Chapter 1

Aldose Reductase Inhibitors Phyto Constituents

1.1 Introduction

India has become the capital of diabetic. According to a report by IDF (international diabetes federation 2015), 1 in 7 births is affected by gestational diabetes,1 in 11 adults have diabetes (415 million), by 2040, 1 adult in 10 (642 million) will have diabetes, Every 6 seconds a person dies from diabetes (5.0 million deaths).

People with diabetes are at higher risk of developing a number of disabling and life-threatening health problems than people without diabetes. Consistently high blood glucose levels can lead to serious diseases affecting the heart and blood vessels, eyes, kidneys and nerves. People with diabetes are also at increased risk of developing infections. In almost all high-income countries, diabetes is a leading cause of cardiovascular disease, blindness, kidney failure and lower-limb amputation (IDF 2015).

Therefore, there is a growing interest in search of drugs that alleviate the various symptoms of diabetic complications. Several studies have suggested that hyperglycaemia may have important role in the pathogenesis of diabetic complications by several mechanisms. Of these, increased aldose reductase (AR) related polyol pathway flux is one important mechanism (Brownlee, 2001). AR is an NADPH-dependent oxidoreductase and one of the important enzymes in the polyol pathway (Figure 1.1) that catalyses the reduction of various sugars to sugar alcohols, such as glucose to sorbitol. Sorbitol is then catalyzed to fructose by sorbitol dehydrogenase, an NADPH-dependent enzyme. Under normal conditions, the affinities of cell based AR for glucose are low, however, in diabetic conditions; an increase in the rate of the AR related polyol pathway augments intracellular concentrations of sorbitol and its metabolite fructose. As shown in Figure 1, accumulation of sorbitol in the cells due to its poor penetration across membranes and inefficient metabolism results in the development of diabetic complications (Kador *et al*., 1980).

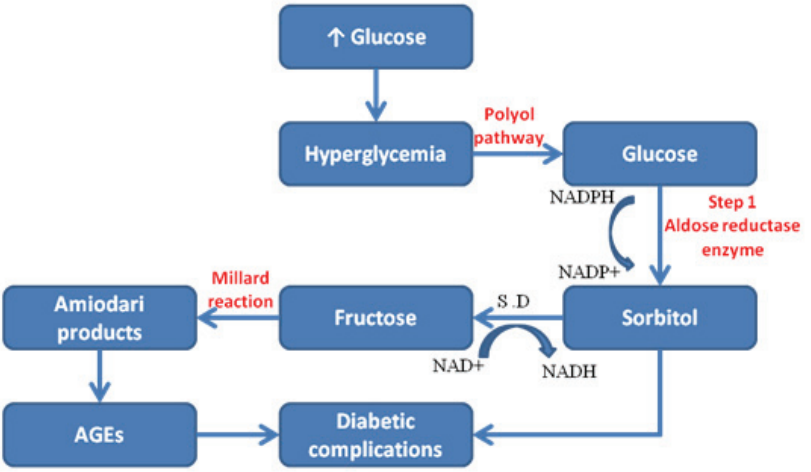


Figure 1.1 Schematic diagram presenting the process for the development of complications of Diabetes mellitus (Chethan *et al*., 2008).
S.D: sorbitol dehydrogenase.

The polyol pathway plays an important role in the development of degenerative complications of diabetes, such as neuropathy, nephropathy, retinopathy, cataract and cardiovascular diseases (Wirasathien et *al*., 2007). The other mechanisms like increased advanced glycation end-product (AGE) formation, activation of protein kinase C (PKC) isoforms and increased hexosamine pathway flux also contribute to diabetic complications. All these mechanisms emphasize hyperglycaemia-induced overproduction of superoxides involving the mitochondrial electron-transport chain (Brownlee., 2001).

In the Western world the incidence of diabetes mellitus is increasing at an almost epidemic rate. Because of this high incidence and the associated morbidity and mortality, it has become a major health hazard. The diabetes control and complications trial (DCCT) undertaken in the USA in 1993; the United Kingdom prospective diabetes study (UKPDS) conducted in 1998, and a Japanese trial have all demonstrated that strict and sustained control of glucose excursions through interventions, including intensive insulin therapy, reduces the risk of developing these complications in diabetics, thereby showing the association between hyperglycaemia and the development of long-term diabetic complications (Ohkubo *et al.,* 1995). However, close control is difficult to maintain, and considerable efforts have been made to find novel and effective antidiabetic agents that act by mechanisms independent of controlling blood glucose. AR inhibitors (ARIs) offer the possibility of preventing or arresting the progression of these long-term diabetic complications, despite the high blood glucose

levels and hence with no risk of hypoglycaemia, since they have no effect on blood glucose (Costantino *et al*., 1999). The present book gives an insight into the screening methods that are commonly employed for AR inhibitory activity and also summarizes phytochemicals and extracts which have been reported to possess AR inhibitory activity.

Screening Methods for AR Inhibitory Activity

AR inhibitory activity is screened by both *in vitro* and *in vivo* methods. *In vitro* assays for AR enzyme are further classified into different models based on source of enzyme.

In vitro Methods

Rat lens AR (RLAR) inhibitory activity. Male albino rats of wister strain weighing 250-280 g are used for isolation of crude AR. Rat lens homogenate is prepared according to the modified method of Hayman *et al*. (1965) whereby the lenses are homogenized in sodium phosphate buffer (pH 6.2) and the supernatant obtained by centrifugation of the homogenate at 10000 rpm at 4 °C for 20 min is frozen until use. Crude AR, with activity of 6.5 U/mg, is used for the evaluation of enzyme inhibition. Reaction solution consisting of 600 µL of 100 mM of sodium phosphate buffer (pH 6.2), 100 µL of AR homogenate, 100 µL of 0.15 µM NADPH, 9 µL of the sample dissolved in 10% DMSO and 90 µL of 50 mM of DL-glyceraldehyde as the substrate. The AR activity is determined by measuring the decrease in NADPH absorption at 340 nm over 4 min period on UV/Visble spectrophotometer.

Rat Kidney AR (RKAR) Inhibitory Activity

In this method male albino rats of wister strain weighing 250-280 g are used for isolation of crude AR. Rat kidney homogenate is prepared according to the modified method outlined by Cerelli *et al.* (1986). The kidneys are first homogenized in sodium phosphate buffer (pH 6.2) and the supernatant obtained by centrifugation of the homogenate at 4000 rpm at 4 °C for 30 min is then frozen until use. Crude AR, with activity of 6.5 U/mg, is used for the evaluation of enzyme inhibition. Reaction solution is made to contain 1.0 mL of 100 mM sodium phosphate buffer (pH 6.2), 100 µL of AR homogenate, 100 µL of 0.15 µM NADPH, 100 µL of the sample (different concentrations prepared in DMSO) and100 µL of 100 mM of DL-glyceraldehyde as a substrate. AR activity is determined by measuring the decrease in NADPH absorption at 340 nm over 1 min period. Quercetin, a well-known ARI, is generally used as a reference standard.

AR Enzyme from Cataracted Human Eye Lens

Cataracted human eye lenses are washed with saline and their fresh weights are recorded. The lenses are pooled and homogenized in (1:2 w/v) sodium

phosphate buffer (0.135 M, pH 7.0) containing 0.5 mM phenylmethyl sulfonyl fluoride (PMSF) and 10 mM β-mercaptoethanol and centrifuged at 8000g for 30 min at 4 °C. The supernatant is used for determination of AR activity (Chethan *et al*., 2008).

AR Enzyme from Bovine Eyes

In this method the AR enzyme is obtained from bovine eyes lenses. The lenses are removed by lateral incision of the eye and homoginized in 135 mM phosphate buffer containing 10 mM β-mercaptoethanol. The homogenate is centrifuged at 10000g for 15 min and the supernatant fluid used for determination of AR activity (Guzman *et al.*, 2005).

Human Recombinant AR (HRAR) Inhibitory Activity

Inhibition of HRAR is determined according to the method described by Nishimura *et al*. (1991). The reaction mixture is prepared by mixing 100 µL 0.15 mM NADPH, 100 µL of 10 mM DL-glyceraldehyde (as a substrate), 5 µL HRAR and various concentrations of the sample with 100 mM sodium phosphate buffer (pH 6.2) to adjust the total volume to 1 mL. AR activity is determined by measuring the decrease in NADPH absorption at 340 nm over a period of 1 min.

PL (porcine lens) AR Inhibitory Activity

Lenses were removed from porcine eyes and homoginized in 3 vol of 135 mM phosphate buffer containing 10 mM β-mercaptoethanol. The homogenate is centrifuged at 10000g for 15 min and the supernatant fluid used for determination of AR activity (Haraguchi *et al*., 1996).

In vivo Methods

Determination of lens galactitol levels by GLC. Lens galactitol level is determined according to the method of Kato *et al*. (2006). After 21 days of feeding galactose, rats are sacrificed by CO_2 asphyxiation and the eyeballs surgically excised. The lenses are carefully dissected under sterile conditions, the lens material weighed and homogenized in 20% ice cold acetonitrile (1 mL). The sample and methyl α-D-mannopyranoside (0.1 µM) used as internal standard are mixed, centrifuged to eliminate proteins and the resulting supernatant lyophilized. Sugar alcohols are trimethysilylated using tri-sil reagent. After addition of 1 mL of the silylating reagent, the tube is placed in an incubating oven at 60 °C for 30 min. Analysis is performed by GLC.

Estimation of Galactitol Levels in Galactosomic Rat Lens by RP-HPLC

Lyophilized samples of five groups of galactosomic rat were derivatized by adding 250µL of pyridine and 500µL of phenylisocynate and the reaction carried out for 1hr at 55^0C on water bath with occasionally shaking. Derivatized samples are analyzed by reverse-phase C 18 column with the ultraviolet detector at 240 nm. HPLC run by using mobile phase consisting of acetonitrile and 0.01M dipotassium hydrogen phosphate buffer (60:40). Flow rate was adjusted to 2 mL/min and the injection volume was 20 µL. A standard graph was plotted by analyzing solutions of different concentrations of galactitol using glucose as internal standard.

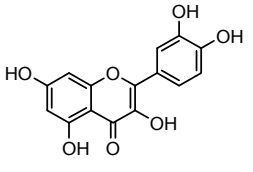
Phytochemicals with AR Inhibitory Activity

Although several synthetic ARIs such as tolrestat, epalrestat and sorbinil exhibit potent effects, either their use was limited, or they have been withdrawn from clinical trials because of relatively low efficacy, poor pharmacokinetics and unsatisfactory safety (Kawannishi *et al*., 2003; Manzanaro *et al*., 2006; Peyrou *et al.,* 2006). At present, only eplarestat, which reached the Japanese market in 1992, is still available in Japan. Thus, there is still an urgent need for development of improved ARIs (Angel de la Fuente and Manzanaro, (2003)).

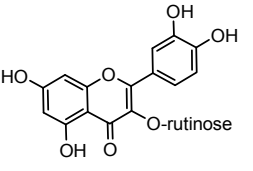
There is growing interest in the benefits of dietary supplements such as naturceuticals and traditional herbal medicines as pharmaceuticals that lack toxicity and other harmful side effects. A vast literature survey showed that cataract progression could be slowed or prevented by inhibition of AR enzyme using natural resources (Crabbe *et al*., 1998; Fuente *et al.*, 2003).

Many structurally diverse phytochemicals and extracts have been reported as potent ARIs *in vitro*. Currently known ARIs can be classified into four main groups based on their structures: acetic acid derivatives e.g. tolrestat and epalrestat, cyclic imides e.g. sorbini, phenolic derivatives e.g. quercetin, and phenylsulfonyl nitromethane derivatives e.g. ZD 5522.

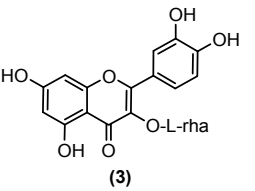
Plant derived compounds having significant AR inhibitory activity can be classified into specific chemical groups such as flavonoids, tannins, phenolics, alkaloids, terpenoids, coumarins and miscellaneous compounds. The structures of these phytochemicals are shown in Figures 2-7.



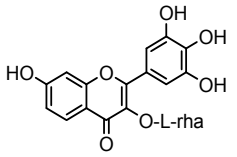
(1)



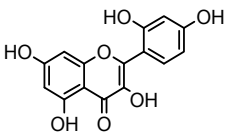
(2)



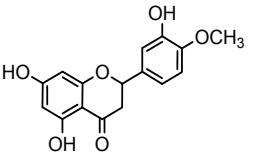
(3)



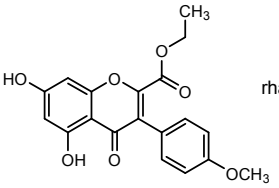
(4)



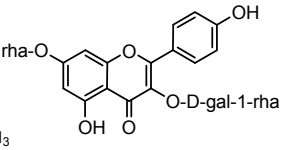
(5)



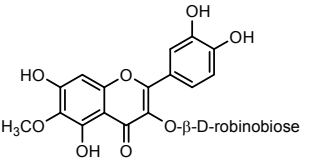
(6)



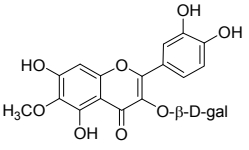
(7)



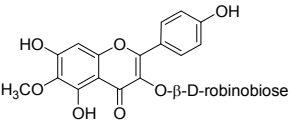
(8)



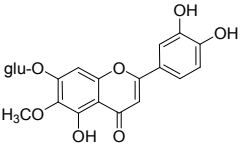
(9)



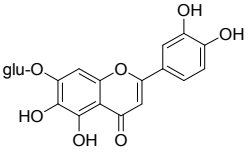
(10)



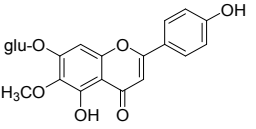
(11)



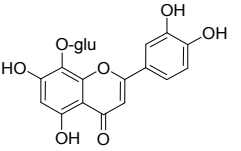
(12)



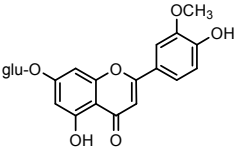
(13)



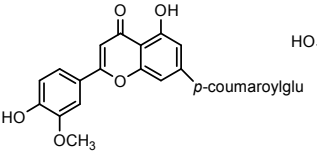
(14)



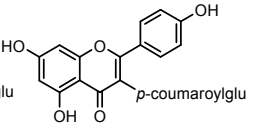
(15)



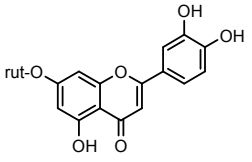
(16)



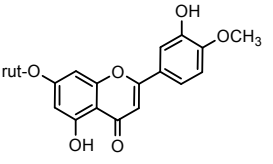
(17)



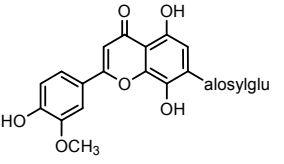
(18)



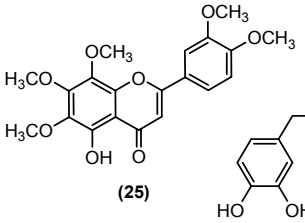
(19)



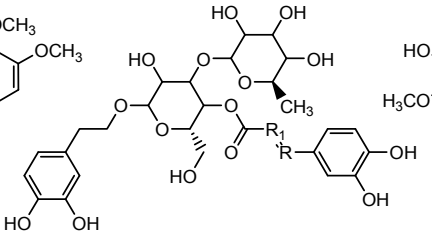
(20)



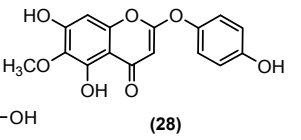
(21)



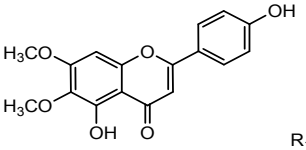
(25)



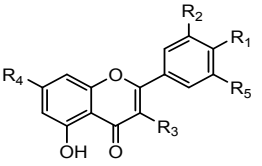
R-R1 =single bond acteoside **(26)**
R-R1 = double bond dehydroacteoside **(27)**



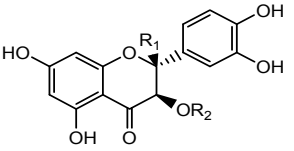
(28)



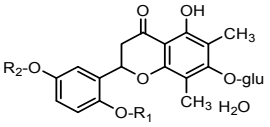
(29)



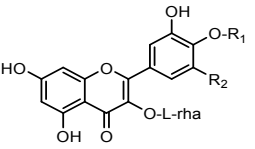
R_1	R_2	R_3	R_4	R_5	
OH	OH	OSO_3K	OH	H	**(30)**
OH	OCH_3	OH	OH	H	**(31)**
OH	OCH_3	OSO_3K	OH	H	**(32)**
OH	OCH_3	OSO_3K	OSO_3K	H	**(33)**
OH	OCH_3	OH	OCH_3	H	**(34)**
OH	OCH_3	OSO_3K	OCH_3	H	**(35)**
OH	OH	O-glu	OH	H	**(36)**
OCH_3	H	O-glu	OSO_3K	OH	**(37)**



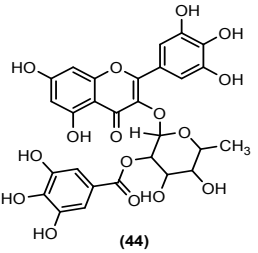
R_1=H R_2=H **(38)**
R_1=H R_2= rha **(39)**



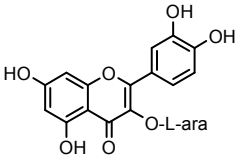
R_1 = R_2 = H **(40)**
R_1 = H R_2 = CH_3 **(41)**



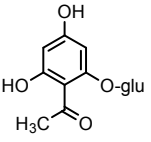
R_1 = H R_2 = OH (**42**)
R_1 = CH3 R_2 = OH (**43**)



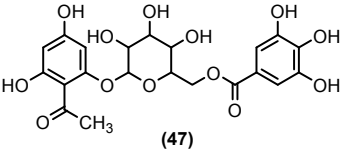
(44)



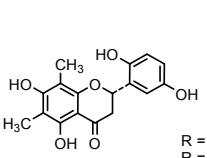
(45)



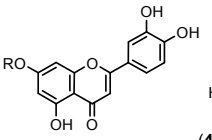
(46)



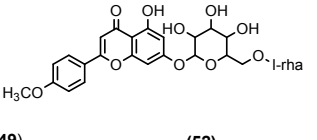
(47)



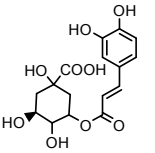
(48)



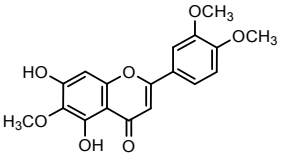
R = H (**49**)
R = β-D-glucopyranosyl (**50**)
R = β-D-glucopyranosiduronic acid (**51**)



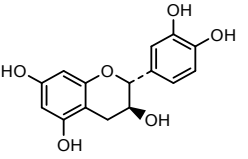
(52)



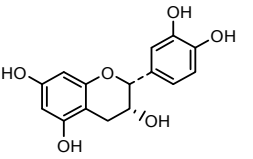
(53)



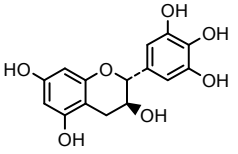
(54)



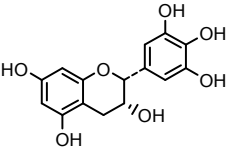
(55)



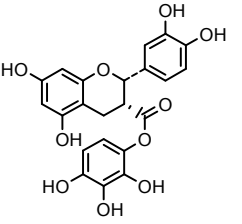
(56)



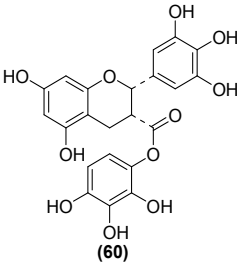
(57)



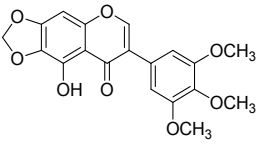
(58)



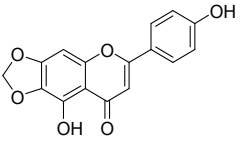
(59)



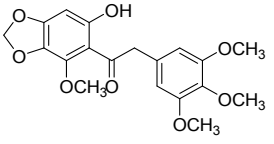
(60)



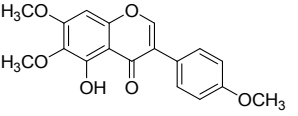
(61)



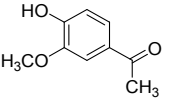
(62)



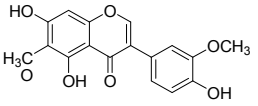
(63)



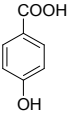
(64)



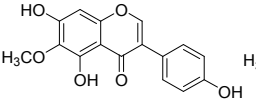
(65)



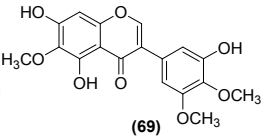
(66)



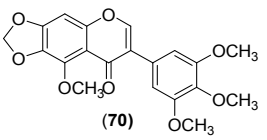
(67)



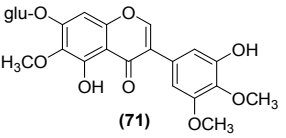
(68)



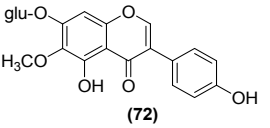
(69)



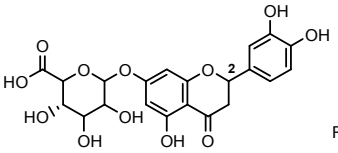
(**70**)



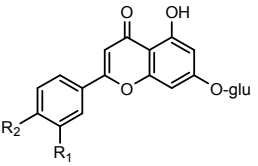
(**71**)



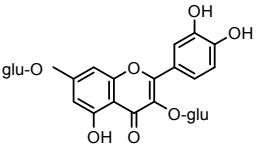
(**72**)



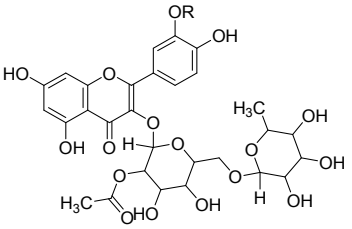
(2S)-(**73**)
(2R)-(**74**)



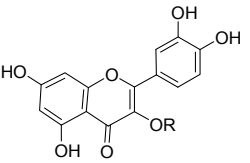
R_1 = H R_2 = OH (**75**)
R_1 = OH R_2 = OCH_3 (**76**)



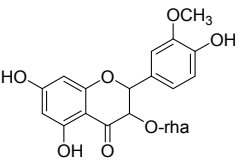
(**77**)



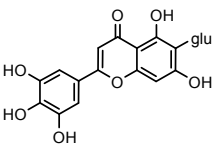
R = H (**78**)
R = CH_3 (**79**)



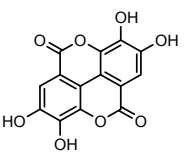
R= dirha(2→6)-gal (**80**)
R= neohesperidoside (**81**)



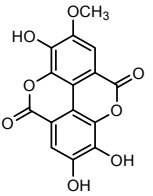
(**82**)



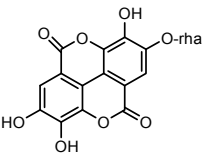
(**83**)



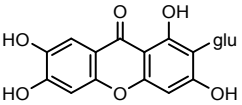
(**84**)



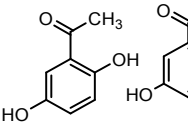
(**85**)



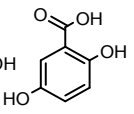
(**86**)



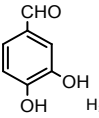
(**87**)



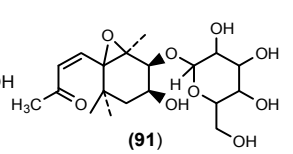
(**88**)



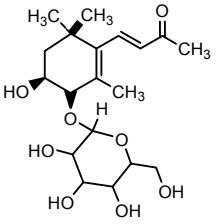
(**89**)



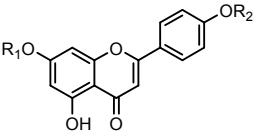
(**90**)



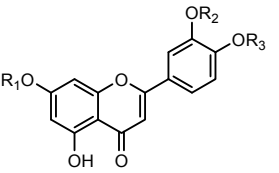
(**91**)



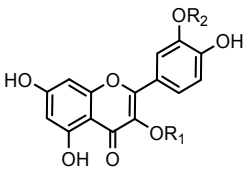
(92)



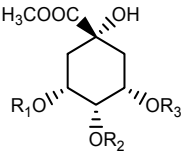
$R_1 = H \quad R_2 = H$ **(93)**
$R_1 = glu \quad R_2 = H$ **(94)**
$R_1 = H \quad R_2 = glu$ **(95)**
$R_1 = rut \quad R_2 = H$ **(96)**

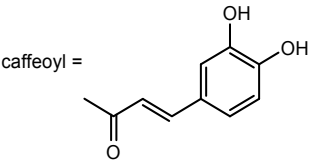


R_1=glu R_2=H R_3=H **(97)**
R_1=H R_2=H R_3=glu **(98)**
R_1=rut R_2=H R_3=H **(99)**
R_1=glu R_2=CH_3 R_3=H **(100)**
R_1=rut R_2=CH_3 R_3=H **(101)**

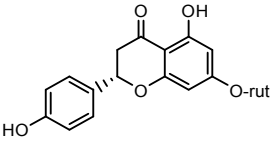


$R_1 = glu \quad R_2 = H$ **(102)**
$R_1 = rut \quad R_2 = CH_3$ **(103)**

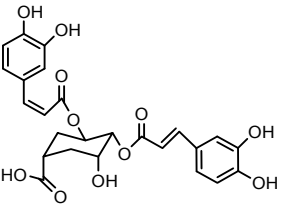




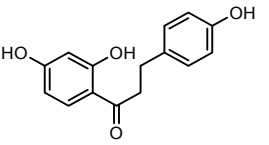
$R_1 = caffeoyl \quad R_2 = H \quad R_3 = H$ **(104)**
$R_1 = H \quad R_2 = caffeoyl \quad R_3 = H$ **(105)**
$R_1 = H \quad R_2 = H \quad R_3 = caffeoyl$ **(106)**



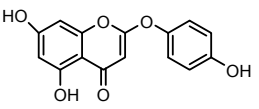
(107)



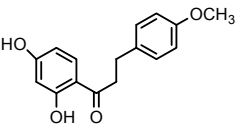
(108)



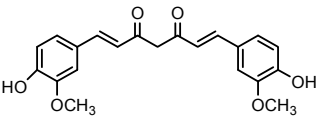
(109)



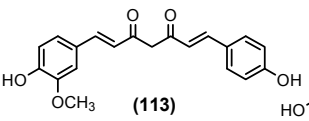
(110)



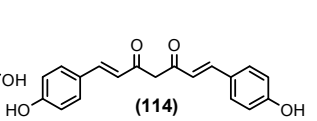
(111)



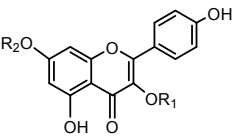
(112)



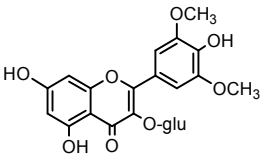
(113)



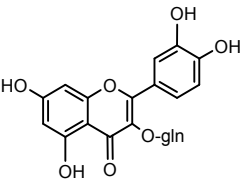
(114)



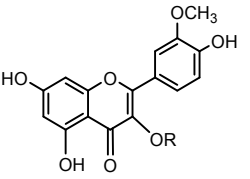
R_1	R_2		R_1	R_2	
H	H	**(115)**	rha(1-2)gln	H	**(120)**
gal	H	**(116)**	rha(1-2)glu	H	**(121)**
H	glu	**(117)**	glu	H	**(122)**
glu	H	**(118)**	gln-methylester	H	**(123)**
rha(1-6)glu	H	**(119)**			



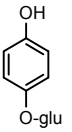
(124)



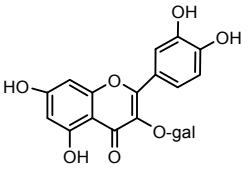
(125)



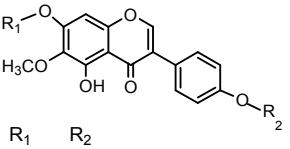
R=glu **(126)**
R=rha(1-6)-glu **(127)**



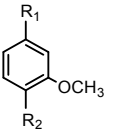
(128)



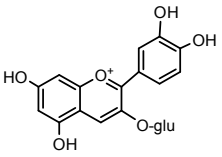
(129)



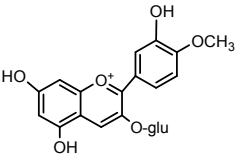
R_1	R_2	
glu	glu	**(130)**
H	glu	**(131)**



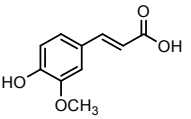
R_1	R_2	
CH_2OH	OH	**(132)**
$(CH_2)_2OH$	OH	**(133)**
CH_2COOH	OH	**(134)**
CH_2COOH	OCH_3	**(135)**
$(CH_2)_2COCH_3$	OH	**(136)**



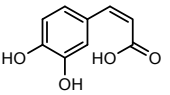
(137)



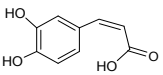
(138)



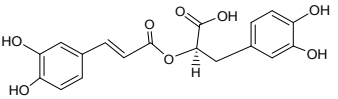
(139)



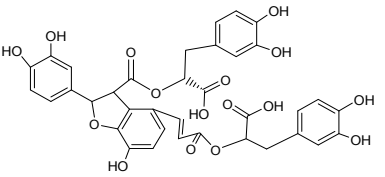
(140)



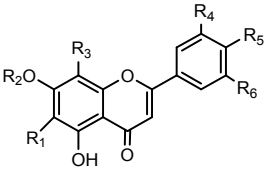
(140)



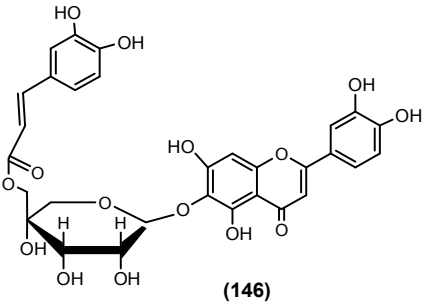
(141)



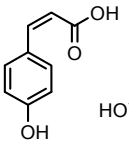
(142)



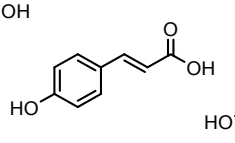
R_1	R_2	R_3	R_4	R_5	R_6	
glu	H	H	H	OH	OH	(**143**)
H	H	glu	H	OH	OH	(**144**)
H	H	glu	H	OH	H	**(145)**
H	glu	H	OCH_3	OCH_3	OCH_3	**(147)**
H	H	H	OCH_3	OH	OCH_3	**(148)**



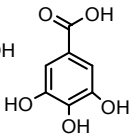
(146)



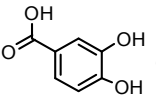
(149)



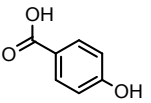
(150)



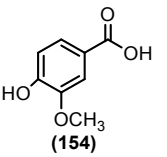
(151)



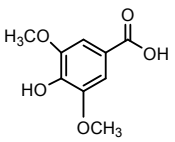
(152)



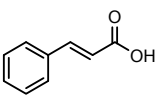
(153)



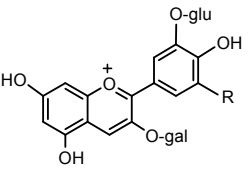
(154)



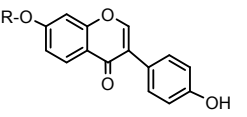
(155)



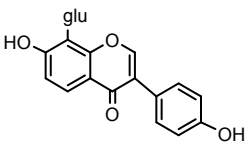
(156)



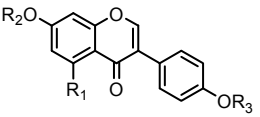
R=O-glu (**157**)
R=OH **(158)**



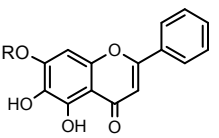
R= H (**159**)
R=glu (**160**)



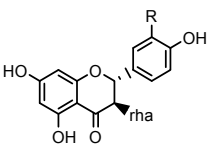
(161)



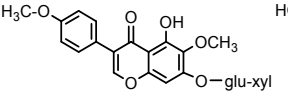
R_1=H R_2 =glu R_3=CH_3 (**162**)
R_1=OH R_2 =glu R_3=H (**163**)
R_1=OH R_2=H R_3=H **(164)**
R_1=H R_2=H R_3=CH_3 **(165)**



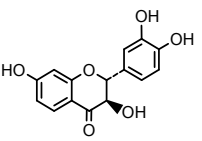
R=gln **(166)**
R=H **(167)**



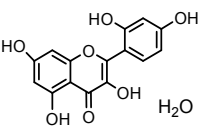
R=H **(168)**
R=OH **(169)**



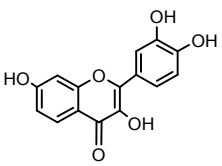
(170)



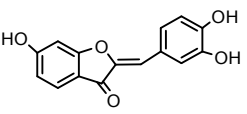
(171)



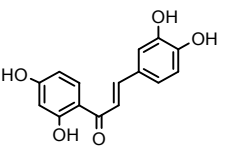
(172)



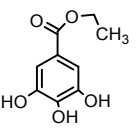
(173)



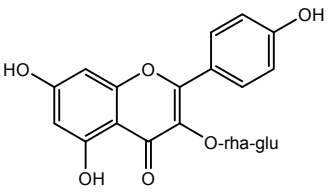
(174)



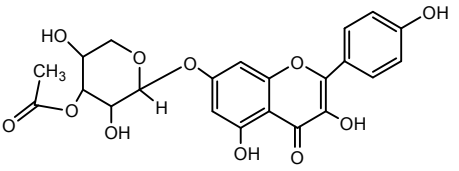
(175)



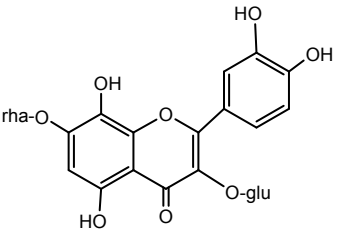
(176)



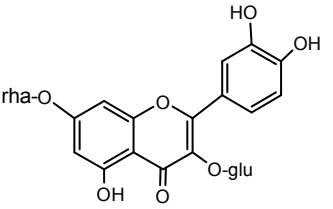
(177)



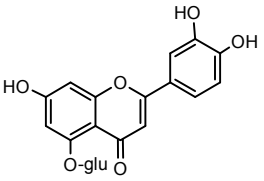
(178)



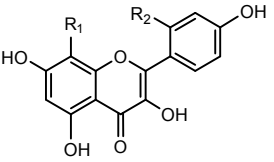
(179)



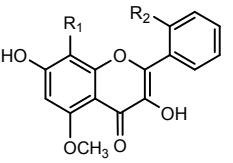
(180)



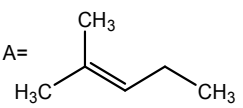
(181)

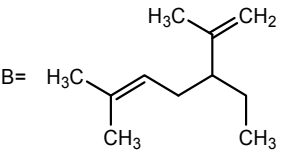


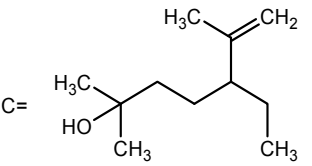
R_1	R_2	
A	H	**(182)**
B	OH	**(183)**
B	OH	**(184)**

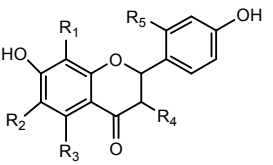


R_1	R_2	
C	OH	**(185)**
B	OH	**(186)**
A	H	**(187)**



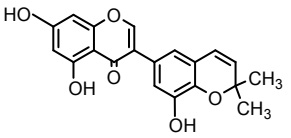




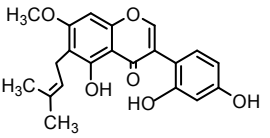


R_1	R_2	R_3	R_4	R_5	
B	H	OH	H	OH	**(188)**
C	H	OCH_3	H	OH	(**189**)
B	H	OCH_3	H	OH	**(190)**
B	H	OCH_3	H	OCH_3	**(191)**

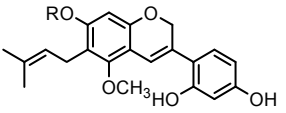
R_1	R_2	R_3	R_4	R_5	
A	H	OCH_3	OH	H	(**192**)
A	H	OCH_3	H	H	(**193**)
A	H	OH	H	OH	(**194**)
A	H	OH	H	OH	(**195**)



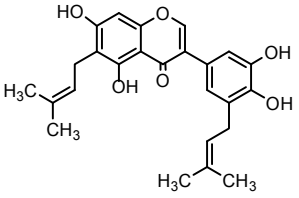
(196)



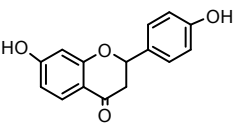
(197)



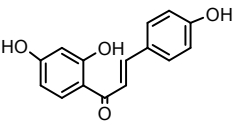
R=H **(198)**
R=CH_3 **(199)**



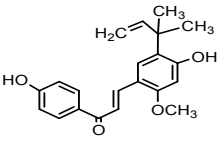
(200)



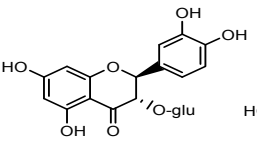
(201)



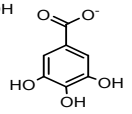
(202)



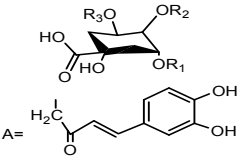
(203)



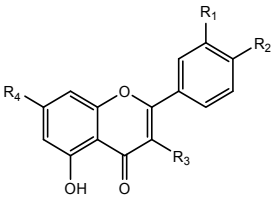
(204)



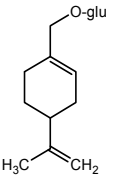
(205)



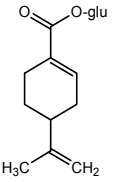
R_1	R_2	R_3	
A	H	A	**(206)**
H	A	H	**(207)**
A	H	H	**(208)**



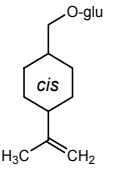
R_1	R_2	R_3	R_4	
OH	OH	O-gal	OH	**(209)**
OH	OH	H	O-rut	**(210)**



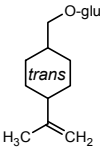
(211)



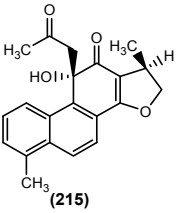
(212)



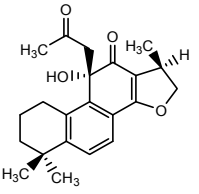
(213)



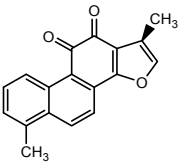
(214)



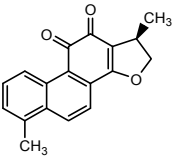
(215)



(216)



(217)



(218)

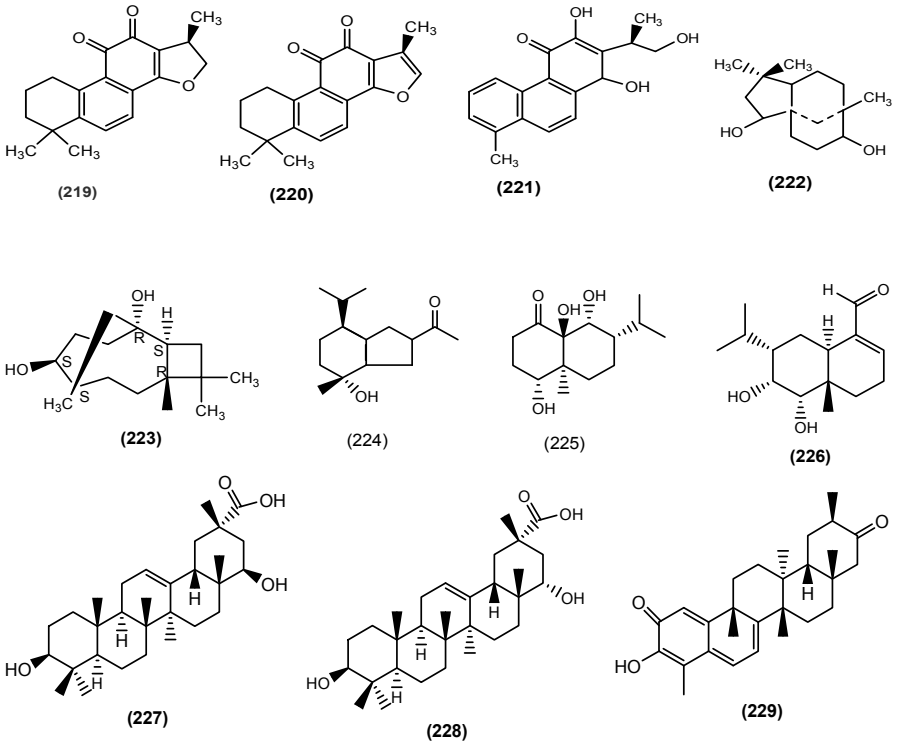


Figure 1.2 Structure of flavonoids and other phenolics with AR inhibition activity (1-208)

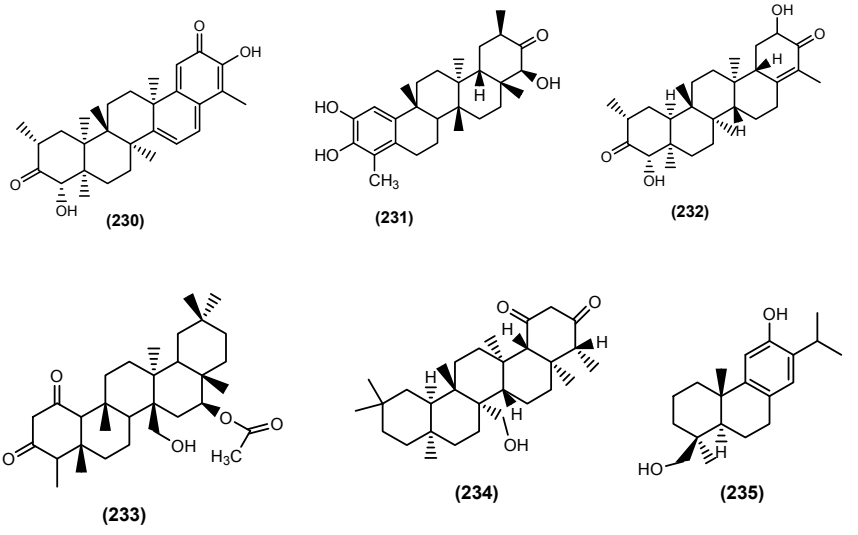


Figure 1.3 Structure of terpenoids with AR inhibition activity (209-239)

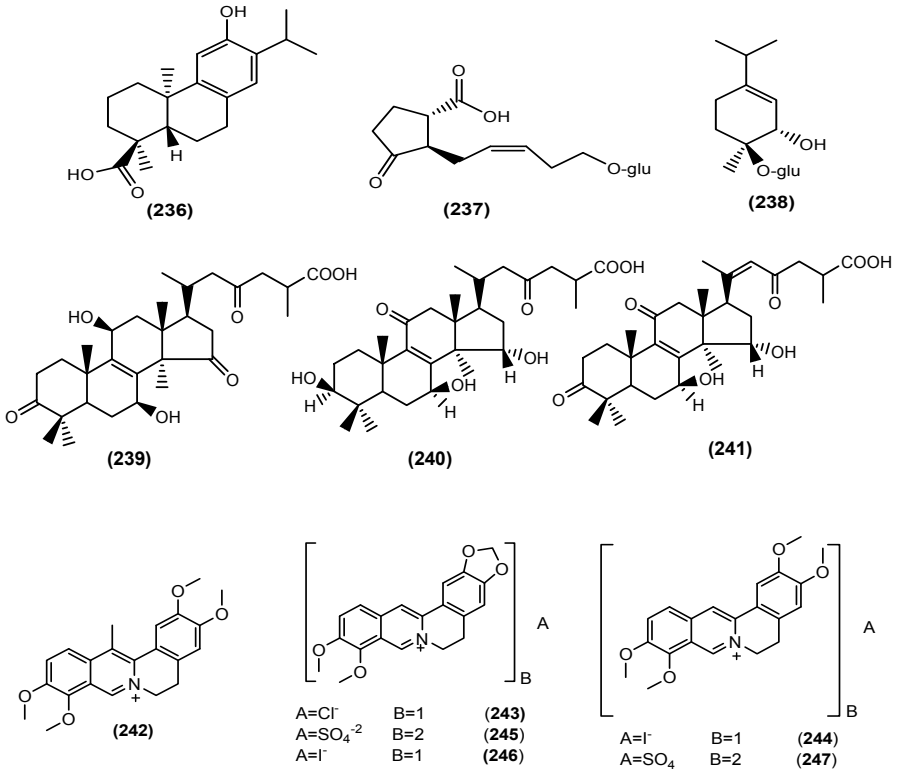
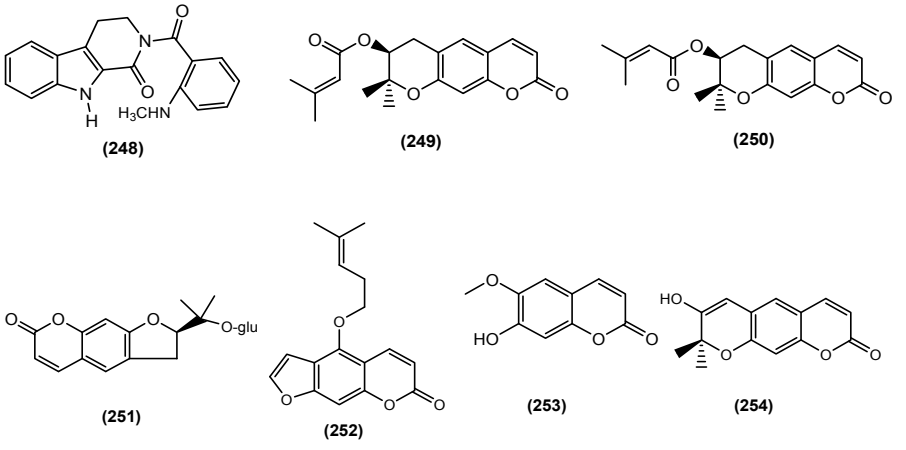


Figure 1.4 Structure of alkaloids with AR inhibition activity (240-246)



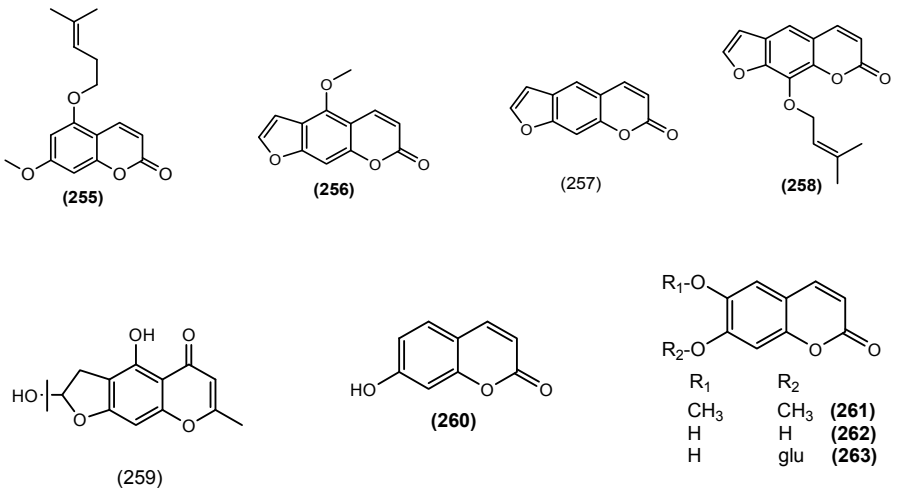
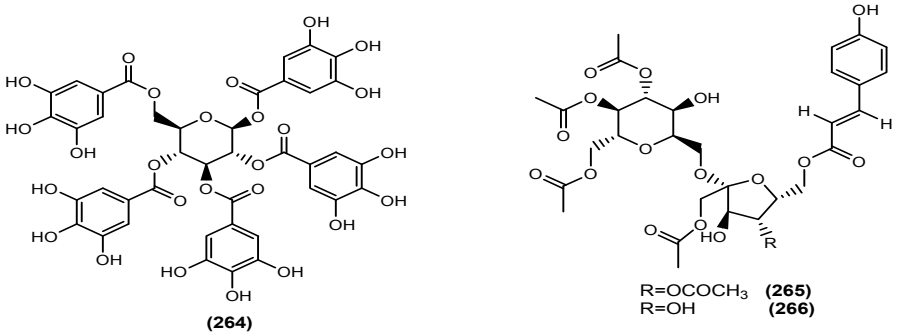


Figure 1.5 Structure of coumarins with AR inhibition activity (247-262)

Figure 1.6 Structure of tannins with AR inhibition activity (263)



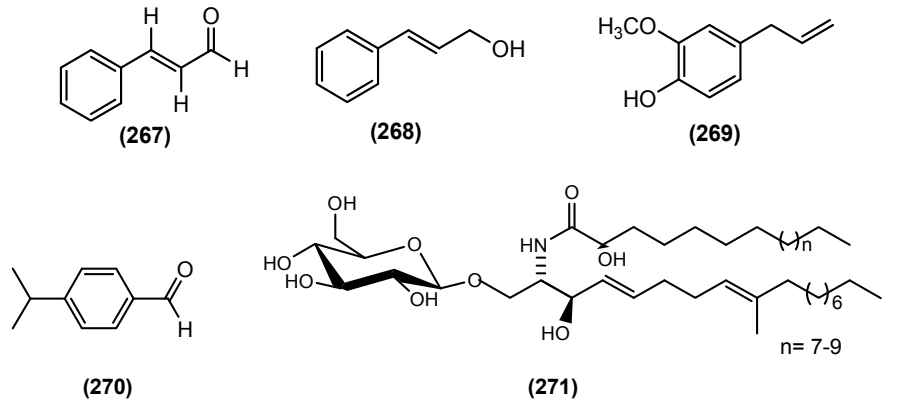


Figure 1.7 Miscellaneous compounds with AR inhibition activity (264-270)

Flavonoids and other Phenolic Compounds

Flavonoids constitute one of the most characteristic classes of compounds in higher plants. They are commonly ingested from fruits and vegetables in the diet. Although flavonoids have no nutritive value, they are capable of exerting various pharmacological activities including antioxidative and AR activities. Perusal of literature reveals that a variety of flavonoids and other phenolic compounds (Figure 2) display powerful AR inhibitory activity in different *in vitro* and *in vivo* test systems.

Varma *et al*., 1975, tested the inhibitory activities of quercetin **(1),** rutin **(2)**, quercetrin **(3)** myrcitrin **(4)** morin **(5)**, hesperetin **(6),** 2-carboxy-5,7-dihydroxy-4′-methoxyisoflavone **(7)** and robinin **(8)** on RLAR. The inhibioy activity of AR shown in table 1.1. It was found that quercetin **(1),** quercitrin **(3)** and myrcitrin **(4)** are much more effective inhibitors than tetramethylene glutaric acid, previously known AR inhibitors (ARIs). They have also reported that quercetin is more potent AR inhibitor than morin, the ortho orientation of the hydroxyl group in meta and ortho of ring C rather than a meta orientation is more favorable to AR inhibitory activity. Hesperetin, in which there is the lack of double bond and the OH in ring B, and the para hydroxyl group in ring C is methylated, has much lower activity than the other aglycones. The glycoside of a flavones may be higher or lower inhibitory activity than its parent non sugar moiety, depending on the nature of the sugar moiety.

Table 1.1 Inhibition of lens AR activities by various compounds (Varma *et al*., 1975).

Inhibitors	% inhibition at the following concentration	
	10^{-5}M	10^{-6}M
tetramethylene glutaric acid	82	35
quercetin **(1)**	83	60
rutin **(2)**	95	20
quercetrin **(3)**	95	88
myrcitrin **(4)**	100	75
morin **(5)**	75	0
hesperetin **(6)**	50	0
2-carboxy-5,7-dihydroxy-4′-methoxyisoflavone **(7)**	77	0
robinin **(8)**	56	0

Brickellia arguta belongs to family compositae and it distributed in south westeren, Mexico, and South and Central America. patuletin-3-*O*-β-D-robinoside **(9),** patuletin-3-*O*-β-D-galactoside **(10)** and 6-methoxykaempferol-3-*O*-β-D-robinobioside **(11),** isolated from the aqueous

extract of the aerial parts of *Brickellia arguta* showed significant inhibitory activity and their potency was comparable to that of the isoquinoline derivative (alrestatin), which is regarded as one of the most promising water soluble ARIs (Rosler *et al.,* 1984). The activity of patuletin-3-*O*-β-D-robinoside **(9)** was considered to be highly significant because of its water solubility at neutral pH at pharmacologically active concentrations. The Inhibitory activity of AR shown in table 1.2.

Table 1.2 Activity of AR inhibitors (Rosler *et al.,* 1984).

Inhibitors	% inhibition at the following concentration	
	10^{-5}M	10^{-6}M
patuletin-3-*O*-β-D-robinoside **(9),**	86	33
patuletin-3-*O*-β-D-galactoside **(10)**	84	38
6-methoxykaempferol-3-*O*-β-D-robinobioside **(11)**	63	-32
Alresatin	90	40

The AR inhibitory activity of 15 typical Lamiaceae flavonoids (Table 1.3) has been evaluated on RLAR by Tomás-Barberán *et al.* (1986). It was shown that the glycoside nepitrin **(12),** and the aglycones sideritoflavone (**23**) and nepetin **(24)** are the active compounds with activities compare to that of quercitrin **(3)**, the positive control used in the study. Among them, there is no single compound have much potential activity than positive control. It is noteworthy that the Incorporated of a p-coumaroyl moiety in the sugar portion of monoglycosides slightly decreased their activity.

Table 1.3 Inhibitory effects of some Lamiaceae flavonoids on rat lens aldose reductase (RLAR) (Tomás-Barberán *et al.*, 1986).

Flavonoid	Common name	Source	% inhibition (10^{-5}M)
5,7,3′,4′-Tetrahydroxy-6-methoxyflavone-7-glucoside **(12)**	Nepitrin	*Rosmarinus officinalis*	72.3
5,6,7,3′,4′-Pentahydroxyflavone-7-glucoside **(13)**		*Thymus mastichina*	61.9
5,7,4′-Trihydroxy-6-methoxyflavone-7-glucoside (**14)**	Hispidulos ide	*Rosmarinus officinalis*	52.0
5,7,8,3′,4′-Pentahydroxyflavone-8-glucoside **(15)**		*Sidertis mugronensis*	38.0
5,7,4′-Trihydroxy-3′-methoxyflavone-7-glucoside **(16)**		*Rosmarinus officinalis*	33.3
5,7,4′-Trihydroxy-3′-methoxyflavone-7-*p*-coumaroyl-glucoside **(17)**		*Phlomis lychnitys*	16.0

Table 1.3 *Contd…*

Flavonoid	Common name	Source	% inhibition (10^{-5}M)
3,5,7,4′-Tetrahydroxyflavone-3-*p*-coumaroyl-glucoside **(18)**	Tiliroside	*Phlomis spectabilis*	32.3
5,7,3′,4′-Tetrahydroxyflavone-7-rutinoside **(19)**		*Teucrium gnaphalodes*	61.4
5,7,3′-Trihydroxy-4′-methoxyflavone-7-rutinoside **(20)**	Diosmin	*Mentha sp.*	45.2
5,7,8,4′-Tetrahydroxy-3′-methoxyflavone-7-alosylglucoside **(21)**		*Sideritis leucantha*	24.0
5,7,3,-Trihydroxy-4′-methoxyflavone-7-neohesperidoside **(22)**	Neohesperidin	*Mentha sp.*	54.0
5,3,4′-Trihydroxy-6,7,8-trimethoxyflavone **(23)**	Sideritoflavone	*Sideritis sp.*	78.4
5,7,3′,4′-Tetrahydroxy-6-methoxyflavone**(24)**	Nepetin	*Rosmarinus officinalis*	62.0
5-Hydroxy-6,7,8, 3′,4′-pentamethoxyflavone **(25)**		*Sideritis mugronensis*	0.0
3,5,7,3′4′-Pentahydroxymethoxyflavone-3-rhamnoside **(3)**	Quercitrin	Roth	86.1

Monochasma savatieri is belonging to the family Rhinantheae, it is a perennial herb used in traditional Chinese medicine. The 70% acetone extract of the aerial parts of *M. savatierii* showed very strong inhibition of rabbit lens AR. Two phenolic glycosides: acetoside **(26),** dehydroacetoside **(27)** along with 5 iridoid glycosides were isolated from this extract. The iridoid glycosides failed to show any activity, whilst the phenolic glycosides displayed activity (table 4) with acetoside **(26),** exhibiting a better inhibition than the positive control, while dehydroacetoside **(27)** was not tested**.** The activity of acetoside **(26)** was 2.5 times more potent than baicalein, a known natural inhibitor of AR (Kodha *et al.,* 1989).

Table 1.4 Activity of AR inhibitors (Kodha *et al.,* 1989).

Compounds	IC_{50} (M)
acetoside **(26),**	3.90×10^{-7}
dehydroacetoside **(27)**	Not tested
Demethylmussaenoside	6.14×10^{-5}
7-*O*-acetyl-8-epi-loganic acid	5.60×10^{-5}
Catalpol	-------
Bartisioside	--------
Aucubin	--------
Baicalein	9.80×10^{-7}

Traditionally in Japan, some kampo medicines have been prescribed for the alleviation of subjective symptoms of diabetic neuropathy. Which contain Glycyrrhizae radix (GR *Glycyrrhizae uralensis* Fischer)) and Paeoniae radix (PR *Paeonia lactiflora* Pallas)) have long been used for the treatment of diabetic neuropathy. Kaoru *et al.,* 1989, isolates the nine compounds from the boiled water extract of GR and PR. Among the seven of GU compounds, GU-2 (isoliquiritin) was the most potent inhibitor of rat lens aldose reductase (RLAR) by inhibiting 86% at the concentration of 1.0 µg/mL (Table 1.5). The IC_{55} of GU-2 was 7.2×10^{-7}M. Compounds PR-1 and PR-2 of PR inhibited RLAR by 77.6% and 61.0%, respectively, at the concentrations of 1 µg/mL. The IC_{50} of PR-1 on RLAR was determined to be 6.3×10^{-7} M**.**

Table 1.5 RLAR Inhibitiory ativity of kampo medicines, (Kaoru et al., 1989).

Compounds	%inhibition (µg/mL)	
	1.0	0.1
Liquiritin	23.5	0
Isoliquiritin	75.4	34.6
liquiritigenin	62.7	12.0
licuraside	74.3	22.1
Naringenin-4-*0*-β-D-glucoside	19.3	0.5
1,2,3,6-tetra-*O*-galloyl-3-β-D-glucose	77.6	3.0
1,2,3,4, 6-penta-*O*-galloyl-3-β-D-glucose	61.0	2.9

3,3',4-Tri-O-methylellagic acid 4'-sulfate potassium salt was isolated from a Mexican herb "Sinfito" (*Potentilla candicans*) as a potent AR inhibitory active constituent. 3,3',4-Tri-O-methylellagic acid 4'-sulfate potassium salt was more potent (IC50 = 8.0 × 10(-8) M) than ellagic acid, which is one of the natural inhibitors of AR.

Anacardium occidentale belongs to the family Anarcardiaceae, Toyomizu et al., 1993 isolated the sixteen compounds from the methanolic extracts of *Anacardium occidentale* and evalavuvated the BLAR activity. Among the tested against BLAR, 6-Pentadecatrienlysalicylic acid is the strongest inhibitor followed by 5-pentadecadienyl, and 5-pentadecatrielnylresorcinol (Table 1.6).

Table 1.6 AR Inhibitiory ativity of compounds isolated from the nuts of *Anacardium occidentale* at a concentration of 100 Mm, (Toyomizu et al., 1993).

Compounds	IC_{50}(M)
1,6-pentadecylsalicylic acid	100.4
6-[8(Z)-pentadeccnyl] salicylic acid;	40.4
6-18(Z), 11 (Z)-pentadecadienyl] salicylic acid;	49.3

Table 1.6 *Contd…*

Compounds	IC_{50}(M)
6-[8(Z),11 (Z), 14-pentadecatrienyll] salicylic acid;	20.4
3-pentadecylphenol; 6, 3-[8(Z)-pentadecenyll phenol;	>328.4
3-[8(Z)-pentadecenyl] phenol	>330.6
3-[8(Z),11 (Z)-pentadecadienyl] phenol;	332.8
3-18(Z), 11(Z), 14-pentadecatrienyll phenol;	180.9
2-methyl-5-pentadecyl resorcinol;	NT
2-methyl-5[8(Z)-pentadecenyl] resorcinol;	300.7
2-methyl-5[8(Z), 11 (Z)-pentadecadienyll resorcinol;	118.0
2-methyl-5[8(Z), ll (Z). 14-pentadecatrienyll resorcinol;	115.7
5-pentadecyl resorcinol;	312.0
5-[8(Z)-pentadecenyl]-resorcinol;	28.3
5-[8(Z), 1l(Z)-pentadecadienyll resorcinol;	28.4
5-[8(Z),11*(Z),*14-pentadecatrienyl] resorcinol.	57.2

rhamnocitrin, Capillarisin **(28)** and cirsimaritin **(29)** isolated from the ethyl acetate extract of *Artemisa capillaris* exhibited a potent inhibitory effect on bovine lens AR (BLAR). Capillarisin **(28)** was found to be much more potent than the others with activity exceeding those of the positive control quercetin and quercitrin Shown in Table 1.7 (Okada *et al*., 1995).

Table 1.7 Inhibitory effect of the test compound on BLAR (Okada *et al*., 1995).

Compounds	Conc(µg/ml)	%inhibition	IC_{50} (M)
rhamnocitrin	10	21	-----
Capillarisin (28)	1	89	0.22
cirsimaritin (29)	10	91	1.6
quercetin	10	88	0.84
Quercitrin	3	81	0.5

Haraguchi *et al*. (1996) isolated nine flavonoids namely, quercetin **(1),** 3-sulfate quercetin **(30),** isorhamnetin (**31**), percicarin **(32)**, isorhamnetin-3,7-disulfate **(33)**, rhamnazin **(34),** rhamnazin-3-sulfate **(35),** isoquercitrin **(36)**, and tamarixetin-3-glucoside 7-sulfate **(37)** from the leaves of *Polygonum hydropiper*. All of them showed varying degrees of inhibitory effect on PL (porcine lens) AR (Table 1.8). But, isorhamnetin-3,7-disulfate **(33)** was the most potent with an IC_{50} value of 1.8 µM. Kinetic analysis proved that isorhamnetin-3, 7-disulfate **(33)** exhibited noncompetitive inhibition against both *dl*-glyceraldehyde and NADPH. In this study, also explain about the importance of sulfonation and methylated derivate of flavonoids, if removal of one or both sulfate moiety from isorhamnetin-3, 7-disulfate **(33) a**bolish the AR inhibitory activity. Similarly, methyalation of quercetin **(1),** 3-sulfate quercetin **(30),** isorhamnetin (31) at C-3' caused a decrease in the inhibitory activity. And other hand, sulfonation at

7th position and methylation at 3' to isoquercitrin (**36)**, to form tamarixetin-3-glucoside 7-sulfate (**37)** with greater PL inhibitory activity.

Table 1.8 Effect of flavonoids isolated from the leaves of *Polygonum hydropiper* PLAR Haraguchi *et al*. (1996). (Inhibitory activity as expressed as the mean of 50% inhibitory concentration of triplicate determination).

Compounds	IC_{50}
quercetin (1)	50.1
3-sulfate quercetin (30)	50.9
isorhamnetin (31)	>95.0
percicarin (32)	69.0
isorhamnetin-3,7-disulfate (33)	1.8
rhamnazin (34)	>91.0
rhamnazin-3-sulfate (35)	30.1
isoquercitrin (36)	16.0
tamarixetin-3-glucoside 7-sulfate (37)	5.0

Engelhardtia chrysolepis is belongs to family juglandaceae, is a subtropical tree grown in Guangdong, Guangxi, and China. Dried leaves of this plant are used as a sweet tea to prevent obesity and are used in folk medicine as an antifebrite and anodyne. The dihydroflavonol, taxifolin **(38)** and its rhammnoside, astilbin **(39)** isolated from the leaves of the *E. chrysolepis* have been reported to inhibit both HRAR and RLAR. In this study It was observed that the aglycone possesses less activity than the glycoside on RLAR assay, whilst the activity of the aglycone was better than its rhamnoside on HRAR (Table 1.9) (Haraguchi *et al*., 1997).

Table 1.9 Inhibitory effect of taxifolin and astilbin on both HRAR and RLAR (Haraguchi *et al*., 1997).

Compounds	Conc(µg/mL)	RLAR %inhibition	HRAR %inhibition
astilbin (39)	10	63	30
	6.1	50	15
taxifolin (38)	10	55	60
	6.1	18	35

In Brazil, the leaves of *Myrcia multiflora* (LAM.) DC. Which is belonging to the family Myrtaceae, which is widely distributed in Brazil and Paraguay. Leaves of *M. multiflora* are used for the treatment of diabetes. Phytochemical analysis of the ethyl acetate-soluble portion of the methanolic leaf extracts of the plant by Yoshikawa *et al*. (1998) resulted in the isolation of secondary metabolites including the flavanone glucosides myrciaacitrin 1 **(40)** and myrciaacitrin 2 **(41**); the flavonol glucosides myricitrin **(42),** mearnsitrin **(43),** quercitrin **(3)** desmanthin-1 **(44)** and

guaijaverin **(45);** and the acetophenone glucosides myrciaphenone A **(46)** and myrciaphenone B **(47).** All the principal constituents including myrciacetin **(48),** the aglycone of the major constituent myrciaacitrin 1 **(40)** showed potent inhibitory activity on RLAR enzyme. But, desmanthin-1 **(44)** (IC_{50} = 8.2 X 10^{-8} M) was the most potent of all with activity equivalent to that of the commercial synthetic AR inhibitor, epalrestat (Table 1.10).

Table 1.10 Inhibitory activity on RLAR enzyme. (Yoshikawa *et al*., 1998)

Compounds	IC_{50}(M)
myrciaacitrin 1 (40)	3.2×10^{-6}
myrciaacitrin 2 (41)	1.5×10^{-5}
myricitrin (42)	3.8×10^{-5}
mearnsitrin (43)	1.4×10^{-6}
quercitrin (3)	1.5×10^{-7}
desmanthin-1 (44)	8.2×10^{-8}
guaijaverin (45)	1.8×10^{-7}
myrciaphenone A (46)	--------
myrciaphenone B (47)	2.9×10^{-5}
myrciacetin (48)	1.3×10^{-5}
epalrestat	7.2×10^{-8}

The flowers of *Chrysanthemum indicum* L. belongs to compositae family are used for the treatment of eye diseases in Chinese traditional medicine. The inhibitory activity of components isolated from the active fractions of this plant has been examined on RLAR. Among the tested compounds, luteolin (**49**), luteolin-7-*O*-β-D-glucopyranoside (**50**), luteolin 7-*O*-β-D-gluopyranosiduronic acid **(51),** acacetin-7-*O*-(6"-α-L-rhamopyranosyl)-β-D-glucopyranoside **(52)** and chlorogenic acid (**53)** showed good inhibition (Table 1.11). But their activity was weaker than that of the commercial synthetic AR inhibitor, eplrestat. In the same experiment the inhibitory effect of the methoxylated flavone, eupatilin **(54),** was much less than the activity of luteolin (49**)** (Yoshikawa *et al.,* 1999).

Table 1.11 Inhibitory activity of compounds from*C. indicum* on RLAR enzyme. (Yoshikawa *et al.,* 1998).

Compounds	IC_{50} at 100µM
luteolin (49),	0.45
luteolin-7-*O*-β-D-glucopyranoside (50)	0.99
luteolin 7-*O*-β-D-gluopyranosiduronic acid(51),	3.1
acacetin-7-*O*-(6"-α-L-rhamopyranosyl)-β-D-glucopyranoside (52)	4.7
and chlorogenic acid (53)	1.8
epalrestat	0.072

Due to the wide biological activities including antioxidative properties reported for green tea, its hot water extract has been examined for AR inhibitory activity. The active fraction purified by solvent fractionation, reversed phase column chromatography, and high performance liquid chromatography gave (+)-catechin **(55)**, (−)-epicatechin **(56)**, (+)-gallocatechin **(57),** (−)-epigallocatechin **(58)**, (−)-epicatechingallate (**59)** and (−)-epigallocatechingallate (**60**) (Murata *et al*., 1994). Among these compounds, (−)-epicatechingallate **(59)** (IC_{50} = 38 μmol/L) inhibited AR most strongly, (−)-epicatechin **(56**) (IC_{50} = 79 μmol/L) was next strongest, while (−)-epigallocatechin (**58)** (IC_{50} = 620 μmol/L) did not inhibit the enzyme at all, and (+)-gallocatechin **(57)** inhibited it very weekly (Table 1.12). The results suggested that catechol type catechins inhibited AR more strongly than pyrogallocatechins, and that *epi*-type catechins with a gallolyl group inhibited more strongly than those without. Unlike the inhibitory actions of flavones and flavonols, the inhibitory activity of each catechin appears to be irreversible, because the inhibition was partially restored by adding the enzyme.

Table 1.12 Inhibitory activity of catechins against RLAR enzyme. (Murata *et al*., 1994).

Compounds	IC_{50} at 100μM
(+)-catechin (55),	280
(−)-epicatechin (56),	79
(+)-gallocatechin (57),	620
(−)-epigallocatechin (58),	>620
(−)-epicatechingallate (59)	38
(−)-epigallocatechingallate (60)	110
Caffeine	480

Sakai *et al*., (2001) investigated the inhibitory activity of the water extract from commercial English tea against human placenta AR (HPAR). The extract was found to possess a potent activity mainly due to the presence of the flavone glycoside isoquercitrin **(36).** The study also showed that the potency of isoquercitrin **(36)** was equal to that of epalrestat. Enzyme kinetic studies revealed that isoquercitrin **(36)** demonstrated its activity by binding at a site independent of the substrate or cofactor (NADPH) binding sites.

Belamcanda chinensis belongs to iridaceae family, is a perennial shrub growing on the hill sides in the East Asia and have been used as Chinese traditional medicine for the treatment of asthama and tonsillitis. Systematic fractionation of the methanol extract of the rhizomes of *B. chinensis* led to the isolation of 9 isoflavonoids and 3 other phenolic derivatives. All the isolated compounds inhibited AR in RLAR *in vitro* assay. The results

summarized in Table 13 indicate that all the compounds possess varying degrees of inhibition (Jung *et al.*, 2002). The isoflavonoids tectoridin **(72)** and tectorigenin **(68)** showed potent activities with IC_{50} values of 1.08 and 1.12 μM, respectively. In the same experiment, the IC_{50} value of tetramethylene glutaric acid was 0.63 μM., the presence of a hydroxyl and a methoxyl group in ring A seem to be essential for the AR inhibitory activity, but the presence of substituents in ring C appeared to have almost no influence on the inhibitory effects. Substitution with methylenedioxy group in ring A markedly reduced the inhibitory activity. As reported by Varma and Kinoshita (1976), inhibition is greater in trihydroxy- than dihydroxyflavones, the hydroxylation at position 4 has beneficial effects, and the abolition of the double bond between C-2 and C-3 leads to a decrease of inhibition. This was shown also to apply for isoflavonoids where trihydroxylated isoflavones such as iristectorene B, tectorigenin and irigenin showed much stronger activity than their dihydroxy counter parts. Furthermore, inhibition was greater in isoflavones with a 4-hydroxyl group.

Table 1.13 Percentage inhibition of isofavonoids and other phenolic compounds isolated from the rhizomes of *Belamcanda chinensis* at a concentration of 10 μM (Jung *et al.*, 2002).

Flavonoid	% Inhibition
Noririsflorentin **(61)**	54.1
Kanzakiflavone-2 **(62)**	60.4
Sheganone **(63)**	37.6
4,7-Di-*O*-Methyltectorigenin **(64)**	45.3
Apocynin **(65)**	33.7
Iristectorene B **(66)**	69.8
p-Hydroxybenzoic acid **(67)**	32.8
Tectorigenin **(68)**	83.5
Irigenin **(69)**	70.9
Irisflorentine **(70)**	40.9
Iridin **(71)**	46.8
Tectoridin **(72)**	83.1

The compositate plant, the flower of *Chrysanthemum indicum* L. has been used for to treat inflammation, fever and eye disease in Chinese traditional preparation. Two flavanone glycosides (2S)- and (2R)-eriodictyol 7-*O*-β-D-glucopyranosiduronic acid (**73** and **74**), and the flavone glycosides apigenin -7-*O*-β-D-glucopyranoside **(75)**, diosmetin 7-*O*-β-D-glucopyranoside **(76)** and quercetin 3,7-di-*O*-β-D-glucopyranoside **(77)** isolated from the flowers of *C. indicum* were found to show inhibitory activity on RLAR (Table 14). Among them, **73** and **74** showed potent inhibitory activity (Matsuda *et al.*, 2002a). The methanolic extracts of several natural medicinal food stuffs were shown to possess inhibitory

effect on RLAR (Matsuda *et al.,* 2002b). In most cases, bioassay-guided separation resulted in the isolation of flavonoids as active constituents, and among them, quercitrin **(3),** guaijaverin **(45)** and desmanthin-1 **(44)** exhibited potent inhibitory activity on RLAR. Desmanthin-1 **(44)** (IC_{50} = 0.082 μM) showed the most potent activity, which was equivalent to that of the synthetic ARI, eplrestat (IC_{50} = 0.072 μM). The structural requirements of flavonoids for AR inhibitory activity have been studied by determining the activities of a number of flavonoids and related compounds including flavones, flavonols, flavanones, dihydroflavonol, flavan-3-ols, isoflavones and stilbenes (Matsuda *et al.,* 2002b). The results suggested the following structural requirements:

1. flavones and flavonols having 7-hydroxy and/or catechol moiety (3′ and 4′ dihydroxy group) at the B ring exhibit strong activity;
2. 5-hydroxyl group does not affect activity;
3. 3-hydroxyl and 7-*O*-glucosyl moieties reduce activity;
4. The 2-3 double bond enhances activity; and
5. Flavones and flavonols having the catechol moiety at the B ring exhibit stronger activity than those having the pyrogallol (3′,4′,5′-trihydroxyl) moiety.

Table 1.14 Inhibitiory ativity of compounds isolated from the flowers of *C.indicum* at a concentration of 100 μM (Matsuda *et al.*, 2002a).

Compounds	IC_{50}(μM)
(2S)- eriodictyol 7-*O*-β-D-glucopyranosiduronic acid (**73**)	2.1
(2R)-eriodictyol 7-*O*-β-D-glucopyranosiduronic acid (**74**)	1.5
apigenin -7-*O*-β-D-glucopyranoside **(75)**	23
diosmetin 7-*O*-β-D-glucopyranoside **(76)**	23
quercetin 3,7-di-*O*-β-D-glucopyranoside **(77)**	84
epalretat	0.072

Prunus mume belongs to family Rosaceae has been widely cultivated as an ornamental pants, and its fruits is used as a food garnish and drink in Japan. In Chinese traditional medicine, various parts of this plant have been used as herbal medicines. The flowers of *P. mume* have been used for detoxification, expectorant, and sedative purpose and it also used for the treatment of eye disease and skin disorders in Chinese traditional medicine. Yoshikawa *et al*., (2002) reported the isolation of two previously unknown flavonol oligoglycosides, 2"-*O*-acetylrutin (78) and 2"-*O*-acetyl-3'-*O*-methylrutin **(79),** together with quercetin 3-*O*-(2",6"-α-L-dirhamnopyranosyl)-β-D-galactopyranoside (**80**), rutin **(2),** quercetin 3-*O*-neohesperidoside **(81),** and isorhamnetin 3-*O*-rhamnoside **(82)** from the methanolic extract of *Prunus mume*, and determined their inhibitory

activity on RLAR. All showed inhibition but the effect of 2"-*O*-acetyl-3'-*O*-methylrutin **(79)** was much higher than the remaining compounds (Table 1.15).

Table 1.15 Inhibitiory ativity of compounds isolated from the flowers of *P. mume* at a concentration of 100 Mm, (Yoshikawa *et al*., 2002).

Compounds	IC_{50}(μM)
2"-*O*-acetylrutin (78) and 2"-*O*-acetyl-3'-*O*-methylrutin **(79)**	9.8
quercetin 3-*O*-(2", 6"-α-L-dirhamnopyranosyl) -β-D-galactopyranoside (**80**)	>30
rutin **(2)**	13
quercetin 3-*O*-neohesperidoside **(81)**	18
isorhamnetin 3-*O*-rhamnoside **(82)**	19
epalretat	0.072

The C-glucosyl flavone, isoaffinetin (83), isolated from the methanolic extract of the dried leaves of *Manilkara indica* showed potent AR inhibitory effect on BLAR, RLAR and HRAR (Haraguchi *et al.,* 2003). Although many ARIs have been reported to inhibit aldehyde reductase, (**83**) failed to show activity against both aldehyde reductase and NADPH oxidase. Like many flavonoidal compounds (**83**) was shown to exert its action by uncompetitive inhibition against both *dl*-glyceraldehyde and NADPH. Structure-activity relationship study revealed that increasing the number of hydroxyl groups in ring B increases inhibition by C-glucosyl flavones.

During a search for possible AR inhibitors from Amazonian plants, the 80% methanol extract of the leaves of *Myrciaria dubia* was found to contain 3 compounds with AR inhibitory activity. The compounds were identified as the phenolic acids: ellagic acid **(84)** and its two derivatives such as 4-*O*-methyl ellagic acid **(85),** 4-(α-rhamnopyranosyl) ellagic acid **(86)** (Ueda *et al*., 2004).The IC_{50} values of the compounds were 0.27, 0.24, 0.041 and 0.047, 0.14, 0.029 μM in HRAR and RLAR assays, respectively. In HRAR assay, the activity of 4-(α-rhamnopyranosyl) ellagic acid (86) was 60 times more than that of quercetin (IC_{50} = 2.5 μM).

Salacia chinensis is a medicinal plant widely used as antidiabetic in Thailand, Myanmar and India. Phytochemical analysis of the hydroalcoholic extract of the stems of this plant resulted in the isolation of a series of secondary metabolites among which the xanthone, mangiferin (**87)** was one (Morikawa *et al.* 2003). Magniferin (IC_{50} = 3.2 μM) was found to be the most active inhibitor of all the isolated compounds when tested on RLAR. Similarly, the ethyl acetate fraction (IC_{50} = 0.8 ug/mL) of the methanol extract of the fruiting bodies of the bracket fungus *Ganoderma applanatum* showed potent AR inhibitory activity on RLAR

(Lee *et al*., 2005). Repeated silica gel chromatography yielded several secondary metabolites including the simple phenolic compounds 2,5-dihydroxyacetphenone **(88),** 2,5-dihydroxybenzoic acid **(89)** and protocatechualdehde **(90)**. Protocatechualdehde **(90)** showed significant inhibitory activity towards RLAR, with an IC_{50} value of 0.7 µg/mL, which is equivalent to that of the positive control tetramethylene glutaric acid (IC_{50} = 0.6 µg/mL). The results suggested that the two phenolic compounds **(89)** and **(90)** having 2,5-dihydroxy benzene moieties exhibit lower AR inhibitory potencies than that carrying a catechol moiety as observed in flavonoids and related compounds.

A number of secondary metabolites have been isolated from the whole plant 80% aqueous acetone extract of *Saussurea medusa* and examined for their inhibitory activity on RLAR (Xie *et al*., 2005). Among the principal isolated constituents, only the flavonoids and quinic acid derivatives presented in Table 1.16 showed activity.

Table 1.16 Inhibitory effects flavonoids and quinic acid derivatives isolated from the whole plant extract of *Saussurea medusa* Maxim on rat lens aldose reductase (RLAR) (Xie *et al*., 2005).

Flavonoid	IC_{50} (µM)
Saussuroside A (91)	>100
Saussuroside B (92)	>100
Apigenin (93)	2.2
Apigenin 7-*O*-β-D-glucopyranoside (94)	4.4
Apigenin 4'-*O*-β-D-glucopyranoside (95)	3.2
Apigenin 7-*O*-rutinoside (96)	4.7
Luteolin(49)	0.45
Luteolin 7-*O*-β-D-glucopyranoside (97)	0.99
Luteolin 4'-*O*-β-D-glucopyranoside (98)	4.8
Luteolin 7-O-rutinoside (99)	0.92
Chrysoeriol 7-*O*-β-D-glucopyranoside (100)	26
Chrysoeriol 7-O-rutinoside (101)	14
Quercetin (1)	2.2
Quercetin 3-*O*-β-D-glucopyranoside (102)	4.5
Isorhamnetin 7-*O*-rutinoside (103)	19
3-Caffeoylquinic acid methyl ester (104)	13
4-Caffeoylquinic acid methyl ester (105)	16
5-Caffeoylquinic acid methyl ester (106)	1.3
Eplarestat	0.072

Goodarzi *et al.* (2006) compared the AR inhibitory effects of quercetin **(1)** and naringin (**107)** in streptozotocin-induced diabetic and healthy rats. It was found that AR activity was reduced by 73% and 69% in diabetic rats fed with quercetin (1) and naringin **(107**), respectively. But, the reduction of enzyme activity in healthy rats was 63% and 59%, respectively. The study revealed that the two flavonoids are effective in reducing of AR activity *in vivo*, particularly in diabetic rats. The seeds of *Aremisia dracunculus*, which have a variety of medicinal uses including as a remedy for diabetes have been investigated for their inhibitory activity on HRAR enzyme. The ethanolic extract of the seeds afforded 4 compounds: 4,5-di-O-caffeoylquinic acid **(108),** davidigenin **(109)**, 6-demethoxycapillasin **(110)** and 2',4'-dihydroxy-4-methoxydihydrochalcone **(111**). The compounds displayed either similar or better inhibition than that caused by quercitrin (Logendra *et al.,* 2006). Curcuminoids, curcumin **(112),** demethoxycurcumin **(113**) and bisdemethoxycurcumin **(114),** isolated from *Curcuma longa* were reported to possess remarkable inhibitory activity on bovine lens AR. It was also observed that curcumin **(112)** exhibited the highest inhibitory activity with IC_{50} value of 6.8 μM (Du *et al.,* 2006). In another study curcumin was shown to delay streptozotocin (STZ)-induced diabetic cataract in rats mainly through its antioxidant property and inhibition of RLAR enzyme (Suryanarayana *et al*., 2005). Du *et al*. (2006) have also reported that curcuminoids isolated from *Curcuma longa* possess inhibitory activities on BLAR. In the same experiment, the authors synthesized analogues of curcumin and evaluated their ability to inhibit the enzyme. Structure-activity relationship studies revealed that the curcumin analogues with ortho-dihydroxyl groups form a tighter affinity with AR to exert potent activities. In another study curcumin was shown to inhibit bovine kidney AR with an IC_{50} value of 10 μM in a non-competitive manner, but is a poor inhibitor of closely related members of the aldo-keto reductase superfamily, particularly aldehyde reductase (Muthenna *et al.*, 2009)

Similarly, of the stamens of *Nelumbo nucifera* were examined for their possible inhibitory activity on RLAR. Thirteen flavonoids with previously known structures have been isolated from the ethyl acetate soluble fraction of the methanol extract and assessed for their inhibitory activity on RLAR (Lim *et al.*, 2006). The results of the study which are summarized in Table 1.17 indicate that among the isolated compounds, those harboring the 3-*O*-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside group in their C ring, including kaempferol 3-*O*-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside **(119)** (IC_{50} = 5.6 μM) and isorhamnetin 3-*O*-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside **(127)** (IC_{50} = 9.0 μM) possess the highest activity. In addition, arbutin (128) showed weak activity.

Table 1.17 Aldose Reductase (AR) inhibitory activities of flavonoids isolated from the stamens of *Nelumbo nucifera* (Lim *et al.*, 2006).

Flavonoid compound	IC_{50} (μg/ml)	IC_{50} (μM)
Kaemferol (115)	6.94	24
Kaemferol-3-*O*-β-D-galactopyranoside (116)	8.26	18
Kaemferol-7-*O*-β-D-glucopyranoside (117)	6.34	14
Kaemferol-3-*O*-β-D-glucopyranoside (118)	5.05	11
Kaemferol-3-*O*-α-L-rhamnopyranosyl-(1 → 6) β-D-glucopyranoside (119)	3.32	5.6
Kaemferol-3-*O*-α-L-rhamnopyranosyl-(1 → 2) β-D-gluccuronopyranoside (120)	---	
Kaemferol-3-*O*-β-L-rhamnopyranosyl-(1 → 2) β-D-glucopyranoside (121)	---	
Kaemferol-3-*O*-β-D-glucuronopyranoside (122)	-----	
Kaemferol-3-*O*-β-D-glucuronopyranosyl methyl ester (123)	5.52	11.6
Myricetin 3',5'-dimethyl-3-O-β-D-glucupyranoside (124)	----	
quercetin-3-*O*-β-D-glucuronopyranoside (125)	----	
isorhamnetin -3-*O*-β-D-glucopyranoside (126)	9.13	19
isorhamnetin-3-*O*-α-L-rhamnopyranosyl-(1 → 6) β-D-glucopyranoside (127)	5.86	9.4
Quercetin	5.49	16

In another study involving the leaf extract of *N. nucifera*, it was shown that the ethyl acetate fraction contains quercetin **(1)** and its four of its glycosides: quercetin 3-*O*-β-D-glucopyranoside **(102),** quercetin-3-*O*-β-D-glucuronopyranoside **(125)**, quercetin 3-*O*-β-D-galactopyranoside (**129**), and quercetin-3-*O*-β-L-rhamnosyl-(1→6)-β-D-glucopyranoside (rutin) **(2)** as active RLAR inhibitors. Rutin **(2)** (IC_{50} = 2.49 ± 0.04 μM) was the most active of all the isolated flavonoids showing more than twice the activity of quercetin (IC_{50} = 5.54 ± 0.15 μM) (Jung *et al.*, 2008a).

Bioassay-guided fractionation of the MeOH extract of the whole *Viola hondoensis* plant resulted in the isolation of four isoflavonoids, tectoridin-4′-*O*-β-D-glucoside **(130)**, tectorigenin **(68),** tectoridin **(72),** and tectorigenin-4′-*O*-β-D-glucoside **(131),** as the active AR inhibitory principles (Moon *et al*., 2006). Tectoridin-4′-*O*-β-D-glucoside **(130)** (IC_{50} = 0.54 ± 0.02 μM), which contains a glucose moiety at C-7 and C-4′ exhibited the most potent inhibitory activity. On the other hand, **(68)** (IC_{50} = 1.12 ± 0.08 μM), which has no substitution at C-7 and C-4′ exhibited significantly lower activity than (**130**). A similar case was observed between compounds **72** and **131**. Tectorigenin-4′-*O*-β-D-glucoside **(131)** without a glucose moiety at C-7 was much more effective than 3, which

contains a glucose moiety. These results indicate that glucosylation of C-4′ increases AR inhibitory activity.

In an attempt to obtain nontoxic inhibitors of diabetic complications from edible plants, Kato *et al*. (2006) investigated the hot water extract of the rhizome of *Zingiber officinalis* Roscoe. Out of the 16 phenolic compounds isolated only 5 displayed good inhibitory activity on HRAR. Their structures were identified as (4-hydroxy-3-methoxyphenyl)methanol **(132),** 2-(4-hydroxy-3-methoxyphenyl)ethanol **(133)**, 2-(4-hydroxy-3-methoxyphenyl) ethanoic acid **(134),** 2-(-3,4-dimethoxyphenyl) ethanoic acid (**135**) and 4-(4-hydroxy-3-methoxyphenyl)-2-butanone (**136**). Compounds **132, 133**, and **134** exhibited slightly better inhibition than quercetin (IC_{50} = 27.0 ± 3.8 μM), with IC_{50} values of 24.4 ± 4.6, 19.2 ± 1.9 and 18.5 ± 1.1 μM, respectively, whilst the inhibitory potentials of **(135)** and quercetin were almost the same. On the other hand, **(136)** (IC_{50} 197 ± 12 μM) was a much weaker inhibitor than quercetin **(1).** It is interesting to note that [6]-gingerol and [6]-shogaol, the well-known major constituents of ginger displayed extremely weak activities. A structure-activity relationship study revealed that the applicable side alkyl chain length and the presence of a C_3 OCH_3 group in the aromatic ring are essential features for enzyme recognition and binding.

In view of the association between the consumption of pigmented rice and the improvement of human health due to the antoxidant potency of phenolic compounds they contain, the secondary metabolites of black and pigmented brown rice varieties (*Oryza sativa* L. *japonica*) have been investigated (Yawadio *et al.*, 2006). Two anthocyanins: cyanidin-3-*O*-β-glucoside **(137)** and peonidin-3-*O*-β-glucoside (**138**) were isolated from black rice, whilst the major component of pigmented brown rice was found to be ferulic acid **(139).** All the isolated compounds showed inhibitory activity on BLAR with compound **(138)** (IC_{50} = 8.7 μg/mL) exhibiting the highest activity that was better than that of quercetin (IC_{50} = 11.4 μg/mL). It was concluded that black and brown pigmented rice varieties possess marked health benefits in preventing diabetic complications by preventing the key enzyme (AR) involved in their development.

Origanum vulgare ssp. hirtum traditionally used in Morocco for the control and treatment of diabetes, was studied for its inhibitory activity against RLAR (Koukoulitsa *et al.,* 2006). The polar extracts of the plant growing wild in Greece yielded 3 phenolic acids: caffeic acid (**140**), rosmarinic acid and **(141),** lithospermic acid B **(142**) along with 2 terpenoidal compounds. The inhibitory activity against RLAR of compounds **140–142** was examined and docking studies on the active site of the enzyme were performed. The most active compound was found to be lithospermic acid B (**142**) inhibiting the enzyme by 96% at a dose of 100 μM. Caffeic acid (**140**) was inactive. Docking results seem to support the

biological data. Despite the fact that carboxylic acids have a potent inhibitory activity *in vitro*, they were less potent *in vivo* due to their complete dissociation at physiological pH.

Black bamboo, *Phyllostachys nigra* grows particularly in Southeast Asia and is widely used as a source of food. The leaves of *P. nigra* were investigated for their inhibitory effect on rat lens ALR2 to evaluate their potential for treatment of diabetic complications. The investigation led to the isolation and identification of the flavones isoorientin (**143**), orientin (**144**), vitexin (**145)** luteolin 6-*C*-(6′′-*O*-*trans*-caffeoyl glucoside) (**146**), vittariflavone (**147**) and tricin (**148**)), and the simple phenolic acids, *cis*-coumaric acid (**149),** and *p*-coumaric acid **(150)** that inhibited ALR2 activity (Jung *et al*., 2007). Of these, luteolin 6-*C*-(6′′-*O*-*trans*-caffeoylglucoside) **(146)** (IC_{50} = 0.0134 μM) was found to exhibit the strongest inhibition. In the same experiment, the inhibitory potency of reference compound tetramethyl glutaric acid (IC_{50} = 0.924 μM) was much lower.

Finger millet, *Eleusine coracana* is a good source of polyphenols among cereals. Finger millet polyphenols being a major antidiabetic and antioxidant components, Chethan *et al*., (2008) evaluated their AR inhibiting activity. It was shown that the phenolic constituents in finger millet such as gallic acid **(151),** protocatechuic acid **(152),** *p*-hydroxy benzoic acid **(153**), *p*-coumaric acid (**150)**, vanillic acid **(154**), syringic acid (**155),** ferulic acid (**139**), *trans*-cinnamic acid (**156)** and the quercetin **(1)** inhibited cataract eye lens effectively, the latter was more potent with an IC_{50} of 14.8 nM. Structure relationship analysis revealed that OH group at position 4 was important for AR inhibitory property. It was also observed that the presence of O-methyl group next to the carbon carrying the phenolic OH moiety eliminates AR activity. The phenolic acids were found to inhibit AR reversibly by non-competitive inhibition.

The methanol extract of the air-dried fruit pericarp of the tropical and subtropical edible fruit, Litchi (*Litchi chinensis Sonn*.) was investigated for its inhibitory activity on RLAR. The ethyl acetate soluble fraction of the methanol extract afforded four compounds of which 2,5-dihydroxybenzoic acid (**89**), delphinidin 3-*O*-β-galactopyranoside-3′,5′-di-*O*-β-glucopyranoside **(157**), and delphinidin 3-*O*-β- galactopyranoside-3′-*O*-β-glucopyranoside (**158**) showed inhibitory activity on RLAR assay (Lee *et al*., 2009). However, the anthocyanin delphinidin 3-*O*-β-galactopyranoside-3′-*O*-β-glucopyranoside (**158**) exhibited the most powerful activity with an IC_{50} value of 0.23 μg/mL, which was twice that of the positive control tetramethylene glutaric acid (IC_{50} = 0.48 μg/mL).

Phytochemical analysis of the 80% methanolic extract of the roots of *Pueraria thunbergiana* led to the isolation of four isoflavonoids; daidzein **(159),** daidzin **(160),** puerarin **(161)** and ononin **(162),** and all showed

inhibitory activity against RLAR. In addition, the isoflavonoids: genistin **(163),** genistein **(164),** and formononetin **(165),** and the flavonoids baicalin **(166**), baicalein **(167),** were examined and showed inhibitory activity against RLAR (Park *et al*., 2007). Structure-activity relationship among these compounds revealed that the aglycones possess better inhibition than the corresponding glycosides and substitution of the C-4′ OH group with a methoxyl group reduce activity. Engeletin (**168)** and astilbin **(169),** dihydro flavonol glycosides isolated from the ethyl acetate extract of the leaves of *Stelechocarpus cauliflorus* R.E. Fr. were found to possess AR inhibitory activity. Although engeletin **(168)** has only one hydroxyl group in its C ring as opposed to astilbin **(39),** which contains two hydroxyl groups at 3′ and 4′ positions, the inhibitory activity of the former against HRAR was 23 times greater than that the latter and twice that of quercetin **(1)** (Wirasathien *et al.,* 2007).

Viola hondoensis belongs to family Violaceae is distributed in the southern part of Korea. In traditional medicine, the herb has been used as an expectorant and a treatment for skin eruption. The isolation and characterization of ARIs from the *V. hondoensis* W. Becker et H Boss has been reported (Chung *et al.*, 2008). The MeOH extract (IC_{50} = 1.2 μg/mL) and EtOAc fraction (0.6 μg/mL) were found to exhibit potent RLAR inhibition *in vitro* (Table 1.18). Kakkalide **(169)** (IC_{50} = 0.3 μg/mL), the major isoflavonoid glycoside isolated from the ethyl acetate soluble fraction was found to be more the active constituent of the plant, which is compared with positive control TMG (tetramethylene glutaric acid).

Table 1.18 Inhibitory Effects of the Extract, Solvent Fractions and Compound of *Viola hondoensis* on Rat Lens Aldose Reductase. (Chung *et al.*, 2008).

Fractions and Compounds	IC_{50}(μg/mL)
MeOH extract	1.28
n-Hexane fraction	6.2
EtOAc fraction	0.62
Chloroform fraction	3.2
n-BuOH fraction	4.3
Kakkalide	0.34
TMG (tetramethylene glutaric acid)	0.48

Rhus verniciflua grows particularly in South East Asia and the biological activities of this plant have been reported as anti-inflammatory, anti-cancer, and anti-rheumatoid arthritis *etc*. In an attempt to find to find potential AR inhibitors, Lee *et al*. 2008 investigated the ethanol extract of the bark of *Rhus verniciflua*, a plant that grows particularly in South East Asia and the pharmacological activities of this plant have been reported as

anti-inflammatory, anti-cancer, and anti-rheumatoid arthritis *etc*. Several compounds including flavanonols, flavones, an aurone, a chalcone and simple phenolics have been isolated from the active ethyl acetate fraction (IC_{50} = 0.6 μg/mL), which showed concentration dependent inhibition. The isolated compounds were identified as fustin **(170),** morin hydrate **(171),** fisetin **(172),** quercetin **(1),** sulfuretin (**173**), butein **(174**), protocatechuic acid (**152**), and ethyl gallate **(175).** The chalcone butein (**174**) exhibited the strongest inhibitory activity against HRAR with an IC_{50} value of 0.7 μM, a better inhibition than that displayed by epalrestat (Table 1.19). The activity of sulfuretin (**173**) with aurone structure also showed inhibition that was equal to the reference drug epalrestat.

Table 1.19 Inhibitory Effects of the Compounds Isolated from the Bark of *R. verniciflua* on rhALR2 (Lee *et al*. 2008)

Compounds	Conc. (μm)	%inhibition	IC_{50} (μM)
Epalrestat	2.5 1.25 0.625	85.8±5.0 49.1±1.7 11.8±4.2	1.3
fustin (170),	2	20.1±0.5	>2
morin hydrate (171)	2	14.1±8.0	>2
fisetin (172),	2	31.1_8.9	>2
quercetin (1),	2	39.1±4.6	>2
sulfuretin (173	2.0 1.0 0.5	69.8_3.3 41.9±1.1 7.0_2.3	1.3
butein (174)	2.0 1.0 0.5	89.9±7.7 65.1_1.1 41.1_2.2	0.7
protocatechuic acid (152),	2	12.6±3.7	>2
ethyl gallate (175). pentagalloyl glucose	2.0 2.0	---- 46.6_5.1	>2 >2

Sorbus domestica fruits (Rosaceae) are widely used in northern Europe as antioxidant agents in beverages. The diethyl ether and ethyl acetate extracts of *S. domestica* fruits possess AR inhibitory activity. Further analysis of these extracts revealed that the AR inhibitory activity is attributed to the high flavonoids and hydroxyl cinnamoyl content of the plant (Termentzi *et al.*, 2008).

From the methanolic extract of the dried whole plant of *Sinocrassula indica* (Crassulaceae) thirty-one flavonoids were isolated. Among the isolated flavonoid constituents, the inhibitory effects of eight principal components were investigated on RLAR enzyme (Morikawa *et al*. 2008). It

was found that luteolin **(49)**, quercetin **(1),** multiflorin B **(176),** quercetin 3-*O*-β-D-glucopyranoside **(102),** kaempferol **(115),** sinocrassosides A_2 (**177**), sinocrassosides D_2 **(178),** and quercetin-3-*O*-β-D-glucopyranosyl-7-*O*-α-L-rhamnopyranoside (**179),** have activities with IC_{50} values shown in Table 1.20.

Table 1.20 Inhibitory Effects of the Compounds Isolated from the whole plant of *Sinocrassula indica* on RLAR. (Morikawa *et al*. 2008).

Compounds	IC_{50}(μM)
kaempferol **(115)**	10.0
quercetin **(1)**	2.2
quercetin 3-*O*-*β* -D-glucopyranoside **(102)**	4.5
sinocrassosides D2**(178)**	47
sinocrassosides A2**(177)**	31
multiflorin B **(176)**	2.7
quercetin 3-*O*-*β* -D-glucopyranosyl-7-*O*-*α* -L-rhamnopyranoside **(179)**	56
luteolin **(49)**	0.45
multiflorin B **(176),**	2.2

Cirsium maackii, a member of the Asteraceae family, is a perennial thistle that grows abundantly in Korea. The whole plants of Cirsium species (Cirsii Radix et Herba) have been used as a folk medicine in the treatment of hemorrhaging, inflammation of the liver and kidney, and a variety of abdominal and intestinal disorders. Jung *et al*. (2009) have assessed the AR inhibitory activity of the leaves, roots, stems, and flowers of the Korean thistle, *C. maackii* along with two major components, luteolin 5-*O*-β-D-glucopyranoside (**180**) and the aglycone luteolin **(49)** against RLAR and HRAR (Table 1.21). HPLC quantitative analysis of the two key flavonoids in each plant parts indicated that the content of **180** and **49** might contribute to the antioxidant and AR inhibitory activities of *C. maackii*.

Table 1.21 AR Inhibitiory ativity of isolated compounds from *Cirsium maackii*, (Jung *et al*. 2009).

Compounds	IC_{50} (μM)	
	RLAR	**HRAR**
luteolin 5-*O*-β-D-glucopyranoside (180)	0.33 ± 0.00	6.07 ± 0.05
luteolin (49)	0.52 ± 0.05	9.18 ± 0.10
Quercetin	1.53 ± 0.20	14.79 ± 0.35
Epalrestat	0.07 ± 0.00	0.07±0.01

Sophora flavescens Ait belongs to family Leguminosceae is a perennial shrub that occurs in the wild and is also cultivated throughout North East Asia. The dried root of *S. flavescens*, Sophorae Radix, is an important herbal medicine that is used in folk medicine as an antipyretic, analgesic, anthelmintic and stomachic, and is used for the treatment of gastrointestinal haemorrhage, diarrhoea and eczema. The root extracts of *Sophora flavescens* and its prenylated flavonoids, which are known to exhibit antidiabetic activities in several enzymatic systems (Kim e*t al*., 2006) and inhibit the Na^+-glucose cotransporter (Sato *et al*., 2007) implicated in diabetes have been examined for their AR inhibitory activities (Jung *et al.,* 2008b). The results summarized in Table 22 indicated that all of the prenylated flavonoids isolated from the active methylene dichloride and ethyl acetate fractions show varying degrees of activity on both RLAR and HRAR assays. The inhibitory effect of the prenylated chalcone desmethylanhydroicaritin **(181)** (IC_{50} = 0.95 ± 0.04 μM), however, was the highest on RLAR assay. In this assay, the IC_{50} values of epalrestat and quercetin were 0.28 ± 0.01 and 7.73 ± 0.29 μM, respectively. Similarly, in the HRAR assay most of the compounds showed marked inhibitory activity with the prenylated flavanone (2S)-7,4'-dihydroxy-5-methoxy-8-(γ,γdimethylally)-flavanone **(192)** (IC_{50} = 0.37 μM) exerting the highest activity, which was better than quercetin (IC_{50} = 2.54 μM) and comparable with that of epalrestat (IC_{50} = 0.28 μM). Overall, the prenylated flavanones and prenylated flavonols showed higher activities than the prenylated chalcones in the RLAR assay, whereas the prenylated chalcones and the prenylated flavonols exhibited greater activity than the prenylated flavanones in the HRAR assay.

Table 1.22 IC_{50} Inhibitory activities values of prenylated flavonoids isolated from the root extract of *Sophora flavescens* against rat lens aldose reuctase (RLAR) and human recombinant aldose eductase (HRAR) (Jung *et al.,* 2008b).

Flavonoid	RLAR		HRAR	
	μgmL^{-1}	μM	μgmL^{-1}	μM
Desmethylanhydroicartin (181)	0.34	0.95	0.16	0.45
8-Lavandulylkaempferol (182)	1.61	3.80	0.33	0.79
Kushenol C (183)	8.12	18.54	0.37	0.85
Kuraridinol (184)	10.10	22.14	0.60	1.32
Kuraridin (185)	9.46	21.60	0.12	0.27
Xanthohumol (186)	3.80	10.73	-----	----
Sophoraflavanone (187)	25.26	59.58	0.60	1.42
Kurarinol (188)	0.97	2.13	2.0	4.39
Kurarinone (189)	1.31	2.99	1.67	3.81
(2S)-2'-Methoxykurarinone (190)	1.70	3.77	5.0	11.0

Table 1.22 *Contd…*

Flavonoid	RLAR		HRAR	
	μgmL^{-1}	μM	μgmL^{-1}	μM
(2S)-3β,7,4'-Trihydroxy-5-methoxy-8-(γ,γ-dimethylallyl)-flavanone (191)	1.34	3.63	1.67	4.50
(2S)-7,4'-Dihydroxy-5-methoxy-8-(γ,γ-dimethylallyl)-flavanone (192)	11.57	32.69	0.13	0.37
Kushenol E (193)	3.29	7.74	0.89	2.09
Leachianone (194)	4.62	12.97	0.89	2.49
Quercetin	2.61	7.73	0.86	2.54
Epalrestat	0.09	0.28	0.09	0.28

The roots and rhizomes of licorice species (*Glycyrrhiza* sp.) have for long been used, worldwide, as herbal medicine and natural sweetener. Licorice is also known to improve glucose tolerance in diabetic mice. Such preventive and inhibitory activities against diabetes, shown by several licorice-derived components led to further investigation of the inhibitory effects of *Glycyrrhiza uralensis* on diabetic complications. The investigation which involved extraction of the dried rhizomes of the plant with methylene chloride resulted in the isolation of 5 prenylated flavonoids: semilicoisoflavone B **(195)**, 7-*O*-methylluteone (**196**), dehydroglyasperin C (**197**), dehydroglyasperin D (**198**), and isoangustone A (**199**), and three non-prenylated flavonoids: liquiritigenin (**200**), isoliquiritigenin (**201**), and licochalcone A (**202)**, among others. Semilicoisoflavone B (**195**) was the most potent inhibitor with IC_{50} values of 1.8 and 10.6 μM against RLAR and HRAR, respectively. The IC_{50} values of epalrestat in the two assays were shown in table 1.23. In the kinetic analyses using Lineweaver–Burk plots of 1/velocity and 1/concentration of substrate, semilicoisoflavone B (**195**) showed noncompetitive inhibition against RLAR. The results of the study indicated that the presence of a γ,γ-dimethylchromene ring is partly responsible for the AR inhibitory activity of isoprenoid-type flavonoids (Lee *et al* 2010).

Table 1.23 Inhibitory Effects of the Compounds Isolated from *Glycyrrhizae uralensis* on Rat Lens AR and Recombinant Human AR. (Lee *et al* 2010).

Compounds	IC_{50} (μM)	
	RLAR	HRAR
Quercetin	2.5	12.7
Epalrestat	0.9	1.0
semilicoisoflavone B (195),	1.8	10.6
7-*O*-methylluteone (196),	28.5	76.5
dehydroglyasperinC (197),	42.7	130.6
dehydroglyasperin D (198),	62.4	176.2
and isoangustone A (199),	99.5	280.8
liquiritigenin (200)	2.0	21.9
isoliquiritigenin (201)	3.4	27.5
licochalcone A (202)	96.3	257.2

Lee *et al*. 2011 reported the isolation of the flavanol glycoside, glucodistylin (**203**) and three polyphenol derivatives: gallate (**204**), (+)-catechin **(55)** and (+)-gallocatechin **(57)** from an aqueous acetone extract of the bark of *Quercus acutissima*. The most active compound glucodistylin exhibited uncompetitive inhibitory activity against RHAR with an IC_{50} value of 7.2 μM, activity that was twice that of quercetin (Table 1.24).

Table 1.24 Inhibitory effects of compounds isolated from *Q. acutissima* on HRAR. (Lee *et al*. 2011).

Compounds	IC_{50}(μM)
quercetin	15.98
glucodistylin (**203**)	7.2
gallate (**204**),	------
(+)-catechin **(55)**	112.5>
(+)-gallocatechin **(57)**	159.4>

The young leaves of *Artemisia montana* (Nakai) Pampan are consumed as foodstuffs, and the mature plant used as a moxibustion in Korea and Japan. Bioassay-guided fractionation of extract of the whole plant yielded RLAR inhibitory active ethyl acetate and n-butanol fractions. Repeated column chromatography of the fractions afforded a series of chlorogenic acids and flavonoids, among others (Jung *et al*., 2011). The isolated acids: 3,5-di-*O*-caffeoylquinic acid (**205**), chlorogenic acid (**53**), cryptochlorogenic acid (**206**) and neochlorogenic acid (**207**) inhibited RLAR with IC_{50} values shown in table 1.25. The flavonoids obtained: apigenin **(93),** luteolin (**49**), quercetin (1), isoquercitrin **(36),** hyperoside **(208**), luteolin 7-rutinoside(scolymoside)**(99**) displayed better activity than the plant acids with (**49**) (IC_{50} = 0.19 ± 0.02) exhibiting the most potent effect followe by (1) (IC_{50} = 0..30 ± 0.03) and (**99**) (IC_{50} = 0.55 ± 0.03).

Table 1.25 Inhibitory effects of compounds isolated from *A. montana* on RLAR. (Jung *et al*., 2011).

Compounds	IC_{50}(μM)
3,5-di-*O*-caffeoylquinic acid (**205**),	5.37±0.25
chlorogenic acid (**53**),	4.36±0.47
cryptochlorogenic acid (**206**)	11.13±1.70
neochlorogenic acid (**207**)	19.19±2.19
apigenin **(93),**	0.67±0.03
luteolin (**49**),	0.19±0.02
quercetin (1),	0.30±0.03
isoquercitrin **(36),**	1.16±0.0
hyperoside **(208**),	1.85±0.06
luteolin 7-rutinoside(scolymoside) **(99**)	0.55±0.03
Umbeliferone (259)	122.10±12.26
Scoparone (260)	44.30±0.47
Scopoletin (251)	64.50±9.08
Esculetin (261)	172.48±9.01
Scopolin (262)	128.15±1.72

Chlorogenic acid (1), 3,5-di-O-caffeoylquinic acid (2), apigenin (3), 1,3, 5-tri-O-caffeoylquinic acid (4), 5,7-dimethoxy-flavanone-40-O-[-Dapiofuranosyl-(12)]-D-glucopyranoside (5), and b-sitosterol (6) from 70% methanolic leaves extact of *Phoradendron* sp. the IC_{50}s of compounds 1, 2, and 4 toward AR were 6.83 lM, 4.62 lM, and 4.28 lM, while compounds 3, 5, and 6 were inactive (Zhiqiang *et al.,* 2017).

Effects of 95% ethanol extracts from the leaves of *C. esculenta* and, its organic solvent soluble fractions, including the dichloromethane (CH_2Cl_2), ethyl acetate (EtOAc), *n*-butanol (BuOH) and water (H_2O) layers, using DL-glyceraldehyde as a substrate. Ten compounds, namely tryptophan (**1**), orientin (**2**), isoorientin (**3**), vitexin (**4**), isovitexin (**5**), luteolin-7-*O*-glucoside (**6**), luteolin-7-*O*-rutinoside (**7**), rosmarinic acid (**8**), 1-*O*-feruloyl-D-glucoside (**9**) and 1-*O*-caffeoyl-D-glucoside (**10**) were isolated from the EtOAc and BuOH fractions of *C. esculenta*. All the isolates were subjected to an *in vitro* bioassay to evaluate their inhibitory activity against rat lens aldose reductase. Among tested compounds, compounds **2** and **3** significantly inhibited rat lens aldose reductase, with IC_{50} values of 1.65 and 1.92 μM, respectively. Notably, the inhibitory activity of orientin was 3.9 times greater than that of the positive control, quercetin (4.12 μM) (Hong *et al*., 2014).

Terpenoids

Terpenoids are the most numerous and structurally diverse family of natural products derived from C_5 isoprene units. For many years, pharmaceutical and food industries have exploited them for their potentials as effective medicines and flavor enhancers. Considering the numbers and diversity of this group of secondary metabolites, however, literature reports on their AR inhibitory activity is not numerous.

Moon *et al.,* 1988 started research on monoterpine derivate to find BLAR enzyme Inhibitory activity. Most of the monoterpine showed the mild inhibitory activity on BLAR. Only 3-carene showed no effect on the enzyme activity at the concentration of 10^{-3}M (Table 1.26). Among them, (+) Pulegon showed maximum activity with 42% inhibition at the 10^{-3}M concentration.

Fujita *et al.,* 1995 reported that the monoterpene glycosides: perillosides A **(209),** B (**210**), C (**211**) and D (**212**) isolated from the leaves of *Perilla frutescens* possess potent inhibitory activity on both RLAR and HRAR enzymes. But, the inhibitory effects of perillosideB (**210**) and perilloside D **(212)** were much lower than perilloside A (**210**) and perilloside C (**211**) though their structures are similar to those of **209** and **211.** Structure-activity relationship among this group of compounds was carried out by synthesizing several related monoterpene glycosides and their tetraactates and determining the AR inhibitory effects. It was concluded that a planner

monoterpene glucoside consisting of a *p*-menthane skeleton with an equatorial side chain and a β-D-glucosyloxy moiety at the C-7 position is expected to have a potent inhibitory effect on AR enzymes. Kinetic studies revealed that the type of inhibition by perilloside A (**209**) and perilloside C (**211**) was competitive with respect glyceraldehydes, whilst the inhibition caused by their tetraacetates was non-competitive.

Table 1.26 RLAR Inhibitiory ativity of some monoterpines (Moon *et al*., 1988).

Compounds	%inhibition (M)	
	10^{-3}	10^{-5}
3-Carene	0	0
4-Caranol	23	17
4-Isocaranon	21	14
3-Hydroxy methyl- caran-4-on	22	17
3-Hydroxy methyl- caran-4-ol	30	16
(+)Carvon	25	14
(-)Carvon	35	14
Carbomethon	37	21
(+)Pulegon	42	20
(-)isopulegol	25	17
(-)Menthon	23	05
4-Hydroxy methyl- Menthon	31	17
Camphor	14	05

The abietane-type diterpenoids: danshenols A **(213)** and B **(214),** dihydrotanshinone I **(215**), tanshinone I (**26),** cryptotanshinone **(217),** tanshinone II A (**218**) and (-)-danshexinkun A **(219**) isolated from the dried root and rhizome of *Salvia miltiorhiza* showed inhibitory activity against RLAR enzyme. Among these danshenol A (**213**) was found to exhibit the most potent inhibitory activity with an IC_{50} value of 0.10 μg/mL. In the same experiment, the IC_{50} value of the reference drug epealrestat was 0.10 μg/mL (Kasimu *et al*., 1997). Yoshikawa *et al.* 1999, isolated 6 sesquiterpenes from the methanol extract of the dried flowers of *Chrysanthemum indicum*, which showed inhibitory activity on RLAR. However, the tested compounds: clovanediol (**220),** caryolane 1,9-β-diol (**221**), oplopanone (**222)**, kikkanol A (**223**) and kikkanol C (**224**) showed weak inhibitory activity, indicating that the sesquiterpenes do not contribute to much of the AR activity of the plant.

The hydroalcoholic extract of the stems of *Salacia chinensis* afforded a series of triterpenes and one sesqiterpene. However, only two of the isolated oleanane-type triterpenes, 3β,22β-dihydroxyolean-12-en-29-oic acid (225) (IC_{50} = 26.0 μM) and maytenfolic acid (226) (IC_{50} = 72.0 μM), and all of the norfriedelane-type triterpenes, tingenone (227) (IC_{50} = 13.0

μM), tingenin B (228) (IC_{50} = 7.0 μM) and regeol A (IC_{50} = 30.0 μM) (229) and triptocalline A (230) (IC_{50} = 14 μM) showed activity on RLAR. The friedelane- and ursane- type triterpenes as well as the eudesmane-type sesquiterpene failed to exhibit appreciable activity (Morikawa *et al.*, 2003). Similarly, investigation of the hydroalcoholic root extracts of another *Salacia* species, *S. oblonga* used in Ayurvedic traditional medicine in India as a remedy for diabetes among others, were investigated for their inhibitory activity against RLAR. The principal components of the active ethyl acetate soluble fraction yielded diterpenes and tritepenes. The triterpenes obtained were kotalagenin 16-acetate (231), maytenfolic acid (226), 3β, 22-α-dihydroxyolean-12-en-29-oic acid (225) and 26-hydroxy-1,3-friedalnedione (232), 19-hydroxyferruginol (233) and lambertic acid (234) were the diterpene constituents of the plant. Among the isolated compounds, 3β, 22-α-dihydroxyolean-12-en-29-oic acid (225) was the most active exerting a percentage inhibition of 75.9% at a concentration of 100 μM (Matsuda *et al.,* 1999). Similarly, 12-hydroxyjasmonic acid 12-*O*-β-glucopyranoside (235), and *p*-menth-3-ene-1, 2-diol-1-*O*-β-glucopyranoside (236) isolated from the polar extract of *Origanum vulgare* showed AR inhibitory activity. At a concentration of 100 μg/mL the compounds showed percent inhibition of 77 ± 1.4 and 41 ± 0.6, respectively (Koukoulitsa *et al.,* 2006).

Fatmawati *et al*. 2010a isolated ganoderic acid Df (237), a lanostane-type triterpenoid from the fruiting body of *Ganoderma lucidum* Df. Ganoderic acid Df (237), showed potent inhibitory activity against HRAR with an IC_{50} value of 22.8 μM. The carboxyl group in the side chain of (237) was found to be essential for eliciting inhibitory activity as its methyl ester derivative was much less active.

In another study, the chloroform extract of the fruiting body of *G. lucidum* was found to show inhibitory activity on HRAR *in vitro*. From the acidic fraction, two potent human ARIs, ganoderic acid C2 (**238**) and ganoderenic acid A (**239)**, were isolated together with three related compounds (Fatmawati *et al*. 2010b). The free carboxyl group of (**238**) and **(239)** was considered to be essential in eliciting the inhibitory activity. The COOH hydrophilic head of (**238**) and (**239**) is similar to that of many ARIs such as tolrestat and zopolrestat, and this head can possibly bind to AR in the form $(COO)^{-}$.

Alkaloids

Although alkaloids are by far the most biologically active secondary metabolites, there appear to have been very few reports in the literature concerning their AR inhibition effect. One such report by Kubo *et al.* (1994) deals with the isolation of 7 alkaloidal components dehydrocorydaline (**240**) from the methanolic extract of the tuber of

Corydalis turtschaninovii. Among these alkaloids only the quaternary alkaloidal component, dehydrocorydaline (**240**) produced inhibition against RLAR. All the tertiary alkaloids failed to show activity. Similarly, Lee, 2002b characterized the isoquinoline alkaloids, berberine chloride (**241**) and palmatine iodide (**242**) as AR inhibitors of methanol extract of the root of *Coptis japonica*. The IC_{50} values of the alkaloids against RLAR were found to be 13.98 and 13.45 μM. In the same experiment the isoquinoline alkaloids, berberine sulfate (**243**) berberine iodide (**244**) and palmatine sulfate (**245**) were also tested. It was observed that inhibitory activities of the chlorinated and sulfated analogues are much greater than those for the iodide (Lee, 2002b).

In the search for components inhibiting AR, Kato *et al*. (2009) isolated an active alkaloid from the hot water extract of *Evodia rutaecarpa* Bentham. The alkaloid identified as N2-(2-methyl amino benzoyl) tetrahydro-1H-pyrido[3,4-b] indol-1-one (rhetsinine) **(246)** inhibited HRAR with an IC_{50} value of 24.1 μM.

Coumarins

The coumarin (benzopyran-2-one, or chromen-2-one) ring system, present in natural products (such as the anticoagulant warfarin) displays interesting pharmacological properties. The AR inhibitory activities of 41 coumarins have been included in the review by Kawannishi et al. (2003). The hot water root extract of *Angelica gigas* has been reported to inhibit BLAR at a concentration of 100 μg/mL. Three linear coumarins: decursunol angelate **(247),** decursin **(248)** and nodakenin (**249)** with AR inhibitory activity have been isolated. Among these, nodakenin **(249)** exhibited significant inhibition with an IC_{50} value of 7.33 μM (Lee *et al*., 2002). Other workers have reported the isolation of 11 coumpounds, 9 of which were coumarins, from the dried stem of *A. gigas* with AR inhibitory activity. Isoimperatorin (**250)**, scopoletin (**251**), and 3'-hydroxyxanthyletin (**252**) showed good inhibitory activity with IC_{50} values of 5.1, 2.59, and 4.23 μM, respectively. 7-Methoxy-5-prenyloxycoumarin (**253**), bergapten (2**54**) and psoralen (**255**) also showed an intermediate activity with IC_{50} values of 32.38, 25.03, and 51.62 μM, respectively. Xanthotoxin (256) (IC_{50} = 103.15 μM) showed weak activity. Imperatorin (**257**) and decursin (**248**) did not show any significant activity. Interestingly, visaminol (**258**), which is not a coumarin but a chromone derivative, showed relatively good inhibitory activity with an IC_{50} value of 26.66 μM (Park *et al.*2011).

In another study, five coumarins: umbelliferone (**259**), scoparone (**260**), scopoletin (**251**), esculetin (**261**), and scopolin (**262**) with AR inhibitory activity were isolated from the whole plant extract of *Artemisia montana*. All the other isolated compounds showed intermediate activities but the

inhibition produced by scoparone (**260**) (IC_{50} = 44.30 ± 0.47 μM) on RLAR was better than the others (Jung *et al*., 2011).

Tannins

Tannins have diverse effects on the biological systems because they are potential metal ion chelators, protein precipitating agents and biological antioxidants. Lee *et al*., 2008. Isolated the one tannin pentagalloyl glucose **(263)** from the *Rhus verniciflua***,** it shows the inhibitory activity against AR.

Miscellaneous

Two polyacylated sucroses prunose I (**264**) and prunose II (**265**) were isolated from the methanolic extract of *Prunus mume*. Whilst (**264**) (IC_{50} = 58 μM) exhibited inhibitory effect against RLAR, the effect of **(265)** (IC_{50} = >100 μM) was very weak (Yoshikawa *et al.,* 2002) The bark of C*innammum cassia*, the commercial source of cinnamon, was subjected to methanol extraction and fractionated with various solvents. Further investigation of the active hexane fraction led to the isolation of *trans*-cinnamaldehyde (**266**), cinnamyl alcohol **(267)** and eugenol (**268**), among others. (**266**) (IC_{50} = 3 μg/mL) exhibited good inhibitory activity, whereas the activities of (**267**) and (**268**) (IC_{50} = 500 μg/mL) was much weaker (Lee 2002a). Cerebrosides (**269**) (30.0 The μg/mL) isolated from the EtOAc soluble fraction of the methanol extract of the fruiting bodies of *Ganoderma applanatum* showed inhibition against RLAR (Lee *et al*., 2005). The essential oil obtained from the seeds of *Cuminum cyminum* was found to completely inhibit RLAR at a dose of 0.5 mg/mL. Chromatographic analysis of the oil by HPLC reveled that cuminaldehyde (**270**) is the active constituent of the oil. Cuminaldehyde (**270**) (IC_{50} = 0.80 μM) displayed a potent activity that could be compared with the reference compound quercetin (IC_{50} = 0.51 μM) (Lee, 2005).

Conclusion

Prevention of diabetic complications has become the current interest of scientists and research workers worldwide. Use of plant derived phytochemicals in the treatment of various chronic disorders is increasing and many phytomedicines are becoming the best alternatives to synthetic drugs. Diabetic and its complications can be prevented using phytomedicines. The promising plant derived compounds like quercetin **(1)**, kaempferol **(115),** and ellagic acid (**84)** have long standing evidences for their AR inhibitory activity. In the present context this review stresses the need to focus on research for potential phytochemical compounds which can be effectively used for the treatment of diabetic complications.

References

Angel de la Fuente J, Manzanaro S. 2003. Aldose reductase inhibitors from natural sources. Nat Prod Rep 20: 243–251.

Brownlee M. 2001. Biochemistry and molecular cell biology of diabetic complications. Nature 414: 813-820.

Cerelli MJ, Curtis DL, Dunn JP et al.1986. Antiinflammatory and aldose reductase inhibitory activity of some tricyclic arylacetic acids. J Med Chem 29: 2347–2351

Chethan S, Dharmesh SM, Malleshi NG et al. 2008. Inhibition of aldose reductase from cataracted eye lenses by finger millet (Eleusine coracana) polyphenols. Bioorg Med Chem 16: 10085-10090.

Chung IM, Kim MY, Park WH et al. 2008. Aldose reductase inhibitors from Viola hondoensis. Am J Chin Med 36: 799-803.

Chung YS, Choi YH, Lee SJ et al. 2005. Water extract of Aralia elata prevents cataractogenesis in vitro and in vivo. J Ethanopharmacol 101: 49-54.

Costantino L, Rastelli G, Vianello P et al. 1999. Diabetes complications and their potential prevention: Aldose reductase inhibition and other approaches. Med Res Rev 19: 3-23.

Crabbe MJ, Goode D. 1998. Aldose reductase: a window to the treatment of diabetic complication?. Prog Retin Eye Res 17: 313-383.

Du ZY, Bio YD, Liu Z et al. 2006. Curcumin analogs as potent aldose reductase inhibitors. Arch Pharm 339: 123-128.

Fatmawati S, Kurashiki K, Takeno S. 2009. The Inhibitory effect on aldose reductase by an extract of Ganoderma lucidum. Phytother Res 23: 28–32.

Fatmawati S, Shimizu K, Kondo R. 2010a. Ganoderic acid Df, a new triterpenoid with aldose reductase inhibitory activity from the fruiting body of Ganoderma lucidum Fitoterapia 81: 1033-1036.

Fatmawati S, Shimizu K, Kondo R. 2010b. Inhibition of aldose reductase in vitro by constituents of Ganoderma lucidum. Planta Med 76: 1691-1693.

Fuente DL, Manzanaro S, Martín MJ et al. 2003. Synthesis, activity, and molecular modeling studies of novel human aldose reductase inhibitors based on a marine natural product. J Med Chem 46: 5208–5221.

Fujita T, Ohira K, Miyatake K et al. 1995. Inhibitory effect of perilloside A and C, and related monoterpene glucoside on aldose reductase and their structure activity relationship. Chem Pharm Bull 43: 920-926.

Gacche RN, Dhole NA. 2011a. Aldose reductase inhibitory, anti-cataract and antioxidant potential of selected medicinal plants from the Marathwada region, India. Nat Prod Res 25: 760–763.

Gacche RN, Dhole NA. 2011b. Profie of aldose reductase inhibition, anti-cataract and free radical scavenging activity of selected medicinal plants: An attempt to standardize the botanicals for amelioration of diabetes complications. Fod Chem Toxicol 49: 1806-1813.

Goodarzi MT, Zal F, Malakooti M et al.. 2006. Inhibitory activity of flavonoids on the lens aldose reductase of healthy and diabetic rats. Acta Medica Iranica 44: 41-45.

Guzmán A, Ricardo OG. 2005. Inhibition of aldose reductase by herbs extract and natural substance and their role in prevention of cataracts. Rev Cubana Plant Med 10: 3-4.

Halder N, Joshi S, Gupta SK. 2003. Lens aldose reductase inhibiting potential of some indigenous plants. J Ethanopharmacol 86: 113-116.

Haraguchi H, Hayashi R, Ishizu T et al. 2003. A flavone from Manilkara indica as a specific inhibitor against aldose reductase in vitro. Planta Med 69: 853-855.

Haraguchi H, Ohmi I, Fukuda A et al. 1997. Inhibition of aldose reductase and sorbitol accumulation by astilbin and toxifolin dihydroflavonols in Engelhardtia chrysolepis. Biosci Biotechnol Biochem 61: 651-54.

Haraguchi H, Ohmi I, Sakai S et al. 1996. Effect of Polygonum hydropiper sulfated flavonoids on lens aldose reductase and related enzyme. J Nat Prod 59: 443-445.

Hayman S, Kinoshita JH. 1965. Isolation and properties of lens Aldose reductase. J Biol Chem.240: 877-882.

Hong Mei Li, Seung Hwan Hwang, Beom Goo Kang, Jae Seung Hong, Soon Sung Lim. Inhibitory Effects of Colocasia esculenta (L.) Schott Constituents on Aldose Reductase. Molecules. 2014; 19: 13212-13224.

Hsieh P-C, Huang G-J, Ho Y-L et al. 2010. Activities of antioxidants, α-Glucosidase inhibitors and aldose reductase inhibitors of the aqueous extracts of four Flemingia species in Taiwan. Bot Studies 51: 293-302.

International Diabetes Federation (IDF), Diabetes Atlas Seventh Edition 2015.

Jung HA, Islam MD, Kwon YS et al. 2011. Extraction and identification of three major aldose reductase inhibitors from Artemisia Montana. Food Chem Toxicol 49: 376–384.

Jung HA, Jung YJ, Yoon NY et al. 2008a. Inhibitory effect of Nelumbo nucifera leaves on rat lens aldose reductase, advanced glycation endproducts formation and oxidative stress. Food Chem Toxicol 46: 3818-3826.

Jung HA, Kim YS, Choi JS. 2009. Quantitative HPLC analysis of two key flavonoids and inhibitory activities against aldose reductase from different parts of the Korean thistle, Cirsiummaackii. Food Cheml Toxicol 47: 2790–2797.

Jung HA, Yoon NY, Kang SS et al. 2008b. Inhibitory activities of prenylated flavonoids from Sophora flavescens against aldose reductase and generation of advanced glycation endproducts. J Pharm Pharmacol 60: 1227-1236.

Jung SH, Lee JM, Lee HJ et al. 2007. Aldose reductase and advanced glycation endproducts inhibitory effect of Phyllostachys nigra. Biol Pharma Bull 30(8): 1569-1572.

Jung SH, Lee YS, Lee S et al. 2002. Isoflavonoids from the rhizomes of Belamcanda chinensis and their effect on aldose reductase and sorbitol accumulation in streptozotocin induced diabetic rat tissues. Arch Pharma Res 3: 306-312.

Kador PF, Kinoshita JH, Tung WH et al. 1980. Differences in the susceptibility of various aldose reductases to inhibition. Invest Opthalmol Visual Sci 19: 980-982.

Kaoru A , Masato T, Hideo S, Toshiinasa O, Hiroshi S,Hiroaki N, Masao C, and Hiroshi M. 1989 The Existence of Aldose Reductase Inhibitors in Some Kampo Medicines (Oriental Herb Prescriptions). Planta Medica 55, 409-38.

Kasimu R, Basnet P, Tezuka Y et al.1997. Danshenols A and B, new aldose reductase inhibitors from the roots of Salvia miltiorhiza. Chem Pharm Bull 45: 564-566.

Kato A, Higuchi Y, Gato H et al. 2006. Inhibitory effects of Zingiber officinale Roscoe derived components on aldose reductase activity in vitro and in vivo. J Agric Food Chem 54: 6640-6644.

Kato A, Yasuko H, Goto H et al. 2009. Inhibitory effect of rhetsinine isolated from Evodia rutaecarpa on aldose reductase activity. Phytomedicine 16: 258-261.

Kawanishi K, Ueda H, Moriyasu M. 2003. Aldose reductase inhibitors from nature. Curr Med Chem 10: 1353-1374.

Kim J, Kim CS, Sohn E et al. 2011. KIOM-79 inhibits aldose reductase activity and cataractogenesis in Zucker diabetic fatty rats. J Pharm Pharmacol 63: 1301–1308.

Kim JH, Ryu YB, Kang NS et al. 2006. Glycosidase inhibitory flavonoids from Sophora flavescens. Biol Phrama Bull 29: 302-305.

Kodha H, Tanaka S, Yamaoka Y et al.1989. Studies on lens- aldose- reductase inhibitor in medicinal plants. II. active constituents of Monochsma savatierii. Chem Pharm Bull 37: 3153-3154.

Koukoulitsa C, Zika C, Geromichalos GD et al. 2006. Evaluation of aldose reductase inhibition and docking studies of some secondary metabolites, isolated from Origanum vulgare L. ssp. Hirtum. Bioorg Med Chem 14: 1653-1659.

Kubo M, Matsuda H, Tokuoka K et al. 1994. Studies of anti-cataract drugs from natural sources.I. Effects of methanolic extract and the alkaloidal components from Corydalis Tuber on in vitro aldose reductase activity. Biol Pharm Bull 17: 458-459.

Lee EH, Song DG, Lee JY et al. 2008. Inhibitory effect of the compounds isolated from Rhus verniciflua on aldose reductase and advanced glycation endproducts. Biol Pharma Bull 31(8): 1626-1630.

Lee HS. 2002a. Inhibitory activity of Cinnamomum cassia bark derived component against rat lens aldose reductase. J Pharm Pharmaceut Sci 5: 226-230.

Lee HS. 2005. Cuminaldehyde: Aldose reductase and α-glucosidase inhibitor derived from Cuminum cyminum L.seeds. J Agric Food Chem 53: 2446-2450.

Lee HS.2002b. Rat lens aldose reductase inhibitory activities of Coptis japonica root derived isoquiniline alkaloids. J Agric Food Chem 50: 7013-7016.

Lee S, Jung SH, Lee YS et al. 2002. Coumarins from Angelica gigas roots having rat lens aldose reductase activity. J Appl Pharmacol 10: 85-88.

Lee S, Shim SH, Kim JS et al. 2005. Aldose reductase inhibitors from the fruiting bodies of Ganoderma applanatum. Biol Pharma Bull 28(6): 1103-1105.

Lee SJ, Park WH, Park SD et al. 2009. Aldose reductase inhibitors from Litchi chinensis Sonn. J Enzyme Inhib Med Chem 24(4): 957-959.

Lee YS, Kim JK, Bae YS et al. 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 YS, Kim SH, Jung SH et al. 2010. Aldose reductase inhibitory compounds from Glycyrrhiza uralensis. Biol Phrama Bull 33(5): 917-921.

Lim SS, Jung YJ, Hyum SK et al. 2006. Rat lens aldose reductase inhibitory constituents of Nelumbo nucifera stamens. Phytother Res 20: 825-830.

Logendra S, Ribnicky DM, Yang H et al. 2006. Bioassay guided isolation of aldose reductase inhibitors from Artemisia dracunculus. Phytochemistry 67: 1539-1546.

Manzanaro S, Salva J, Angel de la Fuente J et al. 2006. Phenolic marine natural products as aldose reductase inhibitors. J Nat Prod 69: 1485-1487.

Matsuda H, Morikawa T, Toguchida I et al. 2002a. Medicinal flowers. Part VI. Absolute stereostructures of two new flavonone glycosides(I) and a phenylbutanoid glycoside(II) from the flowers of Chrysanthem indicum: Their inhibitory activities for rat lens aldose reductase. Chem Pharm Bull 50: 972-975.

Matsuda H, Morikawa T, Toguchida I et al. 2002b.Structural requirements of flavonoids and related compounds for aldose reductase inhibitory activity. Chem Pharm Bull 50:788-795.

Matsuda H, Murakami T, Yashiro K et al.1999. Antidiabetic principles of natural medicines. IV. Aldose Reductase and α-glucosidase inhibitors from the roots of Salacia oblonga Wall. (Celastraceae): Structure of a new friedelane-type triterpene, kotalagenin 16-acetate. Chem Pharm Bull 47: 1725-1729.

Moghaddam MS, Kumar PA, Reddy GB et al. 2005. Effect of diabecon on sugar induced lens opacity in organ culture: mechanism of action. J Ethnopharmacol 97: 397-403.

Moon HI, Jung JC, Lee J. 2006. Aldose reductase inhibitory effect by tectorigenin derivatives from Viola hondoensis. Biorg Med Chem 14: 7592-7594.

Morikawa T, Kishi A, Pongpiriyadacha Y et al. 2003. Structures of new friedelane type triterpenes and eudesmane type sesqiterpene and aldose reductase inhibitors from Salacia chinensis. J Nat Prod 66: 1191-1196.

Morikawa T, Xie H, Wang T et al. 2008. Bioactive constituents from Chinese Natural Medicines xxxvii. Aminopeptidase N and Aldose reductase Inhibitors from Sinocrassula indica: structures of sinocrassosides B4, B5, C1, and D1-D3. Chem Pharm Bull 56: 1438-1444.

Murata M, Iries J, Homma S et al. 1994. Aldose reductase inhibitors from green tea. Lebensm Wiss u Technol 27: 401-405.

Muthenna P, Suryanarayana P, Gunda SK et al. 2009. Inhibition of aldose reductase by dietary antioxidant curcumin: Mechanism of inhibition, specificity and significance. FEBS Lett 583: 3637–3642.

Nishimura.C, Yamaoka T, Mizutani M et al. 1991. Purification and characterization of the recombinant human Aldose reductase expressed in baculovirus system.Biochem Biophys Acta 1078: 171-178.

Ohkubo Y, Kishikawa H, Araki E et al. 1995. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: arandomized prospective 6-year study. Diabetes Res Clin Pract 28: 103-117.

Okada Y, Miyauchi N, Suzuki K et al. 1995. Search for naturally occurring substances to prevent the complication of diabetes.II.Inhibitory effect of coumarin and flavonoid derivatives on bovine lens aldose reductase and rabbit platelet aggregation. Chem Pharm Bull 43: 1385-1387.

Park C-H, Lim SS, 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.

Park HY, Kwon SB, Heo NK et al. 2011. Constituents of the stem of Angelica gigas with rat lens aldose reductase inhibitory activity. J Korean Soc Appl Biol Chem 54: 194-199.

Patel DK, Kumar R, Kumar M et al. 2012. Evaluation of in vitro aldose reductase inhibitory potential of different fraction of Hybanthus enneaspermus Linn F. Muell. Asian Pac J Trop Biomed 2: 134-139.

Peyroux J, Sternberg M. 2006. Advanced glycation end products (AGEs): pharmacological inhibition in diabetes. Pathol Biol 54: 405-419.

Rosler KH, Goodwin RS, Mabry TJ et al.1984. Flavonoids with anti cataract activity from Brickellia arguta. J Nat Prod 47: 316-319.

Sakai I, Izumi SI, Murano T et al. 2001. Presence of aldose reductase inhibitors in tea leaves. Jpn J Pharmacol 85: 322-326.

Saraswat M, Muthenna P, Suryanarayana P et al. 2008. Dietary sources of aldose reductase inhibitors: prospects for alleviating diabetic complications. Asia Pac J Clin Nutr 17: 558-565.

Sato S, Takeo J, Aoyama C et al. 2007. Na+-glucose cotransporter (SGLT) inhibitory flavonoids from the roots of Sophora flavescens. Bioorg med chem 15: 3445-3449.

Suryanarayana P, Saraswat M, Mrudula T et al. 2005. Curcumin and turmeric delay streptozotocin-induced diabetic cataract in rats. Invest Ophthalmol Vis Sci 46: 2092–2099.

Surynarayana P, Kumar PA, Sarasawat M et al. 2004. Inhibition of aldose reductase by tannoid principles of Emblica officinalis: Implications for the prevention of sugar cataract. Mol Vis 10: 148-154.

Terashima S, Shimizu M, Nakayama H, Ishikura M, Ueda Y, Imai K, Suzui A, Morita N.1990.Studies on aldose reductase inhibitors from medicinal plant of "sinfito," Potentilla candicans, and further synthesis of their related compounds. Chem. Pharm bull; 38(10):2733-6.

Termentzi A, Alexiou P, Demopoulos VJ et al. 2008. The aldose reductase inhibitory capacity of Sorbus domestica fruit extracts depends on their phenolic content and may be useful for the control of diabetic complications. Pharmazie 63: 693-696.

Tomás-Barberán FA, Lopez GC, Villar A et al.1986. Inhibition of lens aldose reductase by Labiatae flavonoids. Planta Med 6: 239-240.

Toyomizu M, Sugiyama S, Jin RL, Nakatsu T. 1993. α-Glucosidase and Aldose Reductase Inhibitors: Constituents of Cashew, Anacardium occidentale, Nut Shell Liquids. Phytotherapy research, 7, 252-254.

Ueda H, Kuroiwa E, Tachibana Y et al. 2004. Aldose reductase inhibitors from the leaves of Myrciaria dubia. Phytomedicine 11: 652-656.

Varma SD, Kinoshita JH. 1976. Inhibition of lens aldose reductase by flavonoides –their possible role in the prevention of diabetic cataracts. Biochem Pharma 25: 2505-2513.

Varma SD, Mikuni I, Kinoshita JH et al.1975. Flavonoids as inhibitors of lens aldose reductase. Science 188: 1215-1216.

Wirasathien L, Pengsuparp T, Suttisri R et al. 2007. Inhibitors of aldose reductase and advanced glycation end products formation from the leaves of Stelechocarpus cauliflorus. Phytomedicine 14: 546-550.

Xie H, Wang T, Matsuda H et al. 2005. Bioactive constituents from Chinese natural medicine.XV.Inhibitory effect on aldose reductase and structure of saussureosides A and B from Saussurea medusa. Chem Pharm Bull 53: 1416-1422.

Xu Z, Yang H, Zhou M et al. 2010. Inhibitory effect of total lignan from Fructus Arctii on aldose reductase. Phytother Res 24: 472–473.

Yawadio R, Shinji T, Naofumi M. 2006. Identification of phenolic compounds isolated from pigmented rices and their aldose reductase inhibitory activities. Food Chem 101: 1616-1625.

Yoshikawa M, Morikawa T, Murakami T et al. 1999. Medicinal flowers.I.Aldose reductase inhibitors and three new eudesmane type sesquiterpenes, kikkanols A, B, and C, from the flower of Chrysanthem indicum. Chem Pharm Bull 47: 340-345.

Yoshikawa M, Murakami T, Ishiwada T et al. 2002. New flavonol oligoglycosides and polyacylated sucroses with inhibitory effects on aldose reductase and platelet aggregation from the flowers of Prunus mume. J Nat Prod 65: 1151-1155.

Yoshikawa M, Shimada H, Nishida N et al. 1998. Antidiabetic principles of natural medicines.II. Aldose reductase and α-glucosidase inhibitors from Brazilian natural medicine, the leaves of Myrcia multiflora DC. (Myrtaceae):structures of myrciaphenones A and B. Chem Pharm Bull 46: 113-119.

Zhiqiang Wang, Seung Hwan Hwang, Yanymee N. Guillen Quispe, Paul H. Gonzales Arce, Soon Sung Lim. Investigation of the antioxidant and aldose reductase inhibitory activities of extracts from Peruvian tea plant infusions. Food Chemistry 231 (2017) 222–230.