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Review Article

Emerging Herbal Bio-actives as Reformed Dipeptidyl Peptidase (DPP-IV) Inhibitors Used for the Management of Diabetes Mellitus: A Brief Review

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Abstract

Background: Diabetes mellitus is a severe metabolic disorder affecting nearly half of the population worldwide and increase patient risk by its other related complication. DPP-IV is a serine aminopeptidase, which plays a crucial part in the glucose metabolic process and causes incretin degradation in GLP-1. It is one of the validated targets for the treatment of Type 2 Diabetes because of its effect of incretin hormone. Nearly seven DPP-4 inhibitors are in the market for treating Type -II diabetes (i.e., Sitagliptin, Vildagliptin, Saxagliptin, Linagliptin, and Alogliptin). They all are synthesized chemically, having good therapeutic efficacy, but their long-term safety use is unknown.

Methods: Moreover, plant-derived products are available in the market and found to be safe and effective, and nearly half of the population consumes these natural or bio-active compounds. Therefore, for developing novel anti-diabetic drugs, these natural products or herbal medicine seems to have good utility.

Result: The present study deals with the progress of new herbal medicine, their crude extract with the mechanism of action having DPP-IV inhibitory activity. Therefore, these could be helpful evidence for developing the next generation of anti-diabetes medicines via inhibiting DPP-4 activity.

Conclusion: The researchers investigating the novel lead for managing diabetes (type II) can also search these natural bioactive for future use. We have summarised the reported herbal Bioactives/Plants for the management of Diabetes mellitus from the year 2001- 2022.

Keywords: Diabetes mellitus; Bioactives; DPP-IV; Extract; Incretin; Medicinal plants

Abbreviation: WHO: World Health Organization; DM: Diabetes Mellitus; GIP: Glucose-dependent insulin-tropic hormone; GLP: Glucogen like peptide; DPP-IV: Dipeptidyl peptidase

Introduction

Diabetes Mellitus (DM) is a common metabolic disorder that is increasing rapidly in the growing era, and according to WHO data, it is considered a primary cause of death worldwide [1]. Amongst all types of diabetes, Type 2 is the most common disorder having 90% of cases. Patient with Type 2 diabetes mellitus shows no apparent symptoms, but still, it is a life-threatening condition. According to the International Diabetes Federation, the cases of diabetes will increase from 415 million (in 2015) and might be increased 642 million (in 2040) [2]. Numerous synthetic drugs are introduced to lower the blood glucose level (i.e., biguanides, incretin mimetics, α glucosidase inhibitor, and DPP-IV inhibitor) [3]. The hormone incretin plays a significant role after ingesting food; GIP and GLP-1 are the two essential enzymes secreted by Incretin that stimulate the insulin release from the β pancreatic cells [4]. Incretin shows the insulinotropic effect; it decreases food intake, inhibits glucagon and gastric emptying time, and slows down glucagon secretion [5]. The action of Incretin (GLP- ad GIP-1) mainly depends on the two

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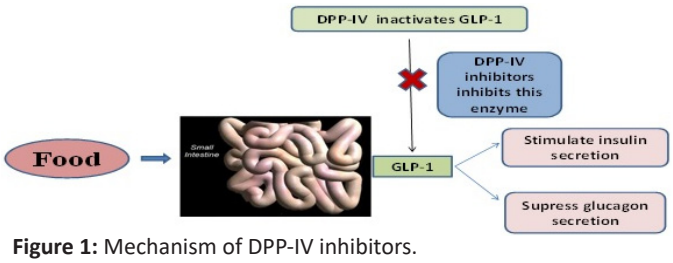


Figure 1: Mechanism of DPP-IV inhibitors.

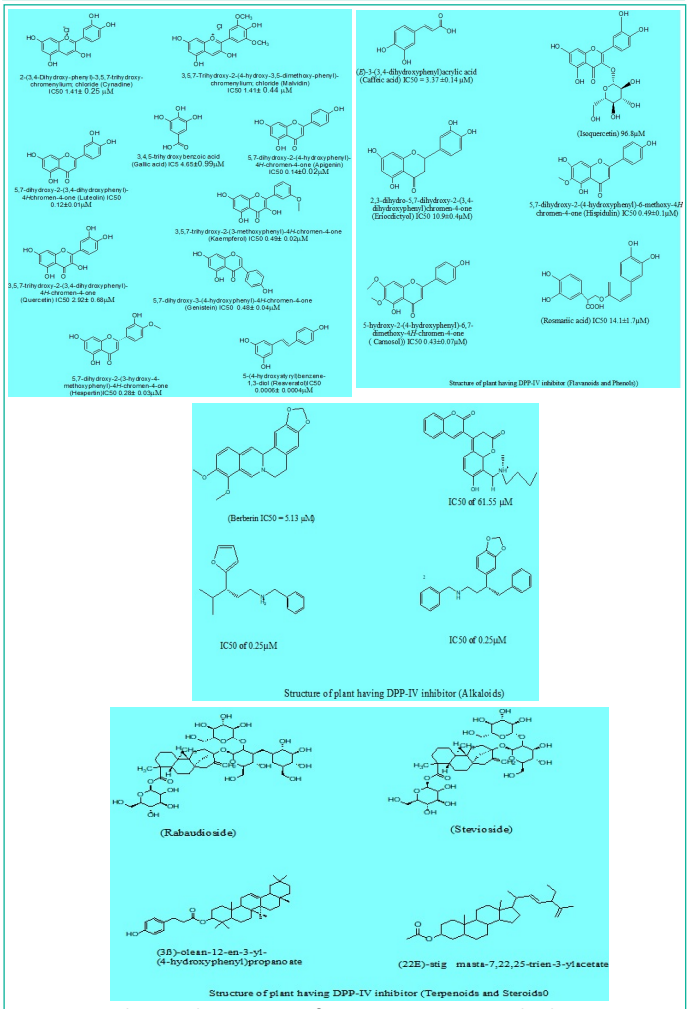
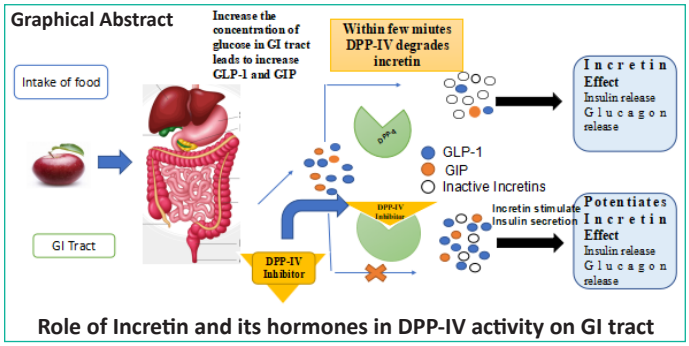


Figure 2: Chemical structure of Bioactive compounds showing DPP-IV inhibition activity along with their IC50 value.



Role of Incretin and its hormones in DPP-IV activity on GI tract

N-terminal amino acids that DPP-IV removes. Within 1-2 min, the Incretin is metabolized into inactive form by enzyme DPP-IV and only (10 to 15%) circulating stimulates the pancreas [6]. DPP-IV is an enzyme belonging to the family of serine proteases which involves the degradation of peptide hormones (i.e., glucagon-like peptide and cytokinin) [7]. DPP-IV inhibitors are now widely used in the market. These inhibitors inhibit the enzyme and promote the glucose homestasis [8]. But these synthetic drugs have good therapeutic activity, but they are not safe for the long term, so there is an increase in attention towards plant-derived products; they're bioactive and used to treat type 2 diabetes. Therefore, this review aims to compile the various herbal plants, their extract, mechanism of action, IC50 value, and structure of chemical compounds during 2000-2022, depicted in Table 1 and Table 2.

Mechanism of DPP-IV Action

DPP-IV is an amino peptidase enzyme with 760 amino acids. It contains two subunits having two domains (N terminal domain and C terminal domain). It is already known that GIP (Glucose-dependent insulin-tropic hormone) and GLP-1 (Glucagon l;ike peptide hormone) are incretin hormones that stimulate the release of insulin from pancreatic islets [10]. After food ingestion, these two incretin hormones release and contribute to insulin secretion [11]. DPP-IV enzymes mainly metabolize the Incretin (GLP and GIP-1), which release in response to food ingestion. DPP-IV inhibitors come under the class of oral hypoglycemic drugs, which competitively inhibit the enzyme DPP-IV and prevent the degradation of incretin hormone (GIP and GLP-1), ultimately increasing insulin secretion [12].

Table 1: List of synthetic DPP-IV inhibitors available in the market [14].

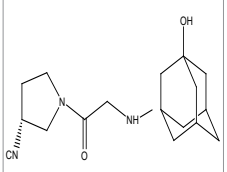
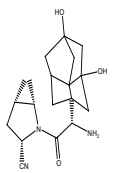
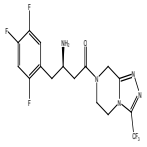
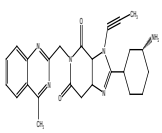
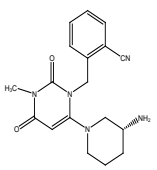
Marketed drugs	Vildagliptin	Saxagliptin	Sitagliptin	Linagliptin	Alogliptin
DPP-IV inhibitory potential	More than 95%	70-85%	More than 85-95%	More than 75%	More than 85%
Effectivity	Highly effective	Moderately effective	Very highly effective	It shows dose-dependent inhibition and highly effective	Shows high-affinity ad inhibition in a dose-dependent manner
Hypoglycemia risk	No risk detected	No risk detected	No risk detected	No risk detected	No risk detected
Half-life	1.4-1.5hr	2.4hr	7-14hr	11-12hr	12.5 to 24hr
Metabolism	Metabolized through kidney	Metabolized through kidney	Only 16% metabolised through kidney	Primary exertion through bile and secondary through kidney	Metabolized by cytochrome enzymes.
Approved countries	Europe	Europe and the United States	United States and Europe	Europe	Under Investigation
Brand name	Galvus	Onglyza	Januvia	Tradjenta	Nesina
Bioavailability	±85%	±67%	±100%	±30%	±100%
Structures					

Table 2: List of reported medicinal plants having DPP-IV inhibitory activity.

S.No	Plant/Family	Common name	Dose mg/kg & ug/ml	Part used	Extract	Mechanism	IC50 value/% inhibition	Reference
1	*Pueraria tuberosa* (Fabaceae)	Kudzu	50 &100	Roots	Water	Inhibit DPP-IV enzyme	-	[15]
2	*Berberi's arista* (Berberidaceae)	Indian barberry	500	Bark	Methanolic	Affect DPP-IV and endocrine system activity	14.46 µg/ml	[16]
3	*Camellia Sinensis*	White tea	200 µM	leaves	Ethanolic	Increase insulin secretion	227µg/ml	[17]
4	*Castanospermum australe* Cunn.	Blackbean	100 &150	Seeds	-	Reduced blood glucose level, HbA1c, and insulin	13.96 µg/ml	[18]
5	*Fagonia critica* (Zygophyllaceae) & Hedera *nepalensis* K. (Araliaceae)	Dhamasa Albumbar	-	Aerial	Ethyl acetate	Inhibit DPP_IV enzyme	38.1 µg/ml 17.2 µg/ml	[19]
6	*Desmodium gageticum* (Legumioiseae)	Sarivan	1000µg/ml	Aerial	Aqueous	Decrease the inactivation of GLP-1 and thereby increase its concentration and its action	255.5µg/ml	[20]
7	*Mangifera indica* (Anacardiaceae)	Mango	-	Leaves	Methanolic	Increase the level of GLP-1, improve glucose tolerance, and enhance insulin secretion	182.7µg/ml	[21]
8	*Withania Somifera* (Solanaceae)	Ashwagandha	5,25,125µg/ml	Roots, leaves, Fruit	Methanolic	It decreases the blood sugar level by increasing the GLP-1 in the body	8.76µg/ml	[22]
9	*Enicostemma littorale* (Gentianceae)	-	100µl	Whole plant	Ethyl acetate	It increases insulin secretion by increasing GLP -1 half-life	165.64µg/ml	[23]
10	*Berberis aristata* (Berberideaceae)	Oregon grapes	500µg/ml	Bark	Methanolic	It increases insulin secretion	14.4µg/ml	[24]
11	*Corylus avellana* L. (Betulaceae)	Hazelnut	50µl	nuts	Aqueous	-	24.7µg/ml	[25]
12	*Commiphora Mukul* (Burseraceae)	Guggul	200mg/kg	Gum	Hydroalcoholic	Decrease in blood glucose level and HA1c	16.45µg/ml	[26]
13	Tinospora crispa L. (Menispermaceae)	Guduchi	-	Stem	-	Increase the incretin and GLP-1 levels, which increases the insulin secretion in the body	65.86±1.02	[27]
14	*Curculigo latifolia* (Hypoxideacea)	Lamba	30µl	Root, Fruit	Aqueous	It increases insulin secretion and glucose uptake	66.15 ± 4.09% 42.79 ± 1.47%	[28]
15	*Eucalyptus citriodora* (Mytraceae)	Lemon scented gum	250 mg/5 mL/ kg	Leaf	Ethanolic	It increases insulin secretion and decreases glucose absorption	9-25%	[29]
16	*Urena Lobata* (Malvaceae)	Caserweed	625, 1 250, 2 500, 5 000 and 10 000 mg/ mL	Leaf	Ethanolic	Prevents GLP degradation and increases insulin secretion	6 489.88 mg/mL	[30]
17	*Abelmoschus manihot (L.)* (Malvaceae)	Hibiscus	312.5; 625; 1250; 2500; 5000; and 10000 µg/mL	Leaves	Ethanolic	-	860.67 µg/mL	[31] `
18	*Senna (Cassia) nigricans* (Fabaceae)	Sannai	17.3 µU/µl)	Whole plant	Methanolic	It breaks the incretin level and increases the GLP level	63.1±4.67%	[32]
19	*Ferula Assafoetida* (Umbelliferae)	Fennel	-	Seeds	Methanolic	It breaks the incretin level and increases the GLP level	24.5%	[33]

20	*Pueraria tuberosa* (Fabaceae)	Kudzu	95µl	Roots	Aqueous	It decreases glucose production and increases GLP-1 circulation in the body.	-	[34]
21	*Lens culinaris* (Fabaceae)	Lentil	-	Seeds	Ethanolic	-	51.69 ± 4.83µm	[35]
22	*Aloe vera* (Liliaceae)		30µl	Leaves	Ethanolic	Increase the plasma insulin ad GLP-1 level	8.59 ± 2.61 mM,	[36]
23	*Trigonella foenum graecum*	Fenugreek	320µg/ml	Seed	Methanolic	Increase the plasma insulin ad GLP-1 level	80.15%	[37]
24	*Annona squamosa* (Annonacin)	-	250mg/5ml	Leaves	Ethanolic	It suppresses the level of the Dpp-Iv enzyme and increases the incretin level	33%	[38]
25	*Spirulina platensis* (Cyanophycean)		200µm	Whole plant	Butanolic	It suppresses the level of DPP-IV enzyme and increases the incretin level	70%	[39]
26	*Boesenbergia pandurata* Roxb (Zingiberaceae)	Fingerroot	-	Whole Plant	Ethanolic	It increases the level of GLP-1 and Incretin	-	[40]
27	Pergularia extensa Chiov (Asclepiadaceae)	Daemia extensa	10-30µm	Whole plant	Methanolic	It suppresses the level of DPP-IV enzyme and increases the incretin level	-	[41]
28	*Ephedra foeminea* (Ephedraceae)	Jordan	0.1ml	Aerial	Methanolic	It increases insulin release and decreases the glucose uptake	50%	[42]
29	*Picrorhiza kurroa* (Plantaginaceae)	Kutki	25µm	Whole plant	-	Increase the plasma insulin ad GLP-1 level	52.51 ± 5.71 nM	[43]
30	*Castanospermum australe*	-	6.4µg/ml	Seed	Ethanolic	It increases glucose utilization and increases the glycogen stores in the liver.	13.96 g/ml	[44]
31	*Coreopsis Lanceolate* (Compositae)	lance-leaved coreopsis	100µg	Flower	Methanolic	It increases insulin secretion and glucose uptake	87.2%	[45]
32	*Nauclea latifolia* (Rubiaceae)	Pin cushion tree	-	Leaf	Aqueous Ethanolic	-	89.6%	[46]
33	*Trillium govanianum* (Melanthiaceae)	Naag Chattri	181.3 ± 30.2 mg/g	Rhizome	-	It helps in managing the glucose level in the body.	17.68 ± 1.32 µM	[47]
34	*Angelica keiskei* Kodzumi (Apiaceae)	-	-	Stem Leaves	Ethanolic	It helps in reducing the plasma glucose level in the body	10.49 µM	[48]
35	*Phaseolus vulgaris L.* (Fabaceae)	Black Bean	1mg/ml	Bean	-	It helps in decreasing glucose uptake and increases the level of Incretin.	96.7%	[49]
36	*Quercus variabilis* Blume (Fagaceae)	Acorn	25µl	-	Ethanolic	It inhibits the digestive enzymes and glucose transporters.	5.25 mg/mL)	[50]
37	*Prunus amygdalus* (Rosaceae)	-	15ml	Seed	Methanolic	It inhibits the enzyme Incretin and DPP-IV	162.9(lg/mL)	[51]
38	*Lagerstroemia speciosa* (Lythraceae)	Banaba	-	Leaves	Methanolic extract	It inhibits the enzyme Incretin	60.22±2.01	[52]
39	*Rhinacanthus nasutus (L.)* (Acanthaceae)	Snake jasmine	-	Leaves	Methanolic	It inhibits the digestive enzymes and glucose transporters	34.4 ìg/mL	[53]
40	Allium Sativum (Alliaceae)	Garlic	10 µL	Bulb	Methanolic	It decreases the blood glucose level, increases the Incretin, and increases insulin secretion.	70.88 µg/mL	[54]
41	*Artemisia Judaica* (Compositae)	Common Mugwort	-	Aerial	Hydro-methanolic	It inhibits the enzyme DPP-IV	85.89 µg/mL	[55]

42	Termialia Arjua (Comitaceae)	Arjun	-	Bark	-	It helps in reducing the plasma glucose level in the body	28%	[56]
43	*Eucalyptus citriodora* (Myrtaceae)	lemon- or citron-scented gum	8 mU/mL	Leaves	Ethanolic	It increases the incretin level and decreases glucagon secretion	52%	[57]
44	*Spirulina platensis* (Cyanophyceae)	-	200 µM	Leaves	Ethanolic	It increases the icreti levele y increasing the GIP-1 ad GLP	-	[58]
45	*Melicope Gabra* (Rutaceae)	Tenggek burung	50µL	Leaves Stem	Chloroform	It helps in reducing the plasma glucose level in the body	619.31±9.21µg/ml	[59]
46	*Tenebrio molitor*	yellow Mealworms	20µL	-	Hydroalcoholic	It increases the incretin level in the body	(57.56 ± 2.59%	[60]
47	*Pisum Sativum* (Fabaceae)	Pea	100µm	seed	-	It formed the hydrophobic bond with the S1 pocket in DPP-IV and inhibited the DPP-IV enzyme.	11.04µm	[61]
48	*Brassica oleracea* (Brassicaceae)	Broccoli	-	Stem Leaves	Hydrolysis	It increases the incretin level in the body	99.68µm	[62]
49	*Chenopodium quinoa Willd* (Chenopodiaceae)	Quinoa	25µl	-	N-hexane	It stimulates gastrointestinal digestion and inhibit the DPP-IV enzyme.	3.40 ± 0.20 mg/mL	[63]
50	*Heritiera fomes*	Sundari	10µl	Bark	Ethanolic	It increases the insulin release	-	[64]
51	*Commiphora Mukul (Combiteacea)* and *Phyllanthus emblica*	Guggul Amla		Gum Fruit	Hydroalcoholic	Increase the incretin and GLP-1 levels, which increases the insulin secretion in body	0.36 µM 0.8 µg/mL	[65]
52	*Ocimum Sativum* (Labiateae) *Momordica Charantia* (Cucurbitaceae)	Tulsi Karela	0.1 to 0.5mg/ml	Leaves	Methanolic	It activates the GLP-1 ad GIP ad increase the incretin level	66.81±0.05% 53.25±0.04%	[66]
53	*Palmaria palmata* (Palmariaceae)	Dulse	-	Species	Aqueous	It helps in reducing the plasma glucose level in body	1.47 ± 0.09mg/ml	[67]
54	*Lippia graveolens* (Verbenaceae)	Wild oregano	50 µL	Seeds	Methanolic	It inhibits the DPP-IV enzyme and decrease glucose secretion in the body	(3.9 ± 0.6 µM	[68]
55	*Rosa Gallica* (Rosaceae)	Gallic source	100µM	Flower buds	Aqueous	It decreases glucose and increases insulin secretion, and increases the GIP and GLP-1 levels.	25.8 µM and 70%	[69]
56	*Antidesma madagascariense Lam.* (Euphorbiaceae)	Bois bigaignon bâtard	-	Leaves	Ethyl acetate	Increase the incretin and GLP-1 levels, which increases the insulin secretion in the body.	79.2 ± 2.8 µg/ml	[70]
57	*Aronia arbutifolia (L.)* (Rosaceae)	Red Chokeberry	-	Juice	Fractioned	It decreases the plasma glucose level in the body and inhibits the DPP-IV enzyme	81%	[71-72]
58	*Allophylus Cominia* (Sapindaceae)	Panigera	-	Leaves	Aqueous	It helps in reducing the plasma glucose level	344.3	[73]
59	*Calocybe Indica*	Mushroom	100µl	-	Ethanolic	It controls the glucose level and increases GLP, GIP-1.	60.91µg/mL	[74]
60	*Senna Nigricans* (Fabaceae)	-	1 µg/µl	Powder	Methanolic	It increases the incretin level	56.43%	[75]
61	*Helichrysum arearium* (Asteraceae)	Dwarf everlasting	-	Flower	Methanolic Ethanolic	It inhibits the increase in the blood glucose level	41.2 µg/ml 16.0µg/ml	[76]
62	*Mytilus edulis* (Mytillidae)	Blue mussel	-	-	Protein	It inhibits the enzyme incretin and increases the half-life of GIP and GLP-1.	0.66±0.17 mg/ml	[77]
63	*Abelmoschus manihot L. Medic* (Malvaceae)	Gedi	20 µL	Leaves	Ethanolic	It inhibits the DPP-IV enzyme and increases the incretin level	860.87 µg/mL	[78]

Table 3: List of herbal phytoconstituents having DPP-IV inhibitory activity.

S.No	Phytoconstituents	Biological plants/ compound	Description	IC50 value/% inhibition	Researchers	Reference
1	Alkaloids	*Coptis chinensis* (Berberine)	From this plant, 9 bioactive were selected for *in vitro* bioassay, of which 7 had DPP-IV activity (IC50<1.00 mM).	13.3 µM	Guasch et al	[79] [80]
2	Glycosides	*Lens culinaris* (kaempferol) *Lens culinaris* (Robinin)	Four compounds were isolated from the seeds of this plant and tested for their DPP-IV inhibitory activity. Robinin was isolated from the seeds of this plant and tested their DPP-IV inhibitory activity.	51.9±4.83 µM 37.01 µM	Hyo Young Kim *et al.* Kim et al. 1998	[81]
3	Flavanoids	*Lippia graveolens* & *Rosmarinus officinalis* L (Naringeni) *Camellia Sinesis (Theaceae)*	In this, it was reported that six bioactive from these plants showed potent DPP-IV inhibitory activity. Epigallocatechin gallate	2.5±0.3 µM 10.21 µM	Fan J *et al*.	[82]
4	Terpeoids and Steroids	*Stevia rebaudiana* (Rebaudioside A) (Stevioside)	Molecular docking identified two main compounds from this plant for DPP-IV inhibitory activity.	-	Ayachi et al.	[83]
5	Phenols and Stilbenoid	*Vitis thunbergii* var. ((+)-Hopeaphenol, (+)-vitamin A, and (−)-vitisin B	The ethanolic extract from the stems and leaves of plants processes DPP-IV inhibitory activity.	401 90.75 15.3 µM	Lin et al.	[84]

Marketed Available Drugs Having DPP-IV Inhibitor Activity

DPP- IV is a new class of oral anti-diabetic drugs. These drugs are active orally, safer, tolerable, and with a low risk of hypoglycemia. Various drugs are available in the market to inhibit the DPP-IV enzyme, out of which three DPP-IV inhibitors are under Investigation. First, reversible drug analogs, including (pyrrolidines and thiazolidines, secondly covalently modifying analogs, including Cyanopyrrolidines and lastly, non-peptidase reversible analogs, including xanthines and aminomethyl pyrimidines [13]. These drugs have specific adverse effects and increase the risk of cardiovascular-related complications and tumor incidence. Table 1 summarises the marketed drugs used in the management of diabetes mellitus which are approved by FDA.

Medicinal Plants Having DPP-IV Inhibitory Activity

In today's era, the use of herbal medicine is increasing very rapidly. This herbal medicine showed a promising effect in managing diabetes and its related complication with a lesser risk of side effects and greater acceptance. In this, we have compiled the data of a list of medicinal plants from natural sources, active parts of plants, their extract, and mechanism of action, along with their IC50 value from 2001-2022, depicted in (Table 2). In this we have summarizes the medicinal plants like *Pueraria tuberosa*, *Berberis arista* (14.46 µg/ml), *Mangifera indica* (182.7µg/ml), *Desmodium gageticum* (255.5µg/ml), *Withania Somifera* (8.76µg/ml).

Natural Phytoconstituents Showing DPP-IV Inhibition Activity

The herbal plants, their extracts, and their phytoconstituents have been encouraging throughout the globe since ancient times. Various herbal-based potent leads have been manufactured through integrated methodologies. Most of the herbal leads showed a potent inhibitory effect against DPP-IV. The numerous medicinal plants are recognized and categorized according to their chemical structure, as depicted in Table 3. The various categories of drugs used for DPP-IV, their characteristics, age group of the patient and number of patients involved in the studies, are tabulated in Table 4 and ongoing clinical trials in Table 4.

Table 4: List of clinical trial data on DPP-IV inhibitors[85].

NCT No.	Condition	Intervention	Characteristics	Age group	Sex	No. of patient
NCT01588587	Diabetes Mellitus (Type II)	1st Drug: Sitagliptin 2nd Drug: Vildagliptin	Observational study type Model: Cohort studies Measures outcomes: Cancer frequency, AGE concentration	25-95years	All type	500 patients
NCT00411411	Diabetes (Type II)	1st Drug: Januvia 2nd Drug: Placebo	Interventional study type Model: Randomized studies, Parallel assessment	18-88 years	All type	49 patients
NCT01545024	Diabetes Mellitus (Type II)	1st Drug: Sitagliptin (50mg one time per day os)	Model: Observational	20-95years	All type	60 patients
NCT00111631	Diabetes Mellitus (Type II)	1st Drug: DPP-IV inhibitor 2nd Drug: Metformin 3rd: Placebo	Model: Interventional (phase 2)	18-75 years	All type	218 patients
NCT03602638	Diabetes Mellitus (Type II) DPP-IV inhibitor GLP-1	1st Drug: Sitagliptin 2nd Drug: Acarbose	Model: Interventional (Phase 4)	18-80 years	All type	300 patients
NCT01937598	Diabetes Mellitus (Type II)	1st Drug: Placebo 2nd Drug: Sitagliptin 3rd Drug: Liraglutide	Model: Interventional (Phase 3)	25-75years	All type	16 patients

Conclusion

Over the past few decades, the enzyme DPP-IV considers a promising target for the management of Diabetes mellitus. Moreover, some synthetically manufactured compounds are commercially available in the market, but they have been associated with several side effects, and their long-term use is still unknown. DPP-IV inhibitors work by inhibiting the incretin hormone or increasing the GLP-1 and GIP levels via stimulating insulin secretion and inhibiting glucagon secretion. Newer drugs like molecular docking can potentially manage diabetes using some natural products. In- *vivo* and *In- vitro* experiments studies are recommended for targeting the DPP-IV enzymes. Traditionally, many natural plants and bioactive extracts are used to treat diabetes. Therefore, the current data gives researchers, the industrial sector, and others a new idea for developing novel formulations but still needs more advanced studies in preclinical and clinical to prove their efficacy and safety in human beings.

Author Statements

Conflict of Interest

The authors declare that there is no conflict of interest.

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