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NATURAL MEDICINE FOR DIABETES AS DIPEPTIDYL PEPTIDASE-IV [DPP-IV] INHIBITOR

Dr. Avani N Doshi[1]*, Bhumi M Shah[2,3], Nidhi H Jadav[4], Geetika S Sharma[5] & Dr. Dhrubo Jyoti Sen[6]

[1]Department of Pharmaceutical Chemistry, K. B. Raval College of Pharmacy, Shertha, Post Kasturinagar, B/h IFFCO township, Gandhinagar, Gujarat, 382443, India.

[2]Department of Pharmaceutical Chemistry, K. B. Institute of Pharmaceutical Education and Research, Gandhinagar, Gujarat 382023, India.

[3]Department of Pharmaceutical Chemistry, L. J. Institutes of Pharmacy, L J University, Ahmedabad, Gujarat 382210, India.

[4,5]Department of Pharmaceutical Chemistry SAL Institute of Pharmacy, Opp Science City, Ahmedabad, Gujarat 380060, India.

[6]School of Pharmacy, Techno India University, Salt Lake City, Sector-V, EM-4/1, Kolkata-700091, West Bengal, India.

ABSTRACT: DPP-IV is the main point of target for the treatment of type 2 diabetes. Plant products are always accessible for the attainable lead generation for various diseases. In this review, we tried to cover many natural sources which exhibit antidiabetic action mainly due to inhibition of DPP-IV. The most potent chemical constituents of the plant as DPP-IV inhibitors were resveratrol, luteolin, apigenin and flavone. Now a day, it is very important to identify DPP-IV inhibitors which can act as forthcoming antidiabetic agent. Already available synthetic inhibitors like sitagliptin, vildagliptin, saxagliptin showed unenviable side effects. Phenolic compound and flavonoids have antioxidant properties as well being present in many functional foods. So, the researchers try to uncover the natural sources for lead generation as DPP-IV inhibitors.

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

INTRODUCTION: Diabetes is a disease that involve problems with the hormone insulin. Diabetes mellitus is a clinical condition which is characterized by an increase in plasma blood glucose. Normally, the pancreas releases insulin to help your body store and use the sugar and fat from the food you eat but in diabetes pancreas is unable to produce insulin or our body cannot utilize the insulin.[1]

Diabetes is a chronic disorder of interference in metabolism characterized by increased fasting and post prandial blood sugar levels. The global preponderance of diabetes expected to be increase 5.4 % by the year 2025. It is estimated that there are approximately 33 million adults with diabetes in India which is going to be increase to 57.2 million by the year 2025. Type I diabetes (Insulin dependent) is caused due to insulin insufficiency because of lack of functional beta cells.[2] Patients suffering from type-I are therefore totally dependent on exogenous source of insulin while patients suffering from Type II diabetes (Insulin independent) are unable to respond to insulin and can be treated with changes in diet, exercise or medication.

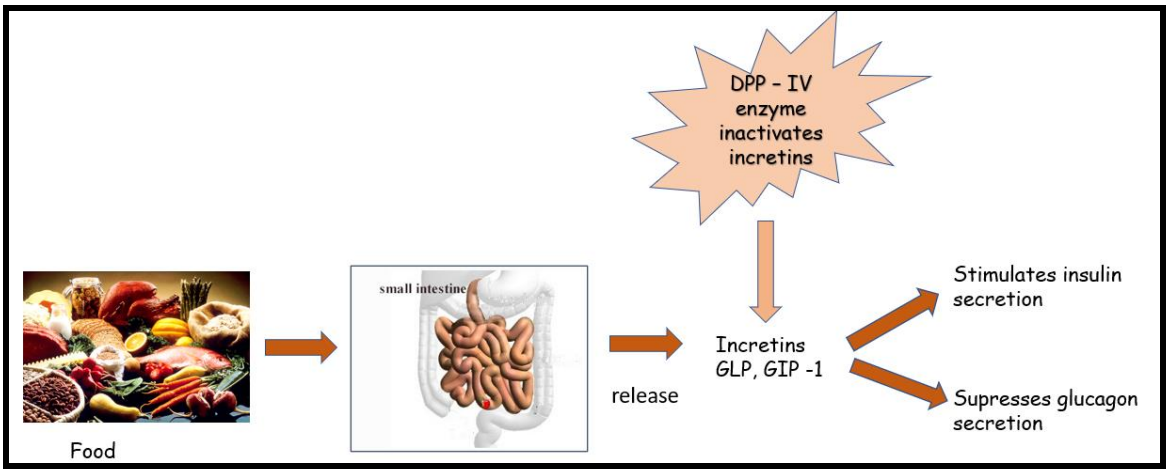

Figure-1: Mechanism of DPP-IV inhibitors

The treatment of Diabetes varied due to its multicomponent pathophysiology therefore it depends on multitude of agents which have ability to tackle many facets of the disease pathophysiology like improving insulin availability by direct insulin supplements or by the agents which increase insulin secretion, increase sensitivity to insulin, delay in absorption and delivery of carbohydrates from GI tract or increase urinary glucose excretion. Dipeptidyl peptidase IV (DPP-IV) enzyme exert its action through degradation of glucagon like peptide -1 (GLP-1) **(Figure-1)**.[3] Now a days, Dipeptidyl peptidase-IV (DPP-IV) inhibitors are a relatively emerging class of oral diabetes drugs. DPP-IV inhibitors commonly prescribed to the patients who have not responded properly for oral antidiabetic agents. DPP-IV inhibitors exert its effect by preventing degradation of GLP -1 thus prolong its action and due to this it increases insulin activity for the glucose lowering effect. DPP-IV inhibitors can overcome side effects of oral antidiabetic agents like weight gain and hypoglycemia but have higher risk of pancreatitis.[4]

Diabetes is a complex condition with a variety of causes and pathophysiology. The currently available approach is not the ideal for correction of disease and its hurdles.[5] Herbal medicine has been used for the management of diabetes over centuries. Many diabetic patients use herbal medicines in addition to their mainstream treatments, which may have some beneficial as well as hazardous effect to effective management of the disease. All Approved DPP-IV inhibitors are shown in **Figure-2**.

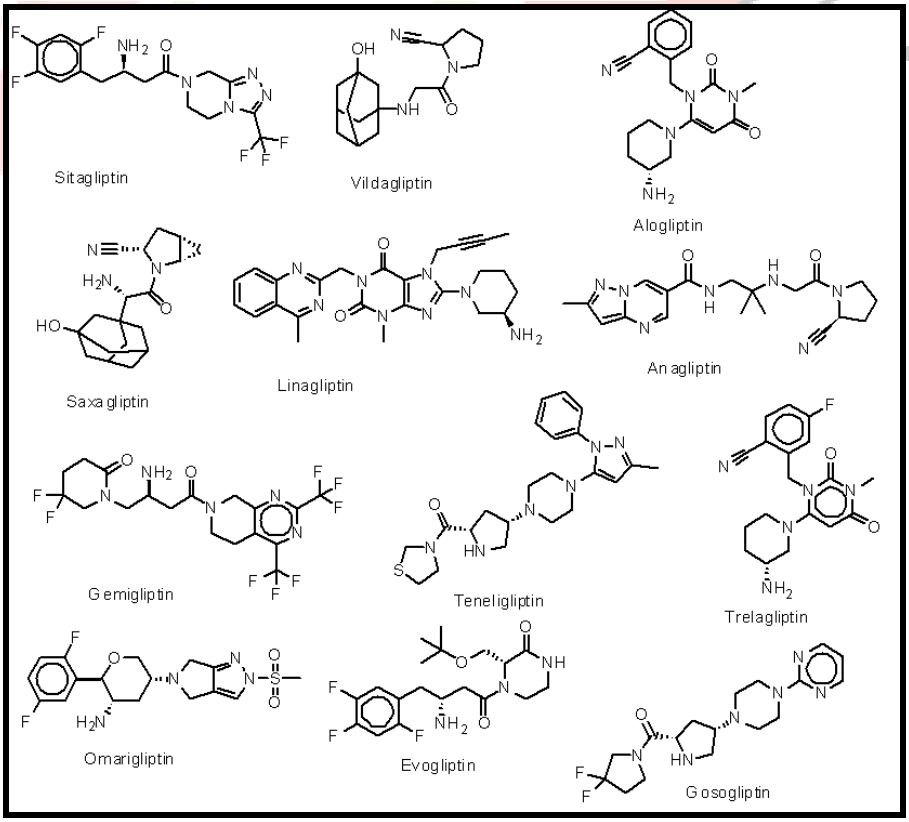

Figure-2: Approved (Synthetic) Drugs used as DPP-IV inhibitors

Plants as DPP-IV inhibitors: *Momordica charantia* (Ayurvedic/Sanskrit name: Karavella, Kathilla; Common name: Karela, Bitter Gourd)

Momordica charantia commonly known as bitter gourd or karela or bitter melon, used for many medicinal purposes like constipation, inflammation, cough, microbial infection, and respiratory diseases, hyperglycaemia etc.[6] Singh J. et al. have isolated an alkaloid, Momordicin **(Figure-3)** and a steroidal saponin, Charantin (momocharin) (**Figure-3**) from fruit of the plant and exhibit hypoglycaemic effect.[7] Bhat G A. et al. have carried out a study effect of aqueous extract of plant. Aqueous extract increases tissue glycogen, serum insulin and GLP-1 non-significantly. The polar molecules of M. charantia depolarize the L-cell through elevation of intracellular Ca^{2+} concentration which releases GLP-1 leads to elevate beta-cell proliferation and insulin secretion.[8] Methanolic extract (0.5 mg/ml) of *M. charantia* showed 53.25 % DPP-IV inhibition and the extract has phenolic content which increases DPPH free radical scavenging activities.[9]

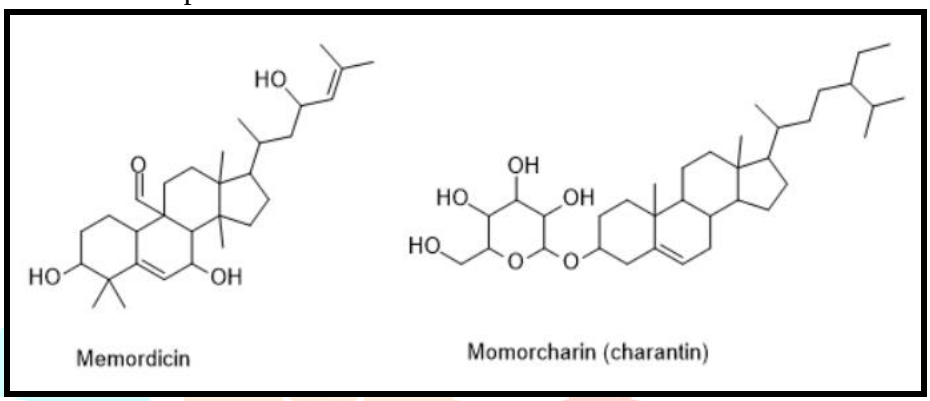

Figure-3: Active constituents of Memordica Charantia as DPP-IV inhibitors

***Cassia nigricans* (Ayurvedic/Sanskrit name: Aragvadha; Common name: Senna)**

Cassia nigricans, Senna is an especially important plant of Ayurvedic medicines which possesses anti-inflammatory, antioxidant, hypoglycemic and anticancer activities.[10] Saidu Y. et al. have prepared methanolic, ethanolic and hexane fractions of the plant. All of them showed 63.1 % inhibition of DPP-IV which is less effective than standard, P32/98.[11] Further *in-vitro* enzyme inhibition was carried out by methanolic extract of *Cassia nigricans* (57.0 ± 1.91%) by Saidu y. et al. which serves as sources of inhibitors of the DPP-IV enzyme in the treatment of Type-2 diabetes mellitus.[12]

***Ocimum sanctum* (Ayurvedic/Sanskrit name: Gouri, Bhuteshta; Common name: Tulsi)**

Inbaraj S. et al. has been reported that *O. sanctum* possess anti diabetic, antifertility, anti-cancer, anti-fungal, hepatoprotective and cardioprotective actions.[13] Somasundaram G. et al. have reported that methanolic extract of *Ocimum sanctum* possesses good DPP-IV inhibition activity with % inhibition 66.81 ±0.05%. The chemical constituents like ursolic acid and oleanolic acid **(Figure-4)** (Triterpenoids) present in leaf extract showed DPP-IV inhibition action and potentiation of insulin release.[14] Singh A K. et al. have showed α-glucosidase and DPP-IV enzyme inhibition effects by *in-vitro* method using leaf extract. *Ocimum basilicum* contains almost 10% eugenol **(Figure-4)** which is found to lower the blood glucose level.[15]

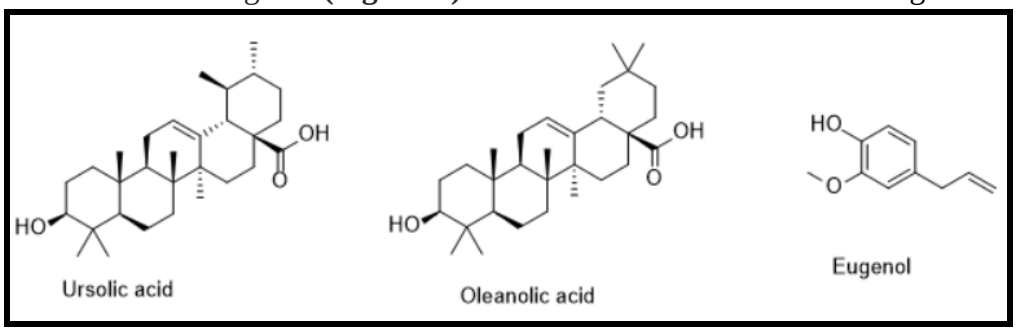

Figure-4: Active constituents of *Ocimum sanctum* as DPP-IV inhibitors

***Gymnema sylvestre* (Ayurvedic/Sanskrit name: Madhunashini; Common name: Gudmar)**

Gymnema sylvestre is used as sugar destroyer because chewing of leaves destroys the ability to identify the sweet taste in case of glycosuria and other urinary diseases. The plant extract of *Gymnema sylvestre* [Gurmar]) was showed better in vitro DPP-IV (60.21±0.35%) inhibitory activity.[16] This plant has the

potential to be developed as a natural alternative to synthetic DPP-IV inhibitors. In terms of utilization by the pharmaceutical companies, research outcomes of this study may play a key role in the development of natural indigenous DPP-IV inhibitors.[17] Laha S. et al. have isolated primary chemical constituents of Gymnema as DPP-IV inhibitors include gymnemic acid **(Figure-5)** identified when leaves of this plant reduces urine glucose in diabetes. Also, Arun L. B. et al. have identified *G. sylvestre* as an alternative to synthetic DPP-IV inhibitors by screening their extract for invitro DPP-IV inhibitory activity.[18]

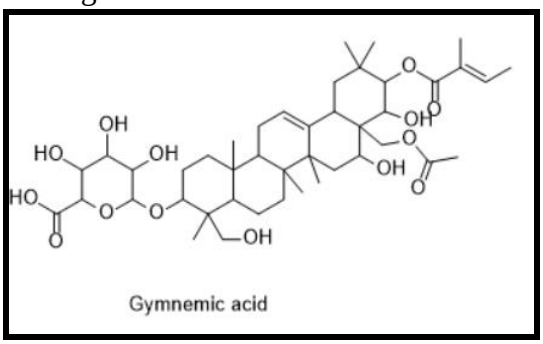

Figure-5: Active constituents of *Gymnema sylvestre* as DPP-IV inhibitors

***Mangifera indica* (Ayurvedic/Sanskrit name: Aamra, Sahakara; Common name: Mango)**

It is commonly known as mango, is a species of flowering plant in the sumac and poison family Anacardiaceae. Mangiferin is a pharmacologically active flavonoids, which having the anti-bacterial, antioxidant, anticancer, antidiabetic, hepatoprotective, anti-inflammatory activities.[19] Suman R k et al. have isolated the chemical constituents from the barks of Mangifera indica. Their structures were identified as mangiferone, mangiferin, myricetin, myricitrin, rutin and quercetin. The active constituent quercetin **(Figure-6)** is act as DPP-IV inhibitors.[20] Methanolic extract of *Mangifera indica* leaves was prepared by Kalita P. et al. which showed potent DPP-IV inhibitory activity (68.22 ± 1.14%).[21] Also, methanolic extract prepared by Yoshida S. et al. showed potent activity with an IC_{50} value of 182.7µg/ml. *Mangifera indica* inhibits the DPP-IV and enhances the GLP-1 for type 2 diabetes. The peptide is rapidly inactivated by the enzyme dipeptidyl peptidase-IV (DPP-IV), resulting in a half-life of active GLP-1 of only approximately 1-2 minutes. Inhibition of DPP-IV increases the levels of endogenous active GLP-1 and prolongs its half-life.[22]

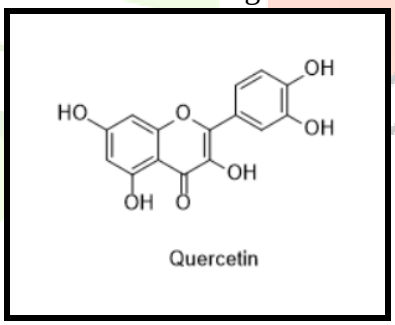

Figure-6: Active constituents of Mangifera indica as DPP-IV inhibitors

Bodhi Leaves (Ayurvedic/Sanskrit name: Bodhivriksha; Common name: Peepal)

It is known as peepal tree family (*F. religiosa* L.). Fruits are used as laxatives, latex is used as a tonic, and fruit powder is used to treat asthma. It is also used traditionally antiulcer, antibacterial, antidiabetic, in the treatment of gonorrhea and skin diseases[23]. The ethanolic extract of Bodhi leaves showed highest (68.98 ± 1.95) inhibitory activity against DPP-IV enzyme that plays a role in improving diabetes[24]. Plant extract of 100, 200 and 400 mg/kg reduced the blood glucose level by 33%, 53% and 54% after three weeks. Plectranthoic acid **(Figure-7)** showed inhibition of glucosidase, amylase and DPP-IV activities.[25]

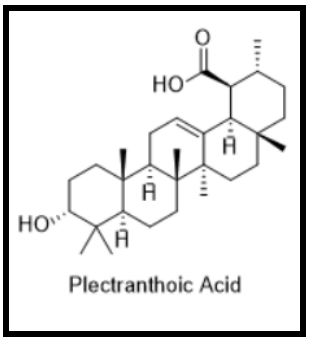

Figure-7: Active constituents of *Ficus religiosa* as DPP-IV inhibitors

Garlic (Ayurvedic/Sanskrit name: Lasunah, Rasonah; Common name: Lasun)

Garlic (*Allium sativum*) naturally belongs to a member of the Alliaceae family, is well recognized as a principal spice, and is additionally used as a remedy for specific ailments and physiological disorders. Allicin, **(Figure-8)** a sulfur-containing compound is responsible for its pungent odour and it has been shown to have significant hypoglycemic activity. This effect is thought to be due to increased hepatic metabolism, increased insulin release from pancreatic beta cells and/or insulin sparing effect.[26] Several other research including studies on effect of garlic extract on blood glucose levels and lipid profiles in streptozotocin/alloxan-induced diabetic rats, alloxan diabetic rabbits have exhibited its antidiabetic activity.[27-30] Apart from this, *Allium sativum* exhibits antimicrobial, anticancer and cardio protective activities also. Ultrasonic-assisted garlic extract has been demonstrated as a promising anti-diabetic agent by inhibiting therapeutic drug target dipeptidyl peptidase IV, results showed that 70.9 µg/Ml of garlic bulb extract inhibited 50% DPP-IV activity.[31]

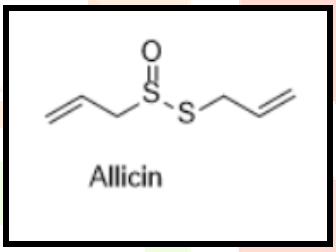

Figure-8: Active constituents of Allium sativum as DPP-IV inhibitors

***Caesalpinia sappan* (Ayurvedic/Sanskrit name: Patangah; Common name: Sappan wood)**

Sappan wood (*Caesalpinia sappan* L.) is a Brazilian plant that is referred to as Brazil wood. Brazilin **(Figure-9)** sappan wood major compound and important bioactive, has been used to treat diabetes through several biomolecular mechanisms. Previously 100 ppm of sappan wood extract had DPP-IV inhibition activity of 84.24%.[32] Sappan wood extract with chlorine chloride-lactic acid of 0.60 ppm, 1.60 ppm and 2.03 ppm showed DPP-IV inhibition 4.54 %, 5.01%, and 5.72 %, respectively while Wood extract with Betaine-Lactic acid of 0.73 ppm, 1.61 ppm, 2.08 ppm showed DPP-IV inhibition with 5.70 %, 6.72 % and 7.74 %, respectively.[33]

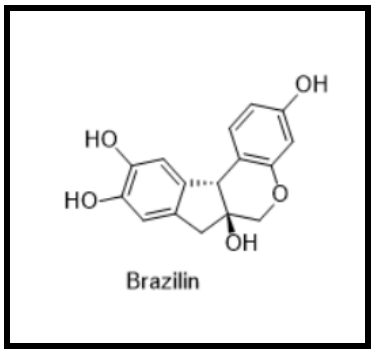

Figure-9: Active constituents of *Caesalpinia sappan* as DPP-IV inhibitors

***Camella senensis* (Ayurvedic/Sanskrit name: Syamaparni; Common name: Tea)**

Camellia sinensis (Tea) is a traditional health beverage in China and Indian medicine, and its antioxidant, antidiabetic, anti-hypertensive functions have been confirmed. For instance, tea polysaccharides can inhibit alpha-glucosidase, which is related to type 1 diabetes[34,35] and tea polyphenol is one of the effective antidiabetic components in decreasing glucose levels and preventing complications.[36-39]

Chinese tea which is used as beverage and food supplements, is made from the leaves and leaf buds of the *Camellia sinensis* species and used for finding DPP-IV inhibitory effects. Aqueous extract of black tea after ultra-filtration showed very good DPP-IV inhibition *in-vitro.*[40]

White tea (*Camellia sinensis* (L.) Kuntze) is a tea bud which is still roll processed without fermentation. The methanol fraction of the tea bud showed IC_{50} value 227 µg /mL which is the most active inhibitor of DPP-IV enzyme. The inhibitory activity determined by using rat blood serum as DPP-IV enzyme source (*ex-vivo*).[41]

EGCG, a major flavonol **(Figure-10)** in tea, was shown to have antidiabetic activities in rodents. EGCG appears to have multiple antidiabetic actions including islet protection, increasing insulin secretion, decreasing insulin tolerance, and decreasing gluconeogenesis and insulin-mimetic action.[42,43] The role of EGCG in islet protection was shown to protect against cell death mediated by islet amyloid polypeptide (IAP) *in-vitro.*[44,45] EGCG was reported to activate AMPK in adipocytes.[46] *In-vitro*, the concentration of Epigallocatechin-3-gallate (EGCG) required to inhibit DPP-IV activity by 50% (the IC_{50} value) was 28.42 μM. These data provide a theoretical basis for intervention in glucose metabolism with EGCG.[47]

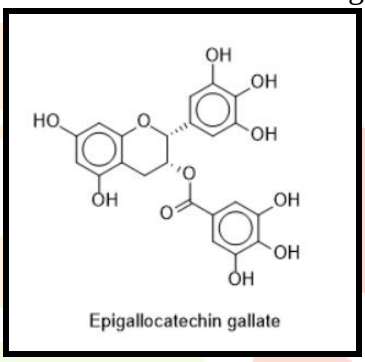

Figure-10: Active constituents of *Camellia sinensis* as DPP-IV inhibitors

Berberine (Ayurvedic/Sanskrit name: India barberry, Daruharidra; Common name: Berberina)

Berberis aristate commonly known as "Dāruhaldhi" and "Citra" used in skin diseases, menorrhagia, diarrhea, jaundice, fever, diabetes, hepato-biliary disorder.[48] Phytochemical screening of methanolic extracts of leaves, stems and roots of *B. aristate* showed the presence of active compounds such as alkaloids (berberine) **(Figure-11)**, reducing sugars, steroids, flavonoids, terpenoids, glycosides and saponins while tannins were found to be absent.[49] Chakrabarti R. et al. have found that methanolic extract of the bark of berberis aristate shown comparable DPP-IV inhibition (IC_{50} - 14.4 µ*g*/ml) with standard diprotin-A (IC_{50} - 15 µ*g*/ml).[50]

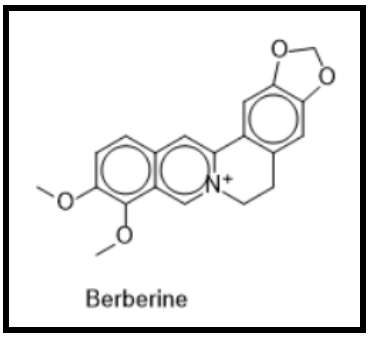

Figure-11: Active constituents of *Berberis aristate* as DPP-IV inhibitors

***Terminalia arjuna* (Ayurvedic/Sanskrit name: Arjuna; Common name: Arjuna tree)**

Terminalia arjuna is widely used in Indian system of medicine as cardioprotective, hypotensive, antidiabetic, hypolipidemic and wound healing activity.[51] Borde M. K. et al. reported that extract of *Terminalia arjuna* exhibited good DPP-IV inhibition activity with the highest percentage of DPP-IV inhibition 83.39±7.58%.[52] Ipseeta et al. concluded that the active ingredient of Terminalia arjuna; Arjunetin, Arjungenin, Ellagic acid

and Arjunic acid **(Figure-12)** showed superior DPP-IV Inhibitory activity as compared to synthetic DPP-IV inhibitors (Sitagliptin and Vildagliptin) based on results of docking studies.[53]

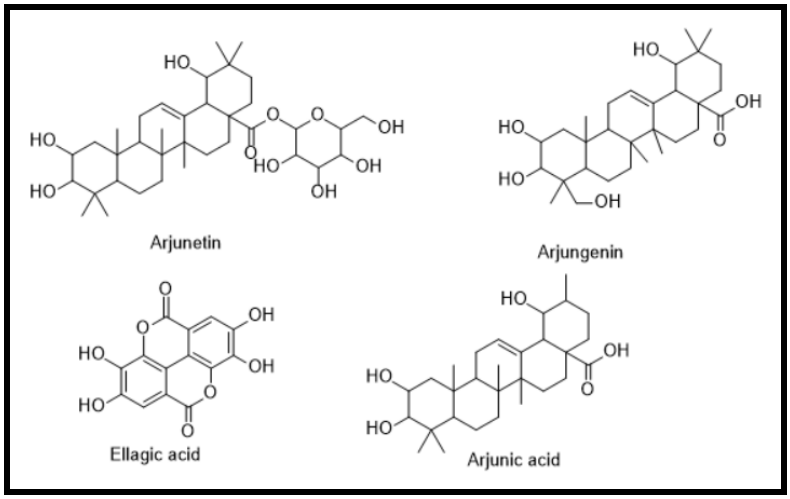

Figure-12: Active constituents of *Terminalia arjuna* as DPP-IV inhibitors

***Withania somnifera* (Ayurvedic/Sanskrit name: Kamrupini; Common name: Indian winter cherry)**

Withania somnifera (L.) is commonly known as Ashwagandha. In the traditional system of Ayurvedic medicine, this plant is claimed to have potent aphrodisiac rejuvenate and useful in the treatment of anti-inflammatory, antitumor, antistress, antidiabetic, antiaging, stimulant for neurotransmitter and life prolonging properties.[54,55] Therefore, Kempegowda P K. et al. have tried to evaluate the extract of roots, leaves and fruits of *Withania somnifera* plant by *in-vitro* inhibitory assay. The methanolic extract of the root showed the maximum DPP-IV inhibition activity compared to other extract. Catechin **(Figure-13)** present in methanolic extract of the root showed the potent DPP-IV inhibition (>80 % inhibition at 125 μg/ml concentration) which is also proved by molecular docking study.[56]

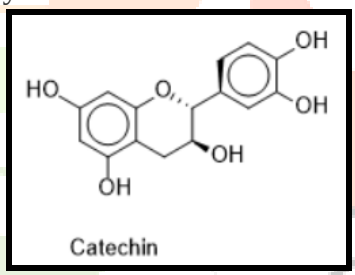

Figure-13: Active constituents of *Withania somnifera* as DPP-IV inhibitors

***Trigonella foenum-graecum* [Fenugreek] (Ayurvedic/Sanskrit name: Samudra methi; Common name: Methi)**

Trigonella foenum-graecum [Fenugreek] is used to treat numerous health problems, including insulin resistance, diabetes, poor appetite, inflammation, digestive problems and menopausal symptoms. 4-hydroxyleucine, a novel amino acid from fenugreek seeds increases glucose stimulated insulin release. In animal experiments, it has been shown that oral administration of plant extract decreased the blood glucose levels. Administration of fenugreek seeds improved glucose metabolism and reduced hepatic and renal glucose-6-phosphatase and fructose−1,6-biphosphatase activity.[57] Chemical constituents of the plant include saponins, many of which are glycosides of diosgenin. The seeds also contain the alkaloids trigonelline, gentianine, and carpaine **(Figure-14)** compounds. Seed constituents include 4-hydroxyisoleucine, an amino acid, and fenugreekine. It has been shown to increase erythrocyte insulin receptors and improve peripheral glucose utilization, thus showing potential pancreatic as well as extra pancreatic effects.[58] Fenugreekine, a steroidal saprogenic peptide ester, may have hypoglycemic properties. Trigonelline, another component, may exert hypoglycemic effects in healthy patients without diabetes, but other studies have shown that fenugreek has no effect on fasting or postprandial blood glucose levels in no diabetic subjects. Fenugreek seeds provided the highest inhibitory activity against DPP-IV enzyme *in-vitro* at a concentration of 2.5 μg/ml. That plays a role in improving diabetes. The highest inhibitory percentage was given by the ethanol extract of fenugreek seeds of *Trigonella foenum-graecum* L. is 71.29 ± 0.33.[59]

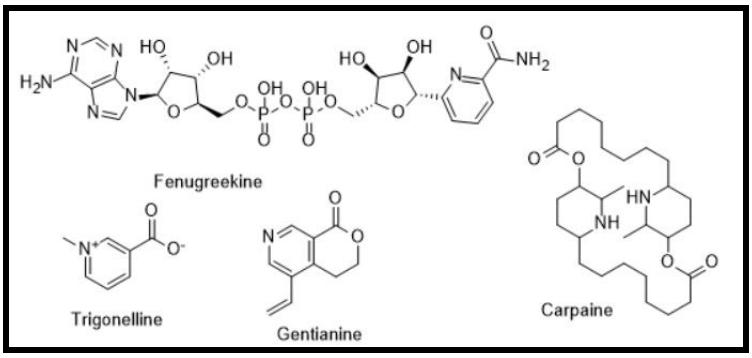

Figure-14: Active constituents of *Trigonella foenum* as DPP-IV inhibitors

Eucalyptus globulus **(Ayurvedic/Sanskrit name: Tailapatra; Common name: Blue gum)**

Eucalyptus which is commonly known as gum tree. The bark and leaves of the eucalyptus tree have been used for many diseases. Dey B. et al. have evaluated leaf extract of *E. globulus, E. citriodora, E. camaldulensis* as natural enzyme inhibitors. Polyphenol and flavonoids are present in these variety. Through correlation study they came to know that the phenolic content has more correlation with the inhibitory potential of enzymes. Triterpenoids and Phenolic compounds **(Figure-15)** of the plant is mainly responsible for DPP-IV inhibition. The leaf extract of *E. globulus, E. citriodora, E. camaldulensis* showed DPP-IV inhibition with IC_{50} 3.098, 6.138, 3.99, respectively.[60] Kato E. et al. have isolated macrocarpals A–C from *Eucalyptus globulus* which is acting as DPP-IV inhibitors. Amongst them macrocarpals C **(Figure-15)** showed the most potent activity.[61]

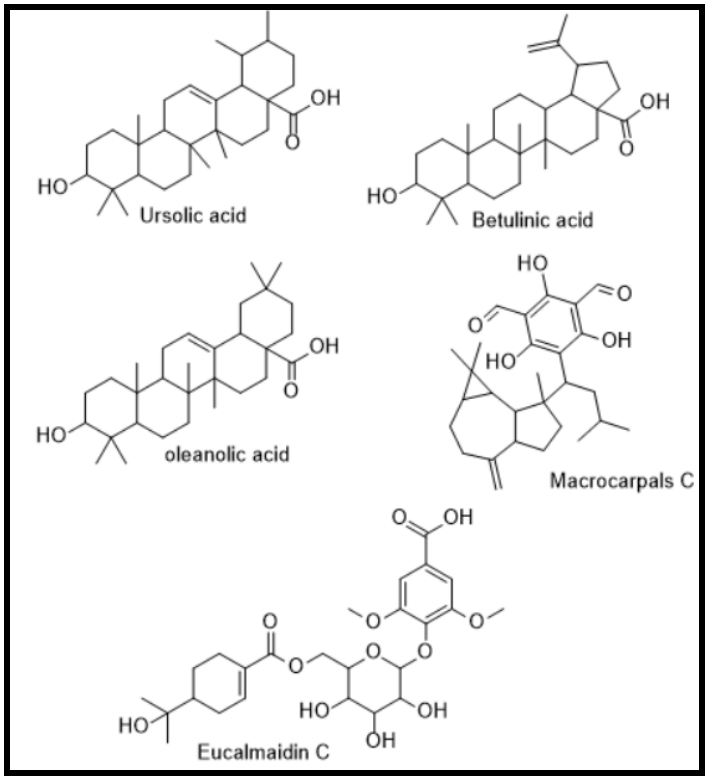

Figure-15: Active constituents of *Eucalyptus globulus* as DPP-IV inhibitors

Emblica officinalis **(Ayurvedic/Sanskrit name: Amalki; Common name: Amla, Indian gooseberry)**

Majeed M. et al. extracted β-glucogallin **(Figure-16)** from the fruits and checked for antidiabetic activity. The fruit extract inhibited α-amylase and α-glucosidase enzyme with IC_{50} values of 135.70 μg mL^{-1} and 106.70 μg mL^{-1}, respectively. Also, the fruit extract showed inhibition of dipeptidyl peptidase-IV enzyme with IC_{50} value 3770 μg mL^{-1}.[62]

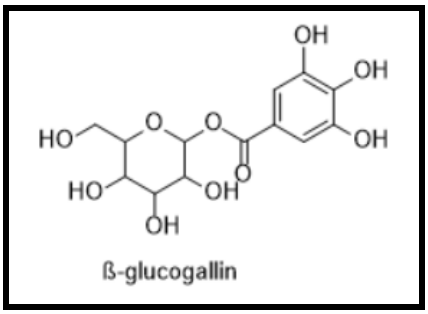

Figure-16: Active constituents of *Emblica officinalis* as DPP-IV inhibitors

***Rosa gallica* (Ayurvedic/Sanskrit name: Devataruni; Common name: Gulab)**

Kato E et al. have evaluated Ellagitannins were isolated as DPP-IV inhibitors from rose bud extract powder. Inhibiting DPP-IV protects GLP-1 from degradation, which enhances the secretion of insulin to help our body decrease the blood sugar level. Rugosin A and Rugosin B act as DPP-IV inhibition at 100µM (%).[63]

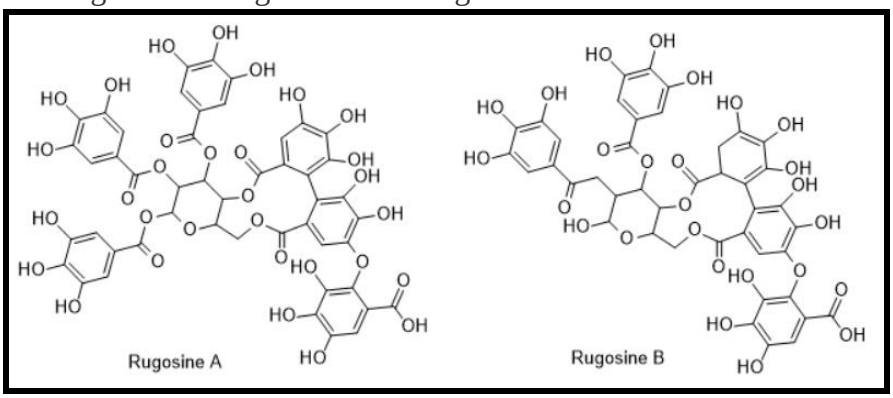

Figure-17: Active constituents of *Rosa gallica* as DPP-IV inhibitors

***Commiphora mukul* (Ayurvedic/Sanskrit name: Guggulu; Common name: Guggul)**

C. mukul is commonly known as Indian bdellium tree. Sharma D. et al. have isolated the percentage inhibition of *C. mukul* (92.97±8.45%) shows that it is a potent inhibitor of DPP-IV enzyme.[64] Sharma B. et al. have tried to evaluated *C. mukul* exerts anti-diabetic activity via DPP-IV inhibition. It guggulsterone act as DPP-IV inhibit enzyme, which can help to cure type II diabetes.[65]

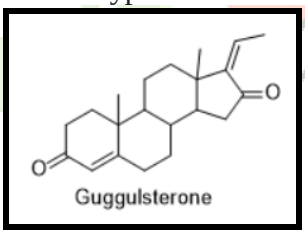

Figure-18: Active constituents of *Commiphora mukul* as DPP-IV inhibitors

***Punica granatum* (Ayurvedic/Sanskrit name: Dadima; Common name: Pomegranate)**

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 plants extract i.e *Trigonella foenum-graecu*, *Cicer arietinum*, and *Punica granatum* has potent inhibition effects on DPP-IV, with IC_{50} values of 0.03, 0.09, and 0.19 mg/mL, respectively.[66] Fruit peel of pomegranate plant *Punica granatum* were subjected to extraction with four solvents (distilled water, 80% methanol, 80% acetone and a mixed solvent that included methanol, ethanol, acetone and n-butanol at proportions (7:1:1:1 v/v/v/v), respectively. Methanol extract recorded the highest DPP-IV activity. (47.1 ± 1.5%).[67] Methanol extraction of pomegranate peels are recommended to be a target for investigations involved in the development of anti-T2DM and anti-cancer therapies. Components in pomegranate (punicalagin and ellagic, gallic, oleanolic, ursolic and uallic acids) were found to have antidiabetic effect. *Punica granatum* inhibit IRS-1 (Insulin receptor substrate 1), GLUT-2 (Glucose transporter 2) and GLUT- 4 (Glucose transporter 4).[68]

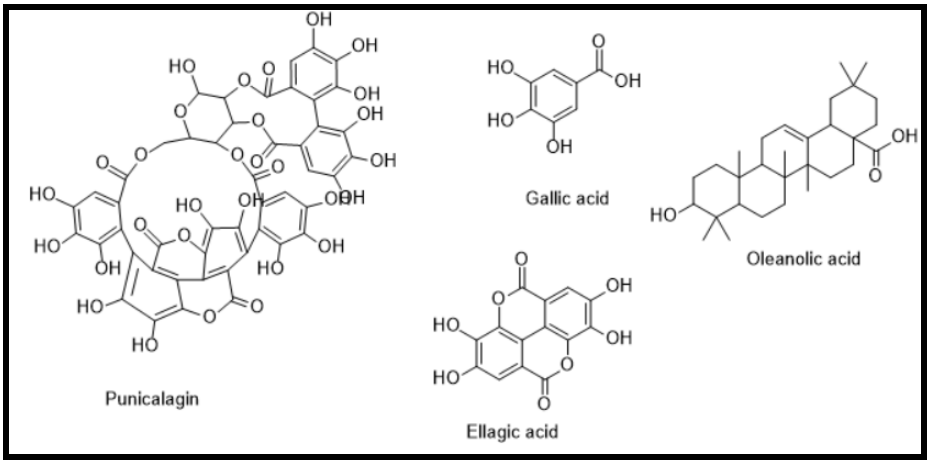

Figure-19: Active constituents of *Punica granatum* as DPP-IV inhibitors

***Calocybe indica* (Ayurvedic/Sanskrit name: Amlika; Common name: Milky white mushroom)**

Calocybe indica belongs to family Tricholomataceae, is rich in protein, flavonoids, lipid, terpenes, polyketides, fiber, carbohydrate and vitamin.[69] The ODE and LE were tested against α-amylase, α-glucosidase, and dipeptidyl peptidase-IV (DPP-IV). The oven dried extract demonstrated 50% inhibitory activity for α-amylase, α-glucosidase and DPP-IV enzyme at 62.18 µg/ml, 47.77 µg/ml and 91.84 µg/ml, respectively. The lyophilized extract revealed 50% inhibitory activity for α-amylase, α-glucosidase and DPP-IV enzyme at 38.11 µg/ml, 28.09 µg/ml and 60.91 µg/ml, respectively.[70]

***Aronia arbutifolia* (Ayurvedic/Sanskrit name: Aronia berry; Common name: Chokeberries)**

Aronia arbutifolia (L.) Pers. *Aronia arbutifolia* (family; Rosaceae) is a genus of deciduous shrubs. It is also known as red chokeberry. Aronia berries exert lipid lowering, cardioprotective, antihypertensive, gastroprotective, anti-inflammatory, anti-oxidant and anti-diabetic activities.[71] Aronia juice was fractionated by column chromatography and eluted fraction was subjected to determine DPP-IV inhibitory activity. 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.[72,73]

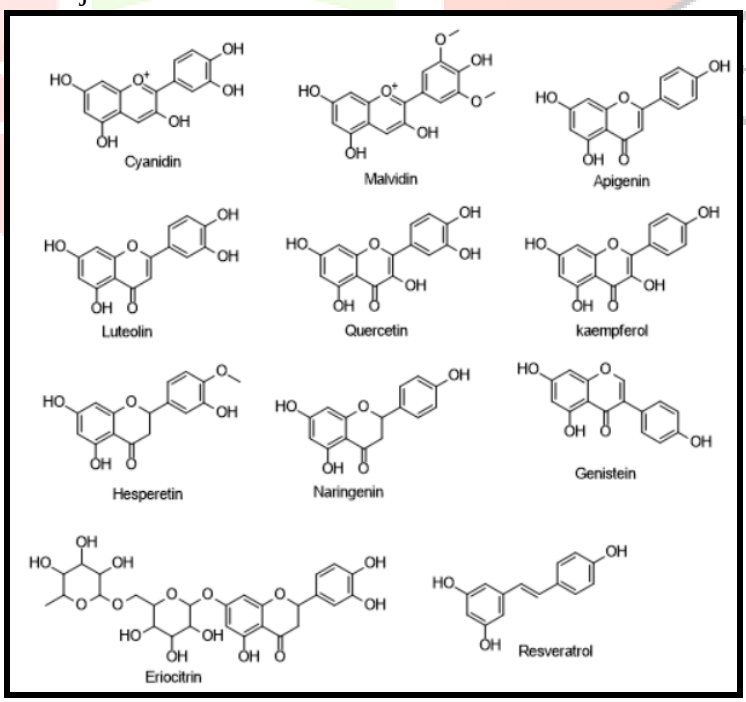

Figure-20: Active constituents of *Aronia arbutifolia* as DPP-IV inhibitors

***Urena lobata* (Ayurvedic/Sanskrit name: Sakhee Kandakeephala; Common name: Malayalam)**

Roots and leaves of *Urena lobata* have been used empirically by Nigerian people to treat Diabetes. DPP-IV inhibitory activity of *U. lobata* ethanolic extract was stronger than water extract during in–vitro testing but opposite was found with *in–vivo* study.[74] Yudi et al. isolate ten active substance include alkaloid, fitosterol

and flavonoid from alcoholic and water extract of *U. lobata*. DPP-IV inhibitory activity was proven by molecular docking study of leaf extract. The study shows mangiferin, stigmasterol, beta sitosterol is responsible for DPP-IV inhibitory activity.[75]

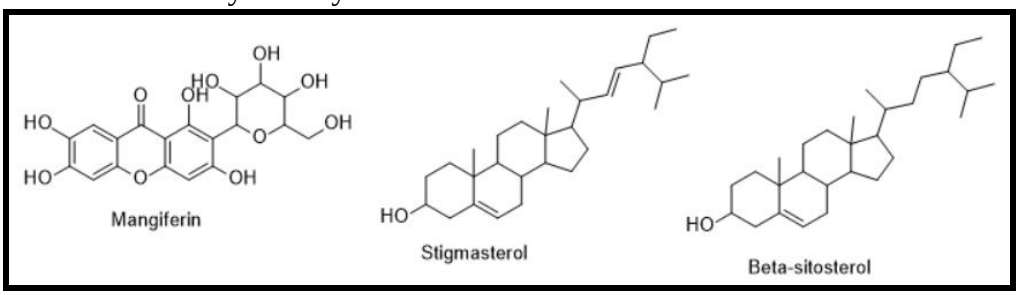

Figure-21: Active constituents of *Urena lobata* as DPP-IV inhibitors

Pueraria tuberose **(Ayurvedic/Sanskrit name: Vidarikand; Common name: Bilaikand, Kudzu)**

Hot water extract of roots of *P. tuberose* showed DPP-IV inhibitory activity. 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. *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.[76] 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. Shrivastava et al. reported that puerarone and robinin are the potential phytochemicals responsible for DPP-IV inhibitory activity of roots of *P. tuberose*.[77]

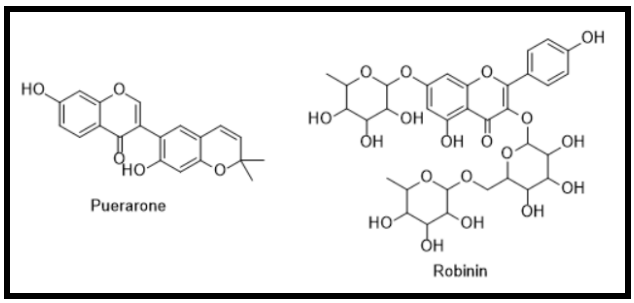

Figure-22: Active constituents of *Pueraria tuberose* as DPP-IV inhibitors

Antidesma madagascariense **(Ayurvedic/Sanskrit name: Antidesma bhasimbilla; Common name: Bois bigaignon batard)**

Antidesma madagascariense leaves showed antidiabetic potential via DPP-IV inhibitory activity *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.[78] Preparative scale HPLC technique was developed for isolation of active constituents responsible for DPP-IV inhibitory activity. Amentoflavone was identified as DPP-IV inhibitor with an IC_{50} value of 3.9±0.5 µM. This is the first report on DPP-IV inhibition by amentoflavone.[79]

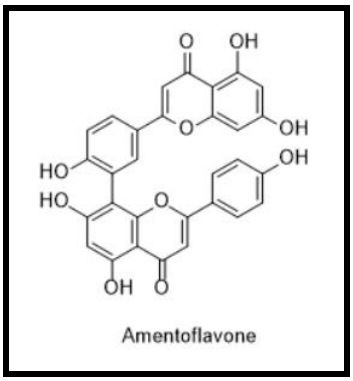

Figure-23: Active constituents of *Antidesma madagascariense* as DPP-IV inhibitors

***Avena sativa* (Ayurvedic/Sanskrit name: Avasa; Common name: Oats)**

Avena sativa known as the common oat, is a species of cereal grain grown for its seed.[80] Wang F. et al. have identified the peptides which released from oat and found out *in-vitro* inhibition activity on DPP-IV. Oats are highly responsible for inhibiting DPP-IV enzyme and showed a significant level of inhibition with IC_{50} 0.99 mg/mL.[81] Bleakley S. et al. have predicted the release of bioactive inhibitory peptides occurring from oat protein hydrolysates followed by in silico hydrolysis using the proteases papain and ficin. The isolated oat proteins showed DPP-IV inhibition between 3.7 ± 3.9% and 46.2 ± 28.8%.[82] Tricin is used for DPP-IV inhibitor in Oat.[83]

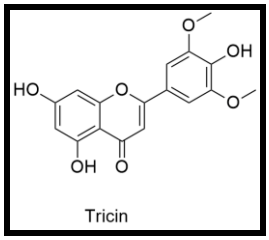

Figure-24: Active constituents of *Avena sativa* as DPP-IV inhibitors

***Eugenia Jabolana* (Ayurvedic/Sanskrit name: Jambu; Common name: Jamun)**

Eugenia jambolana Lam. or *Syzygium cumini* Skeels., a plant of the Myrtaceae family, is commonly known as jambolão in Brazil, jamun in India, and black plum in Europe. *In-vitro* assay suggested that *Eugenia Jambolana* potently inhibits DPP-IV enzyme with IC_{50} values of 278.94 µg/mL.[84] Further, pharmacodynamic and pharmacokinetic interactions of aqueous extract of *Eugenia jambolana* seeds (400 mg/Kg) with other DPP-IV inhibitor drug sitagliptin (10mg/Kg) were studied by Vora A. et al.. These combination drug showed a better hypoglycemic action instead of individual drug.[85] Hispidulin and Petunidin is used for DPP-IV inhibitors.

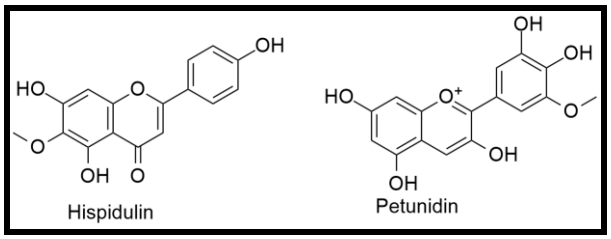

Figure-25: Active constituents of *Eugenia jabolana* as DPP-IV inhibitors

***FerulaAssa-Foetida* L. (Ayurvedic/Sanskrit name: Ramaha; Common name: Hing)**

Phytochemical analyses of Ferula species have confirmed the presence of sesquiterpene coumarins, sesquiterpenes, sulfides and volatile oils.[86-88] Ferulic acid gives activity against DPP-IV inhibitor in ferulaAssa-Foetida L[89].Yarizade A. et al. have extracted *FerulaAssa-foetida* seed using methanol, ethanol, ethanol-methanol, and water and checked for DPP-IV inhibition. All the fractions showed DPP-IV inhibition but ethanolic fraction showed the highest DPP-IV inhibition (24.5 %) [90]. Further, Nagini D. V. et al. have identified active compounds responsible for DPP-IV inhibition through GC-MS which after molecular docking studies identified Ethoxydi (tert-butyl) silane, 9,12-octadecadienoic acid, Methyl tetradecanoate and Hexadecanoic acid as most potent the standard drug saxagliptin.[91]

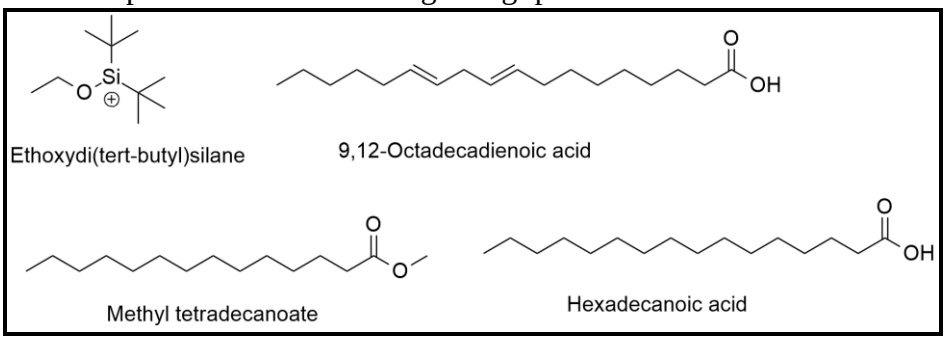

Figure-26: Active constituents of *Ferula foetida* [Asafoetida] as DPP-IV inhibitors

***Fagonia cretica* (Ayurvedic/Sanskrit name: Duhsparsa; Common name: Khorasanthron)**

Saleem S. et al. have identified the chemical compounds responsible for DPP-IV inhibition present in *Fagonic cretica* which was previously reported natural folk medicines for the treatment of diabetes.[92] Crude extract of the plant showed good inhibitory activity with IC_{50} value 38.1 µg/ml. Chemical compounds which showed the inhibitory activity were isolated through bioactivity guided isolation viz. quinovic acid (IC_{50}-30.7 mM), quinovic acid-3β-O-β-D-glycopyranoside(IC_{50}-57.9 mM), quinovic acid-3β-O-β-D-glucopyranosyl-(28-1)-β-D-glucopyranosyl ester(IC_{50}- 23.5 mM), stigmasterol (IC_{50}- 4100 mM).[93] Further Singla R. K. et al. have carried out assessment of pharmacokinetic properties of these naturally originated potent DPP-IV inhibitors like quinovic acid, stigmasterol, quinovic acid-3-beta-D-glycopyranoside.[94]

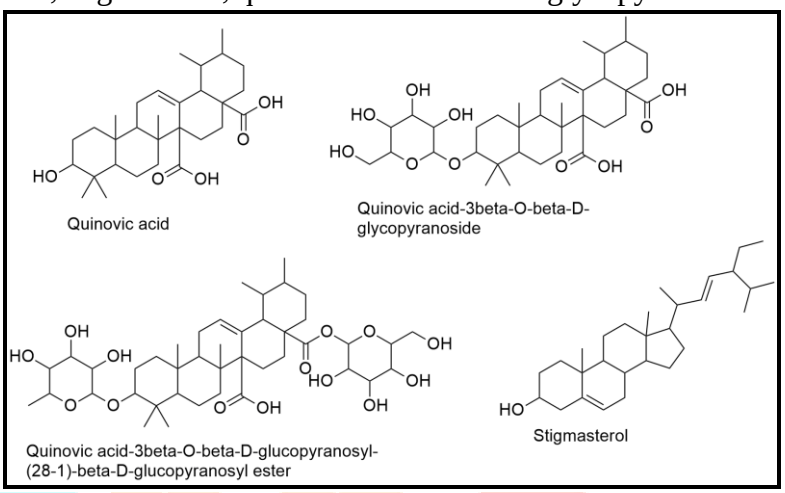

Figure-27: Active constituents of *Fagonia cretica* as DPP-IV inhibitors

***Psidium guajava* (Ayurvedic/Sanskrit name: Perala; Common name: Guava)**

Psidium guajava L. belongs to the Myrtaceae family, have gained attention in the control of diabetes mellitus type II recently[95]. Eidenberger T. et al. have investigated ethanolic extract of leaves of guava for DPP-IV inhibition activity which contain seven main flavanol-glycoside.[96,97] The guava extract showed DPP-IV inhibition of 47.1 ± 7.03%[96]. Amongst seven main flavanol-glycoside, Peltatoside, hyperoside, isoquercitrin and guaijaverin showed 5 to 10 times higher inhibitory effect than that of others. The bioactive compounds guaijaverin and avicularin present in guava leaves are the potent inhibitor of glucose trasporter-4 (GLUT4) and DPP-IV.[98]

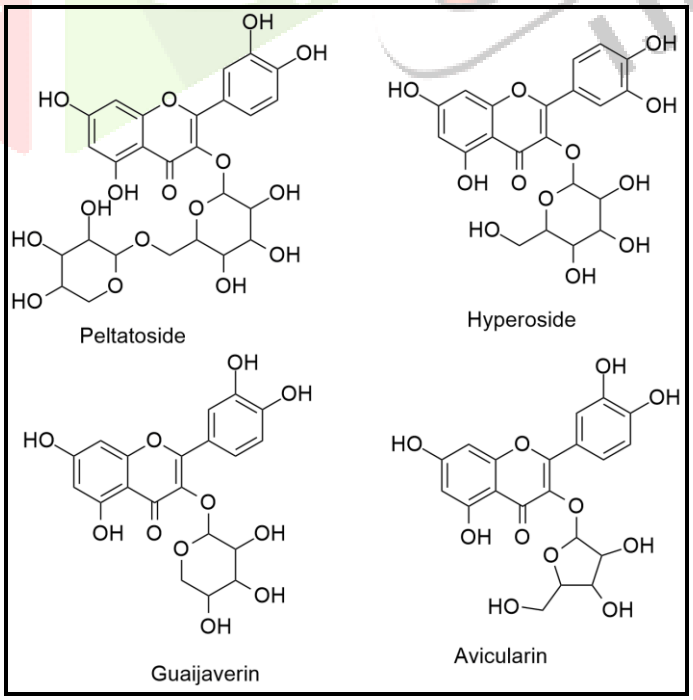

Figure-28: Active constituents of *Psidium guajava* as DPP-IV inhibitors

Morus alba (Ayurvedic/Sanskrit name: Morusalba Common name: Whitemulberry)

Morus alba, moderately fast-growing plant known as White mulberry.[99] The antidiabetic effect of the plant was identified by want H. J. et al. The leaf extract of the plant showed potent *in-vitro* α-glucosidase and DPP-IV inhibitory activities.[100] Agustina M. et al. investigated the effect of acid on ethanolic extract of mulberry stem bark. Apigenin, a bioactive compound of *Morus alba* stem bark extracted using ethanol with acid hydrolysis showed 23 % DPP-IV inhibition.[101]

Some DPP-IV inhibitors from natural origines were listed in **Table-1** with their active chemical constituent and testing methods. Plants with their DPP-IV inhibiting activity were listed in **Table-2** with the part of plant which can be used as DPP-IV inhibitors with other medicinal uses.

TABLE: 1 Natural DPP-IV inhibitors from different origins.

Structure sub class	Compound name	Source	Testing method	References
Alkaloids	Berberine	*Berberis aristata*	Enzymatic	48
	Withanolides	*Withania Somnifera*	Enzymatic	54
	Punicalagin, ellagic, gallic acid	*Punica granatum*	*In-vitro*	68
	Mangiferin, stigmasterol	*Urena lobata*	*In-vitro*	75
	Hispidulin, Petunidin	*Eugeniajam bolana* Lam.	*In vitro*	85
Tanin	Caffeine	*Camellia Senensis (Tea)*	*Ex-vivo*	34-35
	Arjunetin, Arjungenin, Ellagic acid and Arjunic acid	*Terminalia arjuna*	Enzymatic	52
	β-glucogallin	*Emblica officinalis*	Enzymatic	62
	Ellagitannins	*Rosa gallica*	*in-vitro*	63
Flavonoids	Ethanolic extract	*Bodhi leaves*	*in-vitro*	24
	Quercetin, carotenoids	*Mangifera indica*	*in-vitro*	19
	caesalpinianone	*Caesalpinia Sappan*	*in-vitro*	32
	α-amylase	*Calocybe indica*	*in-vitro*	70
	Puerarone and robinin	*Pueraria tuberose*	*in-vivo*	77
	Amentoflavone	*Antidesma madagascariense*	*in-vitro*	78
	Malvidin, luteolin	*Aronia arbutifolia*	*in-vivo*	72-73
	Guaijaverin, avicularin	*Psidium guajava*	*in-vitro*	
Glycoside	Momordicin	*Momordica charantia.*	Enzymatic	6-7
	Emodin, emodic acid	*Cassia nigricans*	Enzymatic	12
	Gymnemic acid	*Gymnema sylvestre*	*in-vitro*	16
	Tricin	*Avena sativa*	Enzymatic	81
	Diosgenin	*Fenugreek seeds*	Enzymatic	57
	α glucosidase	*Morus alba*	*in-vitro*	
Triterpenoids	Eugenol, Urosolic acid	*Ocimum sanctum l.*	*in-vitro*	14
	Allicin	*Garlic (Allium sativum)*	*in-vitro*	26
	Polyphenol and flavanoids	*Eucalyptus globules*	*in-vitro*	60
	Ferulic acid	*Ferula foetida L.*	*in-vitro*	89
Resin	Guggulsterone	*Commiphora mukul*	Enzymatic	65

TABLE 2: Overview of the plants reported as a potent DPP-IV inhibition activity with their inhibition activity.

Plant name	Part of plant used	Medicinal use	DPP- IV inhibition activity (%)	References
Momordica charantia	fruits	Antimicrobial, antihelminthic, anticancer, antifertility, antidiabetic	53.25±0.04	9
Senna migricans	leaves	anticancer, antiinflammatory, antidiabetic, antioxidant	57.0± 1.91	12
Ocimum sanctum L.	leaves	Cough, cold, abdominal pain, antifungal, hepatoprotective, cardioprotective, antidiabetic	66.81±0.05	15
Gymnema sylvestre	leaves	Urinary diseases, antidiabetic, antioxidant	60.21 ± 0.35	17
Mangifera indica	leaves	Anti- lipid, peroxidation, cardiotonic, hypotension, antidiabetes	68.22 ± 1.14	20
Fenugreek	seed	Antiulcer, antifertility, antidiabetic, Immunomodulatory effect	71.29 ±0.33	57
Bodhi leaves	leaves	Antibacterial, gonorrhea, skin diseases, antidiabetes	68.98 ± 1.95	25
Garlic	fruits	hepatoprotective, antiinflammatory, antidiabetic, antioxidant, anthelmintic	50.0±0.01	27
Caeslpinia sappan	leaves	Anticancer, antidiarrhoeal, antifungal	84.25±0.01	32
Camellia sinensis	plants	antioxidant, hypoglycemic agents	63.2 ± 0.01	39
Berberine	plants	Antitumor, antimicrobial, antioxidant	79.2 ± 0.18	50
Terminalia arjuna	bark	Cardio protective, hypotensive, hypolipidemic, wound healing activity, antidiabetes	83.39 ± 7.58	52
Withania somnifera	root powder	Arthritis, anxiety, trouble sleeping, antidiabetes	90.35 ± 0.85	56
Fenugreek	seeds	diabetes, poor appetite, inflammation, digestive problems and menopausal symptoms	71.29 ± 0.33	59
Eucalyptus globules	bark and leaves	diabetes, cough, cold	63.2 ± 0.1	61
Emblica officinalis	fruit	antioxidant, immune modulatory, antipyretic, analgesic, cytoprotective, anti ulser	85.95Â±7.16	62
Rosa gallica	flower	colds, bronchial infections, gastritis, diarrhoea, depression body decrease the blood sugar level	69.01 ± 1.3	63
Commiphora mukul	leaves	anti-diabetic	92.97±8.45	65
Punica granatum	fruit	anti-T2DM and anti-cancer	47.1 ± 1.5	67
Calocybe indica	fruit	anti-diabetic	62.18 ± 1.2	70
Aronia arbutifolia	fruit	cardioprotective, antihypertensive, gastroprotective, anti-inflammatory	28.18 ± 0.92	72
Urena lobata	leaves	stomach-ache, diarrhoea and dysentery	IC_{50} value 57.44 µg/mL	75
Pueraria tuberose	root	anti-diabetic	IC_{50} value 17.4	77

			mg/mL	
Antidesma madagascariense	leaves	anti-diabetic	79.2±2.8	79
Avena sativa	cereals	anti-diabetic	3.7 ± 3.9	82
Eugenia Jabolana	fruits	anti-diabetic	IC_{50} value of 278.94 µg/mL	84
FerulaAssa-Foetida L.	Seeds (species)	Antispasmodics, anti-diabetic	Inhibition 24.5	90
Fagoniacretica	leaves	anti-diabetic	IC_{50} value of 38.1 µg/mL	93
Psidium guajava	fruit	anti-diabetic	47.1 ± 7.03	96
Morus alba	Seeds	anti-diabetic	Inhibition 23	101

Conclusion: Traditional plants are a source of bioactive compounds with diverse scaffolds, well known to treat and manage metabolic disorders like diabetes mellitus. 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. But for the finding of the potential or more advance DPP-IV inhibitors from natural source now a day's molecular docking study is used more prominently. 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 present review will remarkably increase the research to find new DPP-IV inhibitors from natural sources using various modern tools. It is believed that this review will increase the attention of the research group for development of newer natural derivatives which provides better, safe and efficacious DPP-IV inhibitor.

Conflict of Interest

Authors state no conflict of interest

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