Bioorganic Chemistry 86 (2019) 305–315

Contents lists available at ScienceDirect

Bioorganic Chemistry

journal homepage: www.elsevier.com/locate/bioorg

The management of diabetes mellitus-imperative role of natural products against dipeptidyl peptidase-4, α-glucosidase and sodium-dependent glucose co-transporter 2 (SGLT2)

Ghulam Abbas[a,b,c,*], Ahmed Al Harrasi[c], Hidayat Hussain[c,d], Ahmed Hamaed[b], Claudiu T. Supuran[a,*]

[a] Università degli Studi di Firenze, NEUROFARBA Dept., Sezione di Scienze Farmaceutiche, Via Ugo Schiff 6, 50019 Sesto Fiorentino (Florence), Italy
[b] Department of Biological Sciences and Chemistry, University of Nizwa, Birkat Al-Mauz, P.O.Box 33, Nizwa 616, Oman
[c] Natural and Medical Sciences Research Center, University of Nizwa, PC 616, Nizwa, Oman
[d] Department of Bioorganic Chemistry, Leibniz Institute of Plant Biochemistry, Weinberg 3, D-06120 Halle, (Salle), Germany

ARTICLE INFO

Keywords:
Diabetes mellitus
Antidiabetic agents
Dipeptidyl peptidase-4 enzyme
Alpha glucosidase enzyme
SGLT2
Natural products
Structure-activity relationship

ABSTRACT

Diabetes mellitus is a chronic metabolic disorder which is rapidly spreading worldwide. It is characterized by persistent elevated blood glucose level above normal values (hyperglycemia) due to defect in either insulin secretion or in insulin action or both of them. Currently approved oral synthetic antidiabetic drugs such as biguanides, thiazolidinediones, sulfonylureas, and meglitinides have shown undesirable side effects. Therefore, newer approaches and targets for the management of diabetes mellitus are highly desirable. Dipeptidyl peptidase-4 enzyme, α-glucosidase enzyme and sodium-dependent glucose co-transporter 2 (SGLT2) have been recognized as effective therapeutic targets for the management of diabetes mellitus while natural products are alternatives to oral synthetic hypoglycemic agents. During the last two decades, many researchers were working on the identification and the validation of plant-derived products for curing various diseases. Natural products do not only provide useful drugs in their own right but also provide templates for the development of more effective compounds for enhanced therapeutic potential. Herein, we advocated the vital role of natural products as source of new drugs by presenting promising inhibitors of dipeptidyle peptidase-4 enzyme, α-glucosidase enzyme and (SGLT2) obtained from different medicinal plants as potential candidates for drug development against diabetes mellitus. The structure–activity relationship (SAR) of these various inhibitors is also discussed.

1. Introduction

1.1. Diabetes mellitus

Diabetes mellitus characterized by constant hyperglycemia is one of the major health problems of the 21st century. Both, the number of people suffering from diabetes and deaths attributed to diabetes are increasing at an alarming rate [1-3]. It is estimated that the number of people suffering from this disease will exceed 366 million by the year 2030 [4]. According to the world health organization (WHO), type-2 diabetes mellitus is the world's fifth leading cause of death. The most common symptoms of diabetes mellitus are excessive urination, weight loss, abnormally great thrust, and excessive appetite [5]. Diabetes mellitus is associated with many micro- and macro vascular complications such as neuropathy, atherosclerosis, rheumatoid arthritis, retinopathy, end stage renal diseases, and neurodegenerative disorders which severely affect the patient's quality of life and is one of the major causes of mortality [6]. Various complications of diabetes could be also delayed or prevented by the intensive postprandial hyperglycemia control [7]. The diabetic complications reflect the insufficient and less effective glycemic control achieved with presently available treatments. Therefore, more effective therapeutics targets and approaches for glycemic control are urgently needed especially in non-insulin-dependent type-2 diabetes mellitus [8].

1.2. Biological role of dipeptidyl peptidase IV (DPP-4) enzyme

Dipeptidyl peptidase IV (DPP-IV, EC 3.4.14.5), a membrane-bound,

* Corresponding authors at: Università degli Studi di Firenze, NEUROFARBA Dept., Sezione di Scienze Farmaceutiche, Via Ugo Schiff 6, 50019 Sesto Fiorentino (Florence), Italy; Department of Biological Sciences and Chemistry, University of Nizwa, Birkat Al-Mauz, P.O.Box 33, Nizwa-616, Sultanate of Oma.
E-mail addresses: abbashej@unizwa.edu.om (G. Abbas), claudiu.supuran@unifi.it (C.T. Supuran).

https://doi.org/10.1016/j.bioorg.2019.02.009
Received 16 September 2018; Received in revised form 29 January 2019; Accepted 3 February 2019
Available online 04 February 2019
0045-2068/

serine protease ectoenzyme is one of the latest pharmaceutical targets for type 2 diabetes treatment. DPP-IV is distributed to various sites of the body such as the intestine, the kidney, and the capillary endothelium [9,10]. The incretin hormones such as glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are responsible to maintain normal blood glucose level within the body. These incretin hormones are released by the gut in response to food intake and an increase in blood glucose. These incretin hormones bind to their respective receptors to increase insulin secretion and reduce glucose production by the liver consequently a normal blood glucose index is obtained. In diabetic patients, DPP IV is widely expressed at the surface of endothelial and epithelial cells and thus causing the rapid degradation of these incretin hormones and transforming them into inactive peptides. DPP IV enzyme catalyzes the cleavage of GLP-1(7–36) to GLP-1(9–36) and of GIP (1–42) to GIP (3–42), respectively as a result the half lives of these hormones decreases and the blood glucose level increases [11].

Glucagon-like peptide 1 (GLP-1) plays a vital role in this pathway as compared to GIP (being of lower relevance than GLP-1 with reference to type-2 diabetes mellitus) where it accelerates glucose-induced insulin secretion. Hence, inhibition of DPP-4 actually increases the half life and biological activity of GLP-1 peptide and as a result normal glucose level is achieved as shown in Fig. 1 [3].

Currently, several classes of standard antidiabetic agents have been identified such as sulfonylureas, biguanides, glitazones, and glinides. However, these agents have shown some serious side effects, such as digestive problems, weight gain, edema and the most importantly, hypoglycemic conditions. At present DPP IV inhibitors, have gain attraction as therapeutic target as they control diabetes mellitus without any adverse side effects.

Several studies have demonstrated that DPP IV inhibitors have therapeutic potential in

the treatment of long term chronic type-2 diabetes [4,11].

1.3. Biological role of α-glucosidase enzyme

The enzyme α-glucosidase (EC 3.2.1.20) has also attracted lots of interest as important therapeutic target for the treatment of carbohydrate mediated diseases. α-Glucosidase is secreted in the small intestine where it catalyzes the cleavage of oligosaccharides and disaccharides into monosaccharides during the final step in the digestions of the carbohydrates and thus increases glucose concentration in the body as shown in Fig. 2. [12-14].

Various studies have shown that α-glucosidase inhibitors can slow down the digestion and absorption of carbohydrates and thus decrease the postprandial blood glucose level which leads to a decreased demand for insulin. Thus, rapid increase of glucose level after meal can be controlled without insulin participation [15,16] As compared to other oral antihyperglycemic agents, alpha-glucosidase inhibitors are considered as

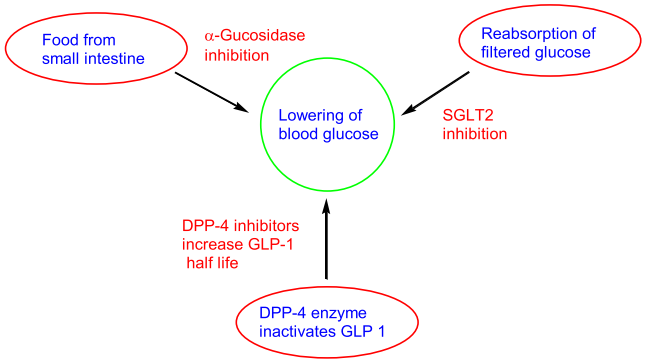


Fig. 1. Effective therapeutic targets and approaches for the management of Diabetes mellitus.

mild due to their confined action in the intestine rather than modulating certain complex biochemical processes within the body. [17]. Therefore, α-glucosidase enzyme is being considered as an important therapeutic target for the management of diabetes mellitus [18].

1.4. Biological role of sodium–glucose co-transporter 2 (SGLT2)

Sodium–glucose co-transporter 2 (SGLT2) actually reabsorbs the filtered glucose in the tubular nephron of the kidney and thus is the major co-transporter. In diabetes mellitus patients, hyperglycaemia may cause upregulation of glucose reabsorption above normal level in the kidneys [19]. Recently, sodium-glucose co-transporter 2 (SGLT2) is being tested for glucose homeostasis in the kidney and thus pharmacological inhibition of SGLT2 is considered as a promising therapeutic approach for the treatment of type 2 diabetes mellitus. Inhibitors of sodium–glucose co-transporter 2 (SGLT2) are hypoglycemic (glucose-lowering) agents which mainly target the kidney with insulin-independent mechanism of action. These inhibitors actually block the reabsorption process of filtered glucose, leading to an increase in urinary glucose excretion (UGE) particularly, during hyperglycemic condition. In this way not only glycaemic control is improved with a limited risk of hypoglycaemia, but also beneficial effects on weight loss and blood pressure are attained. SGLT2 inhibitors exhibited pharmacokinetic characteristics with an excellent oral bioavailability [20,21].

2. Natural products as potential source of antidiabetic drugs

The identification of novel lead compounds is a challenging task whereas drug companies are currently focusing on the use of high throughput screening and fragment-based drug discovery. In fact, despite the high expenditure and the enormous efforts being paid limited number of drugs is being approved every year. On the other hand, screening of natural products were overlooked and infrequently used for lead identification despite the fact that natural products have traditionally played an important role in drug development. Moreover, natural products restrain novel and diverse compounds which are hardly found in synthetically-based commercial screening libraries. Thus, natural products can be excellent leads for drug development despite their complex structures and their limited oral bioavailability [21]. Natural products have been used globally for the treatment of various biological disorders for thousand of years. However, the utilization of natural products for drug discovery is gradually increasing worldwide and there is a growing interest in the promotion of traditional health care systems. About 80% of the world's population uses plant-based traditional health remedies as these are affordable and are safer to use. During the last few decades, researchers have aimed at identifying and validating plants-derived products for the treatment of various diseases including diabetes mellitus [22]. Natural products due to their no or lesser adverse effects have gradually attracted ample interests of the researchers for the treatment of diabetes mellitus [9].

This review article presents an evaluation of the natural products as source of lead compounds mainly with respect to antidiabetic agents. According to as survey, over 1000 plant species are being used as folk medicine against diabetes mellitus [23]. Metformin, the core marketed drug used for the management of diabetes mellitus (type-2), is also derived from the guanidines which were isolated form *Galegine officinalis* plant [24]. As compared to synthetic drugs, plant-based drugs are considered to be less toxic, less side effects and low cost and more effective [25,26]. Here, we advocate more emphasis on the use of natural products to discover more potent and safer antidiabetic agents and their modified derivatives possessing enhanced activity and/or low toxicity.

2.1. Natural products as promising inhibitors of DPP-4 enzyme

In practice, a large number of medicinal plants have been used as traditional medicines for the management of diabetes mellitus which

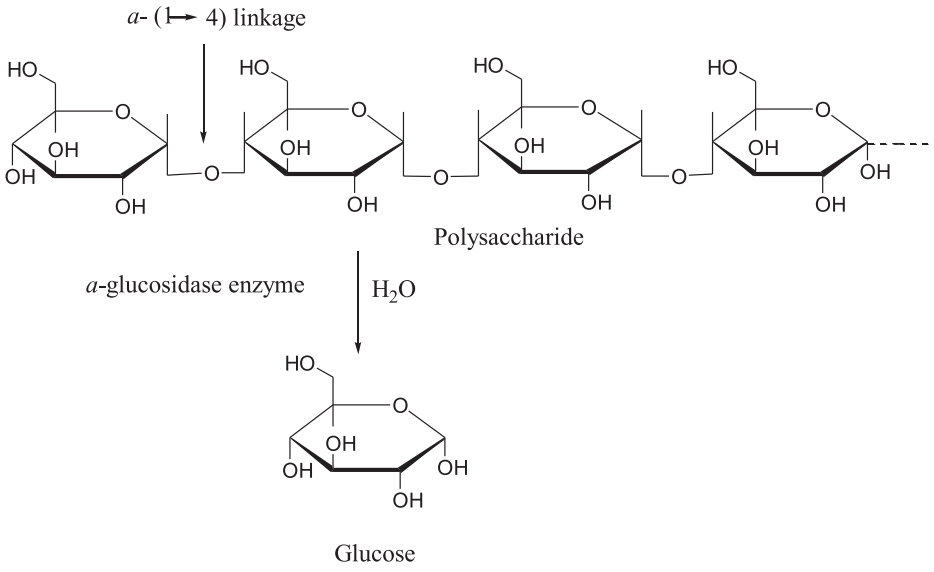


Fig. 2. Mechanism of action of α-glucosidase enzyme.

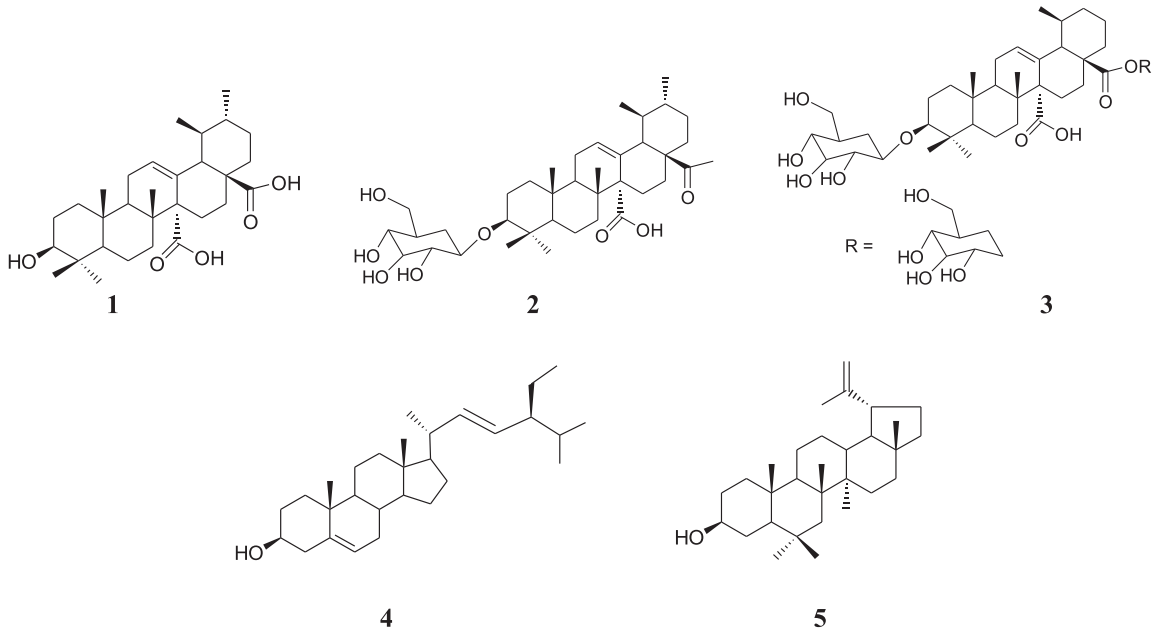


Fig. 3. DPP-4 inhibitors isolated from *Fagonia cretica* and *Hedera nepalensis*.

provided alternative medicines other than existing therapies. It is estimated that > 1,200 medicinal plants have been used as folk medicine to treat diabetes mellitus. The compounds isolated from these medicinal plants have shown more efficient antidiabetic activity than agents being used clinical therapy [9,27]. The inhibition of DPP-IV has an advantage of reduced risk of hypoglycemia because GLP-1 operates in a glucose-dependent manner. Thus the inhibitors of DPP-IV enzyme stimulate the production of postprandial insulin and blood

glucose clearance. Hence, identification of new and effective inhibitors of DPP IV for the management of type 2 diabetes is a dynamic area of research [28,29].

2.1.1. Two medicinally important plants such as Fagonia cretica L. and Hedera nepalensis K. Koch are used as natural folk medicines for the treatment of diabetes.

Two medicinally important plants such as *Fagonia cretica* L. and *Hedera nepalensis* K. Koch are used as natural folk medicines for the treatment of diabetes. In a study, initially plant crude extracts of two plants that is *Fagonia cretica* and *Hedera nepalensis* exhibited potent DPP-4 inhibition activity with IC_{50} values of 38.08 and 17.20 µg/ml, respectively. Subsequently, bioassay-guided isolation resulted in the isolation of promising inhibitors of DPP-4 enzyme by using column chromatography. Four compounds including quinovic acid **(1)**, quinovic acid-3β-O-β-D -glycopyrano-side **(2)**, quinovic acid-3β-O-β-D-glucopyranosyl-(28-1)-β-D-glucopyranosyl ester **(3)** and stigmasterol **(4)** were identified from *Fagonia cretica* while one compound, lupeol **(5),** was obtained from *Hedera nepalensis* (Fig. 3). On DPP-4 inhibition assay, these compounds showed promising activity with IC_{50} values of 30.7, 57.9, 23.5, > 100 and 31.6 µ M, respectively as shown in Table 1.

Structure-activity relationship studies showed that quinovic acid (**1**) exhibited more inhibition than quinovic acid-3 β -O- β - D -glycopyrano-side (**2**) due to presence of "OH" group at C-3 as compared to compound (**2**) with one sugar moiety attached at C-3. However, compound (**3**) showed more inhibition than compound (**2**) due to presence of an ester group at C-28 instead of a keto group [30].

Table 1
DPP-4 enzyme inhibitors from natural products.

S. No.	Name	Source	DPP-4 Inhibition (IC_{50} = μM)	Reference
1.	Quinovic acid	*Fagonia cretica L*	30.7	[30]
2.	Quinovic acid-3 β -O- β - D -glycopyranoside	*Fagonia cretica L*	57.9	[30]
3.	Quinovic acid-3 β -O- β - D -glucopyranosyl-(28–1)- β - D -glucopyranosyl ester	*Fagonia cretica L*	23.5	[30]
4.	Stigmasterol	*Fagonia cretica L*	> 100	[30]
5.	Lupeol	*Hedera nepalensis*	31.6	[30]
6.	Daphneolon	*Daphne odora Thunb*	38.43	[31]
7.	4 0 -trihydroxy-8-ethox-ycarbonyl flavan	*Daphne odora Thunb*	113.76	[31]
8.	betulinic acid	*Daphne odora Thunb*	55.82	[31]
9.	3-O-stigmasterol-(6-O-palmitoyl)-*b*- D -glucopyranoside	*Daphne odora Thunb*	16.58	[31]
10.	Hispidulin	*Bacopa monnieri (L.) Wettst*	0.49 ± 0.1	[32]
11.	eriodictyol	*Bacopa monnieri (L.) Wettst*	10.9 ± 0.4	[32]
12.	Naringenin	*Bacopa monnieri (L.) Wettst*	2.5 ± 0.3	[32]
13.	Cirsimaritin	*Bacopa monnieri (L.) Wettst*	0.43 ± 0.07	[32]
14.	Carnosol	*Bacopa monnieri (L.) Wettst*	> 100	[32]
15.	rosmarinic acid	*Bacopa monnieri (L.) Wettst*	14.1 ± 1.7	[32]
16.	7-Deoxy-6-*epi*-castanospermine	*Seed of Castanospermum australe* Cunn.	(GS = 41.01)	[4]
17.	Australine	*Seed of Castanospermum australe* Cunn.	(GS = 40.07)	[4]
18.	isodaphnetin	Stem bark (*Daphne odora Thunb.)*	14.13	[6]
19.	*trans*-6,7-Dimethoxy-2-(2,4,5-trifluorophenyl)-3,4-dihydro-2H-benzo[*f*]chromen-3-amine	Derivative of natural product	0.0026	[6]
20.	*trans*-6-Methoxy-7-(methylsulfonyl)-2-(2,4,5-trifluorophen-yl)-3,4-dihydro-2H-benzo[*f*]chromen-3-amine	Derivative of natural product	0.00198	[6]
21.	Resveratrol	*Rubus fruticosus*, *Vaccinium corymbosum*	0.0006 ± 0.4	[10]
22.	luteolin	*Rubus fruticosus*, *Vaccinium corymbosum*)	0.12 ± 0.01	[10]
23.	apigenin	*Rubus fruticosus*, *Vaccinium corymbosum*	0.14 ± 0.02	[10]
24.	Flavone	*Rubus fruticosus*, *Vaccinium corymbosum*	0.17 ± 0.01	[10]

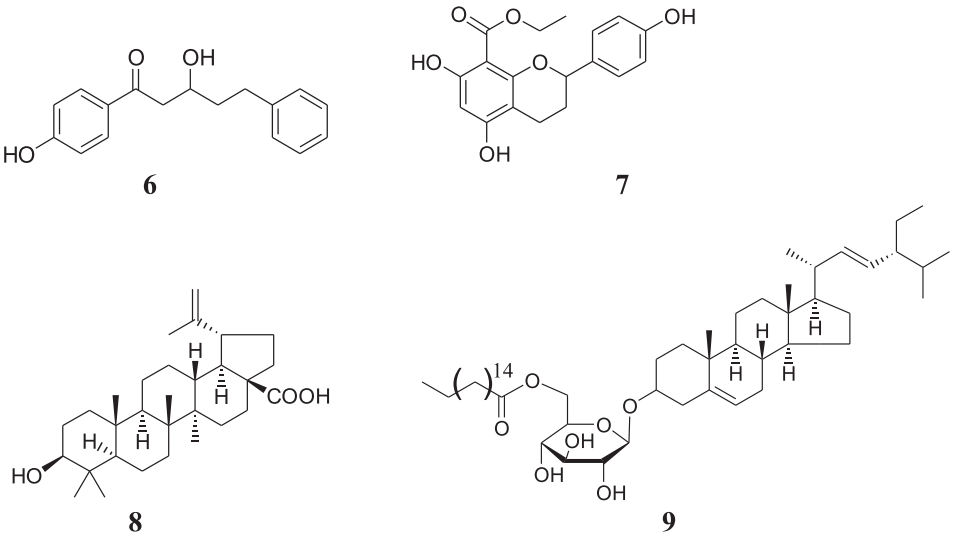


Fig. 4. Inhibitors isolated from *Bacopa monnieri* and *Daphne odora*.

2.1.2. The plants Bacopa monnieri (L.) Wettst and Daphne odora Thunb. var. marginata, are used traditionally in against diabetes mellitus and inflammation

The plants *Bacopa monnieri* (L.) Wettst and *Daphne odora* Thunb. var. *marginata*, are used traditionally in China against diabetes mellitus and inflammation. In a study, initially computational chemical biology strategy- a reverse docking method was successfully employed for natural products isolated from these plants to find out potential binding proteins (DPP-IV). Thus, several natural products obtained from these plants were then evaluated against potential target, dipeptidyl peptidase IV (DPP-IV), as shown in Fig. 4. Among these two compounds daphneticin **(6)**, and 4′-trihydroxy-8-ethoxycarbonyl flavan **(7)** isolated from *Daphne odora Thunb* showed good inhibitory potential with IC_{50} values of 38.43 and 113.76 μM while other two compounds betulinic acid **(8)**, and 3-*O*-stigmasterol-(6-O-palmitoyl)-β-D–glucopyranoside **(9)** obtained from *Bacopa monnieri* (L.) Wettst, showed inhibition with IC_{50} values of 55.82 μM and 16.58 μM, respectively as shown in Table 1. [31].

2.1.3. Culinary herbs from a traditional mediterranean diet such as oregano (Origanum vulgare), marjoram (Origanum majorana), and rosemary (Rosmarinus officinalis) were investigated for their inhibitory potential against DPP-IV enzyme.

Culinary herbs from a traditional Mediterranean diet such as oregano (*Origanum vulgare*), marjoram (*Origanum majorana*), and rosemary (*Rosmarinus officinalis*) were investigated for their inhibitory potential against DPP-IV enzyme. Initially, herbs extracts and fractions were prepared, their total phenolic and flavonoid concentrations were quantified, and then DPP-IV inhibition was measured by using the DPP-IV Glo protease assay. Furthermore, the most potent fractions were analyzed in order to identify the particular compounds responsible for DPP-IV inhibition.

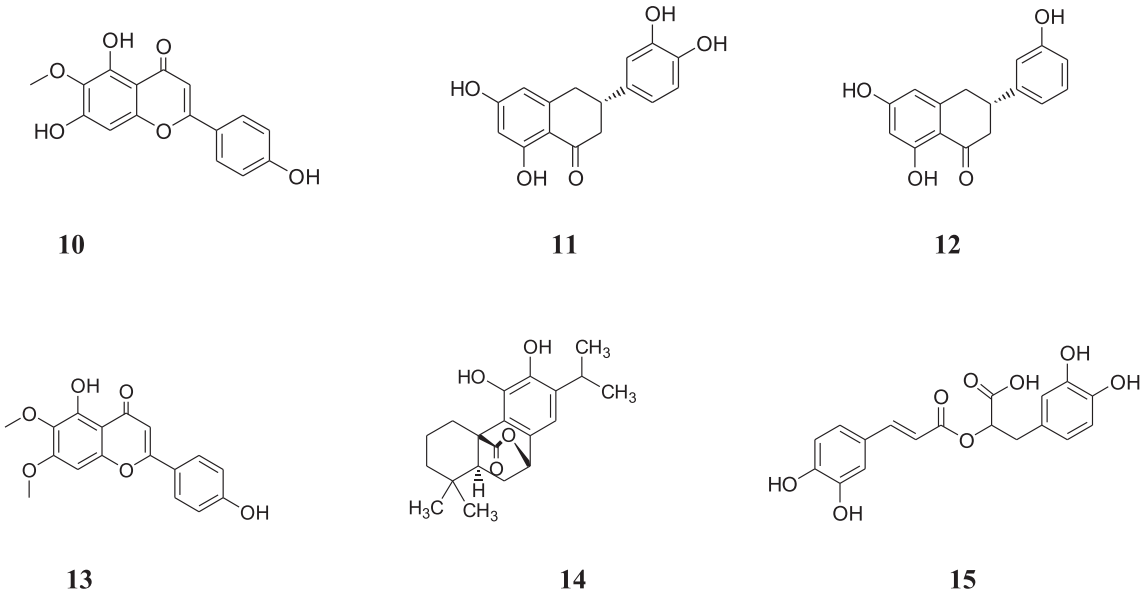


Fig. 5. DPP-IV inhibitors isolated from *Rosmarinus officinalis, Origanum majorana* and *Origanum vulgare.*

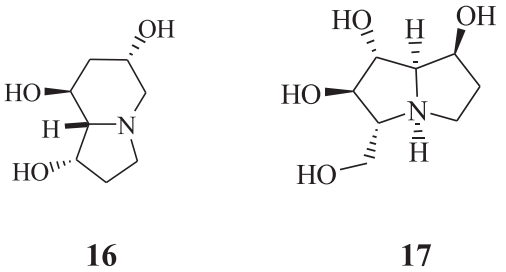


Fig. 6. DPP-4 inhibitors (alkaloids) isolated from *Castanospermum australe*.

Among these compounds cirsimaritin **(10)** with IC_{50} value of 0.43 ± 0.07 μM, hispidulin **(11)** IC_{50} value of 0.49 ± 0.1 μM, and naringenin **(12)** with an IC_{50} of 2.5 ± 0.3 μM, were isolated from *Rosmarinus officinalis* and *Lippia graveolens* respectively, were found to be the most potent inhibitors of DPP-IV. Similarly, eriodictyol **(13)** with IC_{50} value of 10.9 ± 0.4 μM, was isolated from *Rosmarinus officinalis* and rosmarinic acid **(14)** with an IC_{50} of 2 14.1 ± 1.7 μM, was isolated from *Origanum vulgare* both showed good inhibition against DPP-IV (Fig. 5). Carnosol **(15)** was isolated from *Rosmarinus officinalis* found to be the least effective inhibitor, with an IC_{50} value of over 100 μM as shown in Table 1. In this study, sitagliptin with an IC_{50} value of 0.06 ± 0.03 μM was used as standard inhibitor of DPP-IV enzyme [32]. Structure-activity relationship studies showed that compound (**11**) having an extra hydroxyl group at *para*-postion of the benzene ring exhibited 5 fold more inhibition than compound (**12**) which does not have hydroxyl group at *para*-postion. Similarly, compound (**10**) having hydroxyl group at C-3 exhibited potent inhibition as compared to its structural analogue compound (**13**) having ester group at C-3.

2.1.4. Seed extracts of Castanospermum australe showed significant antidiabetic potential when injected in rats with type-2 diabetes mellitus.

Seed extracts of *Castanospermum australe* showed significant antidiabetic potential when injected in rats with type-2 diabetes mellitus. On DPP-IV enzyme inhibitory assay, these extracts exhibited significant inhibitory potential with an IC_{50} value of 1.543 μg/mL. Three alkaloids were isolated from *Castanospermum australe* and then evaluated for DPP-IV enzyme inhibition potential as shown in Fig. 6. Gold docking software was used to calculate the gold score where 7-deoxy-6-*epi*-castanospermine **(16)** and australine **(17)** showed significant inhibition potential against DPP-IV enzyme with gold score = 41.01 and 40.07, respectively which is comparable to the berberin used as standard with glod score of 47.38. (Table 1) [4].

*2.1.5. In another study, isodaphnetin **(18),** a natural product obtained from the stem bark of the medicinal plant Daphne odora Thunb. var. marginata, showed significant inhibition (IC 50 = 14.13 μM) against DPP-4 when applying a reverse-docking based computational chemical biology approach*

In another study, isodaphnetin **(18),** a natural product obtained from the stem bark of the medicinal plant *Daphne odora* Thunb. var. marginata, showed significant inhibition (IC 50 = 14.13 μM) against DPP-4 when applying a reverse-docking based computational chemical biology approach. A new series of isodaphnetin derivatives were synthesized and evaluated for their inhibition potential against DPP-4

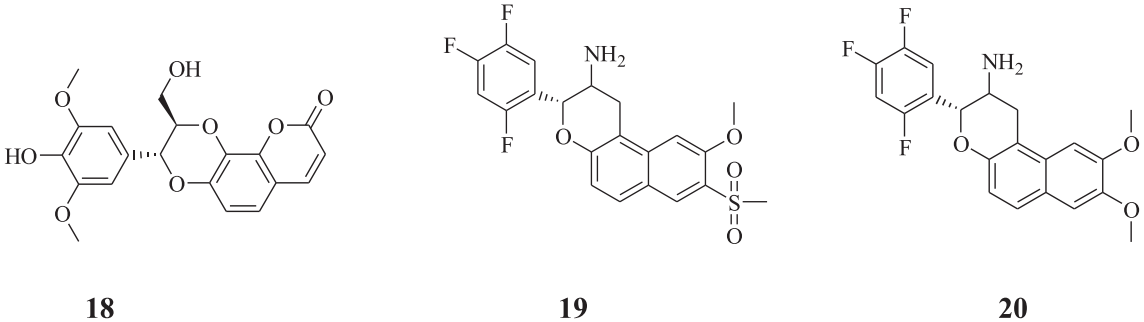


Fig. 7. DPP-4 inhibitor isolated from *Daphne odora* and its derivatives.

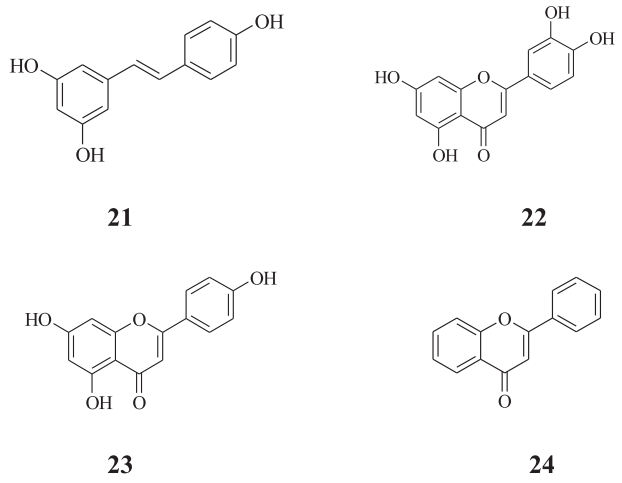


Fig. 8. DPP-4 inhibitors isolated from various fruits.

enzyme as shown in Fig. 7. Among these derivatives the compound *trans*-6-Methoxy-7-(methylsulfonyl)-2-(2,4,5-trifluorophenyl)-3,4-dihydro-2H-benzo[*f*]chromen-3-amine **(19)** and the compound *trans*-6,7-dimethoxy-2-(2,4,5-trifluorophenyl)-3,4-dihydro-2H-benzo[*f*]chromen-3-amine **(20)** which exhibited potent inhibition at sub-nano level with an IC_{50} value of 0.0026 μM and 0.00198 μM, respectively (Table 1). *In vivo* studies also supported the sustained pharmacodynamics effect of these compounds on the inhibition of DPP-4 enzyme and an improvement in the glucose tolerance.

2.1.6. The presence of high amount of flavonoids in the fruits and vegetables makes them beneficial for human health

The presence of high amount of flavonoids in the fruits and vegetables makes them beneficial for human health. In a study, anthocyanins (ANC) isolated from berry wine blends alongwith several other phenolic compounds found in berry, citrus, soybean, and grape were tested for their inhibitory potential on DPP-IV by employing computational modeling and luminescence assay (Fig. 8). Among the tested compounds resveratrol (**21**) showed potent inhibition with an IC_{50} value of 0.6 ± 0.4 nM, luteolin (**22**) with an IC_{50} value of 0.12 ± 0.01 μM, apigenin (**23**) with an IC_{50} value of 0.14 ± 0.02 μM), and flavone (**24**) with an IC_{50} value of 0.17 ± 0.01 μM as shown in Table 1. These IC_{50} values were lower than that of diprotin A (4.21 ± 2.01 μM), a reference standard inhibitory compound [10].

2.2. Natural products as promising inhibitors of α-glucosidase enzyme

One of the most important therapeutic strategies against diabetes mellitus is to decrease the post-prandial glucose levels through the inhibition of the polysaccharides degradation [33]. Therefore, the inhibition of α-glucosidase enzyme is an effective approach to manage the glycemic index independent of insulin [34]. To date, various studies have been performed to evaluate natural products to identify new and effective pharmacologic agents against α-glucosidase enzyme. As a

Table 2
α-Glucosidase enzyme inhibitors from various natural products.

S. No.	Name	Source	Alpha-glucosidase Inhibition (IC_{50} = μM)	Reference
25	Trans-N-(p-coumaroyl)tyramine	*Ipomoea batatas*	4.47 ± 0.19	[35]
26	Trans-*N*-Feruloyltyramine	*Ipomoea batatas*	9.04 ± 1.18	[35]
27	Cis-*N*-Feruloyltyramine	*Ipomoea batatas*	14.35 ± 1.36	[35]
28	3,4,5-tricaffeoylquinic acid	*Ipomoea batatas*	4.61 ± 1.00	[35]
29	3,4-dicaffeoylquinic acid	*Ipomoea batatas*	49 ± 10.09	[35]
30	3,5-dicaffeoylquinic acid	*Ipomoea batatas*	181.86 ± 35.71	[35]
31	4,5-dicaffeoylquinic acid	*Ipomoea batatas*	108.26 ± 8.56	[35]
32	7-Hydroxy-5-methoxycoumarin	*Ipomoea batatas*	64.14 ± 9.23	[35]
33	Quercetin-3-O-glucosidase	*Ipomoea batatas*	22.38 ± 1.73	[35]
34	3,5-Dihydroxyl-6-hydroxymethyl-1-hydroxymethyl phenol ester	Gymnema sylvestre	(EFs = 8.62)	[7]
35	Gymnemic acid A	Gymnema sylvestre	(EFs = 4.32)	[7]
36	8-Hydroxy gymnamine	Gymnema sylvestre	(EFs = 9.24	[7]
37	9, 10, 13-Trihydroxy octadecenoic acid	Gymnema sylvestre	(EFs = 10.35	[7]
38	Hypolaetin	Gymnema sylvestre	(EFs = 8.16	[7]
39	Aromadendrin	Gymnema sylvestre .	(EFs = 1.52	[7]
40	Madecassic acid	Gymnema sylvestre	(EFs = 5.79	[7]
41	Alternoside XVIII	Gymnema sylvestre	(EFs = 3.41	[7]
42	Rutin	*Morus atropurpurea*	13.19 ± 1.10	[36]
43	Astragalin	*Morus atropurpurea*	15.82 ± 1.11	[36]
44	Isoquercetin	*Morus atropurpurea*	116.7 ± 1.17	[36]
45	Kaempferol-3-*O*-rutinoside	*Morus atropurpurea*	365.4 ± 1.05	[36]
46	β-Sitosterol	*Terminalia sericea*	54.49	[37]
47	β-Sitosterol-3-acetate	*Terminalia sericea*	129.36	[37]
48	Lupeol	*Terminalia sericea*	66.48	[37]
49	Stigma-4-ene-3-ol	*Terminalia sericea*	164.87	[37]
50	Phlomisol (15,16-eposy-8,13(16),14-labdatrien-19-ol)	*Phlomis tuberosa*	67 ± 0.003	[38]
51	15,16-Eposy-8,13(16),14-labdatrien	*Phlomis tuberosa*	210 ± 0.010	[38]
52	Flavoglaucin	*Phlomis tuberosa*	229 ± 0.017	[38]
53	Dihydroauroglaucin	*Phlomis tuberosa*	255 ± 0.013	[38]
54	Tetrahydroauroglaucin	*Phlomis tuberosa*	283 ± 0.013	[38]
55	2-(2′,3-Epoxy-1′-heptenyl)-6-hydroxy-5-(3″-methyl-2″-butenyl) benzaldehyde	*Phlomis tuberosa*	371 ± 0.015	[38]
56	Oleanolic acid	*Lagerstroemia speciosa* Leaves	6.29 ± 0.37 μg/mL	[39]
57	Arjunolic acid	*Lagerstroemia speciosa* Leaves	18.63 ± 0.32 μg/mL	[39]
58	Asiatic acid	*Lagerstroemia speciosa* Leaves	30.03 ± 0.41 μg/mL	[39]
59	Maslinic acid	*Lagerstroemia speciosa* Leaves	5.52 ± 0.19 μg/mL	[39]
60	Corosolic acid	*Lagerstroemia speciosa* Leaves	3.53 ± 0.27 μg/mL	[39]
61	23-hydroxyursolic acid	*Lagerstroemia speciosa* Leaves	8.14 ± 0.18 μg/mL	[39]
62	8-methoxyeriodictyol	*Iris unguicularis*	0.338 ± 0.004	[34]
63	kaempferol	*Iris unguicularis*	0.047 ± 0.003	[34]
64	4′,5,7-trihydroxy-6-methoxyflavanone	*Iris unguicularis*	0.097 ± 0.003	[34]

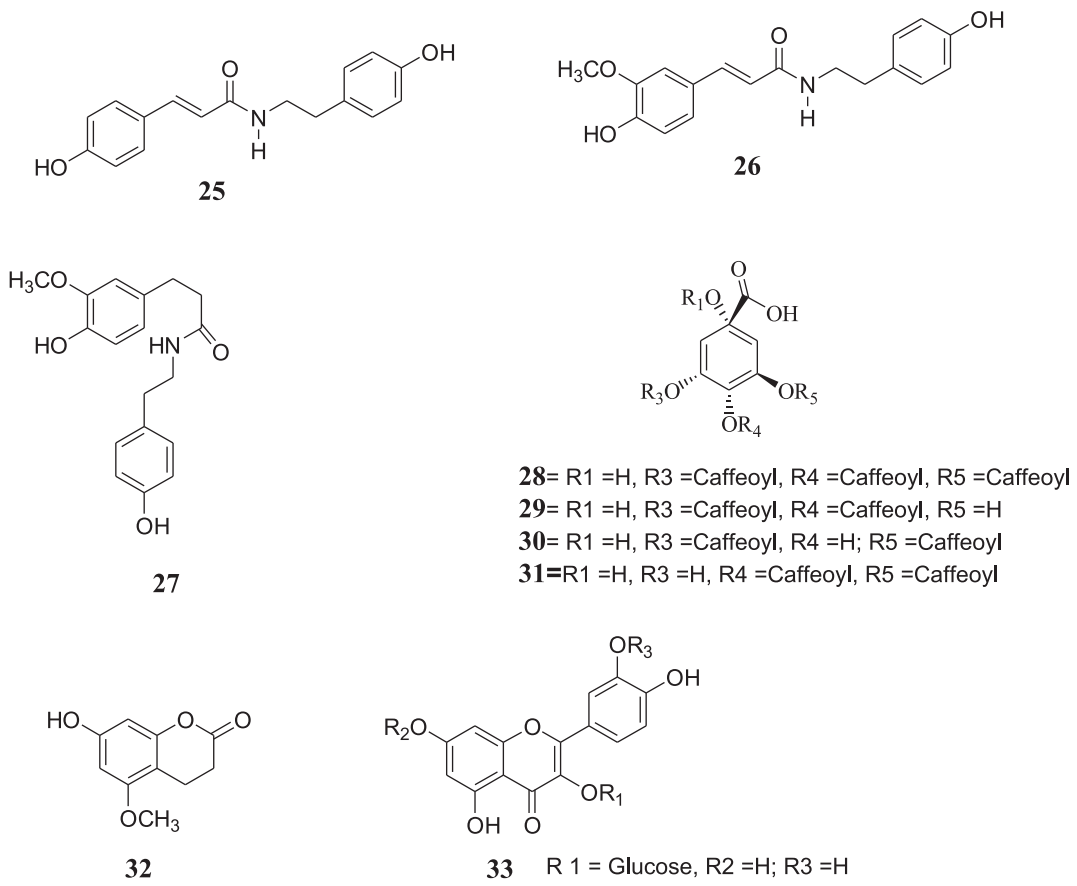


Fig. 9. α-Glucosidase enzyme inhibitors isolated from the leaf of *Ipomoea batatas*.

result several natural products with promising inhibitory potential against α-glucosidase enzyme have been discovered.

2.2.1. The leaf of sweet potato (Ipomoea batatas) is a byproduct of sweet potato products.

The leaf of sweet potato (*Ipomoea batatas*) is a byproduct of sweet potato products. The leaf of sweet potato exhibited considerable bioactivities against various diseases such as cardiovascular diseases, inflammation, hypertension, hyperglycemia tumors and diabetes. The beneficial health effects of sweet potato leaf extract can be attributed to the presence of high polyphenols contents which act as free radical scavengers, singlet oxygen quenchers and hydrogen-donating groups [35].

In another study, several compounds were isolated from the leaf of *Ipomoea batatas* and evaluated for their activities against α-glucosidase enzyme. Among these compounds *trans-N-*(*p*-coumaroyl)tyramine (**25**) with an IC_{50} value of 4.47 ± 0.19 μ M, *trans-N*-feruloyltyramine **(26)** with an IC_{50} of 9.04 ± 1.18 μ M, *cis-N*-feruloyltyramine (**27**) with an IC_{50} value of 14.35 ± 1.36 μ M, 3,4,5-tricaffeoylquinic acid (**28**) with an IC_{50} value of 4.61 ± 1.00 μ M, 3,4-dicaffeoylquinic acid (**29**) with an IC_{50} value of 49 ± 10.09 μ M, 7-hydroxy-5-methoxycoumarin (**32**) with an IC_{50} value of 64.14 ± 9.23 μ M, quercetin-3-*O*-glucosidase (**33**) with an IC_{50} value of 22.38 ± 1.73 μ M exhibited potent inhibition while compounds 3,5-dicaffeoylquinic acid (**30**) with an IC_{50} value of 181.86 ± 35.71 μ M and 4,5-dicaffeoylquinic acid (**31**) with an IC_{50} value of 108.26 ± 8.56 μ M showed comparable inhibitory potential as compared to standard inhibitor acarbose which has an IC_{50} value of 168.95 ± 12.27 μM as shown in Table 2. Structure-activity relationship (SAR) analysis revealed that the methylation of the hydroxyl group in phenethyl cinnamides caused reduction in alpha-glucosidase inhibition activity, while *trans* compounds are more active than their *cis* counterparts as shown in Fig. 9 [35].

2.2.2. The plant Gymnema sylvestre R. Br. (Asclepiadaceae) has shown antidiabetic properties, while gymnemic acids are the main bioactive component in this plant species

The plant *Gymnema sylvestre* R. Br. (Asclepiadaceae) has shown antidiabetic properties, while gymnemic acids are the main bioactive component in this plant species. In a study, the extract of *G. sylvestre* paved significant inhibition against α-glucosidase enzyme with IC 50 = 68.70 ± 1.22 μg/mL as compared to standard inhibitor acarbose (IC 50 = 59.03 ± 2.30 μg/mL). In this study, a rapid method of affinity ultrafiltration coupled with liquid chromatography mass spectrometry (UF-HPLC-MS) was employed to evaluate and identify the α-glucosidase inhibitors in *G. sylvestre*. This bio-affinity method is based on the interactions between the active sites of enzymes and the ligands while its combination with HPLC-MS techniques provides great insights into the biomolecular structures and their binding properties. As a result eight compounds with very high enrichment factors (EFs) were identified.

Among the tested compounds 3,5-dihydroxyl-6-hydroxymethyl-1-hydroxymethyl phenol ester (**34**), gymnemic acid A (**35**), 8-hydroxy gymnamine (**36**), 9, 10, 13-trihydroxy octadecenoic acid (**37**), hypolaetin (**38**), aromadendrin (**39**), madecassic acid (**40**) and alternoside XVIII (**41**) showed enrichment factors (EFs) values of 8.62%, 4.32%, 9.24%, 10.35%, 8.16%, 1.52%, 5.79%, 3.41%, respectively as summarized in Table 2. Structure-activity relationship studies proved that triterpenoid sapogenin (compound **40**) has higher EFs than the saponins (compound **35** and **41**), which also proved that glycosylation could decrease the potential activity of sapogenins (Fig. 10) [7].

*2.2.3. In another study by Hong et al. (2013) the four flavonoids like rutin **(42)**, astragalin **(43)**, isoquercetin **(44)**, and kaempferol-3-O-rutinoside **(45)** were extracted from the leaves of Morus. atropurpurea as shown in Fig. 11*

In another study by Hong et al. (2013) the four flavonoids like rutin

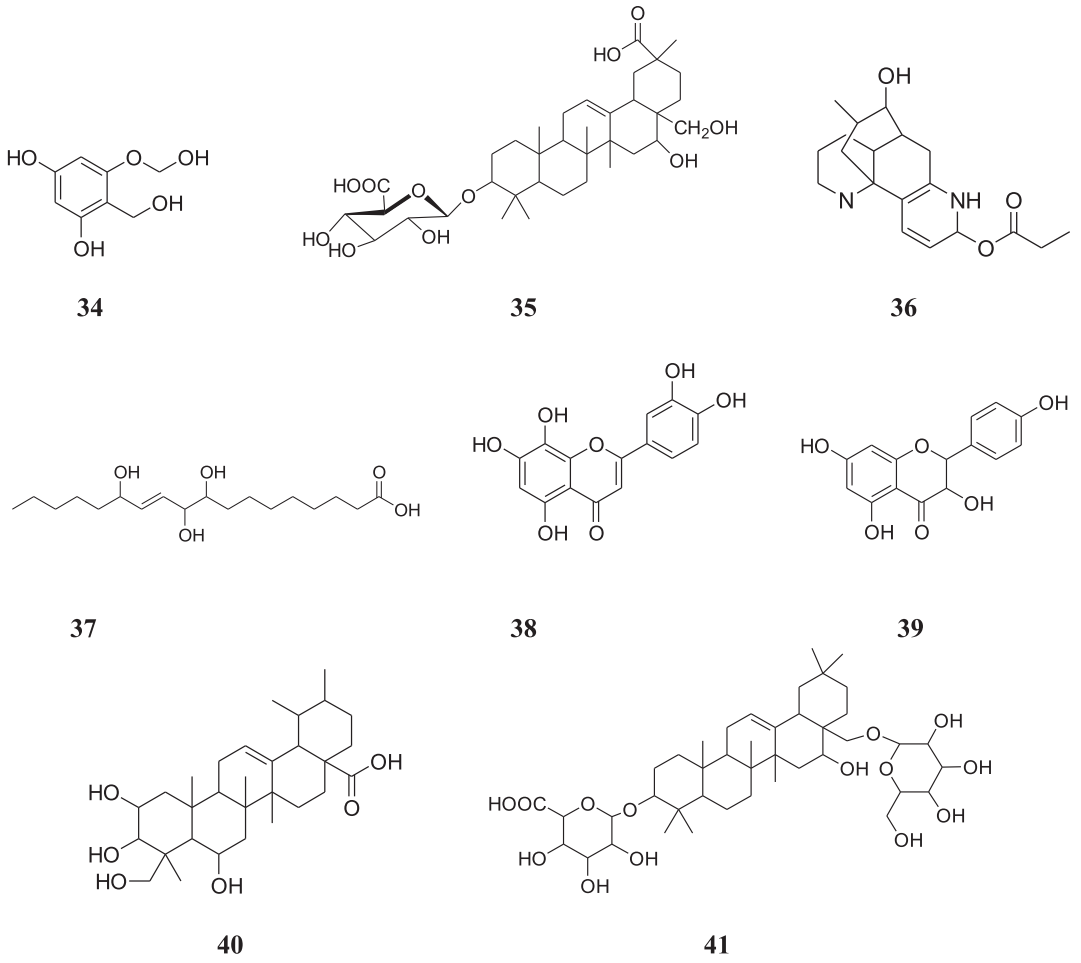
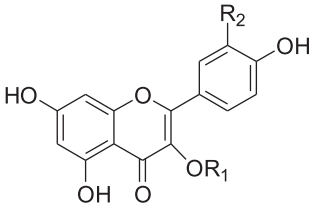


Fig. 10. α-Glucosidase inhibitors from *Gymnema sylvestre.*



Name	R1	R2
42) Rutin	glc (6 →1) rha	OH
43) Astragalin	glc	H
44) Isoquercetin	glc	OH
45) Kaempferol-3-O-rutinoside	glc (6 →1) rha	H

Fig. 11. α-Glucosidase inhibitors isolated from *Morus atropurpurea.*

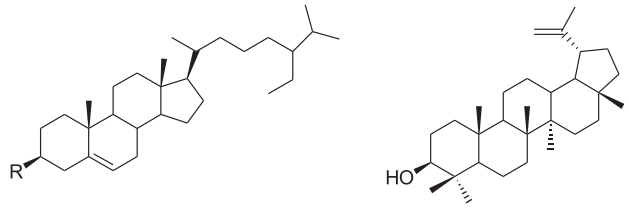


Fig. 12. α-Glucosidase enzyme inhibitors isolated from *Terminalia sericea.*

(42), astragalin **(43)**, isoquercetin **(44)**, and kaempferol-3-O-rutinoside **(45)** were extracted from the leaves of *Morus. atropurpurea* as shown in Fig.11. The four flavonoids like rutin **(42)**, astragalin **(43)**, isoquercetin **(44)**, and kaempferol-3-O-rutinoside **(45)** were extracted from the leaves of *Morus. atropurpurea* as shown in Fig. 11. On α-glucosidase enzyme inhibition assay rutin, astragalin and isoquercetin exhibited potent inhibition with IC_{50} values of 13.19 ± 1.10 μM, 15.82 ± 1.11 μM, and 116.7 ± 1.17 μM, respectively. Kaempferol-3-O-rutinoside showed good inhibition activity with an IC_{50} value of 365.4 ± 1.05 μM. [36]

2.2.4. Air-dried stem bark of the plant Terminalia sericea was used for bioassay guided isolation.

The four compounds such as β-sitosterol **(46),** Lupeol **(47),** β-sitosterol-acetate **(48),** stigma-4-ene-3-one **(49)** were isolated and evaluated against α-glucosidase enzyme as shown in Fig. 12. These compounds exhibited significant inhibition activity against α-glucosidase enzyme with IC_{50} values of 54.49, 66.48, 129.36, 164.87 μM, respectively [37].

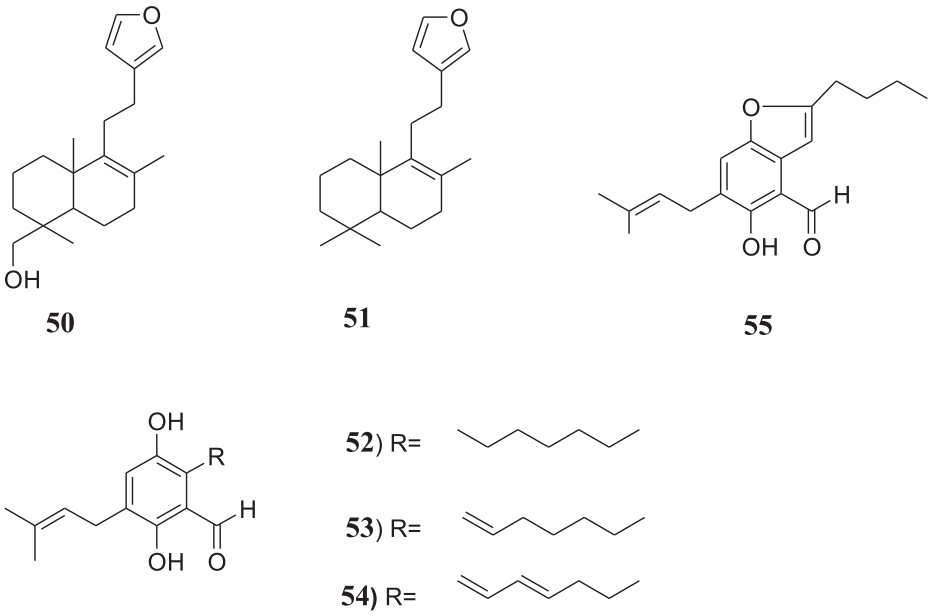


Fig. 13. α-Glucosidase enzyme inhibitors obtained from Phlomis tuberosa.

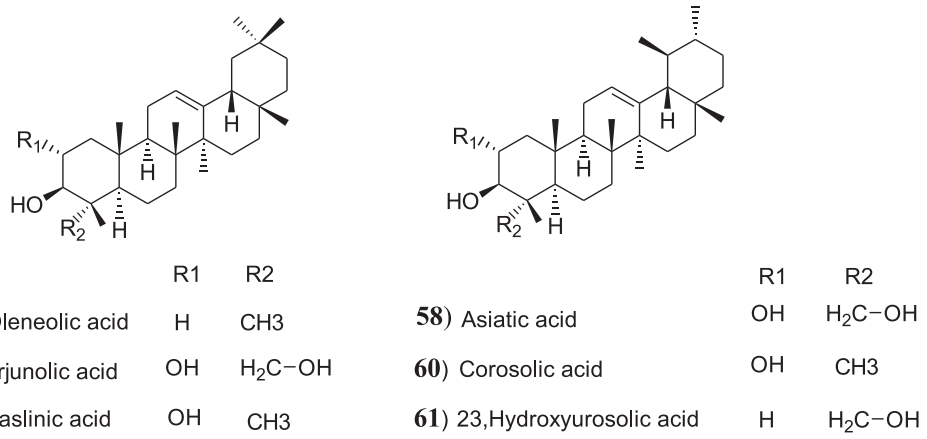


Fig. 14. α-Glucosidase inhibitors from *Lagerstroemia speciosa.*

2.2.5. The plant Phlomis tuberosa belongs to the family lamiaceae (mint family).

The plant Phlomis tuberosa belongs to the family Lamiaceae (mint family). In a study, the roots of the plant *P. tuberose* were collected by Yang et al. (2015) for extraction and isolation of natural products. Twenty compounds were isolated from *P. tuberosa* which were investigated against α-glucosidase enzyme, as shown in Fig. 13. As a result several promising inhibitors were identified such as phlomisol (15,16-eposy-8,13(16),14-labdatrien-19-ol) **(50),** 15,16-eposy-8,13(16),14-labdatrien **(51),** flavoglaucin **(52),** tetrahydroauroglaucin **(53),** dihydroauroglaucin **(54),** and 2-(2 0,3-epoxy-10 -heptenyl)-6-hydroxy-5-(3″-methyl-2″-butenyl) benzaldehyde. **(55)** with IC_{50} values of 0.067 ± 0.003, 0.210 ± 0.010, 0.229 ± 0.017, 0.283 ± 0.013, 0.255 ± 0.013 and 0.371 ± 0.015 mM, respectively as shown in Table 2. [38].

2.2.6. Several terpene acids were isolated form the leaves of plant Lagerstroemia speciosa which were then investigated against α-glucosidase inhibition assay

Several terpene acids were isolated form the leaves of plant *Lagerstroemia speciosa* which were then investigated against α-glucosidase inhibition assay From ethyl acetate extract of *L. speciosa* (LSL) six pentacyclic triterpenes (oleanolic acid (**56**), arjunolic acid (**57**), asiatic acid (**58**), maslinic acid (**59**), corosolic acid (**60**) and 23-hydroxyursolic acid (**61**) were obtained as show in Fig. 14. Among these, corosolic acid, maslinic acid, oleanolic acid and 23-hydroxyursolic acid exhibited significant inhibition with IC_{50} values of 3.53 ± 0.27, 5.52 ± 0.19, 6.29 ± 0.37 and 8.14 ± 0.18 μg/mL, respectively. Moreover,

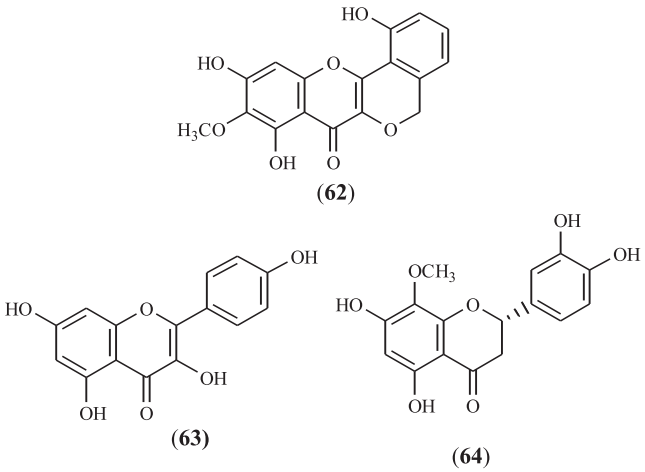


Fig. 15. α-Glucosidase inhibitors from dried rhizomes of *Iris unguicularis.*

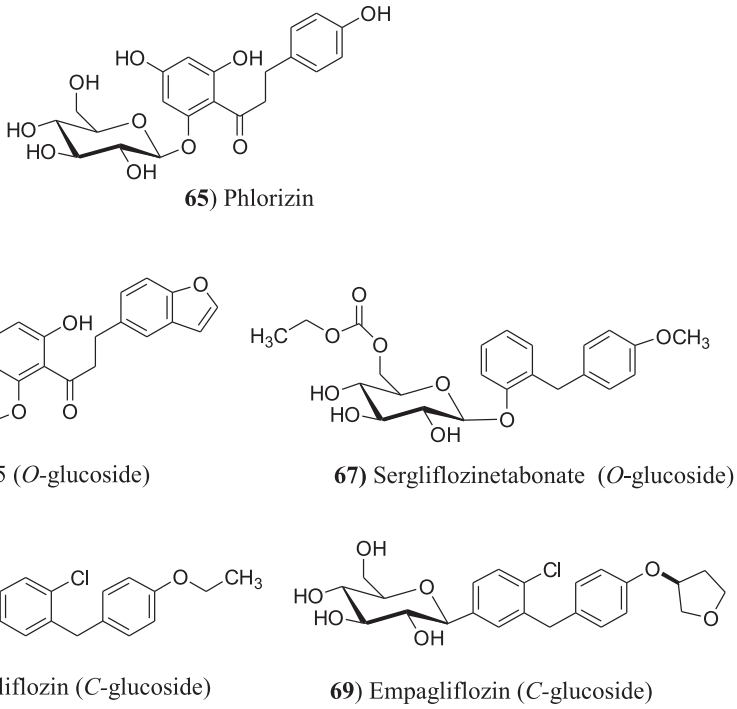


Fig. 16. Phlorizin and its major O and C-glucoside analogues SGLT2 inhibitors.

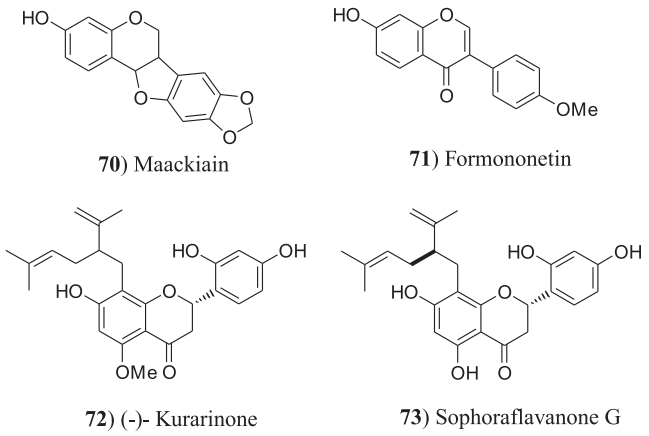


Fig. 17. Chemical structures of SGLT2 inhibitors from *Sophora flavescens*.

arjunolic acid showed good inhibitory potential with an IC_{50} value of 18.63 ± 0.32 µg/mL, while asiatic acid exhibited inhibition activity with IC_{50} an value of 30.03 ± 0.41 µg/mL (Table 2). Structure-activity relationship (SAR) analysis showed that corosolic acid, oleanolic acid and maslinic acid had higher inhibition activity, due to presence of a hydroxyl group in their C-2. Therefore, C-2 is possibly an active group of triterpene acids which could enhance the α -glucosidase inhibition activity. [39].

2.2.7. The plant Iris unguicularis is a rhizomatous flowering plant frequently found in Turkey, tunisia and western Syria

The plant *Iris unguicularis* is a rhizomatous flowering plant frequently found in Turkey, Tunisia and Western Syria. From dried rhizomes of *Iris unguicularis* several compounds were isolated and investigated against α-glucosidase enzyme.

Among the tested compounds 8-methoxyeriodictyol (**62**), kaempferol (**63**) and 4′,5,7-trihydroxy-6-methoxyflavanone (**64**) exhibited promising inhibition activities with IC_{50} values of 0.338 ± 0.004, 0.047 ± 0.003, and 0.097 ± 0.003 mM respectively, as shown in Fig. 15 [34].

2.3. Natural products as promising inhibitors SGLT2

2.3.1. Phlorizin (dihydrochalcone) isolated from the bark of apple trees is the first natural product with SGLT inhibitory activity

Phlorizin (dihydrochalcone) isolated from the bark of apple trees is the first natural product with SGLT inhibitory activity. Because of some critical drawbacks such as the inhibition of both SGLT1 and SGLT2 with low therapeutic selectivity, it was found to be inappropriate for the development of an antihyperglycemic medication. Several pharmaceutical companies performed extensive research to develop novel phlorizin-based analogs with high bioavailability, stability, and SGLT2 selectivity [40].

Initially, *O*-glucoside analogs were developed where an orally-available selective SGLT2 inhibitor T-1095 was developed with the potent IC_{50} values for the human SGLT1 and SGLT2 were approximately 200 nM and 50 nM respectively, which reflected high selectivity and potent inhibitory activities when compared to phlorizin [41]. Similarly, *C*-glucoside analogs were developed where dapagliflozin (Fig. 16), having lipophilic ethoxy substituents at the 4-position on the B-ring of phlorizin (Fig. 15), exhibited over 1200 fold higher potency for human SGLT2 with IC_{50} values of 1.12 nM as compared to SGLT1 (IC_{50} = 1391 nM)[42].

2.3.2. The plant Sophora flavescens (S. flavescens) is one of the widely used plants in traditional chinese medicines.

The plant *Sophora flavescens* (S. flavescens) is one of the widely used plants in traditional Chinese medicines. In a study by Sato et al., nine compounds were isolated from the dried root of *S. flavescens* and evaluated for their potential SGLT inhibition activity. Interestingly, the two compounds such as maackiain and formononetin with isoflavonoid-based structures (Fig. 17), exhibited selective inhibition activity only against SGLT2, but not against SGLT1.

The SAR analysis study showed that the presence of the hydroxyl functional group in isoflavonoid is critical for SGLT2 inhibitory activity. Furthermore, the two most potent compounds (−)–kurarinone (**72**) and sophoraflavanone G (**73**) exhibited good selectivity with IC_{50} values of 10.4 and 18.7 µM for SGLT1, and IC_{50} values of 1.7 and 4.1 µM for SGLT2, respectively [43].

3. Conclusions

Natural products are a continuous and rich source of drug leads due to their chemical novelty and variability. Natural products are equally important and effective against new drug targets. Since diabetes mellitus is one of the most challenging health problems in the world, therefore in this review we summarized the outcomes of the various studies conducted on natural products in different parts of the world for the management of diabetes mellitus. Several promising inhibitors of DPP-4 enzyme, α-glucosidase enzyme and SGLT2 were identified from the traditionally used plants, from the random testing of natural compounds, from the molecular docking studies and from the virtual screening techniques of natural products. These inhibitors belong to diverse classes of natural products such as alkaloids, terpenes, flavonoid, isoflavonoids, arylamines, flavan and glucopyranoside. These inhibitors as long-acting antidiabetic agents are the strong candidates for drug development. Moreover, these inhibitors provided the basic skeletons and structural features responsible for their activity which can be modified to enhance their inhibition potency for future drug discovery.

Conflict of interest

Authors report no conflict of interest.

Acknowledgement:

The author (Hidayat Hussain) thanks the Alexander von Humboldt Foundation for its generous support in providing the opportunity to do work in Germany

References

[1] P. Zimmet, K.G. Alberti, J. Shaw, Global and societal implications of the diabetes epidemic, Nature 414 (2001) 782–787.
[2] K. Connelly, D.J. Kelly, R. Langham, H. Krum, R.E. Gilbert, Drug therapy for the cardiac complications of diabetes, Drug Discovery Today: Therapeutic Strategies 1 (2) (2004) 195–200.
[3] W.L. Wu, J. Hao, M. Domalski, D.A. Burnett, D. Pissarnitski, Z. Zhao, A. Stamford, G. Scapin, Y.D. Gao, A. Soriano, T.M. Kelly, Discovery of novel tricyclic heterocycles as potent and selective DPP-4 inhibitors for the treatment of type 2 diabetes, ACS Med. Chem. Lett. 7 (5) (2016) 498–501.
[4] S.K. Bharti, S. Krishnan, A. Kumar, K.K. Rajak, K. Murari, B.K. Bharti, A.K. Gupta, Antihyperglycemic activity with DPP-IV inhibition of alkaloids from seed extract of Castanospermum australe: Investigation by experimental validation and molecular docking, Phytomedicine 20 (1) (2012) 24–31.
[5] D.W. Cooke, L. Plotnick, Management of diabetic ketoacidosis in children and adolescents, Pediatr Rev. 29 (12) (2008) 431–435.
[6] S. Li, H. Xu, S. Cui, F. Wu, Y. Zhang, M. Su, Y. Gong, S. Qiu, Q. Jiao, C. Qin, J. Shan, Discovery and rational design of natural-product-derived 2-phenyl-3, 4-dihydro-2 H-benzo [f] chromen-3-amine analogs as novel and potent dipeptidyl peptidase 4 (DPP-4) inhibitors for the treatment of type 2 diabetes, J. Med. Chem. 59 (14) (2016) 6772–6790.
[7] G. Chen, M. Guo, Rapid screening for α-glucosidase inhibitors from Gymnema sylvestre by affinity ultrafiltration–HPLC-MS, Front. Pharmacol. (2017) 8.
[8] J. Feng, Z. Zhang, M.B. Wallace, J.A. Stafford, S.W. Kaldor, D.B. Kassel, M. Navre, L. Shi, R.J. Skene, T. Asakawa, K. Takeuchi, Discovery of alogliptin: a potent, selective, bioavailable, and efficacious inhibitor of dipeptidyl peptidase IV, J. Med. Chem. 50 (10) (2007) 2297–2300.
[9] I.M. Al-Masri, M.K. Mohammad, M.O. Tahaa, Inhibition of dipeptidyl peptidase IV (DPP IV) is one of the mechanisms explaining the hypoglycemic effect of berberine, J. Enzyme Inhib. Med. Chem. 24 (5) (2009) 1061–1066.
[10] J. Fan, M.H. Johnson, M.A. Lila, G. Yousef, E.G. de Mejia, Berry and citrus phenolic compounds inhibit dipeptidyl peptidase IV: Implications in diabetes management, Evidence-Based Complementary Alternative Medicine (2013).
[11] L. Juillerat-Jeanneret, Dipeptidyl peptidase IV and its inhibitors: Therapeutics for type 2 diabetes and what else? J. Med. Chem. 57 (6) (2013) 2197–2212.
[12] M.S. Ali, M. Jahangir, ul Hussan SS, Choudhary MI. inhibition of α-glucosidase by oleanolic acid and its synthetic derivatives, Phytochemistry 60 (3) (2002) 295–299.
[13] K. Tadera, Y. Minami, K. Takamatsu, T. Matsuoka, Inhibition of α-glucosidase and α-amylase by flavonoids, J. Nutr. Sci. Vitaminol. 52 (2) (2006) 149–153.
[14] F. Ye, Z. Shen, M. Xie, Alpha-glucosidase inhibition from a Chinese medical herb (Ramulus mori) in normal and diabetic rats and mice, Phytomedicine 9 (2) (2002) 161–166.
[15] E. Standl, O. Schnell, Alpha-glucosidase inhibitors 2012–cardiovascular considerations and trial evaluation, Diabetes Vascular Disease Res 9 (3) (2012) 163–169.
[16] F.A. van de Laar, Alpha-glucosidase inhibitors in the early treatment of type 2 diabetes, Vascular Health Risk Manage. 4 (6) (2008) 1189.
[17] M.A. Phan, J. Wang, J. Tang, Y.Z. Lee, K. Ng, Evaluation of α-glucosidase inhibition potential of some flavonoids from Epimedium brevicornum, LWT-Food Sci. Technol. 53 (2) (2013) 492–498.
[18] B. Elya, K. Basah, A. Mun'im, W. Yuliastuti, A. Bangun, E.K. Septiana, Screening of α -Glucosidase Inhibitory Activity from Some Plants of Apocynaceae, Euphorbiaceae, and Rubiaceae. BioMed Research International, Clusiaceae, 2012.
[19] E. Ferrannini, A. Solini, SGLT2 inhibition in diabetes mellitus: rationale and clinical prospects, Nature Rev. Endocrinol. 8 (8) (2012) 495.
[20] A.J. Scheen, Pharmacodynamics, efficacy and safety of sodium–glucose co-transporter type 2 (SGLT2) inhibitors for the treatment of type 2 diabetes mellitus, Drugs 75 (1) (2015) 33–59.
[21] M.S. Butler, A.A. Robertson, M.A. Cooper, Natural product and natural product derived drugs in clinical trials, Nat. Prod. Rep. 31 (11) (2014) 1612–1661.
[22] M.A. Maciel, A.C. Pinto, V.F. Veiga Jr, N.F. Grynberg, A. Echevarria, Medicinal plants: the need for multidisciplinary scientific studies, Química Nova. 25 (3) (2002 May) 429–438.
[23] P.O. Osadebe, E.U. Odoh, P.F. Uzor, Natural products as potential sources of antidiabetic drugs, British J. Pharmaceut. Res. 4 (17) (2014) 2075–2095.
[24] D.J. Newman, G.M. Cragg, Natural products as sources of new drugs over the 30 years from 1981 to 2010, J Nat Prod. 75 (3) (2012) 311–315.
[25] M. Neelesh, J. Sanjay, M. Sapna, Antidiabetic potential of medicinal plants, Acta Poloniae Pharmaceutica -Drug Res 67 (2) (2010) 113–118.
[26] E.J. Verspohl, Recommended testing in diabetes research, Planta Med. 68 (2002) 581–590.
[27] M. Ahmad, M.A. Khan, M. Arshad, M. Zafar, Ethnophytotherapical approaches for the treatment of diabetes by the local inhabitants of district Attock (Pakistan), Ethnobotanical leaflets 2004 (1) (2006) 7.
[28] S.A. Gilani, R.A. Qureshi, S.J. Gilani, Indigenous uses of some important ethnomedicinal herbs of Ayubia National Park, Abbottabad, Pakistan, Ethnobotanical Leaflets 2006 (1) (2006) 32.
[29] S. Van Goethem, V. Matheeussen, J. Joossens, A.M. Lambeir, X. Chen, I. De Meester, A. Haemers, K. Augustyns, P. Van der Veken, Structure-Activity Relationship Studies on Isoindoline Inhibitors of Dipeptidyl Peptidases 8 and 9 (DPP8, DPP9): Is DPP8-Selectivity an Attainable Goal? J. Med. Chem. 54 (16) (2011) 5737–5746.
[30] S. Saleem, L. Jafri, I. Ul Haq, L.C. Chang, D. Calderwood, B.D. Green, B. Mirza, Plants Fagonia cretica L. and Hedera nepalensis K. Koch contain natural compounds with potent dipeptidyl peptidase-4 (DPP-4) inhibitory activity, J. Ethnopharmacol. 156 (2014) 26–32.
[31] S. Zhang, W. Lu, X. Liu, Y. Diao, F. Bai, L. Wang, L. Shan, J. Huang, H. Li, W. Zhang, Fast and effective identification of the bioactive compounds and their targets from medicinal plants via computational chemical biology approach, Med ChemComm. 2 (6) (2011) 471–477.
[32] A.M. Bower, L.M. Real Hernandez, M.A. Berhow, E.G. De Mejia, Bioactive compounds from culinary herbs inhibit a molecular target for type 2 diabetes management, dipeptidyl peptidase IV, J. Agric. Food. Chem. 62 (26) (2014) 6147–6158.
[33] H. Rasouli, S.M. Hosseini-Ghazvini, H. Adibi, R. Khodarahmi, Differential α-amylase/α-glucosidase inhibitory activities of plant-derived phenolic compounds: a virtual screening perspective for the treatment of obesity and diabetes, Food Funct. 8 (5) (2017) 1942–1954.
[34] M. Mosihuzzman, S. Naheed, S. Hareem, S. Talib, G. Abbas, S.N. Khan, M.I. Choudhary, B. Sener, R.B. Tareen, M. Israr, Studies on α-glucosidase inhibition and anti-glycation potential of Iris loczyi and Iris unguicularis, Life Sci. 92 (3) (2013) 187–192.
[35] L. Zhang, Z.C. Tu, T. Yuan, H. Wang, X. Xie, Z.F. Fu, Antioxidants and α-glucosidase inhibitors from Ipomoea batatas leaves identified by bioassay-guided approach and structure-activity relationships, Food Chem. 208 (2016) 61–67.
[36] H.C. Hong, S.L. Li, X.Q. Zhang, W.C. Ye, Q.W. Zhang, Flavonoids with α-glucosidase inhibitory activities and their contents in the leaves of Morus atropurpurea, Chinese Medicine 8 (1) (2013) 19.
[37] N. Nkobole, Antidiabetic activity of Terminalia sericea Burch. Ex DC constituents, Nat. Prod. Commun. 36 (2011) 3.
[38] Y. Yang, L. Gu, Y. Xiao, Q. Liu, H. Hu, Z. Wang, K. Chen, Rapid identification of α-glucosidase inhibitors from Phlomis tuberosa by sepbox chromatography and thin-layer chromatography bioautography, PloS one 10 (2) (2015) e0116922.
[39] W. Hou, Y. Li, Q. Zhang, X. Wei, A. Peng, L. Chen, Y. Wei, Triterpene acids isolated from Lagerstroemia speciosa leaves as α-glucosidase inhibitors, Phytotherapy Res 23 (5) (2009) 614–618.
[40] C.I. Choi, Sodium-glucose cotransporter 2 (SGLT2) inhibitors from natural products: discovery of next-generation antihyperglycemic agents, Molecules 21 (9) (2016) 1136. Aug 27.
[41] A. Oku, K. Ueta, K. Arakawa, T. Ishihara, M. Nawano, Y. Kuronuma, M. Matsumoto, A. Saito, K. Tsujihara, M. Anai, T. Asano, T-1095, an inhibitor of renal Na+-glucose cotransporters, may provide a novel approach to treating diabetes, Diabetes 48 (9) (1999) 1794–1800.
[42] W. Meng, B.A. Ellsworth, A.A. Nirschl, P.J. McCann, M. Patel, R.N. Girotra, G. Wu, P.M. Sher, E.P. Morrison, S.A. Biller, R. Zahler, Discovery of dapagliflozin: a potent, selective renal sodium-dependent glucose cotransporter 2 (SGLT2) inhibitor for the treatment of type 2 diabetes, J. Med. Chem. 51 (5) (2008) 1145–1149 Feb 9.
[43] S. Sato, J. Takeo, C. Aoyama, H. Kawahara, Na $^{+}$-glucose cotransporter (SGLT) inhibitory flavonoids from the roots of Sophora flavescens, Bioorg. Med. Chem. 15 (2007) 3445–3449.