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Antidiabetic and antiglycation potential of zinc nanoparticles encompassed *Gymnema sylvestre* R. Br. extract

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Abstract

The green approach for the synthesis of nanoparticles has a wide range of applications in modern science due reduced toxicity with increased drug efficiency. In the current study, zinc nanoparticles (Zn NPs) were synthesised from the antidiabetic plant, *G. sylvestre* as a capping and reducing agent. The obtained Zn NPs were examined using techniques including UV-Vis, FTIR, and HR-TEM. Zn NPs were investigated for their potential as antidiabetics and capability to prevent protein glycation *in vitro*. The UV-vis absorption spectrum displays an absorption band at 374 nm, which gives confirmation of synthesised zinc nanoparticles. According to the results from FTIR spectral studies, the presence of various bioactive compounds capped on the surface of Zn nanoparticles was confirmed. HR-TEM micrographs show that the particles were highly mono-dispersed in needle shape. The antioxidant potential of aqueous leaf extract and Zn NPs were measured using the free radical (2, 2-Diphenyl-1-picrylhydrazyl-DPPH) scavenging activity. Zn NPs show the most powerful antioxidant activity when compared to aqueous leaf extract of *G. sylvestre* and was similar to that of ascorbic acid as a standard. Accordingly, the main focus of this study was the alpha amylase inhibition of Zn NPs obtained from the leaves of *G. sylvestre* plant. The result showed that Zn nanoparticles exhibited higher α-amylase inhibition activity when compared with *G. sylvestre* extracts. The percentage of inhibition indicated a concentration-dependent reduction. In addition, bovine serum albumin-fructose assay revealed that Zn NPs significantly inhibited the formation of advanced glycation end (AGEs) products when compared to aqueous plant extract. These results provide evidence that Zn NPs mediated by *G. sylvestre* inhibit the α-amylase enzyme as well as the formation of AGEs. Biogenic Zn NPs synthesised from *G. sylvestre* leaves is an exemplary therapeutic mediator to deliver zinc, have significant implications in the treatment of several diseases, including diabetes mellitus.

1. Introduction

Zinc is a vital micronutrient and is found in human blood plasma concentrations far exceeding those of sea water. It is required for the function of more than 300 enzymes, the stability of DNA, and gene expression. It is necessary for the growth and development of cells, bone metabolism, immunological system, tissue growth, brain function, oxidative stress, and apoptosis (Roohani *et al*., 2013: Jurowski *et al*., 2014). Pancreatic β-cell consist of the highest concentration of Zn, which appears to be crucial for insulin-secreting cells. Zinc elements are essential for the pancreas to store and release insulin, which is responsible for uptake of glucose in the cell (Poudel *et al*., 2017). A recent finding indicated that zinc stimulates glucose transporter type 4 in insulin dependent tissues, which increases the absorption of glucose by cells and regulates blood glucose levels at normal level (Lobene *et al*., 2017). Recent studies show that an increased risk of diabetes is linked to the dysregulation of zinc metabolism.The positive effects of zinc on both type 1 and type 2 diabetes has been demonstrated in numerous of *in vitro* and *in vivo* studies (Ranasinghe *et al*., 2015). Insufficient intake or supplementation of zinc could be leads to the development of diabetes mellitus. An earlier clinical research found that sufficient zinc administration to diabetic patient, had a significantly lowered blood glucose level and increased insulin sensitivity. But in contradiction, the recent report indicates that there is no significant improvement and benefits in preventing diabetes mellitus after zinc supplementation. It is thought that the body lacks a dedicated system for storing zinc (McClung *et al*., 2014). Recent interest has been focused on plant mediated synthesis of ZnO nanoparticles due to their distinctive features, great biocompatibility and low toxicity. Due to its small particle size, nano-Zn is more easily absorbed and accesses target tissue by the body. Recently, zinc nanoparticles have now been considered as GRAS" (generally recognized as safe) substance and have received more attention in biomedical applications (Jiang *et al*., 2018).The use of antidiabetic plants in the biosynthesis of zinc nanoparticles is a unique approach that could be a more effective strategy to treat diabetes. In addition, zinc nanoparticles demonstrate remarkable therapeutic uses in the treatment of diabetes, cancer, drug delivery, and inflammation, wound healing, and bioimaging (Anjum *et al*., 2021). For the treatment of a variety of disorders, several zinc complexes have been developed and their therapeutic effects have been assessed (Nazarizadeh and Asri-Rezaie, 2016). Various secondary metabolites from antidiabetic plants can be delivered to the desired cells using zinc oxide nanoparticles as a carrier.

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Gymnema sylvestre R. Br. is a therapeutic herb, used for the treatment of diabetes mellitus. Gymnema is belongs to Kingdom Plantae with Division Angiospermae and Class Dicotyledoneae and it is found mainly in south-Indian forests (Thakur *et al*., 2012). It has been widely used in the therapy of diabetes and its complications, as well as for the treatment of obesity and snake bites. Recent advancements in experimental research using both animal and human studies have provided evidence-based support for the effectiveness of *G. sylvestre* as diabetic treatment (Khan *et al*., 2019). The Gymnema leaves comprises a mixture of bioactive constituents such as tri-terpenes, glycosides, and saponin, *viz*., gymnemic acid, gymnemagenin, and gurmarin, which exhibit the antidiabetic properties (Altaf *et al*., 2021). The development of a zinc-based agent. Therefore, zinc oxide at the nanoscale is synthesized in the form of Zn NPs from *G. sylvestre* can act as a novel agent for antidiabetic as well as antiglycation potential. Keeping all these in view, the study was planned to synthesize Zn NPs from the *G. sylvestre* leaf extract and potentially examine for its antidiabetic and antiglycation effect. The graphical presentation of work plan shown in Figure 1.

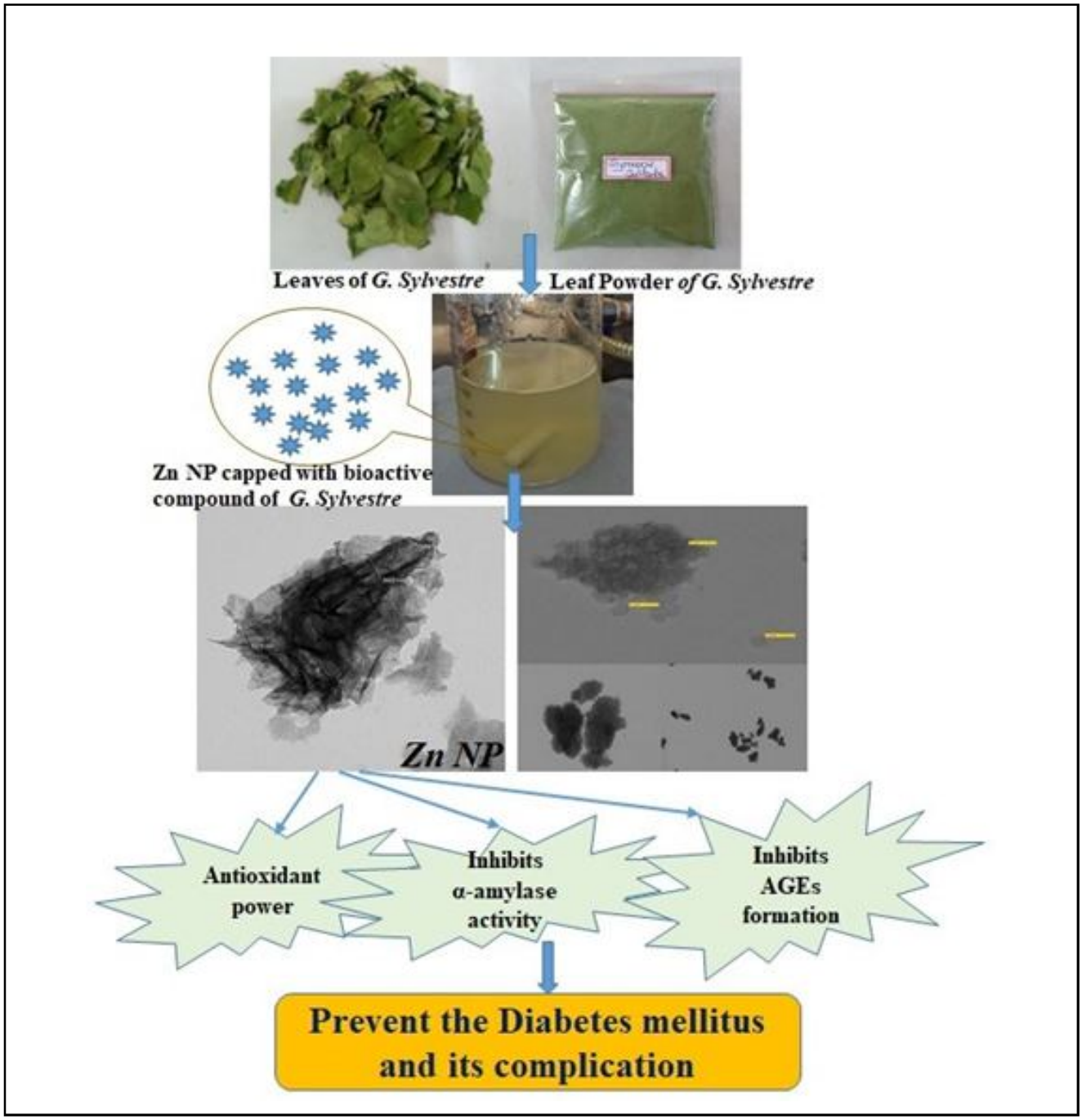

Figure 1: Biogenic synthesis of Zn NPs from leaf extract of *G. sylvestre* for their antidiabetic and antiglycation activity.

2. Materials and Method

2.1 Collection and preparation of extract of *G. sylvestre* leaves

G. sylvestre leaves were identified and collected from the National Research Centre for Medicinal and Aromatic Plants in Boriavi, Anand. *G. sylvestre* leaves were taken and repeatedly cleaned in double-distilled and tap water. The leaves were dried separately under shade, powdered and stored in a closed vessel for further use. *G. sylvestre* dried powder (5 g) was combined with 100 ml of distilled water, and the mixture was then heated continuously at 80°C for 1 h at room temperature with frequent shaking. After that, Whatmann No. 1 filter paper was used to filter the extract. The filtrate was stored at 4°C for future work. This process is appropriate for the extraction of water-soluble constituents.

2.2 Phytochemical analysis of the extract

To detect the presence of various phytochemicals such as phenols, tannins, steroids, carbohydrates, flavonoids, saponins, terpenoids, and alkaloids in the crude aqueous extract of *G. sylvestre* was then subjected to qualitative phytochemical screening of individual components (Shaikh *et al*., 2020).

2.3 Quantitative estimation of total phenolic content (TPC) and total flavonoid content (TFC)

The total phenolic content present in the aqueous extract of *G. sylvestre* leaves was estimated using the FCR (Folin-Ciocalteu reagent) method (Chandra *et al*., 2014) with gallic acid as a standard. Precisely, 0.5 ml of the plant extract was taken and 2.0 ml of the FCR reagent was added. This mixture was then incubated for 2 min at 37°C and was further neutralized by the addition of 2.0 ml of 20% (w/v) sodium carbonate. Optical density was taken at 650 nm and the results were presented in mg of gallic acid equivalent per g of dry weight. The aluminium chloride colorimetric technique was used to determine the crude extract's total flavonoid concentration (Chang *et al*., 2002). The plant extract (0.2 ml) was combined with 2.5 ml of 10% aluminum chloride solution, 2.5 ml of sodium acetate (1.0 M), and 4.9 ml of distilled water. The absorbance was measured at 415 nm on a UV-visible spectrophotometer against a blank with quercetin (0-80 mg/ml) after 15 min of incubation. The total flavonoid content was expressed in mg of quercetin equivalent/g of dry weight.

2.4 Synthesis of Zn NPs by using *G. sylvestre* leaves extracts

A 200 ml solution of 2.0 mM zinc acetate was prepared, and 10 ml of the *G. sylvestre* leaf extract was slowly poured into the solution. After an overnight incubation at room temperature, the appearance of Zn NPs is indicated by the colour alteration from colourless to pale yellow.The sediment pellet of nanoparticles was lyophilized after centrifuging the reaction mixture's colloidal suspension at 2000 rpm for 20 min, and then stored for further characterization.

2.5 Characterization of Zn nanoparticles

At various time intervals, the UV-visible spectrum was used to monitor the nanoparticles. In a double beam UV spectrophotometer, the UV-visible spectra of solution Zn NPs were captured from 250 to 400 nm. Fourier-transform infrared (FTIR) spectroscopy was used to identify the functional groups attached to the surface of nanoparticles.The synthesized nanoparticles were directly subjected to translucent sample discs and were loaded into an FTIR spectroscopy and scannedin the range from 400 to 4000 cm^{-1} having a resolution of 4 cm^{-1}. Furthermore, high-resolution transmission electron microscopy (HR-TEM) was used to investigate the surface morphology like the shape, particle size, and crystallinity of the biosynthesized Zn NPs. Nanoparticles were coated and developed on a copper grid of 200 mesh size and allowed to dry before observation at a voltage of 200 kV (Barzinjy and Azeez, 2020).

2.6 Antioxidant capacity of plant extract and Zn NPs by DPPH free radical scavenging assay

The free radical scavenging activity of aqueous plant extract and Zn NPs was assessed using the DPPH (2, 2-diphenyl-2-picryl-hydroxyl) as stable radical. Initially, 1.0 ml of 0.1 mM DPPH prepared in methanol was added to an equal volume of sample with different concentrations. The reaction mixture was thoroughly shaken before being incubated in the dark for 30 min. Absorbance was taken at 517 nm against methanol as blank. Ascorbic acid (vitamin C) was taken as the standard. The lower the absorbance of the reaction mixture, the greater the percentage of scavenging activity. The IC_{50} value denotes the sample concentration required to scavenge 50% of DPPH free radicals (Baliyan *et al*., 2022). The inhibition or scavenging of free radicals was determined and expressed in percentage by the following formula:

% Inhibition = [(Absorbance of Control-absorbance of the sample) /Absorbance of control] x 100.

2.7 *In vitro* antidiabetic activity

The alpha-amylase inhibitory activities of zinc nanoparticles were carried out as per the method described by Hossan *et al*. (2009). The concentration of zinc nanoparticles was varied from 100- 500 µg/ml. The experiments were conducted in tubes containing starch solution (1.0%), salivary amylase, distilled water, and Zn nanoparticles or acarbose as alpha-amylase inhibitors. The reaction mixtures were incubated at 35°C for 20 min.The reaction was terminated by addition of dinitrosalysilic acid reagent and the tubes were incubated in a water bath at 100° C. The α-amylase inhibitory activity of Zn NP was calculated by using the following formula:

The α-amylase inhibitory activity = [(Ac – As) /Ac] × 100

Ac-absorbance for control; As-absorbance for standard.

2.8 Antiglycation activity

Non-enzymatic glycation of albumin as protein was prepared by taking the mixture of BSA (40 mg/ml) and fructose (125 mM) in potassium phosphate buffer (200 mm with pH 7.4) containing 0.02% sodium azide as preservative for the period of 4 weeks in absence or presence of the Zn nanoparticles separately.

As a positive control, aminoguanidine (AG) was used. As previously reported, the inhibitory effect on fructosamine formation was quantified using a colorimetric method employing nitroblue tetrazolium (NBT) (Adisakwattana *et al*., 2012). Glycated BSA (10 µl) was mixed with 90 µl of 0.5 mM nitroblue tetrazolium in 0.1 M carbonate buffer at pH 10.4 at 37°C temperature. After 15 min, the absorbance was taken at 530 nm. DMF (1-deoxy-1-morpholino-fructose) was considered as a standard.

Inhibition % = [1 - (A0 –A1)/ (A0)] x 100

2.9 Statistical analysis

The data of results were expressed as the mean ± SE of the mean (n = 3). $p<0.05$ was considered to be statistically significant and was calculated by using one-way ANOVA.

3. Results

3.1 Phytochemical screening

The dried leaves converted to powder for extraction of phytochemicals were presented in Figure 2. The determined percentage yield (w/w%) of the *G. sylvestre* aqueous extract was 21.8%.

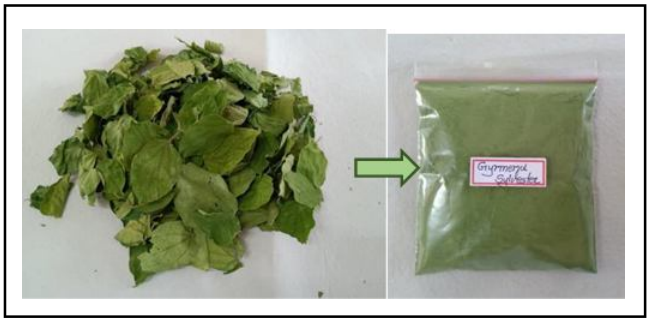

Figure 2: (a) Dried leaves of *G. sylvestre* and (b) it's powder.

Table 1 displays the findings of the initial phytochemical analysis of the *G. sylvestre* aqueous extract screening. Our results indicate the presence of alkaloids, carbohydrates, flavonoids, steroids, tannis and glycosides were detected in aqueous extract.

Table 1: Qualitative phytochemical analysis of the aqueous leaf extracts of *G. sylvestre*. [(+) = Present and (-) = Absent]

Phytochemical	Presence (+)/absence (-)
Alkaloids	++
Flavonoids	+
Phenolics	++
Glycosides	–
Steroids	+
Tanins	+
Saponins	+
Triterpenoids	+

The total phenolic content was determined and calculated using a gallic acid standard curve as a reference. The TPC present in the aqueous extract of *G. sylvestre* leaves was 95.5 ± 4.53 mg GAE/g. The total amount of flavonoid present in plant extract was determined and calculated using a standardization curve of quercetin as a reference. The TFC present in the aqueous extract of *G. sylvestre* leaves was 28.8 ± 7.02 mg of quercetin equivalent/g of dry powder.

3.2 Synthesis and characterization GS-Zn NPs

The Zn NPs synthesis method was first standardized to obtain a determined yield with various concentrations of *G. sylvestre* leaf extract and different concentrations of zinc acetate solution. In a dropwise manner, 1mM of zinc acetate (100 µl) solution and 2 ml of the extract in a dropwise manner produced a stable and maximum amount of zinc oxide nanoparticles. The primary conformation was made within 30 min by observing the color change from colourless to light yellow to brown in the colloidal solution, which shows the formation of zinc nanoparticles. Besides, the color change observation of the synthesis of Zn NPs was confirmed by a UV-visible spectrophotometer for the presence of surface plasmon resonance (SPR) electrons on the nanoparticle surface. UV-vis spectra of the Zn NPs give a sharp peak at 374 nm (Figure 3).

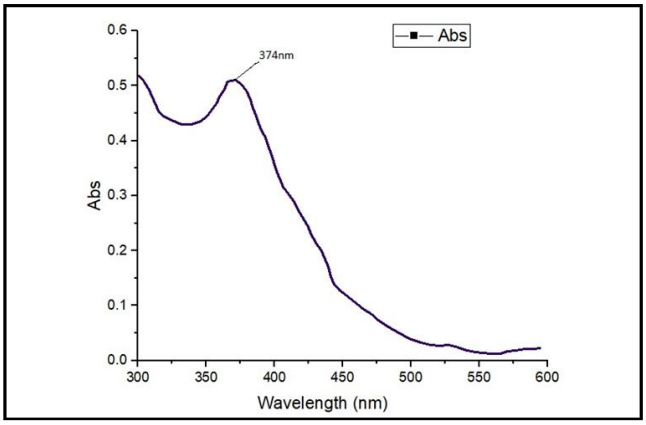

Figure 3: UV-visible spectrum of zinc nanoparticles synthesized by leaf extract of *G. sylvestre*.

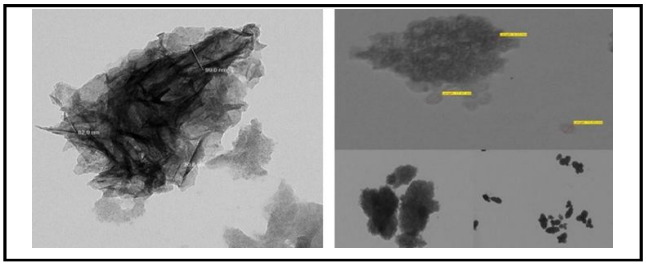

Figure 4: High-resolution transmission electron microscopy (HR-TEM) image of zinc nanoparticles.

The TEM images (Figure 4) indicated that the synthesized Zn NPs were highly mono-dispersed in needle shape and there were a few aggregates also observed in some places due to sedimentation with time. Figure 4 shows the FTIR spectra of synthesized Zn NPs derived from *G. sylvestre* leaf extract.

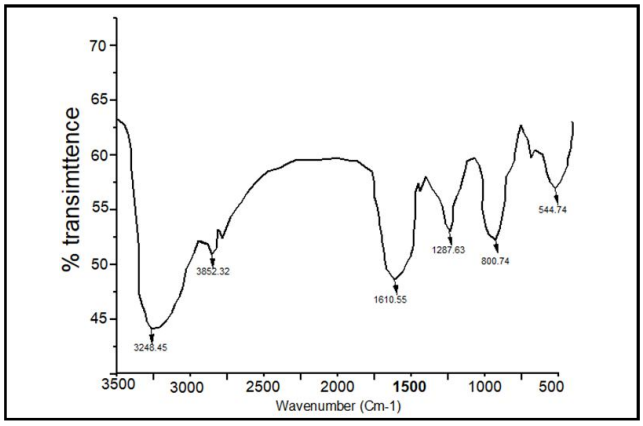

Figure 5: Fourier transform infrared spectroscopy spectrum of Zn NP.

FTIR spectral data in the form of the image revealed the presence of functional groups on nanoparticles that act as capping mediators and are accountable for the stabilization of nanoparticles. The FTIR spectra of the synthesized zinc nanoparticles displayed strong transmittance at 3248.45 cm^{-1}, 3852.32 cm^{-1}, 1610.55 cm^{-1}, 1287.63 cm^{-1}, 800.74 cm^{-1} and 544.7 cm^{-1} (Figure 5). The presence of peaks in FTIR curve are associated with stretching vibrations of –OH groups in alcohols or phenolic compounds, CH_2 and CH_3 functional groups; N-H; C=C groups of aromatic compounds or C=O groups of carboxylic acids; C-N ($CONH_2$) and amide 2 (CONH) groups, C-O or C-O-C functional groups and S=O stretching, respectively.

3.3 Antioxidant activity of *G. sylvestre* medicated Zn NPs

The vanishing of the violet color of free radical DPPH accompanied by a decrease in absorbance measured at 517 nm shows the antioxidant potential of the nanoparticles. Figure 6 shows antioxidant power in terms of the percent radical scavenging activity of crude *G. sylvestre* leaf extract, Zn NPs, and standard reference ascorbic acid with concentrations 10, 50, 100, 200, and 500 µg/ml.

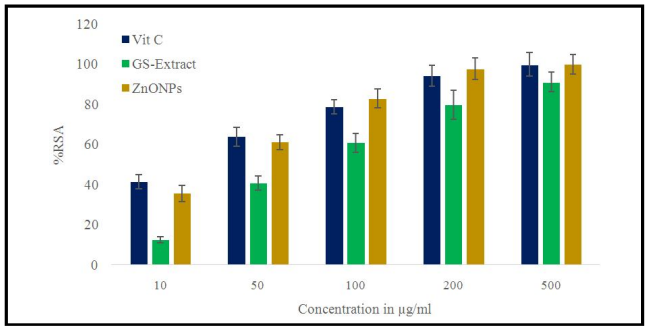

Figure 6: DPPH radical scavenging activity of standard vitamin C, Zn nanoparticles, and leaf extract of *G. sylvestre*.

In the form of fructosamine, the inhibitory effects of biologically synthesised Zn NPs on glycated albumin were measured. The glycated albumin treated with Zn NPs exhibits significantly lowered level of fructosamine level when compared to the untreated glycated control. Furthermore, percentage of inhibition of glycated albumin was nearly parallel when compared with positive control aminoguanidine. In this assay, the Zn NPs shows the % of inhibition with a value range from 30% to 72.8% at the concentration of 1-50 mg /ml and the standard aminoguanidine ranged from 40% to 68.77% (Figure 7).

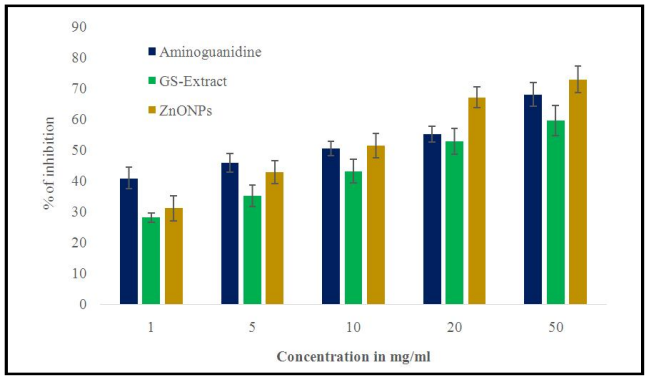

Figure 7: Effect of different concentration of aminoguanidine, Zn nanoparticles, and leaf extract of *G. sylvestre* on fructosamine level using the BSA-glucose system.

4. Discussion

The use of a green approach in the synthesis of nanocarriers has been well documented for its antidiabetic activity *via* pancreatic α-amylase, intestinal α-glucosidase, improved insulin action and secretion, and glucose uptake (Bhardwaj *et al.*, 2020). Nano-based drug delivery systems are the best methods for increasing targeting ability and enhancing the safety and efficacy of medications. The reduction and stabilisation of metal NPs are caused by active phyto-constituents present in plant extract that are attached to them (Mittal *et al.*, 2013). In the present study, the leaves of *G. sylvestre* was taken for the synthesis of Zn NPs due to their potent antidiabetic and hypoglycemic properties. After the treatment with aqueous leaf extract of *G. sylvestre*, a milky white and foamy powder was obtained after centrifugation, indicating the formation of Zn-NPs. It is well reported that nanoparticles have distinct optical absorption spectra due to the surface plasmon resonance (SPR) property. The UV-Vis spectra of the obtained NPs revealed a band at 390 nm, which is typical of Zn NPs (Jiménez-Rosado *et al.*, 2022). FTIR spectra studies confirmed the presence of various biofunctional groups such as –C-O-, -OH, -C=O involved in the green synthesis of Zn NP nanoparticles.

The presence of functional groups on zinc nanoparticles might suggest capping of nanoparticles with active phytoconstituents present in leaves of *G. sylvestre*. It is well explored herbs as potential antidiabetic drug which have ability to stimulate insulin secretion and regenerating pancreatic β-cell. *G. sylvestre* contains bioactive compounds like oleanines (gymnemic acid, gymnema saponins), anthraquinones, and gymnemasides, which strongly reported to have antidiabetic and antioxidant activity (Yadav *et al.*, 2019; Parveen *et al.*, 2015). The aqueous extract of *G. sylvestre* leaves showed good radical scavenging ability as indicated by the percentage of DPPH scavenging activity. As compared to *G. sylvestre* leaf extract, Zn NPs demonstrated higher antioxidant capacity, which could be attributed to the presence of specific antioxidant compounds, such as gymnemagenin, coated on nanoparticles. Free radical scavenging properties of Zn NPs could be attributed by functional groups present in leaves extract of *G. sylvestre*.

The total phenolic and flavonoid content present in the aqueous extract of *G. sylvestre* were quantitatively analysed and shown according to the report previously (Behera, 2020). Flavonoids are a type of polyphenol that play an important pharmacological role as free radical scavengers and have possible therapeutic effects against free radical mediated diseases, particularly diabetes mellitus. Zinc could be enhance the insulin secretion and insulin signalling by several mechanisms including insulin receptor phosphorylation. Umrani *et al.* (2014) reported the antidiabetic effects of Zn NPs in experimental type 1 and 2 diabetic rats induced by streptozotocin. It was observed that Zn NPs increase insulin secretion from pancreatic β-cells, control blood glucose, and improve glucose tolerance. Interestingly, zinc is has been shown to regulate glucagon secretion from pancreatic α-cells.

The results of the present study showed a significant reduction in α-amylase activity in the presence of Zn NPs, which indicates a great antidiabetic activity of zinc nanoparticles. The inhibition of protein glycation is a superior strategy for preventing various pathological complications of diabetes mellitus. We demonstrated the fructosamine inhibitory activity of *G. sylvestre* medicated Zn

NP using fructose induced glycation of albumin an *in vitro* model. The precise mechanism of Zn NPs' antiglycation activity is currently unknown and was not investigated in this study. But, previously, Zn NPs were documented with their ability to reduce the content of glycation products and antioxidant properties (Kumar *et al*., 2022).

5. Conclusion

The results obtained in present work indicated that Zn NPs, which were biologically synthesized from leaf extract of the antidiabetic plant, *G. sylvestre* has been characterized. UV spectral studies and HR-TEM show confirmed synthesis of Zn NPs produced from *G. sylvestre*. By using DPPH analysis, it was confirmed that the biogenic synthesis of zinc nanoparticles possess higher antioxidant properties. The present study shows the ability of zinc nanoparticles (ZnNPs) from the aqueous *G. sylvestre* leaf extract inhibited non-enzymatic protein glycation formation and also reduced the activity of α-amylase. *G. sylvestre* Zn NPs have the potential to be used as a therapeutic agent to maintain glycemic control and postpone the onset of diabetic complications.

Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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