Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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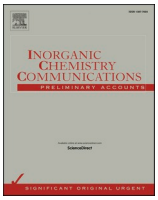

Nanomedicine for drug resistant pathogens and COVID-19 using mushroom nanocomposite inspired with bacteriocin – A review

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ABSTRACT

Multidrug resistant (MDR) pathogens have become a major global health challenge and have severely threatened the health of society. Current conditions have become worse as a result of the COVID-19 pandemic, and infection rates in the future will rise. It is necessary to design, respond effectively, and take action to address these challenges by investigating new avenues. In this regard, the fabrication of metal NPs utilized by various methods, including green synthesis using mushroom, is highly versatile, cost-effective, eco-compatible, and superior. In contrast, biofabrication of metal NPs can be employed as a powerful weapon against MDR pathogens and have immense biomedical applications. In addition, the advancement in nanotechnology has made possible to modify the nanomaterials and enhance their activities. Metal NPs with biomolecules composite prevent the microbial adhesion and kills the microbial pathogens through biofilm formation. Bacteriocin is an excellent antimicrobial peptide that works well as an augmentation substance to boost the antimicrobial effects. As a result, we concentrate on the creation of new, eco-compatible mycosynthesized metal NPs with bacteriocin nanocomposite via electrostatic, covalent, or non-covalent bindings. The synergistic benefits of metal NPs with bacteriocin to combat MDR pathogens and COVID-19, as well as other biomedical applications, are discussed in this review. Moreover, the importance of the adverse outcome pathway (AOP) in risk analysis of manufactured metal nanocomposite nanomaterial and their future possibilities were also discussed.

1. Introduction

MDR Pathogenic bacteria and other microbes induce numerous pathogen associated infections and the sickness in human globally reported by world health organization (WHO) in 2016 [1]. Microbial infections are becoming a serious threat due to the development of resistance. There are several factors responsible for the development of MDR. In past, the introduction of the first antibiotic, penicillin unlocked a new era for treating the infectious diseases which were known as "golden age" in the field of antibiotic research during 1940–1962. The timeline followed the introduction of other antibiotics like streptomycin, chloramphenicol, and tetracycline and much more. Initially, antibiotics were able to cure many of the common bacterial infections and played an important role during 2nd World War [2,3]. The increasing use of antibiotics in infectious diseases resulted in the development of MDR microbes. The MDR microbial pathogens are able to produce a different kind of hydrolyzing enzymes which mainly target the active sites of antibiotics to make them non-functional. β-lactamases

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are one of the major enzymes made by many Gram-positive and negative bacterial cells that plays a key role in the development of resistance. The developing countries are leading the microbial disease burden in the world [3]. MDR is a major concern in developing nations like India, where microbial infections impose a significant cost burden on healthcare and pharmaceutical industries. In India, according to a recent survey performed by the Center for Disease Dynamics, Economics, and Policy (CDDEP), 80–100 percent of *E. coli* can develop resistance by creating Extended-spectrum-lactamases (ESBLs) enzymes, while 50–61 percent of *K. pneumonia* are MBL-producing organisms [4]. ESBLs producing cells target antibiotics like penicillin as well as third generation cephalosporin [5,6].

MDR organisms are able to modify the functional group of antibiotics to render them inactive. Bacteria of this category deactivate the antibiotics mostly by O -acetylation, and N –acetylation. Some resistant organisms can oxidize or reduce the antibiotics to make them nonfunctional. Alteration in the active site of antibiotics can play an key role in the development of resistance. In *S. aureus*, Mec A gene-encoded penicillin- binding protein 2a transpeptidase can help in the development of methicillin resistance [methicillin- resistant *Staphylococcus aureus* (MRSA)] [3,7]. If no action is taken, the number of deaths caused annually by harmful microbes would rise to 10 million by 2050, according to the MDR research 2016 report [8]. Coronavirus infections are currently a serious global pandemic. There have also been two more recent CoV outbreaks. Severe Acute Respiratory Syndrome (SARS-CoV) transmission from civet cats to people was discovered in 2002. It was discovered that the Middle East Respiratory Syndrome (MERS-CoV) of 2012 can spread from dromedary camels to people. Despite the fact that COVID-19 has already demonstrated some parallels to current coronavirus outbreaks. Novel beta-corona virus responsible for COVID-19 likely occurred in a "wet market" in Wuhan, central China [8,9]. The unique coronavirus-related illness was formally referred to as Coronavirus Disease 2019 on February 12, 2020, by WHO (COVID-19). An overall the COVID-19 infections were affected by 292.5 million and 5.4 million deaths occurred globally till December 2021. In particular, first wave of the COVID-19 pandemic conditions arise on 19 April 2020 as reported by WHO, there after increasing the corona cases nearly 152 million confirmed by July 2020 over with 3 million deaths occurred in worldwide [10]. The 2nd wave of COVID-19 pandemic arise in April and May month of 2021 by Delta variant, while 29.27 million cases were confirmed and 1.19 million deaths were occurred up to October 2021 reported by WHO and Institute for Health Metrics and Evaluation (IHME). After the devastating 2nd wave of COVID-19, the SARS CoV-2 has more variants or mutations at globally in the way of silent mutations, deletion, point mutation, synonymous, and non-synonymous due to environmental factors, climatic changes and various circumstance during December 2019 to December 2021. A new mutated version of the Delta variant has made its appearance. It was 1st detected in India. However, this variant named as Delta Plus or B.1.617.2. Scientists have discovered a novel strain of the virus that causes COVID-19 in Southern France, as the rest of the globe struggles with the severely mutated Omicron variety of SARS-CoV-2. Recent research indicates that the Omicron variant, which triggered the horrific second wave of the pandemic, is substantially more contagious than the Delta variety. Over a hundred nations have so far reported finding the Omicron variant. Over the course of 23 states and Union Territories in India, 1,892 instances of the Omicron variant have thus far been identified. India is currently experiencing the third COVID-19 wave, during which the number of cases has actually doubled over the last three days from the original 27,553 patients to 58,097 patients on January 5th 2022, with an increase in Omicron variant cases as well. The COVID-19 variant B.1.640.2 has been identified by researchers at the institution IHU Mediterranean Infection in at least 12 cases and it has been connected to travel to the African nation Cameroon. This discovery comes as COVID-19 cases are once again on the rise around the world. IHU is not well understood, however it is hypothesized to have more mutations than the Omicron variant. 30 amino acid changes and 12 deletions, caused by 46 mutations and 37 deletions, have been recorded by WHO 2022, according to the novel variant IHU. On the theory of this virus variant leading to an 'Endemic' stage, but still we are not yet over the 'Pandemic'.

In order to save thousands of lives, it is important that hospitals are quickly established in a temporary setting. The public must be able to deal with the crisis in the most circumspect and safest possible way because there is no end in sight for it in the coming years. It is obvious that the prevention of this disease is preferable to its treatment, so all practical precautions must be taken, along with implicating and imposing public participation in disease control, strict adherence to COVID-19 appropriate behaviors (such as hand hygiene, the wearing of face masks, and social restriction), and the execution of mini-lockdowns, nighttime curfews, and micro-contained areas. The pandemic situations have significantly affected the economy, safety, health and well-being of both individual and communities. To date, so many COVID-19 vaccines are used for SARS CoV-2 and most of the people are vaccinated. Despite an available COVID-19 vaccine, SARS CoV-2 not lost their virulence and also mutated due to circumstance, to date pandemic is still continuous, so WHO does not conclude that perfect vaccine for COVID-19 and also associated MDR pathogens.

The issue is both pandemics and epidemics that arise rapidly, most probably due to mutation of the viral genome. A change in a single nucleic acid can have a wide destructive effect on the human population. The commonly spread viral diseases can cost billions of dollars, whereas the sudden occurrence and rapid proliferation of a novel extremely virulent viruses result in high mortality. Therefore, rapid and reliable diagnostics have to be part of any successful defense against any kind of pandemic. Globally, conventional molecular diagnostic techniques are generally used in laboratories in order to detect microbes with a high degree of sensitivity and reproducibility. The short shelf half-life of some reagents (enzymes and DNA primers) as well as high cost; limit the relevance of conventional pathogen detection methods in developing nations. In addition to this, despite their sensitivity, current technologies (e.g. PCR and ELISA), require a wide-range of sample preparations and have long readout times, that ends in delayed response as well as disease containment [11,12]. Conventional molecular diagnosis is a consuming time process with lower specificity and accuracy, which is considered a major drawback in clinical diagnosis. Also, most of these methods are not applicable in the fields such as aerodrome and food courts [13]. At present, there are no potential vaccines or drugs that have been shown to prevent or treat COVID-19 effectively, and most countries are currently trying to prevent the spreading of the SARS-CoV-2 virus by implementing control and preventive strategies. Microbiologists and clinicians are recently struggling with increasing drug resistance pathogenic microbes [14]. So, an urgent need to develop novel drug or antimicrobial materials with various chemical compositions and novel mechanisms to combat COVID-19 and MDR pathogens exists.

1.1. Need for novel approach to control the MDR pathogens and COVID-19

Recent studies have focused on developing novel antimicrobial drugs by constructing new or changing the presence of existing compounds and techniques to successfully cope with emerging MDR pathogens because of the obstacles [15]. In this regard, Nanotechnology provides a platform to fabricate and improve bioactive nanomaterials. Nanoparticles (NPs) at the nanoscale aspects attract the researcher's attention because of their unique size and shape explored in the field of advanced bio-nanotechnology [16]. Nanomaterials with at least 1–100 nm size are considered as the initial building blocks of nanotechnology [17]. CRISPR-Cas9 gene editing by nanotechnology is a new golden age in the realm of medical science. The ultimate goal of nano-carrier design is to examine the basic working strategy of CRISPR-Cas9 using NPs, cells, or tissues, and the application of laboratory findings to the clinics [18,19].

NPs have a broad range of potential uses in physics, chemistry, biology, material science, and medicine [20]. Metal NPs, such as gold (Au), silver (Ag) [21,22], platinum [23], titanium [24], copper [25], and zinc [26] have piqued the interest of numerous researchers in recent years, and are being employed for a variety of applications. Among them, Ag and Au were shown to be more important in biological applications than the other metals. Antimicrobials, antioxidants, catalysts, anticancer, and other characteristics of Au and Ag NPs have been documented [27–29].

NPs can be prepared by top-down (physical) and bottom-up (chemical and biological) methods (Fig. 1). The physico-chemical processes of NPs fabrication are costly and lead to the release of toxic by-products. Green chemistry production of metal NPs utilising biological systems has emerged as a feasible remedy to these drawbacks. The biological technique is economical, simple to produce, less toxic to the environment, and does not require extra processing during synthesis [30]. Biological methods of synthesis consisting of the principle of 'Nature' with maximum societal benefits and minimal negative impact on the ecosystem. The green synthesis of metal NPs mediated by biological agents such as bacteria [31,32], fungi [33,34], yeast [35,36], algae [37,38], actinomycetes [39,40], and plants [41–43], which containing bioactive chemicals that to play a key role as reductants in the conversion of metal ions to NPs as well as provide capping agents to stabilize them. However, green synthesized NPs with small size and the high surface area could easily adhere to the cell membrane and enter into the plasma membrane [44].

Among all the type of biological systems, fungi could be a better choice for the mycosynthesis of metal NPs. In the past, people have used mushrooms, which are macro-fungal biological organisms, as both food and medicine since they are a rich source of vitamins, minerals, carbohydrates, and proteins, fibres [45]. Moreover, they have polyphenols, terpenoids, and lectins which are also known for their various biological activities [46]. Mushrooms are an attractive natural system for the green synthesis of metal NPs, because they offer high tolerance to metals; easy to grow, and fungal mycelia provide them with a larger surface area. The mycelial mass of mushrooms is more resistant to agitation and pressure, making them more suitable for large-scale NPs synthesis [47]. Besides, they revealed simple downstream processing during NPs synthesis. Mushroom possess antioxidant, anti-inflammatory, antiviral, antifungal, antibacterial, cardiovascular, hepatoprotective, and lowering hypotensive activities [46]. Edible mushroom extracts contain various biomolecules such as proteins, amino acids, polysaccharides, and vitamins. These molecules contribute to the better reduction of metal ions, biocompatibility, long-term stability and capping actions during NPs synthesis. Additionally, these capping layers offer a surface that is active for the interaction of higher affinity functional groups with biomolecules [48,49]. Furthermore, Ag and Au NPs synthesis utilizing the aqueous extract of edible mushrooms is easy to use, effective, affordable, safe, and doesn't need complicated equipment.

Bacteriocins are ribosomally produced peptides or proteins by many bacterial species, including probiotic strains. Exerting their antimicrobial property versus other microbes, either belonging to the same species (narrow spectrum) or various genera (broad-spectrum) [50,51]. Bacteriocins are, colorless, heat-stable and odorless, having a much amount of biomedical applications [52]. They are generally tiny molecular weight of proteins that enter the target cells through binding to cell surface specific receptors. Recently, bacteriocin-secreting lactic acid bacteria (LAB) has attracted significant attention because they are generally recognized as safe (GRAS) status and effective antimicrobial substance to replace an antibiotics [53]. Bacteriocin act as a perfect augmentation substance for increasing the antimicrobial properties. Ag NPs and Au NPs by themselves have better antimicrobial property, yet increasing of their antimicrobial property is desirable. Moreover, conjugation of metal NPs with effective antimicrobial compounds like bacteriocin helps to prevent their microbial adhesion and kills the microbial pathogens through biofilm formation. Generally, Ag and Au are positively charged with large surface area, which facilitates their binding to the negatively charged bacterial membrane [54]. However, metal NPs were identified as a potential weapon against viral pathogens [12]. Metallic and non-metallic nano-materials showed anti-viral activity by

(i) directly interacting with the viral membranes, (ii) controlled drug delivery, (iii) interacting deleteriously with viral genomic material and proteins, (iv) recruiting host immune cells, and (v) generating reactive oxygen species (ROS). Furthermore, Metallic and non-metallic nano-materials were used to develop materials with a broad spectrum of chemical, mechanical, magnetic, and electrical properties for biomedical applications such as drugs, anti-viral surface and viral diagnostics [12,55]. A wide array of nano bases applications are under investigation to fight against the COVID 19 [56]. Therefore, there is a need to

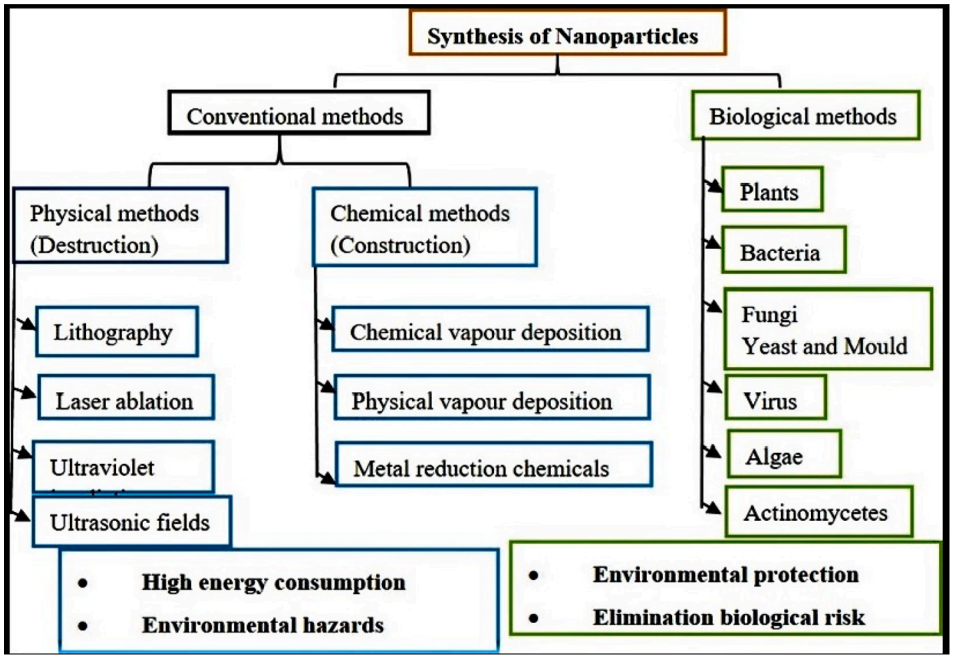

Fig. 1. Different approaches used for synthesis of metal NPs.

investigate the synergistic effect of antimicrobial effects of bacteriocins in combinations with metal NPs. This review will focus on novel approaches of mycofabricated Ag-Au NPs bionanocomposite with bacteriocin to enhance the antimicrobial potential & less cytotoxic effects in humans. This review will also elucidate the synthesis of metallic NPs and its effects on MDR pathogens & COVID-19. An adverse outcome pathway (AOP) process development relevance to risk assessment of nanomaterials and their prospects is critically reviewed.

2. NPs Synthesis: Approaches and their importance

Metal NPs are being fabricated using the different approaches viz., physical, chemical, and biological (Fig. 1).

2.1. Conventional approaches of NPs synthesis

The physical and chemical approaches are much popular and widely adopted for metal NPs synthesis (Fig. 1). Different physical approach are employed for synthesizing NPs viz., ultraviolet irradiation [57], evaporation condensation, lithography, laser ablation, ultrasonic fields [58], high energy ball milling, pyrolysis, sputter deposition, plasma arcing, diffusion, electrolysis [59]. Moreover, fabricating metal NPs are cost-intensive and require high energy consumption by using physical approach methods.

On the other hand, metal NPs are fabricated through different chemical approaches, viz., chemical reduction, microemulsion, electrochemical, and thermal decomposition has been limited by its various factors like costly and lead to the production of toxic by-products as they involve hazardous chemicals that are harmful to the environment [60]. In order to overcome these disadvantages, green chemistry approach has emerged as novel method as they are safe, eco-compatible, cost-effective, non-toxic, and easily scaled up for metal NPs synthesis. Further, the green chemistry approach does not involve toxic chemical, high temperature, energy, and pressure.

2.2. Biological approaches of NPs synthesis

The biological fabrication of NPs is deemed to be a green chemistry approach that interconnects biotechnology and nanotechnology. The biological mode of NPs synthesis used extracts from various organisms including bacteria [32], fungi [33], actinomycetes [61], yeast [62], algae [63], and wide range of plants [64]. Different biological substances are being utilized to synthesize metal NPs (Fig. 2).

2.2.1. Biosynthesis of Ag and Au NPs using plant extracts

Ag NPs synthesis from different parts of plants [41–43]. So far there are a large number of studies regarding the use of plant extract for NPs synthesis [65,66]. According to geographical variation, the plant metabolites may get changed and so the same plant from different parts may give different results. Identification of a single compound which mediates reduction is very tedious as the plant contains a large number of metabolites compared to microbes. Plants contain many medically important metabolites which can initiate the green synthesis of Ag NPs. Plant extracts mediate one-step synthesis of Ag NPs in a rapid, cost effective method [67]. The plant extracts could mediate the green synthesis of Au NPs from reacting solution containing gold ions, which indicates the solution turns red [68]. The green procedure employs extracts from leaves of *Cistus incanus* [69] and *Mentha piperita* [70] to reduce chloroauric acid to Au NPs.

2.2.2. Biosynthesis of Ag and Au NPs using bacteria

Microorganisms are beneficial than plants towards NPs synthesis because they can be easily cultivated and preserved for further use. Plants, when used, are vulnerable to the risk of getting endangered. Bacteria can be used as nanofactories for the synthesis of metal NPs because it is very easy to handle them. The bacteria can effectively use to synthesis NPs by the intracellular or extracellular method. The extracellular method is the most adopted one as it is beneficial compared to intracellular. Extracellular production offers effortless purification steps compared to the intracellular synthesis. The scale up process is easy with the extracellular method and handling of the cell free filtrate is less laborious than managing biomass [31,32]. Various researchers were reported that the important challenges must be addressed before moving into the industrial production of NPs using bacteria [32,44,71]. The main disadvantages associated with the biological system includes comprehensive knowledge on the mechanism involved in the green synthesis of NPs by the organism, control of the size of NPs, time taken for synthesis is more compared to other chemical and physical methods [59].

2.2.3. Biosynthesis of Ag and Au NPs using fungi

Synthesis of NPs by fungi is an exciting and new aspect of current nanotechnology. In recent year's myco-nanotechnology attained considerable popularity. Fungi can bear up to many tough environmental conditions compared to other biological resources used for NPs synthesis. Fungi secrete plenty of extracellular enzymes, which contribute much into synthesis and stabilization of NPs [27,33]. When, proceeding to green synthesis with fungi, the total quantity of NPs obtained is extended to a greater extent than bacteria; the fact behind it is the extracellular enzymes and proteins produced by fungi (Mukherjee *et al.*, 2008). The synthesis arbitrated by fungi can be extracellular or intracellular, extracellular method of synthesis is easy and commonly used. Intracellular production is tedious as it needs additional steps to obtain NPs as it is intracellularly produced [72,73]. Commonly used salt

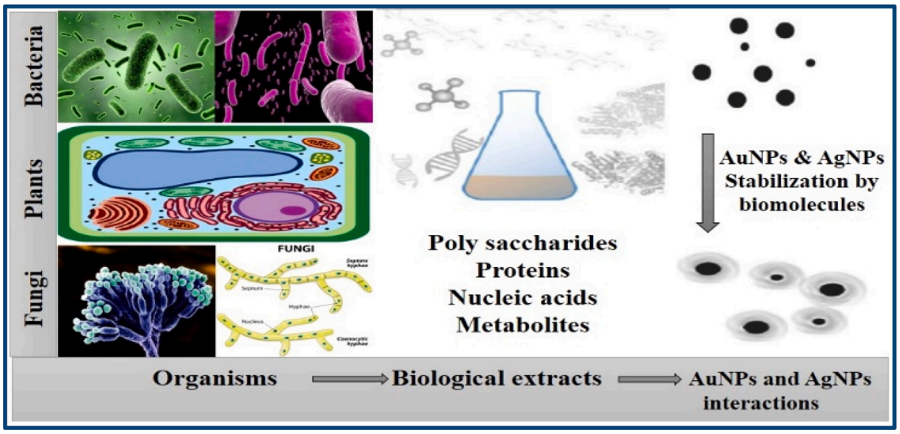

Fig. 2. Biological synthesis of metal NPs involving proteins, polysaccharides, nucleic acids and other metabolites from bacteria, plants and fungi.

$AgNO_3$ is reduced to Ag NPs when it is treated with fungal biomass and the previous studies showed that the particles are visible close to the cell wall and it rationalizes the presence of reducing an enzyme in the cell membrane. The role of nitrate reductase enzyme in reducing $AgNO_3$ to Ag NPs was well studied with *Fusarium oxysporum* [74]. The roles of polyphenols/ flavonoids, proteins, terpenoids, tannins as reducing, capping and stabilizing agents were well documented [75]. El-sonbaty *et al.*, (2013) studied the intracellular synthesis of Ag NPs where they observed a high dispersity and perfect shaped particles [76].

2.2.4. Biosynthesis of Ag and Au NPs using algae

Biosynthesis of Ag NPs by algae is an area with clear prospects. Usage of algae is more convenient because it eliminates the risk of serial subculturing and sophisticated storage [38]. Commonly followed the method of NPs synthesis is extracellular in case of algae. The reaction could be carried out in algal extract and the preparation of extract and the crucial process in NPs synthesis. The extract can be prepared either in water or in a corresponding solvent [77]. Considerable studies on marine algae on this aspect have been reported. Various freshwater algae and microalgae also used for the synthesis of Ag NPs. Algal synthesis is eco-friendly, rapid and stable [37,38]. The main advantage of NPs production by algae is its easy availability and effortless cultivation [77]. Algae and its extract are generally known for the extended bioactive potential and it is witnessed in kinds of literature. Algae possess antimicrobial, anti-inflammatory, antimitotic, antineoplastic, antioxidant and antifouling activities. Algae are effective producers of hydroxyl, carboxyl and amino functional groups, alkaloids, phenols, polysaccharides, saponins, flavonoids steroids. These molecules can contribute well for capping, stabilization and reduction reactions [78]. Phytobioreactors can be designed to establish the commercial production of metal NPs. All the scale-up strategies should be strictly followed to obtain optimum production [37,79].

Compared with different biomaterials utilized in green synthesis approach, the mushroom mediated metal NPs has more advantages like safe to handle, one-step process, environmentally friendly, a rapid rate of synthesis, more stable NPs, and better control over the size and shape of NPs. Owing to these advantages, many researchers aimed to explore the various mushroom species for synthesis of metal NPs.

3. Mycosynthesis of Ag NPs and Au NPs

3.1. Mushroom biology

Mushrooms are eukaryotic organisms classified under macrofungi with rigid cell walls and are non-photosynthetic. They vary from all other groups of organisms of this earth based on their peculiar physiology, lifestyle, biochemistry, and exclusively absorptive mode of nutrition [80]. It grows best in moist and shady places and has a cosmopolitan distribution. Mushrooms are both edible and non-edible fungi. They represent up to 41,000 species, of which about 850 species are recorded from various areas of India, in particular Himalayas and the Western Ghats. However, only a less numbers are commercially cultivated [81]. The most farmed mushrooms are the oyster mushroom (*Pleurotus florida*), straw mushroom (*Volvariella volvacea*), winter mushroom (*Flammulina velutipes*), black forest mushroom (*Lentinus edodes*), button mushroom (*Agaricus bisporus*). Historically, mushrooms have been served as a special kind of functional food and referred to as a storehouse of biological compounds. In this view, many mushrooms are revealed to have high nutritional value with more quantity of proteins, fibers, low or no cholesterol, minerals, and trace elements [82]. Mushrooms are consumed as folk medicine, and it comprises a vast and mostly untapped source of suitable new pharmaceutical materials. Mushrooms are well known for their anti-oxidant, anti-tumor, anti-viral, anti-yeast, anti-bacterial, anti-diabetic, anti-hypercholesterolic, anti-cancer, anti-arthritic, and anti-fungal activities [83,84].

3.2. Mushroom based fabrication of Ag NPs and Au NPs

Many bioactive chemicals with various biological activities may be found in many species of edible and medicinal mushrooms. When compared to chemical synthesis, the rate of mycosynthesis of Ag NPs and Au NPs was substantially faster. The outline protocol employed for NPs synthesis utilize mushroom extracellularly or intracellularly is displayed in Fig. 3.

The mushroom extract has inspired consideration for the biological development of metal NPs due to their tolerance and capability to accumulate metals [85,86]. Further, it was revealed that mushroom contains rich polysaccharides and proteins that attribute to the intracellular and extracellular fabrication of Au/Ag NPs [45]. Ag NPs and Au NPs have been extensively prepared through the biological reduction of Ag NO_3 to Ag NPs and $HAuCl_4$ to Au NPs using different mushroom species extracts viz., A. bisporus, L. edodes, Agrocybe aegerita, Ganoderma lucidium, V. volvaceae, and P. sajor caju, etc. [87]. Another exciting aspects of mushroom fungi as a perfect substance for fabricating NPs is the intracellular metal uptake capacities and high metal binding to the cell walls surface. Besides, mushroom fungi acquires one or more metal tolerance strategies viz., precipitation, intracellular sequestration, complexation, extracellular metal sequestration, increased metal efflux, and suppressed influx, [88].

Furthermore, mushrooms have the capability to synthesize metal NPs with nanoscale structures by the influence of their reducing enzymes and biomimetic mineralization (Fig. 4). The mycelial mesh used for NPs synthesis can bear agitation, other bioreactors conditions, flow pressure and compared with bacteria [89]. It can be easy to handle in downstream method of metal NPs synthesis as the reducing agents like proteins and polysaccharides are readily secreted by mushroom fungi [90]. A wide variety of mushroom species have been explored in many research for the green chemistry synthesis of both Ag and Au NPs through intracellular as well as extracellular processes, and their NPs shape and size are well examined (Table 1). Moreover, the mushroom extracts has been considered as cost-effective, much reliable, and compatible with biomedical research fields [33].

4. Mechanisms of Ag and Au NPs synthesis using mushroom

The mushroom mediated NPs synthesis mechanism involves three steps of nucleation, growth and stabilization. Firstly, a portion of metal ions in a solution is reduced to metal atoms by the available reducing agents. These atoms act as nucleation centers and catalyze the remaining metal ions which are present in the reaction solution. Clusters are formed via atoms aggregation. Secondly, the surface ions are frequently reduced in order to attain the high values of nuclei leading to the formation of larger particles during the process. Finally, the capping agents in the solution function as stabilizer and prevent the further aggregation of the particles.

Various types of mushrooms display diverse kinds of mechanisms; moreover, the reduction response is the main principle for NPs development (Fig. 5**)**. However, the development of NPs occurs by the impact of an enzyme reductase, which exists in the culture extract mixed with metal ions [85]. Mushroom-mediated NPs synthesis can be intracellular or extracellular as stated in the area of NPs development. In general, extracellular fabrication of NPs involved nitrate reductase action and electron shuttle quinones. Nitrate reductase start off NPs development in numerous fungi, including mushrooms. Some enzymes, such as nitrate-dependent reductases, α-NADPH-dependent reductases, and an extracellular shuttle quinone, are correlated with Ag NPs fabrication [108]. It was revealed that the development of NPs was due to the shift an electrons from free amino acids to metal ions [109]. The ninhydrin analysis could be proved the existence of free amino acids in the heat-denatured fungal extract, which may be produce for the NPs synthesis.

Mandal et al. (2006) revealed that the enzymes present in mushroom filtrate could play a crucial part in reducing metal ions by oxidating

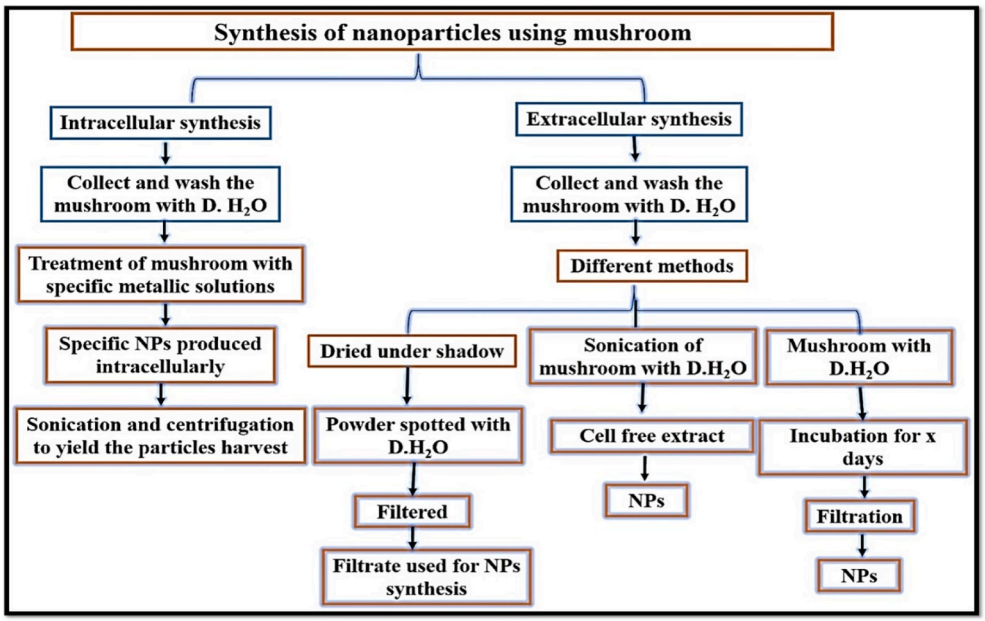

Fig. 3. Steps involved in the mycosynthesis of NPs using mushroom.

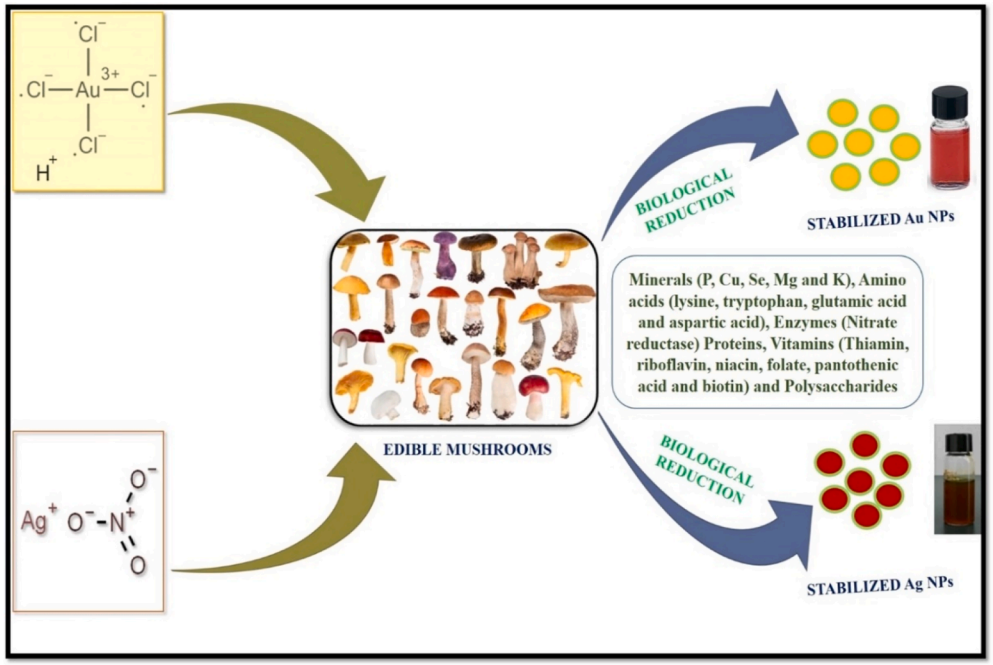

Fig. 4. Mycosynthesis of Ag and Au NPs using edible mushroom.

aldehyde groups to carboxylic acids [110]. A latest findings display that a glucan polysaccharide isolated from P. florida mushroom serves as a reducing and stabilizing material [92]. The mushroom extract of Tricholoma matsutake recommended the potentiality of reducing metal ions to metal NPs due to the existence of proteins [104]. Flavo-proteins present in the mushroom filtrate also play a key role for reducing Ag ions into Ag NPs [103].

The extracellular fabrication of Ag NPs and Au NPs by mushroom is due to the high existence of nitrate reductase enzymes in mushroom cytoplasm, which greatly assist the reduction of Ag and Au ions into Ag NPs and Au NPs, respectively. Molnar et al. (2018) recommended that the fabrication of Au NPs might contain two main concept affair that include stabilization by capping the ligands of NPs and reducing Au^{3+} into Au^{0} fabricate nuclei later the growth of NPs [111]. The safety ligands avert the additional development and agglomeration of NPs due to electrostatic stabilization and in the end promote well solid Au NPs.

In the intracellular development of NPs, the microbial cell serves as a particular ion transport process, where the negatively charged cell wall energetically associate with the metal ions transfer a positive charge that promote an electrostatic interaction force between these two opposite charges [24]. The metal ions are perhaps reduced by the enzymes or polysaccharides within the cell wall, which promote the accumulation of metal ions and the development of NPs [108].

Table 1
List of mushrooms explored for the synthesis of Ag NPs and Au NPs.

NPs type	Mushroom species	Mode of synthesis	Size	Shape	Reference
Au	*Pleurotus florida*	Extracellular	12–15 nm	Crystalline spherical	[91]
Au	*Pleurotus florida*	Extracellular	14.93 ± 2.88 nm	Crystalline spherical	[92]
Au	*Volvariella volvacea*	Extracellular	20–150 nm	Triangular	[21]
Au	*Pleurotus florida*	Extracellular	10–50 nm	Spherical	[91]
Au	*Pleurotus florida*	Extracellular	10–50 nm	Triangular	[91]
Au	*Volvariella volvacea*	Extracellular	20–150 nm	Spherical	[21]
Au	*Volvariella volvacea*	Extracellular	20–150 nm	Prism	[21]
Au	*Agaricus bisporus*	Intracellular	10–50 nm	Spherical	[93]
Au	*Lentinus edodes*	Intracellular	5–15 nm	Spherical	[73]
Au	*Pleurotus ostreatus*	Intracellular	5–15 nm	Spherical	[73]
Au	*Pleurotus ostreatus*	Intracellular	22–39 nm	–	[72]
Au	*Grifola frondosa*	Intracellular	5–15 nm	Spherical	[73]
Au	*Ganoderma lucidum*	Intracellular	5–15 nm	Spherical	[73]
Au	*Pleurotus ostreatus*	Intracellular	7.0 ± 0.5 nm	Crystalline spherical	[94]
Au	*P. cornucopiae* var. *citrinopileatus*	Intracellular	16–91 nm	Spherical	[95]
Au	*Lentinula edodes*	Intracellular	72 nm	Irregular	[96]
Au	*Flammulina velutipes*	Intracellular	10–80 nm	Spherical	[97]
Ag	*Agaricus bisporous*	Extracellular	30 nm	Spherical	[98]
Ag	*Agaricus bisporous*	Extracellular	10–20 nm	Spherical	[99]
Ag	*Fomes fomenterieus*	Extracellular	8–50 nm	–	[100]
Ag	*Lentinula edodes*	Extracellular	–	–	[100]
Ag	*Agaricus bisporous*	Extracellular	20–44 nm	Dispersed spherical	[98]
Ag	*Agaricus bisporous*	Extracellular	–	–	[99]
Ag	*Ganoderma appalanatum*	Extracellular	15–20 nm	–	[21]
Ag	*Pleurotus florida*	Extracellular	20–50 nm	–	[101]
Ag	*Pleurotus citrinopileatus*	Extracellular	6–10 nm	Core-shell spherical	[102]
Ag	*Pleurotus florida*	Extracellular	20 ± 5 nm	–	[21]
Ag	*Volvariella volvacea*	Extracellular	5 nm	–	[103]
Ag	*Pleurotus ostreatus (white)*	Extracellular	–	–	[95]
Ag	*P.salmoneostramineus (pink)*	Extracellular	–	–	[45]
Ag	*Agaricus bisporous*	Extracellular	5–50 nm	Spherical	[100]
Ag	*Calocybe indica*	Extracellular	5–50 nm	Spherical	[100]
Ag	*Pleurotus florida*	Extracellular	5–50 nm	Spherical	[100]
Ag	*Pleurotus florida*	Extracellular	20 ± 5 nm	Spherical	[90]
Ag	*Tricholoma matsutake*	Extracellular	10–20 nm	–	[104]
Ag	*Schizophyllum commune*	Extracellular	–	–	[105]
Ag	*Pleurotus florida*	Extracellular	20 ± 5 nm	Spherical	[91]
Ag	*Agaricus bisporous*	Intracellular	80–100 nm	Spherical	[106]
Ag	*Agaricus bisporous*	Intracellular	40–60 nm	Spherical	[86]
Ag	*Coriolus Versicolor*	Intracellular	10 nm	Spherical	[107]
Ag	*P. comucopiae* var. *citrinopileatus (bright yellow)*	Intracellular	10–20 nm	Spherical	[83]
Ag	*Calocybe indica*	Intracellular	100 nm	Spherical	[106]
Ag	*Pleurotus ostreatus (grey)*	Intracellular	–	–	[45]

5. Antimicrobial peptide as an alternative agent

Nature provides a defence system as a part of innate immunity, which is produced as antimicrobial substances by animals, plants, insects, and bacteria in the form of hydrogen peroxide, fatty acids, organic acids, ethanol, antibiotics, and antimicrobial peptides (AMPs). AMPs possess broad spectrum effectiveness against multidrug-resistant pathogens, which make them very interesting compounds for the search of new drug molecules [112]. AMPs are small-molecular-weight proteins/peptides generally produced by different multicellular organisms. Most of the AMPs possess net positive charge because of the presence of multiple lysine and arginine residues along with $\geq$ 30 % hydrophobic residues. Till date, hundreds of such AMPs have been searched with activity against various pathogenic microorganisms, fungi, yeast, viruses and others [113,114].

5.1. Bacteriocins: Antimicrobial peptide from bacteria

The antimicrobial peptides (AMPs) secreted by the bacterial cells are known as bacteriocins. Limited nutrients in the atmosphere cause production of diverse bacteriocins for survival. Bacteriocins are ribosomally synthesized peptides which display narrow spectrum potential (kills relatively close species) or broad-spectrum activity (kills non-related microbial group). Most of the bacteria have the capability of producing at least one bacteriocin, many of them, are still not identified [115]. Although the antibiotics and bacteriocins have a bacterial origin and pose similar function but they differ. Antibiotics are secondary metabolites of bacterial cells while bacteriocins are synthesized by ribosomes [116].

5.2. Sources of bacteriocin

In the current scenario, bacteriocins have been anticipated as a replacement for antibiotics to which the pathogenic bacteria are developing resistance. In previous studies, bacteriocin was isolated from various genera including *Bifidobacteria*, LAB, and yeast (Table 2). The bacteriocin production is not limited to any specific bacteria as it can be produced by both Gram-positive and Gram-negative bacteria [117]. The first bacteriocin named colicin was isolated and purified from Gram-negative bacteria *E. coli* [118]. Klebicins, marcescins, alveicins, cloacin and pyocin are the other known bacteriocins from Gram-negative bacteria secreted by *K. pneumoniae*, *Serratia marcescens*, *Hafnia alvei*, *Enterobacter cloacae* and *Pseudomonads,* respectively [119]. They are classified into two groups, 30–80 kDa molecular mass bacteriocins secreted by Gram-negative bacteria are known as colicins and 1–10 kDa were known are microcin. Most of the bacteriocins of Gram-negative bacteria belonging to colicin are heat labile peptides which cannot survive in extreme conditions [118].

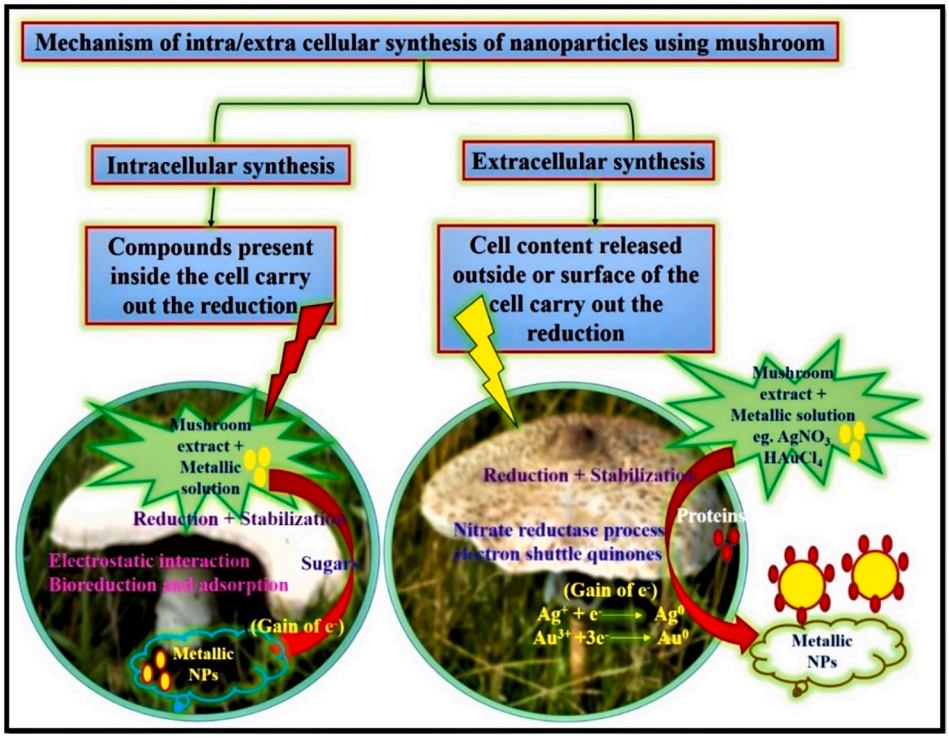

Fig. 5. Mechanisms of intra/extra cellular synthesis of NPs using mushroom.

5.3. Classification of bacteriocin

The classification of bacteriocin is based on their structure, size, and sensitivity towards enzymes, thermo stability and post translational modifications (Table 3).

5.4. Mechanism of action

The detailed study of physical and chemical parameters of bacteriocin is very important for targeting the pathogenic bacteria [146]. The bacteriocin differs in their molecular structure, amino acid composition, molecular weight, thermo stability, pH, antimicrobial activity and mode of action. The *in-vitro* and *in-vivo* investigations reveal the promising compound to become a therapeutic drug molecule [147]. Many of the bacteriocins are bactericidal in action in which lysis of the cell takes place. In few cases, the bacteriocin activity is bacteriostatic in nature. Many of the bacteriocins (e.g. colicins) are acting on sensitive cells by pore formation and weakens the integrity of the membrane thus results in leakage of cellular constituents [148]. The gram-positive bacteria are made up of peptidoglycan whereas the gram-negative bacteria are made up of lipopolysaccharides. This feature greatly influences the mode of action of bacteriocin on pathogenic bacteria. In recent study, it was reported that the inhibitory activity determination is difficult if the producer strain produces several bacteriocins, organic acids and hydrogen peroxide [149]. Various mode of bacteriocin action on microorganisms was represented in Fig. 6**.** The class I peptide bacteriocins attacks on microorganisms by attaching to the cell wall membrane, inserted into the membrane followed by pore formation results in cellular constituents leakage [150,151]. The class II bacteriocins integrate into the cell wall membrane causes depolarization of the membrane and membrane potential disrupts that leads to death of the cell [152]. In a recent study by Colombo et al. (2018) reported that the bacteriocins act on cytoplasmic membrane and dissipate the electric potential of the membrane [153]. Krishnamoorthi et al., (2022) reported that bacteriocin significant antimicrobial effects against *C. albicans, A. fumigatus, S. flexneri, K. pneumoniae, S. aureus* and *S. pyogens*. Moreover, the bacteriocin mode of action against human pathogens was revealed that cell lysis and rupture the cell wall as reported in SEM studies [120]. The bacteriocin mode of action results from its binding to the receptors present on the surface of bacterial membrane of the target. In another mechanism the interaction of charged ions between bacteriocins and membrane lipids results in the generation of electrostatic forces followed by bacteriocin entry into the bacterial cell [154].

Members of class I bacteriocins target the lipid II, an intermediate in the peptidoglycan biosynthesis [155]. Some of the bacteriocins have been reported to form pore by their capability to directly insert themselves into bacterial cells after binding to the lipid II. Bacteriocins from class I have also been reported for depletion of membrane potential which causes efflux of compounds. Type A subgroup of lantibiotics of class I which includes nisin, epidermin, and galidermin, targets the bacterial cells by two mechanisms, one membrane permeabilization and another inhibition of cell wall [156]. Mersacidin, a member of type B has been revealed to inhibit peptidoglycan synthesis by reacting with lipid II without interacting with transglycosylation enzyme [157]. Plantaricin C, the member of type B lantibiotic, targets bacterial cell by direct lipid II-mediated action [155].

Class II bacteriocins have been reported for the disintegration of plasma membrane of the bacterial cell [158]. Class II bacteriocins are a diverse class of short thermostable peptides (10 kDa) having an amphiphilic helical shape that enables their entry into the cytoplasmic membrane of the target cell, leading to membrane depolarization and cell death. They induce the leakage of internal substances such as monovalent cations, phosphate and ATP. The members of class II, PA-1, leucocin A, and mesentericin Y105 are known for binding with specific receptors present on the bacterial cell surface. Mannose phospho transferase system (PTS) and EIIt Man permease act as a receptor for members of class II, which directs its activity against *L. monocytogenes* and *Enterococcus faecalis* [159].

Similar to most bacteriocins, class IIc cyclic bacteriocins permeabilize the membrane of susceptible cells, resulting in the leakage of ions, dissipation of the membrane potential, and cell apoptosis [160]. Class III bacteriocins are bigger in size having molecular

Table 2
List of bacteriocin producing microorganisms.

S. No.	Bacteria	Bacteriocins	Antimicrobial Activity	Reference
Lactic acid bacteria				
1	*L. lactis* strain CH3	Nisin	*C. albicans, A. fumigatus, S. flexneri, K. pneumoniae, S. aureus,* and *S. pyogenes*	[120]
2	*L. lactis* subsp. *lactis B14*	Bozacin B14	LAB and food borne pathogens	[121]
3	*L. lactis* subsp. *lactis Q1-2*	Lactococcin 972	*L. sakei, L. lactis* subsp. *lactis and L. cremoris*	[122]
4	*L. lactis* subsp. *cremoris 2A27*	Lactococcin G	*L. sakei, L. lactis* subsp. *lactis and L. cremoris*	[122]
5	*L. lactis* subsp. *lactis*	Nisin A	*S. aureus, Listeria innocua, L. sakei,* and *L. plantarum*	[123]
6	*L. lactis* subsp. *lactis 1AA17 and 2BB9*	Nisin Z	*S. aureus, L. innocua, L. sakei,* and *L. plantarum*	[123]
7	*Lactiplantibacillus plantarum KLDS1.0391*	Plantaricin MG	*L. monocytogenes, S. aureus, S. typhimurium* and *E. coli*	[124]
8	*Lactococcus garvieae BCC 43578*	Garvieacin Q	*L. garvieae, Enterococcus faecium, and L. monocytogenes*	[125]
9	*Lactobacillus animalis TSU4*	Bacteriocin TSU4	*A. hydrophila, P. aeruginosa, S. flexneri, S. typhimurium, S. aureus, S. paratyphi,* and *E. coli*	[126]
10	*Lactobacillus coryniformis MXJ 32*	Lactocin MXJ 32A	*E. coli, S.aureus, Salmonella* sp., *L. monocytogenes,* and *C. sakazakii*	[127]
11	*L. plantarum JLA-9*	Pantaricin JLA-9	and *M. Luteus, S. aureus, C. sporogenes, C. perfringens, C. difficile, P. polymyxa, A. acidoterrestris, G. stearothermophilus, B. subtilis, B. coagulans,* and *B. cereus,*	[128]
12	*B.animals* BB04	Bifidocin A	E.coli, Listeria monocytogenes, S. aureus	[129]
Yeast				
13	*S. boulardii* CNCM I-745	leucocin C	Antilisterial activity (L. monocytogenes)	[130]
Bacillus				
14	*Bacillus licheniformis*	Bacteriocin BL8	*B. circulans, S. aureus, B. coagulans, B. cereus, C. perfringens* and *B. pumilis*	[131]
15	*Bacillus subtilis*	Bacteriocin	diabetic foot ulcer patients to *Pseudomonas* sp., *S. aureus* sp., *Klebsiella* sp. and *Proteus* sp.	[132]
Streptococcus				
17	*S. thermophilus* ST109	Thermophilin 109	*E. faecalis* and *S. pyogenes*	[133]
18	*S.thermophilus* SBT1277	Thermophilin 1277	*C. butylicum, C. sprogenes* and *B. cereus*	[134]
19	*Streptococcus mutans* N	Mutacin N	*S. pyogenes* and Oral *Streptococci*	[135]
Enterococcus				
20	*E. faecalis* 478	Enterocin 478	multidrug-resistant enterococci and vancomycin-resistant enterococci	[136]
21	*E. faecalis* NKR-4–1	Enterocin W	*B. coagulans, B. circulans, B. subtilis,* and *Listeria innocua*	[137]
22	*Enterococcus durans L28-1*	Durancin L28-1A	LAB and food borne pathogens	[138]
23	*Enterococcus mundtii QU 2*	Mundticin KS	*E. faecalis, E. hirae, L. plantarum, L. sakei* ssp. *sakei, Leuconostoc mesenteroides,* and *P. acidilactici*	[139]

Table 3
Types of bacteriocin and their characteristics.

Class	Subgroups	Characteristics feature of bacteriocin	Examples	Reference
Class I		Lantibiotics, small size peptides, presence of unusual amino acids		
	Type A	Amphipathic peptides, known for voltage-dependent pore formation	Nisin	[140]
	Type B	Small anionic or neutral peptides	Mutacin II	[141]
Class II		Non-lantibiotics Absence of unusual amino acids, heat stable		
	IIa	Bacteriocin possessing anti-listeral activity	Leucocin A	[142]
	IIb	Composed of two complementary peptides whose mechanism depend upon both peptides	Lactococcin Q	[143]
	IIc	Cyclic bacteriocins formed by the linkage of C and N terminals of the peptide	Lactocyclicin Q	[144]
	IId	Non pediocin like linear peptide	Lacticin Q	[145]

weight>30KDa. The bacteriocins are hydrophilic and heat labile in nature. Their action mode differs compared to other bacteriocins in that they encourage the destruction of the target microorganism's cell envelope. Their C-terminal region is in charge of recognising the target cell, while their *N*-terminal region is similar to an endopeptidase responsible for the synthesis of cell walls. The bacteriocins interfere with different cellular functions such as cell wall synthesis, transcription, translation and replication [152]. The peptides possessing good antimicrobial activity have been discovered recently and some of them are under clinical trials [161–163].

6. Bio-functional potential of metal NPs

Nanomaterials reveals antimicrobial property by promoting antibiotics administration effectiveness and safety [86,93,164]. The antimicrobial property of NPs cannot pose direct and severe consequence, while promising toxicity upon long-term exposure. The development of antimicrobial NPs could be non-toxic, cost-effective when compared with antibiotics fabrication, and they are relatively stable enough for long-term storage with an extended shelf-life [86]. Besides, the synthesized metal NPs can tolerate hard state of affairs, such as high-temperature sterilization, under which conventional antibiotics are usually inactivated. Antibiotics distribution using metal NPs offer various superiority: i) reduced side effects, ii) sustained and controlled

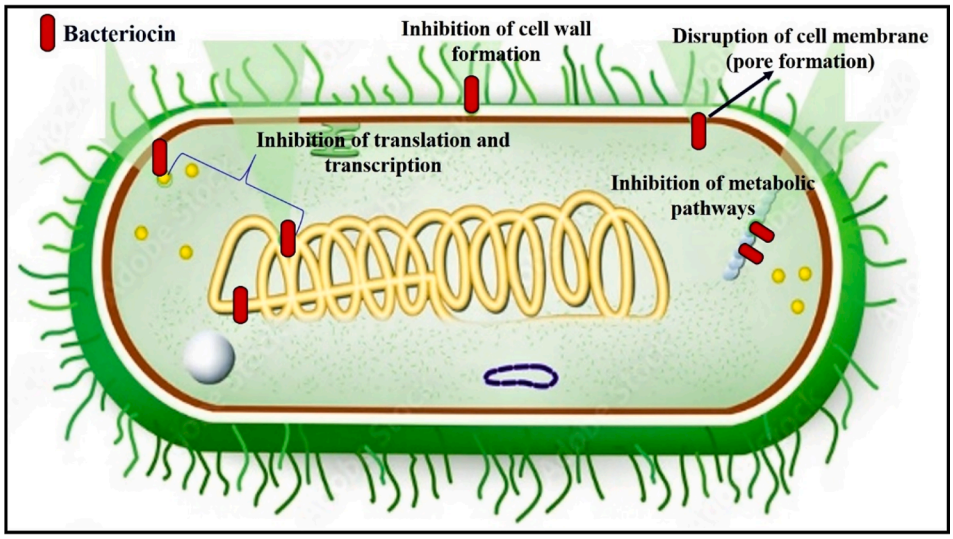

Fig. 6. Mechanism of antibacterial action of bacteriocin.

release, iii) controllable and relatively uniform distribution in the target tissue, iv) enhanced cellular internalization, v) improved patient-compliance, and vi) improved solubility [32,86,93].

Metal NPs make reactive oxygen species (ROS) under UV light and find their increasing applications in antimicrobial formulations and dressings. In particular, silver, gold, zinc, and their compounds fruitfully inactivate many pathogenic microorganisms. Currently, tetracycline hydrochloride development in polymeric NPs has demonstrated increased antimicrobial properties and anti-methicillin resistant *Staphylococcus aureus* (MRSA) properties with non-polymerized forms of penicillin and *N*-methylthio β-lactams [165–167]. Vancomycin-capped Au NPs have also revealed increasing antimicrobial properties against vancomycin-resistant enterococci (VRE), and *E. coli* strains [168]. Metal NPs based bionanocomposite with bacteriocin could enhance their antimicrobial potential against MDR pathogenic microorganisms.

6.1. Antibacterial potential of Ag NPs and Au NPs

In the last few years, bacterial infection is common in healthcare settings, especially in hospital-acquired infections, contamination of water, food, and agriculture sectors worldwide. Hospital patients mostly pneumonia, bacteraemia, meningitis, urinary tract infections, as well as skin and soft-tissue infections caused by *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Acinetobacter* spp. Microbial pollutions are key for the most common clinical infections around worldwide, conveying considerable dangers to the general well-being of humans. Presently, familiar market obtainable antimicrobial agents are antibiotics, metal salt arrangements, and ammonium salt [165]. Unfortunately, most antimicrobial agents are poor, and misapplication has led to MDR of pathogenic bacteria, yeast, and fungal microorganisms. The notable pollution that have happened because of MDR microbes of *Pseudomonas* sp, *Klebsiella* sp., and *Acinetobacter baumannii* are rise at an alarming signal [61]. In this way, it is critical to detect novel antimicrobial agents with less toxic qualities and high potency to combat this catastrophe. Therefore, it is necessary to create innovative antimicrobial treatments based on metal NPs that have high antibacterial effectiveness, low toxicity, and good compatibility. Metal NPs have been considered as possible substitute to commercial antibiotics.

The therapeutic properties of many antibiotics originate from their capability to "inhibit the cell wall synthesis, interfering with essential proteins expression and disrupting the DNA replication machinery". However, bacteria have developed the capability to resist each of these mechanisms of action. One of the fundamental principle of bacterial resistance is the change of the antibiotics target [169]. Over the years, the use of nanomaterials in photo thermal therapy has received considerable attention [170,171]. The light-responsive technique specifically has been used in the development of drugs. It has also found application in the design of drug carrier systems and as an antibacterial agent. The light-responsive structure can be easily regulated and it has low invasiveness. Its mechanism of activity is based on the alteration of the light sensitive molecules when stimulated by light, thus enabling the release of the encapsulated or conjugated drug [172]. Metal NPs can overcome the drug resistance principle owing to their distinctive physicochemical activity, enabling nanomaterials to carry out various new bactericidal pathways (Fig. 7 **and** Table 4) to attain antimicrobial properties such as i) photocatalytic generation of ROS that damage cellular constituents, ii) inhibition of enzyme property and DNA synthesis, iii) interruption of energy transduction, and iv) compromising the bacterial cell membrane [173–175]. The antibacterial mechanisms of metal NPs is naturally relative their core material, shape, size, and surface functionalization. Besides their broad-spectrum antibacterial activity, metal NPs have been used as a vectors to deliver antimicrobial component that outstandingly enhance their biocidal activities [176]. Metal NPs shows entirely new or enhanced activities based on particular characteristics such as size, shape, and NPs distribution. Some of the benefits of using metal NPs as vectors are their protective action against enzymes that would otherwise kills antimicrobial agents; their capability to deliver antibiotics actively, and their capability to combine many therapeutic modalities onto an one individual nanomaterials [165,176].

The Au-Ag NPs, which are positively charged, aggregate on negatively charged bacterial cell walls. They release Ag NPs and generate ROS, which are antibacterial agents. Strong emission under near-infrared (NIR) irradiation allows these bacteria to be easily damaged. The NIR irradiation also increases the antibacterial effect of the NPs through the photo-thermal effect (heat generation using energy converted from the absorbed photons), it brings about a considerable conformational change in the cell wall. It eventually loses permeability control, which generate to cell death [172]. Once metal NPs enter the bacterial cell, they would affect with the bacterial multiplication signalling pathway by modulating tyrosine phosphorylation of putative peptides substrates important for cell division and cell viability [86,177]. The other mechanism is the development of free radicals, which subsequently promote membrane damage leading to an effective antimicrobial activity of metal NPs against *S. flexneri, K. pneumoniae, S. aureus,* and *S. pyogene* at 100 μg/ml. Further, the metal ions interfere with the bacterial cell wall and electron transport at the same time causing DNA damage [86]. Strong antibacterial action by Ag NPs against

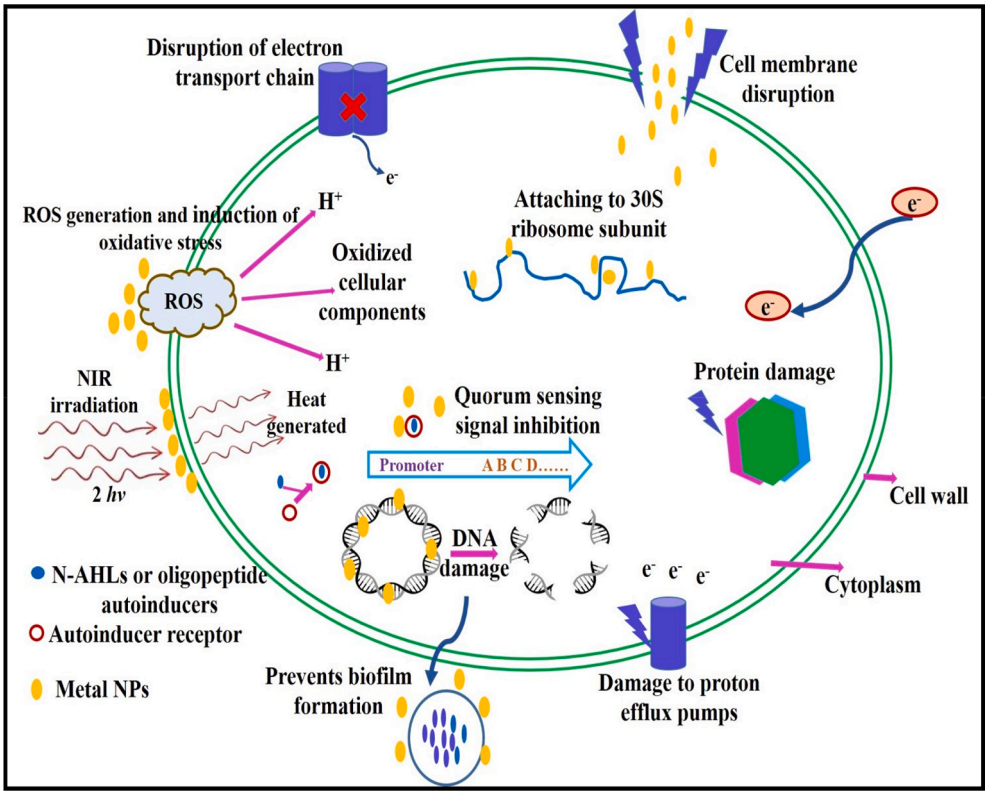

Fig. 7. Mechanisms of antibacterial action of metal NPs.

human bacterial pathogens that are resistant to many drugs has been established.

In previously so many studies was reported that Ag and Au NPs as a broad spectrum of antimicrobial effects. For example, *S. aureus* and *Edwardesiella tarda* bacteria were resistant to Ag NPs inspired with citrus lemon juice as a reducing agent, while *Oscillatoria* species were resistant to the cyanobacterial effects of the latter [178]. Researchers have looked into using Au NPs as an effective antibacterial to inhibit the growth of common waterborne infections like *Salmonella typhi* and *E. coli* that are developing resistance to conventional bactericides [179]. Carrizales et al. documented that AgNPs can reduce bacterial adherence in the early stages of biofilm development and enhance the impact of antibiotics against bacteria that are resistant to them [180]. According to Fernando et al. (2019), Ag NPs containing garcinol from *G. quaesita* Pierre on top effectively suppressed the development of a methicillin-resistant strain of Staphylococcus aureus with a 21.7 mm zone of inhibition [181].

Priyadharshni et al., (2022) reported that, the synergistic antimicrobial effects of Ag NPs and mushroom extract showed efficient antibacterial effects against human pathogens and Ag NPs with mushroom extract may be attributed by their tiny size and large surface area to contact the microbial cells and thus makes them interact effectively with the cell wall of the disease causing microbes [164]. The mushroom based Au NPs may bind with the cytoplasmic membrane and destroys the bacterial cell due to the electrostatic affinity between positively charged Au NPs and negatively charged cell membrane of the pathogenic microbes [111]. Krishnamoorthi et al., (2022) clearly reported that mushroom based Ag NPs may induce the release of reactive oxygen species, which leads to the destruction of proteins and DNA of bacteria cells, ultimately cause cell death [86].

Also, metal NPs could produce ROS that interfere the amino acid synthesis and DNA in bacterial cells. On the other hand, metal oxide-based nanomaterials cause cell wall damage and produce ROS to destroy bacteria [86,167]. Metallic nanomaterial can offer a wide range of antibacterial mechanisms (Fig. 7) could combat drug-resistant superbugs [182]. The Ag NPs and Au NPs reveals efficient antimicrobial activity due to their extensive surface area, which provides superior contact with human pathogens at 100 μg/ml [90,93]. Nanomaterials surface chemistry is important to modulate their interaction with bacteria, enhancing their broad-spectrum property at the same time decreasing their toxicity against mammalian cells [86,165].

6.2. Antifungal potential of Ag NPs and Au NPs

Around the world, fungus infections are the most prevalent infectious disease. Fungal diseases appear in individuals when an invasive fungus invades a body organ and multiplies beyond the capacity of the immune system to manage it. The most frequent fungal pathogens are *Candida albicans*, *Aspergillus* spp., *Pneumocystis* spp., and *Cryptococcus* spp. *C. albicans* is an opportunistic pathogen cause sickness to humans like bloodstream infections and oral thrush [198]. After occasionally it will become acute to die. The Indian public is dealing with a brand-new issue as reports of recent COVID-19 patients who have died with mucormycosis, it is sometimes known as “black fungus,” emerge. Sinus fungus infections are challenging to cure and frequently lethal. Of late, the resistance of fungal pathogens to antifungal drugs has received worldwide recognition. Thus, there is a growing demand for novel antifungal agents. To overcome this issue, metallic NPs as powerful nano weapon to fight fungal pathogens. The Ag/Au NPs are the most frequently studied NPs that demonstrate a potent antifungal effects through various mechanisms viz., induction of cell wall interfere, cell wall depolarization, cell cycle arrest, promotion of bacteria cell apoptosis via metacaspase activation, and cytochrome *c* release [199]. The action of metal NPs and their particular antifungal mechanisms are displayed in Fig. 8.

The interaction of Au NPs with fungal pathogens and effective enzymes may change their regular conformations superior to the activity loss [200]. Thus, the fungal cell wall is impotent of controlling the H^+

Table 4
Mechanism of antibacterial action of Ag/Au NPs against target bacteria.

NPs type	Targeted bacteria	Concentration of NPs	Mechanisms of antibacterial action	Reference
Ag	*Streptococcus pneumoniae*	20 µL	ROS generation, cellular uptake of silver ions, cascade of intracellular reaction.	[183]
Ag	*Streptococcus pyogenes, S. aureu, K. pneumoniae* and *Shigella flexneri*	100 µg/ ml	Disruption of the bacterial cell wall, DNA damage, and ROS generation.	[86]
Ag	*Staphylococcus aureus*	100 µg/ ml	Cell surface damage and loss of the chain integrity.	[31]
Ag	*Pseudomonas aeruginosa* and *E. coli*	1 µg/disc	Evade multidrug efflux pumps.	[30]
Ag	*Enterobacter cloacae* and *Streptococcus mutans*	180 µg/ ml	ROS production and membrane disruption.	[184]
Ag	*S. epidermidis* and *S. aureus*	80 µg/ ml	Penetration in the bacterial biofilm using an external magnetic field.	[185]
Ag	*Escherichia coli* and *P. aeruginosa*	50 mM	Inhibition of cell wall synthesis, protein synthesis and nucleic acid synthesis.	[15]
Ag	*S. aureus* and *E. coli*	80–160 µg/ ml	Physical adhesion to the bacterial cell.	[186]
Ag	*Acinetobacter baumannii*	3.06 µg/ ml	Attach to the cell wall leading to structural changes in the permeability of the cell membrane.	[187]
Ag	*A. calcoaceticus*	50 µg/ ml	Not revealed.	[188]
Ag	*S. aureus* and *E. coli*	100 µg/ ml	Upregulation of the expression of antioxidant genes and ATP pumps.	[189]
Au	*Klebsiella pneumoniae* and *E. coli*	1.009 mg/L	Disruption of the bacterial cell wall, DNA damage.	[190]
Au	*Streptococcus pyogenes, S. aureu, K. pneumoniae* and *Shigella flexneri*	100 µg/ ml	Disruption of the bacterial cell wall, DNA damage.	[93]
Au	*Streptococcus bovis* and *Streptococcus epidermidis*	50 to 512 µg/ml	Disruption of the bacterial cell wall.	[191]
Au	*Acinetobacter baumannii*	40 µg/ml	Disturb of osmotic balance and disrupt the integrity of cell bacterial cell wall.	[192]
Au	*E. coli*	4 mg/mL	Interaction between lysozyme microbubbles and cell wall.	[193]
Au	*P. aeruginosa*	>78 ppm	Interaction with cell surface.	[194]
Au	*S. aureus*	70 µg/mL	Laser excitation of the near IR LSPR lead to an efficient photothermal response with efficient killing of bacteria biofilms.	[195]
Au	*E. coli*	0.005 % v/v	Penetration through biofilm layers and interaction with cellular components.	[196]
Au	*Proteus species*	2 µM	Interaction between proteins and NPs.	[197]

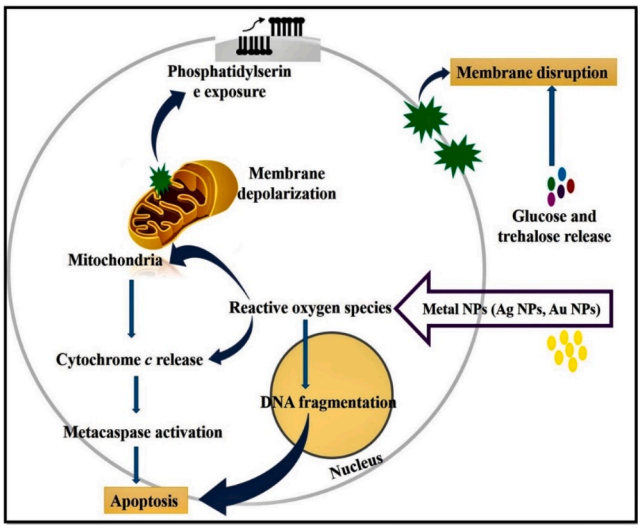

Fig. 8. Mechanism of antifungal action of metal NPs.

transport across the cell wall, leading to the cell growth's retardation, which ultimately causes cell death. The antifungal property of metal NPs is size-dependent and the extent of inhibition enhanced with the particle size decreased. Since, the decreased particle size of Au NPs has an increased surface area that enhances its interaction with the binding sites of the plasma membrane proteins.

A small sized Au NPs may diffuse rapidly through the cell wall to the cells inside. Au (weak acid) has a better tendency to behave with the sulphur and phosphorus-containing soft bases [201]. Therefore, Au NPs may interact with phosphorus-containing bases in DNA or sulfur-containing proteins in cell wall proteins to prevent cells from operating normally, such as replicating, synthesising, repairing, and ultimately cell death. Krishnamoorthi et al. 2021 reported that Au NPs obtained from *A. bisporus*, which have great antifungal potential in *C. albicans* and *A. fumigatus* at 100 µg/ml [111]. The findings of Priyadarshni et al. 2022, green synthesis of Ag NPs with mushroom extract have antifungal efficacy in *A. fumigatus* and *C. albicans* [164]. Various fungal pathogens are more susceptible for Ag/Au NPs and their particular antifungal mechanism are displayed in Table 5.

6.3. Antiviral potential of Ag NPs and Au NPs

Viral infectious diseases like Human Immunodeficiency viruses (HIV) and influenza including Ebola [207], Zika [208] and Avian Influenza as well as corona virus (CoV) are common throughout the world. COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are responsible for huge mortality globally [8–10]. Fruitful remedy of viral infections are limited by enhanced drug

Table 5
Mechanism of antifungal action of Ag/Au NPs against target fungi.

NPs type	Targeted fungi	Concentration of NPs	Mechanisms of antifungal action	Reference
Ag	*Aspergillus niger, and Candida albicans*	25–50 μg/ ml	DNA replication, cellular proteins and enzyme essential for ATP production is inactivated of living cells.	[202]
Ag	*C. albicans* and *A. fumigatus*	100 μg/ ml	Disruption of cell membrane and cell lysis	[86]
Ag	*Candida albicans*	2 μg /ml	Disrupted the cell membrane and inhibited the normal budding process.	[200]
Ag	*Sclerotinia homoeocarpa*	200 μg/ml	Oxidative damage.	[203]
Ag	*C. albicans* and *A. fumigatus*	100 μg/ml	cell membrane disruption and cell lysis	[204]
Ag	*Saccharomyces boulardii* and *C. tropicals*	25 μg/mL	Damage to cell death. Cell wall disruption and osmotic imbalance.	[205]
Ag	*Aspergillus niger*	200 μL	Pitting of the cell membranes and finally cell death.	[206]
Au	*Aspergillus niger* and *Fusarium oxysporum*	100 μL	Inactivation of sulfhydryl groups in the fungal cell wall and disruption of membrane bound enzymes and lipids which causes cell lysis. Disruption of cell membrane and cell lysis	[201]
Au	*C. albicans*	>166 ppm	Interaction with cell surface.	[194]
Au	*C. albicans* and *A. fumigatus*	100 μg/ ml	Disruption of cell membrane and cell lysis	[93]

resistance, mostly related to HIV [209] and influenza [210]. Viruses are rigidly intracellular pathogenic microbes composing of DNA or RNA as genetic factor and a protein coat (capsid). The genetic code for enzymes requires in replication and for many structural proteins which confers infection inducing virulence factor of viruses. All the DNA and RNA viruses enter into the host cell through a particular receptor on the cell membrane of host cells by connection glycoprotein implant in the viral envelope [211,212]. The CoV enters the host cell membrane by binding on the specific receptor of the angiotensin-converting enzyme 2 (ACE2) protein site. Followed by entry into the host cell membrane, the RNA viruses undergo reverse transcription (viral mRNA synthesis) [36]. Utmost severe lung contagions were caused by CoV, such as SARS-Cov, MERS and SARS-CoV-2 [176]. Currently, appropriate, safe, biocompatible, and alternative antiviral materials to avert pandemic contagions is required. Generally, metal NPs possess remarkable antimicrobial and antiviral properties [55]. Therefore, it is crucial to highlight the significance of particular metal NPs to be used as antiviral and drug delivery agents.

Fabrication of metal nanomaterial drugs having various antiviral mechanisms viz., "inhibition of virus fusion with the host cell membrane, anatomization of cell surface receptors, inhibition of uncoating, inhibition of transcription of viral RNA or DNA, inhibition of enzymes involved in virus replication, inhibition of protease as well as neuraminidase production" as displayed in Fig. 9 [213]. The working of metal NPs and their particular antiviral mechanisms are shown in Table 6.

6.3.1. *Therapeutic approaches for COVID-19*

Nowadays, the epidemic of the tremendous contagion novel COVID-19 associated pneumonia is a worldwide pandemic. Various therapeutic approaches for COVID-19 treatment viz., renal replacement/transplant, rescue therapy, immunotherapy, mechanical ventilation, oxygen therapy, antiviral therapy, blood purification and circulatory support and plasma therapy were reported by sheanhan et al., (2012), which was not only to treat the symptoms of COVID-19, and also capability to reduce the viral load [223]. Most of the anti-viral drugs can be used for preliminary treatment of COVID-19 infections likewise Arbidol, Chloroquine phosphate, Ribavirin, Lopinavir/ritonavir, IFN-α, remdesiver and hydroxychloroquine along with azithromycin [224–226]. Due to the global challenge of finding a long-term solution to the issue, various vaccinations, medications, and immunotherapeutic candidates started entering clinical trials concurrently. As per report of WHO and COVID-19 vaccine tracker, 74 vaccine are being completed or in-completed globally. Amid these limited number of vaccines have done 3rd phase trials successfully and now those are in use and the reports were displayed in Table 7. Additionally, the only option to discover efficient and secure COVID-19 remedies is through simultaneous and rapid ambulatory and medical care combined with randomized clinical trials [227,228].

In the regards, the metal NPs in relation to CoV, is that they are capable to suppress viral binding to the host cell- specific surface receptor [239]. Metal NPs perform as superior antiviral drug transporter because of their large surface-to-volume ratios, tiny, modifiable surfaces, and controllable hydrophobicity, which enable the drug-loaded NPs to target particular biological sites [240]. Dendrimers, quantum dot and micelles are the most often used NPs against viruses [241]. In recent times, many researchers dealing with metal NPs against COVID-19, but they have more limitations like NPs effective against CoV was 20 nm size with 50–70 ppm dose concentration which may cause cytotoxicity [221]. Bacteriocin obstruct with viruses entry of host cell by blocking the surface receptor and simultaneously decrease the virus load into the host cells [242]. Bacteriocin have a potential anti-viral effects against SARS-CoV-2 infections, and not only to treat the symptoms of SARS-CoV-2, while act as an immunomodulatory for humans. Balemh et al., (2021) was also reported that bacteriocin have promising antiviral effects against COVID-19 and prophylaxis of SARS-CoV-2 [243].

Kim and colleagues found that the affinity of Au NPs for the thiolated domain of hemagglutinin, a highly conserved fusion protein of influenza virus, is a factor in the antiviral action of Au NPs. The findings demonstrate that after receiving Au NPs therapy, the vitality of virus-infected MDCK cells improved to 96.8 % compared to 33.9 % in the control group. The greater affinity of AuNPs for the disulfide bond with HA, which inhibits the fusion of the viral membrane and is supported by real-time RT-PCR, is thought to be the probable mechanism of the anti-influenza effect of these particles. Because the SARS-CoV-2 virus also includes HA, like the influenza virus, these careful arguments lead researchers to consider using AuNPs as a supplement to the Covid-19 therapy [244,245]. Alghrair et al. examine the anti-influenza effect of Flu-Pep modified Ag and Au NPs in canine MDCK cells. The results suggest that both functionalized nano-systems have high antiviral efficacy, with an IC_{50} value of 2.1 nM, although they are lower effective than Flu-Pep itself, which has an IC_{50} value of 140 pM [246]. While the immunomodulatory action of AgNPs is connected to the down-regulation of pro-inflammatory cytokines including IL-6, IFN, and CCL5, the virucidal efficacy of produced AgNPs may be attributed to their capacity to bind with surface glycoprotein of virus over respiratory epithelium. The authors also stated that A549 epithelial cells are not cytotoxic to when treated to AgNPs at a dosage of 50 μg/ml. These findings inspire researchers to employ AgNPs as a supplement to COVID-19 therapy [247]. Bacteriocin like pediocin PA-1 significantly act

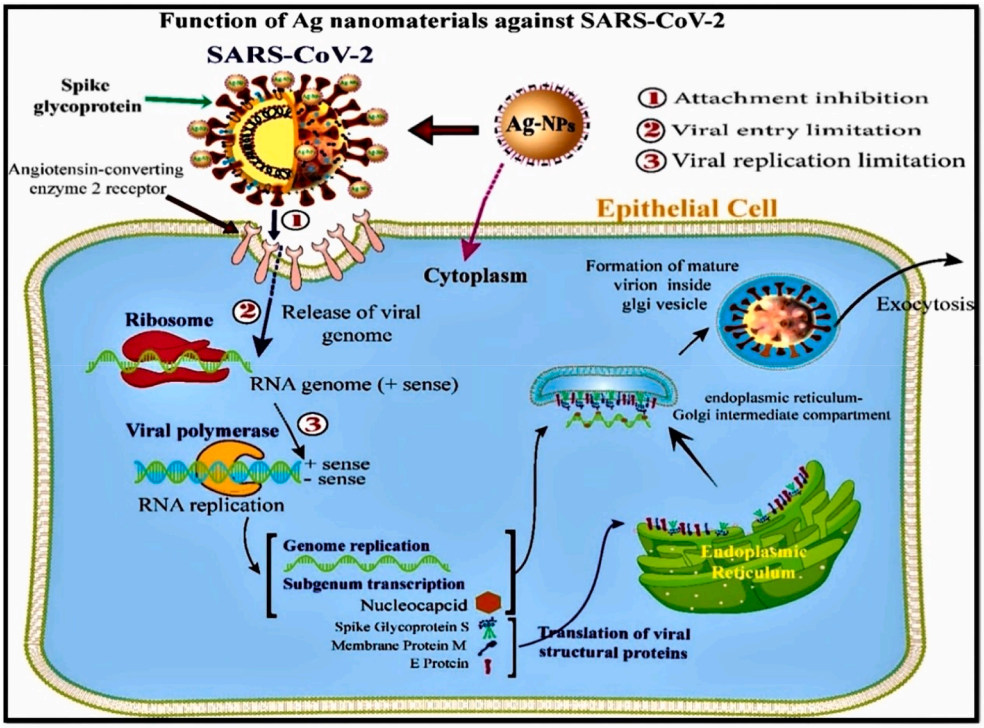

Fig. 9. Mechanisms of antiviral action of metal NPs against SARS-CoV-2 (Source. [213]).

Table 6
Mechanism of antiviral action of Ag/Au NPs against target viruses.

NPs type	Targeted virus	Concentration of NPs	Mechanisms of antiviral action	Reference
PVP-coated Ag	Human immunodeficiency virus type 1 (HIV-1)	50 mM	Interaction with gp120	[214]
Ag	HIV-1	0.44 mg/mL	Interaction with gp120	[215]
Ag	Herpes simplex virus type 1 (HSV-1)	200 μg/ml	Competition for the binding of the virus to the cell	[216]
Au	Herpes simplex virus type 1 (HSV-1)	400 μg/ml	Competition for the binding of the virus to the cell	[217]
Ag	Tacaribe virus (TCRV)	10 or 50 μg/ ml	Inactivation of virus particles prior to entry	[218]
Ag	Hepatitis B virus (HBV)	5–50 μM	Interaction with double-stranded DNA and/or binding with viral particles	[219]
Ag	HIV-1	100 μg/ ml	surface transformation	[220]
Ag	Corona viruses	10 and 100 ppm	viral entry limitation, attachment inhibition, and viral replication limitation	[213]
Ag	SARS-CoV-2	2 ppm	inhibited viral entry step via disrupting viral integrity	[221]
Ag	monkeypox virus and Respiratory syncytial virus	0.3 & 0.5 ml	inhibiting the viral adherence to host cell	[222]

against delta variant (L452R-T478K double mutant) SARS-CoV-2 and to enhance the immune systems [248]. Based on the above facts, novel development of bacteriocin composite with metal NPs as a less toxic compared to other nanomaterials, long-term stability and high efficiency with low volume of drug concentration is developed.

6.4. Cytotoxicity effects of Ag NPs and Au NPs

Human revelation to metal NPs is unavoidable as they become generally used for antimicrobial purposes. This has led to cytotoxicity in humans (Table 8). Because these metal NPs can interact with cells, it is essential to confirm that these activities do not generate any harmful impact on the human body. The harmful impact of metal-based nanoparticles varied with various kinds of nanomaterials. For metal NPs, intracellular aggregate can cause less cytotoxicity to humans because of their small size. Ag NPs can induce dose-dependent toxicity in mammalian cells, as well as oxidative stress and genetic material damage, finally occur in cell death [86,165].

The interaction of metal NPs with cell membrane proteins stimulates signalling pathways that generate ROS, which in turn damages proteins and genetic material due to the strong link between gold and sulphur and ultimately induces death and inhibits cell growth [249]. Thus, metal NPs can cause apoptosis via mitochondria and caspase dependent pathway mediated by Jun amino-terminal kinase (JNK) (Fig. 10). Most of the studies have pointed to the forgoing research in cytotoxicological pathways of metal NPs.

Two main mechanisms underlying the cytotoxicity of metal NPs have been reported: i) production of ROS and ii) causing of apoptosis. In chitosan coated Ag NPs, nanocomposite with zinc oxide NPs are less toxic and have immense potential for cancerous cells [250]. Nano size

Table 7
List of currently available COVID-19 vaccines and their efficacy.

S.No	Trail ID & Vaccine name	Developed countries	Efficiency (%)	Ag Type	Study evolution	Reference
1	CanSino:Convidecia (Ad5-nCoV) NCT04526990	China	65	Viral vector	Tolerability and immunogenicity from different strain	[229]
2	Sinopharm [Vero Cell] BBIBP -CorV NCT04560881	China	79.3	Inactivated	Variant neutralization	[230]
3	Pfizer-BioNTech (BNT162b2) NCT04368728	USA	95	mRNA	Tolerability and immunogenicity from different strain	[231]
4	EpiVacCorona NCT04527575	Russia	90	Peptide	Increased immune response	[232]
5	Sinovac-Corona Vac NCT04456595	China	50.4	Inactivated	Effective against UK, South African variants	[233]
6	Janssen (Johnson & Johnson) Ad26. CoV2.S NCT04505722	USA	66	Viral vector	Effective against severe condition	[234]
7	Sputnik V NCT04530396	Russian	91	Viral vector	Immune system	[235]
8	CovishieldAZD1222 NCT04516746	UK	65	Viral vector	Neutralization against B.1.1.7 variant	[236]
9	Covaxin (BBV152) NCT04471519	India	50	Inactivated	Neutralization against UK variant strain	[237]
10	Moderna (mRNA-1273) NCT04470427	USA	94	mRNA	Neutralization against UK variant strain B.1.351varient	[238]

Table 8
Cytotoxicity of Ag/Au NPs on human cell lines.

NPs Type	Cell line	Cytotoxicity effects	Reference
Ag	HeLa and U937	Induce cytotoxicity in both HeLa and U937	[252]
Ag	HepG2 cell	Induce size-dependent toxicity through autophagy of lysosomal system and inflammasome activation	[254]
Ag, CuO, ZnO	Mammalian cell	Order of cytotoxicity on mammalian cell. Ag > CuO > ZnO	[255]
Ag	MCF-7 (Human breast cancer cell	IC_{50} value of 42.19 mg/mL along with cell shrinkage, blebbing and restricted cell spreading patterns compared to control cells	[256]
Ag	NHDF cell	Less toxicity while using 100 μg/mL	[86]
Ag & Au	Cancerous cells (MCF-7 and RAW 264.7)	ROS generation and induce cytotoxicity	[257]
Au	LoVo cancer cell	Endocytosis	[258]
Au	MCF-7 human breast cancer cell line and NCI-N87 human stomach cancer cell line	Induce size-dependent toxicity and cell membrane disturb and finally cell death	[259]
Au	MCF-7 cell line	ROS generation	[260]
Chitosan coated Ag/ZnO NPs	RAW 264.7 murine macrophages	Inhibition of biofilm through ROS generation	[250]

zerovalent ion of zinc oxide causes toxicity via mixture of oxidative stress to disruption of cell membrane, hypoxia, and chlorosis [251]. Metal NPs can enter into the cell through the action of diffusion, endocytosis or phagocytosis. Inside the cell, metal NPs itself or ionized (Ag^{+} or Au^{3+}) produce ROS and induce oxidative stress (Fig. 11). Over the generation of ROS, it can denature various antiapoptotic proteins and start proapoptotic proteins expression. Thus, expression of apoptotic proteins starts apoptosis signalling pathway (p53, AKT, MAPK activation to inhibit ROS production by metal NPs).

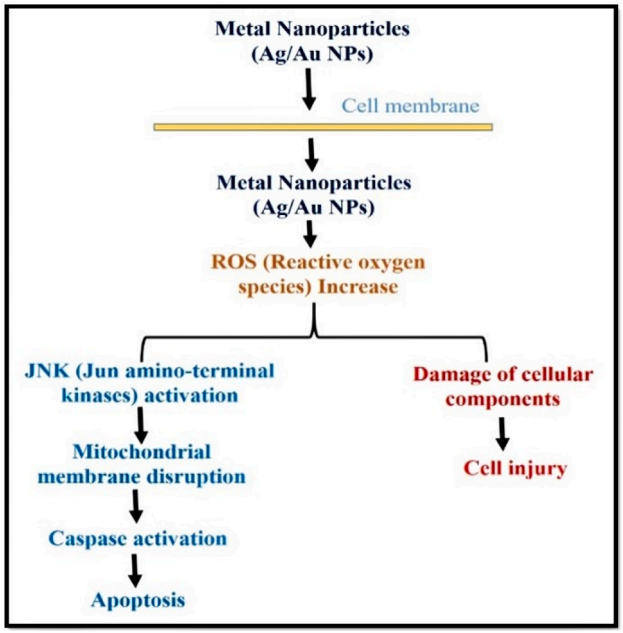

Fig. 10. Antimicrobial mechanism of metal NPs inducing cell death.

In general, very tiny metal NPs are more cytotoxic than the

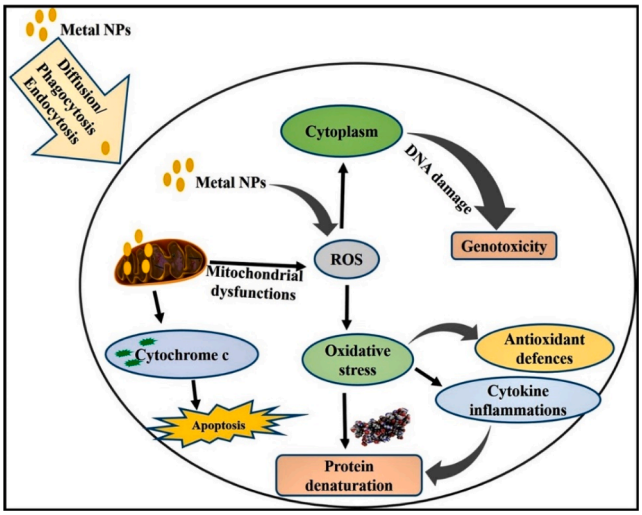

Fig. 11. Mechanisms of cytotoxicity of metal NPs in different cell lines.

highlighted entities, with Ag NPs below 40 nm, commonly induce abundant toxicity [252]. The cytotoxicity of metal-based nanomaterial was correlated with their clinical applications. Various efforts are devoted to decrease the cytotoxicity of metal NPs. Researchers have suggested nanomaterial immobilization in polymeric matrices such as polyethylene glycol, chitosan, silica, proteins, bacteriocins, titania, alginate beads, and dextran to reduce the cytotoxicity of metal NPs [165,253]. Another approach for decreasing the toxicity of metal NPs is to use green chemistry fabrication technique. For example, mushroom-mediated fabrication of metal NPs formed fewer toxic by-products that demonstrate antimicrobial properties on Gram-positive and Gram-negative bacteria as well as fungi, but with little cytotoxicity on mammalian cells.

6.5. *Development process of adverse outcome pathway (AOP) of relevance to metal NPs composite bacteriocin*

In the last decades, the toxicity pathways were recommended by the US "Environmental Protection Agency" and the "National Research Council" as the favored toxicity analyzing approach [261]. The novel research review evaluates the bioanalytical examination approach and techniques for the safety assessment of metal NPs composite peptides. Thus, bioanalysis comes from the findings of the bio-responses of metal NPs at the cell, tissue, and organ levels after exposure. Disruption of cellular properties committed to the toxicity outcomes in biological systems (i.e., fibrosis, DNA damage, necrosis, inflammation, apoptosis, carcinogenesis, and hypertrophy). On keep viewing the mind, toxicity analysis on in vitro cellular models focusing on adverse outcome pathways (AOPs) is the favored approach. Various researchers on the effective toxicity of metal NPs in different animal systems, such as Daphnia, zebrafish, mice, guinea pigs, human skin, etc., have been documented (Table 8) [262,263]. Chemical initiators (Metal NPs-Bacterocin nanocomposite) are used in the development of the AOP

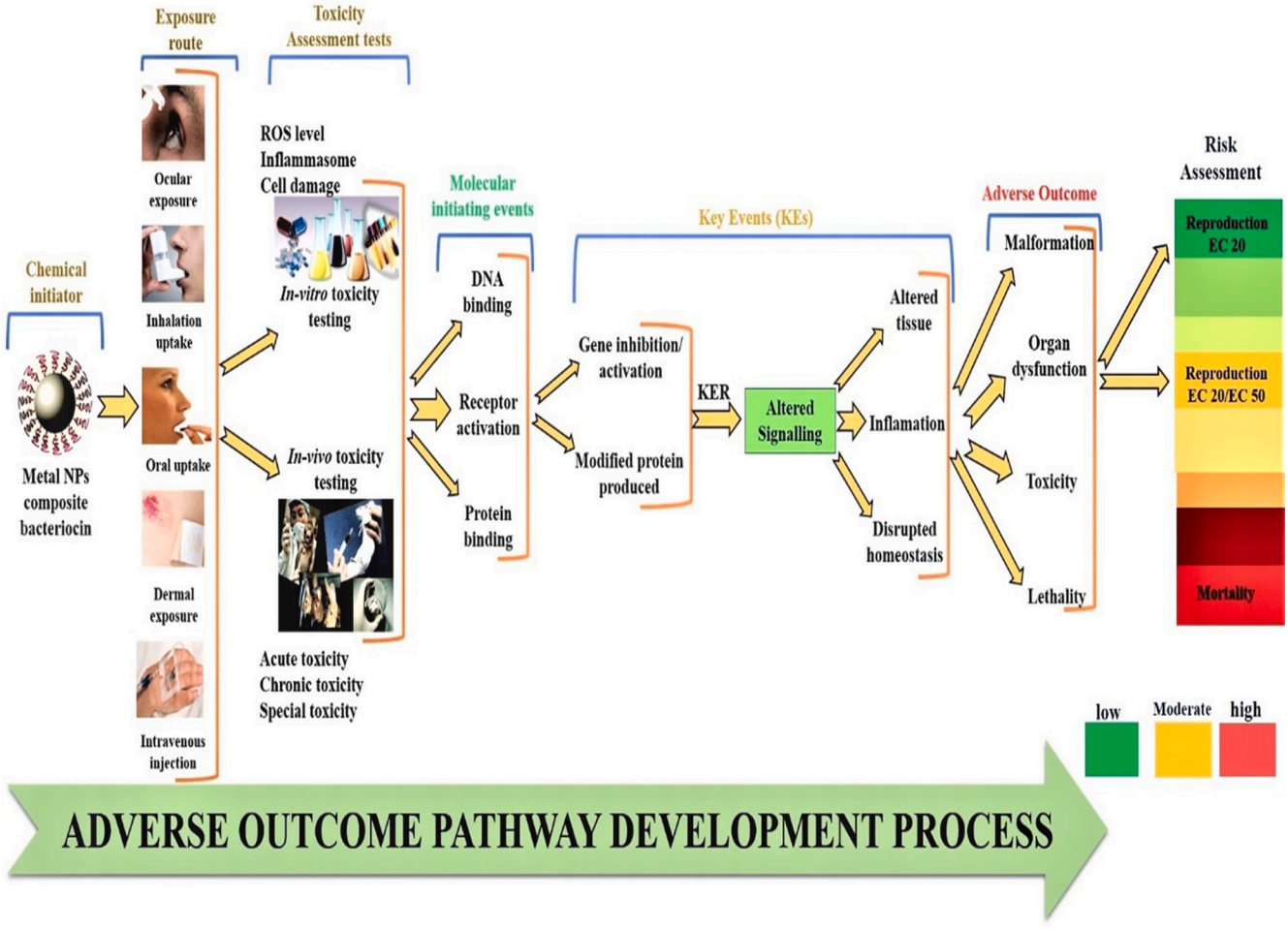

Fig. 12. A schematic representation of the adverse outcome pathway (AOP) framework. The risk assessment for developing occupational exposure limits for metal NPs- bacteriocin nanocomposite.

process and will be linked to proteins, receptors, and DNA to change the signalling pathway in a cascade. The molecular initiating event (MIE) is the first interaction with the biological system; it then spurs the formation of key events (KEs), which ultimately result in apical unfavourable effects (AO). Key event relationships (KER) are used to describe the connection between the two major events, and Fig. 12 illustrates this. Nano-toxicological research requires filling the gap of combined toxicity in the complex system. Fabricated metal NPs must have a maximum level of biocompatibility compared with other agents and have low adverse effects on human health (Table 9). It is an important to understand the biological interactions of combined metal NPs with organisms and design safe nanoproducts for human use. Based on the literature survey, in our knowledge, metal-based NPs composite bacteriocin of in-vitro studies, predictive computational tools, and in-vivo models is efficacious and potentially be used to explore environmental and human hazard assessment in the future.

7. Bionanocomposites strategies for metal NPs with biomolecules

The synthesis of nanomaterials with well-defined surface chemistry, controlled size/shape and unique optoelectronic properties is the basis of their wide range of applications [279]. The large surface to volume ratio and high reactivity with biological systems provide a platform for surface modifications. The modification of NPs provides enhancement in the interaction between NPs and biomolecules. The advancements in the field of nanotechnology have opened a new era of environment friendly and bio-inspired synthesis of NPs. The surface modified NPs plays a key role in the synthesis of non-toxic and biocompatible formulations. They can be conjugated to variety of antibiotic drugs, biomolecules such as peptides, proteins, antibodies, nucleotides and enzymes. These nanocomposite based products can be used in the treatment of various bacterial infections by enhancing the therapeutic efficacy of various antibiotic drugs or biomolecules [280].

In general, the nanocomposite of biomolecules on the surface of metal NPs can be achieved by using four various strategies: (i) Direct attachment, (ii) electrostatic interaction, (iii) covalent attachment, and (iv) encapsulation [281] (Fig. 13).

Direct attachment approaches involves the conjugation of biomolecules to NPs that can attach directly through the high affinity interactions depending on the surface exposure of the NPs to the surrounding environment as shown in Fig. 13**a** [282]. The thiol groups are the most commonly used for this type of interactions, especially

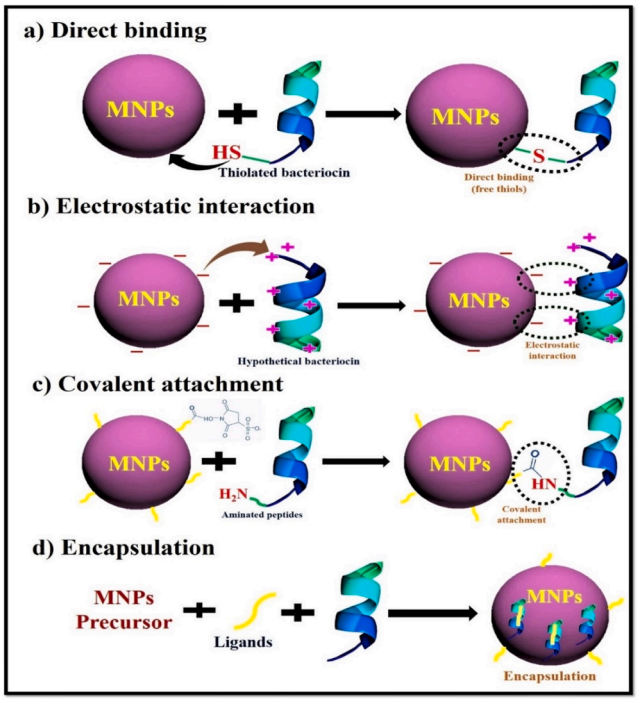

Fig. 13. Methods of formation of metal NPs and bacteriocin nanocomposite.

biomolecules have thiol groups with directly attachment on Au and Ag NPs. Furthermore, the high affinity strength of the solution, which ultimately prevents NPs aggregation owing to the screening of direct attachment between Au-TMA and the oligo anions. Electrostatic interactions have a vital significance in the formation of various self-assembled nanostructures. Although, a positively/negatively charged metal NPs and oppositely charged biomolecules by simply mixing the solution of the NPs and biomolecules [283]. In this method, it is assumed that all the biomolecules would fit on the surface of NPs (Fig. 13**b**). However, it is difficult to control the final orientation of the bio-conjugate because of the possibility of non-specific interactions. This method has been applied successfully to conjugate citrate-stabilized Au NPs to variety of positively charged biomolecules such as peptides, proteins, polymers etc., [284]. They provide stable and robust interaction among various enzymes, peptides, and proteins. Covalent

Table 9
Adverse outcome pathway of metal NPs and their toxicity risk assessment.

NPs type	Test type models	Adverse Outcome	Report of the study	Reference
Ag, Zn O, iron oxide, and TiO2	*In-vitro*	Compromised phagocytosis	NPs interact with membrane/ biomolecules	[264]
Ag, CeO_2, and ZnO	*In-vitro*	Progression of cancer and death	ROS formation	[265]
PVP capped Ag NPs	*In-vitro & In-vivo*	Brain and liver damage	Dopamine receptor antagonism, ROS formation	[266]
CeO_2, ZnO, TiO_2, Ag and silica NPs	*In-vitro*	Cell death	Lysosomal acidification	[267]
Au, Ag, ZnO, CNTs and TiO_2	*In-vitro*	Impaired cytoskeleton	DNA methylation	[268]
Ag NPs (PVP Coated and uncoated)	*In-vitro*	Increased mortality and decreased reproduction	apoptosis stimulation, ROS formation and DNA damage	[269]
Ag NPs, ZnO, and TiO_2,	*In-vitro*	Dysregulation of Immune system	Activation of intracellular pattern recognition receptors	[270]
Ag NPs & Selenium NPs	*In-vitro & In-vivo*	Destroy tumor cell	micronuclei formation & chromosomal aberrations, and DNA damage	[271]
Inorganic nanomaterial	*In-vivo*	Proinflammatory cytokines	ROS and angiogenesis	[272]
Metal NPs	*In-vitro & In-vivo*	Wound healing	angiogenesis pathway, and ATP synthase enzyme inhibiting	[273]
Au NPs	*In-vivo*	Eye defect	Oxidative stress	[262]
Au/ manganese dioxide nanocomposite	*In-vitro & In-vivo*	Destroy malignant cell and melanoma tumor	ROS geenration and oxidative stress	[274]
Metal NPs	*In-vivo*	Liver damage and lung damage	Cell damage, ROS formed	[275]
Ag/80S bioactive nanocomposites	*In-vitro & In-vivo*	Cell death	ROS production, and Cell membrane damage	[276]
Chitosan- Ag NPs composite	*In-vitro & In-vivo*	Cell lysis and promote dissemination	Cell membrane damage, ROS generation	[277]
Au NPs/ gelation fibers nanocomposite	*In-vitro & In-vivo*	Cell proliferation	NADPH oxidase generating a maximum level of ROS in the lysosome	[278]

attachment is the one of the most commonly employed method for the coupling of biomolecules to the metal NPs. In this method primary amines, thiols and carboxyl groups have been used for the conjugation of NPs as these groups are generally present on biomolecules (Fig. 13**c**) [282]. This method includes 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC. HCl) and *N*-hydroxysuccinimide (NHS) as coupling reagents which catalyze the formation of amide bonds [285]. The potential advantage of this method is their bio-orthogonality, as the coupling of two groups takes place in a specific manner without any manipulation of the other groups. Covalent approach has some disadvantages, such as poor scoring functions, and limitations in speed and accuracy. Encapsulation interaction is generally used to encapsulate a variety of antibiotics, targeted molecules etc. on NPs for drug delivery [286]. It includes the encapsulation of biomolecules using organic NPs such as liposomes polymeric NPs, solid lipid NPs etc. Fig. 13**d** revealed that metal precursor strongly encapsulates with biomolecules with the help of ligands. Advantages of encapsulation approach such as protection of API from degradation, targeted drug delivery with surface coating or conjugation, PEGylation for extended circulation time, modification to surface charge can promote cell entry, surface function for cell entry and fluorescent labelling for imaging. Disadvantages of encapsulation approach such as control of the particle size is difficult, special handling and storage conditions can be required, moderate yields for small batches, and can degraded highly temperature sensitive compounds.

8. Synergistic effects of metal NPs with bacteriocin for increased antimicrobial efficacy

The integration of nanotechnology and biotechnology may be considered as the most recent example of this hurdle technology. One of the possible methods to target MDR pathogens is a combination of one or more antimicrobial agents. In combinatorial studies, two or more compounds target the bacterial cell at the same time with their own mode of action which shows the enhanced effect on the antimicrobial potential than the individual compounds. The reason for the enhancement could be the multipronged strategy to target the bacterial cell growth. The combinatorial studies can result in; synergistic, antagonism and indifferent or zero interaction [287]. In the synergistic activity of oil compounds with antibiotics exhibited an enhanced activity at lower concentration and lower down the cytotoxicity against cancerous cells as compared to the individual compound. Currently, several research suggest that metal NPs can be combined with biomolecules to increase their effectiveness.

Ag NPs with peptide molecules has been emerging as a promising candidate for biological applications due to their bioavailability, higher specificity and lower toxicity [288,289]. The antimicrobial activity of individual components was enhanced by the cationic peptide Odorranain-A-OA1 (OA1) conjugated Ag NPs, which had no significant IC50 value compared to Ag NPs, which had an IC_{50} value of 96 μg mL^{-1}, implying non-cytotoxicity of the conjugate against a mammalian cell line [290]. Recently, Ag NPs were conjugated with an antimicrobial peptide nisin [291]. The Ag peptide conjugate showed that the antimicrobial activity of peptide nisin was enhanced after bioconjugation with Ag NPs. Bacteriocin capped Ag NPs have a broad spectrum of antimicrobial property against food spoiling bacteria [292]. In another study, the antibacterial effects of peptide capped Ag NPs on gram-negative bacteria was studied, where, casein peptide stabilized Ag NPs strongly inhibited the biofilm formation of *P. aeruginosa, E. coli*, and *Serratia proteamaculans* at concentration of 10 μg mL^{-1}, 4–5 μg mL^{-1} and 10–20 μg mL^{-1}, respectively [293].

In recent years, peptide functionalized Au NPs have been used in wide number of therapeutic applications. Recently, glucagon like peptide-1 (GLP-1) was modified at the C-terminal by the addition of cysteine to promote the conjugation with Au NPs [294]. The intraperitoneal delivery of the GLP-1 gold conjugate to normoglycemic rats showed a decrease in the level of blood glucose similar to that of a native GLP-1 and demonstrated the stability of the conjugate which maintains the activity of this incretin. In another report, Au NPs were functionalized with therapeutic peptide (NH2-TSFAEYWNLLSP-NH2) and a targeted peptide (CRGDK) to achieve the selective binding with NRP-1 receptor over expressed on the cancer cells which regulates the process of membrane receptor mediated internalization. It has been found that CRGDK peptide facilitates the intracellular uptake of AuNPs which exhibited stronger *in-vitro* anti-cancer activity compared to other conjugates due to strong binding interaction between peptide CRGDK and targeted Nrp-1 receptor [295]. Peng et al. (2016) reported that the integration of antimicrobial peptides with Au NPs had great transfection efficacy and synergetic effects on human pathogens [296]. Bacteriocins produced by

L. plantarum ATM11 and commercial nisin were conjugated with Au NPs having enhance antimicrobial potential against food spoilage microorganisms [297]. The disadvantages of using single drug such as high dose, toxicity, alter cellular metabolisms, and generation of drug resistance with a minimum period of time. The interaction between the NPs and bacteriocins thus holds the potential to lead to a reduction in the requirement of high bacteriocin dosage, and an extension in the shelf life of food. Nano-encapsulations of bacteriocins when used in food preservation, protect them from degradation by gastrointestinal enzymes, and can also increase their commercial yield and stability. However, the advantages of combination of bacteriocins with NPs is more effective than bacteriocins alone owing to their increased antibacterial efficacy with possibly lower doses, synergistic effects, decrease the probability of resistance evaluation, broad spectrum of action, and multiple targets. Hence, metallic NPs can be used to conjugate bacteriocins to increase the antimicrobial spectrum of the former, which in turn can prove to be an efficient weapon in the fight against MDR pathogens.

9. Future prospects

Despite the advantages that NPs offer, such as a broad therapeutic index, controlled drug release, less prone to bacterial resistance, and fewer side effects than chemical antimicrobials [298], to treat infections caused by the ESKAPE pathogens, there are still challenges remaining to be tackled such as improvement of physicochemical properties, better pharmacokinetic profiles, and comprehensive studies on long-term exposure to humans. Metal NPs-based compounds (alone or in combination with other antimicrobial agents) provide promising alternatives to combat the development of antibacterial resistance (Shaikh et al., 2019). The strategies to reduce antibiotic resistance include the limited use of antibiotics and the application of more effective antimicrobial therapies. Because the time of exposure to antibiotics correlates with the development of resistance, it is necessary to use drugs with a broad spectrum of action and pharmacokinetic properties that facilitate their rapid access to the target site. However, most of the available treatments do not have all these characteristics, so an alternative option is the use of combination therapies, which can lead to a synergistic and more effective response. The combination of drugs leads to a considerably more potent effect, compared to the individual drug. Therefore, it is imperative to develop a comprehensive understanding of the mechanisms of action responsible for the bactericidal properties as well as the identification of the most promising antimicrobial agents for future clinical translation [299–301]. For an example, metal NPs will made up wound-dressing materials, catheters, bone cement, cardiovascular implants, and dental restorative materials that are available for clinical uses. Nevertheless, antimicrobial metal NPs are more effective for fighting human contagion diseases involving the entire body and its associated organs were displayed in Fig. 14**.** Ag NPs is a well-known antimicrobial drugs which has a wealth of experience of topical use versus domestic contagion [302]. Still now, there is a need for fabrication of more effective drugs and vaccines for treating pandemic contagion diseases [303] or as antimicrobial drug delivery systems [304]. However, there is

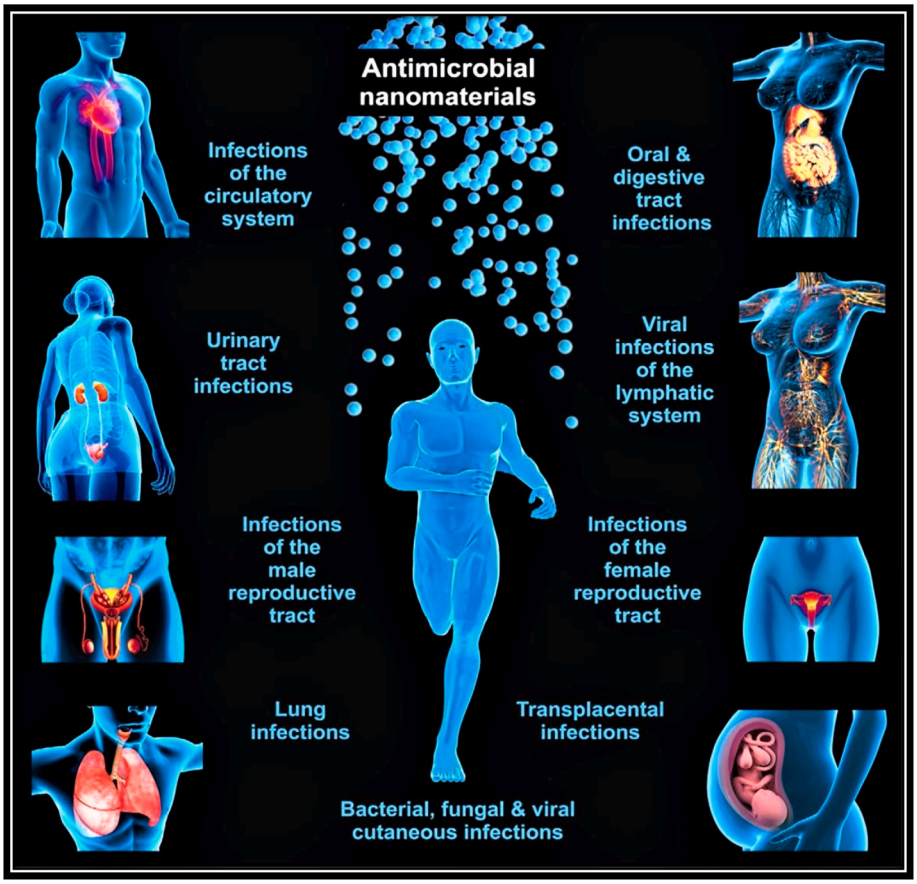

Fig. 14. Antimicrobial efficacy of nanomaterials in fighting infections in various parts of the human body ().
Source: [305]

evidence for many clinical experiments on metal NPs based antimicrobials materials.

Apart from the approach stated above, mushroom as a bio factory, which have wide number of mycomolecules (alkaloids, proteins, polysaccharides, terpenoids, aminoacids, vitamins and polyphenols) could have wide range of food and biomedical applications. Based on the above facts mushroom could be uses in a green chemistry synthesis and is more helpful for increasing biocompatible capabilities of metal NPs. The use of metal NPs is not only narrow to the biomedical field. It can be generally applicable in water treatment, textiles, food packaging, cosmetics industry, and agriculture system (nano fertilizer and nano pesticides). The mycosynthesized metal NPs will be a novel field and finds the right balance between the production cost, scalability, and applicability. Hence, further studies will be required to focus on economical ways of mycosynthesized metal NPs fabricated, producing them readily available for all kinds of future prospects. Metal NPs and nanocomposites with biomolecules play a crucial role in the production of non-toxic and biocompatible formulations, based on the aforementioned valuable discussion points. However, a novel system with distinctive antimicrobial potential of Ag and Au NPs bionanocomposite with bacteriocin obtain many benefits without the use of hazardous chemicals. Bio-nanotechnology-based monoclonal antibodies and vaccines precisely deliver the active agents to targeted tissues and provide very rapid detection of these viruses. Green synthesized nanomaterials could also play a crucial role in developing a vaccine. Nowadays, vaccines are delivered through slow-release implants, single-dose followed by the second dose, and plant viral nanoparticles for drug delivery. That day seems far off in the race to develop a novel SARS CoV-2 vaccine that works, but it remains to be seen whether SARS CoV-2 will be more like flu, requiring an unknown shot every year. The COVID-19 focus is on the solution, and nanomedicine is the part of the solution that enables delivery of bacteriocin composite metal NPs. This paradigm shift from "what are the unknown risks of nanomedicines?" to "what clinical solutions can we solve with nanomedicine" has opened the door to translational nanomedicine applications beyond SARS-CoV-2 vaccines. Finally, the biggest challenge will always remain the possibility of these nanocomposite metal NPs as a potential therapeutic agent for SARS CoV-2. The broad range of antimicrobial properties of metal NPs against MDR pathogens (bacteria, fungi, and viruses), as well as the sustainability of mass manufacturing. Considerations of the bacteriocin composite metal NPs drug delivery mechanisms and effective in vivo safety should be paved to ensure enhanced treatment of COVID-19 and MDR infectious diseases with maximum biosafety.

10. Conclusion

Microbial resistance has emerged as a serious threat to public health due to indiscriminate and abusive use of antibiotics thereby causing a need to search for novel antibiotics. In recent years, metal NPs and nanocomposites with antimicrobial effective biomolecules appear as a promising candidate for various biological applications. However, most of the work in this direction has been performed with antimicrobial macromolecules. Keeping the focus on cost effective synthesis for design of novel nano-antibiotics, mushroom has been found as a suitable green source for nanomaterials synthesis with biomedical applications due their non-toxic, and biocompatible nature. The size, shape, and morphology of metal NPs were well controlled by mushroom-based synthesis. This review focused on evaluating the possible mechanisms of antibacterial, antifungal, antiviral and cytotoxicity of metal NPs. Bacteriocin as a nature source of antimicrobial peptides from probiotic

bacteria has broad spectrum of antimicrobial effects on MDR pathogens and COVID-19. Synergistic effects of metal NPs nanocomposite with various biomolecules to enhance the antimicrobial effects and non-toxic property are reported. Based on the above facts, we focus on metal NPs nanocomposite with bacteriocin as a perfect augmentation to enhance their antimicrobial effects and increasing their long-term stability. We believe that bacteriocin nanocomposite metal NPs would become a more effective approach to combat the ongoing global health emergency and future pandemics.

CRediT authorship contribution statement

Moovendran Srinivash: Writing – original draft. **Raman Krishnamoorthi:** Conceptualization, Writing - original draft, Writing - review & editing. **Pambayan Ulagan Mahalingam:** Validation, Supervision. **Balasubramanian Malaikozhundan:** Writing – review & editing. **Subramanian Bharathakumar:** Resources, Visualization. **Krishnamoorthy Gurushankar:** Formal analysis, Data curation. **Kasi Karuppa Samy:** Validation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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