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EXPLORING THE POTENCY OF NOVEL HERBAL DRUG DELIVERY SYSTEMS: A COMPREHENSIVE REVIEW ON ANTIBACTERIAL STUDIES

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ABSTRACT

In a scenario of the ineffectiveness of the current drugs against antibiotic-resistant pathogens, the herbal extracts can serve as an alternative remedy. *Phyllanthus emblica* (gooseberry) leaf extract to synthesize Boron-doped zinc oxide nanosheets (B-doped ZnO-NSs) is deliberated in this article. B doped ZnO-NSs were tested against both gram-positive and gram negative bacterial strains including *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, and *Escherichia coli*. Against gram-negative bacterium (*K.pneumonia and E.coli*), B-doped ZnO displays enhanced antibacterial activity with 26 and 24 mm of inhibition zone, respectively. In this study, we report low cost, green synthesis of AgNPs using fresh fruit extract of *Phyllanthus emblica*. Copper oxide nanoparticles (CuONPs) have emerged as potential antibacterial agents. In this study, we aimed to synthesize CuONPs using *Terminalia chebula (T. chebula)* dried fruit extract and evaluate their antibacterial activity against specific wound pathogen. In the current research, an aqueous extract of *Terminalia chebula* fruit was used to produce silver nanoparticles (AgNPs) in a sustainable manner. UV-visible spectrophotometry, transmission electron microscopy (TEM), and scanning electron microscopy (SEM) were used to characterize the synthesized nanoparticles.*Terminalia bellerica* (TB) dry fruit parts mediated gold nanoparticles were synthesized using the aqueous extracts. The green synthesized gold nanoparticles show vibrant colours. The clinical species such as *Acinetobacter pneumonia*, *Bacillus subtilis*, and *Enterococcus faecalis* which cause common infections. The TB fruit part extracts, as well as TB fruit parts mediated gold nanoparticles were capable enough to destroy clinical pathogens.

KEYWORDS: *Phyllanthus emblica*, nanoparticles, copper oxide, *Terminalia bellerica*, *Terminalia chebula*, nanosheets, *pseudomonas*, antibacterial.

INTRODUCTION

In recent decades, the development of new and effective antimicrobials against infections caused by antibiotic-resistant bacteria has been increasingly interested. Antimicrobial resistance (AMR) is increasingly recognized as a growing global health problem and accounts for over 700,000 deaths annually. AMR following bacterial infections in particular, is a major concern due to their high prevalence and mortality rates in both developed and developing countries. Scientists have been motivated by the growing environmental issues to avoid using toxic materials that could pose a severe ecological impact. As a result, researchers have recently been looking for novel solutions that are more environmentally friendly and sustainable.

Europe and the United States of America (USA) have been reported to have high rates of AM- resistant bacterial infections and associated mortality rates. More than 20,000 people in Europe and the USA succumb to antibiotic-resistant bacterial infections per annum. Still, multi microbe- resistant broad-spectrum antibiotics with lesser side effects are a big challenge for researchers as microbes are capable enough to obtain resistance to the drugs. Thus, the problems associated with the rise of multi-drug-resistant (MDR) bacterial infections have prompted a need for novel and cost-effective antimicrobial agents. *Salmonella* has coevolved and ensured continuous survival within humans by means of challenging the antibiotic regime and replicating tactfully in new hosts. *Salmonella* is one of the major contributors to the global public health burden with the highest incidence of 40% infection in infants and children under 5 years of age. Earlier investigations have reported an increase in multidrug resistance among *Salmonella Typhi* strains in India.

Several studies have reported that nanoparticles made up of different noble metals like Ag, Cu, and Au, which can be applied to kill both resistant and nonresistant bacteria. In recent years, silver nanoparticles (AgNPs) have received a great deal of attention from many researchers working on multiple disciplines due to their unique features and a wide spectrum of applications. Previous studies have demonstrated that AgNPs have potential antimicrobial activities against *Escherichia coli, Staphylococcus aureus, and Serratia marcescens*. The current study reports on the synthesis of AgNPs using aqueous and methanolic extracts of the *Terminalia mantaly* (TM) plant. The study also investigates the antibacterial activity of TM extracts and AgNPs. Extracts from *Terminalia* species (*Combretaceae*) such as *Terminalia catappa*, *Terminalia bellerica*. *Terminalia* extracts are commonly rich in phenolics, flavonoids, alkaloids, triterpenoids, and tannins.These phytochemicals can potentially be used as reducing agents in the synthesis of colloidal gold and silver metallic NPs.Various techniques, including physical and chemical techniques, can be used to synthesize nanomaterials. Synthesis of nanomaterials using the green chemistry approach is started recently, while these approaches were used in agriculture, consumer items, and health for several years. Zinc oxide (ZnO) is such an important material that has plenty of uses and applications in almost any field of modern technology both in bulk and nano.

Copper oxide nanoparticles (CuONPs) have emerged as potential antibacterial agents. Among the myriad of nanomaterials, copper oxide nanoparticles (CuONPs) have emerged as a particularly promising candidate in the realm of wound healing. Copper, an essential trace element, plays pivotal roles in physiological processes, including angiogenesis, skin regeneration, and immune response. The integration of nanotechnology into wound healing, particularly through the eco-friendly synthesis of copper oxide nanoparticles utilizing *T.chebula*, offers a promising strategy to surmount the limitations of conventional wound healing approaches. There are several reports on the

metallic nanoparticle synthesis using the fruit of *Terminalia bellerica* and its biological activity. To our knowledge this is the first reported work on the synthesis of gold nanoparticles using the *Terminalia bellerica* aqueous extracts of fruit parts such as Epicarp, Mesocarp, and Seed and its antimicrobial activity; comparing it with the whole fruit aqueous extract. The present study aims to identify the fruit part of TB responsible for the formation of gold nanoparticle and an efficient antibacterial agent. We intend to examine the development of a unique ZnO and TiO_2 nanoparticle composite employing separate *Terminalia bellirica* extract as an economical and ecologically friendly approach to close this research gap. Combining ZnO-TiO_2 nanoparticles with *T. bellirica* green separation has several benefits, one of which is a practical and eco-friendly way to handle mixes of nanoparticles. The composites have proven antibacterial activity to possible applications in a range of fields, such as ecological research, agriculture, and medicine. Using the extract from *T. bellirica* is a cheap and safe way to reduce and settle ZnO-TiO_2 nanoparticle mixtures. The design and improvement of novel materials for the treatment of microbial illnesses may benefit from the findings of this study. The antibacterial properties of the ZnO-TiO_2 combination are also advantageous to ecological science.

NOVEL HERBAL DRUG DELIVERY SYSTEM

Phyllanthus emblica

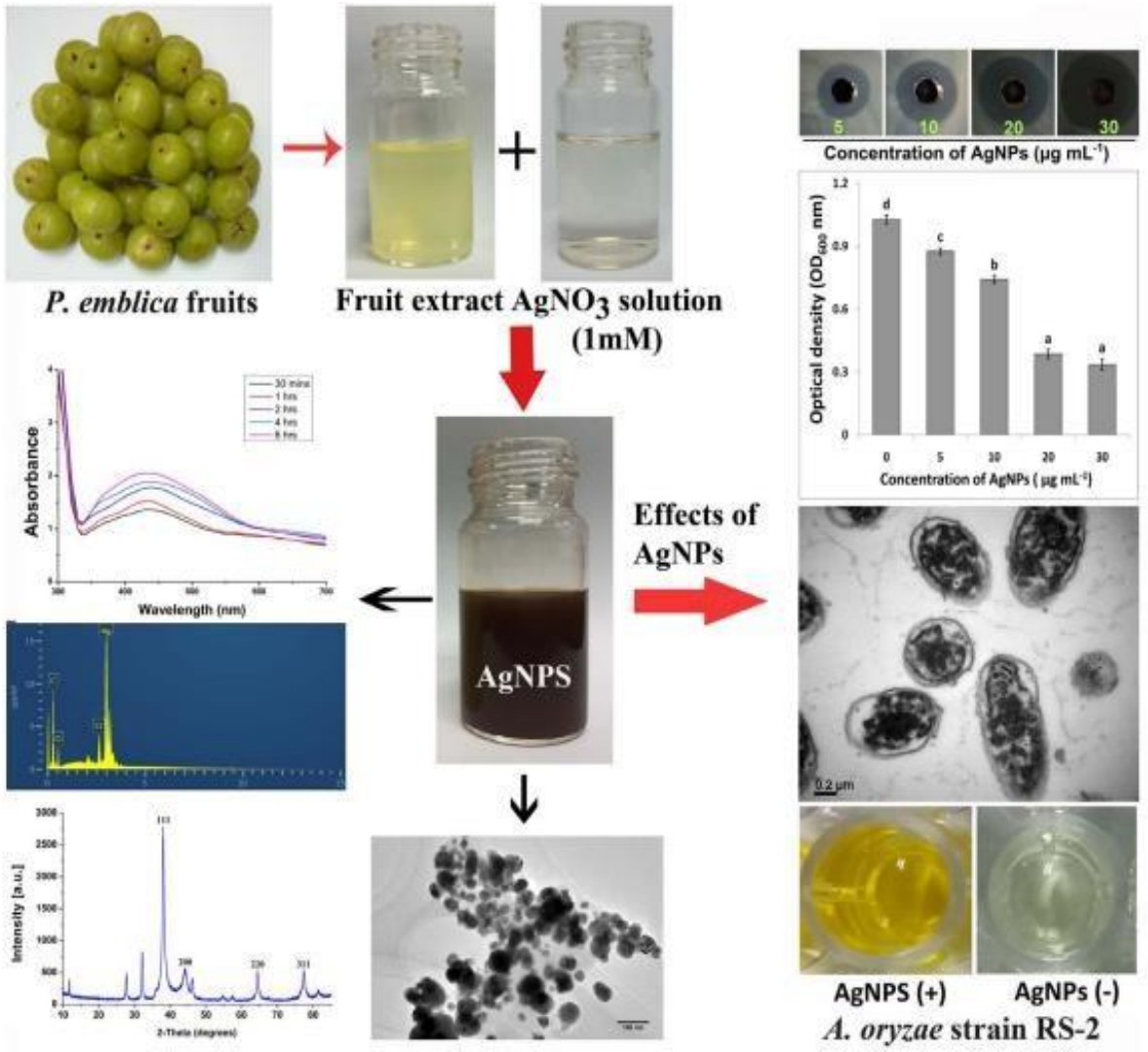
Arya Tjipta Prananda et al (2023) conducted research to evaluate the antimicrobial activity of *Phyllanthus emblica*. This research was conducted utilizing disc diffusion method. The methanolic extract of *P. emblica* was assayed at 500 µg/disc concentrations with standard kanamycin disc against gram positive, gram negative and multi drug resistant strains. The methanolic extract of *P. emblica* at a dose rate of 50 mg/mL and 25 mg/mL, respectively, had a complete bactericidal effect on AMR (antimicrobial-resistant) *S. Typhi and S. Enteritidis*.

Figure 1: *Phyllanthus emblica.*

Biogenic synthesis of Silver nanoparticles

Antimicrobial activity of synthesized AgNPs was evaluated against the pathogen Ao strain RS-2 of rice bacterial brown stripe by agar well diffusion technique as described by Mahidul Islam Masum et al. (2019) with little change. Briefly, 200 ml of bacterial suspension (approximately ~1 × 108 CFU/ml), previously overnight cultivated in LB broth at 30◦C, was spread with 5 ml of LB agar medium on the top of solid LB agar medium in a Petri dish plate. Once the upper inoculated agar medium was air-dried, 40 µl of the final concentration of AgNPs from 5 to 30µg/ml were loaded at the same distance on agar well (6 mm) and grown for 24 h at 30◦C. The same amount of filter-sterilized *P. emblica*

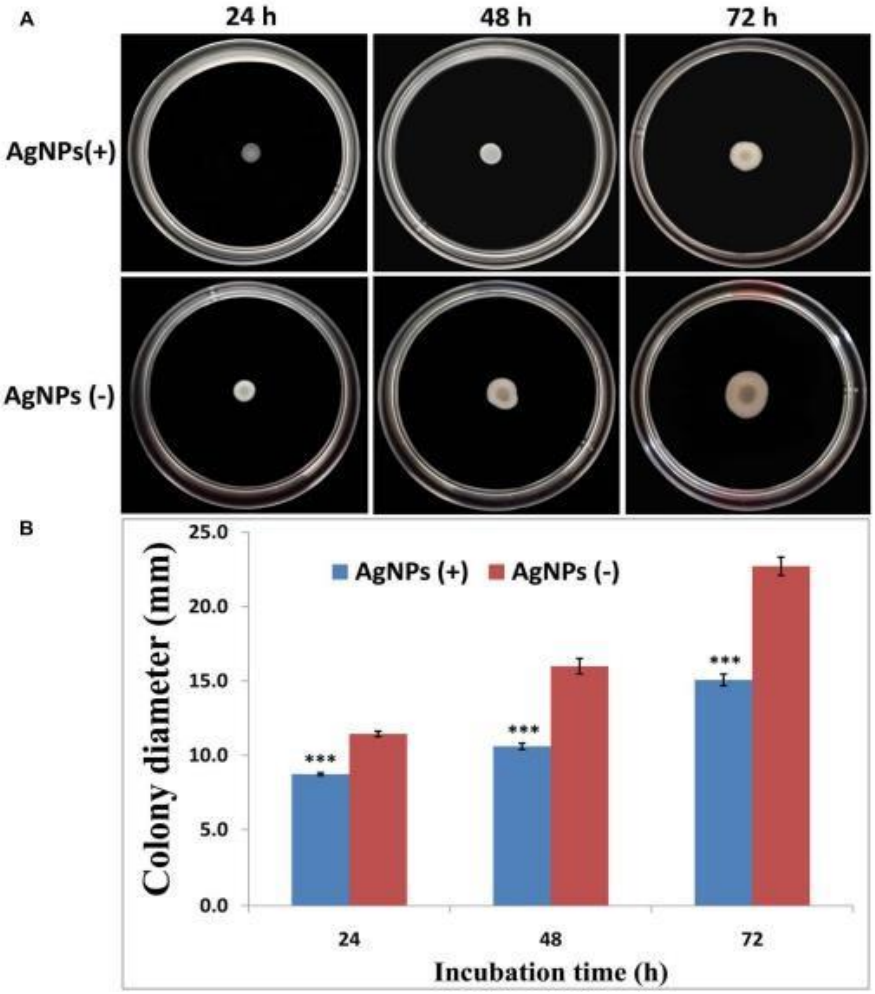
fruit extract was used as a control. Antibacterial activity was determined by averaging the diameter of inhibition zone formed around the center of each well.



Schematic diagram for biosynthesis of AgNPs using fruit extract of *Phyllanthus emblica* and its inhibitory effect on Ao strain RS-2.

Green Preparation of Phyllanthus emblica Extract/Silver Nanoparticles

The antibacterial activity was determined by the disk diffusion test as described by Whijitra Suvandee et al (2022). Four representative bacterial strains typically found in wound infections, including *Staphylococcus aureus (S. aureus,* TISTR 517), methicillin-resistant *Staphylococcus aureus* (MRSA, TISTR 142), *Pseudomonas aeruginosa (P. aeruginosa,* TISTR 1467), and *Escherichia coli (E. coli,* TISTR 887), were incubated on Mueller–Hinton agar (MHA) at 37 °C for 24 h. The bacterial suspension with a turbidity equivalent to the 0.5 McFarland standard was prepared and spread over the Mueller–Hinton agar plate. The test samples were prepared by impregnation of the spray solutions onto 6 mm disks of Whatman filter paper, which were then mounted on the agar plates and incubated at 37 °C for 24 h. Afterward, antibacterial efficacy was determined by measuring the zone of inhibition (mm). The tests were carried out in triplicate and reported as mean diameter ± standard deviation.



Effect of silver nanoparticles (AgNPs) mediated *Phyllanthus emblica* fruit extract on the swarming motility of *Acidovorax oryzae* strain RS-2. The concentration of AgNPs is 20 µg/ml. ***$P < 0.001$. Error bars represent the standard error of the mean ($n = 6$). **(A)** Bacterial swarming motility was determined by measuring the diameters of bacterial colony on the plates from three independent experiments; **(B)** Colony diameter at different incubation time.

Terminalia mantaly

Figure 2: ***Terminalia mantaly.***

Biogenic silver nanoparticles

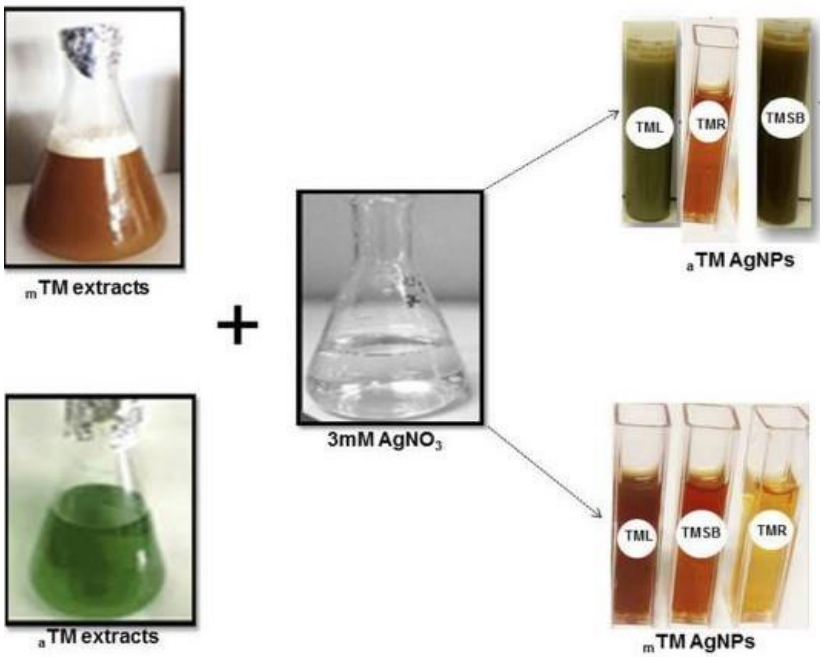
The antibacterial activity of the TM extracts and AgNPs was assessed on eight bacterial strains according to the guidelines set by Clinical Laboratory Standards Institute (M07A9, 2012) with slight modifications as described by Michele stella majoumouo et al Mueller–Hinton broth (Sigma, MO, USA) was inoculated with single bacterial colonies and the cultures were incubated at 37°C with shaking at 400 rpm for 18–24 hrs. The bacterial suspensions were subsequently standardized to 0.5 McFarland (~1.5×10 8 cells/mL) at 450 nm. Each inoculum was diluted to a final concentration of 5×105 cells/mL and further dispensed in a 96 well plate at 100 µL per well. Single point inhibitory effect of TM extracts and TM-AgNPs was determined against the eight bacterial strains. Ampicillin was used as the positive control at128 µg/mL. The turbidity of the bacterial culture, which was visually examined, was used as an indication of bacterial growth. The percentage of bacterial growth inhibition was calculated according to the following formula:

% Growth inhibition: (Number of strains inhibited by the test sample/Total number of tested strains) X 100

Table 1 List Of Bacterial Strains Used For Anti-Bacterial Activity

Bacterial Strains	Acronym	Reference No.	Supplier
Streptococcus pneumoniae	*S. pneumoniae*	ATCC 49619	ATCC
Klebsiella pneumoniae	*K. pneumoniae*	ATCC 13883	ATCC
Haemophilus influenzae	*H. influenzae*	ATCC 49247	ATCC
Shigella flexneri	*S. flexneri*	NR-518	BEI resources
Salmonella enterica	*S. enterica*[a]	NR-13555	BEI resources
Salmonella enterica	*S. enterica*[b]	NR-4294	BEI resources
Salmonella enterica enterica	*S. enterica enterica*	NR-4311	BEI resources
Staphylococcus aureus	*S. aureus*	NR-45003	BEI resources

Notes: *S. enterica*[a] (*Salmonella enterica* subsp. *enterica* A36 (Serovar Typhimurium) vs *S. enterica*[b] (*Salmonella enterica* subsp. *enterica* 2004 Pennsylvania Tomato Outbreak, Serovar Anatum, Isolate 4).
Abbreviations: ATCC, American Type Culture Collection; BEI resources, biodefense and emerging infections research resources repository.



Schematic representation of the AgNP synthesis from TM plant extracts.
Aqueous and methanolic TM extracts were used to reduce $AgNO_3$ into AgNPs, color change indicates NP formation.

The antibacterial effects of TM extracts and AgNPs were evaluated against eight bacterial strains, of which two were Gram positive *(S. pneumoniae and S. aureus*) and the other six were Gram negative. The bacterial cultures were treated with a single dose of 500 µg/mL of TM extracts and 12.5 µg/mL of TM-AgNPs. This was done as a quick and easy test of the antimicrobial activity of the TM extracts and TM-AgNPs. This study,aTML-AgNPs-25°C and aTML-AgNPs-70°C inhibited the growth in all eight strains, while aTMSBAgNPs-25°C and mTMSB inhibited the growth in 80% and 50% of the strains, respectively. mTMSB was the most active extract and inhibited growth in a significant number (four) of the strains. Generally, three of the strains (*K. pneumoniae, H. influenzae and S. flexneri)* were more susceptible to the effects of the treatments, while S. enterica was more resistant.The lowest concentration of the treatments required to inhibit visible growth of the bacteria (i.e. the MIC) was determined after 24 hr treatment with the TM extracts and AgNPs.

Terminalia bellerica

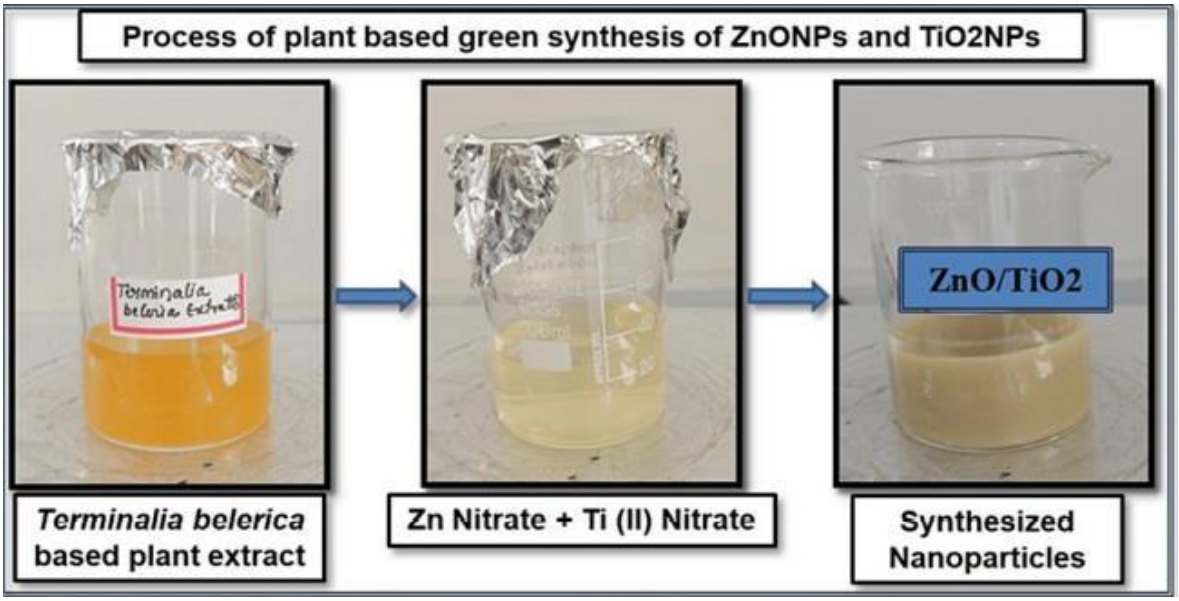
Gold nanoparticles synthesis

Antibacterial activity of formulations was studied by using a well-plate method as described by Akhila chithambaran et al .Clinical Pathogens from clinical samples *Acinetobacter pneumonia, Bacillus subtilis,* and *Enterococcus faecalis* inoculums were prepared by using nutrient broth media. Double strength sterile Mueller Hinton agar media were prepared by autoclaving 7.6 g in 100 ml using sterile cotton swabs, test pathogens were inoculated on the Mueller Hinton agar plates. *Terminalia bellirica* dry fruit part extracts 100 µg/ml (stock solution 1 mg/ml from that 100 µl was taken), synthesized gold nanoparticles 100 µg/ml (stock 1 mg/ml from that 100 µl, was taken) and Amikacin 100 µl/250 µg were placed on agar well. Plates are incubated for 30 min at the refrigerator to diffuse the formulation into the agar plate and finally, plates are incubated at 37 °C for 24 h. Zone of Inhibition (mm) was calculated to determine the antibacterial efficacy. Duplicate studies were done to ensure the reliability of the results.

The antibacterial potency of the aqueous extracts of TB fruit parts and the green synthesized gold nanoparticles es from TB fruit parts were carried out by well diffusion methods. Amikacin was employed as the standard for the study which is administered for the destruction of a broad spectrum of pathogens. Clinical Acinetobacter pneumonia shows resistance to both aqueous extracts of TB fruit parts and TB fruit parts mediated gold nanoparticles. No zone of inhibition (ZOI) was observed for this specific pathogen.

Synthesis of TB-ZnO-TiO(II) Nanoparticles

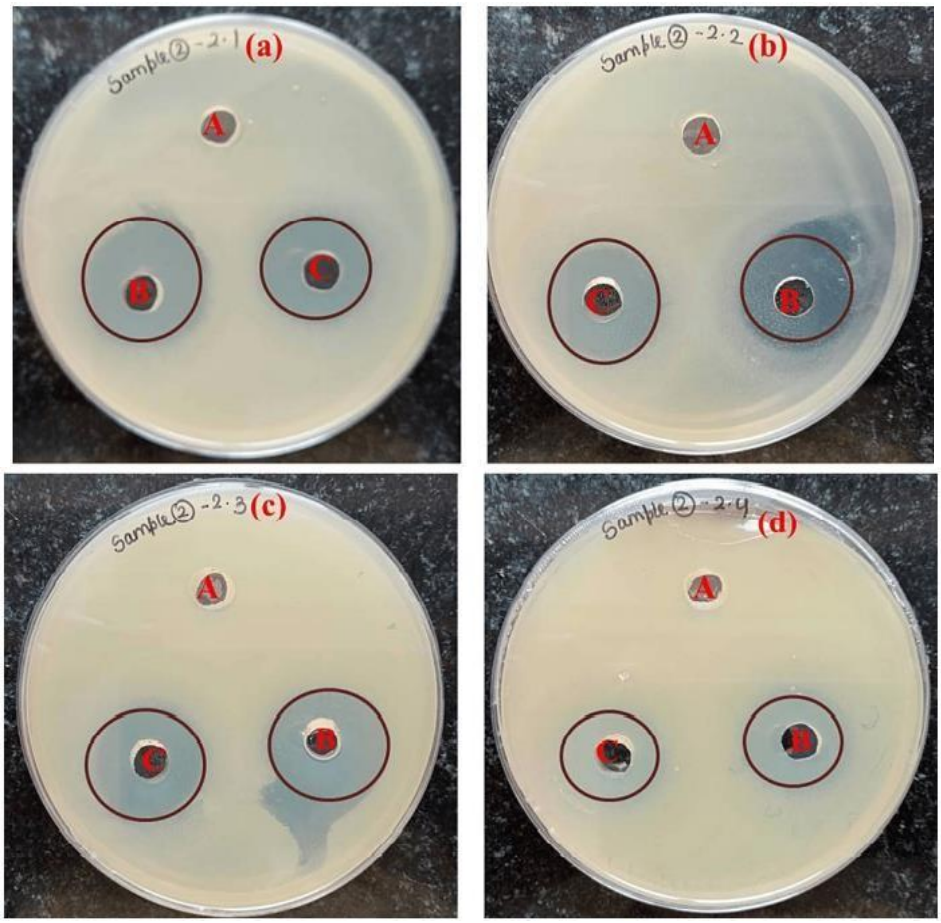
Chitra shivalingam et al described the antibacterial susceptibility experiment was performed on gram positive and gram-negative bacteria, such as *Klebsiella pneumoniae* MTCC 109, *Escherichia coli* MTCC 443, *Streptococcus mutans* MTCC 890, and *Staphylococcus aureus* MTCC 740. The medium used for the bacterial growth and inoculation was MuellerHinton broth. The dried Tb-ZnO-TiO2 NPs composite were measured at a concentration of 25 mg/ml for the antibacterial test with positive control (PBS) and negative control (antibiotics). As the test sample, single dilutions of the dried powder of nanoparticles (Tb-ZnO-TiO2 NPs composite) (25 mg/mL) were used. The diameter of the zone of inhibition was determined during a 24-hour incubation period at 37ºC to evaluate the ability of synthetic nanoparticles (Tb-ZnO-TiO2 NPs composite) to inhibit bacterial growth.



Schematics diagram represent the reaction follow for the synthesis of zinc oxide and titanium (II) oxide nanoparticles

Strain	Concentration	N	Mean (Zone of inhibition)	Standard deviation	P-value
Klebsiella pneumoniae	Negative Control	5	0	0	0
	Sample	5	16	1.5443	0.038
	Positive Control	5	14	1.8567	0.456
Escherichia coli	Negative Control	5	0	0	0
	Sample	5	15	2.1543	0.134*
	Positive Control	5	13	3.1344	0.462
Streptpcoccus mutans	Negative Control	5	0	0	0
	Sample	5	16	2.2352	0.004*
	Positive Control	5	12	2.7455	0.003*
Staphylococcus aureus	Negative Control	5	0	0	0
	Sample	5	16	1.3452	0.256
	Positive Control	5	14	1.2345	0.312

Zone of Inhibition measurement against nanoparticles after 24 h of time interval - One-way ANOVA



Antimicrobial susceptibility activity of prepared samples against gram-negative and gram-positive bacteria

A: Negative control (DMSO), B: Nanoparticles (Tb-ZnO-TiO_2 NPs composite) in 25 mg/mL, C: Positive control (Antibiotics)

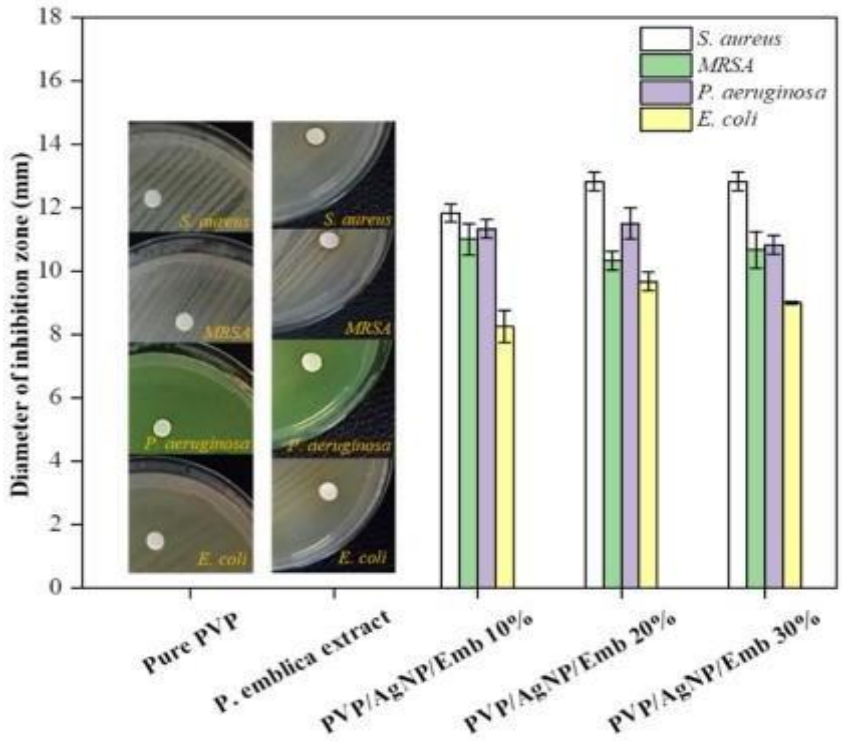
(a) *Klebsiella pneumoniae* MTCC 109, (b) *Escherichia coli* MTCC 443, (c) *Streptococcus mutans* MTCC 890, and (d) *Staphylococcus aureus* MTCC 740)

MTCC: Microbial Type Culture Collection and Gene Bank

RESULT AND DISCUSSION

Preliminary we tested the impact of AgNPs on plant growth promoting bacteria (PGPBs), including *Bacillus amyloliquefaciens* strain D16 isolated from rice and *Paneabacillus polymyxa* strain SX3 from cotton in our laboratory, and hence, we did not observe a significant effect on PGPBs upon exposure the concentration of 5–20 µg/ml (data not shown).However, extrapolation of our observations to more general cases is limited because of in vitro evaluation.

The disk diffusion approach was used to test the antibacterial activity of *P. emblica* extract/silver nanoparticles/polyvinylpyrrolidone spray-on dressing. *P. aeruginosa*, *E. coli*, *S. aureus*, and the resistant MRSA were chosen as typical Gram-negative and Gram-positive bacterial strains often associated with wound infections. PVP spray and *Phyllanthus emblica* extract had no distinct inhibition zones against any of the tested strains as a control, suggesting that PVP and the extract exhibited no antibacterial activity. This suggests that silver nanoparticles are the cause of bacterial growth inhibition.



Antibacterial activity of PVP, *Phyllanthus emblica* extract, and *Phyllanthus emblica* extract-loaded spray-on dressing films against *S. aureus*, MRSA, *P. aeruginosa*, and *E. coli*.

Comparison Of The Bacterial Susceptibility To TM Extracts And AgNPs

Treatment	Bacterial Strains							
	S. enterica[a]	*S. pneumoniae*	*S. aureus*	*K. pneumoniae*	*S. enterica enterica*	*S. enterica*[b]	*S. flexneri*	*H. influenzae*
$_{a}$TMSB	–	–	–	–	–	–	–	✓
$_{a}$TMSB-AgNPs-25°C	–	–	–	✓	–	–	✓	✓
$_{a}$TMSB-AgNPs-70°C	–	✓	✓	✓	✓	✓	✓	-
$_{m}$TMSB	–	✓	–	–	✓	–	✓	✓
$_{m}$TMSB-AgNPs-25°C	–	–	–	–	–	–	–	✓
$_{a}$TML	–	✓	–	–	–	–	–	-
$_{a}$TML-AgNPs-25°C	✓	✓	✓	✓	✓	✓	✓	✓
$_{a}$TML-AgNP-70°C	✓	✓	✓	✓	✓	✓	✓	✓
$_{a}$TMR	–	✓	–	–	–	–	–	✓
$_{m}$TMR	–	✓	–	–	–	–	–	✓
$_{m}$TMR-AgNPs-25°C	–	✓	–	–	–	–	–	–

Notes: Eight bacterial strains were treated with TM extracts and AgNPs for 24 hrs. Inhibitory effects of TM samples were visually assessed to identify the strains that were susceptibility to TM extracts and AgNPs. The $_{a}$TM-AgNPs were the most active and inhibited growth of all bacterial strains, compared to the crude extracts and other AgNPs. *S. enterica*[a] (*Salmonella enterica* subsp. *enterica* A36 (Serovar Typhimurium) vs *S. enterica*[b] (*Salmonella enterica* subsp. *enterica* 2004 Pennsylvania Tomato Outbreak, Serovar Anatum, Isolate 4).

Abbreviations: AgNPs, Silver nanoparticles; TM, *Terminalia mantaly*; $_{a}$, represents aqueous extracts; $_{m}$, represents methanolic extracts; TML, TM leaf extracts; TMR, TM root extracts; TMSB, TM stem bark extracts; *S. pneumoniae, Streptococcus pneumoniae; S. enterica enterica, Salmonella enterica enterica; H. influenzae, Haemphilus influenzae, S. flexineri, Shigella flexineri; K. pneumoniae, Kbesiella pneumoniae; S. aureus, Staphylococcus aureus, S. enterica- Salmonella enterica*; -, no bacterial activity; ✓, bacterial activity.

The absence of antibacterial activity observed in some of the AgNPs may be due to various factors, either the phytochemicals responsible for capping the NPs had adsorbed to the NPs through its active site,or the phytochemicals simply have no antibacterial activity as demonstrated by the crude extracts. Furthermore, the active phytochemicals at specific temperatures might be responsible for the biological activities of the AgNPs. Only *S.enteric* , *S. flexineri* and *H. influenzae* were susceptible to the mTMR, aTMSB and mTMSB extracts. The other strains were not susceptible to the effect of the TM extracts at concentrations up to 500 µg/ml, their respective AgNPs possess enhanced anti-bacterial activities against both Gram negative and Gram-positive strains.

The results demonstrated that the green-synthesized Tb-ZnO-TiO2 NPs composite had exceptional antibacterial activity against both bacterial strains at doses. When compared to the antibiotic standard, the Tb-ZnO-TiO2 NPs composite displayed a larger zone of inhibition, which suggested a noticeably higher level of antibacterial activity. The results of the antibacterial assay in this work are in line with earlier studies that showed the antimicrobial activity of Tb-ZnO-TiO2 NPs composite against both gram-positive and gram-negative bacteria.

CONCLUSION

In conclusion, this study clearly provides an economical, environmental friendly, and straightforward reproducible approach in AgNPs synthesis employing *P. Emblica* fruit extracts as a reducing, stabilizing, and capping agent. The bacteriostatic effect of AgNPs is generally achieved due to direct interaction between AgNPs and bacterial cells, which caused the destruction of biofilm and cell membrane and released intracellular materials from bacteria. In addition, until now, only in vitro studies have been reported. However, our results could be used in the future to detect and catalog AgNPs with antibacterial properties to protect crops. The biogenic AgNPs described in this study can potentially be used as an alternative to conventional antimicrobial agents. Further studies are underway to study the anti-microbial mechanism of TM AgNPs and identify the phytochemicals involved in the synthesis of the NPs. The TB fruit parts mediated gold nanoparticles are capable enough to fight against both gram-positive and gram- negative bacterias. TB fruit is known to be anti-bacterials . However, the active constituent responsible for the reduction of Au^{3+} to Au^{0} and the anti-bacterial efficiency is yet to be determined and it is warranted.

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