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ABSTRACT

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CHARACTERISTICS OF NANOMETRIC PARTICLES OF METAL OXIDES

Introduction. This mini-review examines the mechanisms of damage to bacterial biofilms (BB) by particles of metals (Au, Ag, Fe, Cu, Zn, Mg) and their oxides (AuO, SiO, Fe2O3, Ag2O, CuO, TiO2, ZnO, and MgO). Emphasis is placed on the mechanism which includes the formation of reactive oxygen species that affect the redox state of the bacterial cell and, as a result, its death. The mechanism of the antibacterial action of particles, ZnO, as well as their effect on the porosity and degree of swelling of the apatite-biopolymer composite, were considered in more detail. Due to the emergence of antibiotic resistance of bacterial biofilms, it has become increasingly difficult to treat them effectively.

Materials and Methods. An analytical review of scientific publications was conducted using official databases. The scientific research method was employed to achieve the objective.

Results. The study showed that nanoparticles of metal oxides could have a detrimental effect on bacterial biofilms using various mechanisms of antibacterial action, including oxidative stress, biofilm inhibition, inhibition of protein synthesis and DNA damage, damage to metabolic pathways, penetration through the cell membrane, and interaction with the cell wall and membrane.

Conclusion. To further utilize nanoparticles of metal oxides (copper, gold, silver, titanium, and iron), the primary mechanisms of their influence on the structure of bacterial biofilms (BBs) were studied based on papers published in the world's scientific literature. NPs have different classifications and differ in chemical composition and physical parameters, such as nanosize and surface-to-volume ratio.

Keywords: bacteria, biofilms, bacterial biofilms, nanoparticles, nanomaterials, metal oxides.

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ХАРАКТЕРИСТИКА НАНОМЕТРИЧНИХ ЧАСТИНОК ОКСИДІВ МЕТАЛІВ

Вступ. В міні-огляді розглянуто механізми пошкодження бактеріальних біоплівок (ББ) наночастинками металів (Au, Ag, Fe, Cu, Zn, Mg) та їх оксидів (AuO), (SiO), (Fe_2O_3), (Ag_2O), (CuO), (TiO_2), (ZnO) і (MgO)). Зроблено акцент, зокрема, на механізм, який включає утворення активних форм кисню, які впливають на оксидно-відновлювальний стан бактеріальної клітини і як наслідок – її загибелі. Більш детально розглянуто механізм антибактеріальної дії частинок, ZnO, а також їх вплив на пористість та ступінь набрякання апатит-біополімерного композиту.

Бактеріальні біоплівки – це складні форм мікроорганізмів, що можуть бути прикріплені до поверхні або заховані у позаклітинному матриксі. Матриця біоплівки, що оточує бактерії, робить їх стійкими до антибіотиків та дезінфікуючих хімічних засобів. Через появу антибіотикорезистентності бактеріальних біоплівок стало важко лікувати їх ефективно.

Матеріали та методи. Аналітичний огляд наукових публікацій виконано з використанням офіційних баз даних. Для досягнення поставленої мети використовувався науково-пошуковий метод дослідження.

Результати та їх обговорення. Дослідження показало, що наночастинки оксидів металів можуть згубно впливати на бактеріальну біоплівку за допомогою таких механізмів антибактеріальної дії: окислювальний стрес, інгібування біоплівки, пригнічення синтезу білка та пошкодження ДНК, пошкодження до метаболічних шляхів, проникнення через клітинну мембрану, взаємодія з клітинною стінкою та мембраною.

Висновки. З метою подальшого застосування наночастинок оксидів металів (міді, золота, срібла, титану, заліза) було вивчено на основі опублікованих в світовій науковій літературі досліджень основні механізми їх впливу на структуру ББ. НЧ мають різну класифікацію, відрізняються за хімічним складом та фізичними параметрами: нанорозміри, співвідношення поверхні до об'єму.

Ключові слова: бактерії, біоплівки, бактеріальні біоплівки, наночастинки, наноматеріали, оксиди металів.

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INTRODUCTION / ВСТУП

Abbreviations

BB – bacterial biofilms
NM – nanomaterials
NPs – nanoparticles
NsM – nanosized material
NOM – nanoscale of metal oxides
ROS – reactive oxygen species

Infectious complications associated with surgical intervention during implantation are usually due to the formation of bacterial biofilms (BB). A BB is an association of microorganisms in which microbial cells are concentrated in the middle of a self-created extracellular matrix [1]. Such a bacterial biofilm can interact not only with the implant's surface but also penetrate the surrounding tissues and joints. Currently, one of the promising directions for combating such biofilms is the use of nanoparticles of metals (Au, Ag, Fe, Cu, Zn, Mg) and their oxides, such as (AuO), (SiO), (Fe2O3), (Ag2O), (CuO), (TiO2), (ZnO) and (MgO), which are being thoroughly studied [2, 3, 4]. Nanomaterials (NM) based on nanoparticles (NPs) represent a new class of important materials that are being developed increasingly for use in scientific research and applications related to various areas of human activity. At the same time, it is necessary to remember the difference between true NM and nanosized material (NsM). According to the recommendations of special EU institutions, the size of the particles of true NM in one of its dimensions should not exceed 100 nm. The properties of NsM are practically limited by this dimensional parameter, while for true NMs, the dominant parameter is the surface-to-volume ratio (S/V parameter), which brings additional, qualitatively new properties [5]. In particular, the nanosize of metal oxides (NOM), due to the high value of the S/V parameter, leads to more effective interaction with cells, which makes them universal for strategic effects on BB. The action of such materials is characterized by complex mechanisms that act simultaneously to prevent the generation of genomic mutations of bacteria and suppress their growth [6].

Recent advances in the field of nanotechnology, particularly the ability to create highly ordered nanoparticles of metals, have led to the development of new approaches for using them as antibacterial agents. Studies have shown that preparations based on NPs can be used as effective antimicrobial agents and materials in medicine [7, 8].

According to some scientists (V.F. Marievskyi, B.O. Movchan, Y.G. Gogotsi, Rodney M. Donlan, J. William Costerton), a particularly promising direction in the fight against biofilms of such microorganisms as E coli, S aureus, P. aeruginosa is the use of nanosized metal oxides [9, 10].

Bacterial biofilms are universal. They can cause many problems in various fields of activity: water purification processes, food technologies, and implantology. Biofilms can infect medical devices. Formation of BB is a complex process that begins with the attachment of the bacterium to a living or non-living surface and leads to the formation of microcolonies – three-dimensional structures that peel off from the surface after maturation. Such biofilms are resistant to antibiotics, disinfectant chemicals, phagocytosis, and other components of the body's innate and adaptive defense system [8].

Despite numerous scientific studies on the efficacy of metal oxide nanoparticles against BB, there are still many unanswered questions that require further scientific inquiry and justification. The effectiveness of NPs after entering the biofilm of certain bacteria remains inconclusive. Scientists note that a larger number of studies on the impact of NOM on biofilms are needed to generalize the results and provide substantiated practical recommendations [8, 11, 12].

This article aims to analyze modern research on the classification and characteristics of NOM, as well as the study results on the mechanism of their influence on the destruction of bacterial cells and their biofilms.

Research material and methods

To achieve the goal, an analytical review of scientific publications was conducted using official databases, employing scientific research methods.

Research results

Six main mechanisms of the antibacterial effect on BB are presented in Fig. 1.

The membrane and cell wall are among the main stable cell barriers for bacteria, which enable the adsorption of nanoparticles. The primary component of Gram-positive bacteria is teichoic acid, which facilitates the distribution of NPs along the chain of phosphate molecules, preventing their aggregation [16]. Gram-positive bacteria possess a thick peptidoglycan wall and pores that allow the penetration of smaller molecules that can damage the cell wall of the bacterium, eventually leading to its death [17].

Gram-negative bacteria, on the other hand, possess a higher concentration of lipopolysaccharides, lipoproteins, and phospholipids, which lead to a negatively charged cell wall, thereby improving the interaction with NPs. BBs are likely to establish a barrier that inhibits the penetration of small molecules [18, 19].

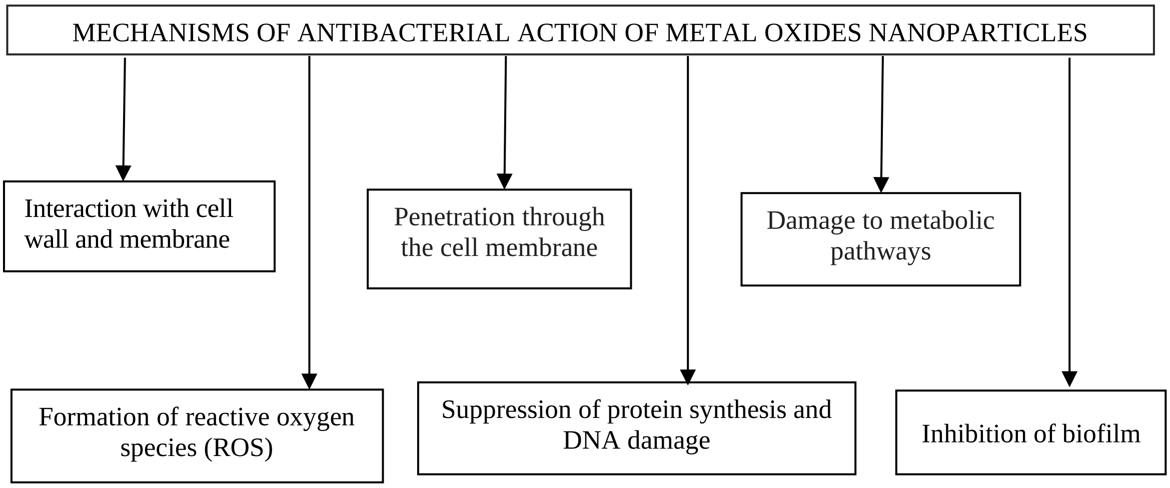

Figure 1 – The main mechanisms of the antibacterial effect of nanoparticles of metal oxides

The primary mechanism by which nanoparticles can damage biofilms is through oxidative stress induced by reactive oxygen species (ROS). Bacteria can maintain a balance in ROS generation under normal conditions. However, contact with certain NPs can disturb this balance, causing an excess of ROS, which eventually alters the redox state of molecules and contributes to cellular oxidation [20].

Upon penetrating the cell wall, NPs tend to release ions and generate ROS through diffusion. Metal ions can bind to negatively charged functional groups of the cell membrane, such as phosphate and carboxyl groups, disrupting its integrity and ultimately causing the death of the bacterial cell [16, 21, 22].

Another well-known mechanism of antimicrobial action of metal nanoparticles is DNA damage and the inhibition of protein synthesis. Typically, NPs cause the breakdown of ribosomal subunit proteins, enzymes, and other proteins synthesized in bacterial cell membranes. In several studies, degradation, compression, and fragmentation of bacterial DNA were observed, leading to a decrease in the physiological activity of genes [23, 24]. A study utilizing zinc oxide (ZnO) against E. coli DNA demonstrated this, where researchers found that NPs caused the most destruction at 10 regions of the bacterial genome. Moreover, the presence of NPs altered gene expression, ribosome composition, molecular structural activity, and RNA modification [25].

It has been shown that silver NPs [10] damage bacterial DNA by upregulating various antioxidant genes, ATP pumps, and genes encoding metal transport in S.aureus and E.coli bacteria. The researchers concluded that silver nanoparticles cause depletion of the antioxidant capacity of bacteria. The metabolic pathways of bacteria are not isolated but are complexly integrated into the activity of cells since their main role is to support the growth and reproduction of bacteria. It has been observed that when entering a bacterial cell, NPs cause changes in metabolism, which leads to cell membrane damage and causes oxidative stress, and bacterial death [26, 27]. It has also been suggested that NPs can directly regulate and damage the metabolic processes of bacterial target proteins to affect bacterial adhesion and the formation of bacterial biofilms [27]. One of the mechanisms of the antibacterial effect of nanoparticles during interaction with BB is the interaction with the extracellular matrix, which provides access to any chemical molecule of the agent to the bacterium and, thus, causes cell damage [28].

When in contact with bacteria, nanoparticles can affect the speed of bacterial adhesion, causing damage to biofilms, which is explained by the processes of metabolic inhibition by released metal ions. Despite numerous studies, the specific mechanisms of the impact of NPs on BB have not yet been fully determined [29].

Substances consisting of two elements, one of which is oxygen, are called oxides. Almost all chemical elements (except Helium, Neon, and Argon) form oxides [30].

According to their chemical properties, oxides are divided into three groups (Fig. 2):

- **basic,** which form salts when interacting with acids and acid oxides, and react with amphoteric oxides and hydroxides;

- **acidic**, which form salts when interacting with bases, basic oxides, amphoteric oxides, and hydroxides;

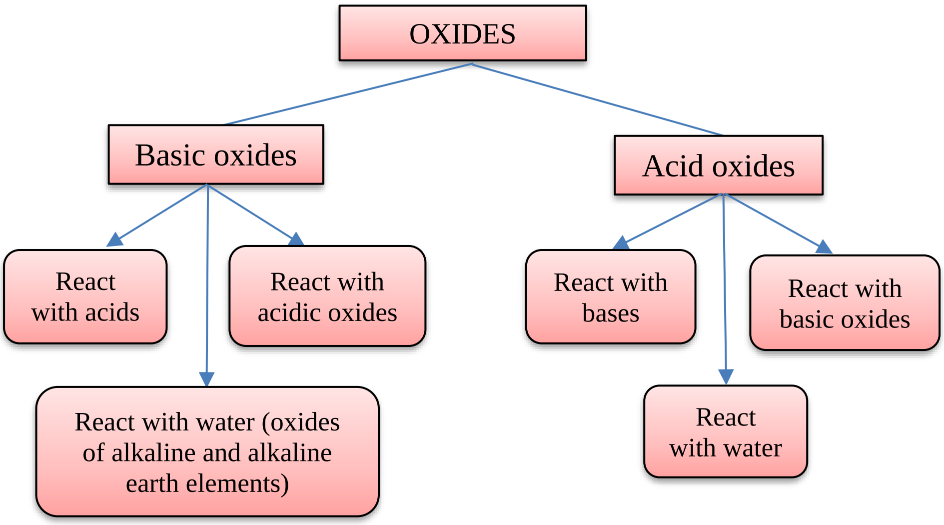

Figure 2 – Chemical properties of metal oxides [30]

- **amphoteric**, which correspond to amphoteric hydroxides, and which form salts when interacting with acids, bases, acidic and basic oxides.

NPs of metal oxides, such as Cu2O, Fe2O3, MgO, Ag2O, Au2O3, and ZnO, are of particular interest (Table 1).

NPs of copper oxide (CuO) have been shown to regulate the levels of cholesterol, sugar, and uric acid in the blood, as well as maintain the balance of intestinal microflora by inhibiting the growth of yeast microorganisms [31, 32]. CuO NPs are characterized by significant biological activity against antibiotic-resistant strains of microorganisms; they are less toxic than the macro-dispersed form of the metal [33]. However, their use in medicinal products requires further research on bioavailability and biocompatibility.

Table 1 – Effect of nanoparticles of metal oxides on bacterial microflora

Nanoparticle	Mechanism of action	Types of bacteria inhibited
Cu_2O	Damage to nucleic acids, disruption of biochemical processes [34]	*Pseudomonas* spp, *E. coli*, *K. pneumonia* , *P. vulgari*
ZnO	Destruction of the cell wall (membranes, proteins, and lipids) slows down gene replication in bacteria [16, 51]	*Staphylococcus aureus*
MgO	Destroy cells with the help of intracellular biomolecules [31]	*S. aureus*
Au_2O_3	Antibacterial action [49]	*S. aureus*, *E. coli*
Ag_2O	The mechanism of action is aimed at cell division and disruption of ROS, destroying the cell [44, 45].	*Escherichia coli* i *Pseudomonas aeruginosa*
Fe_2O_3	Associated with ROS disruption of bacterial cells [51]	*B. subtilis, E. coli*
TiO_2	Photocatalyst for disinfection, antibacterial action [28]	Lactobacillus acidophilus, P. aeruginosa, E. coli, S. aureus

The antimicrobial mechanism of zinc oxide (ZnO) is based on its ability to damage the integrity of the cell membrane, slow down the replication of genes in bacteria, prevent the formation of biofilms, and reduce the hydrophobicity of the cell surface. The antibacterial effect of these nanoparticles is largely determined by their size, which is a decisive factor in their penetration through the nanosized pores on the surface of the bacterial cell. It has been shown that ZnO NPs exhibit activity against cancer cells. This fact is explained by mechanisms based on ROS production, ZnO toxicity, and induction of apoptosis [16, 34].

Let us consider in more detail the mechanisms of their antibacterial action in contact with a microbial cell drawing on the example of ZnO nanoparticles. It should be noted that today several main mechanisms for the damaging effect of ZnO NPs on microbial cells are known [35, 36]. Those can be classified as physical and chemical [37]. The physical process involves the electrostatic interaction of ZnO particles with bacterial cells, which leads to mechanical damage to the cell plasma membrane due to increased surface tension and depolarization. The degree of such interaction is determined by the features of the cell wall structure and thus is the main factor that determines the antimicrobial activity of certain NPs (Fig. 3). After the penetration of ZnO nanoparticles into the cell, chemical interactions occur with the formation of ROS and the release of Zn2+ ions, as well as the leakage of intracellular fluid, which causes the death of the bacterial cell [38, 39]. It's also noteworthy that recent studies have shown interesting results [37, 40], indicating that the introduction of nanostructured ZnO particles into an apatite-biopolymer composite increases its porosity and degree of swelling. Moreover, samples with ZnO content are less conducive to swelling in a neutral environment (pH 7.3) than in an acidic environment (pH 4.5).

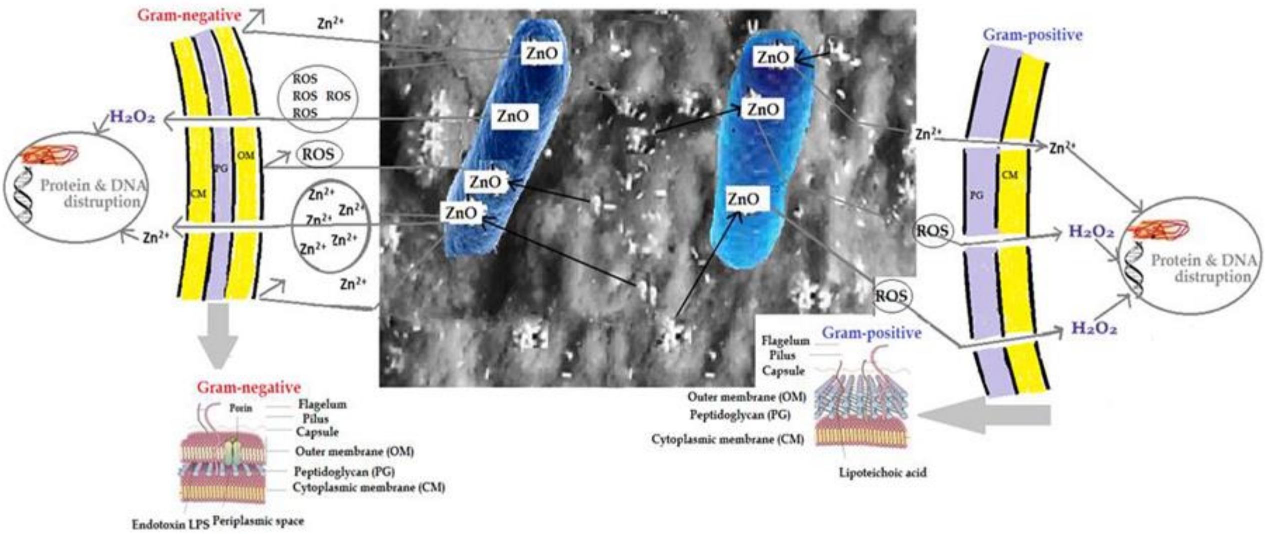

Figure 3 – Various types of interactions of ZnO materials with bacterial cells [36]

Magnesium oxide (MgO) nanoparticles are important antimicrobial agents, in particular, they can produce reactive oxygen species [41, 42]. NPs of magnesium oxide, physically connected to the cell surface, cause dysfunction of the integrity of the cell membrane, which results in its leakage, and also destroy cells with the help of intracellular biomolecules of irreversible oxidation. In addition, some studies have shown that in the absence of lipid peroxidation and ROS, magnesium oxide NPs generate a high antibacterial effect [43].

Iron oxide (Fe2O3) nanoparticles, unlike other nanoparticles, exhibit high ferromagnetism and reduced oxidative sensitivity. Due to the presence of Fe ions, iron oxide nanoparticles are non-toxic and biocompatible materials, which have drawn considerable attention. The stability of cells can also be directly affected by the formation of free radicals [41].

NPs of silver oxides (Ag2O) are used as an antibacterial agent in the composition of compounds such as silver nitrate, and silver sulfadiazine, as well as in the form of a finely dispersed powder for the treatment of infectious, dental diseases, and burn wounds [44]. Silver oxide NPs affect almost all viruses, bacteria, and some eukaryotic microorganisms [45, 46]. Despite silver's wide range of practical applications, from medical dressings to covering surgical devices, its toxicity is also known in the case of high concentrations, often resulting in adverse health consequences, which include permanent skin pigmentation (argyria), loss of vision, organ destruction, inflammation, and changes in the number of blood cells [47, 48].

The action of gold oxide NPs (Au2O3) as antimicrobial agents is primarily based on their electrostatic interaction with the negatively charged bilayer of the cell membrane. Studies have suggested and confirmed that anionic gold oxide particles are not toxic, while cationic ones are toxic [49].

Titanium oxide NPs (TiO2) are an alternative to traditional chemical disinfectants, which are more toxic. TiO2 is an inexpensive, highly efficient, stable, non-toxic substance and, as such, would be of particular value for water treatment systems in developing countries [50]. The antimicrobial properties of TiO2 NPs can be used in industry to increase the safety of food products, hygiene, and cosmetics by photocatalytic disinfection of the antimicrobial nanocrystalline surface TiO2 coating capable of destroying microorganisms resistant to ultraviolet radiation [51].

Application of a nanocrystalline TiO2 coating on the surface of orthodontic products, toothbrushes, and dental implants showed effective antibacterial activity against Lactobacillus acidophilus [51].

CONCLUSIONS / ВИСНОВКИ

To further use nanoparticles of metal oxides (copper, gold, silver, titanium, iron), the main mechanisms of their influence on the structure of BBs were studied based on papers published in the world scientific literature. NPs have different classifications and differ in their chemical composition and physical parameters, as well as their surface-to-volume ratio. Relatively low toxicity to the cells of the human body, low cost, effective inhibition of the growth of a wide range of bacteria, and the ability to prevent not only the formation of BB, but even to destroy spores, makes them promising for use in industry and medicine as antibacterial agents in conditions of the rapidly growing resistance of microorganisms to antibiotics [3, 43]. Analysis of modern research has shown that NPs of metal oxides demonstrate high efficiency in the processes of combating microbial biofilms, as well as (using the example of ZnO) to influence the porosity and degree of swelling of apatite-biopolymer composites.

CONFLICT OF INTEREST / КОНФЛІКТ ІНТЕРЕСІВ

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS / ВКЛАД АВТОРІВ

All authors substantively contributed to the drafting of the initial and revised versions of this paper. They take full responsibility for the integrity of all aspects of the work.

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