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Review Article

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Does manipulation of phyto-based nanoparticles is a promising solution against multi-drug resistant (MDR) pathogens? A critical opinion towards tackling MDR pathogens

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Abstract

In recent decades, microbial resistance to antimicrobial drugs has emerged as a global health crisis. Therefore, it is crucial to develop alternative therapeutic strategies to address the growing threat of multi-drug resistant (MDR) pathogens. Researchers and clinicians are increasingly focusing on plant-based products due to their antibiotic properties and lack of associated antibiotic resistance. Plant-based nanoparticles present several benefits, including their natural origin, biocompatibility, and potential for targeted delivery. Our aims in this review were exploration of the complexities and limitations of plant-based phytochemical extraction processes and addressing the challenges of synthesizing nanoparticles for combating multidrug-resistant (MDR) pathogens. It also examined the effectiveness of phyto-based nanoparticles in drug delivery systems to treat MDR infections; both alone and in combination with antibiotics, and provided a critical assessment of their potentials as a research avenue. For this, we have taken the diverse methodologies that were previously used to select the best possible process to tackle MDR pathogens using plant extracts. Although using plant-derived products and nanoparticles is a novel approach to address the antimicrobial drug resistance; however, detailed researches are necessary to explore their antibacterial attributes. Specifically, transcriptome profiling should be employed to identify therapeutic molecules from plant-based products that can effectively combat MDR bacteria before synthesis of nano-drugs. The outcomes of this study will enable the researchers to obtain the best approaches to tackle MDR pathogens through using the nano-based phytochemicals.

Keywords: Phyto-based nanoparticles, MDR pathogens, Tackling strategies, Nano drugs

1. Introduction

Antimicrobial resistance, led to at least 1.27 million deaths internationally as well as nearly 5 million casualties in 2019, which poses an immediate threat to public health. Over 2.8 million Americans suffer from antibiotic-resistant illnesses each year. Over 35,000 people have lost their lives due to antibiotic-resistance illnesses (Tenover, 2023). Microbes that are resistant to multiple antibiotics are said to exhibit multidrug resistance (MDR). Various resistance mechanisms have been identified in bacteria, including acquired resistance from other species, genetic mutations, and inherent resistance in some bacteria to specific antibiotics (Catalano, 2022). Excessive use of antimicrobial agents is driving to a rise in antibiotic resistance worldwide. This issue affects the nations at all stages of development, making resistant microorganisms difficult to treat and necessitates alternative and/or higher doses of antibiotics resulting in lack of highly effective antimicrobial treatments. The World Health Organization (WHO) has stated that MDR microorganisms, also known as "superbugs," are a major public health concern, resulting in millions of fatalities yearly (Bloom *et al*., 2018). Abuse of antibiotics causes the rise in antimicrobial resistance in bacteria, their widespread use in agriculture, and scarcity of novel medicines (Ventola, 2015). According to WHO, one of the twenty-first century's top three global public health concerns is the escalating problem of antibiotic resistance. Particularly worrisome are a group of bacteria known as ESKAPE pathogens, where each is associated with high mortality rates (Algammal *et al*., 2020). Nanotechnology and nanoparticle-engineered structures with diameters ranging from 1 to 100 nm has been developed in recent years to combat bacterial multidrug resistance (MDR) and bacterial biofilms (Horikoshi and Serpone, 2013). The threat posed by ESKAPE pathogens has been extensively studied, whereas the threat from other MDR bacterial strains has received less attention. This oversight has spurred the development of nanoparticles (NPs). These MDR bacteria's cell membrane and peptidoglycan layer are easily penetrated by NPs because of their tiny size and wide surface area to volume ratio. Since Gram-negative bacteria have a thinner peptidoglycan encapsulation than Gram-positive bacteria, NPs are more efficient against the Gram-negative pathogens (Blecher *et al*., 2011). NPs are effective treatment of infections; especially those carried on by MDR pathogens. NPs and antibiotics can be used either together or individually to provide potent synergistic effects (Mba and Nweze, 2021). The production of NPs using plant-mediated synthesis is extremely quick, easy, reliable, safe, and eco-friendly (Sani *et al*., 2022). Due to biocompatibility, safety, and environmental friendliness of this approach, there are extensive studies being conducted on the use of plant components, including extracts or essential oils from leaves, fruits, roots, stems, or seeds, for *in vitro* production of NPs (Jadoun *et al*., 2021).

Antimicrobial, antibacterial, chemotherapy for cancer, antioxidant, anti-inflammatory, and anti-diabetic properties are all present in plant-mediated metallic nanoparticles (MNPs), which also show effectiveness against genotoxicity, apoptotic alterations, and oxidative damage (Madkour, 2018). NPs have recently been widely used in bio-sensing and bio-imaging because of their remarkable localization efficacy. They are often used in biosynthesis to make it easier for medications and other molecules to reach their intended locations. Currently, NPs are under intensive examinations in anticancer researches because of their capacity to selectively target and destroy cancer cells in a controlled way; with minimum harm to the adjacent healthy cells (Charbgoo *et al*., 2017).

Antibiotic-resistant bacteria (ARB) can be effectively combated by combining MNPs with phytochemicals. Unlike the standard antibiotics, MNPs are less likely to induce resistance despite the evidence that bacteria can develop resistance strategies against them. This is attributed to the nonspecific modes of action of MNPs toward multiple cellular components (Amaro *et al*., 2021). Microorganisms that are resistant to antibiotics exhibit therapeutic potential against plant based NPs. These microorganisms include certain fungi, viruses, and bacteria such as *Escherichia coli*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* (Burlacu *et al*., 2019). Currently, we have limited antibiotic options available to tackle the MDR bacteria. Polymyxin' E' (Colistin) serves as the final option for treating infections caused by MDR bacteria, including *P. aeruginosa*, *E. coli*, *Klebsiella pneumoniae*, and *Acinetobacter baumannii*. NPs significance is heightened due to the rising prevalence of these life-threatening MDR infections globally (Sahoo *et al*., 2023). Besides immunological adaptation, resistance at the molecular level is primarily associated with chromosomal mutations and genes carried by plasmids. For millennia, the naturally occurring bioactive substances obtained from plants or bioactive phyto-compounds (BPCs) have been globally employed to tackle human health challenges. Nowadays, BPCs have become crucial strategies in the quest for discovering contemporary medications. Despite displaying promising biological activities, numerous BPCs face inherent limitations such as low solubility, structural instability, short half-life, poor bioavailability, and non-specific organ distribution; rendering them largely unsuitable for pharmaceutical therapeutic applications. For this reason, researchers have embraced newly developed nano-formulation (NF) technologies, offering potentials for strengthening the stability, pharmacokinetics, and pharmacodynamics of BPCs. Recently, green synthesis approach of silver nanoparticles (AgNPs) has been recorded as effective for development of antibacterial therapeutic applications (Vadakkan *et al*., 2024).

The objectives of this review were to highlight the use of different plant-based phytochemical extraction processes; emphasizing their complexities and limitations, and describes the various types of NPs synthesis, focusing on the challenges associated with their use against MDR pathogens. The review also discusses the challenges in drug delivery systems targeting MDR infections, evaluating whether phyto-based NPs alone are sufficient or should be combined with antibiotics for more effectiveness. Finally, this review provides a critical opinion on the suitability of phyto-based NPs as a viable option for the researchers to tackle MDR pathogens.

2. Extraction of bio-active metabolites from plants

2.1. Phytochemical's extraction and purification

Plants contain bioactive substances called phytochemicals to protect themselves. More than thousand phytochemicals have been identified, which can be obtained from various foods, including whole grains, fruits, vegetables, nuts, and herbs (Wang *et al*., 2020a). Extraction is the first step in separating and purifying the bioactive compounds from plants. While it could be difficult to extract insoluble secondary metabolites such as flavonoids and phenolic acids, certain phenolic compounds are readily extracted and soluble in water, whereas the terpenoids and alkaloids are typically more soluble in non-polar solvents (Jha and Sit, 2021). While heat reflux, maceration, and Soxhlet are all efficient methods for extracting bioactive chemicals (Fig. 1), the equipment needed for each procedure vary. Supercritical fluid, high hydrostatic pressure, ultrasonic, and pulsed electric fields are few of the cutting-edge technologies that represent swiftly outstanding traditional techniques. Higher yields and extraction rates could be achieved with creative and integrated innovative technologies. During the process of phytochemical extraction using different inorganic solvents, we need less energy that shields the loss of final extracts (Wang *et al*., 2020a). People have used plants as a therapy and treatment for various medical conditions since ancient times. Ayurvedic medicine is well-known due to its many benefits and low dangers (Khan *et al*., 2021).

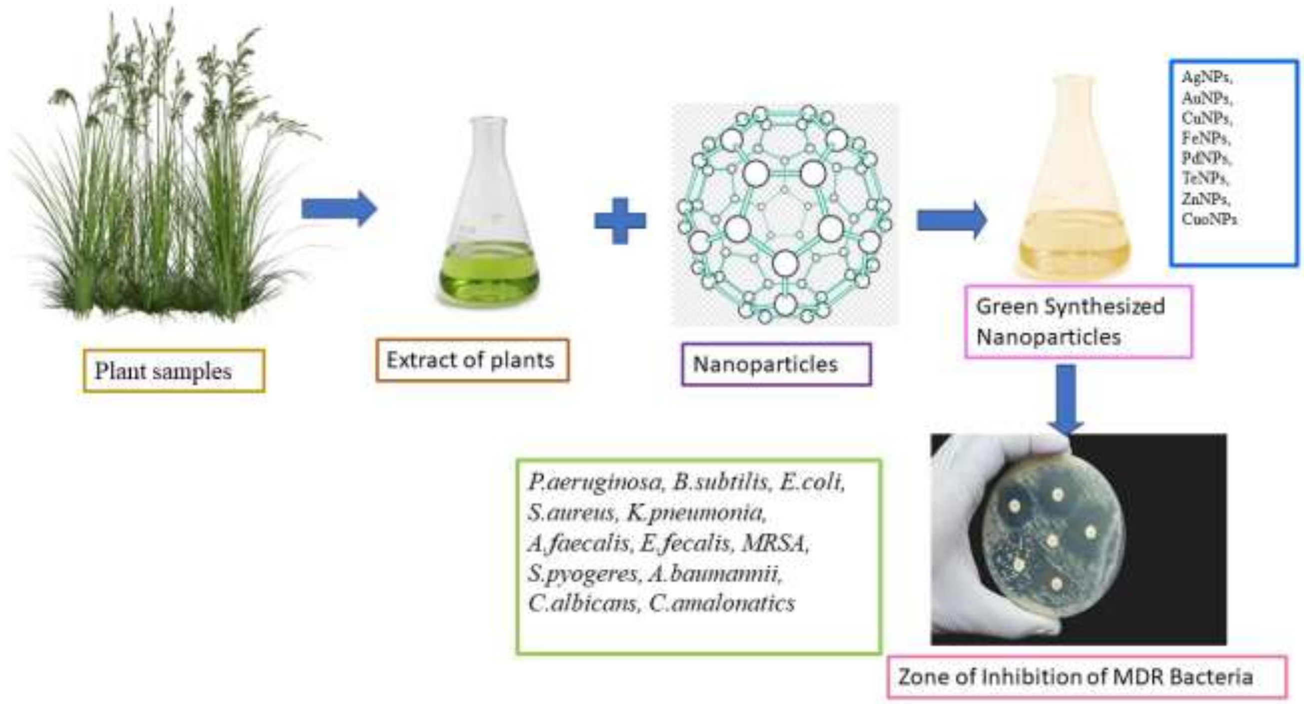

Fig. 1: Extraction of plants, synthesis of green NPs, and their effects against MDR bacteria

2.2. Bioactive phyto-components extraction methods

2.2.1. Traditional extraction methods

Extraction of bioactive compounds from plants can be achieved through advanced traditional methods, including:

Solvent extraction/ Liquid-liquid extraction

The process of separating two liquids that mix well together is known as solvent extraction. There are two different phases: an organic and an aqueous phase. For extraction, the analyte has to be dissolved in the organic phase.

For extraction, the plant or other materials to be treated; together with both of the aqueous and organic phases is held in a separating funnel, where shaking causes the liquid to divide into two layers. During liquid-liquid extraction, the analyte is separated between the two insoluble liquids depending on the soluble state in each solvent (Fig. 2) (Wells, 2003).

Solid-phase extraction

According to the chemical and physical properties of the compound in mixture, separation, purification and identification of lead molecules is carried out using the solid phase extraction process. This process is a solid- liquid extractive method, where the mixture of compounds is dissolved or suspended in the broth medium. The chemical component is eventually eluted and recovered after being bound to the solid sorbent. It is essential to gather as much analytical solute as possible in a consistent and yield-maximizing manner for solid-phase extraction to be successful (Murakami *et al*., 2020).

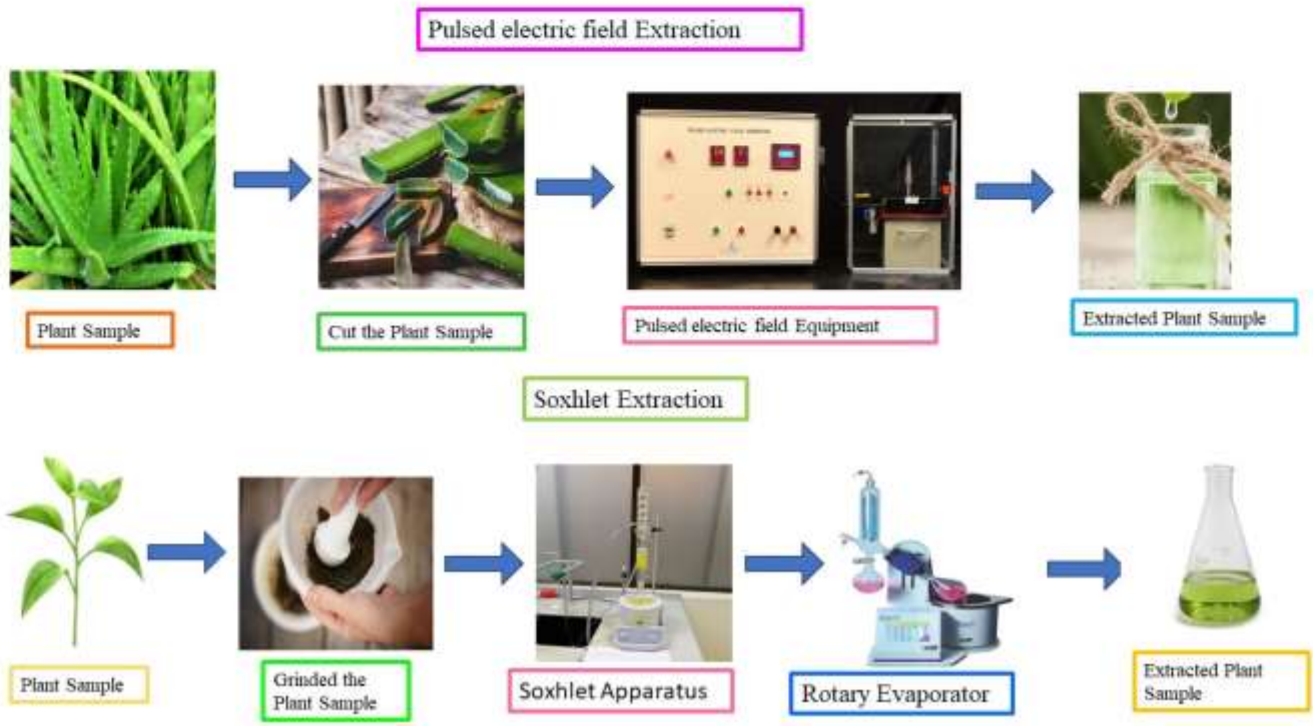

Fig. 2: Image of Soxhlet and pulsed electric field extraction processes

Solid-phase micro-extraction

Solid-phase micro-extraction (SPME) is a simple method that involves applying a sample to solid phase dispersion in a small quantity of extracting phase for a specified interval of time. According to Merkle *et al*., (2015), after being transported for gas or high-performance liquid chromatography (HPLC), the treated particles or sorbents are subjected to a sample or a target material for a particular period of time. A wide range of foods contain trace amounts of bioactive chemicals, which can be evaluated using SPME.

2.2.2. Advanced extraction methods

Ultrasound-assisted extraction (UAE)

Generating high-frequency and high-intensity sound waves to analyse their ability to interact with different materials is one of the most innovative technologies used in the United Arab Emirates. Due to the fact that it doesn't require complex instrument, UAE is a fairly priced technology that may be useful. Both local and large-scale applications are possible with this technique (Dai and Mumper, 2010). According to Jambrak *et al*., (2008), ultrasound enhances the extraction yield by releasing notable amounts of particular chemicals through enhancing mass transfer and disrupting the cellular matrix. UAE involves ultrasonic effects of acoustic cavitations. Diffusion of solutes from a solid phase to a solvent occurs rapidly due to acceleration and vibration of both solid and liquid particles caused by ultrasonic action (Fig. 3) (Cares *et al*., 2010). The ultrasonic extraction efficiency may be attributed to several techniques, including but not limited to cell rupture, more effective permeability, enhanced swelling, capillary effect, and hydration mechanism (Huaneng *et al*., 2007).

Fig. 3: Image of ultrasound assisted and microwave based extractions methodology

When the ultrasound intensity in a liquid is raised, the molecular structure breaks down and bubbles are formed, because the intramolecular forces can no longer hold the molecular structure together. This process is known as cavitation (Baig *et al*., 2010). When bubbles burst, the biological membranes are disrupted, which makes it easier for substances that can be extracted to be released, increases the amount of solvent that can enter the cellular components, and enhances the mass transfer (Metherel *et al*., 2009).

Microwave-assisted extraction (MAE)

According to several studies conducted by Hayat *et al*., (2009), the technology of microwave-assisted extraction (MAE) is useful in extracting valuable compounds from plant materials. Additionally, it functions on both small and large scales and is quite adaptable (*i.e.*, in a laboratory or an industrial setting) (Cravotto *et al*., 2008). MAE is simple-to-utilize, affordable, and an ecofriendly method for extracting the biologically active substances from various plant sources (Hemwimon *et al*., 2007). In microwave absorption, electromagnetic energy of the microwaves is converted into thermal energy by the material. Commercial microwaves typically operate at a frequency of 2450 MHz (2.45 GHz) with an energy output of 600-700 W (Jain *et al*., 2009a). In a previous study, Abu-Samra *et al*., (1975) made the first reference to using microwave radiation. In the laboratory, biological samples are prepared for metal trace analysis using an ordinary microwave oven.

Supercritical fluid extraction (SFE)

Supercritical fluid extraction (SFE) is among the most innovative techniques. It allows for extracting certain compounds from plants at room temperature without causing the material to become thermally denatured. SFE is a well-established solvent extraction method; however, as it requires expensive and complex high-pressure apparatus and technology, its commercial application is reluctant to take off (Tonthubthimthong *et al*., 2001). Due to its critical temperature of 304 °k, which makes it suitable for extracting the heat-labile chemicals, CO_2 is often the most preferred solvent in SFE. Furthermore, CO_2 is a safe solvent that doesn't burn or explode, cheap, noncorrosive, odorless, colorless, and clean. Furthermore, SFE leaves no solvent residue in the product, non-toxic, and widely recognized as a harmless ingredient in food and medicine. Moreover, CO_2 can be easily removed from the extracted oil by simply expanding it. Carbon dioxide has a low surface tension and viscosity and high diffusivity, which makes it attractive as a supercritical solvent (Handa, 2008). According to Brunner *et al*., (2005), when a fluid is heated or pressed above its critical temperature and critical pressure (Pc), it attains its critical state (Tc) (Fig. 4).

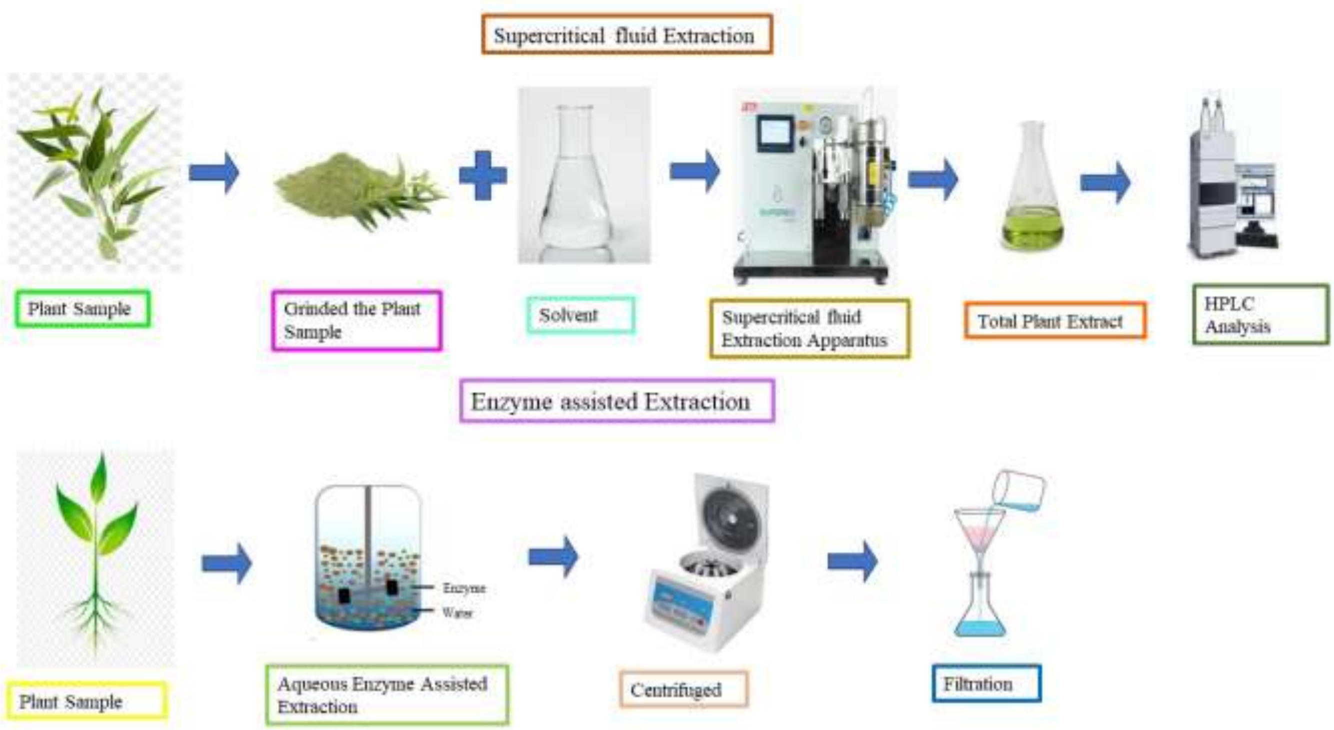

Fig. 4: Advance extraction methods as super critical fluid and enzyme assisted extraction processes

Enzyme-assisted extraction

Effective application of enzymes in extraction is another innovative technique. For extracting biomolecules from plants, enzyme-assisted extraction is becoming increasingly popular as a potential replacement for conventional solvent extraction methods, due to its safety, efficacy, sustainability, and ecological compatibility. The effectiveness of enzyme-based extraction depends on the enzymes' capacity to conduct reactions under mild conditions while retaining biological potencies of the bioactive chemicals. These characteristics include precise specificity, region-selectivity, and adaptability (Puri *et al*., 2012). The fundamental idea behind enzyme-assisted extraction is to hydrolyze plants cell wall utilizing an enzyme as a catalyst under the best possible experimental conditions, thus breaking them down and releasing the internal components. The plant cell wall attaches itself to the enzyme's active site, as a result, the enzyme conforms itself to the substrate's active site, and increases the period of contact between them. When an enzyme's shape changes, the plant cell wall's connections become broken, thus releasing the enzyme's active ingredients (Sheldon and van Pelt, 2013). Enzyme-assisted extraction usually involves carbohydrates hydrolyzing enzymes (Dehghan-Shoar *et al*., 2011).

Pulsed electric field (PEF) extraction

Electric field strengths (EFS) used in Pulsed electric field (PEF) extraction process range from 20-80 kV/ cm in continuous mode extraction and 100-300 V/cm in batch mode. There are two areas where several theories agree on the potentiality of PEF mechanism. The two processes that occur in the biological cell membrane are electroporation and acceleration of chemical reactions involving different substances to improve solvent solubility (Xi *et al*., 2021). To improve permeability of the cell membranes, a process called electro-permeabilization or electroporation, uses an external electrical force (Panja, 2018). A high-voltage electric field is applied between the electrodes and the extracted materials, such as plants. Hydrophilic gaps are created, leading to rupture of cell membrane and release of protein channels. As the plant sample is subjected to an electric field; defined as a force per unit charge, high-voltage electrical pulses are applied across the electrodes. When structural integrity of the membrane is compromised, the plant material is released (Redondo *et al*., 2018).

Soxhlet extraction

In the Soxhlet system, the plant materials are first placed in thimble part of the apparatus and then filled with fresh solvent from a distillation flask. A siphon draws the solution from the thimble-holder and returns it to the distillation flask, transferring the solutes that have been extracted into the main liquid when the liquid level exceeds it. Then, the solute is separated from the solvent by using distillation in a solvent flask. Fresh solvent returns to the plant solid bed while the solute remains in the flask. Until total extraction is accomplished, the process is repeated several times. The solvents that are generally used in the extraction method are ethanol, methanol, and water. The powder form of plant parts is extracted with a proper amount of solvents at 80 $^{\circ}$C for 8 h (Wang and Weller, 2006).

3. Plant-based nanoparticles

Nanotechnology is utilized to mitigate and suppresses multi-drug resistant (MDR) bacteria. NPs represent meticulously engineered structures with dimensions ranging from 1-100 nm. They are pivotal in many medical applications, encompassing medical instrumentation, therapeutic agents, and drug delivery systems (Horikoshi and Sarpone, 2013). Phyto-constituents produced by secondary metabolism have come from various plant parts such as flowers, shoots, bark, stems, roots, and seeds, which are easily increased and influenced by both external signals and environmental factors (Kuppusamy *et al*., 2016). Several previous studies showed that phyto-extracts could be used for safe production of NPs, due to the presence of various beneficial secondary metabolites, including saponins, tannins, flavonoids, alkaloids, steroids, terpenes, phenolic compounds, and coenzymes. For this reason, phyto-extracts act as both reducing and stabilizing agents during the production of NPs (Kuppusamy *et al*., 2016). NPs are mainly categorized into several kinds; mainly carbon-based, metal-based, ceramics, semiconductor, polymeric, and lipid-based. In this category, polymeric and metal NPs are commonly employed due to their antibacterial activities in the field of nanomedicine (Kamaly *et al*., 2016). Polymeric and metal NPs are rapidly synthesized by using phytochemicals (Pal *et al*., 2019).

Utilizing polymeric NPs produced by phytochemicals presents a promising approach for combating MDR bacteria. Examples of several polymeric NPs and their antibacterial potential are summarized in Table (1).

Table 1: Different types of polymers found in various plant leaves and their effects against different bacteria

Polymer	Plant Parts	Phytochemicals	Antibacterial activity	References
Chitosan	Leaf	Cardamom essential oil	Methicillin resistant *Staphylococcus aureus*, Extended spectrum β-lactamase, *Escherichia coli*	Jamil *et al*., (2016)
Chitosan	Leaf	*Eucalyptus globulus* leaf extract	Multidrug resistant *Acinetobacter baumanni*	El-Naggar *et al*., (2022)
Chitosan/ Hydroxypropyl methylcellulose (HPMC)	Leaf	*Schinopsis brasiliensis* leaf extract	Extended spectrum β-lactamase, *Klebsiella pneumoniae* caarbapenemase	De Oliveira *et al*., (2020)
Polylactic acid(PLA)/ Polyvinyl alcohol(PVA)	Leaf	*Pistacia lentiscus* var. *chia* essential oil	*Bacillus subtilis*	Vrouvaki *et al*., (2020)

4. Plant synthesized metal nanoparticles

Metal NPs are nanomaterials produced from pure metals such as Gold (au), copper (cu), Silver (Ag), Palladium (Pd), Iron (Fe), Zinc (Zn), Platinum (pt), and Titanium (Ti), or their compounds form like Copper oxide (Cuo), Iron oxide (Fe_3O_4), Titanium dioxide (TiO_2), and Zinc oxide (Zno), which are characterized by size dimensions ranging from 1- 100 nm. MNPs exhibit distinct physical and chemical attributes that originate from their bulk metal counterparts; primarily attributed to their reduced size and heightened surface area-to-volume ratio (Khan *et al*., 2019). Production of AgNPs using *Aloe vera* extract has demonstrated strong antibacterial activity against *K. pneumonia* (Burange *et al*., 2021). Meanwhile, production of AgNPs using *Cinnamomum tamala* leaf extract has expressed varying minimum inhibition concentration (MIC) values for Gram-negative bacteria such as *E. coli* and *K. pneumoniae* displaying 12.5 µg/ ml, and Gram-positive bacteria such as *Staphylococcus aureus* expressing 10 µg/ ml. Synthesis of AgNPs from *Cotyledon orbiculate* exhibited the highest antibacterial action against *P. aeruginosa* (Kambale *et al*., 2020). AgNPs synthesized from *Mespilus germanica* extract have antibacterial, antibiofilm, and anti-quorum sensing activities against the MDR bacteria such as *K. pneumoniae*. Silver NPs have been biosynthesized using *Stenocereus queretaronesis*, which exhibited a notable antibacterial activity against methicillin-resistant *Staphylococcus aureus* (MRSA). AgNPs produced using *Syzegium cumin* leaf extract have shown outstanding antibacterial potentials against *Staphylococcus aureus* strain resistance to methicillin and vancomycin. The remaining phytobased NPs and their antibacterial activity are mentioned in Table (2).

5. Types of plant-synthesized metal nanoparticles

5.1. Gold nanoparticles

Plant, fungi, bacteria, actinomycetes, algae, and other microorganisms can all be used in green synthesis of AuNPs, which is an economical, biocompatible, and environmentally beneficial method (Kumari *et al*., 2023). Many physical and chemical methods have limited use in AuNPs production and biomedical application due to their high energy consumption and production of vicious by-products (Rudrappa *et al*., 2023). Throughout the duration of green synthesis, a variety of phyto-compounds, including phenolics, terpenoids, flavonoids, and alkaloids, help to reduce and stabilize the metal ions (Khanna *et al*., 2019). Green synthesis of AuNPs produces materials with unique chemical and physical properties such as high surface area-to-volume ratio compared to bulk materials of similar composition. These NPs have a wide range of applications, including drug delivery, catalysis, antibacterial, antimicrobial, and anticancer (Sathishkumar *et al*., 2016). The morphology of AuNPs such as size and form that is important in variety of applications can be controlled using a green strategy (Kumari *et al*., 2023). Plant extract used as a reducing and stabilizing agent is combined with Au metal precursor solution to create AuNPs. There are 3 steps of AuNPs synthesis; mainly reduction, nucleation, and growth of the crystal nuclei (Ahmad *et al*., 2021). The precursor is decreased during the first phase; known as reduction, while the number of Au atoms increases steadily in the second phase (nucleation) (Wu *et al*., 2022). When the concentration of Au atoms falls below the critical super saturation level, Au atoms begin to form crystal nuclei. However, if the concentration has remained below saturation, Au atoms do not form crystal nuclei, resulting in the formation of pure AuNPs (Balkrishna *et al*., 2024) (Fig. 2).

5.2. Nano-silver

Each approach to make NPs has benefits as well as drawbacks. Biological synthesis is environmentally sustainable, cheaper, and can be readily scaled up for enormous scale production of NPs (Ahmed *et al*., 2017). The biological approach is cost effective, cleaner, nontoxic, biocompatible, and frequently single-step method that uses biomolecules such as proteins, enzymes, and DNAs found in algae, fungi, microbes, and plants as well as secondary metabolites (*i.e*., terpenes, phenolics, carbohydrates, flavonoids, etc.) as reducing, capping, and stabilizing agents (Rana *et al*., 2020). A unique nucleation site is provided a by biomolecule-driven synthesis (*i.e*., Proteins, DNA, and enzymes) during synthesis of NPs, leading to the formation of uniformly sized particles with a broad range of biomedical applications, which are selective and sensitive to bio-molecular targets (He *et al*., 2022). However, these methods are highly sensitive to external factors such as temperature (Ocsoy *et al*., 2018). The size of manufactured AgNPs is additionally influenced by the molar ratio of silver salt and biomolecules. Both protein and DNA-mediated AgNPs have expressed sensing applications on spike proteins and demonstrated strong antibacterial activity (Poudel *et al*., 2022). In the field of nanotechnology, the bio-production of functional NPs that is both nontoxic and biocompatible is essential (Nasrollahzadeh *et al*., 2019). Various plant secondary metabolites function as agents that reduce, stabilize, and cap the NPs. The form, size, and production of AgNPs are determined by the distinct classes of secondary metabolites that each plant produces based on its capacity to donate electrons for the reduction of Ag^+ ions to Ag^0 (Wink, 2020).

Table 2: List of plant based nanoparticles, plant sources, and their antibacterial potentials

Plants name	Nanoparticles used	Plant parts used	Antimicrobial activity against	References
Justicia Adhatoda L.	AgNPs	Leaves	*P. aeruginosa*	Bose and Chatterjee, (2015)
Carica papaya L.	AgNPs	Fruit and leaves	*E. coli* and *P. aeruginosa*	Jain *et al*., (2009b)
Artemisia nilagirica	AgNPs	Leaves	*Staphylococcus aureus, B. subtills, E. coli*	Vijayakumar *et al*., (2013)
Trianthema decandra	AgNPs	Roots	*P. aeruginosa* and *E. coli*	Geethalakshmi and Sarad., (2010)
Emblica officinalis	AgNPs	Fruit	*Staphylococcus, B. subtilis, E. coli, K. pneumonia*	Ramesh *et al*., (2015)
Cleome viscosa	AgNPs	Fruit	*Staphylococcus aureus, B. subtilis, E. coli, K. pneumonia*	Lakshmanan *et al*., (2018)
Anabaena spiroides	AuNPs	Leaves	MDR *(Klebsiella oxytoca, Streptococcus pyogeres,* Methicillin-resistant *Staphylococcus aureus*)	Mandhata *et al*., (2021)
Punica granatum	AuNPs	Leaves	Methicillin-resistant *Staphylococcus aureus*	Hussein *et al*., (2021)
Moringa oleifera	FeNPs	Leaves	*E. coli, S. typhae, Staphylococcus aureus*	Aisida *et al*., (2020)
Eichhornia crassipe	FeNPs	Leaves	*P. flurescens* and *Staphylococcus aureus*	Jagathesan and Rajiv, (2018)
Sageretia thea	FeNPs	Leaves	*E. coli, B. subtilis, P. aeruginosa, K. pneumonia, Staphylococcus epidermidis*	Khalil *et al*., (2017)
Punica grantum	FeNPs	Leaves	*P. aeruginosa*	Khan et al., (2017)
Cynometra ramiflora	FeNPs	Leaves	*S. epidermidis, E. coli*	Groiss et al., (2017)
Lantana camara	FeNPs	Leaves	*K. Pneumoniae, Pseudomonas* and *Staphylococcus*	Singh et al., (2020)
Skimmia laureola	FeNPs	Leaves	*Ralstonia solanaceae*	Alam *et al*., (2019)
Padina boryana	PdNPs	Leaves	*Staphylococcus aureus, E. fergusonii P. aeruginosa*	Sonbol *et al*., (2021)
Aloe vera	TeNPs	Leaves	Methicillin-resistant *Staphylococcus aureus,* Multidrug resistant *(E. coli)*	Medina-Cruz *et al*., (2021)
Syzygium cumini , *Prunus africana*	ZnONPs	Flower	Carbpenem resistant *E. coli, K. pneumoniae,* Methicillin-resistant *Staphylococcus aureus*	Ssekatawa *et al*., (2022)
Acacia nilotica, *Bougainvillea*	ZnONPs	Flower	*K. pneumoniae* carbapenemase, Methicillin-resistant *E .coli*	Rasha *et al*., (2021)
Phyllanthus reticulatus	CuONPs	Leaf extract	*E. coli*	Potbhare *et al*., (2019)

When creating NPs, reaction time has an essential role as it enables the salt and the reducing complex components in the extract to interact properly (Barzinjy *et al*., 2023). Plants having higher levels of phytochemicals or secondary metabolites are better for reducing a salt (Sytar *et al*., 2018), while plants that have less reduced chemicals, on the other hand, take longer time to reduce a salt (Acosta-Motos *et al*., 2017). A number of variables, including the reaction mixture's acidity or basicity, temperature, the plant extract's reducing power, light intensity, enzymes, and secondary metabolites, can affect how long a reaction takes (Lade and Patli, 2017). By varying the proportion and ratio of plant extract and precursor utilized, AgNPs size and shape can be designed. AgNPs biosynthesis through using a capping agent as ascorbic acid and a reducing agent as a cylindrical plant extract, gives a quasi-spherical shape (Omran *et al*., 2021). According to their findings, increasing the concentration of $AgNO_3$ (from 0.5 to 0.9 mM) has made a bigger particle size (32.7 to 39.9 nm), which has been obtained by maintaining ascorbic acid and the extract concentration at similar levels (Ansari *et al*., 2023). Additionally, they discovered a narrower absorption peak at 0.5 mM $AgNO_3$ indicating a smaller size distribution (Htwe *et al*., 2019). Aqueous extracts from *Piper betle* L. leaf were used in creating AgNPs and the most favorable circumstances were obtained by experimenting using different concentrations of $AgNO_3$ (1, 2, 3, and 4 mM) and crude extract dilution ratios of 1:2, 1:4, and 1:8 (Nguyen *et al*., 2021). According to their findings, the best outcomes were obtained with 2 mM of $AgNO_3$ and a 1:4 extract dilution ratio. As the $AgNO_3$ concentration has increased, larger NPs are produced by shifting the UV-vis peak to higher wavelengths (Khan *et al*., 2020). AgNPs' application to enhance soil quality, pesticide function, and plant development could considerably assist the agricultural sector, as current estimates take into account the requirement for major augmentation in agricultural productivity for the coming thirty years (Ansari *et al*., 2023).

5.3. Copper nanoparticles

The electrical, mechanical, magnetic, resistance, conductivity, and thermal properties of CuNPs have drawn attention of the general public (Kute *et al*., 2022). These properties have led to several applications such as heat transfer system, water treatment, and antimicrobial coating for surgical instruments (Manjula *et al*., 2022). To attain the required copper concentration, the herb extract has been combined with the copper precursor, where the literature has indicated a wide variety of precursor concentrations (Antonio-Pérez *et al*., 2023). For example, concentrations of 10-250 mM $CuCl_2$, 0.1-100 mM $CuNO_3$, 3-500 mM $Cu(CH_3COO)_2$, and 1-1000 mM $CuSO_4$ have all been examined (Antonio-Pérez *et al*., 2023). Fourier-transform infrared spectroscopy (FTIR) investigation revealed that unlike chemical synthesis, reduction reaction of metal ions such as copper to NPs is independent of a single biomolecule, which raised several questions about the involvement of plant extracts in the production of CuNPs (Husen and Iqbal, 2019). Depending on makeup of the chosen plants, different biomolecules such as alkaloids, phenols, organic acids, and proteins have been involved in green synthesis of CuNPs (Basumatary *et al*., 2024). A study on the phytochemical analysis of an extract of *Ageratum houstonianum* leaves was carried out in 2020 by Chandraker *et al*., (2020), where FTIR studies indicated that this group of chemicals plays a major role in CuNPs synthesis. Except for a few instances, including those of CuNPs made from leaf extracts of *Hagenia abyssinica*, which have produced hexagonal, spherical, prismatic morphologies, and triangular cylindrical shapes; however, the most common reported morphology of CuNPs is spherical (Antonio-Pérez *et al*., 2023). In particular, CuNPs synthesized from *Falcaria vulgaris* extracts have demonstrated a variety of functions, including antioxidant, antifungal, and antibacterial activity, and have the ability to cure cutaneous wounds without causing cytotoxicity (Hurtado *et al*., 2022). One of their main benefits is the fact that the precursors of CuNPs produced by green synthesis have made them inexpensive, non-toxic to humans, and easily tuned (Yazdanian *et al*., 2022). These CuNPs can be employed as antioxidants, anticancer, antimicrobial, and antibacterial agents, due to their ability to interact with various biological systems (Maliki *et al*., 2022).

5.4. Nano-platinum

Numerous primary and secondary metabolites found in plant extracts may operate as organic reducing and capping agents (Abada *et al*., 2023). Biosynthesis of MNPs from a plant extract is a quick and easy procedure that involves combining the metal ions solution and plant extract at the ideal pH and temperature (Prabakaran and Rajan, 2021). The morphology, average size, and surface charge of MNPs should be controlled by optimizing a number of variables, including pH, temperature, and contact duration (Wang *et al*., 2020b). Four main steps make up the mechanism of PtNPs green synthesis: (i) bio-reduction; the first activation step that reduces the metal ions to their zero-oxidation states (Fahmy *et al*., 2020), (ii) agglutination of the small NPs into larger ones making more stable particles according to thermodynamics (Yeap *et al*., 2017), (iii) termination, which involves stabilizing and capping the MNPs to form NPs with a variety of morphologies and average sizes (Fahmy *et al*., 2020), and (iv) the last step, purification and washing of the MNPs typically by centrifugation (Fahmy *et al*., 2024). Furthermore, several analytical techniques, including FTIR, scanning electron microscopy (SEM), UV/Vis spectrophotometry, powder X-ray diffraction (XRD), dynamic light scattering (DLS), and transmission electron microscopy (TEM), have been used to characterize the fabricated MNPs in general and PtNPs in particular (Mitić *et al*., 2017). Plant extracts have long been regarded as safe, environmentally benign, and biocompatible method for producing green PtNPs. The present risky and multi-step synthetic processes have been replaced by photosynthesis of PtNPs (Dheyab *et al*., 2024). Applying green strategies utilizing plants and plant extracts is the subject of few investigations. In one investigation, Pt (IV) ions have been incubated with *Azadirachta indica* leaf extract for 1 h at 100 $^{\circ}$C. The reducing and capping agents are represented by the terpenoids that exist in the leaves of *A. indica* (Dutt *et al*., 2023). To increase the PtNPs monodispersity, they have been sonicated for 30 min. (Thirumurugan *et al*., 2016). To biosynthesize spherical PtNPs, Yang *et al*., (2017) employed *Mentha piperita* (peppermint) leaf extract, and performed the bio-reduction at 60 $^{\circ}$C for 90 min. Tahir *et al*., (2017) used *Taraxacum laevigatum* plant extract to create a simple process for the manufacture of spherical PtNPs. For 10 min., bioreduction was conducted at 90 $^{\circ}$C. Ultimately, gum extract from *Prudus x yedoensis* has been used to create environmentally beneficial PtNPs. The gum extract concentrations of 7 % and 8 % have been used in the reaction conditions that are tuned at pH 8 for 30 min. (Velmurugan *et al*., 2016).

6. Challenges in design of nanoparticles

6.1. Challenges in designing nanoparticles from plants

Numerous studies have concentrated on locally accessible plants, where a wide variety of plant materials are available for eco-friendly synthesis of NPs (Behzad *et al*., 2021). Utilizing the surrounding plants to maximum extent has also been the aim of the green production of CuNPs, AuNPs, NZVI, and Iron oxide NPs (Ruttkay-Nedecky *et al*., 2017). Although pepper mint is native to central and west Asia, fenugreek is used in the synthesis of AuNPs in widely grows of China and along the eastern Mediterranean Coast (Sharma *et al*., 2023). Although other materials such as psoralen can also be used to create Fe_2O_3NPs; however, these materials are primarily found in Sri Lanka, India, and Myanmar (Ying *et al*., 2022). The Ardean blackberry (*Rubus glaucus* Benth), which is mainly found in Colombia, Ecuador, and the Andes of central and south America is used in the synthesis of CuNPs (Kumar *et al*., 2017). Therefore, it is crucial to look into the possibilities of utilizing local plants to produce nano-scaled metals on a large range when choosing synthetic materials (Mitchell *et al*., 2021). It is also challenging to use raw materials for production of NPs when one is short on time. Cotton leaves during the flowering season (Altabbaa *et al*., 2023) or *Sargassum fusiforme*; whose growing season varies greatly from region to region, must provide the ingredients needed to green synthesize AgNPs (Kamaraj *et al*., 2023). Tea extract is used to produce nano-scale zero valent Iron (NZVI) directly from pure tea polyphenols, but the extraction and purification processes are prohibitively expensive (Wang *et al*., 2017a). Carboxymethyl cellulose and cellulase methyl carboxylate are two ecofriendly plant products used for creating PdNPs; however, although cellulose is an ecofriendly raw material, it requires a carboxymethylation process, which uses materials from other plants such as sago pulp (Oyewo *et al*., 2020). Reagents such as sodium hydroxide and sodium mono chloroacetate are used to improve NPs synthesis process, but they may not be compatible with green synthesis (Saputra *et al*., 2014). Despite these challenges, cellulase remains an ecofriendly alternative to synthesis PdNPs (Kamel and Khattab, 2021).

6.2. Challenges in designing synthetic nanoparticles

The main issues with NPs synthesis processes involve the need for additional industrial chemical reagents, excessive energy consumption, and lengthy reaction time (Sheldon, 2012). AgNPS have been made from the leaf and root extract of *Ferula persica* in a 3 h process at 600 °C, whereas CuNPs can be synthesized using guava fruit extract in 800 °C water bath (Wang *et al*., 2017b). CuONPs can be synthesized using ultrasonic stirring for 2 h at 80 °C, which is preferable than the chemical synthesis method (Sharma *et al*., 2023). This means that some green synthesis processes must be run for extended periods of times at very high temperatures and consume a lot of energy that may be harmful to the atmosphere (Shafey, 2020). Despite using ecofriendly raw materials, the process doesn't always adhere to the idea of "green synthesis (González-Ballesteros and Rodriguez, 2020). The brown algae *Cystoseira baccata*, which requires a lot of energy, is used to produce AuNPs at 24 °C, and it is also advisable to store the plant extract at low temperatures (Sampath *et al*., 2022). In order to function at this low temperature energy, intensive equipment such as freezers are needed. It is, therefore, optimal to produce nano-sized metals at room temperature as this simplifies the synthesis process and conserves energy (Bharali *et al*., 2023). The right time to react should be brief because the production costs and efficiency are related. Microwave radiation is necessary to synthesize CuNPS using coffee powder extract. After 3 h of boiling, it is dried for 4-5 h in a hot air oven (Ying *et al*., 2022). However, centrifugation, continuous heating at 60 °C for 1 h, stirring for an extra 30 min., and heating for an additional hour are all are needed conditions to create nano-sized metal oxides using the sol-gel method (Aragaw *et al*., 2021). MNPs are oxidized readily in the air. The disruption of 3-D symmetry and high surface area-to-volume ratio can significantly affect NPs surface coordination. For this reason, chemically inert metals can be oxidized even under mild stress conditions. Therefore, synthesis under inert conditions is described in some published reports to protect MNPs from oxidizing. The difficulty of identifying a precise chemical reaction to describe the synthesis process and lack of knowledge about the biosynthesis mechanism are two other major barriers of green biosynthesis (Santhosh *et al*., 2022). Pomegranate extract (*Punica granatum* L.) peels, for example, can be used as an end capping agent during the green synthesis of ZnO/ Cu_2O/ CuO/ Cu nanostructures. AgNPs can be synthesized using root extract of *Zingiber officinale* and *Sagenetia thea* (Osbeck) acting as occlusive and reducing agents, which can also be used as chelating agents during the synthesis of Fe_2O_3NPs (Javed *et al*., 2023).

6.3. Nanoparticles quality

The qualities of green synthesized NPs produced by various plant extracts are inadequate and their sizes and forms are highly varied. Significant variations in particles size are reported in the current study, which means that green technology is not appropriate for large-scale production of NPs and that managing particles size throughout the production process is significantly difficult. Nano-scale zero valent iron NPs (NZVI-NPs) made from grape seeds have ranged in particle size from 63 to 381 nm (Gao, 2016), whereas AgNPs made from *Nigella arvensis* leaves have ranged in size from 5 to 100 nm (Chahardoli *et al*., 2018). According to SEM analysis, the particle sizes of AuNPs synthesized from *Pistacia integerrima* gall, aqueous *Elaise guineensis* (oil palm), and *Galaxaura elongate* extract varied also significantly, having sizes that ranged from 13 to 97 nm, 2 to 100 nm, and 20 to 200 nm, respectively (Abdel-Raouf *et al*., 2017).

7. Challenges in use of nanoparticles as drug delivery systems against MDR

Based on advanced technology, drug delivery systems (DDS) prepare and store drug molecules in forms appropriate for therapy, including tablets, liquids, and/or other formulations. These systems expedite the delivery of medications to the precise intended site within the body, and optimize the therapeutic efficacy while minimizing the risk of off-target accumulation (Vargason *et al*., 2021). Due to their enhanced systemic circulations and abilities to regulate the drug's pharmacological impact, DDS have been successfully used in treatment of various illnesses and enhancement of overall health. The concept of controlled NPs release has emerged, as advances in pharmacology and pharmacokinetics highlighted the importance of medications release timing in achieving therapeutic success (Verma and Garg, 2001). As in this emerging science era of nanotechnology; it is considered as a good supplier/ provider/ trader of particles ranging in size from 1 to 100 nm that are otherwise known as NPs (Griffin, 2019). The most commonly used NPs are usually biologically processed and have a much better antibacterial effects than the chemically synthesized NPs, and they are specifically used against MDR (Alavi and Raj, 2019). The potential breakthrough to combat antibiotic-resistant microorganisms comes from advanced nanotechnology. In the process of causing bacterial cell death, NPs attach to the bacterial surfaces and break down their cell walls (Wang *et al*., 2017b). It is currently determined that NPs size smaller than 20 nm may enter the bacterial cells and break down their cell walls, disrupting their metabolic processes, and eventually causing death of the bacteria (Arakha *et al*., 2015). Due to its high therapeutic index and efficacy against microorganisms, nanotechnology represents a viable therapeutic approach (Hussain *et al*., 2018). Many bacterial infections may be effectively treated using NPs; particularly when MDR pathogens are involved. When employed alone or combined with antibiotics, NPs have strong synergistic effects. Promising future approaches include nanomaterials that can distribute and release drugs more effectively and react to various endogenous and external stimuli to kill the pathogens (Qiu *et al*., 2018). *Enterobacter* sp. and *P. aeruginosa* are two bacterial spp. that AgNPs have been shown to effectively combat them in urinary tract infections (UTIs) (Jacob Inbaneson *et al*., 2011). Consequently, nano-composites could be useful in many biological applications. Through utilizing a unique bioactive nanostructure with silica-titania sieves acting as carriers, a new antibacterial agent called izohidrafural has been employed. These NPs effectively inhibit the growth of two uropathogens; mainly *K. pneumoniae* and *Proteus mirabilis* (Al Tameemi *et al*., 2017). The leaves of *Berberis aristata* have been utilized to produce ZnONPs, demonstrating significant antibacterial efficacy against clinical isolates of UTIs (Chandra *et al*., 2019). *Candida albicans* has been effectively targeted using AgNPs derived from *Mentha piperita* ethanol extract, which proved to be more effective (Robles-Martínez *et al*., 2020).

8. Phyto-based nanoparticles alone or in combination with antibiotics acting against MDR pathogens

Previous studies expressed that the association of phytochemical-based NPs with antibiotics showed a better impressive results than other forms of phyto-based NPs and antibiotics. Synthesis of phyto-based (*Fagonia indica*) AgNPs that have been combined with the antibiotic Ciprofloxacin resulted in expression of remarkable antibacterial activity against *E. coli*, *Citobacter amaonticus*, and *Salmonella* spp. However, it is noteworthy to recognize the synergetic interaction between AgNPs and antibiotics (Adil *et al*., 2019). The *Zea mays* leaf-based AgNPs combined with two antibiotics such as Kanamycin and Rifampicin, displayed antibacterial activity against 5 strains of bacteria; mainly *Bacillus aureus*, *Listeria monocytogenes*, *Staphylococcus aureus*, *E. coli*, and *S. typhimurium* (Patra and Baek, 2017). Combining phyto-based MNPs with antibiotics seems as a promising approach to fighting MDR bacteria by reducing their resistance and harmful effects (Ruddaraju *et al*., 2020). During the production of AgNPs, choosing eco-friendly methods of green synthesis and considering the use of suitable solvents and chemicals increases the potential of AgNPs to combat microorganisms, thus acting as effective antimicrobial agents (Kaweeteerawat *et al*., 2015). A better activity is obtained when the antibiotic Lincomycin has been combined with AUNPs produced using leave extract of *Piper guineas* (Shittu *et al*., 2017).

Conclusion

Uprising of MDR bacteria has made treating the infectious diseases more difficult by reducing the efficacy of antibiotics and affecting treatment failure rates as well. Phytochemicals are excellent key players in altering the drug resistance of bacteria by killing bacteria or interfering with their pathogenicity. Notably, many plants exhibit inhibitory actions against efflux pumps. The use of edible plants to synthesize NPs is growing in popularity. Although there are multiple challenges associated with the design, selection of type, challenges in delivery system, maintenance of the quality of plant based NPs; however, we found that they have the potential to affect the MDR pathogens both alone and in combination with antibiotics. Propagation of the bacterial class-specific tolerance often requires several genetic elements, including plasmids, transposons, insertion sequences, and integrative conjugative elements. In addition to mutations, bacteria carrying resistance genes are more likely to proliferate and endure in unfamiliar environments. The potential of plant-derived NPs to suppress infections is being evaluated, which is essential in the fight against MDR illnesses. It is important to analyze the plant derived NPs composition to facilitate the effective utilization of medicinal plant extracts in future works. However, the complexity of therapeutic plant extracts presents a challenge; particularly in addressing the impact of antagonism and/or synergism.

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Author's Contributions

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