THE EFFECT OF BIOSYNTHESIZED SILVER NANOPARTICLES IN COMBINATION WITH ANTIBIOTICS ON PATHOGENIC MICROORGANISMS

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CERTIFICATION

This is to certify that this work "The effect of biosynthesized silver nanoparticles in combination with antibiotics on pathogenic microorganisms" was carried out by OJIAKU ADAEZE ANNE (**Reg. No. 20144939998**) in partial fulfillment for the award of degree of Ph.D in Environmental Management, in the Department of Environmental Management of the Federal University of Technology, Owerri, Imo State.

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TABLE OF CONTENTS

CHAPTER ONE: INTRODUCTION

CHAPTER TWO: LITERATURE REVIEW

CHAPTER THREE: MATERIALS AND METHODS

CHAPTER FOUR: RESULTS AND DISCUSSION

CHAPTER FIVE: CONCLUSION AND RECOMMENDATIONS

LIST OF TABLES

LIST OF PLATES

LIST OF FIGURES

ABSTRACT

Antimicrobial resistance (AMR) is an emerging chronic public health issue globally, with the prediction of 10 million deaths per year globally by 2050. In this study, silver nanoparticles synthesized using *Dacryodes edulis* (African pear tree) leaf extract was used in combination with antibiotics and its effects in combination was observed against model gram positive and gram negative microorganisms. Phytochemical constituents of the plant extract, molecular characterization of the microorganisms, biosynthesized silver nanoparticles were characterized, while biosynthesized silver nanoparticles in combination with antibiotics were assessed against the clinically obtained microorganisms. Results revealed presence of alkaloids, tannins, cyanogenic glycosides, flavonoids and anthraquinones. The formation of the silver nanoparticles was established using UV- visible spectrophotometric analysis, exhibiting a characteristic surface plasmon resonance (SPR) band of 390 – 440 nm. Optimization parameters such as extract volume, temperature, and pH revealed 30 ml, 35 ºC, and pH 7 as results for optimal nanoparticle synthesis respectively. The reaction time, however, showed a cascade of intensity from the nucleation phase to the stabilization phase with 90 minutes as optimal time for nanoparticle synthesis. XRD analysis showed face centered cubic crystal nature of the lattices with spectral peaks at 38.17, 43.63 and 64.39 corresponding to (111), (200), and (220) plane, with crystallite size of 16.50±0.79 nm using Scherrer equation. Scanning electron microscope (SEM) analysis displayed spherical shaped nanoparticles with average particle size of approximately 63 nm, while Fourier Transform Infrared Spectroscopy (FTIR) analysis acknowledged the presence of functional groups such as phenolic, carboxylic, alkyl, isothiocyanate, and amine groups corresponding to the phytochemical constituents in the aqueous leaf extract being responsible for the bioreduction of silver ions to silver atoms. The microorganisms were identified as *Staphylococcus saprophyticus* and *Escherichia coli*. In silico analysis revealed the presence of resistant genes, and predicted chromosomal gene mutations especially for *E.coli* that mediated antimicrobial resistance. Antibiotic assay indicated that in *S. saprophyticus*, enhanced inhibition was observed for pefloxacin, ampiclox, ciprofloxacin, streptomycin, cotrimoxazole and erythromycin, while reduced inhibition was observed for gentamycin and rocephin. In comparison with antibiotics alone, and antibiotics in combination with AgNPs, gentamycin and rocephin (ceftriaxone) had a reduced zone of inhibition when combined with AgNPs while the other antibiotics had improved zone of inhibition. For *E. coli,* there was enhanced inhibition for streptomycin, ofloxacin, pefloxacin, amoxicillin, ciprofloxacin, sparfloxacin and chloramphenicol when exposed to antibiotics, while reduced inhibition was noted for cotrimoxazole and gentamycin. However, in comparison with antibiotics alone and antibiotics in combination with silver nanoparticles, it showed that cotrimoxazole and gentamycin had reduced zone of inhibition when AgNPs were added while other antibiotics had improved zone of inhibition in combination with AgNPs. It is recommended that more research on evolutionary associations of microorganisms and antibiotics be performed and also be included in strategies for antibiotic resistance pipeline development and 'One Health' approach in combatting antimicrobial resistance.

Keywords: Dacryodes edulis, Silver nanoparticles, Antimicrobial resistance, Nanotechnology, Antibiotics, Synergistic Interaction.

CHAPTER ONE

INTRODUCTION

1.1 BACKGROUND INFORMATION

The abuse of antimicrobial agents across One Health sectors (agriculture, veterinary and medical sectors) catalyzes an irrevocable upsurge in resistance thereby rendering such important agents ineffective (Dove, Dzurny, Dees, Qin, Nunez Rodriguez, Alt, Elleward, Best, Rudawski, Fujii, & Czyz, 2023). Over 2.8million antimicrobial-resistant infections are responsible for more than 35,000 deaths that occur annually in the United States (Liao *et al.*, 2023). It has been estimated that globally, 4.95 million deaths were associated with antimicrobial resistance (AMR) while 1.27 million deaths were attributed to resistance in bacteria in 2019 (Aguilar *et al.*, 2023). Despite the colossal cost to human health, AMR also imparts heavily on the global economy. The United States loses as high as 20 billion and 35 billion annually in healthcare and productivity simultaneously (Innes *et al.*, 2019). Unethical waste disposal methods, improper discharge of non-degradable antimicrobial agents and their residues in the form of fecal matter, manure or industrial effluents into the environment are factors that lead to antimicrobial resistance (Samreen *et al.*, 2021). It has been predicted that by the year 2050, 10 million deaths would occur globally if no intervention plan is put in place (Murray *et al.*, 2022). Novel strategies are currently being studied by research scientists to combat antimicrobial resistance. Metal nanoparticles are of great interest due to their tremendous characteristics which include electro-optical and surface redox characteristics, as well as flexibility, elasticity, efficiency, longevity and distinctive physicochemical properties (Mubeen *et al.*, 2021). These nanomaterials are of great use in various applications as biosensors (Lee *et al.*, 2018; Malekzad *et al.*, 2017; Yu & Li, 2019), cosmetics (Arroyo *et al.*, 2020; Mohd-Setapar *et al.*, 2022), protective products like coatings (Basova et al., 2021; Farag, 2020), self-cleaning products (Ismail *et al.*, 2023; M. Khan *et al.*, 2024), wastewater treatments (Agarwal *et al.*, 2019; Naseem & Tayyiba, 2021; Shanmuganathan, Karuppusamy, Muthupandian, *et al.*, 2019), cancer treatments (Abdel-Fattah & Ali, 2018; Buttacavoli *et al.*, 2018; Palem *et al.*, 2018; Sun *et al.*, 2019; L. Wang *et al.*, 2019), diagnostics and therapeutics (Klebowski *et al.*, 2018; Singh *et al.*, 2021), agriculture (Ali *et al.*, 2018; Vargas-Hernandez *et al.*, 2020), vector control (A. Ahmad *et al.*, 2020; Foko *et al.*, 2019), antimicrobials (El *et al.*, 2018; Fierascu *et al.*, 2019; Nisar *et al.*, 2019), targeted drug delivery platforms (Anderson *et al.*, 2019; Barman *et al.*, 2018; Kanwar *et al.*, 2019) and pesticides (Ameen *et al.*, 2019). Utilizing nanoparticles and other nanomaterials has become an important alternative either as nanoformulations to minimize their optimal dosage by increasing their efficacy or used alone as nanoadditives, nanophotocatalyst materials to degrade microbial pollutants in their sink, impart better release, minimize the optimal dose, improve cell permeation, better uptake and bioavailability (Kaushik et al., 2023). These can in turn reduce the excretory load in wastewater.

Nanoparticles synthesized using plant extracts already have a functionalized surface that contains biomolecules (Huq *et al.*, 2022) which promote an increase in the stability of the particles (Habibullah *et al.*, 2022), and also facilitate subsequent attachment of functional molecules like antibodies or DNA to nanoparticles (Ahmad *et al.*, 2024). Functionalized nanoparticles are of great use in biolabelling, catalysis, and bioseparation (Azharuddin *et al.*, 2019).

Traditionally, nanoparticles have been synthesized and stabilised using physical and chemical methods (Din *et al.*, 2017). Metal nanoparticles including silver (Ag) are often synthesized in aqueous or non-aqueous solutions by the reduction of a dissolved metal salt precursor with a reducing agent such as sodium borohydride, ascorbic acid, trisodium citrate or alcohols (Cobos *et al.*, 2020; Daruich De Souza *et al.*, 2019), in the presence of a stabilizing agent, which influences the aggregation behavior of the nanoparticles. These stabilizing agents adsorb on a nanoparticle surface and provide via repulsive forces an electrostatic stabilization or a steric stabilization, which suppress further nucleation events or subsequent treatments that increase nanoparticle size homogeneity and size control (Cartwright *et al.*, 2020). Size, shape, stability, and physicochemical properties of the nanoparticles are strongly influenced by process parameters (Sreekumar *et al.*, 2018), and process kinetics (Abbas *et al.*, 2020), involving the reducing agent, stabilizing agent and the nanoparticles. In size control, the reducing and stabilizing agents typically adsorb on the nanocrystal surface, creating an entity which then represents a thermodynamically very stable nanoparticle configuration (Roto *et al.*, 2018). Therefore, these agents are important in nanoparticle synthesis as they control the formation and dispersion stability of the nanoparticles.

Physical and chemical syntheses can be costly, time-intensive and often use toxic materials with potential hazards such as environmental toxicity (Almatroudi, 2020), which arise from the hazardous substances, such as organic solvents, reducing agents, and stabilizers that are used to prevent unwanted agglomeration of the nanoparticles. However, such formed nanoparticles have also been found to be toxic due to factors such as composition, size, shape, and surface chemistry preventing their use in clinical and biomedical applications (Abbasi *et al.*, 2023; Egbuna *et al.*, 2021).

Plant extracts are used for the bioreduction of metal ions to form nanoparticles. Plant biomolecules control the size and shape of nanoparticles and equally facilitate their purification. The mechanism of metal nanoparticle synthesis in plant extracts involves the bioreduction and nucleation of the metal ions (activation phase), the involuntary mixture of the different particles (Ostwald ripening), and production of different shapes of the nanoparticles otherwise known as the terminal phase (Singh *et al.*, 2018). In this termination phase, nanoparticles acquire the most energetically favorable conformation (Timoszyk, 2018) as a result of the plant extract being used to stabilize the metal nanoparticles.

The reduction and stabilization of metal ions by combination of plant biomolecules such as proteins, amino acids, enzymes, polysaccharides, alkaloids, tannins, phenolics, saponins, terpenoids, flavonoids and vitamins, yield nanoparticles with less defects, highly stable and more homogenous chemical composition (Matussin *et al.*, 2020). This bottom-up approach involves the dissolution of metal salt into a solvent, reduction of the metal ions to their element upon addition of a reducing agent and subsequent stabilization of the forming metal nanoparticles using a stabilizing agent to control the size of nanoparticles and prevent agglomeration (Chung *et al.*, 2016). The biological synthesis of silver nanoparticles using plants has attracted significant attention as a result of its economical nature and proven applications in diverse areas including medical, environmental and agricultural sectors. This is due to their ability to convert silver ions to silver nanoparticles through the action of phytochemical constituents such as flavonoids, phenols and alkaloids. This research seeks to examine the use of *Dacryodes edulis* (African pear or Bush butter tree), rich in phytochemical constituents, for the synthesis of silver nanoparticles. It explores the essential secondary metabolites involved in nanoparticle synthesis, the reaction conditions by which optimal synthesis occurs and its effects in combination with antibiotics on selected microorganisms.

1.2 STATEMENT OF THE PROBLEM

Inappropriate use of antimicrobial agents has led to the selection of resistant bacterial strains to conventional antibiotics. This emerging trend of antibacterial resistance to readily available antibiotics presents grave danger to living organisms and the environment. The biological synthesis of silver nanoparticles using plants has attracted significant attention as a result of its economical nature and proven applications in diverse areas including medical, environmental and agricultural sectors. This is due to their ability to convert silver ions to silver nanoparticles through the action of phytochemical constituents. These plants can serve as eco-friendlly alternatives to counter the effects of antibacterial resistance. These newly developed antimicrobial agents should be readily available, effective in combatting resistant infections, cost effective and above all, safe for the environment.

1.3 OBJECTIVES OF THE STUDY

The main objective of this project is to study the synergistic effects of biosynthesized silver nanoparticles and antibiotics for inhibition of antimicrobial resistance.

The specific objectives shall among others include to:

(i) To determine the phytochemical constituents of *Dacryodes edulis* leaf extract

(ii) To synthesize silver nanoparticles using the plant leaf extracts

(iii) To characterize the prepared silver nanoparticles

(iv) Molecular and in silico characterization of the resistant genes of the clinically obtained microorganisms (*Staphylococcus sp.* and *Escherichia sp.*)

(v) To assess the synergistic effects of prepared silver nanoparticles and antibiotics on the microorganisms

1.4 JUSTIFICATION OF STUDY

Silver nanoparticles (AgNPs) and plant extracts can exert antimicrobial activity by rupturing microbial cell walls, denaturing cellular proteins, blocking cell respiration, thereby inducing microbial cell death. On the other hand, they exert limited cytotoxicity to mammalian cells.

1.5 SCOPE OF STUDY

This research project will focus on the characterization of the pathogenic microorganisms (*Staphylococcus sp.* and *Escherichia sp.*), synthesis and characterization of silver nanoparticles from plant extracts, and their effect on these microorganisms in combination with certain antibiotics. The research variables for nanoparticle synthesis will include:

(i) Extract concentration (0 mL,10 mL, 20 mL, 30 mL, 40 mL, 50 mL, 60 mL, 70 mL, 80 mL, 90 mL)

(ii) Reaction time (0 min,15 min, 30 min, 45 min, 60 min)

(iii) Silver nitrate concentration (1 mM, 2 mM, 3 mM, 4 mM, 5 mM)

(iv) Temperature (25 °C, 35 °C, 45 °C, 65 °C, 75 °C)

(v) pH (5, 7, 9, 11,13)

1.6 LIMITATIONS OF STUDY

Challenges encountered during the course of the research work include:

(i) Lack of equipment. Different laboratories in FUTO, research centers and other tertiary institutions were visited or called to identify equipment that were needed for sample analyses to be carried out. Equipment for nanoparticle analysis should be provided to enhance nanotechnology and material science research.

(ii) Faulty results were obtained due to system downtime or lack of updated knowledge on equipment use. This led to repeated laboratory experiments to produce nanoparticles and sending the samples outside the country in most occasions for some of the analyses that were not available within the country.

(iii) There was limited access to literature online which led to sending personal emails to researchers for their articles. They responded positively and were willing to assist.

(iv) Financial constraints. The inability to access funding for the research work led to use of personal funds which in turn, affected number of samples and variables. It is expected that the institution and research supporting organisations assist postgraduate students with grants and scholarships towards innovative research that would benefit the institution and country at large.

CHAPTER TWO

LITERATURE REVIEW

2.1 OVERVIEW

This review focuses on nanotechnology, silver nanoparticle synthesis with emphasis on synthesis methods, secondary metabolites and their mechanism in nanoparticle synthesis, factors that affect the synthesis, bacterial resistance in the environment, mechanism of antimicrobial action, toxicological assessment, environmental applications and its combination with antibiotics against microorganisms.

2.2 NANOTECHNOLOGY

In recent times nanotechnology has infused great scientific advancement in the field of research and technology. Nanotechnology deals with the study of particles with unique functions and size dependent physicochemical properties that differ from their bulk counterparts (Joudeh & Linke, 2022). It is an area of research that cuts across various disciplines (Rafique *et al.*, 2016). Nanoparticles are fascinated by researchers as a result of their unique physical, chemical, and electrical characteristics that differ from its bulk materials. These characteristics are due to the shape and size of the nanoparticles which have a high surface area-to-volume ratio due to their small size. It is being investigated for applications including effective pollution reduction and control through the development of novel nano-based environmental remediation (Guerra *et al.*, 2018), energy efficiency (Abdin *et al.*, 2018; Banin *et al.*, 2021), and sustainable development (Shah & Mraz, 2019). Nanoparticles display distinctive optical, electronic, magnetic and catalytic properties as a result of their size, shape and morphology and high surface area to volume ratio (Siddiqi *et al.*, 2018). High surface energy, large fraction of surface atoms, reduced imperfections and spatial confinement are responsible for these properties (Dauthal & Mukhopadhyay, 2016). They are used in various areas such as catalysis, cosmetics, chemical industries, drug-gene delivery, health care, environment, biomedical, food, electronics, energy studies, optics, mechanics, light emitters, single electron transmitters, nonlinear optical devices, photo-electrochemical fields and space industries (Ahmed, Ahmad, *et al.*, 2016). Nanoparticles can be classified as organic and inorganic nanoparticles. Organic nanparticles include carbon nanoparticles like carbon nanotubes, fullerenes and quntom dots, while inorganic nanoparticles include metal nanoparticles, magnetic nanoparticles and semi-conductor nanoparticles (Rafique *et al.*, 2016).

2.2.1 SILVER AS AN ELEMENT

Silver has been known to possess antimicrobial properties and its mechanism of action is to distort and penetrate bacterial cell wall and membrane, induce cellular toxicity and lead to damage of the DNA architecture leading to cell death (Abdelsattar *et al.*, 2021). Side effects of silver on humans such as damage to human internal organs, and the environment can be curtailed through the use of low concentrations of silver and the use of biological extracts such as plants during the synthesis of silver nanoparticles.

2.2.2 SILVER NANOPARTICLES

Of all the noble metals explored for metal nanoparticle synthesis, silver has received attention due to its physical, chemical, and biological properties that attributes to the catalytic activity and bactericidal effects and is being applied in nanobiotechnological research (Burdusel *et al.*, 2018; Kędziora *et al.*, 2018). Silver nanoparticles (AgNPs) are of special interest because of the unique properties like large surface area, stability, lower melting point and extraordinary mechanical strength (Singh, Gaud & Jaybhaye, 2020a) which can be incorporated into antimicrobial applications, biosensor materials, composite fibers, cryogenic superconducting materials, cosmetic and biomedical applications (drug delivery, cancer therapy, and biofilm inhibition). AgNPs have a high thermal conductivity (Iyahraja & Rajadurai, 2015), electrical conductivity (Dawadi *et al.*, 2021), optical (Mahmudin *et al.*, 2015) and catalytic property

(Saha *et al.*, 2017). The catalytic property of silver nanoparticles degrades effluents (Jyoti & Singh, 2016). It also converts nitrate and nitrite to nitrogen in chemical fertilizer in controlling environmental pollutants (Tyagi *et al.*, 2018). AgNPs exhibit broad spectrum bactericidal and fungicidal activity that has made them extremely popular in a diverse range of consumer products, including plastics, soaps, pastes, food and textiles, increasing their market value (Haider & Kang, 2015). AgNPs of many different shapes (spherical, rod-shaped, truncated, triangular nanoplates) have been developed by various synthetic routes (Khodashenas & Ghorbani, 2019). AgNPs have excellent antimicrobial property compared to other salts due to their extremely large surface area, which provides better contact with microorganisms (Vadlapudi *et al.*, 2014).

AgNPs have been known to be standard nanoantibiotics due to their improved antimicrobial activity towards bacteria, fungi, protozoans and viruses, extraordinarily few instances of bacterial resistance development and low cytotoxicity (Haidari *et al.*, 2019; Jeevanandam *et al.*, 2022). AgNPs possess diverse mechanisms of action that includes rupture of the bacterial cell membrane through AgNP adherence, penetration of AgNPs into the cell and the nucleus, binding interactions with proteins and DNA and leading to ROS production ultimately resulting in bacterial cell killing, and cell death (Malawong *et al.*, 2021). Due to the nonspecific nature of these mechanisms, AgNPs have been known to bear a reduced risk of bacterial resistance since they disrupt numerous facets of bacterial physiology when compared to antibiotics (Stabryla *et al.*, 2021).

2.2.3 NANOPARTICLE SYNTHESIS METHODS

Metal nanoparticles are synthesized either through top-down or bottom-up approach. Top-down approach involves producing nanoparticles from the bulk metal and it is achieved using physical and mechanical methods (Handoko *et al.*, 2019), while bottom-up approach forms nucleation sites which finally grows into nanoparticles using chemical and biological methods

(Kaabipour & Hemmati, 2021).

2.2.3.1 PHYSICAL SYNTHESIS

The physical methods involved in nanoparticle synthesis include laser ablation (Sportelli *et al.*, 2018), electrospraying (Zong *et al.*, 2018), arc discharge (Raniszewski *et al.*, 2017), atomization (Rosa *et al.*, 2018), metal sputtering (Nguyen & Yonezawa, 2018), annealing (Coaty *et al.*, 2019), high energy balling, evaporation-condensation (Dhand *et al.*, 2015) and laser pyrolysis (Kabashin *et al.*, 2019) amongst others. Laser accelerated protons which is as advanced form of laser ablation technology has been utilized to synthesize gold, aluminum and copper nanoparticles (Barberio *et al.*, 2020). YVO4:Eu3+colloidal nanoparticles were synthesized using laser ablation in deionized water (Wang *et al.*, 2016). Electrosprayed chitosan nanoparticles were assessed for antimicrobial and cytotoxic activity (Ibrahim *et al.*, 2021). Silver nanoparticles were synthesized using the arc discharge method (El-Khatib *et al.*, 2018). Coaxial hydrodynamic atomization has been used to prepare drug-loaded particles with core-shell structure (Chen *et al.*, 2019). Manganese nanoclusters were produced using magnetron sputtering (Khojasteh & Kresin, 2017). Sol-gel process and annealing method were used to synthesize MgO nanoparticles (Sutapa et al., 2018). High energy balling technique was employed in preparing Cu-doped Zn nanoceramics (Das *et al.*, 2019). Titanium oxide/graphene nanocomposites were produced using laser pyrolysis for energy applications (Belchi *et al.*, 2019). Advantages of physical methods include no solvent contamination in the prepared thin films, uniform synthesized nanoparticle distribution and high purity of nanoparticles (Xu *et al.*, 2020). However, these physical methods require a lot of time to achieve thermal stability, high energy consumption at high temperatures thereby increasing the environmental temperature around the source material (Beyene *et al.*, 2017). This makes physical synthesis unsuitable for the production of nanoparticles for clinical applications (Pal *et al.*, 2019) .

2.2.3.2 CHEMICAL SYNTHESIS

This synthesis involves the addition of a reducing agent like ascorbic acid, hydrazine, ammonium formate, dimethylformamide, or sodium borohydride (Eswari *et al.*, 2018) and a capping agent to the metal precursor already dissolved in an organic solvent under inert atmospheric conditions (De Matteis *et al.*, 2018). Chemical methods like chemical reduction (De Souza *et al.*, 2019), electrochemical reduction (Mehdi *et al.*, 2020), the template method, ultrasonic-assisted reduction (Deshmukh *et al.*, 2019), photo-induced or photo-catalytic reduction (Alshehri & Malik, 2020), microwave assisted synthesis (Francis *et al.*, 2018), irradiation reduction (Lee & Jun, 2019), microemulsion (Tianimoghadam & Salabat, 2018) amongst others, have many disadvantages. These methods incur use of toxic chemicals like sodium borohydride, hydrazine, ethylene glycol and sodium citrate (Shanmuganathan, Karuppusamy, Saravanan, *et al.*, 2019), ultilize hazardous solvents, and high energy consumption (Gudikandula & Maringanti, 2016). The reducing agents and surfactants are harsh chemical and produce toxic byproducts that pose toxicity issues to living organisms and the environment (Pal *et al.*, 2019). In other words, they are not eco-friendly. In order to protect living organisms and preserve the environment, there is an urgent need to develop cost effective, ecofriendly and less harmful nanoparticles that can be used for biomedical applications.

2.2.3.3 BIOLOGICAL SYNTHESIS

Green chemistry approach is the best alternative compared to physical and chemical methods. It involves using microbial cell biomass (bacteria, fungi, algae, yeast), biopolymers and plant biomass and extracts as cheap and harmless reagents for nanoparticle synthesis (Srikar *et al.*, 2016a). Utilizing green substances has several advantages including low energy consumption and moderate operation conditions (e. g. pressure and temperature) without using any toxic chemicals (Mohammadlou *et al.*, 2016).

There are reports on biological synthesis of silver nanoparticles using microorganisms including bacteria, fungi and plants; because of their antioxidant or reducing properties. Plants contain secondary metabolites while bacteria, fungi, and algae possess enzymes typically responsible for the reduction of metal compounds during synthesis (Marinescu *et al.*, 2020). Recent reviews have critically and holistically examined silver nanoparticle synthesis. Publication scenarios, different methods of silver nanoparticles synthesis; and their pharmacological applications are well documented (Firdhouse & Lalitha, 2015). Zhang *et al.* (2018) discussed the chemical, oxidative dissolution, sulphidation, chlorination and reduction environmental transformation of AgNPs and their environmental significance. Interactions like uptake, accumulation and toxicity of silver nanoparticles with autotrophic plants and heterotrophic microorganisms were highlighted (Tripathi *et al.*, 2017). Srikar *et al.* (2016b) elaborated on the factors that affect the synthesis of silver nanoparticles and microbiological methods for confirming antimicrobial activity of silver nanoparticles and its application. Non-biological methods of synthesizing silver nanoparticles, including characterisation and factors that affect particle size were examined by Natsuki *et al.* (2015). Synthesis, mechanism of action, optimization and applications of fungi-mediated silver nanopaticles (Guilger-Casagrande & Lima, 2019). Chaudhari *et al.* (2016) also laid emphasis on the use of fungi in silver nanoparticles synthesis, antimicrobial activity and application for topical uses, regulation of nanoparticles to avoid environmental toxicity as well as toxicity produced by chemical and physical routes. The use of plants for silver nanoparticle synthesis, antimicrobial property, applications and future prospects (Mohammadlou *et al.*, 2016), the physical properties of biopolymer edible coatings containing silver nanoparticles; silver release from coating to food and applications of these edible nanocomposites (Kraśniewska *et al.*, 2020), different types of nanoparticles, green approach to nanoparticle synthesis and different bioactivities of green synthesized silver nanoparticles by Ahmad *et al.* (2019), the various green methods of silver nanoparticle synthesis, biomedical and agricultural applications of silver nanoparticles (Rafique *et al.*, 2017), synthesis, characterization, mechanisms of action, routes of exposure and biodistribution with respect to human and environmental risk assessment (Ferdous & Nemmar, 2020) are well documented.

Green chemistry approach to nanoparticle synthesis is a simple protocol that is cost effective, ecofriendly, non-toxic with stable end products (Nilavukkarasi *et al.*, 2020a). Green nanotechnology uses natural sources with the aim of minimizing human health and environmental risks through the development of clean technologies. Among the various biological methods of silver nanoparticle synthesis, use of plant extracts for this purpose is potentially advantageous over microorganisms due to the ease of improvement, non-pathogenic, ecofriendly, and economical technique (Abdelghany *et al.*, 2018). To overcome the problem of toxicity in synthesis, plants have come to play a major role in the synthesis of nanoparticles.

2.3 THEORETICAL FRAMEWORK

Use of plants for green synthesis of nanoparticles has gathered remarkable attention as a result of its environmentally friendly, profitability and viability. The theoretical framework for plant mediated silver nanoparticle synthesis is embedded in the use of plant extracts as reducing and stabilizing agents as alternative options to the conventional physical and chemical synthesis methods. The green approach takes advantage of the rich diversity of phytochemical constituents present in the plants including flavonoids, alkaloids, terpenoids, saponins, tannins, and phenolic compounds to promote the bioreduction of silver ions into silver nanoparticles in and eco-friendly manner. This synthesis protocol is simple, economical, and viable, making it an effective method for expansive nanoparticle production. The following sections explores the key concepts of this synthesis method:

2.3.1 FLAVONOIDS

These are prominent phytochemical constituents found in plants and are produced as a result of biotic and abiotic stress and protect the plant. They are polyphenolic low weight compounds that contribute to the organoleptic characteristics in plant compounds (T. Sharma et al., 2022). Abiotic stress include low temperature, salt, drought, heavy metal stress and UV-B radiation (Zhuang et al., 2023). They can be found in plant parts including flowers, fruit skins, and leaves (Shomali et al., 2022). They can have different synthesis pathways and as such, vary in structure. Flavonoids are water soluble as they possess carbohydrate and hydroxyl groups. It has been known that their suitability for nanoparticle synthesis is due to the presence of electron and hydrogen donating capabilities. Classes of flavonoids include antocyanidins, flavonols, flavones, flavon-3-ols, flavanones and isoflavones (W. Liu et al., 2021). Flavonoids have been known to possess widespread therapeutic effects which include pharmaceutical, nutraceutical, cosmetic and medicinal applications, which may be associated with their antioxidative, anti-inflammatory, anticarcinogenic, and anti-mutagenic properties with modulation of significant cellular enzyme function (S. Chen et al., 2023)

2.3.1.1 MECHANISM OF ACTION DURING NANOPARTICLE SYNTHESIS

In nanoparticle synthesis, the enol group of the flavonoid compound is converted to keto group due to the removal of the reactive hydrogen thereby allowing the reduction of the metal ions to the metal nanoparticles. Incorporating the flavonoids into nanoparticles has been known to ameliorate their selectivity and accessibility to target sites (Sysak et al., 2023).

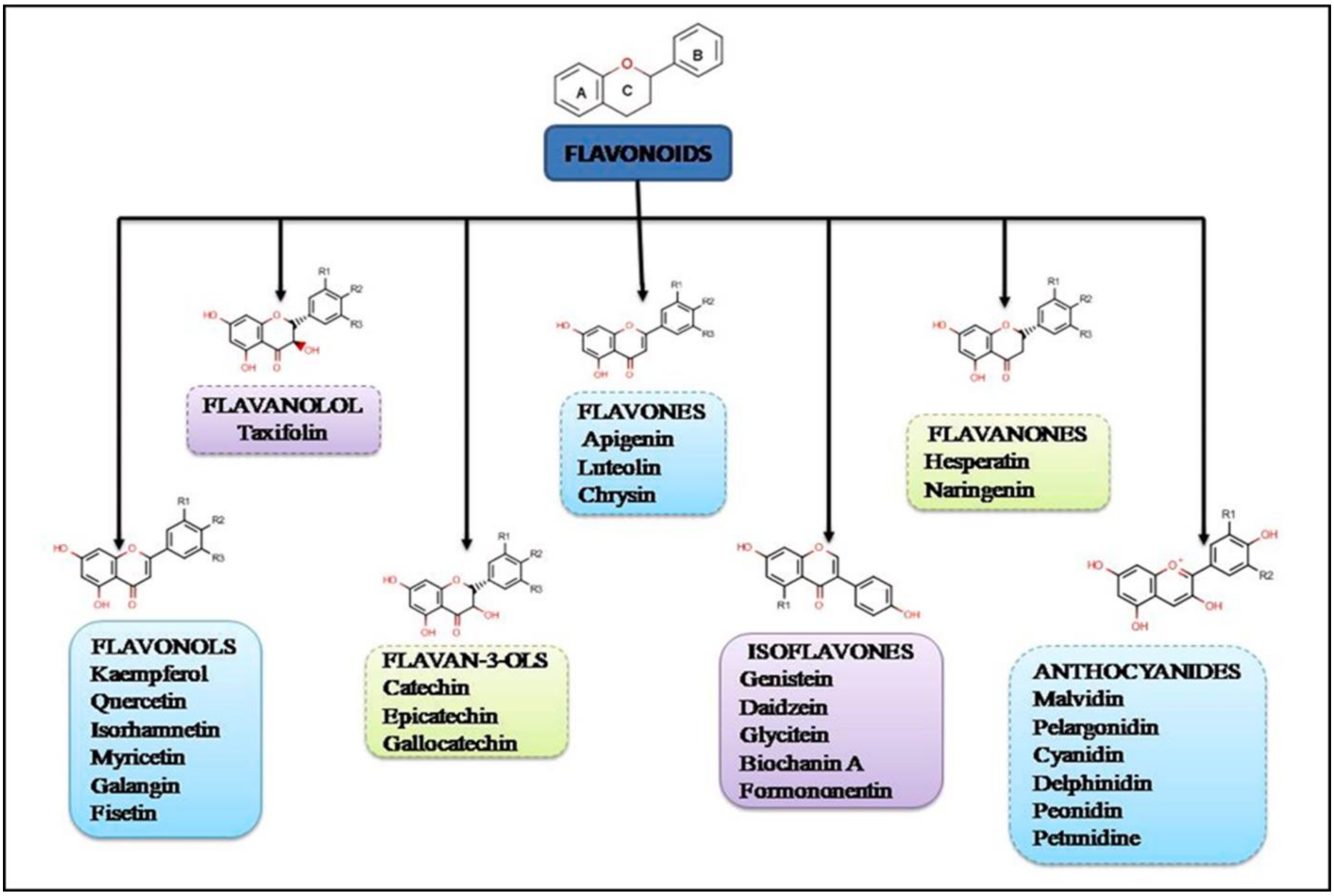


Fig 2.1: Chemical structure of the different classes and examples of flavonoids (T. Sharma et al., 2022)

2.3.2 TERPENOIDS

These are a type of terpenes that possess oxygen molecules synthesized through biochemical transformations. They are synthesized by the melavonic acid pathway in the cytosol and the 2C-methyl-D-erythritol-4- phosphate (MEP) pathway in the plastid, forming isopentenyl pyrophosphate (IPP) and dimethylallyl pyrophosphate (DMAPP) precursors (Masyita et al., 2022). They are found in essential oils in plants and have been reported to be of commercial importance. They have been revealed to possess antimicrobial, antifungal, antiviral, antiparasitic, antihyperglycemic, antiallergenic, anti-inflammatory, antispasmodic, immunomodulatory and chemotherapeutic properties (Abdallah & Quax, 2017). Examples of terpenoids include carvacrol, citronellal, geraniol, linalool, linalyl acetate, piperitone, menthol, and thymol. The different classes of terpenoids include monoterpenoids, hemiterpenoids, sesquiterpenoids, diterpenoids, triterpenoids and tetraterpenoids (Demurtas et al., 2023).

2.3.2.1 MECHANISM OF ACTION:

The hydroxyl group in terpenoids is responsible for the silver ion reduction to form silver nanoparticles, while it oxidises the aldehyde functional groups to carboxylic acid (Balčiūnaitienė et al., 2022). Eugenol for instance, possesses the phenol group on its benzene ring, and two highly inductive groups which are allyl and methoxy groups (Abdou et al., 2021). It discharges a proton which converts it to the activated state. While it stabilizes nanoparticles due to resonance and inductive effect, it releases electrons for reduction of the silver ions thereby increasing its degradation efficiency (Ritu et al., 2023a).

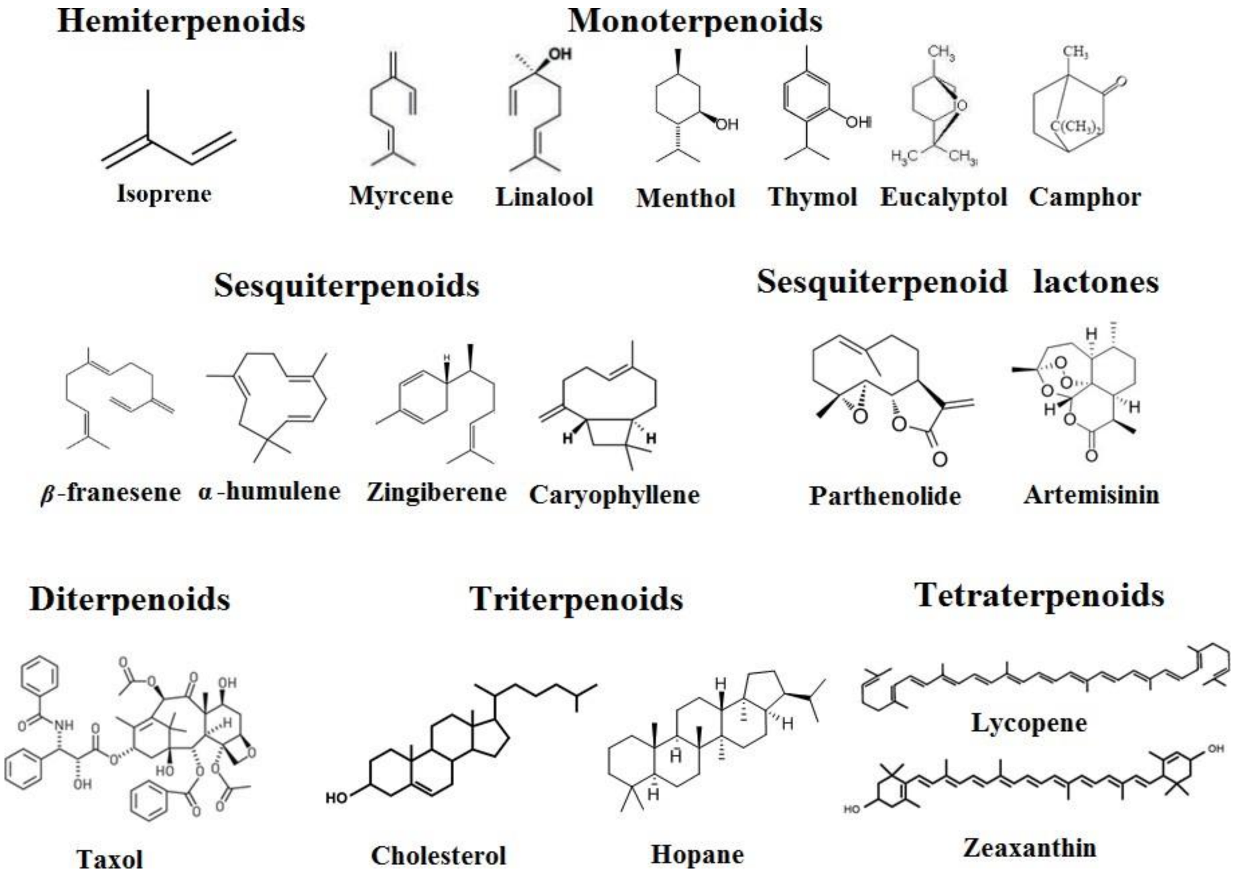
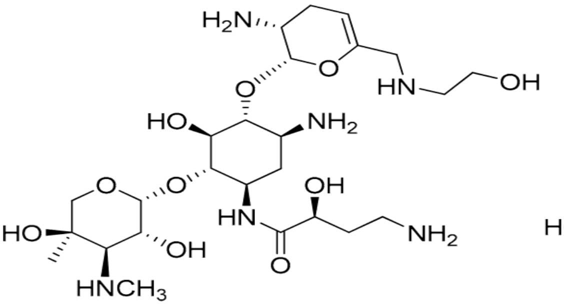


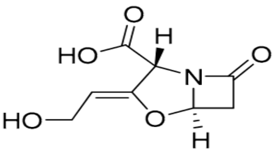
Fig 2.2: Chemical structure of the different classes of terpenoids (Abdallah & Quax, 2017)

2.3.3 ALKALOIDS

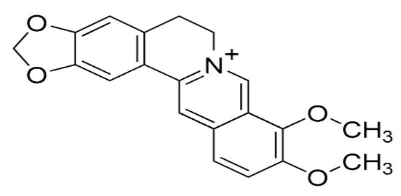
Secondary metabolites with more than 12,000 different structures, alkaloids are found in the meristematic, epidermal and hypodermal tissues, vascular sheaths and root apices (Ritu et al., 2023b). Alkaloids have been known to possess medicinal properties and have been incorporated in pharmaceutical applications (Bhambhani et al., 2021). They include atropine used as an insecticide, quinine present in the bark of trees, and morphine used in relieving pain. Alkaloids can be found in the vacuole in living cells and are transformed from amino acids including proline and ornithine (Heinrich et al., 2021).



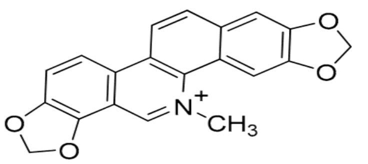
plazomicin (**4**)



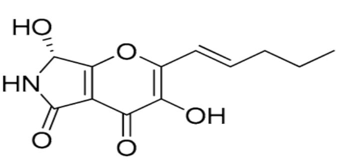
clavulanic acid (**5**)



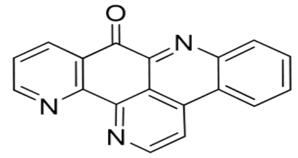
berberine (**6**)



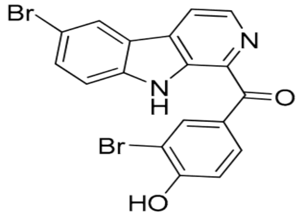
sanguinarine (**7**)



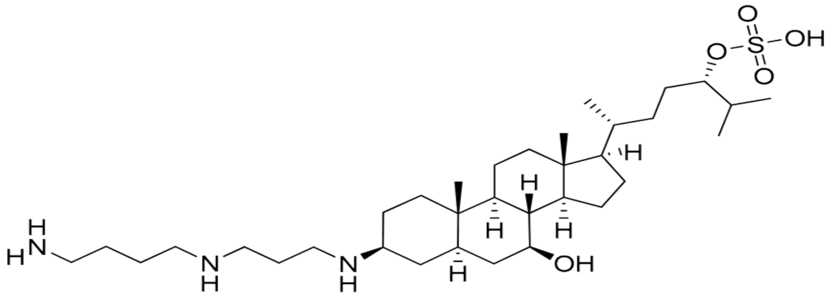
pyranonigrin F (**8**)



ascididemin (**9**)

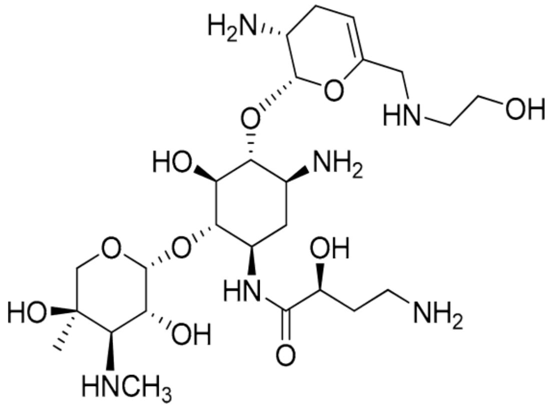


eudistamin Y4 (**10**)

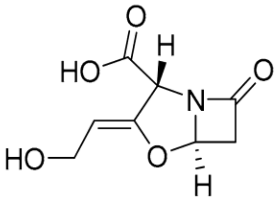


squalamine (**11**)

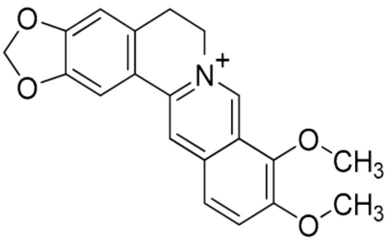
Fig 2.3: Chemical structure of the different classes of alkaloids (Daley & Cordell, 2021)



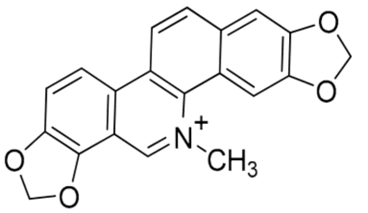
plazomicin (**4**)



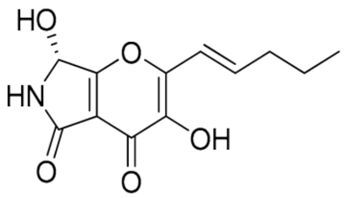
clavulanic acid (**5**)



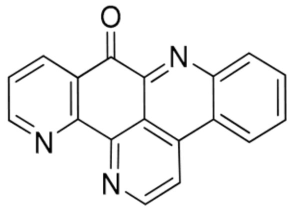
berberine (**6**)



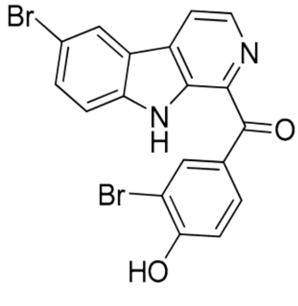
sanguinarine (**7**)



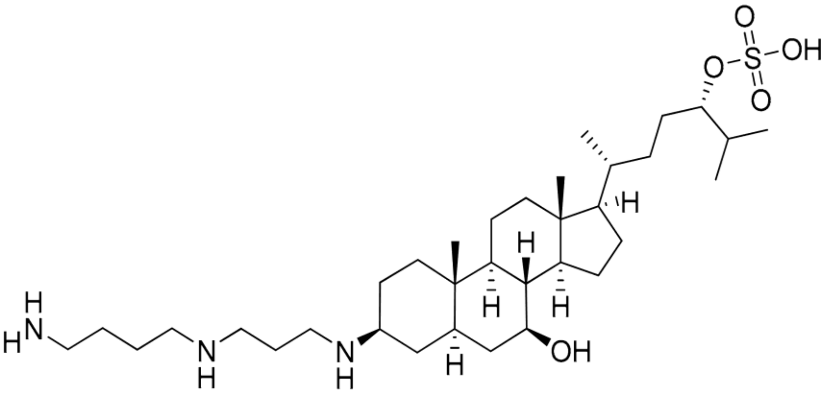
pyranonigrin F (**8**)



ascididemin (**9**)



eudistamin Y4 (**10**)



squalamine (**11**)

Fig 2.4: Chemical structure of alkaloids with antibacterial properties (Daley & Cordell, 2021)

2.3.4 SAPONINS

These are glycosides that can change membrane permeability thereby destabilizing it. These have been known to be responsible for plant defense against pathogens and stress inducing agents (Efimova & Ostroumova, 2021). They have been known to improve blood lipid profile and suppress cancer growth (Zhou et al., 2023). Saponin functionalized nanoparticles have been known to possess encapsulation and stabilization properties that are superior to synthetic surfactants and have the potential of stabilizing nanoemulsions (Schreiner et al., 2022). These properties have been found to be of use in pharmaceutical, supplements and food products, example curcumin (K. Sharma et al., 2023). In medicine, saponin- mediated nanoparticles have been found to be impede bacterial infection, wound burns and wound healing (P. Sharma et al., 2022).

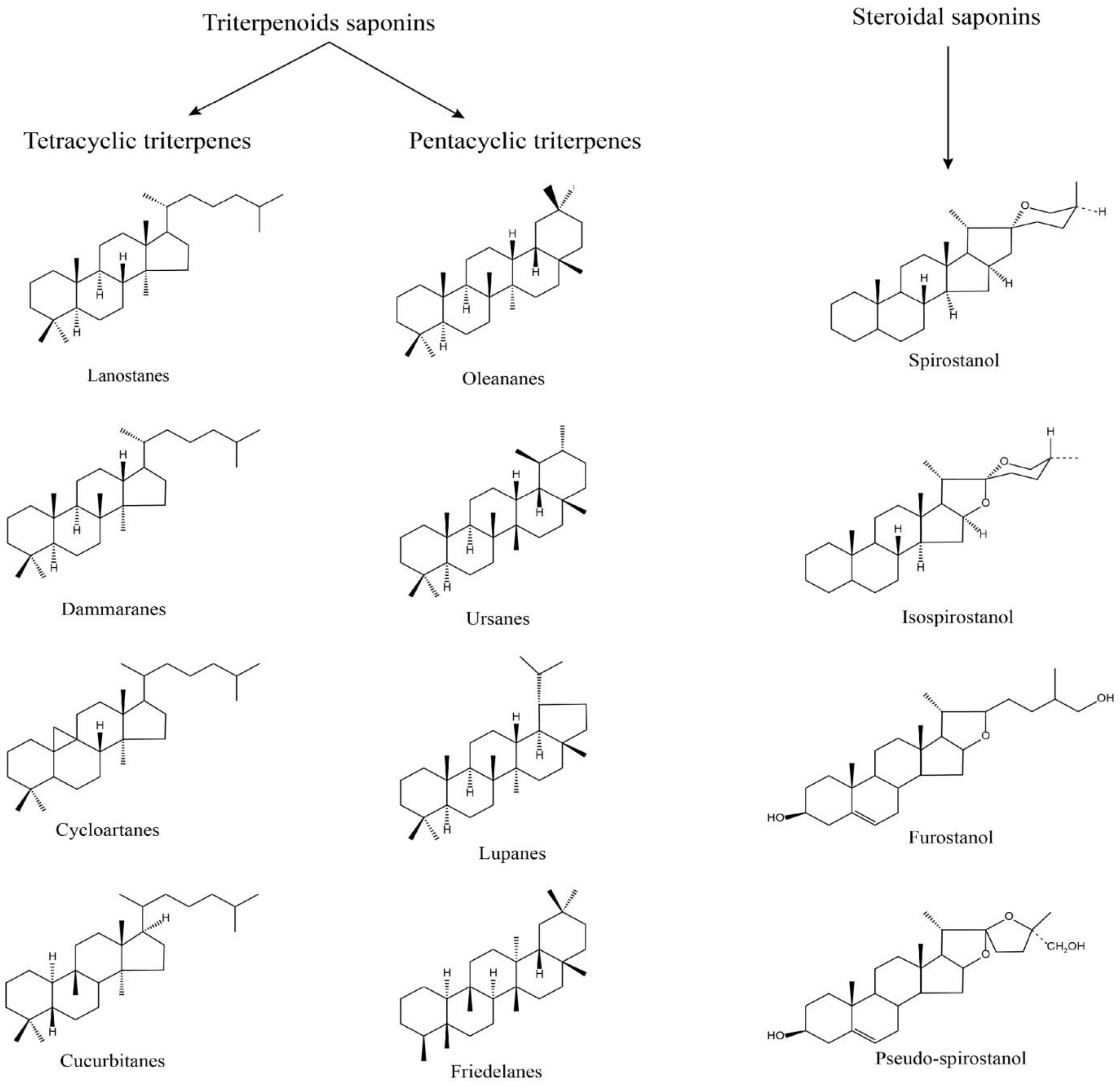


Fig 2.5: Chemical structure of the different classes of saponins (Cao et al., 2024)

2.3.5 TANNINS

These are natural, nontoxic and biodegradable secondary metabolites found in the leaf, fruit, bark and wood of plants. The presence of the hydroxyl groups in tannins makes it possible to combine and form complexes with metal ions (T. L. Nguyen et al., 2023). An example of tannins is tannic acid. Tannic acid, being a polyphenolic compound has glucose molecules at the center with gallic acid and benzoic acid attached at the ends through ester linkages (C. Chen et al., 2022). Tannic acid has been known to be applied in wound healing as it eliminates reactive oxygen species, improves the appearance of capillary vessels and augmentation of the fibroblast (X. Huang et al., 2024).

2.3.5.1 MECHANISM OF ACTION

It has been observed that at low pH, tannic acid begins the extension of nanoparticles at room temperature. However, at high pH, gallic acid form nanoparticles from silver nitrate without stabilizing them, thereby leading to the accumulations of unstable particles (Gibała et al., 2021). Furthermore, glucose has the capability to stabilize the reduced particles at room temperature but lacks reducing capability (Z. Zhang et al., 2022). Therefore, tannic acid cats as both reducing and stabilizing agent to prevent further aggregation of particles. This is as a result of the presence of phenol groups which are electron donors for reducing the metal ions in solution to form metal nanoparticles (T. Ahmad, 2014). Nanoparticles synthesized using tannic acid are more stabilized and is a great green option for metal nanoparticle synthesis (Tian et al., 2022).

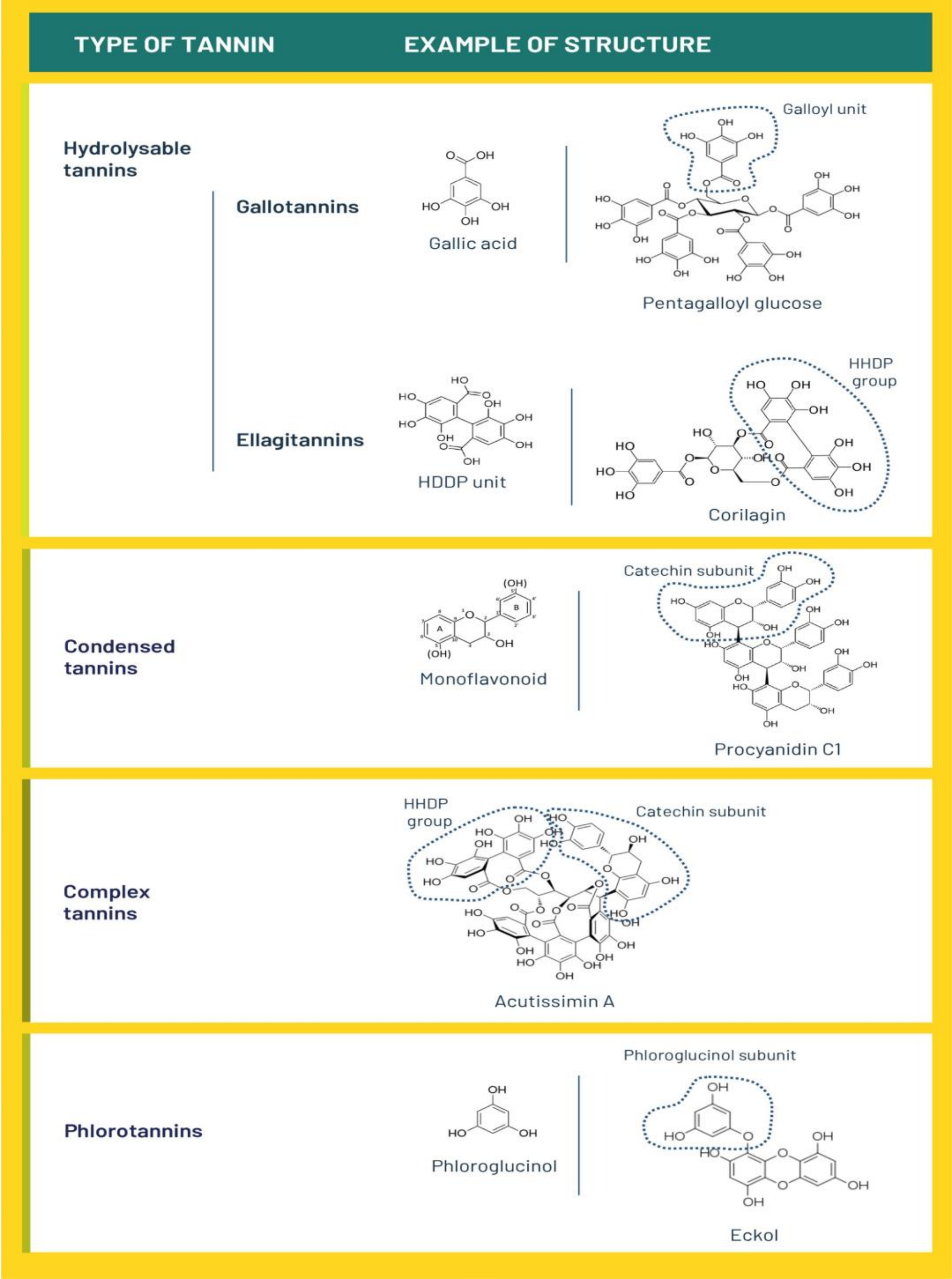


Fig 2.6: Structure of the different classes and examples of the tannins (Molino et al., 2023)

2.4 PHYTOFABRICATION OF SILVER NANOPARTICLES

There are a lot of advantages that make plants better synthesizers. They are in abundance and have a wide variety unlike other microorganisms (Garg *et al.*, 2020). Plants are nontoxic chemicals and provide natural capping agents. Leaf extracts have been used for synthesis of silver nanoparticles, which has highlighted the possibility of rapid synthesis and reduce the steps involved in downstream processing, thereby making the protocol more economical and cost-efficient (Gowri *et al.*, 2017). The use of plant extracts also reduces the cost of isolation and culture media for nanoparticle synthesis by microorganisms (Praba *et al.*, 2015). Plants possess phytochemical constituents otherwise called secondary metabolites. These metabolites existing in plants which include sugars, alkaloids, phenolic acids, terpenoids, polyphenols, and proteins play an important role in the bioreduction of silver ions to silver nanoparticles (Makarov *et al.*, 2014). A number of plants are being currently investigated for their role in the synthesis of nanoparticles. Plant extract has been used as reducing and capping agent for the synthesis of nanoparticles. Plant leaf extract had been used for synthesis of silver and gold nanoparticles, which leads to formation of pure metallic nanoparticles of silver and gold (Meva *et al.*, 2019).

2.5 MECHANISM FOR SILVER NANOPARTICLE SYNTHESIS

The ability of plants to detoxify metal ions, otherwise referred to as bioaccumulation, plays a vital role in the synthesis of silver nanoparticles using plants (Marslin *et al.*, 2018). A possible hypothetical mechanism behind the synthesis of nanoparticles is an enzymatic reaction in which the plant extract contains the complex of reducing enzymes which reduce the chemicals such as silver nitrate into silver ions and nitrate ions (Khan *et al.*, 2017). It has been proposed electrostatic interactions have been responsible for the trappings of Ag ions on the protein surface of the plant extract which leads to formation of silver nuclei which grows by further reduction of Ag ions and build up at the nuclei forming silver (Rajeshkumar & Bharath, 2017). Ahmad *et al.* (2020) postulated that polyols, polysaccharides and aqueous-solvent heterocyclic blends like organic acids, quinones and flavones are the most important plant constituents that are primarily responsible for the reduction of silver particles, leading to the formation of AgNPs. Plants act as reducing and capping agents (Enrique *et al.*, 2018), thereby requiring no addition of capping or stabilizing agent externally. This is made possible by biomolecules which are plant metabolites like alkaloids, enzymes, polysaccharides, terpenoids, proteins, flavones, amino acids, alcoholic compounds, phenolics, flavonols, ascorbic acid, and other vitamins (Handoko *et al.*, 2019). Flavonone and terpenoid components of leaf broth are being predicted to stabilize the formation of nanoparticles (Roy *et al.*, 2015). It is well known that silver nanoparticles exhibit brownish color in aqueous solution due to excitation of surface plasmon vibrations in silver nanoparticles (Prakash *et al.*, 2015; Supraja *et al.*, 2016). In neem leaf broth, terpenoids are the surface-active molecules stabilizing the nanoparticles and reaction of the metal ions is possibly facilitated by reducing sugars (Verma & Mehata, 2016).

Ahmad *et al.* (2020) showed using *Flacourtia jangomas* fruit extract that the proteins which have amine groups played a reducing and controlling role during the formation of AgNPs in the solutions and that the secondary structure of the proteins changed after reaction with silver ions. *Ficus hispida* leaf extract contains antioxidants and polyphenols (flavonoids) and it can also directly scavenge molecular species of active oxygen (Ramesh *et al.*, 2018). Antioxidant action of flavonoids resides mainly in their ability to donate electrons or hydrogen atoms, that is, change keto group to enol form (Khandel *et al.*, 2018). Proteins, enzymes, phenolics, and other chemicals within plant leaf extract reduce silver salts and also provide excellent tenacity against agglomeration (Ravichandran *et al.*, 2019).

2.6 PLANT MEDIATED SILVER NANOPARTICLES RESEARCH

Various researches on plant mediated synthesis and their biomedical, industrial and environmental applications have been performed. However, most of the researchers relied on existing literature for the phytochemical composition of the plants that were involved in silver nanoparticles synthesis. *Lycopersicon esculentum* fruit extract was used as a reducing and capping agent for the green synthesis of silver nanoparticles for anti-biofilm activity of *Candida sp.* (Choi *et al.*, 2019). Colour change from colourless to yellow and then reddish brown after 10 minutes indicated formation of AgNP with UV spectral peak at 445 nm. The peak intensity increased with increase in time as maximum absorbance was observed at 12 minutes marking the end of the reaction. SEM image revealed spherical shapes with size range 10-50 nm. EDAX images confirmed the presence of AgNPs by the signals of silver, carbon, oxygen, Sulphur, and potassium indicating the presence of organic substances in the extract. DLS obtained a polydispersity index (PDI) of 0.232 at 48 hours. FTIR confirmed the presence of flavonoids, terpenoids, and phenolic acids present in the bioreduction of the Ag^+. Antibiofilm and antifungal activities revealed a minimum inhibitory concentration (MIC) of 8 µg/ml for *Candida sp.* whereas no inhibition was obtained for lower concentrations. For pre-formed biofilms, MIC for *C. albicans* and *C. glabrata* was 32 µg/ml while *C. parapsilosis* showed an MIC of 8 µg/ml. this shows that *L. esculentum* –silver nanoparticles as a good antifungal and antibiofilm agent.

Ageratum conyzoides L. leaves rich in tannins and other phytochemicals such as alkaloids, flavonoids, terpenoids, saponins, cardiac glycosides, resins, steroids, phenols, essential and nonessential amino acids (Wuyep *et al.*, 2017) was explored for silver nanoparticle biosynthesis (Chandraker *et al.*, 2019). The leaves extract produced crystalline and spherical silver nanoparticles with size range 11-48 nm with UV spectral peak at 443 nm. The nanoparticles displayed strong antioxidant activity compared to ascorbic acid with confirmed presence of amine, ester, carboxylic, alcohol and methyl functional groups representing the different flavonoids, polyphenols, polysaccharides and triterpenoids involved in the bioreduction of the silver ions. The silver nanoparticles preferably interacted with calf thymus-DNA (CT-DNA) with possible hydrogen binding at N_7 atoms of guaninie-adenine bases and N_3 atoms of cytosine - thymine bases. On addition of 20 mM of H_2O_2 to the biosynthesied silver nanoparticles, the brown colour of the silver nanoparticles became colourless after 25 minutes with decrease in absorbance and disappearance of the characteristic Ag peak. This suggested the use of AgNPs to detect the concentrations of H_2O_2 in unknown samples. The catalytic activity of the green synthesized silver nanoparticles was studied by the solar irradiation mediated degradation of methylene blue. It was observed that there was gradual colour change of methylene blue from blue to colourless after 2hrs of exposure to sunlight. 50% and 100% degradation of methylene blue dye was achieved in 37 and 105 minutes respectively. Photocatalytic degradation followed a Langmuir- Hinshelwood kinetic model with degradation rate constant of 2.8×10^{-2} min^{-1}, showing that *A.conyzoides*- silver nanoparticles can act as a green catalyst for the degradation of methylene blue under visible light.

Riaz *et al.* (2021) reported the formation of spherical silver nanoparticles in the size range of 5-15 nm using *Camellia sinensis* leaves extract. Increase in pH (from pH 7-pH 9) led to shift in surface plasmon resonance (SPR) peak (417 nm-413 nm) indicating efficient reduction of silver ions. Higher pH conditions depicted formation of regular spherically shaped AgNPs. At higher temperatures (25 ^{o}C-85 ^{o}C), the reaction rate increases thereby favouring the nucleation process by forming more nuclei. Higher pH (7,9 and 11) gave rise to more spherical, regular and small size nanoparticles compared to pH 5 which produced irregular and larger size nanoparticles. Zeta potential values varied from -15.32 to -42.90 mV, with particles prepared at 85 ^{o}C having higher zeta potential values than those prepared at 25 ^{o}C indicating increase in AgNP stability with increase in in temperature. Dynamic light scattering (DLS) measurements revealed decrease in hydrodynamic size with increase in pH (5-9) at all temperatures. Antibacterial activity showed higher zone of inhibition on *Escherichia coli* and *Staphylococcus aureus* when nanoparticles produced at pH 9 and 65 ^{o}C was introduced into the agar containing the bacterial strains. However, zone of inhibition for *E. coli* and *S. aureus* were found to be 13 mm and 8 mm respectively. Cytotoxic studies indicated reduction of HeLa cell proliferation when 25 µm AgNPs were added. 50 µm and 75 µm AgNPs addition inhibited cell proliferation altogether, indicating that AgNPs hindered human cervical cancer cell growth in a dose-dependent manner.

Aqueous extract of *Nepeta deflersiana* leaves were employed in green synthesis of silver nanoparticles and assessed for anticancer potentials (Al-Sheddi *et al.*, 2018). It was observed that the nanoparticles with face centred cubic spherical shape of particle size 33 nm was able to cause more than 50% HeLa cell death at 5 µg/ml, showing its huge anticancer potential.

Green silver nanoparticles produced using *Salvia spinosa* plant extract was evaluated for antibacterial activity (Pirtarighat *et al.*, 2019) and the nanoparticles 5.13 nm in diameter were found to contain free –OH group of phenols and alcohols, -NH, alkanes in lipids, COO^-, CΞC, alkynes, N-C, N=C, C=C, amines in proteins, S=O, carboxylic acid groups and alkyl halide groups. Antibacterial analysis showed that the minimum inhibitory concentration for *Bacillus subtilis*, *Esherichia coli* and *Bacillus vallismortis* were 15 mm, 12 mm and 16 mm respectively. It was assumed that the mechanism of action of AgNPs is to disrupt the cell membrane thereby causing intracellular ATP leakage and subsequent cell death. Also positively charged Ag ions have a larger tendency of reacting with phosphorous and sulphur in DNA and RNA which destroys the genetic material in return.

Aerial parts of *Origanum vulgaria* were used to synthesize silver nanoparticles by Shaik *et al.* (2018) for antimicrobial activity. Face-centered cubic, polydisperse and spherical nanoparticles with size range 2-25 nm and average size of 12 nm showed increase in antimicrobial activity as the concentration increased. The zone of inhibition for bacterial strains (*Staphylococcus aureus*, *S. epidermis*, *Micococcus luteus*, Methicillin-resistant *Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Salmonella typhimurium, Shigella sonnei*) were 12-19 nm while that of fungal strains (*Aspergillus flavus, Alternaria alternata, Phialophora alba, Paecilomyces variotti*) were 12-28 nm. Highest zone of inhibition was obtained for *P. aeruginosa* and *S. aureus* (19 nm) while for fungi, *A. alternata* was 28 nm zone of inhibition respectively, which infers the use of *Origanum vulgare*-silver nanoparticles as a good antimicrobial agent.

Mentha arvensis plant extract was employed for green silver nanoparticle synthesis for antibacterial activity for Leishmania and plant pathogens (Javed *et al.*, 2020). It was observed that spherical nanoparticles with size range of 20-100 nm and average size of 20.86 nm was able to kill 100% human red blood cell population (LD_{100}) at 216 µg/ml while minimal dose (10 µg/ml) was effective for *Leishmania tropica*. Lethal activity for *L. tropica* was a dose dependent activity of the synthesized nanoparticles. Dose dependent results for antibacterial activity against the plant bacterial pathogens (*Erwinia carotovora, Xanthomonas vesicatoria, Xanthomonas oryzae* and *Ralstonia solanacearum*) were observed between 2-12 µg/ml against the positive control Ampicillin which was 10 µg/ml. this proves the use of the nanoparticles as plant pesticides in agriculture.

Citrus paradis peel extract was adopted for silver nanoparticle synthesis for catalytic activity against congo red, methylene blue, malachite green, rhodamine B, 4-nitrophenol using hydrogen borohydride as catalyst (Naseem *et al.*, 2020). The spherical bio-synthesized nanoparticles 14.84 nm in size and average diameter of 28 nm were found to contain alcohols, amides, amines, esters, ethers and carboxylic acids. Among the toxic dyes, methylene blue had the highest degradation efficiency (93.29%) while Rhodamine B had the lowest degradation efficiency (60.56%) and this was attributed to the complex structure of Rhodamine B. Aqueous, ethanol and methanol extracts of *Achillea millefolium* plant were utilized for silver nanoparticles and their antibacterial and antioxidant activities compared (Yousaf *et al.*, 2020). The aqueous, ethanol and methanol extract silver nanoparticles had spherical, rectangular and cubic shapes respectively with sizes 20.77 nm, 18.53 nm and 14.27 nm respectively. Methanol extract AgNPs being the smallest in size (18 nm) had the highest antibacterial activity due to their large surface area, followed by ethanol extract and aqueous extracts. Also, in antioxidant activity, the methanol extract had the highest scavenging ability (7.03 µg/ml) compared to ascorbic acid (4.29 µg/ml). Jalilian *et al.* (2020) explored aerial parts of *Allium ampeloprasum* for silver nanoparticle synthesis on antibacterial, antioxidant and cytotoxic activities. Polydisperse and spherical silver nanoparticles of size range 2.3 - 27 nm had zone of inhibition ranges from 8-27 mm for *S. aureus*, *E. coli*, multi-drug resistant *P. aeruginosa* and multi-drug resistant *E. coli*, with *S. aureus* being the smallest (8 mm) and multi-drug resistant *P. aeruginosa* being the largest (27 mm). The total phenolic contents were 10.94 µg/ml compared to that of the extract which is 15.58 µg/ml. For antioxidant activity, the nanoparticles exhibited 81% inhibition while that of the extract is 32%.

Cola nitida pod extract was examined for silver nanoparticle synthesis (Lateef *et al.*, 2016). Polydisperse and spherical nanoparticles with face centred cubic and crystalline structure of size range 12-80 nm were produced. Increase in the AgNPs concentration (50-150 µg/ml) showed strong inhibition for multidrug resistant strains of *Klebsiella granulomatis*, *P. aeruginosa*, and *E. coli*. 5 mg/ml addition of AgNP to paint mixture yielded complete (100%) inhibition of *S. aureus*, *E. coli*, *P. aeruginosa, Aspergillus niger, A. flavus, and A.fumigatus*, making the silver nanoparticles excellent choice as antimicrobial additives in paint coatings. The biosynthesized nanoparticles exhibited antioxidant activity at IC_{50} of 45.98 µg/ml against DPPH (2,2-diphenyl-1-picrylhydrazyl) and iron reduction of 13.62-49.96% at AgNP increasing concentrations. (Aslany et al., 2020)Fresh leaves of *Azolla caroliniana* were involved in producing silver nanoparticles using microwave assisted method (Anjana *et al.*, 2020). Spherical, polydispersed, and crystalline silver nanoparticles of average particle size 23.6 nm were obtained. Addition of AgNPs to crystal violet and fuschine dyes reduced the SPR peak further downwards from 586 nm peak wavelength. Antibacterial analysis showed high microbial inhibition just like streptomycin (positive control) against *S. aureus* and *K.*

pneumoniae growth. Cytotoxic studies revealed minimum inhibitory concentration of 200 µg/ml for 100% lethality of lymphoma ascites cells.

Capparis zeylanica leaves were engaged in silver nanoparticle synthesis for antibacterial and anti-proliferation activities (Nilavukkarasi *et al.*, 2020b). Surface plasmon resonance (SPR) peak was initially observed at 310 nm and later at 395 nm. FTIR analysis showed the presence of NH, OH, C=O, C-N, C-H and C-O groups characteristic of phytochemical constituents present in the silver bioreduction reaction. Average particle size of 28 nm with crystallite size of 35 nm was obtained. For antimicrobial studies, the zone of inhibition ranged from 20-30 mm for *Staphylococcus epidermidis, Enterococcus faecalis, Salmonella paratyphi, Shigella dysenteriae, C. albicans,* and *A. niger*, with *S. dysenteriae* having the smallest (20 mm) and *S. epidermidis* being the largest (30mm). Anti-proliferative analysis revealed reduced cell viability after 48 hours, with higher concentrations like 200 µg/ml and 100 reducing cell viability at 20 and 40% respectively.

Clove (*Syzygium aromaticum*) buds extract-silver nanoparticles of spherical, face-centred cubic nanoparticles of size range 10-27 nm and average size 9.42 nm were analyzed for antidiatom activity (Chand *et al.*, 2020). It showed a decrease in population of algae (*Nitzischia closterium*) successively after 7 day treatment with increase in AgNP concentration. Green thyme (*Thymus vulgaris*) mediated silver nanoparticles with size 75 nm had strong antimicrobial and antibiofilm properties against immune evading methicillin resistant *S. aureus* by distorting the cellular integrity at 1 mg/ml minimum concentration against methicillin-resistant *Staphylococcus aureus* (MRSA) (Singh *et al.*, 2020b). Optimum conditions for high yield of *Hibiscus rosasinensis*-silver nanoparticles were pH 6, 5 mM and 70 °C and the nanoparticles were spherical and face centred cubic structure of size range 12-17 nm and crystallite size 43 nm. Antibacterial activity for *S. aureus* was 19 mm while *E. coli* was 12 mm.

Antifungal activity of *Melia azedarach*-mediated silver nanoparticles was assessed by Jebril *et al.* (2020). Silver nanoparticles were observed with prior colour change after 10 minutes of reaction initiation (addition of extract to silver nitrate) from light yellow to dark brown. The produced nanoparticles were spherical and face centered cubic with size range 18-30 nm. FTIR analysis confirmed the presence of hydrolysable tannic acid as being responsible for the silver bioreduction process and stabilization of the AgNPs. For in vitro and in vivo antifungal studies against *Verticulum dahliae* in eggplants, significant mycelial growth inhibition of 18%, 33% and 55% inhibition with increase in AgNP concentration was observed in vitro. While in vivo assay, the biosynthesized silver nanoparticles displayed a reduction in disease severity and vascular discolouration in the eggplant by 87% and 97% at 20 ppm AgNP concentration when compared to untreated control group. It was concluded that *M. azedarach*-silver nanoaprticles can make for good agricultural pesticides against plant pathogens.

Moringa oleifera flowers were utilized for green synthesis of silver nanoparticles and evaluated for antimicrobial and sensing properties (Bindhu *et al.*, 2020). Nanoparticles produced were spherical and monodispersed with size range 2-31 nm. Lower extract concentrations led to insufficient silver ions hence larger size particles. FTIR analysis showed the presence of proteins and other phytochemical constituents in the nanoparticles. For antibacterial activity, the zone of inhibition exhibited by the nanoparticles was higher for *S. aureus* than for *K. pneumoniae*. For sensing potential, addition of copper (Cu) to the AgNPs was met with gradual decrease in the SPR peak 457 nm wavelength with increase in concentrations of the AgNPs and this was attributed to the formation of steady aggregates.

Spherical nanoparticles with average size 20-50 nm were achieved using *Neurada procumbens* for silver nanoparticle synthesis (Alharbi & Alarfaj, 2020). Antimicrobial assay against multi-resistant pathogens like *K. pneumoniae, Acetinobacter baumannii* and *E. coli* revealed reduced bacterial growth when AgNP concentration was increased.

Carya illinoinensis leaf extract was studied for silver nanoparticle synthesis (Dalir *et al.*, 2020). On addition of the leaf extract to silver nitrate solution, UV spectral peak was observed at 440 nm characteristic of the presence of silver nanoparticles FTIR analysis confirmed the presence of –OH stretching in alcohol and phenolic compounds, aliphatic amines, and alkanes. The nanoparticles were spherical in shape with size range 12-30nm with mean diameter of 20.34 nm. Antimicrobial activities against *S. aureus, Listeria monocytogens*, *E. coli* and *P. aeruginosa* revealed highest zone of inhibition exhibited by *S. aureus* (15 mm) and minimum inhibitory concentration at 16 µg/ml AgNP. Higher doses of AgNPs (64 and 128 µg/ml) were needed to achieve inhibition in the gram positive organisms (*S. aureus* and *L. monocytogens*).

2.7 REACTION KINETICS PARAMETERS

Reaction parameters play important functions in optimizing the maximum yield, size, shape and stability of biosynthesized AgNPs (Latif *et al.*, 2019; Ovais *et al.*, 2016). They include the concentration of the plant material, concentration of the silver salt, pH, time of reaction and temperature Optimization is an important requirement for the large scale production of AgNPs to get smaller size particles at the same time, minimize the use of excess reactants and experimental trials (Rao & Paria, 2015).

2.7.1 EFFECT OF PLANT EXTRACT CONCENTRATION

Increase in extract concentration leads to increase in nanoparticle yield (Heydari & Rashidipour, 2015). A study performed by Mankad *et al.* (2020) showed that at higher plant extract concentration (5-20 ml), there is increase in the presence of reducing agents in the extract which in turn increases the particle size upon longer exposure duration. Also, the observable colour intensity that occurs upon addition of silver nitrate solution to the plant extract deepens with increase in extract concentration, thereby leading to higher concentrations of the biomolecules involved in the reduction and capping processes becoming more available in solution (Ibrahim, 2015). In the UV-Visible spectra, the Surface Plasmon Resonance (SPR) peaks are more intense with maximum peak intensity at higher concentrations of the extract leading to more silver nanoparticle absorption as observed in other studies (Bello *et al.*, 2020; Kedi *et al.*, 2018; Oda *et al.*, 2019).

2.7.2 EFFECT OF SILVER NITRATE CONCENTRATION

Increase in salt concentration leads to high SPR bands which reflect an indication of agglomeration (Velidandi *et al.*, 2020). Concentrations above 10 mM can cause accumulation of silver and unclear surfaces (Ovais *et al.*, 2016). It was observed that at high concentrations, large particles are found varying from 40-90 nm (Mohaghegh *et al.*, 2020). Similar results were reported by Balashanmugam *et al.* (2016). In other studies, 5 mM of silver nitrate supported rapid formation of nanoparticles formation while UV spectral peak shifted at 3 mM and 10 mM concentrations (Singh *et al.*, 2020b). Javed *et al.* (2020) also reported optimal yield at 5 mM silver salt concentration. In a study by Mishra *et al.* (2020), with increase in silver salt concentration from 0.5 mM to 5 mM, good surface plasmon resonance peak was obtained at 1 mM salt concentration. They also reported that particle size of the synthesized nanoparticles increased with increase in silver salt concentration. Increase in silver salt concentration has been known to cause a strong absorbance of UV – visible spectra at 440-500 nm exciting surface plasmon vibrations thereby leading to enhanced formation of AgNPs (Bélteky *et al.*, 2021).

2.7.3 EFFECT OF REACTION TIME

Reaction time is one of the major factors that influence the morphology of nanoparticles. Khan *et al.* (2018) observed the formation of AgNPs through colour change from transparent to light brown within 20 minutes of mixing the reactants. Increase in reaction time leads to increase in the rate of reduction of AgNPs formation and aggregation of smaller particles (Singh *et al.*, 2020). Meanwhile, lesser times (10-20 minutes) which is observed in the UV-Visible spectra as low absorption peaks indicates lower yield of AgNPs (Arya *et al.*, 2018). Nucleation was rapid with formation of AgNPs and appearance of absorbance peak at 430 nm between 90 minutes and 120 minutes of initiation of the reaction with the reaction ending after 120 minutes (Shaik *et al.*, 2018).

2.7.4 EFFECT OF pH

The acidity or alkalinity of the reaction medium determines the shape and size of the nanoparticles as it alters the charge on the metabolites, thereby affecting the redox reaction between the metal ions and the phytochemical capping agent (Ahmed & Mustafa, 2020). In a study by Kedi *et al.* (2018), it was observed that *Selaginella myosurus*-mediated silver nanoparticles were well synthesized with pH ranges from 8-12. It was also noted that the surface plasmon resonance bands increased with increase in pH from 8 to 12 while it decreased with decrease in pH from 6 to 2. Under acidic conditions (pH 2.0), biomolecules become inactivated, making acidic pH unsuitable for AgNP synthesis. At pH 10.0, the peak becomes narrow which shows that there is poor stability of AgNPs at extreme alkaline pH (Ramesh *et al.*, 2015), whereas in another study with rice husk extract for silver nanoparticle synthesis, pH 10 was the optimal pH for high stable yield of silver nanoparticles (Liu *et al.*, 2017) In another study (Rao & Paria, 2015), the optimum pH for the biosynthesis of AgNPs using *Aegle marmelos* leaf extract was found to be at pH 7.0. Similar results were observed (Balashanmugam *et al.*, 2016) upon addition of silver nitrate in the *Cassia roxburghii* leaf aqueous extract. It was also observed that stability was also high at pH 7.0 than at other pH levels. It was reported that change in pH affects the shape and size of the nanoparticles, as well as alters the charge of biomolecules which affects their capping and stabilizing abilities (Verma & Mehata, 2016).

2.7.5 EFFECT OF TEMPERATURE

Temperature influences the size, shape and rate of nanoparticle formation (Vijayaraghavan & Ashokkumar, 2017). It provides the required activation energy to kick start a chemical reaction, catalyzes the collision of reactants to be converted to the needed products (Javed *et al.*, 2021). Silver nanoparticle synthesis can be performed below 25 °C and above 40 °C (Hussain *et al.*, 2019). Increase in temperature increases the rate of the reaction but higher temperature above 60 °C denatures the phytochemical constituents which in turn reduce their potential and cause particle size increase and agglomeration (Kaabipour & Hemmati, 2021). Asimuddin *et al.* (2020) studied the effect of temperature on silver nanoparticle synthesis using *Azadirachta indica* leaf extract and reported that room temperature slows down the nucleation process, produces low UV spectral peak intensity and consequent low AgNP yield whereas higher temperatures 35-65 °C were needed for nucleation processes to occur smoothly and produce high quality nanoparticles with less defects.

2.8 CHARACTERIZATION OF SILVER NANOPARTICLES

Characterization of nanoparticles synthesized through several processes is very important especially when these materials produced in the laboratory will be used for commercial applications. Nanoparticle size, size distribution, crystalline structure, surface charge, degree of aggregation and organic compounds present are also crucial for biomedical and environmental applications (Mourdikoudis *et al.*, 2018).

2.8.1 ULTRAVIOLET VISIBLE (UV-VIS) SPECTROSCOPY

This is a primary technique that can easily monitor the synthesis and stability of AgNPs in a fast, simple and sensitive manner (Patil & Chougale, 2021). Metal nanoparticles absorb optical light usually accompanied by changes in colour because of collective resonance of the conduction electrons in the metal known as surface plasmon resonance (SPR) (Patra & Baek, 2014). The colour changes are from colourless for silver nitrate solution and dark green for the plant extract to light yellow and finally to dark brown. The SPR peak is shown through the absorption band spectra of these metal nanoparticles which is in the range of 400-500 nm for silver nanoparticles (Jalani *et al.*, 2018). Synthesized silver nanoparticles using *Nyctanthes* *arbor-tristis* seed extract showed an absorbance of 420 nm wavelength reflecting the surface plasmon resonance of AgNPs (A. Basu *et al.*, 2020). Silver nanoparticles synthesized using turmeric extract displayed and absorbance peak of 423 nm (Alsammarraie *et al.*, 2018) and they suggested that multi-sized distribution of AgNPs could cause broad plasmon band extension with an absorption tail in the higher wavelength part of the wavelength ranges. *Phyllanthus urinaria, Pouzolzia zeylanica*, and *Scoparia dulcis* leaf extracts were employed in silver nanoparticle synthesis and they displayed wavelength range peaks of 400-600 nm (Nguyen *et al.*, 2020). They also showed characteristic colour changes depicting AgNP formation. Increasing the extract concentration leads to increase in size of nanoparticles produced (Girón-Vázquez *et al.*, 2019). Advantages of UV-Vis spectroscopy are rapid and simple means of analysis, it provides very high precision and accuracy, no need for calibration, short measuring time and useful for a wide variety of chemicals and can be used both quantitatively and qualitatively (Ríos-Reina & Azcarate, 2023).

2.8.2 SCANNING ELECTRON MICROSCOPY (SEM)

This method images the sample surface by scanning it with a high energy beam of electrons which strikes the surface of the specimen and interacts with atoms of the sample, sending out signals in the form of secondary electrons (Modena *et al.*, 2019). Characteristic X-rays are then generated, containing information about the sample's surface topography and morphology of the particles through which the size of the nanoparticle can be calculated using a statistical software (Vijayaraghavan & Ashokkumar, 2017). It measures the elemental mapping of silver nanoparticles including their shape and morphology (Rautela *et al.*, 2019). *Artemisia turcomanica* leaf extract mediated nanoparticles was confirmed to be spherical in shape and of size range 20-60 nm with average particle size of 21.22 nm (Mousavi *et al.*, 2018). Advantages of SEM include the ability to observe multiple specimens, efficient analysis, cost effectiveness, enhanced resolution and contrast, automated stage navigation, ease of sample preparation and use, and provision of digital data forms (Ul-Hamid, 2018).

2.8.3 TRANSMISSION ELECTRON MICROSCOPY (TEM)

This technique can obtain information of nanoparticles such as particle size, size distribution and morphology (Lee *et al.*, 2020). Structural and stability of nanoparticles are revealed using this method of characterization (Bian *et al.*, 2021). It can also be used for the direct study of crystal nucleation and growth of nanoparticles for a better understanding of the morphological and crystallographic structure of such particles (Longo *et al.*, 2016). Advantages of TEM include high quality, detailed and powerful magnification of element and compound structures (Javed *et al.*, 2018).

2.8.4 XRAY DIFFRACTION (XRD)

X-ray diffraction data provides information about crystallanity, crystallite size, phase identification, sample purity and morphology of nanopowders (Holder & Schaak, 2019). Advantages of XRD are simplicity of sample preparation, ability y to probe the 3D structure of the nanoparticle in situ, rapidity of measurement, possibility of rendering macroscopically averaged structural data and determine sample purity (Thijssen *et al.*, 2006).

2.8.5 DYNAMIC LIGHT SCATTERING (DLS)

Dynamic light scattering is a well-established technique for measuring the size of molecules and particles in colloidal suspensions (Hoo *et al.*, 2008). This is made possible when the particles in brownian motion cause a Doppler shift when there is an incidence of light on the moving particle, thereby changing the wavelength (Bahru & Ajebe, 2019). Advantages include short measuring time, less labor intensive process, non-invasive technique and extensive experience is not needed for routine measurements (Lim *et al.*, 2013).

2.8.6 ENERGY DISPERSIVE XRAY (EDX)

This technique is used in conjugation with electron microscopy to generate X-rays that reveal the presence of elements present in nanoparticle samples (Scimeca *et al.*, 2018). It can also determine directly the crystal lattice and chemical structure of the intermetallic phases (Lu *et al.*, 2014). Advantages of EDX are thicker specimen management, identification of contaminant, carbon contamination tolerance and rare elemental X-ray peak overlap (Wenner *et al.*, 2017).

2.8.7 FOURIER TRANSFORM INFRARED SPECTROSCOPY (FTIR)

An Infrared spectrum (IR) spectrum displays absorption peaks corresponding to frequencies of vibrations between chemical bonds of atoms that make up of the nanomaterial, protein morphology or secondary structure that interact with metal ions (Amenabar *et al.*, 2013). These identified functional groups represent reducing and capping agents responsible for synthesis and stabilization of silver ions in solution. Advantages of FTIR include higher signal-to-noise ratio, high energy throughput, high accuracy and stability for solid phase samples (Faghihzadeh *et al.*, 2016).

2.9 TOXICOLOGICAL ASSESSMENT OF SILVER NANOPARTICLES

With the increased use of silver nanoparticles in commercial products flooding the market around the world, especially from the onset of COVID, there is the risk of release into the environment and potential toxicological effects (Ihtisham *et al.*, 2021). However, there has been limited information or knowledge on short and long term toxicity of human, animal and ecological exposure to these nanoparticles (Noga et al., 2023). The toxicity expended on organisms can be ascribed to Ag+ ions release inside the cells, thereby inducing reactive oxygen species (ROS) which in turn, affects signaling pathways and transcription reprogramming mechanisms (González-Vega *et al.*, 2022). AgNPs synthesized using laser ablation technique, upon subacute exposure to Wistar rats, resulted in accumulation of the nanoparticles in the lungs, kidneys and liver thereby inducing systemic toxicity (Nayek et al., 2021). Silver nanoparticles synthesized using Gum-Arabic gave a different outcome when two different organisms were used as the nanoparticles showed toxicity when exposed to Zebrafish while no toxicities were observed among Sprague Dawley rats (Maziero *et al.*, 2020).

2.10 BACTERIAL RESISTANCE

Water, soil and other environments with various ecological niches renders unparalleled diverse gene pool that largely exceeds that of the human and animal microbiota (Endale *et al.*, 2023). A cascade of events that lead to acquisition of these environmental genes by the microbiome occur in a progressive manner. Firstly, the antimicrobial resistant gene moves into the genome either by association with insertion sequences or formation of gene casettes and incorporation into integrons (Che *et al.*, 2021). Secondly, the gene relocates to a mobile element like a plasmid or an integrative conjugative element (Horne *et al.*, 2023). Thirdly, there is a horizontal transfer of the mobilized resistant gene either directly to a pathogen or through several intermediary bacterial hosts (Redondo-Salvo *et al.*, 2020). And finally, at any time in the process, ecological connectivity occurs, which is the physical movement of the bacteria carrying the resistant gene to the human or domestic animal microbiota (Crits-Christoph *et al.*, 2022).

Antimicrobial tolerance in bacterial species dates back to the period before humans started manufacturing them for therapeutic purposes (Larsson & Flach, 2022). Prehistoric drivers of resistance mechanisms among microorganisms include perpetual contention for resources and natural production of secondary metabolites which are similar to the antimicrobial agents manufactured in pharmaceuticals in recent times (Miller *et al.*, 2023). The contemporary initiation of antibiotics as therapeutic agents yielded unusual selection pressures particularly among human and animal microbiota and in antibiotic polluted environments (Ebmeyer *et al.*, 2021), which promoted mobilization and transfer of wide range of antimicrobial resistance genes (ARGs) to many disease causing bacterial species (Jian *et al.*, 2021). The ultimate result of such evolutionary occurrence is the inability to prevent and treat bacterial infections (Larsson & Flach, 2022). Understanding the connections between human, animal and environmental microbiota is of critical importance in managing global health challenges.

2.10.1 FACTORS THAT LEAD TO BACTERIAL RESISTANCE

The worldwide proliferation of excessive use of antimicrobial agents, antimicrobial resistance bacteria (ARB) from anthropogenic sources, release of antimicrobial resistant genes (ARGs), accretion of environmentally relevant microorganisms with related increased cost of hospitalizations and high mortality due to infection, remains a major challenge to environmental health and wellbeing of humans and animals (Berendonk *et al.*, 2015). However, current risk assessment models are insufficient to estimate the effect of antimicrobial agents and ARGs on resistance onset and selection, especially in non-clinical environments (Mortimer *et al.*, 2020; Samreen *et al.*, 2021). Compared to chemical contaminants whose concentrations diminish in the environment as a result of degradation, dilution or sorption, bacterial contaminants and their resistant genes have the capability of persisting and spreading in the environment (Haenni *et al.*, 2022). Their resistant genes can multiply in their hosts, move to other bacterial populations or be subject to further evolution and mutation, and therefore pose serious threats to human and animal health (Uddin *et al.*, 2021). Mechanisms responsible for the spread of ARB in the environment which can occur in combination include: horizontal gene transfer of ARGs, genetic mutation and recombination caused by the existence of hypermutator bacterial strains (Arshad *et al.*, 2021). Environmental factors for the proliferation of ARGs could be due to selective pressures imposed by antimicrobial compounds or other contaminants such as heavy metals and biocides (Skandalis *et al.*, 2021). The intricate interplay of environmental, ecological and evolutionary factors among bacterial communities makes it difficult to ascertain and understand the fate and release of ARBs and ARGs into the environment (Amarasiri *et al.*, 2020). The misuse of antimicrobial agents and other biotic and abiotic factors which include physicochemical conditions, environmental contaminants, induction of stress responses, bacterial adaptation and phenotypic heterogeneity are capable of enhancing the effect of selective pressures and promoting bacterial evolution towards bacterial resistance (Russo & Santaniello, 2023). On the other hand, proper knowledge of the environmental factors can help to ease the spread of antibiotic resistance. Antimicrobial resistance hubs are characterized by excessive bacterial loads together with minimal dose concentrations of antimicrobial agents which contribute to discharge and release ARBs and ARGs into the environment (Cai *et al.*, 2021). They include medical environment, environmental settings exposed to anthropogenic activities such as municipal wastewater systems, pharmaceutical processing plants and effluents, aquaculture and animal husbandry facilities (Samal *et al.*, 2022). Currently, there is poor understanding of the how environmental ARGs and ARBs promote antimicrobial resistance among strictly environmentally relevant bacteria and if their acquisition by these microorganisms are from the same reservoir.

2.10.2 POLLUTION AS A CONTRIBUTING FACTOR

Synthetic antimicrobial agents are largely associated with selection pressures across microbial flora (Spagnolo *et al.*, 2021). They are released into the environment via excretion, direct contamination of fish environment, improper disposal of unused drugs, and disposal of waste streams of production effluents (Wang *et al.*, 2017). Environmental concentrations of antimicrobial agents are much lower than concentrations that select resistant strains in the laboratory (Stanton *et al.*, 2020). On the other hand, sewage treatment plants and hospital settings contain concentrations that exceed those suspected to select antibacterial resistance (Ngigi *et al.*, 2020).

2.11 ANTIMICROBIAL MECHANISM OF SILVER NANOPARTICLES

Many researchers have extensively studied the effect of silver nanoparticles on microorganisms and possible mechanisms in play. The antimicrobial properties of silver nanoparticles depend on size, environmental conditions (size, pH, ionic strength) and capping agent.

It seems that silver ions interact with the bacterial cell envelope. Intracellular molecules like nucleic acid and enzymes and producing reactive oxygen species (Kędziora *et al.*, 2018). Silver nanoparticles displays higher toxicity to unicellular organisms than other forms of silver (Ag) like Ag^+ (Barros *et al.*, 2019). Further, AgNPs could interact with the exposed sulfhydryl groups in bacterial proteins, avoiding DNA replication (More *et al.*, 2021). Although the antibacterial effect of AgNPs is yet to be fully elucidated, certain theories explain their mechanism of action (Nisar *et al.*, 2019). The potent antibacterial and broad-spectrum activity of nanoparticles against different microorganisms seem to correlate with different mechanisms. According to Talapko *et al.* (2020), the first mechanism involves penetration of cell wall by Ag^+ ions and penetration of the peptidoglycan layer, followed by oxidative stress resulting from AgNPs binding to the membrane proteins thereby releasing ions. This binding affects membrane permeability, uptake and release of phosphate ions and disruption of respiratory chain and energy production. Nanoparticles smaller than 20 nm can penetrate the cytoplasm after passing through the cell membrane (Kong *et al.*, 2020). This is particularly important in the case of Gram-negative bacteria where numerous studies have observed the adhesion and accumulation of AgNPs to the bacterial surface. Many studies have reported that AgNPs can damage cell membranes leading to structural changes, which render bacteria more permeable especially for gram negative microorganisms that are more sensitive (Ahmed *et al.*, 2018). Triangular silver nanoprisms have been known to possess higher antibacterial activity due to the sharp edges and vertexes of the nanoprisms. Also, the smaller the particle size, the larger the surface-volume ratio, the more the toxicity and the greater the mode of interaction with bacterial surface (Acharya *et al.*, 2018). AgNPs enhances protein leakage by increasing the membrane permeabilities of *S. aureus* and *E. coli* and finally bacterial cell death (Gomaa, 2017; Rai *et al.*, 2014). There is a proposition that Ag ions enter the cell and intercalate between the purine and pyrimidine base pairs disrupting the hydrogen bonding between the two anti-parallel strands and denaturing the DNA molecule (Kamaraj & Vivekanand, 2020). There is a probability that AgNPs modulate cellular signaling and act by dephosphorylating tyrosine residues on key bacterial peptide substrates thereby inhibiting microbial growth (Bamal *et al.*, 2021). The antibacterial potential of silver ions depends on the thickness and composition of the microbial cell wall, and the difference on the peptidoglycan layer organization (Domínguez *et al.*, 2020). This means that the higher peptidoglycan layer in gram positive bacteria makes such microorganisms less susceptible to AgNP cellular absorption than gram negative microorganisms that contain lesser peptidoglycan layer around the cellular membrane. Resistance to antimicrobial agents causes antigenic shifts or drifts in microorganisms and cannot be properly managed with current treatment conditions (Shim, 2023).

2.12 ENVIRONMENTAL APPLICATIONS OF PLANT MEDIATED SILVER NANOPARTICLES

Nowadays, nanotechnology has spread through all sectors including engineering, medical, pharmaceutical, agriculture and environment, with silver nanoparticles getting widely used in food packaging, clothing, disinfectants, household appliances, bandages and water purification systems (Patil *et al.*, 2015). Also, silver nanoparticles have attracted the attention of researchers owing to their application in areas like integrated circuits (Tavakoli *et al.*, 2018), sensors (Prosposito *et al.*, 2020), bioimaging (Shankar *et al.*, 2017), membrane filters (Bortolassi *et al.*, 2019; Kharaghani *et al.*, 2018), cell electrodes (Lim *et al.*, 2017), cheap and paper batteries (Agrawal *et al.*, 2018).

Below are some of the environmental applications in which silver nanoparticles are employed.

2.12.1 INCORPORATION ON COTTON FABRICS/TEXTILES

The development of protective, decorative, and technical textiles for applications in the textile, pharmaceutical, medical, engineering, agricultural and food industries are of interest to scientists, since they protect users from pathogenic or odour generating microorganisms which cause medical and hygienic problems, and protect the textiles from undesirable esthetic changes and damages due to rot (Simoncic & Tomsic, 2010). There are findings that the use of Ag+ and AgNPs at low concentrations is relatively non-toxic to humans (Simončič & Klemenčič, 2016). However, the research on the safety of AgNPs on humans and the environment is still ongoing. Functionalization of textiles using plant mediated AgNPs through solution-immersion method provides excellent result as they act as novel colourants, and reducing and capping agents for nanoparticle synthesis because of the presence of biomoloecules (Ratnasari *et al.*, 2020). Salem *et al.* (2020) demonstrated the antimicrobial effect of AgNPs as coating on cotton textiles. AgNPs were synthesized using Streptomyces antimycoticus isolated from *Mentha longifolia* plant leaves and loaded onto cotton fabrics at 100ppm (safe dose). Scanning electron microscopy connected to energy dispersive X-ray spectroscopy revealed AgNP distribution as 2% of the total fabric elements. The nano-finished fabric showed antibacterial activity against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherchia coli* and *Pseudomonas aeruginosa* even after 10 washing cycles, indicating the stability of the treated fabrics. Antifungal activity of AgNPs synthesized from lemon leaves extract and loaded on cotton and silk fabrics against *Fusarium oxysporum* and *Alternaria brassicicola* were assessed by Vankar & Shukla (2012). The antifungal activity of the silver nanoparticles showed enhancement in synergistic effect of the silver nanoparticles and the essential oil components of the lemon leaves. The durability and sustainability of the nanofinish on the fabrics were still effective even after 5 washes. The antibacterial effect of *Clerodendron infortunatum*–mediated silver nanoparticles loaded on cotton fabric was assessed against

Staphylococcus aureus (Jha & Prasad, 2016), which showed effective inhibition of the microorganism. It was attributed to the synergy between the silver and the conglomerate of secondary metabolites. Firdhouse & Lalitha (2013) explored the antibacterial potential of *Amaranthus dubius*-silver nanoparticles loaded on perspiration pads and cotton cloth against a sweat bacteria, *Corynebacterium sp*., of which it showed high resistance towards the bacteria. AgNPs synthesized from a plant biomaterial, *Cassia roxburghii* DC aqueous extract, impregnated on cotton fabrics, were tested against *Bacillus subtilis*, *Micrococcus luteus*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli* and *Enterobacter aerogenes*. *Pseudomonas aeruginosa* showed a higher zone of inhibition more than the other bacteria (Balashanmugam & Kalaichelvan, 2015).

2.12.2 INCORPORATION INTO HYDROGELS

Hydrogels are polymeric materials that can absorb and retain significant amount of water within its structures without getting dissolved in the water medium, possessing interesting properties (biocompatibility, functionality, reversibility, sterilizability) which meet material and biological requirements to treat, interact or replace targeted tissues and organs in biological systems (Raza *et al.*, 2018). The intrinsic ability of hydrogels to absorb water is due to the presence of hydrophilic groups such as amine ($-NH_2$), carboxylic (-COOH), and sulphate ($-SO_3$) groups attached to the polymeric chain (Huang *et al.*, 2019). Hydrogels have been applied in many fields which include tissue adhesives, drug delivery carriers, self healing materials, biosensors, wearable electronics, soft robots, electronic skin, tissue engineering scaffolds (Zheng & Zuo, 2021), agricultural applications, food industry, water treatment processes, and environmental remediation (Majcher & Hoare, 2019). In a study by Thi *et al.* (2018), catechol rich gelatin-AgNPs were synthesized during hydrogel formation and its antimicrobial activity was assessed against *Staphylococcus aureus* and *Escherichia coli*. The hydrogels exhibited high inihibition rates with sustainable release of silver for more than 2 weeks. In order to control the release rate of silver ions from AgNPs and increase the antibacterial effect, studies have suggested combining AgNPs with other biocompatible polymers such as chitosan, polyvinyl alcohol, polyvinyl pyrrolidone and polylactic acid to create wound healing application in the type of topical gels, topical dressings and mats (T. D. Nguyen *et al.*, 2019). AgNPs synthesized using *Camellia sinensis* were incorporated into polyvinyl alcolhol/sodium alginate hydrogel and its antibacterial activity was explored against *Staphylococcus aureus* and *Escherichia coli* (Wang *et al.*, 2020). The hydrogels exhibited superior water absorption properties and excellent antibacterial activity.

2.12.3 CATALYTIC ACTIVITY

Dyes are the chemical synthetic organic compounds used to impart colour to fabrics, foods, liquids, fluids and other objects for their beautification and distinction. They are permanently fixed to these materials, not easily biodegradable, resistant to microbial attack, aerobic digestion, and stable to heat, light, oxidizing agents, water, soap, acid and alkalies (Punnoose & Mathew Beena, 2018). Wastewater discharged during textile manufacturing processes such as dying, finishing, scouring and other processes are the sources of continuous water pollution (Mangalam *et al.*, 2019). It is estimated that about 50% of the dyes used in the textile industry are azo dyes and 10%–15% of such dyes do not bind to the fibres and get released as effluent. Azo dyes have one or more azo groups –N=N– which are responsible for their colouration (Mangalam *et al.*, 2019). Even at very low concentrations, textile dyes present in effluents can cause highly carcinogenic and mutagenic effects to humans as a result of their complicated constitution, low biodegradability and high chemical stability in water (Saini, 2017). In aquatic ecosystem, these dyes can cause eutrophication, reduces reoxygenation, and makes severe damage to the aquatic organisms by hindering the infiltration of sunlight and interfering with the growth of aquatic species (Bhatia *et al.*, 2017). So, it remains a challenge to researchers to explore safer methods to degrade these toxic dyes and save the environment from severe pollution. The conventional chemical methods like electrocoagulation (Zazou *et al.*, 2019), carbon sorption (Jasper *et al.*, 2020), redox treatment (Guardado *et al.*, 2019), flocculation (Favero *et al.*, 2020), UV photo degradation (Salama *et al.*, 2018) are ineffective for decolorization and mineralization of these pollutants these methods are energy or chemical intensive leading to introduction of unwanted chemicals and increase in concentration of chemical pollutants in streams and rivers after discharge (Parmar & Shukla, 2018). The photocatalytic mechanism occurs in two phases. In a study by Roy *et al.* (2015), a degradation of methylene blue dye was performed under solar irradiation using silver nanoparticles synthesized from *Cucumis sativus* fruit extract. The percentage dye degradation was found to be approximately 93% after 6 hours. Reductive-degradation of azo dyes such as congo red (CR) and methyl orange (MO) was studied (Edison *et al.*, 2016) using *Anacardium occidentale* testa derived silver nanoparticles (AgNPs) as a catalyst. The calculated rate constant for the reductive-degradation of Congo Red and Methyl Orange were 0.0795 and 0.1178 min^{-1} respectively. The photocatalytic activity of AgNPs synthesized using *Vaccinium floribundum* was evaluated for the degradation of Methylene blue dye, under direct sunlight irradiation (Kumar *et al.*, 2019). The percentage degradation efficiency of the AgNPs was 29.09% at 60 minutes. (Singh *et al.*, 2017) investigated the photocatalytic activity of AgNPs synthesized using gum arabic and ascorbic acid for the degradation of methylene blue. The reaction followed the first-order kinetics with a degradation percentage of 89%.

2.12.4 CORROSION INHIBITION

Not much research has been done in the area of microbiologically influenced corrosion to inhibit these microorganisms that damage steel and cause corrosion. Microbial induced corrosion occurs as a result of microbial metabolic secretions from microorganisms on metallic surfaces that involve toxic organic and inorganic acids, ammonia and sulphides. These compounds have oxidation-reduction and electron transfer properties that initiate electrochemical reaction on metal surfaces (Narenkumar *et al.*, 2017). Metals like stainless steel and many environments including marine, food processing plants, oil and gas facilities, industrial and chemical plants, wastewater and domestic water plants are susceptible to metal degradation by microorganisms (Okeniyi *et al.*, 2018). The current techniques for inhibiting corrosion are expensive and hazardous to man and the environment, hence the need by researchers to explore green and natural corrosion inhibitors that are readily and easily available and environmentally benign. *Nulembo nucifera* plant mediated silver nanoparticles were assessed for anticorrosion activity (Supraja *et al.*, 2017). Stainless steel and iron coupons were immersed in the plant synthesized silver nanoparticle samples and then kept in bacterial cultures and stirred for 16 days. The corrosion rate was lower in the presence of AgNPs. Silver nanoparticles synthesized using Elaeis guineensis (palm oil) leaf extracts were prepared and incorporated in cement composite and examined against reinforcement steel corrosion in natural seawater. Electrochemical, optical property and thermal stability studies were performed on Setaria verticillata mediated silver nanoparticles in a study by Prabhu *et al.* (2016). Results showed that the crystalline silver nanoparticles with 24 nm diameter showed a TGA decrease in the weight of biosynthesized nanoparticles which was due to desorption of biomolecules from silver nanoparticles. Electrochemical characterization revealed good electrochemical activity, making the nanoparticles useful in the construction of electrochemical sensors for the detection of metal impurities and organic effluents present in the environment. Obot *et al.* (2013) synthesized silver nanoparticles using honey mediated by sunlight and assessed its corrosion potential in acidic solution. the nanoparticles exhibited an inhibition efficiency of 93.1% at the highest concentration of 6%v/v silver nanoparticles showing the nanoparticles as excellent corrosion inhibitor. *Artemisia annua* and *Sida acuta* leaves extract were used to synthesize silver nanoparticles and corrosion inhibition was determined (Johnson *et al.*, 2014). An absorption band of 450 nm showed formation of silver nanoparticles while electrochemical analysis revealed that they are good inhibitors for the corrosion of mild steel in 0.5M HCl solution. Also, inhibition efficiency increased with inhibitor concentration.

2.13 ANTIMICROBIAL COMBINATIONS WITH ANTIBIOTICS AND INTERACTIONS

There has been proliferation of multi drug resistant bacterial species as a result of global antibiotic use (de Pontes et al., 2022). This remains a challenge for drug research and development, and health care facilities. Despite the research and development of novel drug discovery which last for 10-17 years at a success rate of less than 10% (Shang *et al*., 2019), there are strategies for combatting antimicrobial resistance. They include combining antibiotics with other non-antibiotic drugs (Xiao et al., 2023), combining antibiotics with other antimicrobials (Browne *et al*., 2020) or adjuvants that are chosen from a plethora of natural bioactive compounds (Dhanda et al., 2023), or by restoring the efficacy of the existing antibiotics through combinations with biological or chemical compounds or molecules *(Murugaiyan et al.*, 2022). This process can lower the drug dosage thereby decreasing toxicity effects and ability to develop resistance (León-Buitimea et al., 2020).

Synergistic interaction occurs when the drug effects of antimicrobial agents in combination with antibiotics are higher than their individual effects (Shyr et al., 2021). Additive interaction exists whereby the combined effects of the antimicrobial agent and antibiotic do not differ from their individual effects (Forslund *et al*., 2021) whereas drug combinations exhibit antagonistic interaction when their combined effects are less than their individual effects (Bobrowski *et al*., 2021). Among antagonistic combinations, there also exists a set of interactions called suppressive interactions which occur when the combined effect is lesser than one or both of the antimicrobial agents (N. Singh & Yeh, 2017), and possesses distinct characteristics and significance which includes to slow down and possibly change the evolution of resistance.

There has been various studies on silver nanoparticles synthesized using different synthesis methods and the effect of their combination with antibiotics on different microorganisms as summarized in Tables, 2.1, 2.2, and 2.3 below.

TABLE 2.1 SILVER NANOPARTICLE SYNTHESIS USING CHEMICAL METHODS AND THEIR COMBINATION WITH ANTIBIOTICS

NP size(nm)	Reducing/stabilizing agent	Antibiotics	Microorganism	Antimicrobial technique	Reference
5-12	Sodium borohydride/trisodium citrate	Polymyxin B, rifampicin, tigecycline	A. baumanni	FIC	(Hwang et al., 2012)
8.6	Gallic acid	Ampicillin, amikacin	P. multocida, S. uberis, S. aureus, E. faecium	FIC	(Lopez-Carrizales et al., 2018)
16	Sodium borohydride, trisodium citrate dihydrate/PVP	Streptomycin, ampicillin, tetracycline	E. coli, S. aureus	ZOI	(Kora & Rastogi, 2013)
19.3	Sodium borohydride, tisodium citrate dehydrate/SDS	Streptomycin, ampicillin, tetracycline	E. coli, S. aureus	ZOI	(Kora & Rastogi, 2013)
20	Sodium citrate	Ampicillin	s. aureus, S. epidermidis, E. coli, P. aeruginosa	MIC	(Rogowska et al., 2017)
20	Ascorbic acid	Amoxicillin	K. pneumonia, E. coli	MIC	(P. Li et al., 2005)
20	Sodium borohydride/PVP	Vancomycin, amikacin	S. aureus, E. coli	ZOI	(A. Kaur & Kumar, 2019)
20-40	Tween 80	Gentamicin	S. epidermidis	FIC	(Mazur et al., 2020)
23	Sodium citrate	Tetracycline, neomycin	S. typhimurium	MIC, ZOI	(McShan et al., 2015)
26	δ – glucose/ starch	Erythromycin, ampicillin, cephalothin, tetracycline, clindamycin,	S. aureus, MRSA, S. mutans, S. oralis, S, gordonii, E. faecalis, E. coli,	ZOI	(Ipe et al., 2020)

		gentamicin, amoxicillin, ciprofloxacin, cefodoxime, cefuroxime	A. actinomycetes, P. aeruginosa		
29.8	Sodium citrate	Ampicillin, enoxacin, kanamycin, neomycin, tetracycline	S. typhimurium	Colony counting, ZOI	(Deng et al., 2017)
29.8	Sodium citrate	Neomycin, kanamycin, enoxacin, tetracycline	S. tyhpimurium	Colony counting, ZOI	(Deng et al., 2017)
15.21	commercial	Kanamycin, colistin, ampicillin, ciprofloxacin, vancomycin, rifampicin	E. coli, K. pneumonia, P. aeruginosa, A. baumannii, S. aureus, S. saprophyticus, S. sciuri, S. epidermidis	MIC	(Alotaibi et al., 2022)
10.84	Trisodium citrate	Gentamycin, ceftazidime, ciprofloxacin, tobramycin, amikacin, imipenem, menopenem, cefepime, levofloxacin, piperacillin, piperacillin/azobactam, azetronam	P. aeruginosa	MIC,ZOI	(Kamer et al., 2024)

TABLE 2.2: SILVER NANOPARTICLES SYNTHESIZED USING MICROORGANISMS AND THEIR COMBINATION WITH ANTIBIOTICS

NP size (nm)	Reducing/stabilizing agent	Antibiotics	Microorganism	Antimicrobial technique	reference
5-32	Streptomyces xinghaiensis OF1 strain	Ampicillin, kanamycin, tetracycline	E. coli, S. aureus, B. subtilis, P. aeruginosa, C. albicans, Malassezia furfur	FIC	(Wypij et al., 2018)
20	Klebsiella pneumoniae	Chloramphenicol, gentamicin, chloramphenicol/gentamicin	E. faecalis	ZOI	(Katva et al., 2018)
35-60	Estuarine Pseudomonas aeruginosa	Ampicillin, ciprofloxacin	S. aureus, V. cholera	ZOI	(Naik et al., 2017)
5-30	Aspergillus flavus	Imipenem, gentamicin, vancomycin, ciprofloxacin	E. coli, P. aeruginosa, E. faecalis, M. luteus, A. baumannii, K. pneumoniae	ZOI	(Naqvi et al., 2013)
5-40	Trichoderma viride	Erythromycin, kanamycin, chloramphenicol, ampicillin	S. typhi, E. coli, S. aureus, M. luteus	ZOI	(Fayaz et al., 2010)
8-12	Acinetobacter calcoaceticus	Amikacin, gentamicin, kanamycin, amoxicillin, ampicillin, penicillin, ceftazidime, vancomycin, ciprofloxacin, doxycycline, tetracycline, chloramphenicol, trimethoprim	E. aerogenes, E. coli, P. aeruginosa, S. sonnei, S. typhimurium, S. aureus, S. mutans, A. baumannii	ZOI, MIC	(R. Singh et al., 2013)
66.7	Emericella nidulans	Amikacin, kanamycin, oxytetracycline, streptomycin	E. coli, P. aeruginosa, S. aureus	FIC	(Barapatre et al., 2016)

81.1	Aspergillus flavus	Amikacin, kanamycin, oxytetracycline	E. coli, P. aeruginosa, S. aureus	FIC	(Barapatre et al., 2016)

TABLE 2.3 SILVER NANOPARTICLES SYNTHESIZED WITH PLANTS AND THEIR COMBINATION WITH ANTIBIOTICS

NP size (nm)	Reducing/stabilizing agent	Antibiotics	Microorganisms	Antimicrobial technique	Reference
5.8	Gum kondagogu	Streptomycin, gentamicin, ciprofloxacin	S. aureus, E. coli, P. aeruginosa	FIC	(Rastogi et al., 2015)
7.4-18.3	Rosa domascenes	Cefotaxime	E. coli, MRSA	ZOI	(Halawani et al., 2020)
15.0	Ulva fasciata	Azithromycin, gentamicin, oxacillin, cefotaxime, neomycin, ampicillin/sulbactam, cefuroxime, fosfomycin, chloramphenicol, oxytetracycline	S. aureus, S. enterica, E. coli	ZOI	(Abo-Shama et al., 2020a)
20-30	Urotica dioica Linn	Streptomycin, kanamycin, vancomycin, tetracycline, ampicillin, cefepime, amoxicillin, cefotaxime	B. cereus, S. epidermidis, S. aureus, B. subtilis, E. coli, S. typhimurium, K. pneumonia, S. marcescens	ZOI	(Jyoti et al., 2016)
45.3	Zea mays leaf extract	Kanamycin, rifampicin	B. cereus, L. monocytogenes, S. aureus, E. coli, S. typhimurium	ZOI	(Patra & Baek, 2017)
114	Anastatica hierochuntica	Bacitracin, ciprofloxacin, tetracycline, cefixime	p. aeruginosa, E. coli, S. aureus, C. albicans	ZOI	(Aabed & Mohammed, 2021)
125.5	Artemisia absinthium	Bacitracin, ciprofloxacin, tetracycline, cefixime	P. aeruginosa, E. coli, S. aureus, C. albicans	ZOI	(Aabed & Mohammed, 2021)

15.20	Starch	Ceftazidime, imipenem, menopenem, gentamicin	Burkholderia pseudomallei	FIC	(Malawong et al., 2021)
4-23	Mentha longifolia	Ceftazidime, cefotaxime, ceftriaxone, cefepime	p. aeruginosa, K. pneumoniae, S. aureus, E. faecalis	ZOI	(Adil et al., 2023)
58.62-72.30	Hibiscus sabdariffa flower extract	Fosfomycin	E. cloacae, MRSA, K. pneumoniae, E. coli	MIC, ZOI	(Aljeldah et al., 2023)

2.14 *DACRYODES EDULIS*

Dacryodes edulis (G. Don) H. J. Lam, also known as African Pear, is an aboriginal fruit tree found in the tropical lowlands and plateau regions of West Africa, Central Africa, and the Gulf of Guinea and well known in the Eastern and Western parts of Nigeria (Hassan-Olajokun *et al.*, 2020). Its edible fruits and other parts, like the leaves, resin, bark, and roots, known to contain saponins, flavonoids, tannins, phenols, and alkaloids, are used for local treatment of diseases including anemia, malaria, hypertension, cardiovascular diseases, and cancer (Swana et al., 2023). Trado-medicinal benefits using the leaves have been reported to include antiemetic purposes, remedy for auditory infections, diabetes, and birth pangs (Akunne & Orhue, 2021; Ononamadu *et al.*, 2019), and antiplasmodial activity (Uzor *et al.*, 2021). Aqueous extracts of *D. edulis* leaves have been known to inhibit tumor growth of induced estrogen-dependent cancer in female Wister rats (Mvondo *et al.*, 2021). For environmental applications, *D. edulis* plant has also been known to have promising environmental applications in crude oil pollution treatment (Nnaji et al., 2016), water treatment (Kamgaing et al., 2017), drilling fluid (Effiom, 2023), paint coatings (Isaac et al., 2014), biodiesel production (Uwem Isong et al., 2020) and natural dye for textiles (Clark et al., 2024). For pharmacological applications, it has also been known to display remarkable therapeutic prospects in the management of long-term diseases such as diabetes and hypertension. The plant's safety profile which has been supported by both folklore use and experimental research, makes it a promising candidate for further research and development in terms of technological innovations and ecofriendly alternatives for incorporation in functional foods, nutraceuticals and environmental applications.

2.15 CONCEPTUAL FRAMEWORK

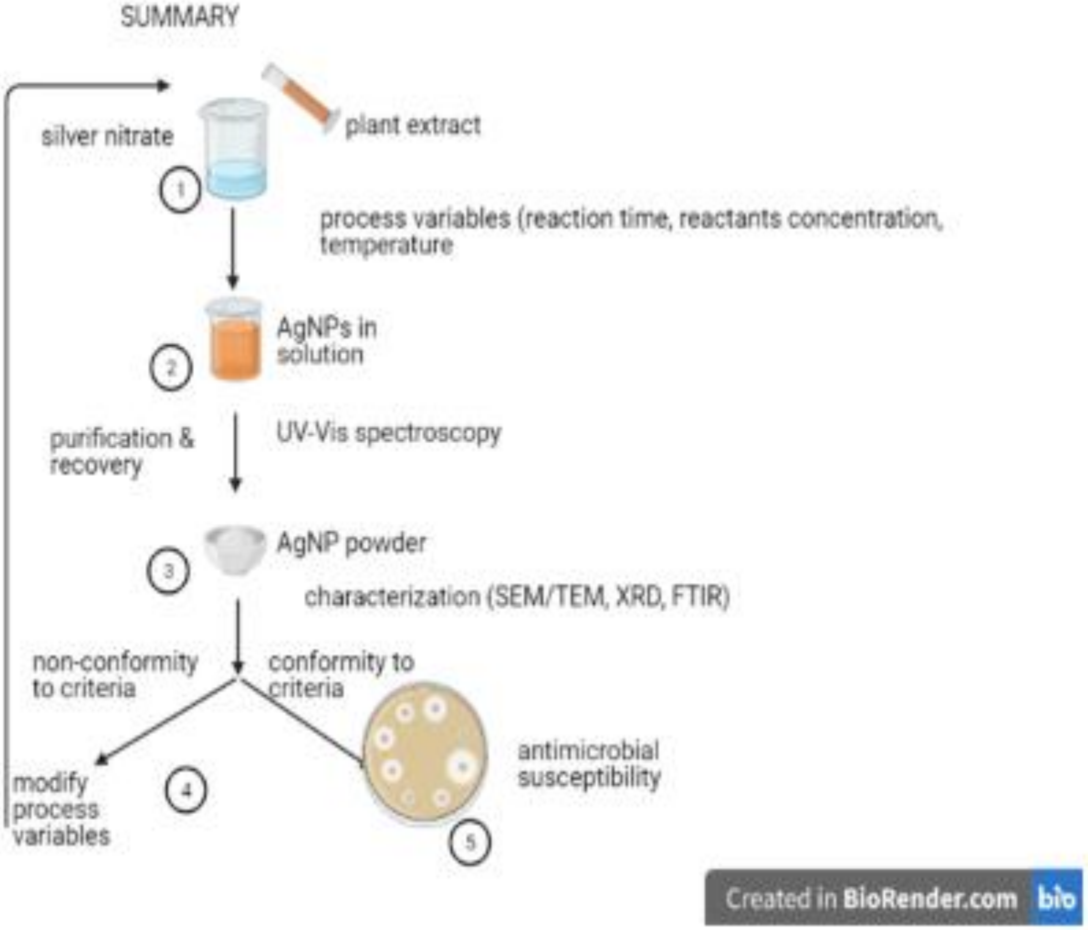


Fig 2.1: Conceptual framework for the use of plants in the silver nanoparticle synthesis

CHAPTER THREE

MATERIALS AND METHODS

3.1 MATERIALS

Silver nitrate (with ≥ 99.9%), hydrochloric acid, (HCl), sodium hydroxide pellets (NaOH), and Mueller Hinton Agar were purchased from Sigma Aldrich and used without further purification. Bacterial isolates (*Staphylococcus sp.* and *Escherichia sp.*) were obtained from the Parasitology Unit, Federal University Teaching Hospital, Owerri, Nigeria.

3.2 METHODS

3.2.1 LEAF SAMPLE COLLECTION AND EXTRACT PREPARATION

D. edulis leaves were harvested by hand, and a pictorial view of the tree is as shown in plate 4.1 overleaf. Fresh green leaves of *D. edulis* were washed thoroughly with distilled water to eliminate dust and biological contamination, and subsequently air-dried away from sunlight. The dried leaves were pulverized to powdery form using a blender and stored in a dry polythene bag. In order to prepare the leaf extract, 10 g of the dried powdered plant material was mixed with distilled water in a beaker (ratio 1:10 w/v). The mixture was boiled at 75 ^{o}C in a water bath for 15 minutes. After it had cooled, it was sieved using Whatman filter paper No.1 and the extract stored in a container at 4 ^{o}C for further use.

Plate 3.1: A pictorial view of Dacryodes edulis tree

3.2.2 ANTIOXIDANT ACTIVITY

1,1-Diphenyl-2-picrylhydrazyl (DPPH) free radical scavenging potential of the plant extracts (aqueous) was determined using the method by Yousaf *et al.* (2020). 50 µg/mL of aqueous plant extracts and ascorbic acid (positive control) was prepared and taken in separate test tubes. About 1 mL of DPPH (1 mM) liquefied in methanol was added in the above sample and vortex thoroughly. Finally, the solution was incubated at room temperature in dark for 30 min and absorbance measured at 517 nm using UV–Vis spectrophotometer. The DPPH without the sample was used as a control prepared using the same procedure as mentioned above. Free radical scavenging activity was calculated with the help of formula:

$$\%\text{DPPH scavenging activity} = \frac{\text{OD control-OD sample}}{\text{control}} \times 100 \tag{3.1}$$

where, OD control is the absorbance of DPPH + methanol and OD sample is the absorbance of DPPH + sample.

3.2.3 DETERMINATION OF PHYTOCHEMICAL CONSTITUENTS

Extraction was performed as described by Yasir *et al.* (2012) but with slight modification. Extraction of the plant leaves was by maceration with distilled water and kept to dry in a water bath at 60 ^{0}C for 72 hours. Phytochemical constituents were determined quantitatively for the presence of compounds such as tannins, phenols, flavonoids, alkaloids, saponins, cyanogenic glycosides.

Tannin determination was performed using Van-Burden and Robinson method as described (G. J. Kaur & Arora, 2009) but with slight modification. 2 g of the powdered D. edulis leaf sample was weighed and poured in to a 250 mL volumetric flask of which distilled water (50 mL) was added and shaken for 1 hour using a mechanical shaker. It was thereafter filtered into a 50 mL flask and distilled water was added to make up the final volume. 5 mL of the filtrate was pippetted out into a test tube and mixed with 2 mL (10 fold diluted) of 0.1 M $FeCl_3$ in 0.1 N Hcl and 0.008 M potassium ferrocyanide, mixed thoroughly and allowed to stand for 10 minutes. The absorbance was measured at 605 nm against the blank. The tannic acid content as tannin was expressed as tannic acid equivalents (TAEs) in milligram per 100 grams of the dry material.

Flavonoid content was determined as reported (Ezeonu & Ejikeme, 2016). 50 mL of 80% aqueous methanol added was added to 2.50 g of leaf sample in a 250 mL beaker and was left to stand for 24 hours at room temperature. The supernatant was discarded while the residue was re-extracted thrice with ethanol. The whole solution was filtered with Whatman filter paper No 42 (125 mm diameter) and the filtrate was transferred in to a crucible, put in a water bath and allowed to evaporate to dryness. The contents in the crucible was cooled in a desiccator and weighed until constant weight was obtained. Flavonoid content was obtained as a percentage of the dry weight.

For alkaloids, the method used was as described (Ezeonu & Ejikeme, 2016; Gurrapu & Mamidala, 2017). 5 g of the dried powdered leaves were dispersed in 10% acetic acid solution and left to stand for 4 hours at 24 ºC and further filtered using Whatman filter paper No 42. The filtrate was concentrated to a quarter of its original volume to which 15 drops of concentrated aqueous ammonium hydroxide (NH_4OH) was added in a dropwise manner until precipitation was complete. The precipitate was then washed in 20 mL of 0.1 M ammonia solution and left to dry in an oven. The alkaloid content was calculated and expressed as percentage of the dried weighed sample.

The cyanogenic glycoside content was determined using the alkaline picrate method (Omar *et al.*, 2012). 5 g of the dried leaf sample was weighed, put into a conical flask and dissolved in 50 mL of distilled water. it was allowed to stay for 24 hours and filtered afterwards. To the filtrate, 4 mL of alkaline picrate solution was added to each sample and put in a water bath to boil for 15 minutes. When there was colour change (reddish brown), the absorbance of the sample was taken at 490nm using a spectrophotometer. Different concentrations were prepared against the blank. Measurements were repeated in triplicates and the cyanide content obtained from the cyanide curve.

3.2.4 DNA EXTRACTION ISOLATION AND WHOLE GENOME SEQUENCING

The bacterial isolates were identified on selective media and confirmed by biochemical test. The isolates were sub-cultured on nutrient agar and incubated @ 37 ºC for 24 hours. A single colony was selected and dispersed in 1X Phosphate Buffered Saline (PBS). The sample was centrifuged for 10 minutes @8000 rpm to pellet the cells. The pelleted cells were resuspended in 560 µL of lysis buffer (QiAamp DNA extraction kit) and the Nucleic acid was recovered using the QIAamp DNA extraction kit (Hilden, Germany) following manufacturer's guidelines. The Nucleic acid was quantified on the Qubit 4 fluorometer (ThermoScientific) using the Qubit 1X dsDNA High sensitivity kit (Thermofisher).

3.2.5 DNA SEQUENCING AND ASSEMBLY

Using the metagenomic approach input DNA within 100 ng-500 ng isolated from the pure isolate was used for the library preparation using illumina DNA prep following the manufacturer's protocol and sequenced on Illumina MiSeq. The raw reads were copied out and uploaded on CZID AMR pipeline for analysis.

3.2.6 PHYLOGENETIC ANALYSIS

After the DNA sequencing was completed, the quality of the compressed fastq files retrieved from the Illumina Miseq was checked using FASTQC. The reads were trimmed, aligned and blasted on NCBI to obtain the reference genome for alignment. The phylogenetic analysis was as performed by Suzuki *et al.* (2020) but with minor modifications. The obtained sequences were compared with those available on the National Center for Biotechnology Information (NCBI) GenBank database website by using the Basic Local Alignment Search Tool (BLASTn) on the webpage (http://blast.ncbi.nlm.nih.gov/Blast.cgi) to determine identical or related DNA sequences. Sequences were aligned using the Clustal W method in the MEGA XI software. Phylogenetic trees were constructed by the neighbour-joining (NJ) method using Molecular Evolutionary Genetics Analysis (MEGA) software (version 11.0). Bootstrap values were estimated for 1000 replicates.

3.2.7 IN SILICO ANTIMICROBIAL RESISTANCE ANALYSIS

The procedure was done as performed by Vieira *et al.* (2023) but with minor modifications. A web version of the ResFinder (New) 4.4.1 tool was used to identify AMR agents and genes in the bacterial sequences. The ResFinder tool uses BLAST (Basic Local Alignment Search Tool) for the detection of acquired AMR genes in the whole genome database. The fasta (.fasta) format of the input genome sequences was used. The threshold for reporting a match between a gene in the ResFinder (New) database and the input sequence was set at a 90% identity with a minimum length of 60%.

3.2.8 GREEN SYNTHESIS OF AgNPs

The AgNPs were synthesized in a procedure reported by Kumar *et al.* (2018) but with slight modification. 30 mL of as-prepared extract of *D. edulis* leaves was poured slowly into 70 mL aqueous solution of 1 mM silver nitrate ($AgNO_3$) that was kept under stirring in a round bottom flask under heat using a magnetic stirrer. The mixture was heated at 50±2 ^{o}C with continuous stirring for 1 hour and left to stand for 24 hours. The gradual change in colour of the reaction mixture was observed within minutes of heating which inferred the reduction of silver ions and formation of AgNPs. The plant mediated synthesis was exposed to different reaction conditions.

3.2.9 EFFECT OF LEAF EXTRACT VOLUME

For the purpose of determining the effect of leaf extract concentration on the biosynthesis of AgNPs, different leaf extract volumes (10 mL, 20 mL, 30 mL, 40 mL, 60 mL, 70 mL, 80 mL, and 90 mL) were added to different test tubes containing silver nitrate aqueous solutions making it up to the 100 mL mark. The reaction was carried out at 50±2 ºC and the absorbance recorded afterwards using UV-Vis spectrophotometer.

3.2.10 EFFECT OF TEMPERATURE

To examine the effect of temperature on nanoparticle synthesis, 10 mL of aqueous leaf extract was added to 90 mL of 1 mM silver nitrate solution and the reaction was subjected to different temperatures (25 ºC, 35 ºC, 45 ºC, 55 ºC, 65 ºC, and 75 ºC).

3.2.11 EFFECT OF pH

In order to study the effect of pH, 10 mL of leaf extract was added to 90 mL of aqueous silver nitrate solution and pH levels adjusted to 3, 5, 7, 9 and 11 for each reaction using 0.1 M HCl for acidic pH and 0.1 M NaOH for alkaline pH under stirring conditions.

3.2.12 EFFECT OF REACTION TIME

The effect of reaction time on the biosynthesis of the silver nanoparticles was ascertained by adding 10 mL of the prepared leaf aqueous extract to 90 mL of aqueous silver nitrate solution and measuring the absorption spectra at different time intervals (0 minute, 30 minutes, 60 minutes, 90 minutes, 120 minutes).

3.2.13 CHARACTERIZATION OF AgNPs

The conversion of $AgNO_3$ to silver nanoparticles was monitored by recording the optical absorption spectra of the reaction mixture using UV–Vis spectrophotometer within a range of 380 to 700 nm wavelength with the use of quartz cuvette of 1cm optical pathway and deionized water as blank. The reaction mixture was subsequently centrifuged at 4000 rpm for 15 minutes, while the resultant nanoparticles were washed thrice using deionized water to eliminate any interfering biological contamination and unwanted by-products. The washed nanoparticles were distributed in deionized water.

In order to ascertain the crystalline phase of the nanoparticles, the analysis was performed using a Shimadzu XRD-7000S X-ray diffractometer using Cu Kα radiation. Data were recorded in steps of 0.04° with a scan step time of 1 s in the 2θ range of 5°– 80°. The average crystallite size was also determined from this measurement using Derby- Scherrer's formula as follows:

$$D = \frac{K\lambda}{\beta \cos \theta} \tag{3.2}$$

where D is the calculated average crystallite size from the XRD pattern, K is the Scherrer's constant, λ is the X-ray wavelength, β is the full width at half maximum (FWHM) of the diffraction, and peak θ is the bragg's angle (in degrees).

For the SEM, morphology of AgNPs were examined by using SEM ZEISS SEM (Germany) to confirm the surface topography and composition of the sample. The AgNPs were suspended in deionized water (1 mg/mL) and sonicated in a sonicate bath. The stock solution (1 mg/mL) was subsequently diluted 20 times to measure the size of AgNPs. This was done by drying one drop of the aqueous solutionon a glass plate. Dried sample was then placed on a carbon-coated copper grid before images were taken.

FTIR measurements were documented in the range of 4000 to 650 cm^{-1} to analyze the biosynthesized nanoparticles for functional groups that are active in the bioreduction of the silver ions.

3.2.14 ANTIMICROBIAL ACTIVITY AND ANTIBIOTIC ASSAY

The procedure was done as described by Aritonang *et al.* (2019). All equipment and growing media were sterilized by autoclaving at 115 °C and 15 psi for 30 minutes. Antimicrobial activity was investigated against *Staphylococcus sp.* as a model for Gram-positive bacteria and *Escherichia sp* as a model for Gram-negative bacteria as representative microorganisms. The antimicrobial activity of plant mediated silver nanoparticles alone, antibiotics alone and silver nanoparticles in combination with antibiotics were assessed against model microorganisms using disc diffusion or Kirby Bauer method on Mueller Hinton Agar plates as described by Jyoti *et al.* (2016) but with minor modifications. Classification of standard antibiotics used for this assay are as presented in Tables 3.1 and 3.2 respectively. Mueller Hinton Agar plates were prepared and inoculated with fresh inoculum of each bacterial culture according to MacFarland's standard (1 X 10^8 CFU/mL). Each standard antibiotic disc was saturated with 10 µL of freshly prepared AgNPs (1 mg/mL). Standard antibiotic discs with and without *D. edulis* synthesized silver nanoparticles were placed on the agar plates and kept in the incubator for 24 hours at 37 °C. The assay was done in triplicates and the zones of inhibition were measured using a set of calipers. Antibiotic disks without zone of inhibition were represented with the disk diameter (7 mm).

Table 3.1: Class of antibiotics and their abbreviations used in this experiment for both model gram +ve microorganism (*Staphylococcus sp.*)

Antibiotics	**Acronym**	**Class of antibiotics**
Gram +ve		
Septrin/cotrimoxazole(30µg)	SXT	sulphonamides
Rocephin/ceftriaxone (25µg)	R	cephalosporins
Ampiclox (30µg)	APX	pencillins
Amoxacilllin (30µg)	AM	penicillins
Gentamycin (10µg)	CN	aminoglycosides
Pefloxacin (10µg)	PEF	fluoroquinolones
Streptomycin (30µg)	S	aminoglycosides

Ciprofloxacin (10µg)	CPX	fluoroquinolones
Erythromycin (10µg)	E	macrolides

Table 3.2: Class of antibiotics and their abbreviations as used in this experiment for gram –ve microorganisms (Escherichia sp.)

Antibiotics	**Acronym**	**Class of antibiotics**
Gram -ve		
Septrin/cotrimoxazole (30µg)	SXT	sulphonamides
Chloramphenicol (30µg)	CH	chloramphenicol
Sparfloxacin (10µg)	SP	fluoroquinolones
Amoxacilllin (30µg)	AM	penicillins
Gentamycin (30µg)	CN	aminoglycosides
Pefloxacin (30µg)	PEF	fluoroquinolones
Streptomycin (30µg)	S	aminoglycosides
Ciprofloxacin (10µg)	CPX	fluoroquinolones
Tarivid/ofloxacin (10µg)	OFX	fluoroquinolones

Cotrimoxazole is a combination of trimethoprim and sulfamethoxazole. Microbial growth inhibition efficiency and synergism parameters were determined from the various zones of inhibition.

Inhibition efficiency (IE) was assessed as used by Oguzie & Onuchukwu (2006) but with slight modification and determined as expressed in percentage:

$$IE = \left(1 - \left(\frac{Do}{Dx}\right)\right) * 100 \qquad 3.3$$

Where IE is inhibition efficiency, Do is the zone of inhibition without the antimicrobial agent while Dx is the zone of inhibition of the antimicrobial agent.

Synergistic interaction between the AgNP and the antibiotics was assessed by a relationship proposed by Aramaki and Hackerman in 1969 (Oguzie *et al.*, 2006):

$$SI = \frac{1-(Ia+Ib)}{1-I(a+b)} \qquad 3.4$$

Where SI is the synergy index, I_a and I_b are the inhibition rates of the AgNP and the antibiotic individually while I_{a+b} is the inhibition rate of the combination. SI<1.00 denotes antagonism, SI=1.00 means additivity while SI>1.00 indicates synergism.

3.2.15 STATISTICAL ANALYSIS

All experiments were run in triplicates and data were expressed as mean±standard deviation. ANOVA and post hoc Tukey's test ($p \leq 0.05$) were employed to analyze the data obtained from the antibacterial activity. Statistical analysis was performed using OriginPro 2018 version.

CHAPTER FOUR

RESULTS AND DISCUSSION

4.1 RESULTS

4.1.1 PHYTOCHEMICAL QUANTITATIVE DETERMINATION

Quantitative determination of phytochemical constituents was performed to ascertain the quantity of phytochemical constituents present in the leaf aqueous extract. Fig. 4.1 shows a graphical representation of the phytochemical results.

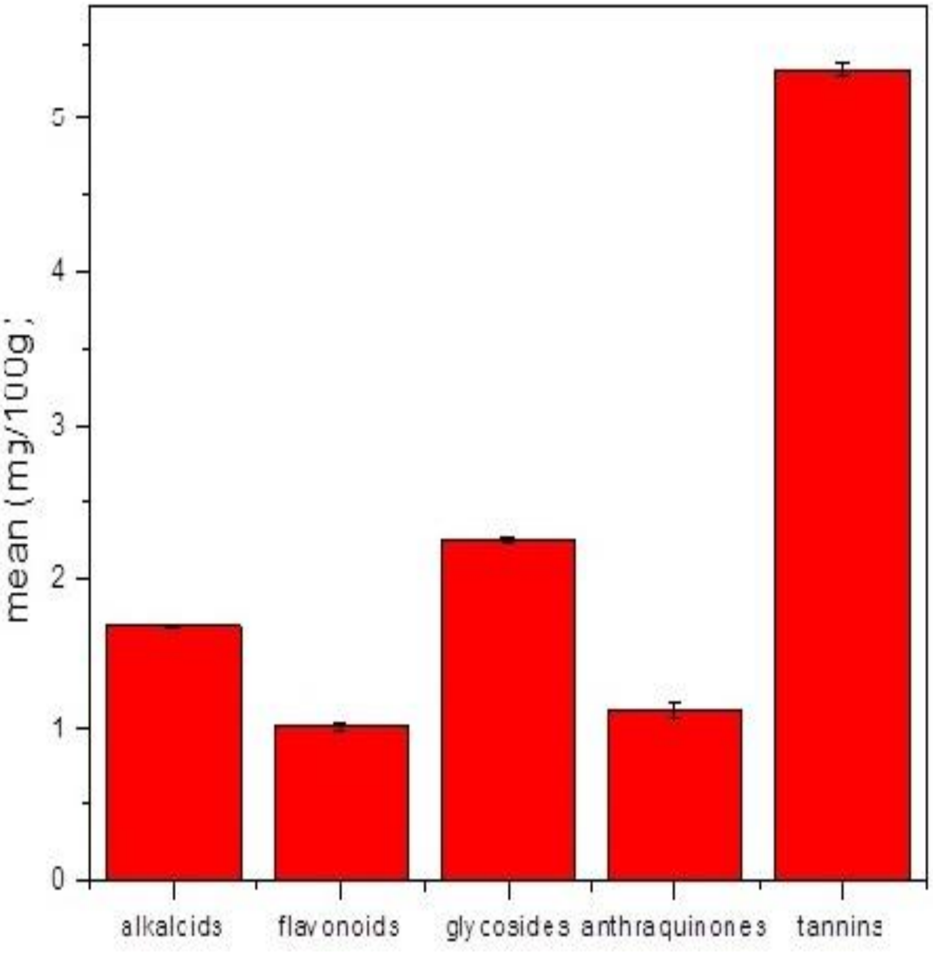


Figure 4.1: Phytochemical analysis of *D.edulis* leaf extract

4.1.2. MOLECULAR IDENTIFICATION OF ORGANISMS

The organisms *Staphylococcus sp.* and *Escherichia sp.* had 97% similarity with *Staphylococcus saprophyticus* and *Escherichia coli*, respectively. The phylogenetic trees were constructed using MEGA XI and are shown in Fig 4.2 and 4.3, respectively.

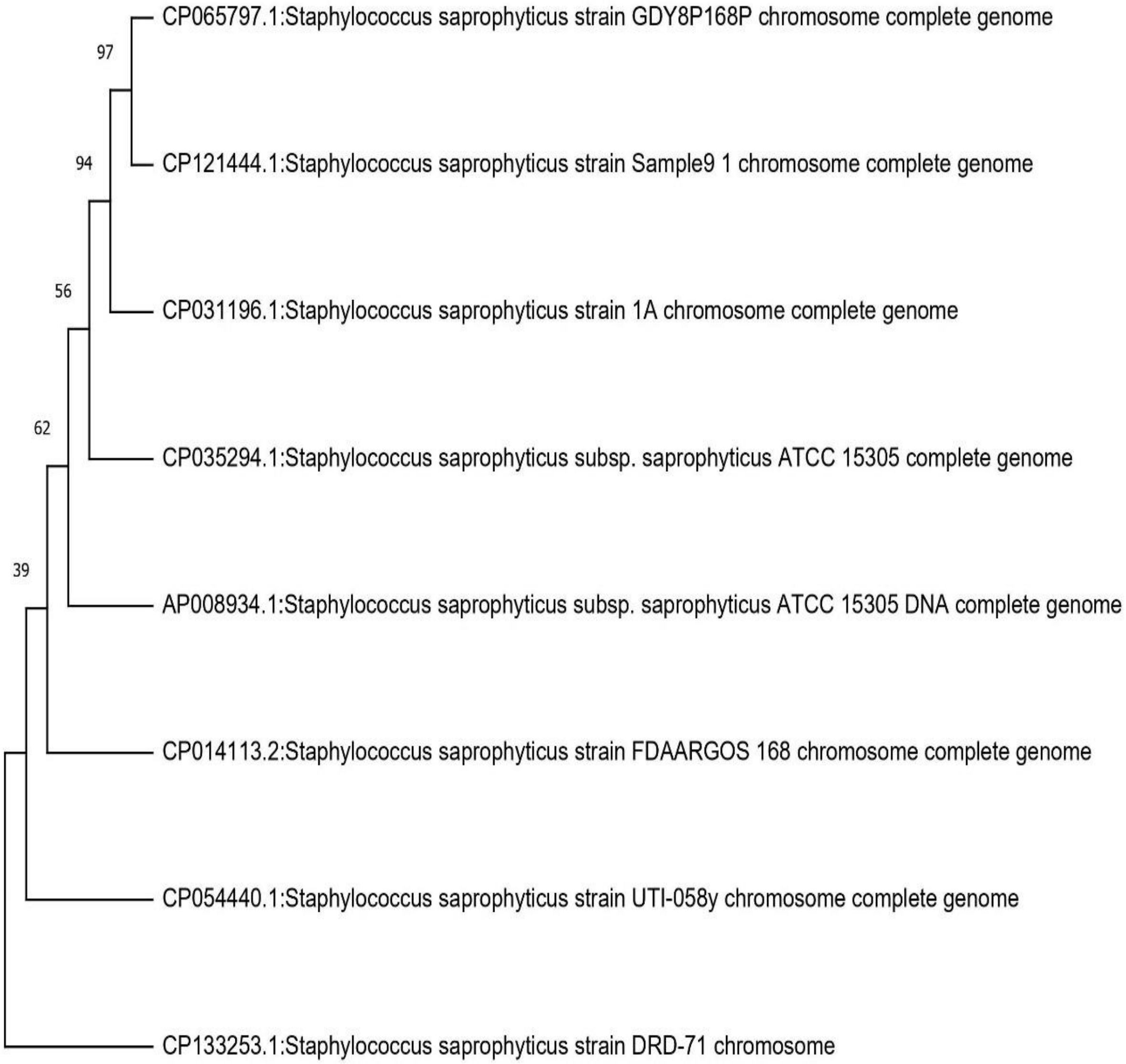


Figure 4.2: Phylogenetic tree for *Staphylococcus saprophyticus*

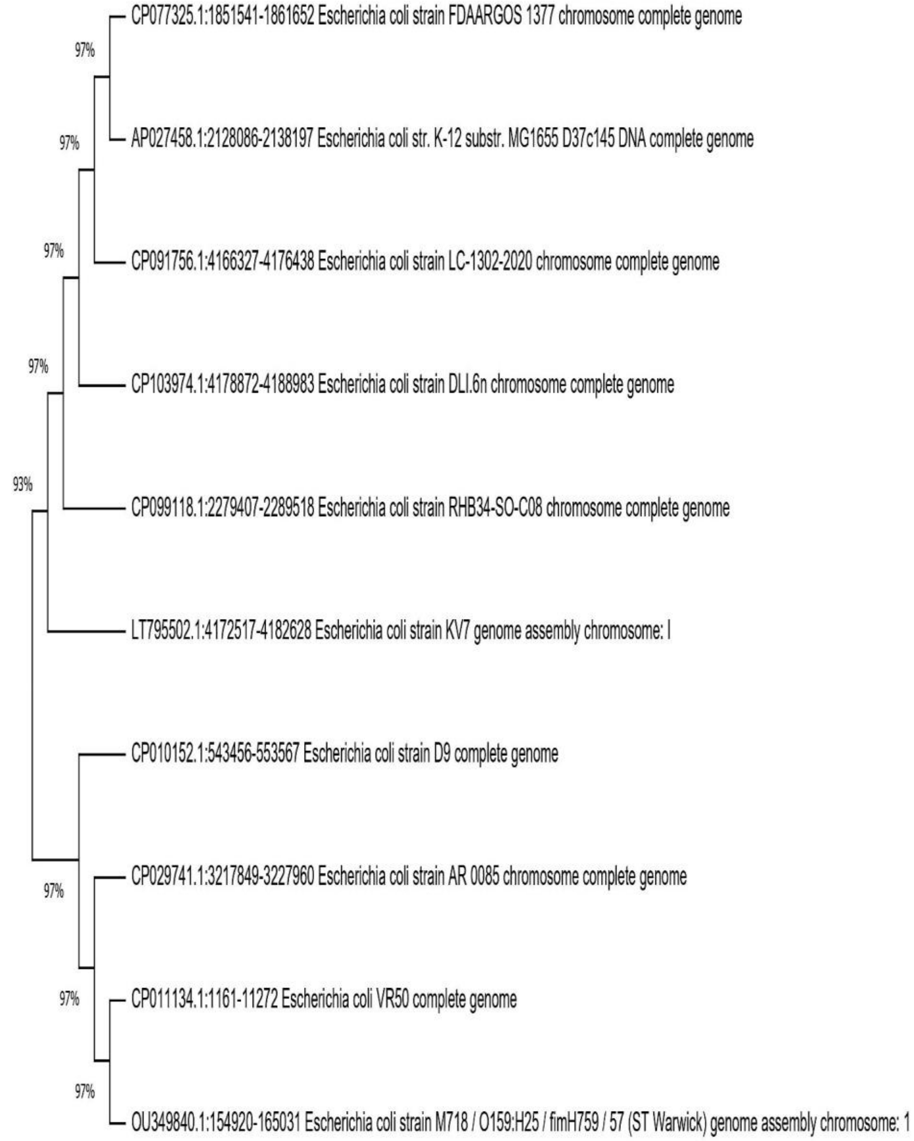


Figure 4.3: Phylogenetic tree for *Escherichia coli*

Accession numbers were assigned to the genome assemblies and their raw reads as shown in Table 4.1, which were submitted to National Centre for Biotechnology Information (NCBI) for reference purposes.

Table 4.1: Genome assembly showing the raw reads and accession numbers assigned by NCBI

Microorganism	**Bioproject number**	**Biosample number**	**Raw reads number**	**Accession number**
***Staphylococcus saprophyticus* AAO1**	**PRJNA1173402**	**SAMN44304559**	**SRR31011620**	**CP172400**
Escherichia coli	**PRJNA1173402**	**SAMN44308692**	**SRR31013689**	**CP183951**

4.1.3. IN SILICO ANTIMICROBIAL RESISTANCE ANALYSIS

Further investigation to reveal WGS-predicted antimicrobial resistance genes was done using ResFinder (www.centerforgenomicepidemiology.com). The specific resistant genes responsible for resistance against these antibiotics in gram positive *S. saprophyticus* were predicted to be *mec*A, *bla*Z and *dfr*G genes as shown in Table 4.2.

Table 4.2: Predicted (In silico) antimicrobial resistant genes using ResFinder

Microorganism	Resistant gene	Antibiotics	Accession number
S.saprophyticus	mecA	Beta-lactams (Amoxicillin, amoxicillin+clavulanic acid (augumentin), ampicillin, ampicillin+clavulanic acid, cefepime, cefixime, cefataxime,cefoxitin, ceftazidime,ertapenem,imipenem, menopenem, piperacillin, piperacillin+tazobactam)	AB546266
	blaZ	Beta-lactams (amoxicillin, ampicillin, penicillin and piperacillin)	JBTH01000015
	dfrG	Trimethoprim	AB205645
E. coli	aph(6)-Id	Streptomycin	M28829
	aph(3”)-Id	Streptomycin	AF321551
	blaTEM-214	Beta-lactams (amoxicillin, ampicillin, piperacillin, ticarcillin, cephatothin	KP050491
	blaTEM-206		KC783461
	blaTEM-1B		AY458016
	sul2	Sulphonamides (Sulfamethoxazole)	FN995456

Table 4.3: Predicted (In silico) chromosomal gene mutations mediating antimicrobial resistance in *E.coli*

Gene	**Accession number**
*gyr*A	CP073768.1
*gyr*B	CP047010.1
*par*C	CP084529.1
*par*E	CP034658.1
*pmr*A	CP047010.1
*pmr*B	CP072802.1
*fol*P	CP047010
23S	CP053604.1
16S-*rrs*B	CP067250.1
16S-*rrs*C	CP053603.1
16S-*rrs*H	CP053603.1
*amp*C-promoter	CP037449.1
*rpo*B	CP047010.1

4.1.4 ULTRAVIOLET- VISIBLE (UV- VIS) SPECTROSCOPY

Below is the colour change that was observed before and during the reaction mixture in Fig 4.4

Figure 4.4: Colour change during silver nanoparticle synthesis showing colour of the extract (1), colour of the silver nitrate solution (2), and colour of reaction mixture upon addition of the extract to the silver nitrate solution (3).

Increase in extract concentration with colour intensity is shown in Fig 4.5.

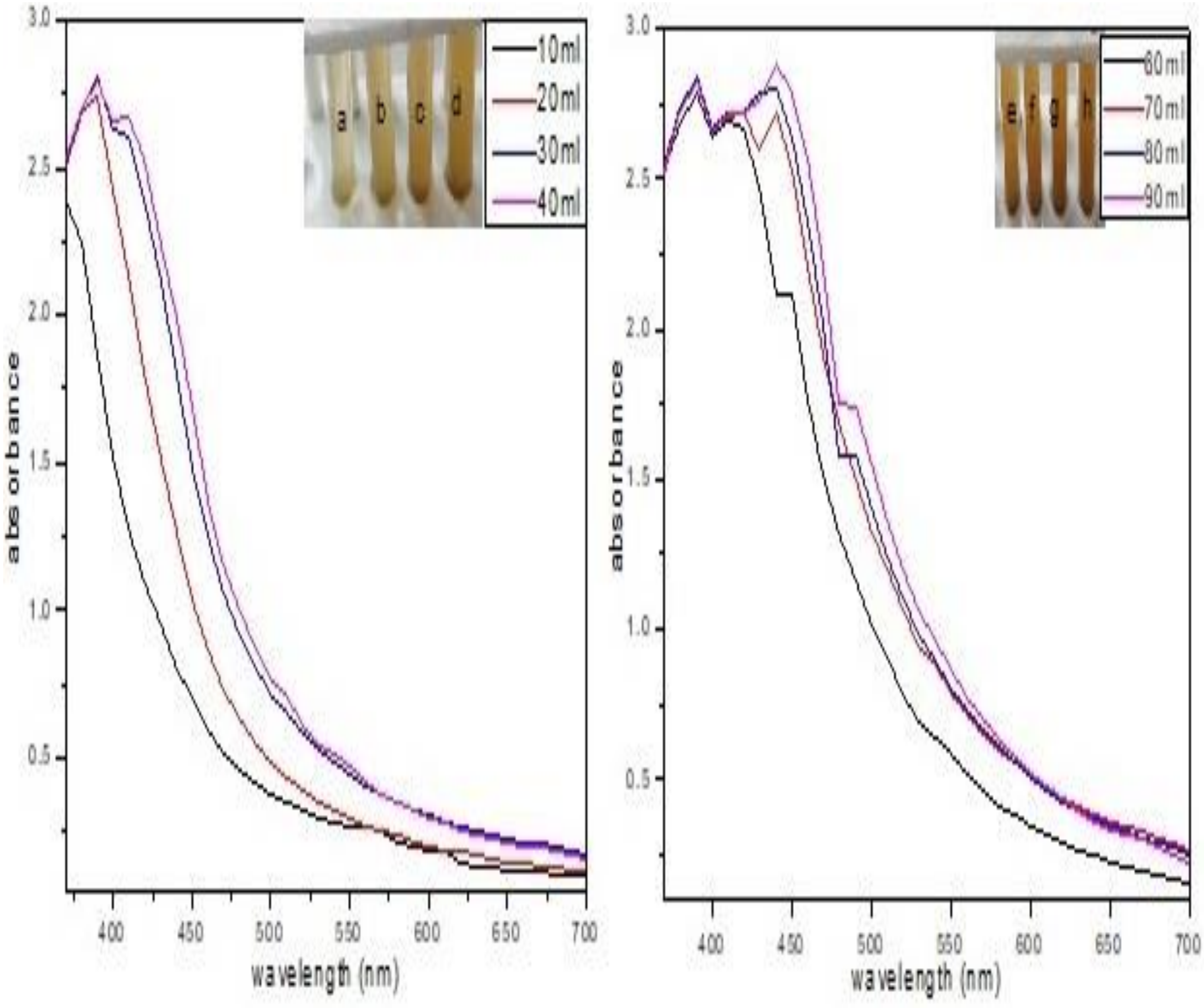


Figure 4.5: UV- Visible spectra of D.edulis derived AgNPs: low volumes of silver nitrate solution – 10 mL-40 mL (left), high volumes of silver nitrate solution – 60 mL – 90 mL (right)

The dynamics of the reaction with respect to temperature was monitored using UV- visible spectral analysis as observed in Fig 4.6.

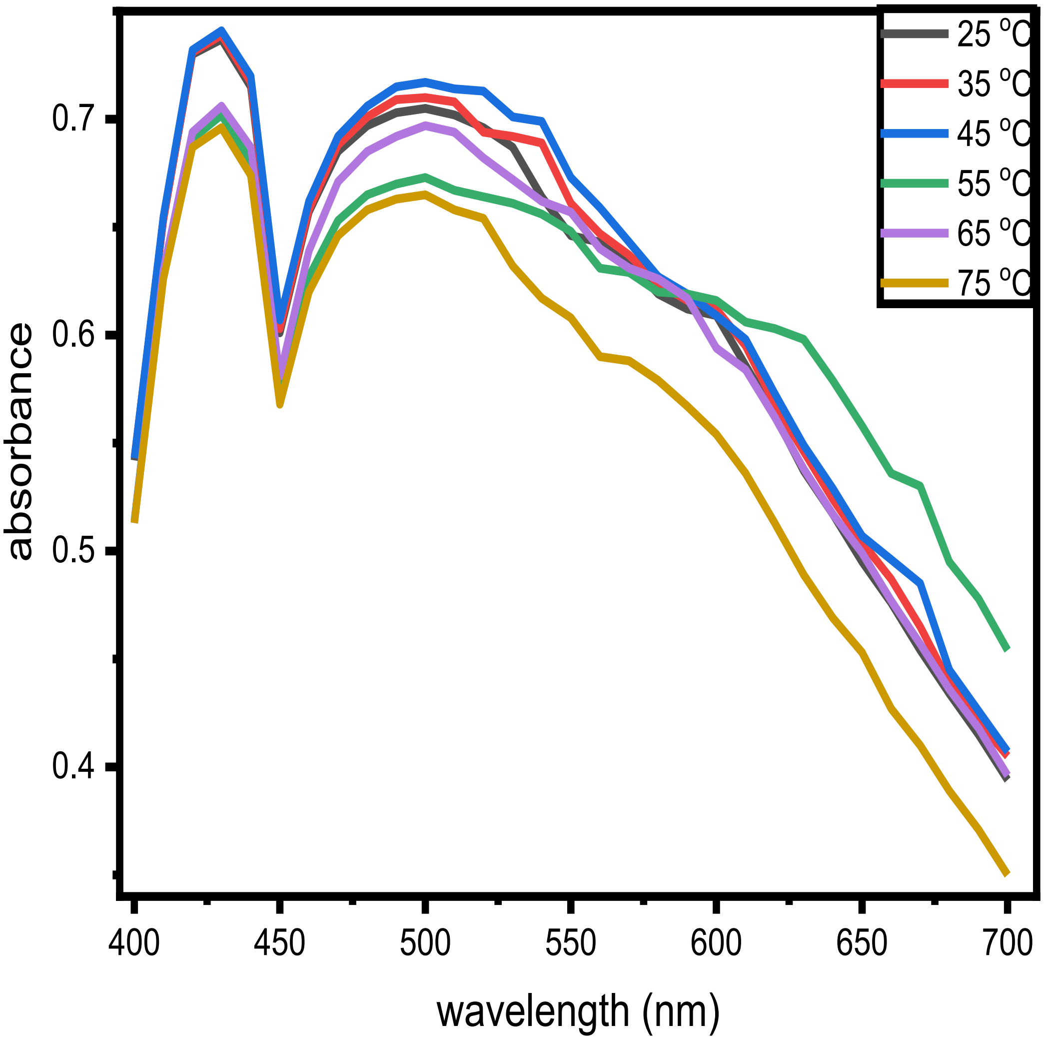


Figure 4.6: UV-Visible spectra with change in temperature

Wavelength absorbance with increase in pH is shown in Fig 4.7.

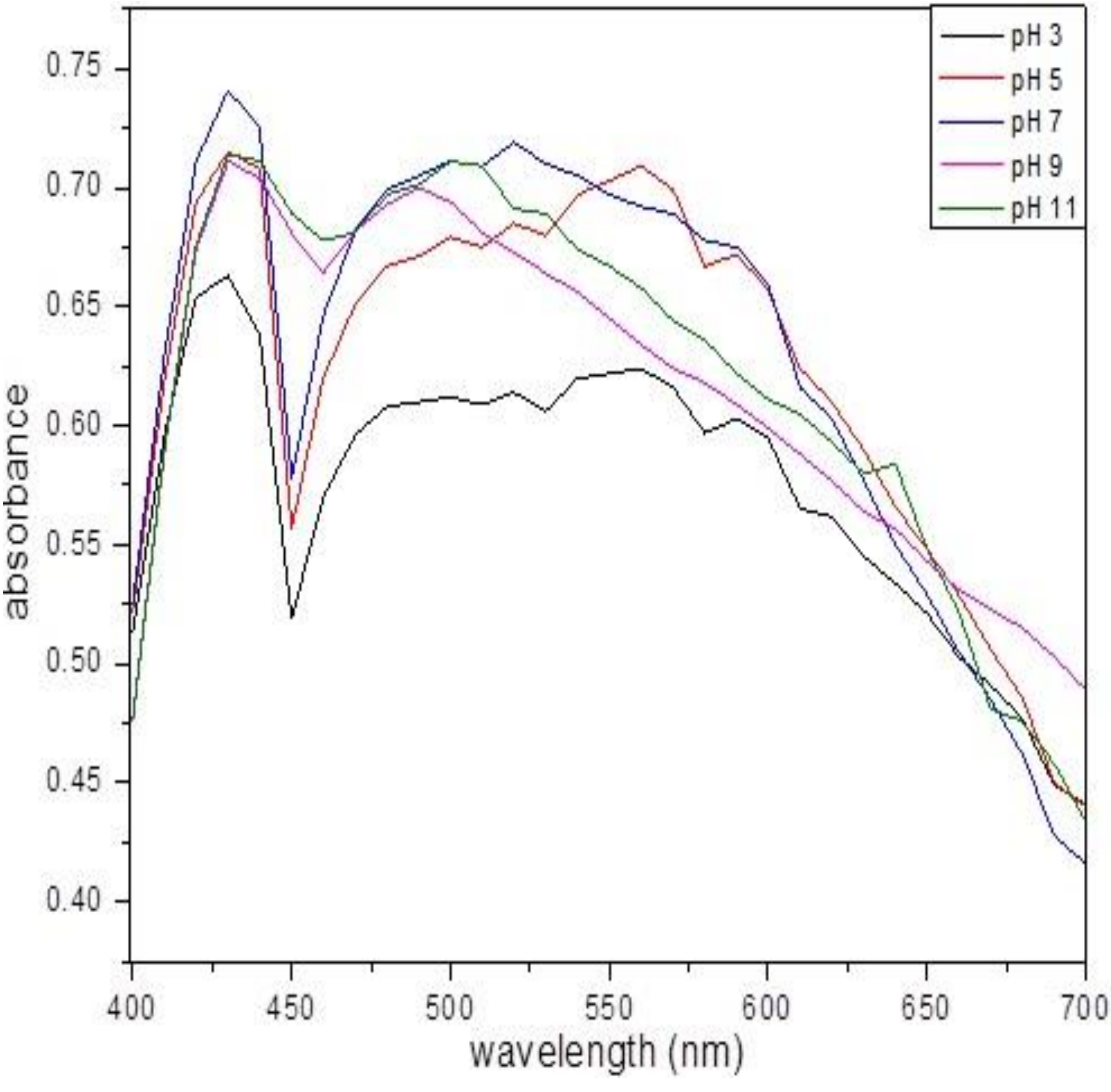


Figure 4.7: UV-Visible spectra showing change in pH

Change in reaction time was monitored and shown in Fig 4.8

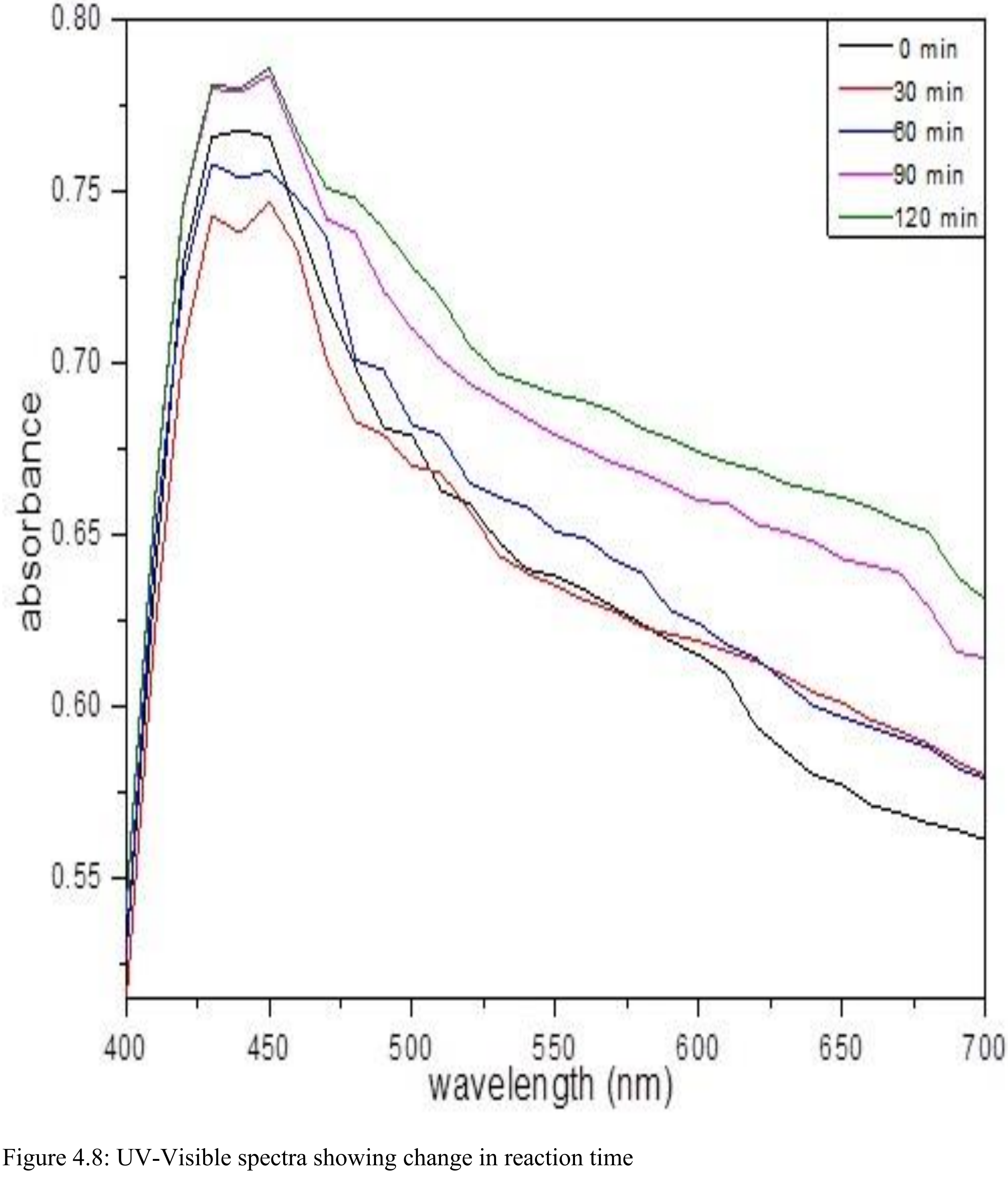


Figure 4.8: UV-Visible spectra showing change in reaction time

Figure 4.9 shows the XRD pattern of the silver nanoparticles synthesized using D. edulis leaf extract.

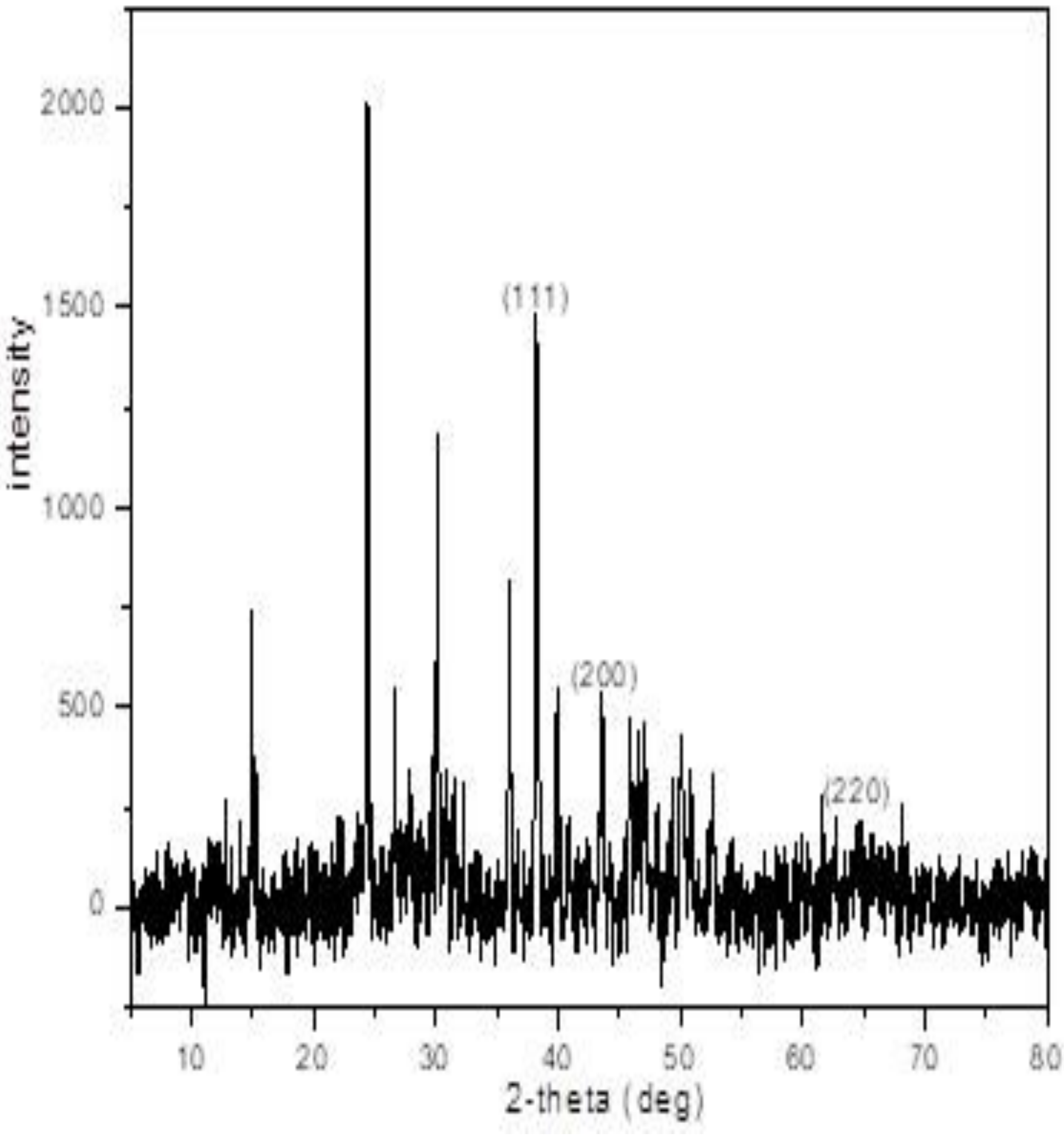


Figure 4.9: XRD pattern of *D. edulis* derived AgNPs

Fig 4.10 shows the SEM image of AgNPs taken at X500 magnification

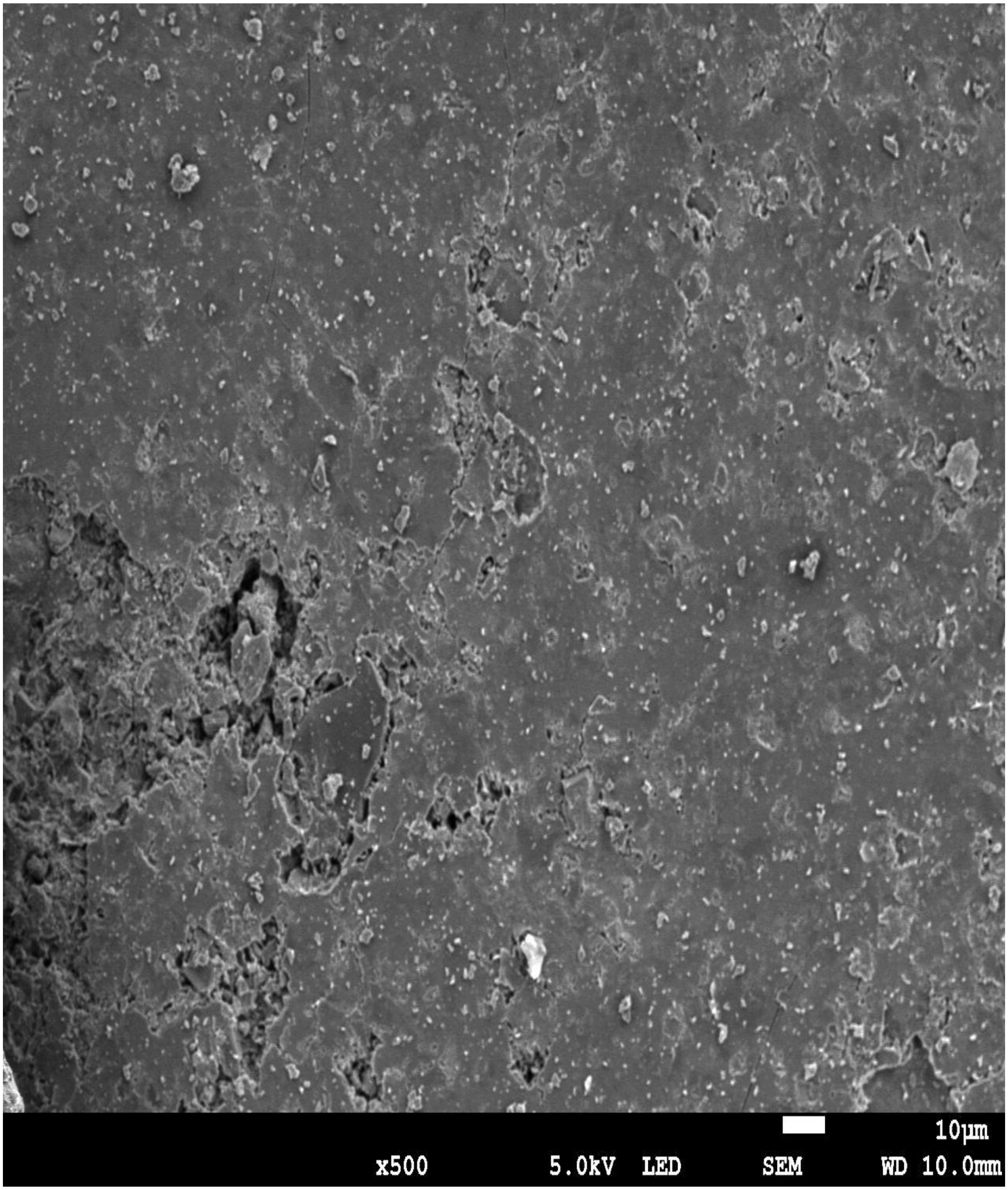


Figure 4.10: SEM image of *D. edulis* AgNPs

The FTIR spectrum of the biosynthesized AgNPs is shown in Fig 4.11.

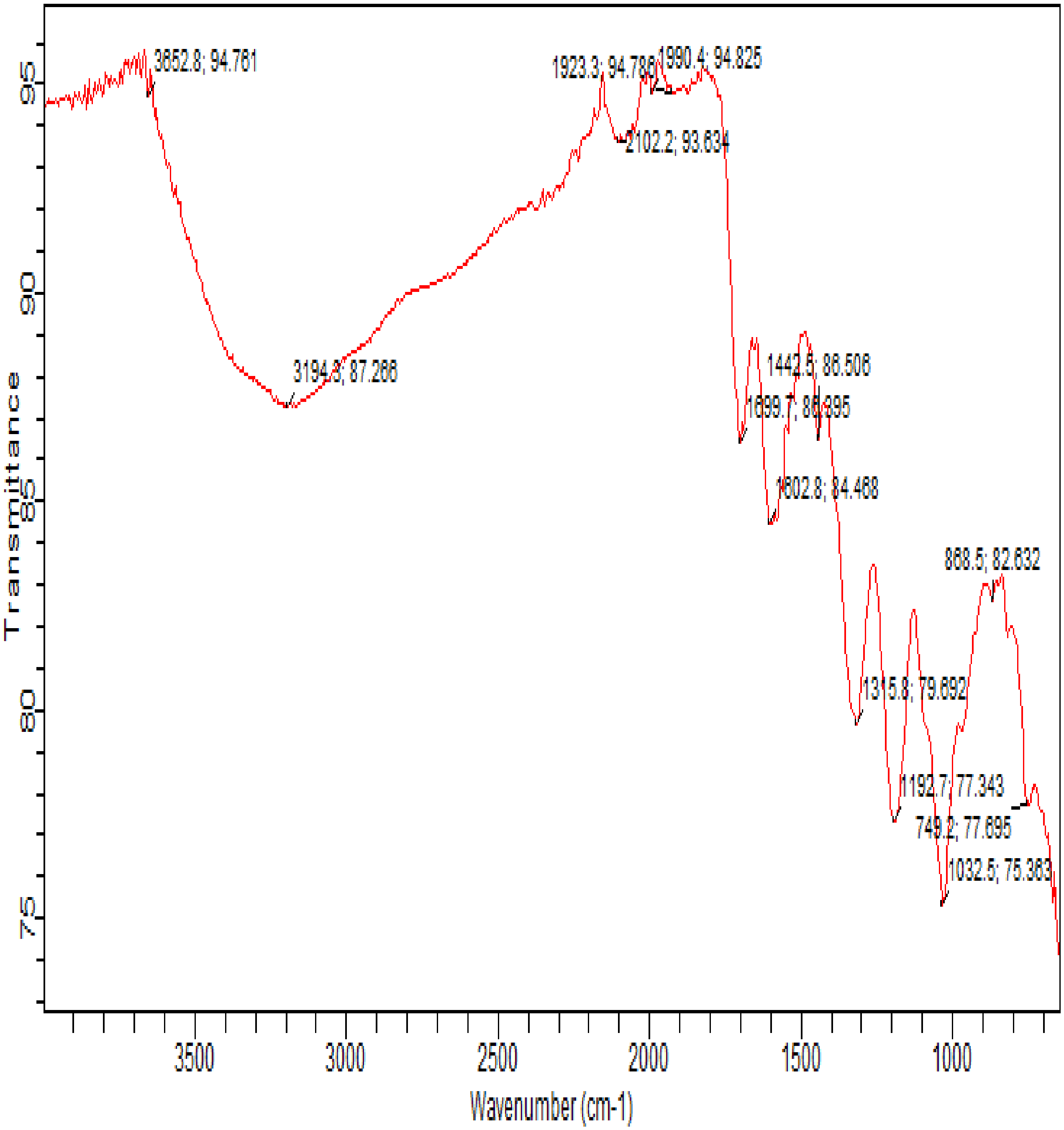


Figure 4.11: FTIR spectra of *D. edulis* mediated AgNPs

Table 4.3: Zones of inhibition and synergy parameters for *S. saprophyticus*

	Zone of inhibition AgNPs and antibiotics (mm)			Inhibition efficiency (%)		Synergy Index
Antibiotics	AgNP	Antibiotics(AB)	Antibiotic+AgNP	Antibiotics	Antibiotic+AgNP	
Gentamycin	10.7±1.2	19±1.00	7.00±0.00	63.2	0	0.018
Pefloxacin		15.17±1.26	20.33±0.76	53.9	65.6	0.32
Ampiclox		7.00±0.00	10.83±0.29	0	35.4	1.01
Ampicillin		7.00±0.00	11.83±0.29	0	40.8	1.09
Rocephin/ceftriaxone		13.17±0.39	7.00±0.00	46.9	0	0.18
Ciprofloxacin		12.13±0.23	17.17±0.29	42.3	59.2	0.56
Streptomycin		14.17±0.29	19.83±0.76	50.6	64.7	0.41
Cotrimoxazole		7.00±0.00	11.30±0.26	0	38.1	1.05
Erythromycin		7.00±0.00	17.17±0.29	0	59.2	1.59

Table 4.4: Zones of inhibition and synergy parameters for *E. coli*

	Zone of inhibition AgNPs and antibiotics (mm)			Inhibition efficiency (%)		Synergy Index
Antibiotics	AgNP	Antibiotics(AB)	Antibiotic+AgNP	Antibiotics	Antibiotic+AgNP	
Cotrimoxazole	11.00±2.70	12.00±0.50	7.00±0.00	41.7	0	0.22
Streptomycin		11.33±1.04	25.17±0.29	38.2	72.2	0.91
Ofloxacin		7.00±0.00	24.33±0.58	0	71.2	2.20
Pefloxacin		7.00±0.00	23.00±0.29	0	69.6	2.09
Gentamycin		10.5±0.5	9.00±0.50	33.3	22.2	0.39
Amoxacillin		7.00±0.00	20.33±0.58	0	65.6	1.85
Ciprofloxacin		15.33±0.58	19.33±0.23	54.3	63.8	0.26
Sparfloxacin		17.17±0.29	22.67±0.76	59.2	69.1	0.14
Chloramphenicol		12.17±0.29	16.30±0.26	42.5	57.1	0.49

Fig 4.12 shows the zones of inhibition exhibited by AgNPs in comparison with some antibiotics against *S. saprophyticus*

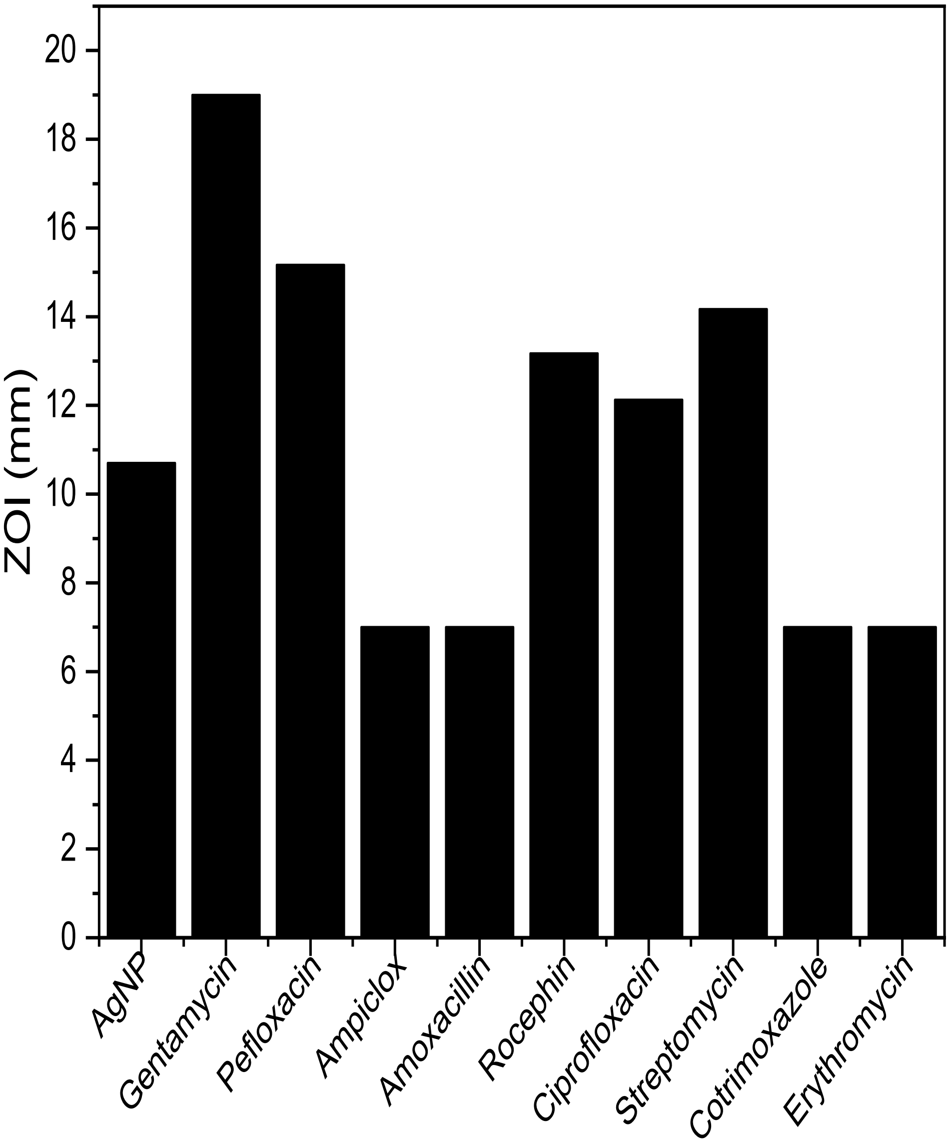


Figure 4.12: Zone of inhibition of AgNP and antibiotics alone for *S. saprophyticus*

Fig 4.13 represents zones of inhibition observed for *E. coli*.

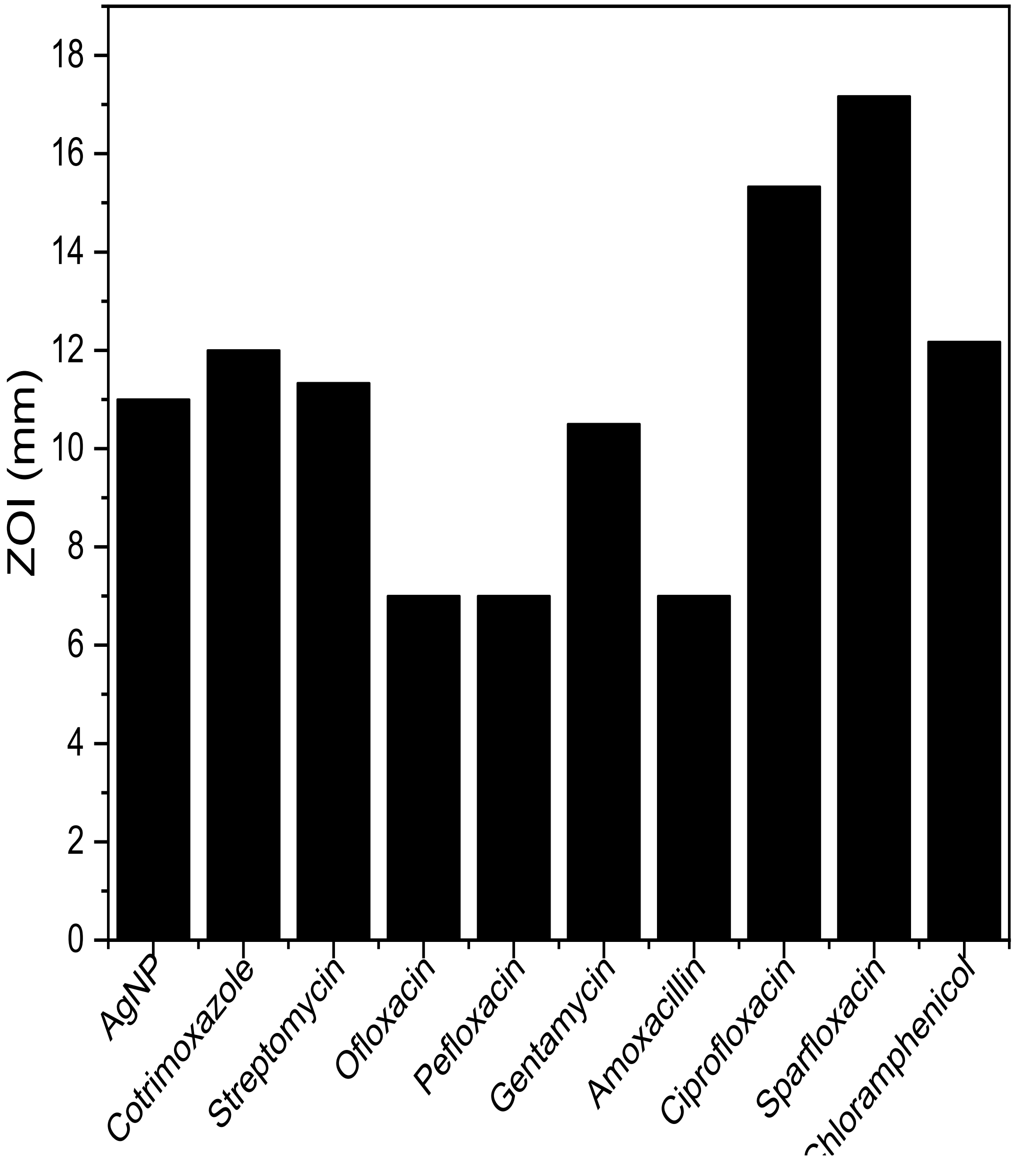


Figure 4.13: Zone of inhibition for AgNPs and antibiotics individually for *E. coli*

Zone of inhibition when AgNPs were in combination with antibiotics for *S. saprophyticus* was shown in Fig 4.14.

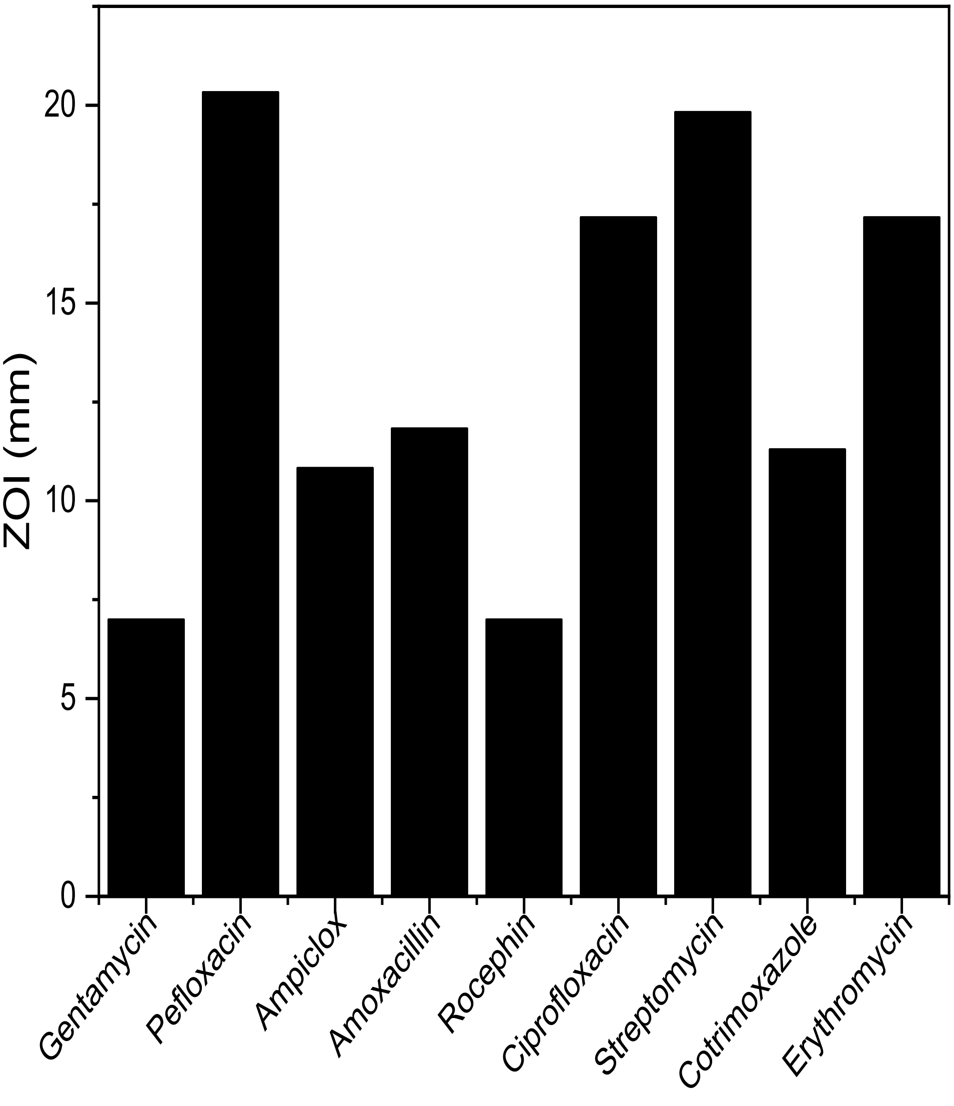


Figure 4.14: Zone of inhibition for antibiotics in combination with the AgNPs for *S. saprophyticus*

Zone of inhibition when AgNPs were in combination with antibiotics for *E. coli* was shown in Fig 4.15.

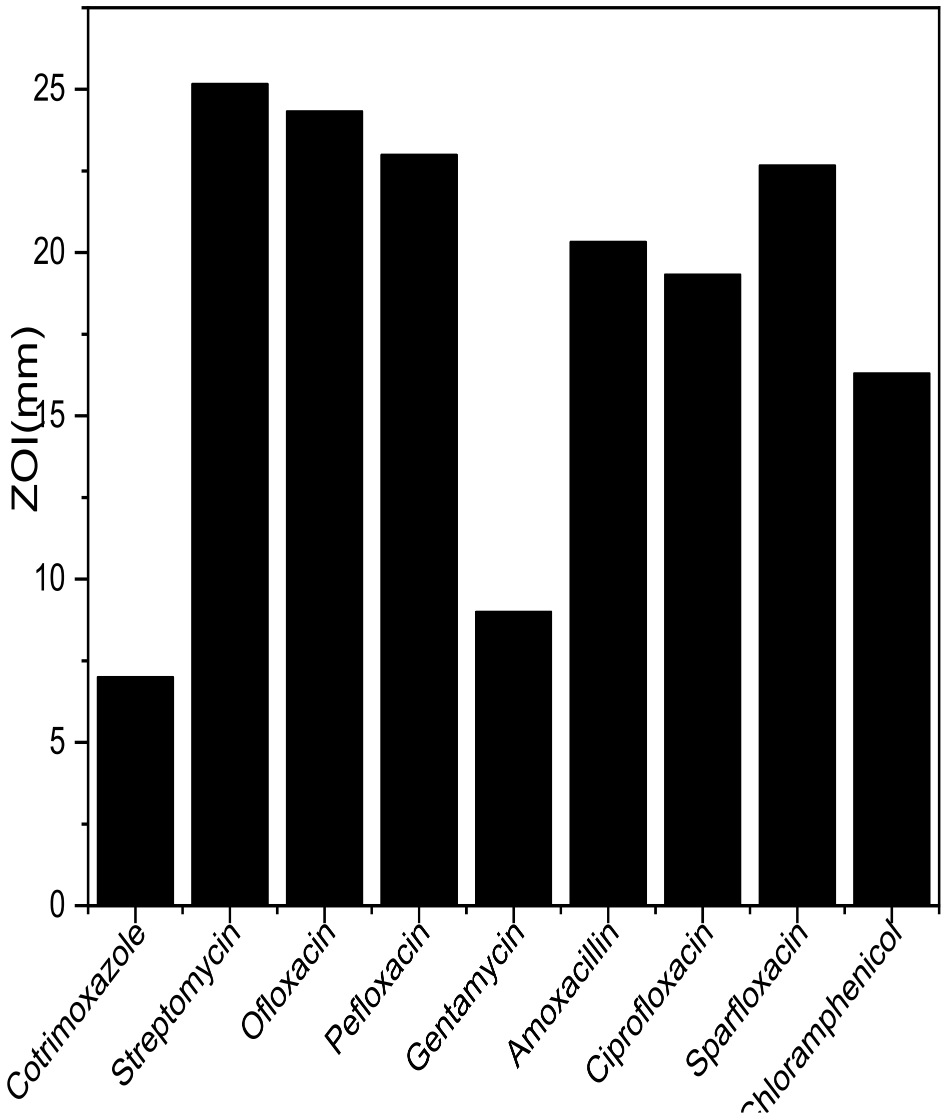


Figure 4.15: Zone of inhibition for antibiotics in combination with the AgNPs for *E. coli*

The comparison of zones of inhibition of antibiotics alone and antibiotics in combination with AgNPs for *S. saprophyticus* are displayed in Fig 4.16.

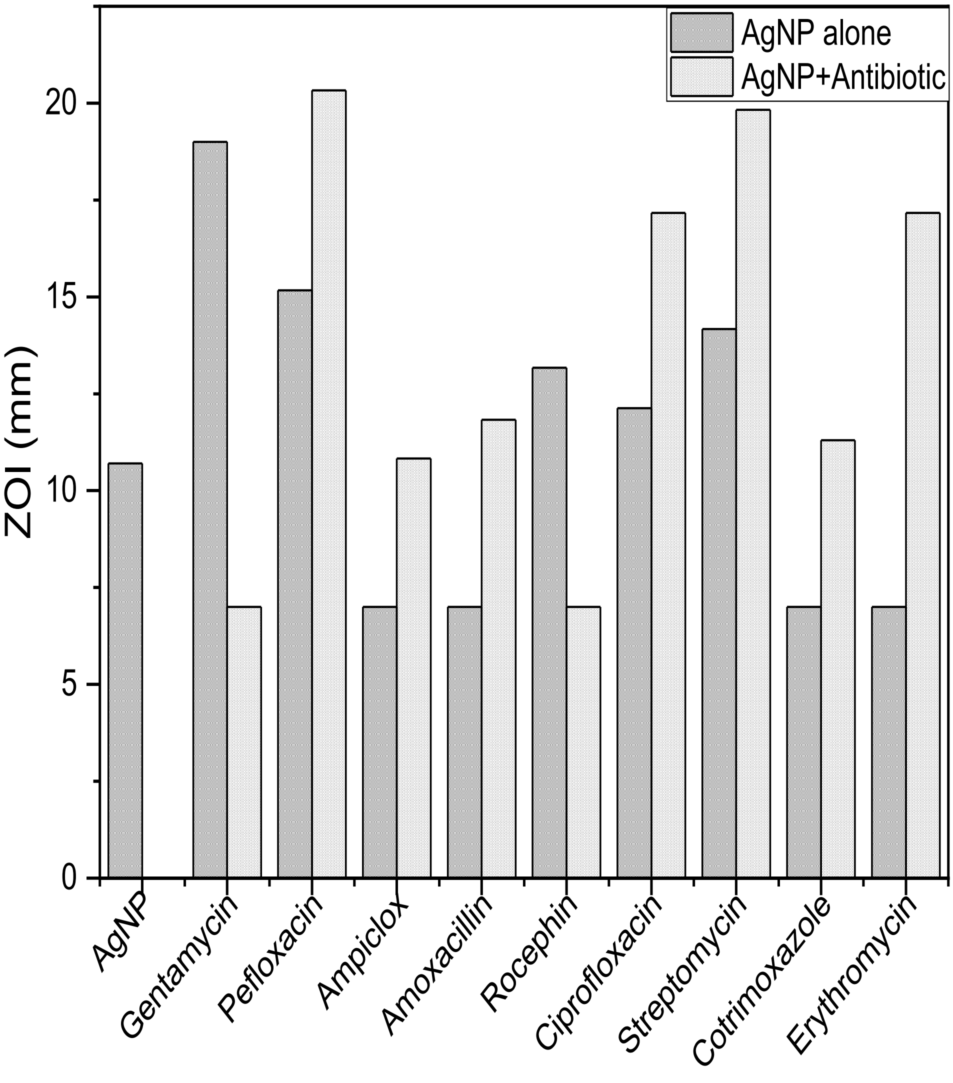


Figure 4.16: Comparison of the zones of inhibition for *S. saprophyticus* for AgNPs and antibiotics alone, and antibiotics in combination with AgNPs.

The comparison of zones of inhibition of antibiotics alone and antibiotics in combination with AgNPs for *E. coli* are displayed in Fig. 4.17

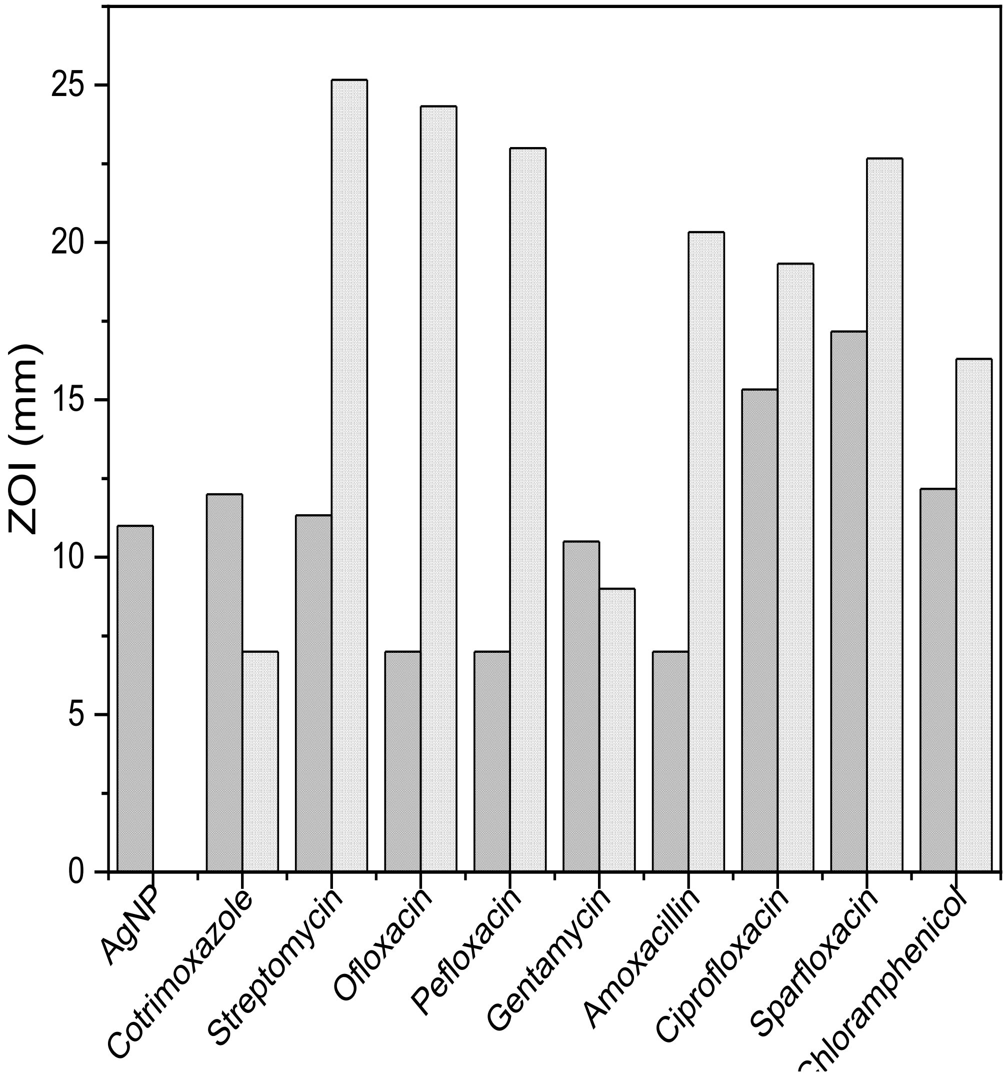


Figure 4.17: comparison of antibiotics alone and antibiotics in combination with AgNPs for *E. coli*

The inhibition efficiency of the AgNPs and antibiotics for *S. saprophyticus* are shown in Fig 4.18

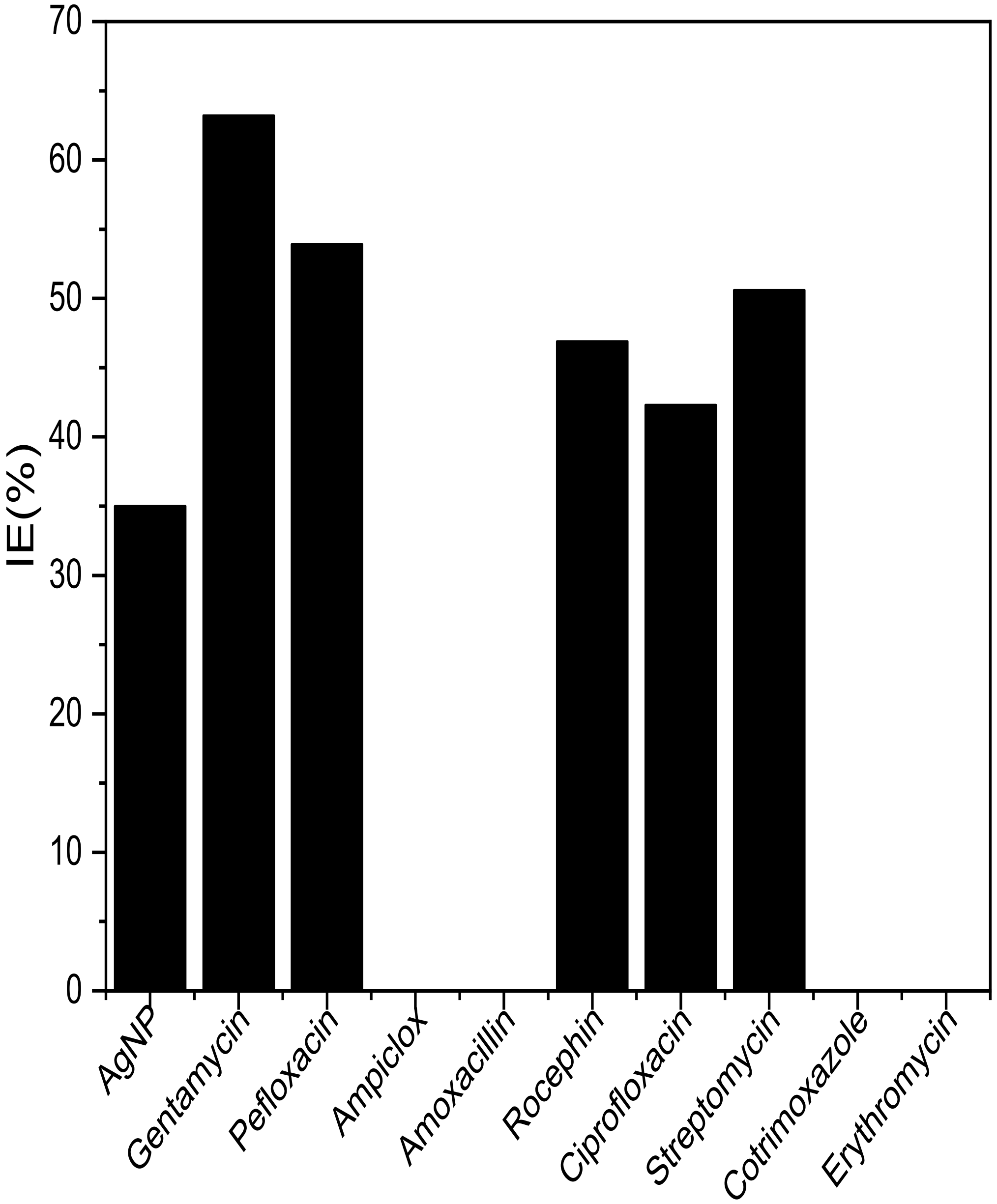


Figure 4.18: Inhibition efficiency of AgNPs and antibiotics for *S. saprophyticus*

The inhibition efficiency of AgNPs and antibiotics for *E. coli* are displayed in Fig. 4.19.

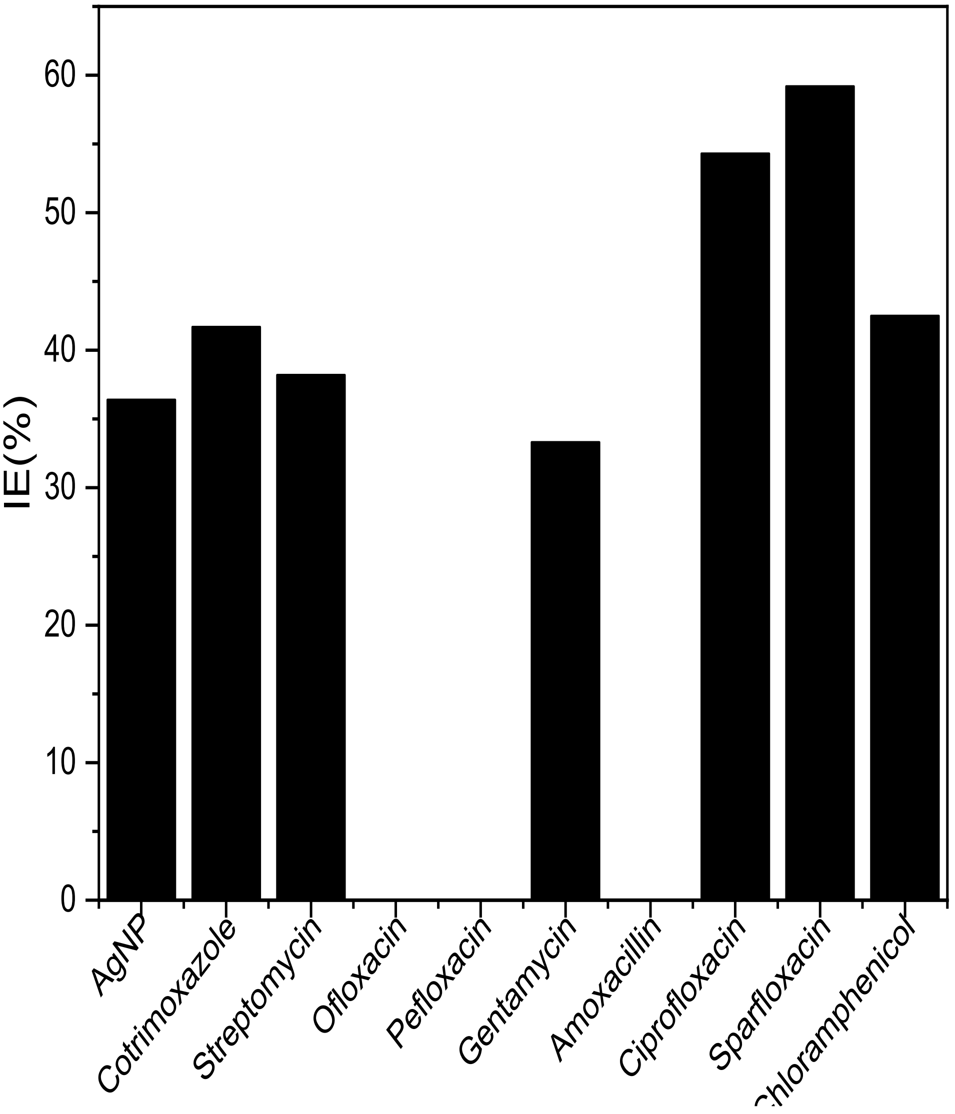


Figure 4.19: Inhibition efficiency of AgNPs and the antibiotics for *E. coli*

Inhibition efficiency for antibiotics in combination with AgNPs for *S. saprophyticus* are displayed in Fig. 4.20.

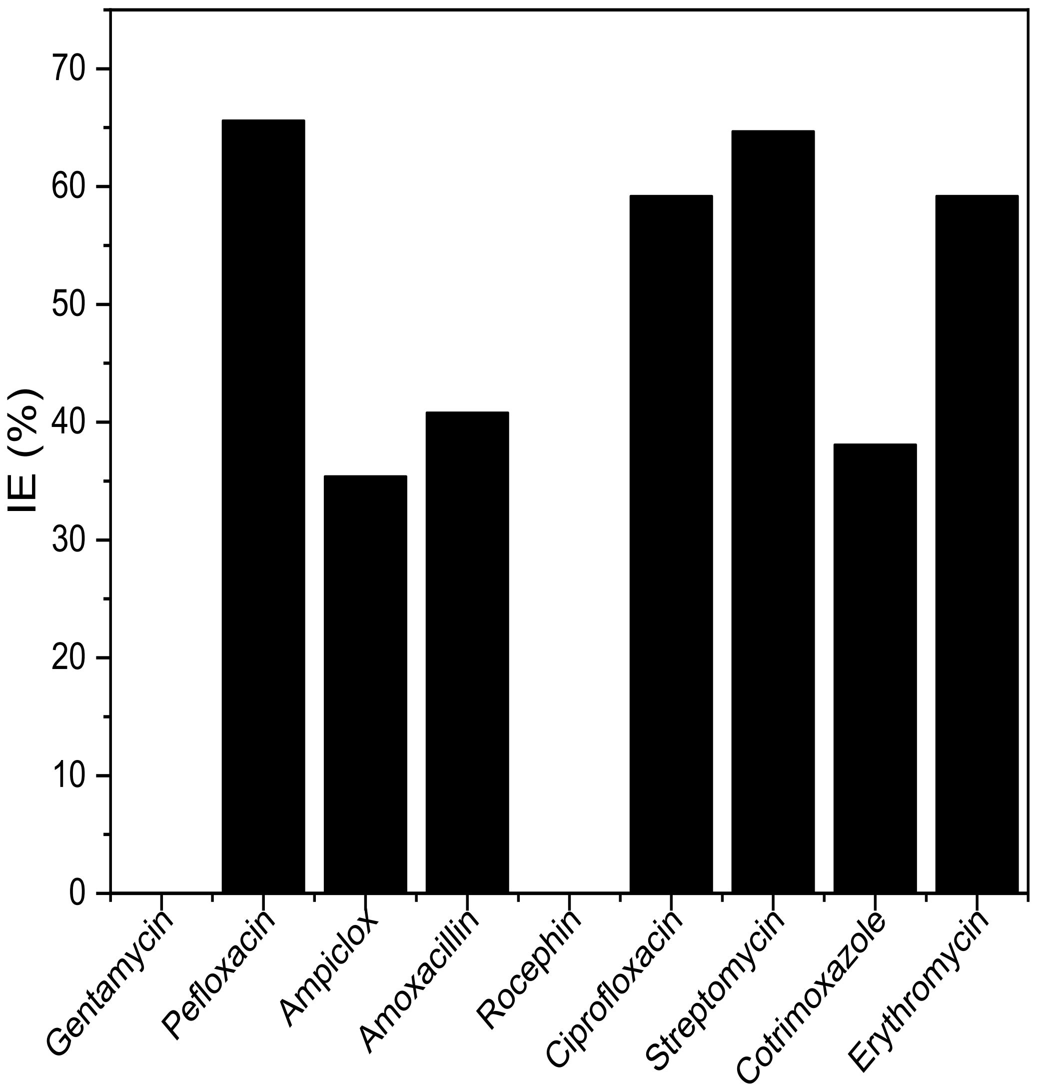


Figure 4.20: Inhibition efficiency of antibiotics in combination with AgNPs for *S. saprophyticus*

Inhibition efficiency of antibiotics in combination with AgNPs for *E. coli* are revealed in Fig. 4.21.

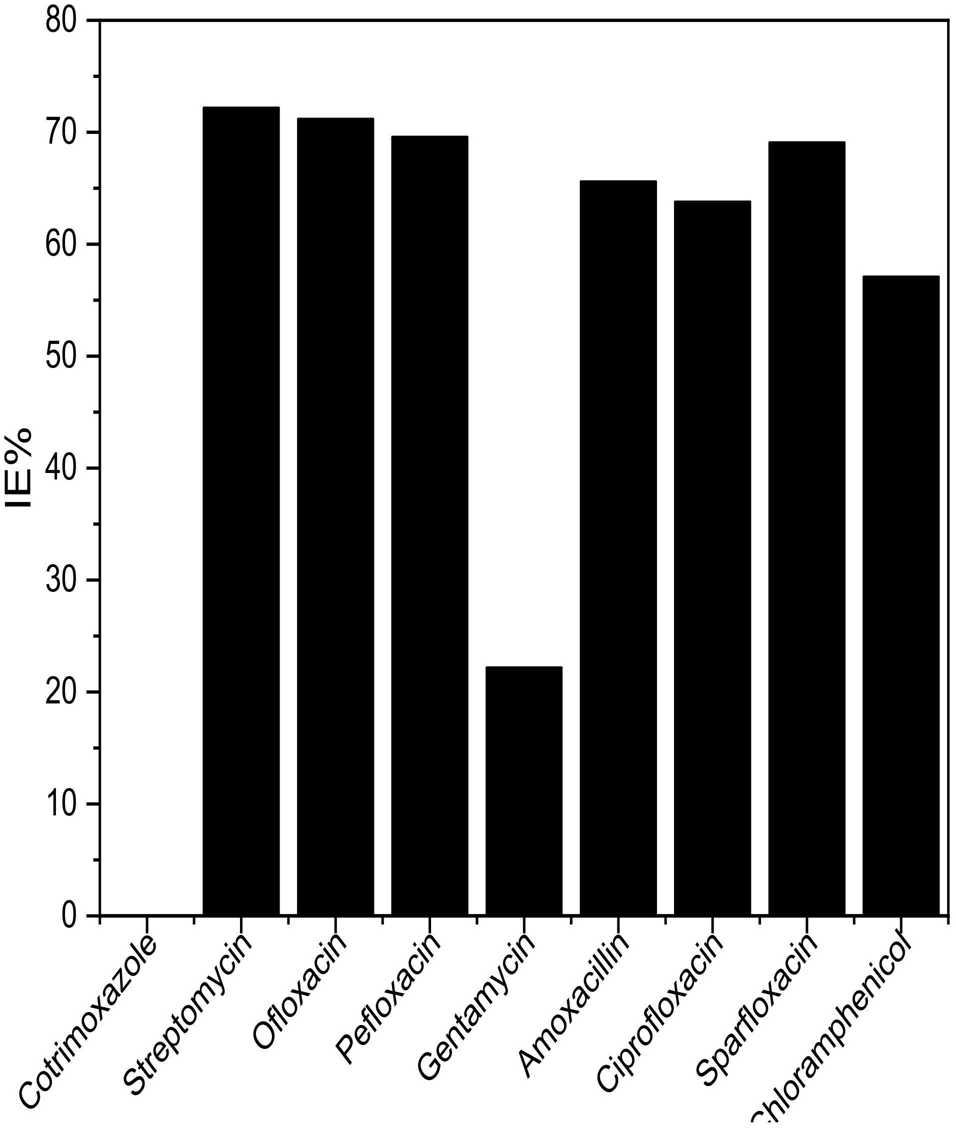


Figure 4.21: Inhibition efficiency of antibiotics in combination with AgNPs for *E. coli*

The comparison of the inhibition efficiency of AgNPs and antibiotics alone and antibiotics in combination with AgNPs for *S. saprophyticus* are displayed in Fig 4.22.

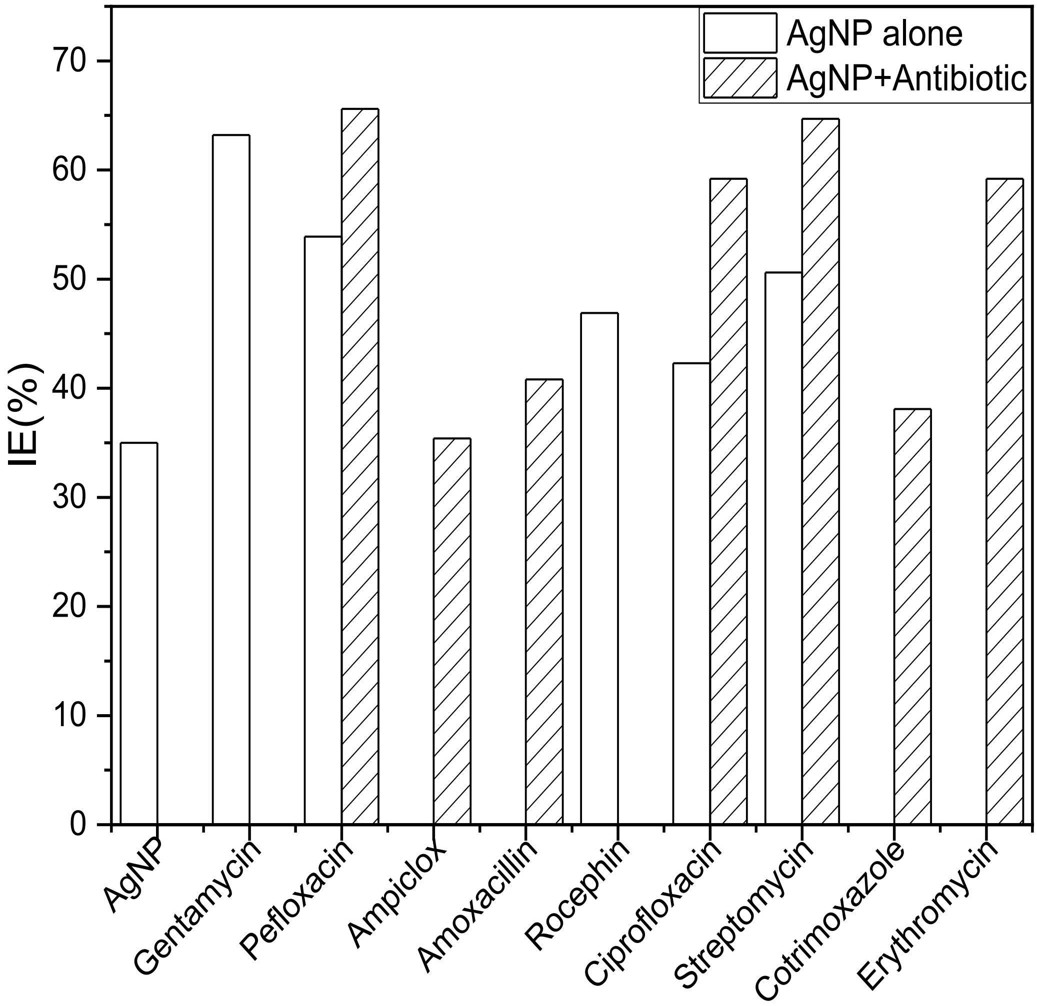


Figure 4.22: Antimicrobial assay showing the comparison of the inhibition efficiency of antibiotics alone and in combination with *D. edulis*-AgNP for *S. saprophyticus*

The comparison of the inhibition efficiency of AgNPs and antibiotics alone and antibiotics in combination with AgNPs for *E. coli* are displayed in Fig 4.23.

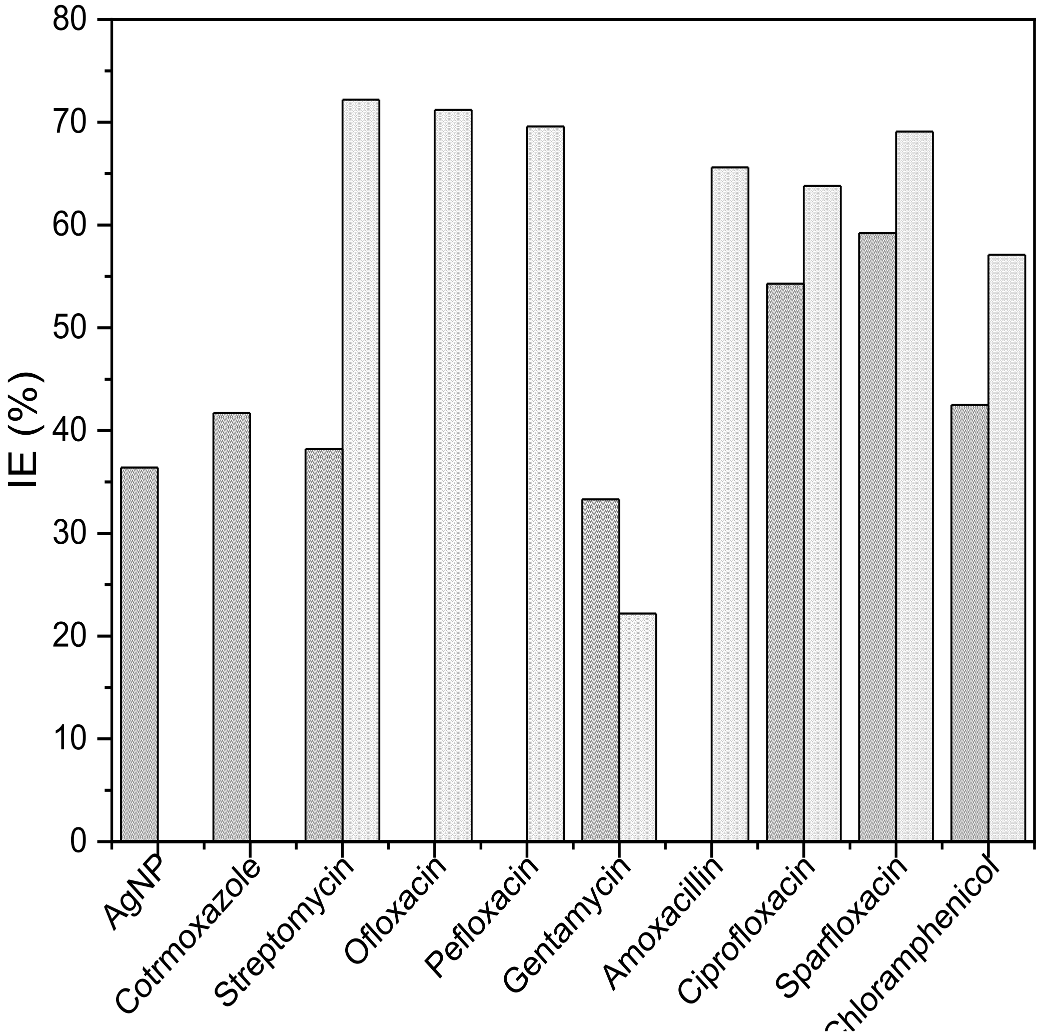


Figure 4.23: Comparison of the antibiotics alone and in combination with AgNPs for *E. coli*

In vitro synergistic assessment for *S. saprophyticus* is as shown in Fig 4.24.

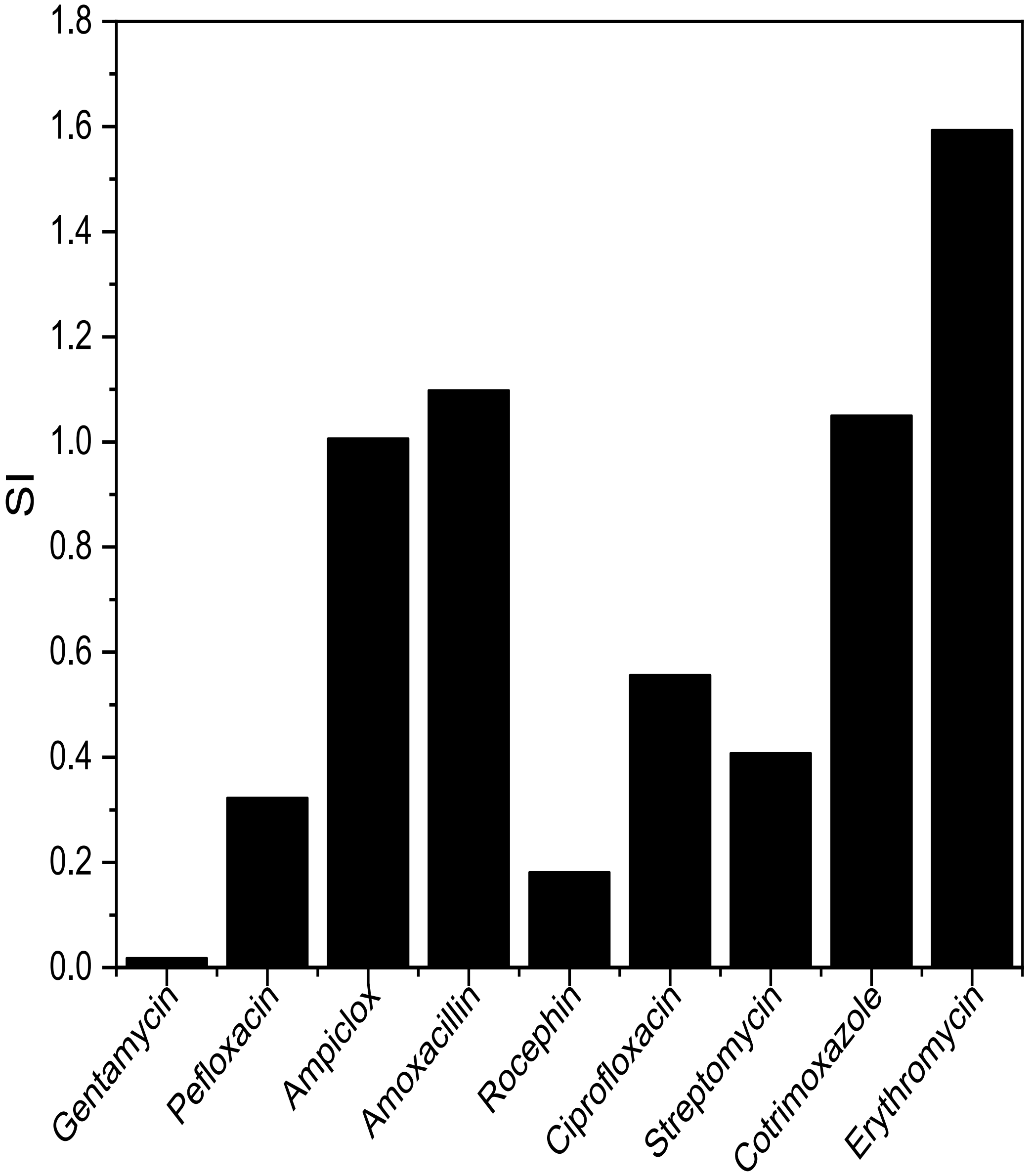


Figure 4.24: Synergistic index of antibiotics in combination with AgNPs for *S. saprophyticus*

In vitro synergistic assessment for *E. coli* is as shown in Fig 4.25.

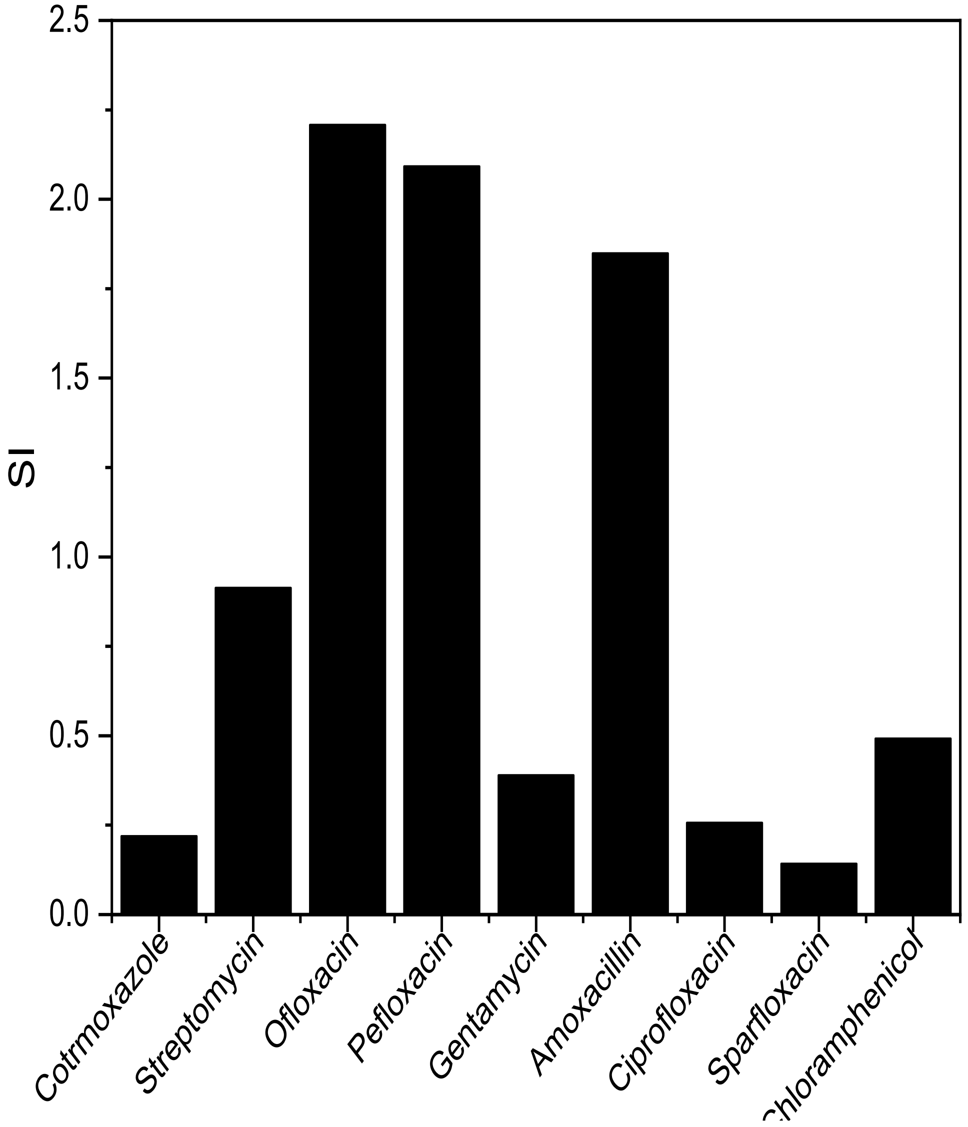


Figure 4.25: Synergistic Index of antibiotics in combination with AgNPs for *E. coli*

4.2 DISCUSSION

The phytochemical constituents as displayed in Fig. 4.1 showed alkaloids (1.68±0.01 mg/100g), tannins (5.33± 0.04 mg/100g), cyanogenic glycosides (2.24±0.02 mg/100g), flavonoids (1.03±0.03 mg/100g) and anthroquinones (1.14±0.05 mg/100g), with tannins being the most predominant biomolecules present in the leaf aqueous extract. Similar results were obtained elsewhere for flavonoids, alkaloids and cyanoglycosides (Ezeabara *et al.*., 2020) at 1.76±0.04mg/100g, 1.66±0.02mg/100g and 2.82±0.07mg/100g respectively from the leaf aqueous extract. Similar low amounts of tannins were obtained in Diospyros mespiliformis (Maitera *et al.*, 2018) and spruce bark (Bello *et al.*, 2022), and this was attributed to the type of solvent that was employed. It has been suggested that cold water extraction by maceration yields low tannin content compared to hot water (Kim *et al.*, 2018).

DPPH scavenging activity was used to determine the ability of the leaf extract to eliminate free radicals in human and plant cells. Percentage scavenging activity of *D. edulis* leaf aqueous extract was obtained as 61.85±0.01%. Similar results were observed for *Acacia nilotica* flowers (Abdel-Farid *et al.*, 2014), typical corn (Li *et al.*, 2007), and *Griffonia simplicifolia* (Akoto *et al.*, 2020). It was reported that the presence of phenolic compounds and flavonoids in plant extracts confers free radical scavenging properties since they release electron or hydrogen to balance the DPPH free radicals (Batool *et al.*, 2019). These free scavenging properties are significant in preventing or reducing acute or long-term diseases including diabetes and cancer (Khalid *et al.*, 2017) and this has been evidenced in some reports concerning *D. edulis* plant extract (Mvondo *et al.*, 2021; Ononamadu *et al.*, 2019; Uzor *et al.*, 2021).

The organisms *Staphylococcus sp.* and *Escherichia sp.* had 97% similarity with *Staphylococcus saprophyticus* and *Escherichia coli*, respectively. The phylogenetic trees were constructed using MEGA XI and are shown in Fig 4.2 and 4.3, respectively. *Staphylococcus saprophyticus* implicated as the next major of urinary tract infections (UTI) in men and women, has also been found in the gut and rectal normal flora of livestock such as cattle and pigs, is a common contaminant of meat and fermented food products, and also found in polluted aquatic environments (Lawal *et al.*, 2021). It is rarely found in men and is known to be the cause of urogenital infections including urethritis, epididymitis, kidney stones, prostatitis and men of all ages using urinary catethers (Shahid *et al.*, 2020; M. Yousaf *et al.*, 2022). *E. coli* has been found to be adaptable microorganisms that occupy a niche in the intestinal microbiota of both humans and animals, capable of causing urogenital, bloodstream, prostate, and other nonabdominal infections in hospital and community settings both local and globally (Manges *et al.*, 2019).

Further investigation to reveal WGS-predicted antimicrobial resistance genes was done using ResFinder (www.centerforgenomicepidemiology.com). The specific resistant genes responsible for resistance against these antibiotics in gram positive *S. saprophyticus* were predicted to be *mec*A, *bla*Z and *dfr*G genes as shown in Table 4.1. In a similar study by Zhang et al (2023), *mec*A gene, a genetic mobile element that encodes for β-lactam resistance was responsible for resistance to drugs such as penicillin, cefotixin and oxacillin. *bla*Z gene was confirmed in another study by Amiri et al (2023). It has also been known to encode β-lactam resistance in S. saprophyticus. *dfr*G gene encodes for trimethoprim resistance as was observed in a different study (Lawal et al., 2021).

However, in *E. coli*, there were predicted chromosomal gene mutations that mediated antimicrobial resistance as shown in Table 4.2. *gyr*A&B, *par*C&E, *pmr*A&B, *fol*P, 16S-*rrs*B, 16S-*rrs*C,16S-*rrs*H, *amp*C-promoter and *rpo*B. Similar results were obtained from various studies (Dehbanipour *et al.*, 2019; Kathayat *et al.*, 2020; Massella *et al.*, 2020; Mukherjee *et al.*, 2021; Neyestani *et al.*, 2023; Patel *et al.*, 2023; Pearcy *et al.*, 2021). Fluoroquinolone resistance in *E. coli* has been known to be associated with chromosome-mediated mutations in the encoding genes DNA gyrase (*gyr*A and *gyr*B subunits) and topoisomerase IV (*par*C and *par*E) which are located at the fluoroquinolone resistance determining region (QRDR), thereby causing reduced affinity for the antimicrobials (Cheng *et al.*, 2020). Fluoroquinolone mechanism of action is to interfere with the activity of the type IIA bacterial topoisomerases, DNA gyrase and topoisomerase IV enzymes which are tetramers made up of heterodimers of homologous *gyr*A, *gyr*B and *par*C and *par*E respectively. However, the reason for the selective resistance to ofloxacin and pefloxacin but not to ciprofloxacin could not be explained.

Sulfonamides target dihydropteroate synthase (DHPS), encoded by the *fol*P gene, whose mechanism of action can be two-fold. Firstly, mutations in *fol*P gene by acquisition of alien, sequence-divergent genes coding for DHPS variants (insensitive to sulfonamides) and secondly resistance associated with *sul* genes typically encoded on plasmids found in gram negative species like *E. coli* (Venkatesan *et al.*, 2023). Point mutations in *fol*P gene have been observed to suppress (tetrahydrofolate) THF production (Pearcy *et al.*, 2021). *fol*P gene has also been identified in the trimethoprim, tetracycline, and ampicillin (machine learning) ML models (Sánchez-Osuna *et al.*, 2019). *pmr*A&B genes have been known to be associated with resistance to the antibiotic colistin. However, the antimicrobial agent Colistin was not among the antibiotics used in the antibiotic assay for this study.

Alterations to 23rRNA gene or 50S subunit proteins (2058 and 2059 *E.coli* positions) lead to antimicrobial resistance in macrolides for example erythromycin (Cho & Misra, 2021; He *et al.*, 2023), which occurs via chromosomal efflux pumps (Gomes *et al.*, 2019). These are bacterial systems that are known to release molecules, toxic substances, antibiotics and other compounds alien to the bacteria from the bacteria into the surrounding environment. *E. coli* isolated from poultry and livestock (calf) were found to possess chromosomal mutations in 16S *rrs*B, 16 *rrs*C and 16S *rrs*H genes (Al-Mustapha *et al.*, 2023; Hickman *et al.*, 2022). According to studies by Kurylo *et al.* (2018), 16S *rrs*H-bearing ribosomes contribute to transcriptional aspects of the general stress response and have been known to be responsible for the resistance to gentamycin. Mutation in *amp*C promoter gene was observed to be responsible for bacterial resistance to amoxicillin (Hoeksema *et al.*, 2019). These mutations in the promoter region is the most common cause of excessive production of β-lactamases especially in clinical isolates, resulting in resistance to antibiotics including ampicillin, cefoxitin, and expanded-spectrum cephalosporins (Singh *et al.*, 2019). *rpo*B gene mutation, a RNA polymerase subunit β, has been known to give rise to tetracycline, tigcycline and rifampicin resistance (Haeili *et al.*, 2022; Shelake *et al.*, 2023).

The UV-Vis spectroscopy studies were employed to ascertain the formation and stability of the silver nanoparticles. Silver nanoparticle formation started off upon addition of leaf extract to the silver nitrate solution as depicted by colour change as seen in Figure 4.4. This colour change is attributed to the excitation of the localized Surface Plasmon Resonance (Urnukhsaikhan *et al.*, 2021). In general, the exhibition of colour change has been linked to the oscillations of the free electrons influenced by an electromagnetic field (Chandraker *et al.*, 2019), which leads to the dispersion of incident radiation and absorption (Madivoli *et al.*, 2020). This is then measured and read using a UV-Visible spectrophotometer.

Colour intensity improved with increase in extract concentration as shown in Figure 4.5 (see insert). Spectral analysis revealed an absorption band at 390 nm which increased with increase in extract concentration.

It has been reported that slight changes in absorbance signifies changes in particle size (Ahmed & Ikram, 2015). Plant extract concentration volumes that are lower than aqueous $AgNO_3$ volumes showed sharp peaks at 390 nm while plant extract concentration volumes higher than

$AgNO_3$ volumes showed sharp plasmon resonance bands of 390 nm – 440 nm respectively which is typical of silver nanoparticles (Rautela *et al.*, 2019). A similar absorption peak was achieved with aqueous silver nanoparticles synthesized from *Achillea millefolium* leaves extract (Yousaf *et al.*, 2020). The absorption peak became broader with increase in plant extract concentrations with peak appearing at approximately 440 nm. Increase in plant extract concentration causes particle aggregation and subsequent formation of colloidal silver (Reda *et al.*, 2019). The dynamics of the reaction with respect to temperature was monitored using UV- visible spectral analysis as observed in Fig 4.6.

Low temperatures (25 °C, 35 °C and 45 °C) showed high absorbance compared to high temperatures (55 °C, 65 °C and 75 °C). A similar result was observed in the formation of silver nanoparticles using *Tropaeolum majus* (Bawazeer *et al.*, 2021). It has been suggested that increase in temperature increases the molecular kinetic energy leading to formation of particles of approximate size distribution (Jain & Mehata, 2017; H. Liu *et al.*, 2020).

Increase in pH led to increase in absorbance which confirms increase in formation of AgNPs as seen in Figure 4.7. However, at pH 7 also known as neutral pH, most silver nanoparticles were formed as seen in the intensity of the absorbance. Further increase in pH (9 and 11) showed reduced intensity in absorbance thereby leading to a decrease in the kinetic energy of the conversion of Ag^+ to Ag^0 ions. Alkaline pH (It has been reported that neutral pH is appropriate for the production of spherical small sized nanoparticles (Elemike *et al.*, 2017). A change in pH has been known to alter the particle size variations and stability by changing the charge of biomolecules thereby affecting their capping and stabilizing potentials (Vanlalveni *et al.*, 2021). In acidic environment, the biomolecules act as oxidizing agents which leads to the formation of highly unstable nanoparticles whereas the silver nanoparticles are more stable in alkaline pH (Gul *et al.*, 2022). pH 9 & pH 11) gave rise to sharper peaks than the acidic pH (pH 3 & pH 5).

Initial addition of plant extract to silver nitrate solution at 70 °C with respect to reaction time, revealed a tremendous increase in intensity of absorbance within the first minute which became steady and gradual at 30 minutes as seen in Fig 4.8. However, increase in time after 90 minutes of the reaction showed no increase in absorbance even at 120 minutes. This was also observed in a related study (Khan *et al.*, 2017). In this study, 90 minutes was the optimal time for the complete formation of AgNPs. The absorbance peaks became sharper with increase in time and minor shift in wavelength of 449 nm. This observation was also reported by Ahmed & Ikram (2015) and Devi & Sathishkumar (2017).

XRD was carried out to assess the crystalline nature of the silver nanoparticles. Figure 4.9 shows the XRD pattern of the silver nanoparticles synthesized using D. edulis leaf extract with Bragg's reflection of the 2θ peaks observed at 38.17°, 43.63° and 64.39° which corresponded to (111), (200) and (220) plane lattice, respectively. These lattice planes have been indexed to the face-centred cubic crystal nature of the nanoparticle. Other prominent 2θ peak values observed in the XRD pattern have been attributed to the organic phases of the plant extract, thereby indicating the involvement of phytochemical constituents in the plant extract as reducing and capping agents in the nanoparticle synthesis (Kambale *et al.*, 2020; Pirtarighat *et al.*, 2019).The average crystallite size of the nanoparticles was calculated using the Scherrer equation and was found to be 51.44 nm. This confirms the crystalline nature of the silver nanoparticles as reported by other studies (Basu *et al.*, 2016; Das *et al.*, 2019).

Fig 4.10 shows the SEM image of AgNPs image taken at X500 magnification. It shows AgNPs are spherical in shape with smooth surface and the average size of the particles approximately 63 nm. Irregular distribution of AgNPs were observed, with varying particle sizes. Similar results were reported by Shah *et al.* (2021) and it was attributed to the silver reduction caused by the interaction between the silver salt and the organic compounds as found in the leaf extract.

SEM has been known to show the enclosure of the AgNPs by the plant extract framework (Abdellatif *et al.*, 2022).

The functional groups involved in the silver bioreduction are identified using FTIR spectroscopy which acknowledges the feasible biomolecules present in D. edulis plant extract which are responsible for reducing and capping Ag^+. The FTIR spectrum of the biosynthesized AgNPs as shown in Fig 4.11 exhibits the existence of different wavenumber peaks at 749 cm^{-1}, 868 cm^{-1},1032 cm^{-1}, 1192 cm^{-1}, 1315 cm^{-1}, 1424 cm^{-1}, 1602 cm^{-1}, 1699 cm^{-1}, 1990 cm^{-1}, 1923 cm^{-1}, 2102 cm^{-1}, 3194 cm^{-1} and 3652 cm^{-1}. Using the FTIR interpretation manual, the peaks at 3652 cm^{-1} and 3194 cm^{-1} refer to the –O-H stretching vibrations of phenolic or carboxylic groups while observed peaks at 2102 cm^{-1} and 1990 cm^{-1} are assigned to the CΞC stretching and N=C=S stretching of alkyne and isothiocynate groups respectively. 1923 cm^{-1} corresponds to the C=C=C stretching of the allene group, 1699 cm^{-1} for C-H bending of the aromatic groups and medium peak C=C stretching belonging to the cyclic or conjugated alkene group. 1424 cm^{-1} and 1315 cm^{-1} indicates the –OH bending of the phenol or carboxylic acid, 1192 cm^{-1} is ascribed to C-O stretching of the ester or tertiary alcohol group while 1032 cm^{-1} was attributed to the C-N stretching of the amine group. 868 cm^{-1} is for C-H bending while 749 cm^{-1} corresponds to 1,2 di-substituted –OH bending. These functional groups represent alkaloids, flavonoids, cyanogenic glycosides, tannins and quinones present in the plant leaf extract. These biomolecules have been known to bind to the nanoparticle surfaces (Shaik *et al.*, 2018) during the nucleation process and promote nanoparticle formation and prevent aggregation (Rezazadeh *et al.*, 2020; Shanmugam *et al.*, 2022). The mechanism of action of these phytochemical constituents collectively in the reduction of silver nitrate solution to silver nanoparticles is unknown. However, tannins possess various mechanisms of action in order to regulate the amplification of resistant microbial strains which include the unique capability to precipitate proteins (Girard *et al.*, 2018), block substrate availability to bacterial cells (Maito *et al.*, 2022), and deprive the extracellular microbial enzyme of substrates needed for their development (Javed *et al.*, 2020).

The antibacterial activity of the plant synthesized AgNPs was investigated against Gram-positive bacteria (*S. saprophyticus*) represented in Table 4.3, and gram-negative bacteria (*E. coli*) using the Kirby-Bauer (disc diffusion) method shown in Table 4.4. Discs with no inhibition was taken as 7.00 mm which is the diameter of the discs utilized for the experiment. The experiment was performed in triplicates and result expressed by means ±standard deviation. The values were subjected to ANOVA and post hoc Tukey analysis and there was significance difference ($p \leq 0.05$).
The zone of inhibition which displays antibacterial activity is the rounded average value of triplicate measurements of the inhibition diameter in the agar plate. The antibacterial activity indicates that <9mm zone was regarded as inactive, 9-12mm as partially active; 13-18mm was evaluated as active while > 18mm was assessed as very active (Uddin et al., 2020). In comparison with the inhibition shown by the antibiotics, it could be said to be partially active. The results indicated that the bio-synthesized AgNPs showed substantial inhibition against the microorganisms, although the inhibition was less for *S. saprophyticus* (10.27±mm) in Fig 4.12 than *E. coli* (11.00±mm) in Fig 4.13. This could be attributed to the thicker peptidoglycan layer which is characteristic of gram-positive bacteria as this obstructs the diffusion of toxins and chemicals, including AgNPs into the cell membrane (Lenart-Boroń et al., 2024).

However, in combination with antibiotics as shown in Fig 4.14, AgNPs exhibited enhanced inhibition and reduced inhibition in both microorganisms. In *S. saprophyticus*, enhanced inhibition was observed for pefloxacin, ampiclox, ciprofloxacin, streptomycin, cotrimoxazole and erythromycin, while reduced inhibition was observed for gentamycin and rocephin (ceftriaxone). Similar results were obtained by Hashemzadeh *et al.* (2021) where *S. saprophyticus* isolated from urine culture were found to be resistant to erythromycin, oxacillin and cotrimoxazole (trimethoprim/sulfamethoxazole).

Whereas, in vitro antimicrobial assessment for *E. coli* in Fig 4.15, there was enhanced inhibition for streptomycin, ofloxacin, pefloxacin, amoxicillin, ciprofloxacin, sparfloxacin and chloramphenicol, while reduced inhibition was noted for cotrimoxazole and gentamycin. Despite the fact that the exact mechanism of the antibacterial activity of AgNPs against infectious agents still require in-depth study (Islam et al., 2021), the catalytic activity and unique infiltrating potential of the silver nanoparticles into the bacterial cells affecting the cellular membranes and their DNA replication may be the most likely reason for their enhanced bacterial inhibition (Hussein et al., 2020). As for the reduced inhibitions, it was suggested that the biomolecules capping the AgNPs could to a certain degree interfere with the antibiotic component and thus limit their availability (Chugh et al., 2021).

For *S. saprophyticus* as seen in Fig 4.16, in comparison with antibiotics alone, and antibiotics in combination with AgNPs, gentamycin and rocephin (ceftriaxone) had a reduced zone of inhibition when combined with AgNPs while the other antibiotics had improved zone of inhibition. However, for E. coli as revealed in Fig 4.17, the comparison showed that cotrimoxazole and gentamycin had reduced zone of inhibition when AgNPs were added while other antibiotics had improved zone of inhibition in combination with AgNPs. Loss of inhibition and improved inhibition occur as a result of the resistant genes and the chromosomal mutations as discovered in the *in silico* analysis.

Inhibition efficiency as displayed in Fig 4.18 shows gentamycin, pefloxacin, and streptomycin had good inhibition efficiency; while ampiclox, amoxicillin, cotrimoxazole and erythromycin had no inhibition efficiency for *S. saprophyticus*. But with AgNP in combination with antibiotics as seen in Fig 4.19, gentamycin and rocephin (ceftriaxone) lost their inhibition efficiency while ampiclox, cotrimoxazole, amoxicillin and erythromycin regained their inhibition efficiency. The comparison is revealed in Fig 4.20.

For E. coli as revealed in Fig 4.21, inhibition efficiency revealed sparfloxacin, ciprofloxacin, cotrimoxazole, chloramphenicol as good inhibitors while ofloxacin, pefloxacin, and amoxicillin had no inhibition efficiency. But in combination with AgNPs, as shown in Fig 4.22, cotrimoxazole lost its inhibition efficiency while ofloxacin, pefloxacin and amoxicillin had their inhibition efficiency restored. Gentamycin, however, had reduced inhibition efficiency. Their comparison is exhibited in Fig 4.23. Similar results of lost and regained inhibition of antibiotics in combination of AgNPs were obtained by Aabed & Mohammed (2021).

Synergistic assessment for antibiotics in combination with biosynthesized silver nanoparticles was calculated from the inhibition effects. In vitro synergistic assessment for *S. saprophyticus* as shown in Fig 4.24, revealed synergistic interactions for amoxicillin, cotrimoxazole and erythromycin. Ampiclox showed additive effect while pefloxacin, gentamycin, rocephin (ceftriaxone), ciprofloxacin and streptomycin showed antagonistic interactions. For *E. coli*, as shown in Fig 4.25, ofloxacin, pefloxacin and amoxicillin had synergistic effect while the other antibiotics had antagonistic effects. Streptomycin, however almost had additive effect with SI≈1.0. Similar results were obtained by Panáček et al (2016) and it was attributed to the various modes of activity of AgNPs which include cooperating with antibiotics to disrupt or damage the bacterial cellular membrane, promoting hydrophilic antibiotic transport to the plasma membrane by aiding membrane permeability, and inhibiting bacterial enzyme activity responsible for bacterial resistance to restore antibacterial activity of antibiotics.

Similar phenomena were observed by various researchers. In a study by Singh *et al.* (2017), there was restored susceptibility to antibiotics (erythromycin, novobiocin, vancomycin, lincomycin, pencillin G, and oleandomycin) when in conjunction with silver nanoparticles against *Pseudomonas aeruginosa*, *Escherichia coli* and *Salmonella enterica*. Same restoration of antimicrobial activity was observed by Naqvi *et al.* (2013), although the reason for the occurrence could not be unraveled. But in a research study by Abo-Shama *et al.* (2020b), silver nanoparticles and zinc oxide nanoparticles simultaneously displayed total restoration of antibiotic susceptibility, decreased susceptibility or total loss of susceptibility when *E.coli*, *S.aureus* and *Salmonella sp* were exposed to antibiotics (oxacillin, cefuroxime and fosfomycin) in combination with the metal nanoparticles. The authors however, did not explain the reason for these phenomena. The loss, decreased or restoration of antibiotic susceptibility when the synthesized silver nanoparticles were added to antibiotics is not clear.

However, a research study by Hoeksema *et al.* (2019), suggests that transferring bacteria to another antibiotic environment depending on the antibiotic combination leads to loss, partial maintenance or full preservation of the original resistance. Therefore, adaptation to a new antibiotic (in this case antibiotic+silver nanoparticles) could either lead to increased/decreased susceptibility or resistance, a phenomenon known as collateral sensitivity or resistance. This phenomenon is important in developing strategies to multidrug resistance pipeline development. They also suggested that cellular accommodations required for the adaptation to the new antimicrobial agent may not always be compatible with previously acquired mutations. Although physiological interactions (synergy, additive and antagonism) in antibiotic combinations have been thoroughly studied and explored for therapeutic purposes (Singh & Yeh, 2017), evolutionary associations leading to collateral effects have lately become of interest to researchers (Aulin *et al.*, 2021). Negative evolutionary associations between antibiotics, known as collateral sensitivity (CS), materializes when the emanation of resistance to an antibiotic is followed by increased sensitivity to a second antibiotic (Hasan *et al.*, 2022). On the other hand, positive evolutionary associations, known as collateral resistance (CR), result in increased resistance to the second antibiotic (Rodriguez de Evgrafov *et al.*, 2021).

CHAPTER FIVE

CONCLUSION AND RECOMMENDATIONS

5.1 CONCLUSION

This research work laid focused on the synergistic relationships between silver nanoparticles and antibiotics when used in combination, against microorganisms. In this research, fresh silver nanoparticles were prepared using eco-friendly *D. edulis* leaves. The phytochemical analysis revealed the presence of alkaloids, tannins, cyanogenic glycosides, flavonoids and anthraquinones in the leaf extract. *D. edulis* leaf extract exhibited a colour change from dark brown to pale yellow with the addition of the silver nanoparticles and the colour darkened with increase in extract concentration. Synthesized silver nanoparticles showed a surface plasmon resonance band at 390 - 440 nm. Optimal parameters revealed lower concentratons of extract, temperatures between 55-75 °C, pH 7 and 90 minutes reaction time for optimal synthesis of AgNPs. XRD analysis confirmed crystalline face cenetred cubic and spherical crystals with crystallite size of 51.44 nm. SEM analysis revealed spherical particles with particle size of approximately 63 nm. FTIR analysis displayed carboxylic, hydroxyl, amine and alkyl groups characteristic of flavonoids, tannins, glycosides, alkaloids and anthraquinones present in the plant extract. This microorganisms were identified as *S. saprophyticus* and *Escherichia coli*. In silico characterization of the bacterial species revealed resistant genes and chromosomal mutations responsible for the resistance and susceptibility in culture media when AgNPs and antibiotics applied alone, and synergistic or antagonistic interactions when AgNPs were applied in combination with antibiotics.

5.2 RECOMMENDATIONS

These results implicate the need to appreciate the role of nanoparticles in combatting antimicrobial resistance. Also, with the emergence and proliferation of animal-human disease transmissions and the resultant increase in antimicrobial resistant infections, molecular surveillance using whole genome sequencing (WGS) as well as existing phenotypic surveillance provide effective tools for antimicrobial resistance surveillance (Zohra et al., 2021). WGS helps scientists to envision resistant genes responsible for bacterial resistsnce to antimicrobial agents in a time efficient and low cost manner (Moo et al., 2019). More research is required to fully understand the different cellular components in microorganisms involved during resistance and susceptibility to antibiotics. Also, molecular identification of microorganisms is very vital and should be encouraged at laboratory, research and clinical level for proper identification of microorganisms. This will aid proper infection diagnosis and targeted therapy for humans and livestock.

5.3 CONTRIBUTION TO KNOWLEDGE

(a)To the best of our knowledge, this is the first time *D. edulis* leaf extract is utilized in producing silver nanoparticles.

(b) To the best of our knowledge, this is also the first time that *D. edulis* – silver nanoparticles is being combined with antibiotics.

(c) To the best of our knowledge, this is the first time *D. edulis* synthesized silver nanoparticles is being used in combination with antibiotics against *Staphylococcus saprophyticus* and *Escherichia coli.*

(d) The genomic sequence analysis and raw reads of *S. saprophyticus* and *E. coli* have been submitted to NCBI database.

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