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Review Article

REVIEW ON ANTI-DIABETIC POTENTIAL OF GREEN SYNTHESIZED NANOPARTICLES W.S.R. RASA SHASTRA

Himanshu Sharma[1*], Pramod Yadav[2], Prajapati PK[3]

1. *PG Scholar, Dept. of Rasa shastra & Bhaishajya Kalpana, All India Institute of Ayurveda, New Delhi, India.*
2. *Assistant Professor, Dept. of Rasa shastra & Bhaishajya Kalpana, All India Institute of Ayurveda, New Delhi, India.*
3. *Professor & Head, Dept. of Rasa shastra & Bhaishajya Kalpana, All India Institute of Ayurveda, New Delhi, India.*

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Abstract

Bhasma is one of the most important contributions of Rasa shastra to Ayurvedic repertoire. Owing to the physical attributes of Bhasma, various scholars have equated Bhasma to nanoparticles (NPs). Presently, researchers are focusing on synthesis of nanoparticles of various metals and metalloids by adopting greener approaches. Gold, silver, zinc etc. have been converted into their nano forms by synthesizing through extracts of various plants. Therefore green synthesized nanoparticles have gained prominence recently in view of many invitro and invivo studies proving their efficacy in management of diabetes. Only gold, silver, zinc and copper have been selected for compiling the review since their *Bhasma* are used in *Rasashastra* and are also indicated in *Prameha / Madhumeha* which can be equated to diabetes mellitus. In the present review, it is found that streptozotocin, alloxan and adult zebra fish models were used for evaluating invivo anti diabetic activity. Pancreatic beta cell lines, yeast models and invitro studies viz. α–amylase and α-glucosidase enzymes inhibition activities have been frequently used for assessing the anti diabetic potential of green synthesized nano particles. In particular, utilization of medicinal plant extracts as potential reducing and stabilization agents to synthesis nanostructures attained many advantages over conventional physical and highly toxic chemical methods. An attempt has been made searching through google scholar and pubmed and various available research articles on gold, silver, copper and zinc having invitro and or invivo activity on diabetes have been included in this review.

Keywords: Green synthesis; Nanoparticles; Gold; Silver; Copper; Zinc; Bhasma.

***Address for correspondence:**
Dr. Himanshu Sharma
PG Scholar, Dept. of Rasa shastra & Bhaishajya Kalpana,
All India Institute of Ayurveda, New Delhi, India - 110076
E-mail: hemuscholar1@gmail.com

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INTRODUCTION

Rasashastra is the latrochemistry of ancient Indian system of medicine. Gradual development of this science led to its evolution in field of medicine and various formulations developed in due course of time. Amongst various dosage forms, Bhasma is one of the most important contributions of Rasashastra to Ayurvedic repertoire. These Bhasmas are prepared from sources of mineral, metal, metalo-mineral or biological origin. Shodhana, Bhavana and Marana are few of the classical processes involved in the manufacture of Bhasma. Owing to the physical attributes of Bhasma, various scholars have equated Bhasma to nanoparticles (NPs).

Presently, researchers are focusing on synthesis of nanoparticles of various metals and metalloids by adopting greener approaches. The process is termed as Green Synthesis of NPs. Gold, silver, zinc etc. have been converted into their nano forms by synthesizing through extracts of various plants. Apart from paramedical uses, green synthesized nanoparticles have also shown to possess an array of biological activities viz. anticancer, antioxidant, antidiabetic, antibiotic etc.

Diabetes is becoming a universal health hazard with severe impact on developing countries. India is presumed to become the diabetic capital of the world in near future. Ignorance towards health coupled with lack of knowledge and delay in early detection has made it difficult to manage and has assumed the status of an epidemic.

Conventional antidiabetics have their respective drawbacks and adverse reactions. Therefore green synthesized nanoparticles have gained prominence recently in view of many invitro and invivo studies proving their efficacy in management of diabetes.

All metals and minerals generally used as a form of bhasma (incinerated form) also considered as nano-particles of Rasashastra. Therefore, an attempt has been made here to compile available references across internet depicting antidiabetic potential of nano particles produced through green synthesis with special reference to their nearest counterpart in Rasashastra.

MATERIAL AND METHODS

A search has been made through google scholar and pubmed with key words green synthesis, nanoparticles, gold, silver, copper, zinc. The available research papers on gold, silver, copper and zinc having invitro and or invivo activity on diabetes have been included for this review.

OBSERVATION AND RESULTS

Metals possessing anti diabetic properties are mentioned in Table 1.

DISCUSSION

Bhasma is very much prevalent amongst Ayurvedic physicians, who use it either through a formulation or by mixing with other herbs with suitable adjuvant. They are well tolerated and reported to be safe on oral ingestion in experimental animals.[1] It has become increasingly difficult to manage diabetes owing to missed diagnosis and ignorance of patients. Reluctance to take medicine for lifelong is also one of the reasons. Contemporary medicine relies on various combinatorial therapies for management of diabetes with difficulty in controlling blood sugar levels. Diet and lifestyle modifications are also advised for proper control of sugar levels. New drug development is time taking and highly expensive procedure. Reverse pharmacology can serve the purpose by exploring leads from traditional medicine and utilizing for therapeutic potentials.

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Table 1: Metals possessing anti diabetic properties

Sl.No.	Nanoparticle	Biological source used for processing	Model
1.	Gold	*Cassia fistula* stem bark [2]	Streptozotocin induced diabetic rats
2.	Gold	*Cassia auriculata* aqueous leaf extract[3]	
3.	Gold nanoparticles	*G. sylvestre* leaf extract[4]	alloxan-induced diabetic rats
4.	Gold nanoparticles	Aqueous extracts of *Sargassum swartzii*[5]	alloxan–induced diabetic rats
5.	Gold nanoparticles	Ethanolic extract of *Costus igneus*[6]	yeast model
6.	Gold nanoparticles	*Bacillus licheniformis*[7]	streptozotocin induced diabetic mice
5.	Gold-Silver Nanocomposite	*Trigonellafoenum graecum* L. Seeds Extract[8]	Streptozotocin Induced Diabetic Rats
7.	Silver	aqueous leaf extract of *Pouteria sapota* [9]	Streptozoticin
8.	Silver nanoparticles	methanol/water bark extract of *Eysenhardtia polystachya* [10]	adult zebrafish model And pancreatic β-cell line INS-1
9.	Silver nanoparticles	*Halymenia poryphyroide* Algae[11]	α–amylase and α-glucosidase enzymes inhibition
10.	Silver nanoparticles	*Bauhinia variegata* flower extract[12]	Alpha-amylase enzyme activity and inhibitor studies
11.	Silver Nanoparticles	*Gymnema sylvestre* extract[13]	streptozotocin
12.	Silver nanoparticles	*Sphaeranthus amaranthoides*[14]	invitro inhibition of alpha-amylase enzyme activity
13.	Copper Nanoparticles	*D. bulbifera* tuber extract[15]	α-amylase and α-glucosidase inhibition
14.	Zinc oxide (ZnO) nanoparticles (NPs)	*Hibiscus subdariffa* leaf extract[16]	streptozotocin (STZ) induced diabetic mice
15.	Zinc oxide nanoparticles	Plant extracts of *Azadirachta indica*, *Hibiscus rosa-sinensis*, *Murraya koenigii*, *Moringa oleifera*, and *Tamarindus indica*[17]	α-amylase and α-glucosidase activity
16.	Zinc oxide nanoparticles	*Andrographis paniculata* leaf extract[18]	a-amylase inhibitory activity

Green syntheses of nanoparticles are being carried out by different macro–microscopic organisms such as plant, bacteria, fungi, seaweeds and microalgae. The biosynthesized nanomaterials effectively control various endemic diseases with less adverse effect. Plant contains abundant natural compounds such as alkaloids, flavonoids, saponins, steroids, tannins and other nutritional compounds. These natural products are derived from various parts of plant such as leaves, stems, roots shoots, flowers, barks, and seeds. Recently, many studies have proved that the plant extracts act as a potential precursor for the synthesis of nanomaterial in non-hazardous ways.

Since the plant extract contains various secondary metabolites, it acts as reducing and stabilizing agents for the bio-reduction reaction to synthesized novel metallic nanoparticles. The non-biological methods (chemical and physical) are used in the synthesis of nanoparticles, which has a serious hazardous and high toxicity for living organisms. In addition, the biological synthesis of metallic nanoparticles is inexpensive, single step and eco-friendly methods. The plants are used successfully in the synthesis of various greener nanoparticles such as cobalt, copper, silver, gold, palladium, platinum, zinc oxide and magnetite.

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Also, the plant mediated nanoparticles are potential remedy for various diseases such as malaria,[19] cancer,[20] HIV,[21] hepatitis and other acute diseases.

Green synthesized nanoparticles have been developed in this sense and are finding greater applications in field of Diabetes.Manytimes the media used for processing the NPs have reported anti diabetic activity. Therefore a review was undertaken to compile the studies reporting anti diabetic potential of green synthesized nano-particles.

Only gold, silver, zinc and copper have been selected for compiling the review since their *Bhasma* are used in *Rasashastra* and are also indicated in *Prameha / Madhumeha* which can be equated to diabetes mellitus.[22]

Classics of *Rasashastra* has described the *Prameha / Madhumeha* hara (Anti-diabetic) property of incinerated Mica (*Abhraka bhasma*), Chalco-pyrite (*Swarna makshika bhasma*), Lead (*Naga bhasma*), Iron (*Louha and Mandoora bhasma*) and Tin (*Vanga bhasma*). However, review of these incinerated metals and minerals are not considered in this compilation.

In the present review, it is found that streptozotocin, alloxan and adult zebra fish models were used for evaluating invivo anti diabetic activity. Pancreatic beta cell lines, yeast models and invitro studies viz. α–amylase and α-glucosidase enzymes inhibition activities have been frequently used for assessing the anti diabetic potential of green synthesized nano particles.

Use of gold nanoparticles synthesized from *C. fistula* stem bark for the treatment of rats with streptozotocin-induced diabetes reduced serum blood glucose concentrations, induced favorable changes in body weight, improved transaminase activity, achieved a better lipid profile, and reversed renal dysfunction to a greater extent that did aqueous extracts from the same plant. This study indicates that phytochemically synthesized gold nanoparticles are better hypoglycemic agents in the treatment of diabetes mellitus and its associated complications.[23]

In another study, gold nano particles were synthesized using *Cassia auriculata* aqueous leaf extract. The size, shape and elemental analysis were carried out using X-ray diffraction, TEM, SEM-EDAX, FT-IR and visible absorption spectroscopy. Stable, triangular and spherical crystalline AuNPs with well-defined dimensions of average size of 15-25 nm were synthesized using *C. auriculata*.

The authors have hypothesized their anti diabetic potential owing to the anti diabetic properties of *Cassia auriculata* leaves.[24]

AuNPs synthesized biologically using the antidiabetic potent *G. sylvestre* plant showed positive effect on alloxan-induced diabetic model. They were effective in reducing the BGL to normal level and have good control over the lipid levels of the treated diabetic rats. AuNPs also have an anti-inflammatory effect on diabetic rats assessed using inflammatory markers TNF, IL-6 and hsCRP. Based on the results, it is suggested that colloidal nanoparticles could be used as a nanomedicine for treatment of diabetes.[25]

Synthesis of gold nanoparticles (AuNPs) using a marine algae has also shown promising results. Dhas TS *et al* used aqueous extracts of *Sargassum swartzii* to synthesize gold nanoparticles and assessed its effect on alloxan–induced diabetic rats. Fasting blood glucose levels, serum insulin, hemoglobin and glycosylated hemoglobin levels in diabetic treated rats with AuNPs were significantly decreased compared to the control group. The results of the blood glucose level and serum insulin levels indicated that AuNPs could significantly improve the insulin resistance and glucose level in diabetic rats.

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AuNPs synthesized using *S. swartzii* exerted antidiabetic effect, accordingly improve pancreas, liver and kidney damage caused by alloxan induced diabetic rats.[26]

AuNPs synthesized using ethanolic extract of *Costus igneusi* were tested for its activity on yeast models and showed good anti diabetic activity.[27]

AuNPs have also been synthesized using *Bacillus licheniformis.* However, it is beyond the scope of this paper. Even though, it is being reported, as authors have found significant activity on streptozotocin induced diabetic mice. The authors conclude that the profound control of AuNPs over the anti oxidant enzymes such as GSH, SOD, Catalase and GPx in diabetic mice to normal, by inhibition of lipid peroxidation and ROS generation during hyperglycemia evidence their anti-oxidant effect during hyperglycemia. The AuNPs exhibited an insistent control over the blood glucose level, lipids and serum biochemical profiles in diabetic mice near to the control mice provokes their effective role in controlling and increasing the organ functions for better utilization of blood glucose. Histopathological and hematological studies revealed the non-toxic and protective effect of the gold nanoparticles over the vital organs when administered at dosage of 2.5 mg/kilogram.body.weight/day.[28]

Another study by Virk P *et al*. used *Trigonellafoenum graecum* L. seeds extract for synthesis of Gold-Silver Nanocomposite and tested its antidiabetic potential on Streptozotocin Induced Diabetic Rats. The green gold and silver (Au/Ag) nano-composite showed a profound anti-hyperglycemic effect which was significantly better than all other treated groups. The results on serum ALT, creatinine levels and blood urea also showed a comparable ameliorative effect of both the bulk *Trigonella* seed extract (TBN) and the green nano-composite (TN), being more efficacious than metformin.[29]

Silver has also been widely explored for anti diabetic potential in its green synthesized nano form (AgNPs).

AgNPs prepared using aqueous leaf extract of *Pouteria sapota* were evaluated on Streptozoticin induced diabetic rats. A significant reduction in blood sugar levels was noted in rats treated with leaf extract or AgNPs. Results of in vitro and in vivo analyses in rats treated with leaf extract or AgNPs show that both the extract and the biologically synthesized AgNPs have antidiabetic activity.[30]

Garcia Campoy AH *et al* prepared AgNPs using methanol / water bark extract of *Eysenhardtia polystachya* and evaluated its anti diabetic potential on adult zebrafish model and pancreatic β-cell line INS-1. They found that EP/AgNPs promote pancreatic β-cell survival, insulin secretion, enhanced hyperglycemia, and hyperlipidemia in glucose-induced diabetic zebrafish. EP/AgNPs also showed protection of the pancreatic β-cell line INS-1 against hydrogen peroxide-induced oxidative injury.[31]

AgNPs synthesized using *Halymenia poryphyroide* algae was evaluated on α–amylase and α-glucosidase enzymes inhibition activity. The assay results of silver nanoparticles showed dose dependentsignificantly ($P<0.005$) increase in percentage inhibitory activity against α–amylase enzyme, at a concentration of0.2 mg/ml 26.20 ± 0.02% inhibition was seen and at 1.0 mg/ml 91.30 ± 0.02% inhibition was observed, similarlydose dependent significantly ($P<0.005$) increase in percentage inhibitory activity against α-glucosidase enzyme wasalso observed where in at lower concentration of 0.2 mg/ml 33.20 ± 0.01% of inhibition and at higher concentrationof 1.0 mg/ml 89.10 ± 0.01% inhibition were recorded.[32]

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Alpha-amylase enzyme activity and inhibitor studies were carried out on AgNPs synthesized using *Bauhinia variegata* flower extract. The synthesized BVF-AgNPs showed potent antioxidant property and α-amylase enzyme activity inhibition. The IC50 value of BVF-AgNPs was found to be 4.64 and 16.6 µg/ml for DPPH and ferric reducing power assay, respectively. The IC50 value of BVF-AgNPs for α-amylase inhibition was found to be 38 µg/ml. The Ki value of BVF-AgNPs for α-amylase inhibitory effect was found to be 21 µg/ml with the non-competitive mode of inhibition.[33]

In a similar study, silver nano particles were synthesized using *Gymnema sylvestre* extract (GSSNPs). Sterptozotocin induced diabetic rats were used for particular study. It was found that GSSNPs at dose level of 200 mg/kg (b.wt p.o.) showed significant inhibition of ($p<0.001$) blood glucose levels and lipid profile as compared with *Gymnema sylvestre* extract treated group. These detections revealed that GSSNPs possess potent anti-hyperglycemic and anti-hyperlipidemic activity and thus preferable over crude extract.[34]

In-vitro inhibition of alpha-amylase enzyme activity of AgNPs synthesized using *Sphaeranthus amaranthoides* extract. It was found that silver nanoparticles showed a dose response inhibitory activity on α-amylase. Acarbose was used a standard drug. The IC50 value for plant extract is 0.28µg/ml where as for acarbose is 0.75µg/ml.[35]

Literature review also showed that copper has also been evaluated for anti diabetic potential for its nano particles. Ghosh S *et al* studied α-amylase and α-glucosidase inhibition activity of Copper Nanoparticles synthesized using *D. bulbifera* tuber extract. Excellent inhibitory potential of the CuNPswas found against α-amylase and α-glucosidase which are considered to be significant pharmacological targets for treatment of T2DM.

Similarly, it exhibited superior antioxidant activity. This is the first ever report on the α-amylase and α-glucosidase inhibitory activity of CuNPs synthesized by DBTE. The high potency of these biogenic CuNPs for radical-scavenging and glycosidase inhibitory activities in vitro provided strong scientific evidence for antidiabetic potential of CuNPs which intensely rationalize its use in therapy and management of T2DM.[36]

Zinc has been traditionally used in Ayurveda for its anti-diabetic activity in *Bhasma* from, either alone or in conjugation with other drugs. *Hibiscus subdariffa* leaf extract was used to prepare Zinc oxide (ZnO) nanoparticles (NPs) and studied on streptozotocin (STZ) induced diabetic mice.

It was observed by enzyme linked immunosorbent assay (ELISA) and real time polymerase chain reaction (RT-PCR) that ZnO can induce the function of Th1, Th2 cells and expressions of insulin receptors and other genes of the pancreas associated with diabetes.[37]

Similarly ZnO nanoparticles prepared using plant extracts of *Azadirachta indica*, *Hibiscus rosa-sinensis*, *Murraya koenigii*, *Moringa oleifera* and *Tamarindus indica* were studied for α-amylase and α-glucosidase inhibition activity. The authors found that ZnO nanoparticles synthesized using T. indica extract displayed remarkable antioxidant and antidiabetic activities.[38]

Alpha-amylase inhibitory activity of ZnO nanoparticles prepared using *Andrographis paniculata* leaf extract was studied by Rajakumar G *et al*. It was found that the synthesized nanoparticles possess strong biological activities regarding anti-oxidant, anti-diabetic, and anti-inflammatory potentials.[39]

The quantum of research available in this topic indicates the vast unexplored area and provide further leads to future researchers.

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CONCLUSION

Green synthesized nano particles are gaining importance for their application in field of medicine in therapeutics, diagnostics etc. They bear close resemblance to Bhasma in their physical properties. In particular, utilization of medicinal plant extracts as potential reducing and stabilization agents to synthesis nanostructures attained many advantages over conventional physical and highly toxic chemical methods. However, the safety aspect in comparison to traditional classical methods is still unrevealed.

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