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FOCUS ON SYNERGISTIC BACTERIOCIN-NANOPARTICLES ENHANCING ANTIMICROBIAL ACTIVITY ASSAY

Antimicrobial resistance is one of the most significant threats to public health worldwide. As opposed to using traditional antibiotics, which are effective against diseases that are multidrug- resistant, it is vital to concentrate on the most innovative antibacterial compounds. These innate bacterial arsenals under the term «bacteriocins» refer to low-molecular-weight, heat-stable, membrane-active, proteolytically degradable, and pore-forming cationic peptides. Due to their ability to attack bacteria, viruses, fungi, and biofilm, bacteriocins appear to be the most promising, currently accessible alternative for addressing the antimicrobial resistance (AMR) problem and minimizing the negative effects of antibiotics on the host's microbiome. Nano-compounds have shown promise in a variety of applications, including antibacterial agents, drug delivery systems, food and drug packaging elements, functional food formulations, and many more. However, there are certain disadvantages in the chemical production of nanoparticles (NPs), such as toxicity and other negative impacts. Due to the dual action of biological sources combined with metallic NPs, the use of conjugated or green-synthesized nanoparticles has become more widespread during the past ten years. Recently, bacteriocin nanoparticles have emerged as a viable remedy and the most effective antibacterial agent in vitro to overcome some of these limitations.

***Keywords**: lantibiotics, green synthesis, antimicrobial resistance, bottom-up synthesis.*

Bacteriocin. A short polypeptide, i.e., a protein, called bacteriocin is synthesized by ribosomes and has antimicrobial effects on bacteria that are unrelated to the strain that created it [1]. Despite the fact that bacteriocin was first discovered in 1925, interest in the method of its production and application in medicine has grown only recently [2]. Microbial community's

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cells can be either bacteriocinogenic (producing bacteriocin) or resistant to each bacteriocin, depending on whether they are sensitive or resistant to it. Few bacteriocinogenic cells are really stimulated to produce and release bacteriocin [3]. Other cells contain mutations that make them robust to the environment and allow them to live, whereas certain fragile cells are promptly killed. Both Gram-positive and Gram-negative bacteria can create bacteriocins, however lactic acid bacteria (LAB) are the primary producers. A wide variety of bacteria produce a large number of bacteriocins, which are then divided into groups according to their molecular weights, sizes, modes of action, producer bacteria, and range of activity [4]. When opposed to other antibiotics, bacteriocins have a natural antibacterial effect in addition to having a narrow spectrum of activity that targets only a few types of bacteria. Additionally, Gram-positive foodborne pathogens are among the large range of microbes against which enterococci bacteriocins are recognized to be effective [5]. In another study, the effect of bacteriocin produced from the genus *Bacillus* spp. was found to be effective against bacteria that cause skin diseases such as *Propionibacterium acnes* [6].

Classification of Bacteriocins. Bacteriocins from Gram-positive bacteria (G+ve), which are more numerous and diverse than those found in Gram-negative bacteria (G-ve), are comparable to the antimicrobial peptides generated by eukaryotes. They normally come in sizes between 2 and 6 Kd and are cationic, amphiphilic, and membrane-permeable peptides. The lantibiotics (class I), which are tiny (10 kDa) and heat stable, are among the several classes of bacteriocins. Pediocin-like and anti-Listeria bacteriocins (subclass IIa), two peptide bacteriocins (subclass IIb) [7]. As shown in Table (1), bacteriocins from Gram- positive bacteria (G+ve) are divided into four classes [8].

The Enterobacteriaceae family produces most bacteriocins found in G-ve bacteria. Based on their molecular weights, these bacteriocins are divided into two classes: colicins and microcins [9].

Antimicrobial resistance (AMR) of bacteriocins. AMR is an important global health issue that requires the creation of fresh tactics. According to several writers [10, 11], the interface between the human and animal environments is currently being taken into account as part of the One Health strategy in order to better understand the ecology and spread of AMR.

A fascinating alternative to using traditional antibiotics is the use of Bacteriocins. These peptides may develop into crucial biological weapons, particularly against newly emerging bacteria that are resistant to antibiotics, and they may

Table 1. **Classification of bacteriocins**

Class	Sub class	Characters	Example
Class I	Type A Type B	Lantibiotics, small (< 5 kDa) peptides, elongated, globular	Nisin Mutacin I
Class II	Class IIa	Non-lantibiotics, small (<10 kDa) peptides one-peptide, pediocin-like bacteriocins	AcidocinA
	Class IIb	Two-peptide bacteriocins	Lactacin F
	Class IIc	Covalently connected N- and C-terminal cyclic bacteriocins One-peptide, linear, non-pediocin-like bacteriocins	Acidocin B Carnobace-riocin A
Class III	—	Large (>30 kDa) heat-labile proteins	Lacstrepsin
ClassIV	—	Bacteriocins with non-protein moieties, i.e. glycoproteins and/or lipoproteins	Lactocin 27

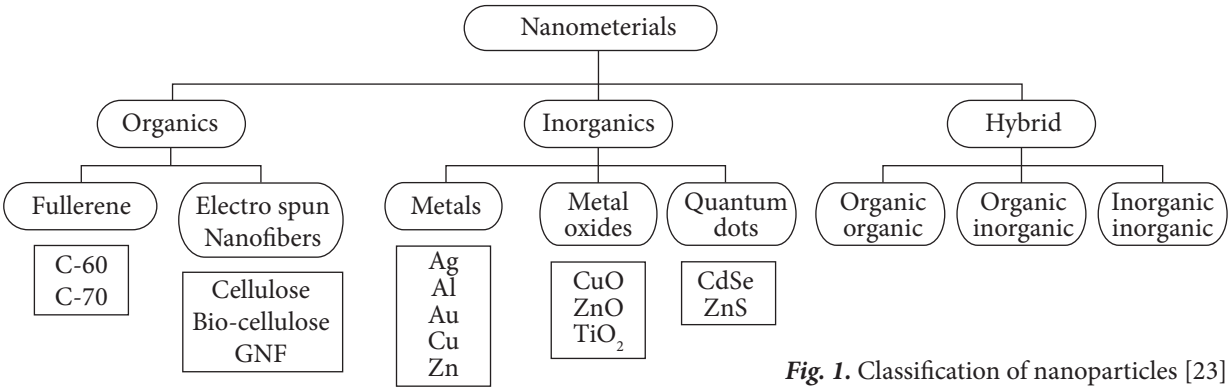


Fig. 1. Classification of nanoparticles [23]

find application in various industries, including the food industry, medicine, veterinary medicine, and agriculture [12].

Antimicrobial peptides known as bacteriocins are generated by ribosomes that are fatal to the cells that make them. These peptides typically work against species that are closely related to the bacterium that produced them. The bacteriocins produced by Gram-positive bacteria exhibit a larger spectrum of inhibitory activity, which may favor a wider range of industrial uses [13]. Due to their activity against closely related bacterial species, bacteriocins are commonly produced to give the producer a selection advantage in terms of the niche colonization potential [14]. Bacteriocins have been found to be potential biopreservatives. Bacteriocin 10A's capacity to specifically prevent the development of diseases and bacteria that ruin food [15]. Bacteriocins, which are peptidic poisons produced by bacteria, have the potential to replace or combine with existing medicinal substances. The multidrug-resistant (MDR) bacteria are particularly vulnerable to these poisonous peptides, yet producer strains are still resistant to the bactericidal peptides [16].

Nanotechnology and Nanoparticles. The study of material properties at the nanoscale is known as nanoscience, which is particularly focused on the distinct, size-dependent features of solid-state materials [17]. For the first time, the process of nanotechnology was outlined at the Tokyo Science University in 1974. The primary functions of nanotechnology are the separation, aggregation, and deformation of materials by a single atom or molecule. The first publication on nanotechnology was published in 1986 [18].

Nanomaterials have become novel antimicrobial agents for the treatment, which result in higher ratios between atoms on the surface and atoms inside of materials compared to the corresponding bulk materials and have shown efficacy against resistant bacteria [19]. Currently, nanomaterials manufactured by biological methods have a synergistic effect with preservatives against pathogenic bacteria [20].

Properties of Nanoparticles. Metal nanoparticles such as gold, silver, platinum, and others, as well as non-metallic, inorganic oxides like zinc oxide and titanium oxide, have been employed widely due to their exceptional electrical, magnetic, and optical capabilities. Furthermore, nanoparticles exhibit peculiar electrical, catalytic, magnetic, and optical properties in contrast to bulk metals [18].

Nanoparticles stand apart from other particles because of their larger surface area-to-volume ratio, larger size, and distinctive shapes like a rod or a circle. They can therefore be utilized for biological purposes, cancer cell diagnostics or monitoring, display devices, optoelectronics, catalysis, the production of biological sensors, drug development, and therapeutic treatment [21].

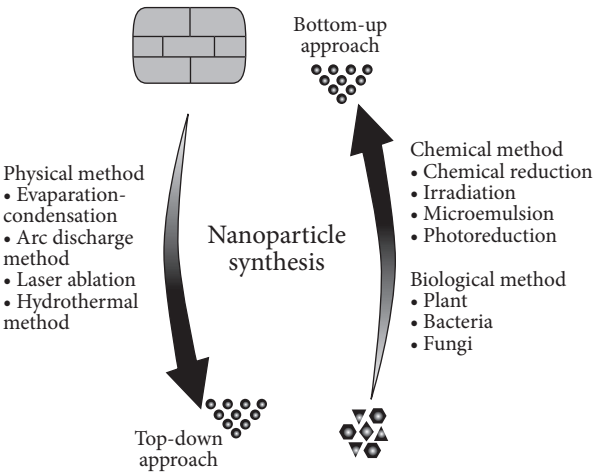


Fig. 2. Schematic illustration of top-down and bottom-up approaches in nanoparticle synthesis [26]

Classification of Nanoparticles. Based on their morphology, shape, size, and content, nanoparticles can be divided into a number of classes. According to their composition, NPs are frequently divided into three groups: organic, carbon-based, and inorganic [22] (Fig.1).

Methods for nanoparticles' synthesis. The most common ways for creating nanoparticles are top-down and bottom-up approaches. Atom-sized components are assembled bottom-up to create the final nanoparticles. The precise synthesis procedure varies depending on the chemical being produced, but some frequent techniques include citrate reduction, gas phase, and microbial synthesis [24]. Milling, laser ablation, and spark ablation are examples of top-down processes where a bulk substance is physically broken down to produce smaller molecules [25]. The methodologies are categorized into three groups: physical, chemical, and biological processes for NP synthesis (Fig. 2).

There are several NP synthesis strategies that have been developed. The physical method of synthesizing NP has advantages since it prevents NP solvent contamination, but it is not insignificant as it uses a significant amount of energy for particle condensation and evaporation. Furthermore, the cost of synthesis of NPs is indirectly increased by substantially raised temperature and pressure modulations, which extend the time for NP fabrication [27].

Green synthesis and mechanism of NP production. Milling, laser ablation, and spark ablation are examples of top-down processes where a bulk substance is physically broken down to produce smaller molecules. The methodologies are categorized into three groups: physical, chemical, and biological processes for NP synthesis for both top-down and bottom-up approaches [28]. Microbes produce NP using a number of metals and metal oxides in both internal and external processes [29]. Microbial NP production is influenced by the biochemical mechanism that controls the reduction with soluble inorganic or toxic ions during cellular detoxification. Using enzymes, microbial species attach to dangerous metal ions in the environment and convert them to elemental metals. The microorganisms capture these ions on the cell surface during the extracellular process and then reduce them through enzyme-catalyzed reactions. The biological manufacture of nanoparticles made from bacteria has proven a broad inhibitory effectiveness. Zinc oxide nanoparticles were produced from MDR with high ability to swarm, and strong biofilm producer *P. mirabilis* isolated by biological method and these synthesized peptides assemble into stable particulate nanostructures. The working principle includes electrostatic interaction: positively charged metal ions are attracted to the negatively charged bacterial cell membranes [30].

During the extracellular process of NP synthesis, the metal ions are reduced by the enzymes, proteins, building blocks of cell walls, or organic components of the culture medium. The nearby intracellular enzymes of the microorganisms transport the ions, and the microbial enzymes of those microbes convert the ions into NPs[31]. One of the most important applications of nanoparticles was the use of kiwi fruit peel

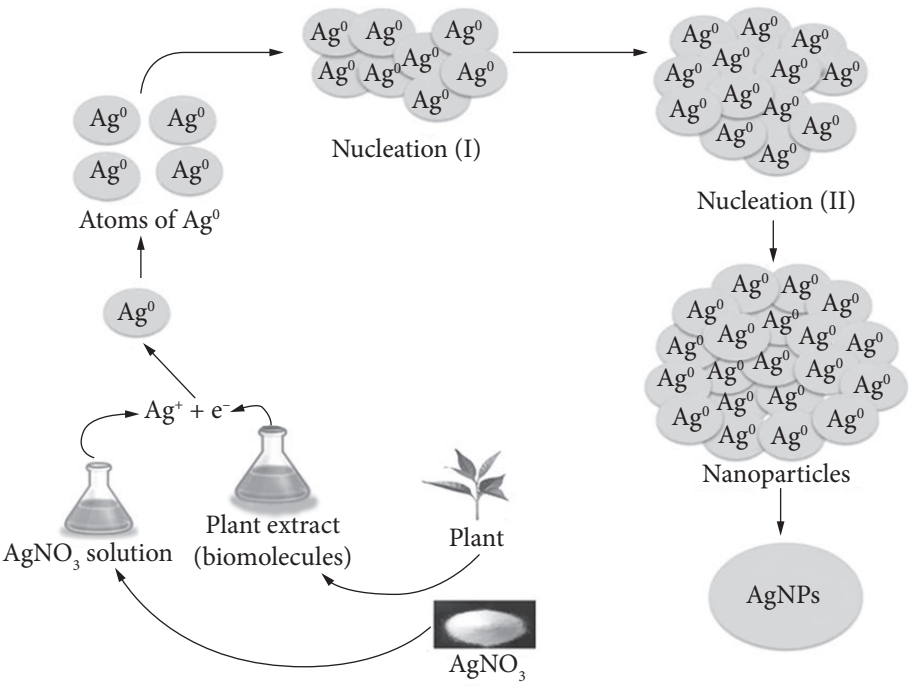
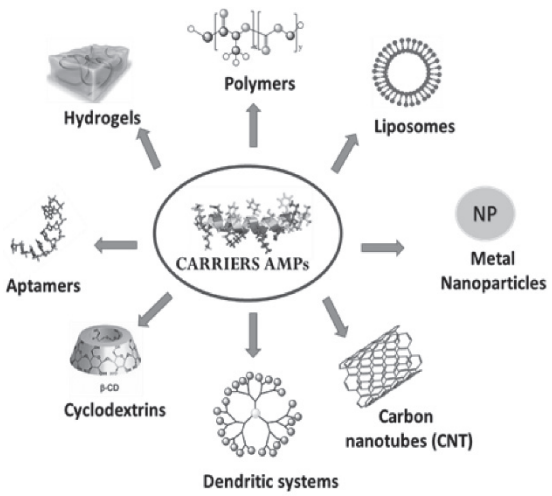


Fig. 3. Mechanism of green synthesis of silver nanoparticles: approach toward cancer nanomedicine [33]



Advanteges	Disadvanteges
Decrease of AMP side-effects	Fast elimination of the vehicle system
Lower frequency of AMP administration	Immune reaction against delivery system
Lower AMP dose is needed	High production cost
Constant blood AMP levels	Difficult to scale-up
Maximization of therapeutic index	
Applicable to a wide range of drugs	
Bioavailability enhanced by protection from degradation	

Fig. 4. Different inorganic nanosystems as delivery systems

residues in the preparation of zinc nanoparticles against *Staphylococcus aureus* isolated from contaminated cosmetics [32].

Explain the process of synthesizes silver nanoparticles using biological method that are beneficial to the environment and the extent of their effectiveness against cancerous cells. Synthesis of silver nanoparticles by the biological method is demonstrated in Fig.3 [33].

Polypeptides targeted nano delivery systems. To make the delivery of target peptides more accurate, nano systems have been adorned or altered with extra moieties [34]. As seen in Fig. 4, a variety of strategies have been

used over time. Other drug delivery systems have used AMPs as ligands to transport other peptides or conventional pharmaceuticals while various chemicals have been used to aid in the dispersion of AMPs. This method allows organisms to cross boundaries created by nature. Low pH, enzymes, mucosa, and epithelial layers in the intestine are some of such barriers that inhibit the proper release of peptides to the right site [35]. For targeted delivery, polymeric nanoparticles and synthesized peptides were used [36]. Two mouse dendritic cell lines that could recognize the target peptide sequence, DC 2.4 and B3Z hybridoma T cells, were used to study uptake and intracellular targeted drug delivery [37].

Nowadays, we have information that metal-based nanoparticle synthesis has reached sizes ranging between 5 and 260 nm suitable for entry into the mitochondrial matrix, so nanosystems not only act as antioxidants but are also fabricated for the delivery of chemotherapeutic agents. The use of nano-engineered metals and their oxide nanoparticles are targeted at the mitochondria that manage many health issues, including different cancers [38].

It is important that we meet the requirements or some conditions for nanoparticles to be used in the medical area. We should obtain nanoparticles that are biocompatible, cost-effective, and environmentally friendly for biomedical applications. The biosynthesis of ZnO NPs was performed using isolated bacteria strains from farm soil in Jeddah, and the green production of NPs has been developed as a viable alternative to the traditional method. These processes are eco-friendly and non-toxic. Microorganisms serve as a nano-factory, converting metal ions into metal NPs with the help of enzymes manufactured by the bacteria [39].

5-Antimicrobial activity of bacteriocin and nanotechnology

The study into edible coatings with antimicrobial compounds is encouraged by the rising standard of food quality and the concern to reduce waste in the environment. Hydrocolloids (proteins and polysaccharides) used in edible cheese coatings and films are biopolymers that recently have received the greatest research attention. They are used to alter the environment around foods and create a barrier between the food and the environment without altering the foods' organoleptic and nutritional qualities, which helps to improve the food products' safety, quality, and functionality [40]. When applied to the covered surface of food, the combination of nisin and chitosan has an excellent antilisterial *antibacterial* effect [41] and inhibits the growth of undesirable germs. By immobilizing the antibiotic bacteriocin by

Table 2. **Comparison of antibiotics and bacteriocins for antimicrobial potential**

Antibiotic used for treatment	Alternative Bacteriocin used as (probiotic)	Producing strain	Bioactivity	Potential application	References
Carbapenems	Plantaricin 423	*Enterococcus mundtii*	Antimicrobial agent	GIT infections	(Kumarasamy et al., 2010) (Dreyer, 2018; Van Zyl, 2018)
Cyclic lipopeptide	Piscicolin 126	*Carnobacterium piscicola*	Antimicrobial agent	GIT infections	(Coates et al., 2011) (Ingham et al., 2003)
Metronidazole	Pediocin PA-1	*Pediococcus acidilactici*	Antimicrobial agent	GIT infections	(Persky and Brandt, 2000) (Cintas et al., 1998; Dabour et al., 2009)
Penecillin	Peptide ST4SA	*Enterococcus mundtii*	Antimicrobial agent	GIT infections	(Tan and Tatsumura, 2015) (Knoetze et al., 2008; Dreyer, 2018; Van Zyl, 2018)

covalent bonding in the packaging method, stability against proteolytic enzymes is provided [42]. Additionally, we can create bacteriocin nanocapsules using nanoliposomes, nanoemulsions, nanoparticles, and nanofibers, which may have been used in the pharmaceutical and food industries. When combined with carvacrol, curcumin, and cymene, nisin, podocin, and sublitosin were evaluated against *Candida lusitaniae, E. coli, S. typhimurium,* and *L. monocytogen* [43]. Nanotechnology improves the antimicrobial activity, enhances the physicochemical properties of bacteriocin [44], increases the applicability of bacteriocins, broadens the antimicrobial spectrum, and promotes stability [45]. Nano-formulated bacteriocins were used experimentally in the treatment of skin injuries, e.g., nisin silver nanoparticles were used for the treatment of *S. epidermidis* skin infection in mice [46].

Nanofibers with ethylene oxide and poly D, L-lactic acid, as well as nisin or plantaricin, can be used to treat deep wounds that have *S. aureus* infections. Several bacteriocins are used as a probiotic in the replacement of antibiotics because they play a crucial role in boosting our immune system [47] (Table 2).

Conclusions. Antimicrobial resistance is a relevant health problem worldwide that needs the development of new strategies. Bacteriocins are a promising alternative to the use of conventional antibiotics. Green synthesis of metal oxide NPs has gained great interest since it is an eco-friendly approach with a wide range of applications in biotechnology and medical field. synthesis of metal nanoparticles using microorganisms represents a novel alternative to chemical and physical approaches. Biological methods are preferred over other methods as they are environmentally friendly.

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ДОСЛІДЖЕННЯ СИНЕРГІЧНОЇ ДІЇ БАКТЕРІОЦИНУ ТА НАНОЧАСТИНОК, ЩО ПОСИЛЮЮТЬ АНТИМІКРОБНУ АКТИВНІСТЬ

Стійкість до протимікробних препаратів є однією з найбільших загроз для охорони здоров›я в усьому світі. На додаток до використання традиційних антибіотиків, які ефективні проти збудників хвороб, стійких до багатьох препаратів, життєво важливо зосередитися на найбільш інноваційних антибактеріальних сполуках. Одні з таких речовин, природні бактеріальні арсенали, позначаються терміном «бактеріоцини» і являють собою низькомолекулярні, термостабільні, мембраноактивні і протеолітично розщеплювані катіонні пептиди, що утворюють пори. Завдяки своїй здатності впливати на бактерії, віруси, гриби та біоплівки, бактеріоцини є найбільш перспективною та доступною альтернативою для вирішення проблеми резистентності до антимікробних засобів та мінімізації негативного впливу антибіотиків на мікробіом хазяїна. Наносполуки є перспективними для застосування в різних галузях, включаючи антибактеріальні засоби, системи доставки ліків, елементи упаковки харчових продуктів і ліків, препарати для функціонального харчування та багато іншого. Однак хімічний спосіб створення наночастинок (НЧ) має певні недоліки, такі як токсичність та інші негативні наслідки. Завдяки подвійній дії біологічних сполук у поєднанні з металевими НЧ, використання кон›югованих або синтезованих шляхом зеленого синтезу НЧ стало більш поширеним протягом останніх десяти років. Нещодавно показано, що поєднання НЧ та бактеріоцинів *in vitro* є перспективним та ефективним антибактеріальним засобом для подолання існуючих обмежень.

Ключові слова: *лантибіотики, зелений синтез, резистентність до антимікробних засобів, висхідний синтез.*