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Role of Silver and Gold Nanoparticles in the Management of Diabetes: Current Trends and Perspectives

Mohammad Amir[1], Manisha Vohra[1], Amit Sharma[1] and Sheetu Wadhwa[2*]

[1]*Department of Pharmacy Practice, ISF College of Pharmacy, Moga, Punjab - 142001, India*

[2]*School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, Punjab - 144401, India*

[*]sheetu.21001@lpu.co.in (Corresponding Author)

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ABSTRACT

Background: Diabetes mellitus is a severe metabolic disease in which a person's body cannot control the glucose level in the blood; it results from a defect in insulin secretion, insulin action, or both. Nanotechnology is a rising area in pharmaceutical sciences as nanoparticles are reported to enhance drug efficacy obtained from plant sources through green synthesis.

Purpose: The purpose of this review is to focus on the antidiabetic potential of various metallic nanoparticles like silver, gold, copper, and selenium by using their secondary metabolites like tannins, alkaloids, saponins, and steroids. The advantages of green nanoparticle synthesis are that they are eco-friendly, high temperature is not required, can be used on large-scale synthesis, and are cost-effective.

Methods: A preliminary search was conducted in PubMed, OVID Medline, Embase, ScienceDirect, Web of Science, and Google Scholar databases using keywords such as "Diabetes, nanoparticles, metallic nanoparticles, gold nanoparticles, silver nanoparticles."

Results: This review includes various marketed formulations of silver and gold nanoparticles particles obtained from various biological sources like allium cepa, argyreia nervosa, callophyllumtomentosum, punica granatum, cassia auriculate, saracaasoka, gymnemasylvestre, etc. along with their research findings for reducing the antidiabetic activity.

Conclusion: This review contains details about the silver and gold nanoparticles obtained from various biological sources used to treat diabetes..

1. Introduction

Diabetes mellitus is a group of metabolic disorders characterized by a chronic hyperglycaemic condition resulting from defects in insulin action, insulin secretion, or both (Ozougwu*et al.*, 2013).Mainly there are three types of diabetes which include type-1 diabetes, type-2 diabetes, and gestational diabetes. Type 1 diabetes is also known as insulin-dependent diabetes mellitus (IDDM). It generally begins in childhood and is also known as juvenile-onset diabetes. It is an autoimmune condition and happens when the pancreas is attacked by antibodies, causing damage to the organand nerfing its ability to make insulin.Type 2 diabetesis known as non-insulin-dependent diabetes mellitus (NIDDM). In this, the pancreas makes insulin, but it is inadequate, or the body does not utilize it as it should. It is also known as adult-onset diabetes.Gestational diabeteselevates blood sugar levels during pregnancy (Goldenberg&Punthakee, 2013).Various approaches are available in the treatment of diabetes, are oral and injectable drugs, but due to their limitations like lower bioavailability, degradation of the drug in the gastrointestinal tract, first-pass metabolism, etc. To tackle these limitations, scientists are approaching novel drug delivery systems, and nanoparticles are one of the novel approaches. A nanoparticle is a tiny particle that ranges in size from 1 to 100 nanometers. Nanoparticles, which are invisible to the naked eye, can have radically different physical and chemical characteristics than their bigger material counterparts. This review contains details about the silver and gold nanoparticles obtained from various biological sources used to treat diabetes.

1.1. Diabetes Prevalence and Incidence Rate

There has beena whopping increase in the number of people with diabetes in India in the last three decades. Diabetic

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patients have increased from 26 million in 1990 to 74.2 million in 2021[3]. The prevalence ratein India was found to be 9.6% (74.2 million), according to International Diabetes Federation (IDF). The global diabetes prevalence in 2021 is estimated to be 10.5% (537 million) which will rise to 643 million by 2030 and 783 million by 2045 (Sun *et al.*, 2022).

1.2. Available Approaches and their Drawbacks

Different types of existing therapies for the treatment of diabetes, along with their challenges, are as follows(Kesavadev*et al.*, 2014)-

1.2.1. TYPE-I

1.2.1.1. Insulin prescription

A large population in India lives in rural areas, so their treatment is carried out by primary healthcare doctors with limited knowledge of insulin regimens(Hayes*et al.*, 2008). Specialist endocrinologists and diabetologists give their treatment in cities, and their fees are also high, which is the primary reason many people are devoid of proper insulin regimen therapy.

1.2.1.2. Monitoring and therapy compliance

Self-monitoring blood glucose, following a proper diet, and exercising according to schedules are very important for patients with type-I diabetes(AADE, 2008). The patients suffering from type 1 diabetes mellitus, when following the mentioned steps, it is observed that they are benefited tremendously in countering diabetes (Povey& Clark-Carter, 2007), (Boulé*et al.*, 2001), (Odegard&Capoccia*et al.*, 2007). A study also shows that only 30% of patient who has diabetes is acquiescent to the prescribed drug regimen (Kotwani*et al.*, 2007).

1.2.1.3. Hypoglycemia

It is the side effect of insulin therapy and can be lethal also. The study has observed that the patients on long-term insulin treatment, around 50% of them have altered awareness of low blood sugar level-related symptoms(Berlin*et al.*, 1997). It is also observed that patients suffering from regular hypoglycemic episodesare afraid of hypoglycemic conditions and reduce insulin usage(Gonder-Frederick*et al.*, 2006).

1.2.2. TYPE-II

Type-II diabetes mellitus cannot be cured completely, but its symptoms and severity can be controlled by the use of drugs and lifestyle changes(Kalsi *et al.*, 2017).

1.2.2.1. Thiazolidinediones

They are insulin sensitizers thatenhance insulin sensitivityin organs like the liver and muscles. They decrease insulin resistance in fat-containing tissue, the liver, and the muscles. Thiazolidinediones activate peroxisome proliferator-activated receptors, which has a significant side effect of increased proliferation of fat-containing tissues situated peripherally to enhance the uptake of free fatty mass(Greenfield & Chisholm, 2004). Another side effect of these drugs is that it causes an increase in fluid reabsorption from nephrons and can cause edema or enhanced kidney volume (Endo *et al.*, 2011).

1.2.2.2. Biguanides

Metformin is the drug prescribed under this class to lower blood glucose levels. It enhances glucose utilization by improving its binding action on receptors and the glucose transporters in the target organs like hepatocytes and skeletal muscles(Bhujbal, 2016). The adverse effect of this drug is that it induces lactic acidosis, which arises in patients with a history of liver disease, pulmonary or cardiac insufficiency, and patients with renal disease (Fowler, 2007).

1.2.2.3. Meglitinides

The meglitinides enhance insulin secretion, and their mechanism to do so is by binding on different sites on beta cells than sulfonylureas. On the other hand, rifampicin enhances the elimination of sulfonylureas, thereby decreasing its availability in the circulatory system and reducing its efficacy(Aquilante, 2010).

1.2.2.4. Insulin

Insulin is a hormone secreted by the pancreas and is responsible for maintaining blood sugar levels in any person. In type 2 diabetic patients, the insulin is secreted, but either it is too low or not utilized properly, so to counter this, insulin therapy is chosen. The side effect of this therapy is gaining weight by the person undergoing this therapy. The symptoms are justified as improved glucose levels in blood and energy utilized by these patients are very low (Miller*et al.*, 2001). However, the adverse effect of this hyperinsulinemia enhances the proliferation of a particular cell and pathways of survival which can result in the risk of cancer in different organs like the colon, liver, pancreas, and many other organs(Giovannucci*et al.*, 2010)**.**

1.2. Advantages of Nanoparticles

The advantages of nanoparticles include that they are biocompatible, have a longer circulation duration, are amphiphilic, can be chemically modified, are efficient carrier systems for hydrophilic drugs, are biodegradable, have increased surface area, and can be tunable for various sizes.

2. Various Methods for the Synthesis of Nanoparticles

Top-down and bottom-up are the two procedures involved in nanoparticle synthesis (Bhardwaj*et al.*, 2020), (Panigrahi*et al.*, 2004), (Li *et al.*, 2008).

2.1. Metallic nano-particles Synthesis

For synthesizing metallic nanoparticles and bio-reduction of ions of metals, secondary metabolites like alkaloids, tannins, phenolic acid, etc., are responsible. These green synthesized nanoparticles possessed hypoglycemic, anti-carcinogenic, anti-inflammatory, and antioxidant properties (Jain *et al.*, 2019), (Santhosh*et al.*, 2020), (Sarli*et al.*, 2020). The biosynthesized metallic nanoparticles contain distinctive, self-assembling properties, larger surface-to-volume ratio, crystalline structure dependent on size ranging from 1-100 nm, highly stable, particular surface structure, and because of their material components, high biocompatibility is observed (Santhoshkumar*et al.*, 2017). Hence due to these characteristics, the interaction of drug molecules with the specific target can be easily achieved for clinical application for a particular tissue; because of this, least or no side effects are observed with maximum efficacy. The formation of nanoparticles is depicted by the reactions of several metals like silver (Tripathy*et al.*, 2010), gold(Thakkar*et al.*, 2010), platinum (Thirumurugan*et al.*, 2016), copper(Ramanathan*et al.*, 2013), iron (Herlekar*et al.*, 2014), titanium (Sundrarajan& Gowri, 2011), selenium (Liu *et al.*, 2018), and zinc (Sangeetha *et al.*, 2011). To reduce metallic nanoparticles, the plant extract contains numerous metabolites like flavonoids comprising several classes like isoflavonoids, flavonoids, anthocyanin, etc. The conversion of tautomer from the enol to keto transformation of flavonoids obtained highly reactive species of hydrogen, which acts as a reducing agent for metal ions(Gardea-Torresdey*et al.*, 1999). A variety of metal ions, including lead, aluminum, copper, ferric and ferrous ions, can be chelated by ketones and carboxylic acid groups(Khan*et al.*, 2013). Organic polymers like terpenoids contain a 5-C isoprene chain primarily and because of their dissociation formation of resonance structure occurs, followed by the formation of nanoparticles due to the presence of hydroxyl groups(Khan*et al.*, 2013). Many studies have observed that several functional groups like amine, cyanide, carboxyl, ester, and hydroxyl act as stabilizing agents for the production of nanoparticles (Shahverdi*et al.*, 2007). To control nanoparticle size, crystallinity, shape, and diversity, we need to understand the mechanism behind its biogenic synthesis.

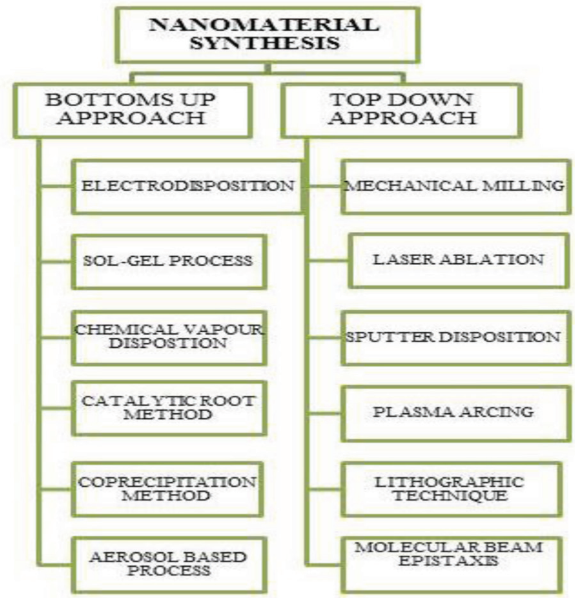

Figure 1: Various methods for synthesis of nano-particles.

2.2. Silver Nanoparticles

Silver metals are the most extensively used metal for the green synthesis of nanoparticles (Akhtar*et al.*, 2013), (Irshad *et al.*, 2020). Silver nitrate is the most widely used precursor for synthesizing silver nanoparticles (Yamamoto&Watarai, 2006). The silver nanoparticles of *argyreia nervosa*(Saratale*et al.*, 2017), *punica granatum*(Saratale*et al.*, 2018), and algae found in sea *colpomeniasinuosa*(Manam*et al.*, 2014)possess hypoglycaemic activity as the action of alpha-amylase, and alpha-glucosidase was hindered in a dose-dependent manner which is higher than a plant extract. In some modern studies, the antidiabetic effect of *ocimumbasilicum* and *ocimum sanctum* decreases the activity of both enzymes after introducing respective silver nanoparticles and also showed the kinetics of both the enzymes that is competitive inhibition of alpha-glucosidase and non-competitive inhibition of alpha-amylase (Rajaram*et al.*, 2015). The activity of alpha-glucosidase and alpha-amylase is prohibited by the nanoparticles obtained from stems of *tephrosiatinctora,* and it also enhances glucose utilization in human beings(Rajaram*et al.*, 2015). Lemongrass has antidiabetic properties because the silver nanoparticles in the leaves reduce the activities of alpha-amylase and alpha-glucosidase. Many other plants have shown antidiabetic activity, like the roots of clausena anisate (Yakoob*et al.*, 2016) and the leaves of *cantella asiatica*(Wilson *et al.*, 2015). Abideen and Vijayshankar(Abideen&Vijayshank

ar, 2015) discovered that seaweeds named *gracillaria edulis* and *syringodiumisoetifolium*have antidiabetic properties. It was observed that both seaweeds causeda decrease in alpha-amylase activity and decreased glucose diffusion rate(Anwar*et al.*, 2018). The antidiabetic potential of nanoparticles obtained from *enhalusacoroids*(Senthilkumar*et al.*, 2016) and *lonicera japonica* (Balan*et al.*, 2016) prohibited the enzymes' enzymal activity. The *lonicera japonica* inhibited alpha-amylase and alpha glycosidase by the non-competitive method. Silver nanoparticles obtained from *solanum nigrum* showed a hypoglycaemic effect.

Table 1: Anti-hyperglycaemic activity of silver nanoparticles from numerous biological sources.

Sr. No	Biological source	Secondary metabolic products	Parameters of testing	Result	Reference
1	*Allium cepa*	Polyphenols, gallic acid, kaempferol, quarcetin, ferulic acid	Assay for the inhibition of alpha-amylase and alpha-glucosidase enzymes	74% reduction of alpha-amylase and 60 % decrement on of alpha-glucosidase at 100 mcg/ml	(Jini& Sharmila, 2020)
2	*Argyreia nervosa*	Saponins, sterols, flavonoids, triterpenoids	An assay of alpha-amylase and alpha-glucosidase was done	70% decrement of both enzymes at 100 mcg/ml	(Saratale*et al.*, 2017)
3	*Callophyllumtomentosum*	Flavonoids, saponins, tannins, alkaloids, phenols, coumarin.	Alpha amylase and alpha-glucosidase	Inhibition of approximately 18% alpha-amylase and 52% alpha-glucosidase	(Govindappa*et al.*, 2018)
4	*Xylocarpus granatum*	Carbohydrates, saponins, tannins, and flavonoids	Alpha amylase and alpha-glucosidase inhibition	92% reduction of both enzymes at 0.5mg per ml	(Bhardwaj*et al.*, 2020)
5	*Zingiber officinalis*	Volatile oils like neral, geranial, and zingiberene	Biochemical parameters like glucose level, body weight, etc., of STZ-induced diabetic rats	Blood glucose levels were restored to normal, and body weight was raised by 200mg per kg.	(Garg*et al.*, 2016)
6	*Saracaasoca*	All food components are flavonoids, tannins, saponins, carbohydrates, and protein.	Alpha amylase inhibition assay	Inhibition of alpha-amylase	(Patra *et al.*, 2018), (Pradhan *et al.*, 2010)
7	*Punica granatum*	Flavonoids, phenols, tannins, and alkaloids	Alpha-glucosidase and alpha-amylase inhibition assay	61% inhibition of alpha-amylase and 60% of alpha-glucosidase at 100 mcg/ml	(Saratale*et al.*, 2018)

2.2. Gold nanoparticles

These nanoparticles are widely researched for their many features related to diagnostics, treatments, and molecular nanoprobes. Gold nanoparticles have gained value in synthesizing numerous metals because of their size-dependent optical and electronic properties(Yeh*et al.*, 2012), (Yang *et al.*, 2017). Gold nanoparticles are unique among other metallic nanoparticles because of their formable surface plasmon resonance, which is why they are used in biosensors for the detection of bacteria and viruses, bio-labeling techniques, and pathogenic identification in clinical specimens by immune-chromatographic technique (Elahi *et al.*, 2018). It has been discovered in a developing field of green chemistry that these nanoparticles are biocompatible, inert, and easily bond with proteins, enzymes, deoxyribonucleic acid (DNA), and amino acids and that they also yield a large surface area for immobilization of these giant molecules.Gold nanoparticles obtained from *cassia auriculata*(Venkatachalam *et al.*, 2013) and *sargassum swertzii*(Dhas*et al.*, 2016) possessed hypoglycemic activities in diabetic rats. Gold nanoparticles from *cassia auriculata* interfered with the biochemical parameters of the sample. Fasting blood sugar(FBS), triglycerides (TG), total cholesterol (TC), and low-density lipoprotein-cholesterol (LDL-C) levels were reduced by the gold nanoparticles obtained from *s.swertzii*, increase in insulin, increase in high-density lipoprotein (HDL-C) level, andserum glutamate pyruvate transaminase (SGPT), serum glutamic oxaloacetic transaminase (SGOT) and creatinine level were maintained. These nanoparticles were synthesized from *cassia fistula,*and they showed antidiabetic potential. Alpha amylase had significant inhibition due to these nanoparticles and alpha-glucosidase, with insulin secretion increasing upto 95 % at 60 micrograms per ml.

Table 2: Antidiabetic activity of gold nanoparticles obtained from numerous biological sources.

Sr. No	Biological Source	Metabolic Products Involved	Testing parameters	Result	Reference
1	*Cassia auriculate*	Extracted propanoic acid from a sample	Biochemical parameters like insulin, cholesterol, etc., in rats	Body weight, cholesterol levels, and insulin levels are all controlled.	(Venkatachalam *et al.*, 2013)
2	*Cassia fistula*	Phenolics, anthraquinones, and flavonoids	Body weight, blood glucose hemoglobin	Body weight returned to normal, as did blood glucose and hemoglobin levels.	(Daisy&Saipriya, 2012)
3	*Fritillaria cirrhosa*	Imperialine, verticine, peimisine.	Biochemical and serum parameters in rats	Body weight, total protein, and plasma insulin levels increase, whereas hemoglobin levels decrease.	(Guo *et al.*, 2020)
4	*Saracaasoka*	Flavonoids, tannins, saponins, carbohydrates, proteins, and amino acids are all present.	Alpha amylase inhibition assay	Enzyme got inhibited	(Patra*et al.*, 2018)
5	*Gymnemasylvestre*	Alkaloids, terpenoids, peptides.	Biochemical parameters of rats of alloxan-induced	All the parameters returned to normal levels.	(Karthick*et al.*, 2014)
6	*Gymnemic acid*	Gymnemic acid	MTT assay and glucose utilization assay	49.43 % of glucose uptake.	(Rajarajeshwari*et al.*, 2014)

2.3. Other Metallic Nanoparticles

Other metals' biologically produced nanoparticles with antidiabetic potential have also been identified from other plants.For example, copper nanoparticles from Plumbago zeylanica and Gnidia glauca (Jamdade*et al.*, 2019) and palladium-reduced grapheme oxide conjugates from Zanthoxylum armatum(Hazarika*et al.*, 2019) were shown to inhibit alpha-glucosidase enzyme activity. Diverse plants have varied phytochemical elements in different ratios and combinations, which account for differences in their antidiabetic efficacy or potential. Furthermore, the nanoparticles differ in form and size, which leads to their differences in efficacy and the final result in a therapeutically antidiabetic medicine that operates on diverse diabetes regulatory components or mechanisms(Sharma*et al.*, 2021), (Sharma*et al.*, 2018), (Sharma*et al.*, 2017), (Sharma*et al.*, 2015).

Table 3: Antidiabetic action of other metallic nanoparticles obtained from different biological sources.

S. No.	The metal used for nanoparticles	Testing parameters	Result	Reference
1	Selenium	STZ-induced mice were taken into consideration for their biochemical parameters	Normal biochemical parameters were observed inthe kidney and liver, and the serum level was lowered too.	(Liu*et al.*, 2018)
2	Copper	Alpha-glucosidase inhibition assay	88.60% of the enzyme at 100mcg/ml	(Jamdade*et al.*, 2019)

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3	Zinc	Streptozotosin-induced type-I and type-II diabetic rats were taken for their biochemical parameter.	It increased serum insulin by 70%. It reduced blood glucose by 29%. Reduced triglycerides by 48%.	(Umrani & Paknikar *et al*., 2014)
4	Vanadium pentoxide	STZ-induced Wistar rats were taken into consideration for their biochemical parameters	Increased the activity of AST and ALT and serum protein and liver glycogen levels.	(Vijay *et al*., 2008)
5	Chromium	STZ-induced mice were taken into consideration for their biochemical parameters	Decreases fasting blood glucose Total cholesterol and Triglycerides levels decrease significantly	(Dong *et al*., 2021)

3. Advantages of Green Synthesis of Nano-Particles

- It is easy to synthesize and is efficient and also environment friendly.
- It eliminates the use of harmful chemicals, and it also consumes less energy, and produces safer products and by-products.
- It prevents the accumulation of waste.
- It has a lower risk of an accident.
- It utilizes safer solvents and reagents.
- It has a high atom economy.
- It is a less hazardous synthesis.

4. Challenges, Biosafety, and Clinical Translation

The challenges of gold and silver nanoparticles in the treatment of diabetes are that there are diverse plants that have varying phytochemical elements in different ratios or combinations, which account for variance in their antidiabetic potential. Furthermore, the nanoparticles differ in form and size, contributing to their variable efficacy and ultimate impact as a therapeutic antidiabetic medicine operating on various diabetes regulatory mechanisms or components (Bhardwaj *et al*., 2020). The majority of clinically approved nanomedicine products are made from soft nanoparticles. Furthermore, a considerable number of soft NPs are liposomal or polymer-conjugated formulations. Most clinical trial reports for nanomedicine products focus on pharmacological therapeutic efficacy rather than biosafety or adverse effects of NPs on the human body. Although the size and shape of these soft nanoparticulate systems are highly influenced by environmental parameters such as temperature, pH, ionic strength, or medium properties, most clinical studies did not offer specific information on the dynamic size of the therapeutic or carrier NPs. Although soft NPs have minimal toxicity, their larger counterparts can amass in key organs and produceharmful issues (Su *et al*., 2018). There are many challenges in the clinical translation of gold and silver nanoparticles,asit is an expensive and very complex process compared to its conventional counterparts. Another major challenge is the large-scale production, biocompatibility issues, government regulations, and commercialization pathways (Hua *et al*., 2018).

Conclusion

The antidiabetic potential of silver and gold metallic nanoparticles synthesized from various biological sources according to their application is discussed here. The secondary metabolite of various biological sources coated with nanoparticles and their effect on diabetes were studied. The advantages of green synthesis over conventional delivery systems are that it is easy to synthesize without using harmful chemicals or excessive heat.Silver and gold nanoparticles can potentially help treat diabetes and its microvascular consequences.This is due to its capacity to inhibit and efficiently disrupt various pathophysiological determinants (disease-causing proteins) involved in the evolution of diabetes complications. More collaborative research on the safe, effective size, and effective dose are needed, although silver and gold nanoparticles are expected to help treat diabetes problems.Overall, applying gold and silver nanoparticles in treating diabetes can potentiallyaffect human health significantly. It has been proposed to aid in the creation of customized medicine for specific patient sub-groups, in which medication is modified based on the patient's unique genetic and illness profile

Conflict of Interest Statement

The authors have declared that no competing interests exist.

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Authors Contributions

Dr. Amit Sharma: Collected data in ongoing study and writing the manuscript, data analysis; Mr. Mohammad

Amir, Miss Manisha Vohra,Dr.Sheetu: Contributed equally in collecting data, writing, drafting the manuscript; all authors read and approved the final manuscript.

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