Indian Journal of Natural Products and Resources
Vol. 10(4), December 2019, pp 227-237

DPP-IV Inhibitors from natural sources: An alternative approach for treatment and management of diabetes

Divya Sharma, Sandeep Kumar, Sunil Kumar* and Dinesh Kumar
Institute of Pharmaceutical Sciences, Kurukshetra University, Kurukshetra 136119, Haryana, India

Received 06 March 2019; Revised 27 October 2019

Diabetes is a chronic metabolic disorder present in almost all countries. According to WHO, T2DM is the World's fifth leading cause of death. Treatment for T2DM depends on the incretin hormone (GLP-1 & GIP). GLP-1 plays a vital role in the body's metabolism, such as insulin secretion but DPP-IV enzyme inactivates these incretin hormones. Therefore, it becomes important to identify DPP-IV inhibitors that act as prospective antidiabetic agents. Synthetic inhibitors like vildagliptin, sitagliptin, and saxagliptin are available in the market but they have some undesirable side effects. There are several natural plants as well as products that provide safe and effective medication against diabetes by DPP-IV enzyme inhibitory mechanism. This review summarizes recent advancement of DPP-IV inhibitors from medicinal plants and isolated phytoconstituents including alkaloids, flavonoids, terpenoids, phenol, and stilbenoids which are responsible for the DPP-IV inhibition.

Keywords: Active constituents, Diabetes, DPP-IV inhibitors, DPP-IV, GLP-1, Natural products.

IPC code; Int. cl. (2015.01)- A61K 36/00, A61P 3/00, A61P 3/10

Introduction

Diabetes mellitus (DM) is the most common metabolic disorders with micro- and macro-vascular complications. According to WHO, DM is considered as one of the leading causes of death in the world[1]. Type 2 DM (T2DM) is the common type of this disease and responsible for at least 90% cases. Although in most patients with T2DM, there may be no obvious symptoms for a long period, it still threatens human health. Blurred vision, drowsiness, weight gain, numbness in hands and feet and gum disease are common symptoms of T2DM in patient[2,3]. In the modern system of medicine, no suitable and effective therapy is available to cure diabetes mellitus. There is a gradual increase in demand to use natural products with antidiabetic activity due to side effects associated with the use of insulin and oral hypoglycemic agent. The most recent medications used to treat T2DM are inhibitors of dipeptidyl peptidase IV (DPP-IV).

DPP-IV is an enzyme mainly found in the capillary bed of the gut mucosa and other body organs like kidney, liver and intestine[4]. It is widely distributed in almost all human cells, tissues and organs. This enzyme belongs to the family of serine proteases, containing 766 amino acids. This enzyme is known for inactivating two incretin hormones glucagon-like peptide 1 (GLP-1) and glucose dependent-insulinotropic polypeptide (GIP)[5,6]. GLP-1 plays a very important role in body metabolism and insulin secretion. It also reduces the gastric emptying time and gastric acid secretion to reduce postprandial glucose spikes[6]. Administration of DPP-IV inhibitors blocks the enzyme (DPP-IV) and thereby enhances the half-life and main functional activity of GLP-I. One of the recent therapies used in the treatment of Type 2 diabetes are synthetic DPP-IV inhibitors[7] like vildagliptin[8], sitagliptin[9], and saxagliptin[10] but they have several side effects, therefore, it is necessary to identify natural DPP-IV inhibitors.

Mechanism of DPP-IV action

It is a well-known fact that glucagon-like peptide-1 (GLP-1) and glucose-dependent insulin tropic polypeptide (GIP) are the two main human incretin hormones that stimulate insulin release in the healthy individuals[11,12].

Glucagon-like peptide-1 (GLP-1) is produced from the proglucagon gene in L-cells of the small intestine. GLP-1 has its main effect by stimulating glucose-dependent insulin release from the pancreatic islets[12,13]. It is responsible to slow down the gastric emptying and inhibit inappropriate post-meal

*Correspondent author
Email: sunilmadhuban@kuk.ac.in, sunilmadhuban@yahoo.com

glucagon release (Fig. 1). It is considered as an incretin hormone and is one among the family of naturally occurring gut hormones that is released in the setting of a meal, but not with intravenous carbohydrate, and stimulates insulin synthesis and secretion[13-15].

DPP-IV inhibitors are a class of oral antidiabetic drugs inhibits the enzyme DPP-IV and therefore, its inhibition affects glucose regulation through multiple effects[16].

It is expected that herbal medicine can be a good option to oral hypoglycemic agents in the treatment of T2DM. It has been assumed that more than 1200 plants have been used to treat diabetes traditionally and at least 136 plants have been evaluated to have anti-diabetic activities. However, few studies indicated that some plants are responsible for DPP-IV inhibition in the treatment of diabetes mellitus.

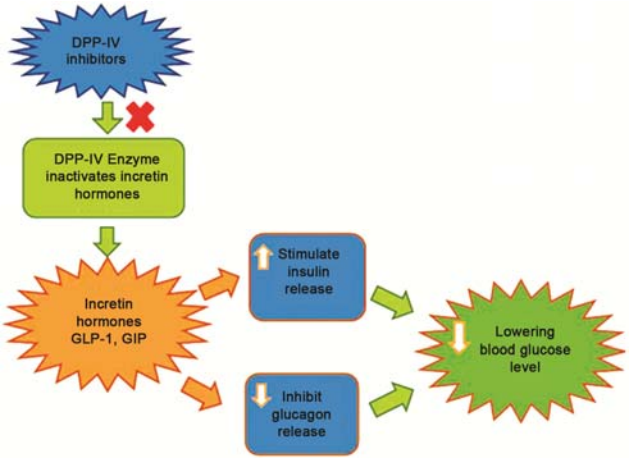

Fig. 1 — Mechanism of action of DPP-IV inhibitors

Medicinal plants showing DPP-IV inhibition activity

The use of herbal medicine in the field of diabetes is increasing day by day. Herbs are a promising therapeutic approach in the treatment of diabetes as complementary and alternative medicine. The purpose of this review is to give details of medicinal plants showing DPP-IV inhibitory activity (Table 1,2).

Apocynum cannabinum L. (Apocynaceae)

It is commonly known as Indian Hemp, a perennial herbaceous plant found in North-Eastern America and can be used as antirheumatic, cardiotonic, diaphoretic, emetic, expectorant and vermifuge. An active compound isoquercetin isolated from the leaves of *Apocynum cannabinum* L. (Apocynaceae) responsible for DPP-IV inhibitory activity with an IC_{50} value 96.8 µM[17].

Avena sativa L. (Poaceae)

It is also known as oats. It has a high protein content of about 12.4 to 24.5%. Three peptides mainly

Table 1 — List of plants showing DPP-IV inhibition with their respective IC_{50} values

S.No.	Name of the plant	Common name	Family	Part of plant used	IC_{50} value	Reference
1	*Apocynum cannabinum* L.	Indian hemp	Apocynaceae	Leaves	96.8 µM	17
2	*Avena sativa* L.	Oat	Poaceae	Seeds	0.99 mg/mL	18
3	*Berberis aristata* DC	Indian berberry	Berberidaceae	Bark	14.4 µg/mL	19
4	*Camelia sinensis* (L.) Kuntze	White tea	Theaceae	Leaves	227 µg/mL	20
5	*Castanospermum australe* A. Cunn. & C. Fraser	Black bean	Fabaceae	Seeds	13.96 g/mL	21
6	*Cicer arietinum* L.	Chickpea	Leguminosae	Leaves and grams	0.09 mg/mL	22
7	*Desmodium gangeticum* (L) DC	Salparni	Leguminosae	Aerial parts	255.5 µg/mL	24
8	*Eugenia jambolana* Lam.	Jamun	Myrtaceae	Seeds	278.94 µg/mL	25
9	*Fagonia cretica* L.	Ustarkhar	Zygophyllaceae	Aerial parts	38.1 µg/mL	26
10	*Fagopyrum esculentum* Moench	Buckwheat	Polygonaceae	Seeds	1.98 mg/mL	18
11	*Ferula assa-foetida* L.	Devil's dung	Apiaceae	Seeds	24.5 µg/mL	27
12	*Gymnema sylvestre* (Retz.) R. Br. ex Sm	Gurmar	Asclepiadaceae	Leaves	773.22 µg/mL	25
13	*Hedera nepalensis* K. Koch	Himalayan ivy	Araliaceae	Aerial parts	17.2 µg/mL	26
14	*Hordeum vulgare* var. *trifurcatum*	Barley	Poaceae	Seeds	1.83 mg/mL	18
15	*Mangifera indica*	Mango	Anacardiaceae	Leaves	182.7 µg/mL	28
16	*Morus alba* L.	White mulberry	Moraceae	Leaves	480 µg/mL	30
17	*Pilea microphylla* (L.) Liebm.	Gunpowder	Urticaceae	Leaves	520.4 µg/mL	31
18	*Psidium guajava* L.	Guava	Myrtaceae	Leaves	380 µg/mL	32
19	*Pterocarpus marsupium* Roxb.	Malabar kino	Leguminosae	Leaves	273.73 µg/mL	25
20	*Punica Granatum* L.	Pomegranate	Leguminosae	Leaves and fruit	0.19 mg/mL	22
21	*Schisandra chinensis* (Turcz.) Baill	Magnolia-vine	Schisandraceae	Fruit	10.8 µg/mL	22
22	*Trigonella foenum graceum* L.	Fenugreek	Leguminosae	Seed	0.03 mg/mL	22
23	*Urena lobate* L.	Caesarweed	Malvaceae	Leaves	1 654.64 µg/mL	34

Table 2 — Plants showing DPP-IV inhibition with their respective % Inhibition values

S. No.	Name of the plant	Common name	Family	Part of plant used	% Inhibition	Reference
1	*Camelia sinensis* (L.) Kuntze	White tea	Theaceae	Leaves	50.487	20
2	*Commiphora mukul* (Hook. ex Stocks) Engl.	Guggul	Burseraceae	-	92.97±8.45	23
3	*Desmodium gangeticum* (L) DC	Salparni	Leguminosae	Aerial parts	73.21	24
4	*Emblica officinalis* Gaertn	Amla	Phyllanthaceae	-	85.95±7.16	23
5	*Momordica charantia* L.	Bitter gourd	Cucurbitaceae	Fruits	53.25±0.04	29
6	*Morinda citrifolia* L.	Indian mulberry	Rubiaceae	-	24.64±2.24	23
7	*Ocimum sanctum* L.	Tulsi	Lamiaceae	Leaves	66.81±0.05	29
8	*Terminalia arjuna* (Roxb. ex DC.) Wight & Arn.	Arjuna	Combretaceae	-	83.39	23
9	*Tinospora crispa* (L.) Hook. f. & Thomson	Guduchi	Menispermaceae	Stem	65.86±1.02	33

derived from oats, buckwheat and barley shows *in vitro* DPP-IV activities. All peptides present in oats shows enzyme inhibition activities at different concentration with a substrate Gly Pro-pNA. It is concluded that oats are highly responsible for inhibiting DPP-IV enzyme and shows a significant level of inhibition with IC_{50} 0.99 mg/mL[18].

***Berberis aristata* DC (Berberidaceae)**

It's a woody plant, native to the Himalayas in India and Nepal. *Berberis aristata* DC root is used in a number of ailments like antibacterial, antiplatelet, anti-inflammatory, analgesic, antipyretic, antioxidant and hepatoprotective activities etc. Methanolic extract of the bark of *B. aristata* has the potential to inhibit DPP-IV enzyme activity (*in vitro*). The crude bark extract had shown the IC_{50} value of 14.4μg/mL[19].

***Camellia sinensis* (L.) Kuntze (Theaceae)**

It is an evergreen shrub, natively found in china and Southeast Asia comes under Theaceae family. Caffeine is the main constituent of *Camellia sinensis* that function as a secondary metabolite. Elya revealed that methanolic extract of white tea had DPP-IV enzyme inhibition with the highest percentage as compared to other plant extracts. The methanolic fraction of the *C. sinensis* has a greater inhibition percentage (50.487%), with an IC_{50} value of 227 μg /mL[20].

***Castanospermum austral* A. Cunn. & C. Fraser (Fabaceae)**

It is commonly known as Black Bean or Moreton Bay Chestnut., native to coastal rainforests and beaches in Australia. It mainly contains three alkaloids castanospermine, 7-deoxy-6-epi-castanospermine and australine. The extract of *Castanospermum australe* shows good DPP-IV inhibitory potential having an IC_{50} value of 13.96 g/mL with the standard Diprotin A shows the IC_{50} value of 1.543 g/mL[21]. HPLC analysis of dry powder extract contains three main alkaloids Castanospermine (RT=10.91), 7-deoxy-6-epi-castanospermine (RT= 7.04) and australine (RT=21.55)[21].

***Cicer arietinum* L. (Leguminosae)**

Three kinds of traditional Chinese medicine from Xinjiang, *Trigonella foenum-graecum*, *Cicer arietinum* and *Punica Granatum* found to have anti-diabetic effects. Research has proved that all three plant extracts have potent inhibition effects on DPP-IV, with IC_{50} values of 0.03, 0.09, and 0.19 mg/mL respectively[22].

***Commiphora mukul* (Hook. ex Stocks) Engl. (Burseraceae)**

Commiphora mukul commonly known as Guggul is found in western India and is commonly used as a valuable herb in Ayurvedic medicine for over 2500 years. *C. mukul* is well known for its anti-inflammatory, antispasmodic, carminative, hypoglycemic, antiseptic, astringent, sedative, stomachic, diaphoretic, diuretic, expectorant, thyroid stimulant, anthelmintic, antiseptic, demulcent, aphrodisiac, lithonotropic, obesity, antidiabetic, antihyperlipidemic, and antiosteoarthritic properties. The percentage inhibition of *C. mukul* (92.97±8.45%) shows that it is a potent inhibitor of DPP-IV enzyme[23].

***Desmodium gangeticum* (L.) DC (Leguminosae)**

It is a perennial non-climbing herb or shrub widely distributed in tropical and sub-tropical habitats and particularly abundant in India and used as a medicinal herb in indigenous system of medicine (Ayurveda) as a bitter tonic, febrifuge, digestive, anti-catarrhal, anti-emetic and in inflammatory conditions. Aqueous extract of *Desmodium gangeticum* exhibited good DPP-IV inhibitory activity at different concentration. Extract of *D. gangeticum* shows maximum percentage inhibition 73.21% with an IC_{50} value of 255.5μg/mL[24] compared with the standard Diprotin A.

***Emblica officinalis* Gaertn. (Phyllanthaceae)**

Emblica officinalis grows in tropical and subtropical parts of China, India, and the Malay Peninsula. The fruit is commonly known as amla or emblic myrobalan. The fruits of *E. officinalis* have been reported to have potent antimicrobial, antioxidant, adaptogenic, hepatoprotective, anti-tumour and antiulcerogenic activities. Manjusha K Borde *et al.,* screened five plants extract (*Terminalia arjuna*, *Commiphora mukul*, *Gymnema sylvestre*, *Morinda citrifolia*, and *E. officinalis*) for DPP-IV inhibitory activities compared with synthetic inhibitors (Vildagliptin and Sitagiptin). However, *C. mukul, T. arjuna*, and *E. officinalis* extract found to be significant DPP-IV inhibitors with inhibition percentage 92.97±8.45, 83.39±7.58, and 85.95±7.16% respectively[23].

***Eugenia jambolana* Lam. (Myrtaceae)**

It is a berry fruit, which grows abundantly in tropical regions of South Asia and South America, and is used in traditional medicines such as Ayurveda. *In vitro* assay suggest that *Eugenia jambolana* potently inhibits DPP-IV enzyme with IC_{50} values of 278.94 µg/mL[25].

***Fagonia cretica* L. (Zygophyllaceae)**

It is natively found in Malta, Spain, Crete and North Africa. It is used in the treatment of general debility, mouth ulcer, nausea, vomiting and diarrhoea. Mirza B *et al.* investigated two plants and their chemical compounds for the DPP-IV enzyme inhibition activity A crude extract of *Fagonia cretica* possessed good inhibitory activity (IC_{50} value: 38.1 µg/mL)[26]. *F. cretica* contains mainly four compounds (1) quinovic acid, (2) quinovic acid-3β-O-β-D-glycopyranoside, (3) quinovic acid-3β-O-β-D-glucopyranosyl-(28-1)-β-D-glucopyranosyl ester, and (4) stigmasterol. These are also responsible for DPP-IV enzyme inhibition with an IC_{50} value of 30.7, 57.9, 23.5 and >100 µM respectively.

***Fagopyrum esculentum* Moench (Polygonaceae)**

It is an annual herb with a green and red stem (when mature) also known as buckwheat. Catechins and rutin are the main constituents of *Fagopyrum esculentum*. It has been used as an antioxidant, anti-inflammatory, cardiovascular and hypolipidemic agent. Peptides isolated from buckwheat shows *in vitro* inhibitory effects on dipeptidyl peptidase IV (DPP-IV) enzyme[18].

***Ferula assa-foetida* L. (Apiaceae)**

It is also known as asafoetida or devil's dung and comes under the family of Apiaceae. Recent pharmacological studies have also shown several activities of *Ferula assa-foetida*, such as antioxidant, antiviral, antimicrobial, antispasmodic and antidiabetic. Seed extract of *F. assa-foetida* exhibit significant DPP-IV inhibition activities and α-glucosidase inhibition activities also. Adel yarizade estimated potent enzyme inhibitory activity of *F. assa-foetida* fractions[27].

***Gymnema sylvestre* (Retz.) R. Br. ex Sm. (Asclepiadaceae)**

It is found in Central and Western India. *Gymnema sylvestre* (Asclepiadaceae) is a slow-growing, perennial, medicinal woody climber found in central and peninsular India. It possesses antimicrobial, antihypercholesterolemic, hepatoprotective activities. Leaves of this plant have been found to cause hypoglycemia in laboratory animals and can be used in herbal medicine to help, treat adult-onset diabetes mellitus (NIDDM). The DPP-IV Inhibitory activity of *G. sylvestre* was calculated as 773.22 µg/mL[25].

***Hedera nepalensis* K. Koch (Araliaceae)**

It is also known as Himalayan ivy, woody climber plant up to 30 m long. It is native to Nepal and Bhutan as well as China, Afghanistan, India, Laos Thailand and Myanmar. Leaves of this plant have been used for the treatment of diabetes. A crude extract of *Hedera nepalensis* (HNC) possesses higher inhibitory activity with IC_{50} value: 17.2 µg/mL[26]. A triterpenoid constituent Lupeol of *H. nepalensis* also shows significant DPP-IV inhibitory activity with an IC_{50} value of 31.6 µM.

***Hordeum vulgare* var. *trifurcatum* L. (Schltdl.) Alef. (Poaceae)**

It is also known as barley and an important miscellaneous grain. Barley is mostly known for its high amount of dietary fibre such as β-glucan that may decrease the risk of coronary heart disease. Barley leaves have high antioxidant activity. It has been found that the constant consumption of whole grains decreased the risk of type 2 diabetes by 31%. Peptides isolated from Highland barley known for the *in vitro* DPP-IV inhibitory activity with an IC_{50} value of 1.83 mg/mL[18].

***Mangifera indica* L. (Anacardiaceae)**

It is a popular tree and serves as food and as an important medicinal plant. It contains a high amount of vitamin A as its main constituent, and also contains

vitamin B and C. The methanolic extract of *Mangifera indica* leaves has *in vitro* DPP-IV inhibitory activity. The extract showed potent activity with an IC_{50} value of 182.7 µg/mL[28]. This plant has been reported to have several pharmacological activities such as antioxidant, anti-inflammatory, antidiabetic, and immune-modulatory activities.

***Momordica charantia* L. (Cucurbitaceae)**

It is also known as karela or bitter gourd. It is a popular plant used for treating diabetes-related conditions especially in indigenous populations of Asia, South America, India, the Caribbean and East Africa. Anand Krishna *et al.* revealed that the methanolic extract of *Momordica charantina* has DPP-IV activities with 53.25±0.04% inhibition[29]. Biochemical and animal model experiments showed the antidiabetic effect of *M. charantia* based on data and hypothesis.

***Morinda citrifolia* L. (Rubiaceae)**

It is also known as Indian mulberry (Noni) is a small evergreen tree. The leaves are 8-10 inches long, oval-shaped, dark, green and shiny, with deep veins. Fruit juice of *Morinda citrifolia* is a popular health drink and possess various pharmacological properties including anti-diabetic, antioxidant and anti-inflammatory. The hydroalcoholic extract of *M. citrifolia* possesses significant inhibition percentage (24.64%) for DPP-IV inhibition[23].

Morus alba* L. *(Moraceae)

It is also known as White mulberry moderately fast-growing, deciduous shrub or tree growing 20-35 meters tall. Its fruit is frequently eaten in various parts of the world. Wang *et al.* showed the antidiabetic effect of Traditional Chinese Medicine formula[30]. Both *in vitro* and *in vivo* studies were carried out to confirm the antidiabetic activity of the formula and found that *Morus alba* leaves extract had potent *in vitro* α-glucosidase and DPP-IV inhibitory activities.

***Ocimum sanctum* L. (Lamiaceae)**

Ocimum tenuiflorum (Ocimum sanctum) is commonly known as Thulasi/Tulsi in India. In the Indian subcontinent, fresh leaves of this plant are used for the treatment of cough, cold, abdominal pain, skin diseases, arthritis, painful eye diseases, measles, and diarrhoea. The preclinical evaluation on various extracts of different parts of *O. sanctum* shows anti-fertility, anti-cancer, anti-diabetic, anti-fungal, hepatoprotective and cardioprotective actions. Methanolic extract of *O. sanctum* possesses good DPP-IV inhibition activity with % inhibition 66.81%[29].

***Pilea microphylla* (L.) Liebm. (Urticaceae)**

It is commonly known as Gunpowder Plant. It is a small, perennial herb. *Pilea microphylla* balances the insulin level and cures diabetes. The infusion of the whole plant acts as a diuretic and promotes urination. *P. microphylla* inhibits dipeptidyl peptidase IV (DPP-IV) *in vitro* with an IC_{50} of 520.4±15.4 g/mL[31]. It is also useful in labour pain and a good remedy to cure infertility.

***Psidium guajava* L. (Myrtaceae)**

Guava leaves serve as popular and traditional medicine. It was originally grown from the tropic belt countries of Asia and Africa belongs to the Myrtaceae family. The main effects for guava extracts are sedative, anti-diarrheic, anticestodals, analgesic, anti-inflammatory, anti-microbial and hepatoprotective. The ethanolic leaves extract of *Psidium guajava* possess significant inhibition of DPP-IV enzyme, with an IC_{50} value of 380 µg/mL[32]. Flavonol glycosides isolated from the guava leaves potentially shows DPP-IV inhibition activity.

***Pterocarpus marsupium* Roxb. (Leguminosae)**

It is also known as Malabar kino or Bijasar. It is a large tree common to the mixed deciduous forests central and Peninsular India. *Pterocarpus marsupium* Roxb. is also used in Indian folk-lore medicine for the treatment of diabetes and controls diabetes in experimental animals. *P. marsupium* inhibits DPP-IV potently with IC_{50} values of 273.73±2.96 µg/mL[25].

***Punica granatum* L. (Leguminosae)**

It is also known as Pomegranate, fruit-bearing shrub belong to the family Leguminosae. Research by Xinjiang has proved that all three plant extracts i.e *Trigonella foenum-graecum*, (Leguminosae), *Cicer arietinum*, (Leguminosae) and *Punica Granatum* (Leguminosae) has potent inhibition effects on DPP-IV, with IC_{50} values of 0.03, 0.09, and 0.19 mg/mL, respectively[22].

***Schisandra chinensis* (Turcz.) Baill. (Schisandraceae)**

An antidiabetic Traditional Chinese Medicine (TCM) formula, consisted of *Schisandra chinensis* (Schisandraceae), *Coptis chinensis* (Ranunculaceae), *Psidium guajava*, (Myrtaceae) and *Morus alba*

(Moraceae), has been studied based on its inhibitory activities against α-glucosidase, DPP-IV and advanced glycation end products that shows good inhibitory actions on DPP-IV[22].

***Terminalia arjuna* (Roxb. ex DC.) Wight & Arn. (Combretaceae)**

It is commonly known as Arjuna and is widely used in Indian system of medicine. It is basically used as cardioprotective, hypotensive, hypolipidemic and wound healing activity. Extract of *Terminalia arjuna* exhibited good DPP-IV inhibition activity with the highest percentage of DPP-IV inhibition 83.39±7.58%[23].

***Tinospora crispa* (L.) Hook. f. & Thomson (Menispermaceae)**

It is a deciduous climbing shrub which has stems up to 15 metres long. *Tinospora crispa* is a medicinal plant used to treat diabetes, by decreasing serum glucose level in diabetic rats and the hypoglycemic effect was surely due to its insulinotropic activity. *T. crispa* also increased peripheral utilization of glucose and inhibited hepatic glucose release[33].

***Trigonella foenum graceum* L. (Leguminosae)**

It is also known as fenugreek, commonly known as methi, popular traditional medicinal herb in Bangladesh, possesses various biological activities and pharmacological functions. *Trigonella foenum-graecum* seeds are also used in high cholesterol, inflammation and gastrointestinal ailments. Soraya Riyanti *et al.* investigated many different Indonesian plants and the inhibitory percentage of *T. foenum graceum* extract was found to be 71.29±0.33%[33] and its IC_{50} value was calculated as 0.03 mg/mL[22].

***Urena lobata* L. (Malvaceae)**

It is also known as caesarwood mainly found in Indonesia and is used to cure many diseases. Traditionally, Nigerian people used *Urena lobata* to treat diabetes mellitus. The ethanolic and water extract of *U. lobata* leaves shows significant *in vitro* DPP-IV inhibition activity with the IC_{50} values of 1 654.64 and 6 489.88 mg/mL, respectively[34].

***Withania somnifera* (L.) Dunal (Solanaceae)**

It is also known as Indian ginseng (Ashwagandha). It grows in dry parts of sub-tropical regions. Rajasthan, Punjab, Haryana, Uttar Pradesh, Gujarat, Maharashtra and Madhya Pradesh are the major Ashwagandha producing states of India. Methanolic extract of the matured root of *Withania somnifera* exhibits very good DPP-IV inhibitory activity[35]. Catechin is the main constituent of *W. somnifera* also shows good DPP-IV inhibitory action.

Natural phytoconstituents showing DPP-IV Inhibition activity

In recent years, with the rapid progress of new technology and the increased research on natural DPP-IV inhibitors, lots of plants, their extracts and their active chemical constituents (Table 3) has been found with powerful inhibitory effects against DPP-IV, which will give us valuable leads to study safe DPP-IV inhibitors. Here, in this review, the natural DPP-IV inhibitors discovered over the last few years are summarized and categorized according to their chemical structures (Fig. 2).

Alkaloids

Guasch et al. have predicted 12 potential DPP-IV inhibitors from 12 different plant extracts that have the potential for antidiabetic activity. Nine molecules were selected for *in vitro* bioassay, out of which seven compounds were identical having DPP-IV activity with IC_{50} values less than 1.00 mM. The other two compounds had no results due to their poor solubilities, the results have shown that Virtual screening process is a highly efficient approach for discovering DPP-IV inhibitors from natural products[36].

Berberine is the main isolated compound from the Chinese herb *Coptis chinensis* French. (Ranunculaceae), It mainly shows the potent DPP-IV inhibitory activity with the in-vitro bioassays (IC_{50} value = 13.3 μM)[37].

Glycosides

Kalhotra *et al*. carried out molecular docking of novel chrysin molecules and found that malvidin is well-known to inhibit DPP-IV enzyme along with other natural products like Hispidulin, Luteolin, Apigenin, Hesperetin, Naringenin, Kaempferol, Genistein, cyanidin, flavone, Cyanidin-3-glucoside and Reserveratol[38].

Bo-Ram Kim, Hyo Young Kim *et al*., isolated four compounds (kaempferol- 3-O-β- gulcopyranosyl-(1→2)-β-galactopyranosyl-7-O-α-rhamnopyranoside, kaempferol-3- O-β-gulcopyranosyl-(1→2)- [α-rhamnopyranosyl (1→6)]-β-galactopyranosyl-7-O- α-rhamnopyranoside, and robinin (kaempferol-3-O-α-rhamnosyl (1→6)-O-β-galactopyranoside- 7-O-α-rhamnopyranoside and kaempferol) from the seeds of *Lens culinaris* Medikus (Fabaceae) and tested for

Table No. 3 — List of active constituents showing DPP-IV inhibition

S. No.	Active principles	Biological source	Family	Plant part used	Enzyme inhibitory activity (IC_{50})	Reference
1	Alkaloids					
	Berberine	*Coptis chinensis* Franch.	Ranunculaceae	Stem and root	14.4 µg/mL	37
2	Glycosides					
	Malvidin	*Anagallis monelli* (L.) U. Manns & Anderb	Primulaceae	Aerial parts	1.41 µM	38
	Kaempferol- 3-O-β-gulcopyranosyl-(1→2)-β-galactopyranosyl-7-Oα-rhamnopyranoside	*Lens culinaris* Medikus	Leguminosae	Seeds	27.89 µM	39
	Kaempferol-3- O-β-gulcopyranosyl-(1→2)-[α-rhamnopyranosyl(1→6)]-β-galactopyranosyl-7-O- α-rhamnopyranoside	*Lens culinaris* Medikus	Leguminosae	Seeds	36.52 µM	39
	Robinin	*Lens culinaris* Medikus	Leguminosae	Seeds	37.01 µM	39
	Kaempferol	*Lens culinaris* Medikus	Leguminosae	Seeds	51.9 µM	39
3	Flavonoids and Phenols					
	Apigenin	*Acacia auriculiformis* A. Cunn. ex Benth.	Fabaceae	Stem and pods	0.14 µM	40
	Caffeic acid	*Coffea arabica* L.	Rubiaceae	Leaves	3.37 µM	40
	Cirsimaritin	*Rosamarinus officinalis* L.	Lamiaceae	Leaves	0.43 µM	41
	Cyanidin	*Rubus fruticosus* L.	Rosaceae	Fruits	1.41 µM	40
	Cyanidin-3-glucoside	*Vaccinum corymbosum* L.	Ericaceae	Fruits	125.1 µM	42
	Emodin	*Rheum palmatum* L.	Polygonaceae	Leaves	5.76 µM	43
	Epigallocatechin gallate	*Camellia sinensis* (L.) Kuntze	Theaceae	Leaves	10.21 µM	40
	Eriocitrin	*Citrus limon* (L.) Osbeck	Rutaceae	Fruits	10.36 µM	40
	Eriocdictyol	*Lippia graveolens* Kunth	Verbenaceae	Leaves	10.9 µM	41
	Gallic acid	*Camellia sinensis* (L.) Kuntze	Theaceae	Leaves	4.65 µM	40
	Genistein	*Psoralea corylifolia* L.	Fabaceae	Leaves	0.48 µM	40
	Hesperetin	*Citrus aurantium* L.	Rutaceae	Fruits	0.28 µM	40
	Hispidulin	*Origanum majorana* L.	Lamiaceae	-	0.49 µM	41
	Luteolin	*Brassica oleracea* L.	Brassicaceae	Leaves	0.12 µM	40
	Naringenin	*Citrus maxima* Merr.	Rutaceae	Fruit	0.24 µM	40
	Quercetin	*Quercus alba* L.	Fagaceae	-	2.92 µM	40
	Rosmarinic acid	*Rosamarinus officinalis* L.	Lamiaceae	-	14.1 µM	41
	Rutin	*Fagopyrum esculentum* Moench	Polygonaceae	Leaves	485 µM	44
	Isoquercitin	*Pilea microphylla* (L.) Liebm.	Urticaceae	Leaves	96.8 µM	45
4	Terpenoids					
	Rebaudioside A	*Stevia rebaudiana* (Bertoni)	Asteraceae	Leaves	-	47
	Stevioside	*Stevia rebaudiana* (Bertoni)	Asteraceae	Leaves	-	47
	Lupeol	*Hedera nepalensis* K. Koch	Araliaceae	Aerial parts	31.6 µM	26
5	Phenol and Stilbenoid					
	Hopeaphenol	*Vitis thunbergii* var. *taiwaniana*	Vitaceae	Stem and leaves	401 µM	48
	Vitisin A	*Vitis thunbergii* var. *taiwaniana*	Vitaceae	Stem and leaves	90.75 µM	48
	Vitisin B	*Vitis thunbergii* var. *taiwaniana*	Vitaceae	Stem and leaves	15.3 µM	48

their DPP-IV–inhibitory activity. Their DPP-IV inhibition activities were reported as 27.89±1.29, 36.52±0.78, 37.01±1.40, and 51.9±4.83 µM, respectively[39].

Flavonoids

Fan J *et al*. isolated sixteen phenolic compounds from the citrus, berry, grape and soybean. Anthocyanin analysis was carried out followed by

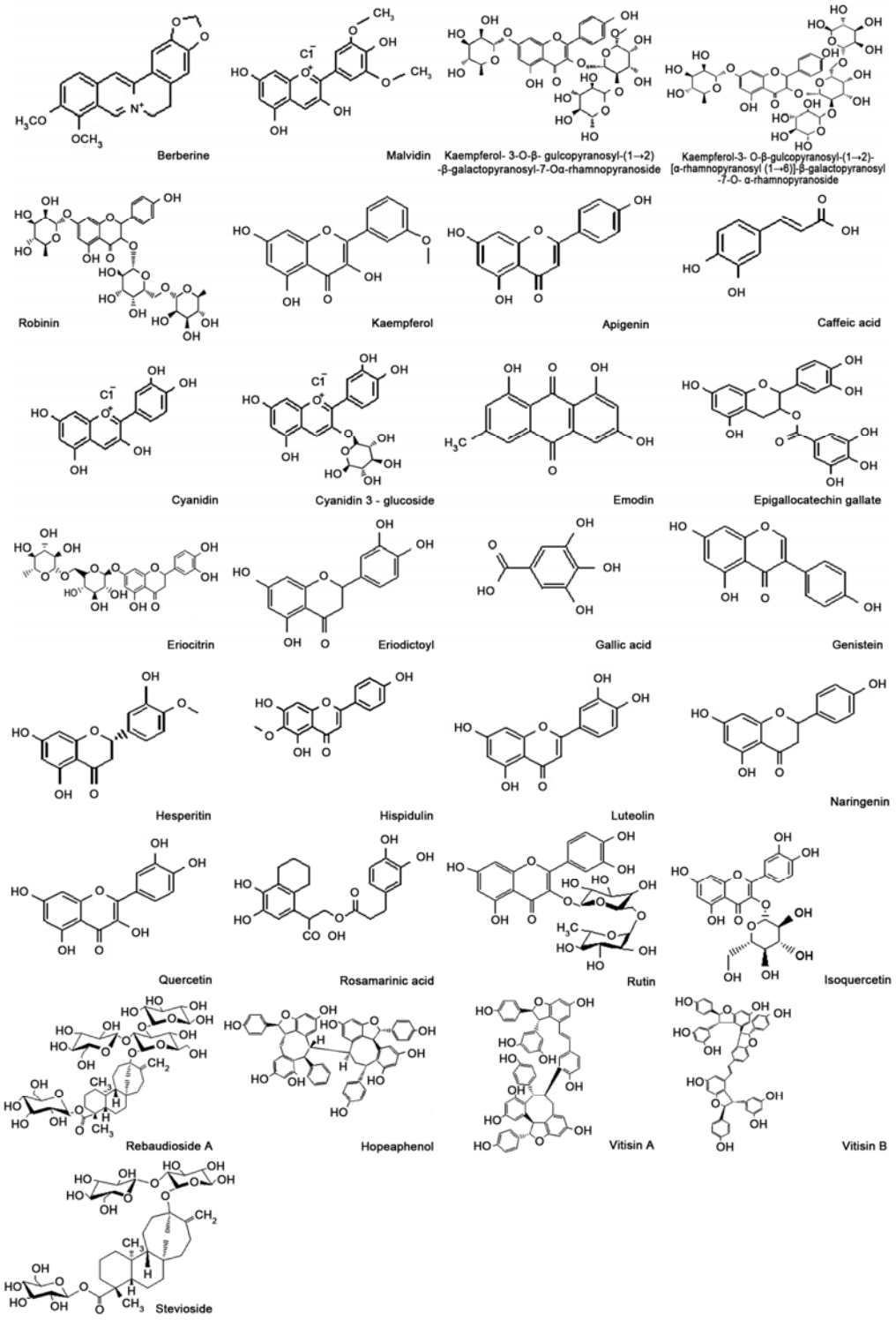

Fig. 2 — Structures of active constituent showing DPP-IV inhibition activity

DPP-IV inhibition assay where blank contained the vehicle only and positive control contained the vehicle and purified DPP-IV enzyme. The results were compared with the positive control diprotin A (Ile-Pro-Ile, IC_{50}, 4.21±2.01 μM) which showed that these varieties of phenolic compounds had DPP-IV inhibitory activities *in vitro* with different IC_{50} values[40], like apigenin (IC_{50} = 0.14±0.02 μM), caffeic

acid (IC_{50} = 3.37±0.14 μM), cyanidin (IC_{50} = 1.41±0.25 μM), epigallocatechin gallate (IC_{50} = 10.21±0.75 μM), eriocitrin (IC_{50}= 10.36±0.09 μM), gallic acid (IC_{50} = 4.65±0.99 μM), genistein (IC_{50} = 0.48±0.04 μM), hesperetin (IC_{50} = 0.28±0.07 μM), luteolin (IC_{50} = 0.12±0.01 μM), naringenin (IC_{50} = 0.24±0.03 μM), quercetin (IC_{50} = 2.92±0.68 μM). Insilico and molecular docking were also performed on these phenolic compounds[40].

Six main active constituents from greenhouse-grown Mexican oregano (*Lippia graveolens* Kunth) (Lamiaceae) and Rosemary (*Rosmarinus officinalis* L.) (Lamiaceae) *in vitro* assay shows that these constituents exhibits potent DPP-IV inhibitory activities[41] and IC_{50} values compare with sitagliptin as positive control (IC_{50} = 0.06±0.03 μM), eriocdictyol (IC_{50} = 10.9±0.4 μM), hispidulin (IC_{50} = 0.49±0.1 μM), cirsimaritin (IC_{50} = 0.43±0.07 μM) and rosamarinic acid (IC_{50} = 14.1±1.7 μM), naringenin (IC_{50} = 2.5±0.3 μM), while carnosol (IC_{50} > 100 μM) is a weaker inhibitor[41].

Casedas G *et al*. discussed the potential role of the anthocyanin (Cyanidin 3-O-Glucoside) as therapeutic candidate to treat chronic diseases like diabetes by inhibiting DPP-IV enzyme. It was evaluated that cyanidin 3-O-glucoside was able to inhibit α-GLU (IC_{50} = 479.8 μM) and DPP-IV (IC_{50} = 125.1 μM) enzyme respectively[42].

Emodin, which is isolated from the *Rheum palmatum* L. inhibit DPP-IV activity *in vitro* without inhibiting DPP-VIII or DPP-IX. The IC_{50} value (5.76 μM) shows the potency of emodin as DPP-IV inhibitor[43].

Citrus flavonoids show significant DPP-IV inhibitory activities in comparison with gliptins IC_{50} values of 0.684 μM (sitagliptin), 0.707 μM (saxagliptin) and 2.286 μM (vildagliptin). *In vitro* studies proves that rutin is the most potent inhibitor of DPP-IV with an IC_{50} value of 485 μM[44].

Isoquercitrin[45], is the main constituent isolate from the apocynum and folium mori, it is widely existing in medicinal plants, food and beverage, fruits and vegetables and shows antioxidant, anti-inflammatory, antidepressant, antihypertensive, and lipid-lowering activities. *In vitro* activities of isoquercetin show its potency as a DPP-IV inhibitor (IC_{50} = 96.8 μM).

Naringin is the main active constituent isolate from peels of *Citrus maxima* Merr. and *Citrus aurantium* L. (Rutaceae), shows significant DPP-IV inhibitory activity. The *in vivo* study shows that naringin has strong activity against DPP-IV[46].

Terpenoids and steroids

Rebaudioside A and stevioside, are the two main sesquiterpene glycoside identifies from the *Stevia rebaudiana* (Bertoni) (Asteraceae), has potential DPP-IV inhibitory activities by molecular docking[47].

Phenols and stilbenoid

Three main compounds from the *Vitis thunbergii* var. *taiwaniana* showed potent DPP-IV inhibitory activity**.** Ethanol extracts from the stems and leaves of plant possess DPP-IV inhibition activity. (+)-Hopeaphenol, (+)-vitisin A, and (−)-vitisin B are the main constituents which has good results against α-glucosidase and DPP-IV with IC_{50} values 401,90.75, and 15.3 μM respectively[48].

Conclusion

In recent years, the enzyme DPP-IV has become an important drug target for diabetes therapy and DPP-IV inhibitors become a popular remedy for it. However, some chemically synthesized compounds are commercially available. Molecular docking is also one of the important tools in finding the potential or advancement of DPP-IV inhibitors from natural products. The *in vivo* and *in vitro* experiments from current literature suggested the potential of medicinal plants, their extracts and their active chemical constituents in inhibiting DPP-IV activity.

Although, nature is a rich source of medicinal plants that have been used to treat diabetes mellitus from ages. Therefore, the discovery of natural DPP-IV inhibitors may suggest a new chance or a new idea for developing newer medications. The reported studies will significantly enhance research to discover new DPP-IV inhibitors from natural products by using modern techniques. It is believed that this review will capture the attention of other research groups to develop newer natural DPP-IV inhibitors that could be better diabetic agents in terms of safety and efficiency.

References

1 Wild S H, Roglic G, Green A, Sicree R and King H, Global prevalence of diabetes: Estimates for the year 2000 and projections for 2030, *Diabetes Care*, **27**(5), 2004, 1047–1053.

2 Baynes H W, Classification, pathophysiology, diagnosis and management of diabetes mellitus, *J Diabetes Metab*, 2015, **6**(5), 1-9.

3 Hackett E and Jacques N, Type 2 diabetes pathophysiology and clinical features, *Clin Pharmacist*, 2009, **1**, 475-478.

4 Kieffer T J and Habener J F, The glucagon-like peptides, *Endocrine Review*, 1999, **20**(6), 876 –913.

5 Deacon C F, Wamberg S, Bie P, Hughes T E and Holst J J, Degradation of glucagon-like peptide-1 by human plasma *in vitro* yields an N-terminally truncated peptide which is a major endogenous metabolite *in vivo*, *J Endocrinol Metab*, 2002, **172**, 355-362.

6 Mentlein R, Gallwitz B and Schmidt W E, Dipeptidyl peptidase IV hydrolyses gastric inhibitory polypeptide, glucagon-like peptide-1 amide, peptide histidine-methionine and is responsible for their degradation in human serum, *Eur J Biochem,* **214**(3), 829–835.

7 Lambeir A M, Durinx C, Scharpé S and De Meester I, Dipeptidyl-peptidase IV from bench to bedside: An update on structural properties, functions, and clinical aspects of the enzyme DPP IV, 2003, *Crit Rev Clin Lab Sci*, **40**(3), 209-294.

8 Villhauer E B, Brinkman J A, Naderi G B, Burkey B F, Dunning B E, *et al.*, 1-[[(3-Hydroxy-1-adamantyl) amino] acetyl]-2-cyano-(S)-pyrrolidine: A potent, selective, and orally bioavailable dipeptidyl peptidase IV inhibitor with antihyperglycemic properties, *J Med Chem*, 2003, **46**, 2774–2789.

9 Kim D, Wang L, Beconi M, Eiermann G J, Fisher M H, *et al.*, (2R)-4-Oxo-4- [3-(trifluoromethyl)-5,6-dihydro [1,2,4] triazolo[4,3-a] pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl) butan-2-amine: A potent, orally active dipeptidyl peptidase IV inhibitor for the treatment of type 2 diabetes, *J Med Chem*, 2005, **48**, 141-151.

10 Augeri D J, Robl J A, Betebenner D A, Magnin D R, Khanna A, *et al.*, Discovery and preclinical profile of saxagliptin (BMS-477118): A highly potent, long- acting, orally active dipeptidyl peptidase IV inhibitor for the treatment of Type 2 diabetes, *J Med Chem*, 2005, **48**, 5025–5037.

11 McKennon S A and Campbell R K, The physiology of incretin hormones and the basis for DPP-4 inhibitors, *Diabetes Educator*, 2007, **33**(1), 55–66.

12 Neumiller J J, Wood L and Campbell R K, Dipeptidyl peptidase-4 inhibitors for the treatment of type 2 diabetes mellitus, *Pharmacotherapy*, 2010, **30**(5), 463-484.

13 Gutzwiller J P, Drewe J, Goke B, Schimdt H, Rohrer B, *et al*., Glucagon-like peptide-1 promotes satiety and reduces food intake in patients with diabetes mellitus type 2, *Am J Physiol Soc*, 1999, **276**(5), R1541- R1544.

14 Gupta V, Glucagon-like peptide-1 analogues: An overview, *Indian J Endocrinol Metab*, 2013, **17**(3), 413-421.

15 Vella A, Mechanism of action of DPP-4 Inhibitors - New insights, *J Clin Endocrinol Metab*, 2012, **97**(8), 2626-2628.

16 Thornberry N A and Gallwitz B, Mechanism of action of inhibitors of dipeptidyl-peptidase-4 (DPP-4), *Best Pract Res Clin Endocrinol Metab*, 2009, **23**(4), 479–486.

17 Gao Y, Zhang Y, Zhu J, Li B, Li Z, *et al.*, Recent progress in natural products as DPP-4 inhibitors, *Future Med Chem*, 2015, **7**(8), 1079-1089.

18 Wang F, Yu G, Zhang Y, Zhang B, and Fan J, Dipeptidyl peptidase IV inhibitory peptides derived from oat (*Avena sativa* L.), buckwheat (*Fagopyrum esculentum*), and highland barley (*Hordeum vulgare trifurcatum* (L.) Trofim) proteins, *J Agric Food Chem*, 2015, **63**(43), 9543−9549

19 Chakrabarti R, Singh B, Narendra P, Varghese N, Vanchhawng L, *et al*., Dipeptidyl peptidase- IV inhibitory activity of *Berberis aristata*, *J Nat Prod*, 2011, **4**, 158-163.

20 Meiliza E, Rani S and Berna E, Dipeptidyl peptidase IV inhibitory activity of fraction from white tea Ethanolic extract (*Camellia sinensis* (L.) Kuntze) ex vivo, *Pharmacogn J*, 2018, **10**(1), 190-193.

21 Bharti S K, Krishnan S, Kumar A, Rajak K K, Murari K, *et al*., Antihyperglycemic activity with DPP-IV inhibition of alkaloids from seed extract of *Castanospermum australe*: Investigation by experimental validation and molecular docking, *Phytomedicine*, 2012, **20**(1), 24–31.

22 Chackalamannil S, Rotella D and Ward I E, *Comprehensive Medicinal chemistry III*, vol. I, General perspective – The Future of Drug Discovery, 2017, 545.

23 Borde M K, Mohanty I R, Suman R K and Deshmukh Y, Dipeptidyl peptidase-IV inhibitory activities of medicinal plants: *Terminalia arjuna*, *Commiphora mukul*, *Gymnema sylvestre*, *Morinda citrifolia*, *Emblica officinalis*, *Asian J Pharm Clin Res*, 2016, **9**(3), 180-182.

24 Bisht R, Bhattacharya S, and Jaliwala Y A, Evaluating the use of *Desmodium gangeticum* as alpha glucosidase and DPP-IV inhibitor for type-II diabetes, *Am J Phytomed Clin Ther*, 2014, **2**(4), 530-539.

25 Kosaraju J, Dubala A, Chinni S, Khatwal R B, Kumar M N S, *et al*., A molecular connection of *Pterocarpus marsupium*, *Eugenia jambolana* and *Gymnema sylvestre* with dipeptidyl peptidase-4 in the treatment of diabetes, *Pharm Biol*, 2014, **52**(2), 268-271.

26 Saleem S, Jafri L, Haq I, Chang L C, Calderwood D, *et al*., Plants *Fagonia cretica* L. and *Hedera nepalensis* K koch contain natural compounds with potent dipeptidyl peptidase-4 (DPP-4) inhibitory activity, *J Ethnopharmacol*, 2014, **156**(28), 26-32.

27 Yarizade A, Kumleh H H and Niazi A, *In vitro* antidiabetic effects of *Ferula assa-foetida* extracts through dipeptidyl peptidase-IV and α-glucosidase inhibitory activity, *Asian J Pharm Clin Res*, 2017, **10**(5), 357-360.

28 Yogisha S and Raveesha A K, Dipeptidyl peptidase IV inhibitory activity of *Mangifera indica, J Nat Prod*, 2010, **3**, 76-79.

29 Singh A K, Jatwa R and Joshi J, Cytoprotective and dipeptidyl peptidase- IV (DPP-IV/CD26) inhibitory roles of *Ocimum sanctum* and *Momordica charantia* extract, *Asian J Pharm Clin Res,* 2014, **7**(1), 115-120.

30 Wang H J and Chiang B H, Anti-diabetic effect of a traditional Chinese medicine formula, *Food Funct*, 2012, **3**(11), 1161-1169.

31 Bansal P, Paul P, Mudgal J, Nayaka P G, Pannakal S T, *et al*., Antidiabetic, antihyperlipidemic and antioxidant effects of the flavonoid rich fraction of *Pilea microphylla* (L.) in high fat diet/streptozotocin-induced diabetes in mice, *Exp Toxicol Pathol*, 2012, **64**(6), 651-658.

32 Eidenberger T, Selg M and Krennhuber K, Inhibition of dipeptidyl peptidase activity by flavonol glycosides of guava (*Psidium guajava* L.): A key to the beneficial effects of guava in type II diabetes mellitus, *Fitoterapia*, 2013, **89**, 74-79.

33 Riyanti S, Suganda A G and Sukandar E Y, Dipeptidyl peptidase –IV inhibitory activity of some Indonesian medicinal plants, *Asian J Pharm Clin Res*, 2016, **9**(2), 375-377.

34 Purnomo Y, Soeatmadji D W, Sumitro S B and Widodo M A, Anti-diabetic potential of *Urena lobata* leaf extract through inhibition of dipeptidyl peptidase IV activity, *Asian Pac J Trop Biomed*, 2015, **5**(8), 645-649.

35 Kempegowda P K, Zameer F, Narasimashetty C K, Kollur S P and Murari S K, Inhibitory potency of *Withania somnifera*

extracts against DPP-IV: An invitro evaluation, *Afr J Tradit Complement Altern Med*, 2018, **15**(1), 11-25.

36 Guasch L, Sala E, Ojeda M J, Valls C, Blade C, *et al*., Identification of novel human dipeptidyl peptidase-IV inhibitors of natural origin (Part I): Virtual screening and activity assays, *Plos One*, 2012, **7**(9), 1–13.

37 Al-masri I M, Mohammad M K and Tahaa M O, Inhibition of dipeptidyl peptidase IV (DPP IV) is one of the mechanisms explaining the hypoglycemic effect of berberine, *J Enzym Inhib Med Chem*, 2009, **24**(5), 1061–1066.

38 Kalhotra P, Chittepu V C, Osorio-Revilla G and Gallardo-Velázquez T, Structure activity relationship and molecular docking of natural product library reveal chrysin as a novel dipeptidyl Peptidase-4 (DPP-4) inhibitor: An integrated in silico and *In vitro* study, *Molecules*, 2018, **23**(6), 1368.

39 Kim B R, Kim H Y, Choi I, Kim J B, Jin C H *et al*., DPP-IV inhibitory potentials of flavonol glycosides isolated from the seeds of *Lens culinaris*: *In vitro* and molecular docking analyses, *Molecules*, 2018, **23**(8), 1998.

40 Fan J, Johnson M H, Lila M A, Yousef G and Mejia E G, Berry and citrus phenolic compounds inhibit dipeptidyl peptidase IV: Implications in diabetes management, *Evid Based Complement Alternat Med*, 2013, **2013**, 1–13.

41 Bower A M, Hernandez L M R, Berhow M A and Mejia E G, Bioactive compounds from culinary herbs inhibit a molecular target for type 2 diabetes management, Dipeptidyl peptidase IV, *J Agric Food Chem*, 2014, **62**(26), 6147-6158.

42 Casedas G, Les F, Burgos E G, Gómez-Serranillos M P, Smith C, *et al*., Cyanidin-3-O-glucoside inhibits different enzymes involved in central nervous system pathologies and type-2 diabetes, *S Afr J Bot*, 2018, **120**, 1-6.

43 Wang Z, Yang L, Fan H, Wu P, Zhang F, *et al*., Screening of a natural compound library identifies emodin, a natural compound from *Rheum palmatum* Linn that inhibits DPP4, *Peer J*, 2017, **5**, 1-14.

44 Gupta A, Jacobson G A, Burgess J R, Jelinek H F, Nichols D S, *et al*., Citrus bioflavonoids dipeptidyl peptidase-4 inhibition compared with gliptin antidiabetic medications. *Biochem Biophys Res Commun*, 2018, **503**(1), 1-5.

45 Zhang L, Zhang S T, Yin Y C, Xing S, Li W N, *et al*., Hypoglycemic effect and mechanism of isoquercetin as an inhibitor of dipeptidyl peptidase-4 in type 2 diabetic mice, *R Soc Chem*, 2018, **8**, 14967–14974.

46 Parmar H S, Jain P, Chauhan D S, Bhinchar M K, Munjal V, *et al*., DPP-IV inhibitory potential of naringin: an in silico, *in vitro* and *in vivo* study, *Diabetes Res Clin Pract*, 2012, **97**(1), 105–111.

47 Ayachi H, Merad M and Ghalem S, Study of interaction between dipeptidyl peptidase-4 and products extracted from the stevia plant by molecular modeling, *Int J Pharm Sci Rev Res*, 2013, **23**(1), 87–90.

48 Lin Y S, Chen C R, Wu W H, Wen C L, Chang C I, *et al*., Anti-α-glucosidase and anti-dipeptidyl peptidase-IV activities of extracts and purified compounds from *Vitis thunbergii* var. *taiwaniana*, *J Agric Food Chem*, 2015, **63**(28), 6393−6401.