Review Article

Polyphenols of Antibacterial Potential – May They Help in Resolving Some Present Hurdles in Medicine?

(polyphenols / drug resistance / microbial / antibiotic resistance / bacterial / biofilms)

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Abstract. The phenomenon of antibiotic resistance has been recognized as one of the greatest threats to humanity. Therefore, there is an enormous need to introduce new antibiotics to the medical practice that will effectively eradicate the resistant bacterial strains threatening human health and life. One solution currently being considered as an alternative to antibiotics involves secondary metabolites of plants that can be used in modern antibacterial therapy. Polyphenols represent a broad and diversified group of plant-derived aromatic compounds. Their antibacterial potential has been recognized via specific mechanisms of action, e.g., by inhibition of bacterial biofilm formation, through synergistic effects with the action of currently used antibiotics, and by inhibition of the activity of bacterial virulence factors.

Introduction

The discovery of penicillin described by Alexander Fleming in 1929 (Fleming, 1929) denoted the beginning of a new era in the fight against bacterial infections. However, the antibacterial effect of several Penicillinum species had been noticed decades earlier (Gould, 2016). Antibiotics are compounds of either natural origin produced by microorganisms, their semi-synthetic derivatives, or synthetic equivalents which, in the appropriate concentration and through various mechanisms of action, affect bacteria by inhibiting their growth and development and/or leading to the cell death (Ferri et al., 2017). In contrast to the period of time before their discovery, antibacterial drugs help to prevent excessive deaths caused by bacterial infections and have accelerated the development of medicine in terms of invasive procedures and operations, especially those in which the opening of the body shell used to carry a huge risk of systemic infections (Mohr, 2016). The beginning of the golden age of antibiotics sparked great enthusiasm in the medical and scientific community, while at the same time Alexander Fleming warned the public about the possible future consequences of excessive and inappropriate use of these innovative drugs (Fleming, 1945).

Indeed, the consequence that Fleming warned about has arisen and is known as the phenomenon of antibiotic resistance. It has been recognized recently by the World Health Organization (WHO) as one of the greatest threats to human health in the whole world. The latest global study, published in The Lancet medical journal, found that drug-resistant bacterial infections were associated with about 4.95 million deaths, including 1.27 million deaths that were caused directly by antibiotic-resistant bacteria in 2019 (Antimicrobial Resistance Collaborators, 2022).

Antibiotic resistance impacts the population, making the entire healthcare system partially or sometimes completely vulnerable in the case of bacterial spread (Gil-Gil et al., 2019). Infections with resistant strains worsen the condition of patients, leading to extension of the hospitalization period, and force the use of alternative therapies that may, in turn, consume huge financial expenses (Hassoun-Kheir et al., 2020). This means that the phenomenon of drug resistance not only affects the healthcare system, but also influences the economy and the state budget (Ahmad and Khan, 2019).

The presence and activity of resistant strains is mostly found within the hospital environment. This is especially dangerous because hospitalized patients are susceptible to many infections. As a result, opportunistic microorganisms, i.e., those being generally non-pathogenic,

Received April 8, 2022. Accepted May 25, 2022.

This study was supported by a research grant from Medical University of Silesia, Katowice, Poland. Grant No. PCN-1-115/N/0/O.

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Abbreviations: ECG – epicatechin gallate, EGCG – epigallocatechin gallate, EPIs – efflux pump inhibitors, GTs – glucosyltransferases, MAPK – mitogen-activated protein kinases, MIC – minimum inhibitory concentration, MRSA – methicillin-resistant *Staphylococcus aureus*, NLRP3 – NOD-like receptor family, pyrin domain-containing 3, SLO – streptolysin O, WHO – World Health Organization.

gain the ability to colonize a devitalized organism. In the situation of the ineffectiveness of antibiotic therapy, virtually all hospital infections may lead to a serious medical crisis (Lerminiaux and Cameron, 2019). Bacteria that are responsible for causing common (hospital) infections belong mainly to the following strains: *Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, Streptococcus pneumonia, Acinetobacter baumannii* and *Pseudomonas aeruginosa* (Antimicrobial Resistance Collaborators, 2022).

Bacteria are microorganisms that are able to acquire, modify and even transfer the mechanisms causing antibiotic resistance in an extremely flexible way (Arzanlou et al., 2017). In addition to the standard route of vertical gene transmission, i.e., inheriting the characteristics of a daughter cell from the parent cell, bacteria can exchange genes horizontally. This means the ability of these organisms to transfer some (favourable) traits between different strains and even between species of bacteria (Bengtsson-Palme et al., 2018).

The ability to develop drug resistance is a natural phenomenon in microorganisms, but the selection of resistant strains and species has been accelerated by excessive and inappropriate antibiotic exposure in healthcare, agriculture and the environment (Holmes et al., 2016). According to some reports from the United States, in the first decade of the 21st century, incorrect diagnoses caused that up to 50 % of antibiotics were unnecessarily prescribed to patients in whom bacteria were not a disease-causing pathogen (Ventola, 2015).

Apart from the use in medicine, agriculture is believed to be a much greater source of antibiotics in the environment (McEwen and Collignon, 2018). The use of antibiotics in agriculture is commonly applied to combat plant and animal infections, and thus to ensure higher yields and profits. It is supposed that agriculture but not medicine is a factor that generates up to 80 % of the total use of antibiotics in the world (Ventola, 2015; Wall et al., 2016).

Due to the very short time line at which bacteria acquire drug resistance, it is not even profitable for pharmaceutical companies to research new antibiotics. The time and costs which must be invested in the development of a new antibiotic may significantly exceed the expected profits from the sale of a functional drug (Plackett, 2020).

Taking into consideration the above-mentioned issues, there is an urgent need for searching for new effective antimicrobial agents. The progress in technology has made it possible to conduct research in many different areas, thus posing a clear difference to the years before antibiotics were discovered. Particularly, modern genetic engineering allows for the development of effective phage therapy. Bacteriophages (or simply phages) are viruses that can infect bacteria, multiply inside their cells, and eventually destroy them. Bacteriophages are characterized by extremely high specificity, they may show activity against certain species or even against particular bacterial strains (Kortright et al., 2019). Another innovative concept in biotechnology is the control of bacterial growth by means of using nanoparticles. Silver-containing nanoparticles possess antimicrobial potential through their interactions with various bacterial structures (Tang and Zheng, 2018). Nanoparticle-based therapies are promising because the structures of molecules differ significantly from the existing antibiotics. It should be kept in mind, however, that the source of new drugs also ought to be cheap and easily available, which will ensure that each patient has access to antimicrobials (Miethke et al., 2021).

A very interesting group of chemical compounds with intended antimicrobial activity are polyphenols. Polyphenols are plant secondary metabolites that are abundant in leaves, seeds, fruits, etc. The chemical structure of polyphenols is based on the presence of at least two hydroxyl groups that are linked to one or more aromatic rings. Polyphenols encompass a large group of organic ingredients, which are divided into numerous subgroups based on their characteristic molecular structure. The largest and most important members of the polyphenol group are flavonoids and phenolic acids (Figs. 1 and 2) (D'Archivio et al., 2007).

Utilization of plant extracts for medicinal purposes has been known for several centuries, but the knowledge of folk medicine was only empirical, based on observations of the effects obtained after the treatment. With time, understanding of the polyphenol molecular structure has explained that their antioxidant activity and subsequent reduction of pro-inflammatory factors is dependent on the presence of numerous hydroxyl groups (Yan et al., 2020). In addition, it was observed that although plants do not have an immune system like animals, most of them can defend themselves against pathogenic factors. This indicates the presence of antimicrobial elements in the plant organisms (Piasecka et al., 2015). It has been documented in plants that in response to the contact with a pathogen, there was a visible increase in the concentration of resveratrol, a naturally occurring polyphenol present, for example, in grapes (Vestergaard and Ingmer, 2019). Intensive research that was conducted for several decades resulted in a significant number of scientific publications reporting the effective antibacterial activity of polyphenols (Barbieri et al., 2017). Therefore, different research centres around the world implied the possible use of polyphenols as compounds with powerful antimicrobial activity. For example, individual molecules inhibit formation of biofilm, acting as interfering factors with intercellular communication, i.e., impede the *quorum sensing* phenomenon. In this setting, polyphenols can act synergistically with the existing antibiotics. Additionally, polyphenols have the ability to bind important bacterial enzymes (Barbieri et al., 2017). The most important features of polyphenols and their promising potential for human needs are discussed in subsequent chapters.

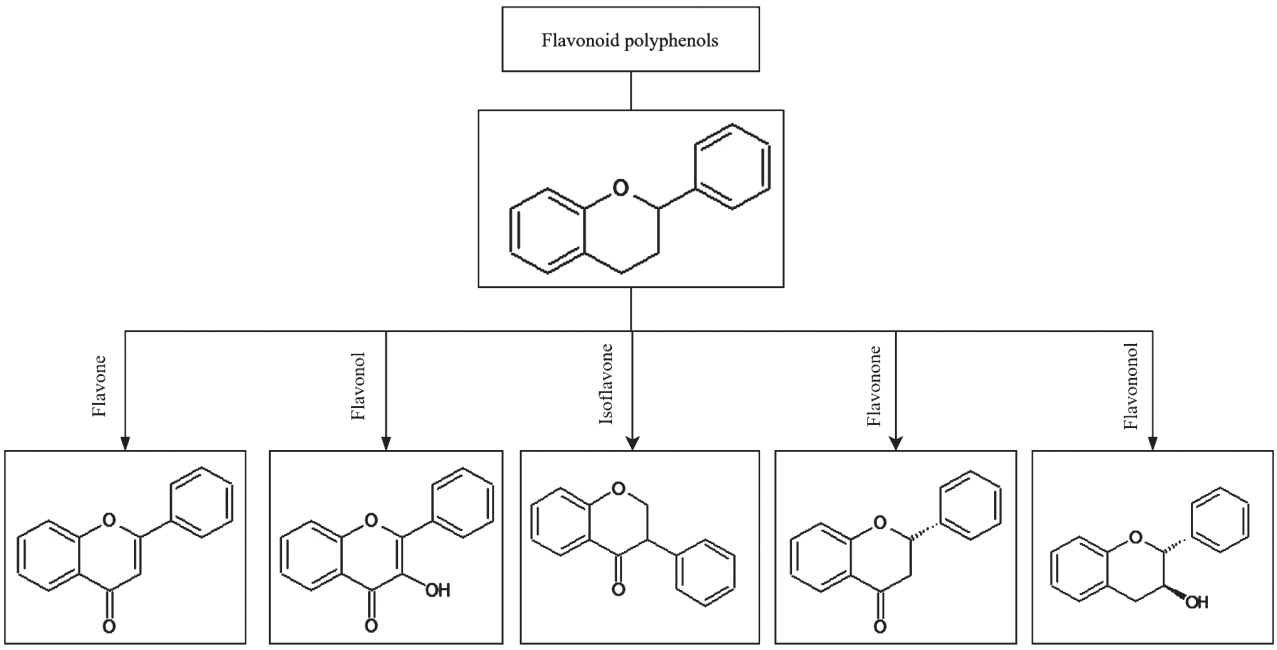

Fig. 1. Basic structure of flavonoids and their subclasses acc. to Alibi et al. (2021).

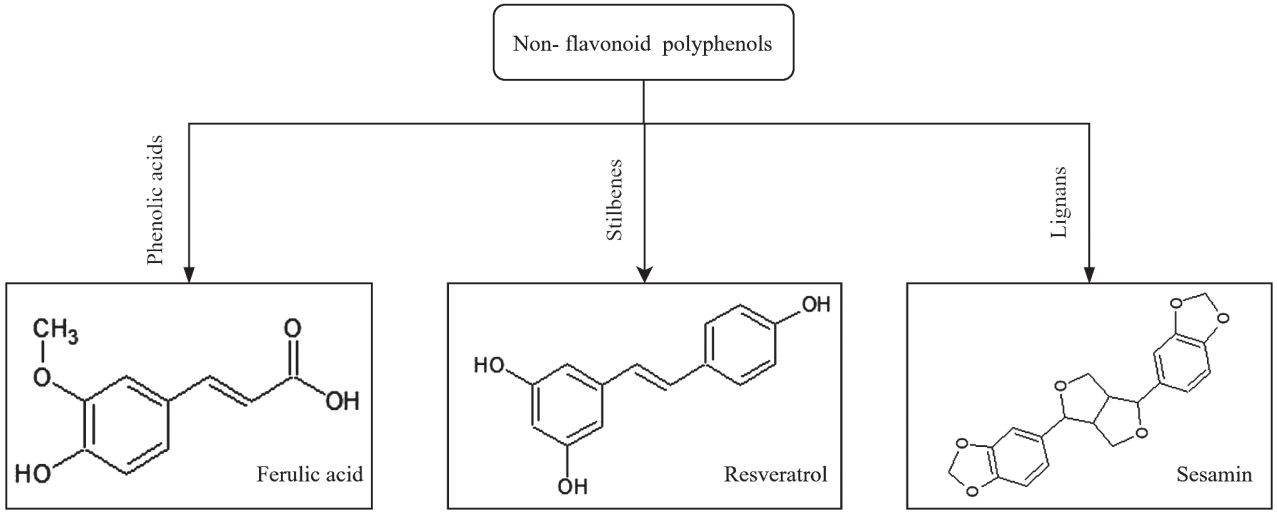

Fig. 2. Classes of non-flavonoid polyphenols and structures of their representatives, acc. to Singla et al. (2019), Di Lorenzo et al. (2021), Makarewicz et al. (2021).

Polyphenol activity against biofilm formation

A unique and interesting phenomenon that some bacteria develop in order to effectively colonize their environment is the ability to produce biofilms. Biofilm is beneficial for bacteria because unicellular organisms, when living in the form of an organized system, acquire greater resistance against the host's immune system. In addition, it has been shown that microorganisms living in the biofilm become up to a thousand times more resistant to the antimicrobial agents' activity than the free-living bacterial forms (Rabin et al., 2015). Biofilm has a spatial structure form consisting of an extracellular matrix in which bacteria are immersed and arranged in multiple layers. Water-binding polysaccharides comprise an essential component of the matrix (Tolker-Nielsen, 2015). During the biofilm formation, bacteria secrete autoinductor molecules that act as signalling factors responsible for bacterial reciprocal communication, i.e., making the so-called *quorum sensing*. When bacterial cells in the biofilm reach the optimal concentration, synchronization between microorganisms occurs, resulting in subsequent changes in the transcriptome. Activated

genes most often encode virulence and resistance factors (Abisado et al., 2018).

Due to the formation of biofilm, possible antibiotic therapy becomes ineffective, as the penetration ability of antibiotics into the biofilm is poor (Tolker-Nielsen, 2015). A simple elevation of the drug doses is not a sufficient remedy to the problem due to the narrow safety margin between the therapeutic and toxic dose of numerous antibiotics and to the risk of patient's intoxication. Recent studies indicate that polyphenols possess the ability to inhibit formation of biofilm by interfering in its development whilst not having a toxic effect on human cells (Fig. 3) (Serra et al., 2016; Stenvang et al., 2016; Eyler and Shvets, 2019; Lee et al., 2019; Qayyum et al., 2019; Schneider-Rayman et al., 2021; Zayed et al., 2021).

Zayed et al., conducting studies on *Streptococcus mutans* strains, observed inhibition of the biofilm formation after addition of green tea extract. It is known that green tea leaves contain numerous flavonoids, mainly epicatechin, epigallocatechin, epicatechin gallate (ECG) and epigallocatechin gallate (EGCG). These compounds are able to prevent the biofilm formation through their interactions with bacterial enzymes glucosyltransferases (GTs). GTs convert sucrose into glucan, which is the basic structural element of polysaccharides in the external environment of bacteria (Zayed et al., 2021). Similar conclusions were made by Schneider-Rayman et al. (2021), authors who also consider the role of EGCG in the direct inhibition of expression of genes that encode proteins involved in the biofilm formation.

In turn, Serra et al. studied the effect of EGCG on the inhibition of biofilm formation by *Escherichia coli*. Authors revealed that some bacteria, including those of the *Enterobacteriaceae* family, may produce a biofilm with specific properties, e.g., an extreme durability, as it

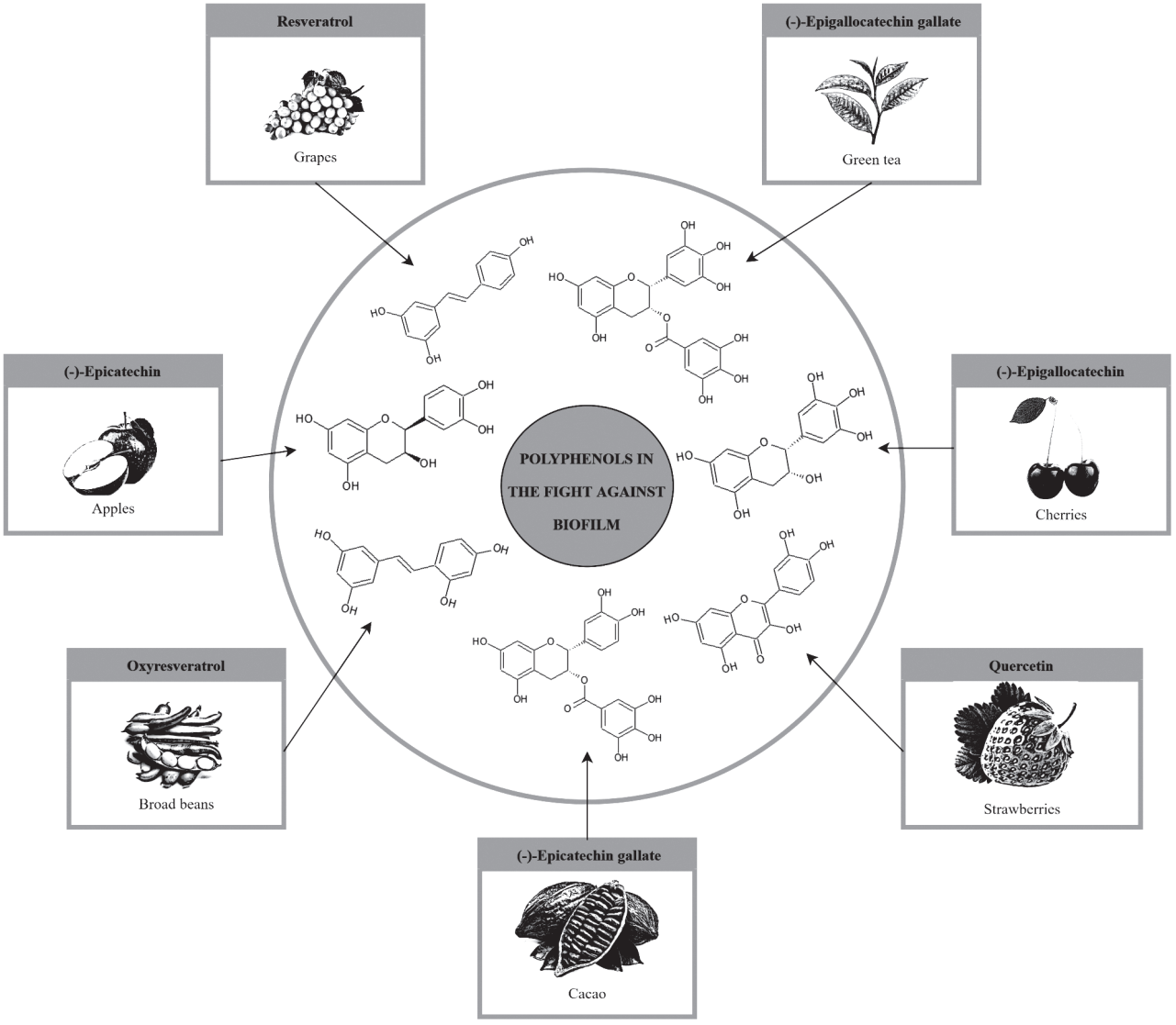

Fig. 3. Polyphenols in the fight against biofilm. Polyphenols are useful tools that may be utilized in the inhibition of biofilm forming. This solution is very promising in medical industry. Polyphenols can be found in different but common plant-derived components.

is composed of amyloid fibres. Amyloids are proteins that exhibit the conformation of a β-sheet in contrast to the conventional, α-helix structured proteins. As a result, the regular structure of unbranched fibres in the β-sheet form makes amyloids extremely resistant to proteolysis. Serra et al. suggest that EGCG weakens formation of curli fimbriae that are composed of amyloid. These studies have confirmed that EGCG present in green tea inhibits biofilm formation in both commensal and pathogenic *E. coli* strains (Serra et al., 2016). Similar studies were carried out by Stenvang et al. based on *Pseudomonas aeruginosa* with a final conclusion that EGCG prevents formation of amyloid fibres in their experimental setting. Moreover, the abnormal structure of curli fimbriae subsequently disrupts formation of *quorum sensing* (Stenvang et al., 2016).

The synthesis of curli fimbriae – a key element in the biofilm structure – may be inhibited by polyphenols such as resveratrol, oxyresveratrol and some oligomers, e.g., suffruticosol A, vitisin A and ε-viniferin. Using uropathogenic *Escherichia coli* strains, Lee et al. proved that resveratrol and oxyresveratrol significantly inhibited expression of genes that are responsible for the formation of biofilm structure-related curli fimbriae as well as for flagella that are necessary for bacterial movement. The results suggest that resveratrol and oxyresveratrol have the potential to reduce the virulence of *E. coli* by inhibiting production of biofilm, both directly and indirectly, by limiting the bacterial motility (Lee et al., 2019).

Quercetin is another member of polyphenol family that influenced production of biofilm in *Enterococcus faecalis*. Qayyum et al., analysing the proteome of bacteria, observed that quercetin interferes with the processes of translation, elongation and protein folding. Eventually, as a result of these interactions, the entire physiology of the bacteria is disturbed, thus preventing transition of bacteria from their planktonic (free) form to the biofilm structure. This research indicates that quercetin can be used as a preventive factor against biofilm synthesis in infections caused by resistant pathogens (Qayyum et al., 2019).

Synergy of antibiotics and potentiation of action

The bacteriostatic and/or bactericidal effect of antibiotics depends on their mechanism of action. The basic activities include: stopping synthesis of the cell wall through interference into peptidoglycan synthesis, inhibition of nucleic acid synthesis, and stopping translation of proteins by binding to a small or large subunit of ribosomes (Eyler and Shvets, 2019).

Unfortunately, antibiotics partially lose their initial potential mainly because bacteria have acquired the ability to alter the structure of molecules that serve as drug targets. This is valid, for example, for the conformational alteration of the topoisomerase active centre or for changes in the structure of ribosome-forming subunits. It is also worthy of note that bacteria gain the ability to produce isoenzymes that degrade the drug molecule such as, e.g., β-lactamases (Wencewicz, 2019). To overcome these barriers, the action of antibiotics must be enhanced, and polyphenols have the potential to be a powerful ally in that context. Combined therapy of polyphenols with antibiotics have a synergistic therapeutic effect, and it has been found that polyphenols potentiate the action of antibiotics. Thus, the benefits of combination therapy using certain antibiotics with polyphenols include: broadening the action spectrum of a drug and lowering the minimum inhibitory concentration (MIC).

In a similar context, Qin et al. conducted research involving analysis of compounds that may sensitize bacterial cells, i.e., increase their sensibility to the action of antibiotics. In their research, authors used catechin and ECG as potentiators of oxacillin action against methicillin-resistant *Staphylococcus aureus* (MRSA). It was reported that a combination of both polyphenols and oxacillin significantly increased the bactericidal efficacy of β-lactams on MRSA strains. Catechin and ECG may act as efflux pump inhibitors (EPIs), and the molecular mechanism of this action may involve inhibition of expression of specific genes that are responsible for the efflux turnover. In this report, a significant decrease in the mRNA copy number of three important MRSA efflux pump genes was documented, which was associated with an increased amount of oxacillin molecules accumulated inside the bacteria (Qin et al., 2013).

A relevant research topic was investigated by Miklasińska et al. (2016), who described the influence of catechin hydrate on the potency of selected antibiotics against MRSA strains. Experimental results revealed that there was an interaction between catechin hydrate and clindamycin or erythromycin potency. This interaction suggested that catechin hydrate can be used as an enhancer of antibacterial activity of selected antibiotics in the *in vivo* system.

Siriwong et al. studied other aspects involving polyphenols and antibacterial drugs. Their work on *Streptococcus pyogenes* strains confirmed that the use of quercetin and luteolin in combination with ceftazidime significantly enhances the antibacterial effect of this antibiotic. Ceftazidime, belonging to the cephalosporin group, inhibits synthesis of bacterial peptidoglycan. The authors observed that both quercetin and luteolin increased the permeability of bacterial cell membranes, changed the shape of bacterial cells, and eventually damaged the cell membranes. Additionally, the bacterial cells of *S. pyogenes* treated with quercetin in combination with ceftazidime and luteolin in combination with ceftazidime showed a decrease in the amount of nucleic acids, while a significant increase in the level of proteins in the cells was detected. In addition, attention was paid to the ability of polyphenols to inhibit peptidoglycan synthesis and to limit the activity of β-lactamases (Siriwong et al., 2015).

Another member of the polyphenol family, namely catechin, is able to modify the antimicrobial activity of

selected antibiotics. Gomes et al., working on antibiotic-resistant strains of *S. aureus*, *E. coli* and *P. aeruginosa*, revealed that catechin in combination with antibiotic drugs – norfloxacin and gentamicin – showed a synergy of action, thus significantly reducing the MIC against *S. aureus* strains. Similarly, a synergistic effect of catechin in combination with imipenem, tetracycline and erythromycin was observed in the case of *E. coli*. However, the best results were obtained using the combination of catechin with norfloxacin, gentamicin and imipenem; this compound was active against resistant strains of *P. aeruginosa*. It is believed that catechin exhibits greater influence on Gram-negative bacteria because of the specificity of the cell wall structure. Catechin increases permeability of the outer membrane, which in turn facilitates penetration of antibiotics into the bacterial interior. Additionally, catechin can form complexes with some cell wall-binding proteins, causing cell wall damage (Gomes et al., 2018).

Polyphenol-mediated inactivation of bacterial virulence factors

Numerous different intra- and extracellular structures as well as molecules secreted from the bacterial cell to the external environment may act as factors of bacterial virulence. These factors enable entry of bacteria into the human body and are responsible for manifestation of the disease symptoms. Some virulence factors e.g. include: fimbriae, cilia, peptidoglycans, lipopolysaccharides and toxins (Diard and Hardt, 2017). These factors may represent a promising antimicrobial drug target, and their neutralization may suppress the bacterial ability to penetrate, adhere, multiply and secrete toxins (Shimamura et al., 2018; Sogawa et al., 2018; Chang et al., 2019; Bhattacharya et al., 2020; Liu et al., 2021).

Staphyloccocus aureus – one of the most harmful microorganisms to human health and life is able to synthesize toxin α-haemolysin. Liu et al. investigated the possible inhibitory effect of EGCG on the signalling pathways involving activation of the inflammatory response induced by α-haemolysin. Experiments confirmed that EGCG suppresses the haemolytic effect of α-haemolysin by reducing its secretion from bacterial cells. In addition, EGCG significantly reduces production of reactive oxygen species and inhibits activation of the mitogen-activated protein kinase (MAPK) signalling pathway, thus diminishing expression of component proteins of the NOD-like receptor family, pyrin domain-containing 3 (NLRP3) inflammasome. NLRP3 is, in turn, responsible for the synthesis of pro-inflammatory cytokines such as IL-1β and IL-18. Moreover, EGCG has the ability to bind directly to α-haemolysin, thereby preventing the toxin from polymerizing and forming its functional structure (Liu et al., 2021).

Catechins can also bind to bacterial enterotoxin A, which is secreted by *Staphylococcus aureus* strains. Shimamura et al. found that catechins bind to staphylococcal enterotoxin A, thereby inhibiting its activity. Detailed investigations showed that the structure of catechins allows for binding with staphylococcal toxin A by means of creating both electrostatic and hydrophobic bonds. Additionally, it was observed that EGCG showed the highest binding strength among other tested catechins (Shimamura et al., 2018).

Bhattacharya et al. in their experiment investigated the anti-virulent activity of polyphenols isolated from kombucha, a fermented drink produced from green or black tea. The main components of the kombucha's isolated polyphenol fraction were catechin and isorhamnetin. Studies have shown that the mobility of *Vibrio cholerae* bacteria was significantly reduced, and the expression of *V. cholera* genes, particularly those involved in flagellum formation, was inhibited. Similar results were observed at the exposure of bacteria to individual polyphenols as well as to their mixture. In addition, polyphenols reduced secretion of bacterial proteases, thus limiting penetration of bacteria through the mucin layer, which is involved e.g. in the protection of intestinal mucosa (Bhattacharya et al., 2020).

Another polyphenol, hydroxytyrosol, possesses similar antibacterial activity to that of catechin and isorhamnetin mentioned above. Sogawa et al. investigated the anti-virulent potential of hydroxytyrosol in relation to streptolysin O (SLO), which is a toxin and a virulence factor in group A streptococci, including *Streptoccocus pyogenes*. Studies have shown that olive (*Olea europaea*)-derived hydroxytyrosol inhibits the haemolytic activity of SLO (Sogawa et al., 2018).

In another study, Chang et al. investigated the inhibitory effect of catechins against the virulence factors of *Aggregatibacter actinomycetemcomitans*, a bacterium that is responsible for causing periodontal infections and inflammation. *A. actinomycetemcomitans* produces a leukotoxin that destroys cells of the immune system, thereby reducing the host's immune response to the infection. Authors stated that catechins cause serious changes in the secondary structure of the leukotoxin. As a result of this conformational change, the toxin lost its ability to bind to the cholesterol present in the cell membrane. The interaction of leukotoxin with molecules present on the host cell surface is an important step in initiating the cytotoxic action of leukotoxin. In the studied group of catechins, the strongest inhibitory effect was shown by EGCG and ECG (Chang et al., 2019).

Polyphenols in practice – what are the most promising approaches today?

The broad availability of polyphenolic compounds and their advantageous properties in respect of the hurdles currently faced in medicine result in the development of several practical approaches. The opportunities to use antibacterially acting polyphenols are not limited to antibiotic therapy *sensu stricto*. The antimicrobial potential of polyphenols enables them to be broadly used in the medical industry. Hospital equipment such as medical devices, implants, chemical reagents, and even

distilled water can be colonized by the same bacteria that threaten humans, or by other strains. Hence, the use of polyphenols with antimicrobial properties in the maintenance of medical equipment could prevent development of infection, as well as directly combat the bacteria-caused disease in patients. Mining of the Scopus database for papers not older that three years gave some interesting findings.

Nanocoating is a promising form of polyphenol usage, making a potential agent to prevent bacterial colonization of medical equipment and accessories. This practical application of polyphenols was investigated using catechins that were distributed on polyamide coatings. Catechins were formulated into special complexes with some rare-earth ions. Later, the possibility of biofilm development by *Pseudomonas aeruginosa* was assessed. The studies confirmed that the coatings covered with catechin nanoparticles did not adhere to bacteria, thus preventing formation of biofilm on the surface of the materials (Liu et al., 2020a).

Dentistry seems to be quite a common area of exploitation of polyphenols for oral treatment and prevention of oral biofilm formation (Furquim Dos Santos Cardoso et al., 2021; Mazur et al., 2021; Schneider-Rayman et al., 2021; Sharifi-Rad et al., 2021). The properties of dental biomaterials have been constantly improving, so that the risk of developing bacterial infections is reduced to the minimum possible. In the studies presented by Guo et al., resveratrol was tested as an additive to dental adhesives. It turned out that the admixture of resveratrol improved the quality of dental adhesives, including limitation of secondary caries development. These results suggest that the addition of resveratrol to dental materials can extend the lifetime of composite fillings (Guo et al., 2021b).

Biomedical sciences are looking for new materials for upgraded implants that will better mimic the physiological characteristics of the organ needed to be replaced or improved in function. Geißler and co-workers conducted studies on polyphenols in the use of bone im-

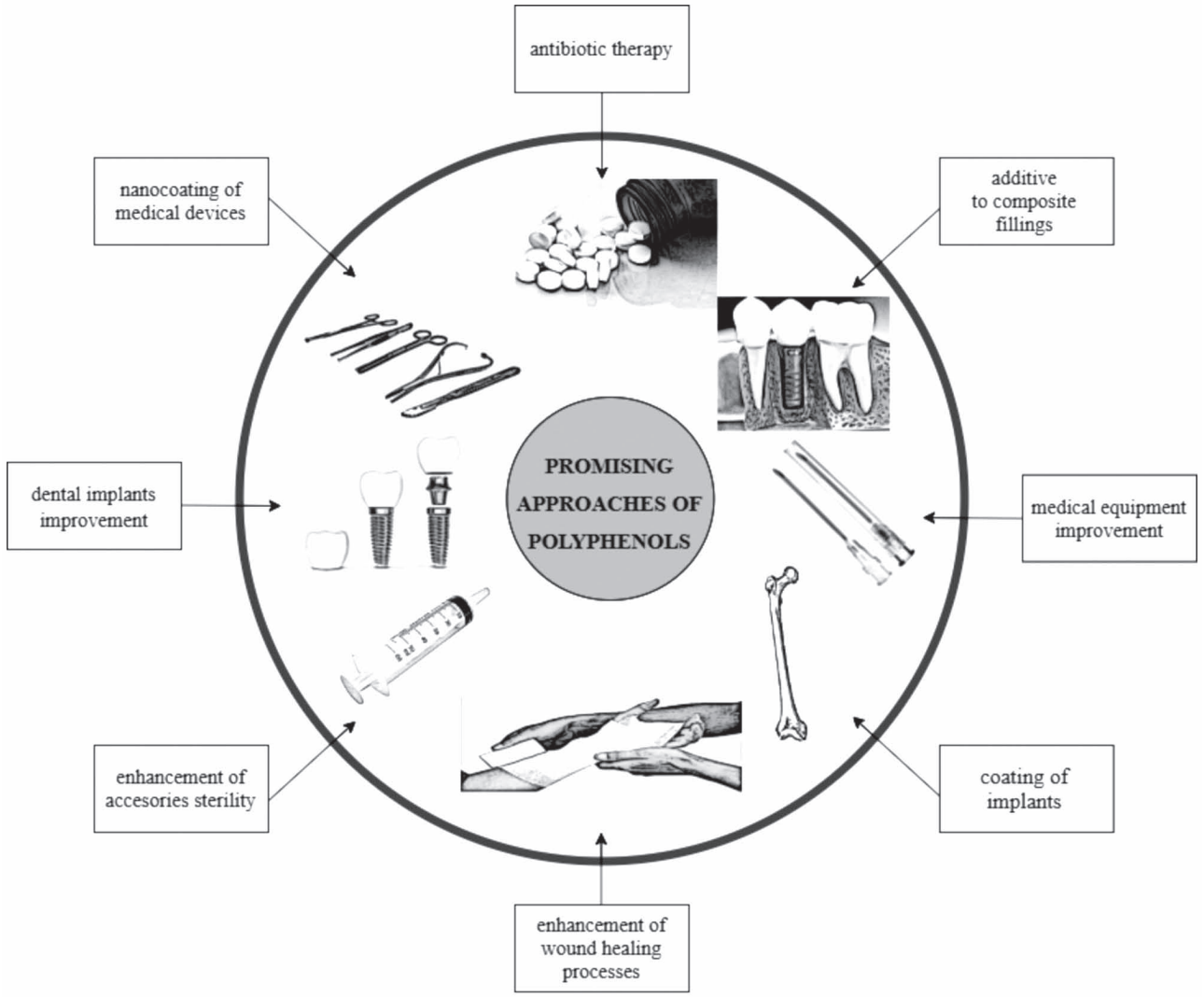

Fig. 4. Promising approaches of polyphenols. Polyphenols may be involved in different areas; these encompass a broad range of antimicrobial activities. Much of them may resolve current problems in the medical and dentistry area of science.

plant improvement. In their approach, the titanium coating of bone implants was additionally covered with polyphenols, such as tannic acid and pyrogallol. Then, human osteoblasts and selected *Staphylococcus epidermidis* and *Staphylococcus aureus* strains were plated on the improved implant surface. The results showed that polyphenol components, when released from the coating located on the titanium implants, inhibited growth of planktonic bacteria. This study suggests that the possibility of using polyphenols in the production of implants represents a versatile functional method that ensures a reduced risk of developing infection, thus providing potential for successful implant applications (Geißler et al., 2019).

Other important scientific and functional interests involve the polyphenolic activity against *Streptococcus mutans*, especially in the context of its methicillin-resistant strains (Miklasińska et al., 2016; Liu et al., 2021; Nuraini et al., 2021; Schneider-Rayman et al., 2021; Souissi et al., 2021; Zayed et al., 2021). The subject of microbial phenomenon *quorum sensing* and its suppression by polyphenols is a very interesting and extensively explored field of science (Abisado et al., 2018; Liu et al., 2020b; Mostafa et al., 2020; Sivasankar et al., 2020). Important findings and approaches include the use of polyphenols as agents supporting antibiotic efficiency (Guo et al., 2021a; Ramata-Stunda et al., 2022) and enhancing wound healing processes (Fabiano et al., 2021; Ekom et al., 2022; Li et al., 2022). A brief graphical summary showing utilization of polyphenols is presented in Fig. 4.

Conclusion

The ability of bacteria to acquire and spread resistance against antibacterial drugs led to the end of the "golden age of antibiotics" in a relatively short period and started the post-antibiotic era that continues to the present day. Unfortunately, the risk related to the phenomenon of antibiotic resistance of bacteria increases every year. Therefore, in order to stop this global medical danger, there is a great need to find or synthesize new substances with antimicrobial properties. Polyphenols are plant-derived compounds that exhibit high potential against bacterial infections. So far, there have been numerous scientific reports describing the antimicrobial properties of polyphenols. The main advantage of these plant secondary metabolites is their mechanism of action, which gives the hope of using polyphenols as individual agents or in combination with antibiotics in the fight against bacteria of various strains. Extended use of polyphenolic compounds may include interference in the formation of biofilm or inhibition of the action of virulent factors. A great goal of the current antibacterial therapy is to find different target points for potential drugs, distant from those of the existing ones. This approach may maintain or even improve the effectiveness of antibacterial therapy. Polyphenols may represent a promising way in this research area, but further studies are needed, for example, to evaluate the doses of polyphenols showing antibiotic activity against specific species of bacteria.

Acknowledgements

The authors wish to thank John Hellewell for his proofreading and suggestions on preparing the manuscript.

Author contributions

Karolina Zapletal (KZ) was principally responsible for the overall concept and design of the study. KZ was also responsible for searching and retrieving publications from databases. KZ and Grzegorz Machnik (GM) performed analysis, selection and interpretation of data. KZ and GM prepared the manuscript and figures. Bogusław Okopień (BO) participated in the processing, and contributed to critical revision of the manuscript, proofreading and supervision. All authors read and approved the final version of the manuscript before sending it to the Editor.

Conflict of interest statement

The authors state that there are no conflicts of interest regarding the publication of this article.

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