigenin, 7. luteolin 7-O-Glc/luteolin, 8. diosmetin 7-O-Glc/diosmetin, 9. luteolin 7-O-GlcA/luteolin, 10. daidzin/daidzein, 11. 3′-OH-formononetin 7-O-Glc/3′-OH-fornmononetin, 12. linarin/acacetin. Data were collected from references (Shin et al., 1995; Yoshikawa et al., 1999; Matsuda et al., 2002; Jung et al., 2004; Liu et al., 2007; Park et al., 2007; Park et al., 2010; Jung et al., 2011).

glucopyranoside (Matsuda et al., 2002; Xie et al., 2005). It revealed that the polyglycosides of flavonoids are stronger than their monoglycosylated forms. Matsuda and others (2002) reported that diosmetin exhibited twice-higher inhibition against AR than that of diosmetin 7-*O*-β-D-glucopyranoside. However, acacetin (IC_{50} = 6.0 μM) showed 210-fold stronger inhibition than its 7-*O*-rutinoside (IC_{50} = 1300.0 μM).

Park et al. (2005) investigated the isoflavone components from the roots of *Pueraria thunbergiana* as ARIs. Genistin and daidzin possessed lower inhibition against aldose reductase than their aglycones, genistein, and daidzein. The activity of *C*-8-glucoside puerarin was also relatively weak. Genistin and genistein possessing a hydroxyl group at the C-5 position showed the most potent inhibition of enzyme activity (IC_{50} = 5.2 and 4.5 μM, respectively) (Park et al., 2005). Park and coworkers (2010) further isolated several isoflavone glycosides from the stem bark of *Sophora japonica*. The glycosylation on the C-7 position of 7,3′-hydroxy-4′-methoxyisoflavone significantly decreased the inhibition by 24.25 times.

Figure 11 shows the inhibitory potency of flavonols and their 3-monoglycosylated compounds (Okuda et al., 1982; Al-Yahya et al., 1988; Matsuda et al., 2002; Xie et al., 2005; Lim et al., 2006; Kim et al., 2013; Mok and Lee, 2013; Zhang et al., 2013). As seen from these data the glycosylation on the C-3 position of flavonoids increased or little affected the inhibition against AR. However, 3-polyglycosylation of flavonols significantly weakened its inhibitory potency (Matsuda et al., 2002). Quercetin 3,7-di-*O*-β-D-glucopyranoside and rutin reduced the inhibitory potency by 38.18 and 4.09-fold, respectively. Rhamnetin 3-*O*-rutinoside and ombuine 3-*O*-rutinoside decreased the inhibition about 7.78 and 6.83 times (Matsuda et al., 2002).

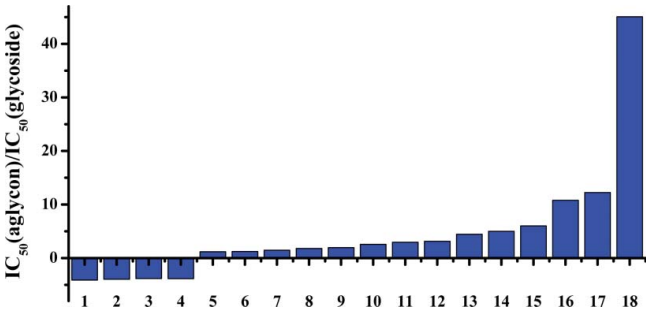


Figure 11. The 3-*O*-glycosylation of flavonoids enhanced or little affected the inhibition against aldose reductase. 1. rutin/quercetin, 2. hyperoside/quercetin, 3. isoquercitrin/quercetin, 4. kaempferol 3-*O*-Glc/kaempferol, 5. quercetin/avicularin, 6. apigenin/apigenin 3-*O*-Glc, 7. quercetin/hirsutrin, 8. quercetin/quercetin, 9. kaempferol/kaempferol 3-*O*-GlcA, 10. kaempferol/afzelin, 11. kaempferol/kaempferol 3-*O*-Rha, 12. quercetin/quercitrin, 13. myricetin/myricitrin, 14. mearnsetin/mearncitrin, 15. quercetin/reyneutrin, 16. quercetin/quercetin, 17. quercetin/guaijaverin, 18. quercetin/quercetin 3-*O*-Rha. Data were collected from references (Okuda et al., 1982; Al-Yahya et al., 1988; Matsuda et al., 2002; Xie et al., 2005; Lim et al., 2006; Mok and Lee, 2013; Kim et al., 2013; Zhang et al., 2013).

The flavonoids glycosylated at the 4′ postion were hardly reported. Xie et al. (2005) isolated luteolin/apigenin and their 4′-glycosides as ARIs from *Saussurea medusa*. It was found that the glycosylation on 4′-hydroxyl of flavones remarkably weakened the inhibition. The IC_{50} values of luteolin, luteolin 4′-*O*-β-D-glucopyranoside, apigenin, and apigenin 4′-*O*-β-D-glucopyranoside inhibiting RLAR were 0.45×10^{-6}, 4.8×10^{-6}, 2.2×10^{-6}, and 3.2×10^{-6} mol/L, respectively (Matsuda et al., 2002; Xie et al., 2005). Luteolin showed ten-fold higher inhibiton than that of luteolin 4′-*O*-β-D-glucopyranoside. The glycosylation on 4′-hydroxyl of 5,3′,4′-hydroxy-6,7-methoxyflavone and 5,4′-hydroxy-3′6,7-methoxyflavone also decreased the inhibition (Okuda et al., 1982; Al-Yahya et al., 1988). The PIC_{50} values of 5,3′,4′-hydroxy-6,7-methoxyflavone and 5,3′-hydroxy-6,7-methoxyflavone 4′-O-Glc were 6.66 and 5.02. 5,3′,4′-hydroxy-6,7-methoxyflavone showed 43-fold higher inhibition than 5,3′-hydroxy-6,7-methoxyflavone 4′-*O*-glucopyranoside inhibition (Okuda et al., 1982; Al-Yahya et al., 1988). Okuda and others (1982) further found the glycosylation on 4′-hydroxyl of 5,4′-hydroxy-6,7-methoxyflavone and 5,7,4′-hydroxy-6,8,3-methoxyflavone also decreased the inhibition. However, 5,4′-hydroxy-6,7,3′-methoxyflavone showed only twice higher inhibition than 5-hydroxy-6,7,3′-methoxyflavone 4′-*O*-glucopyranoside inhibition (Okuda et al., 1982; Al-Yahya et al., 1988). Moreover, the glycosylation on 6 and 4′-OCH_3 of flavones slightly increased the inhibition (Al-Yahya et al., 1988). 5,7- hydroxy-6,8,3′-methoxyflavone 4′-*O*-glucopyranoside and 5,4′-hydroxy-6,7,8,3′-methoxyflavone 6-*O*-glucopyranoside showed slight higher inhibition than those of 5,7-hydroxy-6,8,3′,4′-methoxyflavone and 5,4′-hydroxy-6,7,8,3′-methoxyflavone (Al-Yahya et al., 1988).

Mok and Lee (2013) identified kaempferol, afzelin, quercetin, quercitrin, myricetin and myricitrin from *Rhododendron mucronulatum* and investigated their inhibitory activities against rat lens aldose reductase. The glycosylation on C-3 position of kaempferol, quercetin, and myricetin obviously enhances the inhibition. Kim and others (2013) isolated a 3-*O*-glycosylated quercetin, hirsutrin, which showed a 1.48-fold higher inhibition against rat lens aldose reductase than that of quercetin. Zhang and others (2013) isolated and identified several flavonol 3 or 8-*O*-glycosides, myricetin 3-*O*-β-D-xylopyranosyl(1→2)-β-D-galactopyranoside, 3,3′,4′,5′,5,7,8-heptahydroxyl flavone 3′-*O*-β-D-glucopyranoside, 3,3′,4′,5,5′,7,8-heptahydroxyl flavone 8-*O*-β-D-glucuronopyranoside, 3,3′,4′,7-tetrahydroxyl-5-methoxyl flavone 3-*O*-robinoside, and quercetin 3′-*O*-(6″,-acetyl)-β-D-glucopyranoside, from the

flowers of *Abelmouschus manihot*. All these flavonol glycosides showed significant AR inhibition. Lim and others (2006) isolated kaempferol and its seven glycosides, myricetin 3′,5′-dimethylether 3-*O*-β-D-glucopyranoside, quercetin 3-*O*-β-D-glucopyranoside and two isorhamnetin glycosides from *Nelumbo nucifera*. Among these flavonol glycosides, those with 3-*O*-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside groups in their C rings, such as kaempferol 3-*O*-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside and isorhamnetin 3-*O*-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside, exhibited the highest degree of RLAR inhibitoion (Lim et al., 2006).

In summary, the glycosylation of flavonoids affected the inhibition against AR depending on the conjugation site and the class of the sugar moiety. The *O*-glycosylation on the C-3 position of flavonoids significantly increased or little affected the inhibition. The *O*-glycosylation on the C-7 and C-4′ positions of flavonoids decreased the inhibition.

4.5. Glycogen phosphorylase inhibitors

Glycogen phosphorylase (GP, EC 2.4.1.1) is a key enzyme in the regulation of glycogen metabolism and catalyzes a degradative phosphorylysis of glycogen to glucose 1-phosphate. GP inhibitors are considered to be beneficial in treating type II diabetes. Kato and others (2008) investigated the structure-activity relationships of flavonoids as GP inhibitors. 6-Hydroxyluteolin, hypolaetin, and quercetagetin were identified as good inhibitors for GP with IC_{50} values of 11.6, 15.7, and 9.7 μM, respectively. Quercetin (IC_{50} = 33.5 μM) appears to have much higher inhibition against GP than that of rutin, quercetin 3-*O*-glucopyranoside, and quercetin 3-*O*- galactopyranoside (IC_{50}>200 μM) and luteolin 4′-*O*-glucopyranoside showed much weaker inhibition than that of luteolin. It illustrated that *O*-glycosylation of flavonoids significantly weakens the inhibitory potential against GP. It is not clear the influence of *C*-glycosylation of flavonoids on the inhibition.

4.6. Protection against glucose-mediated protein damage

Kim and coworkers (2011b) investigated the protection effect of quercetin and its glycosides, isoquercitrin, and hyperin against glucose-mediated protein damage. Isoquercitrin and hyperin (50 μM) appeared much higher inhibitory activity against the formation of AGEs in a dose-dependent manner than that of quercetin. Isoquercitrin and hyperin (50 μM) can inhibit AGEs formation by 89.6% and 92.0%, respectively, which is much higher than that of aminoguanidine (50 μM). However, quercetin (50 μM) hardly exhibited any inhibition (Kim et al., 2011b).

5. Impact of the glycosylation of flavonoids on their antiobesity function

5.1. Antiobesity function

The benefits of dietary flavonoids for obesity can be summarized as: prevention the absorption of dietary fat, inhibition of absorption of lipids, accelerating lipid metabolism, and upregulating energy usage, lipolysis, and inhibition of palmatic acid uptake, inhibition of pancreatic lipase, prevention of adipocyte cells grown, and inhibition of lipid droplet accumulation in adipocyte (Calderon-Montano et al., 2011; Afifi and Abu-Dahab, 2012; Bansal et al., 2012; Morikawa et al., 2012; Mulvihill and Huff, 2012). Yahagi and others (2012) isolated flavonol acylglycosides, namely 3″-(E)-p-coumaroylquercitrin, 3″-(E)-feruloylquercitrin, 3″-(E)-cinnamoylquercitrin, and 2″-(E)-cinnamoylquercitrin from the flowers of *Albizia julibrissin*. These compounds inhibited adipogenesis in 3T3-L1 preadipocytes. In particular, 3″-(E)-feruloylquercitrin exhibited potent inhibitory effects on triglyceride accumulation, GPDH activity, glucose uptake in 3T3-L1 adipocytes (Yahagi et al., 2012). Isorhamnetin 3-*O*-β-D-glucopyranoside and quercetin 3-*O*-beta-D-glucopyranoside from *Salicornia herbacea* effectively suppressed adipogenic differentiation in adipocyte cells. Quercetin 3-*O*-β-D-glucopyranoside showed antiadipogenic activity by downregulation of sterol regulatory element-binding protein 1, CCAAT/enhancer-binding proteins, PPAR gamma and the adipocyte-specific proteins (Kong et al., 2012).

5.2. Inhibition of lipid accumulation

Morikawa and others (2012b, 2013) isolated several flavonol glycosides from *Sedum sarmentosum* (Morikawa et al., 2012b) and *Camellia sinensis* (Morikawa et al., 2013).

Flavonol glycosides exhibited strong inhibition against lipid accumulation in HepG2 cells. Kaempferol 3-O-Glc-(1→3)-Rha-(1→6)-Glc and kaempferol 3-O-Glc-(1→3)-Rha-(1→6)-Gal can effectively inhibit TG accumulation in HepG2 cells without detectable cytotoxity (Morikawa et al., 2013).

6. Impact of the glycosylation of flavonoids on their anti-virus capacity

6.1. Anti-HIV activity

Anti-HIV activities of quercetin and its derivatives have been reviewed (Wang et al., 2011; Andrae-Marobela et al., 2013). Inhibition of syncytium formation and protection of HIV-1 induced cytopathic effects (CPE) by quercetin and its 3α/3β-methoxyserrat-14-en-21β-ol conjugate isolated from *Diospyros lotus* has been reported with EC_{50} values of 42.55 and 23.2 μg/mL, respectively using C8166 cells (Wang et al., 2012c; Tanaka et al., 2009). Myricetin and its derivatives myricetin 3-*O*-β-glucuronide and myricetin 3-*O*-α-rhamnoside isolated from the same plant species inhibited syncytia formation with EC_{50} values of 28.37, 16.51, and 14.15 μg/mL, respectively (Wang et al., 2012c). Quercetin 3-*O*-β-D-galactopyranoside from *Alnus firma* inhibited HIV-1 reverse transcriptase (HIV-1 RT) with IC_{50} = 60 μM, while quercetin 3-*O*-(2″,6″-O-digalloyl)-β-D-galactopyranoside and quercetin 3-*O*-(2″-galloyl)-α-L-arabinopyranoside isolated from *Acer okamotoanum* inhibited HIV-1 integrase (HIV-1 IN) with IC_{50} values of 24.2 and 18.1 μg/mL, respectively (Kim et al., 1998; Yu et al., 2007). In a docking study, kaempferol 3-*O*-glucoside was found to be an efficient

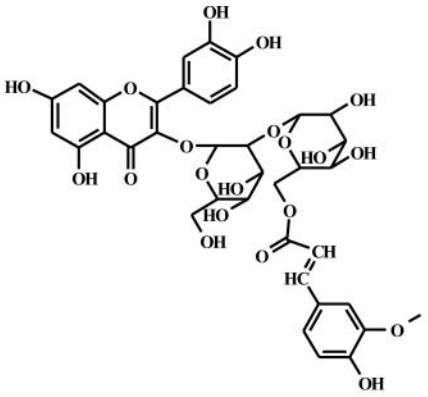
HIV-1 RT inhibitor based on its binding energy and ligand efficiency score (Seal et al., 2011). Sodium rutin sulfate displayed effective suppression of induced syncytia formation and inhibited HIV-1 entry and virus/cell fusion most likely through interaction with HIV-1 envelope glycoprotein (Tao et al., 2007).

The major components in leaves of *Nelumbo nucifera* were found to be quercetin 3-*O*-glycosides, such as quercetin 3-*O*-β-D-glucuronide, rutin, isoquecitrin, hyperin, and quercetin 3-*O*-β-D-xylopyranosyl-(1→2)-β-D-galactopyranoside (Kashiwada et al., 2005). Quercetin 3-*O*-β-D-glucuronide showed moderate anti-HIV activity (EC_{50} = 2 μg/mL) and low cytotoxicity (IC_{50} >100 μg/mL) (TI >50). Quercetin 3-*O*-β-D-xylopyranosyl-(1→2)-β-D-galactopyranoside also showed weak anti-HIV activity (EC_{50} = 4 μg/mL), while quercetin, rutin, isoquecitrin, and hyperin appeared to have no anti-HIV activity. The impact of 3-*O*-glycosylation of flavonols depends on the glycosyl moiety. Tewtrakul and others (2002) isolated flavonol glycosides including a new flavonol glycoside, quercetin 3-*O*-{β -D-glucopyranosyl-(1→2)-[α-L-rhamnopyranosyl-(1→6)]-β-D-galactopyranoside} (peruvianoside III) from the leaves of *Thevetia peruviana*. Quercetin 3-*O*-glycosides, quercetin 3-*O*-[(6-*O*-sinapoyl)-β-D-glucopyranosyl-(1→2)-β-D-galactopyranoside], quercetin 3-*O*-[(6-*O*-feruloyl)-β-D-glucopyranosyl-(1→2)-β-D-galactopyranoside, and quercetin 3-*O*-[β-D-glucopyranosyl-(1→2)-β-D-glucopyranoside] showed appreciably higher HIV-1 RDDP inhibitory activity with values of 33, 20, 41, and 38 μM than that of quercetin (IC_{50} = 43 μM). It suggested that quercetin 3-*O*-glycosides appear to have relatively higher activity than kaempferol 3-*O*-glycosides.

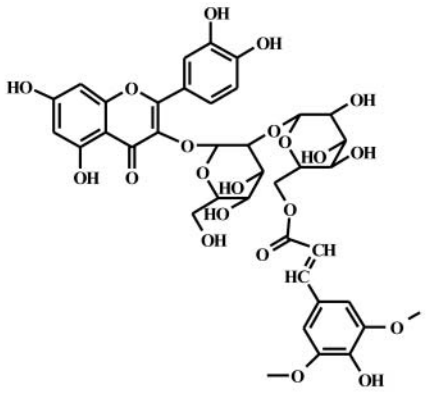
These glycosides exhibited higher inhibition than their aglycones, quercetin, and kaempferol.

Rashed and others (2012) investigated anti-HIV potential myricetin 3-*O*-β-glucuronide, myricetin 3-*O*-α-rhamnoside, myricetin and quercetin isolated and identified from *Diospyros lotus* fruits. Myricetin 3-*O*-β-glucuronide and myricetin 3-*O*-α-rhamnoside showed higher anti-HIV activity in C8166 cell than that of myricetin. Suedee and others (2013) isolated an anti-HIV-1 integrase proanthocyanidin from *Pometia pinnata* leaves. However, three isolated flavonoids, epicatechin, kaempferol 3-*O*-rhamnoside, and quercetin 3-O-rhamnoside showed no anti-HIV-1 integrase activity. Yarmolinsky and others (2012) compared the antiviral poential of quercetin and kaempferol with their 3-*O*-glycosides against HSV-1/2. The 3-*O*-glycosylation of quercetin and kaempferol significantly improved the inhibitory activity against HSV-1/2. The EC_{50} values were determined as quercetin (60 μg/mL) > kaempferol (25 μg/mL) > kaempferol 3-*O*-rutinoside (3.0 μg/mL) > quercetin 3-*O*-rutinoside (1.5 μg/mL) > kaempferol 3-*O*-robinobioside (0.9 μg/mL).

EC_{50} of acacetin 7-*O*-β-D-galactopyranoside, apigenin 7-*O*-β-D-galactopyranoside, luteolin, luteolin 7-*O*-β-D-glucopyranoside, quercetin, and baicalin against HIV-1 replication in H9 lymphocytes were reported to be 8, 61, 10, 7, 132, and 112 μM, repsctively (Olivero-Verbel and Pacheco-Londoño, 2002). The 7-*O*-glycosylation of luteolin obviously improves the anti-HIV activity.



Quercetin 3-*O*-[(6-*O*-feruloyl)-β-D-glucopyrnosyl-(1→2)-β-D-galactopyranoside] vi



quercetin 3-*O*-[(6-*O*-sinapoyl)-β-D-glucopyrnosyl-(1→2)-β-D-galactopyranoside]

In the case of HIV-1 IN inhibitory activity, the inhibition was determined as quercetin The anti-HIV potentials were determined as: quercetin 3-*O*-[(6-*O*-feruloyl)-β-D-glucopyranosyl-(1→2)-β-D-galactopyranoside] > quercetin 3-*O*-[(6-*O*-sinapoyl)-β-D-glucopyranosyl-(1→2)-β-D-galactopyranoside] > quercetin > kaempferol 3-O-[(6-O-sinapoyl)-β-D-glucopyranosyl-(1→2)-β-D-galactopyranoside] > kaempferol 3-*O*-[(6-*O*-feruloyl)-β-D-glucopyranosyl-(1→2)-β-D-galactopyranoside] > kaempferol 3-*O*-{β-D-glucopyranosyl-(1→2)-[α-L-rhamonopyranosyl-(1→6)]-β-D-galactopyranoside} ≈ kaempferol. The flavonol 3-*O*-glycosides with one feruloyl or sinapoyl group in the terminal glucose moiety showed more potent inhibitory activity than unsubstituted ones.

Shahat and others (1998) isolated from (+)-taxifolin, 3-*O*-β-arabinopyranosyl-(+)-taxifolin and 3-*O*-β-xylopyranosyl-(+)taxifolin from *Crataegus sinaica*. The anti-HIV activities were determined as (+)-taxifolin > 3-*O*-β-arabinopyranosyl-(+)-taxifolin and 3-*O*-β-xylopyranosyl-(+)taxifolin. Two new flavanone glucosides, (2R)- and (2S)-5-*O*-β-D-glucopyranosyl-7,4′-dihydroxy-3′,5′-dimethoxyflavanone showed no activity against either HIV-1 RT or HIV-1 IN (Tewtrakul et al., 2002).

In summary, 3-*O*-glycosylation of flavonols (quercetin, myricetin, and kaempferol) and 7-*O*-glycosylation of flavones (apigenin and luteolin) significantly improves the inhibitory activity against HIV-1 RT, HIV-1 IN, and HSV-1/2. Flavanone glucosides showed no activity against either HIV-1 RT or HIV-1 IN.

6.2. Antirotavirus activity

Among enteric viruses, rotaviruses are the major cause of severe diarrhea and it is believed that they would account for about 30–80% of pediatric hospitalizations for acute gastroenteritis. The inhibitory potential of flavanoids against rotavirus was investigated by Bae and others (2000). Among tested flavanoids, hesperidin and neohesperidin showed higher inhibitory activity on rotavirus infection than their aglycone, hesperetin. Naringin and pocirenin also appear to have stronger inhibition against rotavirus infection than their aglycones (narigenin and pocirin). For flavonols, diosmin and rutin showed high inhibition with IC_{50} of 10 μM. However, their aglycones (diosmetin and quercetin) do not exhibit inhibitory activity. All tested isoflavones including alycones and glycosides do not provide antirotavirus activity. It concluded that flavanones and flavonols glycosides appear higher inhibition against rotavirus infection than their aglycones.

6.3. Anti-influenza viral activity

Jeong and others (2009) isolated kaempferol, herbacetin, rhodiolinin, rhodionin, and rhodiosin from *Rhodiola rosea* and studied their neuraminidase inhibitory activity. It illustrated that the 3, 7 or 8 *O*-glycosylation of apigenin, luteolin, herbacetin, kaempferol, and quercetin significantly reduced their neuraminidase inhibition. Ryu and others (2010) isolated eighteen polyphenols with neuraminidase inhibitory activity from the roots of *Glycyrrhiza uralensis*. The inhibitory activities of isoliquiritigenin (IC_{50} = 9.0 μM) and liquiritigenin (IC_{50} = 46.8 μM) were much higher than their 4′-*O*-glycosides, namely isoliquiritin (IC_{50} = 124.0 μM) and liquiritin (IC_{50} = 82.3 μM). It looks like that the glycosylation of flavonoids significantly weakened influenza virus neuraminidase inhibition (Liu et al., 2008; Jin et al., 2012).

6.4. Anti-mayaro virus activity

dos Santos and others (2014) isolated quercetin and quercetin 3-*O*-glycosides, namely guaijaverin, isoquercitrin, and hyperin, from *Bauhinia longifolia (Bong.)* and investigated their anti-Mayaro virus activity. Quercetin (25 μg/mL) displaying a stronger anti-Mayaro virus effect than the licensed antiviral ribavirin; however, quercetin 3-*O*-glycosides showed very weak inhibition against Mayaro virus production.

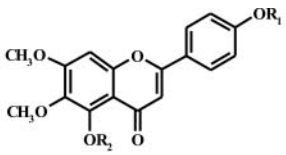
7. Impact of the glycosylation of flavonoids on their preventing and managing of other diseases

7.1. Anti-inflammation activity

Purified flavone aglycones and aglycone-rich extracts can weaken the production of TNF-α and inhibit the transcription of NF-κB, while glycoside-rich extracts showed no significant effects (Hostetler et al., 2012). Deglycosylation of flavonoid glycosides modulates the inflammation by decreasing the production of TNF-α and NF-κB. Mao and others (2011) isolated a new biflavonol glycoside, quercetin 3-*O*-β-D-glucopyranoside-(3′→O-3‴)-quercetin-3-*O*-β-D-galactopyranoside from the leaves of *Machilus zuihoensis* Hayata (Lauraceae). It showed significant superoxide anion scavenging activity (IC_{50} = 30.4 μM) and markedly suppressed LPS-induced high mobility group box 1 (HMGB-1) protein secretion in RAW264.7 cells.

Kim and others (1999) examined the naturally occurring flavonoids for NO production inhibition in LPS-activated RAW 264.7 cells and illustrated that flavonoid glycosides were not active regardless of the types of aglycones. Woo and coworkers (2012) isolated eight new flavonoid glycosides together with 12 known flavonoid derivatives from *Allium victorialis* leaves and evaluated their antineuroinflammatory effects by measuring the production of proinflammatory factor and NO in LPS-activated murine microglia BV-2 cells. The isolated known compounds were identified as kaempferol 7-*O*-β-D-glucopyranoside, 3-*O*-β-D-glucosyl-7-O-β-D-(2-*O*-feruloyl)glucosylkaempferol, kaempferol 3,7,4′-tri-*O*-β-D-glucopyranoside, 3-*O*-β-D-(2-O-feruloyl)glycosyl-7,4′-di-*O*-β-D-glucosylkaempferol, kaempferol 3-*O*-β-D-glucopyranoside, kaempferol 3-*O*-a-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside, kaempferol 3,4′-di-*O*-β-D-glucopyranoside, kaempferol 3,7-di-*O*-β-D-glucopyranoside, quercetin 3,4′-di-*O*-β-D-glucopyranoside, quercetin 3-*O*-β-D-glucopyranoside, quercetin 7,4′-di-*O*- β-D-glucopyranoside and kaempferol 3-*O*-(2″-(E)-p-coumaroylglucoside)-7-*O*-β-D-glucoside. Kaempferol 3-*O*-β-D-[2″-(E)-feruloylglucopyranosyl]-4′-*O*-β-D-glucopyranoside, kaempferol 3-*O*-β-D-[2″-(E)-feruloylglucopyranosyl]-7-*O*-β-D-glucopyranoside, kaempferol 3-*O*-β-D-glucosyl-7-*O*-β-D-(2-*O*-feruloyl)-glucoside, and quercetin 3-*O*-β-D-glucopyranoside exhibited strong inhibitory activities without any influence on cell viability. Quercetin glucopyranosides appear higher inhibition than kaepferol glucopyranosides.

Choi and others (2012) investigated the anti-inflammatory activity of quercetin and its glycosides (isoquercitrin, hyperin, and quercitrin) isolated from mampat (*Cratoxylum formosum*). The anti-inflammatory activity of quercetin appears higher than its glycosides in NO production, iNOS expression, and NF-κB activation. Cirsimaritin displayed higher inhibition activity against nitrite production in RAW264.7 macrophages induced by LPS than its mono- and diglucopyranosides, 4′-*O*-β-D-diglucopyranosyl cirsimaritin, 5-*O*-β-D-glucopyranosyl cirsimaritin and 5,4′-*O*-β-D-diglucopyranosyl cirsimaritin (Bai et al., 2011). The inhibition effects were determined as: cirsimaritin > cirsimaritin monoglucopyranosides > cirsimaritin diglucopyranosides.



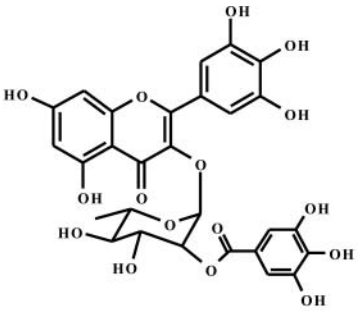
Cirsimaritin R_1=R_2=H

Cirsimarin R_1=-β-D-glucopyranosyl R_2=H

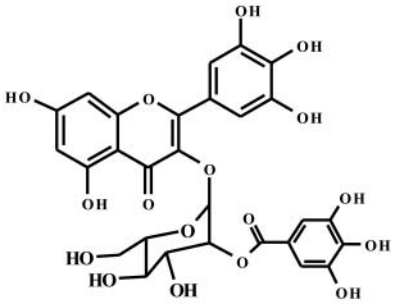
5-O-β-D-glucopyranosyl cirsimaritin R_1=H R_2=-β-D-glucopyranosyl

5, 4′-O-β-Ddiglucopyranosyl cirsimaritin R_1=R_2=-β-D-glucopyranosyl

Kim and others (2008) investigated the inhibition against NO production of kaempferol, kaempferol 3-*O*-α-L-rhamnopyranoside, kaempferol 3-*O*-β-D-(6-acetyl)-glucopyranosyl(1→4)-α-L-rhamnopyranoside, and kaempferol 3-*O*-β-D-glucopyranosyl(1→4)-α-L-rhamnopyranoside, quercetin 3-*O*-α-L-rhamnopyranoside extracted from the seeds of *Prunus tomentosa*. The 3-*O*-glycosylation of kaempferol weakened the inhibition activity on NO and prostaglandin E2 production in INF- γ and LPS-activated RAW 264.7 cells.



myricetin 3-*O*-(2″-*O*-galloyl)-α-L-rhamnopyranoside



myricetin 3-*O*-(2″-*O*-galloyl)-β-D-galactopyranoside

Kim and others (2013) isolated myricetin and its 3-*O*-glycosides (myricitrin, myricetin 3-*O*-(2″-*O*-galloyl)-α-L-rhamnopyranoside, and myricetin 3-*O*-(2″-*O*-galloyl)-β-D-galactopyranoside) from the leaves of *Myrica rubra* sieb. et zucc. Myricetin and its 3-*O*-glycosides significantly and dose-dependently inhibited LPS-stimulated NO production, pro-inflammatory cytokines, and iNOS and COX-2 levels in LPS-stimulated RAW 264.7 macrophages. 3-*O*-Glycosylation of myricetin enhanced the inhibition of pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6) and NO production. Specifically, the location of the galloyl group at the sugar moiety significantly improved the inhibition of pro-inflammatory cytokines. Kwon and others (2004) further examined the role of glycosidation of flavonoids (kaempferol, aromadendrin and quercetin) on the modulation of anti-inflammatory activity by determining the suppression of LPS-induced NO production in BV2 microglial cells. It illustrated that *O*-glycosidation of flavonoids aglycones significantly reduced the suppressive activity against LPS-induced NO production. However, some of flavonoid *C*-glycosides still maintained the inhibitory potential of LPS-induced NO production. Kaempferol 6-*C*-glucoside, taxifolin 6-*C*-glucoside, quercetin 6-*C*-glucoside and luteolin 8-*C*-glucoside showed similar inhibitory activity with their aglycones. Kaemferol 3,7-*O*-L-dirhamnoside, kaempferol 3-rhamnosyl(→2)-glucoside, kaempferol 3-*O*-L-(3-*O*-acetyl) rhamnosyl-7-*O*-L-rhamnoside, kaempferol 3-*O*-L-(4-O-acetyl) rhamnosyl-7-*O*-L-rhamnoside, kaempferol 3-*O*-D-glucosyl-7-*O*-L-rhamnoside, kaempferol 3-rhamnosyl(1→6)-glucoside, kaempferol 3-*O*-D-glucoside, kaempferol 3-rhamnosyl(1→3)-rhamnosyl(1→6)-glucoside appear no inhibitory activity.

Kaempferol glycosides (astragali, icatiin, robinin) and quercetin glycosides (clovin) showed a higher activity against arachidonic acid-induced edema than those for croton-oil induced edema (Lee et al., 1993). These glycosides may show anti-inflammatory activity, at least partly due to olclooxygenase/lipoxygenase inhibition. In general, kaempferol glycosides were found to show higher activity than quercetin glycosides. However, no clear structural-activity relationships depending on the positions or types of sugar substitution was found in the anti-inflammatory activity for flavonoid glycosides. It suggested that flavonoid glycosides (flavone and flavonol) showed anti-inflammatory activity by oral treatment, similar to flavonoid aglycones, or even higher. Recently, kaempferol 3-*O*-rutinoside and kaempferol 3-*O*-glucoside were found to prevent ischemic brain injury and neuroinflammation by inhibition of STAT3 and NF-kappa B activation in vivo (Yu et al., 2013a).

In summary, as for in cell levels (RAW 264.7 macrophages and murine microglia BV-2 cells), the *O*-glycosidation of flavonoid aglycones significantly reduced the inhibition against NO production, iNOS expression, and NF-κB activation. However, some of flavonoid *C*-glycosides still maintained the inhibitory potential of LPS-induced NO production. In vivo (oral treatment), flavonoid glycosides showed similar or even higher anti-inflammatory activity to their flavonoid aglycones.

7.2. Antibacterial and antifungal activities

Antibacterial and antifungal activities of phyto-flavonoids were evaluated against *C. albicans* and *Candida krusei* (Lourenço et al., 2013). These compounds after extraction were tested and showed high antimicrobial potential by the microdilution method. The antifungal activities of the compounds tested showed that these compounds presented similar minimal inhibitory concentrations against *C. albicans* compared to the control ketoconazole and fluconazole. The compounds also exhibited a higher degree of antifungal activity against *C. krusei* as compared with fluconazole (Lourenço et al., 2013).

Orhan and others (2010) investigated the antibacterial and antifungal activities of 5,7-dimethoxyflavanone 4′-*O*-β-D-glucopyranoside, 5,7-dimethoxyflavanone 4′-*O*-[2″-O-(5‴-O-trans-cinnamoyl)-β-D-apiofuranosyl]-β-D-glucopyranoside, rutin, 5,7,3′-trihydroxy-flavanone-4′-*O*-β-D-glucopyranoside, and naringenin 7-*O*-β-D-glucopyranoside isolated from *Galium fissurense Ehrend, Viscum album*, and *Cirsium hypoleucum*. All flavonoid glycodsides showed strong antimicrobial and antifungal activities against isolated strains of *P. aeruginosa, A. baumanni, S. aureus*, and *C. krusei*. Okoth and others (2013) isolated lanneaflavonol, dihydrolanneaflavonol, myricitrin and myricetin 3-*O*-α-arabinofuranoside (betmidin) from the roots of *Lannea alata*. Betmidin, with an arabinose moiety at the C-3 position, showed the best antibacterial activity

against Gram-positive bacteria. Nenaah (2013) investigated the antimicrobial activity of solvent extracts and isolated the 3-*O*-rutinosides of quercetin, kaempferol and isorhamnetin from *Calotropis procera* growing wild in Saudi Arabia. Quercetin 3-*O*-rutinoside showed higher activity than others. The Gram-positive bacteria (*Staphylococcus aureus* and *Bacillus subtilis*) were more susceptible than the Gram-negative (*Pseudomonas aeruginosa* and *Salmonella enteritidis*) and the yeast species were more susceptible than the filamentous fungi. Bello and others (2011) isolated quercetin 3-*O*-rutinoside from the aqueous extract of *Pavetta crassipes* leaves which showed antimicrobial activity against a wide array of microorganisms. Rigano and others (2007) isolated different flavonoids, including the 3-*O*-*β*-rutinosides of quercetin, kaempferol and isorhamnetin from the methanol extract of *Marrubium globosum*, as main constituents responsible for the antibacterial activity, where quercetin 3-*O*-*β*-rutinoside showed higher activity.

Kanwal and others (2009) isolated (−)-epicatechin 3-*O*-*β*-glucopyranoside and (−)-epicatechin from the leaves of mango (*Mangifera indica* L.). (−)-Epicatechin 3-*O*-*β*-glucopyranoside exhibited the very low antibacterial activity against *Lactobacillus* sp., *Escherichia coli, Azospirillium lipoferum* and *Bacillus* sp. However, (−)-epicatechin appears to have the greatest antibacterial activity and the different concentrations decreased the bacterial growth up to 45–99.9%. It illustrated that 3-*O*-glycosylation of (−)-epicatechin weakened the antibacterial activity.

Lee and others (2013b) isolated quercetin 3-*O*-(6″-galloyl)-*β*-D-glucopyranoside (tellimoside) from *Brasenia schreberi* and found that tellimoside showed higher inhibition against the growth of *M. aeruginosa.* Bernard and others (1997) isolated quercetin 3-*O*-*β*-D-glucose-[1,6]-*O*-*α*-L-rhamnoside (rutin), quercetin 3-*O*-*β*-D-galactose-[1,6]-*O*-*α*-L-rhamnoside, and quercetin 3-*O*-*β*-D-glucoside (isoquercitrin) as *Escherichia coli* topoisomerase IV inhibitors. The structure-activitiy relationship showed that quercetin and its disaccharide derivatives (rutin, quercetin 3-*O*-galactose-rhamnoside, quercetin 3-*O*-arabinose-glucoside exhibited similar inhibition against topoisomerase IV-dependent decatenation activity. However, quercetin monosaccharide derivatives (quercetin 3-*O*-rhamnoside, quercetin 3-*O*-glucoside, quercetin 3-*O*-galactoside, and quercetin 3-*O*-arabinoside) showed very weak effect on inhibitory activity (Bernard et al., 1997).

In summary, flavonoid glycosides (flavonol 3-*O*-glycosides) showed the strong antibacterial activity against Gram-positive bacteria, which were more susceptible than the Gram-negative. However, there are very few data on the influence of glycosylation of flavonoids on bacteria and fungi in vivo.

7.3. Antitumor activity

Quercetin presented a weak activity with selectivity for U251 (glioma, TGI = 31.4 μg/mL), MCF-7 (breast, TGI = 31.9 μg/mL), 786–0 (renal, TGI = 42.7 μg/mL) and NCI-ADR/RES (ovarian expressing multidrug resistance, TGI = 44.0 μg/mL) (de Araújo et al., 2013). While rutin did not inhibit cell proliferation of any of the cancer cell lines tested. Moreover, rutin hydrolyzed by hesperidinase displayed a moderate antiproliferative activity with selectivity for OVCAR-3 (ovarian, TGI = 1.5 μg/mL), MCF-7 (breast, TGI = 2.3 μg/mL) and U251 (glioma, TGI = 3.6 μg/mL) (de Araújo et al., 2013). Pick and others (2011) compared the inhibitory potential of apigenin and its glycosides on breast cancer resistance protein (BCRP). Apigenin significantly inhibited BCRP, however, apigenin 7-*O*-glucoside, vitexin-2″-*O*-rhamnoside, and vitexin 4′-rhamnoside hardly inhibited it. It illustrated that *C*/*O*-glycosylation of apigenin significantly weakened the inhibition in despite of the position. Moreover, 3-*O*-glycosylation of quercetin also diminishes its inhibition activity. Genistein remarkably inhibited the growth of estrogen receptor-negative human breast carcinoma cell lines MDA-468 and MCF-7 (Merlino et al., 1994). The effects of biochanin A and daidzein were less pronounced, while genistein and daidzein glycosides exhibited no noticeable activity. Moreover, apigenin appears much higher anti-proliferative activity on HeLa, HepG-2, and MCF-7 cells than apigenin 7-*O*-glucoside (Mamadalieva et al., 2011). Yu and others (2013a) used glycosidase to catalyze flavonoids in *Scutellaria baicalensis* to enhance the herb's anticancer activities. It was found that cellulase can remarkably transform baicalin and wogonoside to their aglycons (baicalein and wogonin). It was also observed that the higher the aglycone content, the stronger the antiproliferation effects. Cai and others (2012) investigated the synthesis and biological activities of diosmetin and its derivatives, 3′-*O*-methyldiosmetin, diosmetin 7-*O*-*β*-D-glucoside, diosmetin 7-*O*-*β*-Dgalactoside, 3′-*O*-methyldiosmetin 7-*O*-*β*-D-glucoside, 3′-*O*-methyldiosmetin-7-*O*-*β*-D-galactoside, diosmetin 7-*O*-*β*-D-acetylglucoside, diosmetin 7-*O*-*β*-D-acetylgalactoside, 3′-*O*-methyl-diosmetin 7-*O*-*β*-D-acetylglucoside, 3′-*O*-methyldiosmetin 7-*O*-*β*-D-galactoside, 7-*O*-isopentyldiosmetin, 7-*O*-prenyl-diosmetin and 7-*O*-farnesyl-3′-*O*-methyldiosmetin and the results showed that only 7-*O*-isopentyldiosmetin exhibited moderate cytotoxicity against SMMC-7721, MCF-7 and SW480 cancer cell lines. Diosmetin 7-*O*-*β*-D-acetylglucoside showed very weak inhibition and other diosmetin hardly innibited this cells. Yu and others (2013b) used glycosidase to catalyze flavonoids (baicalin and wogonoside) in *Scutellaria baicalensis* to enhance the herb's anticancer activity. It illustrated that the higher the aglycone content, the stronger the antiproliferation effects. In summary, flavonoid aglycones showed higher anticancer potential than their glycosides in cell level.

However, Fawzy and others (2012) isolated luteolin 7-*O*-*β*-D-glucopyranoside, luteolin 6-*C*-*β*-D-galactopyranoside and luteolin from *Horwoodia dicksoniae*. The antitumor activity on human cell lines (HEP-G2, HCT-116 and MCF-7) was determined as: luteolin 7-*O*-*β*-D-glucopyranoside > luteolin> luteolin 6-*C*-*β*-D-galactopyranoside.

7.4. Anti-cholinesterase activity

Since the AChE inhibitors became an important therapeutic strategy in Alzheimer's disease (AD) many efforts have been made in the search of new molecules with anti-AChE activity. Naturally occurring compounds from plants are considered a potential source of new inhibitors (Xiao et al., 2008; Xiao and Shao, 2013; Xiao and Tundis, 2013). Although almost all the natural AChE inhibitors are alkaloids, some flavonoids also play an important role in preventing and managing AD. It

appears that the structural elements important for AChE inhibition are not only the 4′-methoxyl group, but also the 7-*O*-substituted sugar and the pattern of substitution on the B-ring (Fan et al., 2008).

Jung and Park (2007) isolated tiliroside, quercitrin and quercetin as AChE inhibitors from *Agrimonia pilosa* ledeb. These compounds inhibited AChE activity in a dose dependent manner and the IC_{50} values of tiliroside, quercitrin and quercetin were determined to be 23.5, 66.9 and 19.8 μM, respectively. Ding and others (2013) isolated quercetin and its glycosides, namely, quercetin 3-*O*-α-L-rhamnopyranoside, quercetin 3-*O*-α-D-glucopyranoside, quercetin 3-*O*-β-D-glucopyranoside, quercetin 3-*O*-α-L-rhamnopyranosyl-(1→2)-β-D-glucopyranoside, quercetin 3-*O*-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside, and quercetin 3-*O*-α-L-rhamnopyranosyl-(1→4)-*O*-α-L-rhamnopyranosyl-(1→2)-β-D-glucopyranoside, from the leaves of *Ginkgo biloba* and investigated their inhibition against AChE. These 13 isolated flavonoids were found to dose dependently inhibit AChE. 3-*O*-glycosylation of quercetin obviously improved the inhibition against AchE. Moreover, kaempferol 3-*O*-α-L-rhamnopyranosyl-(1→4)-*O*-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside also showed higher inhibition against AchE than that of kaempferol.

Mussadiq and others (2013) isolated kaempferol 3-*O*-β-D-[4‴-E-p-coumaroyl-α-l-rhamnosyl(16)]-galactoside (1), kaempferol 3-*O*-β-D-[4‴-E-p-coumaroyl-α-l-rhamnosyl (16)]-(3-E-p-coumaroyl)galactoside (2), and kaempferol 3-*O*-β-D-[4‴-E-p-coumaroyl-α-l-rhamnosyl(16)]-(4-E-p-coumaroyl)galactoside (3) from the ethyl acetate-soluble fraction of the methanolic extract of the flowers of *Aerva javanica*. Compound 1 showed weak inhibitory activity against enzymes, such as AChE, butyrylcholinesterase, and lipoxygenase with IC_{50} values 205.1, 304.1, and 212.3 μM, respectively, whereas compounds 2 and 3 showed weakly inhibition against AChE.

Luteolin showed stronger inhibition activity against AChE, butyrylcholinesterase (BChE), and β-site amyloid precursor cleaving enzyme 1 (BACE1) than its *C*-glycosides, orientin and isoorientin (Choi et al., 2014b).

In summary (Table 2), 3-*O*-glycosylation of flavonols (quercetin and kaempferol) improves the inhibition against AChE. However, all flavonoid aglycones and glycosides show weak inhibition potential against AChE.

7.5. Inhibition of tyrosinase

Tyrosinase catalyzes the hydroxylation of monophenols to *o*-diphenols and the oxidation of *o*-diphenols to *o*-quinones. Tyrosinase inhibitors have been used to treat melanin hyperpigmentation and as cosmetic materials for whitening after sunburn. Arung and others (2011) isolated quercetin 4′-*O*-β-D-glucopyranoside from the dried skin of red onion, which showed tyrosinase inhibition using L-tyrosine or L-DOPA as a substrate with IC_{50} values of 4.3 and 52.7 μM. Fujiwara and others (2011) isolated apigenin, (+)-2,3-trans-dihydrokaempferol, (+)-2,3-trans-dihydrokaempferol 3-*O*-α-L-rhamnoside, (+)-4′,7-dimethoxy-2,3-trans-dihydroquercetin, (+)-2,3-trans-dihydroquercetin, and (−)-2,3-trans-dihydroquercetin 3-*O*-α-L-rhamnoside from the bark of *Peltophorum dasyrachis* (yellow batai). (+)-2,3-trans-dihydrokaempferol and (+)-2,3-trans-dihydroquercetin showed potent inhibition against tyrosinase activity towards L-DOPA as the substrate. Vitexin and isovitexin showed high tyrosinase inhibitory activitie with IC_{50} values of 6.3 and 5.6 mg/mL, respectively (Yao et al., 2012). Kim and others (2012) synthesized astragalin (kaempferol 3-*O*-β-D-glucopyranoside) glucosides with a dextransucrase produced by *Leuconostoc mesenteroides*. Woo and others (2012b) synthesized and characterized ampelopsin 4′-*O*-α-D-glucopyranoside using this dextransucrase from *Leuconostoc mesenteroides*. It suggested the glucosylation of ampelopsin increased water solubility and enhanced bioactivities. Ampelopsin 4′-*O*-α-D-glucopyranoside showed competitive inhibition against tyrosinase with a K_i value of 40.16 μM and was stronger than that of arbutin, which is a commercial active ingredient in whitening cosmetics (Woo et al. 2012b). Astragalin glucosides were identified as kaempferol 3-*O*-β-D-glucopyranosyl-(1→3)-*O*-α-D-glucopyranoside and kaempferol 3-*O*-α-D-glucopyranosyl-(1→6)-*O*-β-D-glucopyranoside for one glucose transferred, and kaempferol 3-*O*-β-D-isomaltooligosacharide (Ast-IMO or Ast-Gn, n = 2–8). The astragalin glucosides showed 8.3–60.6% higher inhibition against the expression of matrix metalloproteinase-1 and 3.8–18.8% increased inhibition against melanin synthesis depending on the number of glucosyl residues linked to astragalin. These novel compounds could be used to in the cosmetics industry. Nugroho et al. (2009) isolated two new flavonol glycosides, kaempferol 3-*O*-[β-D-glucopyranosyl-(1→4)][α-L-rhamnopyranosyl-(1→6)]-β-D-glucopyranoside and quercetin 3-*O*-[β-D-glucopyranosyl-(1→4)][α-L-rhamnopyranosyl-(1→6)]-β-D-glucopyranoside, from the aerial parts of *Lamium amplexicaule*. These flavonol glycosides showed high tyrosinase inhibitory activities. The hot water extract of immature calamondin peel contained a large quantity of 3′,5′-di-*C*-β-glucopyranosyl phloretin, which demonstrated good tyrosinase inhibitory activity in the competitive mode (Lou et al. 2012). The 3-*O*-deglycosylation of phlorizin to phloretin will lead to better inhibitory effect on dihydroxyphenolase activity of mushroom tyrosinase (Zhang et al. 2012). In summary (Table 2), flavonoids glycosides displayed significant inhibitory potential against tyrosinase. However, the impact of glycosylation of flavonoids on tyrosinase inhibition was rarely reported.

7.6. Anticoagulant and antiplatelet activity

Blood coagulation involves the conversion of fluid blood to a solid gel or a clot, and clot formation contributes to hemostasis. Formation of fibrin filaments in combination with adhesion and activation of platelets leads to formation of a haemostatic plug, which blocks damaged blood vessel walls. Thrombin plays an important role in thrombotic processes and is also an activator of inflammation and an inhibitor of fibrinolysis (Furie and Furie, 2005). Blood platelets are implicated in the haemostatic process and also in thrombus formation, which is one of the important contributors to pathogenesis of circulatory diseases and inflammation. Ku and others (2013) investigated the potential anticoagulant activities of isorhamnetin 3-*O*-galactoside and hyperoside from *Oenanthe javanica*. The anticoagulant activities were investigated by measuring

Table 2. Effect of the glycosylation of flavonoids on their biological benefits.

Biological benefits	Flavonoids	Glycosylation		Impact	Ref.
		Type	Local		
Antineuroinflammation	Kaempferol 7-O-β-D-glucopyranoside, 3-O-β-D-glucosyl-7-O-β-D-(2-O-feruloyl) glucosylkaempferol, kaempferol 3,7,4′-tri-O-β-D-glucopyranoside, 3-O-β-D-(2-O-feruloyl) glycosyl-7,4′-di-O-β-D-glucosylkaempferol, kaempferol 3-O-β-D-glucopyranoside, kaempferol 3-O-a-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside, kaempferol 3,4′-di-O-β-D-glucopyranoside, kaempferol 3,7-di-O-β-D-glucopyranoside, kaempferol 3-O-(2′′-(E)-p-coumaroylglucoside)-7-O-β-D-glucoside, kaempferol 3-O-β-D-[2′′-(E)-feruloylglucopyranosyl]-4′-O-β-D-glucopyranoside, kaempferol 3-O-β-D-[2′′-(E)-feruloylglucopyranosyl]-7-O-β-D-glucopyranoside, kaempferol 3-O-β-D-glucosyl-7-O-β-D-(2-O-feruloyl)-glucoside	O-	3,7,4′	↓	Woo et al. (2012a)
	Quercetin 3,4′-di-O-β-D-glucopyranoside, quercetin 7,4′-di-O-β-D-glucopyranoside, quercetin 3-O-β-D-glucopyranoside	O-	3,7,4′	↑	Woo et al. (2012a)
Protection against glucose-mediated protein damage	Isoquercitrin, hyperin	O-	3	↑	Kim et al. (2011b)
Inhibition of lipid accumulation	Kaempferol 3-O-Glc-(1→3)-Rha-(1→6)-Glc kaempferol 3-O-Glc-(1→3)-Rha-(1→6)-Gal	O-	3	↑	Morikawa et al. (2013)
Cardioprotective effects	Quercetin-3-O- β-D-glucopyranoside, avicularin	O-	3	↓	Wang et al. (2013)
Inhibition of AChE, BChE, BACE1	Orientin, isoorientin	C-		↓	Choi et al. (2014a)
AChE inhibitors	Quercitrin	O-	3	↓	Jung and Park (2007)
	Quercetin 3-*O*-α-L-rhamnopyranoside, quercetin 3-*O*-α-D-glucopyranoside, quercetin 3-*O*-β-D-glucopyranoside, quercetin 3-*O*-α-L-rhamnopyranosyl-(1→2)-β-D-glucopyranoside, quercetin 3-*O*-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside	O-	3	↑	Ding et al. (2013)
	quercetin 3-*O*-α-L-rhamnopyranosyl-(1→4)-*O*-α-L-rhamnopyranosyl-(1→2)-β-D-glucopyranoside	O-	3	↓	Ding et al. (2013)
Inhibition of NO production	orientin, isoorientin	C-		↓	Choi et al. (2014a)
Regulation of GABAC receptor channel activity	Rutin, quercetin-3-O-rhamnoside	O-	3	↔	Kim et al. (2014)
	Quercetin-3-(2G-rhamnosylrutinoside)	O-	3	↓	Kim et al. (2014)
Anticancer (living vertebrates)	Quercetin 3-*O*-glucoside	O-	3	↔	Park et al. (2014)
	Quercetin 3-*O*-galactoside, quercetin 3-*O*-rhamnoside, quercetin 4′-*O*-glucoside	O-	3,4′	↓	Park et al. (2014)
Anticancer (HT-29)	Xanthohumol 4′-*O*-β-D-glucopyranoside, xanthohumol 4′-O-β-D-(4′′′-*O*-methyl)-glucopyranoside	O-	4′	↑	Tronina et al. (2013)
	Isorhamnetin diglycosides	O-	4′	↑	Antunes-Ricardo et al. (2014)
Anticancer (U251, MCF-7, 786–0, NCI-ADR/RES)	Rutin	O-	3	↓	de Araújo et al. (2013)
Anticancer (Hep-G2, HCT-116, MCF-7)	Luteolin 7-*O*-β-D-glucopyranoside	O-	3	↑	Fawzy et al. (2012)
	Luteolin 6-*C*-β-D-galactopyranoside	C-	6	↓	Fawzy et al. (2012)
Anticancer (HeLa, HepG-2, MCF-7)	Apigenin 7-*O*-glucoside	O-	7	↓	Mamadalieva et al. (2011)
Anticancer (COLO 205)	5-*O*-β-D-glucopyranosyl cirsimaritin, 4′-*O*-β-D-diglucopyranosyl cirsimaritin	O-	5/4′	↓	Bai et al. (2011)
	5,4′-*O*-β-D-diglucopyranosyl cirsimaritin	O-	5, 4′	↑	Bai et al. (2011)
Anticancer (BCRP)	Apigenin 7-*O*-glucose	O-	7	↓	Pick et al. (2011)
	Vitexin-2′′-*O*-rhamnoside, and vitexin 4′-rhamnoside	C-	8	↓	Pick et al. (2011)
Anticoagulant and antiplatelet activity	Irisolidone, sophorabioside, genistin, quercitrin, and rutin	O-	3	↓	Kim and Yun-Choi (2008)
	Quercetin 4′-*O*-glucoside	O-	4′	↓	Furusawa et al. (2003)
	Rutin, apigenin 7-*O*-glucoside	O-	3	↓	Guerrero et al. (2005)
Anti-Mayaro virus activity	Guaijaverin, isoquercitrin, hyperin	O-	3	↓	dos Santos et al. (2014)
Radioprotective activity	Quercetin 3-*O*-rhamnoside-7-*O*-glucoside, quercetin 3-*O*-rhamnoside	O-	3	↑	Materska et al. (2015)
Antibacterial and antifungal activity	Tellimoside	O-	3	↑	Lee et al. (2013b)
	3,3′-di-*O*-methylquercetin 7-*O*-β-D-glucopyranoside	O-	7	↓	Wang et al. (2012b)
	Isorhamentin 3-*O*-β-D-rutinoside	O-	3	↓	Wang et al. (2012b)
	(−)-epicatechin 3-*O*-β-glucopyranoside	O-	3	↓	Kanwal et al. (2009)
	Myricitrin, myricetin 3-*O*-α-arabinofuranoside	O-	3	↑	Okoth et al. (2013)
		O-	3	↑	Bernard et al. (1997)

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Table 2. (Continued).

Biological benefits	Flavonoids	Glycosylation			Ref.
		Type	Local	Impact	
	Quercetin 3-*O*-β-D-glucose-[1,6]-*O*-α-L-rhamnose quercetin 3-*O*-galactose-rhamnoside, quercetin 3-*O*-arabinose-glucoside				
	Quercetin 3-*O*-rhamnoside, quercetin 3-*O*-glucoside, quercetin 3-*O*-galactoside, and quercetin 3-*O*-arabinoside	O-	3	↓	Bernard et al. (1997)
	Quercetin 3-*O*-rutinoside	O-	3	↓	Nenaah (2013)
	3,3′-di-*O*-methylquercetin 7-*O*-β-D-glucopyranoside	O-	7	↓	Wang et al. (2012b)
	Isorhamentin 3-*O*-β-D-rutinoside	O-	3	↓	Wang et al. (2012b)
Anti-influenza viral activity	Linocinamarin, nicotiflorin, rutin, rhodiolinin, rhodionin, rhodiosin	O-	3,7,8	↓	Jeong et al. (2009)
Inhibition of protein tyrosine phosphatase 1B	Hyperoside	O-	3	↓	Islam et al. (2013)
Antitubercular activity	Apigenin 7-*O*-glucoside, rutin, kaempferol 3-*O*-rhamnoside	O-	3,7	↓	Yadav et al. (2013)
Antiallergic activity	Hesperetin 7-*O*-glucoside Hesperetin 7-*O*-maltoside	O-	7	↑	Shimoda and Hamada (2010)
Inhibition of Na^+/K^+-adenosine triphosphatase	Kaempferol 3-*O*-α-L-(3″-*Z*,4″-*E*-di-*p*-coumaroyl)-rhamnopyranoside, kaempferol 3-*O*-α-L-(3″,4″-di-*Z*-*p*-coumaroyl)-rhamnopyranoside, kaempferol 3-*O*-α-L-(3″,4″-di-*E*-*p*-coumaroyl)-rhamnopyranoside, kaempferol 3-*O*-α-L-(2″-*E*,4″-*Z*-di-*p*-coumaroyl)-rhamnopyranoside, kaempferol 3-*O*-α-L-(2″,4″-di-*E*-*p*-coumaroyl)-rhamnopyranoside, kaempferol 3-*O*-α-L-(2″-*Z*,4″-*E*-di-*p*-coumaroyl)-rhamnopyranoside	O-	3	↑	Lee et al. (2012)
Antileishmanial activity	Kaempferol 3-*O*-(2″,3″-di-*O*-galloyl)-β-D-glucopyranoside, kaempferol 3-*O*-β-D-glucopyranoside, quercetin 3-*O*-β-D-glucopyranoside, quercetin 3-*O*-β-D-galactopyranoside, kaempferol 3-*O*-(2″-*O*-galloyl)-β-D-glucopyranoside, quercetin 3-*O*-(2″-*O*-galloyl)-β-D-glucopyranoside, quercetin 3-*O*-(2″,3″-di-*O*-galloyl)-β-D-glucopyranoside	O-	3	↓	Ercil et al. (2005)
	Apigenin 5-*O*-glucoside, apigenin 7-*O*-glucoside, luteolin 5-*O*-glucoside, luteolin 7-*O*-glucoside	O-	5,7	↔	Tasdemir et al. (2006)
	Apigenin 8-*C*-glucoside	C-	8	↓	Tasdemir et al. (2006)
Inhibition angiotensin converting enzyme	Rohoifolin	O-	7	↑	Guerrero et al. (2012)
	Rutin	O-	3	↑	Guerrero et al. (2012)
	Diosmin, hesperidin	C-	7	↓	Guerrero et al. (2012)
Anti-HIV activity	3-*O*-β-arabinopyranosyl-(+)-taxifolin, 3-*O*-β-xylopyranosyl-(+) taxifolin	O-	3	↓	Shahat et al. (1998)
	(2R)- and (2S)-5-*O*-β-D-glucopyranosyl-7,4′-dihydroxy-3′,5′-dimethoxyflavanone	O-	3	↓	Tewtrakul et al. (2002)
	Quercetin 3-*O*-β-D-glucuronide, quercetin 3-*O*-β-D-xylopyranosyl-(1→2)-β-D-galactopyranoside	O-	3	↑	Kashiwada et al. (2005)
	Rutin, isoquecitrin, hyperin	O-	3	↔	Kashiwada et al. (2005)
	Luteolin 7-*O*-β-D-glucopyranoside	O-	7	↑	Olivero-Verbel and Pacheco-Londoño (2002)
	Myricetin 3-*O*-β-glucuronide, myricetin 3-*O*-α-rhamnoside	O-	3	↑	Wang et al. (2012c)
	kaempferol 3-*O*-rutinoside, quercetin 3-*O*-rutinoside, kaempferol 3-*O*-robinobioside	O-	3	↑	Yarmolinsky et al. (2012)
	Quercetin 3-*O*-[(6-*O*-feruloyl)-β-D-glucopyranosyl-(1→2)-β-D-galactopyranoside], quercetin 3-*O*-[(6-*O*-sinapoyl)-β-D-glucopyranosyl-(1→2)-β-D-galactopyranoside], kaempferol 3-O-[(6-O-sinapoyl)-β-D-glucopyranosyl-(1→2)-β-D-galactopyranoside], kaempferol 3-*O*-[(6-*O*-feruloyl)-β-D-glucopyranosyl-(1→2)-β-D-galactopyranoside], kaempferol 3-*O*-{β-D-glucopyranosyl-(1→2)-[α-L-rhamonopyranosyl-(1→6)]-β-D-galactopyranoside}	O-	3	↑	Tewtrakul et al. (2002)
	Myricetin 3-*O*-β-glucuronide, myricetin 3-*O*-α-rhamnoside	O-	3	↑	Rashed et al. (2012)
	Kaempferol 3-*O*-rutinoside, quercetin 3-*O*-rutinoside, kaempferol 3-*O*-robinobioside	O-	3	↑	Yarmolinsky et al. (2012)
Anti-inflammatory activity	5-*O*-β-D-glucopyranosyl cirsimaritin, 5,4′-*O*-β-D-diglucopyranosyl cirsimaritin, 4′-*O*-β-D-diglucopyranosyl cirsimaritin	O-	5, 4′	↓	Bai et al. (2011)
	Kaemferol 3,7-*O*-L-dirhamnoside, kaempferol 3-*O*-rhamnosyl(→2)-glucoside, kaempferol 3-*O*-L-(3-*O*-	O-	3, 7	↓	Kwon et al. (2004)

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Table 2. (Continued).

Biological benefits	Flavonoids	Glycosylation		Impact	Ref.
		Type	Local		
	acetyl)rhamnosyl-7-*O*-L-rhamnoside, kaempferol 3-*O*-L-(4-O-acetyl)rhamnosyl-7-*O*-L-rhamnoside, kaempferol 3-*O*-D-glucosyl-7-*O*-L-rhamnoside, kaempferol 3-*O*-rhamnosyl(1→6)-glucoside, kaempferol 3-*O*-D-glucoside, kaempferol 3-*O*-rhamnosyl(1→3)-rhamnosyl(1→6)-glucoside				
	Kaempferol 6-*C*-glucoside, taxifolin 6-*C*-glucoside, quercetin 6-*C*-glucoside, luteolin 8-*C*-glucoside	C-	6, 8	↔	Kwon et al. (2004)
	Isoquercitrin, hyperin, quercitrin	O-	3	↓	Choi et al. (2012)
	Kaempferol 3-*O*-α-L-rhamnopyranoside, kaempferol 3-*O*-β-D-(6-acetyl)-glucopyranosyl(1→4)-α-L-rhamnopyranoside, kaempferol 3-*O*-β-D-glucopyranosyl(1→4)-α-L-rhamnopyranoside	O-	3	↓	Kim et al. (2008)
	Myricitrin, myricetin 3-*O*-(2′′-*O*-galloyl)-α-L-rhamnopyranoside, and myricetin 3-*O*-(2′′-*O*-galloyl)-β-D-galactopyranoside	O-	3	↑	Kim et al. (2013)
	Hyperoside, quercitrin, quercetin 3-*O*-β-D-glucopyranoside-(3′→O-3′′′)-quercetin-3-*O*-β-D-galactopyranoside	O-	3	↓	Mao et al. (2011)
Inhibition of tyrosinase	(+)-2,3-trans-dihydrokaempferol 3-*O*-α-L-rhamnoside, (−)-2,3-trans-dihydroquercetin 3-*O*-α-L-rhamnoside	O-	3	↓	Fujiwara et al. (2011)
	Ampelopsin 4′-*O*-α-D-glucopyranoside	O-	4′	↑	Woo et al. (2012a)
	Kaempferol 3-*O*-β-D-glucopyranosyl-(1→3)-*O*-α-D-glucopyranoside, kaempferol 3-*O*-α-D-glucopyranosyl-(1→6)-*O*-β-D-glucopyranoside, kaempferol 3-*O*-β-D-isomaltooligosacharide (Ast-IMO or Ast-Gn, n = 2–8)	O-	3	↑	Woo et al. (2012a)
Antirotavirus activity	Hesperidin, neohesperidin, naringin, pocirenin	O-	7	↑	Bae et al. (2000)
	Diosmin, rutin	O-	3	↑	Bae et al. (2000)
Antidegranulating activity	Hesperidin, narirutin	O-	7	↓	Murata et al. (2013)

activated partial thromboplastin time (aPTT) and prothrombin time (PT). The anticoagulant and profibrinolytic effects of of isorhamnetin 3-*O*-galactoside were greater than those of hyperoside, indicating positive regulation of its anticoagulant function by the methoxy group of isorhamnetin 3-*O*-galactoside (Ku et al., 2013). Kim and Yun-Choi (2008) isolated 4 flavonoid aglycones and six flavonoid glycosides, namely biochanin A, irisolidone, genistein, sophorabioside, genistin, apigenin, quercitrin, and rutin from *Sophora japonica*. All flavonoid aglycones showed much greater inhibitory effects on arachidonic acid and U46619 induced platelet aggregation than those of flavonoid glycosides. Furusawa and others (2003) isolated quercetin dimers, quercetin, and quercetin 4′-*O*-glucoside from brownish scale of onion. Quercetin 4′-*O*-glucoside appears to have a highest inhibition on collagen-induced and ADP-induced platelet aggregation in increasing order of intensity. However, quercetin, but not rutin inhibit human platelet aggregation (Guerrero et al., 2005). Apigenin 7-*O*-glucoside showed significantly weaker inhibition on platelet aggregation than that of apigenin. It illustrated that *O*-glycosylation of flavonoids reduced their antiplatelet activity (Table 2).

7.7. Immunomodulatory function

The saturated groups of *C*-4′ methoxyl and *C*-5 hydroxyl of flavonoids seem to be necessary groups for the immunomodulatory activity, and flavonol glycosides exhibit very weak activity. Quercetin 3-*O*-β-D-rutinoside, myricetin 3-*O*-β-D-galactopyranoside, quercetin 3-*O*-β-D-galactopyranoside and quercetin 3-*O*-β-D-glucopyranoside from *Euphorbia microsciadia* Bioss showed weak inhibitory activity with dose-dependent suppression of lymphocyte proliferation (Ghanadian et al., 2012). Kaempferol 3-*O*-rutinoside-4′-*O*-glucoside and kaempferol 3-(2^G-rhamnosylrutinoside) from *Agave sisalana* do not show any immunomodulatory activity (Chen et al., 2009). Quercetin 3-*O*-rutinoside, kaempherol 3-*O*-rutinoside, and isorhamnetin 3-*O*-glucoside isolated from the aerial parts of *Urtica dioica* showed high intracellular killing activity (Akbay et al., 2003). It looks like that flavonol glycosides exhibit very weak immunomodulatory activity.

7.8. Antitubercular activity

Tuberculosis, an infectious killer disease, is the leading cause of death worldwide from a single human pathogen. Many flavonoids have been identified to possess antitubercular activity (Lin et al., 2002; Gu et al., 2004; Yenjai et al., 2004). According to the structure–activity relationships (Sivakumar et al., 2007; Yadav et al., 2013), the *O*-glycosylation of flavonoids at any of the di- or trihydroxyl substitutions of flavonoids inactivates their antitubercular potential. Apigenin 7-*O*-glucoside, kaempferol 3-*O*-rhamnopyranoside, hesperidin, and rutin are inactive.

7.9. Anti-allergic activity

The structure-activity relationships of flavonoids as inhibitors for IL-4 production illustrated that luteolin, ayanin, apigenin and fisetin were the strongest inhibitors with an IC_{50} value of 2–5 μM (Kawai et al., 2007). Shimoda and Hamada (2010) found that hesperetin 7-*O*-glucoside and 7-*O*-maltoside

showed higher inhibitory effects on IgE antibody production and on O_2-generation from rat neutrophils than those of hesperetin. Makino and others (2013) reported the anti-allergic activity of quercetin, quercetin 3-*O*-glucoside, α-oligoglucosyl rutin and enzymatically modified isoquercitrin (α-oligoglucosyl isoquercitrin, EMIQ) in the murine ear passive cutaneous anaphylaxis (PCA) reaction using ovalbumin as an antigen. α-Oligoglucosyl isoquercitrin showed a significant high inhibition against the PCA reaction. Oral treatments of quercetin and α-oligoglucosyl rutin exhibited no anti-allergic effect, and isoquercitrin showed less effect than that of α-oligoglucosyl isoquercitrin. It looks like *O*-glycosylation of flavonoids increased the anti-allergic potential in vivo.

7.10. Inhibition of aldehyde oxidase

Aldehyde oxidase is a member of the molybdo-flavoenzymes family of enzymes which are involved in biotransformation of some exogenous and endogenous chemicals. Aldehyde oxidase is responsible for metabolism of some therapeutic agents. Quantitative structure-activity relationship studies revealed the glycosylated flavonoids showed relatively weaker inhibition against aldehyde oxidase (Hamzeh-Mivehroud et al., 2003)

7.11. Antileishmanial activity

The leishmaniases are a complex of diseases caused by the protozoan parasite Leishmania and are a major public health problem in many developing countries. Flavonoid glycosides with antileishmanial activity have been reported. Muzitano and others (2006) isolated kaempferol 3-*O*-α-L-arabinopyranosyl (1→2)-α-Lrhamnopyranoside and quercetin 3-*O*-α-L-arabinopyranosyl (1→2)-α-L-rhamnopyranoside from *Kalanchoe pinnata*. It suggested that the quercetin aglycone-type structure, as well as a rhamnosyl unit linked at the C-3 postion, seem to be important for antileishmanial activity. Ercil et al. (2005) islated kaempferol 3-*O*-(2″,3″-di-*O*-galloyl)-β-D-glucopyranoside, kaempferol 3-*O*-β-D-glucopyranoside, quercetin 3-*O*-β-D-glucopyranoside, quercetin 3-*O*-β-D-galactopyranoside, kaempferol 3-*O*-(2″-*O*-galloyl)-β-D-glucopyranoside, quercetin 3-*O*-(2″-*O*-galloyl)-β-D-glucopyranoside and quercetin 3-*O*-(2″,3″-di-*O*-galloyl)-β-D-glucopyranoside from the aerial parts of *Geranium pyrenaicum* Burm. All these flavonol glycosides reduced the intracellular survival of *Leishmania* amastigotes within RAW 264.7 cells. The presence of galloyl groups in quercetin glycosides will dramatically weaken the antileishmanial potential of quercetin. The apigenin and luteolin 5 or 7-O-glucosides showed similar inhibition against *Leishmania donovani* with its aglycones (Tasdemir et al., 2006). However, apigenin 8-*C*-glucoside (IC_{50}> 30 μM) showed much weaker inhibition than apigenin (IC_{50} = 1.9 μM). In summary, most flavonoids glycosides appear to have similar inhibition with their aglycones and 3-*O*-glycosylation of kaempferol and quercetin significantly reduced the inhibitory potential.

7.12. Antitrypanosomal activity

Trypanosomiasis in Africa is also known as sleeping sickness, which is caused by *Trypanosoma brucei rhodesiense* and *T. brucei gambiense*, and is a major cause of mortality and morbidity in sub-Saharan Africa (Tasdemir et al., 2006). It illustrated that *O* or *C*-glycosylation of flavonoids (apigenin, luteolin, kaempferol and quercetin) decreased the inhibition against *T. brucei rhodesiense* and *T. brucei gambiense* (Tasdemir et al., 2006).

7.13. Against protein-energy malnutrition in chronic kidney disease

Hsieh and others (2013) compared the effects of rutin and quercetin on chronic kidney disease induced by doxorubicin in rats. Quercetin and rutin showed different action for doxorubicin induced chronic kidney disease, and rutin was inferior to quercetin with respect to treatment.

7.14. Antidegranulating activity

Murata and others (2013) evaluated the antidegranulating activity of citrus flavonoids in vivo. Hesperetin and naringenin, which are aglycones of hesperidin and narirutin, showed significant stronger antidegranulating activity.

7.15. Antistress activity

Kaempferol 4′-*O*-β-D-glucopyranosyl-(1→2)-α-L-rhamnopyranosyl-(1→6)-β-D- glucopyranoside and its mono and di-*O*-methyl derivatives, kaempferol 4′-*O*-β-D- glucopyranosyl-(1→2)-β-D-glucopyranoside, kaempferol 4′-*O*-α-L-rhamnopyranosyl- (1→6)-β-D-glucopyranoside, kaempferol 3,7-di-*O*-β-D-glucopyranoside, kaempferol 3-*O*-β-D-glucopyranosyl-(1→6)-β-D-glucopyranoside, kaempferol 3-*O*-β-D- glucopyranosyl-7-O-α-L-rhamnopyranoside were isolated and identified from *Evolvulus alsinoides* (Linn) (Gupta et al., 2013). The antistress activity in male Sprague-Dawley rats showed that kaempferol 4′-*O*-β-D-glucopyranosyl-(1→2)-α-L- rhamnopyranosyl-(1→6)-β-D-glucopyranoside and its mono *O*-methyl derivative displayed antistress activity by normalizing hyperglycemia, plasma corticosterone, plasma creatine kinase, and adrenal hypertrophy. Flavonoids (mixture of rutin, orientin, isoorientin, vitexin, and isovitexin) induced increasing corticosterone, glutamic- oxaloacetic transaminase activity, and the amount of thiobarbituric acid-reactive substances in plasma and liver tissues in restrained mice (Watanabe and Ayugase, 2008).

7.16. Radioprotective activity

Materska and others (2015) isolated quercetin 3-*O*-rhamnoside-7-*O*-glucoside and quercetin 3-*O*-rhamnoside from pepper fruits *Capsicum annuum* L. and compared their radioprotective activity on human cell lymphocytes in response to oxidative damage induced by X radiation. It was found that quercetin glycosides showed higher radioprotective activity than that of quercetin.

7.17. Inhibition of Na^+/K^+-adenosine triphosphatase

Lee and others (2012) isolated several acylated kaempferol glycosides from *Laurus nobilis* leaves and invesitigated their

inhibition against Na^+/K^+-adenosine triphosphatase. Kaempferol 3-*O*-α-L-(3″-*Z*,4″-*E*-di-*p*-coumaroyl)-rhamnopyranoside, kaempferol 3-*O*-α-L-(3″,4″-di-*Z*-*p*-coumaroyl)-rhamnopyranoside, kaempferol 3-*O*-α-L-(3″,4″-di-*E*-*p*-coumaroyl)-rhamnopyranoside, kaempferol 3-*O*-α-L-(2″-*E*,4″-*Z*-di-*p*-coumaroyl)-rhamnopyranoside, kaempferol 3-*O*-α-L-(2″,4″-di-*E*-*p*-coumaroyl)-rhamnopyrano side, and kaempferol 3-*O*-α-L-(2″-*Z*,4″-*E*-di-*p*-coumaroyl)-rhamnopyranoside showed much higher inhibitory activitity against Na^+/K^+-adenosine triphosphatase than that of kaempferol. It looks like that the 3-*O*-glycosylation of kaempferol significantly improved the inhibition of Na^+/K^+-adenosine triphosphatase.

7.18. Inhibition of angiotensin converting enzyme

Guerrero and cooworkers (2012) the invesitagated structure-activity relationship of flavonoids as angiotensin converting enzyme (ACE) inhibitors. Rohoifolin and rutin showed higher inhibition against ACE activity than their alycones, apigenin and quercetin. However, diosmin and hesperidin exhibited very lower inhibition against ACE activity than their alycones, hesperetin and diosmetin.

7.19. Protection against methylmercury-induced mitochondrial dysfunction

Franco and others (2010) described the structure–activity relationship of flavonoids in preventing methylmercury-induced mitochondrial dysfunction and it indicated that the protective potencies of the flavonoids against MeHg-induced mitotoxicity were myricetin >myricitrin > rutin.

8. Influence of the glycosylation of flavonoids on their stability and solubility

Even though the effect of glycosylation on the stability of flavonoids has been discussed previously, there is limited information on the stability of flavonoid *O*-glycosides in different solvents. *C* or *O*-Glycosylation of flavonoids obviously enhanced the stability of flavonoids (Plaza et al., 2014; Xiao and Högger, 2015b). Compared with quercetin ($^{10}T_{10}$ = 4.66 min and $^{10}T_{50}$ = 17.96 min), quercitrin and rutin were more stable during 3 h of incubation in DMEM medium with T_{10}>180 min and T_{50}>180 min (Xiao and Högger, 2015b). Luteolin 7-*O*-glucoside, myricitrin, baicalin showed higher stability than their aglycones (Xiao and Högger, 2015b). It was reported *C*-glycosylated flavonoids are more stable in comparison with aglycones or *O*-glycosylated flavonoids (Rawat et al., 2009). However, we found that apigenin *C*- and *O*-glycosides were very stable during 3-h incubation in DMEM, which was similar as their aglycone (Xiao and Högger, 2015b). Glycosylation is a common metabolic fate for majority of flavonoids and structural changes in glycosides may improve the stability. Structural changes in flavonoids 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). Moreover, the extraction methods may also affect the stability of flavonoid glycosides (Biesaga, 2011). Jiang and others (2008) converted puerarin to its 7-*O*-glucoside and 7-*O*-isomaltoside by *Microbacterium oxydans*. The apparent solubilities of puerarin 7-*O*-glucoside and puerarin 7-*O*-isomaltoside were 18 and 100-folds higher than that of puerarin.

9. Conclusion

The flavonoids are the most important dietary polyphenols in human diets and are of great general interest due to their diverse biological activity. The antioxidant potential and inhibition of digestive enzymes of flavonoid glycosides are most frequently reported. Among the flavonoid glycosides, flavonol and flavone glycosides, especially quercetin, kaempferol, apigenin, and luteolin glycosides are more frequently mentioned than other flavonoids (Tables 1 and 2). It seems as though *O*-glycosylation generally reduces the bioactivity of these compounds—this has been observed for diverse properties including antioxidant activity, antidiabetes activity, anti-inflammation activity, antibacterial and antifungal activity, anticancer activity, anticoagulant activity, antiplatelet activity, antidegranulating activity, antitrypanosomal activity, influenza virus neuraminidase inhibition, aldehyde oxidase inhibition, immunomodulatory, and antitubercular activity (Tables 1 and 2). However, *O*-glycosylation can enhance certain types of bioactivity including anti-HIV activity, tyrosinase inhibition, antirotavirus activity, antistress activity, antiobesity activity, anticholinesterase potential antiadipogenic activity, antiallergic activity, and treatment for chronic kidney disease (Tables 1 and 2).

Overall, it is very difficult to draw general or universally applicable comments regarding the impact of glycosylation on flavonoids' bioactivity and capacity for affecting human health. Furthermore, there is a lack of in vivo data that would make it possible to make broad generalizations concerning the impact of glycosylation on the benefits of flavonoids for human health. It is possible that the effects of glycosylation on flavonoid bioactivity in vitro may differ from that seen in vivo. With in vivo (oral) treatment, flavonoid glycosides showed similar or even higher antidiabetes, anti-inflammatory, antidegranulating, antistress, and antiallergic activity than their flavonoid aglycones. Finally, there is a need for more information on how flavonoid glycosylation affects bioactivity in vivo.

In spite of exhibiting diverse bioactivity, flavonoids are yet to achieve the status of promising drug candidates, and only very few these compounds have been approved for clinical application. The reason for this could be the lack of sufficient clinical or in vivo data. Most bioactivy of flavonoid aglycones and glycosides is reported within "tubes" or "plates" and there are very few data from in vivo experiment or clinical practice. The flavonoid glycosylation on their benefit is belived to provide different outcomes between in vitro and in vivo. Flavonoids glycosides maintain higher plasma concentrations and have a longer mean residence time in the blood than aglycones. Although the attached sugar moiety on flavonoid molecules may influence their absorption and metabolic rates, flavonoid aglycones and glycosides show similar absorption and metabolism profiles in vivo. Researchers should pay more attention to the in vivo benefits of flavonoid glycosides.

Moreover, although there are only very few data showing the impact of *C*-glycosylation of flavonoids on their benefits, *C*-glycosylation appears to have positive influences on human health, specifically antioxidant and antidiabetic potential. 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 glycosides and to explore their bioactivities.

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