Research Article

Herbal Drugs and Herbal Mediated Silver Nano Particles as Anti Diabetics: A New Horizon

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ABSTRACT

Diabetes is a chronic metabolic disorder that affects millions of people worldwide and takes a heavy toll on human life. Traditional plant treatments have been used throughout the world for the therapy of diabetes mellitus. Among several medications and other alternative medicines, herbal drugs have been known to cure and control diabetes; additionally they have no side effects. Newer drugs with the least side effects but with highest efficiency are being relentlessly searched by the researchers. Herbal drugs are very common in use in our day to day life easily available and are having least side effects. Nanotechnology is a branch of science and technology conducted at the nanoscale, which is about 1 to 100 nanometers. Nanoscience and nanotechnology are having a wide range of applications in fields, such as green chemistry, herbal drug research. With respect to herbal medicine the drug will take more time to show the anti diabetic activity because herbal drugs are basically more insoluble in nature. To overcome this kind of problems nano herbal medicine is needed. Herbal mediated silver nanoparticles (HMSNP's) are having less particle size, more surface area, more solubility which results in the optimum dose of drug that can reach to systemic circulation and onsite of action is very quick. Recent studies on the use of herbal plant extracts in synthesis of HMSNP's are a relatively new and exciting area of research with considerable potential for development of new methods in nano medicine. HMSNP's capable to treat diabetes effectively by having very less particle size comparatively with herbal medicine current review is an attempt to list of out the anti diabetic plants, biosynthesis and various characterization methods of HMSNP's and their advanced pharmacological applications to treat diabetes.

Keywords: Herbal drugs, Herbal mediated Silver Nanoparticles (HMSNP's), Diabetes mellitus, Optimum dose, Nanoscience and Nanotechnology.

INTRODUCTION

Diabetes is a metabolic disorder; it is mainly caused by dysfunction of the β cells of the pancreas. This in turn leads to decreased production of the hormone insulin and/or increased resistance to the action of insulin in the peripheral tissues[1]. Diabetes can be categorized into two types: type 1 and type 2. Type 1 Diabetes or juvenile-onset diabetes develops when the body's errant immune system damages and destroys the pancreatic β cells that produce the blood glucose regulating hormone insulin.

To survive with type 1 diabetes must need to have an exogenous delivery of insulin hormone. This form of diabetes usually attacks children and young adults, although the onset of the disease may occur at any age[2]. In adults, type 1 diabetes accounts for about 5% of all diagnosed cases of diabetes. Risk factors for type 1 diabetes may be autoimmune, genetic or environmental.

Till now there is no known way to prevent type 1 diabetes exists. Several clinical trials for preventing type 1 diabetes are being planned or currently in progress[3].

Type-2 diabetes (non-insulin-dependent diabetes mellitus; NIDDM) or adult-onset diabetes usually begins as a progressive insulin resistance/insensitiveness, with an ensuing reduction in the ability of the pancreatic hormone to promote peripheral glucose disposal and to suppress hepatic glucose output[4]. The pancreas pumps out increasing amounts of insulin to normalize blood glucose levels as compensation.

Over time, as long as a decade, this ever increasing production becomes unsustainable and the pancreas' ability to produce insulin declines.

As a result, the level of blood glucose rises as a result it begins to appear in the urine and causes increased urination. Established risk factors for type 2 diabetes include genetic polymorphism, family history, physical inactivity, obesity, older age and stress[5].

Type 2 Diabetes Mellitus affected individuals need to follow a diet and perfect exercise programs to control the blood glucose levels. If this first line treatment does not control blood sugar levels effectively, an oral medication can be preferable to the treatment plan. In certain circumstances, patients with type 2 diabetes may also require insulin in the form of injection.

Moreover many patients need to control their blood pressure and cholesterol levels.

Type 2 diabetes accounts for about 90% to 95% of all diagnosed cases of diabetes. African Americans, Hispanic/Latino Americans, American Indians and some Asian Americans are at particularly high risk for type 2 diabetes, along with its complications, and are also being diagnosed, although still rare, as children and adolescents.

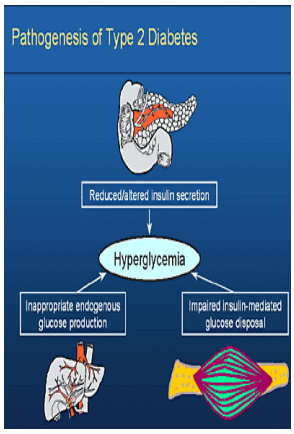


Figure 1(A): Pathophysiology- Diabetes mellitus

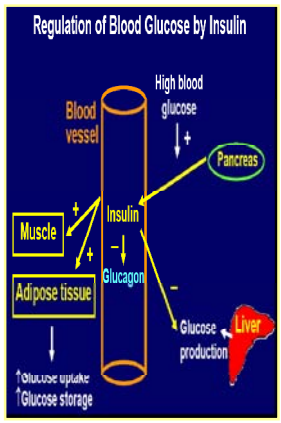


Figure 1(B) Glucose Regulation by Insulin hormone

What is Nanotechnology?

Nanotechnology is defined as the "intentional design, characterization and production of materials, structures and systems by controlling their size and shape in the nanoscale range 1 to 100 nm [6-7]". As the nano particles are similar in scale to biological molecules and systems yet can be engineered to have various functions, nanotechnology is potentially useful for medical applications. The field of nanomedicine aims to use the properties and physical characteristics of nanomaterials for the treatment of diseases at the molecular level.

The field of nanotechnology is one of the upcoming areas of research in the modern field of material science. Nanoparticles show completely new or improved properties, such as size, distribution and morphology of the particles etc. Novel applications of nanoparticles and nanomaterials are emerging rapidly in various research areas such as Pharmacy and medicine etc.[8]

Why Nanoparticles unique from normal size particles?

Nanoparticles have a high specific surface area and unique properties of size and shape. Because of the unique physicochemical characteristics of nanoparticles, including anti cancer, anti diabetic, antibacterial properties and magnetic properties[9-11] they are gaining the interest of researchers for novel methods of synthesis. From the past decade, the synthesis of metal nanoparticles is been a most important topic of research in modern material science and medicine nano technology. Nano-crystalline silver particles have been providing applications in the fields of high sensitivity biomolecular detection, diagnostics, antimicrobials, therapeutics. However, there is still need for economical and easily available and clean synthesis route to synthesize the silver nanoparticles. Silver is well known to possess an inhibitory effect toward many bacterial strains and microorganisms commonly present in medical and industrial processes[12]. In medicines, silver and silver nanoparticles have an ample of applications including skin ointments and cream which containing silver to prevent infection of burns and open wounds[13], medical devices and implants prepared with silver-impregnated polymers[14]. In textile industry, silver-embedded fabrics are now used in sporting equipment [15]. According to present research scenario especially the silver nano particles have been playing an important role in Herbal nano technology to prevent chronic diseases like diabetes and cancer etc.

Table 1: Medicinally Active Plants with Antidiabetic and Related Beneficial Properties

Botanical name	Family	Activity reported
Beta vulgaris L.	*Beta vulgaris* L.	Increases glucose tolerance in OGTT[16]
Bombax ceiba L.	Malvaceae	Hypoglycemic[17]
Butea manosperma	Cesalpinaceae	Anti-hyperglycemic[18]
Cynodon dactylon	Poaceae	Anti-hyperglycemic[19]
Eriobotrya japonica	Rosaceae	Hypoglycemic[20]
Gentiana olivieri L.	Gentianaceae	Hypoglycemic, anti-hyperlipidemic[21]
Globularia alypum L.	Globulariaceae	Hypoglycemic[22]
Glycyrrhiza uralensis	Papilionaceae	Decreases the blood glucose levels[23]
Morus indica. L.	Moracea	Hypoglycemic[24-25]
Morus inignis L.	Moraceae	Hypoglycemic[26]
Murraya koenigii L.	Rutaceae	Hypoglycemic, increases glycogenesis[27]
Nigella saliva	Ranunculaceae	Hypoglycemic[28]
Ocimum gratissinuim	Lamiaceae	Hypoglycemic[29]
Pandanus odorus	Pandanaceae	Hypoglycemic[30]
Parmentieru edulis	Bignoniaceae	Hypoglycemic[31]
Phyllanthus sellowianus.	Euphorbiaceae	Hypoglycemic[32]
Psacalium decompositum	Asteraceae	Hypoglycemic[33]
Psacalium peltatum	Asteraceae	Hypoglycemic[34]
Tinospora crispa	Menispermaceae	Hypoglycemic[35]
Urtica dioica	Urticaceae	Hypoglycemic[36]
Urtica pilulifera L.	Urticaceae	Hypoglycemic[37]
Vinca rosea L.	Apocynaceae	Hypoglycemic[38]
Withania somnifera	Solanaceae	Hypoglycemic, antioxidant[39-40]

Why Silver?

Silver is one of the basic interesting elements with peculiar properties in the multidisciplinary fields of research. It is a naturally occurring element, slightly harder than gold and very ductile and malleable. Pure silver has the highest electrical and thermal conductivity of all metals and has the lowest contact resistance. Silver can be present in four different oxidation states: Ag0, Ag^{2+}, Ag^{3+}. The former two are the most abundant ones, the latter are unstable in the aquatic environment[41]. Metallic silver itself is insoluble in water, but metallic salts such as $AgNO_3$ and Silver chloride are soluble in water (WHO, 2002). Metallic silver is used for the surgical prosthesis and splints, fungicides and coinage. Soluble

silver compounds such as silver slats, have been used in treating mental illness, epilepsy, nicotine addition, gastroenteritis and infectious diseases including syphilis and gonorrhea. Although acute toxicity of silver in the environment is dependent on the availability of free silver ions, investigations have shown that these concentrations of Ag+ ions are too low to lead toxicity (WHO, 2002). Metallic silver appears to pose minimal risk to health, whereas soluble silver compounds are more readily absorbed and have the potential to produce adverse effects[42]. The wide variety of uses of silver allows exposure through various routes of entry into the body. Ingestion is the primary route for entry for silver compounds and colloidal silver proteins. Dietary intake of silver is estimated at 70-90µg/day, since silver in any form is not expected to be toxic to the immune, cardiovascular, nervous or reproductive system and it is not considered to be carcinogenic[43], hence silver is relatively non-toxic[44]. Silver demand will likely to rise as it finds new applications, particularly in medical, textiles and plastics fields, changing the pattern of silver emission as these technologies and products diffuse through the global economy.

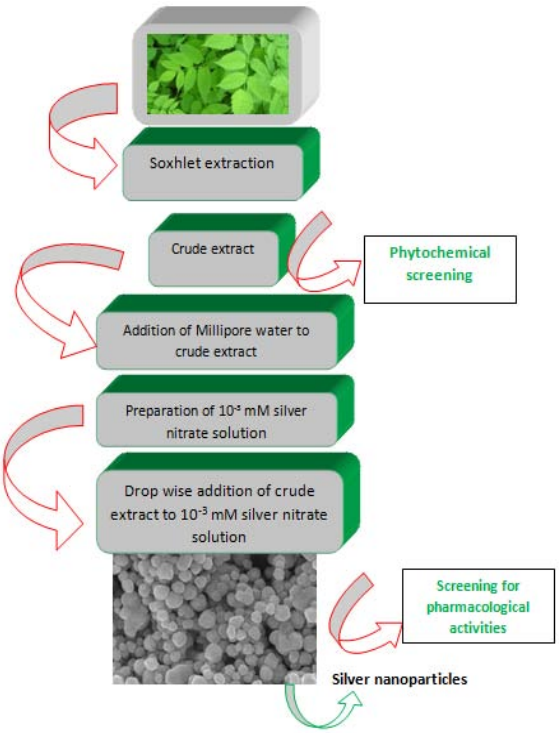
Traditional system of medicine in Nanotechnology

Traditional system of medicine such as Ayurveda can serve as an excellent tool for human in nanomedicine category. A research work shows that traditional medicines such as Ayurveda Bhasma may hold strong relevance in the emerging area of nanomedicine. The purposeful advantage emerges if the traditional system of medicine combines with metal-based nanomedicine[45]. Recent study reveals that Ayurvedic Bhasma are alike the nanocrystalline material. This serves the usage of Bhasma as targeted drug delivery, the reason behind they are biocompatible and non-toxic[46-47].

Synthesis of HMSNP's

Nanoparticles can be synthesized using various approaches including chemical, physical, and biological. Although chemical method of synthesis requires short period of time for synthesis of large quantity of nanoparticles, this method requires capping agents for size stabilization of the nanoparticles. Chemicals used for nanoparticles synthesis and stabilization are toxic and lead to non-eco friendly by products. The need for environmental non-toxic synthetic protocols for nanoparticles synthesis leads to the improving interest in biological approaches which are free from the use of toxic chemicals as byproducts. Thus, "green nanotechnology" has an increasing demand[48]. Many biological approaches for both extracellular and intracellular nanoparticles synthesis have been reported till date using microorganisms including bacteria, fungi and plants[49,50]. Plants provide better results for nanoparticles synthesis as they are free from toxic chemicals as well as provide natural capping agents. Moreover, use of plant extracts also reduces the cost of microorganism's isolation and culture media enhancing the cost competitive feasibility over nanoparticles synthesis by microorganisms[51]. Sometimes the synthesis of nanoparticles using various plants and their extracts can be advantageous over other biological synthesis processes which involve the very complex procedures of maintaining microbial cultures[52-53]. Many such experiments have already been started such as the synthesis of various metal nanoparticles using fungi like *Fusarium oxysporum*[54], *Penicillium species*[55] and using some bacteria such as *Bacillus subtilis* etc.[56, 57]. But, synthesis of nanoparticles using plant extracts is the most adopted method of green, eco-friendly production of nanoparticles and to handle and act as a source of several metabolites[58]. There has also been several experiments performed on the synthesis of silver nanoparticles using medicinal plants such as *Oryza sativa*, *Helianthus annus*, *Saccharum officinarum*, *Sorghum bicolour, Zea mays, Basella alba, Aloe vera Capsicum annuum, Magnolia kobus, Medicago sativa (Alfalfa), Cinamomum camphora and Geranium species* in the field of pharmaceutical applications and biological industries. Besides, green synthesis of silver nanoparticles using a methanolic extract of *Eucalyptus hybrida* was also investigated[59]. In the recent days, silver nanoparticles have been synthesized from the naturally occurring sources and their products like green tea (*Camellia sinensis*), Neem (*Azadirachta indica*), various leaf broth, natural rubber, starch, *Aloe vera* plant extract, lemon grass leaves extract, etc.[60].

Green synthesis of Silver nano particle



Silver nanoparticles

The major advantage of using plant extracts for silver nanoparticle synthesis is that they are easily available, safe, and nontoxic in most cases, have a broad variety of metabolites that can aid in the reduction of silver ions.

The main mechanism considered for the process is plant-assisted reduction due to phytochemicals. The main phytochemicals involved are terpenoids, flavones, ketones, aldehydes, amides, and carboxylic acids. Flavones, organic acids, and quinones are water-soluble phytochemicals that are responsible for the immediate reduction of the ions. Studies have revealed that xerophytes contain emodin, an anthraquinone that undergoes tautomerization, leading to the formation of the silver nanoparticles. In the case of mesophytes, it was found that they contain three types of benzoquinones: cyperoquinone, dietchequinone, and remirin. It was suggested that the phytochemicals are involved directly in the reduction of the ions and formation of silver nanoparticles[61].

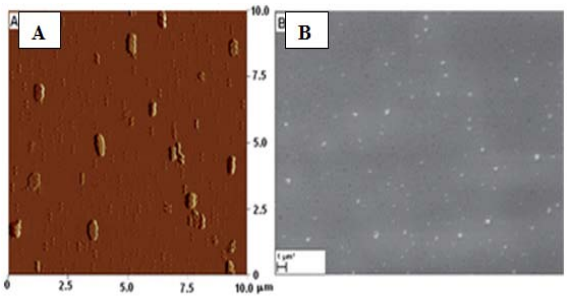


Figure (2A, 2B): AFM images of silver nanoparticles

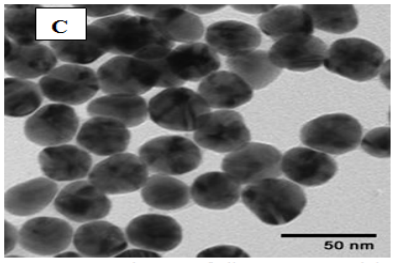


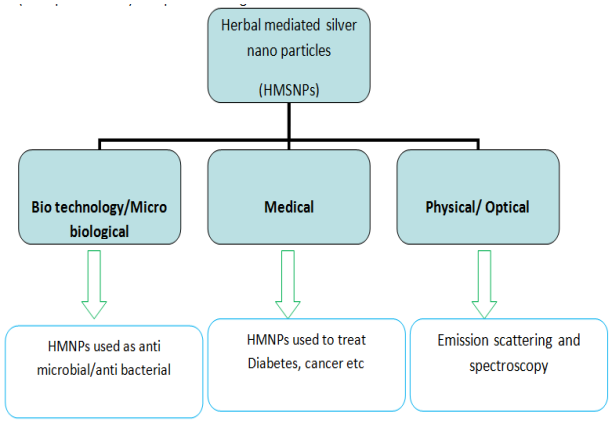
Figure 2C: TEM image of silver nanoparticles

Need for Green Synthesis

Biosynthesis of nanoparticles is a kind of bottom up approach where the reduction/oxidation is the main occurring reaction. The need for biosynthesis of nanoparticles rose as the physical and chemical processes were costly. Often, chemical synthesis method leads to presence of some of the toxic chemical absorbed on the surface that may have adverse effect in the medical applications[62]. This is not an issue when it comes to biosynthesized nanoparticles via green synthesis route[63]. So, in the search of economic pathways for nanoparticles synthesis, scientist used microbial enzymes and plant extracts (phytoconstituents). With their antioxidant or reducing properties they are usually responsible for the reduction of metal compounds into their respective nanoparticles. Green synthesis provides advancement over chemical and physical method as it is cost effective, environment friendly, easily scaled up for large scale synthesis and in this method there is no need to use high pressure, energy, temperature and toxic chemicals.

Applications of Silver Nanoparticles

Nanoparticles are of great interest due to their extremely small size and large surface to volume ratio, which leads to both chemical and physical differences in their properties compared to bulk of the same chemical composition, such as mechanical, biological and sterical properties, catalytic activity, thermal and electrical conductivity, optical absorption and melting point[64]. Hence, designing and production of materials with novel applications can be results by controlling shape and size at nanometer scale. Nanoparticles exhibit size and shape-dependent properties which are of interest for applications ranging from biosensing and catalysts to optics, antimicrobial activity, computer transistors, electrometers, chemical sensors, and wireless electronic logic and memory schemes. These particles also have many applications in different fields such as medical imaging, nano-composites, filters, drug delivery, and hyperthermia of tumors[65-66]. Silver nanoparticles have drawn the attention of researchers because of their extensive applications in areas such as integrated circuits[67], sensors, biolabelling, antimicrobial deodorant fibres[68], low-cost paper batteries (silver nano-wires)[69] and antimicrobials[70]. Silver nanoparticles have been used extensively as antimicrobial agents in health industry, food storage, textile coatings and a number of environmental applications. In general, therapeutic effects of silver particles (in suspension form) depend on important aspects, including particle size (surface area and energy), particle shape (catalytic activity), particle concentration (therapeutic index) and particle charge[71].



Pharmacological applications of HMSNPs

Can Nanotechnology bring relief to Diabetics? Beneficial Role of Nano Herbal Medicine

Several instances of earlier studies reported many possibilities of nanotechnology to implement new ways of treating diabetes.

As the world population increases, improved resources are needed to sustain society. An alternative to this issue is to be highly efficient and this could be achieved through nano science and technology. With this new technology, diabetics may become completely free from dietary regulations and the restrictive systematic regime.

Some devices are so adjustable that diabetics will no longer be dependent on insulin injections and their blood glucose levels will be adjusted according to their glucose level at that moment in time. This would enable them to lead a normal life, especially the young who are always active. It helps the patient to feel more mentally secure/better and confident, as well as being cost-effective in other aspects as it requires fewer resources with a much more effective outcome. Efficiency is essential as the world population increases, hence economic efficiency is the most stable way of supporting the billions of people all over the world with diabetes.

CONCLUSION

Herbal mediated silver nanoparticles: Scope of Future Research

A literature survey of current topic suggests that a lot of work has been undertaken to establish the anti-diabetic potentials of several drugs, ranging from homeopathy and Ayurvedic to formulated nano medicines yet the field of nanotechnology or nanomedicine needs special attention. In this context, there is an open era of research to establish standard nano drugs and to explore more advanced insulin therapy, their nano formulations, delivery and the pathway through which they act. Finding the truth of which drugs are really capable of bringing about corrective modulations of some parameters at molecular level and are scientifically acceptable with protocols/methodologies adopted that can be repeated by others is absolutely mandatory. Exploring this area of research will not only bring a new dimension in the regimen of treatment to diabetic patients, but should also be a step forward towards building a platform for development of newer scientifically tested drugs by following an advanced procedure of drug designing.

The discovery and development of potent antidiabetic drugs have been significantly hampered due to a lack of suitable preclinical models with respect to the optimum dose of the drugs to check the efficacy of candidate agents. To bridge the gap, these drugs should include the kingdom of natural products (KNP), but at the same time need to show enhanced bio availability, target-specific in action and utilize the different aspects of nanotechnology. Synthesized and formulated herbal mediated silver nanoparticles not only biodegradable, biocompatible and non-toxic but also would have a greater ability to enter biological cell membrane and show more quick action thereby providing great bio availability as an alternative system of herbal medicine to treat diabetes.

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