**Antibacterial properties of snake venom components**

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Received: 15 July 2019 / Accepted: 14 September 2019 / Published online: 21 September 2019
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**Abstract**

An increasing problem in the field of health protection is the emergence of drug-resistant and multi-drug-resistant bacterial strains. They cause a number of infections, including hospital infections, which currently available antibiotics are unable to fight. Therefore, many studies are devoted to the search for new therapeutic agents with bactericidal and bacteriostatic properties. One of the latest concepts is to search for this type of substances among toxins produced by venomous animals. In this approach, however, special attention is paid to snake venom because it contains molecules with antibacterial properties. Thorough investigations have shown that the phospholipases A2 (PLA2) and l-amino acids oxidases (LAAO), as well as fragments of these enzymes, are mainly responsible for the bactericidal properties of snake venoms. Some preliminary research studies also suggest that fragments of three-finger toxins (3FTx) are bactericidal. It has also been proven that some snakes produce antibacterial peptides (AMP) homologous to human defensins and cathelicidins. The presence of these proteins and peptides means that snake venoms continue to be an interesting material for researchers and can be perceived as a promising source of antibacterial agents.

**Keywords** Snake venom · Phospholipases A2 · l-Amino acid oxidases · Antimicrobial properties

**Introduction**

The most important clinical problem in the field of microbiology today is growing resistance to antibiotics in bacteria. According to the WHO, bacterial infections involving multi-drug-resistant (MDR) strains are one of the ten leading causes of death worldwide (Lopez et al. 2006). Moreover, antimicrobial resistance is considered to be one of the greatest threats to human health globally (Walker et al. 2009). Unfortunately, new examples of bacteria with antibiotic resistance appear every year. It is estimated that more than 90% of *Staphylococcus aureus* strains are resistant to β-lactam antibiotics (Panlilio 1992). Such resistance is shown, for example, by already long-known strains like methicillin-resistant *S. aureus* (MRSA) and penicillin-resistant *Streptococcus pneumoniae* (PRSP) (Al Ahmadi et al. 2010). Recent studies have also shown that excessive use of antibiotics, such as vancomycin, may lead to developing vancomycin-intermediate (VISA)/vancomycin-resistant (VRSA) strains, like, for example, in the case of enterococci (Appelbaum 2006; Cázares-Domínguez et al. 2015). Other bacteria such as *Pseudomonas*, *Klebsiella*, *Enterobacter*, *Acinetobacter*, *Salmonella* or *Enterococcus* have also developed several ways to resist antibiotics (Al Ahmadi et al. 2010). It is estimated that 23,000 and 25,000 people die every year in the USA and Europe, respectively, from infections caused by multidrug-resistant bacteria (CDC 2013; Blair et al. 2015). Presently existing and still appearing multiple-resistant strains increase the risk of bacterial infections, which become more and more threatening, as currently, we lack proper tools and drugs to combat them. Recently, many antimicrobials are at various stages of development and phases of clinical trials. However, it is still very clear that the discovery of new, potent antibacterial agents capable of overcoming drug resistance as well as the development of antibacterials with a new mechanism of action remains of the highest priority (Guardabassi and Kruse 2003; Ang et al. 2004; Roos 2004; de Lima et al. 2005; Al Ahmadi et al. 2010; Perumal Samy et al. 2017).
The pharmacological potential of snake venom

The composition of snake venom depends mainly on the species, but also on age, sex or type of food consumed (Koh et al. 2006). However, it should be mentioned that some systematic groups do not contain venomous snakes, e.g., boa or pythons. In some other groups, however, all the species classified there are venomous. Venomous snakes belong to following families: Viperidae (viperids, including vipers and rattle snakes), Elapidae (elapids, including cobras, mambas and taipans), Hydrophidae (sea snakes) and Colubridae (colubrids, although only some of them are venomous) (Gold et al. 2002; Warrell 2010; Burbrink and Crother 2011; Warrell 2019).

Snake venoms are complex mixtures of several families of protein-origin components that can be divided into 4 groups. The dominant are three-finger toxins (3FTx), phospholipases A₂ (PLA₂), snake venom metalloproteases (SVMP) and snake venom serine proteases (SVSP). The second group includes proteins commonly present in the venom, but in much smaller amounts: Kunitz peptides (KUN), Cysteine-Rich Secretory Proteins (CRiSP), the venom, but in much smaller amounts: Kunitz peptides, and Colubridae (colubrids, although only some of them are venomous) (Gold et al. 2002; Warrell 2010; Burbrink and Crother 2011; Warrell 2019).

Snake venoms are known to be a complicated mixture of proteases and metalloproteases in different systematic groups (Tasoulis and Isbister 2017).

The toxins present in the venom exert a variety of biological effects such as neurotoxicity, myotoxicity, cardiotoxicity, hemorrhage, pro- and anti-coagulation, etc. (Perumal Śamy et al. 2014a; Munawar et al. 2018). However, snake venoms as a complex mixture of proteins and peptides can also exhibit a wide range of pharmacological activities and may be used to develop new drugs with high therapeutic value (Koh et al. 2006; Waheed et al. 2017). The classic example in this field are the bradykinin-potentiating peptides (BPP), found in Bothrops jararaca venom, the inhibitors of the somatic angiotensin-converting enzyme (ACE) (Ferreira et al. 1970). On the basis of one of them, teprotide, the first active site-directed inhibitor of ACE was developed, which is currently used to treat human hypertension, namely captopril (Cushman and Ondetti 1991; Plosker and McTavish 1995). Past discoveries and developmental works proved that venom proteins can lead to production of drugs that are in clinical use and commercially generate billions of dollars. Besides the most famous example, captopril, there are others. For example epifibatide is an antiplatelet drug with a cyclic heptapeptide structure based on the three amino acid sequence (Lys-Gly-Asp) found in barbourin, which is a disintegrin from Sistrurus miliarius barbouri venom (Fig. 1). Similar pharmacological profile can be seen in tirofiban, peptidomimetic agent based on the RGD sequence (Arg-Gly-Asp) from echistatin, protein from Echis carinatus venom (Diz-Küçükayay and López 2018). There are also some examples of anticoagulant drugs available on the market namely: Reptilase (Batroxobin from Bothrops atrox), Delibrase (Moojenin from Bothrops moojeni) and Vivostat (serine protease from B. moojeni) (Waheed et al. 2017). Moreover, several venom-based compounds show promising pharmacological potential and currently undergo comprehensive investigation during clinical or preclinical studies. These are: cenderitide (Ichiki et al. 2019), Vipegitide (Lazarovici et al. 2019), antifibatide (Masias and Cataland 2017), vicrostatin (Swenson et al. 2018), DisBa-01 (Danilucci et al. 2019), HCA—hemocoagulase agkistrodon (Li et al. 2018a), RPI-NM, and RPI-78M (Waheed et al. 2017). Also, the group of following compounds were currently withdrawn from the market: alfimeprase—potent fibrinolytic recombinant analog of metalloproteinase from Agkistrodon contortrix contortrix venom previously used for thrombolysis (Jones et al. 2001) and ancord-serine protease from Calloselasma rhodostoma previously used as an anticoagulant agent (Nolan et al. 1976; Waheed et al. 2017).

Snake venoms in drug design and development

Snake venoms are known to be a complicated mixture of proteins and peptides with great potential for drug design and development, which can ultimately lead to their clinical use. Unfortunately, the therapeutic use of peptide-origin drugs is problematic, especially due to their low bioavailability through the oral route, poor permeability, metabolic inactivation, the danger of proteolysis or enzymatic degradation, binding to plasma protein and finally, toxicity (Craik et al. 2013). Presently these limitations are being overcome through various approaches, for example, using antimicrobial peptides (AMP) externally in contact lenses coating.
(Dutta et al. 2014), using biocompatible carriers which enhance bioavailability (Lax and Meenan 2012; Maia et al. 2014) or encapsulation in biodegradable polymers (Anthony and Freda 2009). Snake venom toxins, from small peptides to large proteins, are very interesting, pharmacologically active compounds with wide chemical and functional variability, stability and specificity. They may inspire innovative discoveries including development of research tools or invention of new drugs like antibacterial and antitumor compounds. Currently, it is believed that pharmaceutical and biomedical research should lead to routine use of venom toxins as structural templates for the design and synthesis of novel and efficient therapeutic agents (de Oliveira-Junior et al. 2013; Almeida et al. 2017, 2018).

Currently, hundreds of therapeutic peptides are under development and at different stages of clinical tests (Kaspar and Reichert 2013; Uhlig et al. 2014). Majority of them are involved in cancer: e.g., disintegrins with antiangiogenesis effect or LAAOs inducing apoptosis (Li et al. 2018b) and cardiovascular diseases treatment, besides the examples mentioned in the previous paragraph, also, e.g., natriuretic peptides and ion channel blockers (Koh and Kini 2012). However, there are also peptides tested for pain treatment (e.g., mambalgin from Dendroaspis polylepis venom) (Diochot et al. 2012) and infectious diseases, for example LAAOs from Trimeresurus stejnegeri venom inhibit infection and replication of HIV-1 virus (Zhang et al. 2003) and LAAOs from Bothrops jararaca have antiviral (Dengue virus) and antiprotozoal (trypanocidal and leishmanicidal) activities (Sant’Ana et al. 2008).

The use of venom components for drug discovery is rapidly increasing, though it is still mostly an unrealized prospect due to recurrent technical bottlenecks that represent venom exploration (Lewis and Garcia 2003). It is estimated that although all animal venoms consist of over 40 million proteins and peptides, only a very small fraction of them are known (Escoubas and King 2009). The advent and development of -omic techniques has led to discovery of an increasing number of toxins with known sequences and structures, which are available for biomedical and biotechnological exploitation (King 2011). The future direction of venom research with the use of modern ‘omics’ techniques such as genomics, transcriptomics and proteomics should lead to identification and characterization of new therapeutic molecules from animal venoms. According to the authorities in this field, the key for the search of novel antimicrobial molecules is the characterization of previously unexplored and rare animal venoms, as they may be the new source of antibacterial molecules (Perumal Samy et al. 2017).

The antibiotic potential of snake venom

Antimicrobial agents are used in medicine to treat infections caused by microbes from different classes of pathogenic organisms, namely viruses, protozoa, fungi and
bacteria, including among others, rickettsia, mycoplasma and chlamydia. Among them, bacteria are the largest and most diverse group of pathogenic microorganisms (Rouault 2004). Antimicrobial agents normally used to treat bacterial infections are divided into two groups: bacteriostatics and bactericidal. Bacteriostatic agents arrest the growth of bacteria (e.g., sulphonamides, tetracycline, chloramphenicol), bactericidal agents, on the other hand, kill bacterial cells through disruption of cell wall/membrane function (Chao et al. 2013). The effectiveness of both, existing drugs and venom components, depend on the type of bacteria. For example, the bactericidal activity of Bothrops alternatus venom is higher against Escherichia coli and S. aureus versus Pseudomonas aeruginosa and Enterococcus faecalis (Bustillo et al. 2008).

Recent studies prove that many venoms and venom components produced by different venomous animals show potential antibacterial activity. These include snake (Perumal Samy et al. 2007; Al Ahmadi et al. 2010; Ferreira et al. 2011; Perumal Samy et al. 2014b), spider (Haeberli et al. 2000; Budnik et al. 2004; Kozlov et al. 2006; Benli and Yigit 2008), scorpion (Conde et al. 2000; Torres-Larios et al. 2002), honeybee (EL-Feel et al. 2015; Leandro et al. 2015) and wasp venoms (Jalaei et al. 2014).

The antibiotic potency of snake venom is well known and documented and it is mainly dependent on the venom composition as well as on the specific bacterial types (de Oliveira Junior et al. 2013). The major clinical challenge in developing novel antibiotics is the design of new, less toxic molecules that effectively combat the recent emergence of MDR clinical pathogens such as S. aureus, E. coli and enterococci. Therefore, the majority of research is devoted to attempts to break through resistance of these bacteria. Examples of venom tested for antibacterial properties are summarized in Table 1. Both Viperidae and Elapidae venoms have been tested on numerous occasions and much of the obtained data give very promising results indicating antimicrobial activity in vitro that can rival currently used antibiotics. It has also been noted that viperid venoms exhibit a broader spectrum of antibacterial activity against different bacterial strains (Perumal Samy et al. 2007). However, based on the evidence, elapid venoms and their components may also represent valuable resource for future development of novel human therapeutics useful in fighting with bacterial infections (Birrell et al. 2007).

Snake venom components with antimicrobial properties

Generally, components of snake venoms can be divided into peptide-origin and non-peptide-origin. The first group is discussed in the second paragraph of the article and it may constitute more than 90% of venom’s dry weight, while the second group consists of low molecular weight organic compounds such as carbohydrates, serotonin, histamine, citrate, and nucleosides; and inorganic ions such as calcium, cobalt, magnesium, copper, iron, and potassium. The toxic effect of venom, both in the context of victim bite and potential antibacterial effect, is caused by the components of the first group (Izidoro et al. 2014).

Phospholipases A2

One of the most common groups of enzymes present in both elapid and vipersid venoms are phospholipases A2, which can be divided into basic and acidic PLA2s. Basic PLA2s are usually responsible for major toxic effects induced by snake venoms, while acidic PLA2s tend to have a lower toxicity (Doley et al. 2010). The svPLA2s (snake venom PLA2s) are very interesting enzymes due to their potential for being therapeutic lead molecules with antimicrobial properties against enveloped bacteria, viruses, fungi, parasites, and protozoa (Perumal Samy et al. 2007, 2012). Basic PLA2 from Crotalus durissus terrificus has strong bactericidal effects against both Gram-positive and -negative bacteria (Toyama et al. 2003). An acidic PLA2 from Porthidium nasutum venom has bactericidal activity against S. aureus with MIC (minimal inhibitory concentration) value of 32 µg/ml (Vargas et al. 2012). A myotoxic PLA2 (MjTX-II) from B. moojeni demonstrates antimicrobial activity against E. coli (Okubo et al. 2012). Phospholipase A2 from Crotalus adamanteus, called toxin-II (CaTx-II) has antibacterial properties against S. aureus and Burkholderia pseudomallei and also inhibits Enterobacter aerogenes growth causing disintegration of cell wall, by the generation of pores in membrane. Moreover, it has been shown that this protein can promote wound healing (Perumal Samy et al. 2014b). Membrane permeabilization is also caused by basic myotoxin crotonmine from C. durissus terrificus and, what is interesting, this effect is limited to prokaryotic cells because it acts without any haemolytic effects (Oguiura et al. 2011). New PLA2 from Walterinnesia aegyptia venom has antimicrobial properties against several human pathogenic strains (Ben Bacha et al. 2018) and PLA2 from Pseudonaja textilis is able to inhibit the growth of S. aureus (Perumal Samy et al. 2007) and Burkholderia pseudomallei (Perumal Samy et al. 2006). The mechanism of action in this case is associated with pore formation and membrane damaging effects on the bacterial cell wall without any cytotoxic effects on lung and skin fibroblast cells (Perumal Samy et al. 2014b).

What is also interesting, peptides formed from a svPLA2 fragmentation are also able to interact with lipopolysaccharide (LPS), particularly the lipid A component of S. aureus, causing membrane permeabilization, and exerting bactericidal effects (Perumal Samy et al. 2014b). Cysteine-rich
Table 1  Summary of previously tested venoms for antibacterial properties

| Snake species                      | Bacterial species                           | References                  |
|-----------------------------------|---------------------------------------------|-----------------------------|
| Montivipera bornmuelleri          | Staphylococcus aureus                       | Accary et al. (2014)        |
| Echis carinatus                   | Staphylococcus aureus                       | Al-Ahmadi et al. (2010)     |
| Walterinnesia aegyptia Echis      | Staphylococcus aureus                       | Al-Asmari et al. (2015)     |
| pyramidum Echis coloratus         | Staphylococcus aureus                       |                             |
| Cerastes gasperetii Naja arabica  | Staphylococcus aureus                       |                             |
| Walterinnesia aegyptia Echis      | Enterococcus faecalis                       | Al-Asmari et al. (2015)     |
| pyramidum Echis coloratus         | Escherichia coli                            |                             |
| Naja arabica                      | Pseudomonas aeruginosa                      |                             |
| Bothrops alternatus               | Escherichia coli                            | Bustillo et al. (2008)      |
| Bothrops jararaca                 | Staphylococcus aureus                       | Ferreira et al. (2011)      |
| Calloselasma rhodostoma           | Staphylococcus epidermidis                  | Ferreira et al. (2011)      |
| Bothrops atrox                    | Staphylococcus aureus                       |                             |
| Vipera ammodytes                  | Proteus vulgaris                            | Iğci et al. (2016)          |
| Montivipera bornmuelleri          | Salmonella enteritidis                      | Jaoudeh et al. (2017)       |
| Montivipera latifii               | Bacillus subtilis                           | Moridikia et al. (2018)     |
| Crotalus adamanteus              | Burkholderia pseudomallei                   | Perumal Samy et al. (2006)  |
| Daboia russellii russellii        | Staphylococcus aureus                       |                             |
| Pseudechis australis              |                                             |                             |
| Pseudechis guttata                |                                             |                             |
| Agkistrodon halyi                 |                                             |                             |
| Bitis rhinoceros                  | Staphylococcus aureus                       | Perumal Samy et al. (2007)  |
| Daboia russellii russellii        | Staphylococcus aureus                       |                             |
| Echis carinatus                   |                                             |                             |
| Bitis rhinoceros                  |                                             |                             |
| Bitis arietans                    |                                             |                             |
| Pseudechis australis              |                                             |                             |
| Naja naja naja                    |                                             |                             |
| Ophiophagus hannah                | Staphylococcus aureus                       | Rangsinpanurat et al. (2019) |
| Naja naja                         | Escherichia coli                            | Sachidananda et al. (2007)  |
| Pseudomonas aeruginosa Vibrio cholerae |                             |                             |
| Staphylococcus aureus Bacillus subtilis |                                             |                             |
| Calloselasma rhodostoma           | Staphylococcus aureus                       | San et al. (2010)           |
| Ophiophagus hannah                |                                             |                             |
| Bitis arietans                    | Staphylococcus aureus                       | Shebl et al. (2012)         |
| Pseudechis australis              |                                             |                             |
| Cerastes cerastes                 |                                             |                             |
| Naja nigricollis                  |                                             |                             |
| Naja naja naja                    |                                             |                             |
| Vipera lebetina                   |                                             |                             |
| Echis carinatus                   |                                             |                             |
| Naja nigricollis                  | Pseudomonas aeruginosa                      | Shebl et al. (2012)         |
| Naja naja naja                    |                                             |                             |
AMPs in particular may have a broad spectrum of antimicrobial properties. They are characterized by flexibility of structure and positive charge, which are essential for the enrichment of antibacterial activity caused by hydrophobic attraction to bacterial membrane with negatively charged components (Perumal Samy et al. 2017). Different cationic peptides derived from svPLA$_2$s from *Bothrops asper* present antimicrobial activity against *Klebsiella pneumoniae*, fight peritonitis induced by *Salmonella enterica* in mice and cause membrane permeabilization of *S. aureus* (Santamaria et al. 2005). But what is most important, these peptides, which are composed of 10- to 22-odd amino acids, derived from the carboxy terminus of the svPLA$_2$s, are less toxic for eukaryotic cells and more bactericidal than the parent molecules. That is why this type of natural peptides and others may become a base for novel drugs design and lead to the production of new drugs with potential therapeutic value in the near future (White 2000; Koh et al. 2006).

Among PLA$_2$ family, there is a subgroup which can induce tissue damage by mechanisms independent of catalysis. These proteins have a single mutation, changing aspartate residue at position 49 for a lysine residue, and are called Lys49 PLA$_2$s. This substitution prevents the coordination of Ca$^{2+}$ ions in the binding loop, leading to loss of enzymatic activity (Delatorre et al. 2011). Although they do not hydrolyze membrane phospholipids, they have antimicrobial activity against a variety of pathogenic microorganisms (Páramo et al. 1998; Stábeli et al. 2006). It is believed that not a catalytic reaction but the distinctive primary structure consisting of a combination of hydrophobic and cationic residues in the C-terminal region of the molecule is responsible for antimicrobial activity by the destabilization and perturbation of biological membranes (Díaz et al. 1991, 2001). Several synthetic peptides were designed, based on such C-terminal sequence of 13 amino acids from *B. asper* myotoxin II, which is a homolog of Lys49 PLA$_2$ (Fig. 2). In fact, one of

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**Table 1** (continued)

| Snake species          | Bacterial species         | References          |
|-----------------------|---------------------------|---------------------|
| *Pseudechis australis* | *Escherichia coli*        | Shebl et al. (2012) |
| *Cerastes cerastes*   |                           |                     |
| *Naja nigricollis*    |                           |                     |
| *Naja naja naja*      |                           |                     |
| *Vipera lebetina*     |                           |                     |
| *Echis carinatus*     |                           |                     |
| *Pseudechis australis*| *Salmonella typhimurium*  | Shebl et al. (2012) |
| *Cerastes cerastes*   |                           |                     |
| *Naja naja naja*      |                           |                     |
| *Montivipera xanthina*| *Staphylococcus aureus*   | Yalcın et al. (2013) |

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**Fig. 2** Different representations of the monomer of myotoxin II from *B. asper* (PDB: 1CLP; Chain: A). **a** Ribbon visualization of secondary structures of MTX-II (Lys49—in green; C-terminal sequence with bactericidal activity—in red). **b** Surface visualization of MTX-II with Coulombic Surface Coloring (areas with high electron density, which therefore are more negative are blue; white surfaces is neutral, while red color indicates regions with a positive charge). The figure shows that 13 amino acids AMP from myotoxin II has visible cationic nature, which is perceived as important for its overall bactericidal activity (Chimera software)
the derivatives exhibit very high bactericidal, fungicidal and even antitumor activity with low toxicity towards eukaryotic cells (Won and Ianoul 2009). Small peptides designed on the base of primary structure of Lys49 phospholipase A2, namely CoaTx-II, from Crotalus oreganus abyssus have antibacterial effect against drug-resistant clinical isolates. It was proven that presence of charged and aromatic amino acids plays an important role in interaction of peptides with bacterial cell membrane (Almeida et al. 2018). The antibacterial evaluation of LmutTX, Lys49 PLA2 from Lachesis muta muta snake venom and synthetic peptides designed on its base show promising activity against Gram-negative and Gram-positive bacteria (Diniz-Sousa et al. 2018). Also other C-terminal, cationic peptides derived from Lys49 PLA2s have been evaluated for their microbicidal and anti-tumor potential (Páramo et al. 1998; Murillo et al. 2007; Costa et al. 2008), presenting promising results. Furthermore, the synthetic peptides show high specificity, potent action at low dose, low immunogenicity, high diffusion to tissues, and relatively easy chemical synthesis with the possibility of modifications, such as the use of α-amino acids or cyclization. All these advantages make synthetic peptides, developed on the base of snake venom proteins, a very promising alternative to traditional drugs (Almeida et al. 2018).

l-Amino acid oxidases

The second major group of venom enzymes responsible for antimicrobial properties is l-amino acid oxidases (LAAO). They are usually homodimeric proteins with covalently linked cofactors (FAD or FMN), however, their structures, molecular masses, and isoelectric points can be significantly different. Concentration of snake venom LAAOs varies between systematic groups and affects venom toxicity and its color. Those enzymes catalyze the oxidative deamination of hydrophobic and aromatic amino acids in a wide range of pHs and temperatures. In the first step of the reaction the amino acid substrate is oxidized to an imino acid, with a simultaneous reduction of the cofactor. In the second step the imino acid undergoes nonenzymatic hydrolysis, yielding α-keto acid and ammonia. In order for the next reaction to occur, it is necessary to close the catalytic cycle by regenerating the cofactor. Reoxidizing of cofactor takes place in the presence of molecular oxygen and thus generates hydrogen peroxide. It is believed that the production of hydrogen peroxide opens perspectives for new applications of these enzymes as bactericidal, antiviral, and antitumor agents, making them a promising biotechnological agent. In prey’s body they induce changes in platelet function, which cause local effects on plasma clotting disorders among other things. But in vitro, LAAOs also trigger apoptosis in various cell lines and show antimicrobial and antiparasitic activity (Izidoro et al. 2014).

Bactericidal effect of snake venom l-amino acid oxidases was reported in the case of several species of both viperids (e.g., Ciscotto et al. 2009; Costa Torres et al. 2010; Vargas et al. 2013) and elapids (e.g., Samel et al. 2008; Lee et al. 2011). Generally, snake venom LAAs exhibit various levels of antibacterial activity against different bacteria strains. l-Amino acid oxidase from P. australis venom is 17.5 times more effective than tetracycline against Aeromonas hydrophila on a molar basis (Stiles et al. 1999). The venom of Bothrops leucurus inhibits S. aureus growth in a dose-dependent manner, with a MIC of 25 μg/ml. LAAs from C. adamanteus and B. asper exert antibacterial activity against S. aureus and Proteus mirabilis same as svLAAO from Bothrops venoms (Tempone et al. 2001; Izidoro et al. 2006; Costa Torres et al. 2010). Another LAAs from Bothrops pirajai controls the growth of Pseudomonas aeruginosa and Escherichia coli (Izidoro et al. 2006). And as in the case of PLA2s, also small fragments of LAAO show enhanced antimicrobial activity. These small peptides could be promising candidates in the new antibiotics design (Okubo et al. 2012).

There are at least two hypotheses about antibacterial activity of LAAs. The first is related to the oxidized form of the cofactor of the enzyme (FAD or FMN). This cofactor interacts with l-amino acids which can then act on nucleic acids, proteins, and the plasma membrane (Izidoro et al. 2014). The second involves hydrogen peroxide which, after interaction with the bacterial membrane, can provoke lipoperoxidation (Toyama et al. 2006), DNA fragmentation (Braga et al. 2008), and in consequence cell death. It is also probable that LAAO can directly oxidize amino acids in proteins (Ande et al. 2008). Generally it is believed that the most probable mechanism of bactericidal activity of LAAs involves oxidative stress in the bacteria cell, triggering disorganization and permeabilization of the plasma membrane and finally death of the cell, all caused by presence of hydrogen peroxide in the reaction medium (Izidoro et al. 2014).

Antimicrobial peptides

Staphylococcus aureus and the coagulase-negative S. epidermidis, colonizing the nose and skin, are the most common commensal bacteria causing infections in humans and other mammals. The infection develops only when the protective layer of the human epithelium is breached and mechanisms of host immunity fail. These mechanisms include antimicrobial peptides (AMP) present on the skin and in the sweat. They are the first line of innate immune defenses on the human skin and also form part of the mechanisms by which bacteria are eliminated in the neutrophil phagosome after phagocytosis. AMPs in humans belong to two major groups: defensins and cathelicidins and many of them are active against staphylococci (Joo and Otto 2015).
Similarly to humans, other animals including snakes, produce small cationic antimicrobial peptides (cAMP) called cathelicidins. These peptides have a broad-spectrum of antimicrobial activity against a wide variety of bacteria, enveloped viruses, and fungi (Perumal Samy et al. 2017). Transcriptomic analyses of venom glands of several species (Naja atra, Bungarus fasciatus and Ophiophagus hannah) reveal that snakes’ cathelicidins are highly homologous with AMPs found in lysosomes of cells in the immune system and have strong antibacterial properties (Wang et al. 2008, 2011; Zhao et al. 2008). BF-30, cathelicidin-type peptide derived from B. fasciatus is very effective against diverse antibiotic-resistant bacteria, including those that cause wounds (MRSA) (Chen et al. 2011a). It was shown that it reduces number of bacteria at the wound, but also prevents inflammation and accelerates wound healing (Zhou et al. 2011; Du et al. 2015). Cathelicidin (OH-CATH) from Ophiophagus hannah and its analogs exert strong antibacterial and weak hemolytic activity. They are very effective against Acinetobacter spp., including multi-drug-resistant Acinetobacter baumanii (MRAB) and methicillin-resistant Staphylococcus aureus (MRSA) and their effectiveness is higher than that of the 9 routinely used antibiotics (Zhao et al. 2018).

Other proteins

PLA₂s, LAAOs and AMP are the most widely described groups of proteins with antibacterial properties. But there are also single descriptions of peptides and proteins from other groups, which are very promising and open the way to completely new discoveries. Most of antibacterial peptides act by binding, interacting and finally disrupting the lipid plasma membrane. For example, toxin gamma from cobra Naja nigricollis, belonging to three-finger toxin (3FTx) family, increases membrane permeability of S. aureus (Gram-positive) and E. coli (Gram-negative) bacteria which leads to the bactericidal effects of this protein. The direct molecular activity of this protein is binding to the major membrane constituents for Gram-negative and positive bacteria, lipopolysaccharide (LPS) and lipoteichoic acid (LTA), respectively. Destabilization of LPS layer and inhibition of LTA biosynthesis causes bactericidal effects (Chen et al. 2011c). Another 3FTx example—cardiotoxin 3 from Naja naja atra—has the same mechanism of action, but its activity is greater against S. aureus than against E. coli (Chen et al. 2011b). Different venom peptides and proteins interact with bacteria membrane components by electrostatic and ionic interaction. It was observed that most of these toxins have positive molecular net charge and are able to bind with anionic and zwitterionic phospholipid particles. This mechanism of action is distinctive for other 3FTxs, namely cardiotoxins from N. naja atra venom (Kao et al. 2009). On the basis of N. naja atra cardiotoxin 1 (CTX-1), also belonging to the three-finger toxins family, a series of small peptides was designed. The developed peptides consist of sequences that normally build the tip and subsequent β-strand of the first “finger” of this toxin. Thanks to that, new peptides had microbicidal activity towards strains of Gram-positive and Gram-negative bacteria of original protein with the lack of general toxicity (Fig. 3) (Sala et al. 2018).

Another example of an interesting protein is omwaprin originating from Oxyuranus microlepidotus venom. It is an acidic protein belonging to the warprin family (whey acidic proteins) and it has selective antibacterial properties against Gram-positive bacteria. Its action is based on damaging of the cell membrane of bacteria, which in consequence leads to the leakage of cell contents and cell death. Interestingly,
this protein does not damage human cells, which has been proven in tests on erythrocytes (Nair et al. 2007).

Similar to 3FTxs and wapris, C-type lectin-like proteins are an example of venom components without enzymatic activity. Representatives of this group often show contradictory actions: some induce platelet aggregation and agglutination, while others inhibit this effect. Both purified lectins, such as the one from Bothrops leucurus venom, namely BIL, and lectin homologs, have antimicrobial properties. Mentioned BIL protein from B. leucurus is effective against Staphylococcus aureus, Enterococcus faecalis and Bacillus subtilis (Nunes Edos et al. 2011) and the protein from Bothrops jararacussu acts against Staphylococcus aureus (Klein et al. 2015) whereas homologs of convulxin from Crotalus durissus terrificus decrease the growth of Xanthomonas axonopodis and Clavibacter michiganensis michiganensis (Rádis-Baptista et al. 2006).

A final example of a venom component with antibacterial properties is enzyme AHM from Agkistrodon halys belonging to metalloproteinase family. This protein is very effective against Proteus vulgaris, Proteus mirabilis, Staphylococcus aureus and multi-drug resistant Burkholderia pseudomallei. The mechanism of action is associated with damage to the membranes, wrinkling of cell surfaces, leakage of cell contents and formation of vesicles on cell surfaces, with the consequence that the membrane and wall lose their integrity (Perumal Samy et al. 2008).

Conclusions

In the era of great threat posed by antibiotic-resistant strains of bacteria, we face a great challenge which is to develop modern methods of antibacterial therapies. One of the promising trends is the search for compounds with antibacterial potential among venom components. It has been repeatedly proven that both whole snake venom and its individual components, or even their fragments, have the desired properties and are therefore a potential source of new antibiotics. This approach is all the more promising as there are known examples of the development of effective drugs based on proteins and peptides derived from snake venom.

Moreover, much attention should be devoted to understanding the different mechanisms responsible for the antibacterial activity of venom-based drugs. This will certainly enable finding new promising drug templates as well as optimizing existing structures. Therefore, the identification of new venom-origin agents, combined with alternative routes of administration, developed in recent years, make them a very promising line of research with great potential for the future. With increased approval of peptide-based drugs and advances in peptide-associated technologies, they are becoming more and more medically significant.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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