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REVIEW ARTICLE

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Natural drug leads as novel DPP-IV inhibitors targeting the management of type 2 diabetes mellitus

Keddagoda Gamage Piyumi Wasana[a], Anoja Priyadarshani Attanayake[a], Kamani Ayoma Perera Wijewardana Jayatilaka[a] & Thilak Priyantha Weerarathna[b]

[a] Department of Biochemistry, Faculty of Medicine, University of Ruhuna, Galle, Sri Lanka
[b] Department of Medicine, Faculty of Medicine, University of Ruhuna, Galle, Sri Lanka

Abstract

Aim: Number of type 2 diabetes mellitus (T2DM) patients using incretin based therapeutics has significantly increased in past few years. The development of novel incretin based therapeutics from natural sources has become an interesting area of drug discovery. The current review emphasizes the plants having DPP-IV inhibitory activity that can be used in the development of novel anti-diabetic agents.

Methods: The relevant literature was collected form data sources as PubMed, Web of Science and Google Scholar. The references of articles were also examined to obtain further information.

Results: To date, number of plants were documented for its' antidiabetic potential through DPP-IV inhibitory activity either *in vivo* or *in vitro*. The compounds which exert potent DPP-IV inhibitory action have been identified and their structures have been deduced in some research findings. The DPP-IV inhibitory activity has been compared with positive controls in most of the studies.

Conclusion: The present review reports on natural DPP-IV inhibitors through the assessment of plant profile used in the management of DM and highlights a new pathway for the researches to develop novel molecules from herbal sources with DPP-IV inhibitory activity.

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· **Contact**: Piyumi Wasana piyumi089@gmail.com, anoja715@yahoo.com, ayomawijewardena@yahoo.com, thilak.priyantha@yahoo.com Department of Biochemistry, Faculty of Medicine, University of Ruhuna, Galle 80000, Sri Lanka.Tel: +94 71 4428121

Introduction

Incretin effect

Type 2 diabetes mellitus (T2DM) is a long standing disease arise from insulin resistance and/or progressively diminishing *β*-cell functions. Major comorbidities of T2DM include obesity, dyslipidemia, hypertension and high cardiovascular disease burden which lead to mortality associated with diabetes [1]. Management of T2DM has become an increasingly important task because of the high prevalence of T2DM patients, as reported by the WHO [2]. Multiple pharmacotherapies have been developed to date, and of these available treatments, incretin based therapies have been developed relatively recently which target the incretin system.

Glucose taken from meals induces the secretion of insulin in large scale compared to the administration of glucose intravenously. This phenomenon is referred as the 'incretin effect' [3], which is impaired in T2DM patients [4]. The incretin hormones are biological entities which endow signals through absorption and digestion of the meal [3]. The first identified incretin hormone, gastric inhibitory polypeptide (GIP), is a 42-amino acid hormone secreted by K cells in the mucosa of the duodenum and jejunum in response to the ingestion of lipids and carbohydrates [5]. Additionally, GIP reduces gastric acid secretion. Insulinotropic effect of GIP is achieved by binding to its specific receptor called gastric inhibitory polypeptide receptor with an aim of increasing intracellular cyclic adenosine monophosphate (cAMP) and Ca^{2+} levels in β cells [6]. The glucagon-like peptide-1 (GLP-1) was identified as the second incretin. GLP-1 is a post-translational cleavage product of the proglucagon gene [7] and it is also secreted in response to an intake of meal [8]. Insulinotropic effect is achieved by GLP-1 through the binding to its specific receptor with an aim of increasing intracellular cAMP and Ca^{2+} concentration in β cells. However, the incretin potential could be increased therapeutically by supraphysiological dosages of many agents including glucagon-like peptide-1 (GLP-1) or associated components which are stimulating the GLP-1 receptor (GLP-1R) [9].

Table 01 : A list of medicinal plants with DPP-IV inhibitory activity

Plant	Family	Part used in the investigation	Extraction	Reference
Allophylus cominia L.	Sapindaceae	Leaves	Aqueous	[97]
Aloe vera L. Burm.f.	Xanthorrhoeaceae	Leaves	Ethanol	[98]
Calocybe indica	Tricholomataceae	Spawn	Ethanol	[99]
Ficus religiosa L.	Moraceae	Leaves	Ethanol	[100]
Gymnema sylvestre R. Br.	Apocynaceae	Leaves	Hydroalcoholic	[32]
Lagerstroemia loudonii Teijsm. & Binn	Lythraceae	Leaves	Ethanol	[100]
Punica granatum L.	Lythraceae	Rind	Ethanol	[100]
Senna nigricans	Cassia	Whole plant	Methanol	[101]
Tinospora crispa L. Miers ex Hoff.f	Menispermaceae	Stem	Ethanol	[100]
Trigonella foenum-graecum L.	Fabaceae	Seed	Ethanol	[100]

Dipeptidyl peptidase-IV enzyme (DPP-IV)

Dipeptidyl peptidase-IV (DPP-IV) enzyme inactivates several oligopeptides as a serine exopeptidase. The DPP-IV enzyme is located on 2q23 chromosome and acts as a type II transmembrane protein [10]. DPP-IV is widely articulated on endothelial and epithelial cells throughout the vascular bed and in kidneys, intestines, exocrine pancreas and gastrointestinal tract [11]. The DPP-IV enzyme inactivates the incretins further hampering insulinotropic activity [12]. DPP-IV inhibitors blocks DPP-IV enzyme activity extending half-life of incretins. Therefore, inhibition of DPP-IV is one of the modest pharmaceutical targets in the management of T2DM.

Role of incretin based therapies

Incretin therapies have arisen as a positive answer for the inactivation of incretins by DPP-IV enzyme. DPP-IV inhibitors (gliptins) and incretin mimetics are two classes of incretin therapies. Although incretin mimetics and gliptins are based on anti-diabetic properties of incretins, their approaches for the management of T2DM differs from each other. Both gliptins and incretin mimetics therapies control plasma glucose concentration, postprandial glucose concentration and glycated hemoglobin (HbA_{1C}) [13]. In addition to the glucose lowering effect, incretin based therapies exert anti-atherogenic effects with the potential to stabilize atherosclerotic plaques and treat arterial inflammation [14].

Incretin mimetic drugs are a relatively new group of drugs used in the treatment of T2DM and currently recommended by American Diabetes Association in dual therapy with the base line of treatment of T2DM, metformin [15]. Exogenously administered incretin mimetics raise the concentration of GLP-1 in body. Several studies have reported that the incretin mimetics with longer half-life raise the concentration of GLP-1 six to ten fold compared to the postprandial state [16, 17]. The commonly used Food and Drug Administration (FDA) approved incretin mimetics in the management of T2DM are exenatide, liraglutide, lixisenatide, dulaglutide and albiglutide [18]. All these drugs are GLP-1 analogs. Among them, exenatide and liraglutide are oldest incretin mimetics [19]. Exenatide is synthesized from the saliva of *Heloderma suspectum* [20] and it is injected twice a day in T2DM patients who are poor controlled on oral anti-diabetic agents [21]. Amino acid sequence of exenatide is coincides with GLP-1 and therefore, exenatide could cooperate with GLP-1 receptors by mimicking the anti-diabetic potential of GLP-1. Liraglutide is synthesized by the attachment of a C13 fatty acid to an altered GLP-1 molecule with 97 % amino acid homology to native GLP-1and it has been approved to take once daily by the T2DM patients. Furthermore, incretin mimetics impede gastric emptying and also promote body weight losses [22, 20].

DPP-IV inhibitors/gliptins are widely used in clinical practice for the management of T2DM through the inhibition of DPP-IV enzyme activity [23]. Several gliptins are marketed for the management of T2DM such as sitagliptin, vildagliptin, saxagliptin, alogliptin and linagliptin [24]. Sitagliptin (Merck) is the first-in-class DPP-IV inhibitor [25] and is associated with few additional benefits such as reduced risk of hypoglycemia, weight neutral and the potential for regeneration/differentiation of β-cells [26, 27]. The second approved DPP-IV inhibitor is vildagliptin while the third approved one is saxagliptin. Other DPP-IV inhibitors are still under supervisory review. Regular administration of gliptins maintain ≥ 70–90% of DPP-IV inhibition throughout the period of 24 hours [28].

Side effects of incretin drugs

Even though both incretin based therapies of gliptins and incretin mimetics have beneficial effects compared to the currently available other anti-diabetic drugs, several investigators have reported that administration of incretin drugs may cause some adverse events such as pancreatic cancer, pancreatitis, angioedema etc. attach with incretin based therapies [8, 13, 29, 30]. Even though the most serious side effect associated with the use of incretin drug was the development of pancreatic cancer, a meta-analysis comprising 33 studies and 79,971 patients concluded that treatment with incretin drugs is not associated with an increased risk of pancreatic cancer in patients with T2DM [31]. Additionally, incretin based therapies are expensive compared to other anti-diabetic drugs [32]. Moreover currently available anti-diabetic drugs including incretin based therapies are failed to prevent significant cardiovascular morbidity and mortality in diabetic patients. Considering all these facts, the researchers are moving to explore novel therapies that would control glycemia with minimum risk of occurrence of adverse effects and also beneficial effects on lipid profile, hypertension and cardiovascular mortality and morbidity from plant origin.

Medicinal plants as sources of anti-diabetic agents

Natural flora has afforded a large array of therapeutic agents and it has been used from the time immemorial for the management of several pathological conditions including DM by traditional practitioners in the world [33]. Indeed medicinal plants perform an imperative part in the invention of novel pharmaceutical agents. The well-known existing anti-diabetic drug, metformin has derived from plant origin of *Galega officinalis* [34, 35]. This finding was the landmark in the field of anti-diabetic drug discovery from natural plants. Most of the time, the isolated anti-diabetic drug leads from plant extracts belong to bioactive secondary metabolites as alkaloids, glycosides, galactomannan, polysaccharides, peptidoglycans, hypoglycans, guanidine, steroids, carbohydrates, glycopeptides, terpenoids, flavonoids, phenolics, amino acids and several inorganic ions [36]. During the past few years the researchers screened plant extracts for

DPP-IV inhibitory activity and they were able to isolate DPP-IV active compounds from the plant extracts as a new therapeutic approach over the synthetic drug for the management of DM.

The present review is focused for the plants which exert the DPP-IV inhibitory activity that can be used in the field of novel drug discovery for the management of DM. The literature related to plants having DPP-IV inhibitory activity were examined from the data bases as PubMed, Web of Science and Google Scholar.

Natural DPP-IV inhibitors in recent literature

Aronia arbutifolia (L.) Pers.

Aronia arbutifolia (family; Rosaceae) is a genus of deciduous shrubs. It is also known as red chokeberry. *Aronia melanocarpa* (Michx.) Elliott and *Aronia prunifolia* (Marshall) Rehd are other two synonyms of Rosaceae family. *Aronia* berries are indigenous to Eastern North America and usually grow in wet woods and swamps. *Aronia* berries exert lipid lowering, cardioprotective, antihypertensive, gastroprotective, anti-inflammatory, anti-oxidant and anti-diabetic activities [37-42]. Several scientific investigators have reported about the positive effects of *Aronia* juice on plasma glucose concentration in patients with T2DM [43-45]. *In vitro* study on *Aronia* juice revealed DPP-IV inhibitory effects as the anti-diabetic mechanism [46]. Then DPP-IV inhibitory potential was measured as 27% using 50 mM Tris HCl buffer (pH 9.0) Gly-Pro-7-amido-4-methylcoumarin hydrobromide (Gly Pro-AMC) as the substrate. Further, *Aronia* juice was fractionated by column chromatography and eluted fraction was subjected to determine DPP-IV inhibitory activity. A 28% reduction was observed and the fraction was also subjected to reverse phase chromatography. The four fractions were collected and the fraction (in which the cyanidin 3, 5-diglucoside isolated) which was collected at second showed the highest DPP-IV inhibitory potential of 81%. The study also reported that cyanidin, cyaniding-3-glucoside, malvidin, luteolin, apigenin, quercetin, kaempferol, hesperetin, naringenin, eriocitrin, genistein, resveratrol, gallic acid and caffeic acid are responsible for DPP- IV inhibitory activity in *Aronia* juice. DPP-IV inhibitory potential of *Aronia* juice was not compared with a positive control in the study.

Mangifera indica L.

Mangifera indica (family; Anacardiaceae) is available in all tropical countries and it is commonly known as mango. *M. indica* contains vitamin A and C, β-carotene, xanthophylls, humulene, elemene, indicine, terpinine, tannins, flavonoids, linalool, nerol, gallic acid, ethyl gallate, methyl gallate and mangiferin [47]. Every part of the tree exert potent bioactivities such as anti-oxidant, anti-inflammatory, anti-tumor and immunomodulatory [48-51]. The anti-diabetic effect of *M. indica* was reported in several studies [52, 53].

A study carried out by Yogisha and Raveesha [47], underlined that the methanolic leaf extract of *M. indica* could be able to inhibit the DPP-IV enzyme thereby enhancing half-life of GLP-1 *in vitro*. In that study, 50% of inhibition was observed at the extract concentration of 160 µg/mL. Furthermore, the investigation showed that the methanolic extract of *M. indica* leaves inhibit porcine kidney DPP-IV inhibitory activity with an IC_{50} value of 182.7 µg/mL. Diprotin-A was used as reference standard.

Eucalyptus globules Labill.

Eucalyptus globules (family; Myrtaceae) is commonly called as Tasmanian blue gum and it is native to Tasmania and South-East Australia. *E. globules* is a well popular plant with anti-bacterial, anti-fungal, analgesic, anti-inflammatory and anti-diabetic activities in folk medicine [54-56]. Methanol extraction of *E. globules* leaves exerted a potent DPP-IV inhibitory activity. Therefore, the extract was screened for DPP-IV active compounds [57]. The bioactive fraction was subjected to normal phase chromatography and reverse phase High Performance Liquid Chromatography (HPLC), yielded macrocarpals A, B and C as the DPP-IV inhibitors. After that, those compounds were subjected to determine DPP-IV inhibitory activity separately. A 30% inhibition was observed at 500 µM by macrocarpals A and B. Macrocarpal C showed an inhibition of 90% at 50 µM. Although the chemical structures of macrocarpals A, B and C had relative similarities, binding pattern of these molecules to DPP-IV enzyme and inhibition curves showed significant differences. Based on the results of the study, Kato et al [57] suggested that more than one molecule of macrocarpal C aggregated for the DPP-IV inhibitory activity. No positive control was used in the study.

Commiphora mukul (Stocks) Hook.

Commiphora mukul (family; Burseraceae) is available in Northern Africa, central Asia and Northern India. *C. mukul* is commonly known as Indian bdellium tree. It has been used to manage various conditions such as inflammation, hyperlipidemia, hyperglycemia and diabetic cardiomyopathy [58-60]. *C. mukul* exerts anti-diabetic activity via DPP-IV inhibition [32]. The hydroalcoholic extract of *C.*

mukul gum resin was screened for DPP-IV inhibitory potential and compared with the synthetic DPP-IV inhibitors of sitagliptin and vildagliptin (positive controls) using *in vitro* assays. DPP-IV inhibitory activities in vildagliptin, sitagliptin and the hydroalcoholic extract of *C. mukul* were 90%, 85% and 93% respectively. The results of the investigation revealed that the anti-diabetic effect of *C. mukul* is superior to sitagliptin and vildagliptin. Therefore, this anti-diabetic potential could be successfully blended with scientific background for the aim of synthesizing anti-diabetic pharmaceuticals.

Terminalia arjuna (Roxb.) Wight & Arn.

Terminalia arjuna (family; Combretaceae) is commonly known as Arjuna and grown in river banks or near dry river beds in Bangladesh and in India. The plant exerts cardiotonic, anti-diabetic, anti-dysenteric, anti-pyretic and astringent properties. Results of the scientific experiments clearly demonstrated that *T. arjuna* exerts potent anti-diabetic activity [61, 62]. Besides the hypoglycemic effect of *T. arjuna*, positive effects were also showed against dyslipidemia [63].

Another study based on hydroalcoholic extract of *T. arjuna* bark clearly demonstrated that *T. arjuna* exerts potent DPP-IV inhibitory activity [32]. It was evident through an *in vitro* assessment of DPP-IV inhibitory potential of 83% and this value was compared with the DPP-IV inhibitory potential of sitagliptin and vildagliptin as 85% and 90% respectively.

Emblica officinalis Gaertn.

Emblica officinalis (family; Euphorbiaceae) is commonly known as Amla and it is available in tropical South Eastern Asia, central and Southern India. Dried and fresh fruits of the plant have been used in traditional Indian medicine. All parts of the plant exert valuable medicinal properties. Various researchers revealed that *E. officinalis* supplement is effective in reducing the fasting and postprandial blood glucose concentrations and HbA_{1C} levels in patients with T2DM [64, 65]. The *in vitro* study based on a hydroalcoholic extract of *E. officinalis* fresh fruit clearly demonstrated that *E. officinalis* exerts potent DPP-IV inhibitory activity of 86% [32]. This value was compared with the DPP-IV inhibitory activity of sitagliptin (85%) and vildagliptin (90%).

Berberis aristata DC.

Berberis aristata (family; Berberidaceae) is a woody plant native to India and Nepal. *B. aristata* is commonly known as Indian barberry. The bark of *B. aristata* consists of an alkaloid berberine that has an anti-oxidant, anti-microbial, anti-tumor, anti-inflammatory and anti-diabetic potential [66, 67]. Berberine has also shown in the reduction of fasting blood glucose, HbA_{1C} and triglycerides in patients with T2DM [68]. The ethanol extract of the root of *B. aristata* reduces serum glucose concentration along with the increment in high-density lipoprotein (HDL) cholesterol level in alloxan induced diabetic rats [69].

In vitro study on methanolic extract of *B. aristata* bark showed a DPP-IV enzyme inhibition with an IC_{50} value of 14.46 µg/mL [70]. This value was compared with the IC_{50} value of diprotin-A (1.5µg/ml) as the positive control [70].

Rosa gallica L.

Rosa gallica (family; Rose) is native to Europe, Turkey and Caucasus and it is commonly named as Gallic rose or French rose. The water extract of *R. gallica* flower buds exerts anti-diabetic potential via DPP-IV inhibitory activity [71]. After the dissolving of Rose bud extract powder in water, it was partitioned between ethyl acetate and then 1-butanol. The ethyl acetate soluble portion was exposed to silica gel column chromatography and the active fraction was then fractionated using reverse phase column chromatography. Thereafter, active fractions were used to isolate DPP-IV inhibitor compounds. As the results, seven ellagitannins were identified. Among them, the compounds of rugosin A and B showed the highest inhibitory activities of 60% and about 70%, respectively at 100 µM. IC_{50} values of rugosin A and rugosin B were 28.5µM and 25.8 µM, respectively. No positive control was used in the study.

Antidesma madagascariense Lam.

Antidesma madagascariense (family; Euphorbiaceae) is called as Bois bigaignon bâtard indigenous and native to Mascarene region and Madagascar. The population live in Mascarene Islands use this plant for T2DM, skin infections, rheumatic and body aches [72-74]. Preliminary phytochemical screening of the leaves of *A. madagascariense* indicated the presence of phenols, tannins, alkaloids, flavonoids, cyanogenetic heterosides, leucoanthocyanins, sterols and saponins [72].

A. madagascariense leaves showed an anti-diabetic potential via DPP-IV inhibitory activity [75]. *In vitro* studies of using DPP-IV inhibition assays on ethyl acetate extract of *A. madagascariense* leaves showed a DPP-IV inhibitory potential with an IC_{50} value of 79.2±2.8 µg/mL. Furthermore, preparative-scale HPLC technique was developed to isolate DPP-IV

inhibitory active compounds. As a result, amentoflavone was isolated and it indicated the DPP-IV inhibitory potential with an IC_{50} value of 3.9μM. This value was compared with IC_{50} values with diprotin A (4.2μM) and sitagliptin (0.02μM) as positive controls.

Urena lobata L.

Urena lobata (family; Malvaceae) is an annual, variable, erect and ascendant undershrub. It is commonly known as caesarweed or congo jute and widely distributed as a weed in the tropics of both hemispheres including Brazil and Southeast Asia. *U. lobata* is widely used in traditional medicine for the treatment of diarrhea, colic, skin diseases, boils, cough and T2DM [76, 77]. Antibacterial, antidiarrheal and anti-diabetic activities of *U. lobata* have been scientifically proven by several investigators [77, 78-81].

The ethanolic extract of *U. lobata* leaves exerted DPP-IV inhibitory activity [82]. It was demonstrated through an *in vitro* study using gly-pro-p-nitroanilide as the substrate for DPP-IV enzyme. The results of the study showed that the ethanolic extract of *U. lobata* leaves exerts DPP-IV inhibitory activity with an IC_{50} value of 1654.64 μg/mL. This value was compared with IC_{50} value vildagliptin (57.44 μg/mL) as the positive control. of Furthermore, the compounds present in ethanolic extract of *U. lobata* leaves such as mangiferin, stigmasterol and β-sitosterol were identified as DPP-IV inhibitor compounds using liquid chromatography-mass spectrometry.

Castanospermu austral A.Cunn & C.Fraser ex Hook

Castanospermu austral (family; Fabaceae) is a flowering plant native to Australia. The plant can also be seen in India, Pakistan and Sri Lanka. It is commonly known as black bean or moreton bay. The secondary metabolites as alkaloids, saponins and flavonoids present in *C. austral* exert several biological activities such as analgesic and anti-inflammatory properties to the various extents and these components are considered as promising compounds for clinical exploitation [83]. *C. austral* is used in traditional medicine in the treatment of post prandial hyperglycemia in patients with T2DM.

The ethanol extract of *C. austral* seeds exerts potent DPP-IV inhibitory activity [84]. It was assessed through DPP-IV inhibitory *in vitro* assay. The results reported that DPP-IV inhibitory activity with an IC_{50} value of 13.96 μg/mL. This value was compared with an IC_{50} value of Diprotin A (1.543 μg/ml) as the reference standard. Furthermore, the results of molecular docking studies showed that 7-Deoxy-6-epi-castanospermine is an alkaloid present in ethanol extract of *C. austral* seeds which acts as a DPP-IV inhibitor.

Pueraria tuberose (Willd.) DC.

Pueraria tuberose (family; Fabaceae) is a climber with woody tuberculated stem. It is commonly known as kudzu, Indian kudzu or Nepalese kudzu. *P. tuberose* is used in various formulations as restorative tonic, antiaging, spermatogenic and immune booster in traditional medicine [85]. Several scientific investigations have demonstrated that *P. tuberose* exerts potent anti-inflammatory, anti-oxidant and anti-diabetic properties [86-88].

The hot water extract of roots of *P. tuberose* on normoglycemic rats showed that roots of *P. tuberose* exert DPP-IV inhibitory activity [89]. The results showed a DPP-IV inhibitory activity with an IC_{50} value of 17.4 mg/mL. This value was compared with an IC_{50} value of vildagliptin (5 mg/mL) as the positive control. Furthermore, *in vivo* study was carried out on normoglycemic rats by the measurement of increased plasma GLP-1 concentration via GLP-1 enzyme immunoassay kit and DPP-IV activity after a glucose load. The results of the study reported inhibition of DPP-IV activity (35%), an increment of GLP-1 concentration (80%) and decrement in plasma glucose concentration in rats. Another scientific investigation demonstrated that puerarone and robinin are the potential phytochemicals responsible for DPP-IV inhibitory activity of roots of *P. tuberose* [90].

According to these facts several studies have been conducted to evaluate plant based DPP-IV inhibitory activity. In addition to the above mentioned plants, initial screening for DPP-IV inhibition was also carried out for a number of medicinal plants as shown in Table 1.

Discussion

The plant based drug leads possess more properties that could be evolutionary optimized for serving different biological functions. The structural differences between the plant based drug leads and the synthetic drugs found that major differences originate from the introduction of properties during making synthetic drugs as more efficient. For example, the most plant based drug leads have built in chirality whereas most synthetic compounds are achiral [91]. Chiral separation is challenging and expensive. Therefore creating the new analogues with few number of chiral centers is a promising task. Also synthetic molecules in the drugs have low molecular weight, higher number of freely rotatable bonds, higher chain lengths, a lower number of rings,

less oxygen but more nitrogen, sulfur, and halogen atoms with compared to plant based drug leads. Other prominent differences are the complexity of ring systems and the degree of saturation [92, 93]. These structural differences mainly including lower number of chiral centers, low molecular weight and high flexibility make synthetic drugs as weaker and less specific for the target activity [92]. On the other hand, natural products often possess selective biological actions due to binding affinities for relevant specific proteins for their biological functions, superior chemical diversity and complexity developed during biosynthesis [93, 94]. Moreover, the ethanobotnical information regarding the traditional use of medicinally valuable plants has been well documented and it provides more hints on compounds which are therapeutically effective in humans. Therefore, the present review is mainly aimed to highlight DPP-IV inhibitors from the plant origin which are useful in the development of novel anti-diabetic drug discovery with more effective and "druglike" over the synthetic drugs.

However, high prevalence of synthetic drugs over natural drugs obtained from the plant origin may reside because of the several limitations associated with herbal drugs. Identification of the bioactive target compound/s from the plant extract is one of the most challenging steps. Plant materials often varies on quality and composition and this could hamper the assessment of its' therapeutic claims. The chemical composition is not only dependent on species identity and harvest time, but also on soil composition, altitude, actual climate, processing and storage conditions. Moreover during the extraction, isolation and transformation, the degradation of target compounds can occur [95, 96]. Also, the high complexity of plant extracts is a huge problem during the maintenance. Therefore, it is mandatory to carry out sophisticated sample preparation method and fractionation of the crude extract prior to conduct several testing.

Future perspectives

Recently, DPP-IV inhibitors have become a novel therapy for the management of DM. Only few synthetically produced DPP-IV inhibitors are commercially available. Therefore exploration of novel DPP-IV inhibitors especially from plant origin with less adverse effects, low cost and more therapeutic efficacy is important. The present review promotes the researchers to investigate DPP-IV inhibitory activity at the cellular level of the plant, isolate and to elucidate structures of DPP-IV inhibitory compounds from medicinal plant extracts by using modern medicinal chemistry approaches. The above mention plants have not been clinically investigated yet for the assessment or confirm their DPP-IV inhibitory activity. Actually the discovery of novel DPP-IV inhibitors from plant origin with proven clinical efficacy may offer a new pathway to pharmaceutical companies for the extraction of DPP-IV inhibitors from plant origin or synthetically produce that compounds with some modifications to achieve an excellent therapeutic approach for the management of DM.

Conclusions

The present review reports the information on incretin effect, DPP-IV enzyme, role of incretin based therapies, side effects of the incretin drugs, medicinal plants as sources of anti-diabetic agents and natural DPP-IV inhibitors in recent literature. DPP-IV inhibitory activity of the reported plants was comparable with the positive controls used in the experiments. Numerous therapeutic approaches have to be implemented to isolate novel DPP IV inhibitors from natural medicinal plant extracts and to develop new anti-diabetic agents with proven clinical efficacy and safety.

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Nil

Conflicts of interests

None

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