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ANTIMICROBIAL DISCOVERY – IMPACT OF THE NATURAL SOURCES

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This article is the result of an analysis of the most relevant publications in the medical literature on the importance of natural sources in the antimicrobial discovery. Literary sources were selected by searching the following databases: PubMed/Medline, virtual health library (LILACS and SciELO) and Science Direct Publisher Site, Europe PMC free article, Cross Ref.

The purpose of this review was to carry out a bibliographic analysis of scientific articles devoted to the study of the antimicrobial activity of various products of natural origin. The authors of this study evaluated the therapeutic potential of antimicrobial agents from natural sources and identified the main trends in the study of such resources in our country and abroad. They also presented the advantages and disadvantages of natural antimicrobials and emphasized the prospects of using the antimicrobial properties of various natural agents as an alternative to classical antibacterial drugs.

Keywords: *natural agents, antimicrobial properties, alternative to antibiotics.*

DESCOPERIREA ANTIMICROBIANĂ – IMPACTUL SURSELOR NATURALE

Acest articol este rezultatul analizei celor mai relevante publicații din literatura medicală despre importanța surselor naturale în descoperirea antimicrobiană. Sursele literare au fost selectate prin căutarea următoarelor baze de date: PubMed/Medline, virtual health library (LILACS and SciELO) și Science Direct Publisher Site, Europe PMC free article, Cross Ref.

Scopul acestui review a fost de a efectua o analiză bibliografică a articolelor științifice dedicate studiului activității antimicrobiene a diferitor produse de origine naturală. Autorii acestui studiu au evaluat potențialul terapeutic al agenților antimicrobieni din surse naturale și au identificat principalele tendințe în studiul unor astfel de resurse în țara noastră și în străinătate. De asemenea, au prezentat avantajele și dezavantajele antimicrobienelor naturale și au subliniat perspectivele utilizării proprietăților antimicrobiene ale diferiților agenți naturali ca alternativă la medicamentele antibacteriene clasice.

Cuvinte-cheie: *agenți naturali, proprietăți antimicrobiene, alternativă la antibiotice.*

Introduction

The problem of antibiotic resistance has become global and today is one of the most serious threats to human health, food security and development. New mechanisms of sustainability appear and spread everywhere, taking into account their use not only in medicine, but also in veterinary medicine, agriculture, fisheries, food industry and many other areas. It is becoming increasingly difficult for the pharmaceutical industry to create new antibiotics. This is a very long and expensive process, requiring significant economic and scientific resources. Under such conditions, humanity is inexorably approaching the post-antibiotic era, when even a minor infection will be able to lead to death [1]. Thus, the search for alternative medicines with high antimicrobial activity, low toxicity and adequate cost becomes strategically important. The positive experience of the use of medicinal plants by the population for the treatment of diseases makes it necessary to conduct pharmacological research, which will make a great contribution to scientific knowledge and clarify the mechanisms of action of the main bioactive substances present in these plants. Due to the complexity of the fight with the antibiotic resistant microorganisms, antimicrobial agents from natural sources are becoming an inexpensive and effective alternative. A systematic review of ongoing research in the world is a powerful tool that incorporates research variability, providing an overall assessment of the use of such agents as antioxidants of anti-inflammatory and antimicrobial agents [2].

Material and methods

The article provides an overview of the most relevant publications of medical literature in the country and abroad using the databases PubMed, EMBASE, HINARI, virtual health library (LILACS & SciELO) and

Science Direct Publisher Site, Europe PMC free article, Cross Ref. To clarify this topic, 47 bibliographic sources, information published over the past 15 years, were analyzed and systematized. Nine old articles that were not considered suggestive were excluded from the analysis process. Thus, as a result, 34 topical, current publications, 4 older, but very revealing articles (a total of 38 scientific sources) on the antimicrobial activity of various products of natural origin were selected.

Results of literature review

Phytoncides. Plants synthesize a variety of secondary metabolites (phytochemicals), which as is known, are involved in defense mechanisms and in the last few years it has been recognized that some of these molecules have beneficial effects on health, including antimicrobial properties. Biologically active substances formed by plants, which kill or inhibit the growth and development of bacteria, microscopic fungi, and protozoa are called phytoncides. About 85 percent of higher plants have high phytoncide activity, as for example, garlic, onions, lemon, ginger, blackcurrant, juniper, white cabbage, birch, oak, horseradish, nettle, pine, bird cherry, bee products, sea buckthorn, turmeric, lavender, etc. These and many other examples of antimicrobial agents of plant and animal origin are collected and described in the work of Indian authors. They represented very widely the spectrum of resources of plant and animal origin, which were investigated for antimicrobial activity against pathogenic microorganisms, and also presented the spectra of sensitive microorganisms [3].

The chemical nature of phytoncides is different. Usually this is a complex of compounds, the so-called secondary metabolites, not related to the main classes of natural compounds. The main groups of plant compounds that are responsible for antimicrobial activity are phenols, phenolic acids, quinones, saponins, flavonoids, hydrolyzable tannins, catechins, tannins, coumarins, glycosides terpenoids and alkaloids. There are non-excretory phytoncides of cell protoplasm ("tissue juices") and volatile fractions released into the atmosphere, soil, water (in aquatic plants). Volatile phytoncides are able to exert their effect when at a distance. The action of essential oils is based on these properties, i.e. phytoncides of the leaves of oak, eucalyptus, pine, lavender and many others. The power and spectrum of the antimicrobial effect of phytoncides are very diverse in different plant species, and also depend on the growing season, time of day, atmospheric conditions, and season [2,3].

A lot of research is devoted to the mechanisms of action of secondary plant metabolites on microbial cells, which allows a deeper understanding of the prospects and their antimicrobial effectiveness. Hydrolyzable tannins are secondary metabolites of plants that are roughly classified into gallotannins and ellagitannins having gallic acid and ellagic acid residues correspondingly linked to the hydroxyl group of glucose by an ether bond. It is believed that the presence of hexahydroxydiphenyl and nonahydroxyterphenoyl groups determines the antimicrobial property of hydrolyzable tannins. They also show significant synergism with antibiotics. They have a low pharmacokinetic property. Nevertheless, the scope of their application as a future antimicrobial agent, according to some authors, may be quite promising. Other studies examined the mechanism of action of gallic (GA) and ferulic (FA) acids, hydroxybenzoic acid, and hydroxycinnamic acid. The mechanism of their action was evaluated on *Escherichia coli*, *Pseudomonas aeruginosa, Staphylococcus aureus* and *Listeria monocytogenes*. Antimicrobial targets were studied using various bacteriological physiological parameters: minimum inhibitory concentration (MIC), minimum bactericidal concentration (MBC), membrane permeability, intracellular potassium excretion, physicochemical surface properties and surface charge. It was found that FA and GA have antimicrobial activity against bacteria tested by MIC, 500 μg/ml for *P. aeruginosa*, 1500 μg/ml for *E. coli*, 1750 μg/ml for *S. aureus* and 2000 μg/ml for *L. monocytogenes* with GA; 100 μg/ml for *E. coli* and *P. aeruginosa*, 1100 μg/ml and 1250 μg/ml for *S. aureus* and *L. monocytogenes*, respectively, with FA. MBC for *E. coli* was 2500 μg/ml (FA) and 5000 (GA), for *S. aureus* – 5000 μg/ml (FA) and 5250 μg/ml (GA), for *L. monocytogenes* – 5300 μg/ml. (FA) and 5500 μg/ml (GA) and 500 μg/ml for *P. aeruginosa* with both phytochemicals – GA and FA led to irreversible changes in the properties of the membrane (charge, intracellular and extracellular permeability, and physicochemical properties) due to changes in hydrophobicity, reduction in negative surface charge and the occurrence of local rupture or pore formation in cell membranes with subsequent leakage of necessary intracellular components. A general study emphasizes the potential of plant molecules as a green and sustainable source of new broad-spectrum antimicrobial products [4].

Green tea, traditional for Asian countries at the end of the twentieth century, became popular almost everywhere. Its leaves are collected from the same bushes as black tea leaves, but in the process of preparation for use, they undergo minimal fermentation (oxidation). More recently, researchers have began to study the use of green tea in antimicrobial therapy and the potential prevention of infections. The special properties of catechins found in tea showed its antimicrobial effect. Green tea contains four main catechins (polyphenols) found in green tea: (-) - epicatechin (EC), (-) - epicatechin-3-gallate (ECG), (-) - epigallocatechin (EGC), and (-) -epigallocatechin-3-gallate (EGCG). Three of these, ECG, EGC, and EGCG have been shown to have antimicrobial effects against a variety of organisms [5].

Many authors are interested in the antimicrobial action of green tea. Investigations of clinically isolated strains of cariogenic and periodontal bacteria from carious teeth and periodontal pockets of patients with dental caries and periodontal diseases are described. Green tea extract was prepared by water extraction, then dilutions were made. For qualitative and quantitative determination of the antibacterial activity of green tea extract, standard methods were used for each isolate: the disk-diffusion method and serial dilutions. The results of these studies showed a high sensitivity of *S. mutans, A. actinomycetemcomitans, P. intermedia,* and *P. gingivalis* (100%) to green tea extract, and the minimum inhibitory concentration of the extract for *S. mutans* was 4 mg/ml for *A. actinomycetemcomitans* 6.25, for *P. gingivalis* and *P. intermedia* – 12.5 mg/ml. That is, green tea extract showed strong antibacterial activity against tested microorganisms; therefore, it can be used to rinse the mouth or create antimicrobial dentifrices for the prevention of caries and periodontal diseases [6,7].

Another interesting study is the impact of green tea extract on *Fusobacterium nucleatum*. This bacterium plays a key role in creating a pathogenic subgingival biofilm that initiates destructive periodontitis. It is also a frequent resident of the human gastrointestinal tract and is associated with the inflammatory gut disease. The effect of green and black tea extracts and their two biologically active components EGCG and theaflavins on the growth and virulent properties of *F. nucleatum* was studied. Tea extracts and components exhibit varying degrees of antibacterial activity, which may include damage to the bacterial cell membrane and chelation of iron. They also prevented the formation of *F. nucleatum* biofilms in concentrations that did not affect bacterial growth. Extracts of green and black tea, EGCG, and theaflavins reduced adherence of *F. nucleatum* to oral epithelial cells and matrix proteins. In addition, these tea components also attenuate *F. nucleatum*-mediated hemolysis and production of hydrogen sulfide, two other virulence factors that are expressed by this bacterium. Thus, this study showed that tea polyphenols may be of interest for the treatment of disorders associated with *F. nucleatum* [8].

The results of the authors who investigated the effect of green tea on the urinary tract infections caused by *E. coli* are very promising. *E. coli* is an infectious agent for 80–90% of all UTIs. Of the four main catechins, it was shown that only EGC is excreted in the urine in fairly high concentrations. The isolates of *E. coli* from UTI, which are resistant to antimicrobial agents and to standard drugs were studied. Then, 80 of that isolates, representing a wide range of antimicrobial susceptibility patterns, were selected for testing using green tea extract. The studies established minimal inhibitory concentrations and high (99%) antimicrobial activity, which also suggest that green tea may have a potential antimicrobial effect on UTI caused by *E. coli*. To complete the picture of its antimicrobial potential, further collection of data on studies conducted with human consumption during infections and studies on the spread of infections in populations that regularly consume green tea will be required [9,10].

Many authors pay great attention to garlic derivatives. One of the active components of freshly ground garlic homogenates is allicin. It has a variety of antimicrobial properties. It has been found that allicin in its pure form exhibits antibacterial activity against a wide range of gram-negative and gram-positive bacteria, including enterotoxicogenic *E. coli* strains resistant to many drugs; in addition, it has a high antifungal activity, especially against *C. albicans*; its antiparasitic activity is widely known, including in relation to the protozoa of the human intestine (*Entamoeba histolytica, Giardia lamblia*); also, its antiviral activity has long been known [11]. The main antimicrobial effect of allicin is due to its chemical reaction with thiol groups of various enzymes, for example, alcohol dehydrogenase, thioredoxin reductase and RNA polymerase, which can affect the essential metabolism of cysteine proteinase activity involved in the virulence (for example *E. histolytica*) [12].

A series of in vitro experiments have been developed to evaluate the effect of two different industrial products derived from garlic (*Allium sativum*) on fecal microbiota of pigs. *Escherichia coli* and *Salmonella typhimurium*, the two most common pathogens of pigs were tested, resulting in both compounds showing a bactericidal effect against these strains. *In vivo* trials were aimed at exploring the potential use of these products as an alternative to antibiotics in pig feeds [13].

Interesting studies were conducted by Portuguese scientists. They studied different varieties of walnut leaves, their antimicrobial and antioxidant properties. Antimicrobial ability was studied in relation to gram-positive

(*Bacillus cereus, Bacillus subtilis, Staphylococcus aureus*) and gram-negative bacteria (*Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae*) and fungi (*Candida albicans, Cryptococcus neoformans*). Walnut leaves selectively inhibit the growth of gram-positive bacteria, with *B. cereus* being the most susceptible (MIC 0.1 mg/ml). Gram-negative bacteria and fungi were resistant to extracts at a concentration of 100 mg/ml, but their high antioxidant activity was demonstrated. The authors described the high antimicrobial properties of walnut kernels and the oil obtained from them. It has been established that walnut oil exhibits antimicrobial activity against *Staphylococcus, Klebsiella pneumoniae, Pseudomonas aeruginosa, Escherichia coli, Bacillus subtilis* and *Proteus vulgaris*. Walnut oil can be used to fight bacterial infections. The authors also found that walnut oil contains a large amount of phytochemicals [14].

The aim of Brazilian scientists was to provide a systematic review of the antimicrobial and antioxidant properties of cashew nuts (*Anacardium occidentale*), (*Anacardium microcarpum*) and pequi (*Caryocar brasiliense*) [4]. It was also found that cashew bark has a significant bactericidal effect due to the presence of tannins [15].

Essential oils. The use of plants as antimicrobial agents has increased significantly in recent years. A good example of this fact is the phenolic compounds present in the essential oils of many plants, which are known as active substances, such as rosemary leaf essential oil, used in food preservation to suppress microbial contamination and spread, or tea tree oil, which is a well-known antiseptic [16].

There is an interesting work of Egyptian scientists who studied the essential oils of 18 Egyptian plants. Isolated oils were tested for their antimicrobial activity against the most economical lant pathogens *Agrobacterium tumefaciens* and *Erwinia carotovora var. carotovora*, and fungi *Alternaria alternata, Botrytis cinerea, Fusarium oxysporum* and *Fusarium solani*. Isolated oils showed a different, but rather high degree of antibacterial activity. In the analysis of inhibition of mycelial growth, most essential oils showed a pronounced effect. A connection was found between antimicrobial activity and the chemical composition of the isolated oils. The results of this study suggest that the isolated oils could potentially be used as antimicrobial agents [17].

Lavender and basil vegetable essential oils were tested *in vitro* for antimicrobial activity against gram-positive bacteria (methicillin-resistant *Staphylococcus aureus* 1144 (MRSA 1144) and *S. aureus* 1426) and gram-negative bacteria (*Escherichia coli* ATCC 25922 and *Escherichia coli* ESBL 4493) showed antimicrobial good antimicrobial activity of lavender essential oil, with MIC and MBC values of <0.1% for *E.coli* ESBL producing strain and 1.56% for MRSA. These results can make a significant contribution to the development of new antimicrobial infection control strategies [18].

Russian authors studied the method of air purification using phytoncides and essential oils and they proved this is the safest, most affordable and effective way, which at the same time has a beneficial effect on human health. The mechanism of action of volatile phytoncides is that they cause various changes in the microbial cell: suppress respiration, dissolve and destroy the surface layers and components of protoplasm (enzymes, etc.). And more importantly, it was found that microbes with prolonged contact with volatile plant secretions don't develop resistance to them. The number of bacteria in the air was taken as the number of microorganisms that formed colonies visible to the naked eye when growing on the medium for three days. For the cultivation of microorganisms in the air, universal media were used - meat and peptone agar, nutrient agar for the cultivation of microorganisms. It was established that phytoncide formation is a dynamic process and depends on many environmental factors: a) the release of volatile substances in hot weather increases, and decreases with a drop in temperature, b) an increase in the humidity of the greenhouse negatively affects the bacterial and fungicidal activity of plants. All studied greenhouse plants had a pronounced phytoncidal activity, which depended on the species. The following plants possess the greatest antibacterial and fungicidal activity during the entire growing season: laurel, eucalyptus, lemon etc. The results were used for the selection of essential oils in order to disinfect the premises. It was found that the essential oil of laurel noble has more pronounced bactericidal properties than the oil of lemon, eucalyptus and cypress. The activity of essential oils is identical to the activity of volatile emissions of the corresponding plants [19].

Similarly, animal products also contain antimicrobial agents such as exoskeletons, chitosan, milk, egg albumin, beekeeping products, a large collection of marine biomolecules etc. [17,23].

Other natural types of antibiotics are antimicrobial peptides (AMPs), which are abundant in nature. The antimicrobial effect occurs as a result of the rapid interaction of AMP with the microbial membrane, which leads to their destruction, the release of cytoplasmic components and the cessation of cellular activity. For peptides of marine invertebrates living in Ghana, it is reported that the crude peptides *Galatea paradoxa, Patella rustica* have some antimicrobial activity [2,20].

Antimicrobial peptides are molecules consisting of 12-50 amino acid residues that have antimicrobial (antibacterial) activity. For the first time, antimicrobial peptides, cecropins, have been isolated from hemolymph of silkworm caterpillars. *Cecropins* possessed strong antimicrobial activity, and not only this was surprising, but also the very high specificity of the action of these substances. *Cecropins* acted with high efficiency only on *Escherichia coli*. In response to microbial damage or damage the skin of the frog releases a large number of antimicrobial peptides consisting of 23 amino acids. Antimicrobial peptides are produced even by plants. *Thionins* are plant peptides discovered almost 50 years ago. Antimicrobial peptides act on both gram-negative and gram-positive bacteria, as well as fungi, viruses, protozoa. In addition, antimicrobial peptides exhibit antimicrobial activity against bacterial strains resistant to antibiotics [20].

AMPs are often introduced in the literature as "promising alternative to antibiotics", "potential to address the growing problem of antibiotic resistance," and "hold promise to be developed as novel antibiotics". Antimicrobial peptides act on a negatively charged outer membrane of gram-negative bacteria. On the surface of this membrane are magnesium cations, which neutralize the negative charge on the surface of the membrane. Antimicrobial peptides displace these ions and either firmly bind to a negatively charged lipopolysaccharide or neutralize a negative charge on the membrane surface, disrupt its structure and penetrate into the periplasmic space. The cytoplasmic membrane of bacteria is also negatively charged. Antimicrobial peptides can integrate into the cytoplasmic membrane and change their conformation to form structures such as channels that disrupt cell integrity. In addition, when bacteria or another parasite penetrate the cytoplasm, antimicrobial peptides, when positively charged, bind to cellular polyanions (such as DNA and RNA), which also leads to the death of a bacterial cell. In addition, among the existing models of the action of antibacterial peptides on the microbial cell, there is the so-called carpet model. The positively charged peptide molecules line the negatively charged bacterial membrane, forming a molecular carpet. When the entire surface of the bacterium is occupied by peptides, its membrane begins to break into pieces. It is much harder for bacteria to develop resistance to antimicrobial peptides. Therefore, antimicrobial peptides may be a good alternative to antibiotics. Many of these peptides have more than one function: many AMPs have been shown to possess immunomodulatory, anti-cancer and antibiofilm functions in addition to their antimicrobial properties [21].

Currently, a large amount of information is available in the literature on the chemical and biological aspects of beekeeping products, but little information is available on its therapeutic use. The phenolic profile, in vitro antimicrobial activity, and the effect of the propolis hyaluronidase enzyme (widely associated with the inflammation process) collected in Portugal were evaluated. The effectiveness of the three extracts (hydroalcoholic, methanol and water) was also compared. A hydroalcoholic extract was chosen because it was most effective for the extraction of phenolic compounds. Antimicrobial activity was achieved in gram-positive and gram-negative bacteria and yeast isolated from different biological fluids, and the results were then compared with those obtained for control microorganisms. Propolis from Braganza had the highest polyphenol content. A sample from Beja showed less significant inhibition of the hyaluronidase enzyme. Regarding antimicrobial activity, *Candida albicans* was the most stable, and *Staphylococcus aureus* the most sensitive. Control microorganisms were more sensitive than those isolated from biological fluids [21]. Antimicrobial activity was determined against bacteria and yeast isolated from control strains and hospital origin. The chemical composition of the geopropolis included flavonoids, derivatives of glycosylated phenolic acids and terpenoids. GP showed high antioxidant activity, it inhibited the activity of the inflammatory enzyme hyaluronidase and reduced the mutagenic effects in *S. cerevisiae*. As for antimicrobial activity, it contributed to the death of all evaluated microorganisms. In conclusion, this study was first to reveal the chemical composition of GP and demonstrate its pharmacological properties. The presence of phenylpropanoids, flavonoids [2], phenolic acids, hydrolyzable tannins [19], triterpenes, saponins and alkaloids compounds that may be associated with the biological properties of this substance has een described [22].

Another example of bee products. The biological properties of propolis are constantly studied and include antifungal, antimicrobial, antioxidant activity. There are studies showing how the high polyphenol content in *Chilean propolis* inhibits the growth of *Streptococcus mutans* and reduces the formation of biofilms. The multiple therapeutic properties of honey are due to its chemical diversity: peptides, proteins, hydroxymethylfurfural are examples of bioactive compounds. One of these studies led to the isolation of glycoproteins from honey which showed sequence identity with the Major Royal Jelly Protein 1 (MRJP1) which is composed of three antimicrobial peptides: Jelleins 1, 2, and 4. These glycoproteins exhibit a broad-spectrum activity against multi-drug resistant clinical isolates. A better understanding of the mechanism of action (MOA) of AMP is an important part of the discovery of more potent and less toxic AMPs. Many models and methods have been used to describe MOA. However, the use of antimicrobial peptides in the clinic still has a number of obstacles. When administered intravenously, antimicrobial peptides flood healthy tissues and only some of them reach the site of infection. Host proteases cleave antimicrobial peptides even before they reach their destination. The activity of antimicrobial peptides in vivo often differs from the activity of peptides in vitro. Thus, polyphemisin isolated from crustacean hemolymph, which showed high antimicrobial activity in vitro, did not show any antimicrobial activity in animal models. Another obstacle to the widespread use of antimicrobial peptides is their high cost. They cannot yet be obtained on a large scale as antibiotics and the cost of treatment with antimicrobial peptides will be approximately $ 100 per day [23-25].

Spirulina. A lot of research is devoted to the antimicrobial activity of algae, in particular, the activity of spirulina. Spirulina, like many other types of cyanobacteria, has the potential to produce a large number of antimicrobial substances, that's why they are considered suitable organisms for use as biocontrol agents of plant pathogenic bacteria and fungi. The antimicrobial activity of the soluble extracts of Spirulina platensis was studied against a wide spectrum of pathogenic bacteria: *Staphylococcus aureus, Streptococcus epidermidis, Streptococcus pyogenes, Bacillus cereus, Proteus mirabilis, Escherichia coli, Pseudomonegelus fungelifermella flexumella, Campella tropicalis, Candida albicans,* and *Candida glabrata*. The antimicrobial activity of *Spirulina platensis* was determined against pathogenic bacterial and fungal isolates. *Spirulina platensis* methanol extract showed a maximum inhibition zone against all bacterial and fungal isolates. Spirulina platensis hexane extract showed a minimal inhibition zone against bacterial and fungal pathogens compared to other solvent extracts [26,27].

It is very important to understand and it should be noted that the positioning of antimicrobial agents as "natural" does not guarantee advantages and safety, which makes it fundamental that the well-known herbal medicine is widely studied in terms of its pharmacological and toxicological aspects in order to understand its side effects [4]. Adverse effects occur due to the production of plant secondary metabolites, which can be toxic to the body, since, for example, anthraquinone in *Aloe Vera* can cause nephritis when the latter enters the body in high concentration. Alkaloid metabolites of pyrrolizidine present in comfrey (*Symphytum officinale*) are also hepatotoxic [16].

Scientific research by Moldovan scientists

Very active researches are carried out by Moldovan authors. Due to its geographical location, soil richness and the absence of polluting industries, Moldova has a very favorable environment, which allows the growing of different plant crops, vegetables, fruits and their processing in ecological conditions. Numerous studies are underway in Moldova at the Institute of Microbiology and Biotechnology of the Academy of Sciences, Institute of Genetics, Moldova State University, Technical University of Moldova, State University of Medicine and Pharmacy "Nicolae Testemitanu". The Medical University has a specialized botanical garden, where more than 200 species of medicinal plants are grown for deeper study and creation of medicinal products, for biological, phytochemical, pharmacognostic, pharmacological studies, etc. in order to allocate precious plants for the development of local medicinal products. Research work is constantly being carried out there, and highly effective agents have already been created: *Cimpelsept* – antimicrobial ointment with antifungal effect, a remedy with antimicrobial and antibacterial effect [28].

There are very interesting and promising studies on Mountain thyme essential oil. As a result of these studies, it was found that mountain thyme oil has a pronounced antibacterial effect against a wide range of gram-positive and gram-negative microorganisms and fungi (*C. albicans, A.niger, A. fumigatus, Penicillium*) *in vitro*. This is a low toxicity substance. Studies have shown that the LD50 for white rats is 7500 mg/kg body weight. Mountain thyme essential oil can be included in the reserve fund of antibacterial and antifungal substances. Based on these data, an antibacterial ointment, a medicine with pronounced bactericidal and fungicidal properties, where mountain thyme essential oil is used as a biologically active ingredient was created in the Scientific Laboratory of the "Nicolae Testemitanu" SUMPh. The ointment is effective in treating purulent-septic infections caused by fungal infections caused by *Candida* and *Aspergilus*. A very high effectivity has been shown in treating *S. aureus* carriers with a long-term effect. Six months after healing, *S. aureus* was found only in 4.5% of carriers treated with antibacterial ointment. At the same time, in the control group, which included *S. aureus* carriers treated with propylene glycol, the rate was 90% [29].

Eleutherococcus, valerian, ginkgo biloba, thyme, periteum, echinacea, and calendula are well described. There are studied plants - sources of aromatic and medicinal essential oils. So, laboratory studies have shown that the essential oil from *Koellia virginiana* exhibits antimicrobial properties and can be used as an antimicrobial and antifungal substance in production. Laboratory studies have shown in vitro the antibacterial properties of *Koellia virginiana* against gram-positive and gram-negative microorganisms in the range of concentrations of 0.03-0.5%, as well as the antifungal properties: in the range of concentrations of 0.015-0.125%. The oil of *Koellia virginiana* has low toxicity (LD50> 1000 mg/kg). The process of obtaining oil is simple and does not require high costs. It can be widely used in medicine and veterinary medicine, in the treatment of purulent-septic and fungal infections [30].

The studies evaluating the antimicrobial activity of sanguirytrin, sanguine, hyperforin diethylammonium, monarda essential oil with thymoquinone and without one *in vitro*, revealed pronounced antibacterial and antifungal activity of plant products derived from local raw materials [31].

Authors from the Institute of Chemistry and the Institute of Microbiology and Biotechnology of the Academy of Sciences of Moldova have studied and presented data about the possibilities of using plant tannins in the treatment of diseases of microbial origin. Enoxil, which is made from grape seed tannins, has both antibacterial and antifungal activity. Minimum inhibitory and bactericidal/fungicidal concentrations and some antimicrobial mechanisms of the Enoxil have been determined. On that basis, a cream with antimicrobial properties was developed, which is convenient in practical use; additionally, Enoxil is commercially beneficial due to its low price if compared to other creams with antimicrobial properties [32].

As for powders of rosehip and hawthorn, the research focused on the chemical composition and antiradical activity of their extracts, and the antimicrobial activity against pathogenic strains of *S. aureus, E. coli K. pneumoniae*. Rosehip powders exhibit the most pronounced antimicrobial activity in relation to *S. aureus*. In the case of *E. coli* and *K. pneumoniae*, the antimicrobial activity of rose hip is on average 1.3 times higher than that of hawthorn powders. The studied plant powders have shown promising antimicrobial potential against pathogenic microorganisms and can be used in the food industry to reduce microbial contamination of raw materials and food products. It was found that pathogenic and toxigenic microorganisms in foods are affected by various polyphenols. Polyphenols such as carvacrol and thymol, which have the highest level of activity against a wide range of gram-negative and gram-positive bacteria, as well as against fungi spoil food, were studied. Plant-based polyphenols are a rich new source of organic food preservatives and sanogenic substances, which also contribute to maintaining the health of the intestinal microbiota [33].

A lot of research is devoted to cyanobacteria and their active bioproducts. A special role is given to cyanobacteria and microalgae: *Spirulina platensis*, a microscopic cyanophyte algae with spiral threads. The studies of the therapeutic benefits of the biomass of spirulina and some of its extracts are quite numerous, showing various positive effects, especially antiviral, antitumor and immunomodulating. Spirulina doesn't produce and doesn't remove toxins, which is a good pharmacological priority, making it one of the main sources of materials for medicine preparations [34,35].

The antifungal activity of topical preparations, such as spirulina extract, enoxyl and hydroperoxide was investigated. A microbiological study of the antifungal properties of an aqueous-alcoholic extract of spirulina was carried out. Antifungal activity was assessed by the number of colonies on the Sabouraud-agar. As a result of a comparative study, the preparations taken in the experiment showed that the aqueous-alcoholic extract of spirulina has a much more pronounced antifungal effect in vitro than hydroperoxide and enoxyl [33]. In another study of the same authors, 42 fungal cultures were selected, which include: *Trichophyton, Candida albicans, Microsporum, Epidermophyton floccosum* to determine the antimycotic effect of the hydroalcoholic extract of spirulina. The results showed that spirulina extract at a concentration of 1 mg/ml caused complete inhibition of fungal cultures growth. The growth of *Microsporum canis* and *Trichophyton rubrum* cultures was inhibited by 0.5 mg/ml spirulina extract. The study really proved that spirulina extract has a high fungicidal effect [26,37].

Conclusions

1. Natural antimicrobial agents are widespread and they are secondary products of the metabolism of higher plants: phytoncides, volatile essential oils, and antimicrobial peptides – biomolecules of animals and marine organisms etc.

2. Numerous studies from different countries have one common aim – to identify and to study the antimicrobial properties of natural agents, to determine the mechanisms of their antimicrobial action and to prove the perspectives of their using as an alternative to antibiotics.
3. The results of these researches indicate the presence of good antimicrobial potential of natural agents, which suggests the need for further research to create effective antimicrobial agents that will be an alternative to traditional antibiotics.
4. Despite the fact that there are many studies on the antimicrobial activity of plant extracts on resistant micro-organisms, at the same time, it has been shown that not all of them are sufficiently active and harmless to the human body.
5. The authors of many studies which were analyzed, including in this review, emphasize the need to study the mechanisms of action and toxicity of these compounds.

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