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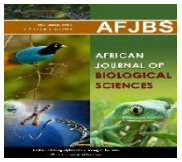

Review Paper **Open Access**

DPP-IV An Emerging Therapeutic Target: Purview from Compounds of Natural Origin

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ABSTRACT
Dipeptidyl peptidase IV (DPP-IV), exerts several physiological functions. It regulates immune system, inflammatory response and particularly manages blood sugar levels through degradation of incretins glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP). The DPP-IV inhibitors terminate the action of DPP-IV to control the degradation of GLP-1 and GIP and increase insulin sensitivity. However, the adverse effects of DPP-IV limit its clinical applications for diabetics especially with comorbid conditions. This firmly demands novel DPP-IV inhibitors from synthetic or natural sources like herbs, plants having lesser side effects for clinical benefits. Surfacing researches provide evidences that phytochemicals from plant sources improve glucose metabolism by increasing insulin sensitivity, stimulation of pancreatic β-cells through signalling pathways like cAMP/PKA, P13K/Akt, SIRT-1, AMPK etc. The plantbased compounds also improve metabolic diseases by improving insulin sensitivity in peripheral tissues. This review attempts to assimilate the data regarding capacity of natural compounds that target DPP-IV for various physiological benefits including diabetes.

Keywords: DPP-IV, Diabetes, Phytochemicals, Flavonoids, Plant sources

1) INTRODUCTION

The dipeptidyl peptidase-IV (DPP-IV), or CD26 is ubiquitous glycoprotein, that exists in two isoforms, soluble and insoluble. The insoluble form is a cell membrane-bound glycoprotein which is expressed on the surface of various cells while the soluble form is present mostly in body fluids [1]. This transmembrane type-II protein is released through a non-classical secretory mechanism from cell membrane. As an exopeptidase it degrades a number of substrates like cytokines, growth factors including gut peptides/incretins. It is present in tissues like monocytes, lymphocytes, intestines, vascular endothelium, adipose tissues, thymus, kidney, spleen etc. Elevated levels of DPP-IV have been observed in diseases of metabolic origin like diabetes and obesity, non-alcoholic fatty liver and cardiovascular diseases. Contemporary researches have expanded the pharmacological profile of DPP-IV inhibitors for the therapy of some metabolic diseases or their complications [2,3]. Among the various substrates of DPP-IV it specifically targets incretins: glucagon-like peptide-1 (GLP- 1) and gastric inhibitory polypeptide (GIP). These incretins are released from small intestine in response to glucose after meal ingestion that consequently causes absorption and digestion of food. This phenomenon is also known as ‘incretin effect’. The metabolic degradation of incretins is associated with insulin resistance and metabolic dysregulation. The enzymatic breakdown of incretins attenuates their insulinotropic effect that causes an increase in blood sugar levels [4].This led to the development of synthetic DPP-IV inhibitors like sitagliptin, vildagliptin, saxagliptin, alogliptin, denagliptin etc. In order to mitigate the associated side effects of drugs of synthetic origin, plant based and functional foods are getting increasingly recognized [5]. **Table 1** shows the side effects of various anti-diabetic drugs presently used in clinical practice.

The plant-based drugs arise majorly from the developed regions with biodiversity which support the primary healthcare [6].The advancement in the researches have put forward herbal medicines as potent substitute with lesser or no side effects. Dietary fruits, vegetables, tea contain abundant quantities of plant flavonoids that have proven benefits in diabetes and obesity. Seeking compounds of natural origin with fewer side effects is the present need. Therefore, these natural compounds shall be utilized as low cost, effective supplements for metabolic disorders including diabetes [7,8].

Several plant-based compounds have exhibited their anti-diabetic effect but a very few have demonstrated the anti-diabetic potential via targeting DPP-IV. The DPP-IV inhibitory potential

of plants and herbs from wide variety of sources can be utilized for the therapy of diabetes and other related complications. These compounds canbe employed

prophylactically, or serve as preventive or alternate to the present therapies. The structural activity analysis of natural compounds can enable the discovery of newer pharmacological compounds. Primary lead candidates from plant-based compounds would help to discover novel prospectives in drug development [6,9]. **Fig.1** shows the benefits of natural compounds in managing diabetes.

Table 1: Currently available anti-diabetic treatments and their side effects

Class	Drug	Mechanism	Side Effect	References
DPP-IV inhibitors	Vildagliptin, Sitagliptin, Alogliptin, anagliptin, Saxagliptin	↓ Degradation of incretins and ↑ insulin sensitivity	Rash indigestion, respiratory tract infections	[10]
Sulphonyl urea	Glimepiride, Glyburide, Gliclazide	Block K^+ channels at pancreatic cells, and ↑Insulin Secretion	Hypoglycaemia and obesity	[11]
Biguanides	Metformin	↓Gluconeogenesis from liver	Indigestion and lactoacidosis	[12]
Meglitinides analogues	Repaglinide, Nateglinide	↑Insulin Secretion	Hypoglycemia and obesity	[13]
Amylase/ Glucosidase inhibitors	Acarbose, Voglibose, Miglitol	↓digestion of carbohydrates	Flatulence and diarrhoea	[14]
Thiazolidinediones	Pioglitazone, Rosiglitazone	↑Insulin sensitivity	Obesity and oedema	[15]
Sodium glucose transporter inhibitor	Dapagliflozin, Empagliflozin, Canagliflozin,	↓Glucose reabsorption in kidneys	Urinary and genital tract infection	[16]

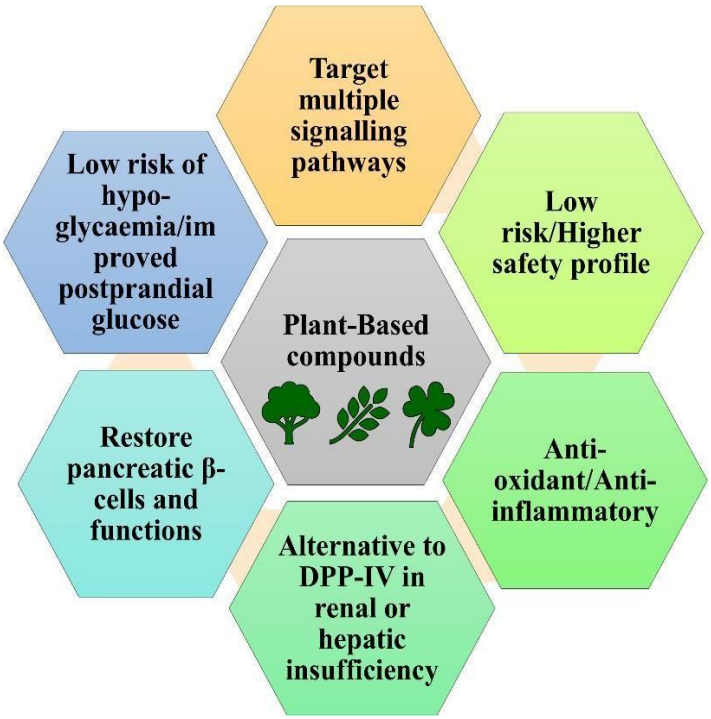

Fig.1: Benefits of natural compounds in managing diabetes.

2) BIOLOGICAL ACTIVITY OF DPP-IV

DPP-IV is an 88 kDa serine protease enzyme, having 766 amino acids containing catalytic domain and cytoplasmic region with transmembrane domain and an extracellular domain. It exists in two isoforms, membrane bound (mDPP-IV) and soluble (sDPP-IV) form. The membrane bound form has complete DPP-IV peptide while the soluble form is devoid of transmembrane and cytoplasmic regions. Both of these forms have their significant pathological and physiological role in human biology [17]. DPP-IV is present in dimer form and cleaves specific peptides with N-terminal region. It is largely expressed in cells like lymphocytes, fibroblasts and endothelial cells. Circulatory DPP-IV in its active enzymatic form undergoes proteolytic cleavage from plasma membrane by matrix metalloproteinase which increases its plasma concentration [1,18,19]. The enzymatic regions remain intact during this process. Major biological actions are carried by sDPP-IV through several cellular signalling pathways. Though there is a knowledge gap that exists regarding the DPP-IV signalling. Ohm *et al.* reported that PAR2 (protease-activated receptor 2 in vascular smooth muscle cells is identified as a functional receptor for DPP-IV. PAR2 is a metabotropic G- protein coupled receptor having seven transmembrane domain and a major receptor for wide variety of responses as it is expressed in most human tissues including immune cells [20].

There are several substrates of DPP-IV and few of which exhibit pleiotropic effect. The protease critically regulates glucose metabolism and is also responsible for cellular signalling, immune response and storage of lipids [21]. sDPP-IV is classified based on its biological function that include hyperglycaemia, damage due to infections, respiratory disease or autoimmune responses. The functions of DPP-IV are dependent on its catalytic activity and ability to bind with several proteins like fibronectin, chemokine receptor, adenosine deaminase, collagen, tyrosine phosphatase and viral proteins like HIV (Human Immunodeficiency Virus). Therefore, cellular processes like T-cell activity, extracellular matrix proliferation are regulated by it. The damage caused by depletion of Th17 cell cause HIV-induced damage to gut is associated with sDPP-IV [22,23].

The physiological role of mDPP-IV is also implicated in hypersensitive reactions, regulation of immune response and autoimmune disease. In a clinical study with Hashimoto's thyroiditis, patients exhibited significant decrease in expression of mDPP-IV in $CD8^+$ T cells [24]. While, in another allergic condition psoriasis, the mDPP-IV expressions were found to be higher than normal skin by 11-folds [25]. Through stimulation of T cell activation, mDPP- 4 was also found to play a crucial role in asthma progression [26]. These researchers indicated potential biological role of both forms of DPP-IV.

3) SIGNIFICANCE OF DPP-4 INHIBITION

DPP-IV inhibitors have earned a lot of attention for their prominent role in regulation of glucose metabolism by preventing the degradation of incretin hormones. The inhibition of DPP-IV has been clinically translated for regulation of glucose in diabetic patients [21]. Molecular sieve partition technique showed that the DPP-IV sequence that impart highest inhibition are is Leu-Pro-Val-Pro-Gln, Phe-Ser-Asp, Trp-Ser-Gly, and Ala-Pro [27].

Several DPP-IV inhibitors with potent and selective activity with novel structures have been investigated and reported. Based on their electivity, absorption, inhibition potential, oral bioavailability and half-life these agents are categorized and designed as peptides, peptide mimetics and non-peptide mimetics. These compounds have shown cardiovascular safety, decrease in blood pressure, attenuation of inflammation, improvement in vascular endothelial function, extra glycaemic effect apart from regulation of glucose metabolism. However, these benefits accompany certain side effects like angioedema, rheumatoid arthritis or haemolysis [28]. The biological activities direct sDPP-IV to essentially regulate the chemotactic activity, immune and inflammatory response. In lieu of this, serum levels of sDPP-IV serve as marker

for physiological inflammation and immunological activity. The substrates of both isoforms of DPP-IV, colony stimulating factor (CSF) and SDF-1/CXCL12 (stromal cell-derived factor-1) attract hematopoietic stem cells. This association increases the chances of success during transplantation [17,29].

Inhibition of mDPP-IV activity attenuated the angiogenesis by suppressing mDPP-IV/SDF- 1α which reversed ventricular dysfunction [30]. DPP-IV inhibitors delayed the progression of pulmonary hypertension by modifying pulmonary artery [31]. DPP-IV inhibitors also altered the activity of macrophages through suppression of natural killer cells was seen that mitigated the lung cancer [32]. Overall, these studies collectively suggest comprehensive biological role of sDPP-IV and mDPP-IV and pathological effect of inhibition of the protease and unanticipated side effects.

4) PHYTOCHEMICALS AND DPP-4 INHIBITION

Pharmacological and phytochemical dimensions of plants in regulating incretin hormones through DPP-IV inhibition is reformative. DPP-IV inhibitors from different natural origins are screened using discrete approaches to achieve the desired inhibition towards the target. It is intriguing to note that the natural compounds with dominant DPP-IV inhibitory activity include phenols, terpenoids, flavonoids and peptides. Surprisingly, alkaloids have not been explored well to have DPP-IV inhibitory potential while crude extracts or protein hydrolysates have demonstrated their DPP-IV inhibition capacity. **Fig. 2** shows the regulation of diabetes with natural plant-based compounds.

A number of plants have been proven to have anti-diabetic efficacy, but this didn't qualify them well enough to be utilized as potential alternate to modern medicines. In-vitro studies have showed that DPP-IV inhibition from aqueous extracts from various plants like *Azadirachta indica* (seeds), *Trigonella foenum-graecum* (seeds), *Mangifera indica* (seeds), *Aegle Marmelos* (leaves), *Anogeissus Latifolia* (bark), *Cratoxylum cochinchinensis* (bark) ranged from 9-96% [33]. Crude extracts of *Hedera nepalensis* and *Fagoniacretica* which are chemically diverse plants, exhibited DPP-IV inhibitory activity. Quinovic acid from *Fagonia cretica* showed highest inhibition against the protease suggesting significant anti-diabetic activity [9].

The anti-diabetic potential of *Pterocarpus marsupium* and *Eugenia jambolana* were explored in diabetic rats. These plant extracts exhibited significant DPP-IV inhibition with $IC_{50}$of 273.73 ± 2.96 and 278.94 ± 6.73 µg/mL, respectively. They also improved the circulating GLP-1 levels

in rodents suggesting their capacity in glucose regulation during diabetes [34]. Interestingly, the same team of researchers explored the role of these plants extracts in neurodegenerative diseases like Alzheimer's disease (AD). The extracts at the doses of 200 and 400 mg/kg exhibited neuroprotection in diabetes-induced AD in Wistar rats. The radial arm maze test and the hole hole-board test showed improvement in cognition. After 30 days treatment a decrease in tau phosphorylation and increase in circulating GLP-1 levels was seen that caused neuroprotection [35]. In the year 2019, another study suggested association of DPP-IV with AD. Quercetin and triterpene rich fraction (F1) and polysaccharide rich fraction (F2) of *Abelmoschus esculentus* were found to suppress DPP-IV-induced apoptosis *in-vitro*. Both F1 and F2 fractions prevented the amyloid beta(Aβ)-mediated neuronal apoptosis. They improved the insulin signalling and Aβ levels. F2 fraction attenuated the activity of caspase 3 at a low dose of 1 µg/ml while F2 could exhibit similar effect at a dose of 25 µg/ml. They improved the AMPK and P13K activity while showed a decrease in p-IRS-1-Ser307and p- Tau. The activity of p-GSK-3β was more pronounced with F1 fractions [36].

Procyanidins have been shown to have extracted from grape-seed were identified to have biological activities like anti-oxidant, anti-tumor, anti-inflammatory including potent anti-diabetic activity. In human intestinal cells, Caco-2, chronic treatment with this procyanidins decrease the activity as well as gene expression of DPP-IV. In addition, 30% decrease in gene expression and 40% decrease in DPP-IV activity was observed in female Wistar rats, cafeteria rats and Zucker rats at 25 and 35 mg/kg dose. The attenuation of enzyme activity and downregulation of expression contributed to the antihyperglycemic effect of procyanidins [37]. Another *in-vivo* study on wild type C57BL/6 male mice decreased the progression of osteoarthritis targeting DPP-IV inhibition. The effect was stipulated to be via activation of Sirt1 that caused a decrease in cellular senescence and apoptosis in chondrocytes leading to amelioration of osteoarthritis. These results suggested involvement of DPP-IV/Sirt1signalling cascade in progression of osteoarthritis [38].

Huang *et al.* evaluated the polyphenols from *Hibiscus sabdariffa* and identified it to have significant potential *in-vivo* in Sprague-Dawley rats. At the dose of 1 mg/ml the polyphenol (in combination with linagliptin) altered the compensated GLP-1 receptor and inhibited DPP- IV activity. It improved the insulin sensitivity and modified the downstream signals cascade induced by palmitate, and epithelial mesenchymal transition mediated by angiotensin receptor-1.These results manifest *Hibiscus sabdariffa* polyphenols as prevent adjuncts for anti-diabetic treatment [39]. Isoflavone phytoestrogen from Glycine max (soybean), genistein also exhibited

suppression against circulating DPP-IV in rodents. At intraperitoneal once daily dose of 2.5, 5, and 10 mg/kg it remarkably decreased the neuronal apoptosis and enhanced cellular viability and increased the concentration of GLP-1 in diabetic Swiss albino male mice with cerebral ischemia-reperfusion [40]. Another study investigated the capacity of anthraquinone emodin from *Rheum palmatum* also inhibited activity of DPP-IV in rodent model. Oral administration of emodin at dose of 3, 10 and 30 mg/kg dose-dependently downregulated the DPP-IV activity in male Balb/c mice and male ob/ob (-/-) mice. These outcome revealed that emodin exhibited anti-diabetic property through a decrease in DPP-IV activity [41]. *In-vitro* and *in-vivo* studies also demonstrated anti-diabetic effect of isoflavones extracted from *Polygala molluginifolia*. At various doses of 10, 25, and 50 mg/kg it inhibited the activity of maltase, enhanced glucose tolerance, insulin secretion and increased glycogen in liver preclinically. It also stimulated the incretin GLP-1 levels in animals with hyperglycaemia exhibiting anti-diabetic effect. While it showed DPP-IV inhibition when given in combination with sitagliptin *in-vitro* [42].

The nutraceuticals supplement containing citrus bioflavonoids (500 mg), vitamin C (500 mg), rutin (900 mg) and hesperidin (37.5 mg) exhibited DPP-IV inhibitory activity comparable to gliptins[43]. By using molecular docking tool, saponins momordicosides D, charantin and cucurbitacin from *Momordica charantia* showed significant role in glucose regulation via GLP-1 and DPP-IV inhibition. When given in diet to rats (5-20%) it elevated the levels of GLP-1 by 295.7% while decreased the activity of DPP-IV by 87.2%. In addition, the potential for anti-diabetic activity also attributed to the activation of TGR-5 (Takeda G- Protein coupled receptor-5) [44]. Another study demonstrated the anti-diabetic prospective of single-dose and long-term administration of 16-hydroxycleroda-3,13-dien-15,16-olide (HCD) which is a diterpenes extracted from *Polyalthia longifolia.* HCD was found to terminate the GLP-I affecting PKA and decreased the ERK phosphorylation induced by lipopolysaccharide *in-vivo* in obese mice and *in-vitro* in AR42J rat pancreatic tumor cells, Caco-2 colorectal adenocarcinoma cells and C2C12 mouse myoblast cells [45].

Myricetin found abundantly in *Macrotyloma uniflorum* (Horsegram) effectively decreased DPP-IV activity when given in combination with horsegram protein (HP). At a concentration of 35 µg/g flour in the presence of HP, the researchers reported anti-diabetic effect in streptozotocin-induced diabetic Wistar rats. Myricetin altered DPP-IV activity, that subsequently raised GLP-1 levels and improved insulin sensitivity. In addition, it also modulated NLRP3 inflammasome activity that contributed towards the anti-hyperglycaemic effect of the myricetin [46]. The ethanolic extract of pods of *Prosopis cineraria* showed its anti-

diabetic potential when the molecular docking showed promising association with DPP- IV. *In-vitro* analysis showed that the extract showed 64.8% inhibition for DPP-IV enzyme. Whereas, *in-vivo* study exhibited its significant potential for glucose control and improved insulin resistant in rodents [47]. Traditionally, garlic bulb has been used to decrease the blood glucose levels though the mechanism remains unclear. To identify the possible mechanism extract of garlic bulb was explored for its DPP-IV inhibitory and anti-oxidant capacity. The results showed that 50% inhibition of enzyme activity was observed at concentration of 70.9 µg/ml while 10 µg/ml exhibited 20% scavenging of reactive oxygen species. These results suggested that phytochemicals from garlic showed their antihyperglycemic activity through DPP-IV inhibition [48]. The folk medicine amla or *Emblica officinalis* has proven pathological benefits in Ayurveda. The fruit extract from amla containing β-glucogallin and hydrolysable tannins (100 gm/kg) were investigated for its anti-diabetic effect *in-vitro*. The extract exhibited significant inhibition of DPP-IV (IC_{50} 3770 µg/ml), and of α-glucosidase (IC_{50} 562.9 µg/ml). It also decreased the pancreatic and salivary α-amylase (IC_{50} 135.70 µg/ml). These results support the pharmacological benefits of amla with potent anti-diabetic effect [49].

Chloroform extract of various phytochemicals from *Melicope latifolia*like protocatechuic acid, methyl p-coumarate and halfordin also showed potential DPP-IV inhibition [6]. Extracts from *Garcinia linii* and active component syringaldehyde also exhibited DPP-IV inhibitory activity. It also altered activity of AMPK, PPARγ and α-glucosidase in diabetic ICR mice and in 3T3-L1 mouse embryo cells as well as in FL83B mouse hepatocytes was observed [8].Phytochemicals from fruit of *Withania coagulans* were evaluated for their anti-diabetic activity through inhibition of DPP-IV activity in diabetic rats. The fruit extract exhibited DPP-IV inhibition (63.2%) and decreased oxidative stress, altered lipid profile, improved insulin sensitivity thus improved glucose homeostasis. Moreover, it also restored the altered pancreatic tissues in rats [50].

In another study on diabetic and obese rat models, the anti-diabetic potency of ethyl acetate extract from *Chlorophytum alismifolium* was evaluated. The oral administration of extract at various concentrations (150-600 mg/kg) decreased the DPP-IV levels, increased the serum insulin activity and PPAR-γ levels. These results suggested anti-diabetic activity of these natural compounds through DPP-IV inhibition [51].

Lim *et al.* investigated the underlying mechanism regarding post-prandial hypoglycaemic effect of the extract from New Zealand pine bark. The study suggested that this extract delays the

digestion of carbohydrates, decrease enzyme activity of α-amylase and α-glucosidase. There was a significant decline in activity of DPP-IV enzyme activity that consequently enhanced the incretin effect exhibiting post-prandial glucose regulation [52]. The *in-vitro* assays of the phytochemicals form fruits of *Passiflora edulis* also showed its anti-diabetic potential in mouse liver. It showed inhibition of DPP-4 (IC_{50} 71.1 ± 2.6 µg/ml) levels in addition to decrease in α-amylase (IC_{50} 32.1 ± 2.7µg/ml) and α-glucosidase (IC_{50} 76.2 ± 1.9µg/ml) activity [53].

Kumar *et al.* also explored the anti-diabetic activity of the phytochemicals of this plant. The *in-vitro* examination showed a 68.3% inhibition in DPP-IV activity by the extract. While *in- vivo* investigations in diabetic rats exhibited that through regulation of DPP-IV activity. It restored the pancreatic cells and enhanced glucose regulation in animals. The extract additionally improved the neurological complication through inhibition of acetylcholinesterase and butyryl cholinesterase that aroused due to insulin resistant [54].

The various *in-vitro* and preclinical studies demonstrated the DPP-IV inhibitory activity of plant-based compounds. This inhibition not only regulated the bold sugar levels but also showed benefitted the diabetic complications and other pathological conditions.

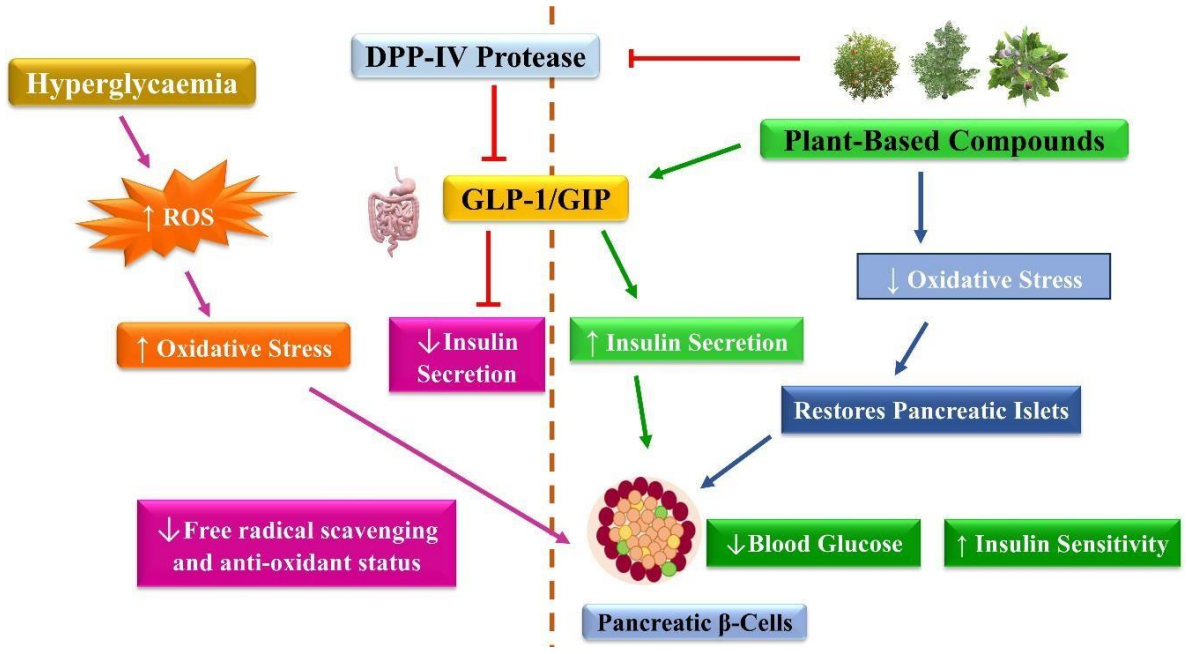

Fig.2: Regulation of hyperglycaemia through plant-based compounds.

5) CONCLUSION & FUTURE DIRECTIONS

The inhibition of DPP-IV appeals as target for anti-diabetic activity as it enhances the life of incretin hormones and improves insulin sensitivity. Therefore, DPP-IV inhibitors/gliptins are utilized clinically for the management of type 2 diabetes mellitus. It also has other significant biological functions like immune regulation, inflammation, lipid regulation and maintenance of vascular endothelium. Despite the availability of several modern treatments such as biguanides, sulphonyl urea, SGLT2 inhibitors etc., their cost and side effects limit their clinical translation owing to diabetic complications. Therefore, plant-based compounds are being researched mindfully for their potential role in controlling diabetes. The emerging evidences regarding multiple roles of DPP-IV directs the researchers to attentively explore phytochemicals from plant sources that may provide safe and effective alternative treatment. DPP-IV inhibition by phytochemicals exhibit their effect by through targeting several signalling pathways including cAMP/PKA, DPP-IV/SIRT-1, P13K/Akt, AMPK, PPARγ etc. Nonetheless, extensive studies with different models and associated co-morbid conditions of diabetes are required to evaluate the improvement in circulating GIP and GLP-1 levels by natural compounds. Moreover, to understand the role of individual or multiple phytochemicals identification, isolation, and characterization of these compounds would support and substantiate the anti-diabetic activity of these compounds. It is also noteworthy that DPP-IV inhibitions also provide other pathological benefits like decreasing the complications in neurological disorders like Alzheimer's disease or skeletal disorders like arthritis and osteoporosis. Hence, compelling researchers with natural compounds that target DPP-IV are desired for exploring its benefits besides glucose control.

Conflict of Interest:

The authors declare that they don't have any Conflict
of interest.

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