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# NOVEL COPPER-LOADED DRESSING FOR WOUND HEALING: A BIBLIOMETRIC ANALYSIS

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**NOVEL COPPER-LOADED DRESSING FOR WOUND HEALING: A BIBLIOMETRIC ANALYSIS**
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**Introduction.** In recent years, there has been a significant increase in the number of patients requiring wound care. The attention is on the time required for wound healing and the growing risk of antibiotic resistance. The 2022 Global Antimicrobial Resistance and Use Surveillance System (GLASS) report highlights alarming resistance rates among common bacterial pathogens. Thus, it is important to emphasize new alternative methods of wound care to address antibiotic resistance. Metal-based nanoparticles, such as copper nanoparticles (CuNPs), are a promising material for tissue regeneration and preventing the development of antibiotic resistance of microorganisms.

The *aim* is a bibliographic analysis of data on the use of copper nanoparticles as an antimicrobial agent for wound healing (and for other medical purposes).

**Materials and methods.** The authors searched for information in electronic databases such as PubMed, Scopus, Web of Science, and Google Scholar using the main keywords. Tools for bibliometrics network visualization (VOSviewer) were used in the analysis.

**Results.** We studied 142 publications in the Scopus database, where the main keywords were "copper nanoparticles" and "wound healing". The results show that over the past 14 years, the number of publications on the research topic has begun to increase. The subject is mostly studied by researchers from China, India, and the USA, which indicates the relevance of the current subject among the scientists. From 2010 to 2024, a bibliometric analysis on the Scopus database identified four chronological stages based on keywords: 1) synthesis of copper nanoparticles and description of the antimicrobial properties; 2) antibacterial activity in wound healing; 3) inception of new biomaterials to wound care.

Thus, copper nanoparticles and their properties are actively studied. The ability of CuNPs to inhibit bacterial growth and promote angiogenesis can be used in wound healing and added to dressings to stimulate tissue regeneration.

**Key words:** copper nanoparticles, CuNPs, wound healing, tissue regeneration, wound dressing.

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**НОВІ КУПРУМ-ВМІСНІ ПОВ'ЯЗКИ ДЛЯ ЗАГОЄННЯ РАН: БІБЛІОМЕТРИЧНИЙ АНАЛІЗ**
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Стаття присвячена аналізу літературних даних щодо використання наночастинок міді як антимікробного засобу для загоєння ран у зв'язку зі збільшенням кількості антибіотикорезистентних бактеріальних патогенів.

На основі досліджень 142 джерел було встановлено, що за останні 14 років кількість публікацій на вказану тему суттєво збільшилася, що пов'язано зі зростаючим інтересом науковців до нанотехнологій та пошуком альтернативних антимікробних речовин. Бібліометричний аналіз показав, що наночастинки міді активно вивчаються вченими в різних країнах світу, зокрема в Китаї, Індії та США. Їхня здатність пригнічувати ріст бактерій та сприяти ангіогенезу може бути використана безпосередньо під час лікування ран або додавання до перев'язувальних матеріалів для стимулювання регенерації тканин.

**Ключові слова:** наночастинки міді, загоєння ран, регенерація тканин, ранова пов'язка.

**Introduction.** In recent years, the number of patients with wounds has increased significantly around the world. This problem has become particularly acute in Ukraine. The number of wounds and injuries among the civil and military population has significantly boosted since the beginning of the full-scale invasion. The main concern is the time it takes to heal and the risk of antibiotic resistance. The 2022 Global Antimicrobial Resistance and Use Surveillance System (GLASS) report underscores resistance rates observed among prevalent bacterial pathogens. In 76 countries, the average of methicillin-resistant *Staphylococcus aureus* (MRSA) causing bloodstream infections is 35% [1].



Thus, new alternative methods of wound care should be found to overcome antibiotic resistance.

The United States Environmental Protection Agency (EPA) acknowledged copper in 2008 as the inaugural metallic antimicrobial agent [2]. Nanomaterials containing copper (CuNPs) promote the synthesis of extracellular matrix (ECM) components, such as fibrinogen, and enhance the activity of matrix metalloproteases (MMPs) in fibroblasts. CuNPs play a role in the formation of collagen and integrins, which are vital for cellular binding to the extracellular matrix [3–5]. Therefore, copper nanoparticles can be promising material in the regeneration of tissue and wound healing.

The basis of wound treatment is different types of dressing. The choice of dressing depends on the specific wound type. It plays a crucial role in wound care by creating an optimal environment for healing, protecting the wound from infection, and promoting faster recovery [6].

There are a lot of dressing materials based on nanomaterials, such as silver and gold nanoparticles, which can be used for wound healing [7–9]. However, the development of dressings with copper nanoparticles is a promising direction, considering the high healing properties of CuNPs combined with antimicrobial action. They can enhance the effectiveness of wound dressings due to their strong antibacterial properties, lower tendency to induce microbial resistance compared to antibiotics, and improve their mechanical strength and absorption capacity, making them more effective and comfortable for patients.

The **aim** is to conduct a bibliographic analysis of data on the use of copper nanoparticles and their antimicrobial action in the dressing material for advanced regeneration capacity in wound care.

**Materials and Methods.** The authors analyzed and systematized scientific publications on material with CuNPs used in wound healing in the electronic database Scopus for the past fourteen years on the keywords “copper nanoparticles” and “wound healing”. The authors analyzed the data of publications, such as year, subject area, and country of the research using the Scopus database. VOSviewer system from the University of Leiden (http://www.vosviewer.com/) was used for the visualization of the bibliometric network.

**Results and Discussion**

***Copper nanoparticles***

Over the last ten years, the development of nanomaterials has expanded in various areas of clinical use. Currently, around 100 nanomedicines have gained approval from both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), with over 500 more undergoing clinical trials [10].

Nanotechnology involves the production and manipulation of materials at the nanoscale level, typically ranging from 1 to 100 nanometers (nm) in size. Nanoparticles (NPs) are a diverse class of materials within nanotechnology, encompassing particulate substances. These nanoparticles can be composed of various materials, including metals, metal oxides, polymers, and carbon-based materials. Due to their small size and unique properties, nanoparticles find applications in a wide range of fields, including medicine, electronics, environmental science, and materials science [11; 12]. One of the promising nanoparticles in recent years are copper nanoparticles.

Copper is a vital dietary element necessary for the proper functioning of the human body. The human body can acquire copper from diverse sources such as shellfish, seeds, nuts, cereals, whole grain products, and chocolate. Despite the availability of various sources for meeting the daily copper requirement, research indicates that the average adult loses about 1.4 mg/day for men and 1.1 mg/day for women [13].

Copper is present in over 30 types of proteins and important in the metabolism of living organisms. Enzymes, which contain copper, contribute to various body functions. Oxygen metabolism, regulation of skin pigmentation, synthesis of collagen, maintenance of blood vessel integrity, as well as iron balance, antioxidant defense, and neurotransmitter synthesis are among them [14; 15].

However, copper can become toxic, when consumed over human tolerance levels. Copper toxicity, or copperiedus, can cause several pathological processes that adversely affect human organisms. Acute copper toxicity causes nausea, vomiting, diarrhea, abdominal pain, headaches, and dizziness, while chronic copper toxicity leads to liver damage, kidney failure, or neurological symptoms [16]. Thus, copper-based medications should be used carefully, in appropriate doses under the supervision of a doctor to avoid the toxic effect of copper on the human body.

***Synthesis of CuNPs***

There are three main methods to synthesize copper nanoparticles: chemical, physical, and green synthesis [17].

Chemical method based on the reduction of copper ions in a solution to form nanoparticles. This can be achieved through various techniques such as chemical reduction, precipitation, or electrochemical methods.

In the reduction technique, Cu (II) salts can be reduced by various reducing agents, such as ascorbic acid, sodium borohydride, or polyol. These agents allow to product nanoparticles with controlled size and shape.

Microemulsion is a method of synthesis of nanoparticles, where a thermodynamically stable dispersion is formed in two immiscible liquids, such as water-in-oil, oil-in-water, or water-in-carbon dioxide supercritical phases, which is facilitated by a surfactant. This category uses the reverse micelle method, which involves two inverted emulsions of water and oil. This method was used to synthesize copper nanoparticles ranging in size from 3 to 13 nm.

The electrochemical method used electricity as a controlling force to produce copper nanoparticles. This technique occurs by passing an electric current between two electrodes separated by an electrolyte. So, synthesis takes place at the electrode/electrolyte interface [18].

Chemical methods are the most widely used approaches to obtain copper nanoparticles. However, a significant drawback is the use of hazardous substances at the synthesis stage. The development of environmentally friendly methodologies becomes extremely necessary, considering the growing prevalence of the use of nanoparticles and their active interaction with people.

The main physical method used to produce copper nanoparticles is based on reducing bulk copper into nanoscale particles and includes the milling technique. Milling involves the reduction of the metal to either micro- or nano-scale dimensions, following the “top-down” approach, or assembling larger structures through the blending of precursor salts, following the “bottom-up” approach.

This method has limitations, such as difficulty in the production of ultrafine particles and long-time production. Contamination, which often occurs during mechanochemical processing, affects the quality of the produced material. Nevertheless, there are several advantages of milling synthesis, such as low-cost production and enabling large-scale production. The average size of nanoparticles, their type, and morphology can be adjusted by milling conditions. Thus, the milling method is a promising approach to developing a scalable synthesis of CuNPs, which can be used in different fields, such as biosensors, pharmaceutical and antimicrobial materials [19; 20].

Green synthesis is one of the most interesting methods of CuNPs production in recent years. According to this approach, synthesis of nanoparticles includes the utilization of biological organisms (bacteria, plants, or fungi) and their extract as a reducing agent of the copper ions [21]. Green synthesis offers several advantages, including environmental friendliness, cost-effectiveness, and the potential for large-scale production without the use of harsh chemicals.

Various plants have been utilized to produce nanoparticles due to their medicinal values and properties. *Fortunella margarita*, *Asparagus adscendens*, *Citrus medica*, *Cissus vitiginea* have been previously used for the synthesis of copper nanoparticles [22–25].

The mechanism of green synthesis includes preparing a biological extract and mixing it with a solution of copper salt (copper sulfate, copper chloride). The reducing agents in the biological extract reduce the copper ions in the precursor solution to form copper nanoparticles [26].

All mechanisms of CuNPs have their advantages and disadvantages. However, green synthesis offers a more ecological approach to the synthesis of nanoparticles due to its use of renewable resources and reduce the generation of hazardous waste. Chemical and physical approaches provide control over particle size, and shape, while scaling up green synthesis is more challenging due to process complexity. Thus, the choice between methods of copper nanoparticles depends on the specific application requirements, desired nanoparticle properties, environmental impact, and scalability considerations.

***Characterization and properties of CuNPs***

Morphological characteristics, such as size and shape of nanoparticles, are crucial in studying because it significantly impacts on their efficacy. The most important techniques to describe CuNPs and determine their efficacy are scanning and transmission electron microscopy (SEM and TEM), atomic force microscopy (AFM), dynamic light scattering (DLS), energy dispersive X-ray (EDX), and X-ray diffractometer (XRD).

Copper nanoparticles have unique properties, which are effectively used in different fields, such as biomedical applications, electronics, the chemical industry, textiles, and agriculture.

One of the main properties of copper nanoparticles is antimicrobial action. CuNPs can reduce the viability of bacteria, viruses, or fungi, depending on the chemical composition, shape, and size of the nanomaterial. The mechanism of antimicrobial activity is based on the contact action of nanomaterials, the release of ions, and the production of reactive oxygen species (ROS).

The first stage of CuNPs effect is direct contact with the cell surface, which leads to a change in the cell wall of microorganisms and the cell membrane. CuNPs and their released ions are positively charged, while the surface of both Gram-positive and Gram-negative bacteria are negatively charged. Thus, copper nanoparticles adsorb on the surface of bacterial cells, which leads to the destruction of the cell wall and, therefore, entry of the nanoparticles and their ions inside the cell [27].

The release of copper ions plays an essential role in antimicrobial action. Once copper ions get into bacterial cells, they can bind to enzymes and disrupt their function, bacterial DNA, leading to DNA damage and interfering with replication and transcription processes. The interaction of ions with bacterial DNA leads to the disruption of genetic material and prevents bacterial growth and proliferation [28].

Although ions play one of the key mechanisms in antimicrobial action, copper can only dissolve a small number of ions, which means that the release of ions is not the main antimicrobial mechanism of copper nanoparticles.

Both CuNPs and their ions can induce oxidative stress by generation of ROS. Reactive oxygen species are oxygen-containing derivatives composed of increasable oxygen radicals, such as superoxide ($O_2$), hydroxyl (OH), and hydrogen peroxide ($H_2O_2$), which are highly reactive and can increase in the presence of copper in the cell. The oxygen radicals damage cellular components such as proteins, lipids, and nucleic acids and lead to apoptosis [29–31].

***Application of CuNPs in the wound healing***

Chronic wounds are injuries that fail to heal in a systematic and timely manner throughout the different stages of the healing process within a 3-month period. Wounds can be classified into four groups: venous, arterial insufficiency, pressure, and diabetic ulcers. The classification is based on the etiology of the cause. Chronic wounds represent a considerable challenge to the healthcare system due to their prevalence and high-cost treatment. [32; 33].

Chronic infection is often associated with multiple bacterial species and, thus, effective care and appropriate treatment are essential. Bacteria, which are part of skin microbiota (*Staphylococcus aureus*, *Pseudomonas aureginosa*), can penetrate wounds and cause chronic inflammation. At the beginning of chronic wound formation, gram-positive bacteria, especially *S. aureus*, are most common. Methicillin-resistant *S. aureus* (MRSA) has become a serious problem. There are only a few antibiotics that are effective against these stains. MRSA often forms a biofilm, where bacteria can transfer the resistance genes between each other and, thus, increase resistance to antibiotics and innate host immunity mechanisms. This biofilm can be formed by antibiotic resistance strains, which is more dangerous because treatment with antibiotics could be ineffective [34–37].

Copper nanoparticles are promising material in wound healing due to their antimicrobial properties. Moreover, they can stimulate tissue regeneration by promoting angiogenesis and collagen synthesis.

CuNPs can be merged with natural or synthetic materials, such as chitosan or poly(vinyl alcohol), due to their biocompatibility and ability to promote tissue regeneration [38; 39]. Wound dressings have been made using different materials (synthetic or natural) and come in various physical forms, such as sponges, hydrogels, hydrocolloids, films, and membranes. Various formulations and unique characteristics of dressing make them appropriate for treating specific types of wounds [40]. Copper nanoparticles can be used in dressing material to repair the skin barrier, promote wound regeneration, and decrease the risk of re-infection. Dressing material is used to enhance the proliferation and migration of fibroblasts and accelerate the formation of epithelial tissue [41].

***Limitations of using copper nanoparticles***

A lot of studies claim the cytotoxicity of metal nanoparticles. Thus, copper nanoparticles are not an exception. The size and shape of nanoparticles determined the result of cytotoxicity. Most of the nanoparticles have a limited therapeutic index, despite their extensive antimicrobial properties [42; 43]. On the one hand, CuNPs have antimicrobial properties that can be used in the treatment of bacterial infections. On the other hand, they can also affect cells, organs, and systems of the human body [44]. Therefore, it is necessary to conduct more research to determine the cytotoxic level of CuNPs and the ways of their effect on the host organism. To achieve this goal, copper nanoparticles should be studied from a physical, chemical, and biological point of view.

**Bibliometric analysis of scientific literature**

We analyzed 142 publications in the Scopus database, which was filtered by the keywords "copper nanoparticles" and "wound healing", although there are more than nine thousand publications that were found by the keyword "copper nanoparticles". Thus, scientific interest in copper nanoparticles started in the early 90s and significantly increased over the past thirty years, while the interest of CuNPs' use in wound healing started in 2010 and increased over the last few years (Fig. 1).

The copper nanoparticles and their effect on wound regeneration are mostly studied by researchers from China, India, and United States.

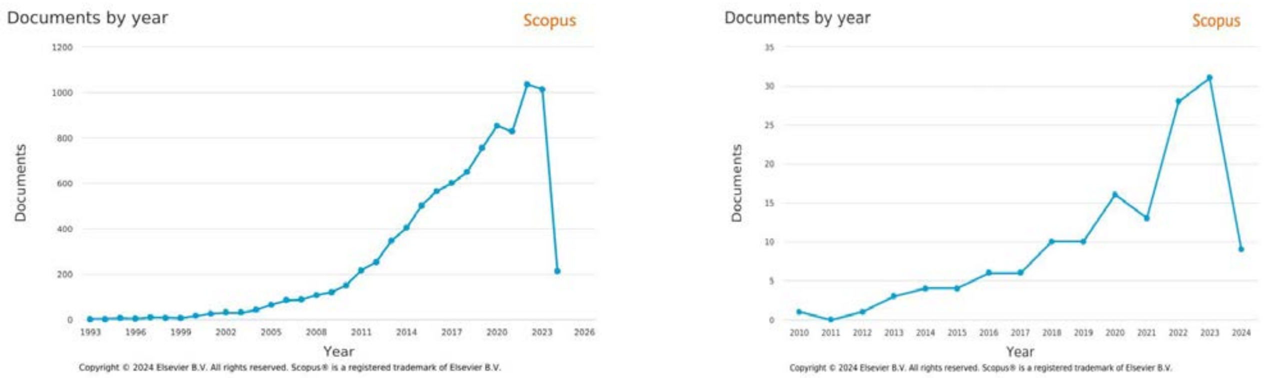
There is also great interest in the dissemination of publications on the subject. According to the data from the Scopus database, copper nanoparticles have been studied from the side of chemistry, material science, and engineering. Only in the past fourteen years the number of publications in biochemistry, molecular biology, and pharmacy increased (Fig. 2).

Thus, copper nanoparticles have been actively studied in the last 30 years mostly for their physical properties, leaving an unfilled niche in the study of properties of nanoparticles in wound healing. The use of nanoparticles in this direction began to be actively studied only in the last 14 years.

We analyzed the 142 publications published from 2010 to 2024 on the research topic. Selected articles were analyzed in the Scopus database using the keywords "copper nanoparticles" and "wound healing". They can be divided into three thematic clusters: 1) copper nanoparticles; 2) antimicrobial activity; 3) wound infections (Fig. 3).

There are also three chronological stages: synthesis of copper nanoparticles and description of the antimicrobial properties; antibacterial activity in wound healing and creation of new biomaterials to wound care (Fig. 4).

**Limitations.** This research includes publications only in the Scopus database from 1993 to March 20, 2024.




A B

**Fig. 1. Comparison of the publication chronology. A. Documents filtered by the keyword "copper nanoparticles". B. Documents filtered by the keywords "copper nanoparticles" and "wound healing"**

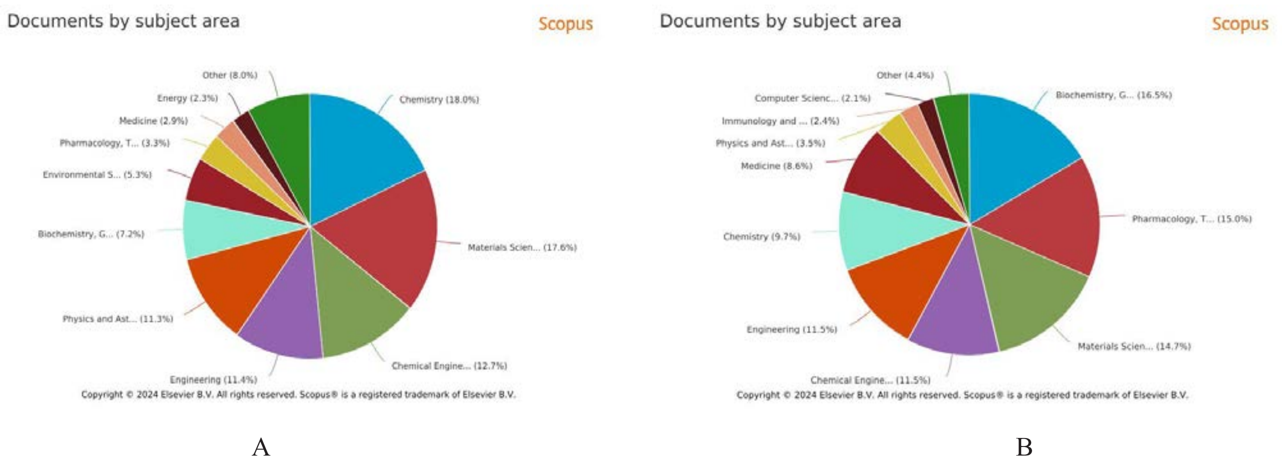



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**Fig. 2. Comparison of the distribution of publications on the subject area. A. Documents filtered by the keyword "copper nanoparticles". B. Documents filtered by the keywords "copper nanoparticles" and "wound healing"**

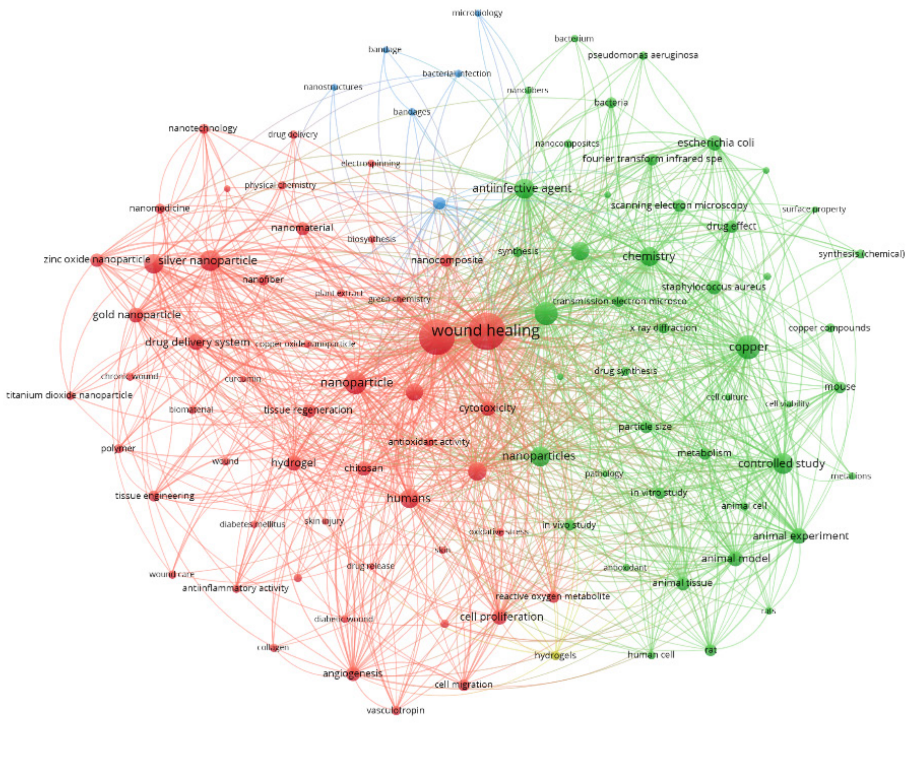


**Fig. 3. Thematic distribution of the analyzed topic using the tools of bibliometric analysis VOSviewer**

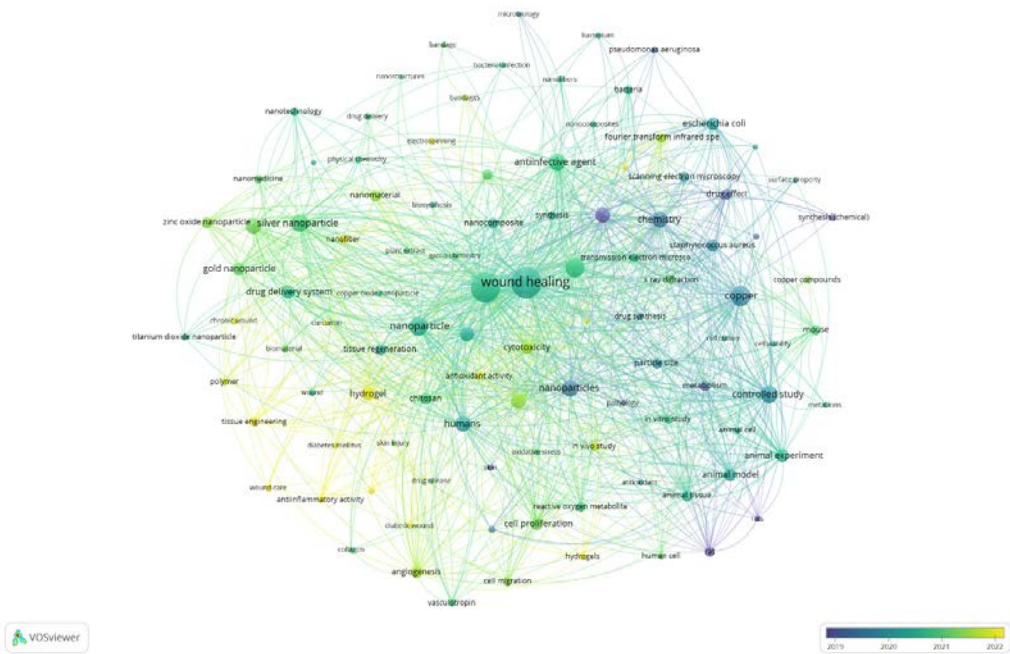


**Fig. 4. Patterns of the chronological development of the analyzed topic using the tools of bibliometric analysis VOSviewer**

**Conclusions.**

Nowadays, the problem of antibiotic resistance requires special attention. More microorganisms are becoming resistant to antibiotics due to lack of control over their use. Thus, it is necessary to investigate alternative materials that could reduce the use of antibiotics in the treatment of infectious diseases, such as wounds.

Analysis of publications of the Scopus database due to the period from 2010 to 2024 shows rising scientific interest in the copper nanoparticles application in medicine, particularly for wound care. Notably, the interest in copper nanoparticles appeared in the 90s, but most publications are dedicated to the physical properties and synthesis of nanoparticles. Meanwhile, research on the use of CuNPs in wound care has increased over the past 14 years. Moreover, due to the active search and study of alternative methods of treating infections, the subject of interest is relevant and is being actively studied now.

We identified three chronological stages using the tool for building and visualizing bibliometrics: synthesis of copper nanoparticles and description of the antimicrobial properties; antibacterial activity in wound healing and inception of new biomaterials to wound care. Scientific publications that were investigated can be split under the three thematic clusters: 1) copper nanoparticles; 2) antimicrobial activity; and 3) wound infections.

Thus, copper nanoparticles are now actively being studied by scientists in different parts of the world. The ability of CuNPs to suppress bacterial growth can be used in wound care. CuNPs promote angiogenesis and collagen synthesis and can be added to the wound dressing. To improve antimicrobial action and decrease the cytotoxicity of CuNPs, different components, such as chitosan, are used due to their synthesis.

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**Conflict of interest.**

The authors declare no conflict of interest.

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