Biological Forum – An International Journal **15(6): 618-627(2023)**

ISSN No. (Print): 0975-1130
ISSN No. (Online): 2249-3239

A Review on Bioactives from Plants against Diabetes mellitus

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(Received: 09 March 2023; Revised: 19 April 2023; Accepted: 23 April 2023; Published: 20 May 2023)
(Published by Research Trend)

ABSTRACT: It has been reported that 25% of world population is affected by diabetes. Diabetes may become the 7th leading cause of death by the year 2030 as reported by World Health Organization (WHO). Among the two different types of diabetes, Type 2 diabetes is known to be treated as well as prevented in a much easier way as compared to the type 1 diabetes. Extensive studies in medical field show that both synthetic drugs and phytochemicals have been used to treat diabetes. However, the synthetic chemical-based drugs have various side effects hampering the general health of the patients, while the phytochemicals (which are mostly secondary metabolites with bioactive properties) have fewer side effects and are also less expensive as compared to synthetic ones. Further, to act as an efficient remedy for diabetes, the binding ability of the phytochemical to a target molecule is a very important criterion.

This review is targeted towards discussing the scopes and applications of various secondary compounds from different types of plants, mainly belonging to the groups of alkaloids, flavonoids, terpenoids& phenolic acids, as an alternative and efficient treatment to diabetes. The study also discusses various results of effects of phytochemicals such as neferine, sanguinarine, indole-type alkaloids, naringenin, catechins, morin, silymarin, anthocyanin, celastrol, gallic acid, caffeic acid, etc. on diabetic rats and describes their mechanism of action. Some recent discoveries about phytochemicals such as teuhetenone A, sulforaphane and chelerythrine as potential antidiabetics have also been brought to light. The targets for antidiabetic molecules were also discussed. An overall perspective of the alternative use of bioactive plant metabolites for treating diabetes will contribute to the future herbal medicine and Ayurveda significantly. Many of these molecules are pre -clinical studies and require further testing in animal model or clinical trials for safety and toxicity. The safety of the herbal medicine is of prime importance because not all phytochemicals are free of side effects. However, this review serves as a catalog of novel experimental antidiabetic phytochemicals with a potential to be used therapeutically in future.

Keywords: Diabetes mellitus, antidiabetic, phytochemicals, target molecules, alkaloids, flavonoids, terpenoids.

INTRODUCTION

Diabetes mellitus (DM) is a condition where the body either fails to produce sufficient insulin or is unable to use the produced insulin effectively. This leads to an imbalanced blood glucose level. Genetic and environmental factors may raise complex disorders involving diabetes. Alcohol, smoking, less physical activity, sedentary lifestyle may lead to overweight and obesity. This in turn, may lead to glucose intolerance & decreased insulin sensitization. As reported by World Health Organization (WHO), from 1980 to 2014, the number of people having diabetes has increased from 108 million to 422 million. There was also a rise in premature mortality by 5% from 2000 to 2016. Approximately 1.5 million people have died due to diabetes in 2019 (WHO, 2021).

Diabetes is associated with various abnormalities & disorders such as diabetic cardiomyopathy, diabetic nephropathy, diabetic retinopathy, diabetic neuropathy, etc. Antidiabetic drugs either modulate pancreatic beta cells or insulin function. Oral hypoglycemic drugs stimulate beta cells to secrete more insulin, some of them inhibit glucose uptake by intestine and kidney cells. This results in less glucose absorption by the intestine and more glucose exit by the kidneys to reduce the blood glucose value.

To address and treat type2 diabetes mellitus (T2DM), many classes of oral hypoglycemic anti-diabetic drugs are being used since generations which have been briefly categorized as follows:

1. Oral Sulfonylureas: These drugs are known to elevate the release of insulin from islets of langerhans. But, this mechanism only works in the presence of insulin. Ex: glimepiride, glyburide (Salehi *et al*., 2019).

2. Biguanides: Major role of these drugs is replenishing the sensitivity of peripheral tissues towards insulin. But, they are only effective in the presence of insulin. Ex: metformin (Salehi *et al*., 2019).

3. α-glucosidase inhibitors: These drugs help in decreasing the absorption of carbohydrates in our body. However, since acarbose reversibly inhibits pancreatic α-glucosidase and α-amylase enzymes, they also reduce post-prandial blood sugar levels along with slower absorption. Ex: acarbose & miglitol (Salehi *et al*., 2019).

4. Thiazolidinediones (TZDs): These drugs improve sensitivity of adipose and muscle tissues towards insulin. Nevertheless, they are selective towards thenuclear peroxisome proliferator-activated receptor gamma (PPARγ), which is present in some tissues of the body. The transcription of certain insulin responsive genes in controlled by activating this PPARγ. Ex: pioglitazone, rosiglitazone (Salehi *et al*., 2019).

5. Non-sulfonylureas secretagogues: These drugs are responsible for increasing the secretion of insulin fromβ-cells. But, they are also known to bind to different types of β-cell receptors (Salehi *et al*., 2019).

Eventually, these synthetic drugs cannot fully reverse the diabetic condition. On the other hand, they can also sometimes worsen the condition by causing various side effects hampering the general health of the patients. Hence, phytochemicals, which are mostly the secondary metabolite bioactive compounds produced in plants as defense mechanisms; have been considered as alternatives. These plant compounds are not only easily available, but also show no side effects and are much cheaper as compared to the synthetic drugs (Gaonkar and Hullatti 2020). The bioactive secondary metabolites from plant sources are known to have antidiabetic, antiparasitic, antimicrobial, antioxidant, anticancer and antitussive properties (Ahmad *et al*., 2017). The bioactive phytomolecules have different mechanisms of actionlike reducing insulin resistance, increasing insulin secretion, protecting pancreatic beta cells, finally resulting in lower blood glucose levels (Jeeva and Sheebha, 2014). The mode of action these plant-based phytochemicals to induce antidiabetic activity have been explained by various mechanisms including the stimulation of insulin secretion from pancreatic β-cells, increase ininsulin binding to receptors, reduction in insulin resistance, and improvement of glucose tolerance, apart from enhancing glucose metabolism, improving β-cell mass and function, and increasing plasma insulin (Oyagbemi *et al*., 2014; Kooti *et al*., 2016; Alam *et al*., 2022; Rafe, 2017). All these mechanisms result in decreased blood glucose levels.

These phytochemical compounds are usually made up of chemicals likesaponins, alkaloids, flavonoids, terpenoids, carotenoids and glycosides. Many of these compounds have been reported to show anti-hyperglycemic effectsby either reducing absorption of glucose in the intestine or by increasing the secretion of insulin by affecting the pancreatic tissue. Tree nuts and peanuts also contain large amount of phytochemicals with antioxidant activities (Stevens-Barrón *et al*., 2019). Many biologically active quinazoline alkaloids also show hypoglycemic activity (Shang *et al*., 2018a; Shang *et al*., 2018b). This opens up avenues to use these metabolites as an alternative medicine against diabetes. The discovery of novel natural antidiabetic compounds offer a great promise to future medicine due to minimal efficacy and safety concerns of current antidiabetic drugs for the hundreds of millions of individuals which are currently seeking better management of diabetes.

Studies on different plant species has revealed that there are many plants with antidiabetic importance like banana, cinnamon, fenugreek, gymnema, soya bean, turmeric, yerba mate, aloe, caper, bitter melon, coffee, cocoa, guava, garlic, sage, nettle, black tea, green tea, walnut, etc (Talwar *et al*., 2023). About 509 plants belonging to 140 genera have already been ascertained with anti-diabetic properties (Salehi *et al*., 2019) among which about 81 plants native to Asian countries show antidiabetic, anti-hyperglycemic, hypoglycemic, anti-lipidemic and insulin-mimetic properties. It has been reported that most of the antidiabetic plants belong to the families of *Lamiaceae*, *Cucurbitaceae*, *Moraceae*, *Euphorbiaceae*, *Leguminoseae*, *Liliaceae*, *Asteraceae*, *Rosaceae* and *Araliaceae* (Patel *et al*., 2012), while *Datura alba* (Khan *et al*., 2019), red morph *Amaranthus* (Sarker and Oba 2019) are reported to show antioxidant properties.

The antidiabetic property of plant metabolites has been attributed to a mixture of phytochemicals or a single component of plant extracts. Medicinal plants produce a wide variety of phytochemicals, including alkaloids, phenolic acids, flavonoids, glycosides, saponins, polysaccharides, stilbenes, and tannin, which have been intensively investigated for their antidiabetic effects (Table 1). From the listed compounds with reference to Table 1, some compounds of high interest identified in plants include phlorizin, gymnemic acids, amorfrutins, berberine, fukugetin, gurmarin, trigonelline, honolciol and palmatine. The genus *Datura* consists of medicinal plants with curative effects in about nine species; also contains various alkaloids (Cinelli and Daniel 2021). Flavonoids like proanthocyanidin, glabrone, galbridin, licochalconetin, eurycarpin A, formonetin, licoflavone, 4'-7 dihydroxyflavone, glabrol, A-C liquiritigenin; phenolic acids such as p-coumaric acid, elgol and rosamic acid show antidiabetic activities (Gaonkar and Hullatti 2020). Citrus fruits like lemons, oranges, grapefruits and mandarins are also rich in flavonoids (Wang *et al*., 2017). Nevertheless, it is very important to regulate a proper intake of any compound because the risk of T2DM also depends on the flavonoid intake (Xu *et al*., 2018). A heterocyclic alkaloid identified from *Melitodes squamata* has shown a mild inhibition of α-glucosidase (Xu *et al*., 2020). Delphinidin and cyanogenic glucosides have been reported to induce insulin secretion (Kaplánek *et al*., 2021). Wogonin, techtochrysin and norwogoninserve are the potential antidiabetic flavonoids (Ahmed *et al*., 2018). Terpenoids like citral, geranic acid, citronellic acid, farnesal, farnesol and farnesyl acetate are reported to be anti-hyperglycemic (Valdes *et al*., 2019). Various types of terpenoids have different mechanisms of action and show antidiabetic effects by targeting different molecules (Bergman *et al*., 2019) as discussed in detail in Table 1.

Table 1: Plant-derived phytochemicals identified with anti-diabetic properties.

Sr. No.		Target molecule	Mechanism of action
I.	**ALKALOIDS**		
1.	Berberine	α-glucosidase; AMPK-dependant pathway	It decreases the transport of glucose into intestinal epithelium by inhibiting α-glucosidase. Thus, it decreases absorption of glucose and shows antihyperglycemic activity. It is an isoquinoline alkaloid, derived from the root & stem-bark of *Berberis thunbergi* (Prabhakar and Banerjee 2017). It affects the AMPK-dependant pathway, thus increasing GLUT4 translocation (MdSayem *et al*., 2018).
2.	Boldine	BMP4 oxidative stress cascade	It is a benzylisoquinoline alkaloid, which participates in the inhibition of BMP4 expression that is stimulated by Angiotensin-II. It thus inhibits the BMP4 oxidative stress cascade mediated by Ang-II which then decreases the ROS (Reactive Oxygen Species) overproduction. This compound is extracted from *Peumusboldus* and *Lindera aggregata* (Bhambhani *et al*., 2021).
3.	Lupanine	KATP channels	It is a quinolizidine alkaloid that influences insulin genes and KATP channels and thus improves homeostasis of glucose. Lupanine is usually extracted from *Lupinus argenteus* and *Laburnum anagyroides* (Liu *et al*., 2017).
4.	Neferine	CCL5 and CCR5 mRNA	It is a bisbenzylisoquinoline alkaloid which reduces expression of CCL5 and CCR5 mRNA in the superior cervical ganglion of T2DM rats. This treatment reduces body weight, FBG, BP, TC, TG & increases high-density lipoproteins (Li *et al*., 2013).
5.	Oxymatrine	p38MAPK/Mrf2 antioxidative signaling	It is a quinolizidine alkaloid which decreases blood urea nitrogen, albumin excretion, serum creatinine, urinary protein and blood glucose in a T2DM high-fat diet streptozotocin (HFD-STZ) nephropathy model for an oral dose of 150 mg/kg per day for about 11 weeks. It improved transduction of p38MAPK/Mrf2 antioxidative signaling in rats (Tareq*et al*., 2021).
6.	Piperine	Blood glucose	Piperine is a Natural Alkaloid known to lower blood glucose levels, which is extracted from *Piper nigrum* and *Piper longum* (Heinrich *et al*., 2021).
7.	Sanguinarine	Nucleic Acids	This is a benzophenanthridine alkaloid known to intercalate DNA & RNA and has been experimented on T2DM rats (Li *et al*., 2013).
8.	Vindoneline	Blood glucose	It is derived from the leaves of *Catharanthus roseous* and is seen to lower blood glucose levels (Heinrich *et al*., 2021).
9.	Vindoline, Vindolidine, Vindolicine, Vindolinine	PTP1B inhibition	These indole-type alkaloids derived from *Catharanthus roseus* showed PTP1B inhibition in different amounts, thus improving glucose uptake (Heinrich *et al*., 2021).
10.	Raubasine	hypoglycemic	It can act as a hypoglycemic agent along with other alkaloids like vinblastine, vincristine and vindesine (Dey *et al*., 2020).
11.	Caulerpin	hPTP1B inhibition	This is an indole alkaloid that can inhibit hPTP1B on the insulin receptor, thus showing antidiabetic activity (Escandón-Rivera *et al*., 2020).
II.	**FLAVONOIDS**		
1.	Naringenin	Gluconeogenesis pathway	Naringenin is a natural Flavanone, derived from gular, *Ficus racemosa*. It is known to show anti-inflammatory, anti-fibrotic, hyperlipidemic and hyperglycemic activities. It also reduces adsorption of glucose at the brush border of intestine and renal, but increases uptake of glucose by muscle & fat tissues. Treatment with this compound reduces gluconeogenesis and TG production in hepatocytes. It is isolated from *Cochlospermum vitifolium* (Ku *et al*., 2020).
2.	Catechins	Glutathione S-transferase	They are found in tea & cocoa products and exhibit enhancing effects towards GST (glutathione S-transferase), SOD, protective when oxidative damage and show CAT activities. According to some studies, green and black tea showed no hypoglycemic effect in T2DM adults (Li *et al*., 2013).
3.	Catechin	Antidiabetic	It can be isolated from *Acacia angustissima* and *Hamelia patens* Jacq. (Zhao *et al*., 2020). Catechin is also found in tea, cocoa, apple, grape, cherry and apricot (Alkhalidy *et al*., 2018).
4.	Epicatechin	NF-kB p65 phosphorylation	It is derived from the bark of *Pterocarpus marsupium* Roxb and helps in reduction in glucose level (Sheehan *et al*., 1983). It can also be derived from *Smilax glabra* Roxb, and can inhibit the NF-kB p65 phosphorylation (Mozaffarian and Wu, 2018).
5.	Epigallocatechin gallate (EGCG)	Antidiabetic	It is derived from the leaves of *Camellia sinensis* Kuntze and protects β-cells in streptozotocin-induced diabetic rats. It is usually found in daily diet products like soybeans, broad beans, apples, pistachio and pecans (Manivannan *et al*., 2020).

6.	Fisetin	Gluconeogenic enzymes	It inhibits the action of certain gluconeogenic enzymes, thus increasing homeostasis of glucose and reducing blood glucose. It also increases the level & activity of glyoxalase 1 (Li *et al*., 2013).
7.	Kaempferol	α-glucosidase inhibition	This is a natural flavonol, derived from gular, *Ficus racemose*, *Tetracera scadens* (L.) and *Equisetum myriochaetum* (Escandón-Rivera *et al*., 2020). It is an antioxidant that promotes sensitivity towards insulin. It also helps in preserving β-cell massand has the potential to inhibit α-glucosidase activity and dipeptidyl peptidase IV thus regulating blood glucose and insulin secretion (Sheehan *et al*., 1983).
8.	Luteolin	α-glycosidase	It is a flavone used to treat diabetic nephropathy, derived from *Glycyrrhiza*. It helps in improving cardiac failure condition in cardiomyopathy of T1DM. Derived from Fabaceae family, this compound inhibits action of α-glycosidase and is prevalent in foods like parsley and celery (Mozaffarian and Wu, 2018).
9.	Quercetin	Akt/cAMP response element-binding protein pathway, α-glucosidase inhibition.	It is a natural flavonol, derived from gular, *Ficus racemose* and *Tetracera scadens* (L.). It is known to activate the Akt/cAMP response element-binding protein pathway, decrease TGF-β (1) mRNA, Type IV collagen, Smad 2/3 expression, laminin levels and G0/G1 phase cell percentage. It has the potential to inhibit α-glucosidase activity and dipeptidyl peptidase IV thus regulating blood glucose and insulin secretion (Li *et al*., 2013). It is also present in watermelon and exhibits antioxidant properties (Proenca *et al*., 2019).It showed maximum pancreatic α-amylase inhibition out of all flavonoids tested (Proenca *et al*., 2019).
10.	Rutin	Insulin-dependent glucose transporter	Rutin is a natural flavonoid glycoside isolated from *Annona cherimola* Mill leaves (Ku *et al*., 2020). It enhances the activity of insulin-dependent glucose transporter and insulin receptor kinase and stimulates glucose uptake. It also alters glycolytic and gluconeogenic enzymes, thus potentiating homeostasis of glucose. It is also present in watermelon and exhibits antioxidant properties (Proenca *et al*., 2019).
11.	Morin	Insulin receptor; Akt/eNOS pathway	Morin is a natural flavonoid, which stimulates the metabolic pathways by activating and sensitizing the insulin receptor. It has been reported to activate the Akt/eNOS pathway in a diabetic mouse model, thus inhibiting dysfunction of endothelium. It also down-regulates miR-29a level, thus showing antidiabetic effects (Li *et al*., 2013).
12.	Silymarin	TGF-β1/Smad signaling	This is a chemical complex formed from silybin, silydianin and silychrisin which has been known to improve diabetic cardiomyopathy by inhibiting the TGF-β1/Smad signaling. It also reduces blood glucose levels and has nephroprotective actions in T2DM.It can be found in apples, asparagus, broccoli, coriander, ginger, okra, etc (Mozaffarian and Wu 2018); in *Silybum marianum*, milk thistle (Tauchen *et al*., 2020).
13.	Chrysine	α-glucosidase inhibition	It is a natural flavone that shows antidiabetic effects (Asadullah *et al*., 2020). It is known to suppress expressions of collagen IV, TGF- β (Transforming Growth Factor- β) and fibronectin in renal tissues. It also helps against CYP (Cytochrome P450 enzymes)-induced kidney, liver, brain, testis and heart toxicity. It also reduces serum levels of IL-6, IL-1β and pro-inflammatory cytokines. It exhibits α-glucosidase inhibition (Proenca *et al*., 2017).
14.	Baicalein	NF-kB (Nuclear Factor kappa B)	This is derived from gular, *Ficus racemosa* (Prabhakar and Banerjee 2017). It inhibits stimulation of NF-kB and decrease oxidative stress and mitigates expression of TGF- β1 and iNOS. It also balances serum levels of liver enzymes and pro-inflammatory cytokines (Li *et al*., 2013).
15.	Glabrin	Superoxide Dismutase activity	It is a flavonoid derived from *Glycyrrhiza glabra* which reduces glucose levels and exhibits superoxide dismutase activity in liver and kidneys, thus triggering an antioxidative pathway (Prabhakar and Banerjee 2017).
16.	Anthocyanin	Gene expression for adipocytokine	This flavonoid showed a change in gene expression of adipocytokine when treated to adipocyte cells. It improves sensitivity to insulin/ reduces glucose intolerance (Sandoval *et al*., 2020).
17.	Hypolectin	α-glucosidase inhibition	It is derived from leaves of *Tetracera indica* Merr. Andshows the potential to inhibit α-glucosidase activity and dipeptidyl peptidase IV thus regulating blood glucose and insulin secretion (Prabhakar and Banerjee 2017).
18.	Isoquercetin	α-glucosidase inhibition.	It has the potential to inhibit α-glucosidase activity and dipeptidyl peptidase IV thus regulating blood glucose and insulin secretion (Prabhakar and Banerjee 2017).
19.	Isorhamnetin	GLUT2	It can be extracted from *Oenanthe avanica*, *Ginkgo biloba* and *Hippophae rhamnoides*. It is known to show inhibitory effects

			on adipogenesis; ameliorate GLUT2 and secretion of insulin (AL-Ishaq *et al*., 2019).
III.	**TERPENOIDS**		
1.	DITERPENOIDS:		
	Triptolide	Caspases 9, 8 and 3	This 3 epoxide groups containing diterpenoid increases caspases 9, 8 and 3 and reduces levels of phosphorylated kappa B inhibitor and phosphorylated protein kinase B (Salehi *et al*., 2019).
	Trans-dehydrocrotonin	Antidiabetic activity	It is a lactone-type clerodanediterpene that showed antidiabetic activity in mice by stimulating pancreatic β-cells (Gushiken *et al*., 2016).
	Andrographolide	α-adrenoreceptors	This diterpenoid lactone has been reported to show antidiabetic effects [44].It ameliorates use of glucose by decreasing the level of plasma glucose. It does so by activating the α-adrenoreceptors thus enhancing the release of β-endomorphin, a peptide (Salehi *et al*., 2019).
2.	TRITERPENOIDS:		
	Boswellic acids	β cells	These are pentacyclic triterpenoids thatstimulateβ-cells so that they release more insulin. They are used in prevention and treatment of islets of langerhans during any inflammation or damage (Salehi *et al*., 2019).
	Celastrol	NF-kB	It is a natural triterpene which inhibits NF-kB thus improving resistance to insulin and treating renal injury. It was tested on diabetic liver injury in T2DM via TLR4/MyD88/NF-*k*B signaling pathway. It ameliorates lipid metabolism thus restraining obesity (Salehi *et al*., 2019).
	Oleanolic acid	Akt/FoxO1; PTP1B and α-glucosidase	This is a pentacyclic triterpenoid which suppresses hepatic gluconeogenesis in T2DM mice via Akt/FoxO1 thus lowering hyperglycemic levels. It is isolated from *S. aromaticum* (Cox-Georgian *et al*., 2019), *Eysenhardtia platycarpa* (Ku *et al*., 2020) and *Myrtus communis* Linn., where it inhibits both PTP1B and α-glucosidase, thus showing antidiabetic activity (Zulcafli *et al*., 2020).
	Ursolic acid	PTP1B and α-glucosidase	It is a pentacyclic triterpenoid that directly inhibits PTP1B and hence, increases insulin sensitivity. In mice with diet-induced obesity, it increases blood glucose levels. In diabetic rats, it also inhibits kidney damage. It is isolated from *Agrimonia pilosa* and it inhibits both PTP1B and α-glucosidase, thus showing antidiabetic activity (Genovese *et al*., 2021). It can be derived from *Origanum majorana* L. and can be used in treatment of diabetic retinopathy along with other phytochemicals (Parveen *et al*., 2018).
	Betulinic acid	PTP1B and α-glucosidase	It is a pentacyclic triterpenoid isolated from *Eysenhardtia platycarpa* (Ku *et al*., 2020) and *Myrtus communis* Linn. (Genovese *et al*., 2021). It inhibits both PTP1B and α-glucosidase, thus showing antidiabetic activity (Genovese *et al*., 2021).
	Lupeol	PTP1B and α-glucosidase	It is a pentacyclic triterpenoid isolated from *Eysenhardtia platycarpa* (Ku *et al*., 2020) and *Pueraria lobate* and it inhibits both PTP1B and α-glucosidase (Genovese *et al*., 2021).
	Gymnemic acids	Glucose absorption	They are a group of triterpenoid saponins isolated from *G. sylvestre* (Tran *et al*., 2020) which are shown to inhibit glucose absorption and the conversion of glycogen to glucose in blood (Salehi *et al*., 2019).
3.	**POLYSACCHARIDES:**		
	Galactomannan	Glucose absorption	It reduces postprandial hyperglycemia by delaying glucose absorption (Salehi *et al*., 2019).
	Inulin	Antidiabetic	It acts as a biogenetic in modulation of liver enzymes and blood metabolites and after dysbacteriosis in regenerating intestinal natural microflora (Salehi *et al*., 2019).
IV.	**PHENOLIC ACIDS**		
1.	Gallic acid	α-amylase and α-glucosidase inhibition; GLUT4	Administration of gallic acid at a dose of 20mg/kg has been reported to reduce the blood glucose level of alloxan-induced diabetic rats to 150 mg/dl. It also showed a mild α-amylase inhibitory effect and high α-glucosidase inhibition when administered along with acarbose. This compound is isolated from *Ibervillea sonorae* (Belobrajdic and Bird 2013) which helps in compartmentalization in plasma membrane for GLUT4 thus improving glucose uptake (Zhao *et al*., 2020).
2.	Salicylic acid	NF-kB signaling pathway, AMPK	It affects NF-kB signaling thus showing anti-inflammatory and antihyperglycemic effects. It is also known to directly activate AMPK thus showing antihyperglycemic effects (Prabhakar and Banerjee 2017).
3.	Ferulic acid	ROS generating oxidative stress-induced pathway.	This compound shows anti-inflammatory, antioxidant, hypoglycemic effects and improves renal tissue impairment by activating JNK, p38, ERK ½, NF-kB signaling pathways,

			inhibiting ROS generating stress-induced pathway. It is present in wholegrain cereals like wheat and barley in high amounts and also present in oat, rice and rye (Belobrajdic and Bird 2013).
4.	Caffeic acid	Autophagy regulatory miRNAs	It is shown to inhibit autophagy regulatory miRNAs, thus modulating autophagy pathway. This improved albumin excretion in STZ induced diabetic rats. It is isolated from *Hamelia patens* Jacq. (Ku *et al*., 2020).
5.	Protocatechuic acid	Oxidative stress	Isolated from *Acacia angustissima*, this is shown to prevent oxidative stress, improve cerebellar, cerebral and pancreatic structures; it is neuroprotective and also prevents oxidative stress in streptozotocin-induced T1D rats (Ku *et al*., 2020).
6.	Ellagic acid	β cells	This is a natural phenol; a dilactone acid, which increases glucose tolerance, secretion of insulin by affecting β cells (Salehi *et al*., 2019).
7.	Butein	NF-kB	Butein is a natural phenolic chalcone that was found to ameliorate homeostasis of glucose by inhibiting the central NF-kB pathway.It inhibits nitric oxide formation in-vitro thus reducing cytokine-induced toxicity (Zhang *et al*., 2015).
8.	Curcumin	NF-kB mediated transcription	It is a natural polyphenolwhich shows keto-enol tautomerism and is known to suppress glycosylated Hb levels, blood glucose. It also inhibits weight loss and can be used for reducing/ preventing diabetes since it has antioxidant & anti-inflammatory activities (Zhang *et al*., 2015). It also helps in reducing the NF-kB mediated transcription, hence also contributing against neuroinflammatory diseases (Subedi *et al*., 2020).
9.	Chlorogenic acid	AMPK	This is a natural polyphenol that activates AMPK in skeletal muscle, thus increasing glucose transport. It is isolated from *Ageratina petiolaris* (Ku *et al*., 2020).
10.	Erianin	HIF-1α-VEGF/VEGFR2 signaling pathway	It is a natural phenolic compound containing 4 aromatic ether groups. It blocks the HIF-1α-VEGF/VEGFR2 (hypoxia-inducible factor 1α-vascular endothelial growth factor-VEGF receptor 2) signaling pathway which is regulated by ERK1/2 (extracellular signal regulated kinases) thus inhibiting retinal angiogenesis induced by high glucose levels (Salehi *et al*., 2019).
11.	Garcinol	Antioxidant	This compund is a polyisoprenylated benzophenone that is responsible in reducing high levels of lipids, glycosylated Hb, blood glucose and also reduces body weight, HDL cholesterol (high density lipoprotein cholesterol), antioxidant activities of enzymes, glycogen, plasma insulin and homeostasis model assessment (HOMA) of β-cell functioning index (Salehi *et al*., 2019).
V.	**OTHERS**		
1.	Resveratrol	SIRT1, GLUT 4	It activates SIRT1 with the help of AMPK (5' Activated Protein Kinase) thus showing antihyperglycemic effect, while it has many effects in animal models like increase in insulin secretion, glucose homeostasis, improvement in metabolic disorders, protection of β cells, decrease in resistance towards insulin, oxidative stress, adipogenic genes, improvement in GLUT-4 translocation (Md sayem *et al*., 2018) and regulation of enzymes involved in carbohydrate metabolism. This is derived from peanuts and purple wine (Forni*et al*., 2019).
2.	Piceatannol	GLUT-4; HMOX1	This is a derivative of resveratrol which stimulates GLUT-4 and increases glucose uptake to the plasma membrane; thus suppressing blood glucose levels in L6 myocytes in mice with T2DM.It also activates HMOX1 (heme oxygenase-1) in human endothelial cells, hence producing endothelial nitric acid and restoring impairment of insulin signaling induced by palmitic acid (Salehi *et al*., 2019).
3.	Vitamin-E	NF-kB	Tocotrienol & tocopherol isomers are seen to reduce high-sensitivity C-reactive protein in patients with T2DM and stimulate the NF-kB pathway, thus reducing diabetic nephropathy (Salehi *et al*., 2019).
4.	Indole-3-Carbinol	Glutathione peroxidase (GPx)	Indole-3-Carbinol and 3, 3′-diindolylmethane (condensation product of Indole-3-Carbinol) act as blocking agents, which increase the levels of Vitamins C & E, glutathione, glutathione peroxidase (GPx), CAT and SOD in diabetic mice (Salehi *et al*., 2019).
5.	Embelin	TNFα	It is a hydroxyl benzoquinone that causes reduction in glycosylated hb, IL6, TNFα (tumor necrosis factor), elevated plasma glucose (Salehi *et al*., 2019).
6.	Gambogic acid	PI3K/AKT pathway	AKA guttic acid, guttatic acid, β-guttilactone, and β-guttiferin is a Natural Pyranoxanthone. It affects PI3K/AKT pathway, thus inhibiting HIF-1α/VEGF expression. This improves proliferative diabetic retinopathy

			(Salehi *et al*., 2019).
7.	Honokiol	PTP1B; Nrf2/ARE pathway	It is a polyphenol lignin that can potentially bind to PTP1B. It is also known to activate Nrf2/ARE pathway and protecting β cells against hypoxia induced injury and high glucose. It enhances insulin signaling factors and also improves phosphorylations (Salehi *et al*., 2019).
8.	Teuhetenone A	α-glucosidase	Teuhetenone A was isolated from *Turnera diffusa* and has been reported to show inhibitory activity on α-glucosidase. It reduced the glycemia levels by 20% in CD1 mice after 6 hours of fasting (Parra-Naranjo *et al*., 2017).
9.	Sulforaphane (SFN)	Lipid peroxidation	This compound can reduce lipid peroxidation, thus decreasing oxidised-LDL and plasma malondialdehyde. As lipid peroxidation is considered one of the indicator of T2DM, SFN can be used as an antidiabetic phytochemical derived from broccoli sprouts (Houghton, 2019).
10.	Chelerythrine	PPARγ inhibition	It is reported to block PPARγ, thus known to be useful in treating insulin resistance. It can be extracted from *Sanguinaria Canadensis* (Croaker *et al*., 2016).

Identification of therapeutic target molecules. To act as an efficient remedy for diabetes, the binding ability of the phytochemical to the drug target molecule is a very important criterion (Prabhakar and Banerjee, 2017). A drug target can be defined as the molecular entity or macromolecule whose function, property is modulated by a particular chemical compound or drug. An ideal drug target has a limited distribution in the body, must be responsive towards the drug and must be patho-physiologically useful to the disease.

A study of various bioactive metabolites in connection with their drug targets would give clarity about the mode of action of the compound in treating diabetes. Plant-derived phytochemicals are seen to target some of the important therapeutic targets for both Type 1 and Type 2 diabetes (Prabhakar and Banerjee, 2017). These targets include:

1. α-glucosidase inhibitors plays a vital role in carbohydrate absorption by slowing down the glucose production resulting in reduction of blood glucose levels.

2. Peroxisome Proliferator-Activated Receptor-Gamma (PPARγ) responsible foractivating the genes involved in adipose tissues for lipid metabolism & adipogenesis. When transcriptionally activated by phytomolecules sensitivity to insulin is activated.

3. G-Protein coupled Receptors (GPR) are preferable therapeutic targets for diabetes mellitus (eg. GPR119, GPR120 & GPR140). GPR120 is a member of the rhodopsin GPR groups and is expressed in adipose tissue & intestinal epithelium. It activates & secretes glucagon which is in turn, responsible for the regulation of insulin secretion.

4. Glucose Transporter Type 4 (GLUT 4) is a polypeptide present in the cell membrane which transports glucose into the cells using a responding mechanism involving insulin. Mutation or gene alteration in GLUT4 causes type 2 diabetes.

5. Nuclear Factor Kappa Light Chain Enhancer of Activated B-cells (NFKB) is a polypeptide complex activated by high plasma glucose levels.

6. P38 Mitogen-Activated Protein Kinase (P38MAPK) activation is reported to be important during treatment of hyperglycemia.

7. Sodium-Glucose Transporter 2 (SGLT 2) is a membrane protein responsible for reabsorption of 90% glucose by kidney cells. Hence, inhibition of this transporter leads to controlling hyperglycemia.

8. Stress Activated Protein Kinase/c-Jun NH (2) terminal Kinase (SAPK/JNK) serve as an important pathway and can lead to resistance of insulin at inhibiting the phosphorylation stage.

9. Dipeptidyl Peptidase-4 (DPP4) degrade GLP-1 (peptide 1 glucagons which when combined with glucose-dependent insulinotropic insulin, stimulate or decrease secretion of insulin, and that of glucagon).

10. 11β Hydroxysteroid Dehydrogenase (11β-HSD) an oxidoreductase enzyme that converts cortisone to cortisol along with NADP/NADPH conversion. This causes hyperglycemia and increases blood sugar levels. Thus, 11β-HSD inhibitors can be potential medicinal targets.

11. Glucose Fructose-6-Phosphatase Amidotransferase (GFAT) is a part of Hexosamine Biosynthetic Pathway where it plays a crucial role in regulating the glucose flux. GFAT is responsible for the glucose-induced insulin resistance and hence, used as a drug target.

12. 17β-Hydroxysteroid dehydrogenase Type 1 an alcohol oxidoreductase enzyme is considered to be a potential biomarker for diagnosing diabetes as it has been reported to cause an increase in insulin resistivity.

13. Solute Carrier Family 16 Member 11 (SLC16A11) a proton coupled transporter that causes increase in chances of Type 2 diabetes.

Different bioactive compounds which act as drugs such as alkaloids, flavonoids, terpenoids and phenolic acids & their drug targets including GLUT4, NFKB, etc. are depicted in Fig. 1. The alkaloids are known to target α-glucosidase, PTP1B and P38MAPK oxidative signaling; whereas, flavonoids target NFKB, α-glucosidase and GLUT. Terpenoids target NFKB, α-glucosidase & PTP1B; while phenolic acids target α-glucosidase, PTP1B, NFKB and GLUT4(Astolfi *et al*., 2015; Ansari *et al*., 2022) (Table 1).

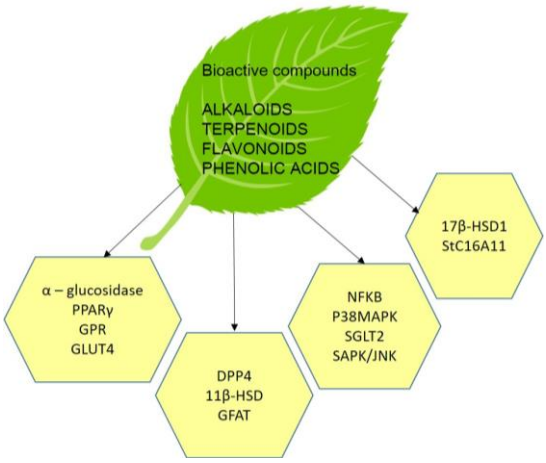

Fig. 1. Antidiabetic drug targets of phytochemicals.

This review is a brief attempt to summarize the existing drug targets of oral hypoglycemic drugs. Further research is required to establish new drug targets as the old targets become saturated or desensitized after repeated administration of these drugs on chronic basis.

CONCLUSIONS

Various plants have been identified whose extracts show hypoglycaemic effects. The antidiabetic effect of plants is attributed to the mixture of phytochemicals or single components of the plant extracts. The phytochemicals responsible for antidiabetic properties mainly are alkaloids, phenolic acids, flavonoids, glycosides, saponins, polysaccharides, stilbenes, and tannins.

Individual compounds from different classes of chemicals have been tested on alloxan-induced T2DM rats and their effectiveness has been described. This has also showed us how due to the diversity of phytochemicals, there is a diversity in the mechanism of action in each compound. They affect various pathways, enzymes by either inhibiting an action; or stimulating it. This results in either an increase in the uptake of glucose or the secretion of insulin. The mode of action of these antidiabetic phytochemicals has been described in detail here. Diverse mechanisms are described, explaining the beneficial effects of phytochemicals, such as regulation of glucose and lipid metabolism, insulin secretion, stimulating β cells, NF-*k*B signaling pathway, inhibition of gluconeogenic enzymes, and ROS protective action. Here, we compiled different plant extracts and their active compounds with their hypoglycemic action and specific drug target.

Knowing the various types of plants that are abundant with these phytochemicals shows us that the sources are not limited. They can be found in various fruits, nuts, vegetables; various families such as *Lamiaceae, Cucurbitaceae, Moraceae, Euphorbiaceae, Leguminoseae, Liliaceae, Asteraceae, Rosaceae and Araliaceae*, etc. Since these compounds do not have to be synthesized pharmaceutically, and only need to be extracted from particular plants, it also makes them cheaper as drugs as opposed to the synthetic ones. The most important reason for considering phytochemicals is the inability of synthetic drugs in reversing the diabetic condition, being able to work only in specific environments such as only in presence of insulin or causing side effects such as reducing post-prandial blood sugar levels, slower absorption and binding to non-specific receptors.

As mentioned in the review, certain phytochemicals have been found that show almost no side effects. Their diversity in the mechanism of action puts aside the setback of being able to work only in specific conditions. Whether they will be able to completely reverse the diabetic condition may be unknown. But, treating DM with plant-derived compounds, which are accessible and do not require laborious pharmaceutical synthesis, seems highly attractive.

FUTURE SCOPE

Diabetes as a lifestyle disease has no signs of decline in the coming years in urban population. Apart from regular antidiabetics the phytochemicals are gaining importance in recent times. India particularly has a lot of Ayurvedic plant derived medicines against Diabetes. In this regard the search for new antidiabetic phytochemical never goes in vain. In future the novel glucose reducing small molecule phytochemicals will be ruling the antidiabetic market. However, a word of caution in using these phytochemicals is for further toxicity and tolerance testing. These molecules may have success in pre-clinical testing. Without further clinical trials these phytochemicals should not be posed as antidiabetic for human use.

Conflict of Interest. None.

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How to cite this article: Biswa Prasun Chatterji, Aarya P. Suthar and Rupasree Mukhopadhyay (2023). A Review on Bioactives from Plants against Diabetes. *Biological Forum – An International Journal*, *15*(6): 618-627.