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A review on biogenic silver nanoparticles as efficient and effective antidiabetic agents

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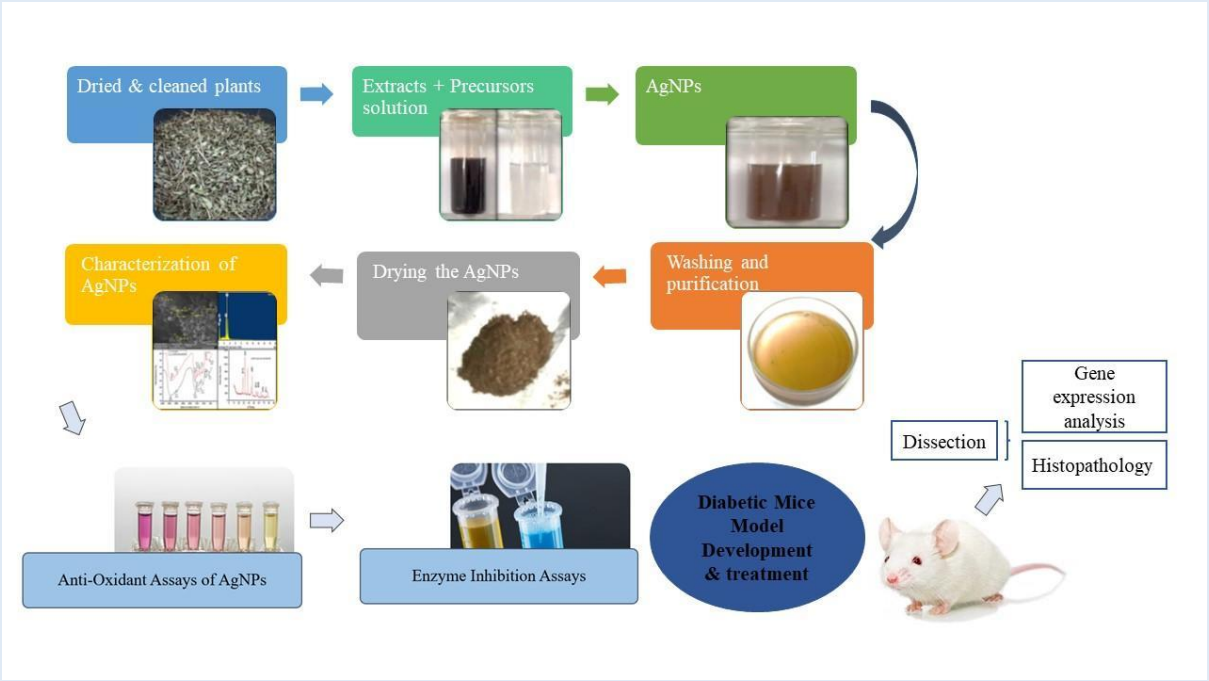
ABSTRACT

The frontiers of nanomedicine are consistently being challenged by the gradually expanding knowledge of the properties of nanoparticles. Toward this end, biogenic synthesis of silver nanoparticles utilizing natural compounds in plants as reducing and capping agents grabbed considerable attention, in lieu of synthetic hazardous physical and chemical techniques. Green synthesis of silver nanoparticles (AgNPs) has proven safe and effective in treating type 2 diabetes mellitus. Currently, biogenic silver nanoparticles have gained importance as safe and efficient antiglycation agents.

Therapeutic strategies by employing nanomedicines from natural sources have been initiated to end the limitations of currently available medications for the treatment of various disorders, including diabetes, Alzheimer's, cancer, and hepatitis. This article highlights the medicinal efficacy of silver nanoparticles synthesized from different plant extracts for their antidiabetic potential characterized through various *in vivo* and *in vitro* assays and unravels their unique properties. This article also focuses on the signaling pathways linked to type II diabetes and the demand for nanomedicine and greener pathways for future pharmacological industries.

Keywords: Biogenic silver nanoparticles, antioxidant, Type 2 Diabetes Mellitus (T2DM), α-glucosidase assay, α-amylase assay



Graphical Abstract: Antidiabetic properties of biogenic silver nanoparticles

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a common metabolic disorder characterized by abnormal blood glucose levels due to impaired insulin secretion and/or reduced insulin action [1]. The rate of diabetes is increasing all over the world. Approximately 537 million adults are diagnosed with diabetes, accounting for 6.7 million causalities in 2021, as per International Diabetes Federation (IDF) 2021 statistics [2]. This number is projected to rise to 783 million by 2045, posing more economic burden with the expenditure of around USD 966 billion in 2020-2021[2]. The prevalence and number of cases have steadily increased over the past few decades, classifying T2DM as the primary cause of stroke, cardiac arrest, lower limb amputation, kidney failure, and blindness, to name a few [3]. The significant T2DM risk factors include physical inactivity, obesity, oxidative stress, inflammation, and genetic and epigenetic factors, making diabetes the seventh driving reason for cessation worldwide [4]. The frontiers of diabetes research focus on updating best analysis, monitoring, and curing. Insulin signaling, adipocytokine signaling, and glycation hexosamine signaling are major pathways in regulating blood glucose homeostasis (Fig. 1), and defects in these pathways are associated with the pathogenesis of T2DM. Genes contributing to these pathways are GLUT2, GLUT4, IRS, IRS1, PI3K, AKT, TNFα, mTOR, and protein kinases, among many others. Activation of upstream gene phosphorylates another target, leading to highly regulated signaling to control glucose homeostasis. [5]. Moreover, the environmental factors superimposed with genetic susceptibility undoubtedly pave the way towards T2DM, making it a disorder of multiple etiology [6]. More than 65 genetic variants have been revealed by Genome-wide association studies (GWAS) on T2DM, potentially of increasing risk of T2D by 10-30%. Most of them are responsible for regulating insulin secretion [7]. An offspring has a 35-39% lifetime risk of developing T2D who has a single type 2 diabetic parent, while the risk rises to 60-70% for an individual with both parents having T2D. In contrast, the risk for the

general population is 10% [8].

There are several complex interacting mechanisms involved in T2DM pathogenesis, like insulin sensitivity, insulin secretion, beta cell functioning, replication of beta cells, obesity, role of adipocytes, hepatic glucose output etc., which various genes themselves may control. The effect of genes may also vary in different populations. This complex etiology explains the difficulty in unraveling the genetic basis of T2DM and identifying the T2DM causal genes [9]. Epigenetics are the inheritable and reversible changes capable of altering the expression of genes while not disturbing the DNA sequence. Epigenetic methylation and histone acetylation have been seen to cause reduced expression of insulin, adiponectin, and insulin-responsive glucose transporter-4 genes in diabetics [10]. Growing evidence suggests that in T2DM pathophysiology, inflammation also owes a significant role, thus linking T2DM to other metabolic disorders which partly or solely are caused due to inflammation, like CVDs. High levels of inflammatory markers and cytokines are responsible for developing glucose intolerance with time; thus, such cytokines can be used as early markers to predict the progression of diabetes [11]. TNF- α also induces insulin resistance in obese rodent models [12].

Environmental factors greatly influence the effect of T2DM genes, as some susceptible individuals would never develop T2DM if they adopt a healthy lifestyle, while some non-susceptible individuals develop T2DM due to their unhealthy practices [9]. In addition, high intake levels of saturated fats and low levels of fiber are characteristics of an unhealthy diet and put individuals at high risk of metabolic disorders like cardiovascular problems and T2DM [13]. Obesity increases the probability four fold for an individual with a family history of T2DM [14]. In obesity, the adipocytes enlarge in size, altering metabolism. Release of free fatty acids [15], or non-esterified fatty acids, and glycerol is increased due to increased lipolysis in obese individuals compared to lean individuals because insulin resistance is caused by these free fatty acids in muscles [16]. Both drugs and changes in lifestyle can manage T2DM. The first line of treatment for hyperglycemia is exercise, and increased physical activity has shown improvement in the regulation of plasma glucose levels and insulin sensitivity [17]. Here are a few available drugs available for the management of T2DM. Metformin is used to lower glucose levels in the blood by suppressing glucose production in the liver and increasing glucose uptake in cells by activating AMPK [18]. Sulfonylureas are a class of drug that stimulates glucose-dependent insulin secretion. However, it can cause hypoglycemia as a potential side effect [19]. Thiazolidinedione is used to increase the levels of receptor molecules, especially peroxisome proliferator-activated receptors that are nuclear receptors and acts as transcription factors for various genes involved in fat and glucose metabolism. However, adverse effects, including increased oedema and cognitive heart failure, have been reported [18]. α-Glucosidase inhibitors are used to decrease glucose digestion by competitive inhibition of enzymes involved in the catalysis of carbohydrate digestion in the intestine. They are also capable of lowering postprandial blood glucose [20]. Repaglinide is administered prior to intake of a meal in order to stimulate insulin secretion, though with a shorter half-life compared to sulfonylureas [21].

As a progressive failure of β-cells occurs in T2DM, the pancreas can no longer synthesize and secrete insulin over time via oral medication. As a result, administration of insulin injections would be recommended. One injection a day would be recommended at the start, along with oral medications, but with time, multiple injections would be administered a day if needed [22].

Prospective future of treatment for diabetes: The current treatment options include oral and injectable medications [23]. Despite their acceptance and widespread practice, some side effects and drawbacks exist. Metformin, which is the first line drug for many

T2DM patients, and alpha-glucosidase inhibitors are known to induce abdominal discomfort, diarrhea, anorexia, and flatulence and also decreases vitamin B12 intestinal absorption [24]. Other oral agents, including thiazolidinedione, sitagliptin, saxagliptin, alogliptin, SGLT2 inhibitors, canagliflozin, empagliflozin, and exenatide are recognized for their ability to manage heart failure, hypoglycemia, and urogenital tract infection in women and balanitis and balanoposthitis in male patients [25]. Injectable agents such as RA-GLP1 cause site reactions like abscess, cellulitis, and necrosis due to excess antibody production and severe gastrointestinal disorders [26]. Insulin is widely prescribed through the injection route, but its preparation and associated distress pose the risk of set weight gain, hyperinsulinemia, and hypoglycemia [27].

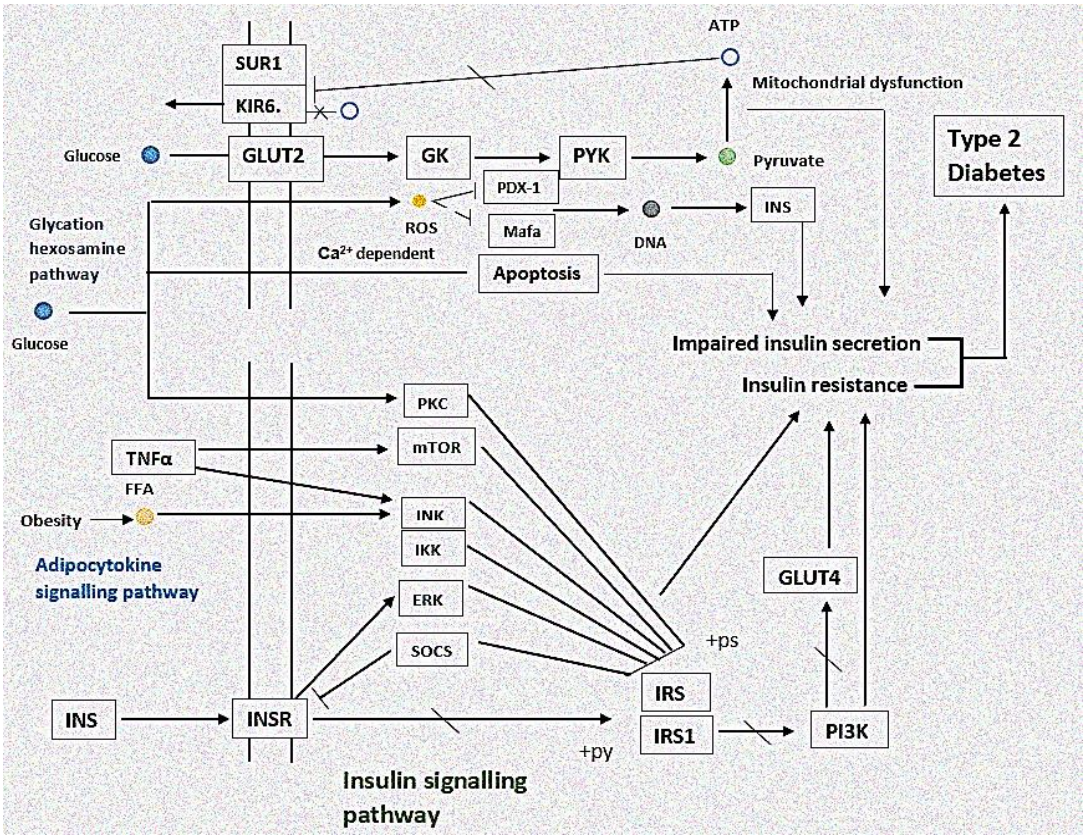


Fig. 1. A schematic representation of different molecular signaling pathways linked to Type 2 Diabetes Mellitus (T2DM). Impaired regulation of many genes involved in various signaling pathways led to insulin resistance and impaired insulin secretion, which are the hallmarks of T2DM. +py = tyrosine phosphorylation, +ps = serine phosphorylation. Utilizing GLUT2, glucose molecules enter into the β-cells of the pancreas after a meal.

ATP molecules are produced by entering intracellular glucose molecules into glycolysis and the Krebs cycle in mitochondria. There is an increase in blood glucose levels when insulin resistance occurs, i.e., when the body's cells cannot respond to the physiological levels of insulin produced. Normally, GLUT4 translocates the glucose from the cytoplasm to the cell membrane due to the binding of insulin peptide to the insulin receptor, initiating a signal cascade based on phosphorylation. GLUT4 helps uptake glucose molecules into the cells and prevents the usage of stored fats for energy [28]. On the other hand, in diabetes, insulin receptors remain inactive in cells, and there is no translocation of GLUT4 from the cytoplasm to the membrane [5]. Therefore, signaling impairment can lead to T2DM pathogenesis via insulin resistance or β cell dysfunction. The interaction information is from KEGG Pathways and the cycle from reference 29.

Keen sightings of insufficiencies of today's medications for diabetes have resulted in a primary push towards fixing diabetes through medications causing minimal adverse effects. This makes one of the emanating interests in research of nanotechnology. Nanotechnology refers to materials at nanoscale dimensions ranging from 1-100 nm [28]. Nanomaterials' tiny size endows their oneness with physical and chemical properties, making them different from massive materials [29]. Swift development in nanotechnology research could be a prospect to cure diseases. The National Institute of Health in the USA has coined this arm of nanotechnology concerning malady monitoring, examination, and cure as "nanomedicine" [30].

Among the various nanomaterials pursued in nanomedicine applications, this review focuses on biogenic silver nanoparticles and their potential as an antidiabetic agent for treating and curing diabetes. Silver nanoparticles (AgNPs) are gaining popularity for various reasons. Their properties, such as good stability, catalytic, antibacterial, antiviral, antifungal, anti-inflammatory, and anticancer activity, have attracted particular attention [31, 32]. The principal properties, such as reducing the formation of advanced glycation end products (AGEs), antioxidant, anti-inflammatory, and digestive enzyme inhibition (e.g., α-amylase), make AgNPs a promising treatment for diabetes [33]. The development of biogenic silver nanoparticles is evolving as an important branch of bionanotechnology. Many review articles on the applications of silver nanoparticles synthesized through green methods have recently been published. However, to our knowledge, there is no orderly compiled data on the plant-mediated synthesis of silver nanoparticles with anti-diabetic properties. Herein, we compiled all the work dealing with the potential antihyperglycemic effect of green synthesized silver nanoparticles are discussed.

ERA OF NANOTECHNOLOGY ADVANCEMENTS

Nanotechnology has been used to obtain novel products since ancient civilizations. The ancient Romans used to color glass with shades of mauve and yellow by using different concentrations of gold and silver [36]. Gold and silver nanoparticles were also used for aesthetic purposes in the famous Lycurgus cup during the 4th century, which is now placed in the British Museum [37]. Similarly, in the Middle Ages, colloidal silver and gold nanoparticles produced brightly colored stained windows, primarily red and purple, in European cathedrals. For example, in Notre Dame, the red and purple color of the rose window of cathedrals is due to the presence of gold nanoparticles [38]. The technique of glass coloring was further refined in the 15th and 17th centuries by using precipitates of different colloids added to the glass [36]. The nanoparticle synthesis by reducing metal oxides upon heating at high temperatures was studied during the 9th century [39]. The first ever documented chemical synthesis of metal nanoparticles was performed in 1857 by Michael Faraday [40], who reduced the solution of chloroauric acid with carbon disulfide to obtain a deep, red-colored gold nanoparticle solution, and then by Zsigmondy in 1906, who reduced chloroauric acid in the presence of formaldehyde to obtain monodisperse gold solutions [41]. Zsigamody's method was further refined in 1951 using the Turkuvish method, which involves the chloroauric acid reduction in the presence of sodium citrate to synthesize gold nanoparticles [42]. Similar protocols are being employed for synthesizing silver nanoparticles.

Nanotechnology's emergence has greatly influenced the field of clinical therapeutics in the last two decades, and a gamut advancement have been made in developing the field of nanomedicine to detect, diagnose, and effectively treat diabetes [43]. Nanomedicine, as per the National Institute of Health, is a formulation of a drug whose end product's size is less than a micron [43]. Nanomedicine has gained advantages due to its ability to overcome biological barriers, enhance the bioavailability of drugs [44], specifically target disease sites, and effectively deliver drugs [43].

Potential role of silver nanoparticles: Silver nanoparticles are employed in biological sciences and biomedical sciences as targeted drug delivery systems [38] and also in the production of products in textile industries, deodorants, cosmetics, and perfumes, food storage, as antimicrobial agents, bandages, biosensors [45], as orthopedic and cardiovascular implants, bone biomaterials, surgical catheters, wounds and burns dressings as therapeutic agents, along with various h household products and cleaning solutions. They also find applications in the burn and wound healing process due to their anti-inflammatory property [46]. Many plants mediated silver nanoparticles are a potent source of antioxidants that reduce the oxidative stress produced as a metabolic response or induced exogenously [47]. Among many, the critical factor affecting the efficiency of the silver nanoparticles is the concentration of reducing compounds, such as phytochemicals like phenols, flavonoids, amides, etc. in the plant extracts that are responsible for the reduction of ions [48], in case of the environmentally friendly synthesis of the nanoparticles.

METHODS OF SILVER NANOPARTICLES PREPARATION

There are three chemical, physical and biological methods for creating AgNPs. Arc discharge and vapor condensation are the physical processes [34], and photochemical and chemical reduction and electrochemical synthesis are the chemical methods [49]. These methods require considerable energy and time and are also toxic. However, biological approaches have fewer side effects and utilize minimal resources [50]. Various shapes of silver nanoparticles could be achieved based on the type of method, stabilizer, and reducing agent. They can be rods, spherical [51], prisms [52], in the form of nanowires[53], Nano pyramids [54], nanobars [55], and cubic [56].

PURPOSE OF THE STUDY

Physical and chemical means are expensive, energy-consuming, and toxic and are not suitable for biological applications [34]. However, biogenic AgNPs could be easily scaled up, inexpensive, and eco-friendly [35]. Those synthesized using plant extract show synergistic effects in reducing inflammation and treating diseases [36]. AgNPs are the least toxic in dermal and ocular toxicity tests in pigs and mice with short-term exposure. Nevertheless, long-term exposure studies are necessary [37]. Green synthesis of nanoparticles does not require temperature, high energy, and is cost effective. Most importantly, green synthesis is not hazardous for human health [38].

Plant-mediated synthesis of silver nanoparticles and their antidiabetic potential: Recently an increase in awareness towards the green synthesis of nanoparticles has been observed. Different metal nanoparticles like copper, gold, zinc, titanium, and silver have been prepared. However, AgNPs are the most effective among them, as silver is a non-toxic, harmless antimicrobial agent with good antidiabetic and antioxidant activity [63].

AgNPs synthesis from plants is more beneficial than microbes and algae, as they do not require the tedious stages of growing the cultures on media. Hence, they are less biohazardous and can be easily improved [15]. Plants possess an array of compounds, such as phenols, flavonoids, terpenoids, and many more, which act as reducing, stabilizing, and capping agents for the nanoparticles and enhance their biomedical properties [39]. The generalized protocol for green synthesis of silver nanoparticles involves a few steps starting with the drying and cleaning of mostly the aerial parts of the plant. The aerial parts are finely ground and powdered and depending on the type of metallic nanoparticles to be synthesized, the required amount of precursor would be added, which also acts as the capping agent. The complex mixture would be kept on stirring, sonicated, and upon the visible color change, it would be centrifuged, purified, and washed. The pellet would be collected, dried through various means, and stored for future use.

The current focus of anti-hyperglycemic drugs is the inhibition of intestinal enzymes such as α-amylase and α-glucosidase, which would decrease the elevation in the post-prandial blood glucose level as in the case of the leaf extract of *Morinda lucida benth [40]*. Nanoparticles synthesized using such plant extracts could potentially inhibit the activity of these digestive enzymes [41]. AgNPs synthesized from different plants assessed for their anti-diabetic potential are summarized in Table 1. Since the current focus for the hyperglycemic therapies is turning towards the inhibition of the intestinal enzymes responsible for digestion, such as alpha amylase and alpha-glucosidase, which would, in turn, decrease the post-prandial blood glucose levels, biogenic silver nanoparticles would be a good fit in this regard.

Lonicera japonica: AgNPs synthesized using the *Lonicera japonica* leaf extract, native to Eastern Asia and traditionally used as an anti-viral and anti-inflammatory agent, possess a spherical and hexagonal shape with an average size of 53 nm [42]. Antioxidant efficacy, through DPPH assay of the radical scavenging response, increased dose-dependently, and the IC50 value of 46.7µg/mL compares well to the ascorbic acid values of 26.45 µg/mL. For diabetes care, the most effective approach considered is the inhibition of α-amylase and α-glucosidase digestive enzymes [43]. These two enzymes were remarkably inhibited by increasing the concentration of *Lonicera-mediated* AgNPs, with the IC50 value of 54.56 and 37.86 µg/mL for alpha-amylose and alpha-glucosidase, respectively. LB and Dixon plot analysis identified AgNPs as reversible non-competitive inhibitors too [42].

Pterocarpus marsupium: The aqueous extract of *Pterocarpus marsupium*, a medicinal plant, bark, and wood, produced AgNPs of 148.5 nm size with a surface zeta potential of -28 mV. The SPR band was found at 279 nm with phenols as capping agents while carboxyl and hydroxyl groups as stabilizing and reducing agents [44, 45].

Table 1. Medicinal plants explored for synthesizing silver nanoparticles to address type 2 diabetes concerns.

Plant name	Plant part	Nanoparticle size (nm)	Reference
Lonicera japonica	Leaves	52	[42]
Pterocarpus marsupium	Bark and wood	148.5	[44]
Clausena anisata	Leaf and root	13-61	[46]
Calophyllum tomentosum	Leaves	24	[47]

Plant name	Plant part	Nanoparticle size (nm)	Reference
Ocimum basilicum	Leaves	17	[48]
Ocimum sanctum	Leaves	15	[48]
Punica granatum	Leaves	35-60	[49]
Azima tetracantha	Leaves	10-80	[50]
Eysenhardtia polystachya	Bark	10-12	[51]
Withania somnifera	Root	123.23	[52]
Alyssum homalocarpum	Seeds	30	[53]
Andrographis echioides	Leaves	-	[54]
Musa paradisiaca	Stem	30-60	[55]
Zingiber officinale	Rhizome	128	[56]
Aloe barbadensis miller	Leaves	30.5	[57]
Thymus serpyllum	Leaves	42	[58]
Azadirachta indica	Seeds	19.27-22.15	[59]
Psidium guajava	Leaves	52.12-65.02	[60]

Clausena anisate: AgNPs were made via the green route with ethanolic leaf and root extract of *Clausena anisata* as a stabilizing and reducing agent. This shrub, native to South Asia and Africa, and dried leaves have multiple medicinal benefits against epilepsy, tuberculosis, migraine, rheumatoid, and diabetes [61, 62]. Exposure to various on-and-off conditions like direct boiling and microwave and sunlight radiations synthesized the AgNPs, whose UV spectral peak was 488.9 nm, and XRD confirmed the crystalline nature. FESEM analysis revealed that the biogenic nanoparticles are spherical with a 13-61 nm size range. Furthermore, the particles exhibited great antioxidant activity, and 500 µg/mL exhibited 80.32% inhibition of α -amylase compared to standard acarbose at 85.24%. In addition, increased glucose uptake by yeast cells was observed with concentration, and the nanoparticles increased the glucose diffusion rate from 30 to 180 minutes [63].

Calophyllum tomentosum: *Calophyllum tomentosum*, commonly grown in Sri Lanka and Western regions of India, leaves were used to make aqueous extract via microwave method and mixed with 5 mM silver nitrate to gain AgNPs of size 24 nm at room temperature. The crystalline nature and the presence of phytochemicals were confirmed with XRD and FTIR, respectively. The *Calophyllum tomentosum-mediated* AgNPs exhibited strong DPPH, H_2O_2, and nitric oxide scavenging activity. Bio-capping of functional groups on AgNPs made them potent inhibitors for α-amylase and α-glucosidase as well as β-glucosidase and DPPIV (dipeptidyl peptidase IV) [47].

Ocimum basilicum and Ocimum sanctum: Antidiabetic properties of AgNPs (3-25 nm) synthesized from a combination of *Ocimum basilicum* and *Ocimum sanctum* were detected using *Bacillus stearothermophilus* as an enzymatic model of α-glucosidase, showing significant inhibitory potential compared to standards [48].

Punica granatum: The leaves of *Punica granatum* were contentedly used as a mediator for the synthesis of AgNPs having crystalline and spherical shapes, which were stable with a surface charge of -26.6mV. The

AgNPs showed a concentration-dependent increase in inhibiting digestive enzymes α-glucosidase and α-amylase with an IC50 value of 53.8 and 65.2 µg/mL, respectively. The results also illustrated that they have potent *in vitro* antioxidant activity determined by DPPH and ABTS with an IC50 value of 67.1 and 52.2 µg/mL, respectively [49].

Azima tetracantha: The synthesis of AgNPs using *Azima tetracantha* leaf extract possesses an efficient anti-hyperglycemic activity and potential antiglycation response in a dose-dependent manner by inhibiting α-amylase and α-glucosidase with an IC50 value of 262.18 and 271.78 µg/mL, respectively [64].

Eysenhardtia polystachya: *Eysenhardtia polystachya*, rich in phenols and flavonoids, was an excellent anti-glycating agent for Type 2 Diabetes by reducing oxidative stress in mice models [65]. The *Eysenhardtia polystachya-loaded* AgNPs were synthesized with an SPR band at 413 nm and a surface charge of -32.25 mV, i.e., higher stability. TEM images revealed that the synthesized nanoparticles are spherical, with a 10-12 nm diameter. In the glucose-induced hyperglycemic zebrafish in-vivo model, these nanoparticles showed improved insulin secretion and better survival of β-cells of the pancreas [51].

Withania somnifera: AgNPs were synthesized using *Withania somnifera* root extracts as reducers and stabilizers in an aqueous medium. SEM images presented the nanoparticles as spherical with an average size of 123.23 nm. These nanoparticles were found to have the greatest potency for acting as inhibitors of metabolic enzymes *in vitro*. The percentage inhibition is higher than the standard acarbose for α-amylase [52]. Similar inhibition for α-glucosidase proves the nanoparticles' therapeutic role as an anti-hyperglycemic agent [66].

Alyssum homalocarpum: The seeds of *Alyssum homalocarpum* were used for the methanolic extract and to synthesize face-centered cubic agglomerated nanoparticles functionalized with rich polyphenols, which possess high antioxidant activity. FTIR measurements revealed that the seed extract attaches to the nanoparticles' surface through amide linkages. The nanoparticles showed strong α-glucosidase inhibitory activity but weak α-amylase inhibition at 221 µg/mL for 100 mg/mL [53].

Andrographis echioides: *Andrographis echioides* is a medicinal herb used for various ailments cure. The purified plant powder was mixed with 80% ethanolic extract and 3 mM silver nitrate to yield AgNPs. These nanoparticles could strongly scavenge the DPPH, ABTS, and nitric oxide assay radicals with a dose-dependent increase. The *in vivo* α-glucosidase percent inhibition in Wistar rats was found to be statistically significant [54, 67].

Musa paradisiaca: The synthesis process was noticeably fast, and spherical AgNPs (on average 30-60 nm) were generated within a few minutes as the stem extract of *Musa paradisiaca* came in contact with silver ions. These nanoparticles were tested *in vivo* for the combined treatment of diabetes and malaria on streptozotocin-induced diabetic rats and were found to be effective in improving and moderating insulin, galactose, and glucose [55].

Zingiber officinale: Ginger rhizome ethanolic extract was used as a reducer for silver nitrate for the first time to obtain biogenic crystalline nanoparticles of 128 nm. The 200 mg/kg dose of these AgNPs on diabetic rats showed a gradual decrease in glucose levels compared to the standard metformin. Similarly, male albino diabetic rats responded to 10 mg/kg dose and exhibited a sufficient reduction in glucose levels. Furthermore, the nanoparticles elevated the serum insulin levels and the insulin receptors along with the higher expression of GLUT-2 [56, 68].

Aloe barbadensis miller: Advanced glycation end products (AGE) formation is the primary cause of inflammation and is considered a derivative of the

oxidation [69]. AGE products are proven as potential risk factors for hyperglycemia and peripheral insulin resistance [70]. To overcome and inhibit AGEs, an average of 30.5 nm spherical particles of AgNPs using Aloe vera leaf extract as a stabilizer and reducer were produced. These particles showed a favorable response to the protein structure and inhibited AGE in a dose-dependent manner [57].

Thymus serpyllum: The aqueous extract of the medicinal plant "*Thymus serpyllum"* was reported to synthesize an average size of 42 nm spherical AgNPs. These 10 mg/kg particles reduce hyperglycemia in BALB/c mice and inflammation and help restore the morphology of pancreatic islets. They also upregulate the gene expression of AMPK and IRS1 during the treatment, wherein the glucose uptake by the cells improved. These AgNPs also inhibited the α-amylase with an IC50 value of 8 µg/mL [58].

Azadirachta indica: The aqueous kernel extract of the exemplary botanical specimen, *Azadirachta* indica, was subjected to thorough analysis, and the obtained results verified its propensity of synthesizing silver nanoparticles. The UV visible spectroscopy revealed the peak at 430 nm, a characteristic of silver nanoparticles. The spherical-shaped nanoparticles were in the range of 19.27-22.15 nm, displaying an anti-inflammatory effect of 69.8% and a substantial anti-diabetic effect of 73.5 %, respectively, at 100 µg/mL [59].

Psidium guajava: The aqueous leaf extract of *Psidium guajava* was utilized with silver nitrate as the precursor to prepare the silver nanoparticles and their antidiabetic potential was evaluated on streptozotocin induced diabetic rats by administering the doses of 200 mg/kg and 400 mg/kg for 21 days. A significant decrease in the blood glucose levels and the biochemical parameters were observed for both the extract and the nanoparticles. However, nanoparticles exhibited more promising results and improved and restored the morphology of the liver and pancreas [60].

MARKET OPPORTUNITIES FOR PHYTO-NANOMEDICINE

Phyto-pharmaceuticals are used globally in developing and developed countries [71,72]. In China, around 50%, in Africa, about 80%, and in the US, roughly 50% of the population relies on plant-based medicine [73]. The effect of nanoparticles from plant extracts has elevated patenting and nanomedicine sales and demand. Thus, the nanomedicine market is expected to grow and show substantial influence globally and is expected to surpass 350.8 billion dollars by 2025 [74] [75].

CONCLUSIONS AND FUTURE DIRECTIONS

Diabetes Mellitus is a multifactorial disorder encountering insulin resistance or failure of insulin action. The currently available therapeutic approaches need revision in their management due to side effects or inefficacy in targeting the right pathway or mechanism. However, nanobiotechnology efforts, emphasizing digging the solution for diabetes management, appear to be favorable. One of the aspects of nanotechnology is nanomedicine, which aids in overcoming the side effects of conventional drugs through better pharmacokinetic control and sustained release of therapeutic substances. Presently, nanoparticles are employed in diabetes management for monitoring blood glucose levels, biosensing, and imaging, and also as delivery vehicles for insulin to eradicate the use of injectable insulin in Type 1 Diabetes Mellitus (T1DM) [100]. Recently, plant extract-mediated nanoparticles are gaining popularity owing to the presence of phytochemicals with the dual functionality of capping and reducing agents to stabilize the nanoparticles [101].

Silver nanoparticles from biogenic sources have been elucidated to reduce the oxidative stress in diabetes and act as alpha-amylase inhibiting agents [102], gaining them more attention as a captivating tool for diabetes treatment. Plant-mediated silver nanoparticles are economical, safe, and therapeutically effective. Their phytoconstituents decrease the intensity of micro and macrovascular complications

associated with diabetes by providing natural antioxidants that scavenge free radicals. Nanomedicine aims to efficiently utilize the nanoparticles to lower blood glucose levels, improve insulin secretion and prevent beta cell destruction causing the most negligible side effects. However, due to lesser data available on antidiabetic plant extract-mediated nanoparticles, more extracts must be explored. This review examines available *in vitro* studies of these nanoparticles' application as anti-hyperglycemic agents without toxicity, predominantly in mice or rat models. The availability of fewer in vivo evaluations is a predicament for large-scale applications.

Furthermore, silver nanoparticles' antiglycation ability and the mechanism through which they prevent the glycation of proteins and lipids need critical evaluation. Indeed, "nanodrugs" stand the potential to cure diabetes, and, in this regard, silver nanoparticles could hold a special place in providing a sustainable solution with minimal risk. However, larger-scale controlled studies on human subjects must be established to comprehend the role of genetics, epigenetics, and widespread applications.

Abbreviations: GLUT2: Glucose Transporter Protein Type-2, GLUT4: Glucose Transporter Protein Type-4, IRS: Insulin Receptor Substrate, PI3K: Phosphoinositide 3-Kinase, AKT: Protein Kinase B, Also known as PKB, TNFα: Tumor Necrosis Factor alpha, mTOR: Mammalian Target of Rapamycin, T2D: Type 2 Diabetes, AMPK: Adenosine Monophosphate Kinase, α-Glucosidase: alpha-glucosidase, α-amylase: alpha-amylase, SGLT2: Sodium-Glucose Cotransporter-2, RA-GLP1: Glucagon-like peptide-1 receptor agonists, KEGG: Kyoto Encyclopaedia of Genes and Genomes, DPPH: 2,2-Diphenyl-1-picrylhydrazyl, IC50: Half-maximal Inhibitory Concentration, ABTS: 3-ethylbenzothiazoline-6-sulfonic acid.

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