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LL-37: Review of antimicrobial profile against sensitive and antibiotic-resistant human bacterial pathogens

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Abstract

Background: By the development of drug-resistant bacterial infections, the world is rapidly heading towards the post-antibiotic era. Antimicrobial peptides are highly potential to be used as a promising alternative to antibiotics. One of the most widely known members of this group is a cationic peptide with an alpha-helical structure, called LL-37, naturally produced by many human cells. The aim of this study was the quantitative determination of the antimicrobial profile of LL-37 against human pathogens.

Methods: All articles in which the antimicrobial activity of LL-37 was evaluated quantitatively were selected and assessed using the Google Scholar search engine and three databases of Scopus, Web of Science, and PubMed.

Results: LL-37 was able to combat a wide range of resistant and sensitive bacterial pathogens which classified into three groups. 1. Gram-positive: at least one of the species in the genus of *Staphylococcus*, *Streptococcus*, *Enterococcus*, *Clostridium*, *Listeria*, *Nocardia*, *Bacillus*, *Aggregatibacter*, *Peptostreptococcus*, *Capnocytophaga*, and *Actinomyces*. 2. Gram-negative: at least one of the species in the genus of *Acinetobacter*, *Pseudomonas*, *Escherichia*, *Salmonella*, *Klebsiella*, *Yersinia*, *Vibrio*, *Neisseria*, *Moraxella*, *Haemophilus*, *Porphyromonas*, *Helicobacter*, *Campylobacter*, *Fusobacterium*, *Prevotella*, *Eikenella*, *Tannerella*, *Burkholderia*, and *Stenotrophomonas*. 3. Other bacterial pathogens (non-detectable or poor results of gram-staining): at least one of the species in the genus *Leptospira*, *Borrelia*, *Treponema*, *Mycoplasma*, *Ureaplasma*, and *Mycobacterium*.

Conclusion: Due to the broad-spectrum activity, ability to combat drug-resistant bacterial pathogens, and having a human source, LL-37 could be an appropriate candidate for research, development, and production of novel antimicrobial drugs based on antimicrobial peptides.

Keywords: Antimicrobial peptide; LL-37; Bacteria; Resistance

Background

Microbial infections have been one of the main causes of death in humans throughout history (Rasch 2019). Since about 70 years ago, weapons were developed to fight microbial infections. The discovery of antibiotics greatly reduced the mortality of microbial pathogens (Nicolaou and Rigol 2018). Due to the excessive use of antibiotics in recent years, resistant bacteria are being increased (Khaledi et al. 2016; Esmaeili et al. 2019). Evidence suggests that the world is rapidly moving toward the post-antibiotic era and many health organizations considered this as a ticking time bomb (Ribeiro da Cunha et al. 2019; Krishnamurthy 2018; Organization 2018).

The fear of returning to the era in which the human could not combat infectious disease, have forced the researchers to discover and develop alternative antimicrobial agents (Allen, Mulvihill, and Hiscock 2019; Safdari et al. 2014). Antimicrobial peptides (AMPs) are one of the agents with high potential for research and investment in this field (Neshani, Zare, Akbari Eidgahi, Khaledi, et al. 2019).

AMPs are usually composed of less than 50 amino acids with broad-spectrum antimicrobial activity (Wang, Li, and Wang 2015). Many of these peptides were discovered when the scientists observed antimicrobial properties in some body fluids and secretions of living organisms. Therefore, natural AMPs are considered as an important part of the innate immunity of organisms (Zharkova et al. 2019; Neshani, Zare, Akbari Eidgahi, Hooshyar Chichaklu, et al. 2019) However, with the progression of computer science in drug manufacturing, many synthetic AMPs were also designed (Torres, de la Fuente-Nunez, and Fuente-nunez 2019). According to the antimicrobial peptide database (APD), 3128 AMPs are registered up to now (2019.09.16) (Wang, Li, and Wang 2015).

Cathelicidins are a family of natural AMPs which have attracted considerable attention from the researchers due to their effective role in innate immunity (Scheenstra et al. 2019). Human cathelicidin is a member of this family that is converted to the LL-37 multifunctional AMP after processing. LL-37 (LLGDFFRKSKEKIGKEFKRIVQRIKDFRLRNLVPRTES) has a secondary alpha-helical and amphipathic structure with the strong charge of +6 at a physiological pH (Fabisiak, Murawska, and Fichna 2016). Although this peptide was first discovered in leucocytes and testis, it was found that many other human cells were able to produce that. Typically, this peptide is highly expressed during acute inflammation (Kahlenberg and Kaplan 2013; Fabisiak, Murawska, and Fichna 2016).

Several studies have been conducted on LL-37 and the antimicrobial effects proved on a wide range of microbes (Fabisiak, Murawska, and Fichna 2016). In addition to the antimicrobial activity, this peptide has other effects including immunomodulatory (Zsila, Kohut, and Beke-Somfai 2019), wound healing (Carretero et al. 2008), angiogenesis (Koczulla et al. 2003), chemotaxis (Agerberth et al. 2000), and high-affinity binding to bacterial LPS (neutralizing the inflammatory effects of LPS) (Ahmad et al. 2019).

Although the antimicrobial profile of many antibiotics (Woldemariam et al. 2019; Van et al. 2019; Patel et al. 2019) and other antimicrobial agents (Ochwoto et al. 2017) in exposure to

bacterial pathogens have been determined so far, no comprehensive efforts have been made for AMPs till now. Therefore, this review aimed to investigate the studies on antimicrobial effects of LL-37 as one of the famous available AMPs and the antimicrobial profile was provided in tables against the bacterial pathogens.

Methods

The search protocol was performed in two steps. First, important bacterial pathogens were extracted from the book Jawetz, Melnick, Adelberg Medical Microbiology (Brooks et al. 2015). Then, studies which simultaneously included the bacteria of the previous step and LL-37 AMP were selected using the Google Scholar search engine and three databases of Scopus, Web of Science, and PubMed. It should be noted that only the articles containing quantitative antimicrobial effect included in our study.

The search formula LL-37 [All Fields] AND ("selected bacteria" [MeSH Terms] OR "selected bacteria" [All Fields]) was used for PubMed. The search formulas for Scopus and Web of science were similar to the PubMed. In addition, the cited studies to our selected articles and references were reviewed.

Results

A total of 75 studies were found with the direct or indirect investigation of LL-37 antimicrobial effects. 63 studies had quantitative reports based on minimum inhibitory concentration (MIC), minimum bactericidal concentration (MBC), the half maximal inhibitory concentration (IC_{50}), The 99% effective dose (ED_{99}) and 90% lethal dose (LD_{90}), The concentrations giving 50% growth inhibition (GI_{50}) and the 50% effective concentration (EC_{50}) that included in our review. The results are classified into three groups of gram-positive bacteria with 29 studies (Table 1), gram-negative bacteria with 38 studies (Table 2), and other bacterial pathogens (non-detectable or poor results of gram-staining) with 7 studies (Table 3).

Discussion

The LL-37 cationic AMP is a part of human innate immunity and plays an active role against pathogens during the initial invasion and spread of microbial infection (Fabisiak, Murawska, and Fichna 2016). Although there might be still unknown mechanisms for the antimicrobial activity of this peptide, two mechanisms of membrane attack (de Miguel Catalina et al. 2019), and regulation of host immunity (Zsila, Kohut, and Beke-Somfai 2019), are currently among the most well-known methods. The strong positive charge of this peptide results in the absorption and penetration into the bacterial membrane containing a negative charge. Since eukaryotes contain less negative surface charge, they are less sensitive to the toxicity of peptide (Li et al. 2017). When a critical concentration of LL-37 molecules accumulate on the

bacterial surface, alteration of membrane structure results in the formation of channels or aqueous pores, leading to hypoosmotic lysis of bacteria and death (Xhindoli et al. 2016; Gutsmann et al. 2001).

In this study, the antimicrobial profile of LL-37 against bacterial pathogens was provided in three tables according to the investigated studies. Based on the results, LL-37 is able to kill a wide range of bacterial pathogens. A large number of studies were related to bacteria in which the drug resistance is a serious problem such as *Acinetobacter baumannii*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, Enterococci, and *Escherichia coli*. Although the antimicrobial power of LL-37 is lower in exposure to drug-resistant bacteria, it can effectively inhibit the growth of resistant pathogens in higher concentration. However, it should be noted that the inhibition power of LL-37 was higher against vancomycin-resistant *Enterococcus faecalis* than the sensitive form. Also, there was not any significant difference in the bactericidal activity of LL-37 between pandrug-resistant (PDR) *A. baumannii* and drug-sensitive strains.

An important note we noticed during the data collection was the lack of coordination in the quantitative results of some articles published in reliable journals. As in a few articles, the reported antimicrobial results were different despite the identical bacterial strains. This problem occurs due to the lack of comprehensive reference containing the antimicrobial profile of LL-37.

Conclusion:

Since the study on AMPs is increasingly developed and some of these peptides are at clinical trial step to be introduced as novel antimicrobial drugs (Costa et al. 2019; Neshani, Tanhaeian, et al. 2019), it is suggested that studies be performed by the health organizations for the determination of antimicrobial profile of AMPs.

Abbreviations:

AMPs: antimicrobial peptides **APD:** antimicrobial peptide database

MIC: minimum inhibitory concentration **MBC:** minimum bactericidal concentration

IC₅₀: half maximal inhibitory concentration **ED₉₉:** 99% effective dose

LD₉₀: 90% lethal dose **GI₅₀:** 50% growth inhibition

EC₅₀: 50% effective Concentration **PDR:** pandrug-resistant

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

AN, HZ, MRA, KG conceived and designed the study. All authors contributed to the study protocol and analyzed the data. AN, HZ, KG drafted the manuscript, critically reviewed it and prepared the final version. All authors read and approved the final manuscript.

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Table 1. Quantitative antimicrobial activity of LL-37 against gram-positive human bacterial pathogens (the values are in µg/mL)

Organism	MIC	MBC	Other methods	Reference
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<i>Staphylococcus aureus</i>	Standard strains	14->128	-	-	(Pacor et al. 2018; Shurko et al. 2018; de Miguel Catalina et al. 2019; Leszczyńska et al. 2013; Hai et al. 2012; Geitani et al. 2019)
	Clinical isolates	>128-143.7	-	-	(Geitani et al. 2019; Kang, Dietz, and Li 2019)
	MRSA	>128 -256	-	-	(Zharkova et al. 2019; Shurko et al. 2018; Geitani et al. 2019; Rajasekaran et al. 2019)
	VISA	64	-	-	(Shurko et al. 2018)
<i>Staphylococcus epidermidis</i>	Standard strains	36-53.9	-	-	(Hai et al. 2012; de Miguel Catalina et al. 2019)
	Clinical isolates	56-66	-	-	(Martínez-García et al. 2019; Leszczyńska et al. 2013)
<i>Enterococcus faecalis</i>	Susceptible strains	24.9-32	56	-	(Bals et al. 1998; Leszczyńska et al. 2013; Krahulec et al. 2010)
	VRE standard strains	71.8-1000	2000	-	(Rajasekaran et al. 2019; Caiaffa et al. 2017)
	Clinical isolates	5->20	-	-	(Lieberman 2018)
<i>Enterococcus faecium</i>	Standard strains	35.9-143.7	-	-	(Sakoulas et al. 2015)
	VRE standard strains	9	-	-	(Sakoulas et al.

					2015)
<i>Streptococcus</i> spp.	Group A	4.5-71.8	-	-	(Dorschner et al. 2001; Leszczyńska et al. 2013)
	Group B	143.7- >143.7	-	-	(Dorschner et al. 2001)
	Group c	71.8	-	-	(Dorschner et al. 2001)
	<i>S.salivarius</i> (ATCC 13419)	14-62.5	-	-	(Leszczyńska et al. 2013; Ji et al. 2007)
	<i>S.sanguinis</i> (ATCC 10556)	14	28	IC_{50} 2.5	(Leszczyńska et al. 2013; Bruce et al. 2018)
	<i>S.gordonii</i>	31.3 - > 125	-	-	(Ji et al. 2007)
	<i>S.mutans</i>	28-250	28-1000	IC_{50} 22.4	(Caiaffa et al. 2017; Leszczyńska et al. 2013; Bruce et al. 2018)
<i>Clostridium</i> spp.	<i>S.pneumoniae</i>	14	14	IC_{50} 1.5-7.2	(Leszczyńska et al. 2013; Bruce et al. 2018)
	<i>C.difficile</i>	8-48	-	-	(Sarker et al. 2014; Mcquade et al. 2012; Woods et al. 2018)
	<i>C.perfringens</i> clinical	128	256	-	(Durna et al. 2017)
<i>Listeria</i> spp.	<i>L.monocytogenes</i>	0.5-2.2	-	-	(Kumaraswamy et al. 2018; Turner et al. 1998)
<i>Aggregatibacter</i> spp.	<i>A.actinomycetemcomitans</i>	15.7-62.5	-	-	(Tanaka, Miyasaki, and Lehrer 2000; Ji et al. 2007)
<i>Peptostreptococcus</i> spp.	Clinical isolates	8-62.5	-	-	(Ji et al. 2007; Durna et al. 2017)
	<i>P.anaerobius</i> ATCC 27337	224	224	-	(Leszczyńska et al. 2013)
<i>Capnocytophaga</i> spp	Standard strains	-	-	ED_{99} 7.5-11	(Tanaka,

					Miyasaki, and Lehrer 2000)
<i>Actinomyces</i> spp.	<i>A.naeslundii</i>	31.3	-	-	(Ji et al. 2007)
	<i>A.israeli</i>	7.81	-	-	(Caiaffa et al. 2017)
<i>Nocardia</i> spp.	<i>N.farcinica</i> (ATCC 3318)	-	-	LD ₉₀ 32	(Rieg et al. 2010)
	<i>N.nova</i> (ATCC 33726)	-	-	LD ₉₀ 32	(Rieg et al. 2010)
<i>Bacillus</i> spp.	-	32->250	-	GI ₅₀ 1-68	(Thwaite et al. 2006; Blower, Popov, and van Hoek 2018; Fox et al. 2012)

Table 2. Quantitative antimicrobial activity of LL-37 against gram-negative human bacterial pathogens (the values are in µg/mL)

	Organism	MIC	MBC	Other methods	Reference
<i>Acinetobacter baumannii</i>	Standard strains	4-32	-	-	(Zharkova et al. 2019; Feng et al. 2013; Hashemi et al. 2019; Jaskiewicz et al. 2019)
	MDR	16 - >250	-	-	(Spencer et al. 2018; Feng et al. 2013; Lin et al.

					2015)
	PDR	32-64	128-256	-	(Guo et al. 2017)
<i>Pseudomonas aeruginosa</i>	Standard strains	16-64	32-64	-	(Hashemi et al. 2019; Geitani et al. 2019; Dosler and Karaaslan 2014; Bals et al. 1998; Hai et al. 2012)
	MDR	32-287.5	32->128	-	(Geitani et al. 2019; Rajasekaran et al. 2019; Lin et al. 2015; Dosler and Karaaslan 2014)
<i>Escherichia coli</i>	Standard strains	9- 44.9	-	-	(Zharkova et al. 2019; Pacor et al. 2018; Aghazadeh et al. 2019; Bals et al. 1998; Hai et al. 2012)
	Drug resistant	15-128	30-718	-	(Aghazadeh et al. 2019; Wnorowska et al. 2019; Scheenstra et al. 2019)
<i>Salmonella</i> spp.	-	4-143.7	-	-	(Martynowycz et al. 2019; Sakoulas et al. 2017; Hai et al. 2012; Honda et al. 2015)
<i>Klebsiella pneumoniae</i>	Standard strains	32	-	-	(Hashemi et al. 2019)
	MDR	64-143.7	-	-	(Lin et al. 2015; Ulloa et al. 2019)
<i>Yersinia</i> spp.	<i>Y. pestis</i>	-	40- >160	-	(Galván, Lasaro, and Schifferli 2008)
<i>Vibrio</i> spp.	<i>V.cholerae</i>	50	-	-	(Duperthuy et al. 2013)
<i>Neisseria</i> spp.	<i>N. meningitidis</i>	0.98 -44.9	56-112	-	(Leszczyńska et al. 2013; Jones et

					al. 2009; Tzeng et al. 2005)
	<i>N. gonorrhoeae</i>	0.9-8	3.6-8	-	(Kiattiburut et al. 2018; Bergman et al. 2005)
<i>Moraxella</i> spp.	<i>M.catarrhalis</i>	28-34.6	28	-	(Leszczyńska et al. 2013; Cederlund, Agerberth, and Bergman 2010)
<i>Haemophilus</i> spp.	<i>H.influenzae</i>	28-42.8	56	-	(Leszczyńska et al. 2013; Cederlund, Agerberth, and Bergman 2010)
<i>Porphyromonas</i> spp.	<i>P.gingivalis</i>	7.81-224	224	-	(Leszczyńska et al. 2013; Ji et al. 2007; Caiaffa et al. 2017)
<i>Helicobacter</i> spp.	<i>H.pylori</i>	8.9-300	8.9-300	-	(Leszczyńska et al. 2013, 2009; Mcgee et al. 2011)
<i>Campylobacter</i> spp.	<i>C. jejuni</i>	1.42-12.13	-	-	(Naito et al. 2010)
<i>Fusobacterium</i> spp.	<i>F. nucleatum</i>	3.9-250	224-250	-	(Leszczyńska et al. 2013; Ji et al. 2007; Caiaffa et al. 2017)
<i>Tannerella</i> spp.	<i>T.forsythensis</i>	>125-224	224	-	(Leszczyńska et al. 2013; Ji et al. 2007)
<i>Eikenella</i> spp.	<i>E.corrodens</i>	7.8-15.6	-	-	(Ji et al. 2007)
<i>Burkholderia</i> spp.	<i>B. thailandensis</i>	-	-	EC ₅₀ 8.43	(Blower, Barksdale, and van Hoek 2015)
	<i>B. pseudomallei</i>	212	416.6	-	(Lee et al. 2016)
<i>Stenotrophomonas</i> spp.	<i>S.maltophilia</i>	0.03-256	-	-	(Kumaraswamy et al. 2016; Pompilio et al. 2011)
<i>Prevotella</i> spp.	<i>P.nigrescens</i>	> 125	-	-	(Ji et al. 2007)
	<i>P.intermedia</i>	15.7	-	-	(Ji et al. 2007)

	<i>P.melaninogenica</i>	128	128	-	(Durna et al. 2017)
	<i>P.oralis</i>	8	8	-	(Durna et al. 2017)
	<i>P. bivia</i>	64	64	-	(Durna et al. 2017)
	<i>P.disiens</i>	16	16	-	(Durna et al. 2017)

Table 3. Quantitative antimicrobial activity of LL-37 against other bacterial pathogens (non-detectable or poor results of gram-staining, the values are in µg/mL)

	Organisms	MIC	MBC	Other methods	Reference
<i>Leptospira</i> spp.	<i>L. interrogans</i>	143.8 -224.7	143.8 -224.7	-	(Sambri et al. 2002)
<i>Borrelia</i> spp.	-	40-449.4	449.4	-	(Sambri et al. 2002; Lusitani, Malawista, and Montgomery 2002)
<i>Treponema</i> spp.	<i>T. pallidum</i>	449.4	449.4	-	(Sambri et al. 2002)
	<i>T. denticola</i>	31.3-62.5	-	-	(Ji et al. 2007)
<i>Mycobacterium</i> spp.	<i>M. tuberculosis</i>	5	-	-	(Rivas-Santiago et al. 2013)
	<i>M. smegmatis</i>	31.8	-	-	(Gupta, Singh, and van Hoek 2015)
<i>Mycoplasma</i> spp.	<i>M. pulmonis</i>	32	-	-	(Park et al.

					2013)
<i>Ureaplasma</i> spp.	<i>U. parvum</i>	-	-	IC ₅₀ 65	(Xiao et al. 2014)
	<i>U. urealyticum</i>	-	-	IC ₅₀ 65	(Xiao et al. 2014)

Highlights

- LL-37 is one of the most attractive multi-functional antimicrobial peptides
- Investigating all quantitative studies related to the LL-37 antimicrobial properties
- Providing an antimicrobial profile of this peptide in exposure to human pathogens

Journal Pre-proof