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; Görski 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 diphosphate, 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...
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
microarray 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 inter-
actions of OA in combination with isoniazid, rifampicin
or ethanbutol against Mycobacterium tuberculosis.
The third pentacyclic triterpenoid with similar chemi-
cal 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; Hab.termaria 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 abun-
dant compound was totarol, exhibited potent bacteri-
cidal activity 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).

Phenolics and polyphenols. Phenolics and poly-
phenols constitute a very large group of chemical
compounds. Simple phenols consist of a single sub-
stituted 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, caffic acid isolated from
perennial thorny shrub, Paliurus spina-christi was
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 diterpenes isolated
from hairy roots of Salvia sclarea L was also studied.
The results showed that abietane diterpenoids: salvi-
sipone, aethiopinone, 1-oxoaethiopinone and ferruginol
were bacteriostatic as well as bacteriocidal for cul-
tures of S. aureus and S. epidermidis but not for the
Gram-negative species, E. coli and Pseudomonas
aeruginosa (Kuzma 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 phe-
nomenon was due to the probable alternation of cell
surface hydrophobicity and cell envelopes permeabil-
ity (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).
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 sulphydryl groups in proteins (Urs and Dunleavy, 1975; Mason and Wasserman, 1987).

Flavonoids 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 Hypericum perforatum (St. John’s wort) were active against Gram-positive species – S. aureus, S. epidermidis, E. faecalis and Bacillus subtilis (Males et al., 2006; Saddique 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 antioxidant 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 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, cumarins, 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 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 co-workers (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 acuminatum 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 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 Sakhivel, 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

Fig. 3. Different types of silver and gold nanoparticles
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 (Panceck 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, dressings 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 (Zharov 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). Pre-operative 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 (Lakatos, 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 antileishmanial 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 \( \frac{1}{2} O_2 \) 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 strongly 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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