Synergistic Multi-Enzyme Inhibition by Sri Lankan Medicinal Plants: A Promising Strategy for Effective Diabetes Management - A Comprehensive Review

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Received: 23.06.2025 Revised: 09.01.2025 Accepted: 11.09.2025 Online: 15.12.2025

Abstract Diabetes mellitus (DM) remains a major global health burden, characterized by chronic hyperglycemia that leads to severe complications such as cardiovascular diseases, nephropathy, and neuropathy, significantly contributing to its high mortality rates. Effective management of post-prandial hyperglycemia is a key therapeutic strategy, with enzyme inhibition emerging as a promising approach. While targeting individual enzymes like alpha-amylase and alpha-glucosidase—responsible for starch breakdown—has shown efficacy, growing evidence suggests that the simultaneous inhibition of multiple key enzymes, including dipeptidyl peptidase-IV (DPP-IV), offers superior glucose regulation by preserving incretin hormones like Glucagon-Like Peptide-1 (GLP-1) and Glucose-Dependent Insulinotropic Peptide (GIP). Medicinal plants, rich in bioactive compounds, have demonstrated the ability to exert multi-targeted inhibitory effects on these enzymes, exhibiting potent synergistic activity that enhances their therapeutic potential. This comprehensive review explores the pivotal roles of alpha-amylase, alpha-glucosidase, and DPP-IV in glucose metabolism and highlights medicinal plants with multi-enzyme inhibitory properties. By emphasizing the significance of synergistic inhibition, this review provides insights into the development of next-generation plant-based anti-diabetic therapeutics, offering a more effective, natural, and safer approach to managing DM.

Keywords: Alpha-amylase, Alpha-glucosidase, Diabetes mellitus, Dipeptidyl Peptidase-IV, Inhibitory effects, Medicinal plants

Introduction

Diabetes mellitus (DM) is a metabolic disorder corresponding with chronic hyperglycaemia resulting from deficiency in insulin secretion, insulin action, or both, promoting disturbances of carbohydrate, fat and protein metabolism (ADA, 2014; ADA, 2018). According to the worldwide survey by the World Health Organization (WHO, 2016), 422 million people are globally affected by DM and it will be the seventh leading cause of death by 2030. Moreover, the number will rise to 700 million by 2045 (IDF, 2017). DM is generally divided into four categories: Type 1 diabetes mellitus (T1DM) is autoimmune beta cell destruction usually accompanied by absolute insulin deficiency. Type 2 diabetes mellitus (T2DM) is a gradual decrease in beta cell insulin secretion and insulin resistance. Gestational diabetes is a temporal hyperglycemic condition seen in pregnant women and the fourth category is named as other specific types of diabetes (ADA, 2018). T1DM affects about 5-10% of total diabetic patients (Li et al., 2014) and the prevalence of T2DM is about 90% among the global diabetic patients (Zimmet et al., 2001).

Hyperglycaemia is the characteristic of all types of DM and its consistency leads to various acute and chronic complications that are mostly related to high mortality in DM and the chronic complications responsible for the most devastating consequences. Among the chronic complications, microvascular lesions can cause diabetic retinopathy, diabetic nephropathy and diabetic

neuropathy (Labazi and Trask, 2017). Additionally, the macrovascular complications include cardiovascular and cerebrovascular diseases (Konig et al., 2013). T2DM can also cause the morbidity of depression (Semenkovich, 2015), sexual dysfunction (Tameler and Deveney, 2010) and dementia (Ninomiya, 2014).

The major conventional classes of drugs for the treatment of hyperglycaemia includes insulin secretagogues (enhance release of insulin from pancreatic islets); biguanides (reduce hepatic glucose production); insulin sensitizers (boost the action of insulin); Alpha-glucosidase inhibitors (interfere with the absorption of glucose in the gut); incretin mimetics (stimulate glucose dependent insulin release) and SGLT2 inhibitors (prevent glucose reabsorption in the proximal convoluted tubule) (Padhi et al., 2020). These drugs either administered as monotherapy or given in combination with other oral hypoglycaemics. However, it has been discovered that these drugs have failed to restore the glucose homeostasis completely and reduce the mortality rate associated with DM as expected (Wasana et al., 2021). Severe hypoglycaemia, weight gain, lower therapeutic efficacy owing to improper or ineffective dosage regimen, low potency and altered side effects due to drug metabolism have identified as the major drawbacks associated with above mentioned conventional drugs (Feingold et al., 2000). Furthermore, to highlight the unavailability of effective anti-diabetic drugs, it is important to mention that after the approval of SGLT-2 inhibitors as the newest antidiabetic agent by Food and Drug Administration in 2013, new oral hypoglycaemic drugs have not been introduced to date (Wasana et al., 2021). Thus, there is an urgent need for the development of safe and effective novel pharmaceutical agents with scientific validation of alternative therapies for the management of DM and its associated complications.

Globally, the prevalence of patients who use medicinal plants for the management of DM has noticeably increased in recent years. Moreover, the WHO estimated that 25% of the currently available drugs have derived from various plants. Metformin (dimethyl biguanide) is a reputed to be most widely prescribed pharmaceutical in the treatment of DM. Metformin is derived from galegine a natural product from *Galega officinalis* (also known as Goat's rue), used in herbal medicine in medieval Europe (Bailey, 2017; Rena et al., 2017). Among the small molecule drugs developed over the past 25 years or so, 5% was from natural products, 27% was derivatives of natural products and 30% was synthetic drugs inspired by natural products (Prakash et al., 2015). Therefore, it is evident that there is a great potential to identify more effective anti-diabetic drugs from the plant sources. In recent updates of the treatment of DM alpha amylase, alpha glucosidase and DPP-lV enzyme inhibitors from various plant sources are trending for their ability in the reduction of post-prandial hyperglycaemia. Notably, the simultaneous inhibition of multiple enzymes through synergistic interactions has been shown to be more effective in achieving better glycemic control than targeting a single enzyme alone. Herein, this review summarizes the potential of medicinal plants in providing synergistic therapeutic effects for diabetes management. Given the complex nature of diabetes, we suggest that synergistic inhibition of multiple key enzymes, rather than targeting a single enzyme, offers a more effective strategy for controlling post-prandial hyperglycemia. By simultaneously inhibiting alpha-amylase, alpha-glucosidase, and DPP-IV, plant-derived compounds can enhance glycemic control through complementary mechanisms, thereby improving overall therapeutic outcomes.

Alpha-amylase and alpha-glucosidase enzyme activity and inhibition

Alpha-amylase and alpha-glucosidase are the key enzymes responsible for the metabolism of carbohydrates. Understanding their activities is crucial in the context of glucose metabolism and can be relevant to conditions such as DM. Alpha-amylase is an enzyme that catalyzes the first step in the breakdown of complex carbohydrates (starches) into simpler sugars such as glucose, maltose, maltriose and limit dextrins (Ahmed, 2020). This enzyme catalyzes the hydrolysis of 1,4-glucan linkages present in starch (Gong et al., 2020). It is produced in the salivary glands and pancreas. Alpha-amylase begins its action in the mouth (salivary amylase) and continues in the small intestine (pancreatic amylase) (Kim et al., 2014).
Alpha-glucosidase is an enzyme located in the brush border of the small intestine. It plays a key

role in catalyzing the breaking down of disaccharides (such as maltose and sucrose) and complex carbohydrates into absorbable monosaccharides, primarily glucose (Rahman et al., 2022). This enzyme cuts glucose from the non-reducing end of the polysaccharide by hydrolyzing α- 1,4-glycosidic bond (Gong et al., 2020). Alpha-glucosidase acts on the carbohydrates present in the small intestine before they are absorbed into the bloodstream (Rahman et al., 2022).

Inhibiting these two enzymes can slow down the digestion and absorption of carbohydrates, leading to a more gradual increase in blood glucose levels after meals (Wehmeier et al., 2004)). This is relevant for individuals with DM who need to manage their blood glucose levels.

One effective therapeutic approach for controlling hyperglycemia associated with type 2 diabetes is to target alpha-amylase and alpha-glucosidase, enzymes that catalyzes starch hydrolysis in the intestine. Alpha-glucosidase inhibitors delay the process of carbohydrate absorption in the gastrointestinal track by moving the undigested carbohydrate into the distal part of the small intestine and colon. At present, the approved inhibitors for these enzymes are restricted to Acarbose, Miglitol and Voglibose. They are alpha-glucosidase inhibitors which are oligosaccharides that act as competitive inhibitors for the enzymes, alpha amylase and alpha glucosidase to slow down the digestion of carbohydrates such as starch leading to the reduction in postprandial hyperglycaemia (Narita et al., 2011, Wehmeier et al., 2004). These antidiabetic drugs may cause some adverse effects such as weight gain, hypoglycemia and abdominal distension (Padhi et al. 2020; Xu et al., 2018). It has been suggested that these side effects might be caused by excessive inhibition of the pancreatic alpha-amylase leading to the abdominal bacterial fermentation of undigested carbohydrates in the colon (Salehi et al., 2013). Most of the inhibitors contain sugar moieties and their synthesis involves tedious multistep procedures. Therefore, inhibitors from non-sugar sources could be considered better as they cause lesser side effects (Ahmed et al., 2020).

DPP-IV enzyme activity and inhibition

Recently, considerable interest has been generated by novel class anti-hyperglycaemic agents that act at distinct levels of the incretin pathway. Incretins are group of gastrointestinal hormones, predominantly glucagon like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP) which increase post-prandial insulin release from pancreatic beta cell in glucose dependent manner (Ban et al., 2009). Dipeptidyl peptidase-IV is responsible for the rapid degradation of GLP-1 and GIP (Figure.1) (Makrilakis, K ;2019). Thus, preventing the degradation of incretin hormones, by DPP-IV inhibition became an attractive therapeutic strategy. Several DPP-IV inhibitors such as gliptins currently approved for the treatment of T2DM (Dhillon, 2015; Keating, 2014; Plosker, 2014).

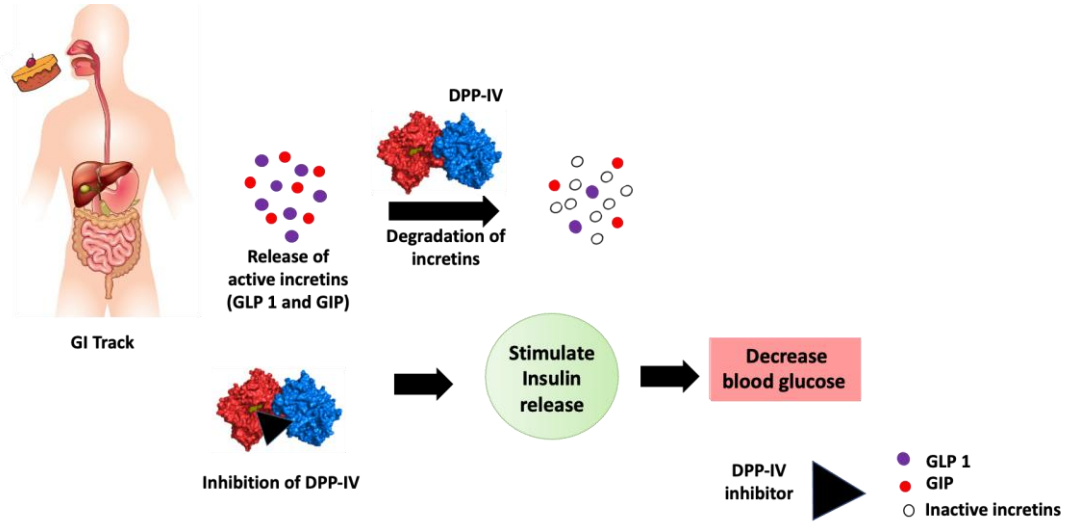

Figure 1: DPP-IV functions and mechanism of DPP-IV inhibitors' action (Makrilakis, 2019)

Natural product extracts of plant origin as sources of alpha-amylase and alpha-glucosidase inhibitors

Natural products of plant origin have been a valuable source of therapeutic agents with lesser toxicity and side effects (Dirir, 2022). Natural products which have been shown to possess a low inhibitory effect against alpha- amylase and high inhibition activity against alpha- glucosidase can be used as an effective means to reduce postprandial hyperglycaemia with minimal adverse effects (Kim et al., 2009; Tarling et al., 2008). Therefore, the search for more effective and safer oral hypoglycaemic compounds from medicinal plants has continued to be an important area of active research. Several studies reported to show ability of various medicinal plants in inhibition of alpha-amylase and alpha-glucosidase. Majority of the studies have been done with crude extracts (organic or aqueous), and some have studied pure components (Kim et al., 2014; Ali et al., 2013). Most of the plant extracts and the pure compounds were effective against alpha amylase or alpha glucosidase with few exceptions being effective against both enzymes (Mohamed et al., 2012; Perez-Gutierrez et al., 2012). A wide range of plant-derived compounds mainly alkaloids, glycosides, terpenoids, polysaccharides, tannins, flavonoids, galactomannan gum and phenolic acids have demonstrated bioactivity against hyperglycaemia inhibiting alpha-amylase and alpha-glucosidase enzymes (Mentreddy, 2007). A list of plants reported to have significant alpha-amylase inhibitory activity and alpha- glucosidase inhibitory activity is shown in Table 1.

Table 1. List of plants having significant alpha-amylase and alpha-glucosidase inhibitory activity

Plant Scientific Name	Common English name	Family	Parts used	Type of extract	Inhibited enzyme	Reference
Ficus racemosa	Cluster Fig	Moraceae	Stem bark	Methanol	Alpha-Amylase & Alpha-Glucosidase	Poongunran et al., 2015
Phyllanthus debilis	Niruri	Euphorbiaceae	Whole plant	Methanol	Alpha-Amylase & Alpha-Glucosidase	
Coccinia grandis	Ivy Gourd	Cucurbitaceae	Leaves	Methanol	Alpha-Glucosidase	
Gymnema lactiferum	Ceylon cow plant	Apocynaceae	Leaves	Methanol	Alpha-Glucosidase	
Gymnema sylvestre	Gurmar (Masbedda)	Asclepiadaceae	Leaves	Methanol	Alpha-Glucosidase	
Musa paradisiaca	Banana	Musaceae	Yam	Methanol	Alpha-Glucosidase	
Phyllanthus embilica	Indian gooseberry	Phyllanthaceae	Fruit	Methanol	Alpha-Amylase & Alpha-Glucosidase	
Pterocarpus marsupium	Indian kino	Fabaceae	Latex	Methanol	Alpha-Amylase & Alpha-Glucosidase	
Strychnos potatorum	Clearing nut tree	Loganiaceae	Seeds	Methanol	Alpha-Glucosidase	
Tinospora cordifolia	Moonseed	Menispermaceae	Leaf	Methanol	Alpha-Glucosidase	
Costus speciosus	Crepe Ginger	Costaceae	Leaves	Methanol	Alpha-Glucosidase	Perera et al., 2016

Plant Scientific Name	Common English name	Family	Parts used	Type of extract	Inhibited enzyme	Reference
Cinnamomum zeylanicum	Dalchini (Kurundu)	Lauracae	Bark	Methanol	Alpha-Amylase & Alpha-Glucosidase	Sindhu et al., 2013
Momordica charantia	Bitter gourd	Cucurbitaceae	Fruits	Methanol	Alpha-Glucosidase	Hussain et al., 2022
Azadirachta indica	Neem	Meliaceae	Leaves, Bark, Seeds	Aqueous & Acetone	Alpha-Amylase & Alpha-Glucosidase	Kazeem et al., 2013
Salacia reticulata	Kothala himbutu	Celastraceae	Root, Stem	Aqueous	Alpha-Glucosidase	Ozaki et al., 2008
Osbeckia octandra	Heen Bovitiya	Melastomataceae	Leaf & flowers	Aqueous	Alpha-Amylase	Wickramasinghe et al., 2022
Passiflora suberosa L.	Corky Passionflower	Passifloraceae	Leaves	Ethyl acetate	Alpha-Glucosidase Alpha-Amylase	Sewwandi and Peiris, 2020
Acacia catechu	Black catechu	Fabaceae	Bark	Methanol	Alpha-Amylase	Khadayat et al., 2020
Calyptranthes caryophyllifolia	Java plum	Myrtaceae	Bark, Fruits, Seeds	Aqueous and Ethanol mixture	Alpha-Amylase Alpha-Glucosidase	Ishartati et al., 2020
Terminalia arjuna	Arjun tree	Combretaceae	Bark	Aqueous	Alpha-Amylase	Thomson et al., 2014
Cassia fistula	Golden Shower Tree	Fabaceae	Flowers	Aqueous and Ethanol	Alpha-Amylase	Fathima et al., 2018
Trigonella foenum-graecum	Fenugreek	Fabaceae	Leaves	Aqueous and ethyl acetate	Alpha-Amylase Alpha-Glucosidase	Ganeshpurkar et al., 2013

The aqueous extracts of *Syzygium cumini* L. (syn: *Eugenia Jambolana* Lam.*)* (Black plum) and *Psidium guajava* (Guava) leaves both showed a dose dependent inhibitory effect on alpha- amylase activity (Karthic et al., 2008). The 50% methanol extracts of *Terminalia arjuna* (Arjun Tree) Roxb bark, *Eugenia cumini* (Black plums) seeds and *Aegle marmelos* (Bael Tree) leaves showed a dose dependent inhibition on pancreatic alpha- amylase activity (Saha and Verma, 2012). Various extracts of *Bixa Orellana* L. (Sindhuri), *Ficus bengalensis* L. (Banyan), *Cinnamomum verum (Cinnamon), Murraya koenigii* L. *(Curry leaves) Syzygium cumini* L. (Black plums) and *Curcuma Longa* L. (turmeric) are known for their hypoglycaemic property, were found to exhibit strong inhibitory action on human pancreatic alpha- amylase even better than acarbose (Ponnusamy et al., 2011). The phytochemicals in the extracts causing this exhibition were identified as alkaloids, proteins, glycosides, flavonoids and saponins (Mentreddy, 2007). Li et al., (2023) investigated the inhibitory activity of raspberry leaf tea (*Rubus corchorifolius* L.) (RLT) extract on digestive enzymes and found potent alpha- amylase inhibitory activity for its ethanolic, methanolic and aqueous extracts.

The polar extracts of *Tetracera loureiri* (Mempelas) leaves showed highly potent alpha-

glucosidase inhibitory effect than the positive inhibitor, acarbose (Kittiwisut et al., 2021). Likewise, the alpha-amylase inhibitory activity of the polar extracts showed stronger activity. These antidiabetic enzyme inhibitor fractions additionally displayed antioxidant activity discovered via

Aqueous extract of *Morinda lucida* Benth (brimstone tree) leaves showed highest inhibitory activity against alpha-amylase and alpha-glucosidase when compared with the acetone and ethanolic extracts. Kinetic analysis revealed that the aqueous extract of this plant leaves inhibited the alpha-amylase competitively but displayed mixed noncompetitive mode of inhibition towards alpha-glucosidase (Kazeem et al., 2013). Inhibitory activity of protein extracts from two kinds of *Momordica charantia* (Bitter melon) on alpha-amylase and alpha-glucosidase showed that their inhibition rate (66% to 69%) and IC50 (0.26 to 0.29) were comparable to acarbose (Poovitha and Parani, 2016).

Alpha-glucosidase and alpha-amylase inhibitory activities of nine Sri Lankan antidiabetic plants was investigated (Poongunran et al., 2015). The study revealed very significantly high alpha-glucosidase and alpha-amylase inhibitory activity of methanol extracts of *Ficus racemosa* (cluster fig) stem bark*, Phyllanthus emblica* (Indian gooseberry) fruit*, Phyllanthus deblis* (Niruri) whole plant and *Pterocarpus marsupium* (Indian kino tree) latex exhibiting promising leads as inhibitory molecules with hypoglycaemic effects. The findings also provided scientific support for their use in traditional Ayurvedic Medicine. *Musa paradisiaca (Banana)* yam and *Tinospora cordifolia* (Moonseeds) leaves also showed considerable inhibitory effects on alpha-glucosidase activity. Therefore, the known hypoglycaemic effects of these plants should be at least partly due to their effects on carbohydrate digestion and absorption. Leaves of *Coccinia grandis* (Ivy gourd), *Gymnema sylvestre* (Masbedda) and seeds of *Strychnos potatorum* (Clearing-nut plant) did not show any considerable inhibitory activity on the two enzymes and they may have other mechanisms for their hypoglycaemic effects. The fruit pulp and leaf of *Annona muricata* (Soursop) demonstrated significantly high abilities to inhibit alpha-amylase and alpha-glucosidase and minimize the rate of glucose assimilation into the blood after feeding (Agu et al., 2019). This is evident in the obtained standard DPPH radical scavenging and Ferric Reducing Ability of Plasma (FRAP) assay. Furthermore, Methanol extract of avocado fruit pulp and seed exhibited significant alpha-amylase and alpha-glucosidase inhibition activity (Dhakal et al., 2022).

IC50, B_{max} (Maximum binding capacity), K_d (Dissociation constant) and V_{max} (Maximum velocity) values which further suggested that the mechanism of inhibition is that of uncompetitive inhibition, thus conferring an appreciable potency and efficacy for the plant compared to standard drugs.

The extracts of *Allium sativum* (Garlic) exhibited a dose dependent inhibition of alpha-glucosidase in comparison to acarbose (Obih et al., 2019). *Allium cepa* (Onion) bulb have been evaluated for its several physiological effects including anti-diabetic properties (Wu and Xu, 2014). However, for onion outer skin and peels very few studies have done to investigate their anti-diabetic potential even though they present great concentrations of phytochemicals (Masood et al., 2021). It was stated that methyl alcohol extracts of *Allium cepa* had potent ability to inhibit alpha-glucosidase activity (Lee et al., 2008). In order to have better understanding of onion's antioxidant potential, the glucosidase inhibitory activity of bulb and peel extract were evaluated and compared in this study. Ethanolic extract of onion peel reported greater inhibition potential as compared to the ethanolic bulb extract being 80% vs 40% respectively which is in accordance with the previously published studies (Kim et al., 2010) while, water extract of bulb reported the lowest activity. The comparative analysis of alpha-glucosidase and alpha-amylase inhibition potential of various extracts was also done, and it was revealed that the onion bulb and peel extracts caused prominent alpha-glucosidase inhibition but depicted significantly lower potential against inhibition of alpha-amylase. In previous studies, alpha-amylase and alpha-glucosidase inhibition mechanism of several phenolic compounds and quercetin in particular which is the major flavonoid of onion has been thoroughly investigated (Nile et al., 2021; Chen et al., 2020).

It was shown that inhibitory activity of anthocyanin rich bilberry extract on alpha-glucosidase and alpha-amylase and their interaction mechanism *in vitro* (Ji et al., 2021). The enzyme kinetics revealed

the bilberry extract acts as a mixed type of inhibitor against alpha-glucosidase. A morphological observation of starch granules found that bilberry extract inhibited the activity of alpha-amylase to postpone the hydrolysis of starch. Different concentration of the aqueous extract of *Costus igneus* (Insulin plant) and solution of metformin and acarbose (standard drug) were taken and assessed for the antidiabetic activity based on their alpha-amylase and alpha-glucosidase inhibition (Sanjana et al., 2022). The alpha-amylase inhibitory action of *Costus igneus* was 89% of that of metformin at concentration of 500 □g. The alpha-glucosidase inhibitory action of *Costus igneus* was 66.6% of that of metformin at same concentration. The study has shown that the aqueous extract of the leaves of *Costus igneus* could serve as an alternative to the commonly used antidiabetic drug metformin. The inhibitory activities of methanolic extracts of *Artocarpus altilis* (Breadfruit), *Artocarpus heterophyllus* (Jackfruit), *Cinnamomum Zeylanicum* (Kurundu) and *Piper betel* (Betel Pepper) were evaluated on wheat alpha-amylase and baker's yeast alpha-glucosidase at varying concentrations (Sindhu et al., 2013). Out of the four extracts *Artocarpus heterophyllus* (Jackfruit) showed the maximum alpha-amylase and alpha-glucosidase inhibitory activity. Chili peppers have demonstrated the ability to control diabetes through inactivation of alpha-amylase and alpha-glucosidase (Watcharachaisoponsiri et al., 2016). Both enzyme inhibitions were dose-dependent, in which the inhibition was elevated with increasing concentration of chili pepper extract.

Natural product extracts of plant origin as sources of dipeptidyl peptidase-iv inhibitors

Various naturally available plant-based compounds are investigated as DPP-IV inhibitors. Different plant parts such as leaves, seeds, flowers, buds and bulbs are analyzed to identify their inhibitory capacity against DPP-IV activity. A list of plants reported to have significant DPP-IV inhibitory activity is shown in Table 2. The DPP-IV inhibitory compounds abundantly present in the leaves compared with other parts of the plant. *Mangifera Indica* (Mango) leaf extract has been shown to have hypoglycaemic properties (Aderibrigbe et al., 2001). The extract of it leaves exhibited DPP-IV inhibitory activity (Yogisha and Raveesha, 2010). The main phytochemical in *Mangifera indica* mangiferin lowered serum DPP-IV levels, improved insulin resistance and improved beta cell function (Suman et al., 2016). *Pterocarpus marsupium* (Indian kino tree), *Eugenia jambolana* (Black plum) and *Gymnema sylvestre* (Insulin plant) are the most important medicinal plants in the Indian system of traditional medicine for the treatment of hyperglycaemia. *P. marsupium* and *E. Jambolana both had potent* inhibitory effects on DPP-IV (Kosaraju et al., 2014). Extract of *Camellia sinensis* (Tea plant) leaves showed inhibitory activity on DPP-IV activity (Ekayanti et al., 2018). The principal component of *C. sinensis* is caffeine which acts as secondary metabolites.

Ethanolic leaf extract of *Psidium guajava* (Guava) and flavonol glycosides isolated from the extract inhibited DPP-IV in a dose dependent manner (Eidenberger, 2013). Ethyl acetate fraction of *Lilium longiflorum* (Easter lily) bulbs was shown to inhibit DPP-IV (Kim, 2020). *Emblica Officinalis* (Indian gooseberry) fruit extract, inhibited DPP-IV and alpha-glucosidases and exhibited antioxidant properties (Majeed et al., 2020). An ethanol extract of *Hibiscus rosa-sinensis* (Chinese hibiscus) significantly inhibited DPP-IV activity, increased insulin release, and thus improved glucose tolerance in type 2 diabetic rats (Ansari et al., 2020). *Urena lobata* (Caesarweed) root extract had anti-hypoglycaemic effects on streptozotocin-induced diabetic rats (Onoagbe, 2010) and in *in vitro*, an ethanolic extract of *U. lobata* showed 4-fold greater DPP-IV inhibitory activity than water extract (Purnomo et al., 2015).

Table 2. List of plants having significant DPP-IV inhibitory activity

Plant scientific Name	Common English Name	Family	Parts used	Type of extract	Reference
Avenia sativa	Oats	Graminaceae	Seeds	Proteins	Wang et al.,2015
Momordica charantina	Bitter gourd	Cucurbitaceae	Fruits	Aqueous	Bhat et al.,2018
Gymnema sylvestre	Gurmar (Masbedda)	Apocynaceae	Leaves	Ethanol/ Hydroalcoholic	Kosaraju et al.,2014
Aloe vera L.	Aloe vera	Xanthorrhoeaceae	Leaves	Ethanol	Raja and Venkataraman, 2016
Allophylus cominia	Cafe Marron	Sapindaceae	Leaves	Aqueous	Calero et al.,2014
Ficus religiosa	Sacred bo tree	Moraceae	Leaves	Ethanol	Riyanti et al.,2016
Punica granatum	Pomegranate	Lythraceae	Rind	Ethanol	Riyanti et al., 2016
Senna nigricans	Senna	Cassia	Whole plant	Methanol	Saidu et al., 2016
Tinospora crispa	Bitter grape	Menispermaceae	Stem	Ethanol	Riyanti et al., 2016
Trigonella foenum-graecum L.	Fenugreek	Fabaceae	Seeds	Ethanol	Riyanti et al., 2016
Pterocarpus marsupium	Indian Kino Tree	Fabaceae	Heart wood	Ethanol	Kosaraju et al.,2014
Syzygium cumini	Black plum	Myrtaceae	Fruits	Ethanol	Kosaraju et al.,2014
Vitis vinifera	Grapes	Vitaceae	Seeds	Acetone and Methanol	Gonza´lez-Abui´n et al.,2014
Moringa peregrina	Ben tree	Moringaceae	Leaves	Methanol	Ullah et al.,2015
Psidium guajava	Guava	Myrtaceae	Leaves	Ethanol	Eidenberger et al.,2013

Natural phytoconstituents as inhibitors of alpha-amylase, alpha-glucosidase and DPP-IV

The scientific literature offers a plethora of reports concerning the *in vitro* alpha-amylase, alpha-glucosidase and DPP-IV inhibitory activity of plants as anti-diabetic remedies (Kashtoh and Baek, 2023; Kashtoh and Baek, 2022; Shaikh, 2021; Xu et al., 2018; R'ios et al., 2015). The extracts that show alpha-amylase, alpha-glucosidase and DPP-IV inhibition *in vitro* comprise extensive lists of natural products incorporated into human diets. Their effects are due to the ambiguous pool of compounds including flavonoids, alkaloids, phenolic acids, anthocyanins, terpenoids, tannins, xanthones, saponins and polysaccharides (Kashtoh and Baek, 2023; Kashtoh and Baek, 2022: Shaikh et al., 2021 ;Tundis et al., 2010).

Acarbose, a well-known drug widely used for clinical treatment of diabetes mellitus is a pseudo-tetrasachcharide, is obtained from *Actinomyces urahensis*. It is a competitive inhibitor of alpha-amylase (Yoon and Robyt, 2002) and alpha-glucosidase (Wehmeier and Piepersberg, 2004).
Two classes of compounds, flavonoids and tannins, are known to inhibit alpha-amylase and alpha-glucosidase and play an important role in carbohydrate metabolism (Shahwan et al., 2022). The most abundant secondary metabolites found in plants are flavonoids. The beneficial health effects

of fruits and vegetables have been linked to flavonoid content. Approximately 500 flavonoid compounds have been reported to display alpha-amylase and alpha-glucosidase inhibitory effect which demonstrates their value in the search for novel safer alternatives for post-prandial hyperglycaemic control (Proença, 2020). Several flavonoids have also been shown DPP-IV inhibitory activity (Singh et al., 2020; Gupta et al., 2018; Wang et al., 2017; Bower et al., 2014).

Tannins are another heterogeneous polyphenol widely distributed in plants that are often present in unripe fruits. However, they can disappear during ripening. They have relatively high molecular weight and can be classified into two major classes: hydrolysable tannins and condensed tannins. Hydrolysable tannins are subdivided into two types, one which consist of esters of gallic acid (i.e. gallotannins) and ellagic acid (i.e. ellagitannins) while condensed tannins are complex polymers which are also called proanthocyanidins (Papoutsis et al., 2021; Tundis et al., 2010; Koleckar et al., 2008). McDougall et al., (2005) showed that strawberry and raspberry extracts, which contained appreciable amounts of soluble tannins, effectively inhibited alpha-amylase. Other tannin-rich extracts (red grape, red wine, and green tea) were also effective inhibitors of alpha-amylase. The inhibitory components were identified as ellagitannins. The ability of tannins to strongly bind to proteins, forming insoluble and indigestible complexes, is probably the action mechanism that underlies alpha-amylase inhibition. However, the extent of alpha-glucosidase inhibition was related to anthocyanin content.

Terpenoids are compounds that comprise various structures commonly found in nature with several functions in plants and animals. They usually arise from head-to-tail joining of isoprene units divide the terpenoids in monoterpene (C_{10}), sesquiterpene (C_{15}), diterpene (C_{20}), seterterpene (C_{25}), triterpene (C_{30}) and tetraterpene (C_{40}) (McGarvey, 1995). Triterpenoids represent a promising and expanding source for biologically active natural compounds whose potential for research and development of new substances with pharmacologic activity. However, even though terpenoids are widely distribute in plants inhibitory alpha-amylase activity was only related oleanane, ursane and lupane types and the mechanisms by which this activity occur still not known.

Synergistic multi-enzyme inhibition potential of medicinal plants

The inhibition of key carbohydrate-metabolizing enzymes such as alpha-amylase, alpha-glucosidase, and dipeptidyl peptidase-IV (DPP-IV) plays a crucial role in managing postprandial hyperglycemia, a hallmark of DM. While conventional enzyme inhibitors are available, they often come with side effects, necessitating the search for safer and more effective alternatives. Synergistic antidiabetic potential of medicinal plants, which contain a diverse range of bioactive compounds that can simultaneously target multiple enzymes such as alpha-amylase, alpha-glucosidase, and dipeptidyl peptidase-IV (DPP-IV) increasing the potential therapeutic strength. The multi-enzyme inhibition approach offers a more comprehensive and effective glycemic control strategy compared to single-enzyme inhibitors. Many plant extracts, rich in flavonoids, tannins, alkaloids, and terpenoids, have demonstrated significant inhibitory effects on alpha-amylase, alpha-glucosidase, and dipeptidyl peptidase-IV (DPP-IV) enzymes, with possibility of exhibiting greater potency than synthetic drugs.

Several medicinal plants exhibit synergistic enzyme inhibition, making them extremely valuable in DM management by targeting key carbohydrate-metabolizing enzymes alpha-amylase**,** alpha-glucosidase**,** and DPP-IV. Many plants such as *Syzygium cumini* (Java Plum) contains flavonoids and tannins that inhibit alpha-amylase and alpha-glucosidase (Karthic et al., 2008) (Shinde et al., 2008). While *Trigonella foenum-graecum* (Fenugreek) inhibits DPP-IV and α-glucosidase, enhancing insulin secretion and sensitivity (Hannan et al., 2007). *Cinnamomum verum* (Cinnamon) provides synergistic enzyme inhibition, improving glucose transporter activity (Shang et al., 2021) (Mohsin et al., 2023). *Ocimum sanctum* (Holy Basil) contains eugenol and **ursolic** acid, which not only inhibit multiple enzymes but also exhibit anti-inflammatory effects (Ahmad et al., 2018). *Gymnema sylvestre* (Gurmar) reduces sugar absorption and supports **β**-cell regeneration through DPP-IV inhibition (Rohani et al**.,** 2023**)**. The combined action of these plants offers a natural**,** multi-target approach to glycemic control, making them promising alternatives or

adjuncts to conventional anti-diabetic drugs. However, despite promising *in vitro* findings, the lack of extensive *in vivo* and clinical studies limits the translation of these plant-based inhibitors into synergistic therapeutic applications. Future research should focus on mechanistic studies, pharmacokinetics, and large-scale clinical trials to validate their efficacy and safety toward multi-enzyme inhibition.

Conclusion

Alpha-amylase is a prominent enzyme found in the pancreatic juice catalyzes the initial step in hydrolysis of starch to alpha-limit dextrins, maltotriose and maltose. Alpha-glucosidase is an intestinal brush border enzyme that catalyzes the liberation of absorbable monosaccharides such as glucose from the substrate which eventually facilitates the absorption by the small intestine. An effective means of lowering the postprandial hyperglycemia have been offered by alpha-amylase and alpha-glucosidase inhibitors. Acarbose, Miglitol and Voglibose being the only commercially available alpha-amylase and alpha-glucosidase inhibitors. Incretins are group of gastrointestinal hormones, predominantly glucagon like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP) which increase post-prandial insulin release from pancreatic beta cell in glucose dependent manner (Ban et al., 2009). Dipeptidyl peptidase-IV (DPP-IV) is a serine protease that is responsible for the rapid degradation of GLP-1 and GIP (Barnett, 2006). Thus, preventing the degradation of incretin hormones, by DPP-IV inhibition became an attractive therapeutic strategy. Several DPP-IV inhibitors such as gliptins currently approved for the treatment of T2DM. Plants-derived compounds represent a natural source for bioactive compounds that can be used for the development of effective drugs against DM. Herbs have immense potential to provide bioactive compounds that can be developed into antidiabetic agents. Despite the potential, antidiabetic plants remain grossly understudied and under-utilized as a source of novel drugs. This review article compiles the medicinal plants and their bioactive compounds that inhibit alpha-amylase, alpha-glucosidase and DPP-IV enzymes giving insights to the mechanism of action of the enzyme activity of these enzymes. Most of the reported research focuses on *in vitro* investigations of the inhibitory effect of plant extracts and the identification of bioactive molecules. However, only a limited number of additional studies have conducted for *in vivo* settings. It is prominent that the tests done in animals, and human trials were extremely rare making the potential use of these natural therapeutics in medical practice a challenging task. Therefore, more research and scientific analyses are needed to assimilate the pharmacological activity of natural extracts and compounds to be used as anti-diabetic therapeutics. We present the available knowledge on this important area of research in antidiabetic drug discovery from natural sources hoping to direct the interest of research community on these unexploded areas and accelerate the process of novel drug discovery against DM.

Author Contributions

MMK wrote the main manuscript. DNK wrote few parts of the main text, reviewed and edited the manuscript. SJ and KDPPJ reviewed the manuscript.

Data Availability

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Ethical Approval

No ethical approval was required for this study.

Conflict of Interest

The authors declare that they have no conflict of interest.

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