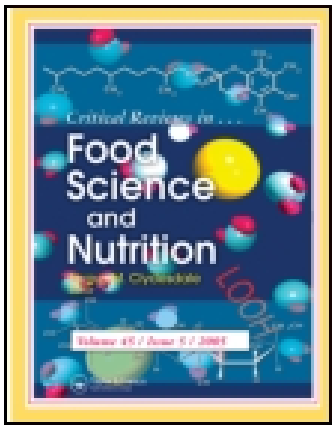

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Advance in Dietary Polyphenols as Aldose Reductases Inhibitors: Structure-Activity Relationship Aspect

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Advance in Dietary Polyphenols as Aldose Reductases Inhibitors: Structure-Activity Relationship Aspect

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The dietary polyphenols as aldose reductases inhibitors (ARIs) have attracted great interest among researchers. The aim of this review is to give an overview of the research reports on the structure-activity relationship of dietary polyphenols inhibiting aldose reductases (AR). The molecular structures influence the inhibition of the following: (1) The methylation and methoxylation of the hydroxyl group at C_3, $C_{3'}$, and $C_{4'}$ of flavonoids decreased or little affected the inhibitory potency. However, the methylation and methoxylation of the hydroxyl group at C_5, C_6, and C_8 significantly enhanced the inhibition. Moreover, the methylation and methoxylation of C_7-OH influence the inhibitory activity depending on the substitutes on rings A and B of flavonoids. (2) The glycosylation on 3-OH of flavonoids significantly increased or little affected the inhibition. However, the glycosylation on 7-OH and 4′-OH of flavonoids significantly decreased the inhibition. (3) The hydroxylation on A-ring of flavones and isoflavones, especially at positions 5 and 7, significantly improved the inhibition and the hydroxylation on C3′ and C4′ of B-ring of flavonoids remarkably enhanced the inhibition; however, the hydroxylation on the ring C of flavones significantly weakened the inhibition. (4) The hydrogenation of the C2=C3 double bond of flavones reduced the inhibition. (5) The hydrogenation of $\alpha=\beta$ double bond of stilbenes hardly affected the inhibition and the hydroxylation on $C_{3'}$ of stilbenes decreased the inhibition. Moreover, the methylation of the hydroxyl group of stilbenes obviously reduced the activity. (6) The hydroxylation on C_4 of chalcone significantly increased the inhibition and the methylation on C_4 of chalcone remarkably weakened the inhibition.

Keywords Polyphenols, flavonoids, aldose reductases inhibitors (ARIs), structure-activity relationship

INTRODUCTION

Polyphenols are the most abundant antioxidants in human diet and are the most common and widespread constituents in plants (Cohen and Kennedy, 2010; Côté et al., 2010a, 2010b; van Dorsten et al., 2010; González et al., 2011). They are considered to be secondary metabolites and have no specific metabolic function in plant cells. Polyphenols contain at least one aromatic ring with one or more hydroxyl groups in addition to other substituent. The most important polyphenols classes are phenolic acids, such as compounds with one C_6 aromatic ring of hydroxybenzoic acids such as hydroxytyrosol, tanins, and gallic acid, those with a C_6–C_3 structure of hydroxycinnamic acids such as caffeic acid and coumaric acid, those with the C_6–C_2–C_6 structure of stilbenes such as resveratrol and polydatin, those with the C_6–C_3–C_6 structure of flavonoids and others with the C_6–C_4–C_6 structure of lignans such as secoisolariciresinol (Xiao et al., 2013a; 2013b).

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Authors Jianbo Xiao and Xiaoling Ni have contributed equally to this work.

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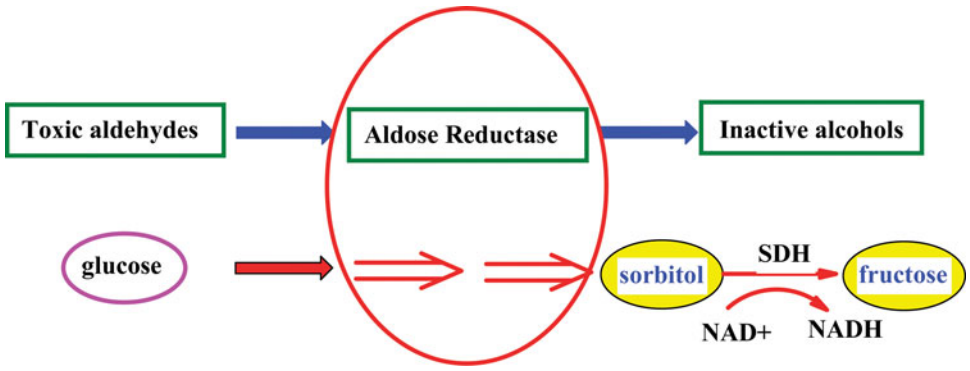


Figure 1 Aldose reductase and the polyol pathway.

Flavonoids are the most important polyphenols in plant sources (Blade et al., 2010; Morabito et al., 2010; Natella et al., 2010; Xiao et al., 2009; Xiao et al., 2010; Xiao et al., 2011a, 2011b). Their structures are represented by a benzene ring (A), condensed with a heterocyclic sixmembered pyran or pyrone ring (C), which in the 2 or 3 position carries a phenyl ring (B) as a substitute. *Flavonoids: Chemistry, Biochemistry and Applications* is one of the most comprehensive books published in this century available to date on this group of natural products (Andersen and Markham, 2006; Veitch and Grayer, 2008). Over 10,000 flavonoids have been separated and identified from plants and most of which are divided into subclasses, including anthocyanidins, flavanones, flavonols, flavones, and isoflavones (Blade et al., 2010; Brand et al., 2010).

Aldose reductase (AR; alditol/$NADP^+$ oxidoreductase, E.C.1.1.1.21, ALR2) is the first enzyme of the polyol pathway that reduces excess D-glucose into D-sorbitol with concomitant conversion of NADPH into $NADP^+$ (Figure 1; de la Fuente and Manzanaro, 20003; Matsuda et al., 2003). Aldose reductase, using NADPH as a coenzyme, has a molecular weight of 37,000 Dalton. Aldose reductase in eyes, kidney, muscle, and brain can cause accumulation of sorbitol in the presence of diabetes mellitus (Kador, 1988; Nishimura-Yabe 1998; Brownlee 2001). The polyol pathway seems to play an important role in the development of degenerative complications of diabetes. Accumulation of sorbitol under normal physiological conditions is not much important. However, in diabetes mellitus with increased glucose levels, sorbitol would be accumulated in cells due to its slow metabolization by sorbitol dehydrogenase and it has severe effects in the formation of cataract. Sorbitol does not easily diffuse through the cell membranes, so it accumulates in the cells, causing the osmotic pressure to construct eventually to the cells burst, resulting in the tissue damage. Therefore, the inhibition of AR is important to prevent the incidence of cataract formation in diabetes mellitus. 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 (Lim et al., 2001).

An understanding of how these inhibitors bind to this enzyme should provide a rational basis for the development of new molecules for human AR. The inhibitory effects of dietary polyphenols for ARs have attracted great interests among researchers (Feng et al., 2005; Wang et al., 2005; Zhu, 2009). The aim of this review is to give an overview on the structure-activity relationship of dietary flavonoids inhibiting ARs.

FLAVONOIDS

Methylation and Methoxylation

The methylation and methoxylation of the free hydroxyl groups on flavonoids dramatically prevent the formation of glucuronic acid and sulfate conjugates and improve the intestinal absorption and metabolic stability (Wen and Walle, 2006; Walle, 2009). Recently, Walle reported that the oral administration of methylated flavonoids resulted in high bioavailability and tissue distribution than their unmethylated forms. It looks like that the methylation and methoxylation appears to be an effective method to enhance metabolic resistance and transport of the flavonoids (Walle, 2007a and 2007b).

That methylation and methoxylation of the hydroxyl groups on flavonoids on inhibiting d methoxylation of flavonoids obviously affected the inhibitory effect for ARs was widely reported (Okuda et al., 1982; Al-Yahya et al., 1988). As summarized in Table 1, the methylation and methoxylation of flavonoids obviously affected the inhibitory effect against AR in vitro depending on the replaced sites (Table 1).

The methylation and methoxylation of the hydroxyl group at C_3, $C_{3'}$, and $C_{4'}$ of flavonoids decreased or little affected the inhibitory potency. And, the methylation and methoxylation of the hydroxyl group at C_5, C_6, and C_8 significantly enhanced the inhibitory capacity. However, the methylation and methoxylation of the hydroxyl group at C_7 influence the inhibitory potency depending on the substitutes on rings A and B.

5,7,3′,4′-Trihydroxy-3,6-dimethoxyflavone (1), 3′,4′-dihydroxy-5,6,7,8-tetramethoxyflavone (2), 6,3′,4′-trihydroxy-5,7,8-trimethoxyflavone (3), 5,3′,4′-trihydroxy-6,7,8-trimethoxyflavone (4), 3′,4′-dihydroxy-5,7,8-trimethoxyflavone (5), and 5,3′,4′-trihydroxy-7,8-dimethoxyflavone (6) exhibited very high inhibition against rat lens aldose reductase (RLAR) (Okuda et al., 1984) with IC_{50} values of 3.02×10^{-8},

Table 1 Effects of methylation and methoxylation of flavonoids on inhibiting AR

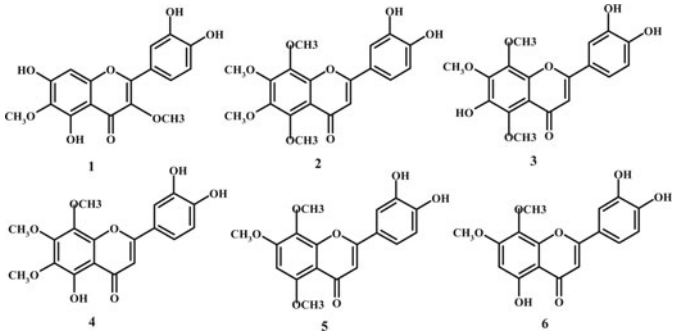
Site	Model	Example	Effect	Ref
3	H→OCH_3	5,6,7,3′,4′-OH→5,6,7,3′,4′-OH;3-OCH_3	Little effect	Okuda et al. (1984)
		5,6,3′,4′-OH;7-OCH_3→5,6,3′,4′-OH;3,7-OCH_3	↓	Okuda et al. (1984)
		5,3′,4′-OH;6,7-OCH_3→5,3′,4′-OH;3,6,7-OCH_3	↓	Okuda et al. (1982); Okuda et al. (1984)
		6,3′,4′-OH;5,7-OCH_3→6,3′,4′-OH;3,5,7-OCH_3	↓	Okuda et al. (1984)
		4′-OH-wogonin→4′-OH-3-OCH_3-wogonin	Little effect	Liu et al. (2007)
		3′,4′-OH;5,6,7-OCH_3→3′,4′-OH;3,5,6,7-OCH_3	↓	Okuda et al. (1984)
		5,7,3′,4′-OH;8-OCH_3→5,7,3′,4′-OH;3,8-OCH_3	↓	Okuda et al. (1984); Liu et al. (2007)
		7,3′,4′-OH;5,8-OCH_3→7,3′,4′-OH;3,5,8-OCH_3	↓	Okuda et al. (1984)
		3′,4′-OH;5,7,8-OCH_3→,3′,4′-OH;3,5,7,8-OCH_3	↓	Okuda et al. (1984)
		Quercetin→Quercetin-3-methyl ether	Little effect	Enomoto et al. (2004)
5	OH→OCH_3	5,6,3′,4′-OH;7-OCH3→6,3′,4′-OH;5,7-OCH3	↑	Okuda et al. (1984); Al-Yahya et al. (1988)
		5,6,3′,4′-OH;3,7-OCH3→6,3′,4′-OH;3,5,7-OCH3	↑	Okuda et al. (1984)
		5,6,3′,4′-OH;7,8-OCH3→6,3′,4′-OH;5,7,8-OCH3	↑	Al-Yahya et al. (1988)
		5,3′,4′-OH;7,8-OCH3→3′,4′-OH;5,7,8-OCH3	↑	Okuda et al. (1984); Al-Yahya et al. (1988)
		5,3′,4′-OH;6,7-OCH3→3′,4′-OH;5,6,7-OCH3	↑	Al-Yahya et al. (1988)
		5,7,3′,4′-OH;8-OCH3→7,3′,4′-OH;5,8-OCH3	↑	Okuda et al. (1984); Al-Yahya et al. (1988)
		5,8,3′,4′-OH;7-OCH3→8,3′,4′-OH;5,7-OCH3	↑	Okuda et al. (1984)
		5,6,4′-OH;7,8-OCH3→6,4′-OH;5,7,8-OCH3	↑	Okuda et al. (1982)
		5,7,3′,4′-OH;3,8-OCH3→7,3′,4′-OH;5,3,8-OCH3	Little effect	Okuda et al. (1984)
		5,3′,4′-OH;6,7,8-OCH3→3′,4′-OH;5,6,7,8-OCH3	↑	Okuda et al. (1984)
		7,3′,4′-OCH_3-luteolin→5,7,3′,4′-OCH_3-luteolin	↑	Matsuda et al. (2002)
6	OH→OCH_3	5,6,3′,4′-OH;7-OCH_3→5,3′,4′-OH;6,7-OCH_3	↑	Okuda et al. (1984); Al-Yahya et al. (1988)
		6,3′,4′-OH;5,7-OCH_3→3′,4′-OH;5,6,7-OCH_3	↑	Okuda et al. (1984); Al-Yahya et al. (1988)
		5,6,3′,4′-OH;3,7-OCH_3→5,3′,4′-OH;3,6,7-OCH_3	↑	Okuda et al. (1984)
		6,3′,4′-OH;3,5,7-OCH_3→3′,4′-OH;3,5,6,7-OCH_3	↑	Okuda et al. (1984)
		5,6,7,3′,4′-OH;3-OCH_3→5,7,3′,4′-OH;3,6-OCH_3	↑	Al-Yahya et al. (1988)
		6,3′,4′-OH;5,7,8-OCH_3→3′,4′-OH;3,5,6,7 -OCH_3	↑	Okuda et al. (1984); Al-Yahya et al. (1988)
		6,4′-OH;5,7,8-OCH_3→4′-OH;5,6,7,8-OCH_3	↑	Al-Yahya et al. (1988)
		6,4′-OH;5,7,8-OCH_3→4′-OH;5,6,7,8-OCH_3	↑	Okuda et al. (1982)
		5,6,4′-OH;7,8-OCH_3→5,4′-OH;6,7,8-OCH_3	↑	Okuda et al. (1982)
		5,6,7-OH; 8-OCH_3→5,7-OH;6,8-OCH_3	↑	Al-Yahya et al. (1988)
		Quercetagetin→Patuletin	↑	Li et al. (1991)
	H→OCH_3	5,3′,4′-OH;7,8-OCH_3→5,3′,4′-OH;6,7,8-OCH_3	↑	Okuda et al. (1984)
		3-OH→4′-OH;3-OH;6-OCH_3	↑	Al-Yahya et al. (1988)
7	OH→OCH_3	5,7,3′-OH;4′-OCH_3→5,3′-OH;7,4′-OCH_3	↓	Matsuda et al. (2002)
		7-OH→7-OCH_3	↓	Costantino et al. (1999); Verma and Pratap (2010)
		5,6,7,3′,4′-OH→5,6,3′,4′-OH;7-OCH_3	↓	Okuda et al. (1984)
		5,6,7,3′,4′-OH;3-OCH_3→5,6,3′,4′-OH;3,7-OCH_3	↓	Okuda et al. (1984)
		3,5,7,3′-OH;4′-OCH_3→3,5,3′-OH;7,4′-OCH_3	↓	Liu et al. (2007)
		5,7,3′,4′-OH;3,6-OCH_3→5,3′,4′-OH;3,6,7-OCH_3	↓	Okuda et al. (1984)
		5,7,4′-OH;6,8-OCH_3→5,4′-OH;6,7,8-OCH_3	↓	Okuda et al. (1982)
		5,7,3′,4′-OH;3,8-OCH_3→5,3′,4′-OH;3,7,8-OCH_3	↓	Al-Yahya et al. (1988)
		5,6,7,3′,4′-OH→5,6,3′,4′-OH;7-OCH_3	↓	Al-Yahya et al. (1988)
		5,6,7, 4′-OH→5,6, 4′-OH;7-OCH_3	↓	Al-Yahya et al. (1988)
		Rutin→Rhamnetin 3-*O*-Rut	↓	Matsuda et al. (2002)
		5,6,7,3′,4′-OH;3-OCH_3→5,6,3′,4′-OH;3,7-OCH_3	↓	Al-Yahya et al. (1988)
		5,6,7-OH;8-OCH_3→5,6-OH;7,8-OCH_3	↓	Okuda et al. (1982)
		5,7-OH→5-OH;7-OCH_3	↓	Matsuda et al. (2002)
		5,7,3′,4′-OH;8-OCH_3→5,3′,4′-OH;7,8-OCH_3	↑	Okuda et al. (1984)
		7,3′,4′-OH;5,8-OCH_3→3′,4′-OH;5,7,8-OCH_3	↑	Okuda et al. (1984)
		7,3′,4′-OH;3,5,8-OCH_3→3′,4′-OH;3,5,7,8-OCH_3	↑	Okuda et al. (1984)
		5,6,7,3′,4′-OH;8-OCH_3→5,6,3′,4′-OH;7,8-OCH_3	↑	Okuda et al. (1984); Al-Yahya et al. (1988)
		7,3′,4′-OH;5,6-OCH_3→3′,4′-OH;5,6,7-OCH_3	↑	Al-Yahya et al. (1988)
		5,7,3′,4′-OH;8-OCH_3→5,3′,4′-OH;7,8-OCH_3	↑	Al-Yahya et al. (1988)
		7,3′,4′-OH;3,5,8-OCH_3→3′,4′-OH;3,5,7,8-OCH_3	↑	Al-Yahya et al. (1988)
8	OH→OCH_3	5,8,3′,4′-OH;7-OCH_3→5,3′,4′-OH;7,8-OCH_3	↑	Okuda et al. (1984)
		8,3′,4′-OH;3,5,8-OCH_3→3′,4′-OH;3,5,7,8-OCH_3	↑	Okuda et al. (1984)
		5,8,3′,4′-OH;7-OCH_3→5,3′,4′-OH;7,8-OCH_3	↑	Al-Yahya et al. (1988)
	H→OCH_3	Luteolin→8-OCH_3-luteolin	↑	Liu et al. (2007)
		3′,4′-OH;5,6,7-OCH_3→3′,4′-OH;5,6,7,8-OCH_3	↑	Al-Yahya et al. (1988)
		5,3′,4′-OH;6,7-OCH_3→5,3′,4′-OH;6,7,8-OCH_3	↑	Al-Yahya et al. (1988)
		6,3′,4′-OH;5,7-OCH_3→3′,4′-OH;5,7,8-OCH_3	↑	Al-Yahya et al. (1988)
		5,6,3′,4′-OH;7-OCH_3→5,6,3′,4′-OH;7,8-OCH_3	↑	Al-Yahya et al. (1988)

(Continued on next page)

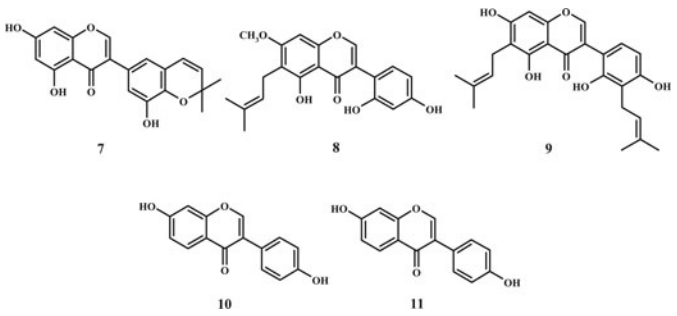
Table 1 Effects of methylation and methoxylation of flavonoids on inhibiting AR *(Continued)*

Site	Model	Example	Effect	Ref
3′	H→OCH_3	5,6,7,4′-OH;8-OCH_3→5,6,7,4′-OH;3′,8-OCH_3	↓;No effect	Okuda et al. (1982); Al-Yahya et al. (1988)
		5,7,4′-OH;6,8-OCH_3→5,7,4′-OH;6,8,3′-OCH_3	↓	Okuda et al. (1982)
		5,4′-OH;6,7-OCH_3→5,4′-OH;6,7,3′-OCH_3	↓	Okuda et al. (1982)
		6,4′-OH;5,7,8-OCH_3→6,4′-OH;5,7,8,3′-OCH_3	↓	Al-Yahya et al. (1988)
		4′-OH;5,6,7,8-OCH_3→4′-OH;5,6,7,8,3′-OCH_3	↓	Okuda et al. (1982)
		5,4′-OH;6,7,8-OCH_3→5,4′-OH;6,7,8,3′-OCH_3	↓	Okuda et al. (1982)
		5,6,4′-OH;7,8-OCH_3→5,6,4′-OH;7,8,3′-OCH_3	↓	Okuda et al. (1982)
	OH→OCH_3	5,3′-OH;6,7-OCH_3;4′-O-Glc→5-OH;6,7,3′-OCH_3;4′-O-Glc;	↓	Okuda et al. (1982)
		5,6,7,3′,4′-OH;8-OCH_3→5,6,7,4′-OH;3′,6,8-OCH_3	↓	Al-Yahya et al. (1988)
		6,3′,4′-OH;5,7,8-OCH_3→6, 4′-OH;5,7,8,3′-OCH_3	↓	Al-Yahya et al. (1988)
		5,3′,4′-OH;6,7-OCH_3→5,4′-OH;6,7,3′-OCH_3	↓	Al-Yahya et al. (1988)
		Ombuine 3-O-Rut→3′-OCH3-ombuine 3-O-Rut	↓	Matsuda et al. (2002)
		Quercetin→3′-OCH_3-quercetin	↓	Haraguchi et al. (1996)
		Pilloin→3′-OCH_3-pilloin	↓	Matsuda et al. (2002)
		3-Sulfatedquercetin→3′-OCH_3-3-sulfatedquercetin	↓	Haraguchi et al. (1996)
		Luteolin 7-*O*-β-D-glucopyranoside→Chrysoeriol 7-*O*-β-D-glucopyranoside	↓	Xie et al. (2005)
		Luteolin 7-*O*-rutinoside→Chrysoeriol7-*O*-rutinoside	↓	Xie et al. (2005)
4′	OH→OCH_3	5,7,4′-OH;6,8-OCH_3→5,7-OH;6,8,4′-OCH_3	↓	Okuda et al. (1982); Al-Yahya et al. (1988)
		5,7,4′-OH;6,8,3′-OCH_3→5,7-OH;6,8,3′,4′-OCH_3	↓	Okuda et al. (1982)
		4′-OH→4′-OCH_3	↓	Al-Yahya et al. (1988)
		Mearnsetin→Mearncitrin	↓	Liu et al. (2007)
		Genistein→Biochanin A	↓	Matsuda et al. (2002)
		Luteolin→Diosmetin	↓	Matsuda et al. (2002)
		Rhamnetin 3-*O*-Rut→Ombuine 3-*O*-Rut	↓	Matsuda et al. (2002)
		Hypolaetin-7-O-glucopyranoside 1→4′-Methoxyhypolaetin-7-O-glucopyranoside 1	↓	Güvenç et al. (2010)
		Hypolaetin-7-O-glucopyranoside 2→4′-Methoxyhypolaetin-7-O-glucopyranoside 2	↓	Güvenç et al. (2010)
		Genistin→Ononin	↓	Park et al. (2007)
		Daidzein→Formononetin	↓	Park et al. (2007)
		Cyanidin-3-glucoside→Peonidin-3-glucoside	↓	Yawadio et al. (2007)

3.34×10^{-8}, 3.39×10^{-8}, 3.89×10^{-8}, 4.47×10^{-8}, and 7.8×10^{-8} mol/L, respectively.

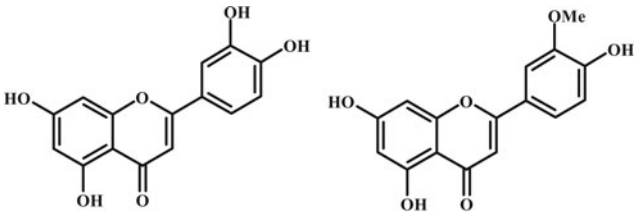


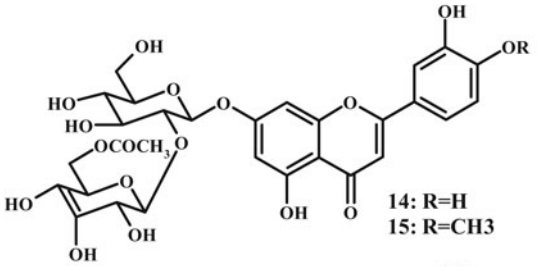
Recently, Lee et al. (2010) evaluated the inhibitory effects of components from the root of *Glycyrrhiza uralensis* on RLAR. Semilicoisoflavone B (7), 7-O-methylluteone (8), and isoangustone A (9) were isolated and identified. Semilicoisoflavone B showed a strong inhibition against RLAR with IC_{50} of 1.28×10^{-6} mol/L. The prenylated flavonoids 7-O-methylluteone (8) and isoangustone A (9) have relative low inhibitory activities (Lee et al., 2010). Park et al. (2007) isolated daidzein (10) and formononetin (11) from *Pueraria thunbergiana* and found that the methylation of the hydroxyl group at $C_{4'}$ of isoflavone significantly weakened the inhibition.

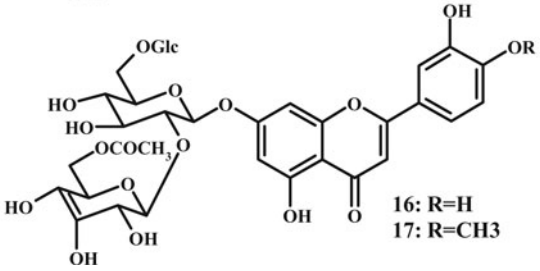


Xie and coworkers (2005) identified luteolin (12) and chrysoeriol (13) glycosides ARIs from *Saussurea medusa*. Luteolin 7-O-β-D-glucopyranoside, luteolin 7-O-rutinoside, chrysoeriol 7-O-β-D-glucopyranoside, and chrysoeriol 7-O-rutinoside inhibited RLAR with IC_{50} values of 0.99×10^{-6}, 0.92×10^{-6}, 26×10^{-6}, and 14×10^{-6} mol/L, respectively. Güvenç and coworkers (2010) investigated the AR inhibitory activities of phenolic compounds from *Sideritis brevibracteata*. Hypolaetin 7-O-[6‴-O-acetyl-β-D-allopyranosyl-(1→2)]-β-Dglucopyranoside (14), 3′-hydroxy-4′-O-methylisoscutellarein 7-O-[6‴-O-acetyl-

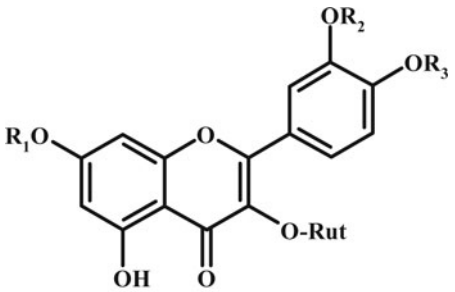
β-D-allopyranosyl-(1→2)]-β-D-glucopyranoside (15), Isoscutellarein 7-O-[6‴-O-acetyl-β-D-allopyranosyl-(1→2)]-β-D-glucopyranoside (16), and 3′-hydroxy-4′-O-methylisoscutellarein 7-O-[6‴-O-acetyl-β-D-allopyranosyl-(1→2)]-6″-O-acetyl-β-D-glucopyranoside (17) as ARIs were identified with IC_{50} values of 0.61×10^{-6}, 1.25×10^{-6} 1.16×10^{-6}, and 2.11×10^{-6} mol/L, respectively (Güvenç et al., 2010). As seen form these data, the methylation of the hydroxyl group at $C_{3'}$ and $C_{4'}$ of flavonoid glycosides obviously decreased the inhibitory potency.



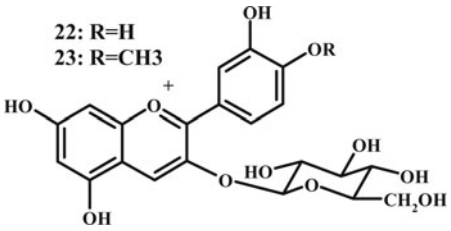




Matsuda et al. (2002) reported the AR inhibitory effects of rutin (18) and its methylated forms rhamnetin 3-O-Rut (19), ombuine 3-O-Rut (20), and 3′-methoxy-ombuine 3-O-Rut (21). It was found that the inhibition decreased with increasing methylation at C_7, $C_{3'}$, and $C_{4'}$ of rutin.



Yawadio et al. (2007) identified cyanidin-3-glucoside (22) and peonidin-3-glucoside (23) from pigmented rices and studied their AR inhibitory activities. Compound 22 exhibited higher inhibition than that of Compound 23, which illustrated that the methylation of the hydroxyl group at and $C_{4'}$ of anthocyanidin glycosides also weakened the inhibitory potency.



Glycosylation

The dietary flavonoids in nature exist almost always as β-glycosides (Day et al., 1998). The flavonoids are found mainly as the 3 and 7-O-glycoside, although the 5, 8, and 4′ positions may also be glycosylated in some cases (Fossen et al., 1998; Park et al., 2007; Jung et al., 2009). Other classes of favonoids are found mainly glycosylated in the 7 position.

The inhibitory potency of flavones (apigenin and luteolin)/isoflavones (genistein and daidzein) and their 7-glycosylated compounds were widely studied as ARIs (Figure 2) (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 (Glc), β-D-glucopyranosiduronic acid (GlcA), α-L-rhamnopyranosyl (Rha), neohesperodosyl (Neo), or Glc (6→1)Rha (Rut). As shown in Figure 2, the glycosylation on the 7 position of flavones significantly decreased the inhibition against AR by 1.16 to216.7 times (Shin et al., 1995; Yoshikawa

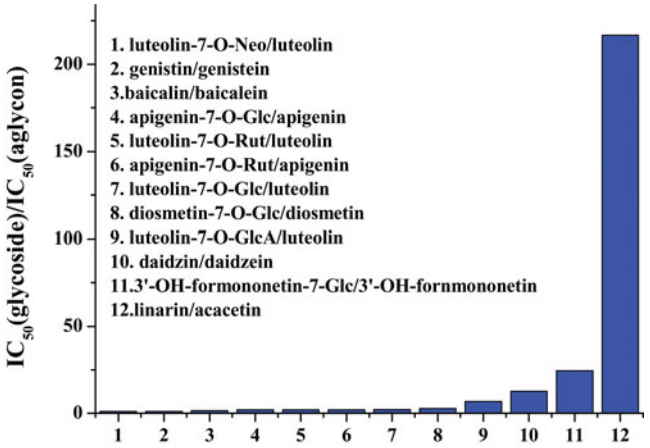
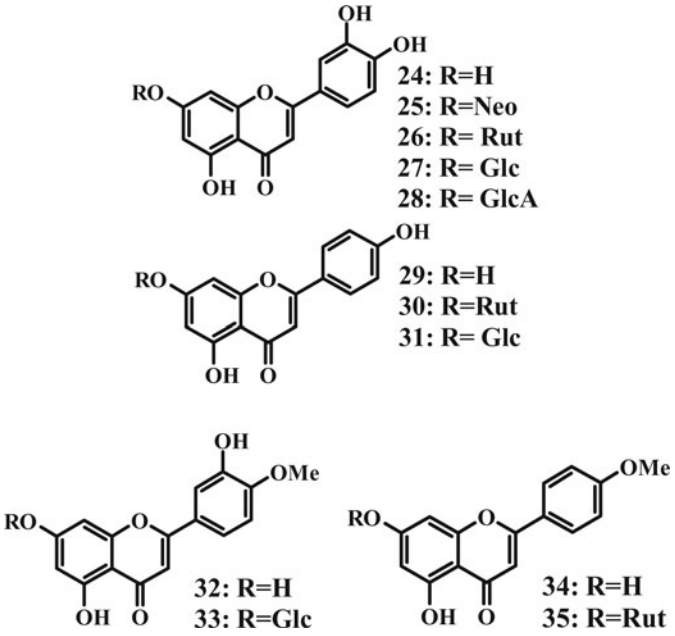


Figure 2 The glycosylation on C_7 position of flavonoids significantly decreased the inhibition against AR. Data were collected from Jung et al. (2011); Liu et al. (2007); Yoshikawa et al. (1999); Jung et al. (2004); Matsuda et al. (2002); Park et al. (2007); Shin et al. (1995); Park et al. (2010).

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 (24) > luteolin-7-O-Neo (25, lonicerin) > luteolin-7-O-Rut (26) > luteolin-7-O-Glc (27) > luteolin-7-O-GlcA (28) (Yoshikawa et al., 1999; Jung et al., 2004; Xie et al., 2005; Park et al., 2007; Jung et al., 2011). The inhibition of apigenin and its glycosides were determined as: apigenin (29) > apigenin-7-O-Rut (30) ≈ apigenin-7-O-Glc (31) (Matsuda et al., 2002; Xie et al., 2005). It revealed that the polyglycosides of flavonoids are stronger than their monoglycosylated forms. Matsuda et al. (2002) reported that diosmetin (32) exhibited twice higher inhibition against AR than that of diosmetin 7-O-β-Dglucopyranoside (33). However, acacetin (34, $IC_{50} = 6.0\ \mu M$) showed 210-fold stronger inhibition than its 7-O-rutinoside (35, $IC_{50} = 1300.0\ \mu M$).



Park et al. (2007) investigated the isoflavone components from the roots of *P. thunbergiana* as ARIs. Genistin and daidzin possessed lower inhibition against AR than their aglycones, genistein, and daidzein. The activity of C_8-glucoside puerarin (38) 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 $4.5\ \mu M$, respectively) (Park et al., 2007). Park and coworkers (2007) further isolated several isoflavone glycosides from the stem bark of *Sophora japonica*. The glycosylation on C_7 position of 7,3′-OH-4′-OCH_3-isoflavone significantly decreased the inhibition by 24.25 times (Park et al., 2010).

Figure 3 shows the inhibitory potency of flavonols and their 3-monoglycosylated compounds (Data from Haraguchi et al., 1996; Matsuda et al., 2002; Jung et al., 2004; Liu et al., 2007; Yoo et al., 2008; Lee et al., 2009a; Park et al., 2009; Jang et al., 2010; Jung et al., 2011). As seen from these data, the glycosylation on C_3 position of flavonoids increased or little affected the inhibition against AR.

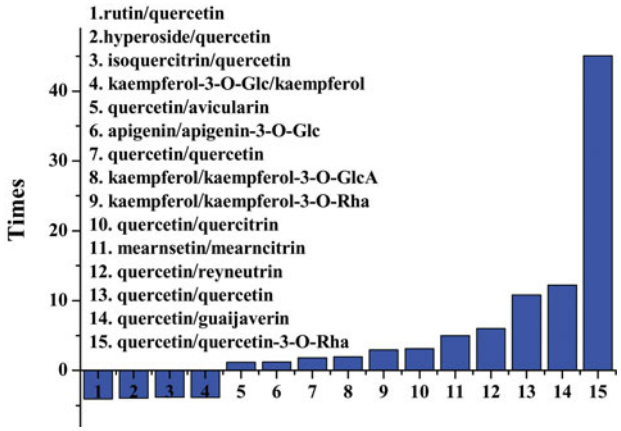
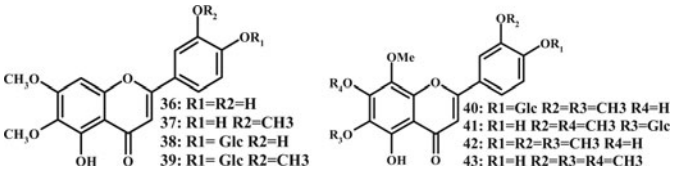


Figure 3 The glycosylation on C_3 position of flavonoids significantly increased or little affected the inhibition against AR. Data were collected from Haraguchi et al. (1996); Jang et al. (2010); Lee et al. (2009a); Park et al. (2009); Jung et al. (2004); Jung et al. (2011); Liu et al. (2007); Yoo et al. (2008).

However, 3-polyglycosylation of flavonols significantly weakened its inhibitory potency (Matsuda et al., 2002). Quercetin 3,7-di-*O*-Glc and rutin reduced the inhibitory potency by 38.18 and 4.09-fold, respectively. Rhamnetin 3-*O*-Rut and ombuine 3-*O*-Rut decreased the inhibition about 7.78 and 6.83 times (Matsuda et al., 2002).

The flavonoids glycosylated at 4′ were hardly reported. Xie et al (2005) isolated luteolin/apigenin and their 4′-glycosides as ARIs from *S. medusa*. It was found that the glycosylation on 4′-OH 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 10-fold higher inhibiton than that of luteolin 4′-O-β-D-glucopyranoside. The glycosylation on 4′-OH of 5,3′,4′-OH-6,7-OCH_3-flavone (36) and 5,4′-OH-3′6,7-OCH_3-flavone (37) also decreased the inhibition (Okuda et al., 1982; Al-Yahya et al., 1988). The PIC_{50} values of 5,3′,4′-OH-6,7-OCH_3-flavone (36) and 5,3′-OH-6,7-OCH_3-flavone-4′-O-Glc (38) were 6.66 and 5.02. 5,3′,4′-OH-6,7-OCH_3-flavone showed 43-fold higher inhibition than 5,3′-OH-6,7-OCH_3-4′-O-Glc (Okuda et al., 1982; Al-Yahya et al., 1988). Okuda et al. (1982) furthermore found the glycosylation on 4′-OH of 5,4′-OH-6,7-OCH_3-flavone and 5,7,4′-OH-6,8,3-OCH_3-flavone also decreased the inhibition. However, 5,4′-OH-6,7,3′-OCH_3-flavone showed only twice higher inhibition than 5-OH-6,7,3′-OCH_3-flavone-4′-O-Glc (39) (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-OH-6,8, 3′-OCH_3-flavone-4′-O-Glc (40) and 5,4′-OH-6,7,8,3′,-OCH_3-flavone-6-O-Glc (41) showed slight higher inhibition than those

of 5,7-OH-6,8,3′,4′-OCH_3-flavone (42) and 5,4′-OH-6,7,8, 3′,-OCH_3-flavone (43) (Al-Yahya et al., 1988).



Lim et al. (2006) isolated kaempferol and seven of its 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 flavonoid glycosides, those harboring 3-O-α-l-rhamnopyranosyl-(1→6)-β-d-glucopyranoside groups in their C rings, including kaempferol 3-O-α-l-rhamnopyranosyl-(1→6)-β-d-glucopyranoside and isorhamnetin 3-O-α-l-rhamnopyranosyl-(1→6)-β-d-glucopyranoside, were determined to exhibit the highest degree of RLAR inhibitory activity in vitro, evidencing IC_{50} values of 5.6 and 9.0 μM, respectively.

In summary, the glycosylation of flavonoids affected the inhibitory effect on AR depending on the conjugation site and the class of sugar moiety. The glycosylation on 3-OH of flavonoids significantly increased or little affected the inhibition. The glycosylation on 7-OH and 4′-OH of flavonoids significantly decreased the inhibition. The decreasing inhibitory effect on AR after glycosylation may be caused by the increasing molecular size and polarity and transfer to the nonplanar structure. After the hydroxyl group is substituted by a glycoside, steric hindrance may take place, which weakens the binding interaction between flavonoids and AR. These results give direct evidences to support that the flavonoid aglycones are easier absorbed than the flavonoid glycosides (Walle, 2004). The fairly large and highly polar flavonoid glycosides cannot be absorbed after oral ingestion, but are hydrolyzed to their aglycones by bacterial enzymes in the lower part of the intestine (Walle et al., 2005).

Hydroxylation

The presence of a C2=C3 double bond on the ring C, a dihydroxyl group (catechol-type) or three adjacent hydroxyl group (pyrogallol-type) on the ring B, and the presence of C-5 and C-7 hydroxyl group on the ring A are usually listed as requirements for antioxidant and antiradical activity of flavonoids. Hydroxylation of flavonoids also significantly affected the inhibitory activity against AR (Table 2).

Hydroxylation on A-ring

There are several works evaluating the effects of the A-ring hydroxyl group of flavonoids on AR inhibition. A series of flavones and isoflavones were tested. As shown in Table 2, the hydroxylation on A-ring of flavones and isoflavones, especially at positions 5 and 7, significantly enhanced the inhibition. The 5,7-dihydroxyflavone structure of flavones was concluded to be crucial for the potent inhibitory activity on AR. Lee et al. (2008) investigated inhibitory effect of flavones isolated from *Rhus verniciflua* against AR. 2.0 μM of 3,7,3′,4′-OH-flavone (fisetin) and 3,5,7,3′,4′-OH-flavone (kaempferol) showed inhibition percentages of 31.1% and 39.1%, which illustrated that hydroxylation at C_5 slightly increased the inhibition. However, it also illustrated the hdroxylation—at C-5 of the A-ring of fisetin to kaempferol—slightly decreased the inhibition (Matsuda et al., 2002).

Research over the past two decades has provided significant epidemiological and other evidence for the health benefits of the consumption of soy-based foods (Larkin et al., 2008). A large number of dietary intervention studies have examined the effects of soy isoflavones on risk factors for cardiovascular disease and hormone-dependent cancers (Larkin et al., 2008). Recent isoflavones as AR inhibitors have attracted great interests among researchers (Matsuda et al., 2002; Enomoto et al., 2004; Liu et al., 2007). As shown in Table 2, the hydroxylation on A-ring of isoflavones, especially at position 5, significantly improved the inhibition.

Hydroxylation on B-Ring

As seen from Table 2, the hydroxylation on C3′ and C4′ of B-ring of flavonoids remarkably enhanced the inhibition. However, the hydroxylation on C5′ of B-ring of flavonoids slightly decreased the inhibition. Matsuda et al. (2002) also illustrated that the flavones and flavonols having catechol moiety at the B ring (the 3′,4′-dihydroxyl moiety) exhibited the strong activity.

Hydroxylation on C-Ring of Flavones

As shown in Table 2, it appears that the hydroxylation on the ring C of flavones significantly weakens the inhibitory activity against AR.

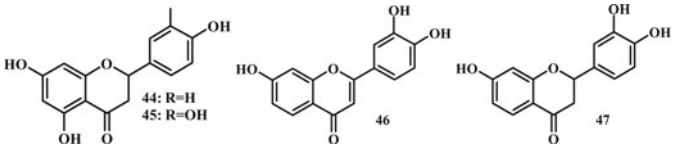
Hydrogenation of the C2=C3 Double Bond

The C2=C3 double bond in conjugation with a 4-oxo group plays a very important role for inhibiting AR. It was found that hydrogenation of the C2=C3 double bond of flavones weakened their activities. The inhibitory activity of apigenin (29) (IC_{50} = 25.32 μM) against RHAR was much higher than that of narigenin (44) (IC_{50} = 120.63 μM) (Kim et al., 2011). The inhibitory activity of luteolin (24) (IC_{50} = 0.45 μM) against rat lens AR was obviously stronger than that of eriodictyol (45) (IC_{50} = 7.7 μM) (Matsuda et al., 2002). 3,7,3′,4′-tetrahydoxyflavone (46) showed a moderate inhibition (IC_{50} = 20.1 μM); however, its hydrogenation compartment, 3,7,3′,4′-tetrahydoxyflavanone (47), hardly inhibits recombinant human AR (Lee et al., 2008). Planarity of the C ring in flavonoids maybe important for binding interaction with proteins, as the molecules with saturated C2–C3 bonds (flavanones and certain others) permit more twisting of

Table 2 Effects of hydroxylation of flavonoids on inhibiting AR

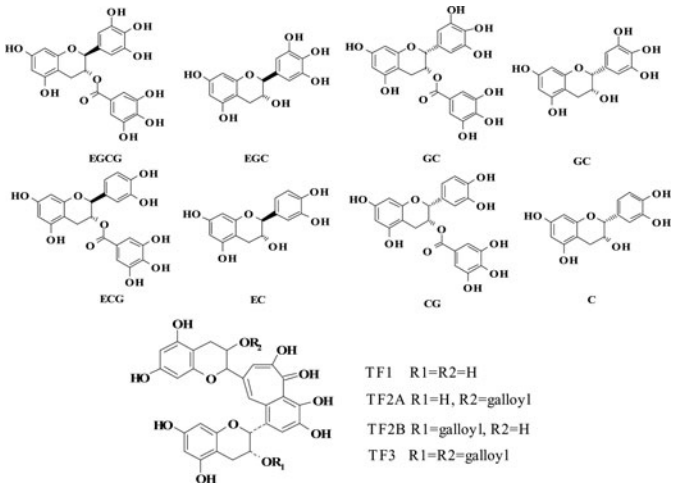
Class	Site	Example	Effect	Ref
Flavone	5	7-OHflavone→Chrysin	↑	Matsuda et al. (2002)
	6	7-OHflavone→6,7-OHflavone	↑	Verma and Pratap (2010)
	7	Flavone→7-OHflavone	↑	Matsuda et al. (2002)
	3′	Apigenin→Luteolin	↑	Shin et al. (1995); Matsuda et al. (2002); Xie et al. (2005); Yoo et al. (2008); Jung et al. (2011); Kim et al. (2011)
		7,4′-OHflavone→7,3′,4′-OHflavone	↑	Matsuda et al. (2002); Verma and Pratap (2010)
		Apigenin-7-O-Glc→luteolin-7-O-Glc	↑	Matsuda et al. (2002); Xie et al. (2005)
		5,7,4′-OHflavone-8-Glc→5,7,3′,4′-OHflavone-8-Glc	↑	Jung et al. (2007)
		Hypolaetin 7-O-[6‴-O-acetyl-β-D-allopyranosyl-(1→2)]-β-D-Glc→Isoscutellarein 7-O-[6‴-O-acetyl-β-D-allopyranosyl-(1→2)]-β-D-Glc	↑	Güvenç et al. (2010)
		Hypolaetin 7-O-[6‴-O-acetyl-β-D-allopyranosyl-(1→2)]-6″-Oacetyl-β-D-Glc →Isoscutellarein 7-O-[6‴-O-acetyl-β-D-allopyranosyl-(1→2)]-6″-Oacetyl-β-D-Glc	↑	Güvenç et al. (2010)
		5,6,7,8-OCH_3-4′-OHflavone→5,6,7,8-OCH_3-3′,4′-OHflavone	↑	Al-Yahya et al. (1988)
		5,7,8-OCH_3-6,4′-OHflavone→5,7,8-OCH_3-3′,6,4′-OHflavone	↑	Al-Yahya et al. (1988)
		7,8-OCH_3-5,4′-OHflavone→7,8-OCH_3-5,3′,4′-OHflavone	↑	Al-Yahya et al. (1988)
		7,8-OCH_3-5,6,4′-OHflavone→7,8-OCH_3-5,6,3′,4′-OHflavone	↑	Al-Yahya et al. (1988)
		8-OCH_3-5,6,7,4′-OHflavone→8-OCH_3-5,6,7,3′,4′-OHflavone	↑	Al-Yahya et al. (1988)
		6,7,8-OCH_3-5,4′-OHflavone→6,7,8-OCH_3-5,3′,4′-OHflavone	↑	Al-Yahya et al. (1988)
	4′	7-OHflavone→7,4′-OHflavone	↑	Matsuda et al. (2002); Verma and Pratap (2010)
		8-OCH_3-5,6,7-OHflavone→8-OCH_3-5,6,7,4′-OHflavone	↑	Al-Yahya et al. (1988)
		7,8-OCH_3-5,6-OHflavone→7,8-OCH_3-5,6,4′-OHflavone	↑	Al-Yahya et al. (1988)
	3	Apigenin→Kaempferol	↓	Matsuda et al. (2002); Kim et al. (2011)
		Luteolin→Quercetin	↓	Matsuda et al. (2002); Xie et al. (2005)
		Luteolin-7-O-Glc→Quercetin-7-O-Glc	↓	Matsuda et al. (2002)
Flavonol	5	Fisetin→Kaempferol	↓	Matsuda et al. (2002)
	3′	Kaempferol→Quercetin	↑	Matsuda et al. (2002)
		Kaempferol-3-O-Glc→Quercetin-3-O-Glc	↑	Park et al. (2009)
		Kaempferol-3-O-Rha→Quercetin-3-O-Rha	↑	Lee et al. (2009b)
	5′	Quercetin→Myricetin	↓	Matsuda et al. (2002)
		Quercetin-3-O-Rha→Myricetin-3-O-Rha	↓	Lee et al. (2009a)
Isoflavone	5	Daidzein→Genistein	↑	Matsuda et al. (2002); Enomoto et al. (2004); Liu et al. (2007); Park et al. (2007)
		Glycitein→Tectorigenin	↑	Matsuda et al. (2002); Liu et al. (2007)
		3′-OH-4′-OCH_3-isoflavone→5,3′-OH-4′-OCH_3-isoflavone	↑	Enomoto et al. (2004)

the B ring with reference to the C ring. A C2=C3 double bond increases the p-conjugation of the bond linking the B and C rings, which favors near-planarity of the two rings. The molecules with near-planar structure easily enter the hydrophobic pockets in enzymes.



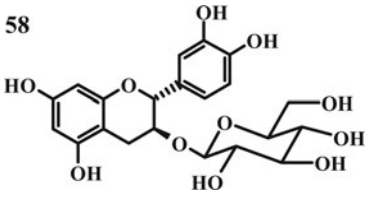
CATECHINS

Catechins are the major polyphenols in green tea leaves. The major catechins of green tea extract are (–)-epicatechin (C, 48), (–)-epicatechin (EC, 49), (–)-epigallocatechin (EGC, 50), (–)-epicatechin gallate (ECG, 51), (–)-epigallocatechin gallate (EGCG, 52), and gallocatechin gallate (GCG, 53). Recent catechins as ARIs have attracted great interests among researchers (Murata et al., 1994; Liu et al., 2006; Lee et al., 2008).



Liu et al. (2006) observed the inhibitive effect of RLAR by tea polyphenols. The inhibition of AR by tea polyphenol

was similar to quercetin. Moreover, the inhibition of AR by tea polyphenol was the stronger than EGCG, ECG, and EGC. EC and GC hardly inhibited AR (Liu et al., 2006).



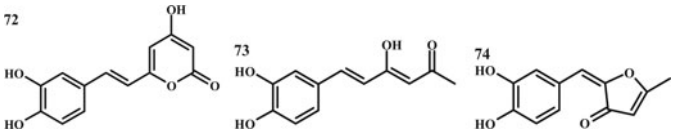
Lee et al. (2011) isolated gallate, (+)-C and (+)-GC from an aqueous acetone extract of the bark of *Quercus acutissima*. Gallate hardly inhibited HRAR. (+)-C and (+)-GC showed very weak inhibitory effects on HRAR with IC_{50} values of 112.5 and 159.4 μM, respectively (Lee et al., 2011). However, glucodistylin (58) showed a very high inhibition ($IC_{50} = 7.2$ μM). Matsuda et al. (2002) found the inhibion pecentages of 30 μM of C, EC, and EGC were about 38%, 41%, and 19%, respectively. It illustrated that inhibitory activities of flavan-3-ols were weaker than flavone, flavonol, and flavanone type compounds. The gallated catechins—GCG, ECG, and EGCG—showed higher inhibition against AR. There are many reports that showed the galloylated catechins having higher inhibition on enzymes than nongalloylated catechins (Kamiyama et al., 2010; Matsui et al., 2007). These results revealed that the galloylation or glycosylation of catechin is a possible method to improve the inhibition.

STILBENES

Stilbenes are phytoalexins that become activated when plants are stressed and are important polyphenols with the C_6–C_2–C_6 structure (Wang et al., 2010; Glauert et al., 2010). The typical natural stilbenes are resveratrol and its 3-glucoside, polydatin (Zhou et al., 2009). These compounds exist in foods and are widely consumed. Resveratrol is a grape-derived polyphenol, which possesses a wide range of bioactivities including antioxidant, anti-inflammatory, and antitumor effects (Weng et al., 2010; Cottart et al., 2010).

Matsuda et al. (2002) investigated the inhibitory activity of stilbenes for RLAR (Table 3). As shown in these data, the hydrogenation of the α=β double bond of stilbenes hardly affected the inhibition and the hydroxylation on $C_{3'}$ of stilbenes decreased the inhibition. The glycosylation on C_5 position of stilbenes significantly increased the inhibition and the glycosylation on $C_{3'}$ position of stilbenes significantly weakened their activities. Moreover, the methylation of the hydroxyl group obviously reduced the activity.

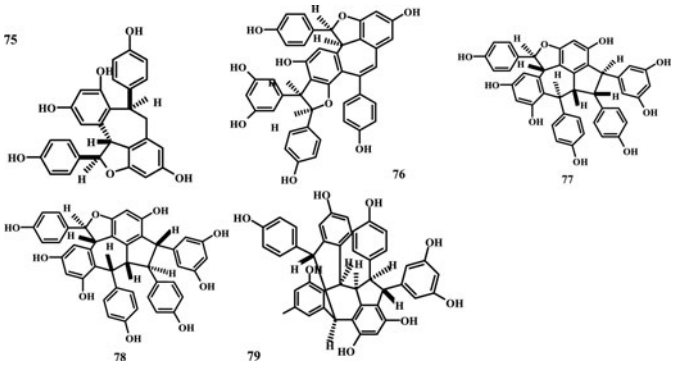
The inhibitory activity of polyphenols from *Phellinus merrillii* was evaluated against RLAR and compared to the quercetin as an ARI (Huang et al., 2011). The ethanol extracts of *P. merrillii* showed the strong inhibition. Aldose reductase inhibitors were identified as hispidin, hispolon, and inotilone, which were isolated from EtOAc-soluble fractions of *P. merrillii*. Among them, hispidin, hispolon, and inotilone exhibited potent against AR with IC_{50} values of 48.26 ± 2.48, 9.47 ± 0.52, and 15.37 ± 0.32 μg/mL, respectively.



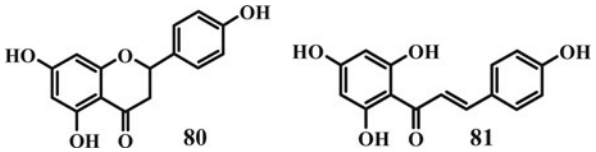
Matsuda et al. (2009) isolated several stilbene dimers and trimers from the wood extract and bark extract of *Cotylelobium melanoxylon*. Melanoxylin A (75) and B (76) vaticanols A (77), E (78), and G (79), (+)-ampelopsin F, (+)-isoampelopsin F, (+)-ε-viniferin, and cis-(+)-ε-viniferin were obtained. The compounds 77 and 78 moderately inhibited enzyme activities of AR, but compound 79 showed only very weak inhibition (Matsuda et al., 2009).

CHALCONES

Chalcones—considered as the precursors of flavonoids and isoflavonoids—are abundant in edible plants; they have also been shown to display a diverse array of pharmacological activities, e.g., antiprotozoal, anti-inflammatory, immunomodulatory, nitric oxide inhibitory, anticancer, anti-HIV, and inhibitory activity against AR (Lee et al., 2010; Liu et al., 2007).

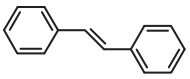
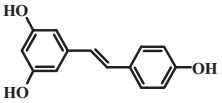
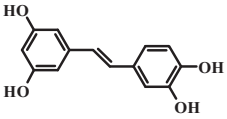
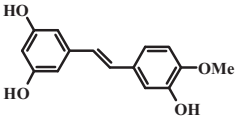
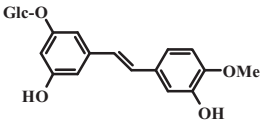
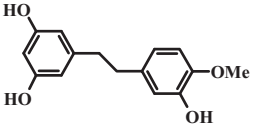
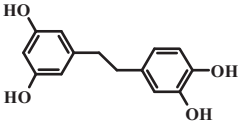
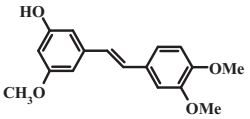
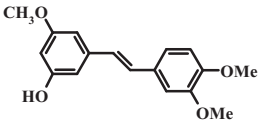
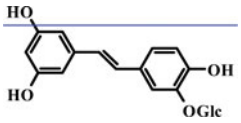
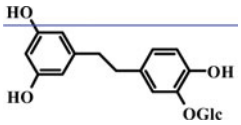
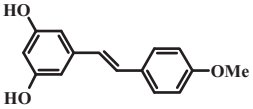
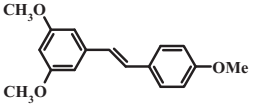


Recently, Lee et al. (2010) isolated 7,4′-OH-flavanone (80) and 4,6,4′-OH-chalcone (81) as ARIs from *Glycyrrhiza uralensis*. Compared with compound 80, the inhibitory potency of compound 81 on RLAR and HRAR slightly decreased.

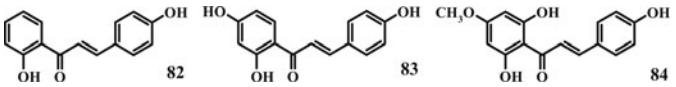


The hydroxylation on C_4 of 2,4′-OH-chalcone (82) to 2,4,4′-OH-chalcone (83) significantly increased the inhibition. The inhibition of 2,4,4′-OH-chalcone (83, $IC_{50} = 0.4$ μM) was about ten-times higher than that of 2,4′-OH-chalcone (82, IC_{50} = 4.25 μM; Liu et al., 2007). More over, the methylation on C_4

Table 3 The inhibitory activity of stilbenes for RLAR (Matsuda et al., 2002)

Compounds	Structure	IC 50/μM	Inhibition At 100 μM/%
Trans-stilbene (59)		>100	6
Resveratrol (60)		25	–
Piceatannol (61)		36	
Rhapontigenin (62)		>100	39
Rhaponticin (63)		80	
Dihydrorhapontigenin (64)		>100	39
Dihydropiceatannol (65)		32	
3,3′,4′-Trimethylpiceatannol (66)		>100	22
3,4′,5-Trimethylpiceatannol (67)		>100	23
Piceatannol 3′-*O*-Glc (68)		85	
Dihydropiceatannol 3′-*O*-Glc (69)		>100	41
Desoxyrhapontigenin (70)		>100	45
3,4′,5-Trimethylresveratrol (71)		>100	13

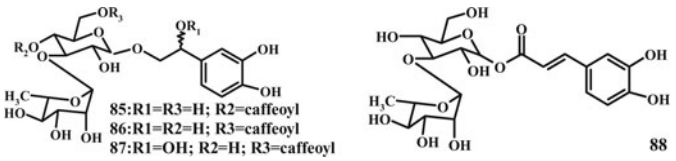
of 2,4,4′-OH-chalcone (83, $IC_{50} = 0.4\ \mu M$) to 2, 4′-OH-4-OCH_3-chalcone (84, $IC_{50} = 5.24\ \mu M$) remarkably weakened the inhibition (Liu et al., 2007).



HYDROXYCINNAMIC ACIDS

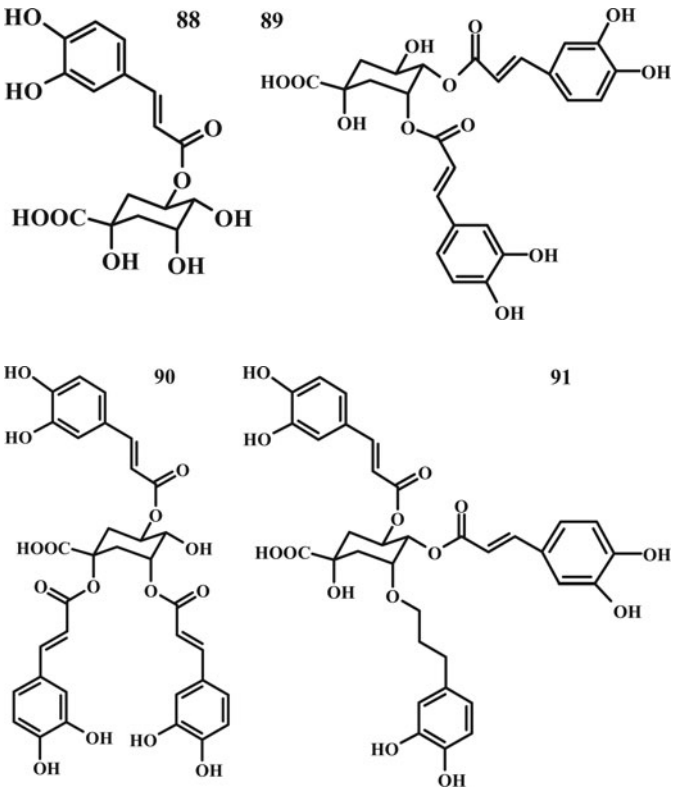
Chlorogenic acids (CGAs) refer to a family of esters between quinic acid and one or plural cinnamic acid derivatives such as caffeic, ferulic, and *p*-coumaric acids. They are richly contained in green coffee beans; 34 kinds of CGAs were reported in green coffee beans (Clifford and Kazi, 1987; Clifford et al., 2006). The typical hydroxycinnamic acids are caffeic acid, chlorogenic acid, and caffeoylquinic acid. Recently, hydroxycinnamic acids as ARIs have attracted great interests among researchers (Kim et al., 2011).

Kim et al. (2011) identified phenylpropanoid glycosides, verbascoside (85), isoverbascoside (86), isocampneoside II (87), cistanoside F (88) from *Paulownia coreana* seeds. The inhibitory effects on RHAR were determined as: isocampneoside II (87) > verbascoside (85) > isoverbascoside (86) > cistanoside F (88) (Kim et al., 2011).

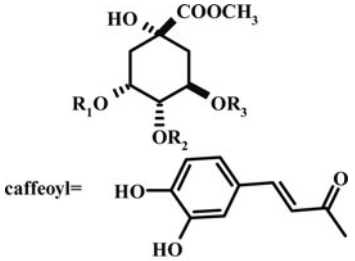


In order to determine the type of the inhibition activity of compounds 85–88, a kinetic study was conducted using glyceraldehydes as a substrate (concentration 0.02–0.2 mM). The Lineweaver–Burk plots (of 1/velocity and 1/concentration) for compounds 85–88 indicated that the inhibition type of rhAR by isoverbascoside (86) and isocampneoside II (87) was uncompetitive, i.e., these inhibitors could bind neither to the substrate-binding region nor to the NADPH binding region of rhAR. Further, verbascoside (85) exhibited a noncompetitive inhibition, whereas cistanoside F (88) showed a competitive inhibition (Kim et al., 2011).

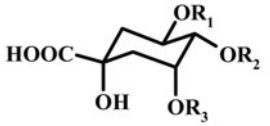
Cui et al. (2009) isolated chlorogenic acid (88) (3-O-caffeoylquinic acid) and caffeoylquinic acids from the acetone-soluble fraction of the aerial parts of Artemisia princes and studied the inhibitory activity of on RLAR. 3,4-di-O-caffeoylquinic acid (89), 1,3,5-tri-O-caffeoylquinic acid (90), and 3,4,5-tri-O-caffeoylqunic acid (91) were studied. These three caffeoylquinic acids were found to have IC_{50} values in the range of 1.78–2.40 μM, illustrating a 5- to 10-fold greater efficacy in RLAR inhibition as compared to the quercetin control, which had an IC_{50} value of 17.91 μM (Cui et al., 2009).



Xie et al. 2005 identified 3-O-caffeoylquinic acid methyl ester (92), 4-O-caffeoylquinic acid methyl ester (93), and 5-O-caffeoylquinic acid methyl ester (94) as ARIs from *S. medusa*. 5-O-caffeoylquinic acid methyl ester (94, $IC_{50} = 1.3\ \mu M$) showed stronger activity than 3-O-caffeoylquinic acid methyl ester (92, $IC_{50} = 13\ \mu M$) and 4-O-caffeoylquinic acid methyl ester (93, $IC_{50} = 16\ \mu M$) for AR (Xie et al., 2005). Jung et al. (2011) compared RLAR inhibitory activities of 3,5-di-O-caffeoylquinic acid, chlorogenic acid, cryptochlorogenic acid (95), and neochlorogenic acid (96) isolated from *Artemisia montana*.



92: R1=caffeoyl R2=R3=H
93: R1=R3=H R2=caffeoyl
94: R3=caffeoyl R1=R2=H



95: R1=caffeoyl, R2=R3=H
96: R1=R3=H, R2=caffeoyl

Chethan et al. (2008) evaluated AR inhibiting activity of gallic, protocatechuic, *p*-hydroxy benzoic, pcoumaric, vanillic, syringic, ferulic, trans-cinnamic acids from *Eleusine coracana*. Among these phenolic acids, protocatechuic and trans-cinnamic acids showed four- to five-fold higher activity with an IC_{50} of 42.7 and 68.1 μg/ml than synringic (172.1 μg/ml) and *p*-coumaric (162.3 lg/ml) acids. Gallic acid also showed an IC_{50} at 97.3 μg/ml. *p*-Hydroxy benzoic, vanillic, and ferulic acids showed negligible or no AR inhibitory activity (Chethan et al., 2008).

ANTHOCYANIDINS

Anthocyanins are the largest group of water-soluble pigments in the Plant Kingdom. They have been recently demonstrated to have potential health benefits and disease prevention properties in animals and humans. Anthocyanins are included in the list of natural compounds known as potential antioxidants. Consumption of anthocyanin-enriched foods is associated with a reduced risk of several diseases such as atherosclerosis, dyslipidemia, and diabetes (Akkarachiyasit et al., 2010). Cyanidin and its glycosides are naturally dietary anthocyanidins, which have been indicated as promising candidates to have potential benefits for humans, especially in the prevention and treatment of diabetes mellitus (Akkarachiyasit et al., 2010).

Lee et al. (2009b) isolated delphinidin 3-O-beta-galactopyranoside-3′,5′-di-O-beta-glucopyranoside and delphinidin 3-O-beta-galactopyranoside-3′-O-beta-glucopyranoside from the active EtOAc fraction of *Litchi chinensis* (Sapindaceae). Delphinidin 3-O-beta-galactopyranoside-3′-O-beta-glucopyranoside was found to be the most potent RLAR inhibitor (IC50 = 0.23 μg/mL) and may be useful in the prevention and/or treatment of diabetic complications.

LIGAND BINDING SITE OF AR AND QSAR ANALYSIS

AR consists of a single polypeptide chain with 315 residues. Their crystal structures have been solved by X-ray crystallography (Wilson et al., 1992). It folds into a β/α barrel with a core of eight parallel β strands. The ligand-binding site is a large, deep, elliptical pocket with the nicotinamide ring of the NADPH cofactor at the base. Figure 4 showed the complex crystal structure of AR and its typical inhibitor, tolrestat (Urzhumtsev et al., 1997). The naphthalene group of tolrestat was found to fit into the hydrophobic pocket of AR (Wilson et al., 1993; Figure 4). Moreover, the conformation of pocket was changed in a loop (residues 121–135) as well as in a short segment (residues 298–303) (Miyamoto, 2002). This conformation change of the enzyme provides the ligand specificity toward AR over aldehyde reductase. Sivakumari et al. (2010) used molecular docking study the binding interaction between cinnamic acid on AR.

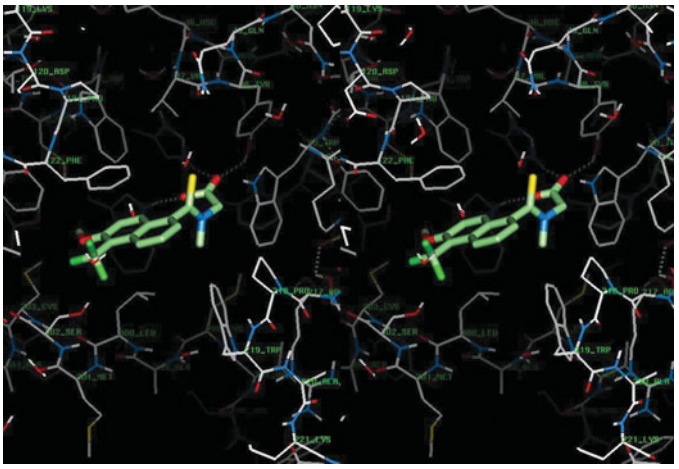


Figure 4 Complex crystal structure model of AR (white) and tolrestat (1) (green) (Wilson et al., 1993). In this model, polar hydrogen atoms are added and oxygen, nitrogen, and sulfur atoms are shown in red, blue, and yellow, respectively. Dashed lines represent hydrogen bonds (Miyamoto, 2002).

Liu et al. (2007) used molecular docking to study the mechanism of flavonoids inhibiting AR. Six flavonoid compounds were used to dock into ALR2 active site by using InsightII/Affinity soft. Comparison between the pharmacophore model and the docking results suggested that the C_7 and $C_{4'}$ hydroxyls on the flavonoids were key functional groups affecting the inhibition activity. When flavonoids enter into the hydrophobic pocket of AR, C_7-OH as a hydrogen acceptor will interact with HIS110 and TRP111 and $C_{4'}$-OH as a hydrogen donor will interact with TYR48 to form hydrogen bonds (Figure 5(1); Liu et al., 2007). TYR48, VAL47, GLN49, HIS110, and TRP111 at the active site of ALR2 were the key residues for the binding (Liu et al., 2007). If the methylation or glycosylation takes place at C_7, the hydrogen bonds between C_7-OH and HIS110/TRP111 will disappear; then the steric hindrance may repel the ligand to VAL47, TYR48, and GLN49, which resulted in forming the hydrogen bonds between $C_{4'}$-OH and TYR48/GLN49 and $C_{3'}$-OH and VAL47 (Figure 5(2); Liu et al., 2007). The steric hindrance will influence the formation of hydrogen bonds between acceptors and donors. These results explained that the glycosylation on 7-OH and 4′-OH of flavonoids significantly decreased the inhibition.

The quantitative structure-activity relationship (QSAR) studies have been successfully applied for modeling biological activities of natural compounds (Caballero, 2010). QSAR studies have been carried out for modeling activities of several kinds of ARIs. Some recent reports have linked structural features of the ligands with their AR inhibition by using topology indexes (Prabhakar et al., 2006; Mercader et al., 2008), three dimensional (3D)-QSAR methodologies (Liu et al., 2009), artificial neural networks (Fernandez et al., 2005; Hu et al., 2006; Patra and Singh, 2009; Thareja et al., 2010; Scotti et al., 2011), pharmacophore (GALAHAD) (Liu et al., 2007; Caballero, 2010), etc.

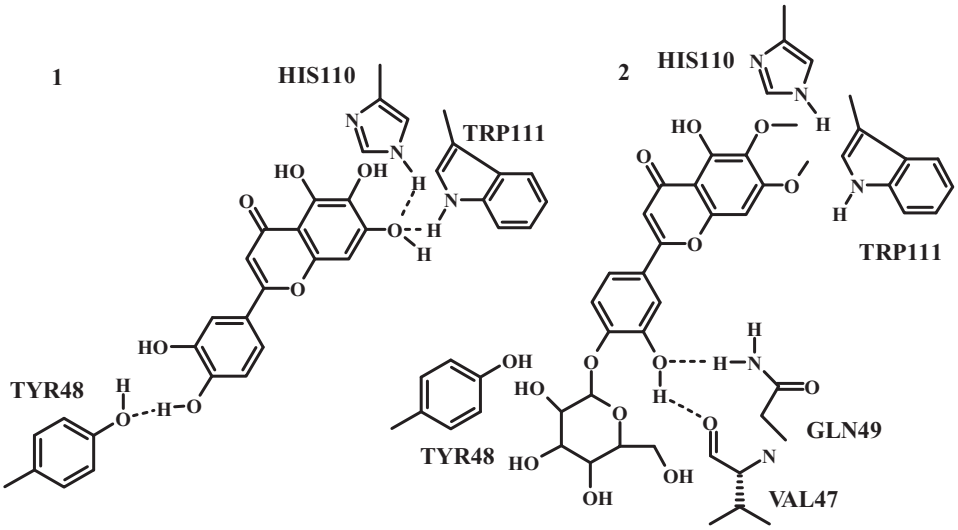


Figure 5 The docking results of flavonoids to AR from human being (Liu et al., 2007).

Caballero studied the QSAR model of AR inhibitory activities of flavonoid derivatives by using CoMFA, CoMSIA, and GALAHAD methods. The best CoMFA model included both steric and electrostatic fields; meanwhile, the best CoMSIA model included steric, hydrophobic, and H-bond acceptor fields. These models had a good predictive quality according to both internal and external validation criteria. GALAHAD was used for deriving a 3D pharmacophore model (Caballero, 2010). Twelve active compounds were used for deriving this model. The obtained model included hydrophobe, hydrogen bond acceptor, and hydrogen bond donor features; it was able to identify the active AR inhibitors from the remaining compounds (Caballero, 2010). These in silico tools might be useful in the rational design of new AR inhibitors.

Prabhakar et al. (2006) investigated the QSAR of the AR inhibitory activity of flavonids by Free-Wilson, Combinatorial Protocol in Multiple Linear Regression, and Partial Least Squares procedures. For the latter two procedures, 152 Molconn-Z parameters and six indicators corresponding to the hydroxyls of flavones were used as molecular descriptors. The CP-MLR procedure identified 26 descriptors to model the activity. They suggested that structures rich in aromatic CH fragments, with a limited number of aliphatic fragments such as –CH2–, –CH<, and free hydroxyls at 7-, 3′-, and 4′-positions of the 2-arylbenzpyran-4-one core would be preferred for the activity (Prabhakar et al., 2006).

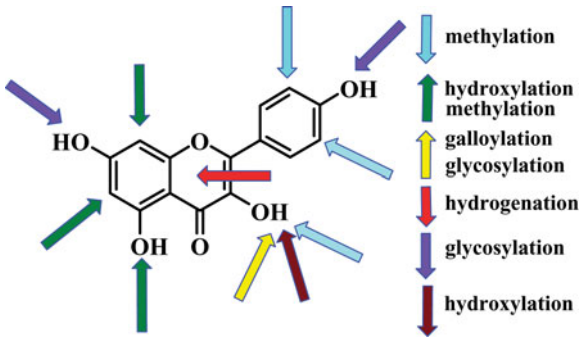


Figure 6 The potential sites of flavonoids affecting the inhibitory effect against α-glucosidase are schematically illustrated. The *up arrows* represent increasing the inhibition and the *down arrows* represent decreasing the inhibition activity.

CONCLUSIONS

Flavonoids are the typical polyphenols and widely studied as ARIs. The typical structure properties of flavonoids affect the inhibitory effect against AR are schematically illustrated in Figure 6. The methylation and methoxylation of the hydroxyl group at C_3, $C_{3'}$ and $C_{4'}$ of flavonoids decreased or little affected the inhibitory potency. The methylation and methoxylation of the hydroxyl group at C_5, C_6, and C_8 significantly enhanced the inhibitory capacity. However, the methylation and methoxylation of the hydroxyl group at C_7 influence the inhibitory potency depending on the substitutes on rings A and B. The glycosylation on 3-OH of flavonoids significantly increased or little affected the inhibition. The glycosylation on 7-OH and 4′-OH of flavonoids significantly decreased the inhibition. The hydroxylation on A-ring of flavones and isoflavones, especially at positions 5 and 7, significantly enhanced the inhibition and the hydroxylation on C3′ and C4′ of B-ring of flavonoids remarkably enhanced the inhibition; however, the hydroxylation on the ring C of flavones significantly weakens the inhibitory activity against AR. The hydrogenation of the C2=C3 double bond of flavones weakened the inhibition. The inhibitory activities of flavan-3-ols were weaker than flavone, flavonol, and flavanone type compounds. The galloylation of catechins enhanced the inhibition against AR.

ACKNOWLEDGMENTS

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ABBREVIATION

AR = Aldose reductase
HRAR = Human recombinant aldose reductase
RLAR = Rat lens aldose reductase
ARIs = Aldose reductase inhibitors
C = (–)-epicatechin
EC = (–)-epicatechin
EGC = (–)-epigallocatechin
ECG = (–)-epicatechin gallate
EGCG = (–)-epigallocatechin gallate
GCG = Gallocatechin gallate
Glc = β-D-glucopyranosyl
GlcA = β-D-glucopyranosiduronic acid
Rha = α-L-rhamnopyranosyl
Neo = Neohesperodosyl
Rut = Glc (6→1)Rha
QSAR = Quantitative structure-activity relationship

REFERENCES

Akkarachiyasit, S., Charoenlertkul, P., Yibchok-anun, S. and Adisakwattana, S. (2010). Inhibitory activities of cyanidin and its glycosides and synergistic effect with acarbose against intestinal α-glucosidase and pancreatic α-amylase. *Int. J. Mol. Sci.* **11**:3387–3396.

Al-Yahya, M. A., El-Sayed, A. M., Mossa, J. S., Kozlowski, J. F., Antoun, M. D., Ferin, M., Baird, W. M. and Cassady, J. M. (1988). Potential cancer chemopreventive and cytotoxic agents from *Pulicaria crispa*. *J. Nat. Prod.* **51**:621–624.

Andersen, Ø. M. and Markham, K. R. (2006). Flavonoids: Chemistry, Biochemistry and Applications. CRC Press, Boca Raton,

Blade, C., Arola, L. and Salvado, M. J. (2010). Hypolipidemic effects of proanthocyanidins and their underlying biochemical and molecular mechanisms. *Mol. Nutr. Food Res.* **54**:37–59.

Brand, W., Padilla, B., van Bladeren, P. J., Williamson, G. and Rietjens, I. M. C. M. (2010). The effect of co-administered flavonoids on the metabolism of hesperetin and the disposition of its metabolites in Caco-2 cell monolayers. *Mol. Nutr. Food Res.* **54**:851–860.

Brownlee, M. (2001). Biochemistry and molecular cell biology of diabetic complications. *Nature*. **414**:813–820.

Caballero, J. (2010). 3D-QSAR (CoMFA and CoMSIA) and pharmacophore (GALAHAD) studies on the differential inhibition of aldose reductase by flavonoid compounds. *J. Mol. Graph. Model.* **29**:363–371.

Chethan, S., Dharmesh, S. M. and Malleshi, N. G. (2008). Inhibition of aldose reductase from cataracted eye lenses by finger millet (*Eleusine coracana*) polyphenols. *Bioorg. Med. Chem.* **16**:10085–10090.

Clifford, M. N. and Kazi, T. (1987). The influence of coffee bean maturity on the content of chlorogenic acids, caffeine and trigonelline. *Food Chem.* **26**:59–69.

Clifford, M. N., Knight, S., Surucu, B. and Kuhnert, N. T. (2006). Characterization by LC-MSn of four new classes of chlorogenic acid in green coffee beans: Dimethoxycinnamoylquinic acids, diferuloylquinic acids, and feruloyldimethoxycinnamoylquinic acids. *J. Agric. Food Chem.* **54**:1957–1969.

Cohen, S. D. and Kennedy, J. A. (2010). Plant metabolism and the environment: Implications for managing phenolics. *Crit. Rev. Food Sci. Nutr.* **50**: 620–543.

Costantino, L., Rastelli, G., Gamberini, M. C., Vinson, J. A., Bose, P., Iannone, A., Staffieri, M., Antolini, L., Corso, A. D., Mura, U. and Albasini, A. (1999). 1-Benzopyran-4-one antioxidants as aldose reductase inhibitors. *J. Med. Chem.* **42**:1881–1893.

Cottart, C. H., Nivet-Antoine, V., Laguillier-Morizot, C. and Beaudeux, J. L. (2010). Resveratrol bioavailability and toxicity in humans. *Mol. Nutr. Food Res.* **54**:7–16.

Côté, J., Caillet, S., Doyon, G., Sylvain, J. F. and Lacroix, M. (2010a). Analyzing cranberry bioactive compounds. *Crit. Rev. Food Sci. Nutr.* **50**:872–888.

Côté, J., Caillet, S., Doyon, G., Sylvain, J. F. and Lacroix, M. (2010b). Bioactive compounds in cranberries and their biological properties. *Crit. Rev. Food Sci.* 2010, **50**:666–679.

Cui, C. B., Jeong, S. K., Lee, Y. S., Lee, S. O., Kang, I. J. and Lim, S. S. (2009). Inhibitory activity of caffeoylquinic acids from the aerial parts of *Artemisia princeps* on rat lens aldose reductase and on the formation of advanced glycation end products. *J. Korean Soc. Appl. Biol. Chem.* **52**:655–662.

Day, A. J., DuPont, M. S., Ridley, S., Rhodes, M., Rhodes, M. J. C. and Williamson, G. (1998). Deglycosylation of favonoid and isofavonoid glycosides by human small intestine and liver L-glucosidase activity. *FEBS Lett.* **436**:71–75.

de la Fuente, J. Á. and Manzanaro, S. (2003). Aldose reductase inhibitors from natural sources. *Nat. Prod. Rep.* **20**:243–251.

Enomoto, S., Okada, Y., Güvenc, A., Erdurak, C. S., Coşkun, M. and Okuyama, T. (2004). Reductase (AR) and hematological activity, and on AR inhibitory activity of quercetin-3-O-methyl ether isolated from *Cistus laurifolius* L. *Biol. Pharm. Bull.* **27**:1140–1143.

Feng, C. G., Zhang, L. X. and Liu, X. (2005). Progress in research of aldose reductase inhibitors in traditional medicinal herbs. *Chin. J. Chin. Mater. Med.* **30**:1496–1500.

Fernandez, M., Caballero, J., Helguera, A. M., Castro, E. A. and Gonzalez, M. P. (2005). Quantitative structure-activity relationship to predict differential inhibition of aldose reductase by flavonoid compounds. *Bioorg. Med. Chem.* **13**:3269–3277.

Fossen, T., Pedersen, A. T. and Anderson, Ø. M. (1998). Flavonoids from red onion (Allium cepa). *Phytochemistry*. **47**:281–285.

Glauert, H. P., Calfee-Mason, K., Stemm, D. N., Tharappel, J. C. and Spear, B. T. (2010). Dietary antioxidants in the prevention of hepatocarcinogenesis: A review. *Mol. Nutr. Food Res.* **54**:875–896.

González, R., Ballester, I., López-Posadas, R., Suárez, M. D., Zarzuelo, A., Martínez-Augustin, O. and De Medina, F. S. (2011). Effects of flavonoids and other polyphenols on inflammation. *Crit. Rev. Food Sci. Nutr.* **51**:331–362.

Güvenç, A., Okada, Y., Akkol, E. K., Duman, H., Okuyama, T. and Çaliş, I. (2010). Investigations of anti-inflammatory, antinociceptive, antioxidant and aldose reductase inhibitory activities of phenolic compounds from *Sideritis brevibracteata*. *Food Chem.* **118**:686–692.

Haraguchi, H., Ohmi, I., Sakai, S. and Fukuda, A. (1996). Effect of *Polygonum hydropiper* sulfated flavonoids on lens aldose reductase and related enzymes. *J. Nat. Prod.* **59**:443–445

Hu, L., Chen, G. and Chau, R. M. (2006). A neural networks-based drug discovery approachand its application for designing aldose reductase inhibitors. *J. Mol. Graph. Model.* **24**:244–253.

Huang, G. J., Hsieh, W. T., Chang, H. Y., Huang, S. S., Lin, Y. C. and Kuo, Y. H. (2011). α-Glucosidase and aldose reductase inhibitory activities from the fruiting body of *Phellinus merrillii*. *J. Agric. Food Chem.* **59**:2702–5706. doi: 10.1021/jf2003943.

Jang, D. S., Yoo, N. H., Kim, N. H., Lee, Y. M., Kim, C. S., Kim, J. H., Kim, J. H. and Kim, J. S. (2010). 3,5-Di-O-caffeoyl-epi-quinic acid from the leaves and stems of erigeron annuus inhibits protein glycation, aldose reductase, and cataractogenesis. *Biol. Pharm. Bull.* **33**:329–333.

Jung, H. A., Islam, N., Kwon, Y. S., Jin, S. E., Son, Y. K., Park, J. J., Sohn, H. S. and Choi, J. S. (2011). Extraction and identification of three major aldose reductase inhibitors from *Artemisia Montana*. *Food Chem. Toxicol*. **49**:376–384.

Jung, H. A., Kim, Y. S. and Choi, J. S. (2009). Quantitative HPLC analysis of two key flavonoids and inhibitory activities against aldose reductase from different parts of the Korean thistle, *Cirsium maackii*. *Food Chem. Toxicol*. **47**:2790–2797.

Jung, S. H., Kang, S. S., Shin, K. H. and Kim, Y. S. (2004). Inhibitory effects of naturally occurring flavonoids on rat lens aldose reductase. *Nat. Prod. Sci.* **10**:35–39.

Jung, S. H., Lee, J. M., Lee, H. J., Kim, C. Y., Lee, E. H. and Um, B. H. (2007). Aldose reductase and advanced glycation endproducts inhibitory effect of *Phyllostachys nigra*. *Biol. Pharm. Bull.* **30**:1569–1572.

Kador, P. F. (1988). The role of aldose reductase in the development of diabetic complications. *Med. Res. Rev*. **8**:325–352.

Kamiyama, O., Sanae, F., Ikeda, K., Higashi, Y., Minami, Y., Asano, N., Adachi, I. and Kato, A. (2010). *In vitro* inhibition of α-glucosidases and glycogen phosphorylase by catechin gallates in green tea. *Food Chem.* **122**: 1061–1066.

Kim, J. K., Lee, Y. S., Kim, S. H., Bae, Y. S. and Lim, S. S. (2011). Inhibition of aldose reductase by phenylethanoid glycoside Isolated from the seeds of *Paulownia coreana*. *Biol. Pharm. Bull.* **34**:160–163.

Larkin, T., Price, W. E. and Astheimer, L. (2008). The key importance of soy isoflavone bioavailability to understanding health benefits. *Crit. Rev. Food Sci. Nutr.* **48**:538–552.

Lee, E. H., Song, D. G., Lee, J. Y., Pan, C. H., Um, B. H. and Jung, S. H. (2008). Inhibitory effect of the compounds isolated from *Rhus verniciflua* on aldose reductase and advanced glycation end products. *Biol. Pharm. Bull.* **31**, 1626–1630.

Lee, E. H., Song, D. G., Lee, J. Y., Pan, C. H., Um, B. H. and Jung, S. H. (2009a). Flavonoids from the leaves of *Thuja orientalis* inhibit the aldose reductase and the formation of advanced glycation endproducts. *J. Korean Soc. Appl. Biol. Chem.* **52**:448–455.

Lee, S. J., Park, W. H., Park, S. D. and Moon, H. I. (2009b). Aldose reductase inhibitors from *Litchi chinensis* Sonn. *J. Enzyme Inhibit Med. Chem*. **24**:957–959.

Lee, Y. S., Kim, J. K., Bae, Y. S., Won, M. H., Kang, I. J. and Lim, S. S. (2011). Inhibitory effect of glucodistylin from the bark of *Quercus acutissima* on human recombinant aldose reductase and sorbitol accumulation. *Arch. Pharm. Res*. **34**:211–215.

Lee, Y. S., Kim, S. H., Jung, S. H., Kim, J. K., Pan, C. H. and Lim, S. S. (2010). Aldose reductase inhibitory compounds from *Glycyrrhiza uralensis*. *Biol. Pharm. Bull.* **33**:917–921.

Li, S. Z., Mao, W., Cao, X. Y., Liang, S. W., Ding, Z. and Li, N. M. (1991). Inhibition of rat lens aldose reductase by quercetagetin and patuletin. *Eye Sci.* **7**:29–33.

Lim, S. S., Jung, Y. J., Hyun, S. K., Lee, Y. S. and Choi, J. S. (2006). Rat lens aldose reductase inhibitory constituents of *Nelumbo nucifera* stamens. *Phytother. Res*. **20**:825–830.

Lim, S. S., Jung, S. H., Ji, J., Shin, K. H. and Keum, S. R. (2001). Synthesis of flavonoids and their effects on aldose reductase and sorbitol accumulation in streptozotocin-induced diabetic rat tissues. *J. Pharm. Pharmacol.* **53**:653–668.

Liu, H., Liu, S., Qin, L. and Mo, L. (2009). CoMFA, CoMSIA analysis of 2,4-thiazolidinediones derivatives as aldose reductase inhibitors. *J. Mol. Model.* **15**:837–845.

Liu, H. B., Wang, Z. L., Qiao, Y. X. and Zhou, J. J. (2007). Flavonoids with aldose reductase inhibiting activity: Pharmacophore modeling and implications for mechanism. *Acta Phys. Chim. Sin.* **23**:1059–1064.

Liu, Y. H., Xue, C. Y., Ou, Y. H., Zhang, R. X. and Zhang, Y. (2006). Inhibition of aldose reductase from rat lens by tea polyphenol. *Pract. Prevent. Med.* **13**:1162–1164.

Matsuda, H., Asao, Y., Nakamura, S., Hamao, M., Sugimoto, S., Hongo, M., Pongpiriyadacha, Y. and Yoshikawa, M. (2009). Antidiabetogenic constituents from the thai traditional medicine *Cotylelobium melanoxylon*. *Chem. Pharm. Bull.* **57**:487–494.

Matsuda, H., Morikawa, T., Toguchida, I. and Yoshikawa, M. (2002). Structural requirements of flavonoids and related compounds for aldose reductase inhibitory activity. *Chem. Pharm. Bull.* **50**:788–795.

Matsuda, H., Wang, T., Managi, H. and Yoshikawa, M. (2003). Structural requirements of flavonoids for inhibition of protein glycation and radical scavenging activities. *Bioorg. Med. Chem.* **11**:5317–5323.

Matsui, T., Tanaka, T., Tamura, S., Toshima, A., Tamaya, K., Miyata, Y., Tanaka, K. and Matsumoto, K. (2007). α-Glucosidase inhibitory profile of catechins and theaflavins. *J. Agric. Food Chem.* **55**:99–105.

Mercader, A. G., Duchowicz, P. R., Fernandez, F. M., Castro, E. A., Bennardi, D. O., Autino, J. C. and Romanelli, G.P. (2008). QSAR prediction of inhibition of aldose reductase for flavonoids. *Bioorg. Med. Chem.* **16**:7470–7476.

Miyamoto, S. (2002). Molecular modeling and structure-based drug discovery studies of aldose reductase inhibitors. *Chem-Bio. Informatics J.* **2**(3):74–85.

Morabito, G., Trombetta, D., Brajendra, K. S., Ashok, K. P., Virinder, S. P., Naccari, C., Naccari, C., Mancari, F., Saija, A., Cristani, M., Firuzi, O. and Saso, L. (2010). Antioxidant properties of 4-methylcoumarins in in vitro cell-free systems. *Biochimie* **92**:1101–1107.

Murata, M., Irie, J. and Homma, S. (1994). Aldose reductase inhibitors from green tea. *LWT—Food Sci. Technol*. **27**:401–405.

Natella, F., Lorrain, B., Prasad, A. K., Parmar, V. S., Saso, L. and Scaccini, C. (2010). 4-Methylcoumarins as antioxidants: Scavenging of peroxyl radicals and inhibition of human low-density lipoprotein oxidation. *Biochimie* **92**:1147–1152.

Nishimura-Yabe, C. (1998). Aldose reductase in glucose toxicity: A potential target for the prevention of diabetic complications. *Pharmacol. Rev.* **50**:21–33.

Okuda, J., Miwa, I., Inagaki, K., Horie, T. and Nakayama, M. (1982). Inhibition of aldose reductases from rat and bovine lenses by flavonoids. *Biochem. Pharmacol.* **31**:3807–3822.

Okuda, J., Miwa, I., Inagaki, K., Horie, T. and Nakayama, M. (1984). Inhibition of aldose reductase by 3ċ,4ċ-dihydroxyflavones. *Chem. Pharm. Bull.* **32**:767–772.

Park, H. Y., Kim, H. K., Jeon, S. H., Kim, S. H., Chun, W. J., Lim, S. S., Kim, M. J. and Kwon, Y. S. (2009). Aldose reductase inhibitors from the leaves of *Salix hulteni*. *J. Korean Soc. Appl. Biol. Chem.* **52**:493–497.

Park, H. Y., Kim, S. H., Kim, G. B., Sim, J. Y., Lim, S. S., Kim, M. J., Chun, W. and Kwon, Y. S. (2010). A new isoflavone glycoside from the stem bark of *Sophora japonica*. *Arch. Pharm. Res.* **33**:1165–1168.

Park, C. H., Lim, S. S. and Lee, D. U. (2007). Structure-activity relationships of components from the roots of *Pueraria thunbergiana* having aldose reductase inhibitory and antioxidative activity. *Bull. Korean Chem. Soc.* **28**:493–495.

Patra, J. C. and Singh, O. (2009). Artificial neural networks-based approach to design ARIs using QSAR for diabetes mellitus. *J. Comput. Chem*. **30**:2494–2508.

Prabhakar, Y. S., Gupta, M. K., Roy, N. and Venkateswarlu, Y. (2006). A high dimensional qsar study on the aldose reductase inhibitory activity of some flavones: Topological descriptors in modeling the activity. *J. Chem. Inf. Model.* **46**:86–92.

Scotti, L., Fernandes, M. B., Muramatsu, E., Pasqualoto, K. F. M., Emereciano, V. P., Tavares, L. C., da Silva, M. S. and Scotti, M. T. (2011). Self-organizing maps and VolSurf approach to predict aldose reductase inhibition by flavonoid compounds. *Rev. Bras. Farmacogn.* **21**:170–180.

Shin, K. H., Kang, S. S., Seo, E. A. and Shin, S. W. (1995). Isolation of aldose reductase inhibitors from the flowers of *Chrysanthemum boreale*. *Arch. Pharm. Res.* **18**:65–68.

Sivakumari, K., Rathinabai, A. F. M. C., Kaleena, P. K., Jayaprakash, P. and Srikanth, R. (2010). Molecular docking study of bark-derived components of Cinnamomum cassia on aldose reductase. *Indian J. Sci. Technol.* **3**:1081–1088.

Thareja, S., Aggarwal, S., Bhardwaj, T. R. and Kumar, M. (2010). 3D-QSAR studies on a series of 5-arylidine-2,4-thiazolidinediones as aldose reductase inhibitors: A selforganizing molecular field analysis approach. *Med. Chem.* **6**:30–36.

Urzhumtsev, A., Tête-Favier, F., Mitschler, A., Barbanton, J., Barth, P., Urzhumtseva, L., Biellmann, J. F., Podjarny, A. D. and Moras, D. A. (1997). A 'specificity' pocket inferred from the crystal structures of the complexes of aldose reductase with the pharmaceutically important inhibitors tolrestat and sorbinil. *Structure*. **5**:601–612.

van Dorsten, F. A., Grun, C. H., van Velzen, E. J. J., Jacobs, D. M., Draijer, R. and van Duynhoven, J. P. M. (2010). The metabolic fate of red wine and grape juice polyphenols in humans assessed by metabolomics. *Mol. Nutr. Food Res.* **54**:897–908.

Veitch, N. C. and Grayer, R. J. (2008). Flavonoids and their glycosides, including anthocyanins. *Nat. Prod. Rep.* **25**:555–611.

Verma, A. K. and Pratap, R. (2010). The biological potential of flavones. *Nat. Prod. Rep.* **27**:1571–1593.

Walle, T. (2004). Absorption and metabolism of flavonoids. *Free. Radical Bio. Med.* **36**:829–837.

Walle, T. (2007a). Methylation of dietary flavones greatly improves their hepatic metabolic stability and intestinal absorption. *Mol. Pharmaceut.* **4**:826–832.

Walle, T. (2007b). Methoxylated flavones, a superior cancer chemopreventive flavonoid subclass? *Semin. Cancer Biol.* **17**:354–362.

Walle, T. (2009). Methylation of dietary flavones increases their metabolic stability and chemopreventive effects. *Int. J. Mol. Sci.* **10**:5002–5019.

Walle, T., Browning, A. M., Steed, L. L., Reed, S. G. and Walle, U. K. (2005). Flavonoid glucosides are hydrolyzed and thus activated in the oral cavity in humans. *J. Nutr.* **135**:48–52.

Wang, Q., Zhou, L. X. and Luo, X. D. (2005). Advances in studies on aldose reductase inhibitors from plants. *Chin. Trad. Herb. Drugs* **36**:298–303.

Wang, T. T. Y., Schoene, N. W., Kim, Y. S., Mizuno, C. S. and Rimando, A. M. (2010). Differential effects of resveratrol and its naturally occurring methylether analogs on cell cycle and apoptosis in human androgen-responsive LNCaP cancer cells. *Mol. Nutr. Food Res.* **54**:335–344.

Wen, X. and Walle, T. (2006). Methylated flavonoids have greatly improved intestinal absorption and metabolic stability. *Drug Metab. Dispos.* **34**:1786–1792.

Weng, Y. L., Liao, H. F., Li, A. F. Y., Chang, J. C. and Chiou, R. Y. Y. (2010). Oral administration of resveratrol in suppression of pulmonary metastasis of BALB/c mice challenged with CT26 colorectal adenocarcinoma cells. *Mol. Nutr. Food Res.* **54**:259–267.

Wilson, D. K., Bohren, K., Gabbay, K. H. and Quiocho, F. A. (1992). An unlikely sugar substrate site in the 1.65 A structure of the human aldose reductase holoenzyme implicated in diabetic complications. *Science*, **257**:81–84.

Wilson, D. K., Tarle, I., Petrash, J. M. and Quiocho, F. A. (1993). Refined 1.8 A structure of human aldose reductase complexed with the potent inhibitor zopolrestat. *Proc. Natl. Acad. Sci. USA* **90**:9847–9851.

Xiao, J. B., Cao, H., Wang, Y. F., Yamamoto, K. and Wei, X. L. (2010). Structure-affinity relationship of flavones on binding to serum albumins: Effect of hydroxyl groups on ring A. *Mol. Nutr. Food Res.* **54**:S253–S260.

Xiao, J. B., Cao, H., Wang, Y. F., Zhao, J. Y. and Wei, X. L. (2009). Glycosylation of dietary flavonoids decreases the affinities for plasma protein. *J. Agric. Food Chem.* **57**:6642–6648.

Xiao, J. B., Chen, T. T., Cao, H., Chen, L. and Yang, F. (2011a). Molecular property-affinity relationship of flavanoids and flavonoids for human serum albumin in vitro. *Mol. Nutr. Food Res.* **55**:310–317.

Xiao, J. B., Kai, G. Y., Yang, F., Liu, C. X., Xu, X. C. and Yamamoto, K. (2011b). Molecular structure-affinity relationship of natural polyphenols for bovine γ-globulin. *Mol. Nutr. Food Res.* **55**:S86–S92.

Xiao, J. B., Ni, X. L., Kai, G. Y., Chen, X. Q. (2013a). A review on structure-activity relationship of dietary polyphenols inhibiting α-amylase. *Crit. Rev. Food Sci. Nut.r.* **53**:497–506.

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

Xie, H. H., Wang, T., Matsuda, H., Morikawa, T., Yoshikawa, M. and Tani, T. (2005). Bioactive constituents from Chinese natural medicines. XV. Inhibitory effect on aldose reductase and structures of Saussureosides A and B from *Saussurea medusa*. *Chem. Pharm. Bull.* **53**:1416–1422.

Yawadio, R., Tanimori, S. and Morita, N. (2007). Identification of phenolic compounds isolated from pigmented rices and their aldose reductase inhibitory activities. *Food Chem.* **101**:1616–1625.

Yoo, N. H., Jang, D. S., Yoo, J. L., Lee, Y. M., Kim, Y. S., Cho, J. H. and Kim, J. S. (2008). Erigeroflavanone, a flavanone derivative from the flowers of *Erigeron annuus* with protein glycation and aldose reductase inhibitory activity. *J. Nat. Prod.* **71**:713–715

Yoshikawa, M., Morikawa, T., Murakami, T., Toguchida, I., Harima, S. and Matsuda, H. (1999). Medicinal flowers. I. Aldose reductase inhibitors and three new eudesmane-type sesquiterpenes, kikkanols A, B, and C, from the flowers of *Chrysanthemum indicum* L. *Chem. Pharm. Bull.* **47**:340–345.

Zhou, S. Y., Yang, R. T., Teng, Z. H., Zhang, B. L., Hu, Y. Z., Yang, Z. F., Huan, M. L., Zhang, X. and Mei, Q. B. (2009). Dose-dependent absorption and metabolism of trans-polydatin in rats. *J. Agric. Food Chem.* **57**:4572–4579.

Zhu, C. J. (2009). Aldose reductase inhibitors as potential drugs for diabetic complications. *Chin. J. New Drugs* **18**:302–306.