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Silver Nanoparticles Synthesis using Banana Peels Extract and Its in Silico Evaluation for Antibacterial Activity against *Escherichia coli*

Cheong Wei Yi, Syazwani Itri Amran, Huszalina Hussin, Nurliyana Ahmad Zawawi*

Department of Biosciences, Faculty of Science, Universiti Teknologi Malaysia, 81310 Johor Bahru, Johor, Malaysia.

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*Corresponding author
nurliyana@utm.my

Abstract

Metal nanoparticles (NPs) are widely used in biomedical research. One of the potential metal nanoparticles known for its potent antibacterial properties is silver nanoparticles (AgNPs). However, its detrimental consequences on human health have been a significant concern. In this study, AgNPs was synthesized using banana peels by environmentally friendly approach, and their antibacterial activity against Escherichia coli as well as mechanisms were studied in silico. Total phenolic content (TPC), total flavonoid content (TFC), and total tannin acid content (TTC) of the BPE were initially determined by extraction using aqueous and methanolic solutions. A disc diffusion test (DDT) against E. coli was used to confirm the antibacterial activity of the BPE and BPE-AgNPs. An in silico approach was used to conduct molecular docking research to assess the potential antibacterial mechanism of BPE phytochemicals with the proteins of E. coli. The phytochemical content analysis shows that flavonoid has the highest content in the aqueous and the methanol extract, with respective concentrations of 439.60±57.84 mg QE/g DW and 222.42±14.56 mg QE/g DW. According to the results of DDT, BPE-AgNPs demonstrated positive antibacterial activity, while BPE demonstrated negative result. Several flavonoid chemical compounds, including rutin, quercetin, myricetin, naringenin, apigenin, luteolin, morin, galangin, catechin, and chrysin, were examined for their ability to bind to E. coli proteins such penicillin-binding protein, dihydrofolate reductase, and glutamate racemase. Rutin with penicillin-binding protein demonstrated the highest binding affinity, with the lowest free binding energy of -9.96 kcal/mol and the inhibition constant of 0.05 μM. The in silico and molecular docking analysis demonstrated the ability of active components of banana peels to inhibit the activity of the E.coli proteins. These elements not only function as reducing and stabilising agents for AgNP synthesis but also prevent E. coli from growing, which is potential in future antibacterial uses.

Keywords silver nanoparticles, biosynthesis, molecular docking, antibacterial activity, *in silico*

1.0 INTRODUCTION

Nanotechnology is one of the most extensive and popular technologies for research and development in improving products, treating diseases, and serving humanity in many aspects of life (Zhang et al., 2020). It has commanded much interest for its applications in biomedical, agriculture, renewable energy, chemical sensor, and aeronautics (Khan et al., 2021). Several most common nanomaterials were employed for material science and biology studies, for instance, fullerenes, carbon nanotubes (CNT), silver nanoparticles (AgNPs), gold nanoparticles (AuNPs), titanium oxide nanoparticles (TiO_2), zinc oxide nanoparticles (ZnO), iron oxide nanoparticles (FeO), and silica nanoparticles (SiO) (Wei et al., 2015). Among the various metallic nanoparticles, silver nanoparticles (AgNPs) have gained strong interest due to their excellent antibacterial capabilities, catalytic activity, chemical stability, high thermal properties, and non-linear optical behavior (Salleh et al., 2020).

The synthesis of AgNPs has been significantly performed by the chemical and physical approaches (Wei et al., 2015). However, the methods of synthesizing the AgNPs using these approaches may cause hazardous substance production problems (Gudikandula & Charya Maringanti, 2016). Besides its high biosynthesis for the antibacterial activity, AgNPs have great potential for other applications such as pharmaceutical, personal care products including textiles (Shu et al., 2020). Up to now, the exact mechanism of the action of green AgNPs for antibacterial activity has not been well documented, although it is known that AgNPs have strong biological material as a reducing agent. AgNPs may elicit the desired pharmaceutical response and safer silver synthesis through its reaction with receptors responsible for yielding antibiotic activity. Several proteins within the bacteria working together with the phytochemical compounds from the banana peels for antibacterial activity have been identified (Siddique et al., 2018). However, no specific method is still satisfactory for this task. Thus, an *in silico* study using targeted protein *E.coli* is essential to know the mechanism of the interaction between phytochemicals of BPE with the bacterial protein that leads to the antibacterial effect. The study of BPE-AgNPs inhibitory activity and its mechanism of binding through *in silico* study provides an insight into the antibacterial properties of green AgNPs using a biological approach. This research not only reduces the emissions of hazardous chemicals to the environment by using fruit waste, but also reduces energy consumption. The study of the inhibitory activity of BPE-AgNPs is also important to establish the exact mechanism of antibacterial activity towards pathogenic bacteria, *E.coli*. The biocomputational method may play an important role in making the process rapid and cost-effective along with the experimental studies performed in the laboratory (Basu et al., 2020).

2.0 MATERIALS AND METHOD

2.1 Materials

Banana peels were collected from Kedai Goreng Pisang Nurul Faqar in Taman Universiti, Skudai, Johor. The deionized water used to clean the banana peels was prepared from Sartorius Arium pro DI Ultrapure Water in Nanomaterial Laboratory, Universiti Teknologi Malaysia (UTM).

2.2 Banana peels extracts preparation and phytochemical contents analysis

This study focuses on the biosynthesize of AgNPs by using banana peel extract as the stabilizing and reducing agent for antibacterial activity against *E. coli*. Firstly, the banana peels were collected randomly, and some pretreatment steps were undergone. The banana peels were washed with deionized water and died at 55°C for 24 hours. The dried banana peels were ground until they became powder, and the banana peels extract was prepared using different extract solvents, aqueous and methanol. The analysis of the phytochemical contents of banana peel extract was performed by undergoing total phenolic content (TPC), total flavonoid content (TFC), and total tannin content (TTC). The Folin-Ciocalteau method was used to analyze the total phenolic contents of the BPE. Flavonoid content was estimated using the aluminium chloride colorimetric method, while total tannic acid was determined by preparing 35% of Na_2CO_3.

2.3 Biosynthesis silver nanoparticles and antibacterial assay

Subsequently, the antibacterial activity of BPE-AgNPs against Gram-negative bacterium, *E. coli* was conducted using disc diffusion test (DDT). Nutrient agar was prepared to undergo bacterial inoculum, while Mueller-Hinton agar was prepared to perform the antibacterial test. Disc diffusion test (DDT) was performed to evaluate the antibacterial activity of BPE-AgNPs against *E.coli.* 4 to 5 colonies of the *E. coli* were taken by inoculation loop, and the colonies were transferred into 0.9% (w/v) of saline water. They were mixed well before streaking on the MHA plate. The sterile cotton swab was used to dip into the standardized bacterial suspension and spread evenly on the MHA plate. Before spreading on the MHA plate, the cotton swab was pressed against the test tube wall to ensure the inoculum is not in excess. The bacteria suspension was spread on the MHA plates evenly by swabbing 6 times at different angles and around the plates on the MHA. Discs were prepared using the Whatman filter paper and sterilized before use. Each of the sterilized discs was pipetted with 0.1µl of the BPE-AgNPs. BPE, and deionized water were allowed to dry before placing the disc with the test samples on the agar plates with *E. coli*. Commercial antibiotics ampicillin which acts as the positive control was used. Around 10 minutes after drying the discs sample, the discs were placed on the agar plates with *E. coli* and pressed gently. To ensure reliability, the steps above were repeated at least three times. The plates were incubated at 37°C overnight. The presence of inhibition zone around the disc indicated the positive result of BPE-AgNPs and showing antibacterial activity.

2.4 *In silico* study and antibacterial evaluation

Using *in silico* approach, a molecular docking studies was conducted to study possible mechanism between the target protein *E.*

coli and binding interaction between the target proteins of *E. coli* and the phytochemicals of the BPE. The selected proteins, which are penicillin-binding protein, dihydrofolate reductase, and methionine aminopeptidase are bacterial *E. coli* proteins that are deemed a good target with antibacterial agents. The crystal structures of the selected target proteins from *E. coli* were retrieved from RCSB PDB (https://www.rcsb.org/) with PDB ID as follows: penicillin-binding protein (PDB ID: 3VMA), dihydrofolate reductase (PDB ID: 1RF7), and glutamate racemase (PDB ID: 5HQT) (King et al. 2017, Cao et al., 2018, Liu et al., 2016). The phytochemicals that were selected for docking with bacterial proteins are based on the BPE flavonoid content that was the highest in section 2.2. Rutin, quercetin, myricetin, naringenin, apigenin, luteolin, morin, galangin, and catechin and chrysin are among the flavonoid chemicals chosen for study, according to findings from Behiry et al. (2019). The molecular formula and molecular weight of each ligand are exported from PubChem while each of 2D molecular structures was extracted from OpenBabel.

Binding affinity of these compounds against selected bacterial proteins were predicted using computational docking analysis. Using AutoDock 4, these compounds were visualized, Gasteiger charges were added and the rotatable bonds were determined (Almutairi et al., 2014).

3.0 RESULTS AND DISCUSSION

It is well known that banana peel extracts contain significant amounts of phenolics and that silver salts are efficiently converted into nanoparticles to form AgNPs. The total flavonoid content (TFC) extracted from the aqueous solution demonstrated the highest value (439.6 mg QE/g DW), followed by the total tannic acid content (343.2 mg TAE/g DW), and the total phenolic content (267.7 mg GAE/g DW), as shown by the data obtained in **Table 1** and **Figure 1**.

Table 1 A comparison of total phenolic content (TPC), total flavonoid content (TFC) and total tannic content (TTC) from banana peels extracted in aqueous and 80% (v/v) methanol.

Solvents	TPC (mg GAE/g DW)	TFC (mg QE/g DW)	TTC (mg TAE/g DW)
Aqueous	267.7 ±13.426	439.6 ±57.84	343.2 ±6.70
80% (v/v) Methanol	215.6 ±0.531	222.4 ±14.56	151.9 ±1.41

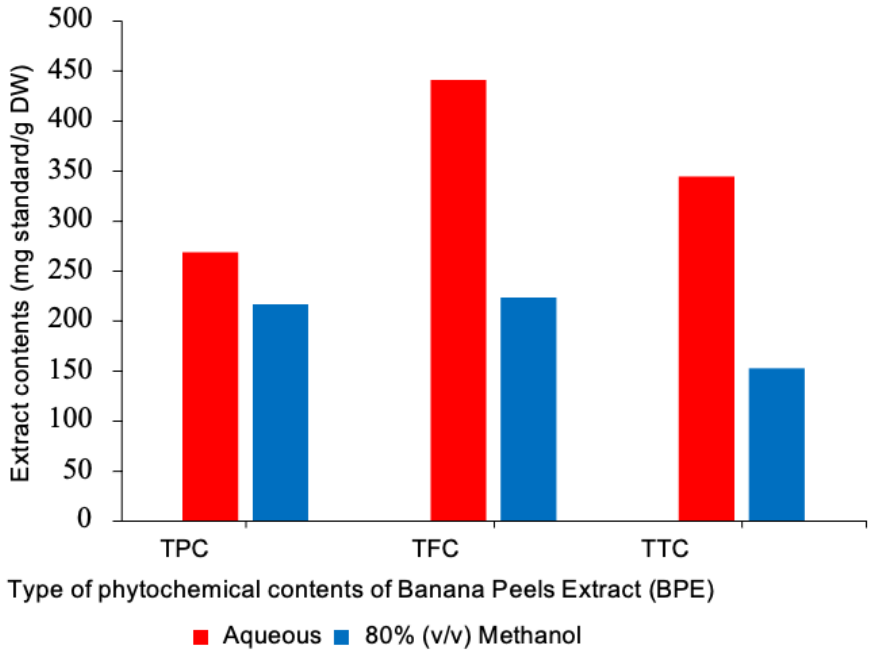

Figure 1 A comparison of total phenolic content (TPC), total flavonoid content (TFC) and total tannic content (TTC) of banana peel extract in aqueous and 80% methanol.

From the results, the maximum amounts of flavonoids, total phenolics and total tannic acid were present in the methanolic extract. The TFC which showed as the largest content in the banana peels, was selected for the upcoming in silico study. The choice of the ligands from PubChem was exported from Protein Data Bank for docking analysis with the *E. coli* proteins. For preparing BPE-AgNPs for antibacterial assessment *in vitro*, banana peel extract was utilized for its safe, eco-friendly following method by Sarah (2020).

In the biosynthesis of BPE-AgNPs, the confirmation of BPE-AgNPs formation was determined through colorimetric analysis. After mixing the silver salt with the extract, the colour turned brownish after three days incubation at 70 ºC. The colour changes demonstrate that the reduction of silver ions produces silver atoms, which are then formed by the growth of oligomeric clusters, ultimately forming colloidal silver particles (Paul et al., 2014). Additionally, the BPE-AgNP was also detected at 430 nm in UV-Vis spectrophotometer, confirming the successful synthesis of silver nanoparticles (Dehghanizade et al., 2018).

To demonstrate AgNPs antibacterial activity, the banana peel extract (BPE) and BPE-AgNP were tested against *E. coli* through a disc diffusion test (DDT). The deionized water and ampicillin were used as a control for the study. **Figure 2** depicts the result of DDT's antibacterial activity against the Gram-negative bacteria *E. coli*. The results of the diagram depicting the inhibition zone of the antibacterial activity of the investigated materials were given in millimetres (mm).

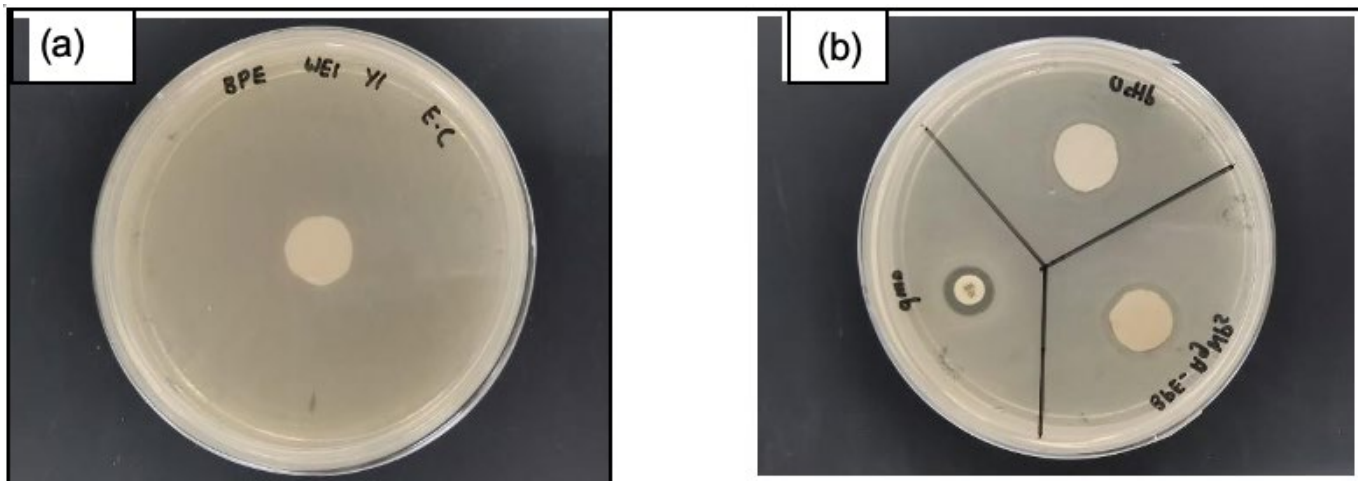

Figure 2 Antibacterial activity of BPE (a) as compared to BPE-AgNPs , deionized water , and ampicillin (Amp) in (b) against *E.coli* by disc diffusion test (DDT). BPE-AgNP showed smaller inhibit zone of 4±0.05 mm compared to control Amp with 5±0.05 mm, and no inhibition zone were observed in discs of BPE and deioinized water sample.

Based on **Figure 2**, BPE-AgNPs that showed 4 mm inhibition zone around the disc indicated its antibacterial activity against *E.coli*. Both BPE sample (without AgNPs) and deionized water (negative control plate) showed no inhibitory activity. AgNPs' antibacterial action in BPE- AgNPs is likely due to the silver cations they create, which serve as storage spaces for the Ag^{+} bactericidal agent. It is thought that Ag ions bind to sulfhydryl groups and reduce disulfide bonds to denaturate proteins. AgNPs may have been attached to the cell membrane's surface to interfere with its function, penetrate bacteria, and release Ag (Dakal et al. 2016).

The molecular docking approach was used to study the binding affinity of phytochemical compounds from BPE against bacterial proteins. Before starting the molecular docking using AutoDock4, control docking was carried out to mimic the crystal structure using the docking procedure. From the result of control docking, the x, y, and z coordinates for three of the bacterial proteins, penicillin-binding protein, glutamate racemase, and dihydrofolate reductase were indicated to show the position of active site in the protein structure to which the library compounds going to bind. **Table 2** shows the Root Mean Square Deviation (RMSD), free binding energy, and constant inhibition value of redocking of the co-crystal ligand into the protein structure. According to the free binding energy, the docking models were ordered. Since low binding energy adds to the complex's high stability, the docking model will be organised higher the lower the free binding energy (Fu et al., 2018). However, the most careful parameter in the control docking was the value of RMSD. The RMSD calculates the difference between the protein's initial structural configuration and final conformation. The deviations made throughout the simulation determine the stability of the protein's structural structure (Mangat et al., 2022). As a result, the smaller the divergence, the higher the RMSD value, indicating that the docking pose corresponded to the binding site.

Table 2 The Root Mean Square Deviation (RMSD), free binding energy, and inhibition constant of control proteins.

Control Protein	Co-crystal ligand	Root Mean Square Deviation (RMSD)	Rank model	Free binding energy, kcal/mol	Inhibition constant Ki, μM
Penicillin-binding Protein (PDB ID: 3VMA)	M0E	2.14	31	-3.62	2210
Dihydrofolate reductase (PDB ID: 1RF7)	DHF	0.60	16	-7.80	1.90
Glutamate racemase (PDB ID: 5HQT)	NHE	2.39	49	-3.39	3280

The molecular docking method was used to investigate the binding affinity of phytochemical compounds from BPE against certain proteins from *E. coli*. According to research that examined the phytochemical contents of BPE, flavonoids have the highest concentration of phytochemicals. To explore the binding affinity against the chosen *E. coli* proteins that are the targets of antibacterial action, chemical compounds from flavonoids were chosen. The results of the free binding energy, inhibition constant, and rank model of the chosen chemical compounds of flavonoids from BPE against penicillin-binding protein, dihydrofolate reductase, and glutamate racemase, respectively, were used to illustrate the molecular docking study between chemical compounds from flavonoids and proteins in **Tables 3, 4, and 5**.The three most effective chemical compounds of flavonoids from BPE against the targeted proteins, penicillin-binding protein (PDB ID: 3VMA), dihydrofolate reductase (PDB ID: 1RF7), and glutamate racemase (PDB ID: 5HQT), are rutin, naringenin, and luteolin, according to the analysis of molecular docking. LigPlot was used to predict the interaction between them in a 2D structure to confirm that there is contact between the chemical compounds and the active site of the targeted proteins. Among three chemical compounds, rutin showed the strongest binding energy, and inhibition constant followed by luteolin and naringenin (**Table 3, 4 and 5**).

Table 3 Molecular docking results of selected chemical compounds of flavonoids from BPE against the penicillin-binding protein (PDB ID: 3VMA).

Protein PDB ID	Compound	Free binding energy, kcal/mol	Inhibition constant Ki, μM	Rank model
3VMA	Control: M0E	-3.62	2210	31
	Rutin	**-9.96**	**0.05**	**38**
	Quercetin	-7.37	3.96	15
	Myricetin	-7.14	5.83	49
	Naringenin	-7.41	3.69	24
	Apigenin	-6.90	8.72	18
	Luteolin	-7.49	3.23	4
	Morin	-7.09	6.36	20
	Galangin	-7.26	4.77	15
	Catechin	-7.02	7.20	30
	Chrysin	-7.18	5.49	13

Table 4 Molecular docking results of selected chemical compounds of flavonoids from BPE against dihydrofolate reductase (PDB ID: 1RF7).

Protein PDB ID	Compound	Free binding energy, kcal/mol	Inhibition constant Ki, μM	Rank model
1RF7	Control: DHF	-7.80	1.90	16
	Rutin	**-9.55**	**0.10**	**17**
	Quercetin	-8.08	1.19	33
	Myricetin	-8.03	1.29	22
	Naringenin	-8.62	0.48	27
	Apigenin	-8.25	0.90	40
	Luteolin	-8.47	0.62	18
	Morin	-7.70	2.28	32
	Galangin	-8.20	0.97	28
	Catechin	-6.01	39.32	18
	Chrysin	-8.23	0.93	32

Table 5 Molecular docking results of selected chemical compounds of flavonoids from BPE against glutamate racemase (PDB ID: 5HQT).

Protein PDB ID	Compound	Free binding energy, kcal/mol	Inhibition constant Ki, μM	Rank model
5HQT	Control: NHE	-3.39	3280	49
	Rutin	**-7.63**	**2.55**	**10**
	Quercetin	-5.61	76.91	30
	Myricetin	-5.33	124.43	24
	Naringenin	-5.80	55.74	37
	Apigenin	-5.62	76.31	17
	Luteolin	-5.87	50.22	27
	Morin	-5.09	185.81	5
	Galangin	-5.06	196.02	33
	Catechin	-5.78	58.07	20
	Chrysin	-5.70	65.85	31

The docking results reported in **Table 6** demonstrated that hydrophobic bonds, which are potential antibacterial agents against penicillin-binding protein, dihydrofolate reductase, and glutamate racemase, have contributed more to the interaction of binding sites than hydrogen bonds. Adding a functional group or metal atom to the ligand or target site can increase specificity and binding affinity for one of the targets. To improve binding sites and binding affinity to that ligand's more polar amino acids, new polar ligand-receptor interactions are likely to have led to the inclusion of polar functional groups (Andrew, 2008). Additionally, by focusing hydrogen bonding to the hydrophobic core of the complex, hydrophobic interactions can be improved, increasing binding affinity (Varma et al., 2010).

Table 6 Binding interaction of Rutin, Naringenin, and Luteolin with the residues of active sites of the protein.

Protein	Ligand	Interacting Residues	
		Hydrogen Bonds	Hydrophobic Bonds
Penicillin-Binding Protein (PDB ID: 3VMA)	M0E	ALA-357, TRY-315, LYS-274	SER-358, ILE-359, GLY-356, GLU-281, LYS-355, VAL-354, ASN-275, VAL-314, SER-280
	Rutin	GLN-271, LYS-274	VAL-354, VAL-314, GLU-281, SER-280, TYR-315, ARG-325, ASN-275
	Naringenin	LYS-355, GLU-233, GLN-271, TYR-310, TYR-315	ALA-357, GLY-356, VAL-354, VAL-314, ASN-275
	Luteolin	ALA-357, GLN-271, TYR-310, LYS-355	TYR-315, GLY-356, VAL-354, VAL-314, ASN-275, GLN-271, TYR-310
Dihydrofolate reductase (PDB ID: 1RF7)	DHF	ARG-57, TRP-22, ASP-27, ARG-52, LYS-32	LEU-54, PHE-31, ILE-50, GLU 17, ALA-7, LEU-24, LEU-28
	Rutin	SER-138, PHE-140	PHE-137, GLU-139
	Naringenin	ASP-27, GLY-15, TYR-100	PHE-31, ILE-14, ALA-6, ALA-7
	Luteolin	TYR-100, ILE-5, ALA-7, GLY-15, ILE-94	ALA-6, ILE-14, MET-20, TRP-22, PHE-31
Glutamate racemase (PDB ID: 5HQT)	NHE	GLN-131, LYS-88	ARG-53, TYR-127, GLN-52, TRP-57, GLY-55, ARG-126
	Rutin	GLN-52, GLN-131, TRP-57, GLU-130, ARG-126	ARG-54, GLY-55, TYR-127, ARG-53
	Naringenin	ARG-53, GLU-130, GLN-52	GLY-55, TYR-127, GLN 131, TRP-57
	Luteolin	GLN-130, GLN-52, ARG-53	ARG-126, TRP-57, GLY-55, GLN-131, TYR-127, GLU-130

4.0 CONCLUSION

Extract of banana peels contained a huge percentage of flavonoid than that of phenolic and tannic acids. Molecular docking study revealed that rutin, naringenin and luteolin from the flavonoid of banana peels demonstrated high binding affinity with the bacterial protein of *E.coli.* Rutin displayed as the most potent antibacterial agent with great affinity and lower binding energy with penicillin-binding protein, dihydrofolate reductase and glutamate racemace. Although qualitative antibacterial activity demonstrated the efficacy of BPE-AgNP against *E. coli,* additional studies are required to prove the antibacterial capabilities of rutin in order to fully comprehend the mechanisms behind its coexistence with silver. This information will allow elucidation of BPE-AgNP as therapeutic agents with less or reduced toxicity.

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