Science of the Total Environment 821 (2022) 153472

Contents lists available at ScienceDirect

Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv

Review

Safer plant-based nanoparticles for combating antibiotic resistance in bacteria: A comprehensive review on its potential applications, recent advances, and future perspective

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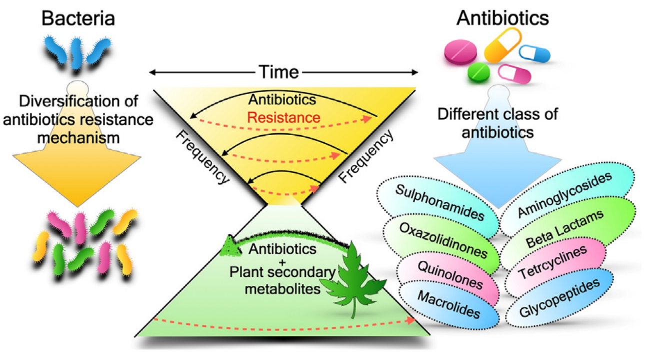
HIGHLIGHTS

- Plant-based NPs have advantages and applications in the field of medicine and the pharmaceutical industry.
- NPs can exert antimicrobial properties alone or in combination with antibiotics.
- Need to assess the safety of its use and diminish the environmental impact of their synthesis.
- Studies of the action mechanisms that mediate the antibacterial effect of NPs are necessary.
- They are a realistic strategy for satisfying society's demand for an effective solution against antibiotics resistance.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 21 October 2021
Received in revised form 22 January 2022
Accepted 24 January 2022
Available online 29 January 2022

Editor: Yolanda Picó

ABSTRACT

Background: Antibiotic resistance is one of the current threats to human health, forcing the use of drugs that are more noxious, costlier, and with low efficiency. There are several causes behind antibiotic resistance, including overprescription of antibiotics in both humans and livestock. In this scenario, researchers are shifting to new alternatives to fight back this concerning situation.

Scope and approach: Nanoparticles have emerged as new tools that can be used to combat deadly bacterial infections directly or indirectly to overcome antibiotic resistance. Although nanoparticles are being used in the pharmaceutical industry, there is a constant concern about their toxicity toward human health because of the involvement of well-

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Abbreviations: NPs, Nanoparticles; AgNPs, Silver nanoparticles; MDROs, Multidrug-resistant organisms; IONPs, Iron oxide nanoparticles; IC_{50}, Half-maximal inhibitory concentrations; NiNPs, Nickel nanoparticles; AuNPs, Gold nanoparticles; HIV, Human immunodeficiency viruses; EOs, Essential oils; ARB, Antibiotic resistant bacteria; ARGs, Antibiotic resistance genes; ROS, Reactive oxygen species; ATP, Adenosine triphosphate; Amp-AgNPs, Ampicillin nanoparticles; NOCs, Organic carbon-based nanoparticles; SCCs, Silver carbene complexes; PVDF, Polyvinylidene fluoride; SLNPs, Solid lipid nanoparticles; ACE2, Angiotensin-converting enzyme 2; DDD, Antibiotic-defined daily dose; HGT, Horizontal gene transfer.

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http://dx.doi.org/10.1016/j.scitotenv.2022.153472

Keywords:
Plant-derived nanoparticles
Antibiotic-resistant bacteria (ARB)
Nanoparticles and their applications
Environmental and health impact
Nanoparticles toxicity/nanotoxicology
Global economies and public health

known toxic chemicals (i.e., sodium/potassium borohydride) making their use very risky for eukaryotic cells.
Key findings and conclusions: Multiple nanoparticle-based approaches to counter bacterial infections, providing crucial insight into the design of elements that play critical roles in the creation of antimicrobial nanotherapeutic drugs, are currently underway. In this context, plant-based nanoparticles will be less toxic than many other forms, which constitute promising candidates to avoid widespread damage to the microbiome associated with current practices. This article aims to review the actual knowledge on plant-based nanoparticle products for antibiotic resistance and the possible replacement of antibiotics to treat multidrug-resistant bacterial infections.

Contents

1. Introduction

Nanotechnology constitutes an emerging science proceeding from nature, which can be considered a supplier of different particles ranging from those derived from inorganic soot, ash, and minerals to sulfur and selenium nanoparticles (NPs) produced by many bacteria and yeasts (Griffin et al., 2018) or cellulose that is present in wood, hemp, cotton, and other plant-based materials (Hitam and Jalil, 2022), including propolis that consists of resinous exudates from various plant parts which are collected by bees, transported to hives, and then modified with bee enzymes (Tiri et al., 2022). In addition to these naturally occurring particles, the possibility of creating NPs has been known for decades now, with the quantity and variety of methods increasing year after year. Fig. 1 shows the NPs currently used as drug delivery systems. Currently sold nanostructures include liposomes and lipid NPs, polyethylene glycated polymer nanodrugs, other polymers, nanocrystals, protein and metal-based NPs (Farjadian et al., 2019; Mitra et al., 2022). Metals NPs, such as nanosilver or nanogold of various shapes and sizes, were created by methods such as laser ablation, during vacuum sputtering, chemical reduction, photochemical reduction, microwave irradiation (Kowalska-Góralska et al., 2010), gamma and electron irradiation, thermal decomposition of silver oxalate in water and in ethylene glycol, and biological synthetic methods (Iravani et al., 2014). However, physical and chemical methods of synthesizing NPs are costly and environmentally toxic. Thus, there is a need to produce NPs using nontoxic, environmentally friendly, and reliable methods to expand their use. The best option to achieve this goal is to use biological entities such as plants and microorganisms (Nayantara and Kaur, 2018) which can be a good strategy especially for remediating metal contaminants and waste (Iravani, 2014).

In the biological synthesis of nano-elements, strictly controlled parameters during the processes are important, including the choice of the biological source, incubation period, pH, and temperature (Iravani, 2011; T. Khan et al., 2019; Mirzaei and Darroudi, 2017; Mittal et al., 2013; Singh et al., 2016). For example, pH played an important role in controlling the size of NPs (Sathishkumar et al., 2010) and, in general, green-based synthesis methods, including plant-based ones, can provide NPs with controlled size and morphology (Mirzaei and Darroudi, 2017). Furthermore, the biological synthesis of metallic NPs is an inexpensive, one-step and environmentally friendly method (Kuppusamy et al., 2016) and seems to be developing in the future (Mirzaei and Darroudi, 2017), especially with the great hope placed on nanoparticles produced with the participation of plants.

The so-called green nanotechnology is gaining great interest in pharmacy and medicine (Griffin et al., 2018) as it uses, for example, plants that are convenient ‘eco-friendly nano-factories’ (Nayantara and Kaur, 2018) and encourage their deeper exploration to meet the demand for nano-products in various fields (Singh et al., 2016). According to the previous literature, most reports on the production of green NPs have focused on the green biosynthesis of silver nanoparticles (AgNPs). This environmentally friendly technique involves the use of biological agents, especially plants, as reducing and encapsulating agents. For example, AgNPs synthesized by green chemistry are a new and potential alternative to chemically synthesized NPs (Roy et al., 2019). Therefore, this is the simplest method to create conditions for spontaneous creation of NPs inside living organisms, including plants and even diatoms (as in phyco-nanotechnology (Griffin et al., 2018; Iravani, 2011) with their nanopatterned silica-based cell walls (biosilica) that, when modified in vivo and along with potentially low culturing costs (Malabadi et al., 2012), make them an attractive raw material for industrial applications, and thus are a promising source of synthesis of ‘green’ material (Pytlik and Brunner, 2018)). In the case of ‘green’ synthesis, most of the costs will be supported solely by the cost of the metal salts, as, for example, vegetable waste from the food industry can serve as reducing agents (when chemical synthesis is used, there are also other costs for reducing agents). Thus, it is also conceivable that companies involved in the food industry and interested in recycling waste will partially pay for the production of NPs, which also highlights the environmental benefits of ‘green’ synthesis compared to traditional methods of production (Makarov et al., 2014).

Interestingly, NPs naturally obtained are surrounded by capping layers and seem to be more stable and biocompatible (Kowalska-Góralska et al., 2010; P. Singh et al., 2018), which is of the utmost benefit to the use of this method (Vilando et al., 2019) and thus also supports the use of plants in the production of nanoparticles. These capping layers provide an active surface for interaction with biological components. Their free active surface functional groups are available for modification, such as conjugation with antimicrobial drugs, genes, and peptides, to increase their efficacy and delivery (P. Singh et al., 2018). A comparison of NPs formed by biological and chemical processes has shown that biogenic NPs (formed in living organisms, including plants) have a better antibacterial effect than chemically

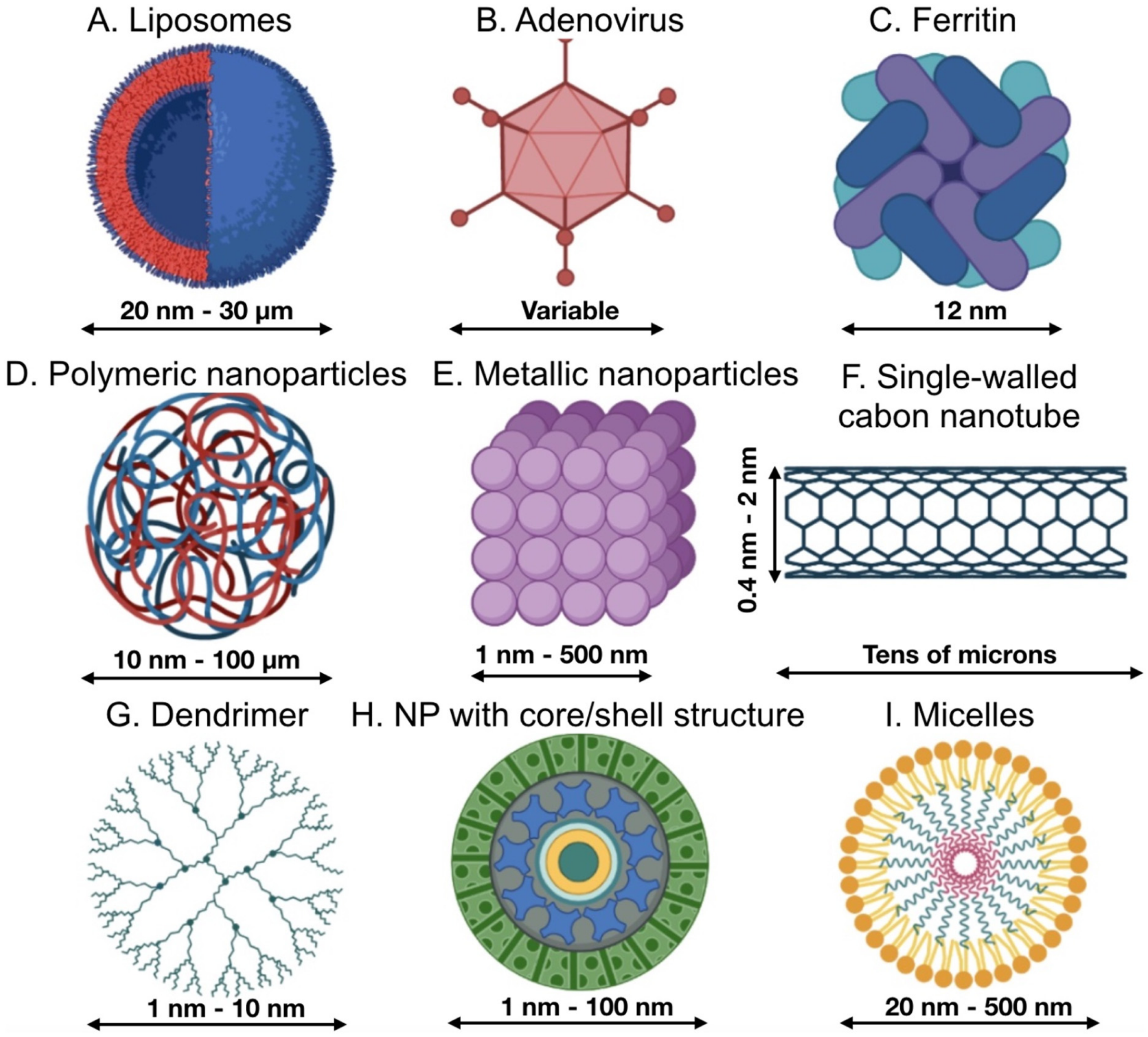


Fig. 1. Nanoparticles used as drug delivery systems: A. Liposomes. B. Viral vector. C. Self-assembled proteins. D. Polymeric nanoparticle. E. Metallic nanoparticle. F. Single-walled carbon nanotube. G. Astruc's 54-ferrocene dendrimer. H. Coated magnetic NPs with core/shell structure. I. Micelle formulation. Figure adapted from (Beltrán-Gracia et al., 2019).

synthesized NPs, especially against recently developed multidrug-resistant organisms (MDROs), both individually and in synergy with current/conventional antibiotics (P. Singh et al., 2018). Therefore, especially in terms of biocompatibility, it is important to understand how active groups from biological sources attach to the surface of NPs and which active groups are involved to produce NPs with greater efficacy (Singh et al., 2016). Also importantly, biogenic NPs are easy to produce, biocompatible, and environmentally friendly (P. Singh et al., 2018) and for these reasons, the use of plant-based NPs in agriculture, which have some beneficial effects on crops, will be a promising step toward nano-revolution in the agriculture industry (Nayantara and Kaur, 2018).

Inorganic NPs may also have interesting properties, which can be used in medicine, as is the case of magnetic iron oxides (IONPs) in the nano-size version. IONPs show magnetic properties and can be used to carry drugs in place of, for example, developing tumors (Wu et al., 2015) or in a selected organ, tissue, using an external magnetic field for hyperthermic treatment of patients. The non-toxic conduct and biocompatible applications of magnetic NPs can be further enriched with a special surface coating with organic or inorganic molecules, including drugs, proteins, enzymes, antibodies, starch, nucleotides, surfactants, non-ionic detergents, polyelectrolytes, polymers, silica, and metals (Ali et al., 2016; Wu et al., 2015, 2008). The interest in magnetic NPs of ferrite materials, as well as fullerenes and carbon nanotubes, is explained by the potential use of magnetic NPs in catalysis, biomedicine, magnetic resonance imaging, magnetic separation and visualization, and hyperthermia of malignant tumors (Vedernikova, 2015).

Regarding other iron nanoparticles, nanosized zero-valent iron (nZVI) is a new material in the field of industrial and municipal wastewater treatment and remediation of contaminated soil and groundwater due to its high reactivity and expected low environmental impact due to the high iron content in the earth's crust (Pasinszki and Krebsz, 2020). Furthermore, the nZVI particles showed striking disinfecting properties compared to other widespread disinfection technologies such as chlorination. Therefore, the results obtained introduce nZVI particles as a promising disinfection technology (Sadek et al., 2021).

Similarly, sulfidated nanoscale zero-valent iron (S-nZVI) has been successfully used to remove antibiotic resistance genes (ARGs) and mobile gene elements (MGEs) from secondary effluents in wastewater treatment plants and weaken their ability to regrow their bacterial carrier (W. Z. Zhang et al., 2020). Bacterial death and vivid staining experiments and transmission electron microscopy also showed that the cellular structure of antibiotic resistant bacteria (ARBs) and intracellular DNA were severely damaged after S-nZVI treatment (Wang et al., 2020). As a result, S-nZVI may be an available reductive approach to dealing with bacteria and ARGs (W. Z. Zhang et al., 2020) and to control antibiotic resistance, especially in the aquatic environment (Chowdhury et al., 2021; Wang et al., 2020). Therefore, both (nZVI and S-nZVI) are important because present and past anthropogenic pollution of the hydrosphere and lithosphere is a growing problem worldwide for sustainable development and human health (Pasinszki and Krebsz, 2020; Yin et al., 2021; Zhang et al., 2022). However, numerous studies also explain their phytotoxicity in terms of plant growth and their fate in the plant system, and these issues should also be taken into account when planning to use them (Ghosh et al., 2017).

Concerning microbial-derived NPs, the extracellular mode of bacterial synthesis is preferable to the intracellular mode because of the easy recovery of NPs. Therefore, the bacterial synthesis of extracellular and intracellular AgNPs is possible using biomass, supernatant, cell-free extract, and derivative components (Singh et al., 2015). For example, in the case of AgNPs, silver-resistant genes, peptides, c-type cytochromes, enzymes (such as nitrate reductase) and reducing cofactors play a significant role in their synthesis. Additionally, the fungus *Aspergillus niger* in the research by Ninganagouda et al. (2014) research was grown in 250 ml Erlenmeyer flasks that contained malt extract, glucose, and yeast extract. After incubation, the mycelium was separated by filtration and distilled in water for about 48 h. The suspension was then filtered. Cell filtrate was challenged with silver nitrate (1 mM) for AgNPs biosynthesis. In parallel, simpler methods are used most often to produce NPs, also using seaweeds and microalgae, including cyanobacteria (Iravani, 2011; Kuppusamy et al., 2016). Recently, the AgNPs biosynthesis by the human gut microbiota has also been reported (Yin et al., 2019). It seems to be interesting, as the perspective of effects on intestinal health when using AgNPs may prevail over antibiotics to some extent (Li and Zhang, 2021).

However, plants are suggested to be the best candidates for large-scale biosynthesis of NPs due to the occurrence of secondary metabolites (Anand et al., 2019), also conferring high stability and a faster rate of NPs (Malabadi et al., 2012) than those of microorganisms.

Naturally occurring nanomaterials, as well as artificially produced nanomaterials of natural products and naturally occurring or manufactured nanomaterials of natural products, exhibit their own specific chemical and physical properties, biological activity, and promising applications, especially in the fields of medicine, nutrition, cosmetics, and agriculture (Griffin et al., 2018). For example, silver, silica and platinum NPs are used as ingredients in various products such as sunscreen, toothpaste, anti-aging creams, hair care products (shampoo), mouthwashes (soap, detergent), and perfumes (Kumar and Yadav, 2009). According to this, we can also anticipate specific optimized biogenic factories, valuable new waste-based materials, effective removal of nano-bioremediation contamination, and conversion of poorly soluble substances and materials into bioavailable forms for practical applications (Ahmed et al., 2022; Griffin et al., 2018). Among the different applications, potentially attributed to natural NPs, current worldwide trends in the abuse of antibiotics in different sectors such as the human, veterinary and aquatic industries have led to the emergence of antibiotic-resistant microorganisms (Aguilar-Pérez et al., 2021; Anand et al., 2019; Reddy et al., 2022; Ruddaraju et al., 2020), leading to a burst of persistent infections that have become one of the major concerns in health systems due to their associated high mortality (Baptista et al., 2018; Khare et al., 2021).

As a solution, the design of plant-based NPs with antimicrobial activity becomes an efficient and modern strategy to counter the microbial resistance to antibiotics (Anand et al., 2020), thus helping their treatment and alleviating the complications attributed to a plethora of infectious diseases. Thus, this review focuses on the recent approaches developed for the synthesis of plant-based NPs, which are committed to providing a sustainable and efficient platform for the design of novel antibiotics with promising exploitation in the food and pharmaceutical industries.

2. Study design

To provide a systematic, critical, and comprehensive analysis of the literature on plant-based nanoparticles products for antibiotic resistance, this work was organized by a literature search and analysis using specific criteria. A search in the SCOPUS database (in the titles, abstracts and keywords fields) for ‘nanoparticles’, ‘plant’, and ‘antibiotic resistance’ showed the existence of 205 articles, with India as the leading publishing country (with more than 60 papers). The first dedicated document was published in 2007, showing the relative novelty of this research activity. In the last year, more than 50 papers have been published, reaching the higher annual publication number, also because of COVID-19 and related environmental pollution aspects. Patents concerning the same keywords resulted in 6836 (the first was published in 1985). They are 6584 considering data from 2007 to December 16, 2021. Most patents were deposited at the United States Patent & Trademark Office (5397), followed by the Japan Patent Office (861), and the European Patent Office (469). Some of the last year published patents are expressly addressed to SARS-CoV-2.

The data extracted from the SCOPUS platform includes all the papers document titles, authors, abstracts, and keywords, for the analysis and interpretation, allowing to obtain a good synthesis of available information. The bibliographic search was followed by cluster analysis. This makes it possible to investigate the co-occurrence text data deriving from the bibliometric database, allowing to perform a systematic analysis of the literature (see Fig. 2). For this purpose, the VOSviewer software (‘VOSviewer version 1.6.16’, 2020) has been used. The study design (with the connected literature) was updated on December 16, 2021.

Fig. 2a is obtained by the analysis of co-occurrence of bibliography abstracts and highlights that the available literature can be grouped in 2 clusters. The first one (35 items), represented by red bubbles, is mainly devoted to the study of antibiotic resistance mechanisms. The second cluster (35 items), shown by green bubbles, is mainly addressed to characterization activities, involving specific instruments (spectroscopies, microscopies, and X-ray techniques).

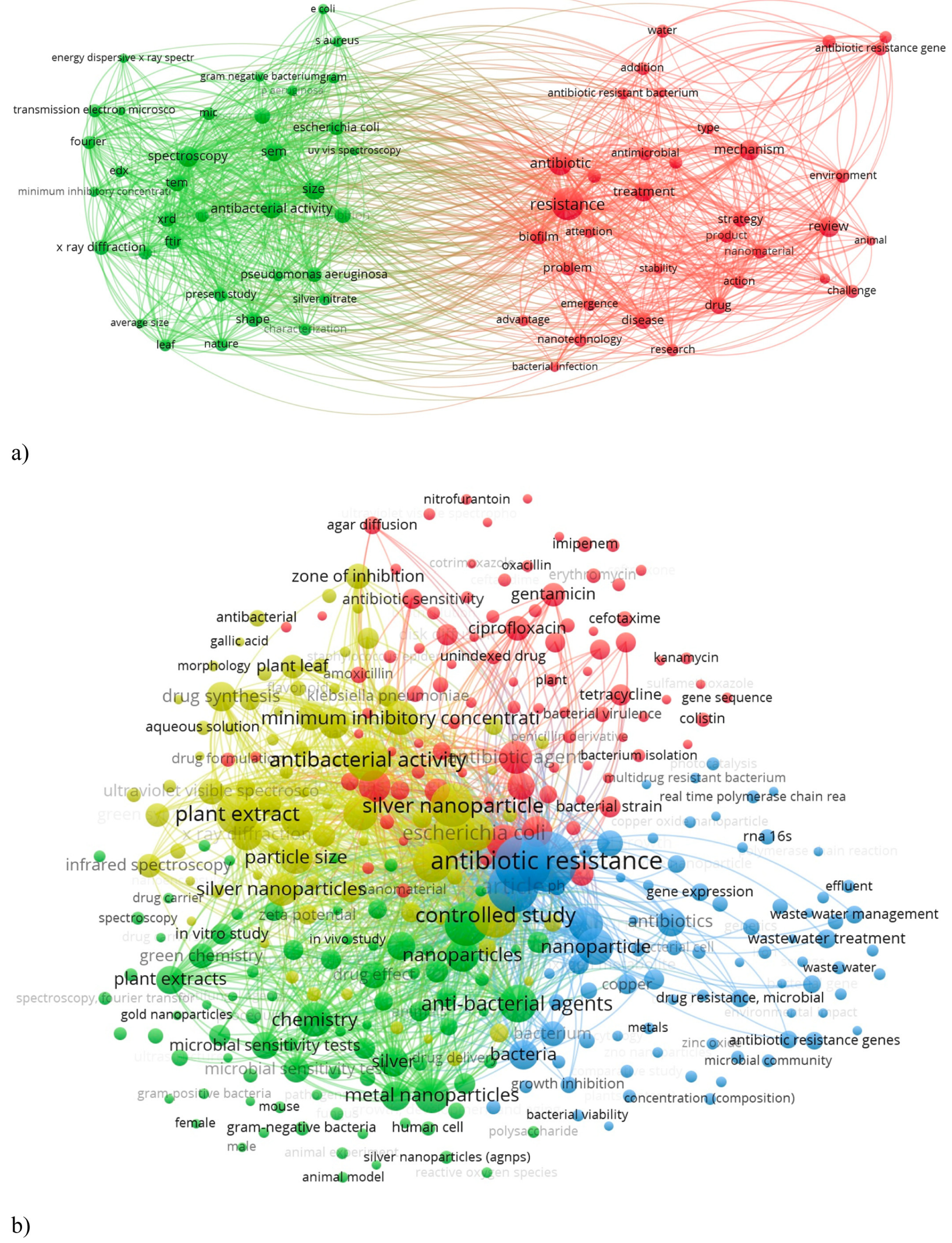
Fig. 2b shows the cluster data analysis resulting from the co-occurrence network of keywords of the papers extracted from the SCOPUS search. Data shows that 4 clusters can be highlighted. The first one (91 items) highlighted by red bubbles is mainly devoted to the antibacterial (or antimicrobial) activity, with great attention to inhibitory mechanisms. The second cluster (85 items) represented by green bubbles, concerns the chemistry of anti-infective (and antibacterial) agents, with great attention to metal nanoparticles (mainly zinc, copper and iron). The third cluster (82 items) highlighted by blue bubbles contains keywords related to antibiotic resistance. The fourth one (79 items), represented by yellow bubbles, essentially concerns plant extracts, also involving several keywords related to their characterization.

Based on the resulted cluster analysis (see Fig. 2), the literature was carefully analyzed, and through the reading of the selected full-text articles, the work was conceived as presented in the following.

3. Plant-based nanoparticles

Plant natural products are derived from different plant tissues and organs, including leaves, stems, shoots, flowers, bark, seeds, and roots, as a result of plant secondary metabolism, which can be easily enhanced by external signals, since it is highly influenced by environmental conditions (García-Pérez et al., 2021; Kuppusamy et al., 2016). Due to the high stability and fast rate of plant-based NPs, the biosynthesis of metal NPs raised interest in the elucidation and characterization of the mechanisms of uptake and bioreduction of metal ions by plants (Iravani, 2011). In this sense, many studies have shown that plant extracts can act as potential precursors for the safe synthesis of nanomaterials, caused by the presence of multiple secondary metabolites, such as alkaloids, saponins, flavonoids, tannins, steroids, phenolic compounds, terpenoids, and many others, and coenzymes, thus acting as reducing and stabilizing agents in the bioreduction reaction involved in the synthesis of metallic NPs (Aromal and Philip, 2012; Kuppusamy et al., 2016; Mittal et al., 2013). Consequently, plants have

Fig. 2. a) Cooccurrence of abstract data for articles extracted from SCOPUS, on ‘nanoparticles’ and ‘plant’, and ‘antibiotic resistance’; b) Cooccurrence of keywords for articles used for cluster analysis in a). Updated on December 16, 2021 by ‘VOSviewer version 1.6.16’, 2020. In a 2D representation of a research field, related terms, that strongly correlate, are located close to each other. The bubble diameter indicates the publications number where the reported term (or keyword) appears.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nanomaterial
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stability
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cotrimoxazole
oxacillin
zone of inhibition
ceftazidime
erythromycin
antibiotic sensitivity
gentamicin
antibacterial
cefotaxime
gallic acid
ciprofloxacin
disk diffusion
staphylococcus epidermidis
unindexed drug
kanamycin
morphology
plant leaf
amoxicillin
plant
flavonoid
sulfamethoxazole
drug synthesis
klebsiella pneumoniae
tetracycline
gene sequence
minimum inhibitory concentrati
bacterial virulence
colistin
aqueous solution
penicillin derivative
drug formulation
antibacterial activity
antibiotic agent
bacterium isolation
photocatalysis
multidrug resistant bacterium
ultraviolet visible spectrosco
real time polymerase chain rea
green
plant extract
silver nanoparticle
bacterial strain
copper oxide nanoparticle
x ray diffraction
escherichia coli
rna 16s
polymerase chain reaction
infrared spectroscopy
particle size
antibiotic resistance
nanoparticle
effluent
drug carrier
silver nanoparticles
nanomaterial
ph
gene expression
waste water management
spectroscopy
zeta potential
controlled study
antibiotics
genetics
drug
in vitro study
in vivo study
nanoparticle
wastewater treatment
green chemistry
drug effect
waste water
plant extracts
copper
spectroscopy, fourier transfor
drug resistance, microbial
gold nanoparticles
anti-bacterial agents
environmental impact
chemistry
metals
bacterium
zinc oxide
antibiotic resistance genes
microbial sensitivity tests
zno nanoparticle
microbial community
silver
drug delivery
bacteria
microbial sensitivity test
comparative study
gram positive bacteria
growth inhibition
concentration (composition)
metal nanoparticles
mouse
bacterial viability
female
gram-negative bacteria
human cell
polysaccharide
male
animal experiment
silver nanoparticles (agnps)
reactive oxygen species
animal model
b)

been successfully used in the synthesis of different biobased NPs such as cobalt, copper, silver, gold, palladium, platinum, zinc oxide and magnetite (Amarnath et al., 2012; Kuppusamy et al., 2016; Ramanathan et al., 2013), and extracts from a wide range of plant species have already been applied to the biosynthesis of NPs (Mittal et al., 2013). In addition to plant extracts, live plants can also be used for synthesis (Mittal et al., 2013). Some plants, e.g., *Brassica juncea* (Mustard greens, Brassicaceae), *Medicago sativa* (Alfalfa, Fabaceae), or *Helianthus annuus* (Sunflower, Asteraceae) can accumulate a significant amount of silver when it is present in the substrate. Ni, Co, Zn, and Cu NPs have also been synthesized in living plants (Gardea-Torresdey et al., 2003; Prathna et al., 2011).

Interestingly, NPs produced by plants have a more varied shape and size compared to those produced by other organisms (Iravani, 2011). Makarov et al. (2014) pointed out that their size and shape depend greatly on the location of the NPs. Thus, when acquiring the NPs accumulated in one plant, it should be taken into account that the others will be different depending on the part of the plant from which they are isolated. In the study by Zhang et al. (2016), AgNPs, formed as a result of green synthesis, had an antibacterial and antifungal effect in direct proportion to concentration, while AgNPs formed from fungi appeared to have better antifungal properties against superficial mycoses, viz. *Candida albicans* and *Malassezia furfur* (= *Pityrosporum ovale*) (Roy et al., 2019) or even in methylene blue dye degradation activities (Mechouche et al., 2022). For example, the synthesis of AgNPs from *Curcuma longa* (Zingiberaceae) was higher in the tuber extract compared to the powder, which was attributed to the high and easy availability of water-soluble reducing agents in the extract, which were mainly responsible for the reduction of silver ions in AgNPs (Sathishkumar et al., 2010). Rapid synthesis of AgNPs, within 5 h, by reduction of aqueous Ag^+ ions using *Dioscorea bulbifera* tuber extract (Dioscoreaceae) has also been reported, and the AgNPs obtained have strong antibacterial activity against both Gram-negative and Gram-positive bacteria. This plant species also has profound therapeutic uses due to its unique phytochemistry (Ghosh et al., 2012).

AgNPs are the most investigated plant-based NPs, being primarily associated with the development of potent antimicrobial and antifungal properties (Table 1). Malabadi et al. (2012) used cell cultures from leaves, callus, and roots of *Catharanthus roseus* (Apocynaceae) in the form of an aqueous extract to synthesize AgNPs. Their studies were carried out against different clinical pathogens such as *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Candida albicans*. The highest effectiveness of the stabilized AgNPs obtained against all pathogens tested has been shown. This alternative, quick possibility of producing NPs with specified properties, efficient, with relatively low costs (Malabadi et al., 2012) and environmentally friendly, gives hope that plant-based NPs will be used (Makarov et al., 2014). *Brillantaisia owariensis* (= *B. patula*, Acanthaceae), *Crossopteryx febrifuga* (Rubiaceae), and *Senna siamea* (Fabaceae) were successfully used for the green production of AgNPs using their aqueous leaf extracts. AgNPs derived from them showed higher antimicrobial activity against the three human skin bacterial pathogens compared to their respective crude extracts and $AgNO_3$. This indicates that the biomolecules coating the NPs can increase the biological activity of metal NPs (Kambale et al., 2020).

The AgNPs from *Fagonia indica* (Zygophyllaceae), a widely known medicinal plant, had a better effect on *E. coli*, *Citrobacter amalonaticus*, *Shigella sonnei*, and *Salmonella typhi* when combined with ciprofloxacin than AgNPs alone. Therefore, it is worth noting the possible interactions between antibiotics and AgNPs (Adil et al., 2019) (Table 1). Prasher et al. (2018) and Jyoti et al. (2016) confirm a beneficial synergistic effect between ‘green’ AgNPs and mainstream antibiotics compared to AgNPs alone. For example, maximum effect, with a 17.8-fold increase in inhibition zone, was observed for amoxicillin with easy bottom-up ‘green’ synthesized AgNPs against *Serratia marcescens*, confirming the synergistic augmenting role of the aqueous extract of *Urtica dioica* (Urticaceae) leaves capped AgNPs-amoxicillin (Jyoti et al., 2016). Other synergies of plant-based NPs and antibiotics have also been observed. For example, AgNPs and corn leaf waste of *Zea mays* extract (Poaceae), and a combination of kanamycin and rifampicin against five

Table 1
Plant-based nanoparticles (NPs) with antimicrobial activity.

Plant (Family)	Part	NPs	Microorganism	Antibiotic	Ref.
Curcuma longa (Zingiberaceae)	Tuber	AgNPs	*Escherichia coli* BL-21 strain	n.c.	(Sathishkumar et al., 2010)
Dioscorea bulbifera (Dioscoreaceae)	Tuber	AgNPs	MDROs: *Acinetobacter baumannii* *Pseudomonas aeruginosa* *E. coli*	Piperacillin, erythromycin Chloramphenicol, vancomycin Streptomycin	(Ghosh et al., 2012)
Catharanthus roseus (Apocynaceae)	Cell cultures from leaves, callus, roots	AgNPs	*Bacillus subtilis*, *Staphylococcus aureus*, *E. coli*, *Klebsiella pneumoniae*, *Candida albicans*	n.c.	(Malabadi et al., 2012)
Brillantaisia owariensis (Acanthaceae), *Crossopteryx febrifuga* (Rubiaceae), *Senna siamea* (Fabaceae)	Aqueous leaves extracts	AgNPs	Gram (+): *S. aureus*. Gram (−): *E. coli*, *P. aeruginosa*	n.c.	(Kambale et al., 2020)
Fagonia indica (Zygophyllaceae)	Callus cell cultures	AgNPs	*E. coli*, *Citrobacter amalonaticus*, *Shigella sonnei*, *Salmonella typhi*	Ciprofloxacin	(Adil et al., 2019)
Urtica dioica (Urticaceae)	Aqueous leaves extracts	AgNPs	Gram (+): *Bacillus cereus*, *B. subtilis*, *S. aureus*, *Staphylococcus epidermidis*. Gram (−): *E. coli*, *Klebsiella pneumoniae*, *Serratia marcescens*, *Salmonella typhimurium*	Amikacin, kanamycin, tetracycline, cefotaxime, amoxicillin, ampicillin, cefepime vancomycin streptomycin	(Jyoti et al., 2016)
Ocimum tenuiflorum	Leaves extract	NiNPs	Gram (−): *Klebsiella pneumoniae*, *Salmonella typhi* and *E. coli*, Gram (+): *Staphylococcus epidermidis*, *Bacillus subtilis*; Fungi: *Candida albicans*, *C. tropicalis*, *Aspergillus fumigatus*, *A. clavatus* and *A. niger*	n.c.	(Pandian et al., 2016)
Piper guineense (Piperaceae)	Aqueous leaves extracts	AuNPs	*S. aureus*, *Streptococcus pyogenes*	n.c.	(Shittu et al., 2017)
Zea mays (Poaceae)	Corn leaf waste extract	AgNPs	*B. cereus, Listeria monocytogenes*, *S. aureus*, *E. coli*, *S. typhimurium*	Kanamycin, rifampicin	(Patra and Baek, 2017)
Typha angustifolia (Typhaceae)	Leaf extract	AgNPs	*E. coli* and *K. pneumoniae*	Gentamicin, cefotaxime, meropenem	(Gurunathan, 2015)
Phyllanthus reticulatus (Phyllanthaceae), *Erigeron bonariensis* (= *Conyza bonariensis*) (Asteraceae)	Leaf extract	CuONPs	*E. coli*	n.c.	(Potbhare et al., 2019)

Abbreviations: n.c.: not combined with antibiotics.

strains of bacteria (Patra and Baek, 2017), or AgNPs and leaf extract of *Typha angustifolia* (Typhaceae) and a combination of gentamicin, cefotaxime, meropenem against *E. coli* and *Klebsiella pneumoniae* were effective (Gurunathan, 2015). Thus, the combination of synthesized green metallic NPs with antibiotics appears to be a viable form to combat MDROs by mitigating resistance and toxicity (Ruddaraju et al., 2020). The identification of green synthesis routes taking into account the need for harmless solvents, reducing and capping agents along these routes also places AgNPs' candidacy in a strong position as potential antimicrobial agents (Kaweeteerawat et al., 2017), including the possibility to reduce the stability of the structure of the bacterial community in microplastic (MP) biofilms in eutrophic water (Niu et al., 2022).

On the other hand, Kaweeteerawat et al. (2017) suggest that AgNPs increase bacteria's resistance to antibiotics, as bacteria preexposed to a sublethal dose of AgNPs exhibited increased resistance to antibiotics with IC_{50} (half-maximal inhibitory concentrations), elevated 3 to 13 times. However, biosynthesized AgNPs show good antibacterial activity, and their combination may be more effective having the synergistic potential to enhance the antimicrobial effect of broad-spectrum antimicrobials. Beta-lactam antibiotics (piperacillin) and macrolides (erythromycin) showed a 3.6 and a 3-fold increase in efficacy, respectively, when combined with the synthesized *Dioscorea bulbifera* (Dioscoreaceae) tuber extract AgNPs selectively against MDROs *Acinetobacter baumannii.* Clear synergy was also observed between such AgNPs and chloramphenicol or vancomycin against *Pseudomonas aeruginosa* and streptomycin-AgNPs against *E. coli*. The extract of *Dioscorea bulbifera* tuber was rich in flavonoids, phenols, reducing sugars, starch, diosgenin, ascorbic acid and citric acid, which can also have an impact on the results obtained (Ghosh et al., 2012).

Therefore, the development of an ecological NP synthesis process with the use of plant extracts is justified, which is an important step in the field of nanotechnology applications (Malabadi et al., 2012). However, even though AgNPs are the most studied biobased metallic NPs with antimicrobial properties, such properties are not restricted to them. Nickel NPs (NiNPs) obtained from *Ocimum tenuiflorum* (=*O. sanctum*, Lamiaceae) leaf extract has also been shown to be an effective disinfectant against pathogenic Gram-negative bacteria (*K. pneumoniae*, *Salmonella typhi*, and *E. coli*), Gram-positive (*Staphylococcus epidermidis*, *Bacillus subtilis*) and fungi (*Candida albicans*, *C. tropicalis*, *Aspergillus fumigatus*, *A. clavatus*, and *A. niger*) compared to leaf extract alone and antibiotics (Pandian et al., 2016). TiO_2 nanoparticles (TiO_2NPs) are highly active in biological activities such as antimicrobial (and antitumor) activity compared to other metal oxides, including the possibility of their interaction with antibiotics in water (Peterson et al., 2015; Van Wieren et al., 2012). TiO_2 photoexcitation also promotes horizontal transfer of resistance genes mediated by phage transduction (Xiao et al., 2021), however, there is still a need to evaluate the influence of NPs on bacterial survival and resistance genes in bacteria with higher NP resistance than NP-sensitive bacteria (Yuan et al., 2021). Many plant extracts have been used to synthesize TiO_2NPs or treat NPs obtained before, for example, Clove (Myrtaceae), Cardamom (Zingiberaceae), Cinnamon (Lauraceae), *Withania somnifera* (Solanaceae), *Eclipta prostrata* (Asteraceae), *Glycyrrhiza glabra* (Fabaceae) (Maheswari et al., 2021; Shiva Samhitha et al., 2021). It was also observed that herb-modified TiO_2NPs exhibit better antibacterial and anti-cancer properties compared to pure nanoparticles, for example, using *Ledebouria revoluta* (Asparagaceae) extract (Aswini et al., 2021). Moreover, biosynthesized selenium NPs (SeNPs) by the aqueous extract of nettle leaves (*Urtica dioica*, Urticaceae) showed potential antibacterial, antifungal, and antitumor activity, which makes them useful in general medicine (Hashem and Salem, 2022).

However, gold NPs (AuNPs) are recognized as the most potent, biocompatible, and environmentally friendly ones. AuNPs have also been designed by modifying sizes and shapes for increased activity and optimal performance in a wide variety of applications, including biomedical, antimicrobial, diagnostic, and environmental ones (T. Khan et al., 2019). For example, the high liver protective capacity of AuNPs mediated by *Azolla microphylla* (Salviniaceae) has been attributed to its high antioxidant activity, which has been assigned to the high polyphenols present in its methanol extracts that are absorbed onto the AuNP surface during synthesis (T. Khan et al., 2019). Improvement in lincomycin delivery was also reported when the drug was encapsulated in AuNPs synthesized by bioreduction with an aqueous extract of *Piper guineense* leaves (Piperaceae) (Shittu et al., 2017). Other recent studies report the use of leaf extracts of *Euphrasia officinalis* (Orobanchaceae) (H. Singh et al., 2018), *Ziziphus jujuba* (=*Z. zizyphus*, Rhamnaceae) (Aljabali et al., 2018) and *Indigofera suffruticosa* (=*I. tinctoria*, Fabaceae) (Vijayan et al., 2018) for ecological, extracellular synthesis of stable AuNPs. Similar reports also refer to the use of grape polyphenols for the synthesis of palladium NPs and their effective prevention of bacterial diseases (Amarnath et al., 2012). Examples of effective use of exogenous biomatrices (peptides, proteins, and virus particles) for the preparation of NPs in plant extracts have also been discussed (Makarov et al., 2014).

Metal plant-based NPs can also effectively control the malaria population in the environment (Kuppusamy et al., 2016). For example, AuNP-mediated leaf extracts of *Cymbopogon citratus* (Poaceae) have been tested for malaria and dengue larvae and pupae vectors (Murugan et al., 2015), but much work is needed to solve the problem. Plant-derived NPs are also a potential cure for other acute diseases such as human immunodeficiency viruses (HIV) and hepatitis (Kuppusamy et al., 2016). That is, bio-AgNPs have a convincing effect against HIV at an early stage of the reverse transcription mechanism, and therefore are promising antiviral drugs against retroviruses (Suriyakalaa et al., 2013). Biosynthesized nanomaterials are effective in combating various endemic diseases with fewer negative effects as well (Kuppusamy et al., 2016).

Namely, plant-based nano-zero-valent iron (nZVI) was found to be nontoxic to human keratinocytes, and cell viability tests did not show a stress response depending on the lactate dehydrogenase assay, confirming a lesser stress to the cell membrane (Nadagouda et al., 2010). NZVI can be synthesized using *Camellia sinensis* extract (green tea, Theaceae), which is very useful as tea polyphenols play an important role in reducing and capping NPs (Hoag et al., 2009). Similar biosynthesis of iron NPs at room temperature is also possible with the use of aqueous *Sorghum* sp. bran extract (Poaceae) (Njagi et al., 2011). The leaf extract of *Eucalyptus globulus* (Myrtaceae) was also used as a reducing agent for the synthesis of nZVI (Oza et al., 2020). It was found that a polyphenol such as oenothein B was responsible for the reduction and stabilization of this nanoparticle (T. Wang et al., 2014; Wang, 2013). Moreover, NZVI modified with *Ginkgo biloba* leaf extract (G-nZVI) as an effective catalyst exhibited excellent activation of sodium persulfate (PS), which allowed the removal of antibiotic resistance genes (ARGs) to be achieved more efficiently than the PS + nZVI system. In this way, G-nZVI can be used for the treatment of secondary effluents from wastewater treatment plants (Duan et al., 2021). The leaves of *Eucalyptus tereticornis*, *Melaleuca nesophila* (both from the Myrtaceae family) and *Rosmarinus officinalis* (Lamiaceae) were also used for the synthesis of FeNPs (Z. Wang et al., 2014).

Fe^0/Fe_3O_4 NPs synthesized using pomegranate leaves (*Punica granatum*, Lythraceae) can be coated on heat-killed *Yarrowia lipolytica* to effectively remove hexavalent chromium, which is an important contaminant of groundwater (Rao et al., 2013). The iron oxide/reduced graphene oxide nano-hybrid was capable of removing 10 ppm of tetrabromobisphenol A in 30 min, while lead and cadmium could be removed in 10 min. This type of NPs can be synthesized using banana peel ash extract (*Musa* sp., Musaceae), while the aqueous leaf extract of *Colocasia esculenta* (Araceae) reduced graphene oxide (Thakur and Karak, 2014). In situ sampling of tetracycline antibiotics in culture wastewater using diffusive gradients in thin films equipped with graphene nanoplatelets also exhibited good precision and accuracy (You et al., 2020). Similarly to the novel ZnO/biochar composites (produced from *Salvinia molesta* (*Salviniaceae*), sugarcane bagasse (Poaceae), and exhausted black wattle bark (*Acacia mearnsii*, Fabaceae)) (Gonçalves et al., 2020), the catalytic activity of rod-shaped magnetic FeO NPs was also investigated for the removal of dyes from wastewater, and thus it can serve as a potent wastewater treatment agent. Their biological synthesis was prepared from the leaf extract of *Peltophorum pterocarpum*

(Fabaceae) (Anchan et al., 2019). Other magnetic FeO NPs, which demonstrated excellent photocatalytic activity in the degradation of methylene blue dye, are synthesized from inedible fruit waste, i.e., using the fruit extract of *Cynometra ramiflora* (Fabaceae) (Bishnoi et al., 2018). Several other plant extracts have also been used to synthesize FeO NPs, e.g., leaf extracts of *Ruellia tuberosa* (Acanthaceae) and *Tridax procumbens* (Asteraceae) (Senthil and Ramesh, 2012; Vasantharaj et al., 2019), or *Terminalia chebula* aqueous extract (Combretaceae) (Kumar et al., 2013). Rod-shaped FeO NPs synthesized with *Eichhornia crassipes* (Pontederiaceae) show antibacterial activity against *Staphylococcus aureus* and *Pseudomonas fluorescens*, with the highest inhibition zone observed at a concentration of 100 μg/ml (Jagathesan and Rajiv, 2018). Furthermore, the ultrasonic method has recently been applied to the ecological synthesis of FeO NPs (as well as AgNPs), in which the *Trigonella foenum-graecum* seed extract (fenugreek, Fabaceae) acts as a reducing, caping, and stabilizing agent (Deshmukh et al., 2019).

Polyphenol-coated $Fe_3O_4@\gamma Fe_2O_3$ NPs, synthesized from *Cinnamomum verum* (Lauraceae) and *Vanilla planifolia* (Orchidaceae), showed the phenomenon of in vitro magnetic hyperthermia, which has a huge impact on therapeutic and diagnostic applications (Ramirez-Nuñez et al., 2018). Similarly, Fe_3O_4 NPs with desirable physicochemical properties for potential magnetic hyperthermia and colon cancer treatment were synthesized using *Garcinia* × *mangostana* (Clusiaceae) fruit peel extract, which turned out to be a new good stabilizer of this biosynthesis (Yusefi et al., 2021). Superparamagnetic magnetite/gold (Fe_3O_4/Au) nanohybrid NPs have been used as contrast agents for computed tomography (CT) and have been found to be biocompatible in various biomedical applications. They were synthesized from the seeds of *Vitis vinifera* (grape, Vitaceae) proanthocyanidin (GSP) (Narayanan et al., 2012).

It should be noted here that the antimicrobial activity of FeNPs is different from that of AgNPs. Recently, the antimicrobial properties of reduced iron and FeONPs, which damage bacterial cells by disrupting the bacterial membrane and generating oxidative stress within the cell, have been investigated (Baranwal et al., 2018; N. Y. Lee et al., 2019). Semicrystalline biogenic iron oxide nanoparticles (FeONPs) with a size of 80–100 nm, which were developed from *Tridax procumbens* leaf extract (Asteraceae), showed bactericidal activity against gram-negative bacteria such as *P. aeruginosa* (Senthil and Ramesh, 2012). The extract mediated by FeNPs *Gardenia jasminoides* (Rubiaceae) and *Lawsonia inermis* (Lythraceae) leaves successfully inhibited the growth of *S. aureus*, *S. enterica*, *P. mirabilis* and *E. coli* (Naseem and Farrukh, 2015). Antibacterial activity against *P. aeruginosa*, *E. coli*, *S. aureus*, *S. typhi*, and *P. multocida* was also confirmed when using FeNPs synthesized from *Moringa oleifera* leaf extract (Moringaceae) (Aisida et al., 2020).

Amazing antimicrobial potential against both Gram-positive and Gram-negative bacteria has been shown when positively charged FeNPs easily attach to the surface of negatively charged bacterial cells, resulting in cell wall rupture and subsequent cell death (Singh et al., 2020). Such bioreductively prepared FeNPs using root and leaf extracts of *Ageratum conyzoides* (Asteraceae) exhibited maximum activity against *P. aeruginosa* compared to *E. coli*, *B. subtilis*, *S. aureus*, and *C. albicans* due to the physical interaction between bacterial cells and FeNPs (Madivoli et al., 2019). Leaf extract of *Eichhornia crassipes* (Pontederiaceae) was used to bioproduce rod-shaped FeNPs that showed good inhibitory activity against *S. aureus* and *P. fluorescens* with maximum efficiency at 100 mg/ml of aqueous FeNPs (Jagathesan and Rajiv, 2018). FeNPs synthesized using an aqueous extract of *Sageretia thea* (Rhamnaceae) were also found to inhibit the growth of *P. aeruginosa*, *S. epidermidis*, *B. subtilis*, *E. coli* and *K. pneumoniae*, and the first two bacteria mentioned were the most sensitive at a minimum inhibitory concentration of 7.8 mg/l (Khalil et al., 2017). Biocompatible FeNPs synthesized from the peel extract of *Punica granatum* (Lythraceae) also showed effective antibacterial activity against *P. aeruginosa* (Irshad et al., 2017). Antibacterial activity against Gram-negative bacteria such as *K. pneumoniae* MTCC 530, *E. coli* MTCC 2939, and *S. typhi* MTCC 3917 was confirmed better than against Gram-positive *S. aureus* MTCC 96 when using FeNP *Couroupita guianensis* fruit extract (Lecythidaceae) (Sathishkumar et al., 2018). Pure hematite phase magnetic FeNPs were synthesized from *Callistemon viminalis* (Myrtaceae) flower extract, which was further used as a new antibacterial agent that was most effective against *S. typhi*, *S. aureus*, *S. enterica*, and *K. pneumoniae*, while *S. dysenteriae* was moderately inhibited (Hassan et al., 2018). Also, hematite (α-Fe_2O_3) nanosized materials synthesized using *Anacardium occidentale* (Anacardiaceae) leaf extract were confirmed to be convincingly effective in inhibiting *S. aureus* and *E. coli* strains (Rufus et al., 2017). The spherical and crystalline FeNPs obtained in the bioreduction process induced by the leaf extract of *Cynometra ramiflora* (Fabaceae) showed significant bactericidal potential against *E. coli* and *S. epidermidis* at 37 °C (Groiss et al., 2017). Highly stable FeNPs from *Lantana camara* plant extract (Verbenaceae) were used for effective inhibition of *Pseudomonas*, *Klebsiella*, and *Staphylococcus* species (Singh et al., 2020). Furthermore, polydispersed FeNPs synthesized using *Skimmia laureola* (Rutaceae) extract showed remarkable antibacterial activity through disintegration of the cell wall of a wild pathogen *Ralstonia solanacearum* (Alam et al., 2019).

Taking all of these into account, however, it should be noted that the influence of plant-based NPs on resistance genes in the treatment of biological wastewater is still not well understood. Some strategies to counter antibiotic resistance (AR) are being explored, for example, the combined use of plant-derived NPs and antimicrobials to overcome toxicity problems (Ebomah and Okoh, 2020). Genes conferring resistance to critical stress factors were found to increase both the survival and performance of the designed catalyst in biological wastewater treatment. Furthermore, combined ecological approaches such as nanoremediation with phytotechnologies can address current challenges and upgrade existing and emerging technologies in biological wastewater treatment (Benjamin et al., 2019) and the in situ remediation of soils and groundwaters (Marcon et al., 2021).

Among plant products, essential oils (EOs) have significant antimicrobial properties, making them promising agents in the fight against drug-resistant human pathogens (Carpena et al., 2021). EOs in combinatorial and nanotechnology-based strategies may also deal with infections caused by drug-resistant bacteria and may offer opportunities to reduce antibiotic use (Trifan et al., 2020). EO encapsulation in nanometric systems is one of the most promising tools for increasing antimicrobial efficacy. Such systems enable efficient delivery and release of EOs for microbiological purposes (especially for 'ESKAPE' pathogens: *Enterococcus* spp., *Staphylococcus aureus*, *Klebsiella* spp., *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp.), prolonged activity and weakening of bacterial biofilms (Trifan et al., 2020). Many of these bacteria, including clinically relevant resistant organisms, can also be easily imported from mainly Asian and African countries and their international markets, where plant-based foods are sold (Jung and Rubin, 2020), or simply from hospital sewage to be discharged into the environment and the community to increase health outcomes (Cai et al., 2021; Wang et al., 2021). All these examples confirm that green chemistry has many advantages, such as fast production, cost-effectiveness, and an easy way to produce plant-based NPs (Malabadi et al., 2012).

4. The multifaceted effects of nanoparticles on antibiotic resistance

As stated before, during the 21st century there is increasing consumption of antibiotics (Fig. 3), which has involved a growing concern about the exponential emergence of antibiotic-resistant bacteria and the subsequent development of a crisis in global public health. Due to the ineffectiveness of previously existing antibiotics in alleviating these persistent diseases and the lack of new antimicrobials (Khare et al., 2021), nanomaterials, especially NPs, have been widely explored as alternatives. It is generally assumed that antimicrobial nanomaterials present a wide range of mechanisms, thereby overcoming antibiotic resistance simultaneously (Smerkova et al., 2020). Therefore, three main mechanisms have been proposed for the effectiveness of antibiotics, affecting different physiological processes in bacteria cells: 1) cell wall synthesis, 2) translational machinery, and 3) inhibition of DNA replication (Beyth et al., 2015) (Fig. 4).

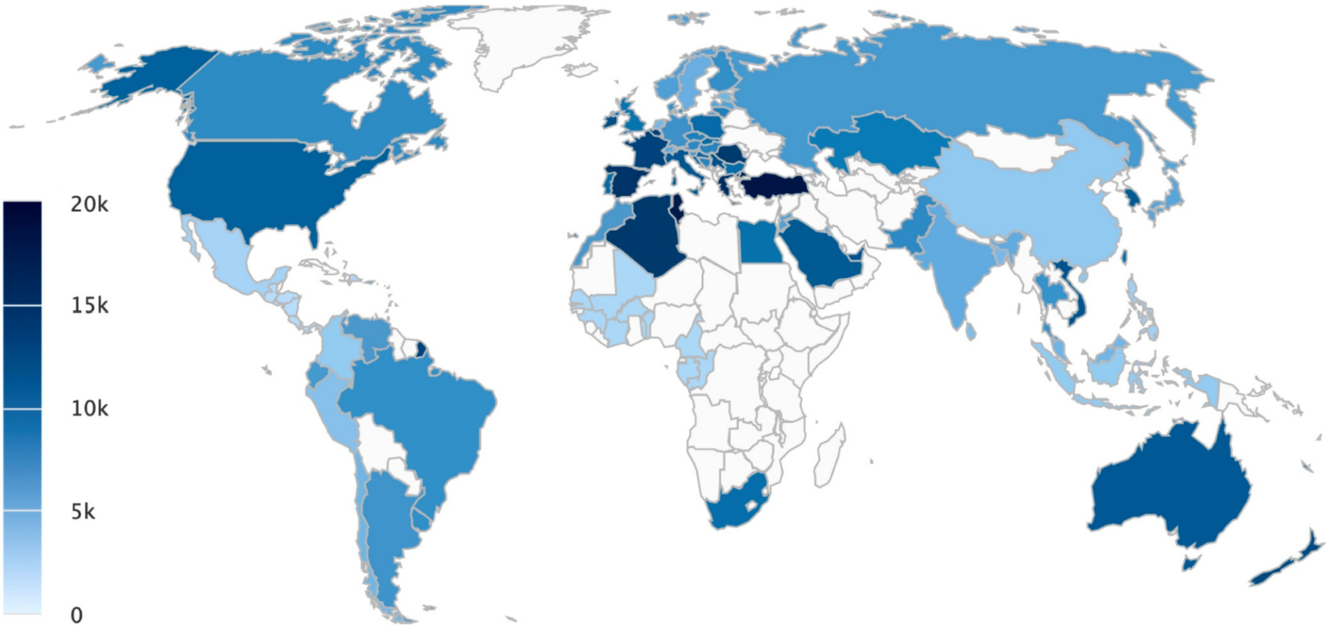

Fig. 3. Antibiotic-defined daily dose (DDD) per 1000 individuals (from The Center for Disease, Dynamics Economics & Policy. Resistance map: Antibiotic resistance 2021, https://resistancemap.cddep.org/AntibioticUse.php. Date accessed: 21 September 2021). Data were derived from antibiotic sales. Sales (expressed in kilograms) were converted into the DDD using the Anatomical Therapeutic Chemical Classification System.

Extreme, not necessarily imperative, use and misuse of antibiotics increases selection pressure and genetic association that can increase antibiotic resistance and virulence in pathogens through various adaptations (Allen et al., 2010; Anand et al., 2020; Sharma et al., 2016). For example, antibiotic-resistant bacteria (ARB) and antibiotic resistance genes (ARGs) in the aquatic environment, including drinking water resources and sewer biofilms, have become an emerging pollution problem with ramifications for human health and the environment (Anand et al., 2021b; Li et al.,

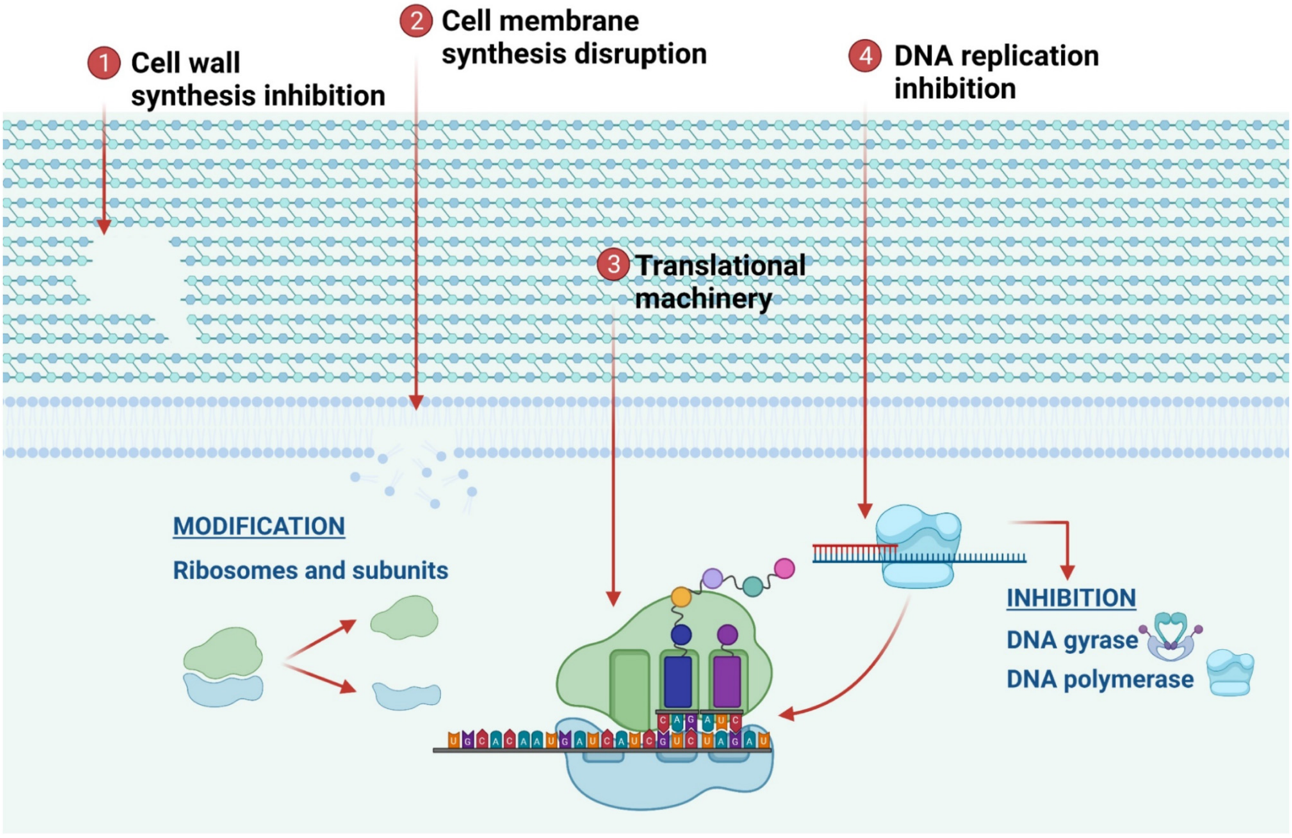

Fig. 4. Antibiotics' effects on bacterial cells. The main mechanisms that have been proposed for the effectiveness of antibiotics are 1) cell wall synthesis inhibition, 2) cell membrane synthesis disruption 3) translational machinery, and 4) inhibition of DNA replication (Beyth et al., 2015).

2019; Sharma et al., 2016). Bacteria have evolved in many ways that have made them resistant to antimicrobials. These include, but are not limited to, enzyme inactivation, decreased cell permeability, altered target site/enzyme, target protection, target overproduction, increased efflux due to overexpression of efflux pumps Fig. 5 (Anaya et al., 2015; Khare et al., 2021). Other more complex phenotypes, such as biofilm formation and quorum detection, do not appear from exposure to bacteria to antibiotics, although it is known that biofilm formation can be induced by antibiotics. These phenotypes are related to the tolerance of bacteria to antibiotics (Baptista et al., 2018). The development of resistance may be intrinsic, acquired through spontaneous mutations (de novo), or may occur as a result of the horizontal transfer of genes from donor bacteria, phages, or free DNA to the recipient bacteria (Sharma et al., 2016; Sultan et al., 2018) and may be increased by sub-lethal concentration of NPs, especially in wastewater and receiving environments (Cui and Smith, 2022).

Recently, antimicrobial nanomaterials have been used to fight MDROs (Kaur et al., 2021; Singh et al., 2014). The use of nanoelements as disinfectants brings hope for their prophylactic use: their action proves effective in the fight against pathogenic bacteria (Aruguete et al., 2013; Ruddaraju et al., 2020) and fungi so as well as in food sensing and storage (Singh et al., 2019) and also against indoor mould growth (Ogar et al., 2015). Nano-structured materials can be used to transport antimicrobial agents, aid in the delivery of new drugs, or, ultimately, have antimicrobial activity on their own. Additionally, NPs (e.g., metallic, organic, carbon nanotubes, etc.) can bypass bacterial drug resistance mechanisms and, due to their antimicrobial potential, inhibit biofilm formation or other important processes (Baptista et al., 2018). For example, TeNPs (tellurium NPs) showed a greater ability to inhibit *E. coli* biofilm than *S. aureus* one, reducing nearly a 90% of the biovolume (Gómez-Gómez et al., 2020). Other strategies are also being explored, including the combined use of plant-based antimicrobials (Chandra et al., 2017) and NPs to overcome toxicity problems (Ruddaraju et al., 2020).

Studies on NPs are based on numerous factors. Apart from the structure of NPs, many other essential elements influence the operation of NPs, namely the environment. The reaction, exposure time, temperature, and oxygen content – all of these parameters can affect the properties of NPs, except for their size, shape, or chemical structure. This multitude of influencing factors does not help the search for their antibacterial properties, and some of the published results may sometimes seem contradictory because the applied conditions have significantly affected their properties. Passive targeting of nanomaterials is an often-used treatment strategy for bacterial infections, including intracellular macrophage infections. Furthermore, specific targeting increases the effectiveness of antimicrobials and reduces side effects (Smerkova et al., 2020). It is similar in the case of NPs used in studies on antifungal properties (Kowalska-Góralska et al., 2020; Ostaszewska et al., 2016) or in studies on toxicity of NPs (Bubel et al., 2013; Kowalska-Góralska et al., 2019, 2015) especially on planktons and microbes in the water environment (Chen et al., 2016; Zhu et al., 2019). This is important since population growth and urbanization, as well as poor water supply and environmental hygiene, are the main reasons for the increase in the incidence of infectious pathogens, including re-emerging influenza (A/H5N1), diarrhea (*E. coli*) and cholera (*Vibrio cholerae*) outbreaks that are a significant burden on global economies and public health (Anand et al., 2019; Tran et al., 2013).

It should also be said that bacterial resistance to NPs has also been observed, which is a clinical concern (Zhao and Jiang, 2013). Although rare, bacteria resistant to Ag, Au, or Cu-NPs have been reported even after exposure to a single dose of NPs (Finley et al., 2015; Zazo et al., 2016; Zhao and Jiang, 2013). However, functional Au-NPs are potent antimicrobial agents against multidrug resistant bacteria (MDRB), e.g., they were effective against both Gram-negative and Gram-positive uropathogens. These AuNPs showed low toxicity to mammalian cells and no bacterial resistance was observed after 20 generations (Li et al., 2014). Thus, the use of Ag, Au, or Cu-NPs remains a therapeutic challenge, and more research is needed to address this problem (Baptista et al., 2018), especially since antibiotic options for infections caused by MDROs are often limited (Kaur et al., 2021). However, such infections are appearing as causes of morbidity and mortality around the world. These clinical challenges highlight the critical need for alternative and effective antimicrobial strategies (N. Y. Lee et al., 2019). Consequently, the most popular topics published on nanopharmaceuticals and nanonutraceuticals in the 2000s included drug delivery, toxicity/biocompatibility, biodistribution, and cancer as well (Das et al., 2021; Yeung et al., 2020).

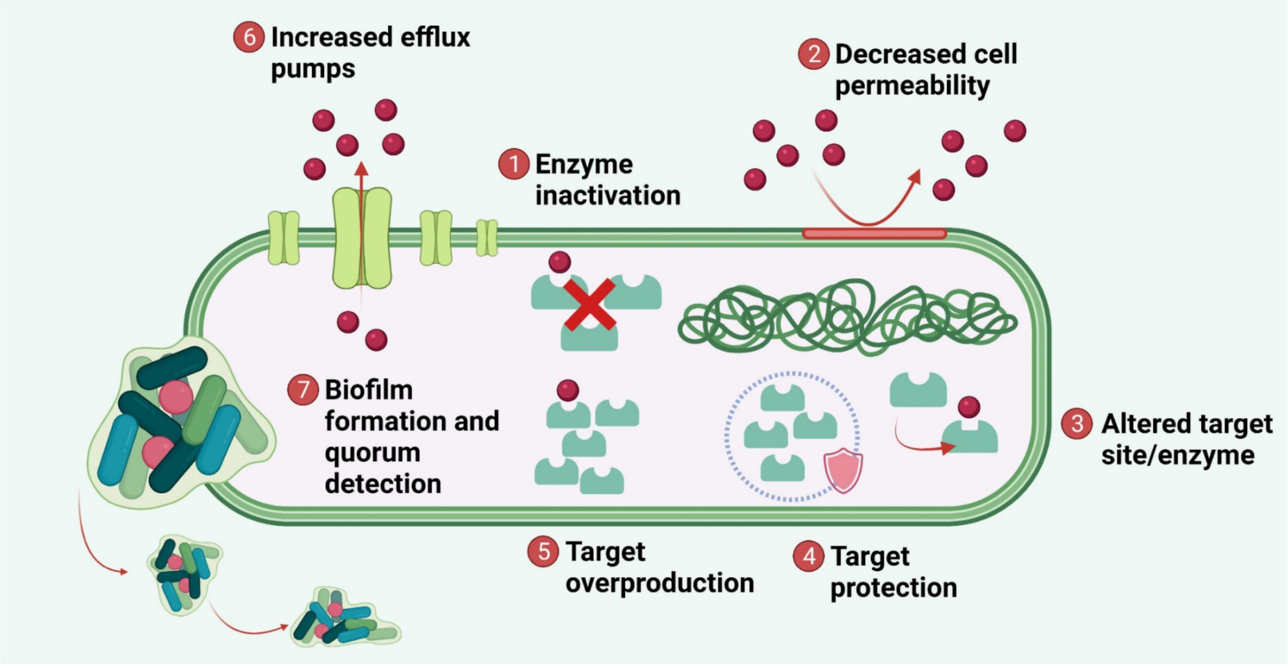

Fig. 5. Antibiotic resistance can be of two types: intrinsic (or inherent) resistance and acquired resistance. Intrinsic antibiotic resistance mechanisms are usually encoded by the chromosomes. Acquired resistance mechanisms are typically acquired through horizontal gene transfer (HGT) and include plasmid-encoded and transposons-mediated antibiotic resistance. Antibiotic resistance is caused by changes in membrane components that reduce cell membrane permeability, modification of cell wall proteins as antibiotic targets, limiting drug uptake, bypassing the drug-inhibited pathway, degrading a drug by enzymes, and pumping out a drug.

Furthermore, NP-based therapies in plants are also increasingly popular, allowing the study of ways to treat plant diseases and prevent the development of phytopathogens (including bacteria, fungi, oomycetes, and viruses) (Malandrakis et al., 2020), leading to the growing use of engineered nanomaterials (Singh et al., 2019). Recent studies also show that green-synthesized or biogenic metallic NPs using plants and microbes without hazardous chemicals hold promise for combating plant pathogens (Ali et al., 2020).

4.1. Interaction of bacteria with nanoparticles

Bacteria bind to the surface and secrete molecules such as proteins that cause them to become irreversibly attached (Zhao et al., 2017). Once settled, they form colonies in peptidoglycan envelopes, which leads to the creation of a biofilm (Riga et al., 2017). Then, bacteria are not available for antibacterial agents and the body's immune system cannot fight against them either (Rex et al., 2019; Watnick and Kolter, 2000). In addition, biofilms react poorly to antibiotics, causing antibiotic resistance (Høiby et al., 2010).

NPs can exert antimicrobial activity through a number of mechanisms, such as (1) direct interaction with the bacterial cell wall; (2) inhibiting biofilm formation; (3) triggering an innate and adaptive host immune response; (4) production of reactive oxygen species (ROS); and (5) inducing intracellular effects (e.g., interactions with DNA and/or proteins) (Baptista et al., 2018). For example, one of the mechanisms of action of NPs is as follows: NPs induce ROS generation; the generated radicals induce oxidative stress and influence membrane lipids by changing the structure of mitochondrial DNA and cell proteins (Oberdörster et al., 2005), sometimes mutagenesis or oxidation of lipids. This affects the development of the inflammatory process and consequently can lead to cell death or inflammation. Beyth et al. (2015) pointed out that nano-elements can be used; however, it is important to constantly remember their toxic properties also against human cells. Based on them, different interactions of the NPs do not create resistance mechanisms such as bacteria do when in contact with antibiotics. Therefore, NPs seem to be useful to combat pathogenic bacteria (Trifan et al., 2020), and since they do not exhibit the same mechanisms of action as standard antibiotics, they can be extremely useful against MDROs (Baptista et al., 2018; Kaur et al., 2021).

Physicochemical properties are crucial for the antimicrobial activity of NPs. It is worth noting, however, that the bacterial strain (the structural and chemical composition of the surface of the bacteria) or the environmental conditions are also very important for the interaction of microorganisms with NPs (N. Y. Lee et al., 2019; Westmeier et al., 2018). The temperature and pH of test media have already been shown to influence the dissolution and antimicrobial activity of NPs in vitro (Smerkova et al., 2020). Lowering the pH increases the solubility of NPs and enhances the antimicrobial effect. The solubility of NPs is, therefore, better in an acidic environment (Peretyazhko et al., 2014; Saliani et al., 2015). When testing AgNPs and AuNPs, the diffusion method was found to be suitable for AgNPs due to the release of toxic and highly diffusive ions into the culture medium. On the contrary, the antibacterial activity of AuNPs is due to the physical interaction with the bacteria, and Au ions are not released into the medium (Kourmouli et al., 2018).

4.2. Bacterial membrane penetration by nanoparticles

NPs can act as nanoscale molecules to interact with bacterial cells, regulate cell membrane penetration, and disrupt molecular pathways (Dakal et al., 2016; Durán et al., 2016; Hemeg, 2017; Rai et al., 2012). In general, NPs, including AgNPs, are generally easy to penetrate into cells (Brandenberger et al., 2010; Kim et al., 2012; Limbach et al., 2005; Sahay et al., 2010; Sokolova and Epple, 2008; Teeguarden et al., 2007). Non-transforming cells absorb AgNPs by endocytosis and macropinocytosis, and this depends on the cell type. On these bases, the influence of NPs on a bacterial membrane is twofold: first, disruption of membrane potential and integrity occurs, and then ROS production follows (Fig. 6). Currently accepted mechanisms also include: triggering host immune responses, inhibition of biofilm formation; and inhibition of RNA and protein synthesis by inducing intracellular effects (Beyth et al., 2015; Pelgrift and Friedman, 2013).

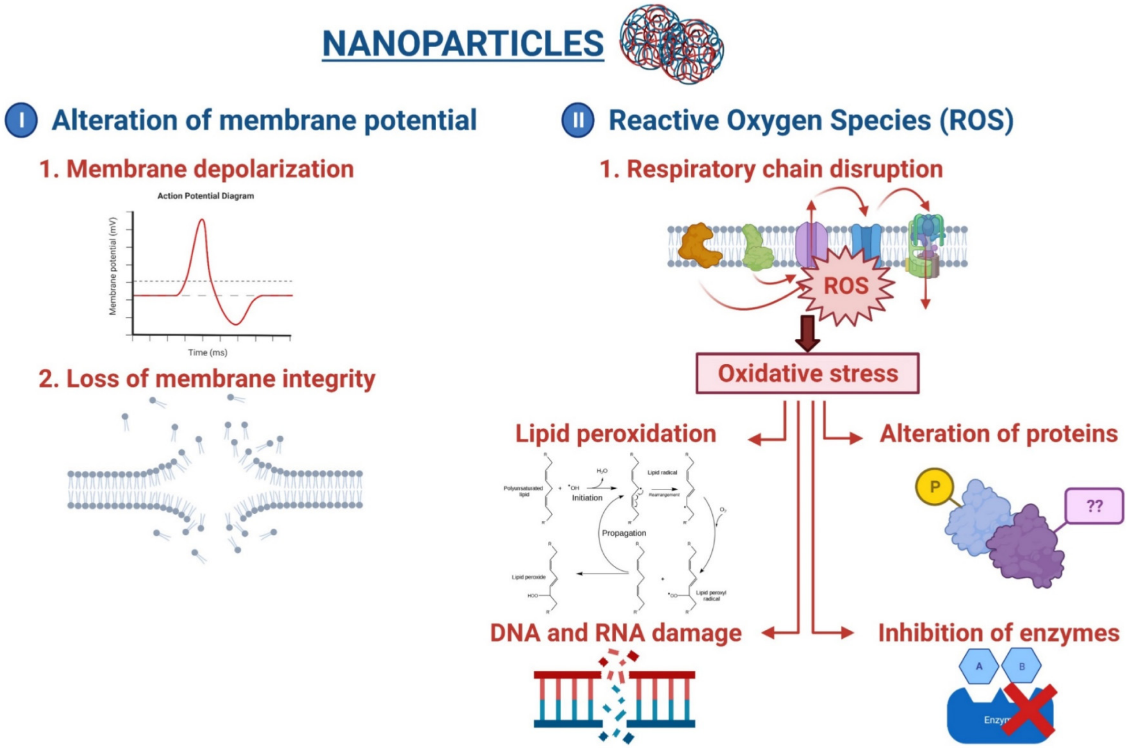

Fig. 6. The influence of nanoparticles (NPs) on a bacterial membrane is twofold: I) disruption of membrane potential and integrity, and II) reactive oxygen species (ROS) production.

Gram-positive and Gram-negative bacteria differ in their membrane components and structure and have different adsorption pathways for NPs (Lesniak et al., 2013). In some cases, bacterial resistance to NPs may be associated with changes in the permeability of the outer membrane and high expression of efflux pumps (Finley et al., 2015; Zhao and Jiang, 2013). Disorders caused by NPs lead to abnormal transport through the membrane, abnormal cell respiration, and energy deficiencies, which affect even the lysis of these cells (Barros et al., 2018; Gahlawat et al., 2016; Lok et al., 2006; Pelgrift and Friedman, 2013; Sondi and Salopek-Sondi, 2004). The method of action in this way, although not yet fully understood, states that the smaller the NPs, the more effective they are, due to their larger surface area (Panáček et al., 2006). However, the larger surface area also has some disadvantages: together with the smaller molecule, the aggregates are formed faster, which usually reduces the antibacterial effectiveness.

Moreover, before switching to the use of NPs, many different concentrations need to be carefully studied to determine precisely those whose effects on organisms will only be beneficial (Bartłomiejczyk et al., 2013; Drake and Hazelwood, 2005; Tolaymat et al., 2010) and only unfavorable for bacteria, fungi, or viruses. It is also necessary to check the question of the adaptation of bacteria to the NPs used. There are also reports that NPs affect not only the respiratory chain. Some studies point out the affinity of Ag for sulfur and nitrogen, which may affect protein structure (Choi et al., 2008) and through the photocatalytic properties of Ag (Kumar et al., 2014) can induce ROS (Carlson et al., 2008; Ninganagouda et al., 2014; Piao et al., 2011; Zhang et al., 2015) causing cytotoxicity by apoptosis and damage to cellular components, although ROS depends on the type of cells (Greulich et al., 2011; Luther et al., 2011; Piao et al., 2011). However, bimetallic Au-Pt NPs have an antibacterial effect against multi-drug resistant *E. coli* by dissipating the bacterial membrane potential and increasing the levels of adenosine triphosphate (ATP) (Baptista et al., 2018). The antibacterial properties of reduced iron and FeO NPs that damage bacterial cells by disrupting the bacterial membrane and generating oxidative stress inside the cell were also investigated (Baranwal et al., 2018). Synergistic antibacterial activity of Ag, Au, and ZnO NPs and antibiotics have been observed against *S. aureus*, *E. faecium*, *E. coli*, *A. baumannii*, and *P. aeruginosa* by penetrating the bacterial cell membrane and interfering with important molecular pathways, creating unique antimicrobial mechanisms (Hemeg, 2017). At this time, there are reasons to believe that bacteria are less susceptible to develop resistance to AgNPs than to antibiotics (Chernousova and Epple, 2013; Leid et al., 2012).

4.3. Antimicrobial mechanisms of nanoparticles

Once NPs interact and penetrate bacteria, several mechanisms of action have been reported to them, whose efficiency depends on multiple factors including particle size and shape and their superficial coating, among others. In this sense, different authors have addressed the various antimicrobial mechanisms of action of NPs, as described by countless examples previously available in the literature.

Monodispersity is another significant parameter to be controlled during nanoparticle synthesis, which can be controlled by adjusting the reaction conditions, such as the inclusion of stabilizers and reducing agents, as part of different synthetic methods. For example, the diverse morphology of bioreduced AgNPs obtained with *Dioscorea bulbifera* tuber extract covered spheres, triangles, and hexagons (Ghosh et al., 2012). Therefore, effective control of the morphology, size, and monodispersity of NPs should be investigated to define the effects of reaction conditions facing synthesis optimization. By using screened organisms with high production capacity and controlling reaction conditions, well-characterized NPs can be obtained faster (Malabadi et al., 2012) and more consistently, compared to chemical and physical methods. This environmentally friendly method has the potential to be used in a variety of fields, including pharmacy, medical applications, cosmetics, and food (Iravani et al., 2014).

Regarding the importance of NPs size, *E. coli* susceptibility to antimicrobial NPs was stable between different particle sizes, showing similar effectiveness in different ranges of AuNPs, while *B. subtilis* exhibited a higher size-dependent sensitivity (Hayden et al., 2012). The shape of NPs also plays an important role, as it has been found for *Klebsiella pneumoniae* whose susceptibility to antibiotics was higher using spherical AgNPs compared to rod-shaped AgNPs (Acharya et al., 2018). Regarding coating, bacteria-released products act as natural protectors and stabilizers on AgNPs, thus preventing aggregation and ensuring their long-term stability, promoting at the same time coordinated activity combined with their anticancer and antioxidant properties (Singh et al., 2015). Such a superficial coating is also known as biofunctionalization, which stands for an efficient strategy to improve the effectiveness of NPs. Thus, biofunctionalized ZrO_2NPs may also have antibacterial properties when coated with glutamic acid (Khan et al., 2020), promoting the regulation of the morphology, dispersion, and yield of NPs (Singh et al., 2015). The highly effective AgNP coated gloves (ex situ coated using *Corymbia citriodora* (=*Eucalyptus citriodora*) ethanolic leaf extract (Myrtaceae) as reducing and capping agents) have the potential to provide additional protection against the transmission of healthcare associated infections (Paosen et al., 2021). Biofunctionalization can, in the last term, improve the effectiveness of AgNPs in terms of antimicrobial activity by promoting new chemical entities, as proven by the synthesis of AgNPs using ampicillin (Amp-AgNPs), resulting in the production of a compound with properties combined from those of both antibiotic and silver (Khatoon et al., 2019). The results of Khatoon et al. (2019) also show that the analyzed bacterial strains do not show resistance to these Amp-AgNPs even after exposure to 15 consecutive cycles. This compound proved to be more effective against *E. coli* and *S. aureus* than chemical NPs or antibiotics. This variety of research and interesting results give hope for the still undiscovered possibilities of NPs applications.

Among the multiple examples of antimicrobial mechanisms of NPs, Sinha et al. (2011) described the effect of nano Ag and ZnO on various mesophilic and halophilic bacteria in cell cultures. The results proved to depend on the nature of the NP and the type of bacteria, as nanotoxicity was more pronounced toward Gram-negative bacteria. Sondi and Salopek-Sondi (2004) and also Sharma et al. (2009) indicated that AgNP cytotoxicity toward *E. coli* was due to the induction of proton leakage through cell membranes. Sinha et al. (2011) pointed out the high dependence of cell membrane charge on the effectiveness of metal NPs, as positively charged Ag and ZnO NPs undergo an electrostatic interaction with the negatively charged cell surface and influence the change of membrane permeability, thus affecting cytotoxicity (Feng et al., 2013a, 2013b; Morones et al., 2005). Therefore, the main cause of nanotoxicity is the interaction of NPs with the walls of bacterial cells, being highly influenced by the structure, as Gram-negative cells have a thin layer of peptidoglycan, rich in lipopolysaccharides, which presents a higher negative charge compared to Gram-positive cells, which possess a thicker layer of peptidoglycan, making the penetration of NPs more difficult (Sanpui et al., 2008). This differential wall composition constitutes a relevant cause of Gram-positive resistance to AgNPs, as reported by Stoimenov et al. (2002). In contrast to the enhanced resistance of Gram-positive strains, halophilic bacteria are Gram-negative microorganisms that present a thinner layer of peptidoglycan substituted with negatively charged cardiolipins, which makes them more susceptible to metallic NPs (Ventosa et al., 1998). This electrostatic-mediated susceptibility to NPs was studied in depth by Sinha et al. (2011) in the Gram-negative *Marinobacter* sp. and the Gram-positive EMB4 strain, showing that ZnO was harmful to both species, showing a clear effect on growth restriction caused by the accumulation of NPs in the cytoplasm, while AgNPs did not affect the development of EMB4, as they were unable to penetrate bacteria. Indeed, the electrostatic incorporation of NPs can also be mediated by the interaction with proteins, as demonstrated by Chwalibog et al. (2010) on *Staphylococcus aureus* and the fungal species *Candida albicans*. Compared to AgNPs, AuNPs molecules have different mechanisms of action and accumulation, which interacted without contact with microorganisms but nonetheless damaged fungal cells, while PtNPs caused cell damage as a consequence of the disintegration of the cytoplasmic membrane and the cell wall (Chwalibog et al., 2010).

In addition to metallic NPs, Rusciano et al. (2009) paid attention to the effectiveness of organic carbon-based NPs (NOCs) produced by normal combustion processes, reporting that NOCs were able to cause oxidative damage to liposome membranes by induction of lipid peroxidation, which influenced changes in membrane permeability through fullerene formation (Zhang et al., 2013). Therefore, four silver carbene complexes (SCCs) showed a high antimicrobial efficiency against resistant bacterial strains at low concentrations (0.5–90 mg/l), such as *Staphylococcus aureus* and MDRO such as *Acinetobacter baumannii*, *Bacillus anthracis*, and *Yersinia pestis* (Leid et al., 2012).

Besides the general antimicrobial mechanisms of action of NPs mentioned above, other relevant mechanisms were also spotted to a lesser extent. For example, Ninganagouda et al. (2014) pointed out the reduction in *E. coli* growth by induction of cell death through ROS production after AgNP application at 10 mg/l, which was similar to the studies of Zhou et al. (2012) on *E. coli*. Consequently, research on NP functional characterization is constantly evolving, but more information is still needed on the mechanisms behind the antimicrobial activity of nanomaterials (Aruguete et al., 2013).

5. Nanoparticles in medicine and pharmaceutical industry

NPs have different properties due to their small size (1–100 nm) (Gadad et al., 2014), compared to other similar materials, such as powdered matter, thus conferring novel perspectives in the field of pharmacological and biomedical research, considered as major elements that make up the new advances in biosensors and bio-nanotechnology (J. Lee et al., 2019; Medina et al., 2007; Mirzaei and Darroudi, 2017) (Table 2). NPs, due to their associated antimicrobial properties, revolutionized medicine through their pharmaceutical applications, opening a new paradigm for the treatment of infectious diseases (N. Y. Lee et al., 2019). Initially, silver and gold were used for this purpose due to their disinfection properties and ease of obtaining (Garncarek et al., 2019; Kowalska-Góralska et al., 2015, 2010; Perelshtein et al., 2015), for example, making the hospital a safer place thanks to the sonochemical coating of textiles with AgNPs that demonstrated excellent bactericidal effect (Perelshtein et al., 2015). AgNP immobilization in cotton fabric with sterile water showed better bactericidal activity compared to polyvinylidene fluoride (PVDF) immobilized fabric, but after another wash, this activity decreased drastically in a cloth immobilized in sterile water (Sathishkumar et al., 2010). NPs with specific antibacterial properties also include ZnO, CuO, and MgO (Ma et al., 2020; X. Zhang et al., 2020), all produced by a simple, efficient, inexpensive, and one-step procedure using environmentally friendly reagents (Perelshtein et al., 2015), and which must be free of toxic contaminants as required in therapeutic applications (Mirzaei and Darroudi, 2017). Among the potential contaminant, metal nano-oxides are one of the major examples, as they strongly adhere to the NPs, although they can be easily removed by successive washes without affecting their effectiveness (Perelshtein et al., 2015). Concerning the antimicrobial properties of NPs, these are mostly used for pharmaceutical purposes as disinfectants due to their inherent antipathogenic properties and/or their ability to inactivate viruses, bacteria, fungi, or yeasts photothermally (Kaur et al., 2021) or by the generation of via photocatalysis-induced ROS (Weiss et al., 2020). Such properties have motivated the development of other potential applications of nanomaterials as antibiotic nanocarriers to overcome bacterial defense mechanisms (Smerkova et al., 2020). Because of their small size and unique surface properties, nanocarriers enable the effective delivery of various drugs by changing solubility, permeability, and pharmacokinetics. Nanocarriers protect encapsulated molecules against degradation and thus increase stability (Saka and Chella, 2021) and also alter and improve the pharmacokinetic and pharmacodynamic properties of various types of drugs. NPs have been used in vivo to protect drug molecules in the systemic circulation, to target the drug to specific parts of the body (Farjadian et al., 2019), and to deliver the drug at a controlled and constant rate at the site of action (Gadad et al., 2014).

Regarding the dosage, different forms of administration of NPs can be distinguished: magnetic microcapsules, fluids, and plasters, magnetorheological suspensions, magnetic ointments, and suppositories. The magnetic behavior of small particles is essentially dependent on the properties of the individual particles and the collective general effects that are caused by the magnetic interaction between the particles (Vedernikova, 2015). The development of methods for the mixed ferrites synthesis with a nanometric range and the study of their properties are aimed at solving the problem of searching for new structures with unique functional properties, which certainly has practical importance and contributes to the development of nanotechnology in pharmacy. However, the use of magnetic NPs as a magnetic filler in

Table 2
Applications of NPs in medicine and pharmaceutical industry.

NPs	Application	Advantages	Ref.
ZnO-NPs	Sonochemical coating of textiles	Bactericidal effect against MDROs	(Perelshtein et al., 2015)
AgNPs	Immobilization on cotton fabric with sterile water	Better bactericidal activity compared to PVDF	(Sathishkumar et al., 2010)
ZnO-NPs	Treatment of skin conditions and anti-cancer properties	Drug delivery and detection horizon	(Mirzaei and Darroudi, 2017)
QL-NPs	Topical application skin layers, intended for skin cancer	Gradual release, dose and frequency reduction of drug administration, and permanence in the body	(Sahu et al., 2013)
PAA-DOXL-NPs	Transdrug® Abraxane®	Multi-drug resistant liver cancer Treatment of metastatic breast cancer	(Couvreur, 2013)
Squalene-NPs	Improved concentrations of drugs absorbed in the space of nanostructures	Slow down release	(Couvreur et al., 2006)
CPEO	Entrapment of proteins and delivery system	Protein release by a simple desorption process mechanism	(Calvo et al., 1997)
Insulin-loaded polymer-coated NPs	Diabetes, oral administration on in vivo systems	Sustained and controlled release	(Zhu et al., 2016)
Polysorbate-coated NPs	Administration of proteins and peptides	Penetration through the blood-brain barrier	(Kreuter, 1996)
pVNPs	Prevention of autoimmune diabetes or alleviate rheumatoid arthritis	Peptide-related mechanism: peptide scaffold and adjuvant	(Zampieri et al., 2020)
AgNPs	Reduced inflammation and tissue regeneration promotion	Inhibition of PI3K/Akt signaling pathways	(Gurunathan et al., 2009)
NPs	Treatment of viral infections (SARS-CoV2)	Inhibition of the interaction between ACE2 receptors and the viral S protein at the respiratory tract	(Weiss et al., 2020)
mRNA-NPs	Vaccines' design	mRNA-based vaccines delivered via lipid NPs	(Shin et al., 2020)
Polymeric NPs	Drug or antigen delivery system	Controlled and permanent drug release, enhanced bioavailability	(Gadad et al., 2014; Reis et al., 2006)

Abbreviations: Polyvinylidene fluoride (PVDF), quercetin-loaded (QL), polyalkylcyanoacrylate (PAA), doxorubicin-loaded (DOXL), chitosan–polyethylene oxide (CPEO), solid lipid NPs (SLNPs), Plant-viral NPs (pVNPs), angiotensin-converting enzyme 2 (ACE2).

pharmaceuticals requires the study of the collective effects of magnetic NPs (Vedernikova, 2015). The contribution of medical, biological, and pharmaceutical nanotechnologies is projected to peak in 2025–2035 (Gusev, 1998).

In practical terms, NPs have been classically used in the pharmaceutical industry in the form of independent preparations, but their combination with different pharmacological agents has grown exponentially in the last years. For example, ZnO-NPs are widely used in the treatment of a wide variety of skin conditions and also have anticancer properties and have emerged as a suitable tool in drug delivery and detection horizon (Mirzaei and Darroudi, 2017). On the other hand, the release and retention of quercetin-loaded NPs in a sustained and controlled manner in topically applied skin layers, intended for skin cancer, has also been described, showing a gradual release of this compound from NPs, thus reducing the dose and frequency of drug administration and its permanence in the body (Sahu et al., 2013). One of the first papers on the application of nanotechnology in pharmacy was concerning the slow release of antigen during preventive vaccination (Birrenbach and Speiser, 1976). The same team, in a slightly wider composition, discovered the lysosomotropic action of NPs, which facilitate the incorporation of drug compounds into cells (Couvreur et al., 1977). Transdrug® developed by BioAlliance Pharma, France is now most likely in the second phase of the clinical trial and is also a poly (alkyl cyanoacrylate) NPs loaded with doxorubicin. They can be used to treat multidrug-resistant liver cancer. Abraxane® for the treatment of metastatic breast cancer is paclitaxel linked to albumin. These and others nanocarriers have been used in the treatment of various diseases such as the liver or retina due to their ability to concentrate in these tissues after intravenous application (Bandopadhyay et al., 2022; Couvreur, 2013). Such molecular addressing attributed to NPs constitutes a promising role in the treatment of tumors (Das et al., 2021), as well, as the use of NPs may direct the release of chemotherapeutic drugs toward a specific malignant tissue, without interfering with healthy tissues (Birrenbach and Speiser, 1976). As a result, NP technology has emerged as an efficient solution not only as a drug delivery platform of choice for cancer treatment (Liao et al., 2019; Ray et al., 2016), but also playing a key role in tumor diagnosis at the initial stage by allowing photothermal therapy and bioimaging (Barabadi et al., 2017). Among the different strategies aimed at the design of drug nanocarriers, the synthesis of polymeric NPs constitutes an efficient solution to achieve a controlled and permanent drug release, with enhanced bioavailability toward tissue and cells, which gives hope for an ideal drug or antigen delivery system (Gadad et al., 2014; Reis et al., 2006). There is also a potential possibility to deliver genes, nucleic acids by means of NPs (Ramasamy et al., 2021), although their effectiveness is not yet satisfactory (Reis et al., 2006).

However, the effectiveness of drug nanocarriers in the targeted treatment of different diseases is not applicable as a general rule, as shown by Couvreur (2013), who indicated that NP technologies have failed to improve the activity of some drugs, potentially due to weak drug-NP interactions, resulting in abnormal drug release. As a solution, squalenylation (Couvreur et al., 2006) emerged as a reliable strategy to improve the concentrations of drugs absorbed in the space of nanostructures, and perhaps even slow down their release, which will result in their greater effectiveness. Furthermore, the targeted efficacy of nanodrug carriers, especially for cancer treatment, motivated the establishment of personalized diagnostics and treatment regimens, collectively known as 'Nanotheranostics' (Arias et al., 2011).

In addition to drug administration, another major concern on pharmacology is the administration of macromolecules, as is the case of proteins, whose gradual administration is commonly considered a difficult task. As a solution, the inclusion of NPs as part of hydrophilic polymers can be regarded as a promising strategy, as they can retain up to 80% of protein without losing their ability to release them over time, as already proved for bovine serum albumin (Calvo et al., 1997). Other authors also highlighted the role of insulin-loaded polymer-coated NPs in sustained and controlled diabetes release, as already reported for oral administration of these nanomaterials in in vivo systems (Zhu et al., 2016). Additionally, such a strategy has gained much attention for the administration of proteins and peptides that should penetrate the blood-brain barrier, by injecting 80-coated polysorbate NPs (Banerjee et al., 2021; Kreuter, 1996). In the same way, liposomal NPs, solid lipid NPs (SLNPs), and nanoemulsions can be expected to target different neurotherapeutic agents to treat different neurological disorders (Naqvi et al., 2020). Furthermore, the use of modified NPs can affect the prevention of autoimmune diabetes or alleviate rheumatoid arthritis and can now be tested for clinical treatment (Zampieri et al., 2020). Finally, inflammation is another pathogenic process that can be treated by the application of NPs, as biosynthesized AuNPs and AgNPs were shown to be effective in reducing inflammation and promoting tissue regeneration (Gurunathan et al., 2009).

Pharmacological research on NPs for the treatment of viral infections has grown exponentially due to the current paradigm related to the SARS-CoV2 pandemic (Anand et al., 2021a). In this regard, nanomaterials have already been considered efficient drug delivery systems to inhibit the interaction between angiotensin-converting enzyme 2 (ACE2) receptors and the viral S protein in the respiratory tract (Weiss et al., 2020). Thus, nanotechnology may find an important place in the fight against viruses and most infectious diseases in general, including in preparation for future pandemics (Anand et al., 2021a; Weiss et al., 2020). It is already known that there are possibilities of introducing mRNA or siRNA into NPs, with the aim of designing vaccines, as it was already recorded as a result of different clinical trials focused on the production of mRNA-based vaccines delivered via lipid NPs, known as nano-vaccines (Anand et al., 2021a; Shin et al., 2020).

6. Toxicity of nanoparticles toward human health

The application of NPs as part of therapeutic strategies for human diseases is limited by their toxicity, as already found for cell cultures from different tissues, including red blood cells, human peripheral blood mononuclear cells, liver cells, human bronchial epithelial cells, human umbilical vein endothelial cells, immortal human keratinocytes, etc. (Yang et al., 2012). As a general rule, biogenic metallic NPs also have the potential to be toxic to plants and beneficial plant-related microorganisms and ultimately to humans (Ali et al., 2020). Medina et al. (2007) already warned about the simultaneous threats attributed to the application of nanotechnology on human health. Because of the above-mentioned health-promoting and therapeutic properties of NPs, there is an urgent need to characterize the toxicological profile of these substances, as limited research has been conducted on this concern. Thus, there are several factors affecting NP toxicity and individual studies should be performed for each nanopreparation and its application conditions (Garncarek et al., 2019; Kowalska-Góralska et al., 2020, 2019), with the aim of determining the balance between the benefits and drawbacks of each preparation, in terms of the benefit-risk ratio (Medina et al., 2007).

Among the different NPs, AgNPs are the most characterized nanomaterials in terms of toxicity, being found to be toxic to several human cell lines in a dose-, size-, and time-dependent manner, especially those with size ≤10 nm (Liao et al., 2019). However, in absolute terms, AgNPs and AuNPs have been shown to be the least toxic to human cells, which gives hope for their use in antibacterial therapy and other therapeutic purposes (Chandran et al., 2012). To date, most studies on NP toxicity are conducted in animal models (Wei et al., 2015), in which AgNPs have been found to cross the murine blood-brain barrier, reaching the circulatory system in in vivo assays (Recordati et al., 2016). Mo et al. (2018) discovered that plasmatic administration of black phosphorus nanomaterials increased immunotoxicity, inducing inflammatory cytokine secretion in human macrophages, and macrophage-mediated immune disorders through higher production of nitric oxide and tumor necrosis factor-α. Therefore, AgNPs tend to accumulate in mice organs, such as the liver, kidneys, brain and spleen, after intravenous, intraperitoneal, and endotracheal administration, thus considering AgNPs as a double-edged sword that can promote beneficial effects on health, but also induce cytotoxicity in mammalian cells (Liao et al., 2019). As a consequence, AgNP toxic effects may cause reproductive disorders, malformations, and morphological deformities in many nonmammalian animal models, as well, due to the induction of oxidative stress, DNA damage, and apoptosis (Tran et al., 2013). Thus, the definition of the therapeutic window for nongreen AgNPs is narrower than is often assumed and should eventually be characterized prior to their use in human applications (Chernousova and Epple, 2013).

Despite the inherent toxicity of metallic NPs, it is important to note that such preparations show lower toxicity than those attributed to pure metal. It was evaluated in the case of zinc, where ZnO-NPs were determined to be less toxic than Zn itself (Vicario-Parés et al., 2014). The widespread use of ZnO-NPs in the global consumer market makes people more susceptible to their adverse effects, especially at the hepatic level. Such hepatoxicity of ZnO-NPs was recorded in HepG2 cells exposed to ZnO-NPs for 12 h, showing a decrease in cell viability by induction of apoptosis and DNA oxidative damage (Sharma et al., 2012). In contrast, other authors revealed that ZnO-NP mediated by *Amaranthus caudatus* (Amaranthaceae) leaf extract did not cause any toxic effect on zebrafish embryos while preserving their excellent antimicrobial activity against *Staphylococcus epidermidis* and *Enterobacter aerogenes* (Jeyabharathi et al., 2017; Vicario-Parés et al., 2014). The accumulation of NPs (of CuO and ZnO) in silkworm tissues was also found, and the treatment with NPs reduced body weight, survival, and cocoon production. Treatment induced changes in the gene expression and activity of antioxidant enzymes, impaired the metabolism of nutrients and caused dysbiosis of the gut microbiota. CuONPs are less toxic than ZnO NPs for silkworms (Muhammad et al., 2022).

Keeping all this in mind, greater efforts are now being made to counter NP toxicity with respect to their use in nanomedicine, thus overcoming their main disadvantages: cytotoxicity and low bioavailability (Min et al., 2015). Therefore, the combination of NPs with biopolymers, such as chitosan, polylactic acid, or collagen, emerged as an efficient solution (Alavi and Rai, 2019). Consequently, it is essential to assess the half-life of nanomaterials in plasma and their rate of degradation, tissue cytotoxicity, immunogenicity, and genotoxicity (Naeem et al., 2018). In fact, to evaluate promising candidates for the development of therapeutic nanomaterials with antimicrobial properties, the design of experiments aimed at maximizing their activity while lowering their associated toxicity at the same time is required (Marassi et al., 2018), together with the characterization of their pharmacokinetic profile and mechanism of action prior to their clinical application (Wei et al., 2015). In this sense, promising results are seen in NP-mediated cancer treatment, as these nanopreparations were shown to be toxic to neoplastic lesions without affecting healthy cells at the same dose (Barabadi et al., 2017).

7. Environmental safety and quality control

In addition to characterization of their mode of action and toxicity evaluation, there is a growing interest in the determination of the biological and environmental safety faced by the large-scale production of metallic NPs, which is an important aspect of current nanotechnology research (Ghosh et al., 2012). In this concern, the nonbiological methods used in the synthesis of NPs (either chemical or physical procedures) pose a serious risk and high toxicity to living organisms, including not only microorganisms but also plants and animals (Kuppusamy et al., 2016; Makarov et al., 2014). In the case of plant toxicity, the implementation of nanofertilizers emerged as a reliable solution to overcome such limitations, as has been the case of ZnNPs, successfully used in the fields of agricultural nutrition and protection due to their dual role as nanofertilizers and nanopesticides (Sturikova et al., 2018). For example, foliar spraying of Fe-based NPs increased the photosynthesis rate and chlorophyll content in maize plants and increased the biomass of maize seedlings (Li et al., 2020). However, the use of metallic NPs for agricultural purposes is not exempt from negative effects, mainly due to their associated phytotoxicity (Kole et al., 2016; Yang et al., 2017), which depends on the type of NPs and their concentration. In fact, several authors have indicated the deleterious impact of metallic NPs on plant physiology. For example, the treatment of seeds with quantum dots loaded with cadmium selenide inhibited rice seed germination (Nair et al., 2011), while carbon, aluminum, and zinc NPs adversely affected the germination of lettuce, radish, corn, cucumber, and ryegrass seeds and rape canola (Lin and Xing, 2007; Zuverza-Mena et al., 2016). In addition to the impairment of seed germination, Al_2O_3-NPs caused phytotoxic effects by inhibiting corn, soybean, cucumber, cabbage, and carrot root growth (Yang and Watts, 2005). On the other hand, the use of metallic NPs has also been shown to develop positive plant physiological responses, contributing to the improvement of radiation absorption, CO_2 assimilation, and delaying chloroplast aging, although the molecular mechanisms involved in these processes remain to be investigated (M. R. Khan et al., 2019).

Among metallic NPs, AgNPs have been revealed, as they are the main metallic NPs characterized in terms of synthesis, mode of action, and safety, but due to the inherent toxicity of Ag as metal, many efforts are being currently conducted in the characterization of other metals with lower related toxicity, such as Zn, Fe, Mg, and Mn. Regarding their effectiveness as antimicrobial agents, the minimum inhibitory concentration of metallic NPs should be determined in vitro and in vivo for each microorganism, referring to their effect on plant growth and development at the working concentration, as well (Ali et al., 2020). Additionally, with this agricultural safety assessment, the environmental impact of metallic NPs is another concern that should be carefully addressed, as the administration of NPs to crop plants also influences the surrounding ecosystem, including the soil microflora and nitrifying microorganisms (Parada et al., 2019). Thus, the positive and negative effects of metallic NPs on agriculture and the environment, along with an assessment of their potential risks, should be analyzed in detail prior to their commercial use in plant disease management directly in the field (Ali et al., 2020). Furthermore, the synthesis of NOCs also shows a negative environmental impact, since it involves a harsh combustion procedure that produces a significant proportion of total human carbon emissions yearly (Rusciano et al., 2009). Consequently, one of the challenges proposed for nanotechnology in the upcoming years should be directed at this concern, finding revolutionary applications to improve the performance of agri-food systems, especially for better crop production and food preservation and safety, especially in the context of high population growth and climate change (Yata et al., 2018).

In addition to the environmental impact of metallic NPs due to their exploitation in agriculture, the presence of NPs in wastewater and sludge derived from inefficient industrial waste management has gained ecological relevance in recent decades. As a consequence, the presence of nanomaterials in industrial waste has been identified as a possible cause of the promotion of antibiotic resistance in the environment (Aruguete et al., 2013). However, little is known about the induction of such resistance, which includes both the proliferation of antibiotic-resistant bacteria (ARBs) and antibiotic resistance genes (ARGs) (Anand et al., 2021b; Peterson and Kaur, 2018; Sharma et al., 2016). Thus, further research may focus on unraveling the contribution of nanomaterials to the development of antibiotic resistance in environmental systems (Aruguete et al., 2013). As a result, comprehensive environmental strategies should be adopted to prevent the proliferation of resistant bacteria, which would eventually lead to efficient control of epidemics (Tran et al., 2013).

8. Concluding remarks and future perspectives

There is an interesting future for NPs to combine them so that they could act as ‘nanomachines’: their mode of interaction through the use of multiple NPs would have a non-linear dependence on changed parameters, such as temperature or pH. This approach seems to be working and the nanotechnology future is nearer; however, its potential threats must be considered, and before implementing new procedures, their effects must be carefully examined. For example, the toxicity of NPs is critically discussed to reflect potential problems before they are widely used in medicine. On the other hand, synthesis mediated by plant extracts is said to be environmentally benign. One of the most outstanding trends in the synthesis of metallic NPs from plant extracts, which could be a positive strategy from the point of view of characterizing the mode of action of NPs. It is a controlled synthesis that can be transferred to a large scale with ease and that ensures environmental safety while at the same time reducing the environmental impact of the process.

Taken together, the use of plant-based NPs has shown different advantages and applications in the field of medicine and the pharmaceutical industry. More precisely, studies confirm that NPs can exert antimicrobial properties alone or in combination with antibiotics, thus diminishing the present issue of acquired resistance due to the overconsumption or misuse of antibiotics. Considering this potential application, future research should focus on two directions: assessing the safety aspects of the use of plant-based NPs (toxicity toward human health and environmental safety) and diminishing the environmental impact of their synthesis. More detailed development of synthesis procedures is necessary, but also the study of action mechanisms that mediate the antibacterial effect of NPs is necessary to turn plant-based NPs into a realistic strategy capable of satisfying the society's demand for an effective solution against antibiotic resistance.

CRediT authorship contribution statement

All the authors of this manuscript have substantially contributed to the concept, literature mining, writing and methodology of the review, provided critical feedback and revised the manuscript critically. All authors contributed to the writing or revision of the final manuscript. **Uttpal Anand**: Conceptualization/conceived the study idea, planned and designed the review structure, wrote the first draft of the manuscript, data validation, visualization, figure captions, arranged references, revision, responded to reviewer comments, final draft. **M. Carpena**, **Monika Kowalska-Góralska**, and **P. Garcia-Perez**: Writing—original draft preparation, prepared the tables and figures, revised the manuscript, visualization. **Kumari Sunita**: Literature survey, writing—review & editing, arranged references, response, suggestions. **Elza Bontempi**: Writing—review & editing, investigation, study design, methodology, software, formal analysis, prepared the figures, validation, response, addressed referee comments. **Abhijit Dey**: Writing—review & editing, suggestions. **M.A. Prieto**: Writing—review & editing, response, suggestions, project administration and funding acquisition. **Jarosław Proćków**: Writing—original draft preparation, data validation, resources, arranged references, completed the critical revision of the manuscript, response, suggestions, addressed reviewer comments, final draft. **J. Simal-Gandara**: Conceptualization, completed the critical revision of the entire manuscript, supervised the drafting process of the review, response, final draft, resources, project administration and funding acquisition. All authors have read and approved the final version of the manuscript for submission to this journal.

Declaration of competing interest

The authors declare no conflict of interest.

Acknowledgments

The research leading to these results was supported by MICINN supporting the Ramón y Cajal grant for M.A. Prieto (RYC-2017-22891); by Xunta de Galicia for supporting the program EXCELENCIA-ED431F 2020/12 and the predoctoral grant of M. Carpena (ED481A 2021/313). Authors are grateful to Ibero-American Program on Science and Technology (CYTED—AQUA-CIBUS, P317RT0003), to the Bio Based Industries Joint Undertaking (JU) under grant agreement No 888003 UP4HEALTH Project (H2020-BBI-JTI-2019) that supports the work of P. Garcia-Perez. The JU receives support from the European Union's Horizon 2020 research and innovation program and the Bio Based Industries Consortium. The project SYSTEMIC Knowledge hub on Nutrition and Food Security, has received funding from national research funding parties in Belgium (FWO), France (INRA), Germany (BLE), Italy (MIPAAF), Latvia (IZM), Norway (RCN), Portugal (FCT), and Spain (AEI) in a joint action of JPI HDHL, JPI-OCEANS and FACCE-JPI launched in 2019 under the ERA-NET ERA-HDHL (n° 696295). Funding for open access charge: University of Vigo/CISUG. All the authors are highly grateful and acknowledge to the authority of the respective departments and institutions for their support in carrying out this research. The authors also express their sincere gratitude to the unknown referee for critically reviewing the manuscript and suggesting useful changes.

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