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Reveiw Article

Enzymes Inhibitors From Plants: An Alternate Approach To Treat Diabetes

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ABSTRACT: Diabetes is one of the major medical complications the world faces today. It is a common metabolic disease characterized by abnormally high plasma glucose levels, leading to major complications such as diabetic neuropathy, retinopathy, and cardiovascular diseases. The management of blood glucose levels is a critical strategy in the control of diabetes complications. Inhibitors of carbohydrate hydrolyzing enzymes (such as α-glucosidase and α-amylase) have been useful as oral drugs for the control of hyperglycemia, especially in patients with type II diabetes mellitus. Other enzymes such as DPP4, aldose reductase and angiotensin converting enzyme also play an important role in diabetes. Inhibition of these factors plays an important role in management of diabetes. Various research studies have been performed to examine the effectiveness of natural sources as the inhibitors of all these enzymes. In the present review, we discuss the various constituents isolated from plants which have inhibitory properties against these enzymes.

KEY WORDS: diabetes, flavonoids, α-glucosidase, α-amylase, DDP4, ACE inhibitor

INTRODUCTION

Diabetes mellitus is a metabolic disorder of multiple etiology. It is characterized by chronic hyperglycemia with disturbance of carbohydrate, fat and protein metabolism resulting from the defect in insulin secretion, insulin action or both.[1] The majority of diabetes cases are divided into two broad etiopathogenic categories. The first category (type 1 diabetes) occurs due to the absolute deficiency of insulin. Only 5-10 % diabetics are affected by this type of diabetes. The other more prevalent category (type 2 diabetes) occurs mostly due to combination of insulin resistance and inadequate compensatory insulin secretary response.[2] One therapeutic approach to treat diabetes is to decrease post – prandial hyperglycemia. This is done by retarding and reducing the digestion and absorption of glucose through the inhibition of carbohydratehydrolyzing enzymes such as α- glucosidase and α – amylase in the digestive tract. Inhibition of these enzymes delays the digestion of the carbohydrates, causing a reduction in the rate of glucose absorption.[3] Stabilization of blood glucose prevents hyperglycemia and the complications associated with the diabetes.[4] Long-term secondary complications are the main cause of morbidity and mortality in diabetic patients.[5] The major microvascular complications of diabetes include nephropathy, neuropathy and retinopathy. Cataract is another vascular complication.[6] Several metabolic factors contribute to the dysfunction observed in diabetic vasculopathy.[7] These include increased glucose flux through the polyol pathway, increased production of reactive oxygen species by the mitochondrial respiratory chain, nonenzymatic glycations, protein kinase-C activation and increased flux through the hexosamine pathway.[5] The increase in the level of ROS in diabetes may be due to their increased production and/ or decreased destruction by enzymic catalase (CAT), glutathione peroxidase (GSH-Px), and superoxide dismutase (SOD) antioxidants. The level of these antioxidant enzymes critically influences the susceptibility of various tissues to oxidative stress and is associated with the development of complications in diabetes.[6].

Aldose reductase is the first and rate-limiting enzyme in the polyol pathway.[8] Another long term complication of the diabetes is hypertension (high blood pressure). Angiotensin converting enzyme is an important enzyme involved in vascular tension.[9] Along with Oxidative stress, this also plays a central role in the onset of diabetes mellitus.

α-Glucosidase (α-D-glucoside glucohydrolase) is an exo-type carbohydrase distributed widely in microorganisms, plants,

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and animal tissues[10]. The α-amylase mainly synthesizes in plants, near the starch deposit sites and also presents along the digestive tract of phytophagous animals range from insects to mammals.[11] Pancreatic α-amylase is the key enzyme in the digestive system. It catalyses the initial step in the hydrolysis of starch to a mixture of small oligosaccharide consisting of maltose, maltotriose and a number of α-(1-6) and α-(1-4) oligoglucans. These are then acted on by α-glucosidases and further degraded to glucose which on absorption enters to bloodstream. Degradation of dietary starch proceeds rapidly and leads to elevated post-prandial hyperglycemia.[12] Plants with inhibitory activity against α-glucosidase enzyme have been summarized in table 2.

Inhibition of α-amylase delay carbohydrate digestion and prolongs overall carbohydrate digestion time, causing a reduction in the rate of glucose absorption, consequently blunting increased post – prandial plasma glucose levels. [3] Because of their purported ability to prevent starch breakdown and absorption, α-amylase inhibitors have been used for weight loss in humans.[13] Acarbose and viglibose are currently used as α-amylase and α-glucosidase inhibitors, but also induce side effects such as abdotension, bloating, flatulence and diarrhea.[14] It has been suggested that such adverse effects might be caused by the excessive inhibition pancreatic α–amylase resulting in the abnormal bacterial fermentation of undigested carbohydrates in the colon.[15] Therefore, natural α-amylase inhibitors from the dietary plants can be used as effective therapy for post prandial hyperglycemia with minimal side effects.[16] Plants with inhibitory activity against α-glucosidase enzyme have been summarized in table 1.

Table1: Plant extracts with α-amylase inhibition activity

Plant	Part used	Extract/Fraction/Compound	IC_{50} and % inhibition	References
Acalypha indica (Euphorbiaceae)	Healthy plant part	Chloroform extract Ethanol extract	173.53 ± 0.21 µg/ml 180.80 ± 0.23 µg/ml	32
Allium sativum (Alliaceae)	Corm	Ethanol extract	17.95 mg/ml	33
Allium Akaka (Alliaceae)	Leaves	Ethanol extract	16.74 mg/ml	33
Allium cepa (Liliaceae)	Whole plant	Chloroform extract	166.38 ± 0.48 µg/ml	32
Allium cepa (Liliaceae)	Bulb	Ethanol extract	16.36 mg/ml	33
Allium porrum (Liliaceae)	Leaves	Ethanol extract	15.73 mg/ml	33
Amaranthus caudatus (Amaranthaceae)	Seeds	Methanolic extract	19.233µg/ml	34
Amaranthus spinosus (Amaranthaceae)	Whole plant	Methanolic extract	46.02 µg/ml	35
Andrographis paniculata (Acanthaceae)	Leaves	20 % (v/v) ethanol extract Andrographolide	50.09 ± 0.17 mg/ml 11.3 ± 0.29 mg/ml	36
Asystasia dalzelliana (Acanthaceae)	Leaves	AD-3 (50:50 methanol:ethylacetate) AD-4 (75:25 methanol:ethylacetate) AD-5 (100 % methanol)	25.78 µg/ml 52.78 µg/ml 56.46 µg/ml	37
Asystasia gangetica (Acanthaceae)	Leaves	Methanolic extract	3.75 µg/ml	38
Azardirachta indica (Meliaceae)	Whole plant	Aqueous extract Ethanol extract	124.62 ± 0.18 µg/ml 62.99 ± 1.20 µg/ml	32
Bergenia ciliate (Saxifragaceae)	Rhizomes	(-)- 3-O- galloylepicatechin (-)- 3-O- galloylcatechin	739 µM 401 Mm	39
Bougainvillea spectabilis (Nyctaginaceae)	Leaves	Chloroform extract	3.20 µg/ml	40

Continued...

Table1: *Continued*

Plant	Part used	Extract/Fraction/Compound	IC_{50} and % inhibition	References
Clerodendrone Multiflorum Linn. (Verbenaceae)	Stem	Methanolic extract Ethylacetate extract	25.33 µg/ml 36.86 µg/ml	41
Cinnamomum tamala (Lauraceae)	Dried bark	Methanol extract Water extract	1.80 µg/ml 5.53µg/ml	42
Curcuma longa (Turmeric)	Rhizomes	Turmerin	31 mg/ml	43
Dioscorea bulbifera (Dioscoreaceae)	Bulb	Petroleum ether extract	61.65 %	44
Elaedendron transvaalense (Celastraceae)	Stembark	Acetone extract	1.12 ± 0.079 µg/ml	45
Elaedendron undulata (Celastraceae)	Rootbark	Acetone extract	2.80 ± 0.063 µg/ml	45
Eleusine coracana L. (millet seeds) (poaceae)	Grains	Acidified methanol extract	23.5 µg/ml	46
Gnidia glauca (Thymelaeaceae)	Leaves Flowers	Petroleum ether extract Petroleum ether extract Ethylacetate extract Methanol extract	34.88 µg/ml), 31.82 µg/ml 33.84 µg/ml 33.92 µg/ml	44
Gymnema montanum (Asclepidaceae)	Leaves	Ethanolic extract	5 µg/ml	47
Lagerstroemia speciosa L. (banaba) (Lythraceae)	Leaves	Valoneaic acid dilactone	333 µg/ml	48
Linum usitatisumum (Linaceae)	Seeds	Isopropanol extract	540 µg/ml	49
Marrubium radiatum (Lamiaceae)	Whole plant	Methanol extract	61.6 µg/ml	50
Mangifera indica (Anacardiaceae)	Stem	Ethanol extract (Mangiferin)	74.35 ± 1.9 µg/ml	51
Merremia emarginata (Convolvulaceae)	Whole plant excluding flowers	Hexane extract Ethyl acetate extract Aqueous Methanol Methanol extract	133.4 µg/ml 421.8 µg/ml 218.0 µg/ml 104.5 µg/ml	52
Morus alba (Moraceae)	Leaves	Ethanolic extract	17.60 mg/ml	53
Morus alba var. nigra (Moraceae)	Leaves	Ethanolic extract	13.26 mg/ml	53
Murraya koenigii (Rutaceae)	Leaves Whole plant	Chloroform extract Pet. Ether extract (Mahanimbine)	1.96 µg/ml 83.72 ± 1.4 µg/ml	54 40
Ocimum basilicum (Lamiaceae)	Leaves	Aqueous Extract	42.50 mg/ml	55
Ocimun sanctum (Lamiaceae)	Whole plant	Ethanol extract	178.55 ± 0.45 µg/ml	32
Ocimum tenuiflorum (Lamiaceae)	Seeds Leaves	Isopropanol extract Aqueous Extract	8.9 µg/ml 1.55 µg/ml	49 40
Phyllanthus amarus (Phyllanthaceae)	Whole plant	Ethanol extract Hexane extract	36.05 ± 4.01 µg/ml 48.92 ± 3.43 µg/ml	56
Pine densiflora (Pinaceae)	Bark	Pine bark extract	1.69 µg/ml	57

Plant	Part used	Extract/Fraction/Compound	IC_{50} and % inhibition	References
Pongamia pinnata L. Pierre (Fabaceae)	Seeds	Methanolic extract	77.92 %	58
Psidium guajava Linn. (Myrtaceae)	Leaves	Ethanol extract further extracted with n- butanol Quercetin Kaempferol Myricetin	4.8 mM 5.3 mM 4.3 Mm	59
Pteronia divaricata (Asteraceae)	Whole plant	Acetone extract	36.30 ± 4.624 µg/ml	45
Saliva verticillata (Lamiaceae)	Aerial parts	Ethanol extract	18.34 mg/ml	60
Saliva virgata (Lamiaceae)	Aerial parts	Ethanol extract	19.73 mg/ml	60
Syzygium cumini (Myrtaceae)	Leaves	Chloroform extract	4.28 µg/ml	40
Terminalia chebula (Combretaceae)	Fruits	Alcoholic extract	52%	61
Tinospora cordifolia (Menispermacea)	Stem	Dichloromethane extract	83%	62
Vaccinium arctostaphylos (Ericaceae)	Berries	malvidin-3-O-beta-glucoside	0.329 mM	63
Varthemia iphionoides (Compositea)	Aerial part	Water extract	14.8 ± 0.8%	64
Vigna sublobat (Fabaceae)	Seeds	Crude protein extract	80.50 % inhibition by 13.5 mg protein content in per gram seeds	65
Ziziphus spina – Christi (Rhamnaceae)	Leaves	Ethanolic extract	0.3 mg/ml	66

IC_{50} = Fifty percent inhibitory concentration

Aldose reductase is a member of the aldo-keto reductases (AKR) super family. It is the first and rate-limiting enzyme in the polyol pathway and reduces glucose to sorbitol, utilizing NADPH as a cofactor. Sorbitol is then metabolized to fructose by sorbitol dehydrogenase.[17] In diabetes mellitus, the increased availability of glucose in insulin-insensitive tissue such as lens, nerve, and retina leads to increased formation of sorbitol through the polyol pathway. Sorbitol does not readily diffuse across the cell membranes. Intracellular accumulation of sorbitol has been implicated in chronic complications of diabetes such as cataract, neuropathy and retinopathy. Aldose reductase inhibitors prevent the conversion of glucose to sorbitol and may have the capacity to prevent diabetic complications.[18] Quercetin, quercitrin, and myricitrin are potent aldose redutase inhibitors.[19] Some plants show inhibitory activity against this enzyme and are summarised in table 3.

Angiotensin I-converting enzyme (ACE) is an important enzyme involved in maintaining vascular tension. ACE activates a histidyl-leucine dipeptide called angiotensin I, into a potent vasoconstrictor called angiotensin II.[10] Angiotensin II stimulates the synthesis and release of aldosterone, which increases blood pressure by promoting sodium retention in the distal tubules.[20] Inhibition of ACE is considered a useful therapeutic approach in the treatment of high blood pressure in both diabetic and non-diabetic patients.[21] Some plants which show inhibitory activity against this enzyme are discussed in table 5.

Another novel approach for treatment of type- 2 diabetes is based on the gut hormone glucagon-like peptide-1 (GLP-1) which is anti-diabetic due to its combined action of stimulating insulin secretion, increasing beta-cell mass, inhibiting glucagon secretion, reducing the rate of gastric emptying and inducing satiety. The peptide is rapidly inactivated by dipeptidyl peptidase-IV (DPP-4), resulting in a half-life of active GLP-1 of only approximately 1-2 minutes. Inhibition of DPP-IV increases the levels of endogenous active GLP-1 and prolongs its half-life. Studies on animals have shown genetic deletion of DPP-IV improved glucose tolerance and increased insulin secretion in response to oral glucose.[22] Some plant extracts which have shown inhibitory activity against this enzyme are summarised in table 4.

Oxidative stress plays a central role in the onset of diabetes mellitus as well as in the development of vascular and neurologic complications of the disease.[23] The source of oxidative stress is a cascade of reactive oxygen species

Table 2: Plants with α–glucosidase inhibitory activity[73]

Plants name	Part	Extract and active constituents	IC_{50}
Acosmium panamense (Onychiuroidea)	Bark	Butanolic extract	109 µg/ml
Adhatoda vasica Nees (Acanthaceae)	Leaves	Vasicine	125 µM
		Vasicinol	250 µM
Euclea undulata (Ebenaceae)	Root Bark	Acetone extract	49.95 ± 0.007 µg/mL
Malmea depressa (Annonaceae)	Roots	Butanolic extract	21 µg/ml
Mangifera indica (Malpighiaceae)	Bark	Ethanolic extract	314 µg/ml
Morus alba (Moraceae)	Leaves	1-deoxynojirimycin (s)	7.7 × 10−5 mM
		1-deoxynojirimycin (m)	1.7 × 10−4 mM
Penares schulzei (Ancorinidae)	Bark	Schulzeines A	48–170 nM
		Schulzeines B	48–170 nM
		Schulzeines C	48–170 nM
Pine densiflora (Pinaceae)	Bark	(Pycnogenol)	5 µg/mL
Pine needle (Pinaceae)	Bark	Ethanolic extract	155 µg/mL
Syzygium malaccense (Myrtaceae)	Bark	Casuarine 6-O-β-glucoside	5.7 µg/mL

Table 3: Plants with aldose reductase inhibitory action

Plants	Part used	Extract used and chemical constituents	IC_{50}	References
Allium cepa (Alliaceae)	Bulbs	Aqueous extract	>1 mg/ml (RLAR)	74
Allium sativum(Alliaceae)	Bulbs	Aqueous extract	>1 mg/ml (RLAR)	74
Belamcanda chinensis (Iridaceae)	Rhizomes	Tectoridin	1.08×10^{-6} M	75
		Tectorigenin	1.12×10^{-6} M (RLAR)	
Centella asiatica L (Apiaceae)	Aerial part	Methanol extract (Centellasapogenol A (17) and its oligoglycoside, Cenlellasaponin A)	0.80 µg/ml (RLAR)	76
Cassia fistula (Caesalpiniaceae)	Plant	Water, ethanol, and chloroform extract	0.15 mg/ml	77
Chrysanthemum boreale (Asteraceae)	Flowers	Luteolin	5×10^{-7} M (RLAR)	78
Cinnamomum cassia (Fabaceae)	Bark	Cinnamaledehyde	0.003 mg/ml	79
		Eugenol	>0.5 mg/ml	
		Cinnamy alcohol	>0.5 mg/ml	
		Cinnamic acid	0.38 mg/ml (RLAR)	
Citrus lemon (Rutaceae)	Fruits	Aqueous extract	0.25 ± 0.01 mg/ml (RLAR)	80
			0.18 ± 0.01 mg/ml (RHAR)	
Coptis japonica (Ranunculaceae)	Roots	Berberine chloride	13. 98 nM	81
		Berberine sulfate	13.45 nM	
		Berberine iodide	32.84 nM	
		Palmitate iodide	68.00 nM	
		Palmitate sulphate	51.78 nM (RLAR)	
Cuminum cyminum (Apiaceae)	Seeds	Cuminaldehyde	0.00085 mg/ml (RLAR)	82

Plants	Part used	Extract used and chemical constituents	IC_{50}	References
Emblica officinalis (Euphorbiaceae)	Fruits	Aqueous extract Hydrolysable tannoids	0.72 mg/ml (RLAR) 0.88 mg/ml (RHAR) 6 µg/ml (RLAR) 10 µg/ml (RHAR)	83
Flemingia lineata (Fabaceae)	Roots	Aqueous extract	108.69 ± 1.40 µg/ml (RLAR)	84
Flemingia macrophylla (Fabaceae)	Roots	Aqueous extract	79.36 ± 3.20 µg/ml (RLAR)	84
Flemingia prostratu (Fabaceae)	Roots	Aqueous extract	172.41 ± 3.13 µg/ml (RLAR)	84
Flemingia strobilifera (Fabaceae)	Roots	Aqueous extract	112.12 ± 2.32 µg/ml (RLAR)	84
Foeniculum vulgare (Apiaceae)	Seeds	Aqueous extract	0.18 ± 0.02 mg/ml (RLAR) 0.19 ± 0.02 mg/ml (HRAR)	84
Ganoderma applanatum (Ganodermataceae)	Fruits	Methanol extract Ethyl acetate fraction Protocatechualdehyde Ergosterol peroxide	1.70 µg/ml 0.8 µg/ml 0.7 µg/ml 15.4 µg/ml (RLAR)	85
Hybanthus enneaspermus Linn F. Muell (Violaceae)	Whole plant	Ethanol extractDifferent Fractions) Pet. Ether fraction Chloroform fraction Ethylacetate fraction Water fraction	118.89 ± 0.71 µg/ml 98.52 ± 1.80 µg/ml 49.26 ± 1.76 µg/ml 70.83 ± 2.82 µg/ml (RLAR)	86
Lagerstromeia indica (Lythraceae)	Leaf, Stem	Methanol extract	0.069 µg/ml	87
Manikara indica Lamk (Sapotaceae)	Plant	Isoaffineyin (5,7,3',4.5'-pentahydroxy flavone - 6 - C - glucoside) (18)	4.6 µM (PLAR)	88
Murraya koenigii (Rutaceae)	Leaves	Aqueous extract	0.31 ± 0.01 mg/ml (RLAR) 0.28 ± 0.03 mg/ml (HRAR)	80
Myrciaria dubia (Myrtaceae)	Leaves	4-(α-rhamnopyranosyl) ellagic acid (19)	4.1×10^{-8} M (HRAR)	89
Myrcia multiflora DC (Myrtaceae)	Leaves	Quercitrin (20) Guaijaverin (20) Desmanthin-1 (20)	0.15 µM 0.18 µM 0.082 µM (RLAR)	87
Ocimum sanctum (Lamiaceae)	Leaves	Aqueous extract	0.20 ± 0.01 mg/ml (RLAR) 0.12 ± 0.01 mg/ml (RHAR)	80
Paeonia lactiflora Pall (Ranunculaceae)	Roots	Tetra - 0 - galloyl - β- d - glucose. (21)	6.3×10^{-7} M (RLAR)	90
Phellinus merrillii (Hymenochaetaceae)	Fruit	hispidin, hispolon inotilone	48.26 ± 2.48 µg/ml 9.47 ± 0.52 µg/ml 15.37 ± 0.32 µg/ml	91
Psidium guajava (Myrtaceae)	Fruits	Aqueous extract	0.70 ± 0.03 mg/ml (RLAR)	80
Salix hulteni (Salicaceae)	Leaves	Diosmetin - 7 - O - β - D – glucoside Isoquercitrin Diosmetin - 7 - O - β - D - xylosyl - (1→6) - β - D – glucoside Armadendrin - 3 - O - β - D – glycosideAstragalin	1.9 mM 1.4 mM 4.2 µM 5.8 µM 3.4 µM (HRAR)	92
Camellia sinensis (Theaceae)	Leaves	Isoquercitrin (22)	1×10^{-6} M (HPAR)	93

Continued...

Table 3: *Continued*

Plants	Part used	Extract used and chemical constituents	IC_{50}	References
Vitis vinifera (Vitaceae)	Fruits	Aqueous extract	>1 mg/ml (RLAR)	80
Zingiber officinalis (Zingiberaceae)	Roots	Aqueous extract	>1 mg/ml (RLAR)	80

RLAR = Rat Lense Aldose Reductase
HPAR = Human Planceta Aldose Reductase
HRAR = Human Recombinant Aldose Reductase
PLAR = Procine Lense Aldose Reductase

Table 4: Plants with activity against the DPP4 enzymes

Plants	Part Used	Extract and active constituents	IC_{50}	References
Berberis aristata (Berberidaceae)	Bark	Methanol extract	14.4 µg/ml	94
Mangifera indica (Anacardiaceae)	Leaves	Methanolic extract	182.7 µg/ml	95
Syzygium cumini (Linn.) (Myrtaceae)	Seed kernel	70% ethanol extract Ellagitannin	65.8 ± 3.6 µg/ml 4.4 ± 0.3 µg/ml	96

Table 5: Plants shows inhibitory activity against the ACE

Plants	Part Used	Extract	IC_{50}	References
Mangifera indica (Anacardiaceae)	Aerial part	Ethyl acetate	8.6%	97
Senecio vulgaris (Compositae)	Aerial part	Ethyl acetate	327.8 ± 3.4 µg/ml	98
Senecio ambiguous subsp. Ambiguous (Compositae)	Aerial part	n-hexane Ethyl acetate	30.6 ± 3.7 µg/ml 219.4 ± 1.7 µg/ml	98
Senecio inaquidens (Compositae)	Aerial part	n-hexane Ethyl acetate	>330 µg/ml 192.1 ± 1.8 µg/ml	98

(ROS) leaking from the mitochondria.[24] This process has been associated with the onset of type 1 diabetes via apoptosis of pancreatic beta-cells and the onset of type 2 diabetes via insulin resistance.[25] The underlying mechanisms in the onset of diabetes are complex because hyperglycemia may be both a cause and an effect of increased oxidative stress.[26]

Hyperphysiological burden of free radicals causes an imbalance between oxidants and antioxidants in the body. This imbalance leads to oxidative stress that is being suggested as the root cause of ageing and various human diseases including atherosclerosis, stroke, diabetes, cancer and neurodegenerative diseases such as Alzheimer's and Parkinsonism.[27] Alloxan is a chemical used for the induction of diabetes in animals. It has been shown to damage pancreatic β-cell by the liberation of oxygen radicals, with reduction in the antioxidant status.[28] Insulin deficiency promotes β- oxidation of fatty acids , which results in the increased formation of hydrogen peroxide.[29] The harmful influence of diabetes mellitus metabolism of tissues on various organ is well known. Glucose control plays a role in the pro-oxidant/antioxidant balance.[30] Antioxidants, which can scavenge free radicals have an important role in biological systems and may be helpful in the prevention of the cancer, heart diseases, ageing and diabetes mellitus.[31] A list of plant extracts which show inhibitory activity against antioxidant enzymes are summarised in table 6.

Inhibition of α-Amylase by Flavonoids

The inhibitory activity of six groups of flavonoids (1-4) against porcine pancreatic α-amylase was compared and chemical structures of flavonoids responsible for the inhibitory activity were evaluated.[67] In porcine pancreatic α-amylase, luteolin, myricetin and quercitin were potent inhibitors with $IC_{50\ values}$ of 0.36, 0.38 and 0.50 mM respectively. The inhibitory activity increased appreciably with an increase in the number of hydroxyl group on the B ring, while the hydroxyl substitution on the position 3 reduces it. Among the six group of flavonoids,

Table 6: Plants with inhibitory activity against oxidation

Plants	Part used	Extract used	IC_{50}	References
Apium graveolens L. (Umbelliferae)	Fruit	Methanol extract	34.75 ± 0.50 µg/ml	99
Cordia myxa L. (Borraginaceae)	Fruit	Methanol extract	132.53 ± 5.75 µg/ml	99
Flemingia lineate (Fabaceae)	Roots	Water extract	187.34 ± 1.28 µg/ml	84
Flemingia macrophylla (Fabaceae)	Roots	Water extract	36.34 ± 1.22 µg/ml	84
Hybanthus enneaspermus Linn F. Muell (Violaceae)	Plant material	Ethanolic extract	164.52 ± 1.48 µg/ml	86
Lactuca sativa L. (Compositae)	Seed	Methanol extract	14.28 ± 1.32 µg/ml	99
Ocimum basilicum L. (Labiatae)	Seed	Methanol extract	4.78 ± 1.77 µg/ml	99
Plantago ovate (Plantaginaceae)	Seed	Methanol extract	126.56 ± 3.23 µg/ml	99
Scoparia dulcis (Scrophulariaceae)	Aerial part	Ethanolic extract	243.82 µg/ml	100

isoflavone show maximal and flavanone show minimum inhibitory effect.[67]

The flavonoid compounds quercetin, kaempferol, myricetin isolated from the 70% ethanol extract of the *guava* leaf (further extracted with the n- butanol) show the inhibitory activity against α-amylase with IC_{50} values of 4.8mM, 5.3mM, 4.3mM respectively. Further extraction of the 70 % ethanol leaf extract of the leaf with the ethyl acetate also show the potent inhibitory activity against the α-amylase due to presence of these flavonoids with the same value of IC_{50}.[59]

Phenolics

(-)-3-O–galloylepicatechin (5) and (-) – 3-O –galloylcatechin (6) isolated from 50 % methanolic extracts of *Bergenia ciliata* show the α -amylase inhibitory activity with the value of IC_{50} 739 µM and 401 µM, respectively.[39]

Tannins and ellagic acid (7) derivatives isolated from *Lagerstroemia speciosa* (banaba) (Lythraceae) leaves are potent inhibitors of α-amylase. Valoneaic acid dilactone (8) is the main active constituent isolated from the leaf extracts. It shows potent inhibitory activity against the α- amylase.[48]

Phenolic compounds such as gallic acid (9), gentisic acid, caffeic acid (10), ferulic acid (11) etc. isolated from *Elusine coracana* acidified methanol extracts show the inhibitory activity towards the α–amylase with a IC_{50} value of 23.05Mg/ml.[46]

Alkaloids

Carbazole alkaloid *mahanimbine* (12) isolated from pet. ether extracts of the leaves of *Murraya koenigii* (Rutaceae) showed the inhibitory effect against α–amylase with an IC_{50} value of 83.72 ± 1.4 mg/ml.[54]

Terpinoids

A mixture of oleanolic acid (13) and ursolic acid (14), triterpenoid isolated from *Phyllanthus amarus*, (Phyllanthaceae) exhibit inhibitory activity against α–amylase with an IC_{50} value of 2.01 µg/ml.[68]

Miscellaneous

The bioactivity assay-guided study of a methanolic extract of the *Spondias mombin* (Anacardiaceae) lead to the isolation of the active compound 3β-olean -12 -en-3 yl (9z)-hexadec-9-enoate which shows the 57 % inhibitory activity against α-amylase.[69]

Xanthone Glucoside

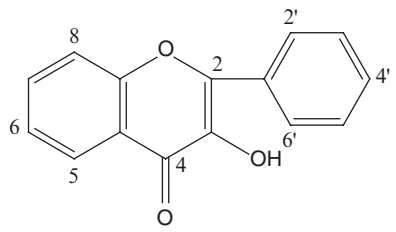
Mangiferin (15) (xanthone glucoside) isolated from the ethanolic extract of *Mangifera indica* (Anacardiaceae) showed appreciable α–amylase inhibitory effects with an IC_{50} value of 74.35 ± 1.9 mg/ml.[51]

p-cymene, 1,8 – cineole, 1-(S)- α-pinene, are the major components isolated from the essential oil of the *Eucalyptus camaldulensis Dehnh* (Myrtaceae). These compounds show inhibitory activity against α–amylase with the percentage inhibition 36.50 ± 1.50, 43.23 ± 2.57, 32.22 ± 1.73 respesctively at the conc. of the 0.015, 0.075, 0.075 µl/ml.[70]

Anthocyanin

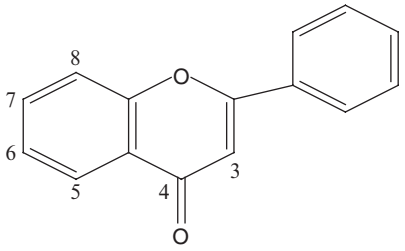
Cyanidine (16) and its glycoside cyanidine-3-glucoside (anthocyanins) are widely distributed in various in

human diets. They show inhibitory effects against α–amylase with IC_{50} values of 0.38 ± 0.01 mM and 0.30 ± 0.01 mM respectively.[71] Cyanidine-3-rutinoside is a colorant found in plants including litchi and capulin. It inhibits pancreatic α-amylase with an value of IC_{50} 24.4 ± 0.1 μM.[72] Some of the common phytochemicals used in the treatment of diabetes are shown in Figure 1



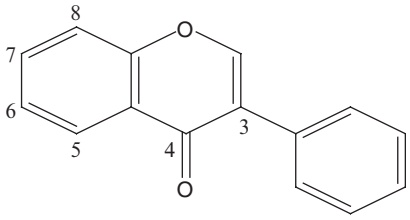
(1)

Flavonol
Myricetin: 5,7,3',4',5' = OH
Quercetin: 5,7,3',4' = OH
Kaempferol: 5,7,4', = OH
Fisetin: 73',4' = OH



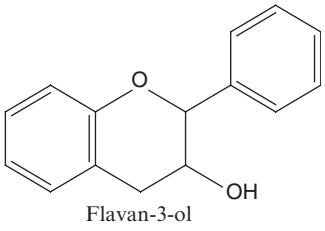
(2)

Flavanone
Naringenin: 5,7,4' = OH
Hesperetin: 5,7,3' = OH



(3)

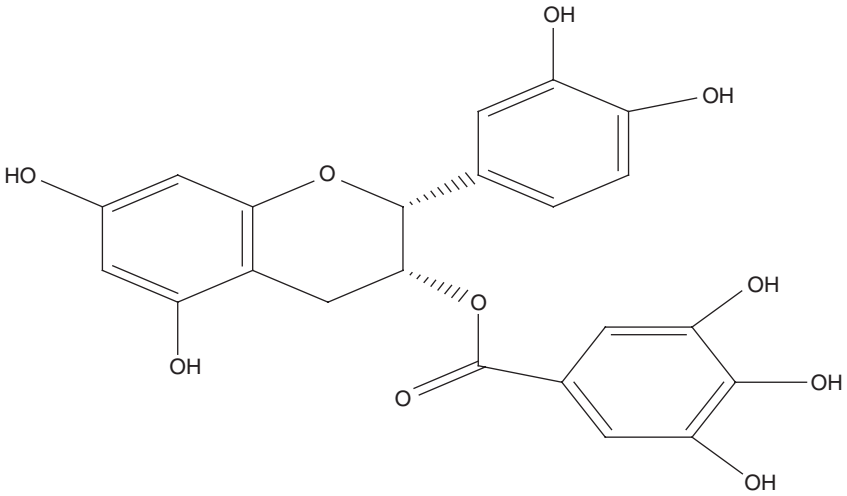
Isoflavone
Daidzein : 7,4' = OH
Genistein: 5,7,4' = OH



Flavan-3-ol

(4)

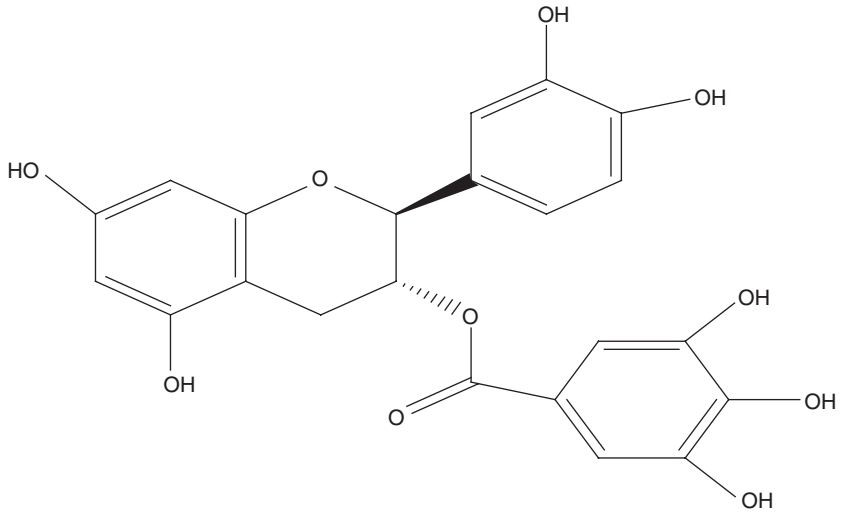
(+) Catechin (2R,3S): 5,7,3',4' = OH
(-)Epicatechin (2R,3R): 5,7,3',4' = OH
(-)Epigallocatechin (2R,3R): 5,7,3',4',5' = OH
(-)Epigallocatechin gallate (2R,3R): 5,7,3',4',5' =OH



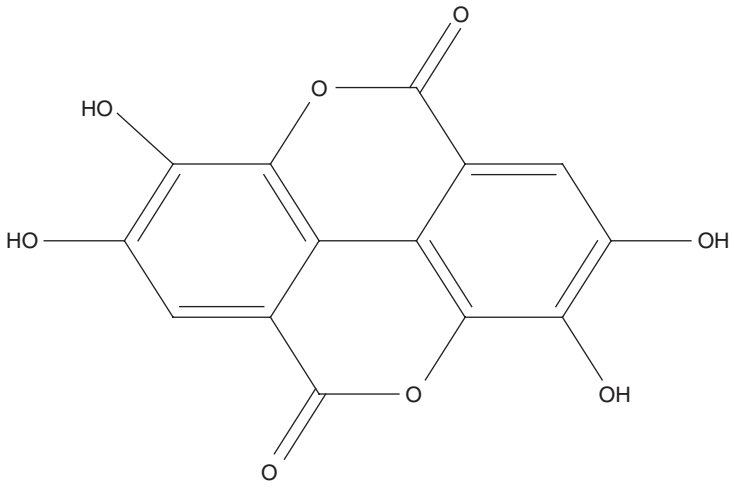
(5)

Anthocyanidine
Cyanidin: 5,7,3',4' = OH
(-)-3 - O –galloylepicatechin

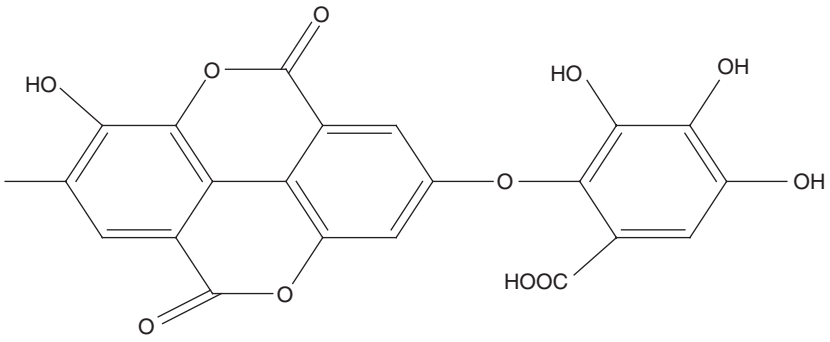
Figure 1: *Continued*



(6)
(-) – 3-O -galloylcatechin



(7)
Ellagic acid



(8)
Valoneaic acid dilactone

Figure 1: *Continued*

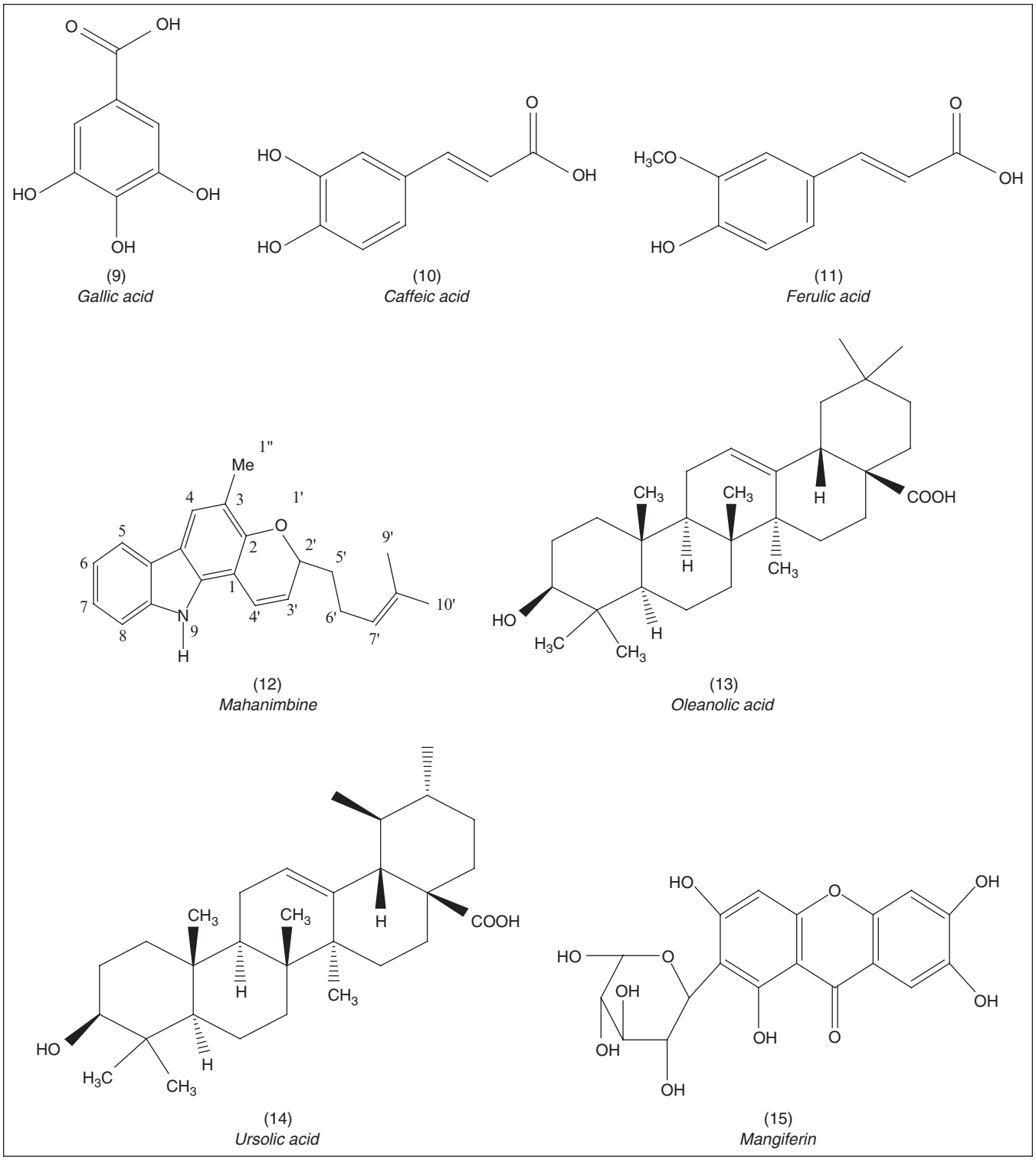


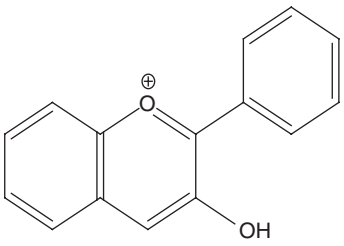
Figure 1: *Continued*

Inhibitory effects of Flavonoids on Aldose reductase

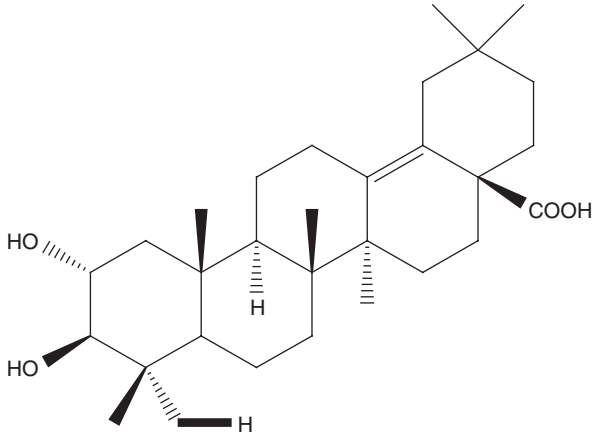
Flavonoids also show inhibitory effects against the aldose reductase enzymes. Among the flavone constituents, 3',4'-dihydroxyflavone, 3',4',7-trihydroxyflavone, luteolin, and luteolin 7-*O*-β-D-glucopyranoside potently inhibit aldose reductase enzyme activity IC_{50} values of 0.37, 0.30, 0.45, 0.99, μM respectively.[76]

CONCLUSION

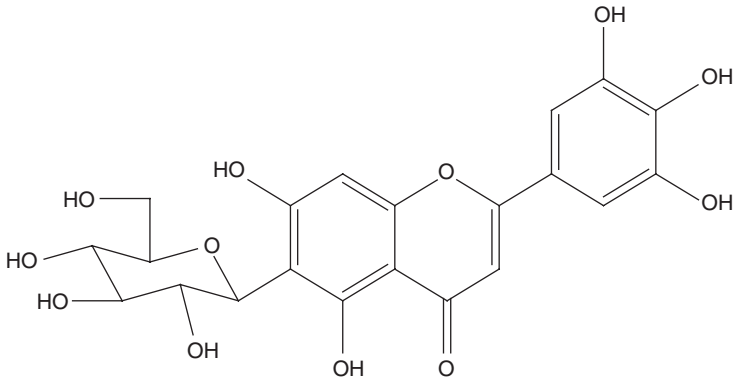
Diabetes mellitus is the one of the major health problem, affecting around 194 millions of the population worldwide, and that number is expected to increase to 300 million by 2025.[101] Most of these will dominated by the type 2 diabetes mellitus.[102] This increasing trend in type 2 diabetes has



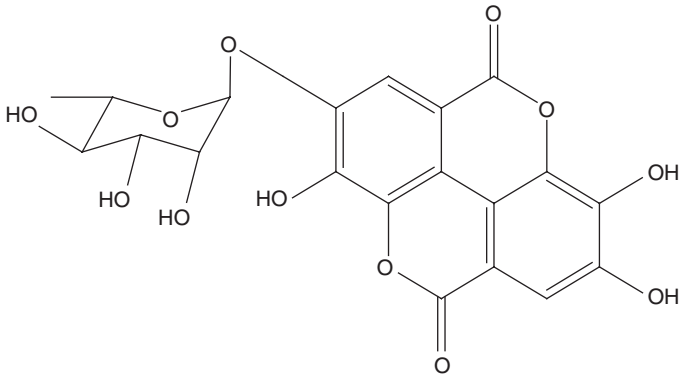
(16)
Anthocyanidine
Cyanidin: 5,7,3',4' = OH



(17)
Centellasapogenol A



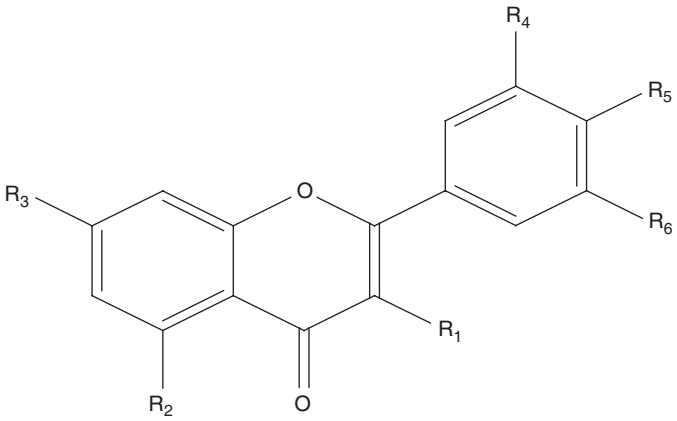
(18)
Isoaffineyin



(19)
4-(α-rhamnopyranosyl) ellagic acid

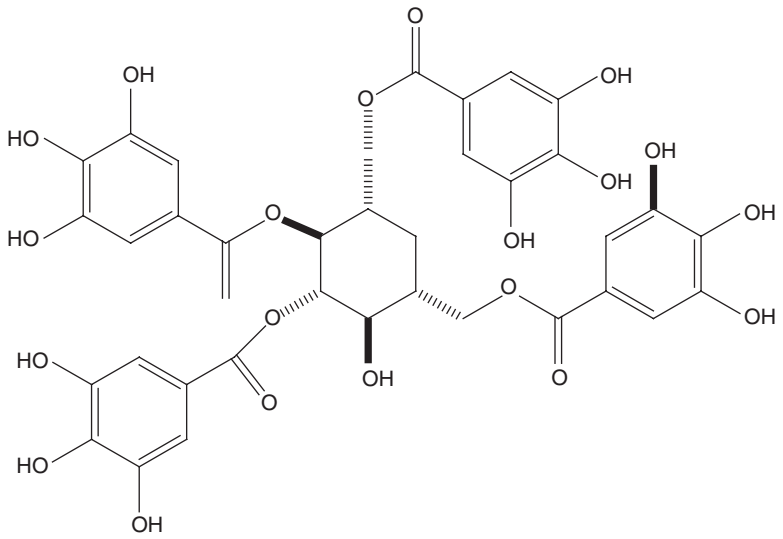
Figure 1: *Continued*

become a serious medical concern worldwide, which accounts for 9 % of deaths. One of the therapeutic approach to control the diabetes is to control the hyperglycemia.[3] The modern medicines available for the management of diabetes show various side effects such as hepatotoxicity, abdominal pain etc. and drug resistance to these medicine also reported.[103,104] Therefore apart of these medicines herbal medicine are recommended for treatment of diabetes.[105] One of the therapeutic approach to treat the diabetes is to control the blood glucose level, and this can be done by inhibiting the all enzymes such as alpha amylase, alpha glucosidase, DPP-4, and aldose reductase, etc. Thus, natural

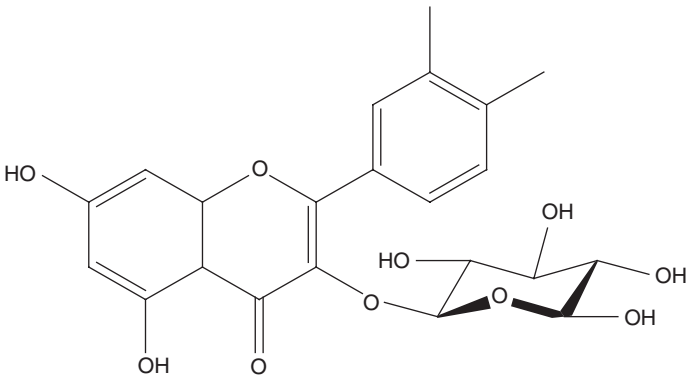


(20)

	R_1	R_2	R_3	R_4	R_5	R_6
Quercetrin	*O- Rha*	*OH*	*OH*	*OH*	*OH*	*H*
Guaijaverin	*O- Ara*	*OH*	*OH*	*OH*	*OH*	*H*
Desmanthin – 1	*O-(2'-galloyl)-Rha*	*OH*	*OH*	*OH*	*OH*	*OH*



(21)
Tetra - O- galloyl - β - d – glucose



(22)
Isoquercitrin

Figure 1: Some phytochemicals with known anti-diabetic activity

products are still a good source of all these inhibitors therefore motivating the use of the natural products. Thus, natural products of great structural diversity are still a good source for searching for such inhibitors, thereby motivating to explore biologically active compounds from the highly diverse plants.

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