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MINIREVIEW

New Antibacterial Therapeutics and Strategies

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Abstract

Studies on new antibacterial therapeutics and strategies are currently being conducted in many microbiological, pharmaceutical and biochemical laboratories. The antibacterial activity of plant-derived compounds as well as silver and gold nanoparticles is the subject of this minireview. The application of photodynamic therapy is also discussed.

Key words: nanoparticles, new antimicrobials, phototherapy, plant compounds

Introduction

The growing antibiotic resistance of pathogenic bacterial species is a serious problem for public health. It can be assumed, that although the bulk of traditional antibiotics can still manage drug-resistant bacteria, many commonly used antibiotics are no longer effective (Levy, 1998; Wright, 2010). This situation is aggravated by a decline in the development of new antibiotics, so recently few substances have appeared in the market (Donadio *et al*., 2010; Högberg *et al.*, 2010). In view of above, the growing interest in the studies aimed at developing new antibacterial therapeutics and strategies is very important not only from medical point of view but also for agriculture and animal breeding (Myles, 2003). The list of such therapeutics is long with stress on the use of bacteriophages as antibacterial agents (Chibani-Chennoufi *et al*., 2004; Górski *et al*., 2009). Many papers cover this problem so it will not be the subject of our publication. The present article describes the antibacterial potency and application of plant-derived compounds, nanoparticles and also the very promising photodynamic therapy.

Plant-derived compounds

Plant-derived compounds of therapeutic value are mostly the secondary plant metabolites (Cowan, 1999). Antibacterial phytochemicals are divided in several categories, this article describe two of them – terpenes and phenolics including polyphenols. As a matter of fact, these compounds cannot be considered a new group of antimicrobials because people have applied plants and plant extract for medical purposes for centuries (Rios and Recio, 2005).

Terpenes. Terpenes, also referred to as isoprenoids, are based on an isoprene structure with general chemical formula $C_{10}H_{16}$ and are biosynthesized from the same basic units, isopentenyl diphosphate, IPP, and its isomer dimethylallyl diphophate, DMAPP (Fig. 1A). Their derivatives containing additional elements, usually oxygen, are called terpenoids. These compounds have a lot of biological functions and are applied as pharmaceuticals, fragrances, colorants. Terpenes constitute a very diverse group of compounds isolated not only from higher plants but also from microorganisms (Sacchettini and Poulter, 1997). Successful approaches in engineering *Escherichia coli* towards biosynthesis of functional isoprenoids were recently described (Harada and Misawa, 2009).

Of special interest are two pentacyclic triterpenoids oleanolic acid (OA) and ursolic acid (UA) and their derivatives containing sugar moieties – glucosides and glucuronides. The chemical formulas of OA/UA are presented in Figure 1B. The antibacterial activity of these compounds was recently reviewed (Wolska *et al*., 2010a). The data described in many papers are contrasting and indicate either a strong or weak

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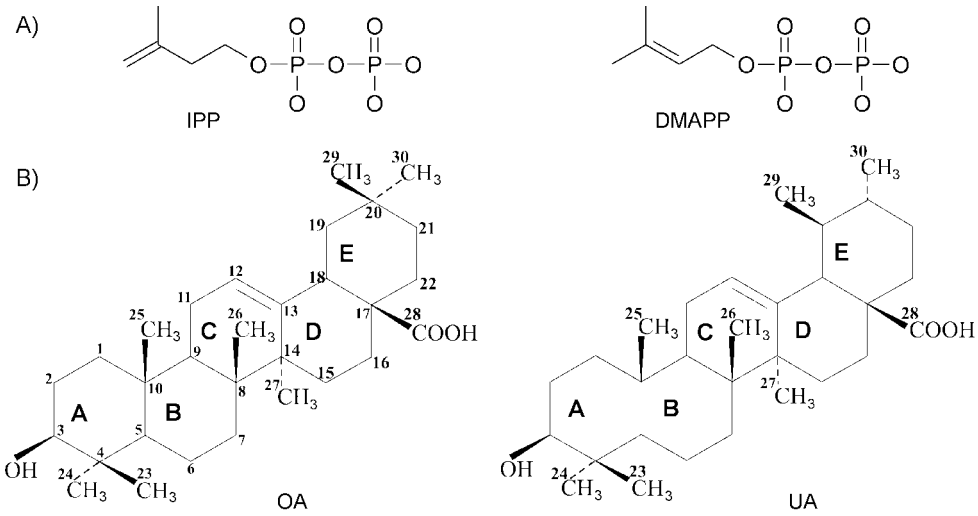

Fig. 1. Chemical formula of IPP and DMAPP (A) and OA and UA (B)

antibacterial effect of OA and UA which likely results from the method of compound purification and the bacterial strain used. A relatively small number of studies has been performed to investigate the basis of OA/UA antibacterial activity. It has been shown that both acids affected peptidoglycan metabolism in *Listeria monocytogenes* (Kurek *et al*., 2010), oleanolic acid cyclodextrins inhibited insoluble glucan synthesis by *Streptococcus mutans* (Kozai *et al*., 1999) and oleane-type triterpenoid, glycyrrhizin acted as a potent *E. coli* heat-labile enterotoxin inhibitor (Chen *et al*., 2009). In turn Ren and coworkers (2005) using microaaray techniques demonstrated that UA caused differential gene expression in *E. coli* and inhibited biofilm formation in several bacterial species. Recently Ge and coworkers (2010) proved the synergistic interactions of OA in combination with isoniazid, rifampicin or ethanbutol against *Mycobacterium tuberculosis*. The third pentacyclic triterpenoid with similar chemical structure – betulic acid (BA) is inactive against a large number of Gram-positive and Gram-negative bacteria. This result illustrates the strong structure-function influence of the antibacterial potential of terpenes (Fontanay *et al*., 2008; Wansi *et al*., 2010).

Other terpenes or terpenoids, such as monoterpenes and sesquiterpenes and their derivatives, also display antimicrobial activity (Ahmed *et al*., 1993; Amaral *et al*., 1998; Habtermariam *et al*., 1993). Many publications describe the antibacterial potential of diterpenoids. It was demonstrated that six diterpenoids isolated from the bark of *Podocarpus nagi*, of which the most abundant compound was totarol, exhibited potent bactericidal activity against Gram-positive bacteria: *Propionobacterium acnes*, *S. mutans* and *Staphylococcus aureus* (Kubo *et al*., 1992). Naturally occurring diterpenoids with a dehydroabietane skeleton are highly bioactive (Savluchinske-Feio *et al*., 2006) *e.g.* isopimaric acid extracted from immature cones of *Pinus nigra* inhibited the growth of multidrug-resistant and methicillin-resistant *Staphylococcus aureus* – MRSA (Smith *et al*., 2005). Antibacterial activity of diterpenoids isolated from hairy roots of *Salvia sclarea* L was also studied. The results showed that abietane diterpenoids: salvisipone, aethopinone, 1-oxoaethopinone and ferrugiol were bacteriostatic as well as bacteriocidal for cultures of *S. aureus* and *S. epidermidis* but not for the Gram-negative species, *E. coli* and *Pseudomonas aeruginosa* (Kuźma *et al*., 2007). Salvipisione and aethiopinone expressed staphylococcal anti-biofilm activity, the reduction in the number of live biofilm cells and changes of biofilm morphology were observed. Both diterpenoids showed synergy with several classes of antibiotics, in case of β-lactams this phenomenon was due to the probable alternation of cell surface hydrophobicity and cell envelopes permeability (Walencka *et al*., 2007). It was also demonstrated that diterpenes inhibited the growth of *M. tuberculosis* (Copp and Pearce, 2007) and recently the Chinese group showed that diterpenes isolated from the genus *Scutellaria* possessed the substantial antimicrobial and antiviral activities (Shang *et al*., 2010).

Phenolics and polyphenols. Phenolics and polyphenols constitute a very large group of chemical compounds. Simple phenols consist of a single substituted phenolic ring, flavones and their derivatives – flavanoids and flavanols are phenolic structures containing one carbonyl group, while quinones contain two carbonyl groups. Tannins are polymeric phenolic substances and coumarins are phenolic compounds made of fused benzene and pyrone rings (Cowan, 1999). The chemical formulas of exemplary phenolic compounds are shown in Figure 2.

The simple phenol, caffeic acid isolated from perennial thorny shrub, *Paliurus spina-christi* was

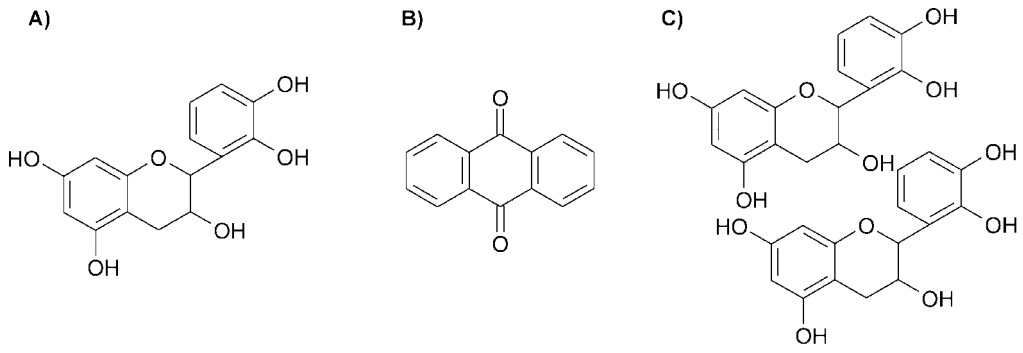

Fig. 2. Chemical formulas of exemplary phenolic compounds with antibacterial activity. Catechin (A), Antraquinone (B), Tannin (C)

effective against Gram-positive bacterial species (Brantner *et al*., 1996). *p*-guanidinethyl and its simple parent phenols were active against *S. aureus*; the simple phenolic species showed lower activity that their calixarene analogues (Mourer *et al*., 2009). Other groups demonstrated that more highly oxidized phenols were also more active probably due to their ability to oxidize of sulfhydryl groups in proteins (Urs and Dunleavy, 1975; Mason and Wasserman, 1987).

Flavones and their derivatives, flavonoids and flavonols, due to their extremely large amount of biological properties, including the antibacterial activity, are placed among the most attractive plant derivatives enriching the current therapy options (Cazarolli *et al.*, 2008). These compounds can form complexes with cell wall and also disrupt bacterial envelopes (Tsuchiya *et al.*, 1996; Nakayama *et al*., 2000). Of special interest are catechins, the subgroup of flavonoids present in the oolong green teas which beneficial effect on human health is well known (Cabrera *et al*., 2006). These compounds are active against food-borne pathogenic bacteria and therefore exert the beneficial effect in gastrointestinal diseases (Friedman, 2007; Dryden *et al*., 2006; Koo and Cho, 2004). It was shown that catechins inhibited *in vitro* the growth of several bacterial species such as *Vibrio cholerae*, *S. mutans* and *Shigella* spp. (Borris, 1996; Sakanaka *et al.*, 1992; Vijaya *et al.*, 1995). Inactivation of specific bacterial enzymes, *V. cholerae* toxin and glucosyltransferases in *S. mutans*, was also reported (Borris, 1996; Nakahara *et al*., 1993). Chrysin, another flavonoid abundant in propolis, also displays substantial antimicrobial activity, preferentially against Gram-positive species, *e.g. Streptococcus sobrinus*, *Enterococcus faecalis and Micrococcus luteus* (Uzel *et al*., 2005). Its activity against certain oral pathogens, such as *Peptostreptococcus anaerobius*, *Peptostreptococcus micros* and *Lactobacillus acidophilus* creates the possibility of propolis application in the treatment of oral cavity diseases (Koru *et al*., 2007). Recently novel C(7) modified chrysin was synthesized. This modification was deliberately designed in order to enhance the antibacterial effect. The biological assays indicated that this compound is a potent inhibitor of beta-ketoacyl-acyl carrier protein synthetase (FabH) in *E. coli* (Suresh Babu *et al*., 2006; Li *et al*., 2009).

A number of papers are concerned with the antibacterial activity of quinones. This activity is based on their high chemical reactivity inactivating the chemical compounds, mainly proteins. Surface-exposed bacterial adhesins, cell wall polypeptides and membrane bound enzymes are their probable targets (Cowan, 1999; Koyama, 2006). Because the redox-potential of these compounds was so essential to their activity, electrochemical techniques along with biochemical and medical knowledge were successfully combined to design and develop therapeutically efficient derivatives (Hillard *et al*., 2008). It should be also mentioned that quinones are strong poisons for bacterial type II topoisomerases – gyrase and TopoIV (Pommier *et al*., 2010). Potent antibacterial activity is attributed to the anthraquinones. It was demonstrated that anthraquinone isolated from *Cassia italica* is bacteriostatic for *Bacillus antracis*, *Corynebacterium pseudodiphtericum* and *P. aeruginosa* (Kazumi *et al*., 1994), in turn hypericin and hyperforin isolated from *Hypericium perforatum* (St. John's wort) were active against Gram-positive species – *S. aureus*, *S. epidermidis*, *E. faecalis* and *Bacillus subtilis* (Males *et al*., 2006; Saddiqe *et al*., 2010). Recently it was shown that the antibacterial activity of anthraquinone derivatives from *Heterophyllaea postulata* against *S. aureus* involved an increase in the level of superoxide anion and singlet molecular oxygen (Comini *et al*., 2010). The antimycobacterial activity of quinones was also described (Copp and Pearce, 2007).

Tannins are divided in two groups – hydrolysable (derivatives of gallic acid) and condensed, also called proanthocyanidins (derived from flavonoid monomers). Among the various health beneficial activities of tannins their antimicrobial activity is often referred to. These compounds are characterized by strong antiperoxidation properties which may be responsible for the inactivation of microbial adhesions, enzymes and

cell envelope transport proteins (Okuda, 2005). The antioxidation activity of tannins is based on their ability to scavenge free radicals, to chelate metals and to inhibit of prooxidative enzymes and lipid peroxidation (Koleckar *et al*., 2008). It was well documented that tannins inhibited the growth of aquatic and foodborne bacteria, so they can be used in food processing to increase the storage time of certain foods (Chung *et al*., 1998). Tannins, especially proanthocyanins, inhibit the growth of uropathogenic *E. coli* (Cimolai and Cimolai, 2007), *S. mutans* (de la Iglesia *et al*., 2010) as well as ruminal bacteria. For the latter it was documented that condensed tannin (sainfoin) inhibited the growth and protease activity of *Butyrivibrio fibrisolvens* A38 and *Streptococcus bovis*. The morphological changes of these species implicated the cell wall as a target of tannin toxicity (Jones *et al*., 1994). In turn, both hydrolysable tannins and proanthocyanidines suppressed the oxacillin-resistance of MRSA (Hatano *et al*., 2005).

The number of publications dealing with antimicrobial activity of yet another group of phenolics, cummarins, is scarce and generally it can be concluded that this property has not been evaluated systematically (Borges *et al*., 2005; Cechinel Filho *et al*., 2009).

Silver and gold nanoparticles

Nanoparticles (NPs) are defined as the clusters of atoms of size ranged from 1 to 100 nm. Their network forms are called nanowires. NPs are characterized by a very large surface area to volume ratio (Rai *et al*., 2009). Copper, zinc, magnesium but especially silver and gold NPs display antibacterial activity and are used for various healthcare, hygiene and personal care purposes and also in water-treatment (Edwards-Jones, 2009; Gurunathan *et al*., 2009). The conventional methods of NPs preparation involves the use of highly toxic chemical agents, however more friendly techniques have also been developed (Baker *et al*., 2005; Wangoo *et al*., 2008). Recently the biological systems for nanoparticles synthesis were elaborated, the process is known as "green synthesis". Sharma and coworkers (2009) described the production of silver nanoparticles (AgNPs) by plant extract containing proteins able to reduce Ag cations. Bacteria and fungi can also be explored for AgNPs production. Their biosynthesis was achieved through reduction of Ag^+ ions by *Klebsiella pneumoniae* (Shahverdi *et al*., 2007), *E. coli* (Gurunathan *et al*., 2009) and *Bacillus licheniformis* (Vaidyanathan *et al*., 2010). Ingle *et al*. (2008) and Gade *et al*. (2008) reported the use of fungi, respectively *Fusarium accuminatum* and *Aspergillus niger*, for the production of AgNPs. In turn He *et al*. (2008) described the synthesis of gold nanowires using an extract of *Rhodopseudomonas capsulata*. It

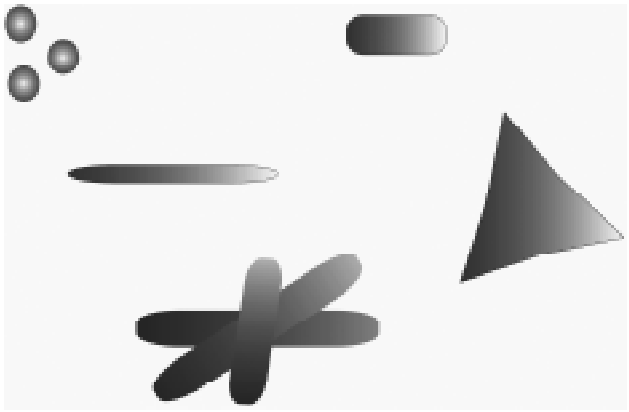

Fig. 3. Different types of silver and gold nanoparticles

should be noted that recently microbial synthesis of selenium, tellurium platinum, thitania, uranitnie and other nanoparticles by bacteria, actinomycetes, fungi, yeasts and viruses was also reported (Narayanan and Sakthivel, 2010).

Silver in ionic form has been known for centuries to cure venereal diseases, bone and perianal abscesses, eye diseases and burns. It was proved that Ag^+ was active against various bacterial species *e.g. E. coli*, *S. aureus*, *Klebsiella* sp. and *Pseudomonas* sp. (Rai *et al*., 2009; Chopra, 2007). AgNPs have an advantage over ionic silver because they show reduced toxicity and 1.4–1.9 times higher antibacterial potential (Ingle *et al*., 2008). Reports pointing to silver toxicity, including arygria and the deposition of silver in liver are rather scarce (Tomi *et al*., 2004; Landsdown, 2006).

The antibacterial effect of AgNPs depends on their size. Smaller-sized particles show stronger antibacterial activity due to their higher surface area to volume ratio (Morones *et al*., 2005). It was also proved that the truncated triangular AgNPs displayed stronger bacteriocidal action against *E. coli* compared with spherical and rod-shaped nanoparticles, suggesting shape-dependent interaction at least with Gram-negative bacteria (Pal *et al*., 2007). Different shapes of silver and gold nanoparticles are shown in Figure 3. Several studies demonstrated that bacterial membranes constituted the main target of AgNPs antibacterial activity, nanoparticles caused their disruption probably due to the production of reactive oxygen species (ROS), including free radicals. Production of ROS is one of the primary mechanisms of nanoparticle toxicity; it may result in oxidative stress, inflammation, and consequent damage not only of membranes but also of DNA and proteins (Singh *et al.* 2008). The model of bacterium – nanoparticle interactions presented by Neal (2008) is based on contact-mediated membrane lipid peroxidation by arising reactive oxygen species. Contact was facilitated by electrostatic forces between nanoparticles and negatively charged cell envelopes. Scanning and transmission electron

microscopy images confirmed the formation of pits in the *E. coli* cell wall and the accumulation of silver in bacterial membranes which increases permeability and therefore results in cell death (Sondi and Salopek-Sondi, 2007). AgNPs may target the bacterial membrane, leading to a dissipation of the proton motive force as shown by proteomic data and biochemical studies. Short exposure of *E. coli* cells to AgNPs resulted in alterations in the expression of several envelope proteins (OmpA, OmpC, OmpF, OppA, MetQ) and heat shock proteins, (IbpA, IbpB and 30S ribosomal subunit) (Lok *et al*., 2006).

AgNPs interaction with membrane sulfur-containing proteins was also proven (Rai *et al*., 2009). Membrane disruption allowed the passage of AgNPs into cytoplasm causing subsequent damage of DNA and other phosphorus containing compounds and impairing the respiratory chain and cell division. The antibacterial activity of AgNPs is enhanced by their decomposition and the release of Ag ions within bacterial cell (Feng *et al*., 2000; Morones *et al*., 2005).

The antibacterial activity of AgNPs was well proven basing on *in vitro* experiments. Activity against MRSA (Panacek *et al*., 2006), *E. coli* (Sondi and Salopek-Sondi, 2007; Morones *et al.*, 2005; Pal *et al*., 2007; Yoon *et al*., 2007), *P. aeruginosa* (Morones *et al*., 2005), *Vibrio cholera* (Morones *et al*., 2005) and *B. subtilis* (Yoon *et al*., 2007) was reported. Kim and coworkers (2007) demonstrated that *E. coli* was inhibited at low concentration of AgNPs whereas the growth-inhibitory effect of *S. aureus* was mild. The efficient antibacterial activity of AgNPs impregnated with bacterial cellulose against *E. coli* and *S. aureus* has also been demonstrated (Castellano *et al*., 2007). Sucrose and soluble and waxy corn starch can also serve as stabilizers (Valodkar *et al.*, 2010). Synergistic antimicrobial activity of AgNPs with penicillin G, amoxicillin, erythromycin, clindamycin and vancomycin against *S. aureus* and *E. coli* was observed (Shahverdi *et al.*, 2007). It was also shown that AgNPs prevent the formation of bacterial biofilms, *e.g*. biofilms formed by *P. aeruginosa* and *S. epidermidis* were inhibited in more than 95% (Kalishwaralal *et al*., 2010). This property made these nanoparticles especially useful in controlling biofilms within the oral cavity (Allaker, 2010). Biofilm formation was inhibited due to the ability of AgNPs to prevent the initial step in biofilm development *i.e*. microbial adhesion to various surfaces (Monteiro *et al*., 2009).

AgNPs are characterized by so many medical and technological applications that they are considered as new antibacterial agents revolutionizing applied medicine. They are used in wounds and ulcers healing, usually in the form of dressings and creams (Cortivo *et al*., 2010; Jun *et al*., 2007). They are also utilized to coat medical devices such as catheters, dentures or surgical masks (Li *et al.*, 2006). Silver, together with copper, is commonly used to inhibit bacterial and fungal growth in chicken farms and in post harvested cleaning of oysters (Singh *et al.*, 2008). AgNPs and other nanoparticles can be used in water filtration and disinfection (Li *et al*., 2008; Jain and Pradeep, 2005) as well in the production of textiles, both non-toxic and possessing antimicrobial properties (Dastjerdi and Montazer, 2010) and in the production of antimicrobial nanopaints (Kumar *et al*., 2008).

Gold nanoparticles (AuNPs) also can be used as antimicrobial agents. In this case the majority of papers describes their application as a tool to deliver other antimicrobials or as a factor enhancing photodynamic destruction of bacteria (Pissuwan *et al*., 2009). AuNPs were very suitable for delivering drugs, including antibiotics; AuNPs conjugates with vancomycin proved to be 50-fold more active that the free antibiotic against *Enterococcus faecium* and *E. faecalis* (Gu, 2003). The AuNPs-ciprofloxacin and aminoglycosidic antibiotics conjugates were also described (Tom *et al*., 2004; Grace and Pandian, 2007). The role of AuNPs was to facilitate the attachment of conjugated antibiotic to bacterium and therefore penetrating of cell wall. However it should be stressed that there is no consensus concerning the efficacy of AuNPs-antibiotic conjugates compared with the same dosage of free antibiotic, *e.g*. Rosemary *et al*. (2006) found that AuNPs enhanced the efficacy of ciprofloxacin against *E. coli* what was not observed for gentamycin (Burygin *et al*., 2009).

AuNPs were also used as stabilizers for various antimicrobial photosensitizers. Four-fold increase of *S. aureus* elimination was observed when toluidine blue O-AuNPs conjugates and methylene blue-AuNPs conjugates were used in photodynamic therapy compared to dyes alone (Gil-Tomás *et al*., 2007; Perni *et al*., 2009). AuNPs enhanced the absorption of light due to their plasmon resonance (Pitsillides *et al*., 2003) which could cause local hyperthermic effect leading to the efficient destruction of *E. coli* irradiated with X-rays (Simon-Deckers *et al*., 2009), *P. aeruginosa* exposed to near-infrared laser (Norman *et al*., 2008) or *S. aureus* irradiated with strong laser light (Zharov *et al*., 2006).

AuNPs are very useful for detection and diagnosis of bacteria even in complex media like blood (Kaittanis *et al*., 2010), this being mainly based on the detection of bacterial DNA by change of color (Elghanian *et al*., 1997). They have been used for fast, accurate and sensitive detection of *Staphylococcus* sp. (Storhoff *et al*., 2004) and *M. tuberculosis* (Baptista *et al.*, 2006; Veigas *et al*., 2010). AuNPs were also applied to improve the sensitivity of bacterial detection methods based on flow cytometry and fluorescence (Zaharov *et al*., 2007; Wang *et al*., 2009).

Natural and synthetic dyes and photodynamic therapy

The antimicrobial effect of natural and synthetic dyes has been known for many decades. Already in the beginning of the last century proflavine, acriflavine, crystal violet and brilliant green were used against bacterial infections, mainly to cure infected wounds (Wainwright, 2008; Wainwright, 2010). Preoperative use of iodine still remains a common practice. Gentian (crystal) violet was shown to be very efficient in the eradication of MRSA from skin lesions (Saji *et al*., 1995). Recently it was shown that the tiazol dye, thioflavin T, exerted a strong inhibitory effect on *S. aureus*, the effect on *E. coli* was less pronounced (Lakatoš, 2010). The list of dyes with antibacterial properties included also pigments synthesized by microorganisms (Wolska *et al.*, 2010b). The pigment produced by *P. aeruginosa* – pyocyanin, due to its unique redox properties, actively eliminated many bacterial species, especially Gram-positive aerobes (Baron and Rove, 1981). In turn violacein extracted from *Chromobacterium violaceum* displayed a potent antileishamanial activity (Leon *et al.*, 2001).

Many dyes can serve as photosensitizers, sometimes called photomicrobial agents, and are applied in photodynamic antimicrobial therapy (PACT). Photosensitizers can be activated by visible light to generate cytotoxic radicals, superoxide radicals and singlet oxygen ½ O_2 which are the reactive oxygen species (ROS). ROS are highly toxic to various type of cells, including bacteria, causing the damage of the outer membrane, cell wall, ribosomes and nucleic acids and thus impairing many cellular functions (for review see Wainwright, 2010; Ryskova *et al.*, 2010). Photosensitizers are usually dyes such as methylene blue (Gad *et al*., 2004), porphyrins (Hamblin *et al*., 2005), crystal violet (Saji *et al.*, 1995), iodocyanine green (Unno *et al.*, 2008) and erytrosine (Wood *et al*., 2006).The latter is of special interest because it can be used for the therapy of oral plaque biofilms (Wood *et al*., 2006). Positively charged (cationic) photosensitizers such as methylene blue and crystal violet act as broad-spectrum antimicrobials, while the negatively charged (anionic) compounds lack efficacy against Gram-negative species (Demidova *et al*., 2005). This is because anionic photosensitizers are not able to penetrate the lipopolysaccharide outer membrane of Gram-negative bacteria. In practice photosensitizers are usually activated by red light and the preferable source of light is low-power lasers (Ryskova *et al*., 2010). The stabilization of various photosensitizers by AuNPs was described in the previous chapter. Beside dyes, also fullerenes which are stable chemical molecules composed of 60 carbon atoms arranged in a soccer ball-shaped structure are proved to be the efficient photosensitizers (Krokosz, 2007).

Photodynamic therapy is used mainly in the treatment of local infections. Its efficacy was proved in healing cutaneous infections *e.g*. poor-healing wounds caused by *Mycobacterium marinum* (Rallis and Koumantaki-Mathioudaki, 2007) and oral microbial related diseases such as periodontitis (Liu *et al*., 2009). It was clinically studied for leishmaniasis (Dai *et al.*, 2009). It should be stressed that photodynamic therapy can be applied in the eradication of antibiotic-resistant pathogens *e.g*. MRSA (Griffiths *et al*., 1997), VRE (Soncin *et al.*, 2002) and *P. aeruginosa* (Minnock *et al.*, 1996) which are life-threat danger in hospitals. Recently it was shown that two water soluble photosensitizers: methylene blue and neutral red enclosed in liposomes gave a stronger antibacterial effect than their free forms (Nisnevitch *et al*., 2010). It should be also noted that photodynamic therapy was applied and found to be efficient in treating lung, stomach and skin tumors (Maisch *et al*., 2005).

Conclusions

The huge and constantly growing amount of papers describing new antibacterial therapeutics reflects an urgent need to find efficient antimicrobials which can be an alternative to antibiotics. Plants and their extracts have been used even in ancient times for medical purposes. Recently, studies are focused on the activity of purified compounds. Trials aimed at resolving the mechanism of their action are also performed. The majority of studies are held *in vitro* but the results of preclinical and clinical trial have also been reported. As it was shown that many plant compounds exert a cytotoxic effect (Zhang *et al*., 2007) efforts have been made to synthesize derivatives with less toxicity and better water solubility (*e.g*. Farina *et al*., 1998; Liu, 2005), which can enhance the possibility of their therapeutic application. Studies on the antibacterial activity of silver and gold nanoparticles are more advanced and also comprise their synergism with commonly used antibiotics and the application of AuNPs in stabilizing photosensitizers used in photodynamic therapy, which is a very proficient new antibacterial strategy.

Considering the enormous scientific effort put in elaborating new antibacterial compounds and strategies, alternative possibilities to cope with bacterial diseases can emerge in the near future.

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