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Article

Gold nanoparticles as a promising treatment for diabetes and its complications: Current and future potentials

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Diabetes and its complications represent a major cause of morbidity and mortality in diabetes patients. This review is aimed to find the potential of gold nanoparticles (AuNPs) to act as therapeutic agents for diabetes and its complications. Here, we outline the literature related to the self-therapeutic effects of AuNPs. The first goal of this review is to highlight and summarize some of the existing studies (10 years ago) in terms of several parameters such as the size of AuNPs, dose, administration route, experimental model, experimental analysis, and findings. The second goal is to describe the self-therapeutic effects of AuNPs against the pathogenesis determinants of diabetic complications. AuNPs have been found to have inhibitory effects on transforming growth factor-β, antiglycation, antiangiogenic, anti-hyperglycemic, anti-inflammatory, and antioxidant effects. AuNPs treatment effectively disrupts multiple pathogenesis determinants in an animal model of diabetes and diabetic complications. The present review provides insight into the potential applications of AuNPs, which may help reduce the incidence of diabetes and its complications.

Keywords: Gold nanoparticles. Therapeutic effects. Diabetes. Diabetic complications. Pathogenesis determinants.

INTRODUCTION

According to the World Health Organization WHO, and the International Diabetes Federation, a total of 171 million people (2.8% of the global population) have diabetes. This number is expected to rise to 336 million (about 4.4% of the global population) by 2030 (Matough *et al.*, 2012; Pourghasem, Shafi, Babazadeh, 2015). Diabetes account for a significant portion of health care, cost and death rate due to the high opportunity of malfunction and failure of body organs. Diabetes is associated with long-term complications (retinopathy, nephropathy, and peripheral neuropathy). All these complications are related to the uncontrolled blood glucose level (*hyperglycemia*) (Kashihara *et al.*, 2010; Matough *et al.*, 2012). One of the pathogenic pathways of these complications that are activated in diabetes due to *hyperglycemia* is the promotion of mitochondrial respiration, resulting in release of reactive oxygen species (ROS) into the cytoplasm. The generation of ROS lead to occurrence of the oxidative stress which lead to the diabetic complications (Barathmanikanth *et al.*, 2010; Kashihara *et al.*, 2010; Afifi, Abdelazim, 2015).

Recent years have witnessed a great development of nanotechnology in the field of science and technology. Nanomaterial have been used in several biomedical applications for their unique properties (Zhao, Castranova, 2011). Recently, pharmacological industries have shown interest in nanotechnology-based drug development. Nanomedicine has been found to have vital effect in treating various fatal diseases. Among other nanoparticles, gold nanoparticles (AuNPs) received great attention as they have anti-inflammatory (Ali *et al.*, 2017), antioxidative (Opris *et al.*, 2017), anti-angiogenic (Arvizo *et al.*, 2011), anti-proliferative (Saha *et al.*, 2016), anti-diabetic (Shaheen *et al.*, 2016) effects.

The anti-hyperglycemic, antioxidant effects of AuNPs were notable in the recovery and amelioration of

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different diseases in diabetes models (Opris *et al.*, 2017) diabetic wound healing (Chen *et al.*, 2012), autistic diabetic model (Selim, Abd-Elhakim, Al-Ayadhi, 2015), diabetic nephropathy (Hamza, Bashuaib, 2018). In this review we are trying to discuss the ability of AuNPs to act as therapeutic agents for diabetes and its complications through exploring its anti-hyperglycemic, antioxidant, antiglycation, antiangiogenic, anti-inflammatory, and anti-fibrotic effects. This review conveys the recent studies into the therapeutic effects mediated by AuNPs, with primary emphasis on anti-hyperglycemic, anti-oxidant, anti-inflammatory and antiangiogenic potential, highlighting the effect of AuNPs on diabetic animal models and diabetic complications.

Different search engines including PubMed, SpringerLink, ISI Web of Science, and Scopus databases were used to identify *in vitro,* and *in vivo* peer-reviewed original research articles published in the last 10 years. The identified research articles investigated the therapeutic effects caused by AuNPs exposure in cell lines and laboratory animals. We carried out the search for the terms ‘‘gold nanoparticles’’ and linked it with different terms related to the pathogenesis determinants of diabetes and its complications such as “hyperglycemia”, “oxidative stress”, “TGF-β”, “angiogenic effects (VEGF)”, “inflammatory effects”, ‘‘diabetic complications’’. A critical evaluation was made of the full texts of papers considered valuable for the aim of our review.

GOLD NANOPARTICLES

Nanoparticles (NPs) range in size from 1 to 100 nm. They have different chemical, physical, and biological representatives from their bulk counterparts (Zhao, Castranova, 2011). NPs are colloidal dispersions consisting of an inner core and an outer shell or a matrix structure that can encapsulate a drug, protein, imaging agent or combination of therapeutic and imaging agent in a single nanostructure (Brede, Labhasetwar, 2013).

NPs, which are 100 to 10,000 times smaller than human cells, offer unprecedented interactions with biomolecules on both the surface and inside of the cells (Ashraf *et al.*, 2016; Bodelón *et al.*, 2017). NPs have several advantages as therapeutic materials because they can pass through biological barriers and enhance the bioavailability of therapeutic agents. Inorganic NPs such as gold, silver, and silica nanospheres exhibit ‘self-therapeutic’ effects without surface modification. These therapeutic effects of NPs are governed by their physicochemical properties. Size, surface characteristics, and shape are major determinants of the actions of NPs in biological systems. Furthermore, tissue-specific microenvironments should be considered in the design of NP-based therapeutics (Jo *et al.*, 2015).

If NPs are used in biomedical applications, it is necessary to determine the possible biological interactions as well as cytotoxicity. Interactions of NPs and biological molecules could lead to unpredictable effects (Kim *et al.*, 2009). Toxicity of NPs result from the release of toxic ions, or their nonspecific interaction with the biological structures facilitated by NPs shape, in addition to the specific interactions of these NPs with biomacromolecules through their surface modifications (Khan *et al.*, 2007). Due to the properties of NPs, particularly the small size with a large surface area, they have recently become the focus of many studies especially in their applications in biomedical imaging and nanomedicine (Mateo *et al.*, 2015).

In its natural form, gold has been deemed as an inactive noble metal, with medicinal and therapeutic effects (Lopez-Chaves *et al.*, 2018). The main disadvantage of the ionic gold is that it can simply be neutralized by complexation and precipitation, therefore, limiting their expected purposes in living systems (Barathmanikanth *et al.*, 2010). Of the different inorganic NPs, nanogold (also called gold NP or colloidal gold) that has been actively investigated for its different biomedical applications. This is primarily due to its stability, straightforward and easy synthesis, low-cost preparation technique, size-controlled synthesis, biocompatibility, relatively easy surface modification, and low-toxicity profile (Khan *et al.*, 2007; Spivak *et al.*, 2013; Shah, Badwaik, Dakshinamurthy, 2014; Aziz *et al.*, 2017; Si *et al.*, 2017). The non-cytotoxicity, non-immunogenicity, and biocompatibility of many AuNPs make them a good prospect in several nanomedicine applications (Spivak *et al.*, 2013). Another great advantage of AuNPs over other NPs is that they show no cytotoxicity in human cells (Connor *et al.*, 2005). AuNPs with dimensions between 1 and 100 nm are being increasingly administered to animals and humans. They have shown great potential in various biomedical applications, including diagnostic imaging (Aziz *et al.*, 2017), cancer photothermal therapy, and drug delivery (Lim *et al.*, 2011).

AuNPs have a strong ability to bind to –SH- and –NH_2-containing molecules. Thus, biological molecules, particularly proteins, can serve as important substrates

in binding to AuNP through cysteine and lysine residues. The preferential binding of cysteine/lysine-rich proteins to AuNP may then alter their structure and biological functions, allowing AuNPs to be exploited as a therapeutic agent (Arvizo *et al*., 2013). Naked AuNPs (uncoated but still possessing a protective electrostatically-adsorbed layer of ions such as citrate) have been shown to have a higher rate of cellular uptake compared to conjugated ones. This is due to the adsorption of serum proteins unto their surface, while conjugation with materials such as polyethylene glycol can reduce cell surface interactions (Chen *et al*., 2013). The uncoated spherical AuNPs is the focus of this review.

It is worth noting that AuNPs are considered to be relatively biologically non-reactive and therefore suitable for *in vivo* applications (Lim *et al*., 2011). However, from the available studies, there are conflicting reports with no obvious conclusion regarding AuNPs toxicity or of their therapeutic effects. This seems to be due to physicochemical properties (i.e. surface chemistry, shape, and size), method of synthesis, and concentration and time of exposure that may potentially affect the interaction of AuNPs with biological systems (either cellular growth media or cellular components of living organisms or cells) (Siddiqi *et al*., 2012). These ultimately influence their toxicity, cellular uptake, and change its functional surface charge and accumulation state, pharmacokinetics, biodistribution, drug delivery efficiency, and biological effects (Alkilany, Murphy, 2010; Xia, Li, Xiao, 2016). However, the main determining factors for the toxicity or therapeutic effects of AuNPs in the biological systems are their physicochemical properties. Specifically, the size, shape and surface charge as well as other factors such as dose and dosing time. All these properties and factors are modifiable, resulting in a varied range of AuNPs with specific features and performance (Campos *et al*., 2017). Direct targeting to the organs is another promising strategy to improve AuNPs therapeutic index for the treatment of different diseases (Williams *et al*., 2018). This allows scientists to find the suitable characteristics of AuNPs according to their goal to target diseases and organs.

Therapeutic effects of AuNPs on different diseases including diabetes and its complications

One incontrovertible fact confirmed in different studies is that the factor most responsible for nanomaterials toxicity is the creation of ROS which lead to oxidative stress (Mateo *et al*., 2015). However, AuNPs were found to act as an antioxidant agent by preventing the release of ROS, scavenging free radicals and raising the level of antioxidant enzymes (Khan *et al*., 2012; Bednarski *et al*., 2015). Different *in vivo* studies reveal that AuNPs have anti-oxidative and anti-*hyperglycemic* activities as shown in table I. According to Opris *et al*., the 21 nm nanogold increases the antioxidant capacity in the blood as well as in liver and muscle, and decreases blood glucose level and reduces inflammation and oxidative stress induced by *hyperglycemia* (Opris *et al*., 2017).

BarathManiKanth *et al*. investigated a biologically synthesized AuNPs on streptozotocin induced diabetic mice, and proved that the 50 nm AuNPs, formed by the reduction of $AuCl_4$ - ions by *Bacillus licheniformis,* have anti oxidative effects that inhibit the formation of ROS and scavenge free radicals. They found that AuNPs improved antioxidant defense enzymes and also have anti-*hyperglycemic* activities, causing the regeneration of pancreatic β cells and reducing blood glucose level (Barathmanikanth *et al*., 2010). These results are the same as Karthick *et al*. and Daisy and Saipriya, who found that AuNPs are promising in the treatment of hyperglycaemia (Daisy, Saipriya, 2012; Karthick *et al*., 2014). Venkatachalam *et al*. (2013) found that blood glucose level, cholesterol and triglyceride significantly reduced after diabetic rats were treated with AuNPs (12–41 nm in size) synthesized using propanoic acid (PAT) isolated from *Cassia auriculate* plant. Edrees, Elbehiry, Elmosaad (2017) found that 10 nm AuNPs have improved blood glucose level, liver enzymes and proinflammatory cytokines, as well as reducing blood urea nitrogen and creatinine levels indicating the curative effect of AuNPs on renal function.

The effects of AuNPs on different diabetic complications have been studied recently. Selim, Abd-Elhakim, Al-Ayadhi, (2015) examined the therapeutic effects of AuNPs on Autistic diabetic rats, and found that 50 nm AuNPs, 2.5 mg/kg, significantly reversed almost all liver redox parameters including glutathione (GSH) and oxidized glutathione (GssG) levels, activities of superoxide dismutase (SOD) and glutathione peroxidase (GPx), as well as oxygen radical absorbance capacity. In addition, there was enhanced glucose and lipid profile levels and apparent reversibility of damage in pancreatic B cells (regenerative capacity) (Selim, Abd-Elhakim, Al-Ayadhi, 2015).

TABLE I – Therapeutic effects of Gold nanoparticles on diabetic animal models

Size nm	Shape/coating	Dose	administration rout & Exposure time	Target tissue/ diabetic animal model	Animal model/ sample size	Assay methods	findings	reference
50	Spherical/ formed by the reduction of $AuCl_4$ - ions by *Bacillus licheniformis*	2.5 mg/kg	IP /15 days	Liver, kidney, spleen, lung. STZ induced diabetic model	Mice 24 mice / 4 groups n=6	-toxicity studies: -hematological and -histological -analysis, NPs -biodistribution.	- Nontoxic, protective effect of AuNPs on liver and pancreas with regeneration of β cells. - normal kidney, liver and lung. - creatinine level is normal in treated diabetic mice. -AuNPs have anti-oxidative and anti-hyperglycemic activities.	(Barathmanikanth et al., 2010)
55.2to 98.4	Reduction of gold ions by C. fistula stem bark with different morphology	60 mg/kg	via gastric intubation for 30 days	Blood parameters, liver and kidney. STZ induced diabetic model	35 male albino Wistar rats/7 groups	-Biochemical analysis of blood parameters, liver and kidney functions	- Serum urea, creatinine and uric acid levels steadily returned to near normal. Reduce serum glucose and Glycosylated hemoglobin. - promising in the treatment of *hyperglycemia*.	(Daisy, Saipriya, 2012)
50	spherical-shaped synthesized using *Gymnema sylvestre* plant	0.5 mg/kg	orally using gavage for 28 days.	Pancreas alloxan-induced diabetic rats	30 male Wistar albino rats/5 groups n=6	-Biochemical analysis for blood glucose serum levels of TNF- α, IL-6 and high-sensitive CRP. -histopathological analysis.	- reduction in blood glucose level. - AuNPs have anti-inflammatory effects.	(Karthick *et al*., 2014)
12 to 41	Spherical/ synthesized using *Cassia auriculate* plant	0.5 mg/kg	fed with AuNPs for 28 days.	blood parameters. alloxan-induced diabetic rats	36 male albino rats/ 6 groups	- Estimation of Serum glucose, total cholesterol, triglyceride and Insulin.	-Blood glucose level, cholesterol and triglyceride significantly Reduced. - body weight and plasma insulin increased significantly. (antidiabetic activity).	(Venkatachalam *et al.*, 2013)
10	Not reported	of 2.5 mg/kg	intraperitoneal injection for7 days	blood parameters. STZ induced diabetic model	30 male albino rats/ 3 groups n=10	Analysis of serum glucose, insulin, liver enzymes, creatinine, BUN and proinflammatory cytokines in Streptozotocin (STZ) induced diabetic rats.	- improved blood glucose level, liver enzymes& proinflammatory cytokines. - control of *hyperglycemia*, reduction of blood urea nitrogen and creatinine levels indicating the curative effect of AuNPs on renal function.	(Edrees, Elbehiry, Elmosaad, 2017)

(continuing)

TABLE I – Therapeutic effects of Gold nanoparticles on diabetic animal models

Size nm	Shape/coating	Dose	administration rout & Exposure time	Target tissue/ diabetic animal model	Animal model/ sample size	Assay methods	findings	reference
21	Spherical/ functionalized with *Sambucus nigra*. Aqueous fruit extract	0.3 mg/kg	orally, for 2 weeks	blood, liver and muscle in STZ induced diabetic model	18 Wistar male rats (n = 6)	Blood parameter measurement. western blot analysis Histology and immunohistochemistry evaluations	- No morphological abnormalities in liver except the increase no. of Kupffer cells, - increase the antioxidant capacity in the blood and tissue. - decreases blood glucose level and reduce inflammation and oxidative stress induced by *hyperglycemia*.	(Opris *et al.*, 2017)
50	Spherical/ sodium citrate	2.5 mg/kg	I.P for 7 days	liver and pancreas Autistic diabetic rats. STZ induced diabetic model	Male Wistar albino rats pup/27 per group	-Oxygen radical absorbance capacity (ORAC) assay. -biochemical assay - ultrastructural study	- improve oxidative stress markers, plasma antioxidant capacity, lipid profile, reversibility of the pancreatic B cells. - 50nm nontoxic and produced no systemic or local adverse effect at the given dose.	(Selim, Abd-Elhakim, Al-Ayadhi, 2015)
3 to 5	AuNP prepared from gold bulk without any surface modifiers or stabilizers.	0.07 mg/g AuNP	-ointment applied directly to the wound site once daily 3, 5, 7 days - 24 hr for cell culture.	Diabetic wound healing (skin). STZ induced diabetic model	135 Male BALB/c mice/6 per group -Human foreskin fibroblasts.	-Real-time PCR -Western blot analysis -Diabetic full-thickness wounds and wound measurement -histological study.	- AuNP may serve as an adjuvant to increase the skin absorption and the functional ability of anti-oxidants.	(Chen *et al.*, 2012)
13	Spherical/ chemical reduction method	0.25 mg/kg	Ip, for 21 days	Diabetic nephropathy. STZ induced diabetic model	60 male adult albino rats (n=10).	-Histopathological study for Kidney and Pancreases. -Analysis of serum glucose, insulin, creatinine, BUN. -ELISA	- significant decrease in serum and urinary urea, creatinine and uric acid level -significant regression in TGF-β, transferring and cystatine C. -AuNPs ameliorate diabetic nephropathy through anti-fibrotic and anti-diabetic effect.	(Hamza, Bashuaib, 2018)

The effect of AuNPs combined with anti-oxidants also has shown a notable acceleration in diabetic wound healing. A study by Chen *et al.* (2012) reported the effect of 3-5 nm AuNPs prepared without any surface modifiers or stabilizers. They suggest that combination of AuNP with epigallocatechin gallate (EGCG), and a-lipoic acid (ALA) significantly accelerated diabetic cutaneous wound healing through angiogenesis regulation and anti-inflammatory effects. AuNP may also serve as an adjuvant to increase the skin absorption and the functional ability of anti-oxidants.

Another *in vivo* and *in vitro* study by Kim *et al.* shows the effect of the 20 nm AuNPs on the retina of C57BL/6 mice pups, and human retina microvascular endothelial cells. It has been found that AuNPs could inhibit retinal neovascularization via suppression of VEGFR-2 signaling pathway. The researchers conclude that AuNPs could be safely applied to retina without retinal toxicity (Kim *et al*., 2011). Shen *et al.* (2018) suggested that the possible mechanism for AuNPs to improve retinopathy in an oxygen induced retinopathy model might be that AuNPs were able to encourage autophagy. Muller *et al.* (2017) found that the 20 nm AuNPs treatment was able to prevent cognitive damage, oxidative stress and neuroinflammation in a sporadic Alzheimer's disease rat model. Spivak *et al.* (2013), in a study of doxorubicin-induced heart failure in rat model, found that 30 nm AuNPs was biosafe (in cytotoxicity, genotoxicity, and immunoreactivity), and have significant cardioprotective effects in heart failure.

The effect of AuNPs was notable in the recovery and amelioration in many other different diseases such as in pleurisy (acute inflammation model induced by carrageenan) (Paula *et al*., 2015), systemic metabolism disorder (Xu, Wang, Yang, 2017), inflammatory disorders (Sumbayev *et al*., 2013), pancreatic ductal Adenocarcinoma (Saha *et al*., 2016), and Ovarian tumour growth and metastasis (Arvizo *et al*., 2013).

Therapeutic effect of AuNPS on the pathogenesis determinant of diabetic complications

Diabetic complications represents a major cause of morbidity and mortality in diabetic patients (Sheetz, King, 2002). Continued exposure to hyperglycaemia is documented as the primary factor in the pathogenesis of diabetic complications (Aronson, 2008). hyperglycemia is considered as the key motivator for diabetic retinopathy, nephropathy, and neuropathy, and also shares in the progress of diabetic cardiovascular diseases (King, 2008). The effects of hyperglycaemia are often irreversible and lead to progressive cell dysfunction, as in diabetic nephropathy and neuropathy. Therefore, it is extremely important to identify novel interventions to halt the progression of diabetic complications (Chow *et al*., 2004; Zent, Pozzi, 2007).

Oxidative stress has been suggested to be a common pathway linking diverse mechanisms for the pathogenesis of diabetes complications (Rahimi *et al*., 2005). Oxidative stress result from the excessive production of ROS in multiple cell types, including mesangial cells and podocytes in diabetic nephropathy (Kanwar *et al*., 2008), or glial cells in neuropathy (Gonçalves, Vægter, Pallesen, 2018), pericytes and endothelial cells in diabetic retinopathy. Oxidative stress to cavernous tissue is considered as an important contributing factor to erectile dysfunction in diabetics, and also plays a crucial role in atherogenesis in cardiovascular disease (Rahimi *et al*., 2005). ROS in turn can up-regulate the expression of profibrotic molecules such as transforming growth factor-β (TGF-β), thus increasing the glomerular extracellular matrix (ECM) deposition. Hyperglycaemia also increases the production of advanced glycation end-products (AGEs) of ECM components in the mesangium and glomerular basement membrane (GBM), resulting in changes in permeability of the filtration barrier (Kanwar *et al*., 2008). Diabetic-induced microvasculature injury by up-regulating the expression of vascular endothelial growth factor (VEGF) also plays a key role in the pathogenesis of diabetic microvascular diseases. The increased density of blood capillaries, resulting from neovascularization, is accompanied by increased vessel leakage (Zent, Pozzi, 2007). Different studies reveal that AuNPs have inhibitory effects on TGF-β, VEGF, as well as antiglycation, anti-hyperglycemic, anti-inflammatory, and antioxidant effects as shown in table II.

Anti-hyperglycemic, Antioxidant effect of AuNPs

The anti-hyperglycemic, antioxidant effects of AuNPs were notable in the recovery and amelioration of different diseases such as in diabetes models (Opris *et al*., 2017), Alzheimer's disease (Muller *et al*., 2017), wound healing (Chen *et al*., 2012), autistic diabetic model (Selim, Abd-Elhakim, Al-Ayadhi, 2015), diabetic nephropathy (Hamza, Bashuaib, 2018), and in pleurisy (acute inflammation model induced by carrageenan)

TABLE II – Therapeutic effects of Gold nanoparticles on different disorders

Size nm	Shape/coating	Dose	administration rout & Exposure time	Target tissue/ or disease	Animal model/ sample size	Assay methods	findings	reference
50	AuNPs Synthesis using *Bacillus licheniformis*	100–1,000 nM	24 hr	retinal endothelial cells	Bovine retinal endothelial cells (BRECs)	-Cell proliferation assay (MTT), -Cell migration assay, -Tube formation assay, -Transwell monolayer -permeability assay, -Plasmid constructs -transient transfection assay. -Western blot analysis.	- 500 nM suppressed proliferation, migration and tube formation. - increase in cytotoxicity of AuNPs in a dose-dependent manner. - high concentrations greater than 500 nM of AuNPs caused significant cell death. - dose from 0 to 500 nM did not induce any cytotoxic effects.	(Kalishwaralal *et al*., 2011)
20	commercial	1 & 5 µM/1 mL phosphate-buffered saline.	intravitreal injection once on the day 14 postnatal	retinopathy of prematurity.	-C57BL/6 mice (5-7 pups)/group -Human retina microvascular endothelial cells.	-Histological analysis -Cell proliferation assay (MTT) -Wound migration assay -Tube formation assay -Western blotting -Cell viability assay (MTT) assay -(TUNEL) assay.	- AuNP inhibit retinal neovascularization. - AuNP could be safely applied to retina without retinal toxicity.	(Kim *et al*., 2011)
20	Spherical/ sodium citrate a reducing agent and stabilizer	2.5 mg/kg.	IP, every 48 h until 21 days	Alzheimer's disease (brain)	Wistar male rats (n= 30 per group	- analyse Oxidative, mitochondrial parameters and neuroinflammatory parameters -western blot -Parameters of oxidative stress analysis -object recognition task.	- AuNPs prevent cognitive damage, oxidative stress and neuroinflammation.	(Muller *et al*., 2017)
30	spherical AuNPs, AuNPs-Simdax conjugate,	12.7 µg/mL by metal in cell line - 0.06 mL per animal.	intrapleural and intravenous -observed until natural death.	heart failure rat model.	Wistar rats (n = 54)/7group. U937 (human leukemic monocyte lymphoma) cell line.	- comet assay - light optical microscopy studies, - laser correlation spectroscopy, - scanning electron microscopy. - sonoporation cardioprotective efficacy.	- AuNPs are biosafety, -Intrapleural (local) delivery is favored over intravenous delivery. - AuNPs-Simdax and AuNPs have similar significant cardioprotective effects.	(Spivak *et al*., 2013)
20	Spherical/ sodium Citrate	10, 25, or 50 mg/kg	administered into the pleural cavity, four hours later, the rats were sacrificed	Pleurisy (acute inflammation model induced by carrageenan)	Adult male Wistar rats nine groups (n=5 animals per group).	-ELISA for Inflammatory parameters and oxidative damage parameters -Protein determination.	- AuNP exhibited antioxidant and anti-inflammatory actions.	(Paula *et al*., 2015)

(continuing)

TABLE II – Therapeutic effects of Gold nanoparticles on different disorders

Size nm	Shape/coating	Dose	administration rout & Exposure time	Target tissue/ or disease	Animal model/ sample size	Assay methods	findings	reference
5, 15, 20, and 35	citrate-stabilized	100 nmol Au/kg	IP, after 4 h animals were euthanized	Interleukin 1beta. dependent inflammatory disorders, such as rheumatoid arthritis and psoriasis	-THP-1 human myeloid leukaemia cells. -Primary human basophils -C57BL/6 male mice	-Western Blot Analysis -PI3K Activity Assay -In-Cell Analysis of Cell-Bound IL-1β -Cytokine Analysis -Analysis of Histamine Release	- AuNPs clearly displayed anti-inflammatory properties on THP-1 cells. - 5 nm AuNPs completely blocked the inflammatory process. - 20and 15 nm AuNPs were less effective, 35 nm AuNP did not display a statistically significant effect. - *In vivo*: down-regulatory effects of AuNPs on IL-1β.	(Sumbayev *et al*., 2013)
20	spherical/ Citrate stabilized	*In vitro*: 5, 25, 50 µg/mL AuNP *In vivo*: 100 µg of AuNP in 100 µL volume	various doses of AuNP for 48 h. *In vivo*: IP for 21 days.	pancreatic ductal adenocarcinoma.	pancreatic cancer cells and the pancreatic stellate cells. *in vivo*: 48 Female athymic nude mice/ 8 per group.	-Immunoblotting -Real-time PCR (qRT-PCR). -Cell viability assay for conditioned media treatment. -Antibody Arrays. -Transmission Electron Microscopy. -Immunocyto and histochemistry	- AuNPs inhibit proliferation and migration of PCCs and PSCs. - *In vivo* AuNP treatment significantly reduced tumour Growth.	(Saha *et al*., 2016)
5, 20, 50, or 100	AuNPs synthesized by the citrate reduction method	100 µg 200 µg 400 µg	After 3 wk of 3 d/wk of i.p. injection of AuNPs	Ovarian tumor growth and metastasis	-ovarian cancer cell lines-A2780, and SKOV3-ip cells -normal ovarian surface epithelial. *in vivo*: athymic nude female mice, (n = 5)	-quantitative RT-PCR -Confocal -immunofluorescence studies -Western blot analyses. -Cell Proliferation Assay. - Transmission Electron Microscopy. -Cellular Apoptosis Assay. -Human Angiogenic Cytokine Array.	- AuNPs inhibit the proliferation of cancer cells in a size- and concentration-dependent manner, with 200 µg or 400 µg of 20 nm showing the greatest efficacy. - AuNPs reverse epithelial mesenchymal transition in cancer cells. - histological analysis of the organs did not reveal any sign of inflammation or toxicity in AuNP-treated groups - 200 µg/mouse demonstrated the highest therapeutic efficacy to inhibit tumour.	(Arvizo *et al*., 2013)

(continuing)

TABLE II – Therapeutic effects of Gold nanoparticles on different disorders

Size nm	Shape/coating	Dose	administration rout & Exposure time	Target tissue/ or disease	Animal model/ sample size	Assay methods	findings	reference
21	spherical citrate	single dose of AuNPs (7.85 mg AuNPs/g)	IP, Tissues collected at 1 h, 24 h and 72 h post-injection.	Brain, heart, spleen, liver, kidney, abdominal fat tissue.	Male C57BL/6 mice.	-Electron microscopy. - real-time PCR.	- A reduction in TNFα and IL-6 mRNA levels in the fat were observed from 1 h to 72 h post AuNP injection, with no observable changes in macrophage number. - no detectable toxicity to vital organs (liver and kidney).	(Chen *et al.*, 2013).

(Paula *et al.*, 2015). AuNPs elicited important actions against oxidative damage in biomolecules, including the addition of free SH groups associated with the decreased profile of antioxidant enzymes (Paula *et al.*, 2015). Oxidative stress has been considered to be a pathogenic factor of diabetic complications including nephropathy, neuropathy, retinopathy, cardiovascular disease, and erectile dysfunction (Rahimi *et al.*, 2005). Recent studies have revealed that antioxidants capable of neutralizing ROS are effective in preventing experimentally induced diabetes as well as reducing the severity of diabetic complications (Kumar *et al.*, 2014). Based on the antioxidant, anti-hyperglycemic actions of AuNPs (as described in therapeutic effect section), we anticipated that AuNPs might be effective in amelioration diabetic complications.

Anti-inflammatory effect of AuNPs

Inflammatory processes are inculpated in the upgrade of diabetes and the development of its complications (King 2008). Recent studies have shown that kidney inflammation is crucial in promoting the development and progression of diabetic nephropathy (Donate-Correa *et al.*, 2015). Several inflammatory cytokines have emerged as being closely involved in the pathogenesis of diabetic retinopathy (Tang, Kern, 2011) and diabetic neuropathy (Doupis *et al.*, 2009). Furthermore, some of the major inflammatory cytokines, which are believed to play an important role in diabetic complications are tumor necrosis factor- α (TNF-*α*), interleukin-1 (IL-1), and IL-6. TNF-*α* promotes the production of ROS, induces cell injury, and increases endothelial permeability. IL-1 stimulates expression of cell adhesion molecules and profibrotic growth factors and increases endothelial permeability. In diabetic nephropathy, IL-6 promotes mesangial proliferation, glomerular hypertrophy, fibronectin production and increases endothelial permeability (Lim, Tesch, 2012; Donate-Correa *et al.*, 2015).

Although *in vitro* studies have demonstrated both inflammatory and anti-inflammatory effects of AuNPs (Almeida *et al.*, 2011), AuNPs have also received a great deal of attention as anti-inflammatory agents *in vivo* because of their capability to prohibit IL-6 and TNF-α (Chen *et al.*, 2013). After treatment with 50 nm AuNPs, the serum levels of TNF-α and IL-6 were significantly brought down to normal levels as compared to that of the diabetic group and standard drug (Glibenclamide), indicating the effect of AuNPs on suppressing the inflammation (Karthick *et al.*, 2014). Paula *et al.* (2015) observed that acute administration of 20 nm AuNP exhibited pronounced anti-inflammatory actions, as characterized by the inhibition of IL-1b and TNF-α and an increase in levels of IL-10 (a cytokine with anti-inflammatory profile) in the pleural exudate of an acute model of inflammation caused by intrapleural administration of carrageenan. AuNPs treatment was also able to prevent cognitive damage, oxidative stress and neuroinflammation in a sporadic Alzheimer's disease rat model (Muller *et al.*, 2017).

Sumbayev *et al.* (2013) suggest that the size of NPs is a critical parameter in the mechanism by which AuNP inhibits IL-1β dependent inflammation, with small AuNPs < 10 nm displaying unique advantages over larger NPs in

terms of their ability to interact with cells. They suggest that in the mechanism of inhibition of inflammatory processes of AuNPs that the IL-1β molecules aggregate around AuNPs; these aggregates therefore reduce the number of available IL-1β molecules that can interact with the interleukin cellular receptor, thus significantly inhibiting the biological activities of IL-1β.

Antiangiogenic properties of AuNPs

Vascular endothelial growth factor (VEGF) is the most potent angiogenic factor and its up-regulation is often observed in pathologic conditions, including cancer, wound healing, rheumatoid arthritis, diabetes and chronic inflammation (Bhattacharya *et al*., 2004; Zent, Pozzi, 2007). Increase VEGF expression has been implicated in the pathophysiology of diabetic retinopathy (Pereira *et al*., 2017) and diabetic nephropathy (Nakagawa *et al*., 2009), while the reduction of VEGF expression was demonstrated in diabetic neuropathy (Quattrini *et al*., 2008). Upregulated VEGF synthesis is accompanied by increased endothelial cell migration, proliferation and formation of immature vessels which characterized by leakiness and decreased vascular resistance (Zent, Pozzi, 2007). There is an awareness for aiming angiogenic route to prevent diabetic nephropathy, and various studies have now obstructed VEGF-A activity as a therapy to prohibit the irregular angiogenesis (Nakagawa *et al*., 2009). AuNPs may find wide applications as therapeutic agents in angiogenesis dependent disorders. Kalishwaralal *et al.,* (2011) found that 50 nm AuNPs (500 nM) inhibit VEGF induced angiogenesis significantly in Bovine retinal endothelial cells (BRECs) in the presence of VEGF. The mechanism of action indicates that AuNPs can block VEGF signaling pathways, which may take part in blocking VEGF-induced retinal neovascularization by the inhibition of the proliferation, migration and tube formation.

Bhattacharya *et al.* (2004) examined 5nm AuNPs effect on VEGF165-induced human umbilical vascular endothelial cells (HUVECs) proliferation. Results indicate that AuNPs selectively prevent VEGF165-induced proliferation of HUVEC cells. These NPs directly bind heparin-binding growth factor VEGF165 through sulphur/amines present in the amino acids of the heparin-binding domain and inhibit VEGF165-induced signalling.

Arvizo *et al.* (2011) also demonstrate that AuNPs inhibit the VEGF signalling cascade *in vitro* using HUVECs and NIH3T3 fibroblast cells and confirmed that the naked gold surface as well as the size of the NPs are important and essential to inhibit the function of VEGF165. They studied different sizes (5 nm, 10 nm, and 20 nm), and found the 20 nm AuNP is the most powerful of all 3 sizes tested in inhibiting the function of VEGF165. They suggest that the inhibitory effect of AuNPs is due to the direct binding with VEGF165, probably leading to the conformational changes in the protein structure and emphasize the role of the naked AuNPs surface in its inhibitory effect.

Taken together, because nanogold has antiangiogenic effects, it may find beneficial applications as therapeutic agents in angiogenesis dependent disorders such in diabetic nephropathy and retinopathy.

Inhibitory Effect of AuNPs on TGF- β

The TGF-β overexpression is implicated in the pathogenesis of experimental and human diabetic nephropathy (Border, Noble, 1998) and diabetic neuropathy (Figueroa-Romero, Sadidi, Feldman, 2008). Many features of the diabetic state stimulate renal TGF-β activity. Hyperglycaemia and increased nonenzymatic glycation end products are found to increase the expression of TGF-β *in vivo* and *in vitro* (Chen, Jim, Ziyadeh, 2003). TGF-β inhibits the cell cycle in most types of cells, leading to hypertrophy. TGF-β mRNA levels were found to be elevated early in diabetic nephropathy. This suggests that repression of TGF-β should be a therapeutic target in order to achieve a greater anti-fibrotic effect (Border, Noble, 1998).

Arvizo *et al.* (2013) demonstrated that AuNPs inhibited ovarian tumour growth and metastasis by inhibiting (Heparin-binding growth factors) HB-GFs like TGF-β, in a dose-dependent manner. They also demonstrated that 20 nm AuNPs do not affect the proliferation of normal cells like ovarian surface epithelial cells nor do they show systemic toxicity after multiple injections over a period of 3−4 weeks. Saha *et al.* (2016) used the 20 nm AuNPs 25 μg to disrupt cellular communications between pancreatic stellate cells (PSCs) and pancreatic cancer cells (PCCs) to improve therapeutic efficacy of pancreatic ductal adenocarcinoma. They found that AuNPs effectively disrupt multiple signalling pathways that are involved in the perpetual activation of PSCs and the PCC−PSC crosstalk. They found that AuNPs significantly decreased the expression of fibronectin, TGF-β, and inhibit matrix deposition.

In a dose dependent manner, AuNPs was also found to reduce the hepatocellular carcinoma weight and volume as a result of reducing serum TGF-β concentration (Zhao *et al*., 2016).

Anti-Glycation Effect of AuNPs

AGEs are complex groups of macromolecules that are formed via irreversible non-enzymatic reaction between reducing sugars and free amino groups of proteins, lipids, and nucleic acids (Kanwar *et al*., 2008). Glycation process leads to damage or alter the physiological and the structural properties of several important tissue proteins. ECM proteins in kidney like collagen, laminin, elastin, and plasma proteins including hemoglobin and albumin are all prone to nonenzymatic glycation, which will reduce their susceptibility to catabolism (Singha *et al*., 2009; Kim *et al*., 2012; Kumar Pasupulati, Chitra, Reddy, 2016). Glycation leads to numerous chronic diabetic complications including renal failure, atherosclerosis, cataract formation (Liu *et al*., 2014), and neuropathy (Figueroa-Romero, Sadidi, Feldman, 2008). Many studies have reported that AuNPs can act as an antiglycation agent reducing the formation of AGEs (Liu *et al*., 2014). The activity of AuNPs against glycation may come from its competitively binding to the free amino groups of Lysine and Arginine which are potent sites for glycation. It has been observed that the glycation will decrease upon masking of the free amino groups such as those residing on the lysine. Singha *et al.* (2009) studied the anti-glycating activity of AuNPs on eye protein α-crystallin, suggesting its possible utility to inhibit cataract formation. Kim *et al.* (2012) also investigated the inhibitory effect of the 20 nm AuNPs of the glycation of collagen, a major protein component of the human dermis.

Liu *et al*. (2014) studied the inhibitory effect of citrate coated spherical AuNPs (ranging from 2 nm to 20 nm) on the glycation of bovine serum albumin (BSA's) by D-ribose. Their results demonstrate that the addition of AuNPs to BSA and D-ribose reduced the formation of AGEs and the degree of inhibition correlated with the total surface area of the NPs. AuNPs of highest total surface area yielded the most inhibition. The antiglycation effect of AuNPs in human serum albumin (HSA) was also studied by Seneviratne *et al.* (2012) and it was found that AuNPs of 2 nm in size can reduce the rate of glycation of HSA by glyceraldehyde, and that was in a concentration-independent manner in which AuNPs can change the secondary structure of HAS. Findings of these studies further support the view of the anti-glycation properties AuNPs and may offer useful link with therapeutic applications in reducing AGE related disease conditions.

In view of these properties that suggested the combination of lower toxicity of AuNP with its inhibitory effects on TGF-β, its anti-glycation effects, anti-angiogenic effects as well as anti-*hyperglycemic* effects, anti-inflammatory effects, and anti-oxidant effects, we hypothesized that AuNPs treatment can effectively be used to affect these pathogenesis determinants in an animal model of diabetic diseases.

CONCLUSION

It must be borne in mind that AuNPs must be thoroughly characterized before their application to avoid its potential toxicity and to guarantee its safe applications. We suggest that AuNPs could be potentially effective to treat diabetes and microvascular complications of diabetes. That was based on its ability to inhibit and effectively disrupt multiple pathophysiological determinants (disease-causing proteins) that are inculpated in the progression of diabetic complications. However, more organized studies concerning the safe effective size and effective dose are required, and it is believed that AuNPs will be efficient in treating diabetic complications.

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CONFLICT OF INTEREST

The authors state they have no conflict of interest.

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