

# The role of antimicrobial peptides in the prevention of sexually transmitted infection (STI)

## Abstract

Development of sexually transmitted infections (STI) has existed in human societies along the history of mankind. It is still an important issue and research to diagnose and treat this group of diseases is growing. Due to the microbial antibiotic resistance to classical antibiotics, finding new antimicrobial compounds is essential. Antimicrobial peptides (AMPs) are of the most important of these compounds. AMPs usually show a broad spectrum of activities. Defensins, secretory leukocyte protease inhibitors (SLPI), calprotectin, lysozyme, lactoferrin and elafin are families of antimicrobial peptides that are involved in vaginal innate immunity. Some of AMPs such as LL-37, magainin 2 and nisin A have dual spermicide and microbicide effects. LL-37 is the most suitable peptide for this purpose with both spermicide/microbicide properties. LL-37 formulated gel administered into the vagina would exert microbicidal action on uropathogenic microbes. However, LL-37 is a long peptide and its synthesis is very expensive, hence the shortest truncated active form of LL-37 peptide or its mimetic, has to be designed. Also, setting up production method for recombinant LL-37 is necessary. In addition *in silico* methods can help this process and modification of AMPs. So, the proper formulation of the LL-37 as a vaginal spermicide/microbicide can play a role in the health of women.

**Keywords:** antimicrobial peptide, STI, defensin, LL-37, spermicide

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## Introduction

Sexually Transmitted Infections (STIs) such as *Chlamydia* infection, chancroid, gonorrhea, crabs (Pubic Lice), genital herpes, hepatitis B, HIV/AIDS, Human Papillomavirus (HPV), scabies, trichomoniasis and Molluscum Contagiosum (MCV) also known as Sexually Transmitted Diseases (STDs) or Venereal Diseases (VD)[1]. STIs are diseases that are passed on from one person to another through sexual contact, and sometimes by genital contact - the infection can be passed on via vaginal intercourse, oral sex, and anal sex.<sup>1</sup> Development of sexually transmitted infections (STI) in human societies, caused that research on diagnosis and treatment of these diseases is growing. Despite successes in antimicrobial drug development, resistance to every new antibiotic molecule has appeared in bacterial populations within a few years of its introduction determining a reduction in the therapeutic efficacy. Antimicrobial peptides (AMPs) have received an increasing attention as potential therapeutic agents.<sup>2</sup> AMPs are important components of innate immune systems. On one hand, there is an urgent demand for novel antimicrobials due to the current trend of reduction in the potency of commonly used antibiotics.<sup>3</sup> AMPs show a broad spectrum of activities against gram-negative and gram-positive bacteria, including antibiotic-resistant bacterial strains and some fungi, viruses, and parasites.<sup>4</sup> Also some of them have spermicidal properties.<sup>4</sup> Many of these peptides such as natural vaginal peptides and synthetic spermicide and microbicide to prevention and treatment of sexually transmitted diseases can be investigated. In this review, we introduce some of the most important AMPs in this regard.

### Antimicrobial peptides that are involved in vaginal innate immunity

Defensins, secretory leukocyte protease inhibitors (SLPI), calprotectin, lysozyme, lactoferrin and elafin are families of antimicrobial peptides that are involved in vaginal innate immunity.<sup>5</sup>

Both  $\alpha$ - and  $\beta$ -defensins have been shown to have anti-HIV activity.  $\alpha$ -defensins directly inhibit viral replication.<sup>5,8</sup>  $\beta$ -defensins have also been shown to decrease the expression of coreceptors required for virus entry into the host cell.<sup>5,9</sup> Some of these AMPs, can regulate the level of sex hormones. Concentrations of  $\alpha$ - and  $\beta$ -defensins from cervicovaginal lavage can vary greatly throughout the menstrual cycle, a variation of up to 50-folds.<sup>5,10</sup> This change in concentration is evidence that levels of estrogen can influence the operational status of the vaginal innate immune system.<sup>5,11</sup> SLPI has also been shown to inhibit HIV-1 activity[9]. Reduced SLPI levels have also been found in women with lower genital tract infections from *Trichomonas vaginalis*, *C. trachomatis*, *N. gonorrhoeae* and *Candida*.<sup>11</sup> Levels of calprotectin also correlate positively with inflammatory cytokines in cervical mucus, indicating that it plays a role in local inflammation. Also, calprotectin have been shown to have anti-Candida activity.<sup>5,12</sup> Elafin like defensin and SLPI has anti-HIV activity. *In vivo* studies have shown that elafin can cause resistance to HIV infection.<sup>13</sup>

### Spermicide and microbicide peptides

Some of AMPs such as LL-37, maximin 1, maximin3, magainin 2, dermaseptin-S1, dermaseptin-S4, subtilisin A, pediocin PA-1/ AcH, nisin A, lactacin 3147, sarcotoxin Pd and gramicidin A have dual spermicide/microbicide activity (Table 1). LL-37, magainin 2 and nisin A are the only AMPs with confirmed *in vivo* contraceptive effects in experimental animals.<sup>14,15</sup> The acidic pH in the healthy human vagina is attributed to the presence of commensal lactobacilli. nisin A is not a good candidate to be developed into a vaginal microbicide, since it exerts microbicidal activity on vaginal *Lactobacillus* spp.<sup>15</sup> LL-37 is produced by cervicovaginal epithelial cells naturally, however, this question arises that can it cause infertility? Therefore, it seems that high concentration of natural LL-37 may cause infertility by spermicide effects. What factors can increase naturally production of LL-37 by cervicovaginal epithelial cells?

**Table 1** sequence and source of spermicide and microbicidal Peptides (Retrieved from Antimicrobial peptide data base.<sup>16</sup>)

Peptide name	Sequence	Source
Maximin 1	Gigtkilggvktalkgalkelastyan	Bombina maxima
Maximin 3	Giggkilsglktalkgaakelastyh	Bombina maxima
Magainin 2	Gigkflhsakkfgkafveimns	Xenopus laevis
Dermaseptin-S1	Alwktmlkkltmalhagkaalgaadtsiqgtq	Phyllomedusa sauvagii
Dermaseptin-S4	Alwmtllkkvkaakaalnavlgana	Phyllomedusa sauvagii
Nisin A	Itsislctpgcktgalmgcnmktatchcsihvsk	Streptococcus lactis
LL-37	Llgdffrkskekigkefrivqrikdflrnlvprtes	Homo sapiens
Gramicidin A	Vgalavvvwlvwlvw	Bacillus brevis
PediocinPA-I/ AcH	Kyyngvtcgkxhscsvdwtgkattciinngamawatgghqgnhkc	Pediococcus acidilactici
Subtilosin A	Nkgcatcsigaacldvgpipdfeiaatgglfglwg	Bacillus subtilis
Lactacin 3147	Cstntfslsdywngngawctthecmawck	Lactococcus lactis
sarcotoxin Pd	Gwlkkigkkiervqhtrglgiaqiaanvaatar	Paederus dermatitis

## Discussion

Bacteria, fungi, yeasts, viruses and protozoa cause sexually transmitted infection. There are many antimicrobial peptides against viruses, bacteria, fungi and protozoa. Several of AMPs have direct anti microbial activity and therefore protect the host from pathogens. Others serve as chemotactic agents, thus recruiting inflammatory cells to the site of infection.<sup>5</sup> Although some natural AMPs are already in clinical and commercial use,<sup>2,6</sup> the future design and optimization of novel AMPs will need to improve their antimicrobial activity and stability, minimize the cytotoxicity, immunogenicity and reduce the proteolytic degradation or the biological fluid inhibition.<sup>2,7</sup> Synthesis of antimicrobial peptides are known to be expensive and time-consuming, therefore *in silico* methods to AMPs design can reduce production costs and the time required for evaluation of activity and toxicity.<sup>2</sup> LL-37 as a spermicide and microbicide peptide has antimicrobial effect against *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Treponema pallidum*, *Candida albicans*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Prevotella intermedia*, *Porphyromonas gingivalis*, *Klebsiella pneumoniae*, *Escherichia coli*, *Enterococcus faecalis* and HIV and HSV.<sup>15</sup> Therefore, LL-37 exerts microbicidal effects on most of microorganisms that involved in STIs, vaginitis and urinary Tract Infection.<sup>15</sup> Also, LL-37 completely inhibits human and mouse sperm motility within 5 min at 10.8 μM and 3.7 μM, respectively. This inhibition is likely due to the specific disruptive effects of LL-37 on sperm surface membranes.<sup>15</sup> LL-37 formulated gel administered into the vagina would exert microbicidal action on uropathogenic microbes that opportunistically form a reservoir in the vagina<sup>15</sup> The vaginal secretion, which can travel upwards into the urinary tract, would also likely contain LL-37 released from the gel, which then can fight against microbes in this tract.<sup>15</sup>

## Conclusion

As mentioned above, the STIs are inhibited by AMPs. LL-37 is the most suitable peptide for this purpose with both spermicide/microbicide properties. LL-37 is a long peptide and its synthesis is very expensive, so the shortest truncated LL-37 peptide or its mimetic, which still bears spermicidal and microbicidal activity, has to be discovered. Also, it is necessary to produce recombinant LL-37.

*In silico* methods can help this process. On the other hand, an effective method to deliver LL-37 into the vaginal lumen has to be established.<sup>15</sup> with further studies; modifications and changes in AMPs such as LL-37 can overcome the limitations of their use. Eventually, modified AMPs can be formulated in the form of ointments and topical lotions and play an important role in the health of women.

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## Conflicts of interest

The author declares there are no conflicts of interest.

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