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Review Article

Applications Of Gold Nanoparticles In Treating Diabetes And Complications Emerging From It: A Review

Sachin J. Kamble*[1], Valmiki B. Koli[2]

[1]*Department of Chemistry, Sanjay Ghodawat Institute, Atigre, Maharashtra, India 416118*
[2]*School of Nanoscience and Biotechnology, Shivaji University, Kolhapur (MS) India 416004*

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ABSTRACT

For patients with diabetes, diabetes-related complications are a primary cause of morbidity and death. This has become a major contributor for many deaths now days. The purpose of this review is to determine whether gold nanoparticles have the ability to treat diabetes and its side effects. Here, we provide a summary of the research on gold nanoparticles' potential for self-treatment. This review's primary objective is to highlight and provide an overview of some of the previous research in relation to many factors including the size of the gold nanoparticles, the dose quantity and its mode of administration, the experimental analysis & its findings. The second objective is to explain how gold nanoparticles work as a self-therapeutic against the complications of diabetes. It has been shown by several studies that gold nanoparticles have anti-inflammatory, anti-glycation, anti-angiogenic, antioxidant, and anti-hyperglycaemic properties. This review sheds light on gold nanoparticles' possible uses, which could lower the prevalence of diabetes & associated complications.

INTRODUCTION

Diabetes has a substantial impact on health care costs, mortality rates, and other factors because it increases the risk of organ failure and dysfunction. It has a long-term complication which are due to the high and uncontrolled blood sugar level that is hyperglycaemia [1, 2]. The complications aroused out of diabetes include retinopathy, nephropathy and peripheral neuropathy. As per the sources of WHO (World Health Organization) and IDF (International Diabetes Federation) the total of 2.5% to 3% global population has diabetes. If it's not kept under control then in next decade this number may rise to 4% to 4.5% of global population [3]. The hyperglycaemia is responsible for the mitochondrial respiration which releases ROS (reactive oxygen species) into the cytoplasm which consequentially leads to oxidative stress causing the diabetic complications [4, 5]. Recently nanoscience and nanotechnology has been

***Corresponding Author:** Sachin J. Kamble
Address: *Department of Chemistry, Sanjay Ghodawat Institute, Atigre, Maharashtra, India 416118*
Email : sachin.kamble305@gmail.com

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developed tremendously which has synthesized different nanomaterials which has been employed in biomedical fields. Nanomaterials have a big demand in pharmacology for preparing nanomedicines which have found to be played a very important role in treating number of lethal diseases. Among all nanoparticles it is found that the gold nanoparticles attracted great attention due to its significant and effective anti-oxidative [6], anti-inflammatory [7], anti-proliferative [8], anti-angiogenic [9], anti-diabetic [10] activities. The remarkable anti-hyperglycaemic and anti-oxidant properties of gold nanoparticles were observed in amelioration and recovery of various diseases in diabetes model [6] including diabetic wound healing, diabetic nephropathy [11] and the autistic diabetes model [12]. The therapeutic effect of gold nanoparticles against diabetes and the complications emerges out of it have been discussed in this review. This review conveys the anti-hyperglycaemic, antioxidant, anti-inflammatory and antiangiogenic potential of gold nanoparticle. The original research publications (peer-reviewed) published in last ten years were found using a variety of search engines like PubMed, Springer Link, Scopus databases and Web of Science.

Gold Nanoparticles:

Nanoparticles are materials having at least one dimension and size ranging between 1 to 100 nm. They have dissimilar physical and chemical properties from its bulk. Nanoparticles are very much smaller than the human cell which offers extraordinary dealings on both the surface as well as inside of the cells [13, 14]. Due to their potential to overcome biological barriers and increase the bioavailability of therapeutic drugs, nanoparticles offer a number of benefits as therapeutic materials. Nanoparticles like gold and silver exhibits self-therapeutic effect without surface modification which is ruled by their physicochemical properties. The action of nanoparticles in any biological system is depending upon the various morphological characteristics like shape and size and surface charge. Cytotoxicity and potential biological interactions with nanoparticles must be determined before using them in biomedical applications. It is to be noted that the unpredictable outcomes could result from interactions between biological molecules and nanoparticles. The discharge of harmful ions or the non-specific interaction of nanoparticles with bio-structures is what causes them to be poisonous. Due to small size and bigger surface area, nanoparticles in recent times have become a focus of several studies especially in its applications in nanomedicine and biomedical imaging [15]. Gold has been considered an inert noble metal with therapeutic and medicinal properties in its native state [16]. The ionic gold can be neutralized by precipitation hence it has limitations for its application in living systems [4]. Gold nanoparticles have been investigated actively because of its high stability; can be synthesized easily with controlled size with simple surface modification and high biocompatibility and lower toxicity [17-21]. Gold nanoparticles have great potential for use in various nanomedicine applications due to their high biocompatibility and lack of cytotoxicity [18]. Gold nanoparticles can bind to molecules that contain -SH- and -NH2- strongly. Hence bio-molecules like proteins can function as a significant substrate in binding gold nanoparticles through cysteine & lysine residues. The favoured binding of cysteine-rich or/and lysine-rich proteins to gold nanoparticles takes place. This then may alter their structure and biological functions that allow gold nanoparticles to get exploited as therapeutic agent [22]. The interaction of gold nanoparticles with biological systems may potentially be affected by several factors like surface morphology, shape and size, method of synthesis, concentration and time of exposure. This in turn shows effect on their

toxicity, cellular uptake, pharmacokinetics, bio-distribution, drug delivery efficiency [23, 24]. The main toxicity determining factors are shape and size, surface charge, quantity of dose and doing time of gold nanoparticles. . All these determining factors can be modified which creates a wide range of gold nanoparticles with special features and performance [25]. Another effective tactic to raise gold nanoparticles therapeutic index for the management of various illnesses is direct targeting to the organs [26]. This enables researchers to identify the ideal properties of gold nanoparticles based on their intended target organs and disorders.

Gold nanoparticles: Its therapeutic effects on various diseases involving diabetes and its complications:

Different studies have confirmed an undeniable fact that the formation of ROS (Reactive Oxygen Species) in biological system is responsible for the oxidative stress within it. This makes the nanoparticles more toxic [15]. However, it was shown that gold nanoparticles functioned as an anti-oxidant agent by increasing the amount of anti-oxidant enzymes, scavenging free radicals, and inhibiting the generation of ROS [27, 28]. This anti-oxidant effect and anti-hyperglycaemic effect shown by gold nanoparticles is presented in Table I. For instance, gold nanoparticles with size 21 nm have found to be with increased anti-oxidant capability in the blood, liver and muscles. It is found to decrease the glucose level in blood and also reduces the inflammation and oxidative stress caused by hyperglycaemia [6]. Gold nanoparticles synthesized using Bacillus licheniformis by biological method with particle size 50 nm when implemented and investigated on streptozotocin induced diabetic mice, it has shown prominent anti-oxidative effect which inhibits the formation of ROS (Reactive Oxygen Species). Gold nanoparticles also improve the antioxidant enzyme in the cells along with anti-hyperglycaemic effect which causes regeneration of pancreatic β cells & hence lowering the glucose level of blood [4]. Similar results were found from the studies performed by other group of investigators and researchers like Daisy and Saipriya and Karthick et al for effect of gold nanoparticles treating hyperglycaemia [29, 30]. Similar effects of gold nanoparticles with particle size 12-41 nm and 10 nm were observed by Venkatachalam et al. (2013) [31] and Edrees, Elbehiry, Elmosaad (2017) [32] respectively. Recent research has examined the impact of gold nanoparticles on several problems associated with diabetes. Selim, AbdElhakim, Al-Ayadhi showed gold nanoparticles with particle size 50 nm and 2.5 mg/kg dose on Autistic diabetic rats impressively reversed majority of liver redox parameters like oxidized glutathione (GssG) levels, glutathione (GSH) and glutathione peroxidase (GPx) [12].

Table I. Therapeutic effects of Gold nanoparticles on diabetic animal models

Size, Shape and Coating	Dose, administration Rout &Exposure time	Target tissue/ diabetic animal model	Animal model/ Sample Size	Assay methods	Findings	Reference
50 nm Spherical Formed by the reduction of	2.5 mg/kg IP /15 days	Liver, kidney, spleen, lung. STZ induced diabetic model	Mice 24 mice / 4	Toxicity studies: hematological and histological Analysis,	• Nontoxic, protective effect of AuNPs on liver and pancreas with	4

AuCl4 - ions by Bacillus licheniformis			groups n=6	NPs bio-distribution.	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.	
55.2 to 98.4 nm 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 per 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.	29
50 nm spherical-shaped Synthesize 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.	30
12-14 nm 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 per groups	• Estimation of Serum glucose, total cholesterol, triglyceride and Insulin.	• Blood glucose level, cholesterol and triglyceride significantly Reduced. • Body weight and plasma insulin	31

					increased significantly. (Antidiabetic activity).	
21 nm Spherical Functionalized with *Sambucus nigra*. Aqueous fruit extract	0.3 mg/kg orally for 2 weeks	Blood, liver and muscle 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*.	6
50 nm 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 • ultra structural 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.	12
3-5 nm	0.07 mg/g	Diabetic wound healing (skin).	135 Male BALB/c mice	-Real-time PCR • Western blot analysis	• Au_NP may serve as an adjuvant to increase the	33

Prepared from gold bulk without any surface modifiers or stabilizers.	Ointment applied directly to the wound site once daily 3, 5, 7 days - 24 hr for cell culture.	STZ induced diabetic model	6 per group • Human foreskin fibroblasts.	• Diabetic full-thickness wounds and wound measurement • histological study.	skin absorption and the functional ability of anti-oxidants.	
13 nm 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.	11

Notable acceleration of diabetic wound healing has also been shown when gold nanoparticles are coupled with other antioxidants. Gold nanoparticles synthesized without any surface modifier with particle size 3-5 nm in combination with EGCG (Epigallocatechin Gallate) and ALA (A-Lipoic Acid) have significantly increased cutaneous wound healing caused by diabetes by angiogenesis regulation and an anti-inflammatory effect [33]. Gold nanoparticles with size 20 nm when employed on the human retina microvascular endothelial cells and the retina of nanoparticles wit 30 nm particle size was found to be safe in genotoxicity, immune-reactivity and cytotoxicity when studied on doxorubicin-induced heart failure in rat model with excellent cardio-protective effects [18]. Gold nanoparticles are C57BL/6 mice pups, they inhibited retinal neovascularization through suppression of VEGFR-2 signalling pathways. It can be concluded from this study that gold nanoparticles can be safely applied to the retina [34, 35]. The possible mechanism behind improvement of retinopathy (oxygen induced retinopathy model) might be encouraged autophagy due to gold nanoparticles. The oxidative stress, neuro-inflammation and cognitive damage from sporadic Alzheimer's disease rat model can be prevented by gold nanoparticles of size 20 nm [36]. Gold notable candidates in recovery of number of different ailments like pleurisy [37], inflammatory disorders [38], metastasis [22] pancreatic ductal Adenocarcinoma [8], systemic metabolism disorder [39].

Gold nanoparticles: Its therapeutic effect on pathogenesis determinant of complications emerged out of diabetes:

One of the main causes of morbidity and death in patients with diabetes is diabetic complications [40]. The main cause of diabetes complications is prolonged exposure to hyperglycaemia [41]. This prolonged hyperglycaemia causes diabetic retinopathy, nephropathy, and neuropathy. It also becomes responsible for progressing diabetic cardio-vascular ailments [42]. The effects shown by hyperglycaemia are irreversible and take to progressive cell malfunction. Consequently, finding cutting-edge therapies to stop the advancement of diabetes problems is crucial [43, 44]. It has been proposed that oxidative stress serves as a common channel that connects many systems involved in the pathophysiology of problems related to diabetes [45]. Oxidative stress is caused by increased ROS production in a variety of cell types for example podocytes (diabetic nephropathy) or mesangial cells [46], glial cells (neuropathy) [47] and pericytes or endothelial cells (diabetic retinopathy). It is thought that oxidative stress to cavernous tissue has a significant role in atherogenesis in cardiovascular disease and is a major contributing factor to erectile dysfunction in diabetics [45]. The pathophysiology of diabetes micro-vascular disorders is significantly influenced by diabetic-induced micro-vasculature injury, which is caused by upregulating the production of vascular endothelial growth factor (VEGF). Neovascularization causes an increase in blood capillary density, which is correlated with an increase in vessel leakage [44]. Different studies revealing the inhibitory effects of gold nanoparticles against VEGF and other complications emerged from diabetes are shown in Table II.

Anti-hyperglycaemic and Antioxidant effect of gold nanoparticles:

The anti-hyperglycaemic and anti-oxidant potentials of gold nanoparticles were noteworthy in recovering diseases like Alzheimer's disease, wound healing, autistic diabetic model, and diabetic nephropathy and in pleurisy. Important action against oxidative damage in bio-molecules was promoted by gold nanoparticles including addition of free -SH group linked to a reduced profile of anti-oxidant enzymes [37]. Diabetes-related problems like cardiovascular disease, neuropathy, nephropathy, retinopathy and erectile dysfunction have linked to oxidative stress as a pathogenic component [45]. Recent research has shown that antioxidants with ROS neutralization ability can both prevent experimentally generated diabetes and lower the severity of diabetic consequences [48]. Given that gold nanoparticles have antioxidant and anti-hyperglycaemic properties, we expected that they could be useful in reducing the consequences of diabetes.

Table II. Therapeutic effects of Gold nanoparticles on pathogenesis determinant of complications emerged out of diabetes:

Size of NPs	Dose, administration rout & Exposure time	Target tissue/ or disease	Animal model/ sample size	Assay/methods	Findings	Reference
50	100-1000 nM 24hrs	Retinal endothelial cells	Bovine retinal endothelial cells (BRECs)	• Cell proliferation assay (MTT), • Cell migration assay,	• 500 nM suppressed proliferation, migration and tube formation. • Increase in cytotoxicity of	59

				• Tube formation assay, • Transwell monolayer • Permeability assay, • Plasmid constructs • Transient transfection assay. • Western blot analysis.	AuNPs in a dose dependent manner. • Concentrations greater than 500 nM of AuNPs caused significant cell death. • Dose from 0 to 500 nM did not induce any cytotoxic effects.	
20	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 inhibits retinal neovascularization. • AuNP could be safely applied to retina without retinal toxicity.	34
20	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 neuro-inflammatory parameters • Western blot • Parameters of oxidative stress analysis • Object recognition task.	• AuNPs prevent cognitive damage, oxidative stress and neuro-inflammation.	36
30	12.7 µg/mL by metal in cell line - 0.06 mL per animal. Intrapleural and intravenous - observed	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.	• AuNPs are biosafety; -Intrapleural (local) delivery is favoured over intravenous delivery. • AuNPs-Simdax and AuNPs have similar significant	18

	until natural death.			• Sonoporation cardio protective efficacy.	cardio protective effects.	
20	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.	37
5, 15, 20, 35	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*: downregulatory effects of AuNPs on IL-1β.	38
20	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 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.	8

5, 20, 50, 100	100 µg 200 µg 400 µg After 3 week of 3 d/week of i. p. injection of AuNPs	Ovarian tumour 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.	22
21	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).	54

Anti-inflammatory effect of gold nanoparticles: The progression of diabetes and the emergence of associated consequences are attributed to inflammatory mechanisms [42]. According to recent research, renal inflammation plays a critical role in fostering the onset and advancement of diabetic nephropathy [49]. Numerous inflammatory cytokines have been identified as having a key role in the diabetic retinopathy pathogenesis [50] and diabetic neuropathy [51]. Furthermore, tumour necrosis factor-α (TNF-α), interleukin-1 (IL-1) and IL-6 are some of the main inflammatory cytokines that are thought to be crucial in diabetic complications. TNF-α stimulates ROS generation, which causes cellular damage and raises endothelial permeability. IL-1 enhances endothelial permeability and promotes the development of pro-fibrotic growth factors and

cell adhesion molecules. IL-6 stimulates glomerular hypertrophy, mesangial proliferation, fibronectin synthesis and endothelial permeability in diabetic nephropathy [52, 49]. While in vitro research has shown that gold nanoparticles have both inflammatory & anti-inflammatory properties [53], since gold nanoparticles can prevent TNF-α and IL-6 from being produced, they have also drawn a lot of interest as in vivo anti-inflammatory drugs [54]. When compared to the diabetic group and standard medication (Glibenemclamide), the serum levels of TNF-α & IL-6 were considerably reduced to normal levels following treatment with 50 nm gold nanoparticles. It clearly indicates that gold nanoparticles have suppressing effect of the inflammation [30]. An acute administration of 20 nm gold nanoparticles displayed prominent anti-inflammatory action [37] in the pleural exudate of an acute model of inflammation caused by intra-pleural administration of carrageenan. In a rat model of sporadic Alzheimer disease, therapy with gold nanoparticles also prevented neuro-inflammation, oxidative stress, and cognitive impairment [36]. One important factor in the method by which gold nanoparticles suppresses IL-1β-dependent inflammation is NP size; gold nanoparticles smaller than 10 nm have a distinct advantage over bigger NPs in terms of their capacity to engage with cells [38]. They propose that IL-1β molecules aggregate around gold nanoparticles as part of the mechanism of inhibition of inflammatory processes; this reduces amount of IL-1β molecules available to interact with interleukin cellular receptor, thereby significantly inhibiting biological activities of IL-1β.

Anti-angiogenic properties of gold nanoparticles:

The most powerful angiogenic agent is vascular endothelial growth factor (VEGF), which is frequently up-regulated in pathologic situations such as diabetes, rheumatoid arthritis, cancer; wound healing & chronic inflammation [55, 44]. Reduction of VEGF expression was shown in diabetic neuropathy [56], however an increase in VEGF expression have been linked to the pathogenesis of diabetic retinopathy [57] and diabetic nephropathy [58]. Increased migration and proliferation of endothelial cells, as well as the creation of juvenile arteries characterized by leakiness and lower vascular resistance, are associated with upregulated VEGF synthesis [44]. The goal of the angiogenic route is known to be to prevent diabetic nephropathy; hence, a number of studies have demonstrated that blocking VEGF-A activity can prevent irregular angiogenesis [58]. Gold nanoparticles have a broad range of potential uses as therapeutic treatments for conditions dependent on angiogenesis. 50 nm gold nanoparticles strongly suppress the angiogenesis that VEGF induces in bovine retinal endothelial cells (BRECs) [59]. According to their method of action, gold nanoparticles can limit the proliferation, migration, and tube formation of VEGF signalling pathways, which may contribute to the prevention of VEGF-induced retinal neovascularization. The impact of 5 nm gold nanoparticles on the proliferation of human umbilical vascular endothelial cells (HUVECs) stimulated by VEGF165 was examined by Bhattacharya et al. (2004) [55]. These findings suggest that gold nanoparticles specifically stop HUVEC cell growth brought on by VEGF165. Through the presence of sulphur and amines in amino acids of heparin-binding domain, these nanoparticles directly bind the heparin-binding growth factor VEGF165, thereby inhibiting the signalling caused by this factor. Arvizo et al. (2011) [9] also demonstrate that using HUVECs and NIH3T3 fibroblast cells, gold nanoparticles block the VEGF signalling cascade in vitro. It has been established that both the size and the bare gold surface of the NPs are crucial for inhibiting the activity of VEGF165. After examining three

different sizes 5 nm, 10 nm, and 20 nm, they discovered that 20 nm gold nanoparticles is the most effective at blocking VEGF165 function out of the three. They emphasize the relevance of the bare gold nanoparticles surface in its inhibitory action and propose that the direct binding of gold nanoparticles with VEGF165 is responsible for the inhibitory impact, likely resulting in conformational changes in the protein structure. Considering all things, due to their antiangiogenic properties, gold nanoparticles may prove useful as therapeutic agents for conditions involving angiogenesis, such as diabetic retinopathy and nephropathy.

Anti-Glycation effect of gold nanoparticles:

An irreversible non-enzymatic interaction between reducing sugars and free amino groups of proteins, lipids, and nucleic acids forms AGEs, which are complex groupings of macromolecules [46].The process of glycation causes damage to or modifications to the structural and physiological characteristics of a number of significant tissue proteins. Non-enzymatic glycation can cause kidney ECM proteins like collagen, laminin, and elastin, as well as plasma proteins like albumin and haemoglobin, to become less susceptible to catabolism [60, 61]. Glycation leads to several chronic diabetic complications like renal failure, atherosclerosis, cataract formation [62] and neuropathy [63]. Numerous investigations have revealed that gold nanoparticles can function as an anti-glycation agent, preventing the production of advanced glycation end products [62]. Gold nanoparticles' ability to bind competitively to the free amino groups of arginine and lysine, two powerful glycation sites may be the source of their anti-glycation efficacy. It has been noted that when free amino groups, like those on lysine, are masked, the glycation would diminish. Singha et al. (2009) [60] investigated the anti-glycation effect of gold nanoparticles on the α-crystallin eye protein, indicating that they may be useful in preventing the development of cataracts. The study conducted by Kim et al. (2012) [64] also examined the potential of 20 nm gold nanoparticles to suppress glycation of collagen, a significant protein constituent of the human dermis. The study conducted by Liu et al. (2014) [62] investigated the potential of citrate-coated spherical gold nanoparticles with a size range of 2 to 20 nm to block the glycation of bovine serum albumin (BSA) by D-ribose. According to their findings, AGE production was inhibited when gold nanoparticles were added to BSA and D-ribose and degree of inhibition was connected with nanoparticles total surface area. The most inhibition was produced by gold nanoparticles with the largest total surface area. The anti-glycation effect of gold nanoparticles on human serum albumin (HSA) was also studied by Seneviratne et al. (2012) [65]. They observed that gold nanoparticles with 2 nm size can decrease the rate of glycation of HSA by glyceraldehyde. The results of these investigations provide more evidence for the anti-glycation characteristics of gold nanoparticles and may provide a valuable connection for therapeutic applications aimed at mitigating AGE-related medical disorders. Given these characteristics, which suggested that gold nanoparticles may have a combination of reduced toxicity, anti-inflammatory, anti-glycation, antiangiogenic, anti-hyperglycaemic and anti-oxidant effects, we postulated that treating animals with gold nanoparticles may successfully influence these pathogenesis determinants in diabetic disease models.

CONCLUSION

It is important to remember that in order to prevent potential toxicity and ensure safe uses, gold nanoparticles must be fully described prior to use. We propose that gold nanoparticles may be useful in the treatment of diabetes and its microvascular complications. This was due to its capacity to successfully inhibit and disrupt a variety of

pathophysiological determinants or disease-causing proteins, implicated in the development of problems associated with diabetes. It is thought that gold nanoparticles will be beneficial in treating diabetes problems, however further systematic research about the safe effective size and effective dose is needed.

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