Antimicrobial activity of alkaloids

Seniuk I., Filimonova N.

National University of Pharmacy (Kharkiv, Ukraine)

citochrom@gmail.com

Introduction. The ability to successfully treat infectious diseases is threatened due to the rise of antimicrobial resistance (AMR). According to the Centers for Disease Control and Prevention (CDC), about 2.9 million antibiotic-resistant infections occur in the United States each year, resulting in 35 900 deaths. The CDC lists sixteen bacteria and two fungi as urgent, serious or concerning threats, including Mycobacterium tuberculosis, of which there are extensively drug-resistant strains, resistant to two of four first-line antibiotics and at least one of the three second-line antibiotics.

Several factors are involved in the rise of antibiotic resistance, especially the overuse and misuse of antibiotics in human and animal health and the lack of development of new antibiotics. The field of antibiotic discovery and development is in dire need of innovation in order to reinvigorate the pipeline that has not seen a new class of drugs discovered and approved by the FDA since the late 1980s. This status quo can be in large part explained by the economics of antibiotics post-approval, which has become so unfavorable to companies and investors that antibiotic start-ups and large pharmaceutical companies alike are unable to survive in the antibiotics development space.

Alkaloids are one of the largest groups of plant NPs, including more than 20 000 different molecules with a vast diversity of structures and routes to biosynthesis. Alkaloids are low-molecular-weight nitrogen-containing compounds and, due to the presence of a heterocyclic ring containing a nitrogen atom, are typically alkaline. Alkaloids are biosynthetically derived from amino acids such as phenylalanine, tyrosine, tryptophan, ornithine, and lysine. Building blocks from the acetate, shikimate, or deoxyxylulose phosphate pathways are also frequently incorporated into alkaloid structures. The biogenesis of alkaloids is used for their classification, as this is directly linked to their molecular skeleton; for example, the largest groups are indole alkaloids and isoquinoline alkaloids. Other relevant groups are tropane alkaloids, steroidal alkaloids, pyridine, and pyrrolizidine alkaloids. The botanical origin of the alkaloids is also used as a classification method, e.g., *Papaver* (opium) alkaloids, *Cinchona* alkaloids, *Rauvolfia* alkaloids and others.

The aim of the study. To conduct an analysis of literature and experimental data on the antimicrobial activity of alkaloids.

Materials and methods. Major Chemical Classes Investigated Antibacterial plant NPs were categorized into four major chemical classes: alkaloids, phenolic derivatives, terpenoids, and other metabolites. Of the compounds tested, 50.8% belong to the major class phenolic derivatives. Terpenoids compromise 26.6% of the compounds, other metabolites account for 17% of compounds, and alkaloids account for the fewest compounds at 5.7%.

Results and their discussion. Alkaloids are known for their numerous pharmacological effects. They impact different metabolic systems, and their mechanism of action (MOA) may be through enzymatic alterations affecting physiological processes. Such processes include inhibition of DNA synthesis and repair mechanisms by intercalating nucleic acids. Research by Tan et al. on a chloroform extract of Artabotrys crassifolius Hook. & Thomson (*Annonaceae*) bark led to the isolation of three aporphine alkaloids: lysicamine, artabotrine and liridine. Lysicamine exhibited high activity Against *L. monocytogenes* and *S. pneumoniae*, and *S. agalactiae*. Artabotrine displayed high activity against a broad

array of gram-positive bacteria, including *B. cereus*, *L. monocytogenes*, *Staphylococcus sp.*, and *S. aureus*. They also found that liridine displayed high activity against *Bacillus subtilis*, *L. monocytogenes*, *Staphylococcus sp*., and *Streptococcus agalactiae*. All three compounds (liridine, lysicamine, and artabotrine) were highly active against extended-spectrum beta-lactamase-producing *K. pneumoniae*. Additionally, Proteus vulgaris growth was significantly inhibited by lysicamine and artabotrine.

Hamound et al. investigated the benzophenanthridine alkaloid sanguinarine, which can be isolated from several members of the *Papaveraceae* family, including *Sanguinaria canadensis L*., *Macleaya cordata R.Br*. and *Eschscholzia californica Cham*. The authors found that the antibacterial activity of sanguinarine was strongest against gram-positive bacteria, with high activity against *Staphylococcus epidermidis* and vancomycin-resistant *Enterococcus faecalis*. Additionally, sanguinarine inhibited the growth of gram-negative bacteria with high activity against *Escherichia coli* and moderate activity against *Acinetobacter baumannii* and *Klebsiella pneumoniae*. Furthermore, the authors observed synergistic activity against a panel of clinically relevant gram-positive and gram-negative strains with a drug cocktail consisting of sanguinarine, an antibiotic (streptomycin), and a chelating agent (ethylenediaminetetraacetic acid, EDTA).

Four quaternary benzylisoquinoline alkaloids, isolated from *Berberis integerrima* Bunge (*Berberidaceae*) roots, including berberine, jatrorhizine, columbamine, and palmatine were investigated by Azimi et al. for growth inhibition against *Brucella abortus*. This study found these compounds to all have high activity against *B. abortus*, with jatrorhizine being the most effective. Another phytochemical study reported that palmatine, isolated from *Tinospora sagittata Gagnep (Menispermaceae)*, showed a bactericidal effect and high growth inhibitory activity against Helicobacter pylori, both *in vitro* and in a murine model. In addition, Xie et al. evaluated the antibacterial efficacy of berberine against selected endodontic pathogens using a multispecies biofilm tooth model. They found berberine to have high activity against *Prevotella intermedia* and moderate activity against *Fusobacterium nucleatum*. Additionally, in a randomized controlled clinical trial of patients with diarrhea due to enterotoxigenic *E. coli* or *Vibrio cholerae*, berberine sulfate treatment was found to produce a significant reduction in stool volume.

Tankeo et al. isolated the benzophenanthridine alkaloid, buesgenine; it is one of the main active constituents of the roots of *Zanthoxylum gilletii (De Wild.)* P.G.Waterman (*Rutaceae*). The authors found buesgenine to have high activity against a panel of gram-negative bacteria, including multidrug-resistant (MDR) phenotypes. Buesgenine was found to have high activity against *E. coli* and *K. pneumoniae*, and moderate activity against *Enterobacter aerogenes*, *P. aeruginosa* and *Providencia stuartii*. Additionally, buesgenine was found to be nontoxic to mouse hepatocytes.

Other Alkaloid Derivatives A phytochemical investigation by Yu et al. on the lateral roots of *Aconitum carmichaelii Debeaux (Ranunculaceae)* led to the isolation of a vakognavine-type C20-diterpenoid alkaloid, carmichaedine. The authors found carmichaedine to have high antibacterial activity against *Bacillus subtilis*. Of the three other alkaloids derivatives found in our review, carmichaedine is the only one exhibiting a high in vitro antibacterial activity.

Conclusions. Alkaloids demonstrated the lowest mean MIC value against reported bacteria. Alkaloid distribution is restricted in plants, with only 300 families producing these compounds. They are also known to be highly toxic in animals and to possess allelopathic effects on plants. A number of

antibacterial drugs are alkaloids, including the antituberculosis medicine bedaquiline with its quinoline scaffold and the synthetic quinolones derived from quinine. Many alkaloids also fall well within the parameters for being considered drug-like by Lipinksi's Rule of Five, and they have more skeletal structural and functional group diversity than other chemical classes. Cordell et al. noted that only 702 out of 21 120 known alkaloids have been evaluated in more than five bioassays and that many new alkaloid skeletons could be discovered from plant families that are already studied for alkaloids. Alkaloids thus represent a promising source of antibacterial compounds, and further research should be performed while considering their potential toxicity at an early stage of the drug discovery process.

Mechanisms of the biological effects of phytoestrogens

Seniuk I., Kravchenko V., Benarafa Ibrahim Amin
National University of Pharmacy (Kharkiv, Ukraine)
citochrom@gmail.com

Introduction. Interest of both public and specialists in medicine and functional food production in the physiological role and practical application of plant bioactive compounds has increased dramatically over the last decade. Of particular interest in relation to human health are the class of compounds known as the phytoestrogens, which includes several groups of non-steroidal estrogens that are widely distributed within the plant kingdom. There is a growing body of evidence, that consumption of some these plants or their molecules could be an additive efficient tool to prevent and to treat several dysfunctions and diseases related to aging, mental processes, metabolism, malignant transformation, cardiovascular diseases and reproduction - breast and prostate cancers, menopausal symptoms, osteoporosis, atherosclerosis and stroke, and neurodegeneration.

The aim of the study. To analyze the literature data on biochemical mechanisms of biological and pharmacological effects.

Materials and methods. Scientific articles on experimental studies of biochemical studies of phytoestrogens on the processes that provide pharmacological activity have been used.

Results and their discussion. Phytoestrogens are strikingly similar in chemical structure to the mammalian estrogen, estradiol, and bind to estrogen receptors alpha and beta with a preference for the more recently described estrogen receptor beta. These receptors after binding with ligand are able to move from cytoplasm to the nucleus, bind and affect the transcription-control regions of DNA or small RNAs and therefore the expression of specific genes. Furthermore, steroids are able to bind to receptors of cell surface, promote formation of cytoplasmic cyclic nucleotides and related protein kinases, which in turn via transcription factors control the expression of target genes. Therefore, phytoestrogens can potentially affect all the processes regulated by estrogens including induction sex hormone binding globulin and inhibition aromatase. Estrogen receptors are present in different tissues – central nervous system (including hypothalamo–hypophysial axis), gonads, reproductive tract, placenta, mammary gland, bones, gastrointestinal tract, lung a.o. This suggests that phytoestrogens may exert tissue specific hormonal effects. The estrogen receptor-specific effects may occur too. For example, estrogen receptors alpha are considered as promoters of cell proliferation, whilst estrogen receptors beta are in charge for promoting mainly cellular apoptosis.

Phytoestrogens besides their ability to bind to estrogen receptors, have other biological effects, which