SECONDARY METABOLITES OF PLANTS AND THEIR POSSIBLE ROLE IN THE "AGE OF SUPERBUGS"

V.M. Nesterovich[1], D.A. Belykh[1], N.V. Gorokhovets[1], L.K. Kurbatov[2], A.A. Zamyatnin[1,3], L.N. Ikryannikova[1]*

[1]Sechenov University,
8/2 Trubetskaya str., Moscow, 119991 Russia; *e-mail: larisa.ikryannikova@gmail.com
[2]Tyumen State University, 6 Volodarskogo str., Tyumen, 625003 Russia
[3]Lomonosov Moscow State University, Moscow, 119234 Russia

Bacterial infections are a serious cause of high morbidity and mortality worldwide. Over the past decades, the drug resistance of bacterial pathogens has been steadily increasing, while the rate of development of new effective antibacterial drugs remains consistently low. The plant kingdom is sometimes called a bottomless well for the search for new antimicrobial therapies. This is due to the fact that plants are easily accessible and cheap to process, while extracts and components of plant origin often demonstrate a high level of biological activity with minor side effects. The variety of compounds obtained from plant raw materials can provide a wide choice of various chemical structures for interaction with various targets inside bacterial cells, while the rapid development of modern biotechnological tools opens the way to the targeted production of bioactive components with desired properties. The objective of this review is to answer the question, whether antimicrobials of plant origin have a chance to play the role of a panacea in the fight against infectious diseases in the “post-antibiotic era”.

Key words: secondary metabolites of plants; phyto metabolites; drug resistance; bacterial pathogens; antimicrobial properties

DOI: 10.18097/PBMC20236906371

INTRODUCTION

Since ancient times, people have used plants and their derivatives for various purposes: for cooking, making clothes and household items, as well as for treating various diseases, including infectious diseases. Perhaps the most striking example of the “pharmaceutical history” of plants is quinine, an alkaloid from the bark of the cinchona tree (*Cinchona spp*.), which is widely known as an effective antimalarial agent, but it was also used to treat other infectious diseases such as pneumonia, typhoid fever, and even common nasopharyngeal infections [1]. The history of two other alkaloids is no less bright and dramatic: morphine from the opium poppy (*Papaver somniferum*) was widely used in anesthesiology, while atropine from belladonna (*Atropa belladonna* L.) found greatest use in ophthalmology.

In the modern world, the above-mentioned compounds have largely lost their importance, giving way to more advanced drugs. However, other phytoderivatives are still used in folk medicine, often as adjuncts in addition to routine therapy. Moreover, some commercial drugs used in modern clinical practice have their origins in traditional medicine of the past. One classic example is aspirin, a derivative of salicylic acid found in significant quantities in willow bark extracts, which were used in ancient times as an antipyretic and antifever agent [2, 3]. Well-known compounds derived from plants that exhibit biological activity, particularly antimicrobial properties, include, for example, allicin (an organosulfur compound from *Allium spp*. of the onion subfamily), piperine (an alkaloid from the genus *Piper* L. of the pepper family), curcumin (*Curcuma longa* of the ginger family), eugenol, the main component of clove oil (*Syzygium aromaticum*, or *Eugenia caryophillis*), chlorogenic acid from the fruits of the coffee tree (*Coffea* L.), etc. [4, 5].

The therapeutic effect of the components of plant raw materials is largely due to a mixture of compounds known as secondary plant metabolites (SMPs). SMPs are substances of varying chemical structure and properties that are not necessary for the growth and functioning of plants; they play an important role in interspecific competition or protection from herbivores and pathogenic microorganisms. To date, about two hundred thousand SMPs have been identified, and there are reasons to believe that this number may be much higher. Many compounds still escape the attention of researchers due to their very low content or short lifetime in changing environmental conditions [6–8].

The search for new SMPs that are promising in terms of biological activity and, in particular, antimicrobial potential, has recently acquired extreme relevance due to the significant spread of drug resistance of pathogenic microorganisms to routinely used antibacterial drugs (ABDs) [5, 9]. It is particularly interesting to explore the possibility of using SMPs as both independent medicinal substances and adjuvants that can potentiate the effect of antibiotics or improve the condition of patients.

1. SMP CLASSIFICATION

There is currently no unified approach to the SMP classification. The principles of SMP classification changed as these metabolites were studied and new data accumulated. The most ancient method of classification is based on certain properties of SMPs: for example, essential oils are a group of volatile liquids with a strong odor, alkaloids are metabolites with alkaline properties, saponins are substances that form foam (from *Saponaria* — soapwort), etc. From the point of view of applied research, the most popular approaches to classification are based on chemical structure and/or methods of biosynthesis of compounds (Fig. 1) [6–8, 10, 11]. Typically, three large groups are distinguished: terpenoids, phenolic derivatives, and alkaloids. Together, these groups account for about 90% of all SMPs [11]. Minor groups include saponins, lipids, essential oils, tannins, and others [9, 10]. A classification method based on the functions of secondary metabolites in the intact plant is also considered. Among the functions of SMPs, one can distinguish protective, attractive and others. In general, the classification of phytoderivatives is complex and is still in its infancy due to their abundance and diversity

2. ANTIMICROBIAL POTENTIAL OF SMPs: NEW PLAYERS VERSUS OLD TARGETS?

Modern scientific literature contains many reports about the antimicrobial activity of SMPs. Some examples are given in Table 1.

SMPs employ various mechanisms for their action on microbial cells (Fig. 2). For different classes of phytometabolites, disruption of the structure and functions of the bacterial cytoplasmic membrane was noted. These include impaired functioning of efflux systems, complex formation with membrane proteins, interruption of synthesis and functioning of DNA or RNA, and prevention of enzyme synthesis; induction of coagulation of cytoplasmic components and interruption of cellular communication (“quorum sensing”) [9, 46, 47]. For example, alkaloids interact with nucleic acids, disrupting transcription and replication processes, and also inhibit cell division [48, 49]. One example is berberine, a known phytochemical agent of the *Berberis spp*. alkaloid group; interacting with *S. agalactiae* streptococci, it can seriously damage the bacterial cell membrane structure and inhibit protein and DNA synthesis [22]. The antimicrobial activity of flavonoids is also associated with the effect on the microbial cell membrane; these molecules interact with membrane proteins on the bacterial cell wall thus increasing membrane permeability [49, 50]. The bactericidal effect of terpenes and terpenoids, as well as essential oils, is also based on the interaction with membrane proteins [49, 51]. For example, carvacrol and thymol, two of the most studied monoterpenes, contained in common thyme (*Thymus vulgaris*), are integrated into the membrane due to their hydrophobic nature, impair its normal functioning [34] and stimulate release of cellular contents as it was demonstrated using SEM in a model interaction with the *E. coli* lipid bilayer [52]. The main targets of plant quinones in microbial cells are presumably cell surface adhesins, cell wall polypeptides, and membrane-bound enzymes present on the surface [49, 53].

SMPs can also influence key events of the pathogenic process. For example, treatment with subinhibitory concentrations of thymol or eugenol reduced production of α-hemolysin

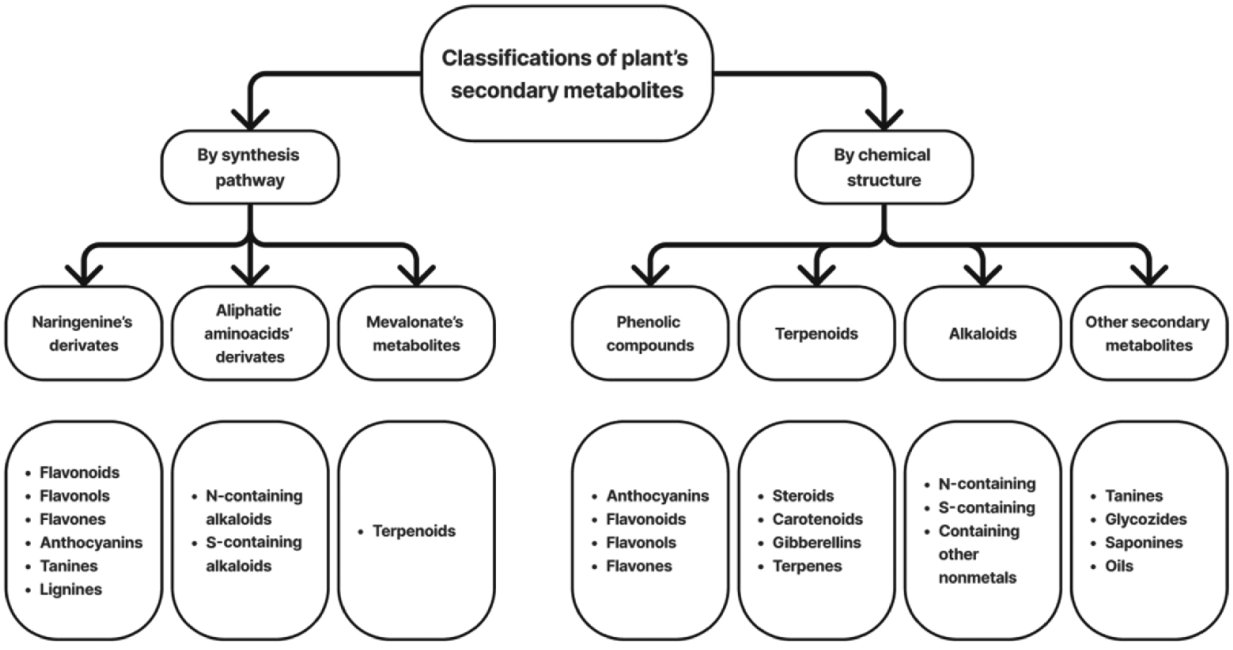

Figure 1. An example of SMP classification based on chemical structures or ways of plant metabolite biosynthesis.

Table 1. The inhibitory effects of some SMPs on viability of clinically important human pathogens

Compound	Chemical class	The most known plant source	Mechanism of action	Antibacterial activity (MIC*, μg/ml)
Piperine	Alkaloids	*Piper nigrum*	Prevention of biofilm formation; impaired efflux pump functioning	*Staphylococcus aureus* (>1000) [12], (100) [13]; *Pseudomonas aeruginosa* [14]; *Mycobacterium tuberculosis* (50–100) [15]
Berberine		*Berberis vulgaris*	Impaired DNA synthesis; membrane damage; inhibition of protein synthesis; inhibition of biofilm formation; impaired utilization of reactive oxygen species	*S. aureus* (MRSA) (256) [16], (64–256) [17, 18]; *Streptococcus pyogenes* (80) [19]; *Salmonella typhimurium* (900) [20]; *P. aeruginosa* (4 mM) [21]; *Streptococcus agalactiae* (0.78) [22]
Eugenol	Phenols	*Syzygium aromaticum*	Inhibition of superoxide dismutase; impaired membrane permeability; impaired efflux pump functioning; inhibition of biofilm formation	*Shigella flexneri* (500) [23]; *Shigella sonnei* (500) [24]; *S. aureus* (≥1024) [25]; *Helicobacter pylori* (2) [26]; *Salmonella typhi* [27]; *Escherichia coli* (>2000) [28]; *P. aeruginosa* (150–300) [29]
Chlorogenic acid		*Coffea* L.	Inhibition of biofilm formation, impaired membrane functioning	*Yersinia enterocolitica* [30]; *Salmonella enteritidis* (2 mM) [31]; *S. aureus* (40), *Streptococcus pneumoniae* (20), *Bacillus subtilis* (40), *E. coli* (80), *Shigella dysenteriae* (20), *S. typhimurium* (40) [32]
Carvacrol		*Origanum vulgare*	Inhibition of biofilm formation; impaired efflux pump functioning, impaired membrane functioning; interference with QS-processes	*E. coli* (100) [28], (8) [33]; *S. aureus, P. aeruginosa* (7) [33]; *Salmonella enterica* [34]
Curcumin		*Curcuma longa*	Inhibition of biofilm and capsule formation; impaired efflux pump functioning; impaired bacterial adhesion; influence on gene expression	*Clostridium difficile* (4-32) [35]; *Klebsiella pneumoniae* [36]; *P. aeruginosa* (25–100) [37]
Resveratrol		*Vitis vinifera*	Inhibition of biofilm formation; impaired efflux pump functioning; interference with QS-processes	*E. coli* (1300) [28], (456) [38]; *Campilobacter spp.* (313) [39]; *S. aureus* [40]
Allicin	Sulfoxides	*Allium sativum*	Inhibition of DNA gyrase; inhibition of alpha-toxin synthesis (*S. aureus*); inhibition of biofilm formation; interference with QS-processes	*S. aureus* (32-64) [41]; *P. aeruginosa* [42]; *Acinetobacter baumannii* (16), *K. pneumoniae* (128), *S. pneumoniae* (32, 64) [43]
Quercetin	Flavonoids	*Quercus robur*	Cell wall and cell membrane damage; decreased ATPase activity; inhibition of biofilm formation; interference with QS-processes	*S. aureus* (75), *E. coli* (300), *H. pylori* (100–200) [44]; *S. typhimurium* (250) [45]

*MIC is minimal inhibitory concentration expressed in μg/ml (except other units are shown in parenthesis)

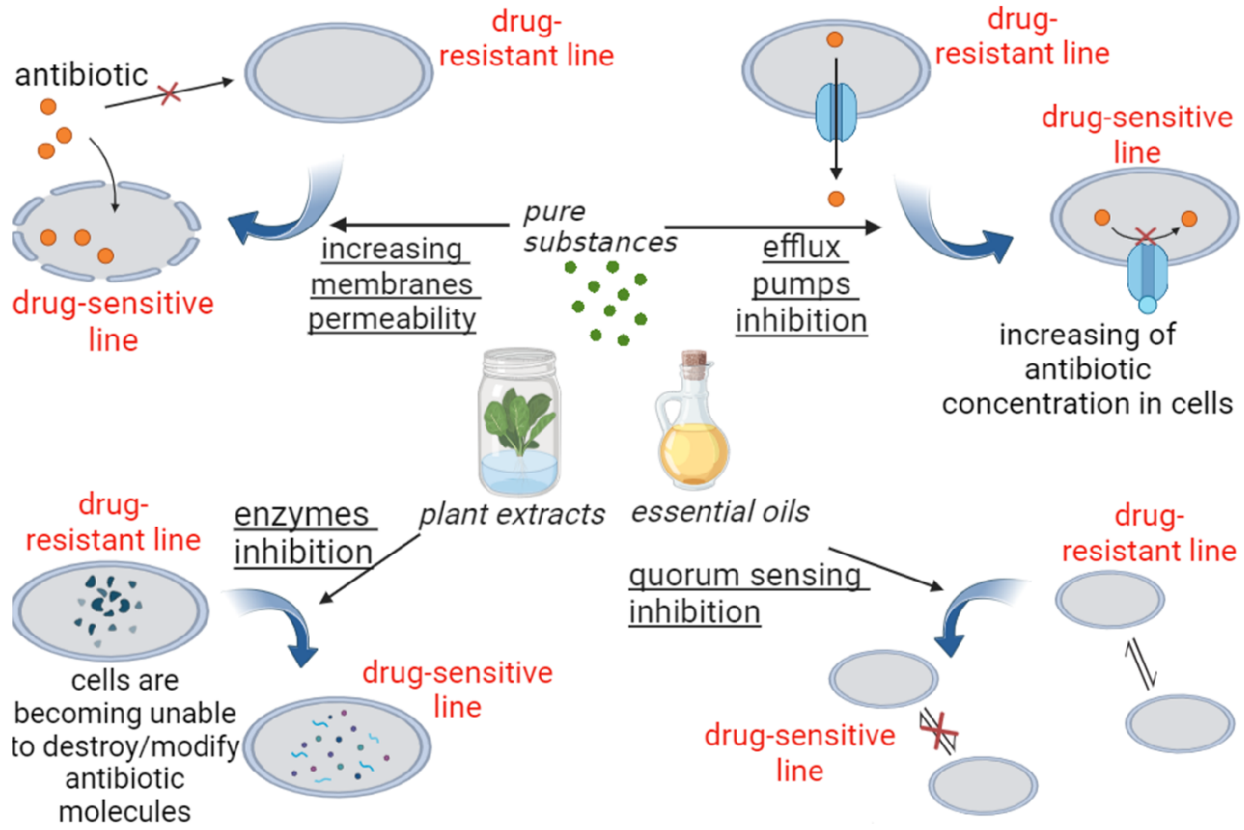

Figure 2. Possible ways of SMP action on the microbial cells.

and staphylococcal enterotoxins A and B in susceptible and methicillin-resistant (MRSA) isolates of *Staphylococcus aureus* [54, 55]. Different studies have obtained similar results demonstrating a decrease or even inhibition of the production of staphylococcal α-hemolysin after treatment with allicin [41], the alkaloid capsaicin from hot peppers of the genus *Capsicum* L. [56], the flavonoids farrerol (*Rhododendron* L.) [57] or gallate epicatechin [58]. Allicin, the main biologically active component of garlic, has been shown to effectively neutralize the toxin pneumolysin, one of the key virulence factors produced by *S. pneumoniae* [59].

A separate issue is the SMP ability to inhibit growth of drug-resistant bacterial strains (i.e. the strains with already formed resistance to routinely used antibiotics). A bacterial cell has many ways to protect itself against antibacterial agents. These include modification of molecular targets of the antibiotic action, active removal of antibacterial preparations from the cell (efflux) or their enzymatic inactivation, as well as formation of stable microbial communities, biofilms, which impede contacts of the antibacterial agent with the bacterial cell. Certain evidence exists that some phytocompounds are able to overcome pathogen defense, for example, by "turning off" the efflux pumps. It has been reported that extracts of many medicinal plants, possessing antimicrobial potential, contain membrane pump inhibitors, including piperine, the flavonoid quercetin,

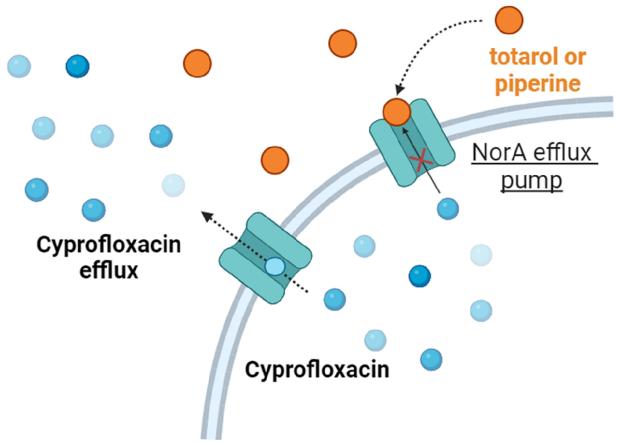

Figure 3. Inhibition of ciprofloxacin efflux via the *S. aureus* NorA pump

resveratrol, etc. [60, 61]. These compounds can block a channel, involved in the process of substrate removal. For example, totarol, a diterpene from *Podocarpus totara*, acts as a competitive inhibitor of the *S. aureus* NorA pump [62, 63] (Fig. 3). In addition, polyphenol molecules can bind to the structure-forming proteins of the channel, causing conformational changes and blocking its operation [64].

Many studies have been undertaken to investigate the possible impact of SMPs on bacterial biofilms: complex structures that promote survival

of microorganisms in unfavorable environmental conditions (including the antibacterial pressure). A number of phytometabolites have been identified that can control biofilm formation. For example, phenylpropanoids such as eugenol and cinnamaldehyde, terpenoids (thymol and carvacrol), betulinic and ursolic acids, alkaloids such as berberine, indole or chelerythrine found in celandine (*Chelidonium majus*), and other plant-derived compounds exhibit significant activity against biofilms formed by *P. aeruginosa* [65–69], *K. pneumoniae* [70, 71] or *S. aureus* [72–74], both growing and already formed. It is suggested that the SMP action is realized in various ways, such as disruption of cell coaggregation, inhibition of their motility or inactivation of bacterial adhesins [28, 75], as well as disruption of intercellular communications ("quorum sensing"). The latter is worth to consider in more details. Quorum sensing (QS) is a complex system that regulates intercellular communication in microbial populations, and the ability to interfere with QS (and thus interrupting bacterial communication) would open new therapeutic prospects. A number of SMPs have been identified that reduce the expression of genes mediating QS in *P. aeruginosa*, including the organosulfur ajoene from garlic or the isothiocyanate iberine from horseradish [76, 77], sulforaphane found in cabbage (*Brassica oleracea*), [78], flavonoids naringenin, taxifolin [79], and quercetin [80]. It has also been shown that caffeine exhibits anti-QS properties against *P. aeruginosa* by inhibiting production of N-acyl homoserine lactone (AHL) signaling molecules [81]. Similar observations have been also reported for other pathogens [82].

3. STAPHYLOCOCCUS AUREUS IN A JAR WITH GARLIC: DEVELOPMENT OF DRUG RESISTANCE TO SMP

Perhaps the most interesting question is whether and how quickly bacterial resistance to plant-derived antibacterials will develop?

As in the case of microbial antibiotics, some microorganisms may demonstrate insensitivity to phytomedicines or their components, possibly being naturally resistant to them. For example the authors [83] demonstrated that extracts of *Terminalia arjuna* and *Eucalyptus globulus* plants suppressed growth of *S. aureu*s, *E. faecalis*, and *S. mutans* but not *E. coli*, *K. pneumoniae*, *P. aeruginosa*, and *S typhimurium*. Moreover, using *E. coli* as an example, it was demonstrated that the minimum inhibitory concentration of phytoextracts of plants such as *Acacia nilotica*, *Syzygium aromaticum* or *Cinnamomum zeylanicum* against this bacterium was significantly higher in the case of hospital-acquired multi-resistant strains of *E. coli* than in community-acquired ones. Some bacterial strains (e.g. *Staphylococcus spp., Enterobacter cloacae, Bacillus spp.* or *Erwinia spp*.) have been isolated during microbiological studies of plant products such as garlic, onion, ginger, rosemary or mustard powder, which are supposed to have strong antibacterial properties [84, 85].

The details of the process by which microorganisms develop resistance to SMPs have so far been studied sporadically. There is a viewpoint that the development of resistance to phytomedicines occurs slowly, or at least the level of resistance to SMPs is still low [47]. However, taking into consideration the fact that many plant components are currently actively used in food products, in "non-traditional" or alternative medicine, as well as in the production of cosmetics, it can be assumed that the spread of strains resistant to "medicines of plant origin", as in the case of traditional antibiotics of microbial origin, is only a matter of time.

There is, however, another side to the coin. It is known that the positive therapeutic effect of crude plant extracts, used for centuries in folk medicine, is often determined by the combined or synergistic effects of many SMPs aimed at various targets in the bacterial cell rather than by action of one biologically active compound. This means that one would expect that the development of bacterial resistance to such synergistic compositions would occur more slowly than to individual compounds [49].

4. ALONE IN THE FIELD IS NOT A WARRIOR? SYNERGISTIC INTERACTION OF METABOLITES BETWEEN THEM OR WITH TRADITIONAL ABPs

As mentioned in the previous section, a single phytocompound that exhibits a high level of bactericidal activity has the potential to stimulate the development of drug resistance in microorganisms. However, in a mixture (extract), SMPs can potentiate actions of each other thus enhancing the overall bioactivity of the phytomedicine [49, 86]. Indeed, it has been repeatedly demonstrated that isolating individual phytochemicals from a plant extract results in a loss or reduction of the overall effect. One good example is the work [87], which compared the minimum inhibitory concentration of one of the most popular dietary supplements — oregano essential oil (from *Origanum vulgare* L.), and its two main components — thymol and carvacrol, as well as their mixtures for *P. aeruginosa* and *S. aureus* strains. The antimicrobial properties of the oil, as well as the additive antimicrobial effect of the mixture of carvacrol and thymol, were higher than for either of these two components used separately [87]. Also, a potentiation effect may occur when SMPs are combined with routinely used antibiotics [88, 89]. Table 2 shows examples of synergistic combinations of SMPs and antibiotics, illustrating a certain decrease in the inhibitory concentrations as compared to antibiotics without phytometabolites.

Table 2. Examples illustrating synergistic interactions between SMPs and ABDs

SMP	ABD	MIC (ABD), μg/ml	MIC decrease	Pathogen
Piperine	Tetracycline	200	4-8-fold	*E. coli (MDR)* [90]
	Gentamycin	32	4-fold	*S. aureus* (*MRSA*) [13]
Eugenol	Tetracycline	128	4-fold	*S. aureus* [91]
Quercetin	Amoxicillin	16	4-fold	Amoxicillin-resistant strain of *S. epidermidis* [92]
	Meropenem	128	4-fold	Carbapenem-resistant strains of *P. aeruginosa* and *A. baumannii* [93]
	Rifampicin	>256	4-fold	*S. aureus* [94]
Carvacrol	Tetracycline	256	4-fold	*Enterococcus faecium* [91]
	Tetracycline	128	2-fold	*S. aureus* [91]
Allicin	Levofloxacin, ceftriaxone	256	2-fold	*Shigella spp.* [95]

Mechanisms of the synergistic interaction between SMPs and antibiotics are diverse, and their study continues. It is clear that knowledge of these mechanisms would culminate in developments of new ways to fight against rapidly growing populations of multidrug-resistant pathogens, thereby reducing the overuse of antibiotics and their side effects.

5. "PHYTOANTIBIOTICS": A STEP INTO THE MEDICINE OF THE FUTURE OR AN ETERNAL BENCH?

For centuries, people have used the healing power of plants for medicinal purposes. Components extractable from plants by using extraction, infusion, distillation, digestion, and other methods available in ancient times always represented a complex mixture of many compounds, and it was impossible to control their ratios. The therapeutic effect of such drugs was weak and often unpredictable, depending on the synergistic interaction of individual components and the presence of some substances in extremely small quantities in these mixtures [96].

Less than a century ago, people received serious support in the war against infectious diseases in the form of highly effective antibiotics of microbial origin. However, this powerful weapon contained "a built-in mechanism of self-destruction": increased drug resistance in bacteria led to a crisis in the treatment of infectious diseases after just a few decades of using antibacterial drugs.

In the "post-antibiotic era," it seems logical to return to the centuries-old experience of using an endless supply of plant natural resources. The 21st century science is offering new approaches to detect and identify even ultra-small amounts of SMPs produced by plants. Modern instruments make it possible not only to detect a new compound and elucidate its structure, but also to accumulate the substance in the amounts necessary to determine the clinical effect [97–99]. The search for effective approaches to the production of drugs based on plant raw materials includes two pathways. The first involves the development of high-tech methods for extracting SMPs from plant materials [100]. In contrast to traditional resource- and energy-consuming techniques that require time and significant consumption of solvents, modern innovative technologies are based on extraction with supercritical fluids [101] or membrane extraction [102], the use of microwave or ultrasonic energy [103], separation in a high-voltage electric discharge or pulsed electric field [100, 104]. Another rapidly developing area includes biotechnological methods that make it possible to modify a plant to produce a large number of SMPs of interest with potential biological activity. This creates conditions to produce high quantities of compounds that normally exist in plants in low and very low concentrations. Currently, plant cells, tissues, and organs are grown in specially created bioreactors, known as "green factories". Such technologies for growing plants *in vitro* are considered as cost-effective and environmentally friendly alternatives to collecting wild biomass for processing and production of phytomedicines [100, 105, 106]. An absolute advantage is the complete independence of the bioprocess from seasonal and geographical conditions [97].

Isolation, purification and careful characterization of potential bioactive metabolites from crude plant extracts are important steps in this process. Modern developments in analytical chemistry, such as mass spectrometry complemented by gas/liquid chromatography or capillary electrophoresis and nuclear magnetic resonance (NMR) spectroscopy, have led to the development of highly efficient tools for analyzing the plant metabolome [98, 107, 108]. The final step is to screen the bioactivity of the isolated and characterized compounds in cell lines or animal models to evaluate the pharmacological potential of the candidate compounds.

Finally, another important area of research is the structural modification of natural phytocompounds with potential biological activity to develop new compounds with desired properties. Chemical modification allows not only to increase the activity of natural SMPs, but also to improve their selectivity, stability or solubility [109].

CONCLUSIONS

The growing resistance of bacterial pathogens to routinely used antibiotics underlies importance of the search for new effective antibacterial agents. Over the past two decades, it has become clear that overcoming antibiotic resistance through the development of increasingly powerful antibiotics based on already known classes of chemical compounds can results only in limited and temporary success; moreover it can contribute to the further development of even higher bacterial resistance. In this context, the plant world appears to be an endless source of new potential inhibitory agents that is unlikely to be rapidly exhausted. Plant raw materials are cheap and available; extracts or even individual phytocompounds often exhibit broad spectrum activity against pathogenic bacterial species; they rarely have serious side effects in humans, and sometimes exhibit immunomodulatory properties. The variety of chemical structures that can be obtained from plants can satisfy numerous requests for both new mechanisms of antimicrobial action and new targets inside the bacterial cell, and the rapid development of modern biotechnologies opens the way to get bioactive compounds in environmentally friendly and low-toxic ways. Advances in bioscreening make it possible to detect pharmacologically attractive phytometabolites even at extremely low concentrations, and modern methods of computer modeling and organic synthesis promote optimization of the chemical structure of potentially promising compounds to improve their properties and reduce toxicity.

The medical practice of the present and future needs new effective antibacterial drugs, and the plant kingdom is basically ready to satisfy these needs. Various combinations of plant-derived metabolites with routinely used antibiotics are being developed and this appear to be more optimal than individual SMPs, even with a high level of biological activity. Indeed, it has been repeatedly shown that combining antibiotics with SMPs or plant extracts leads to enhanced pharmacological properties with simultaneous reduction of probability of dose-related toxicity. It can be assumed that the number of such studies will only increase in the near future.

FUNDING

The work was supported by the Russian Science Foundation (project No. 22-25-00804).

COMPLIANCE WITH ETHICAL STANDARDS

This article does not contain any studies with human participants or animals.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

1. *Achan J., Talisuna A.O., Erhart A., Yeka A., Tibenderana J.K., Baliraine F.N., Rosenthal P.J., d'Alessandro U.* (2011) Quinine, an old anti-malarial drug in a modern world: Role in the treatment of malaria. Malaria J., **10**, 144. DOI: 10.1186/1475-2875-10-144
2. *Li Y., Kong D., Fu Y., Sussman M.R., Wu H.* (2020) The effect of developmental and environmental factors on secondary metabolites in medicinal plants. Plant. Physiol. Biochem., **148**, 80-89. DOI: 10.1016/j.plaphy.2020.01.006
3. *Bilal M., Rasheed T., Iqbal H.M.N., Hu H., Wang W., Zhang X.* (2017) Macromolecular agents with antimicrobial potentialities: A drive to combat antimicrobial resistance. Int. J. Biol. Macromol., **103**, 554-574. DOI: 10.1016/j.ijbiomac.2017.05.071
4. *Arip M., Selvaraja M.R.M., Tan L.F., Leong M.Y., Tan P.L., Yap V.L., Chinnapan S., Tat N.C., Abdullah M.K.D., Jubair N.* (2022) Review on plant-based management in combating antimicrobial resistance — mechanistic perspective. Front. Pharmacol., **13**, 879495. DOI: 10.3389/fphar.2022.879495
5. *El-Saadony M.T., Yang T., Imam M.S., Alghamdi S., Salem H.M., Korma S.A., Soliman S.M., Abd El-Mageed T.A., Selim S., Al Jaouni S.K., Mahmmod Y., El-Wafai N.A., Zaghloul R.A., Abd El-Hack M.E., Khafaga A.F., El-Tarabily K.A., Saad A.M.* (2022) Medicinal plants as alternative antimicrobial agents to combating the multi-drug resistant human pathogens: A comprehensive review. Front. Microbiol., **13**, 998425. DOI: 10.3389/fmicb.2022.998425
6. *Kabera J.N., Semana E., Mussa A.R., He X.* (2014) Plant secondary metabolites: Biosynthesis, classification, function and pharmacological properties. J. Pharm. Pharmacol., **2**, 377-392.
7. *Ashraf M.A., Iqbal M., Rasheed R., Hussain I., Riaz M., Arif M.S.* (2018) Environmental stress and secondary metabolites in plants: An overview. In: Plant Metabolites and Regulation under Environmental Stress, Academic Press: Cambridge, MA, USA, Elsevier Inc.: Amsterdam, The Netherlands, pp. 153-167. DOI: 10.1016/B978-0-12-812689-9.00008-X
8. *Delgoda R., Murray J.E.* (2017) Evolutionary perspectives on the role of plant secondary metabolites. In: Pharmacognosy. Fundamentals, Applications and Strategies, Academic Press: Cambridge, MA, USA, Elsevier Inc.: Amsterdam, The Netherlands, pp. 93-100. DOI: 10.1016/B978-0-12-802104-0.00007-X
9. *Anand U., Jacobo-Herrera N., Altemimi A., Lakhssassi N.* (2019) A comprehensive review on medicinal plants as antimicrobial therapeutics: Potential avenues of biocompatible drug discovery. Metabolites, **9**, 258. DOI: 10.3390/metabo9110258

10. *Hussein R.A., El-Anssary A.A.* (2018) Plants secondary metabolites: The key drivers of the pharmacological actions of medicinal plants. In: Herbal Medicine, Builders P.H. (ed.), IntechOpen: London, UK. DOI: 10.5772/intechopen.76139
11. *de Filippis L.F.* (2016) Plant secondary metabolites: From molecular biology to health products. In: Plant-environment Interaction: Responses and Approaches to Mitigate Stress, 1st ed., Azooz M.M., Ahmad P. (eds.), Wiley Blackwell: Hoboken, NJ, USA.
12. *Das S., Paul P., Chatterjee S., Chakraborty P., Sarker R.K., Das A., Maiti D., Tribedi P.* (2021) Piperine exhibits promising antibiofilm activity against *Staphylococcus aureus* by accumulating reactive oxygen species (ROS). Arch. Microbiol., **204**(1), 59. DOI: 10.1007/s00203-021-02642-7
13. *Khameneh B., Iranshahy M., Ghandadi M., Ghoochi A.D., Fazly B.B.S., Iranshahi M.* (2015) Investigation of the antibacterial activity and efflux pump inhibitory effect of co-loaded piperine and gentamicin nanoliposomes in methicillin-resistant *Staphylococcus aureus*. Drug. Dev. Ind. Pharm., **41**, 989-994. DOI: 10.3109/03639045.2014.920025
14. Liu *Y., Zhu R., Liu X., Li D., Guo M., Fei B., Ren Y., You X., Li Y.* (2023) Effect of piperine on the inhibitory potential of MexAB-OprM efflux pump and imipenem resistance in carbapenem-resistant *Pseudomonas aeruginosa*. Microb. Pathog., **185**, 106397. DOI: 10.1016/j.micpath.2023.106397
15. *Birdi T., d'Souza D., Tolani M., Daswani P., Nair V., Tetali P., Carlos T.J., Hoffner S.* (2012) Assessment of the activity of selected Indian medicinal plants against *Mycobacterium tuberculosis*: A preliminary screening using the microplate alamar blue assay. Eur. J. Med. Plants, **2**, 308-323. DOI: 10.9734/EJMP/2012/1638
16. *Zhang C., Li Z., Pan Q., Fan L., Pan T., Zhu F., Pan Q., Shan L., Zhao L.* (2022) Berberine at sub-inhibitory concentration inhibits biofilm dispersal in *Staphylococcus aureus*. Microbiology, **168**(9), 001243. DOI: 10.1099/mic.0.001243
17. *Zhao N., Isguven S., Evans R., Schaer T.P., Hickok N.J.* (2023) Berberine disrupts staphylococcal proton motive force to cause potent anti-staphylococcal effects *in vitro*. Biofilm, **5**, 100117. DOI: 10.1016/j.bioflm.2023.100117
18. *Xia S., Ma L., Wang G., Yang J., Zhang M., Wang X., Su J., Xie M.* (2022) *In vitro* antimicrobial activity and the mechanism of berberine against methicillin-resistant S*taphylococcus aureus* isolated from bloodstream infection patients. Infect. Drug. Resist., **15**, 1933-1944. DOI: 10.2147/IDR.S357077
19. *Du G.F., Le Y.J., Sun X., Yang X.Y., He Q.Y.* (2020) Proteomic investigation into the action mechanism of berberine against *Streptococcus pyogenes*. J. Proteomics, **215**, 103666. DOI: 10.1016/j.jprot.2020.103666
20. *Xu C., Wang F., Huang F., Yang M., He D., Deng L.* (2021) Targeting effect of berberine on type I fimbriae of *Salmonella typhimurium* and its effective inhibition of biofilm. Appl. Microbiol. Biotechnol., **105**(4), 1563-1573. DOI: 10.1007/s00253-021-11116-1
21. *Boberek J.M., Stach J., Good L.* (2010) Genetic evidence for inhibition of bacterial division protein FtsZ by berberine. PLoS One, **5**, e13745. DOI: 10.1371/journal.pone.0013745
22. *Peng L., Kang S., Yin Z., Jia R., Song X., Li L., Li Z., Zou Y., Liang X., Li L., He C., Ye G., Yin L., Shi F., Lv C., Jing B.* (2015) Antibacterial activity and mechanism of berberine against *Streptococcus agalactiae*. Int. J. Clin. Exp. Pathol., **8**, 5217-5223.
23. *Bai X., Li X., Liu X., Xing Z., Su R., Wang Y., Xia X., Shi C.* (2022) Antibacterial effect of eugenol on *Shigella flexneri* and its mechanism. Foods, **11**(17), 2565. DOI: 10.3390/foods11172565
24. *Su R., Bai X., Liu X., Song L., Liu X., Zhan X., Guo D., Wang Y., Chang Y., Shi C.* (2022) Antibacterial mechanism of eugenol against *Shigella sonnei* and its antibacterial application in lettuce juice. Foodborne Pathog. Dis., **19**(11), 779-786. DOI: 10.1089/fpd.2022.0046
25. *Bezerra S.R., Bezerra A.H., de Sousa Silveira Z., Macedo N.S., Dos Santos Barbosa C.R., Muniz D.F., Sampaio Dos Santos J.F., Melo Coutinho H.D., Bezerra da Cunha F.A.* (2022) Antibacterial activity of eugenol on the IS-58 strain of *Staphylococcus aureus* resistant to tetracycline and toxicity in *Drosophila melanogaster*. Microb. Pathog., **164**, 105456. DOI: 10.1016/j.micpath.2022.105456
26. *Ali S.M., Khan A.A., Ahmed I., Musaddiq M., Ahmed K.S., Polasa H., Rao L.V., Habibullah C.M., Sechi L.A., Ahmed N.* (2005) Antimicrobial activities of eugenol and cinnamaldehyde against the human gastric pathogen *Helicobacter pylori*. Ann. Clin. Microbiol. Antimicrob., **4**, 20. DOI: 10.1186/1476-0711-4-20
27. *Devi K.P., Nisha S.A., Sakthivel R., Pandian S.K.* (2010) Eugenol (an essential oil of clove) acts as an antibacterial agent against *Salmonella typhi* by disrupting the cellular membrane. J. Ethnopharmacol., **130**(1), 107-115. DOI: 10.1016/j.jep.2010.04.025
28. *Gutiérrez S., Morán A., Martínez-Blanco H., Ferrero M.A., Rodríguez-Aparicio L.B.* (2017) The usefulness of non-toxic plant metabolites in the control of bacterial proliferation. Probiotics. Antimicrob. Prot., **9**, 323-333. DOI: 10.1007/s12602-017-9259-9
29. *Rathinam P., Kumar V.H.S., Viswanathan P.* (2017) Eugenol exhibits anti-virulence properties by competitively binding to quorum sensing receptors. J. Bioadhesion Biofilm Res., **33**, 624-639. DOI: 10.1080/08927014.2017.1350655
30. *Chen K., Peng C., Chi F., Yu C., Yang Q., Li Z.* (2022) Antibacterial and antibiofilm activities of chlorogenic acid against *Yersinia enterocolitica*. Front. Microbiol., **13**, 885092. DOI: 10.3389/fmicb.2022.885092
31. *Sun Z., Zhang X., Wu H., Wang H., Bian H., Zhu Y., Xu W., Liu F., Wang D., Fu L.* (2020) Antibacterial activity and action mode of chlorogenic acid against *Salmonella enteritidis*, a foodborne pathogen in chilled fresh chicken. World J. Microbiol. Biotechnol., **36**(2), 24. DOI: 10.1007/s11274-020-2799-2
32. *Lou Z., Wang H., Zhu S., Ma C., Wang Z.* (2011) Antibacterial activity and mechanism of action of chlorogenic acid. J. Food Sci., **76**(6), M398-M403. DOI: 10.1111/j.1750-3841.2011.02213.x
33. *Althunibat O.Y., Qaralleh H., Al-Dalin S.Y.A., Abboud M., Khleifat K., Majali I.S., Aldalin H.K.H., Rayyan W.A., Jaafraa A.* (2016) Effect of thymol and carvacrol, the major components of *Thymus capitatus* on the growth of *Pseudomonas aeruginosa*. J. Pure Appl. Microbiol., **10**, 367-374.
34. *Kachur K., Suntres Z.* (2019) The antibacterial properties of phenolic isomers, carvacrol and thymol. Crit. Rev. Food Sci. Nutr., **60**(18), 3042-3053. DOI: 10.1080/10408398.2019.1675585
35. *Mody D., Athamneh A.I.M., Seleem M.N.* (2019) Curcumin: A natural derivative with antibacterial activity against *Clostridium difficile*. J. Glob. Antimicrob. Resist., **21**, 154-161. DOI: 10.1016/j.jgar.2019.10.005

36. *Karami-Zarandi M., Ghale H.E., Ranjbar R.* (2022) Characterization of virulence factors and antibacterial activity of curcumin in hypervirulent *Klebsiella pneumoniae*. Future Microbiol., **17**, 529-540. DOI: 10.2217/fmb-2021-0222
37. *Tyagi P., Singh M., Kumari H., Kumari A., Mukhopadhy K.* (2015) Bactericidal activity of curcumin i is associated with damaging of bacterial membrane. PLoS One, **10**, e0121313. DOI:10.1371/journal.pone.0121313
38. *Hwang D., Lim Y.H.* (2019) Resveratrol controls *Escherichia coli* growth by inhibiting the AcrAB-TolC efflux pump. FEMS Microbiol. Lett., **366**(4), fnz030. DOI: 10.1093/femsle/fnz030
39. *Klancnik A., Sikic P.M., Trost K., Tusek Z.M., Mozetic V.B., Smole M.S.* (2017) Anti-campylobacter activity of resveratrol and an extract from waste pinot noir grape skins and seeds, and resistance of *Camp. jejuni* planktonic and biofilm cells, mediated via the CmeABC eux pump. J. Appl. Microbiol., **122**, 65-77. DOI:10.1111/jam.13315
40. *Fatima M., Amin A., Alharbi M., Ishtiaq S., Sajjad W., Ahmad F., Ahmad S., Hanif F., Faheem M., Khalil A.A.K.* (2023) Quorum quenchers from *Reynoutria japonica* in the battle against methicillin-resistant *Staphylococcus aureus* (MRSA). Molecules, **28**(6), 2635. DOI: 10.3390/molecules28062635
41. *Leng B.F., Qiu J.Z., Dai X.H., Dong J., Wang J.F., Luo M.J., Li H.E., Niu X.D., Zhang Y., Ai Y.X., Deng X.M.* (2011) Allicin reduces the production of α-toxin by *Staphylococcus aureus*. Molecules, **16**(9), 7958-7968. DOI: 10.3390/molecules16097958
42. *Lihua L., Jianhuit W., Jialini Y., Yayin L., Guanxin L.* (2013) Effects of allicin on the formation of *Pseudomonas aeruginosa* biofilm and the production of quorum-sensing controlled virulence factors. Pol. J. Microbiol., **62**(3), 243-251.
43. *Reiter J., Levina N., van der Linden M., Gruhlke M., Martin C., Slusarenko A.J.* (2017) Diallylthiosulfinate (allicin), a volatile antimicrobial from garlic (*Allium sativum*), kills human lung pathogenic bacteria, including MDR strains, as a vapor. Molecules, **22**, 1711. DOI: 10.3390/molecules22101711
44. *Wu D., Kong Y., Han C., Chen J., Hu L., Jiang H., Shen X.* (2008) d-Alanine:d-alanine ligase as a new target for the flavonoids quercetin and apigenin. Int. J. Antimicrob. Agents, **32**, 421-426. DOI: 10.1016/j.ijantimicag.2008.06.010
45. *Roy P.K., Song M.G., Park S.Y.* (2022) Impact of quercetin against *Salmonella typhimurium* biofilm formation on food-contact surfaces and molecular mechanism pattern. Foods, **11**(7), 977. DOI: 10.3390/foods11070977
46. *Khameneh B., Iranshahy M., Soheili V., Bazzaz B.S.F.* (2019) Review on plant antimicrobials: A mechanistic viewpoint. Antimicrob. Res. Infect. Control., **8**, 118. DOI: 10.1186/s13756-019-0559-6
47. *Radulovic N.S., Blagojevic P.D., Stojanovic-Radic Z.Z., Stojanovic N.M.* (2013) Antimicrobial plant metabolites: Structural diversity and mechanism of action. Curr. Med. Chem., **20**, 932-952. DOI: 10.2174/0929867311320070008
48. *Savoia D.* (2012) Plant-derived antimicrobial compounds: Alternatives to antibiotics. Future Microbiol., **7**, 979-990.
49. *Gupta P.D., Birdi T.J.* (2017) Development of botanicals to combat antibiotic resistance. J. Ayurveda Integr. Med., **8**, 266-275. DOI: 10.1016/j.jaim.2017.05.004
50. *Cazarolli L.H., Zanatta L., Alberton E.H., Figueiredo M.S., Folador P., Damazio R.G., Pizzolatti M.G., Silva F.R.* (2008) Flavonoids: Prospective drug candidates. Mini Rev. Med. Chem., **8**, 1429-1440. DOI: 10.2174/138955708786369564
51. *Guimarães A.C., Meireles L.M., Lemos M.F., Guimarães M.C.C., Endringer D.C., Fronza M., Scherer R.* (2019) Antibacterial activity of terpenes and terpenoids present in essential oils. Molecules, **24**, 2471. DOI: 10.3390/molecules24132471
52. *Khan I., Kumar B.P.A., Bajpai V.K., Kang S.C.* (2017) Antimicrobial potential of carvacrol against uropathogenic *Escherichia coli* via membrane disruption, depolarization, and reactive oxygen species generation. Front. Microbiol., **8**, 2421. DOI: 10.3389/fmicb.2017.02421
53. *Pandey A.K., Kumar S.* (2013) Perspective on plant products as antimicrobial agents: A review. Pharmacologia, **4**, 469-480. DOI: 10.5567/pharmacologia.2013.469.480
54. *Qiu J., Feng H., Lu J., Xiang H., Wang D., Dong J., Wang J., Wang X., Liu J., Deng X.* (2010) Eugenol reduces the expression of virulence-related exoproteins in *Staphylococcus aureus*. Appl. Environ. Microbiol., **76**, 5846-5851. DOI: 10.1128/AEM.00704-10
55. *Qiu J., Wang D., Xiang H., Feng H., Jiang Y., Xia L., Dong J., Lu J., Yu L., Deng X.* (2010) Subinhibitory concentrations of thymol reduce enterotoxins A and B and α-hemolysin production in *Staphylococcus aureus* isolates. PLoS One, **5**, e9736. DOI: 10.1371/journal.pone.0009736
56. *Qiu J., Niu X., Wang J., Xing Y., Leng B., Dong J., Li H., Luo M., Zhang Y., Dai X., Luo Y., Deng X.* (2012) Capsaicin protects mice from community-associated methicillin-resistant *Staphylococcus aureus* pneumonia. PLoS One, **7**, e33032. DOI: 10.1371/journal.pone.0033032
57. *Qiu J., Xiang H., Hu C., Wang Q., Dong J., Li H., Luo M., Wang J., Deng X.* (2011) Subinhibitory concentrations of farrerol reduce α-toxin expression in *Staphylococcus aureus*. FEMS Microbiol. Lett., **315**, 129-133. DOI: 10.1111/j.1574-6968.2010.02183.x
58. *Shah S., Stapleton P.D., Taylor P.W.* (2008) The polyphenol (-)-epicatechin gallate disrupts the secretion of virulence-related proteins by *Staphylococcus aureus*. Lett. Appl. Microbiol., **46**, 181-185. DOI: 10.1111/j.1472-765X.2007.02296.x
59. *Arzanlou M., Bohlooli S., Jannati E., Mirzanejad-Asl H.* (2011) Allicin from garlic neutralizes the hemolytic activity of intra- and extracellular pneumolysin O *in vitro*. Toxicon, **57**, 540-545. DOI: 10.1016/j.toxicon.2010.12.009
60. *Kumar R., Pooja Patial S.J.* (2016) A review on efflux pump inhibitors of gram-positive and gram-negative bacteria from plant sources. Int. J. Curr. Microbiol. Appl. Sci., **5**, 837-855. DOI: 10.20546/ijcmas.2016.506.092
61. *Prasch S., Bucar F.* (2015) Plant derived inhibitors of bacterial efflux pumps: An update. Phytochem. Rev., **14**, 961-974. DOI: 10.1007/s11101-015-9436-y
62. *Shi C., Che M., Zhang X., Liu Z., Meng R., Bu X., Ye H., Guo N.* (2018) Antibacterial activity and mode of action of totarol against *Staphylococcus aureus* in carrot juice. J. Food Sci. Technol., **55**, 924-934. DOI: 10.1007/s13197-017-3000-2
63. *Khan I.A., Mirza Z.M., Kumar A., Verma V., Qazi G.N.* (2006) Piperine, a phytochemical potentiator of ciprofloxacin against *Staphylococcus aureus*. Antimicrob. Agents Chemother., **50**, 810-812. DOI: 10.1128/AAC.50.2.810-812.2006
64. *Piddock L.J.V., Garvey M.I., Rahman M.M., Gibbons S.* (2010) Natural and synthetic compounds such as trimethoprim behave as inhibitors of efflux in Gram-negative bacteria. J. Antimicrob. Chemother., **65**, 1215-1223. DOI: 10.1093/jac/dkq079

65. *Lou Z., Letsididi K.S., Yu F., Pei Z., Wang H., Letsididij R.* (2019) Inhibitive effect of eugenol and its nanoemulsion on quorum sensing-mediated virulence factors and biofilm formation by *Pseudomonas aeruginosa*. Food Prot., **82**, 379-389. DOI: 10.4315/0362-028X.JFP-18-196
66. *Xu Z., Zhang H., Yu H., Dai Q., Xiong J., Sheng H., Qiu J., Jiang L., Peng J., He X., Xin R., Li D., Zhang K.* (2019) Allicin inhibits *Pseudomonas aeruginosa* virulence by suppressing the rhl and pqs quorum-sensing systems. Can. J. Microbiol., **65**, 563-574. DOI: 10.1139/cjm-2019-0055
67. *Rajkumari J., Borkotoky S., Murali A., Suchiang K., Mohanty S.K., Busi S.* (2018) Attenuation of quorum sensing controlled virulence factors and biofilm formation in *Pseudomonas aeruginosa* by pentacyclic triterpenes, betulin and betulinic acid. Microb. Pathog., **118**, 48-60. DOI: 10.1016/j.micpath.2018.03.012
68. *Plyuta V., Zaitseva J., Lobakova E., Zagoskina N., Kuznetsov A., Khmel I.* (2013) Effect of plant phenolic compounds on biofilm formation by *Pseudomonas aeruginosa*. APMIS, **121**, 1073-1081. DOI: 10.1111/apm.12083
69. *Soumya E.A., Saad I.K., Hassan L., Ghizlane Z., Hind M., Adnane R.* (2011) Carvacrol and thymol components inhibiting *Pseudomonas aeruginosa* adherence and biofilm formation. Afr. J. Microbiol. Res., **5**, 3229-3232. DOI: 10.1155/2014/471580
70. *Qian W., Sun Z., Wang T., Yang M., Liu M., Zhang J., Li Y.* (2020) Antimicrobial activity of eugenol against carbapenem-resistant *Klebsiella pneumoniae* and its effect on biofilms. Microb. Pathog., **139**, 103924. DOI: 10.1016/j.micpath.2019.103924
71. *Magesh H., Kumar A., Alam A., Sekar U., Sumantran V.N., Vaidyanathan R.* (2013) Identification of natural compounds which inhibit biofilm formation in clinical isolates of *Klebsiella pneumoniae*. Indian. J. Exp. Biol., **51**, 764-772.
72. *Qian W., Wang W., Zhang J., Liu M., Fu Y., Li X., Wang T., Li Y.* (2020) Sanguinarine inhibits mono- and dual-species biofilm formation by *Candida albicans* and *Staphylococcus aureus* and induces mature hypha transition of *C. albicans*. Pharmaceuticals, **13**, 13. DOI: 10.3390/ph13010013
73. *Agrawa A., Chaudhary U.* (2018) Effect of natural compounds on inhibition of biofilm formation of multi drug resistant *Staphylococcus aureus* and *Staphylococcus epidermidis* — An *in vitro* study. Int. J. Curr. Microbiol. App. Sci., **7**, 2921-2926. DOI: 10.20546/ijcmas.2018.702.354
74. *Yadav M.K., Chae S.-W., Im G.J., Chung J.-W., Song J.-J.* (2015) Eugenol: A phyto-compound effective against methicillin-resistant and methicillin-sensitive *Staphylococcus aureus* clinical strain biofilms. PLoS One, **10**, e0119564. DOI: 10.1371/journal.pone.0119564
75. *Silva L.N., Zimmer K.R., Macedo A.J., Trentin D.S.* (2016) Plant natural products targeting bacterial virulence factors. Chem. Rev., **116**, 9162-9236. DOI: 10.1021/acs.chemrev.6b00184
76. *Jakobsen T.H., van Gennip M., Phipps R.K., Shanmugham M.S., Christensen L.D., Alhede M., Skindersoe M.E., Rasmussen T.B., Friedrich K., Uthe F., Jensen P.Ø., Moser C., Nielsen K.F., Eberl L., Larsen T.O., Tanner D., Høiby N., Bjarnsholt T., Givskov M.* (2012) Ajoene, a sulfur-rich molecule from garlic, inhibits genes controlled by quorum sensing. Antimicrob. Agents Chemother., **56**, 2314-2325. DOI: 10.1128/AAC.05919-11
77. *Jakobsen T.H., Bragason S.K., Phipps R.K., Christensen L.D., van Gennip M., Alhede M., Skindersoe M., Larsen T.O., Høiby N., Bjarnsholt T., Givskov M.* (2012) Food as a source for quorum sensing inhibitors: Iberin from horseradish revealed as a quorum sensing inhibitor of *Pseudomonas aeruginosa*. Appl. Environ. Microbiol., **78**, 2410-2421. DOI: 10.1128/AEM.05992-11
78. *Ganin H., Rayo J., Amara N., Levy N., Krief P., Meijler M.M.* (2013) Sulforaphane and erucin, natural isothiocyanates from broccoli, inhibit bacterial quorum sensing. Med. Chem. Commun., **4**, 175-179. DOI: 10.1039/C2MD20196H
79. *Vandeputte O.M., Kiendrebeogo M., Rasamiravaka T., Stevigny C., Duez P., Rajaonson S., Diallo B., Mol A., Baucher M., El Jaziri M.* (2011) The flavanone naringenin reduces the production of quorum sensing-controlled virulence factors in *Pseudomonas aeruginosa* PAO1. Microbiology, **157**, 2120-2132. DOI: 10.1099/mic.0.049338-0
80. *Ouyang J., Sun F., Feng W., Sun Y., Qiu X., Xiong L., Liu Y., Chen Y.* (2016) Quercetin is an effective inhibitor of quorum sensing, biofilm formation and virulence factors in *Pseudomonas aeruginosa*. J. Appl. Microbiol., **120**, 966-974. DOI: 10.1111/jam.13073
81. *Norizan S., Yin W.-F., Chan K.-G.* (2013) Caffeine as a potential quorum sensing inhibitor. Sensors, **13**, 5117-5129. DOI: 10.3390/s130405117
82. *Kalia V.C., Patel S.K.S., Kang Y.C., Lee J.-K.* (2019) Quorum sensing inhibitors as antipathogens: Biotechnological applications. Biotechnol. Adv., **37**, 68-90. DOI: 10.1016/j.biotechadv.2018.11.006
83. *Khan R., Islam B., Akram M., Shakil S., Ahmad A., Ali S.M., Siddiqui M., Khan A.U.* (2009) Antimicrobial activity of five herbal extracts against multi drug resistant (MDR) strains of bacteria and fungus of clinical origin. Molecules, **14**, 586-597. DOI: 10.3390/molecules14020586
84. *Ujam N.T., Oli A.N., Ikegbunam M.N., Adikwu M.U., Esimone C.O.* (2013) Antimicrobial resistance evaluation of organisms isolated from liquid herbal products manufactured and marketed in South Eastern Nigeria. Br. J. Pharm. Res., **3**, 548-562. DOI: 10.9734/BJPR/2013/3554
85. *Brown J.C., Jiang X.* (2008) Prevalence of antibiotic-resistant bacteria in herbal products. J. Food Prot., **71**, 1486-1490. DOI: 10.4315/0362-028x-71.7.1486
86. *Mundy L., Pendry B., Rahman M.* (2016) Antimicrobial resistance and synergy in herbal medicine. J. Herb. Med., **6**, 53-58. DOI: 10.1016/j.hermed.2016.03.001
87. *Lambert R.J.W., Skandamis P.N., Coote P.J., Nychas G.J.* (2001) A study of the minimum inhibitory concentration and mode of action of oregano essential oil, thymol and carvacrol. J. App. Microbiol., **91**, 453-462. DOI: 10.1046/j.1365-2672.2001.01428.x
88. *Ayaz M., Ullah F., Sadiq A., Ullah F., Ovais M., Ahmed J., Devkota H.P.* (2019) Synergistic interactions of phytochemicals with antimicrobial agents: Potential strategy to counteract drug resistance. Chem. Biol. Interact., **308**, 294-303. DOI: 10.1016/j.cbi.2019.05.050
89. *Bhardwaj M., Singh B.R., Sinha D.K., Kumar V., Vadhana P., Vinodhkumar O.R., Singh V.S., Nirupama K.R., Shree P., Saraf A.* (2016) Potential of herbal drug and antibiotic combination therapy: A new approach to treat multidrug resistant bacteria. Pharm. Anal. Acta, **7**, 11. DOI: 10.4172/2153-2435.1000523

90. *Dwivedi G.Raj., Maurya A., Yadav D.K., Singh V., Khan F., Gupta M.K., Singh M., Darokar M.P., Srivastava S.K.* (2019) Synergy of clavine alkaloid "chanoclavine" with tetracycline against multi-drug-resistant *E. coli*. J. Biomol. Struct. Dyn., **37**, 1307-1325. DOI: 10.1080/07391102.2018.1458654
91. *Miladi H., Zmantar T., Kouidhi B., Al Qurashi Y.M.A., Bakhrouf A., Chaabouni Y., Mahdouani K., Chaieb K.* (2017) Synergistic effect of eugenol, carvacrol, thymol, *p*-cymene and gamma-terpinene on inhibition of drug resistance and biofilm formation of oral bacteria. Microb. Pathog., **112**, 156-163. DOI: 10.1016/j.micpath.2017.09. 057
92. *Siriwong S., Teethaisong Y., Thumanu K., Dunkhunthod B., Eumkeb G.* (2016) The synergy and mode of action of quercetin plus amoxicillin against amoxicillin-resistant *Staphylococcus epidermidis*. BMC Pharmacol. Toxicol., **17**, 39. DOI: 10.1186/s40360-016-0083-8
93. *Pal A., Tripathi A.* (2019) Quercetin potentiates meropenem activity among pathogenic carbapenem-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. J. Appl. Microbiol., **127**(4), 1038-1047. DOI: 10.1111/jam.14388
94. *Lin R.D., Chin Y.P., Hou W.C., Lee M.H.* (2008) The effects of antibiotics combined with natural polyphenols against clinical methicillin-resistant *Staphylococcus aureus* (MRSA). Planta Med., **74**, 840-846. DOI: 10.1055/s-2008-1074559
95. *Jia Y., Wu.X.* (2017) *In vitro* activity of allicin combined with two antibiotics on intestinal *Shigella*. Infect. Int., **6**, 25-29. DOI: 10.1515/ii-2017-0152
96. *Altemimi A., Lakhssassi N., Baharlouei A., Watson D.G., Lightfoot D.A.* (2017) Phytochemicals: Extraction, isolation, and identification of bioactive compounds from plant extracts. Plants, **6**, 42. DOI: 10.3390/plants6040042
97. *Li Y., Kong D., Fu Y., Sussman M.R., Wu H.* (2020) The effect of developmental and environmental factors on secondary metabolites in medicinal plants. Plant. Physiol. Biochem., **148**, 80-89. DOI: 10.1016/j.plaphy.2020.01.006
98. *Salem M.A., de Souza L.P., Serag A., Fernie A.R., Farag M.A., Ezzat S.M., Alseekh S.* (2020) Metabolomics in the context of plant natural products research: From sample preparation to metabolite analysis. Metabolites, **10**, 37. DOI: 10.3390/metabo10010037
99. *Demarque D.P., Dusi R.G., de Sousa F.D.M., Grossi S.M., Silvério M.R.S., Lopes N.P., Espindola L.S.* (2020) Mass spectrometry-based metabolomics approach in the isolation of bioactive natural products. Sci. Rep., **10**, 1051. DOI: 10.1038/s41598-020-58046-y
100. *Fierascu R.C., Fierascu I., Ortan A., Georgiev M.I., Sieniawska E.* (2020) Innovative approaches for recovery of phytoconstituents from medicinal/aromatic plants and biotechnological production. Molecules, **25**, 309. DOI: 10.3390/molecules25020309
101. *Yoshioka T., Nagatomi Y., Harayama K., Bamba T.* (2018) Development of an analytical method for polycyclic aromatic hydrocarbons in coffee beverages and dark beer using novel high-sensitivity technique of supercritical fluid chromatography/mass spectrometry. J. Biosci. Bioeng., **126**, 126-130. DOI: 10.1016/j.jbiosc.2018.01.014
102. *Williams S.R., Oatley D.L., Abdrahman A., Butt T., Nash R.* (2012) Membrane technology for the improved separation of bioactive compounds. Procedia Eng., **44**, 2112-2114. DOI: 10.1016/j.proeng.2012.09.064
103. *Gil-Chávez G.J., Villa J.A., Ayala-Zavala J.F., Heredia J.B., Sepulveda D., Yahia E.M., González-Aguilar G.A.* (2013) Technologies for extraction and production of bioactive compounds to be used as nutraceuticals and food ingredients: An overview. Compr. Rev. Food Sci. Food Saf., **12**, 5-23. DOI: 10.1111/1541-4337.12005
104. *Puértolas E., Koubaa M., Barba F.J.* (2016) An overview of the impact of electrotechnologies for the recovery of oil and high-value compounds from vegetable oil industry: Energy and economic cost implications. Food Res. Int., **80**, 19-26. DOI: 10.1016/j.foodres.2015.12.009
105. *Pyne M.E., Narcross L., Martin V.J.J.* (2019) Engineering plant secondary metabolism in microbial systems. Plant. Physiol., **179**, 844-861. DOI: 10.1104/pp.18.01291
106. *Cardoso J.C., Oliveira M.E.B.S., Cardoso F.C.I.* (2019) Advances and challenges on the *in vitro* production of secondary metabolites from medicinal plants. Horticultura Brasileira, **37**, 124-132. DOI: 10.1590/S0102-053620190201
107. *Thomford N.E., Senthebane D.A., Rowe A., Munro D., Seele P., Maroyi A., Dzobo K.* (2018) Natural products for drug discovery in the 21st century: Innovations for novel drug discovery. Int. J. Mol. Sci., **19**, 1578. DOI: 10.3390/ijms19061578
108. *Tebani A., Afonso C., Bekri S.* (2018) Advances in metabolome information retrieval: Turning chemistry into biology. Part I: Analytical chemistry of the metabolome. J. Inherit. Metab. Dis., **41**, 379-391. DOI: 10.1007/s10545-017-0074-y
109. *Yao H., Liu J., Xu S., Zhu Z., Xu J.* (2017) The structural modification of natural products for novel drug discovery. Expert Opin. Drug Discov., **12**, 121-140. DOI: 10.1080/17460441.2016.1272757

Received: 14. 11. 2023.
Revised: 17. 11. 2023.
Accepted: 20. 11. 2023.

ВТОРИЧНЫЕ МЕТАБОЛИТЫ РАСТЕНИЙ И ИХ ВОЗМОЖНАЯ РОЛЬ В “ЭПОХУ СУПЕРБАКТЕРИЙ”

В.М. Нестерович[1], Д.А. Белых[1], Н.В. Гороховец[1], Л.К. Курбатов[2], А.А. Замятнин[1,3], Л.Н. Икрянникова[1]*

[1]Первый Московский государственный медицинский университет им. И.М. Сеченова (Сеченовский университет), 119991 Москва, ул. Трубецкая, 8/2; *эл. почта: larisa.ikryannikova@gmail.com
[2]Тюменский государственный университет, 625003 Тюмень, ул. Володарского, 6
[3]Московский государственный университет имени М.В. Ломоносова, 119234 Москва

Бактериальные инфекции являются серьёзной причиной высокой заболеваемости и смертности во всём мире. За последние десятилетия лекарственная устойчивость бактериальных патогенов неуклонно возрастает, в то время как скорость разработки новых эффективных антибактериальных препаратов остаётся стабильно невысокой. Царство растений иногда называют бездонным колодцем для поиска новых средств противомикробной терапии. Это связано с тем, что растения легкодоступны и дёшевы в переработке, а экстракты и компоненты растительного происхождения часто демонстрируют высокий уровень биологической активности при незначительных побочных эффектах. Многообразие полученных из растительного сырья соединений способно обеспечить весьма широкий выбор разнообразных химических структур для взаимодействия с различными мишенями внутри бактериальной клетки, а стремительное развитие современных биотехнологических инструментов открывает путь к направленному получению биоактивных компонентов с желаемыми свойствами. Задачей данного обзора стал ответ на вопрос, имеют ли шанс противомикробные препараты растительного происхождения сыграть роль панацеи в борьбе с инфекционными заболеваниями в “эпоху пост-антибиотиков”.

Полный текст статьи на русском языке доступен на сайте журнала (http://pbmc.ibmc.msk.ru).

Ключевые слова: вторичные метаболиты растений (ВМР); фитопроизводные; лекарственная устойчивость; бактериальные патогены; антимикробные свойства

Финансирование. Работа выполнена при финансовой поддержке Российского Научного Фонда (проект № 22-25-00804).

Поступила в редакцию: 14.11.2023; после доработки: 17.11.2023; принята к печати: 20.11.2023.