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REVIEW

WILEY

Enzymes inhibitors from natural sources with antidiabetic activity: A review

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Natural products have been extensively investigated for antidiabetic therapy. Many of the natural products have direct or indirect effect in diabetes pathways as enzyme inhibitors. The most involved mechanisms are inhibition of intestinal alpha-glucosidase and alpha-amylase, lens aldose reductase, oxidative stress protection, inhibition of formation of advanced glycation end products, inhibition of aldose reductase, lowering plasma glucose levels, altering enzyme activity of hexokinases and glucose-6-phosphate, synthesizing and releasing of insulin, postprandial hyperglycemia inhibition, stimulation of GLUT-4, decreasing activity of G6P, lowering the level of skeletal hexokinases, etc. The following medicinal plants products or extracts showed promising effects as enzyme inhibitors: *Abelmoschus moschatus*, *Alangium salvifolium*, *Azadirachta indica*, *Bidens pilosa*, *Boerhaavia diffusa*, *Capsicum frutescens*, *Cassia alata*, *Eclipta alba*, *Embellica officinalis*, *Ficus carica*, *Gentiana Olivier*, *Glycyrrhiza glabra*, *Gymnema sylvestre*, *Hordeum vulgare*, *Ipomoea aquatica*, *Juniperus communis*, *Mangifera indica*, *Momordica charantia*, *Ocimum sanctum*, *Punica granatum*, and *Zingiber officinale*. Some of the group of phytochemicals isolated with enzyme inhibition activities are Alkaloids, sesquiterpene and saponins, polysaccharides, flavonoids, dietary fibers, ferulic acid, tannins, limonene, and oleuropeoside. This review will provide very useful material to enhance the efficiency of rational antidiabetic drug design.

KEYWORDS

diabetes, drug design, enzyme inhibitors, medicinal plants, natural products

1 | INTRODUCTION

Diabetes mellitus has grown into a major health risk worldwide. It has been observed to increase with time. The chronic disease has hurt more than 171 million persons globally in 2000, and the frequency is estimated to grow gradually to 366 million by 2030 (Zhu, 2013). Diabetes is a metabolic disorder, which was previously associated with the sedentary lifestyle, but now, it is observed in children (Johnson, Ermolieff, & Jirousek, 2002). Chronic hyperglycemia results in mortality and morbidity due to microvascular complications such as neuropathy, nephropathy, retinopathy, cataracts, and even stroke damaging blood vessels, peripheral nerves, and nephrons (Kitada, Zhang, Mima, & King, 2010).

List of abbreviations: ADP, Adenosine diphosphate; AGEs, Advanced glycation end products; AKR_1B_1, Aldo-keto reductase family1, member 1; ALR, Aldose reductase; ATP, Adenosine triphosphate; CoA, Coenzyme A; DHAP, Dihydroxy acetone phosphate; DM, Diabetes mellitus; G-6PD, Glucose-6-phosphate dehydrogenase; GFAT, Glutamine fructose-6 phosphate amidotransferase; GK, Glucokinase; GKRP, Glucokinase regulatory protein; GLUT4, Glucose transporter type 4; IR, Insulin receptor; IRS, Insulin receptor substrate; IRS1, Insulin receptor substrate 1; IRS2, Insulin receptor substrate 2; NADP+, Nicotinamide adenine dinucleotide phosphate; NADPH, Nicotinamide adenine dinucleotide hydrogen phosphate; PKC, Protein tyrosine kinase; PTP1B, Protein tyrosine phosphatase 1B; RAAS, Rennin Angiotensin Aldosterone System; ROS, Reactive oxygen species; T2DM, Type 2 diabetes mellitus; UDP, Uridine diphosphate

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Type 2 diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia in which the body becomes resistant to the normal effects of insulin and slowly loses the capacity to produce insulin in the pancreas. As a result, the β cells in the pancreas respond by producing more amount of insulin, in order to achieve some degree of management of the blood glucose levels. Thus, this overproduction of insulin causes β cells to wear themselves out (Cerf, 2013).

Different enzymes act in diabetic pathway each having its specific role in the progression of the disease. Each enzyme plays its specific role as they are involved in the pathogenesis of the disease, control and modulate auto-phosphorylation of insulin receptors, and uptake of glucose by glucose transporter type 4 (GLUT4; Kitada et al., 2010). The principle mediator for glucose uptake in the cells is an insulin-regulated glucose transporter known as GLUT4 (Huang & Czech, 2007).

In this review, the role of these enzymes in the pathogenesis of diabetes is discussed. These enzymes could be targeted for treating this metabolic disorder. This review summarizes the inhibitors of different enzymes in diabetes pathways and natural products that target these enzymes. Moreover, it will provide very useful material for improving the competence of rational antidiabetic drug design (Figures 1–4).

2 | METHODS

The data about enzyme inhibitors acting on different diabetes pathways were searched and obtained using databases such as PubMed, Science Direct, Scopus, research gate, and Google Scholar. The plant's scientific name was validated using the plant name index databases, Plantlist.org.

2.1 | Activation of protein kinases and phosphatases

There is a variety of signaling pathways for insulin to produce its effect (Gum et al., 2003). Pancreatic β cells secrete insulin in response to the upsurge in glucose concentrations in the blood. Binding of insulin to the extracellular alpha subunits triggers the activation of the intrinsic tyrosine kinases (Fountas, Diamantopoulos, & Tsatsoulis, 2015). Insulin receptor substrate is phosphorylated by tyrosine kinases. This series of phosphorylation on the signaling molecules causes the uptake of glucose into cells by the glucose transporter GLUT4. Protein tyrosine phosphatase IB (PTP1B) functions to inactivate the insulin receptor and dephosphorylate the insulin receptor substrate. PTP1B negatively regulates the insulin receptor and its substrates, such as insulin receptor substrates 1 and 2, by dephosphorylating them and serves as the negative regulator of insulin signaling (LeRoith, Taylor, & Olefsky, 2004; Tables 1, 2).

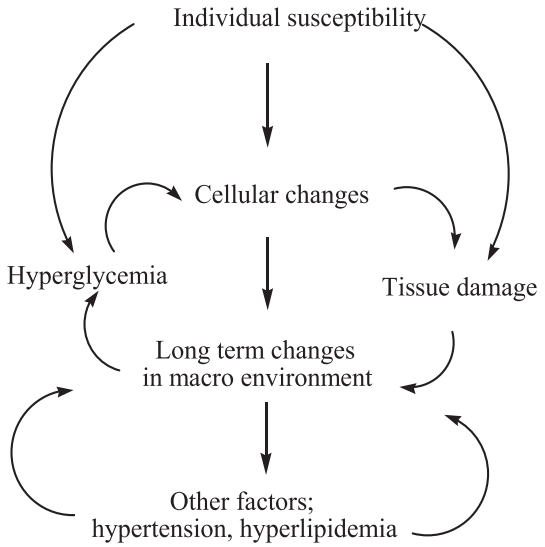

FIGURE 1 Hyperglycemia-induced damage (Kitada et al., 2010)

2.2 | Activation of polyol pathway

Aldose reductase AKR_1B_1 is a member of monomeric nicotinamide adenine dinucleotide hydrogen phosphate (NADPH) dependent oxidoreductases with the molecular weight of 37kD. The reduction of glucose to sorbitol is accompanied by the oxidation of NADPH to NADP+ via AKR_1B_1 (Dunlop, 2000). In a state of hyperglycemia, the affinity of aldose reductase for glucose increases initiating much sorbitol to accumulate more NADPH is consumed and leaving less NADPH for other processes of cellular metabolism (El-Kabbani & Podjarny, 2007). After sorbitol has been formed, it does not easily diffuse across cell membranes; this intracellular buildup of sorbitol may be a reason in the etiology of diabetic complications. Higher concentration of cellular sorbitol results in osmotic stresses on cells and is then associated mainly in microvascular destruction to the retina, kidney, and nervous systems (Gabbay, 1973).

The end product of the polyol pathway is fructose which enters in the hexosamine pathway (Shimoshige, Enomoto, Aoki, Matsuoka, & Kaneko, 2010) leading to activation of protein kinase C and advanced glycation end product (AGE). The oxidation of NADH by NADH oxidase produces reactive oxygen species, which can attack the mitochondrial membrane and results in mitochondrial dysfunction.

2.3 | Advanced glycation end products (AGEs)

After effects of long-term diabetes results in accumulation of AGEs in the kidneys. The receptors of AGEs exist either alone or grouped with other ligands. When the AGEs receptors are activated, it results in promotion of damage of kidney, inflammatory conditions, and fibrosis, which are related with diabetic nephropathy.

In the diabetic kidney, the effect of AGEs is to synergize and potentiate the actions of other pathogenic mediators such as oxidative stress, protein kinase C, and renin-angiotensin system activation. It results in the advancement of kidney disease. It is found that direct exposure to AGEs results in similar lesions as seen in diabetic nephropathy. The innate defense against AGEs buildup exist, but in diabetes, this ability is reduced. A variety of agents have been tested to reduce the AGEs. Many of such agents proved effective but their clinical utility remains unproven (Thomas, 2011).

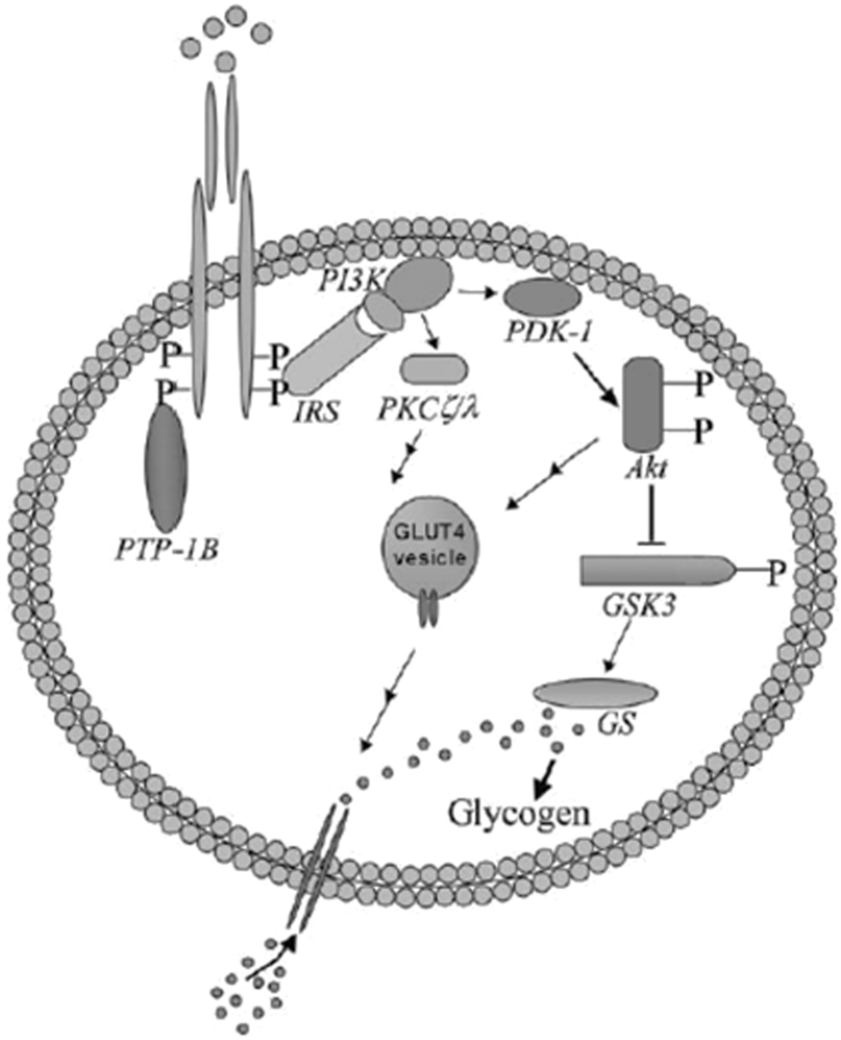

FIGURE 2 PTP1B in insulin transduction pathway (Asante & Kennedy, 2003). PTP1B: protein tyrosine phosphatase 1B; IRS: insulin receptor substrate; GLUT4: glucose transporter type 4; PKC: protein tyrosine kinase

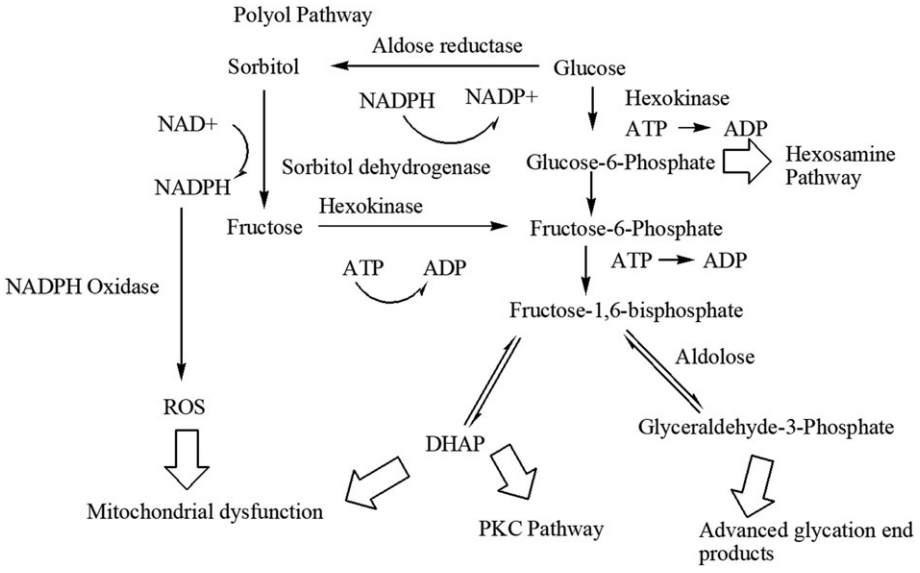

FIGURE 3 Interlinked pathways in diabetes (Unwin, Whiting, Gan, Jacqmain, & Ghyoot, 2009). NADPH: nicotinamide adenine dinucleotide hydrogen phosphate; NADP+: nicotinamide adenine dinucleotide phosphate; ADP: adenosine diphosphate; ATP: adenosine triphosphate; ROS: reactive oxygen species; DHAP: dihydroxy acetone phosphate; PKC: protein tyrosine kinase; NAD+: nicotinamide adenine dinucleotide

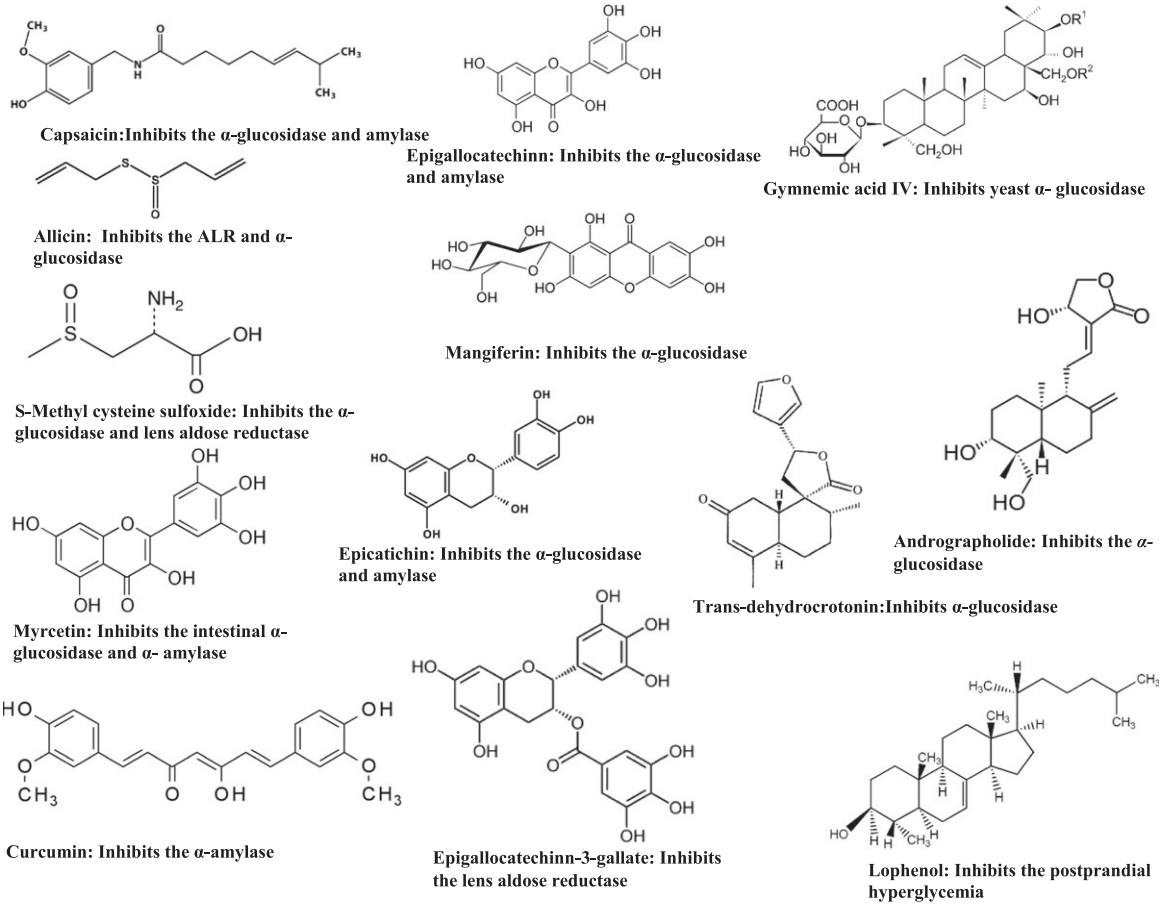

FIGURE 4 Structures and activities of the enzyme inhibitors. ALR: aldose reductase

In the hyperglycemic state, glucose forms covalent bonds with the proteins via a nonenzymatic process, that is, glycation resulting in the formation of AGEs. These are involved in transcription of genes and alter the cellular signaling causing cellular dysfunction (Goldin, Beckman, Schmidt, & Creager, 2006). These AGEs play the central role in the pathogenesis of diabetic complications including diabetic nephropathy, retinopathy, and neuropathy (Singh, Bali, Singh, & Jaggi, 2014).

2.4 | Activation of the hexosamine pathway

When the concentration of glucose is elevated in a cell, the process of glycolysis takes place to metabolize glucose. On the other hand, fructose-6 phosphate diverts into a signaling pathway where it is converted by enzyme glutamine fructose-6 phosphate amidotransferase into glucosamine-6-phosphate and lastly to uridine diphosphate N-acetyl glucosamine. N-acetyl glucosamine gets put onto serine and threonine residues of transcription factors, that is, transforming growth factor-1 and plasminogen activator inhibitor-1 resulting in microvascular complications (Fantus, Goldberg, & Whiteside, 2006).

2.5 | Activation of alpha-glucosidase

The alpha-glucosidase is an important enzyme found in human body. Inhibition of this enzyme in intestine results in delayed carbohydrates digestion. It also results in lowering of glucose level after meal. Consequently, the mechanism of alpha-glucosidase inhibition signifies the pharmacological optimization of the nutritional principle of late carbohydrate absorption. Acarbose when given orally inhibited the enzymes alpha-glucosidase in the brush border of the small intestines and reduces the rate of digestion of complex carbohydrates. So the inhibitors of alpha-glucosidase work in a similar fashion and retard the glycation of proteins and therefore reduced the glycated hemoglobin and glycation end products in collagen. The result is the improvement of biochemical parameters and act against the neuropathy and diabetic nephropathy. Therefore, treatment of diabetic animals with alpha-glucosidase inhibitors improves the metabolic state and prevents the onset of diabetic complications (AG, 1994). Alpha-glucosidase is found in the brush border of intestinal mucosa where they catalyze the end product of digestion into carbohydrates. It is involved in postprandial hyperglycemia (Lebovitz, 1997).

2.6 | Renin Angiotensin Aldosterone System (RAAS)

RAAS is a hormonal system that produces physiologically active Angiotensin II to regulate blood pressure and fluid and electrolyte homeostasis. Moreover, many tissues have been found to have their own local RAAS that can express many of the components of RAAS at these site in order to manipulate the expression of receptors (Cooper, 2004). Genetic variations in RAAS increase the risk of hypertension, premature atherosclerosis, and incidence of Type 2 diabetes.

TABLE 1 Natural enzyme inhibitors from different plant sources involved in diabetic pathways

Sr no.	Name of plant	Family	Common name	Part used	Chemical constituent	Bioactivity in relation to the chemical constituent	
1	*Abelmoschus moschatus*	Malvaceae	Musk okra	Leaves	Myricetin	Inhibited the intestinal alpha-glucosidase in vitro	(Tadera et al., 2006)
2	*Acacia arabica*	Leguminosae	Gum acacia, Babool	Seeds, leaves, and bark	Epicatechin, strictinin, and Arabin	Inhibited the alpha-glucosidase and amylase in vitro	(Aadil et al., 2012)
3	*Acacia catechu*	Leguminosae	Black catechu, Gambirr	Leaves and bark	Epicatechin	Inhibited the lens aldose reductase in STZ induced diabetic rats	(Srivastava et al., 2011)
4	*Aegle marmelos*	Rutaceae	Indian bael, Bel giri, Quince	Leaves	Tannins, pectin, essential oils, eugenol, and cineole	Protects against oxidative damage caused by hyperglycemia	(Kumar et al., 2013)
5	*Agrimonia eupatoria*	Rosaceae	Church Steeples	Leaves	Essential oils, querticin, tannins, and luteolin	Inhibited the formation of AGEs	(Kuczmannová et al., 2016)
6	*Alangium salvifolium*	Alangiaceae	Sage-leaved alangium	Leaves	Alangidiol, alangol, glycosides, and tannins	Inhibited the ALR	(Kumar, Pate, et al., 2011)
7	*Allium cepa*	Amaryllidaceae	Onion	Bulb and leaves	Flavinoids and organo-sulphur compounds and allyl propyl disulphide	Lowers plasma glucose levels in alloxan induced diabetic rats, alters enzyme activity of hexokinases and glucose-6-phosphate	(Wu et al., 2015)
8	*Allium sativum*	Alliaceae	Garlic	Bulb and leaves	Allin, Allicin, essential oils, sapponins, and steroids	Inhibited the ALR and alpha-glucosidase	(Wu et al., 2015)
9	*Aloe barbedensis*	Liliacae	Aloe	Leaves	Barbaloin, isobarbaloin, resin, pseudoprototinosaponin AIII, and prototinosaponins AIII	Stimulate synthesis and release of insulin from pancreatic β cells in vivo	(Kumar, Sharma, et al., 2011)
10	*Aloe vera* Tourn	Asphodelaceae	Aloe	Whole plant	Aloin glycoside	Inhibited the postprandial hyperglycemia	(Mishra et al., 2010)
11	*Anacardium occidentale*	Anacardiaceae	Cashew, Kaju	Whole plant	Flavonols, terpenoid, caumarin, phenolic compound, and essential oil	Increase glucose metabolism and inhibited alpha-glucosidase	(Toyomizu et al., 1993)
12	*Andrographis paniculata*	Acanthaceae	Kalmegh, Green chirayta	Whole plant	Diterpenoid lactone andrographoloid	Delay absorption of glucose	(Subramanian et al., 2008).
13	*Annona squamosa*	Annonaceae	Sugar apple	Leaves	Acetogenins-squamosin B, squamosamide,reticulatain-2, isosquamosin	Stimulate and enhance glucose uptake	(Davis et al., 2012)
14	*Artemisia pallens*	Asteraceae	Davana	Aerial parts	Artabsin	Increase utilization of glucose via GLUT4	(Subramoniam et al., 1996)
15	*Averrhoa bilimbi*	Oxalidaceae	Bilimbi	Leaves		Decrease activity of G6PD	(Ali et al., 2006)
16	*Azadirachta indica*	Meliaceae	Neem	Leaves	Nimbidin, Nimbin, Nimbidol, Nimbosterol	Inhibited intestinal glucosidases	(Bhat et al., 2011)
17	*Beta vulgaris*	Chenopodiaceae	Chukandar, Beetroott	Leaves and root	Betaines	Lower the level of skeletal hexokinases	(Kabir et al., 2015)

(Continues)

18	*Bidens pilosa*	Asteraceae	Spanish needle	Whole plant	Polyyne, that is, 2-β-D-Glucopyranosyloxy-1-hydroxytrideca-5,7,9,11-tetrayne	Protects β cells of the pancreas and regenerate them	(Kabir et al., 2015)
19	*Boerhaavia diffusa*	Nyctaginaceae	Red spiderling	Entire plant	Alkaloid punarnavaine and punarnavoside	Retards intestinal absorption of glucose	(Gulati et al., 2012)
20	*Brassica juncea*	Cruciferae	Rai	Leaves and seed	Isothiocyanate Glycosides sinigrin, protein, and fixed oil	Lowers plasma glucose and postprandial hyperglycemia	(Mun'im et al., 2013)
21	*Camellia sinensis*	Theaceae	Green tea	Leaves	Polyphenolic constituents (EGCG)	Increase insulin secretion in vivo and affects gene expression	(Vinholes & Vizzotto, 2017)
22	*Capsicum frutescens*	Solanaceae	Redchilii	Entire plant	Capsaicin protein	Inhibited the alpha-glucosidase and alpha-amylase in vitro	(Watcharachaisoponsiri et al., 2016)
23	*Carum carvi*	Apiaceae	Zeera, Caraway	Seeds	Limonene, carvacrol, carvone, α-Pinene, linalool, and p-cymene	Lowers serum glucose level and inhibited the ALRA	(Lee, 2005)
24	*Cassia alata*	Caesalpiniaceae	Ringwrm senna	Leaves	Saponins and glycosides	Leaf extract showed hypoglycemic effect by inhibiting alpha-glucosidase	(Varghese et al., 2013)
25	*Cassia auriculata*	Fabaceae	Senna	Flower, root	Trepnoids, flavonoids, and glycosides	Enhances the activity of hepatic hexokinase and phosphofructokinase and suppresses glucose 6-phosphatase and fructose l,6-bisphosphatase in diabetic animals after15-day treatment (400 mg/kg)	(Nanumala et al., 2015)
26	*Catharanthus roseus*	Apocynaceae	Sadabahar	Leaves, twig, and flower	Indole alkaloid and vincristine vinblastin	Increase glucose metabolism and inhibited the PTP1B	(Tiong et al., 2013)
27	*Cinnamomum zeylanicum*	Lauraceae	Cinnamonm	Bark	Essential oils, tannins, flavonoids, glycosides, terpenoids, coumarins, and anthraquinones	Inhibited the alpha-glucosidase in vivo	(Shihabudeen et al., 2011)
28	*Citrus paradisi*	Grapefruitt	Rutaceae	Fruit	Essential oils, linalool, and limonene	Regenerates pancreatic β cells and lowers the level of key enzymes in starch digestion	(de la Garza et al., 2013)
29	*Coriandrum sativum*	Umbelliferae	Dhania, Parsley	Leaves and seeds	Volatile oil, fixed oil, and protein	Increase glucose uptake and glucose oxidation in vivo and acts as a secretagogue in vitro	(Brindis et al., 2014)
30	*Coscinium fenestratum*	Menispermaceae	Yellow wine	Stem	Barberine, glycoside, and saponin	Inhibited the intestinal sucrase	(Adisakwattana et al., 2009)
31	*Croton menyharthii*	Euphorbiaceae	Castor oil	Bark	Fixed oils and trans-dehydrocrotonin	Inhibited the alpha-glucosidase	(Aderogba et al., 2013) (Aderogba et al., 2013).
32	*Cryptolepis sanguinolenta*	Asclepidaceae	Senegal	Roots	Cryptolepine, quindoline, and neocryptolepine	Increase glucose uptake by 3T3-L1 cells	(Ajayi et al., 2012)

(Continues)

						and inhibited the alpha-glucosidase	
33	*Curcuma longa*	Turmeric	Zingiberaceae	Rhizome	Sesquiterpene, phenols, and essential oils	Inhibited the of human pancreatic alpha-amylase in vitro	(Puneeth & Sharada, 2015)
34	*Eclipta alba*	Compositae	False daisy	Leaves	Ecliptin alkaloid	Decrease activity of glucose 6-phosphatase and fructose 1,6-bisphosphatase	(Jaiswal et al., 2012)
35	*Embellica officinalis* Gaertn	Euphorbiaceae	Amla	Fruits	Vit. C and tannin	Reduce levels of 5-hydroxymethylfurfural, creatinine albumin in STZ diabetic rats	(Suryanarayana et al., 2004)
36	*Eucalyptus globulus*	Myrtaceae	Eucalyptus	Leaves	Essential oil and cineole	Increase insulin secretion from clonal pancreatic beta line BRIN-BD 11	(Dey et al., 2014)
37	*Eugenia jambolana*	Myrtaceae	Jaman, Purple berries	Seed, fruit, leaves, and kernel	Raffinose, gallic acid, anthocyanins, and cyanidin diglycoside	Lowers plasma glucose level in vivo by altering glucose metabolism	(Omar et al., 2012)
38	*Ficus bengalensis* Linn	Moraceae	Bargad	Bark	Tannins	Acts as insulin secretagogue in vivo	(Gayathri & Kannabiran, 2008)
39	*Ficus carica*	Moraceae	Fig, Anjeer	Fruit, leaves	Ferulic acid, quercetin-3-O-glucoside, triterpenoids, and sesquiterpenes	The glucose-lowering effect in vivo by stimulating insulin secretion	(Mopuri & Islam, 2016)
40	*Gentiana olivier*	Gentianaceae		Flower and root	α-Pinene, limonen, and β-myrcene, Iso-orienti, and C-glycoside	Lowers blood glucose in vivo	(Orhan et al., 2014)
41	*Glycyrrhizaa glabra*	Leguminosae	Mulathi	Rhizome	Triterpenoid, saponin, and glycyrrhizin	Lowers blood glucose in vivo by inducing hepatic enzymes	(Guo et al., 2015)
42	*Gymnema sylvestre*	Apocynaceae	Periploca of the woods	Leaves and flower	Gymnemic acid and quercetin	Lowers blood glucose in vivo	(Chen & Guo, 2017)
43	*Helicteres isora*	Indian screw tree	Sterculiaceae	Roots	Antioxidants, proteins, fibers, phytosterols, carotenoids, saponin, tannin, and lignins	Initiate insulin release and lower plasma triglycerides	(Rungprom, 2014)
44	*Hordeum vulgare*	Barley	Gramineae	Seeds	Beta-glucan, proteins, and vitamins	The dietary supplement to control diabetes	(Ha et al., 2016)
45	*Hovenia dulcis*	Japanese raisin tree	Rhamnaceae	Entire plant	Flavonoids	Induce hepatic enzymes to lower plasma glucose levels	(Meng et al., 2016)
46	*Ipomoea aquatica*	Water spinach	Convolvulaceae	Leaves	Carotene	Hypoglycemic in vivo	(Lee et al., 2014)
47	*Ipomoea batata*	Sweetpotatoe	Convolvulaceae	Rhizome	β-carotene, manganese, and vitamins	Reduce insulin resistance in vivo	(Matsui et al., 2001)
48	*Juniperus communis*	Common juniper	Cupressaceae	Fruit	Essential oils	Increase peripheral glucose consumption and induce insulin secretion	(Orhan et al., 2014)
49	*Leucas lavandulaefolia* Rees	Halkusha	Labiatae	Entire plant	Essential oils and flavonoids	Lowers plasma glucose in vivo	(Ali et al., 2006)
50	*Mangifera indica*	Mango	Anacardiaceae	Leaves and fruit	Mangiferin	Inhibited the alpha-glucosidase	(Prashanth et al., 2001)

(Continues)

51	*Momordica charantia*	Bitter gourd	Cucurbitaceae	Fruit	Momordicine alkaloid and ascorbic acid	Increase oral glucose tolerance	(Suryanarayana et al., 2004)
52	*Morrus indica* L.	Shehtoot, Mulberry	Moraceae	Fruit	Polyphenols and flavonoids	Regulates glucose uptake and aldose reductase in vivo	(Yang et al., 2012)
53	*Murraya koeingii*	Cury leaf	Rutaceae	Leaves	Essential oils	Increase glycogenesis and decrease glycogenolysis and gluconeogenesis	(Narkhede, 2012)
54	*Musa sapientum*	Banana	Musaceae	Leaves and fruit	Starch, vitamins, and minerals	Reduce blood glucose and glycosylated hemoglobin	(Sheng et al., 2014)
55	*Myrtus communis*	Common mtryle	Myrtaceae	Leaves	Salicylic acid, mirtii oleu, and essential oils	In vivo reduction in blood glucose	(Önal et al., 2005)
56	*Nelumbo nucifera* Gaertn	Lotus	Nymphaeaceae	Rhizome	Nuciferin and nornuciferin	Reduce sugar level in diabetic rats	(Liu et al., 2013)
57	*Ocimum sanctum*	Holy basil	Labiatae	Leaves	Volatile oil, phenol, aldehyde, fixed oil, alkaloid, tannin, and ascorbic acid	Leaf extract showed hypoglycemic effect in vivo	(Malapermal et al., 2017)
58	*Olea europia*	Olive	Oleaceae	Leaves and fruit	Oleuropeoside	Potentiation of glucose, induced insulin released, and increase peripheral uptake of glucose	(Komaki et al., 2003)
59	*Phaseolus vulgaris*	Redd beans	Papilionaceae	Pod, seed, and whole plant	Iridoid, flavonoids, lignins, and phenols	Hypoglycemic, hypolipidemic, inhibit alpha-amylase activity, and antioxidant	(Chiang et al., 2014)
60	*Punica granatum*	Pomegranate	Punicaceae	Fruit, seeds	Vit. C, protein, tannin, gallic acid, and pelletierine	alpha-amylase	(Li et al., 2005)
61	*Trigonella foenum graceum*	Methi	Leguminosae	Seeds and leaves	Protein, fat, V-oil, fixed oil, and carbohydrate	Inhibited alpha-amylase	(Salehi et al., 2013)
62	*Zingiber officinale* Roscoe	Ginger	Zingiberaceae	Rhizome	Sesquiterpene, phenols, and essential oils	Stimulate insulin secretion	(Kato et al., 2006)

Note. STZ: streptozotocin; AGEs: advanced glycation end products; ALR: aldose reductase; GLUT4: glucose transporter type 4; PTP1B: protein tyrosine phosphatase 1B.

TABLE 2 Mode of action of different chemical groups involved in diabetic pathways

Sr no.	Chemical constituents	Mode of action
1	Alkaloids	They inhibited alpha-glucosidase enzyme
2	Sesquiterpene and saponins	Stimulate insulin secretion
3	Polysaccharides	Elevate serum insulin
4	Flavonoids	Stimulate islets of Langerhanss
5	Dietary fibers	Inhibited alpha-amylase
6	Ferulic acid	Act as a secretagogue
7	Tannins	Efficiently absorb glucose in the blood stream
8	Limonene	Inhibited the glucokinase
10	Oleuropeoside	Improve pancreatic secretion of insulin

Improvement of blood flow and microcirculation in skeletal muscles causes enhancement in insulin signaling at the cellular level and prevents diabetic complications (Zhou, Schulman, & Zeng, 2012).

2.7 | Activation of pyruvate dehydrogenase complex

Increased carbohydrate intake causes elevated levels of enzyme pyruvate dehydrogenase. Insulin mediates the release of pyruvate kinase. Pyruvate is the key intermediate in the glucose oxidation and acts as a precursor for glucose, glycerol, fatty acid, and amino acid synthesis. Pyruvate dehydrogenase complex when activated converts coenzyme A and pyruvate, oxidizes nicotinamide dinucleotide into acetyl coenzyme A, and reduces nicotinamide dinucleotide and carbon dioxide (Lee, 2014).

2.8 | Glucokinase in diabetes

The enzyme glucokinase plays an important role in glucose hemostasis. It is regulated by a protein known as glucokinase regulatory protein (Matschinsky et al., 2011). In the pancreas, glucokinase activity is regulated by transcriptional factors, whereas in the liver, it is regulated by glucokinase regulatory protein. Glucokinase catalyzes the first step in glucose metabolism and mutation in this enzyme is related to maturity-onset diabetes of young. Increase carbohydrate diet caused high levels of this enzyme and increased glucose tolerance (Slosberg et al., 2001).

2.9 | Decreased activity of glucose-6-phosphate dehydrogenase

Oxidative damage is one of the major risk factors for diabetes. Glucose-6-phosphate dehydrogenase deficiency predisposes individuals to degenerative diseases such as diabetes and is a major risk factor in the pathogenesis of diabetes. Together, oxidative stress and decreased level of glucose-6-phosphate dehydrogenase caused microvascular complications in diabetic patients (Wan, Tsai, & Chiu, 2002). There is a dramatic change in the management of diabetes during the past many thousand years. The existing pharmacological armamentarium applied to manage diabetes has dramatically reduced the morbidity and mortality. However, most of the therapies are long-term use and have serious side effects in many cases (Sanders, 2002).

Currently, many synthetic drugs are available in the market prescribed for the management of diabetes. The restrictions of these drugs are side effects and postcomplications in the patient. Therefore, it is important to explore the natural products, mostly medicinal plants, for their beneficial potentials in diabetes therapy. The natural products including medicinal plants have the advantage of having more acceptability toward patients because they are mostly edible and safe to use (Ganesan & Xu, 2017). Furthermore, medicinal plants have the ability to inhibit many of the enzymes involved in diabetes pathways. These can be consumed as functional food among the diabetic individuals for treatment. Therefore, this review presents the updated literature revealing the use of natural products as enzyme inhibitors that could be the potential candidate for as phytomedicine for the treatment of diabetes. This review may contribute to set a future direction for search on targets for treatment of diabetes. Moreover, the review purpose to offer basic knowledge for research on the enzymes involved in diabetic pathways, the functions, and working regulation.

2.10 | Enzyme inhibitors from natural products

Many studies have taken place to study the behavior of plants extracts and isolated compounds as enzyme inhibitors. *Artemisia pallens* is an aromatic herb belonging to family Asteraceae. Methanolic extract of aerial parts increased the peripheral utilization of glucose via GLUT4 and also inhibited the intestinal reabsorption of glucose in a dose-dependent manner (Subramoniam et al., 1996).

Myricetin an isolated compound from *Abelmoschus moschatus* showed IC_{50} of 0.38 mM, inhibiting rat intestinal alpha-glucosidase and porcine alpha-amylase by 29% and 64%, respectively (Tadera, Minami, Takamatsu, & Matsuoka, 2006).

Bidens pilosa referred as "Black jack" is a perennial flowering plant belonging to family Asteraceae. It showed its effect by protecting pancreatic β cells (Bnouham, Ziyyat, Mekhfi, Tahri, & Legssyer, 2006). Its methanolic extract inhibited the alpha-glucosidase in vitro (Ezuruike & Prieto, 2014). *Acacia arabica* belongs to family Leguminosae and is commonly known as "Babool." Aqueous extract of bark showed 25.2% inhibition of alpha-amylase (Aadil, Barapatre, Rathore, Pottam, & Jha, 2012).

Aegle marmelos protected against oxidative damage produced by hyperglycemia. Umbelliferone β-D-galactopyranoside an isolated

compound from *Aegle marmelos* raised the hexokinase level at a dose of 10 kg/mg body weight to 112.6 ± 1.77 while decreasing the level of 1,6-fructose biphosphate to 32.2 ± 0.82 at a dose of 40 mg/kg body weight (Kumar et al., 2013).

Ethanolic and aqueous extract of *Acacia catechu* showed concentration-dependent inhibition of aldose reductase with the IC_{50} of 9.08 and 4.91 1 μg/ml against diabetic lens (Srivastava, Mishra, Bhatia, Narender, & Srivastava, 2011). Aqueous extract of *Agrimonia eupatoria* showed IC_{50} of 46.31 ± 8.76 μg/ml against alpha-glucosidase. It also inhibited the formation of AGEs with the IC_{50} of 156.48 μg/ml. Alcoholic extract of dried leaves of *Alangium salvifolium* inhibited the rat lens aldose reductase with an IC_{50} of 106.6 ± 5.11 (Kumar, Pate, Prasad, Sairam, & Hemalatha, 2011). *Allium sativum* is commonly known as "Garlic" that belongs to onion family Amaryllidaceae. It showed a dose-dependent inhibitory effect against alpha-glucosidase and aldose reductase with IC_{50} greater than 500 mg/ml (Wu, Luo, & Xu, 2015).

Methanolic extract of the shade-dried bark of cinnamon reduces postprandial intestinal glucose absorption by inhibiting alpha-glucosidase with IC_{50} of 676 μg/ml while stimulating glucose uptake in the cells via GLUT4 and reduces hyperglycemic response by 42.5% (Shihabudeen, Priscilla, & Thirumurugan, 2011).

S-methyl cysteine and quercetin from *Allium cepa* are responsible for inhibition of alpha-glucosidase and lens aldose reductase. IC_{50} value for inhibition of alpha-glucosidase is 22.0 ± 1.26 (Wu et al., 2015). Lyophilized aloe gel from *Aloe barbedensis* contains aloe-emodin-8-O-glycoside, which enhances glucose transport by modulating the proximal and distal markers involved in glucose uptake and its transformation into glycogen while modulating the expression level of GLUT4 and decreasing the activity of hexokinases (Kumar et al., 2011). It also inhibited the protein tyrosine phosphatase in a dose-dependent manner (Anand et al., 2010).

Luteolin isolated from *Aloe vera Tourn* showed inhibition of procaine pancreatic alpha-amylase with IC_{50} of 50–500 μg/ml (Kumar et al., 2011; Mishra, Rao, Ojha, Vijayakumar, & Verma, 2010). Isolated compounds anacardic acids and cardols from *Anacardium occidentale* are reported to be potent inhibitors of alpha-glucosidases with IC_{50} ranging from 1.1–6.1 μM (Toyomizu, Sugiyama, Jin, & Nakatsu, 1993). Ethanolic extract of *Andrographis paniculata* inhibited the alpha-glucosidases in a concentration-dependent manner with IC_{50} of 17.2 ± 0.15 mg/ml) and a weak alpha-amylase inhibition with IC50 of 50.9 ± 0.17 mg/ml, delaying the absorption of glucose while reducing postprandial hypoglycemia (Subramanian, Asmawi, & Sadikun, 2008).

The hexane extract of *Annona squamosa* showed potent inhibition of protein tyrosine phosphate with an IC_{50} of 17.4 μg/ml. It also increased the glucose uptake with phosphorylation of insulin receptor substrate 1 (Davis et al., 2012). Water extract of *Averrhoa bilimbi* decreased the activity of hepatic glucose 6-phosphatase (Ali, Houghton, & Soumyanath, 2006) and also inhibited the alpha-glucosidase and alpha-amylase (Lawag, Aguinaldo, Naheed, & Mosihuzzaman, 2012). Its diethyl ether extract showed 93% inhibition of protein tyrosine phosphatase (Teng et al., 2011). Chloroform and methanolic extract of *Azadirachta indica* at a dose of 100 μg/200 μl in 0.5% dimethyl sulfoxide inhibited intestinal glucosidases by 51% and 35%, respectively, with an IC_{50} of 7.5 mg/ml (Bhat, Kothiwale, Tirmale, Bhargava, & Joshi, 2011). Aqueous extract of *Beta vulgaris* lowered the activity of skeletal hexokinases while it raises the level of glucose-6 phosphates by 76.71% when a dose of 200 mg/kg is administered orally (Kabir et al., 2015). Ethanolic extract of *Boerhaavia diffusa* inhibited the alpha-glucosidase with an IC_{50} of 1.72 μg/ml (Gulati, Harding, & Palombo, 2012).

Aqueous extract of *Brassica juncea* showed weak inhibition of alpha-glucosidase with IC_{50} of 541.71 ppm (Mun'im, Andriani, Mahmudah, & Mashita, 2013). Two percent epigallocatechin-3-gallate from *Camellia sinensis* inhibited the alpha-glucosidase with IC_{50} of 10.2 ± 2.02 μg/ml (Vinholes & Vizzotto, 2017).

Capsaicin isolated from *Capsicum frutescens* showed weak alpha-glucosidase inhibition of 48.8% ± 2.8% and inhibited the alpha-amylase to 55.5 ± 1.58% (Watcharachaisoponsiri, Sornchan, Charoenkiatkul, & Suttisansanee, 2016). Quercetin from red pepper showed an IC_{50} of 1.59 μg/ml against alpha-glucosidase (Ranilla, Kwon, Apostolidis, & Shetty, 2010).

Cumin-aldehyde isolated from *Carum carvi Linn* inhibited the lens aldose reductase with the IC_{50} of 0.85 μg/ml and showed weak inhibitory potential for alpha-glucosidase with IC_{50} of 0.5 mg/ml (Lee, 2005). The crude extract of *Cassia alata* inhibited the alpha-glucosidase with an IC_{50} of 63.75 ± 2.81 μg/ml whereas Kaempferol 3-O-gentiobioside an isolated compound showed IC_{50} of 82.5 ± 13.7 μg/ml (Varghese, Bose, & Habtemariam, 2013). Vindolicine and vindolinine isolated from dichloromethane extract of *Catharanthus roseus* potently inhibited the protein tyrosine phosphatase with an IC_{50} of 11.6 and 14.1 μM, respectively (Tiong et al., 2013). Ethanolic seed extract of *Cassia articulata* inhibited the yeast alpha-glucosidase with an IC_{50} of 149.6 ± 0.21 μg/ml (Nanumala, Tulasi, & Sujitha, 2015).

Pectin isolated from *Citrus paradise* inhibited the alpha-glucosidase and alpha-amylase in a similar manner with IC_{50} of 0.42 and 0.41 mg/ml, respectively (de la Garza et al., 2013). Ethanolic seed extracts of *Coriandrum sativum* showed an IC_{50} of 0.294 mg/ml against alpha-amylase whereas it exhibited an IC_{50} of 0.211 against alpha-glucosidase (Rayar & Manivannan, 2016). Its water extract competitively inhibited the alpha-glucosidase from *Saccharomyces cerevisiae* with an IC_{50} of 1.63 mg/ml (Brindis, González-Andrade, González-Trujano, Estrada-Soto, & Villalobos-Molina, 2014). Ethanolic extract of *Coscinium fenestratum* stem inhibited the intestinal sucrase and maltase with an IC_{50} of 11.22 and 3.89 mg/ml (Adisakwattana, Chantarasinlapin, Thammarat, & Yibchok-Anun, 2009). Quercetin-3-O-rhamnoside isolated from *Croton menyharthii* showed an IC_{50} of 47.0 ± 1.7 against alpha-glucosidase (Aderogba, Ndhlala, Rengasamy, & Van Staden, 2013).

Quercetin from *Cryptolepis sanguinolenta* inhibited the alpha-glucosidase with an IC_{50} of 0.5 ± 7 mM/L (Ajayi et al., 2012). Curcumin pyrazole derivatives from *Curcuma longa* inhibited the alpha-amylase with an IC_{50} ranging from 37.35 ± 0.15 to 53.87 ± 0.57 μmol/L (Puneeth & Sharada, 2015). Ethanolic extract of *Curcuma longa* inhibited the alpha-glucosidase with an IC_{50} of 28.4 μg/ml (Hasimun & Lisnasari, 2016). Ethanolic extract of *Eclipta alba* inhibited the alpha-glucosidase in noncompetitive manner with an IC_{50} of 54 μg/ml and also inhibited lens aldose reductase with an IC_{50} of 4.5 μg/ml (Jaiswal, Bhatia, Srivastava, Srivastava, & Tamrakar, 2012).

Aqueous fruit extract of *Embellica officinalis Gaertn* showed potent inhibition of rat lens aldose reductase and human recombinant aldose reductase with an IC_{50} of 0.72 and 0.88 mg/ml, respectively (Suryanarayana, Kumar, Saraswat, Petrash, & Reddy, 2004). Aqueous extract of *Eucalyptus globulus* inhibited the alpha-glucosidase, alpha-amylase, Angiotensin-converting enzyme (ACE), and aldose reductase with the IC_{50} of 2.08 ± 0.01, 3.01 ± 0.01, 4.31 ± 0.09, and 2.06 ± 0.03, respectively (Dey, Mitra, Katakam, & Singla, 2014).

Hydrolysable tannins, oenothein C, cornussin B, and swertisin from *Eugenia jambolana* seeds inhibited the alpha-glucosidase with an IC_{50} of 75.1 ± 5.9, 12.2 ± 1.8, and 146.5 ± 1.3 μM, respectively (Omar, Li, Yuan, & Seeram, 2012). Oral administration of aqueous extract of the bark of *Ficus bengalensis Linn* at a dose of 500 mg/kg lowered the level of glucokinase to 8.36 ± 1.54 (Gayathri & Kannabiran, 2008). Ethanolic extract of the fruit of *Ficus carica* inhibited the alpha-glucosidase and alpha-amylase with an IC_{50} of 255.57 ± 36.46 μg/ml and 315.89 ± 3.83 μg/ml, respectively (Mopuri & Islam, 2016). Licochalcone B and total flavonoids from *Glycyrrhiza glabra* inhibited intestinal alpha-glucosidase and PTP1B. Licochalcone B showed inhibition of both enzymes with an IC_{50} of <0.1 μM and < 0.1 μg/ml, whereas total flavonoids inhibited these enzymes with an IC_{50} of 97.33 μM and 15.84 μg/ml, respectively (Guo et al., 2015). Gymnemic Acid IV from *Gymnema sylvestre* is responsible for inhibitory activity against yeast alpha-glucosidase with an IC_{50} of 68.70 ± 1.22 μg/ml (Chen & Guo, 2017). *Gentiana Olivier* showed weak inhibition of alpha-glucosidase with an IC_{50} of 0.1982 mg/ml (Orhan, Hoçbaç, Orhan, Asian, & Ergun, 2014).

Ethanolic extract of *Helicteres isora* inhibited alpha-glucosidase and sucrose with an IC_{50} of 3.71 ± 0.21 and 2.15 ± 0.48, respectively (Rungprom, 2014). Powdered seeds of *Hordeum vulgare* showed dose-dependent maltase inhibition, and it also inhibited the intestinal alpha-glucosidase with an IC_{50} of 79.33 and 18.88 mg/ml, respectively (Ha, Jo, Mannam, Kwon, & Apostolidis, 2016). Myricetin and Quercetin isolated from *Hovenia dulcis* inhibited intestinal alpha-glucosidase and alpha-amylase. Myricetin showed an IC_{50} of 662 μg/ml against alpha-amylase and 3 μg/ml against alpha-glucosidase. Quercetin showed an IC_{50} of 770 μg/ml against alpha-amylase and 32 μg/ml against alpha-glucosidase (Meng et al., 2016); 3,5-di-O-caffeoylquinic acid, 4,5-di-O-caffeolyquinic acid, and Quercetin 3-O-β-D-glucoside isolated from *Ipomoea aquatica* inhibited alpha-glucosidase with an IC_{50} of 18.7 ± 0.17, 14.5 ± 0.19, and 20.5 ± 0.21 μM, respectively (Lee, Mediani, Nur Ashikin, Azliana, & Abas, 2014). Anthocyanins isolated from *Ipomoea batata* inhibited alpha-glucosidase with an IC_{50} of 193 μM (Matsui et al., 2001). Hydro-alcoholic extracts of leaf and fruit of *Juniperus communis* showed potent inhibition of alpha-glucosidase with IC_{50} of 0.0843 and 0.004 mg/ml, respectively (Orhan et al., 2014).

Lupeol isolated from *Leucas lavandulaefolia Rees* inhibited the alpha-amylase with the IC_{50} of 2.01 μg/ml (Ali et al., 2006). Ethanolic extract of *Mangifera indica* inhibited the alpha-glucosidase (in vitro) with an IC_{50} of 314 μg/ml (Prashanth, Amit, Samiulla, Asha, & Padmaja, 2001). Aqueous extract of *Momordica charantia* inhibited the rat and human lens aldose reductase with the IC_{50} of 0.28 ± 0.02 and 0.25 ± 0.01 mg/ml, respectively (Suryanarayana et al., 2004). Ethyl acetate soluble extract of *Morrus indica Linn*. (200 mg/kg) inhibited alpha-glucosidase with IC_{50} of 72.01 ± 4.18 mg/ml (Yang, Wang, Wang, & Zhang, 2012). Dried leaves of *Murraya koeingii* inhibited the alpha-amylase to 63.28% (Narkhede, 2012). Isolated compounds from the flower of *Musa sapientum* inhibited alpha-glucosidase. Vanillic acid, ferulic acid, β-sitosterol, daucosterol, and 9-(4′-hydroxyphenyl)-2-methoxyphenalen-1-one showed IC_{50} of 2,004.58, 1258.35, 283.67, 247.35, and 3.86 mg/L, respectively (Sheng et al., 2014). Myrtucommulone D and myrtucommulone B isolated from *Myrtus communis* inhibited alpha-glucosidase with an IC_{50} of 84.3 ± 3 and 39.99 ± 1.00, respectively (Önal, Timur, Okutucu, & Zihnioğlu, 2005). Flavonoids from *Nelumbo nucifera* inhibited alpha-amylase and alpha-glucosidase with IC_{50} of 2.20 ± 0.18 and 1.86 ± 0.018 mg/ml, respectively (Liu et al., 2013). Silver nanoparticles of *Ocimum sanctum* have inhibitory potential against alpha-amylase and alpha-glucosidase with IC_{50} of 0.70 and 0.009 mg/ml, respectively (Malapermal, Botha, Krishna, & Mbatha, 2017). Aqueous extract of *Ocimum sanctum* inhibited the alpha-glucosidase with IC_{50} of 26.75 whereas its ethanolic extract showed IC_{50} of 230.41 μg/ml (Rege & Chowdhary, 2014).

Ethanolic leaf extract of *Olea europia* inhibited the human alpha-amylase from saliva and pancreas with an IC_{50} of 4 and 0.02 mg/ml, respectively (Komaki et al., 2003). Oleanolic acid isolated from *Olea europia* inhibited the pancreatic alpha-amylase with an IC_{50} of 0.1 mg/ml (Komaki et al., 2003). Alcoholic extract of *Phaseolus vulgaris* inhibited the lens aldose reductase and alpha-glucosidase with the IC_{50} of 0.36–0.46 mg/ml against lens aldose reductase and 1.32–1.94 mg/ml against alpha-glucosidase (Chiang, Chen, Jeng, & Sung, 2014). Methanolic extract of *Punica granatum* showed potent alpha-glucosidase inhibitory activity in vitro with an IC_{50} of 1.8 μg/ml (Li et al., 2005). Methanolic extract of *Trigonella foenum graceum* weakly inhibited the alpha-glucosidase with an IC_{50} of 34.1 ± 2.9 μg/ml (Salehi, Asghari, Esmaeili, Dehghan, & Ghazi, 2013); 2-(4-hydroxy-3-methoxyphenyl) ethanol and 2-(4-hydroxy-3-methoxyphenyl) ethanoic *acid* from *Zingiber officinale Roscoe* inhibited human recombinant aldose reductase with an IC_{50} of 19.2 ± 1.9 and 18.5 ± 1.1 μM, respectively (Kato et al., 2006).

3 | CONCLUSIONS

There are many enzymes involved in diabetic pathways, and finding an appropriate enzyme inhibitor can be useful to identify new sources of antidiabetic drugs. Such inhibitors synergistically with natural products may play a crucial role in the development of a drug for diabetes. This review highlights the impacts of natural sources from plants on different mechanism pathways involved in diabetes such as inhibition of intestinal alpha-glucosidase, inhibition of amylase and lens aldose reductase, protection against oxidative, inhibition of formation of AGEs and aldose reductase, by lowering plasma glucose levels, by altering enzyme activity of hexokinases and glucose-6-phosphate, by synthesis and release of insulin from pancreatic β cells, inhibition of postprandial hyperglycemia, delaying absorption of glucose, increase utilization of glucose via GLUT4, decrease activity of G6PD, and lower the level of skeletal hexokinases. In this article, we showed the possible involvement of the natural products in diabetes pathways. Based on the investigation, this review concludes that natural products are excellent sources for prevention and treatment of diabetes.

CONFLICT OF INTEREST

Authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

Fiaz Alam conceived, designed, and wrote the review. Zainab Shafique and Sayyeda Tayyeba Amjad conducted the literature survey, structures, and figures. Mohammad Hassham Hassan Bin Asad has reviewed and proofreads the article.

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