Review Article

Mechanistic Approach Involved in Antidiabetic Efficiency of Plant Based Nanoparticles: A Review

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ABSTRACT

Diabetes mellitus is considered as one of the top causes of morbidity among the top major causes of mortality. Numerous drugs and treatment options are available which can lower blood glucose levels but complications related to diabetes and side effects of drugs is the major challenging issue which needs to be handled. During the past few years, plant based nanoparticles have become popularized as antidiabetic agents with effective approach and minimum side effects. In the present review, various in vitro and in vivo studies based on antidiabetic potential of phyto-nanoparticles have been incorporated along with the mode of actions involved which will assist to understand the current status of phyto-nanoparticles as antidiabetic agents.

Keywords: Diabetes; nanoparticles; glucose; plants; antidiabetic.

INTRODUCTION

Diabetes mellitus is a dangerous and widespread physiological illness which can be defined as an imbalance in the metabolism of carbohydrates and lipids that lead to hyperglycemia. It may cause a variety of diseases including blindness, neurotoxicity, nephrotoxicity, heart or arterial disease, cardiomyopathy and strokes [1]. It can be classified as type 1 and type 2 diabetes. Type 1 diabetic mellitus is an insulin-dependent disorder where the pancreas doesn't produce adequate insulin. It generally occurs in children and youngsters. On the other hand, in Type 2 diabetes mellitus, sufficient insulin is available but the body is not able to effectively use it. The number of incidents has become more common over the last few years. In 2014, roughly 422 million persons were identified as diabetic which accounts for 8.5 percent of the whole world population and it was predicted that nearly 642 million people will be diabetic by 2040 [2].

Glucose control is known as the primary treatment strategy for diabetes mellitus. Insulin therapy alone or along with hypoglycemic medications are used to cure diabetes mellitus. Metformin, glibenclamide, Alpha-glucosidase inhibitors and other medications are used to treat Type 2 diabetes [3]. Prolonged uses of these drugs may lead to drug resistance, drug toxicity, weight gain, disturbances in digestion, lactic acidosis and liver diseases also. During the last few decades, herbal medications have become more popular due to their effectiveness, negligible side effects and low cost. The medicinal plant contains a variety of bioactive molecules such as alkaloids, phenolic acids, flavonoids, glycosides, saponins, polysaccharides, stilbenes, and tannins are present in plants which showed various medicinal properties including antimicrobial, antioxidant antidiabetic etc. Phytoconstituents showed antidiabetic effect via reduction in carbohydrate assimilation and absorption, imitating insulin action or stimulating insulin production [4,5]. However, phytochemicals showed significant antidiabetic activity in-vitro but results of *in-vivo* research are not much satisfactory which might be due to their rapid metabolism and poor bioavailability. To overcome the pharmaceutical incompetence of these compounds, Nanoscience and nanotechnology have emerged with a broad array of applications in the medical field. It has also been proven as the leading strategy in treatment of diabetes mellitus because of its eco-friendly nature, consistency, bioactivity, bioavailability, and effectiveness in release of drugs [6]. A variety of phytonano-particles such as Azadirachta indica, Catharanthus Roseus, Moringa oleifera, Nigella sativa, Punica granatum, Ocimum sanctum, Zingiber officinales etc. have been developed that delivers the medications to the target location efficiently. This review article has been framed to discuss efficiency of various phyto-nanoparticles and their mechanistic approach in diabetes and its complications.

METHODS

Relevant articles were searched on various search engines such as PubMed, Scopus, Google scholar, Web of Science etc by using the terms diabetes, Nanoparticles, Plants, phyto-nanoparticles, treatment of diabetes etc. Review and original research articles published during the last 10 years were included in this review.

Antidiabetic potential of phyto-nanoparticles

Plants and plant extracts have been used in the field of medicine since long ago. Various phytochemicals such as phytosterols, flavonoids, terpenoids, saponins, alkaloids, carotenoids, aromatic acid, organic acid, essential oils and protease inhibitors are known to possess antimicrobial,

antiinflammatory and antioxidant activities due to which they are being utilized in the treatment of metabolic, respiratory, circulatory, neurological and immunological disorders etc. In Spite of their beneficial effects in various areas, their use is limited essentially due to poor systemic delivery, low bioavailability, and water solubility concerns. To eradicate these problems and to improve availability of drugs, Nanotechnology has emerged as a promising approach for the delivery of natural products. During the last few years, usage of plant based nanoparticles in diabetes treatment has increased with more positive results. A review of the *in vitro* and *in vivo* studies done in the field has been summarized in table 1 and 2 respectively.

Table 1: Antidiabetic potential of phyto-nanoparticles based on *in-vitro* studies

Plant name	Nanoparticle used	Reference	Methodology	Observation
Allium cepa (onion)	AgNPs (20–100 mg/mL)	12	α amylase and α glucosidase enzyme inhibition assay	At 100 µg/ml, alpha amylase and alpha glucosidase ($P \geq 0.05$) inhibition was 74% and 60% respectively.
Allium sativum (garlic)	AgNPs (100-500µg/ml)	13	α amylase inhibition assay	At 500µg/ml, alpha amylase inhibition was 50%.
	AgNPs (30mg/ml)	14	α amylase inhibition assay	Nanoparticles showed greatest inhibition activity (75.55%) at 50 µg/mL and the IC50 value of AgNPs was noted as 2.38 µg/mL.
Annona muricata (soursop)	AgNPs (20µl)	15	α-amylase and α-glucosidase enzyme inhibition assay	Both α-amylase and α- glucosidase ($P < 0.001$) are inhibited with IC50 values of 0.90 and 3.32 µg/ml, respectively.
	Fe3O4 (10-500µg/ml)	16	α amylase inhibition assay	Fe3O4 nanoparticles using Annona muricata exhibit a good level of inhibition under *in vitro* conditions.
Argyreia nervosa (elephant creeper)	AgNPs (20–100 mg/mL)	17	α amylase and α glucosidase enzyme inhibition assay	At 100µg/ml, 70% inhibition was shown by both α amylase and α glucosidase enzyme inhibition assays.
Avicennia officinalis (Indian mangrove)	AgNPs (0.1 mg/ml to 0.5 mg/ml)	18	α amylase and α glucosidase enzyme inhibition assay	Activity of α-amylase and (IC50- 0.28 mg/ml) and α glucosidase (IC50- 0.15 mg/ml) was inhibited 98% and 90% respectively at 0.5 mg/ml.
Andrographis paniculata (Green chirette)	ZnONPs (0.1 mg/ml to 0.5 mg/ml)	19	α amylase inhibition assay	The IC50 value of ZnONPs was 121.42 µg/ml, which was 28.23 g/ml lower than the leaf extract.
Azadirachta indica (Neem)	ZnONPs (100–1.52 µg/mL)	20	α-amylase and α-glucosidase inhibition assay	At 100 µg/ml, α amylase inhibition was 85.7±1.53% and α glucosidase inhibition was 86.93± 0.84 percent.
Callophylum tomentosum (bintangur)	AgNPs (10, 25, 50, 100 and 150 µg/ml)	21	α-amylase, α-glucosidase and DPPIV inhibition assay	At 500 µg/ ml, inhibition of amylase, glucosidase and DPPIV was approximately 18%, 52% and 58% respectively.
Catharanthus Roseus	ZnNPs (10, 20, 40, 80, 160, and 320 µg ml)	22	α-amylase inhibition assay	The normal drug (Acarbose) had an IC_{50} of 13.085434 micrograms per millilitre, whereas the IC50 for the provided sample was 35.64165 micrograms per millilitre. The existence of the Zn-doped *C. roseus* extracts has a profound effect on blood sugar management, a process that Zn acts upon as an actuator. When used to treat diabetes, the produced Zn-doped C. roseus extract shows an enhanced inhibitory action and effectively lowers fasting blood glucose levels.
Cantella asiatica (gotu kola)	AgNPs (250-1000µg/ml)	23	Glucose uptake by Yeast cells, α- amylase inhibition assay, non-enzymatic glycosylation of Haemoglobin inhibition assay	At 200 µg/ml, increment was observed in glucose absorption (63.27 ± 0.57) and non-enzymatic glycosylation of Hb (52.91± 0.421). Percent inhibition of α amylase.43.96± 0.91

Clausena anisata (horsewood)	AgNPs(100- -500 µg/ml)	24	α-amylase inhibition assay, Glucose uptake by yeast cells Glucose 17 diffusion assay	Maximum amylase inhibition was 83.60% (P<0.001) at 500 µg/ml, maximum glucose absorption was 69.51% at 10 mM concentration of glucose, and maximum GDRI was 78.33% (P<0.001) at 600 g/ml glucose.
Colpomenia sinuosa (oyster thief)	AgNPs(0.2-1 mg/ml)	25	α-amylase and α-glucosidase enzyme inhibition assay	At 1 mg/ml, the inhibition of amylase (IC50-490±0.02) and glucosidase (IC50-385±0.02 mg/ml) was 94.30% and 90.50% respectively.
Cympogon citratus (lemon grass)	AgNPs (20, 40, 60, 80, 100 µL)	26	α-amylase inhibition assay and GDRI (Glucose diffusion retardation index assay)	After 120 minutes, α-amylase inhibition was around 90% at 100 µg/ml and GDRI inhibition was 81.30%.
Costus igneus (insulin plant)	ZnONPs (20-100µg/ml)	27	α-amylase and α-glucosidase inhibition assay	74% inhibition of α-amylase and 82% inhibition of α-glucosidase were noted at 100 µg/ml respectively. Nanoparticles showed 12% stronger impact than the plant extract.
Costus pictus (Spiral flag)	AgNPs (200-1000µg/ml)	28	α-amylase and α-glucosidase inhibition assay	Methanolic extract of AgNPs showed strong α-glucosidase inhibitory and α-amylase inhibitory activity as compared with Methanolic extract. The IC50 values of the MECP, MECPAgNPs and Acarbose were found to be 639.83, 534.39 & 513.97µg/ml.
Dioscorea bulbifera	CuNPs of Dioscorea bulbifera tuber extract (DBTE; 10 µg/ml)	29	α-amylase and α-glucosidase inhibition assay	Copper nanoparticles of Dioscorea bulbifera showed 99.09 ± 0.15% inhibition against α-glucosidase while 90.67 ± 0.33% inhibition against murine intestinal glucosidase, respectively.
Enhalus acaroides (Tape seagrass)	AgNPs (0.25 ml) with different concentration (10–100 µg/ml)	30	α-glucosidase enzyme inhibition assay	At 100 µg/ml, the enzyme was inhibited by 76%, with an IC50 value of 47 µg/ml.
Gracillaria edulis	AgNPs (10–100 µg/ml)	31	α-amylase inhibition assay and glucose inhibition assay	98.75% suppression of α-amylase enzyme and 78.75 percent reduction in glucose concentration by diffusion at 400 µg/ ml
Heriteria fomes (jekanzo) and *Sonneratia apetala* (Sonneratia mangrove)	AgNPs(10–100 µg/ml)	32	α-amylase inhibition assay	The enzymes were inhibited by HF-AgNPs and SA-AgNPs, with IC50 values of 280.39 and 273.48 µg/ml, respectively.
	ZnONPs(10–100 µg/ml)	32	α-amylase inhibition assay	The enzymes were inhibited by HF-ZnONPs and SA-ZnONPs, with IC50 values of 334.40 and 394.38µg/ml, respectively.
Hibiscus rosa-sinensis (Chinese hibiscus)	ZnONPs(100–1.52 µg/mL)	33	α-amylase and α-glucosidase inhibition assay	At 100 µg/ml, the inhibition of -amylase was 82.8± 0.95 percent while the inhibition of -glucosidase was 92.03±1.50 percent.
Justicia diffusa (Spreading justicia)	AgNPs 10–100 µg/ml)	34	α-amylase inhibition assay	61.70% inhibition of α-amylase at 200 µg/ml concentration; 6.40% inhibition from plant extract at similar concentration.
Lonicera japonica (Japanese honey suckle)	AgNPs (20–100 mg/mL)	35	α-amylase and α-glucosidase enzyme inhibition assay and their enzyme kinetics activity	α-amylase and α-glucosidase was noted to be inhibited by 80% and 96% at 100 µg/ml with IC values of 54.56 and 37.86 µg respectively. Inhibition of both enzymes by AgNPs is about 20 and 24% higher than plant extract.
Nigella sativa	AuNPs ((100, 200, 300, 400 and 500 µg/mL)	36	α-amylase and α-glucosidase enzyme inhibition assay	Highest enzymatic activity of alpha amylase was reduced by 78% and 81 %, respectively, by the seed extracts and the Phyto fabricated Au-NPs at highest dose (500 g/mL).
Ocimum bascilicum (basil)	AgNPs (2mg/ml)	37	α-amylase and α-glucosidase enzyme inhibition assay and their enzyme kinetics activity	59.79±6.91% inhibition of α-amylase (competitive inhibition) and 79.74±9.51 percent inhibition of α-glucosidase (uncompetitive inhibition) at 3 mg/ml; -1.44% (α-amylase) and 44.99% (α-glucosidase) increase in inhibition from crude extract.

	RGO-ZnO NPs & ZnO NPs (200 µg/mL and 400 µg/mL)	38	α-amylase and α-glucosidase enzyme inhibition assay	ZnO NPs and RGO-ZnO NCs showed 44.4% and 51.19% at the concentration of 200µg/mL for a-amylase inhibition. Inhibition activity was increased for ZnO NPs at 67.12% and 72.41% for RGO-ZnO NCs at 600 mg/mL. For a-glucosidase, ZnO NPs and RGO-ZnO showed 50.38% and 53.24% inhibition activity at 200 mg/mL concen-tration whereas inhibition activity of 67.17% and 72.13% at the maximum concentration of 600 mg/mL for ZnO and RGO-ZnO.
Ocimum sanctum (Tulsi)	AgNPs(3mg/ml)	37	α-amylase and α-glucosidase enzyme inhibition assay and their enzyme kinetics	At 3 mg/ml, competitive inhibition of α-amylase and α-glucosidase was 59.57 ±3.72% and 89.31± 5.32%, respectively. Inhibition from crude extract increased by -1.66 (α-amylase) and 27.06 % (α-glucosidase).
Momordica charantia (Bitter-melon)	ZnONPs (100-200mg/mL)	39	α-amylase and α-glucosidase inhibition assay	82.31± 0.034 % inhibition of α-amylase and 88.57± 0.04% inhibition of α-glucosidase at 100 µg/ml; about 24.59% and 25.67% increase in inhibition of α-amylase and α-glucosidase from plant extract, respectively.
Moringa oleifera (Drumstick tree)	ZnONPs (100–1.52 µg/mL)	40	α-amylase and α-glucosidase inhibition assay	At 100µg/ml, α-amylase inhibition was 90.36 ±1.11 percent and α-glucosidase inhibition were 96.37 ±0.67 percent.
Murraya koenigii (Curry leaf tree)	ZnONPs(100–1.52 µg/mL)	40	α-amylase and α-glucosidase inhibition assay	87.33±1.11 % inhibition of α-amylase and 82.37± 2.16 % inhibition of α-glucosidase were observed at 100µg/ml.
Tamarindus indica (Tamarind)	ZnONPs(100–1.52 µg/mL)	40	α-amylase and α-glucosidase inhibition assay	At 100µg/ml, 89.56± 2.17 percent inhibition of α-amylase and 96.2±1.34 percent inhibition of α-glucosidase was observed.
Leucosidea sericea (Old wood)	AuNPs (20µg/mL)	41	α-amylase and α-glucosidase inhibition assay	The enzymatic activity of Leucosidea sericea total extract, procyanidins fractions of Leucosidea sericea total extract (F1 and F2) and their corresponding AuNPs showed strong inhibitory alpha-amylase activity where F1 Au NPs demonstrated the highest with IC50 of 1.88 µg/mL. On the other hand, F2 Au NPs displayed the strongest alpha-glucosidase activity at 4.5 µg/mL. F2 and F2 Au NPs also demonstrated the highest antioxidant activity, 1834.0 ± 4.7 µM AAE/g and 1521.9 ± 3.0 µM TE/g respectively.
Saraca asoca (Ashoka tree)	AuNPs (100,200 and 400µl)	42	α-amylase inhibition assay	With an IC50 value of 1.5 mM, the enzyme was inhibited.
Pouteria sapota (Mamey sapota)	AgNPs (10mg/kg)	43	In-vitro assays- Non-enzymatic glycosylation of haemoglobin assay, αamylase inhibition assay, glucose uptake assay in yeast cells	52.0 ± 0.5 percent inhibition of α-amylase, 62.1 ±0.6 percent inhibition of non-enzymatic glycosylation of haemoglobin at 250 µg/ml, 67.3 ±0.4 percent increase in glucose uptake at 5 mM concentration of glucose; approximately 11 percent increase in inhibition of α-amylase and non-enzymatic glycosylation of haemoglobin, and approximately 15% increase in glucose uptake of yeast cells when compared to plant extract
Punica granatum (Pomegranate)	AgNPs ((20–100 µg/mL)	44	α-amylase and α-glucosidase enzyme inhibition assay	At 100 µg/ml, α-amylase and α-glucosidase enzymes were inhibited by 61 and 60 percent, respectively; plant extract increased the inhibition of both enzymes by 19 and 17 percent, respectively.
Solanum nigrum (black nightshade)	AgNPs (10mg/kg)	45	Oral glucose tolerance test in rats	Reduces blood glucose levels from 250 mg/dl to 125 mg/dl (P <0.001) after 21 days and increases body weight; 25 mg/dl increase in blood glucose level decrease in comparison to crude extract.

Syringodium isoetifolium (Noodle seagrass)	AgNPs (500µl)	46	α-amylase inhibition assay and glucose inhibition assay	77.25 % inhibition of α-amylase enzyme and 45.25 percent reduction in glucose concentration by diffusion at 400 µg/ ml.
Tephrosia tinctoria (Orange tephrosia)	AgNPs (75 µg/ml)	47	α-amylase and α-glucosidase enzyme inhibition assay and glucose uptake in human RBCs	83.52± 0.71 percent and 94.76±0.86 percent inhibition of α amylase and α glucosidase, respectively, and an increase in glucose uptake to 3.80±0.028 folds at 75 µg/ml; 32.78 %, 20.69 %, and 1.19-folds increase in α-amylase and α glucosidase inhibition and glucose uptake in RBCs after AgNPs treatment, respectively.
Murraya koenigii and *Zingiber officinale*	Ag/CuONPs (100–1.52 g/mL)	48	α-amylase and α-glucosidase enzyme inhibition assay and glucose 6-phosphate inhibition assay	The Ag/CuO NC synthesized using Zingiber officinale extract (1.52g/mL) displayed higher α-amylase and α-glucosidase inhibition activity when compared to that synthesized using Murraya koenigii extract and other nanomaterials. Similarly The nanocomposite synthesized using Zingiber officinale extract (1.52g/mL) showed higher activity among the nanomaterials with respect to their IC50 values because of the rich amount of phytochemicals present in the green extract, which leads to reduce the glucose formation.

Table 2: Antidiabetic potential of phyto-nanoparticles based on *in-vivo* studies

Plant name	References	Methodology	Observation
Cassia auriculate (Sena)	49	Alloxan induced diabetic rats were treated with gold nanoparticles synthesized using PAT of *C. auriculata* (0.5 mg/kg body weight in aqueous solution) for 28 days.	Body mass index, total cholesterol, triglycerides, and In diabetic rats, insulin levels were considerably higher ($P < 0.001$) at 0.5 mg/kg dosage. PTP1B is prevented with an IC50 of 1.79µg/ml.
	50	Streptozotocin (STZ)-induced diabetic rats were treated with aqueous extract of *C. fistula* (60 mg/kg bw) and phytochemically synthesized gold nanoparticles containing *C. fistula* (60 mg/kg bw) for 30 days.	Blood glucose was found to be significantly reduced ($p<0.01$) in Streptozotocin induced diabetic rats after treatment with silver nanoparticles of Cassia. The characteristic damage and disorganization in the cells, alterations in the lipid profile, hyperglycaemia, reduced serum protein and liver glycogen, enhanced liver function and kidney function markers in diabetic rats were found normalized in the treated group of rats
Coumestan wedelolactone (False daisy)	51	DEHP induced diabetic rats were treated with different doses of WDL-AuNPs (10,20,4 mg/kg b.w) for 46 days.	Insulin levels have risen to 95% at 60 µg/ml, while IR, IRS-1, and GLUT2 expression was raised in cells.
Dittrichia viscosa (False yellowhead)	52	Diabetes was induced by maintaining the rats on HFD for 2 weeks, followed by a single intraperitoneal injection of 45 mg/kg of STZ. Diabetic group treated intraperitoneally with a daily injection of AuNPs (2.5 mg/kg) prepared from leaf extract of *Dittrichia viscosa* for 21 days.	Treatment with AuNP significantly lowered the blood glucose level, the gene expression, and the activity of hepatic phosphoenolpyruvate carboxykinase (PEPCK) in comparison to the diabetic untreated group
Datura stramonium	53	Alloxan induced diabetic rats were treated with different doses of phytosynthesized AuNPs (500, 700,1000 µg/ml; synthesized by seed extract of *Datura stramonium)* for 21days.	After inducing diabetes in rats, the animals weight decreases, but after 21 days of therapy, the weight of the treated groups rose as compared to the untreated group. In addition, following treatment with 500 and 750 g/ml AuNPs, while it was reduced in the untreated groups. Increases in serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), urea, and creatinine caused by alloxan induction were significantly attenuated by treatment with Datura stramonium seed extract and the synthesized nanoparticles at 500, 750, and 1000 g/ ml.
Eysenhardtia polystachya	54	Glucose induced diabetic fish were treated with different doses of EP/AgNPs (5,10µg/mL) for 14 days.	Insulin production increased considerably from INS-1 ($P< 0.05$), blood glucose was somewhat reduced, and

(Mexican kidneywood)			the expression of insulin receptor isoform GLUT-2 was enhanced at 10 µg/ml.
Fritillaria cirrhosa (Yellow Himalayan fritillary)	55	Streptozotocin induced diabetic rats were treated with AuNPs at the dose of 10&20 mg/kg body weight for 28 days.	Body weight rises, total protein and plasma insulin, whereas ALT, AST, ALP levels, creatinine, and glycosylated hemoglobin reduced and hepatic enzymes recovered to normal levels (P≤ 0.01).
Musa paradisiaca (Edible banana)	56	Streptozotocin induced diabetic rats were treated with AgNP orally (50 µg/kg body weight) for 56 days.	Insulin levels improved (16.12 1.63 µU at 50 µg/kg), glucose levels fell (281.08 0.74 to 207.99 2.33 mg/dl), and glycogen levels increased (38.51 1.01 to 29.42 0.87 mg/g wet tissue). At 50 µg/kg, hemoglobin raised and glycosylated hemoglobin fell to normal levels.
Silybum marianum (Milk thistle)	57	Alloxan monohydrate induced diabetic rats were treated with aqueous seed extract of Silybum marianum (SME 150 mg/dL) and Silybum marianum zinc oxide nanoparticles ZnONPs (10 & 8 mg/dL) dissolved in saline for 16 days.	FBS levels drop (207 mg/dl to 96 mg/dl), whereas insulin and HDL levels increase considerably (P < 0.05); FBS levels reduced more (24 mg/dl) than crude extract levels.
Psidium guajava (Common guava)	58	Streptozotocin (STZ)-induced diabetic rats were treated with aqueous leaf extract of Psidium guajava (PGE 200 mg/kg) and Psidium guajava silver nanoparticles (PGAg NPs; 400 mg/kg) for 21 days.	PGAg NPs has potent antidiabetic activity due to its enhanced surface area and smaller particle size of nanoparticles. PGE and PGAg NPs produced a drastic decrease in the blood glucose level, ameliorated lipid profile parameters in diabetic rats. Histopathological findings also revealed the improvement in pancreas and liver cells.
Pouteria sapota (Mamey sapota)	59	Streptozotocin (STZ)-induced diabetic rats were treated with aqueous leaf extract of P. sapota leaf extract (100 mg/Kg b.w) and P.sapota AgNPs (10 mg/kg b.w) for 28 days.	In vivo studies show that body weight and insulin levels rise while FBS levels fall considerably (P< 0.05). AST, ALT, ALP, Creatinine, urea, uric acid, and albumin levels in the rat body restored to normal.
Pterocarpus marsupium (Malabar kino)	60	Streptozotocin (STZ)-induced diabetic rats were treated with plant extract of Pterocarpus marsupium 200 mg/kg, p. o and Pterocarpus marsupium silver nanoparticles 200 mg/kg, p. o for 28 days.	Positive effects on lipid levels and pancreatic ß-cell regeneration were seen in STZ- and nicotinamide-induced diabetic rats treated with silver nanoparticles isolated from the Pterocarpus marsupium.
Taverniera couneifolia	61	Alloxan induced diabetic rats were treated with 10 mg/kg of methanolic T. couneifolia extract, and 10 mg/kg of body weight of synthetic AgNPs derived from T. couneifolia in the DAgNPs group for 21days.	Rats with diabetes caused by Alloxan were fed Through the administration of phytosynthesized AgNPs, the dyslipidemia status of diabetic rats was significantly improved as compared to diabetic control rats. Blood sugar levels were also reduced gradually over time. There was a decrease in blood sugar, an increase in body weight, and a significant enhancement of lipid, liver, and renal profiles.
Urtica dioica (stinging nettle)	62	Streptozotocin (STZ)-induced diabetic rats were treated with ZnO (10 mg/dL), plant extract (150 mg/dl), and ZnO extract (8 mg/dl) for 16 days.	Insulin levels increased up to 181 percent, HDLC levels increased up to 130 percent, and FBS, TG, and TC levels decreased up to 51.69 percent, 38.9 percent, and 17.4 percent, respectively, compared to diabetic controls; 134.4 percent and 38.47 percent more increase in insulin and HDLC, respectively, and 6.64 percent, 13 percent, and 1.7 percent more decrease in FBS, TG, and TC, respectively.
Vaccinium arctostaphylos (Caucasian whortleberry)	63	Alloxan monohydrate induced diabetic rats were treated with plant extract (150 mg/dl) and biologically synthesized ZnO nanoparticles dissolved in saline (8 mg/dl) for 16 days.	Fasting blood glucose level decreased from 174.8±5.97 to 50.4± 3.55 mg/dl, and HDL level decreased significantly, but insulin, TG, and TC levels did not change significantly; FBG level decreased 29.4 mg/dl more than plant extracts, and other outcomes were also significantly larger than the crude extract.
Zingiber officinales (common ginger)	64	Streptozotocin (STZ)-induced diabetic rats were treated with silver nanoparticles SNEG (200mg/kg of body weight) for 7 days.	Blood glucose returned to normal level (86 mg/dl after 7 days of treatment) and body weight was increased at 200 mg/kg.

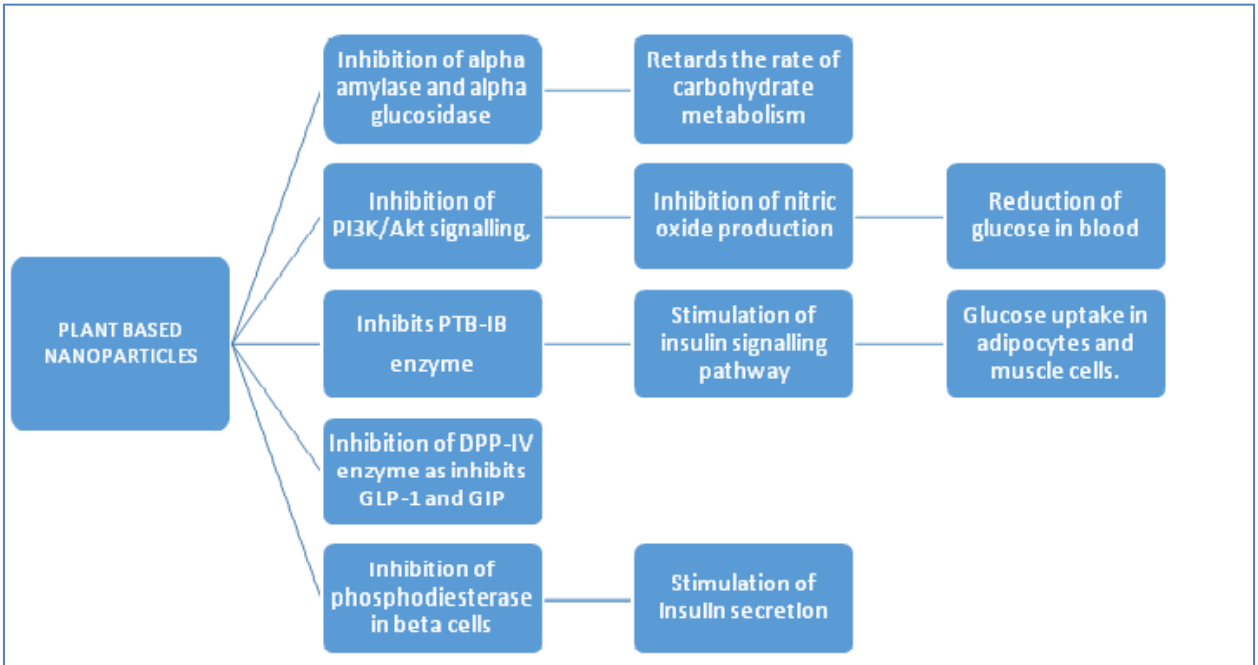

Figure 1: Mechanism involved in antidiabetic activity of phytonanoparticles

Mechanism of action

Nanoparticles have emerged as an alternative for diabetes treatment with least side effects. These act by a variety of mechanisms including Inhibition of α-amylase and α-glucosidase, Stimulation of Insulin Secretion, improvement in beta cell function, Upregulation of glucose transporters, activation of insulin signaling cascade etc.

Inhibition of α-amylase and α-glucosidase

Pancreatic α-amylase and α-glucosidase enzymes break down complex polysaccharides into simple monosaccharides. When these enzymes are repressed, the conversion process of polysaccharides into monosaccharides is delayed and accumulation of glucose level is reduced. So inhibition of these enzymes is considered as an effective strategy in managing type 2 diabetes mellitus via lowering the blood glucose level [7].

A number of in vitro studies indicated that plant based Nanoparticles inhibit activity of α-amylase and α-glucosidase [11, 14, 16, 17, and 25].

Stimulation of Insulin Secretion

Phyto-nanoparticles stimulate insulin secretion by inhibiting activity of dipeptidyl peptidase-IV (DPP-4) and PTP1B or via stimulating activity of GLP 1 and PPAR. Dipeptidyl peptidase-4 (DPP-4) is a multi-functional protein which has catalytic activity. It also acts as a binding protein and a ligand for a variety of extracellular molecules. It is also known as the T-cell antigen CD26. It suppresses insulin synthesis by pancreas via cleaving glucagon-like peptide-1 (GLP-1). A number of studies have indicated that phyto-nanoparticles show inhibitory activity on dipeptidyl peptidase-IV which in turn stimulates synthesis of insulin [8].

Protein tyrosine phosphatases act as signaling molecules. These molecules control a variety of cellular processes including cell growth, differentiation, mitotic cycle, and oncogenic transformation. PTP1B can dephosphorylate the phosphotyrosine residues of insulin receptor kinase and thus it can suppress insulin synthesis via disturbing insulin signaling pathways [9, 10]. Phyto-nanoparticles have been reported to exhibit remarkable Protein Tyrosine Phosphatase 1B (PTP 1B) inhibitory activity [10, 12, 13].

Improvement in beta cell function

Dysfunction of β cells in pancreas might also lead to hyperglycemia. Phyto-nanoparticles may improve the functionality of beta cells by variety of mechanisms including suppression of the phosphodiesterases activity in β cells, by stimulate insulin release through activating the K+/ATP/sulfonylurea receptor channels, through regulation of phospholipase C (PLC), protein kinase C (PKC), protein kinase A (PKA), cyclic adenosine monophosphate (cAMP), via activating GLUT2, PDX1, Akt, insulin receptor substrate (IRS), B-cell lymphoma 2 (Bcl2), and heat shock protein (Hsp)70/90 genes [11]. Phyto-nanoparticles which inhibit dipeptidyl peptidase 4 (DPP-4) also assist in improving β-cell function by preventing the degradation of incretins which inhibits glucagon release and increases insulin secretion [8].

Activation of the insulin signaling cascade

Insulin receptors belong to the receptor tyrosine kinases family. When Insulin binds to the receptor, it induces a conformational change in the receptor autophosphorylation of tyrosine residues on the β subunits and stimulates interaction of Insulin receptor with insulin receptor substrate (IRS-1) containing phosphotyrosine-binding (PTB) domains. In the glucose regulatory pathway,

activated IRS-1 initiates the subsequent signal transduction pathway by binding and activating phosphoinositide 3-kinase (PI3K), which then activates several other kinases, most notably protein kinase B (PKB-Akt) [49].

The phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) pathway and Adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK) play a central role in glucose homeostasis. Phytonanoparticels may lower blood glucose levels by increasing expression of the IRS1 (insulin receptor substrates), GLUT2 (Glucose transporters2)and AMPK that facilitate the translocation of glucose into the cell [47,53].

CONCLUSIONS

Based on the review, it is concluded that the plant based nanoformulations may enhance the compliance and clinical efficacy of phytochemicals. The phyto-nanoparticles have multiple advantages including increased bioavailability, prolonged drug circulation time, multiple drug loading due to which they showed enhanced efficacy and decreased toxicity. Therefore, it is suggested that more research is needed in the direction of phyto-nanoparticles so that more effective treatment of diabetes can be discovered by eliminating the pharmacokinetic and biopharmaceutical obstacles associated with the phytochemicals.

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