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Characterization, antibacterial, antioxidant, antidiabetic, and anti-inflammatory activities of green synthesized silver nanoparticles using *Phragmanthera austroarabica* A. G. Mill and J. A. Nyberg extract

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Introduction: Diabetes mellitus is a chronic metabolic disorder that exhibited great expansion all over the world. It is becoming an epidemic disease adding a major burden to the health care system, particularly in developing countries.

Methods: The plant under investigation in the current study *Phragmanthera austroarabica* A. G. Mill and J. A. Nyberg is traditionally used in Saudi Arabia for the treatment of diabetes mellitus. The methanolic extract (200 mg/kg) of the plant and pure gallic acid (40 mg/kg), a major metabolite of the plant, as well as their silver nanoparticle formulae (AgNPs) were evaluated for their antidiabetic activity.

Results and Discussion: The results showed a decrease in body fat, obesity, an improvement in lipid profiles, normalization of hyperglycemia, insulin resistance, and hyperinsulinemia, and an improvement in liver tissue structure and function. However, the results obtained from AgNPs for both extract and the pure gallic acid were better in most measured parameters. Additionally, the activity of both the crude extract of the plant and its AgNPs were evaluated against a number of gram-positive, gram-negative bacteria and fungi. Although the activity of the crude extract ranged from moderate to weak or even non-active, the AgNPs of the plant extract clearly enhanced the antimicrobial activity. AgNPs of the extract demonstrated remarkable activity, especially against the Gram-negative pathogens *Proteus vulgaris* (MIC 2.5 µg/ml) and *Pseudomonas aeruginosa* (MIC 5 µg/ml). Furthermore, a promising

antimicrobial activity was shown against the Gram-positive pathogen *Streptococcus mutants* (MIC 1.25 µg/ml).

KEYWORDS

sustainability of natural resources, *Phragmanthera austroarabica*, silver nanoparticle, antioxidant, antidiabetic, antimicrobial activity

1. Introduction

Family Loranthaceae comprises many genera that are characterized by the accumulation of phenolic compounds as major active constituents (Kim et al., 2004; Badr et al., 2013). Additionally, these plants demonstrated solid evidence of antidiabetic, anticancer and antilipidemic activities (Kim et al., 2004; Osadebe et al., 2010; Peter and Obi, 2010). Diabetes triggers the production of reactive oxygen species (ROS) (Savu et al., 2012; Son, 2012). Consequently, agents exhibiting radical-scavenging activity can abolish ROS-induced oxidative damage (Pietta, 2000; Kucharska et al., 2004). *Phragmanthera austroarabica* A. G. Mill and J. A. Nyberg is a semi-parasitic plant belonging to the family Loranthaceae and traditionally used in Saudi Arabia to treat diabetes mellitus (Hanafy and Badr, 2014). Our previous research concerning this plant afforded the isolation and identification of many metabolites with promising biological activity. Additionally, the plant revealed antidiabetic activity that agrees with its traditional use (Bamane et al., 2012; Badr, 2014; Hanafy and Badr, 2014; Aldawsari et al., 2017). Among the significant constituents of *P. austroarabica* is gallic acid, a phenolic compound with potent antioxidant and antidiabetic activities (Bak et al., 2013; Daglia et al., 2014; Abdel-Moneim et al., 2018). Gallic acid is reported to have hypoglycemic activity by activating pancreatic cells (Fatima et al., 2017). Others reported the antioxidant potential of gallic acid as an agent for protection against diabetes-induced diseases (Patel and Goyal, 2011). Variya et al. (2020) suggested its action is due to improved Glut4 translocation leading to improved glucose uptake in 3T3-L1 cells and stimulation of adipogenesis and lipid accumulation in 3T3-L1 adipocytes. Additionally, previous investigation of *P. austroarabica* revealed preliminary screening of the antimicrobial activity of the plant extract toward a number of microorganisms. The results exhibited a promising activity against *Staphylococcus aureus* and *Bacillus subtilis* (Waly et al., 2012). Nanotechnology provides a platform to enhance the action of medicinal plant extracts and plant-derived active ingredients, modify their release, and prevent their undesired side effects. Among the most commonly used nano-forms for delivering phytomedicines are silver nanoparticles (AgNPs). Silver curative and protective properties have been known for centuries (Raymond et al., 2008), and recently, AgNPs have proved antimicrobial (Muhammad et al., 2022), anticancer and antidiabetic effects (Muhammad et al., 2022). It was suggested that the antidiabetic activity of AgNPs is related to the efficient inhibitory action of carbohydrate digestive enzymes such as α -amylase and α -glucosidase (Kannan et al., 2016). AgNPs can be synthesized by different

methods, either physical, chemical or biological, which is known as biosynthesis. Biosynthesis is also known as green synthesis, which employs unicellular and extracellular biological organisms such as bacteria, algae and plants to act as reducing and capping agents for the synthesized AgNPs. This technique is now widely used as it is relatively simple, cost-effective, scalable and eco-friendly (Oloruntoyin et al., 2022). For these mentioned reasons, our current study aims to apply biosynthesized nanotechnology-based formula to boost both antimicrobial and antidiabetic activities of *P. austroarabica* extract. Different biological parameters are compared with the conventional methanolic plant extract.

2. Results and discussion

2.1. Quantitative estimation of gallic acid

The linearity of the suggested GC–MS method was inspected by analyzing the standard solution of gallic acid in a series of different concentrations. The calibration curve of gallic acid was obtained by plotting different concentrations against the corresponding peak area (applied in triplicate). Statistical investigation of the received data was verified using linear regression analysis. The linear relationship was obtained over the concentration ranges of 1.5–10.4 µg/ml with a correlation coefficient (R^2) equal 0.9857, and the linear regression equation was $Y = 3506.3 X + 101,700$. The limit of detection of gallic acid based on the signal-to-noise approach was 0.18 µg/ml, while the limit of quantitation was 0.41 µg/ml. The precision was determined based on the analysis of three different concentrations of gallic acid applied in triplicate. The method precision was indicated by the low value of RSD (3.1%). The specificity of the method was confirmed as no endogenous interference was detected at the retention times of the analyte (Figure 1). Upon application of the GC–MS method, gallic acid was determined as 44.8 mg/g of *Phragmanthera austroarabica* crude extract.

2.2. Total phenolic and antioxidant activity of *Phragmanthera austroarabica*

The phenolic compounds generally play a significant role in the studied biological activities (Tatipamula and Kukavica, 2021). In the current study, total phenolic content of the plant extract was determined as 423.19 ± 19.75 mg/g of dry plant

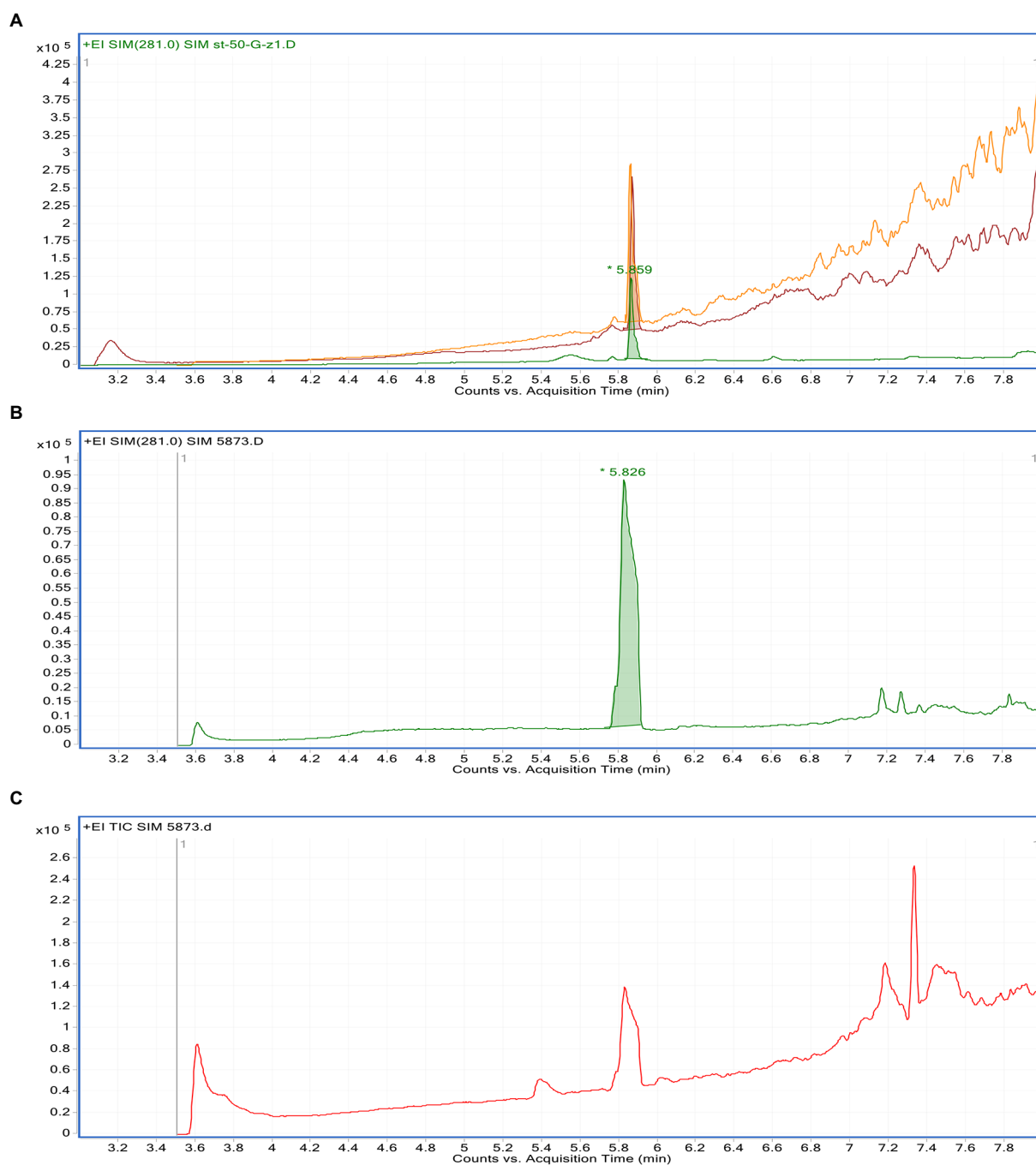


FIGURE 1

GC-MS chromatograms of: a mixture of methanolic *Phragmanthera austroarabica* crude extract and gallic acid standard solution (A), gallic acid standard solution (B), methanolic *P. austroarabica* crude extract (C).

extract. To assess the antioxidant potential of the plant extract, three different methods were implemented. The results demonstrated that *P. austroarabica* crude extract exhibited scavenging activity on DPPH with IC_{50} values of $17.62 \pm 3.41 \mu\text{g/ml}$ while the positive control H_2O_2 demonstrated $IC_{50} = 11.58 \pm 2.13 \mu\text{g/ml}$. Results of FRAP showed that *P. austroarabica* crude extract had promising reduction ability with 1.95 ± 3.41

$\text{mMol Fe}^{+2}/\text{g}$ compared to ascorbic acid as a positive control which showed $2.95 \pm 0.91 \text{ mMol Fe}^{+2}/\text{g}$. Finally, the total antioxidant capacity of the extract and ascorbic acid as a positive control exhibited antioxidant potential equal 31.75 ± 1.23 and 71.28 ± 4.34 , respectively. From these data, *P. austroarabica* crude extract could be a promising antioxidant agent.

2.3. Biosynthesis of AgNPs using *Phragmanthera austroarabica* crude extract

AgNPs were successfully prepared using the crude extract of the *P. austroarabica*. The plant accumulates a number of important chemical constituents (Badr, 2014). Different secondary metabolites previously isolated from the extract are used as reducing and capping agents. It is well known that polyphenol-rich plant extracts are used in the green synthesis of AgNPs (Oliver et al., 2018; Khedr et al., 2022). Among the different constituents present in *P. austroarabica* extract that plays an important role as reducing and capping agents is catechin. Catechin is a polyphenol that was previously used in the green synthesis of AgNPs (Oliver et al., 2018). Another important constituent in the used extract is gallic acid. Gallic acid is a phenolic acid that is naturally occurring in many plants, fruits, and vegetables and known for its antioxidant activity. Gallic acid was used by Nemčková and colleagues in the synthesis of AgNPs (Nemčková et al., 2022). Quercetin also was previously isolated compound from *P. austroarabica* and was involved in the green quercetin-mediated synthesis of AgNPs (Tasca and Riccarda, 2020). Abdallah et al., who synthesized AgNPs using *L. lalambensis* extracts mentioned that some secondary metabolites could be responsible for the reduction and capping of AgNPs. Among these metabolites lupeol and β -sitosterol glucoside, both were isolated from the *P. austroarabica* plant extract used in the current study for reduction and capping of AgNPs (Abdallah and Ali, 2021).

2.4. UV-vis absorbance spectroscopy

In the current study, the AgNPs were synthesized using *P. austroarabica* crude extract and gallic acid. The extract and gallic acid are used as reducing and capping agents to convert silver ions to atomic form and capping the prepared nanoparticles to enhance the stability of colloids. UV-Vis spectroscopy is a reliable technique to confirm AgNPs formation and monitor nanoparticle dispersion stability. Gallic acid AgNPs dispersion was brown and showed UV-Vis spectrum similar to that obtained by Li et al. (2015). The dispersion was dark yellowish brown for *P. austroarabica* crude extract AgNPs. The color intensity increased over time, as shown in Figure 2. The characteristic surface-plasmon resonance absorption band appeared at 400–500 nm, and the maximum absorbance was at 421 nm. This was similar to several studies such as the carob leaf extract AgNPs prepared by Awwad and colleagues, who found the maximum absorbance at 420 nm (Awwad et al., 2013) and Tripathi et al. (2013), who detected the same wavelength as the current study for AgNPs biosynthesized using *Ficus* bands leaf extract.

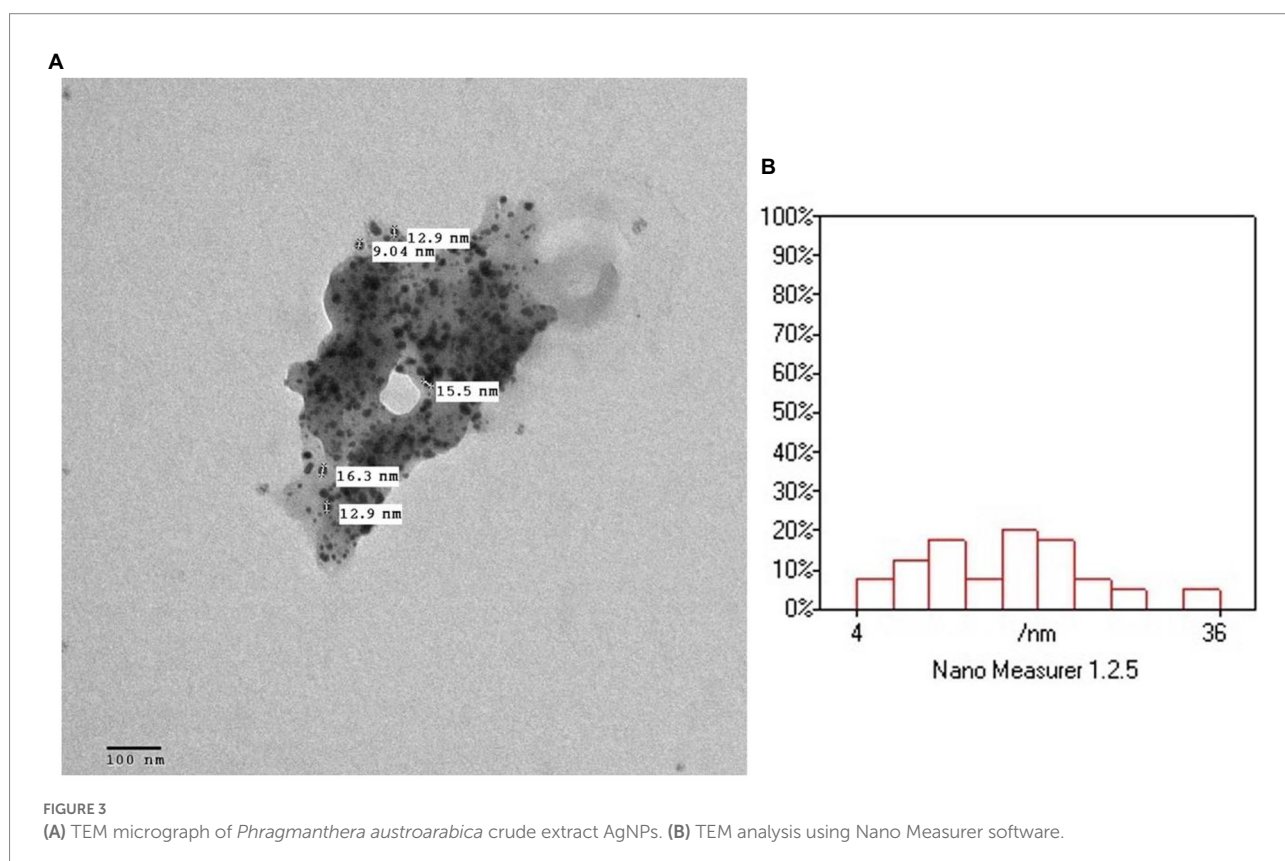
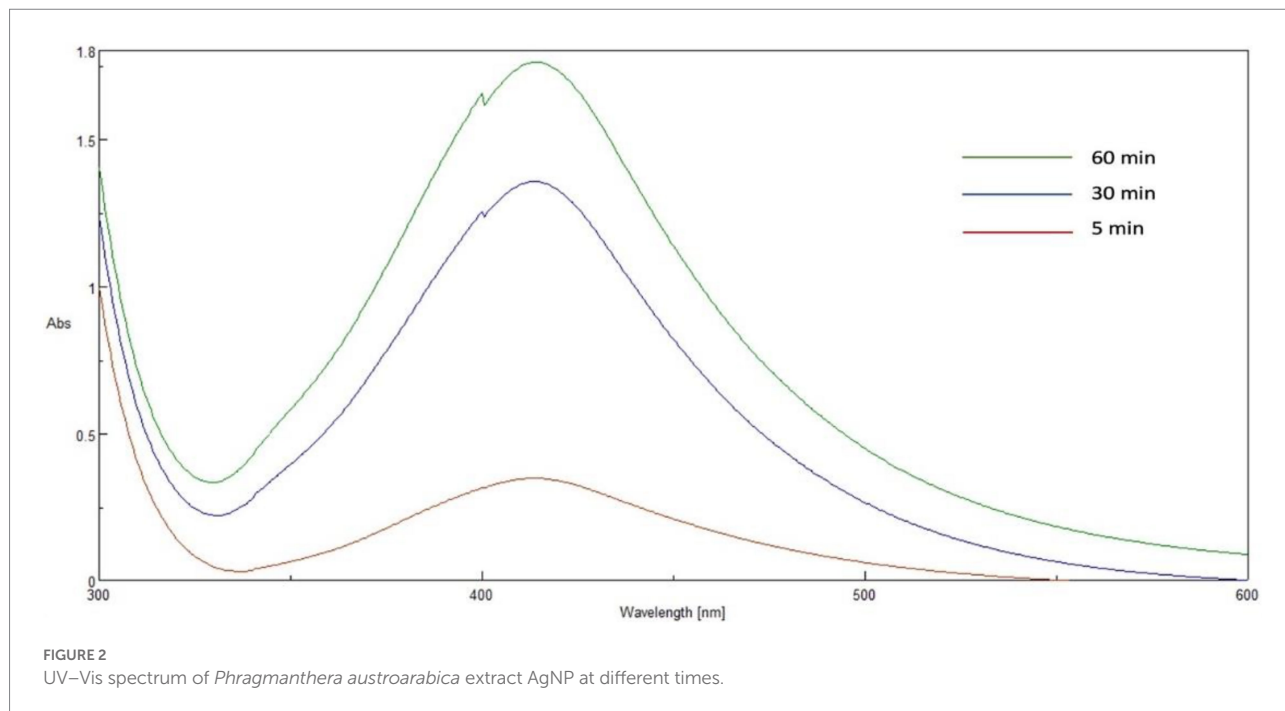
2.5. Transmission electron microscopy

The surface morphology, size and shape of the synthesized *P. austroarabica* crude extract AgNPs are investigated by

TEM. Figure 3 shows that the AgNPs are spherical, with a minimum particle size of around 13 nm. The TEM technique ensures the dry diameter of the dried sample of the nanoparticles, not the hydrodynamic diameter in the dispersion. High density of the particles appears in the field as an indication of the successful preparation of a large number of AgNPs. Similar size range obtained by Ameen et al. (2020), who prepared AgNPs with green synthesis with cyanobacterium *Spirulina platensis*, and Suriyakalaa et al. (2013), who prepared biosynthesized AgNPs using *Andrographis paniculata*, where the TEM revealed the size range from 13 to 27 nm.

2.6. AgNPs size and surface charge determination

The DLS is a useful technique for determining the prepared nanoparticles' hydrodynamic diameter and the surface charge of the particles in the dispersion. Smaller nanoparticles have a higher surface area to volume ratio, enhancing activity. The *P. austroarabica* crude extract AgNPs showed a mean hydrodynamic diameter of 46.22 nm, while gallic acid AgNPs showed a mean diameter of 44.90 nm. Although both preparations were comparable in size, it was noticed that there is a difference in the diameter measured by TEM and DLS techniques. It is clear that they are different techniques, as the former measures the dry diameter in a dried sample, while the latter measures the hydrodynamic diameter of the nanoparticles in dispersion (Cumberland and Jamie, 2009). This finding was also discussed by Diegoli and colleagues who stated that the difference in size between the two techniques is because the DLS technique is sensitive to the double layer surrounding the nanoparticles in dispersion, which is expected to lead to overestimating the mean particle diameter (Diegoli et al., 2008). Khedr et al. (2022), found similar difference in the mean particle size of AgNPs synthesized using *Cynara scolymus* L. crude extracts between the two techniques. Similar results were obtained in the literature where Ahmadi and colleagues prepared AgNPs of *Aloe vera* leaf extract, and the mean diameter was 46 nm (Omid et al., 2018). For gallic acid AgNPs, the diameter value in the current study was intermediate between the value obtained by Li et al. (2015) and by Ahani and Khatibzadeh (2022), which were 17.6 nm, 78.7 nm, respectively. Both studies prepared the nanoparticles at the same pH as the current study (pH 11.0). Regarding the surface charge, a high zeta potential value ensures the stability of colloidal dispersion, which helps the nanocarrier to resist agglomeration leading to sedimentation. When zeta potential is very low, attractive forces overcome repulsion resulting in instability of the colloidal dispersion. So, nanoparticles with higher zeta potential are electrically stabilized (Parmar et al., 2011). The zeta potential of the *P. austroarabica* crude extract AgNPs was -27.4 mV, and the value for gallic acid AgNPs was much higher and was -50.1 mV. These values indicate high stability of the prepared dispersions, especially for the gallic acid AgNPs, which exceeds



the value of good stability of -30 mV. Park et al. (2016) who designed green synthesized AgNPs of gallic acid, stated that the zeta potential was -53.47 mV which indicates excellent stability of the system. The zeta potential value of the *P. austroarabica*

crude extract AgNPs was comparable to AgNPs prepared by Ezealisiji and coworkers. They biosynthesized the dispersion root bark aqueous extract of *Annona muricata*, where the zeta potential value was -27.90 mV (Ezealisiji et al., 2017).

2.7. Impact on the obesity index and the percentage of weight gain

Compared to the normal group, the diabetic group's treatment with a high-fat diet and STZ (30 mg/kg) led to a significantly higher final body weight, the percent increase in body weight, and an obesity index at $p \leq 0.05$ (Table 1). In comparison with the diabetic group, both extract (200 mg/kg) and its corresponding AgNPs for 4 weeks after induction of diabetes significantly ameliorated the % rise in obesity index and body weight (Table 1). In comparison with the diabetic group, gallic acid (40 mg/kg) treated diabetic rats significantly reduced their obesity index %. Conversely, the gallic acid AgNPs formula (40 mg/kg) significantly ameliorated the % increase in obesity index and body weight at $p \leq 0.05$ (Table 1). Overall, the results achieved by the treatment with the AgNPs formulation for both the extract and the gallic acid were the best in improving the reduction in % change in body weight, final body weight and obesity index (Table 1).

2.8. Biochemical measurements

According to the current findings, the diabetic group had significantly higher blood glucose levels (Mm/L), serum insulin levels (ng/L), HOMA-IR scores, and serum leptin levels (ng/L) than the normal group at the time of the study $p \leq 0.05$ (Table 2).

TABLE 1 Effect of *Phragmanthera austroarabica* extract and pure gallic acid versus their AgNPs formulae on the percent increase in obesity parameters.

Group	Final body weight (g)	Obesity index	% Change in body weight	Baseline body weight (g)
Normal	209.5 ± 9.9	0.82 ± 0.06	42.4 ± 9.1	146.9 ± 2.5
Diabetic	353 ± 7.4 ^a	5.8 ± 0.5 ^a	152 ± 14.3 ^a	139.9 ± 5 ^a
Diabetic + pioglitazone (10 mg/kg)	226.8 ± 17.7 ^b	1.8 ± 0.35 ^b	57.9 ± 13.6 ^b	143.3 ± 1.4 ^{ab}
Extract (200 mg/kg)	277 ± 17 ^b	3.6 ± 0.11 ^{ab}	66 ± 17 ^b	167 ± 7 ^{abc}
Extract in AgNPs (200 mg/kg)	173 ± 1.01 ^{bc}	0.86 ± 0.2 ^{bc}	20.1 ± 1.5 ^b	144 ± 1 ^{abcd}
Gallic acid (40 mg/kg)	280 ± 6 ^d	2.5 ± 0.7 ^{abd}	98.8 ± 43 ^d	141 ± 1.01 ^{acde}
Gallic acid in AgNPs (40 mg/kg)	250 ± 5.5 ^{bc}	1.71 ± 0.6 ^{bc}	73.3 ± 8.01 ^b	145 ± 10 ^{abcdf}

Obesity parameters are expressed as mean ± S.E and analyzed using one-way ANOVA followed by Bonferroni's test for multiple comparisons.

^a $p \leq 0.05$ versus normal group; ^b $p \leq 0.05$ versus Diabetic group; ^c $p \leq 0.05$ versus Diabetic + pioglitazone (10 mg/kg); ^d $p \leq 0.05$ Diabetic + Extract (200 mg/kg); ^e $p \leq 0.05$ versus Diabetic + Extract in AgNPs (200 mg/kg); ^f $p \leq 0.05$ versus Diabetic + Gallic acid (40 mg/kg) group, $n = 5$.

However, 4 weeks after diabetes was induced, *P. austroarabica* extract and its AgNPs (200 mg/kg) were administered. This considerably improved the diabetic group's blood glucose level (Mm/L), serum insulin level (ng/L), HOMA-IR, and serum leptin level (ng/L) at $p \leq 0.05$ (Table 2). Additionally, when compared to the diabetic group, treatment with gallic acid (40 mg/kg) significantly decreased HOMA-IR, serum insulin, and blood glucose levels Mm/L, Mm/L, and ng/L, respectively (Table 2). Moreover, treatment with the gallic acid (40 mg/kg) in AgNPs significantly decreased blood glucose level (Mm/L), serum insulin level (ng/L), HOMA-IR and serum leptin level (ng/L) in comparison with diabetes. Generally, the results achieved by the treatment with the AgNPs for both the extract and the gallic acid were better than *P. austroarabica* extract and pure gallic acid in improving blood glucose level (Mm/L), serum insulin level (ng/L), HOMA-IR and serum leptin level (ng/L; Table 2).

2.9. Liver enzymes

Both the liver index and the serum levels of the liver enzymes AST and ALT were significantly higher in the diabetic group than in the normal group in the current investigation at $p \leq 0.05$ (Table 3). Additionally, 4 weeks of administration of *P. austroarabica* extract (200 mg/kg) to diabetic rats were able to considerably normalize the liver index as compared to the diabetic group at $p \leq 0.05$ (Table 3). Additionally, treatment with the *P. austroarabica* AgNPs (200 mg/kg) compared to the diabetes group considerably reduced the levels of the two blood liver enzymes ALT and AST at $p \leq 0.05$ (Table 3). On the other hand, treatment with gallic acid and its AgNPs (40 mg/kg) significantly improved the liver index and serum enzymes ALT and AST levels when compared with diabetic control group at $p \leq 0.05$ (Table 3).

2.10. Lipid profile

When compared to the normal group, the diabetic group had significantly higher levels of serum triglycerides (TG), total cholesterol (TC), and low-density lipoprotein (LDL), and significantly lower levels of high-density lipoprotein (HDL) at $p \leq 0.05$ (Table 4).

In comparison to the diabetes group, treatment with the extract (200 mg/kg) for 4 weeks led to a considerable drop in serum triglycerides (TG), total cholesterol (TC), and low-density lipoprotein (LDL), as well as a significant increase in high-density lipoprotein (HDL) at $p \leq 0.05$ (Table 4). Additionally, when compared to the diabetic group, treatment with the extract (200 mg/kg) in AgNPs for 4 weeks resulted in a substantial drop in serum triglycerides (TG), total cholesterol (TC), and low-density lipoprotein (LDL), as well as a non-significant increase in HDL at $p \leq 0.05$ (Table 4). Additionally, when compared to the diabetic group, treatment with gallic acid (40 mg/kg) regularly significantly improved serum levels of

TABLE 2 Effect of *Phragmanthera austroarabica* extract and pure gallic acid versus their AgNPs formulae on Biochemical Measurements in the experimental groups of type II diabetes in rats.

Group	HOMA-IR	Serum insulin (ng/L)	Blood glucose level (Mm/L)	Serum leptin (ng/L)
Normal	14.4 ± 0.87	2.29 ± 0.06	96 ± 3.8	3.7 ± 0.3
Diabetic	73.99 ± 16.7 ^a	7.7 ± 0.28 ^a	171 ± 24 ^a	13.9 ± 1 ^a
Diabetic + pioglitazone (10 mg/kg)	26.4 ± 1.5 ^b	3.8 ± 0.02 ^{ab}	111 ± 5.7 ^b	4.8 ± 0.3 ^b
Extract (200 mg/kg)	21.7 ± 0.73 ^{ab}	4.9 ± 0.06 ^{abc}	101 ± 3.46 ^b	11.5 ± 1.01 ^{ab}
Extract in AgNPs (200 mg/kg)	25.13 ± 2.09 ^{ab}	4.5 ± 0.1 ^{abc}	125.3 ± 7.8 ^b	5.95 ± 0.05 ^{abc}
Gallic acid (40 mg/kg)	21.9 ± 1.22 ^{ab}	4.43 ± 0.16 ^{abc}	111 ± 2.03 ^b	13.25 ± 0.54 ^{abcd}
Gallic acid in AgNPs (40 mg/kg)	18.56 ± 0.43 ^{abd}	4.06 ± 0.06 ^{abcd}	102 ± 0.67 ^b	7.45 ± 0.15 ^{abce}

Biochemical Measurements are expressed as mean ± S.E.M. and analyzed using one-way ANOVA followed by Bonferroni's test for multiple comparisons.

^a $p \leq 0.05$ versus the normal group; ^b $p \leq 0.05$ versus the Diabetic group; ^c $p \leq 0.05$ versus Diabetic + pioglitazone (10 mg/kg); ^d $p \leq 0.05$ Diabetic + Extract (200 mg/kg); ^e $p \leq 0.05$ versus Diabetic + Extract in AgNPs (200 mg/kg); ^f $p \leq 0.05$ versus Diabetic + Gallic acid (40 mg/kg) group, $n = 5$.

TABLE 3 Effect of *P. austroarabica* extract and pure gallic acid versus their AgNPs on liver Enzymes.

Group	Liver index	AST(U/L)	ALT(U/L)
Normal	2.4 ± 0.1	38.9 ± 1	33.8 ± 1.5
Diabetic	3.6 ± 0.2 ^a	92.4 ± 0.5 ^a	77 ± 2.72 ^a
Diabetic + pioglitazone (10 mg/kg)	2.48 ± 0.3 ^b	51.1 ± 1.5 ^{ab}	25.8 ± 2.5 ^b
Extract (200 mg/kg)	2.72 ± 0.038 ^b	88 ± 4.04 ^a	70.5 ± 1.5 ^a
Extract in nano formula (200 mg/kg)	3.5 ± 0.036 ^{bc}	44 ± 1.01 ^{bc}	31 ± 1.01 ^b
Gallic acid (40 mg/kg)	2.8 ± 0.25 ^b	118.5 ± 4.5 ^{abcd}	89.5 ± 1.5 ^{abd}
Gallic acid in nano formula (40 mg/kg)	2.9 ± 0.24 ^b	56 ± 2.02 ^{abcde}	37.5 ± 1.5 ^{bce}

Liver Enzymes are expressed as mean ± S.E.M. and analyzed using one-way ANOVA followed by Bonferroni's test for multiple comparisons.

^a $p \leq 0.05$ versus the normal group; ^b $p \leq 0.05$ versus the Diabetic group; ^c $p \leq 0.05$ versus Diabetic + pioglitazone (10 mg/kg); ^d $p \leq 0.05$ Diabetic + Extract (200 mg/kg); ^e $p \leq 0.05$ versus Diabetic + Extract in AgNPs (200 mg/kg); ^f $p \leq 0.05$ versus Diabetic + Gallic acid (40 mg/kg) group, $n = 5$.

triglycerides (TG), total cholesterol (TC), and low-density lipoprotein (LDL) at $p \leq 0.05$ (Table 4). Additionally, compared to the diabetic group, the AgNPs of gallic acid (40 mg/kg) results were the best because they demonstrated a significant reduction in serum triglycerides (TG), total cholesterol (TC), and low-density lipoprotein (LDL), as well as an increase in serum high-density lipoprotein (HDL) at $p \leq 0.05$ (Table 4).

2.11. Hepatic histopathological analysis

The normal group in the current study showed typical liver architecture with uniform morphology. On the other hand, the

diabetic group showed no abnormal architecture, lobular inflammation or portal tract injury. All treated groups showed enhancement in liver architecture and a significant decrease in the percent of steatosis compared with the diabetic group at $p \leq 0.05$. The percent of steatosis and the histopathological abnormalities were improved in both AgNPs formulae for the extract and the pure compound gallic acid (Figures 4A,B).

Induction of diabetes mellitus type II, with a high fat diet followed by a small dose of STZ (30 mg/kg) accompanied with metabolic disorders such as elevation in blood glucose and serum insulin level, with a decrease in the sensitivity of cellular receptors to insulin, on the other hand, there were alterations in serum hepatic enzymes, leptin and lipid profile. So obesity and all of these results came in line with preceding studies which showed the biochemical metabolic abnormalities that concurrently occurred with the incidence of diabetes mellitus type II (Khodeer et al., 2016, 2019; Eltamany et al., 2020; Zeinab et al., 2020).

The displayed auspicious activity of *P. austroarabica* extract could be attributed to its accumulation of many biologically active secondary metabolites. For example, it comprises gallic acid, methyl gallate and catechin, which were also isolated from most of the genera of the family Loranthaceae (Badr et al., 2013, 2016; Badr, 2014). The three compounds are well-known for potent antioxidant activity (Colon and Nerin, 2012; Asnaashari et al., 2014; Zanwar et al., 2014; Badhani et al., 2015; Rahman et al., 2016; Variya et al., 2020; Liu et al., 2021). Additionally, gallic acid, considered a principal constituent of the plant (determined as 44.8 mg/g of the crude dry extract in the current study) was previously announced as a hypoglycemic agent (Adefegha et al., 2015; Xu et al., 2021). Catechin also had an antidiabetic effect (Samarghandian et al., 2017; Mrabti et al., 2018). Other plant constituents which occur in a lower percentage are also phenolic. For examples; chrysophanic acid, emodin, chrysophanic acid-8-O-glucoside, emodin-8-O-glucoside, pectolinarigenin, quercetin, dillennetin-3-O-glucoside and catechin-4'-O-gallate (Badr, 2014). Many previously published studies have shown that phenolics exhibit potential therapeutic benefits in alleviating diabetes and obesity

TABLE 4 Effect of *Phragmanthera austroarabica* extract and pure gallic acid versus their AgNPs formulae on lipid profile.

Group	Serum TC (mg/dL)	Serum TG (mg/dL)	LDL (mg/dL)	HDL (mg/dL)
Normal	64 ± 2.99	55.1 ± 3.3	23.9 ± 0.3	46 ± 1.1
Diabetic	116.6 ± 3.3 ^a	160 ± 16.3 ^a	55.4 ± 4.4 ^a	20 ± 2.04 ^a
Diabetic + pioglitazone (10 mg/kg)	88.6 ± 1.6 ^{ab}	41.9 ± 2.4 ^b	29 ± 1.99 ^b	40.4 ± 3.4 ^b
Extract (200 mg/kg)	95 ± 2.02 ^{ab}	103.5 ± 2.5 ^{ab}	38 ± 1.01 ^{ab}	39 ± 1.01 ^b
Extract in AgNPs (200 mg/kg)	51.5 ± 1.5 ^{abc}	61 ± 1.01 ^{bc}	29.5 ± 0.5 ^{bc}	29.5 ± 0.5
Gallic acid (40 mg/kg)	79.5 ± 0.5 ^{abcd}	86 ± 7.07 ^{ab}	42.5 ± 0.5 ^{abd}	21.5 ± 0.5 ^{ac}
Gallic acid in AgNPs (40 mg/kg)	59.5 ± 1.5 ^{abcde}	95.5 ± 4.5 ^{abd}	37.5 ± 4.5 ^{ab}	34 ± 5.05 ^b

Lipid profile are expressed as mean ± S.E.M. and analyzed using one-way ANOVA followed by Bonferroni's test for multiple comparisons.

^a $p \leq 0.05$ versus the normal group; ^b $p \leq 0.05$ versus the Diabetic group; ^c $p \leq 0.05$ versus Diabetic + pioglitazone (10 mg/kg); ^d $p \leq 0.05$ Diabetic + Extract (200 mg/kg); ^e $p \leq 0.05$ versus Diabetic + Extract in AgNPs (200 mg/kg); ^f $p \leq 0.05$ versus Diabetic + Gallic acid (40 mg/kg) group, $n = 5$.

complications (Ademiluyi and Oboh, 2013; Ibrahim et al., 2014; Striegel et al., 2015; Rupasinghe et al., 2017).

According to our study, the whole crude plant extract showed promising antioxidant activity. There is an undoubtful correlation between antioxidant and antidiabetic activity. The plants exerting antioxidant impact can conserve β -cells from reactive oxygen species and consequently prevent the occurrence of diabetic disorders (Patel et al., 2012; Sheela et al., 2013; Sekhon-Loodu and Rupasinghe, 2019). However, the results obtained from AgNPs for both extract and the pure compound gallic acid were the best in most measured parameters.

2.12. Antimicrobial activity

Total extract of *P. austroarabica* showed weak antimicrobial activity against *S. aureus*, *Staphylococcus epidermidis*, methicillin-resistant *S. aureus* (MRSA), *B. subtilis*, *Streptococcus mutants*, *Enterococcus faecalis*, *Proteus vulgaris*, *Pseudomonas aeruginosa* and, *Cryptococcus neoformans*. The activity of the extract ranged from 33 to 67% relative to the activity of positive control, where the highest antimicrobial activity was shown against MRSA. However, *P. austroarabica* extract showed no antibacterial activity against *Bacillus cereus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Salmonella typhimurium*. Similarly, *P. austroarabica* extract demonstrated no antifungal activity against *Candida albicans*, *Aspergillus fumigatus*,

Aspergillus flavus, or *Aspergillus niger*. In consistence with others, there was a remarkable enhancement in the antimicrobial activity of *P. austroarabica* extract (1.3 up to 2.7-fold increase in inhibition zone diameters) when formulated with green synthesized AgNPs using only 10-fold less than the crude extract concentration (Marrez et al., 2019). Inhibition zone diameters of *P. austroarabica* extract and AgNPs obtained using agar plate diffusion assay are shown in Table 5. The fold change in antimicrobial activity of green synthesized AgNPs relative to *P. austroarabica* extract is shown in Figure 5.

The AgNPs demonstrated remarkable activity against the Gram-negative pathogens *P. vulgaris* (MIC 2.5 μ g/ml), *P. aeruginosa* (MIC 5 μ g/ml) in addition to *K. pneumoniae* (MIC 10 μ g/ml). Furthermore, a promising antimicrobial activity was shown against the Gram-positive pathogen *S. mutants* (MIC 1.25 μ g/ml) and MRSA (MIC 10 μ g/ml). Minimum inhibitory concentrations (μ g/ml) of *P. austroarabica* extract and AgNPs obtained using agar plate diffusion assay are shown in Table 6. Our results coincide with previous reports (Xu and Lee, 2001; Cushnie and Lamb, 2005; Li et al., 2015; Jaisinghani, 2017; Abhishek et al., 2019; Marrez et al., 2019; Yang et al., 2020; Albutti et al., 2021; Nguyen and Bhattacharya, 2022; Qanash et al., 2022) that demonstrated the strong antimicrobial activity of either phenolics (namely gallic acid), flavonoids (in particular quercetin) or plant extract rich in these chemical constituents toward a number of microorganisms including *P. vulgaris*, *P. aeruginosa*, *K. pneumoniae*, and MRSA. These pathogens are well-documented eitological agents that were previously reported to be associated with hospital acquired infections (Khan et al., 2015; Haque et al., 2018; Centers for Disease Control and Prevention (CDC), 2019). The remarkable antimicrobial activity of the AgNPs-based extracts suggests its usage as efficective disinfectants in health care yards. Furthermore, similar to others (Yi et al., 2011; Osonga et al., 2019), we demonstrated remakable antimicrobial activity against some oral pathogens such as *S. mutants* and to a lesser extent against *E. faecalis* which play a central role in dental carries and root canal infections (Krzyszciak et al., 2014; Blancas et al., 2021; Tu et al., 2022). This implies the potential benefits of the AgNPs-based extracts in preventing dental diseases and promoting oral health. The *P. austroarabica* extract under investigation in the current study is rich in gallic acid and quercetin. Based on previous literature (Simoes et al., 2009; Borges et al., 2013; Kang et al., 2018; Osonga et al., 2019; Alvarado-Martinez et al., 2020), the proposed antibacterial activity of these compounds is primarily through disruption of outer membrabe integrity and permeabilization. Additional antibacterial activity has been reported for quercetin through targetting DNA gyrase and interfering with nucleic acid synthesis (Simoes et al., 2009; Osonga et al., 2019). Moreover, antibiofilm activity aginst oral pathogens forming dental plaques have also been demonstrated (Albutti et al., 2021). Furthermore, anti-proteus activity of natural plant extracts rich in gallic acid and quercetin have also been reported for *Proteus mirabilis*, a principle cause for urinary tract infections and kidney stone

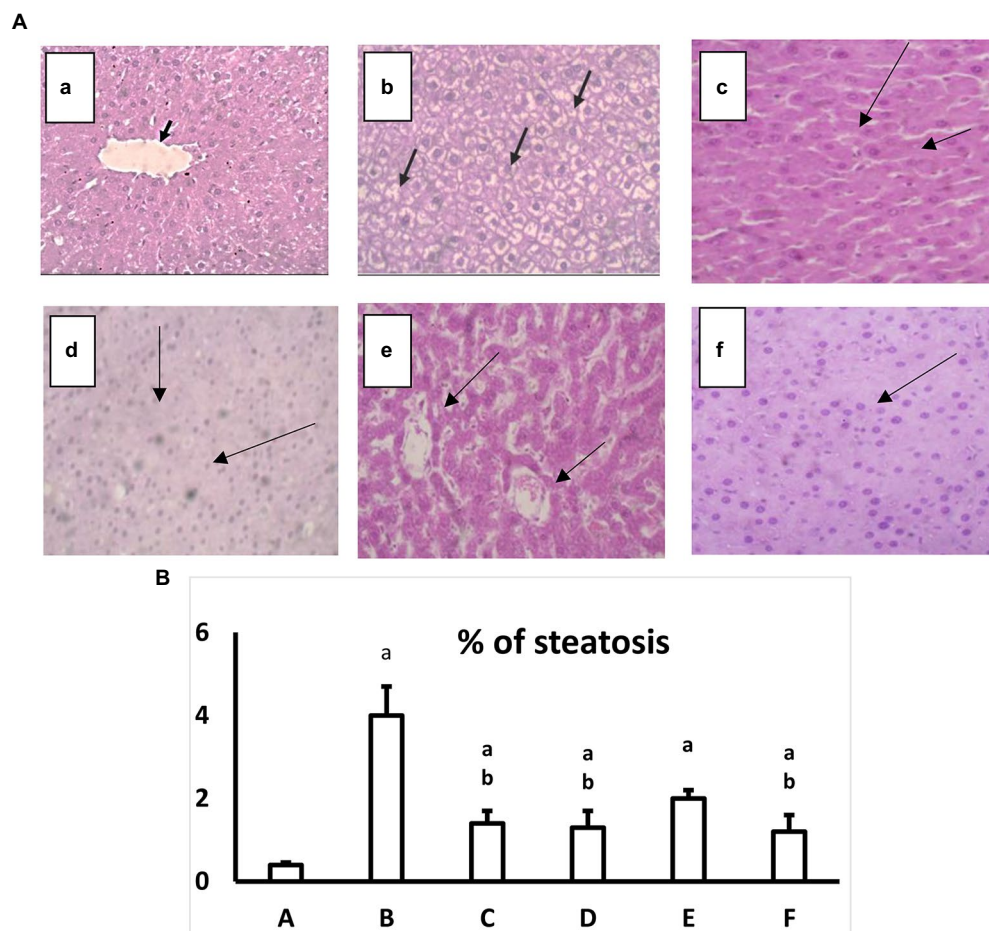


FIGURE 4

(A) Hematoxylin and eosin-stained liver specimen histopathological image at a high magnification $\times 40$. a: Normal group where hepatocytes uniformly distributed in plates radiating from the central vein may be seen in the histopathology photos for liver slices from the normal group (black arrows; H&E, $40\times$). b: Diabetic group, where hepatocytes exhibit signs of damage, including hydropic degeneration and steatosis (black arrows; H&E, $40\times$). c: Diabetic+ extract (200mg/kg) shows Significant hydroponic degeneration in hepatocytes (arrows; H&E, $40\times$). d: Diabetic+extract in AgNPs (200mg/kg) group, which shows There is a mild reduction in hydropic degeneration of hepatocytes (Black arrows) with Congested sinusoids (H&E, $40\times$). e: Diabetic+ Gallic acid (40mg/kg) the group which shows mild hydropic degeneration (Black arrows), with some hepatocytes, regain uniform morphology (H&E, $40\times$). f: Diabetic+ Gallic acid (40mg/kg) in AgNPs group shows Uniform hepatocytes (H&E, $40\times$). (B) Effect of regular and AgNPs of the extract versus the pure gallic acid in regular and AgNPs on a percent of liver steatosis. a: Normal group. b: Diabetic group. c: Diabetic+Extract (200mg/kg). d: Diabetic+Extract (200mg/kg) in AgNPs. e: Diabetic+ Gallic acid (40mg/kg). f: Diabetic+ Gallic acid (40mg/kg) in AgNPs. One-way ANOVA is used to evaluate the data, which is then followed by Bonferroni's test for multiple comparisons. Results are shown as means S.E.M. ^a $p \leq 0.05$ versus the normal group. ^b $p \leq 0.05$ versus the Diabetic group, $n=5$.

formations. [Smanthong et al. \(2022\)](#) have shown the ethanolic extract of *Sida acuta* Burm. F. which is rich in gallic acid and quercetin, to exhibit potent antiviral activity through interfering with swarming motility and urease activity of *P. mirabilis*. In addition, *Sida acuta* Burm. F. extract showed modest potency on anti-struvite crystallization, hence interfering with kidney stone formation. In the present study, we have shown remarkable antimicrobial activity of the AgNPs-based extract of *P. austroarabica* against *P. vulgaris*. A similar mechanism of action can be hypothesized against *P. vulgaris* as both *P. mirabilis* and *P. vulgaris* account for the vast majority of proteus species clinical isolates, in particular nosocomial urinary tract infections. They both are urease positive and display swarming motility as major virulence factors ([Bennett et al., 2019](#)).

3. Materials and methods

3.1. Plant material and extraction process

P. austroarabica was gathered from Abha, in the Southwestern region of King of Saudi Arabia. The plant was taxonomically identified at the Faculty of Science, King Abdulaziz University. To prepare the extract, 600 g of the dry plant were finely powdered and extracted with methyl alcohol ($4 \times 1,000$ ml) at ambient temperature, then concentrated under vacuum by rotary evaporator to give finally 75 g of dry extract. The dry extract was maintained in a refrigerator till use.

TABLE 5 Inhibition zone diameters of *Phragmanthera austroarabica* extract (10mg/ml) and AgNPs (1mg/ml) obtained using Agar plate diffusion assay.

Strain	Diameter of inhibition zone (mm)		
	Extract	AgNPs	Positive control
Gram positive bacteria			
<i>Staphylococcus aureus</i> ATCC 25923	10 ± 1	13 ± 1	24 ± 0
<i>Staphylococcus epidermidis</i> RCMB 009-(2)	10 ± 1	17 ± 1	28 ± 1
Methicillin-Resistant <i>Staphylococcus aureus</i> (MRSA) ATCC 4330	10 ± 0	15 ± 1	15 ± 0.58
<i>Bacillus subtilis</i> NRRL B-543	11 ± 0.58	16 ± 0.58	26 ± 1
<i>Bacillus cereus</i> RCMB 027-(1)	NA	13 ± 1	25 ± 0
<i>Streptococcus mutants</i> ATCC 25175	11 ± 0.58	18 ± 0.58	22 ± 0.58
<i>Enterococcus faecalis</i> ATCC 29212	12 ± 0.58	15 ± 0.58	26 ± 1
Gram negative bacteria			
<i>Escherichia coli</i> ATCC 25922	NA	10 ± 0.58	30 ± 1
<i>Klebsiella pneumoniae</i> ATCC 13883	NA	15 ± 1	21 ± 0.58
<i>Enterobacter cloacae</i> ATCC 23355	NA	15 ± 0.58	30 ± 0.58
<i>Salmonella typhimurium</i> ATCC 14028	NA	13 ± 0.58	17 ± 1
<i>Proteus vulgaris</i> ATCC 13315	10 ±	27 ± 0.58	25 ± 1
<i>Pseudomonas aeruginosa</i> ATCC 27853	9 ±	22 ± 1	27 ± 0
Fungi			
<i>Candida albicans</i> ATCC 10231	NA	NA	20 ± 0.58
<i>Aspergillus fumigatus</i> RCMB 002008	NA	NA	17 ± 1
<i>Aspergillus flavus</i> RCMB 002002	NA	NA	16 ± 1
<i>Aspergillus niger</i> RCMB 002005	NA	NA	15 ± 0
<i>Cryptococcus neoformans</i> RCMB 0049001	9 ± 0.58	12 ± 1	25 ± 0

NA, No Antimicrobial Activity. The results shown in bold underwent further testing to determine minimum inhibitory concentration (MIC).

3.2. Preparation of standard solution

The analytical standard (gallic acid) was obtained from Sigma Chemical Co. Stock solution was prepared by accurately weighing 100 mg of gallic acid, dissolved in 10 ml of methanol, then the volume was adjusted to 100 ml. Serial dilutions were prepared using this stock solution to construct the calibration graph.

3.3. Determination of gallic acid using GS-MS

Quantitation of gallic acid was achieved by GC (Agilent Technologies 7890A) interfaced with a mass-selective detector (MSD, Agilent 7000) equipped with a polar Agilent DB-5 ms (5%-phenyl methyl poly siloxane) capillary column (30 m × 0.25 mm i. d. and 0.25 μm film thickness). Helium was the carrier gas, and the linear velocity was 1 ml/min. The temperatures of the injector and detector were 200°C and 250°C, respectively. The injected volume was 1 μl. Mass operating parameters were 70 eV for ionization potential and 250°C as interface temperature.

3.4. Determination of the antioxidant activity of *Phragmanthera austroarabica*

The antioxidant activity of the plant extract was assessed using the DPPH free radical scavenging test as previously described (Yen and Duh, 1994; Eltamany et al., 2020). Data was recorded at intervals of one min. to measure the decline in absorbance at 515 nm, and H₂O₂ was used as a positive control.

The extract performed the Ferric reducing antioxidant power assay (FRAP) spectrophotometrically according to the previously described method (Oyaizu, 1986; Ferreira et al., 2007). Absorbance was assessed at 700 nm, and ascorbic acid was used as a positive control. The data were displayed as mMol Fe+2 equivalent/g dry sample.

The extract's total antioxidant capacities (TAC) were defined spectrophotometrically using phosphomolybdenum assay. The method was done as previously declared (Prieto et al., 1999; Eltamany et al., 2022). The absorbance was measured at 695 nm, and the effect was expressed as mg equivalents of gallic per g of extract (mg GAE/g). In all the measurements, UV/Vis spectrophotometer (Milton Roy, Spectronic 1,201, Houston, TX, United States) was utilized.

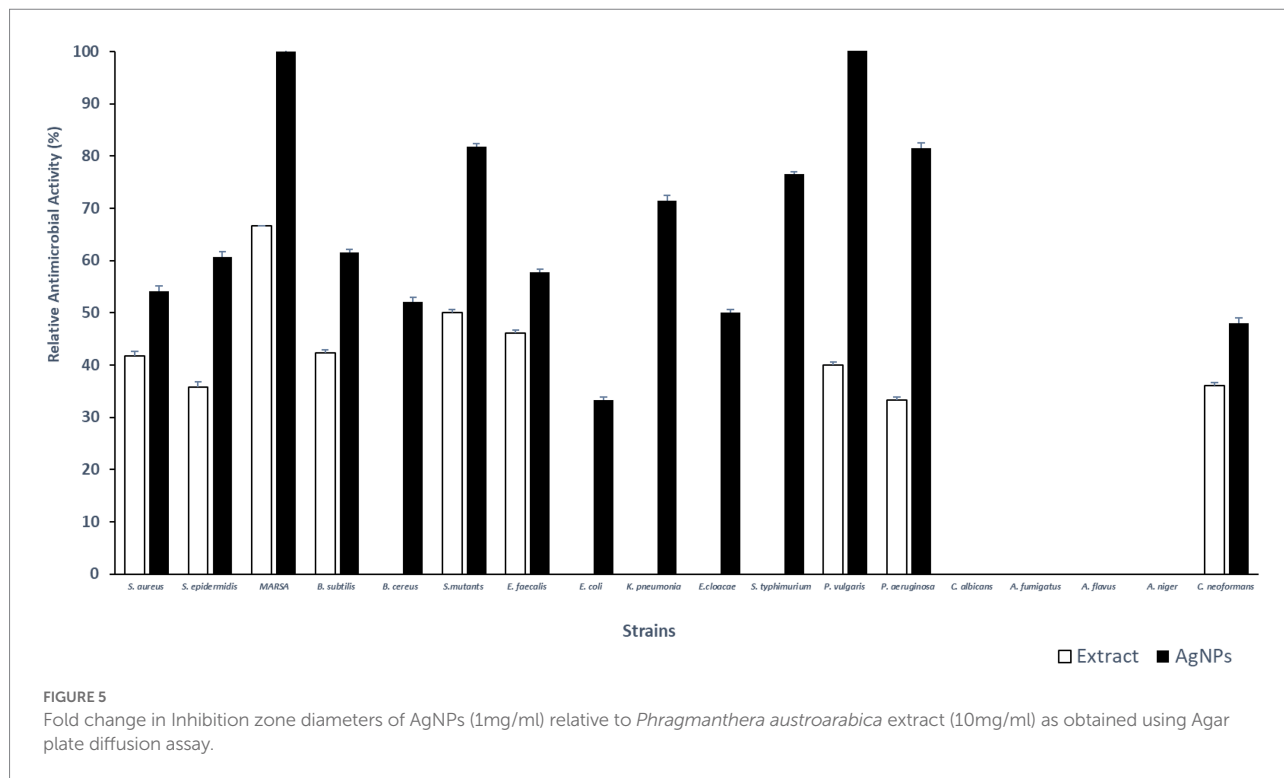


TABLE 6 Minimum inhibitory concentrations ($\mu\text{g/ml}$) of *Phragmanthera austroarabica* extract (10mg/ml) and AgNPs (1mg/ml) obtained using Agar plate diffusion assay.

Strain	Minimum inhibitory concentration ($\mu\text{g/ml}$)
Methicillin-Resistant <i>Staphylococcus aureus</i> (MRSA) ATCC 4330	10
<i>Streptococcus mutants</i> ATCC 25175	1.25
<i>Klebsiella pneumoniae</i> ATCC 13883	10
<i>Salmonella typhimurium</i> ATCC 14028	10
<i>Proteus vulgaris</i> ATCC 13315	2.5
<i>Pseudomonas aeruginosa</i> ATCC 27853	5

3.5. Determination of total phenolic content of *Phragmanthera austroarabica*

The total phenolic contents of *P. austroarabica* extract was assessed by the Folin–Ciocalteu colourimetric method as previously reported (Prieto et al., 1999).

3.6. Biosynthesis and preparation of silver nanoparticles

The biosynthesis of AgNPs of the total extract of *P. austroarabica* was done using a modified method, as previously reported by Mortazavi-Derazkola et al. (2021), with slight

modifications. Initially, 10 mg of the extract were dissolved in 1 ml ethanol, then added to 10 ml of 10 mM AgNO_3 . The pH of the solution is adjusted by adding drops of 1 M NaOH. The mixture was agitated in dark at 600 rpm for 60 min at room temperature. The color was changed gradually till yellowish brown, and the color change was observed at 5, 30 and 60 min.

For gallic acid coated AgNPs, the method used by Li et al. (2015) was used. Briefly, 4 ml of 10 mM AgNO_3 were added to 22 ml of double-distilled water under magnetic stirring at room temperature. Then, 4 ml of 10 mM gallic acid were added, and the pH value was adjusted to 11.0 with 1 M NaOH. Subsequently, the reaction was maintained at room temperature for 30 min.

The AgNPs of both *P. austroarabica* extract and gallic acid were purified by the same procedure. Centrifugation at 15,000 rpm for 1 h. at 4°C was done using a cooling centrifuge (PRO-Research K241R; Centurion, West Sussex, United Kingdom). The AgNPs were re-dispersed in double-distilled water and sonicated for 30 s in the sonicating water bath. Then centrifuged at 15,000 rpm for 1 h at 4°C. The washing procedures using double-distilled water were repeated three times, and then the nanoparticles were stored at 4°C for further investigations.

3.7. Characterization of silver nanoparticles

3.7.1. UV-vis absorbance spectroscopy

The UV-Vis spectrum of the prepared AgNPs at predetermined time intervals was acquired using a double-beam

spectrophotometer (V630, Jasco, Tokyo, Japan). The spectrum was recorded throughout a range of 300–600 nm.

3.7.2. Transmission electron microscopy

The morphology and the size of the prepared AgNPs were examined using transmission electron microscopy (TEM). The samples were further diluted 50 times with double distilled water. Then the diluted samples were negatively stained with phosphotungstic acid and dried on carbon-coated copper grids. The thin film formed was air-dried at room temperature and observed using a transmission electron microscope (JTEM model 1,010, JEOL®, Tokyo, Japan) with an accelerating voltage of about 80 kV. The size distribution of AgNPs was analyzed using Nano measurer 1.2.5 software.

3.7.3. Size analysis and surface charge determination

Average particle size expressed as Z-average, particle size distribution, is described by polydispersity index (PDI) and zeta potential, indicating a surface charge. Furthermore, they were measured using the dynamic light scattering technique (DLS) by Malvern Zetasizer (Nano ZS, Malvern Instruments Ltd., Malvern, United Kingdom). Before analysis, samples were diluted 20 times with distilled water and added to the cell for measurement. All measurements were performed at ambient temperature (25°C).

3.8. Antidiabetic activity

3.8.1. Animal experimentation

In the current investigation, 35 male Wistar rats were employed. The body's initial weight was anywhere between 130 and 170 g. They were kept in clean cages at 21.6°C with regular light and dark cycles. They were given unrestricted access to water and a regular diet or HFD. Under 202209RA2, the Suez Canal University Research Ethics Committee accepted the study's protocol.

3.8.2. Experimental design

Wistar male rats were distributed into six groups, with 5 rats in every group. During the experimentation period, the first group of rats was designated as the normal group and fed a typical chow diet (14 weeks). The other five groups had a diet of HFD (regular diet, lard fat, glucose 7:1:2) for 7 weeks before receiving a low dose of streptozotocin (STZ) of 30 mg/kg (Srinivasan et al., 2005). Rats in all groups had their fasting blood glucose levels measured after 5 days of administration of STZ. Each rat had blood drawn from the tip of its tail, and an automated blood glucometer was used to measure each animal's fasting blood sugar (Super Glucocard, Japan). Then for a further 4 weeks rats in Group II (diabetic control group) were given distilled water (1 ml/kg/day, p.o.). Rats in group III were given the methanolic extract of *P. austroarabica* (200 mg/kg/day, p.o.), while rats in group IV were given the AgNPs formula of *P. austroarabica* (200 mg/kg/day, p.o.). Groups V and VII got gallic acid extract and AgNPs (40 mg/kg). The final body weight was collected when the

treatment regimens were finished. The following equation was used to compute the change in body weight.

$$\Delta \text{Body weight} = \left[\frac{\text{The final body weight} - \text{the initial body weight}}{\text{initial body weight}} \right] * 100$$

The obesity index was similarly determined by

$$\text{Obesity index} = \left(\frac{\text{weight of total adipose tissue}}{\text{final body weight}} \times 100 \right)$$

3.8.3. Processing of liver

Rats were sacrificed under anesthesia. Each rat's liver was removed and washed with a cold saline solution. After weighing the livers, the following formula was used to calculate the liver index: (liver weight/body weight × 100).

The largest hepatic lobe's portion of liver tissue was extracted, formaldehyde-fixed, then hematoxylin–eosin-stained tissue.

3.8.4. Biochemical measurements

3.8.4.1. Liver enzymes

Alanine transaminase enzyme (ALT) and aspartate transaminase enzyme (AST) are measured in accordance to (Pan et al., 2006).

3.8.4.2. Lipid profile

Serum total cholesterol (TC), triglycerides (TGs), high-density lipoprotein (HDL), and low-density lipoprotein (LDL), according to (Allain et al., 1974; Fossati and Prencipe, 1982).

3.8.4.3. Insulin, leptin and HOMA-IR

Following the manufacturer's instructions, the rat insulin and leptin kits were used to measure insulin and leptin serum levels. Insulin resistance was measured using HOMA-IR model (Matthews et al., 1985).

3.9. Antimicrobial assay

The antimicrobial activity was screened against Gram-positive bacteria (*S. aureus* ATCC 25923, *S. epidermidis* RCMB 009-(2), Methicillin-Resistant *S. aureus* (MRSA) ATCC 4330, *B. subtilis* NRRL B-543, *B. cereus* RCMB 027-(1), *S. mutants* ATCC 25175, *E. faecalis* ATCC 29212), Gram-negative bacteria (*E. coli* ATCC 25922, *K. pneumoniae* ATCC 13883, *E. cloacae* ATCC 23355, *S. typhimurium* ATCC 14028, *P. vulgaris* ATCC 13315, *P. aeruginosa* ATCC 27853) and fungi (*C. albicans* ATCC 10231, *A. fumigatus* RCMB 002008, *A. flavus* RCMB 002002, *A. niger* RCMB 002005, *C. neoformans* RCMB 0049001). These strains were obtained from the Regional Center for Mycology, and Biotechnology (RCMB), Al-Azhar University, Cairo, Egypt. Bacterial strains were maintained in Brain-Heart infusion broth,

and fungal strains were maintained in Potato-Dextrose broth. Agar plate diffusion assay was used to screen the antibacterial and antifungal activities as described before (Tomás et al., 2003; Magaldi et al., 2004; Rojas et al., 2006; Valgas et al., 2007; Synytsya et al., 2017; Gonelimali et al., 2018) with some modifications. Briefly, bacterial suspensions with an inoculum size of 1×10^8 CFU/ml were prepared by making a direct suspension of fresh overnight colonies in phosphate-buffered saline. Bacterial inocula were prepared to a density equivalent to a 0.5 McFarland standard. Fungal inocula were prepared using 48 h cultures of potato dextrose broth and adjusted to a spore density of 10^6 spores/ml. A sterile cotton swab was dipped into the adjusted suspension. The dried surface of Mueller-Hinton agar plate was inoculated by streaking the swab over the entire sterile agar surface. Holes with diameters of 6 mm were cut into inoculated plates. Holes were then filled with 100 μ l aliquots *P. austroarabica* extract (10 mg/ml) and AgNPs formula (1 mg/ml). The plates were incubated at room temperature for 5 h and then incubated at 37°C for 24 h for bacteria and 48 h for fungi. A clear inhibition zone of > 6 mm diameter was defined as a positive result. A concentration of 4 μ g/ml of Gentamicin was a positive control for antibacterial activity, and Ketoconazole at a concentration of 100 μ g/ml served as a positive control of antifungal activity. DMSO was a negative control for *P. austroarabica* extract, and distilled water was used as a negative control for AgNPs formula. Strains showing positive results were further tested using holes filled with two-fold serial dilutions (10, 5, 2.5, 1.25, 0.625, 0.3125, 0.15625, 0.078, 0.039, and 0.019 mg/ml) to determine the minimum inhibitory concentration (MIC). Only strains showing inhibition zone diameters comparable to the positive controls (70% or more relative to positive controls) underwent further MIC testing. MIC was recorded as the lowest concentration inhibiting bacterial growth.

3.10. Statistical analysis of the data

Results from the current study were analyzed using the SPSS program version 16 and presented as mean \pm S.E.M. Quantitative variables were analyzed using a one-way analysis of variance (ANOVA), which was then followed by the Bonferroni multiple comparison test. Significant differences were determined at $p \leq 0.05$.

4. Conclusion

The AgNPs prepared using the *P. austroarabica* extract and the phenolic compound gallic acid as reducing and capping agents are small in size, uniform in shape and of uniform size distribution. The nanoparticles show a high negative charge on the surface, indicating high colloidal particles' stability. The presence of the extract or gallic acid on the surface of nanoparticles offers a high surface-to-volume ratio, enhancing their pharmacological activity. Our study deduced that the application of AgNPs was a promising technique for enhancing the efficiency of *P. austroarabica* extract

and gallic acid as antidiabetic agents. These formulae ameliorated body weight, lipid profile, insulin resistance, hyperinsulinemia, liver tissue structure and function. Moreover, the AgNPs formula of the crude extract of *P. austroarabica* potentiated the activity against the Gram-negative pathogens *P. vulgaris*, *P. aeruginosa*, and the Gram-positive pathogen *S. mutants*.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The study protocol was approved by the ethical committee of the Faculty of Pharmacy at Suez Canal University (approval number: 202109RA2).

Author contributions

JB, DK, and SaS: conceptualization. DK, AN, ShS, and SaS: methodology. JB, DK, AN, ShS, MR, and SaS: validation. DK, AN, ShS, RK, MR, and MA: formal analysis. RK and MA: resources. JB and DK: data curation. DK, AN, ShS, and SaS: writing—original draft preparation. JB, DK, and SaS: writing—review and editing. JB, AN, and ShS: supervision. JB, DK, and AN: project administration. RK and MA: funding acquisition. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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