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Green biosynthesis of berberine-mediated silver nanorods: Their protective and antidiabetic effects in streptozotocin-induced diabetic rats

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ABSTRACT

Poor control of blood glucose levels remains a serious challenge for diabetic patients. Silver nanoparticles were employed as antidiabetic agents due to their unique biological capabilities in growing insulin levels in diabetic animal models. In this study, a cost-effective and eco-friendly process for the production of silver nanorods (AgNRs) is described, and berberine extract has been successfully employed as a capping and reduction agent using an innovative method of green chemistry. UV–vis spectroscopy, field emission scanning electron microscopy (FESEM), and X-ray diffraction (XRD) studies were employed to characterize AgNRs. The objective of the current research was to treat or avoid hyperglycemia in rats caused by streptozotocin. Therefore, 25 male albino rats were split into five categories: Healthy control rats; diabetic rats untreated; diabetic rats treated with Glimepiride as a standard drug; diabetic rats treated with AgNRs; rats treated with AgNRs before being streptozotocin-induced diabetes. The diabetic group getting AgNRs exhibited significantly lower fasting blood glucose (FBG) readings than the diabetic control group ($p < 0.001$). The effects of AgNRs were also tested on serum lipid profile levels, which serve as an important biomarker in diabetes. Significantly, Ag NRs were found to improve lipid metabolism in the diabetic rats' group ($p < 0.001$). Additionally, pre-treatment with AgNRs was found to maintain normal blood glucose and lipid profile levels in rats receiving streptozotocin ($p < 0.001$). Together, these findings show a novel potential protective and anti-diabetic impact, which may be applied in designing novel future therapies for treating DM.

1. Introduction

Nearly 425 million individuals worldwide suffer from a serious metabolic illness known as diabetes mellitus (DM) [1]. The World Health Organization (WHO) estimates that diabetes directly contributes to approximately 1.5 million deaths every year worldwide [2], and it is estimated that 552 million individuals will have diabetes by 2030 [3]. Hyperglycemia caused by insulin resistance or an absolute or relative deficiency of insulin is a feature of DM and is often related to age, heredity, and dietary habits. Individuals with diabetes usually are at risk of severe complications such as neurological disorders, cardiovascular issues, hypertension, and kidney disease [4,5]. The three main types of DM are type I diabetes (T1D), type II diabetes (T2D), and gestational diabetes. A Large proportion of patients are suffering from T2D, which occurs as a result of decreased insulin action as liver cells, fatty tissue, and muscle become resistant to insulin, or as a result of poor insulin production by pancreatic beta cells [6]. Numerous synthetic substances can control hyperglycemia in diabetic individuals, which have recently been approved as antidiabetic drugs such as sulfonylureas, meglitinides, biguanides, natural extract products (Hesperidin, genistein, astilbin) and rDNA technology (Recombinant insulins) [7]. Based on the literature review, various synthetic strategies, such as green chemistry and nano-catalysis have been utilized to optimize the production, purity, and selectivity of certain substances as antidiabetic agents [8–10]. Nanomaterials have recently been utilized as a new, successful diabetes management approach.

Synthesis of medicinal plants-based nanoparticles via a green chemistry approach has diverse biological benefits since the plants have a multitude of secondary metabolites that perform a crucial reducing agent role and aid in the stability of the generated nanomaterials [11,12]. The physiological systems of plants contain various chemical components such as alkaloids, phenols, enzymes, amines, ketones, and

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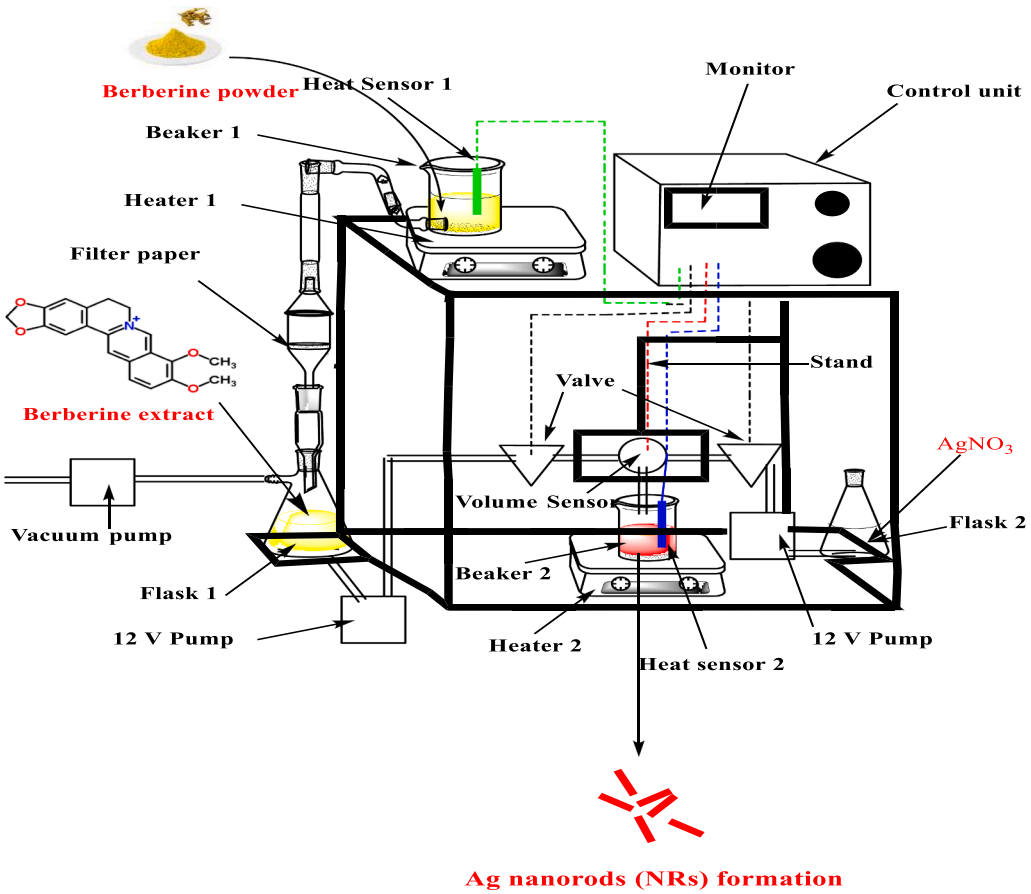

Fig. 1. Schematic diagram of AgNRs synthesis by a novel automated system. The figure is adopted with modification and permission from Elsevier [33].

carboxylic acids. These substances are crucial in the creation of metallic nanoparticles by reducing bulk minerals [13]. The green synthesis approach appears to be a simple, rapid, eco-friendly, and one-step manufacturing method of nanoproducts compared to other traditional conventional procedures, which appear to be costly and unsafe [14–16]. This approach, also known as sustainable chemistry, involves the preparation of Ag NRs using medicinal plants. Silver nanomaterials have acquired abundant attention because of their distinct physicochemical and biological features [17–19]. Nanomaterials' biological and therapeutic potential mainly depends on their physical and chemical composition. An important aspect in influencing the cytotoxicity of these substances is indeed the origin of the reductants utilized in their biosynthesis [20]. Silver nanoparticles (AgNPs) can be produced in several shapes, including flower-like, hexagonal, rod, spherical, octagonal, and so on. However, the control of nanoparticle production in the form of nanorods is limited [21]. Recently, various types of these nanostructures including nanorods have been used in the biomedical field [22].

Over the last few years, AgNPs were employed in many applications such as anticancer agents, antibacterial, drug delivery, cosmetics, and the pharmaceutical industry [23]. AgNRs have recently been used because of their distinct antibacterial characteristics [24,25]. Additionally, AgNPs were utilized as a novel and effective medication option for the treatment of DM [26,27] by stimulating the liver glucokinase (GK) enzyme, the hepatic glucose transporter-2 (GLUT-2) gene, and serum insulin levels [28].

To date, work assessing the use of nano-rods for therapeutic purposes, particularly as a treatment for diabetes, is restricted to very few papers. Several medicinal plants were employed in the biosynthesis of AgNPs. However, a few of them have been successful in treating diabetes [18]. Berberine, a tetra isoquinoline alkaloid, has been utilized as a traditional drug in North America, China, and India due to its therapeutic potential as an anti-diabetic, cardioprotective, antihepatoma, and anti-cancer [29,30]. Previous investigations have also shown that plant alkaloids like berberine have a high reducing potential [31,32]. Therefore, it is critical to create sustainable nanomaterials with high therapeutic efficacy to decrease the likelihood of hyperglycemia. Herein, this work was designed to synthesize AgNRs using berberine extract in a novel way employing green chemistry, we also addressed the in-vivo investigation to look into the AgNRs' potential role in the control or avoidance of DM and its subsequent complications.

2. Experimental

2.1. Materials

2.1.1. Chemicals

Glimepiride, streptozotocin (STZ), silver nitrate ($AgNO_3$), and berberine were supplied from sigma chemicals com. (St Louis, Missouri, USA). Chemicals have been utilized as provided without further modification or purification. All dilution and experiments utilized deionized water.

2.1.2. Experimental animals

Twenty-five adult male Wistar-albino rats (weighing 180–200 g) with an average age at the beginning of the study 3 months were supplied by the Iraqi center for cancer and medical genetics research (ICCMGR), Baghdad, Iraq. The rats were housed in individual stainless-steel cages. The rats were kept in an air-conditioned room with a 12 h light/dark cycle and temperatures between 20 and 22 °C. Before the experiment, the animals were given ten days to acclimatize and provided with a healthy diet and tap water ad libitum. The experimental

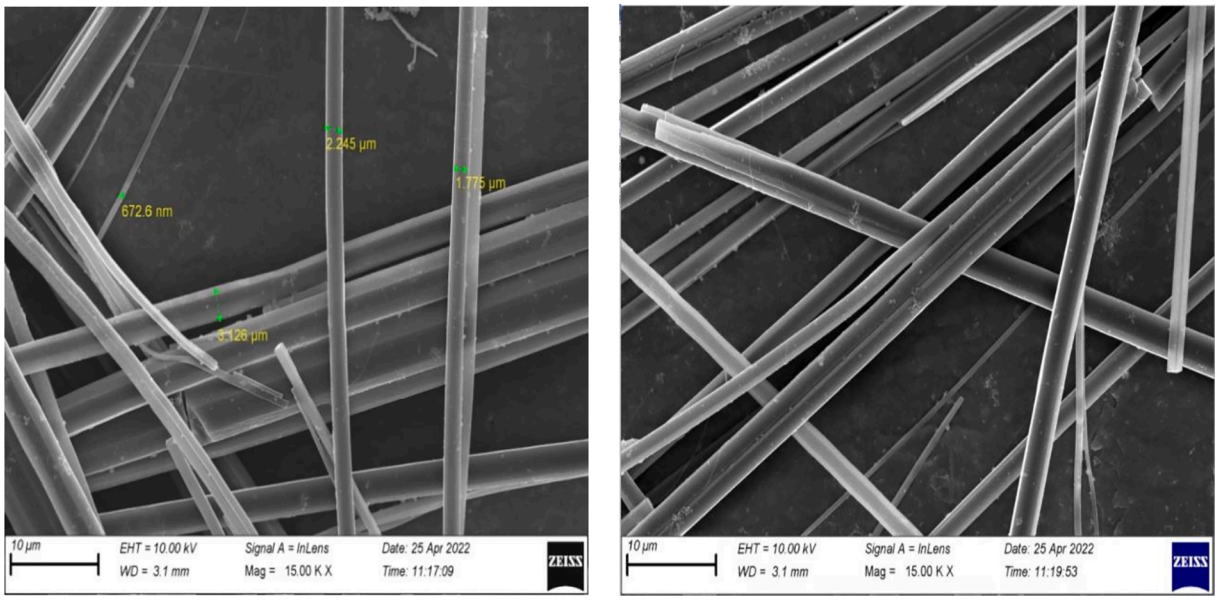

Fig. 2. SEM images of green synthesized AgNRs.

procedure was authorized by the Research Ethical Committee of Anbar University (Approval number: 72–27-06–2022), and International Guidelines for the Care and Use of Laboratory Animals were followed.

2.2. Methods

2.2.1. The formation of AgNRs using a green chemistry approach

To synthesize AgNRs, a novel computerized automated system was developed [33]. The transition between the stages, the operation of pumps and heaters, and the calculation of the required quantities are carried out automatically by entering information through the programming unit as shown in Fig. 1. 1 g of berberine powder, as the reducing agent, was put in the system's beaker 1, 100 ml of deionized water was then added and placed on heater 1 with a magnetic stirrer. When the system is on, heater 1 is operated when the temperature hits 70 °C, running for 60 min with stirring at 200 rpm. Then, the vacuum filtration automatically starts to collect the filtered aqueous extract in flask 1. The second stage involved pumping 20 ml of the pure extract from flask 1 to beaker 2, which was set in heater 2. Afterward, 20 ml of $AgNO_3$ 0.1 M solution was pulled from flask 2 into beaker 2. The third stage, heater 2 is running for 20 min when the temperature reaches 70 °C. Finally, AgNRs were separated from the solution by centrifugation at 12000 rpm for 15 min and then washed five times using deionized water. AgNRs were obtained successfully using the green chemistry approach.

2.2.2. Characterization of AgNRs

The absorption spectrum of the AgNRs was measured by a T80 UV/VIS spectrophotometer in the wavelength range of 200–600 nm. AgNRs were further described by field emission scanning electron microscopy (FESEM) (Carl Zeiss, Germany) to identify their morphology and size. Additionally, using an automated diffraction meter, X-ray diffraction (XRD) (Shimadzu 6000 XRD) was used to examine the crystalline size and structure of Ag NRs [34].

2.2.3. Streptozotocin-induced diabetes

STZ was freshly dissolved at a pH of 4.5 in a buffer containing 0.1 M sodium citrate. A single intraperitoneal (IP) injection of STZ at a dose of 45 mg/kg body weight was administered to induce diabetes. Blood samples from the rat's tail artery were collected 48 hrs following STZ administration and following overnight fasting. A fasting blood glucose test was then employed to confirm DM development [35]. Rats were categorized as diabetic if their fasting blood glucose levels were above 200 mg/dl. Next, the rats underwent treatment for two weeks. The concentration of AgNRs was determined based on previously established work [36].

2.2.4. Experimental design

Randomly, five groups of five rats each were established. All groups underwent a 12-hour fast. Except for the healthy control group, all other groups were injected with STZ. One intraperitoneal (IP) injection of freshly prepared STZ was given to induce diabetes. After two days of STZ injection, diabetes in the rats was validated using a one-touch glucometer to measure FBG concentrations in blood samples taken from the tail vein. The blood drops were collected and FBG levels were measured to monitor the treated diabetic groups. After the trial, sera were also used to measure the lipid profile. Rats were categorized as follows: Group I: Healthy control rats received only 0.1 M citrate buffer; Group II: Diabetic untreated control rats; Group III: Diabetes-related rats were given Glimepiride orally at a dose of 10 mg/kg each day for 14 days, which served as a positive control [37]; Group IV: Diabetes-related rats were given AgNRs orally at a dose of 40 mg/kg each day for 14 days, the dose of AgNRs as an antidiabetic agent was selected based on a previous study [38]; Group V: Rats pre-treated with AgNRs orally at a dose of 40 mg/kg each day for 14 days before streptozotocin injected to the prevention of diabetes. The oral delivery route was by gavage. Silver nitrate concentration was chosen based on a previous study.

2.2.5. Biochemical analysis

Following the research has been completed, all rats were sedated before being sacrificed, blood samples were collected and sera were separated immediately for biochemical analysis. FBG level from the peripheral blood of the tail was measured using a one-touch glucometer. Total cholesterol levels in the blood, triglycerides (TGs), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were calculated utilizing respective commercial kits purchased from BD, Biosciences, USA.

2.3. Analytical statistics

All data shown were expressed as mean ± s.e.m and were representative of three separate experiments. The data were calculated using

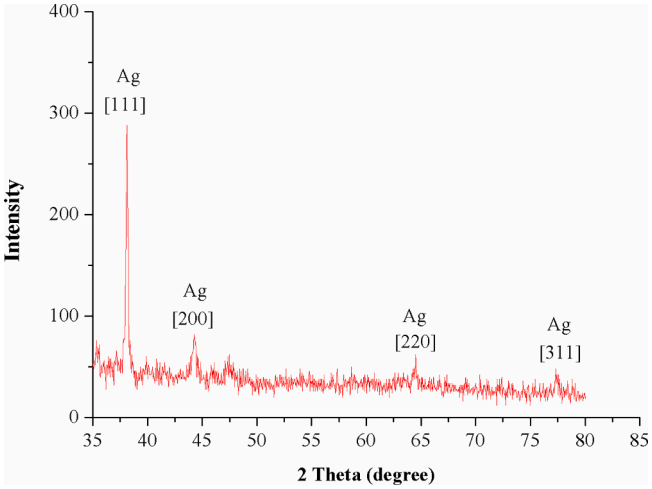

Fig. 3. XRD spectrum of green synthesized AgNRs.

GraphPad Prism version 5.01. One-way analysis of variance (ANOVA) with Dunnett's post-test and two-way analysis of variance (ANOVA) was performed to determine the statistical significance of differences. P values < 0.05 were regarded as significant.

3. Results and discussion

3.1. Characterization of silver nanorods

3.1.1. UV–Visible spectroscopic analysis

Monitoring of the distinctive surface plasmon resonance (SPR) band is the initial confirmation of Ag nanoparticle formation using UV–visible spectroscopy [39,40]. Berberine was utilized as a precursor to reduce Ag^{+} to Ag^{o} and stabilize the formation of AgNRs according to a green chemistry approach. In this study, a distinctive absorption peak of the SPR was formed at 470 nm wavelength, which is in line with the formation of AgNRs. This result is consistent with earlier research that showed AgNPs prepared using Acacia rigidula and T. tinctoria extract as a reducing agent to have a broad absorption peak at 480 nm [36,41]. The broad peaks accompanied by a shift toward higher wavelengths indicate that larger sizes of AgNRs were generated, which may have been caused by the abundance of reducing particles that required more fixing groups [42,43].

3.1.2. SEM analysis

Generally, FE-SEM analysis is conducted to predict the shape and dimensions of the nanoparticles. The scale and form of the AgNRs obtained by berberine extract were displayed in Fig. 2. FE-SEM micrographs revealed rods shaped particles with a smooth surface of pure silver varying in length and diameter of around 672 nm. Recently, it was reported that AgNRs synthesized using Mango leaf extract and aqueous Seed extract of Nigella Sativa were in rods shape [44–46].

3.1.3. XRD analysis

Fig. 3 illustrates the X-ray diffraction pattern obtained from berberine-mediated AgNRs. This technique was employed to determine the crystal structure of pure Ag nanorods. The XRD pattern is indexed with the Joint Committee on Powder Diffraction Standards (JCPDS) data file card No. 00–004-0783 as a standard reference database. Ag nanorods present typical diffraction peaks at (2θ) 38.12°, 44.62°, 64.54°, and 76.81° which are attributed to 111, 200, 220, and 311 planes, respectively, of face-centered cubic (fcc) for the Ag nanorods. The inset exhibits that the broad diffraction peak was at 38.2°, which suggests that the preferential growth of Ag nanorods prepared is along the 111-crystal plane [47]. The XRD spectrum shows no other peaks, indicating that there is no contamination and that the synthesized silver nanorods are pure.

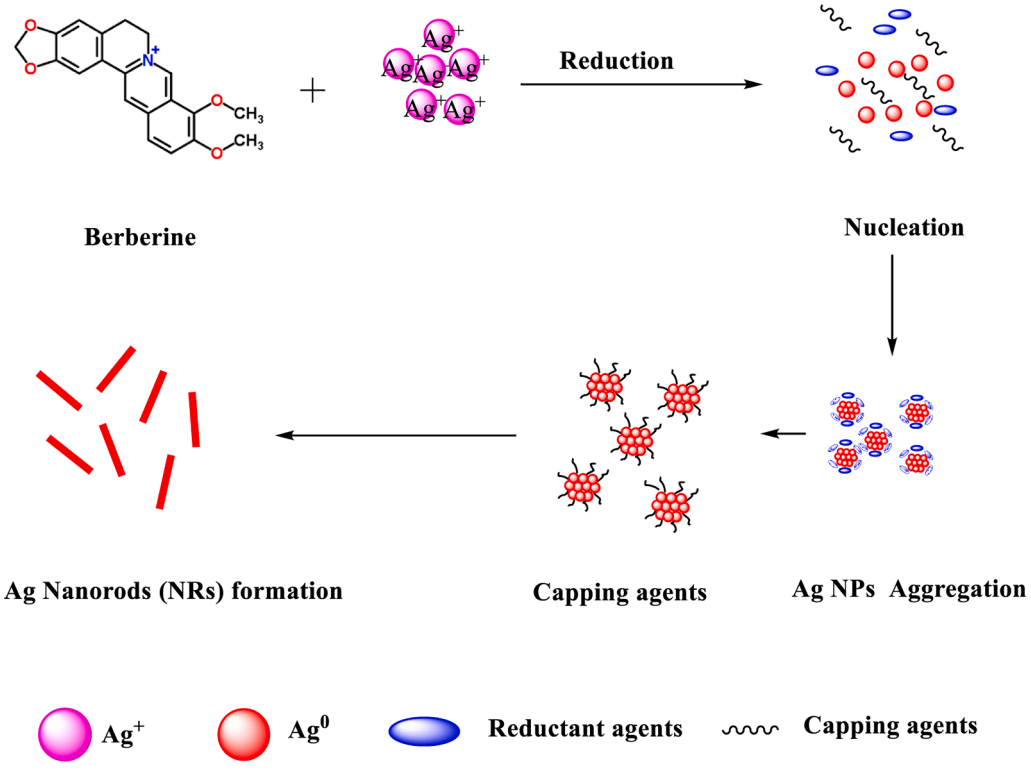

Fig. 4. Representation of AgNRs formation involving reductants and capping agents.

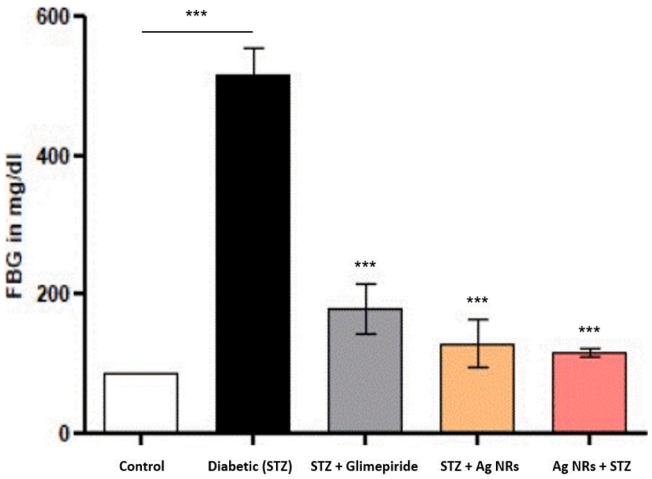

Fig. 5. The effect of AgNRs and Glimepiride on blood glucose concentration in diabetic rats triggered by streptozotocin at the end of the study. Diabetic rats were treated with AgNRs or Glimepiride for 14 days following stimulation with STZ. Group V of rats was pretreated with AgNRs for 14 days before stimulation with STZ. Each value is indeed the mean ± s.e.m of three separate experiments. An ANOVA one-way test was used to assess the data. ***$p < 0.001$ versus normal control group and untreated diabetic control group (STZ).

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3.2. AgNRs formation mechanism

Three major processes are critical to the formation of nanoparticles, which control the shape and size of these particles: Nucleation, development, and capping [48,49]. All of the nuclei are synthesized with the same shape and size as a result of the nucleation of the whole bulk material [50,51]. The second phase is nuclei growth; if all of the nuclei are generated simultaneously, the nanoparticles will all grow at the same rate, which brings us to the final step of the synthesis, the coating of grown nuclei to prevent the clustering of nanomaterials in bulk structures [52]. Recently, scientists have employed a variety of medicinal plants to biosynthesis silver nanoparticles; this method is environmentally safe and has demonstrated excellent efficacy for usage in the medical industry [53].

Alkaloids, which are plant secondary metabolites, belong to the multiple functional groups present in berberine and seem to be important in the reduction of Ag^{+} to Ag^{o}. They give plant-generated nanoparticles the modifications and capabilities to support their prospective use in pathogen resistance [29]. Numerous investigations have shown that the hydroxyl, carboxylic, and amine groups of secondary phytometabolites are crucial to the reduction of silver salt [13,49]. In Fig. 4, the synthesis of AgNRs from berberine is depicted.

Another way to understand the biosynthesis of AgNPs is to consider how secondary metabolites of phytochemicals reduce, chelate, and stabilize the nanomaterials. Redox reactions reduce silver salt, generating ions and molecules as a result [48,54]. Throughout the chelation procedure, both ions and molecules establish bonds with the metallic ions. The functional groups of phytochemicals also act as capping agents and prolong the stability of AgNPs. It is worth mentioning that the precise process underlying the formation and stabilization of nanoparticles produced by plant secondary metabolites is yet unknown and requires further research [48,55].

3.3. The impact of AgNRs and Glimepiride on diabetic rats caused by streptozotocin

STZ is known to be a cytotoxin specific to pancreatic β cells, it decreases the antioxidant content of pancreatic islet cells, causing oxidative stress that severely damages the cell's components such as proteins, lipids, and DNA. Therefore, it is used in animal models of diabetes as a causative agent [56–58]. Many studies clarify that the alkaloids, flavonoids, phenolic acids, and terpenoids that belong to the secondary metabolites play an essential role in the conversion of Ag ions to metallic Ag atoms inside the plant, which form the nanostructures and their potential applications against diseases including diabetes [13,49,59]. The phyto-synthesis of AgNPs is safe, non-toxic, and cost-effective. The creation of silver-based nanoparticles has made advantage of several medicinal plants. However, only a small number of these substances have been proven to have anti-diabetic effects [18]. According to Kulkarni, berberine has a beneficial impact on managing diabetes by regulating blood glucose levels [29].

In continuation with earlier research, the impact of berberine-mediated AgNRs on diabetic rats induced by streptozotocin was assessed in the current study. A previous study revealed that poor glucose regulation caused by a change in cellular metabolism led to weight loss in diabetic rats [60]. As shown in Fig. 5, the group of diabetic rats induced by streptozotocin exhibited noticeably higher glucose values than those in the control group ($p < 0.001$), which showed normal blood glucose concentration. Interestingly, the diabetic rat group that received 40 mg/kg of AgNRs restored normal glucose levels ($p < 0.001$). Suggesting that Ag NRs have a significant anti-hyperglycemic impact. Likewise, 10 mg/kg of Glimepiride as a standard drug in the diabetic rats (Group III) caused a substantial decline in the blood glucose concentration ($p < 0.001$) compared to the diabetic rats caused by streptozotocin. It was shown that Glimepiride has a better antidiabetic effect and a less hypoglycemic effect than other conventional sulfonylureas [61]. In addition, Badian et al demonstrated that glimepiride has been completely bioavailable after oral administration. Therefore, the present study compared the antidiabetic effect of AgNPs in comparison with Glimepiride as a positive control drug [62].

Our study also highlighted the impact of berberine-mediated AgNRs to protect rats from streptozotocin-induced diabetes. Interestingly, the rats that were pre-treated with 40 mg/kg of AgNRs (Group V) for 14 days displayed normal glucose levels following being subjected to streptozotocin as an inducer of diabetes in rats. Our findings revealed that AgNRs have protective and anti-streptozotocin effects to maintain blood glucose levels. This suggests that AgNRs may have reset aberrant pancreatic functions by lowering oxidative stress, which can stabilize the pancreatic shape and secretory control. Our findings concurred with those of other studies, which stated that AgNPs cause elevated serum insulin concentrations [27,28]. Additionally, earlier studies that showed a significant decline in FBG of treated diabetic groups in comparison to the diabetic control group give evidence to the role of AgNPs as a potential antidiabetic [27,28,58].

To date, despite AgNPs having been explored as a potential treatment for a variety of illnesses, however, investigation of the potential risks of giving AgNPs to animal models is limited to a few studies [63,64]. Hyun and co-workers, on the other hand, reported the absence of any measurable toxicity in rats that received AgNPs treatment for 28 days [65]. In another study, when AgNPs were employed as an in vivo therapeutic during short-term therapy, the histology of the liver, kidney, and pancreas showed minor toxic effects. Therefore, future research is required to evaluate the safety of AgNPs in animal models [57].

In this study, the glycemic-lowering effect of the Ag nanorods is expected to be consistent with earlier studies. Numerous investigations have been carried out to understand the processes that mediate the function of AgNPs as antidiabetic agents. AgNPs are believed to act as an antihyperglycemic drug by enhancing the stimulation of serum insulin level, liver GK activity, and hepatic GLUT-2 gene expression [56]. The antidiabetic mechanical actions of AgNRs could also be related to their effect in impeding STZ-induced ROS and RNS synthesis. Since the plant-fabricated AgNPs utilized receptor-mediated endocytosis for internalization, they inhibit NOS and ROS formation by raising the antioxidant content in STZ-induced diabetes rats [4,56]. On the other hand,

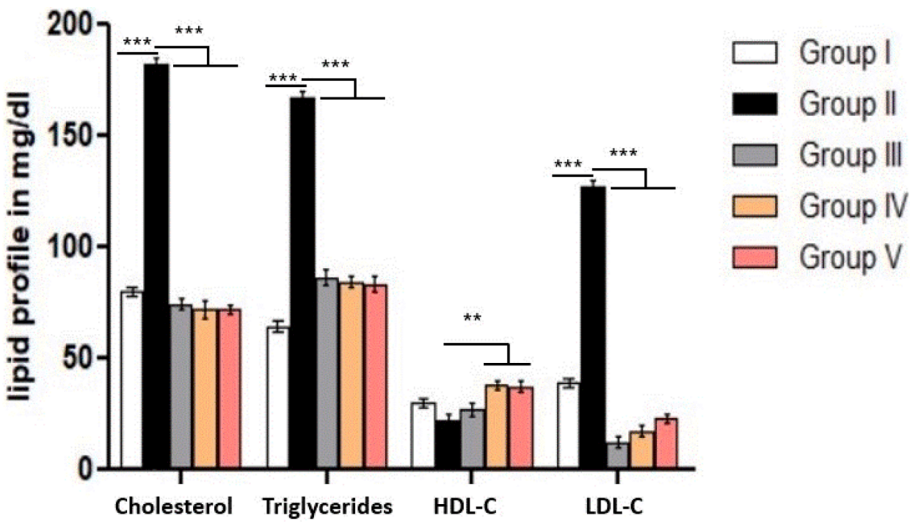

Fig. 6. The effect of AgNRs and Glimepiride on the serum lipids of streptozotocin-induced diabetic rats at the end of the study. Diabetic rat groups were treated with AgNRs or Glimepiride for 14 days following stimulation with STZ. Group V of rats was pretreated with AgNRs for 14 days before stimulation with STZ. Each value is indeed the mean ± s.e.m of three separate experiments. An ANOVA two-way test was used to assess the data. $^{**}p < 0.01$, $^{***}p < 0.001$ versus normal control group and untreated diabetic control group (STZ).

α-amylase and α- glucosidase are considered major enzymes in carbohydrate metabolism. Thus, inhibiting these enzymes is an ideal therapeutic approach for lowering high glucose levels by impairing glucose uptake [66]. Previous studies showed that plant-based AgNPs produced by nanobiotechnology as an antidiabetic medication selectively inhibited glucosidase and -amylase enzymes [67–69]. Nevertheless, the actual mechanism by which the plant-mediated AgNPs exert their antidiabetic effect is unclear. Thus, it is necessary to conduct more research for a clearer understanding of the physiological mechanism of plant-based AgNPs as antidiabetics [70].

3.4. The lipid profile assessment in diabetes rats given AgNRs and glimepiride

In uncontrolled diabetes, lipid profiling is a critical parameter that should be evaluated. The most severe complications of diabetes are cardiovascular disease, which is aggravated by high lipid levels [71]. Diabetes affects lipid metabolism because it increases the recruitment of fats from adipose tissue into circulation [72].

In our research, the impact of AgNRs on the lipid profile levels in STZ-induced diabetic rat groups was further investigated. Interestingly, diabetic rat groups treated with either AgNRs or Glimepiride showed restored lipidogram as shown in Fig. 6. In diabetic rats caused by streptozotocin, total cholesterol, LDL-C, HDL-C, and TGs were all considerably altered. The diabetic rats had significantly higher levels of LDL-C, TGs, and total cholesterol compared to the healthy rats group ($P < 0.001$), while the level of HDL-C was slightly decreased compared to the healthy rats group. The change in lipid profile levels may be caused by reduced lipid production driven by increased cyclic adenosine monophosphate [73]. Interestingly, treatment with either AgNRs or Glimepiride significantly reduced total cholesterol, LDL-C, and TGs values compared to diabetic rats triggered by streptozotocin ($p < 0.001$). Moreover, HDL-C value was found to be markedly raised following treatment with AgNRs ($p < 0.01$). On the other hand, pretreatment with AgNRs also maintained lipid profile levels in rats stimulated by streptozotocin. Intriguingly, rats in Group V pretreatment with AgNRs had significantly lower levels of total cholesterol, TGs, and LDL-C than untreated diabetic rats ($p < 0.001$). Pre-treatment with AgNRs, moreover, also markedly raised HDL-C levels ($p < 0.01$). The potential mechanism of AgNRs as an antihyperlipidemic agent could be related to the effects of AgNRs-stabilized on beta cells in the pancreas that stimulate or imitate insulin via the active chemicals from berberine. A study published in 2016, reported that the AgNPs caused a significant decline in cholesterol and triglycerides in diabetic rats caused by alloxan [58]. Another study revealed that exposure to AgNPs significantly raised HDL levels [57].

4. Conclusion

In this study, Ag NRs have been successfully produced using an innovative green chemical methodology. The formation of crystalline nanorods shape was confirmed by UV–visible, SEM, and XRD analyses. AgNRs synthesized biologically using berberine provide an opportunity to develop new anti-diabetes drugs by studying their impact as antihyperglycemic agents in rats with STZ-induced diabetes. According to our findings, using AgNRs in a rat model reversed pancreatic dysfunction by treating or avoiding diabetes mellitus among the diabetic cases. AgNRs were effective in reducing glucose and lipid profile levels compared to diabetic rats triggered by streptozotocin. Pretreated with AgNRs also showed a protective effect against STZ-induced diabetes. The current research showed that AgNRs can have strong anti-diabetic capabilities. These preliminary findings imply that berberine-mediated AgNRs may represent a brand-new potential treatment approach in the management of diabetes and its side effects.

CRediT authorship contribution statement

Yousif H. Khalaf: Writing – original draft, Writing – review & editing, Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization. **Yousaf Dawood:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization. **Atheer A. Khashan:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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