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REVIEW ARTICLE

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

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ABSTRACT

Background/Aim: The number of type 2 diabetes mellitus (T2DM) patients using incretin-based therapies has significantly increased in the past few years. The development of novel incretin-based therapies from natural sources has become an interesting area of drug discovery. This review emphasizes the plants having dipeptidyl peptidase-IV (DPP-IV) inhibitory activity that can be used in the development of novel antidiabetic agents.

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

Results: To date, a 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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Introduction

Incretin effect

Type 2 diabetes mellitus (T2DM) is a long-standing disease arising 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, recently, incretin-based therapies have been developed relatively, which target the incretin system.

Glucose taken from meals induces the secretion of insulin on 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]. In addition, GIP reduces gastric acid secretion. The insulinotropic effect of GIP is achieved by binding to its specific receptor called GIP receptor with an aim

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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]. The insulinotropic effect is achieved by GLP-1 through binding to its specific receptor with the aim of increasing intracellular cAMP and Ca^{2+} concentration in β-cells. However, the incretin potential could be increased therapeutically by supraphysiological doses of many agents including GLP-1 or associated components which are stimulating the GLP-1 receptor (GLP-1R) [9].

Dipeptidyl peptidase-IV (DPP-IV) enzyme

DPP-IV enzyme inactivates several oligopeptides as a serine exopeptidase. The DPP-IV enzyme is located on the 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 the kidneys, intestines, exocrine pancreas, and gastrointestinal tract [11]. The DPP-IV enzyme inactivates the incretins and further hampers the insulinotropic activity [12]. DPP-IV inhibitors block DPP-IV enzyme activity extending the 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 antidiabetic properties of incretins, their approaches for the management of T2DM differ from each other. Both gliptin and incretin mimetic 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 antiatherogenic 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 the American Diabetes Association in dual therapy with the baseline treatment of T2DM, metformin [15]. Exogenously administered incretin mimetics raise the concentration of GLP-1 in the body. Several studies have reported that the incretin mimetics with longer half-life raise the concentration of GLP-1 from 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 the 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 antidiabetic agents [21]. Amino acid sequence of exenatide coincides with GLP-1, and therefore, exenatide could cooperate with GLP-1 receptors by mimicking the antidiabetic potential of GLP-1. Liraglutide is synthesized by the attachment of C13 fatty acid to an altered GLP-1 molecule with 97% amino acid homology to native GLP-1, and it has been approved to take once daily by the T2DM patients. Furthermore, incretin mimetics impede gastric emptying and also promote body weight losses [20,22].

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, whereas the third approved one is saxagliptin. Other DPP-IV inhibitors are still under supervisory review. Regular administration of gliptins maintains ≥70%–90% of DPP-IV inhibition throughout the period of 24 hours [28].

Side effects of incretin drugs

Even though both the incretin-based therapies of gliptins and incretin mimetics have beneficial effects compared to the currently available other antidiabetic drugs, several investigators have reported that the administration of incretin drugs may cause some adverse events such as pancreatic cancer, pancreatitis, and angioedema 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]. In addition, incretin-based therapies are expensive compared to other antidiabetic drugs [32]. Moreover, currently available antidiabetic 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 the 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 antidiabetic 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 antidiabetic drug, metformin, has derived from a plant origin of *Galega officinalis* (family; Fabaceae) [34,35]. This finding was the landmark in the field of antidiabetic drug discovery from natural plants. In most of the times, the isolated antidiabetic drug leads from plant extracts belong to bioactive secondary metabolites such 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 the 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 on the plants which exert the DPP-IV inhibitory activity and 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 was examined from databases such as PubMed, Web of Science, and Google Scholar.

Natural DPP-IV inhibitors in recent literature

Aronia arbutifolia (L.) Pers.

A. arbutifolia (family: Rosaceae) is a genus of deciduous shrubs. It is also known as red chokeberry. *Aronia melanocarpa* (Michx.) Elliot and *Aronia prunifolia* (Marshall) Rehd. are other two synonyms of the family Rosaceae. *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, antioxidant, and antidiabetic 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]. An *in vitro* study on *Aronia* juice revealed DPP-IV inhibitory effects as the antidiabetic mechanism [46]. Then, DPP-IV inhibitory potential was measured as 27% using 50 mM Tris-HCl buffer (pH 9.0) and Gly-Pro-7-amido-4-methylcoumarin hydrobromide as the substrate. Further, *Aronia* juice was fractionated by column chromatography and eluted fraction was subjected to determine the 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 positive control in the study.

Mangifera indica L.

M. indica (family: Anacardiaceae) is available in all tropical countries and it is commonly known as mango. *M. indica* contains Vitamins 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 exerts potent bioactivities such as antioxidant, anti-inflammatory, antitumor, and immunomodulatory [48–51]. The antidiabetic 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 and to enhance the 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 inhibits porcine kidney DPP-IV inhibitory activity with an IC_{50} value of 182.7 μg/ml. Diprotin A was used as a reference standard.

Eucalyptus globulus Labill.

E. globulus (family: Myrtaceae) is commonly called as Tasmanian blue gum, and it is native to Tasmania and Southeast Australia. *E. globulus* is a well popular plant with antibacterial, antifungal, analgesic, anti-inflammatory, and antidiabetic activities in folk medicine [54–56]. The methanolic extract of *E. globulus* 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), yielding 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.

C. 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 antidiabetic activity through 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 hydroalcoholic extract of *C. mukul* were 90%, 85%, and 93%, respectively. The results of the investigation revealed that the antidiabetic effect of *C. mukul* is superior to sitagliptin and vildagliptin. Therefore, this antidiabetic potential could be successfully blended with scientific background with the aim of synthesizing antidiabetic pharmaceuticals.

Terminalia arjuna (Roxb.) Wight and Arn.

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

Another study based on the hydroalcoholic extract of *T. arjuna* bark clearly demonstrated that *T. arjuna* exerts a 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.

E. officinalis (family: Euphorbiaceae) is commonly known as amla, and it is available in tropical Southeastern Asia and 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 a 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.

B. 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 antioxidant, antimicrobial, antitumor, anti-inflammatory, and antidiabetic potential [66,67]. Berberine has also shown in the reduction of fasting blood glucose, HbA_{1C}, and triglycerides in patients with T2DM [68]. The ethanolic root extract of *B. aristata* reduces serum glucose concentration along with the increment in high-density lipoprotein cholesterol level in alloxan-induced diabetic rats [69].

An in vitro study on the 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 (1.5 μg/ml) as the positive control [70].

Rosa gallica L.

R. gallica (family: Rosaceae) 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 antidiabetic potential through DPP-IV inhibitory activity [71]. After dissolving of rosebud extract powder in water, it was partitioned between ethyl acetate and 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 B were 28.5 and 25.8 μM, respectively. No positive control was used in the study.

Antidesma madagascariense Lam.

A. madagascariense (family: Euphorbiaceae) is called as Bois bigaignon bâtard, and it is indigenous and native to Mascarene region and Madagascar. The population who 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, cyanogenic heterosides, leucoanthocyanins, sterols, and saponins [72].

A. madagascariense leaves showed an antidiabetic potential through DPP-IV inhibitory activity [75]. The *in vitro* studies of using DPP-IV inhibition assays on the 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 3.9 μM. This value was compared with IC_{50} values of diprotin A (4.2 μM) and sitagliptin (0.02 μM) as positive controls.

Urena lobata L.

U. lobata (family: Malvaceae) is an annual, variable, erect, and ascendant undershrub. It is commonly known as Caesar weed or Congo jute and widely distributed as a weed in the tropics of both the 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 antidiabetic 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 an IC_{50} value of vildagliptin (57.44 μg/ml) as the positive control. Furthermore, the compounds present in the 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.

Castanospermum australe A. Cunn. and C. Fraser. ex Hook.

C. australe (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 such as alkaloids, saponins, and flavonoids present in *C. australe* 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. australe* is used in traditional medicine in the treatment of postprandial hyperglycemia in patients with T2DM.

The ethanolic extract of *C. australe* seeds exerts a potent DPP-IV inhibitory activity [84]. It was assessed through DPP-IV inhibitory *in vitro* assay. The results reported a 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 the ethanolic extract of *C. australe* seeds which acts as a DPP-IV inhibitor.

Pueraria tuberosa (Willd.) DC.

P. tuberosa (family: Fabaceae) is a climber with woody tuberculated stem. It is commonly known as kudzu, Indian kudzu or Nepalese kudzu. *P. tuberosa* is used in various formulations such as restorative tonic, antiaging, spermatogenic, and immune

booster in traditional medicine [85]. Several scientific investigations have demonstrated that *P. tuberosa* exerts potent anti-inflammatory, antioxidant, and antidiabetic properties [86–88].

The hot water extract of *P. tuberosa* roots on normoglycemic rats showed that the roots of *P. tuberosa* 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, an *in vivo* study was carried out on normoglycemic rats by the measurement of increased plasma GLP-1 concentration through GLP-1 enzyme immunoassay kit and DPP-IV activity after a glucose load. The results of the study reported the inhibition of DPP-IV activity (35%), an increment of GLP-1 concentration (80%), and a 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 the roots of *P. tuberosa* [90].

According to these facts, several studies have been conducted to evaluate plant-based DPP-IV inhibitory activity. In addition to the abovementioned plants, an 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 while 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 analogs with a few number of chiral centers is a promising task. Furthermore, synthetic molecules in the drugs have low molecular weight, higher number of freely rotatable bonds, higher chain lengths, a lower number of rings, and less oxygen but more nitrogen, sulfur, and halogen atoms 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 a 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 ethanobotanical 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 antidiabetic drug discovery with more effective and "druglike" over the synthetic drugs.

However, a 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 vary on quality and composition, and this could hamper the assessment of its' therapeutic

Table 1. 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	Hydroalcohol	[32]
Lagerstroemia loudonii Teijsm. and 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]

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 extraction, isolation, and transformation, the degradation of target compounds can occur [95,96]. Furthermore, the high complexity of plant extracts is a huge problem during maintenance. Therefore, it is mandatory to carry out a sophisticated sample preparation method and fractionation of the crude extract before conducting several tests.

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 and to isolate and elucidate the structures of DPP-IV inhibitory compounds from medicinal plant extracts using modern medicinal chemistry approaches. Still, the abovementioned plants have not been clinically investigated for the assessment or confirmation of 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 the 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 antidiabetic 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 antidiabetic agents with proven clinical efficacy and safety.

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Nil.

Conflicts of interests

None.

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Table of comments

Reviewers' comments	Investigator's comments	Page number
Reviewer 02		
Title needs more clarity like "Natural drug leads as a novel DPP-IV inhibitors targeting the management of type 2 diabetes mellitus"	Title was edited.	Please refer page 01.
Abstract and introduction section could be improved further	It was edited.	Please refer pages from 02 to 07.
In abstract, the result section needs to highlight the result based on collated literature. Currently, it seems like the results are from their own studies	It was edited.	Please refer page 02.
Need further improvement with respect to readability and clarity. The grammar and scientific language can be further improved. It is too long, as your focus is on the herbal sources with DPP-IV inhibitory activity. I suggest shortening it to 2–3 pages and reviewing the most recent development in incretin field during last few years. Since large number of reviews gets published on this topic you should limit your thought to plant herbs and DPP-IV inhibition. There are several repetitive statements.	It was edited.	Please refer pages from 03 to 07.
The objective for this article is to review natural plants which exert DPP-IV inhibition potential. Is it requiring reviewing role of incretins in physiology?	Description related to incretin physiology was reduced.	Please refer pages 03 & 04.
Other changes in introduction section are in track change mode	Track changers were edited.	Please refer pages from 03 to 07.
Correct the DPP-IV substrate name as "Gly Pro AMC"	It was corrected.	Please refer page 07.
Most of the reviewed studies on plants have reported DPP-IV inhibition activity. However, authors have not presented any information whether these studies have used any positive control such as sitagliptin, vildagliptin, and so on for comparison	It was edited.	Please refer pages from 07 to 14.
Authors should include expert opinion as they have reviewed the plants for the DPP-IV inhibition. Something like what's the recent update on the use of these plants clinically. Whether any clinical studies are available to confirm translation of DPP-IV activity using these plants. Also provide your perspective on this interesting area.	It was included.	Please refer pages from 07 to 14.
Conclude with the focus on the herbal drugs as DPP-IV inhibitors	It was edited.	Please refer page 14.
Be specific what you mean by concerns with GLP-1 receptor agonists and DPP-IV inhibitors. They have some GI related issues but not serious concern	It was omitted.	Please refer page 14.
Reviewer 03		
In this review article, the layout of the article is presented as an original article. Please, review author's guidelines for review articles. In general, a review article do not have neither material and methods, nor results section nor study selection with inclusion and exclusion criteria.	It was edited.	Please refer pages from 02 to 14.
In addition, as for the DPP-IV natural compounds from plants section. Some sections are properly elaborated, however, most of the sections appears as if the authors only cited articles without clearly describing the findings from such scientific discoveries. Such sections are the heart of the review, and not properly elaborated. Please, elaborate those sections (see section 7 of major).	It was included.	Please refer pages from 07 to 14.

Continued

Reviewers' comments	Investigator's comments	Page number
The manuscript requires a thorough English revision as regards to the use of general terminology instead of scientific terminology.	The whole manuscript was corrected.	Please refer pages from 02 to 14.
I suggest the authors to better present the abstract of the review article. From a reader point of view, it appears the authors prefer DPP-IV over GLP-1 analogs because of the side effects. Make clear to the reader that this review article aims to provide a more clear view of DPP-IV natural compounds as potential therapeutic approach compared to synthetic forms, and not because of the side effects of incretin drugs.	It was corrected.	Please refer pages 05 and 06.
Could the authors elaborate on the side effects? The most serious side effects associated with incretin drug use was pancreatic cancer, however a meta-analysis comprising 33 studies and 79,971 patients concluded that treatment with incretin drugs is not associated with increased risk of pancreatic cancer in patients with T2DM. Furthermore, I strongly recommend the authors to include following review article on the role of incretin drugs and side effects.	The information on side effects was included.	
The authors should mention that the first line of treatment for T2DM is metformin. In addition, please include that incretin mimetic drugs are a relatively new group of drugs used in the treatment of diabetes and currently recommended by American Diabetes Association in dual therapy with metformin for the treatment of T2D.	It was included.	Please refer page 04.
Shorten the introduction, consider the use subheadings. In addition, address the difference or beneficial effects of natural vs. synthetic DPP-IV inhibitors.	It was included.	Please refer pages from 03 to 07.
Include the references related to the following sentence: "Ability of these compounds to target incretin related pathways via DPPIV inhibitory action has been proven over the past few decades."	It was included.	
Pharmaceutical companies extract DPP-IV from natural compounds or produced synthetically. It would be interesting for the manuscript that the authors emphasize whether or not any natural compounds is the active principle of a current FDA-approved DPP-IV drug.		
How natural DPP-IV compounds are more beneficial than synthetic DPP-IV? Why the authors emphasize on natural compounds in this review?	It was included.	Please refer page 06.
For all the species selected, the authors should adequately describe the experimental design and the results of the experiments performed. A citation is not enough. A review article should be more specific. An original article can be more vague and refer to the citation, but a review article should not. Please, complete and clarify those sections	It was included.	Please refer pages from 07 to 14.
As for the results presented from original articles, the authors should make an effort of consistency when presenting the data.	It was edited.	Please refer pages from 07 to 14.
What are the benefits of natural compounds versus already existing synthetic drugs. Please include a paragraph in conclusion section. How did the authors "highlighting the importance of DPP-IV inhibitors from plant sources"?	It was included.	Please refer page 06.

Continued

"Increased in a large scale" is a bit exaggerated term, please replace. Provide values.	It was edited.	Please refer page 02.
Reviewers' comments	**Investigator's comments**	**Page number**
How does extraction of the natural compound differ from synthetically produced drug. The prevalence of synthetic drugs over natural compounds may reside in the purity of the process as well as efficiency and efficacy. Please, include a paragraph.	It was included.	Please refer page 06.
Page 4, Line 3. The incretin GIP is discharged with respect to ingestion of nutrition. Please specify, and elaborate about GIP. 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. Additionally, GIP reduces gastric acid secretion. Include: Baggio LL, Drucker DJ. Biology of Incretins: GLP-1 and GIP. Gastroenterology. 2007;132(6):2131-2157. doi:10.1053/j.gastro.2007.03.054	It was included.	Please refer page 03.
Page 5, line 1. DPP-IV inhibitors obstructs the DPP-IV enzyme. Please, replace this sentence by. DPP-IV inhibitors block the actions of the DPP-IV enzyme.	It was replaced.	Please refer page 04.
Page 5, line 5. Spelling: incretin memetics. Replace by incretin mimetics	It was corrected.	Please refer page 05.
The following sentence by the authors: Nauck and co-workers [17] have reported that the developed incretin mimetics with long half-lives raise the concentration of GLP-1 receptor agonists six to ten fold compared to the postprandial state. Nauck in his article indeed mentions 6-10 fold, however, other authors have reached to that number. Please review references 14, 15, 22 of the article referenced by the authors (17). Please, include appropriate references	It was included.	Please refer page 04.
What do the authors mean in page 5 line 14 by "approved drugs". Please, specify if the drugs are FDA approved or not. If so, include the FDA website: https://www.fda.gov/drugs/information-drug-class/incretin-mimetic-drugs-type-2-diabetes The authors have not included other incretin drugs such as sitagliptin, linagliptin. Please specify whether the authors are only referring to GLP-1 analogs within the incretin mimetic group.	It was included.	Please refer page 5.
Page 7, line 3. Boon is not a scientific nor accurate word in scientific writing, please replace.	It was corrected.	Please refer page 07.
Please replace the title: Overview of the plants reported as potent DPP-IV inhibitors in recent literature, by: Natural DPP-IV inhibitors in recent literature.	It was replaced.	Please refer page 07.