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Review Article

# Highlights on the alternatives to antibiotic therapy against bacterial infection

Bijayanta Sircar, Shyamapada Mandal*

*Laboratory of Microbiology and Experimental Medicine, Department of Zoology, University of Gour Banga, Malda-732103, India*

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Abstract

The antibiotic resistance among gram-positive and gram-negative pathogenic bacteria is of global health concern. This has prompted the development of new effective drugs. But the discovery and development of new drugs is slow, and the emergence of resistance to such new drugs, on the other hand, is rapid as well as continuous among the bacteria. Therefore, in tackling the emergence of antibiotic resistant pathogenic bacteria finding alternative ways is vital. This communication, based on the published scientific data, summarizes the antibacterial capacity of some naturally derived agents such as honey, phytocomponents, probiotics, and antimicrobial peptides that might bring new essence in biomedicine.

**Keywords:** Bacterial resistance, alternative therapeutics, honey, phytomedicine, probiotics, antimicrobial peptides.

*Address for Correspondence:

Dr. Shyamapada Mandal, Professor, Department of Zoology, University of Gour Banga, Malda-732103, India E-mail: samtropmed@gmail.com

## 1. Introduction

Emergence of bacterial antibiotic resistance developed through an array of mechanisms is a severe threat to humans, and such phenomenon has been marked as an global alarming problem, which in developing countries including India, as recognised by the WHO, is reaching critical levels[1]. The multidrug resistant (MDR) ESKAPE (gram-positive: *Enterococcus faecium* and *Staphylococcus aureus*, and gram-negative: *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp.) bacteria are among the most notorious to cause life threatening nosocomial infections[2]. The continuous antibiotic therapy as well as the lack of effective antibiotics in the existing global treatment regimen has directed to a major upsurge in antibiotic resistance[3]. The increasing trend of development of antibiotic resistance among pathogenic bacteria has been associated with a marked economic cost worldwide. As the consequences there are great mortality and morbidity, high treatment costs, diagnostic doubts, and deficiency of trusted conventional medicine[2]. Of the six notorious ESKAPE pathogens, the four gram-negative bacteria, have been associated with four main types of multi-drug resistance, specifically the extended-spectrum β-lactamase-producing *K. pneumoniae* and *Enterobacter* spp., carbapenemase-producing *A. baumannii* and metallo-β-lactamase producing *Ps. aeruginosa* limiting the therapeutic choices[4]. *K. pneumoniae* is presently developing as a noticeable opportunistic pathogen and the most challenging agent of nosocomial infections[5].

Exposure of the pathogenic bacteria to antibiotics surges the risk of the emergence of carbapenem resistant Enterobactericeae, too. Carbapenems and cephalosoprins are cause of resistance that increased the risk up to 15-fold and 6 - 29 folds, respectively[1]. The widespread antibiotic usage in communities and hospitals cause severe multidrug resistance among gram-negative bacteria. The ESBL-mediated MDR gram-negative ESKAPE pathogens are progressively associated with several conditions that are difficult to treat in both developed and developing nations[4]. Current researches have shown pronounced interest in the use of alternative agents including honey, phytomedicine, probiotics, and antimicrobial peptides, in targeting the bacterial resistance corroborating their potential in the treatment of diseases caused by a large number of bacteria displaying resistance to almost all the antibiotics. This study thus provides a highlight on the antibacterial capacity of some naturally available agents, based on the scientific information published in the field.

## 2. Antibacterial activity

The indiscriminate use of antibiotics causes the development of antibiotic resistance among pathogenic bacteria leading to high morbidity and mortality from infections caused by such pathogens[6]. In the current times, there has been an increasing interest in exploring and evolving new antimicrobial biotherapeutics from various sources to fight bacterial resistances[7]. Along with the growing incidence of antibacterial resistance, complete and effective investigation is needed to look for the natural antibacterial sources, such as honey, plants, probiotics providing several active compounds having antibacterial activity that could inhibit life threatening bacterial diseases (Figure 1).

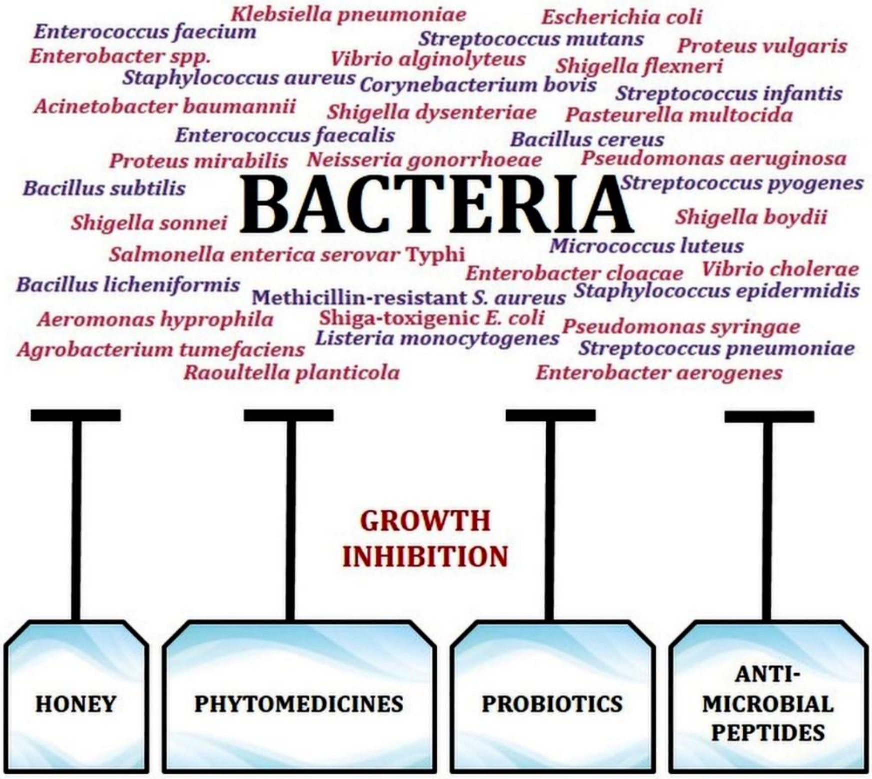


**Figure 1:** Schematic representation of different alternative antibacterials against human pathogenic bacteria.

### 2.1. Honey

Recently it has been proved experimentally that honey display antibacterial, anti-inflammatory and antioxidant activities, which may be useful in opposing MDR bacteria as well as in inhibiting many prolonged inflammatory processes[8]. The antibacterial activity of honey against clinical isolates of *Escherichia coli, Pseudomonas aeruginosa* and *Salmonella enterica* serovar Typhi has been reported previously[9]. Some factors that present in the honey as antimicrobials include hydrogen peroxide ($H_2O_2$) and inhibin, and also the osmotic effect of honey, its low pH (3.2 – 4.5), defensin-1, as well as the presence of phytochemical components display antibacterial activity[10].

Most of the researchers performed the disc diffusion or well diffusion method to study the antibacterial activity of honey. Several articles on antibacterial activity of different honey samples from diverse region of the world that has been published are summarised in Table 1.

**Table 1: Antibacterial activity of honey**

| Honey type | Geographical location | Using condition | Activity against bacteria | Antibacterial activity | | Ref |
|---|---|---|---|---|---|---|
| | | | | ZDI (mm) | MIC (%) | |
| Commercial grade honey | Malda, India | Aqueous honey | **Gram negative:** *Escherichia coli, Pseudomonas aeruginosa, Proteus vulgaris, and E. coli* ATCC 25922 **Gram positive:** *Staphylococcus aureus* | 6 – 30 | ND | 8 |
| Natural jujube honey | Saudi Arabia | Methanol extract | **Gram negative:** *E. coli* ATCC 35218, *Klebsiella pneumoniae* ATCC 700603, and *K. pneumoniae* ATCC 27736 **Gram positive:** *S. aureus* ATCC 25923, *Staphylococcus epidermidis* ATCC 12228, *Enterococcus faecalis* ATCC 29212, *Bacillus cereus* ATCC 10876, | 6 – 17 | ND | 11 |
| Eucalyptus honey and commercial grade honey | Mauritius | Undiluted | **Gram negative:** *Proteus* sp., *Klebsiella* sp., *Pseudomonas* 161 sp., and *E. coli, E. coli* ATCC 25922, and *Ps. aeruginosa* ATCC 27853 **Gram positive:** *Streptococcus* sp., *S. epidermidis* ATCC 35984, *and S. epidermidis* ATCC 14990 | 6 – 28 | ND | 12 |

**Table 1:** (*Continued*)

| Honey type | Geographical location | Using condition | Activity against bacteria | Antibacterial activity | | Ref |
|---|---|---|---|---|---|---|
| | | | | ZDI (mm) | MIC (%) | |
| Blossoms honey | Slovakia | 50% honey solution | **Gram negative:** *Ps. aeruginosa* CCM1960<br>**Gram positive:** *S. aureus* CCM4223 | ND | 3 – 27 | 13 |
| Wildflower and bitter leaf honey | Nigeria | Raw honey | **Gram negative:** *Salmonella typhimurium* ATCC 14028, *Sal. typhimurium* clinical, *Shigella dysenteriae* ATCC 11836, *Sh. dysenteriae* (clinical), *E. coli* ATCC 700728, *E. coli* (clinical)<br>**Gram positive:** *B. cereus* ATCC 14579, *B. cereus* (clinical), *S. aureus* ATCC 29213 and *S. aureus* (clinical) | 6 – 26 | ND | 14 |
| Natural honey | Ethiopia | Aqueous honey | **Gram positive:** Methicillin-resistant *S. aureus* | 6 – 39 | 9.38–37.5 | 15 |
| Citrus honey and mango honey | Malda, India | Aqueous honey | **Gram negative:** *Salmonella enterica serovar* Typhi, *Ps. aeruginosa* and E. coli ATCC 25922<br>**Gram positive:** *S. aureus* | 15 – 35 | ND | 16 |
| Local honey | Pakistan | Aqueous honey | **Gram negative:** *E. coli* ATCC 25922, *Ps. aeruginosa* ATCC 27853, *S. typhi ATCC 19943 and K. pneumoniae ATCC 27736*<br>**Gram positive:** *S. aureus* ATCC 6538, *En. faecalis* ATCC 19433 | 14 – 37 | ND | 17 |
| Natural (Kombu and Vembu) and commercial grade honey | Vellore, India | Honey diluted with dimethyl sulfoxide | **Gram negative:** *E. coli, S. typhi, Proteus mirabilis, K. pneumoniae, Shigella flexneri and Ps. aeruginosa*<br>**Gram positive:** *S. aureus, B. cereus and Enterococcus casseliflavus* | 6 – 38 | ND | 18 |
| Acacia, abies, sideritis, herbs, polyfloral and conifers honeys | Mount Olympus area, Greece | Raw honey | **Gram negative:** *A. baumannii, Citrobacter freundii, K. pneumoniae, and Salmonella typhimurium*<br>**Gram positive:** *Streptococcus infantis* | ND | 6.25–12.5 | 19 |

MIC: minimum inhibitory concentration, ND: not done, ZDI: zone diameter of inhibition

### 2.2. Phytomedicines

Roots, leaves, seeds, bark or other part of medicinal plants possess therapeutic, tonic, purgative or other pharmacologic activity under *in vitro* as well as *in vivo* conditions. Several plants are used in various countries as the source of potent and powerful medicines[20]. Alkaloids, norsecurinines, phyllanthine, phyllochrysine, saponins, quercetin, quercetol, rutin, quercitrin, astragalin, gallocatechins, niruretin, nirurin, brevifolin, ellagic acid ellagitannins, repandusinic acids, geraniin, carboxylic acids, corilagin, cymene, lupeols, phyllanthenol, lignans, hypophyllanthin, niranthin, nirtetralin, lintetralins, methyl salicylate, niruriside, triacontanal, tricontanol etc. type of bioactive compounds are present in various plants as the source of therapeutic components[21].

The innovation of medicinal plants in different parts of the globe is vital to the agriculture and medicine sectors, in defining the new guidelines towards spread of unconventional medicinal crops that offer improved commercial welfares[22]. Some tribal communities are mostly dependent upon the natural resources for their traditional food habits as well as for treating common illnesses such as diarrhoea, dysentery, vomiting, headache, cold, and fever[23].

Indian flora deals countless possibilities for the detection of new compounds with important medicinal uses in opposing infection. The antimicrobial compounds found in plants may inhibit bacterial toxicities by alternative mechanisms than the conventional one[24]. Phytomedicine, prepared from different plant materials, such as Ayurvedic traditional medicine, are relatively safe, cost effective and have less or no side effects[25].

Most of the current *in vitro* study on different medicinal plants with their experimental particulars, in terms of the antibacterial activity, are summarized in Table 2, where some research on bioactive fruit plants and spice herbs are also included.

**Table 2: Antibacterial activity of different plant extracts**

| Plants | Plant parts | Extracting solvent | Activity against Bacteria | Antibacterial activity | | Ref |
|---|---|---|---|---|---|---|
| | | | | ZDI (mm) | MIC (µg/ml) | |
| **Medicinal plants** | | | | | | |
| *Aegle marmelous* (Bael) | Leaves | Hexane, acetone, ethanol, and aqueous | **Gram negative:** *E. coli, Ps. aeruginosa, Salmonella enterica*, *Shigella sonnei* **Gram positive:** *Bacillus cereus, Strep. faecalis, Listeria innocua*, *Micrococcus luteus* | ND | 297 – 551 | 23 |
| *Azardirchata indica* | Leaves and bark | Ethanol, chloroform and methanol | **Gram negative:** *Aeromonas hyprophila*, *A. hyprophila* ATCC 7966, *Ps. aeruginosa*, *Proteus mirabilis*, Shiga-toxigenic *E. coli* **Gram positive:** *S. aureus*, *S. aureus* ATCC 25923**,** *Enterococcus faecalis*, Methicillin-resistant *S. aureus* | 6 – 27 | 500 – 12500 | 26–29 |
| *Withania somnifera* (Aswagandha) | Leaves | Ethyl acetate and methanol | **Gram negative:** *E. coli* ATCC 25922, *Proteus mirabilis* ATCC 35659, *Ps. aeruginosa* ATCC 27853, *Pseudomonas syringae pv. Phaseolicola* and *Xanthomonas campestris pv. Phaseoli* **Gram positive:** *S. aureus* ATCC 25923, *Streptococcus pneumoniae* ATCC 49619, *En. Faecalis* ATCC 29212 | 7 – 13 | 6.25 – 2500 | 30, 31 |
| *Bacopa monnieri* (Brahmi) | Whole plant and leaves | Methanol, acetone, ethanol and methanol | **Gram negative:** *E. coli* K 88, *Ps. aeruginosa, Salmonella typhii 62, Shigella dysenteriae 3, E. coli, K. pneumoniae* and *K. pneumoniae* MTCC 109 **Gram positive:** *S. aureus* ATCC 6571, *Streptococcus faecalis* 52, *En. faecalis* ATCC 29212, *S. aureus* MTCC 3160 and *B. subtilis* MTCC 441 | 8 – 22 | 30 – 25000 | 32, 33 |
| *Santalum album* (Sandal wood) | Heartwood | n-hexane, water chloroform, acetone, butanol ethylacetate and ethanol | **Gram negative:** *E. coli* 25922, *E. coli* 35318 and *Shigella sonnei* BB-8 **Gram positive:** *S. aureus* 25923, *S. aureus* 38541, *Streptoccs pyrogenes* Tc-11-2 and *Neisseria gonorrhoeae* 4c-11 | 6 – 17 | ND | 34 |
| *Ranwolfia serpentina* (Sarpa gandha) | Leaves, Roots and leaves | Acetone, methanol and ethanol | **Gram negative:** *E. coli* and *S. typhi* **Gram positive:** *S. aureus, B. cereus* and *B. subtilis* | 7 – 22 | 4000 - 9000 | 20, 35 |
| *Ocimum sanctum* (Tulsi) | Leaves | Aqueous, acetone and ethanol | **Gram negative:** *K. pneumoniae***,** *E. coli, Pr. vulgaris, Ps. aeruginosa, S. typhi, Acinetobacter baumannii* and *E. coli* MTCC 443 **Gram positive:** *Streptococcus mitis, Streptococcus viridans, S. aureus, B. cereus* and *Listeria monocytogenes* MTCC 657 | 6 – 28 | ND | 36, 37 |
| *Mentha pipertia* (Pippermint) | Leaves | Ethanol, chloroform and hexane | **Gram negative:** *E. aerogenes* and *S. typhimirium* **Gram positive:** *S. aureus, B. subtilis* and *Propioni bacterium acnes* MTCC 1951 | 7 – 8 | 312 – 1150 | 38, 39 |

**Table 2:** (*Continued*)

| Plants | Plant parts | Extraction solvent | Activity against bacteria | Antibacterial activity | | Ref |
|---|---|---|---|---|---|---|
| | | | | ZDI (mm) | MIC (µg/ml) | |
| *Phyllanthous amarus* (Bhumi amla) | Whole plant and leaves | Aqueous, n-hexane, ethyl acetate and methanol | **Gram negative:** *E. coli, Ps. aeruginosa* and *Pseudomonas spp.*<br>**Gram positive:** Coagulase positive *S. aureus* and *S. aureus* | 9 – 26 | ND | 21, 40 |
| *Enhydra fluctuans* (helencha) | Whole aerial parts (stem and leaves) | Methanol and aqueous | **Gram negative:** *A. baumannii*, *Ps. aeruginosa* and *E. coli* ATCC25922<br>**Gram positive:** *B. cereus, Listeria monocytogenes* and *L. monocytogenes* MTCC657 | 6 – 24 | 2500 - 10000 | 41 |
| **Fruit plants** | | | | | | |
| *Elaeocarpus floribundus* (Indian olive) | Seed and mesocarp-epicarp of mature fruits | Ethanol and aqueous | **Gram negative:** *E. coli, Pr. vulgaris and Ps. aeruginosa* ATCC 27813<br>**Gram positive:** *B. cereus*, *S. aureus* and *L. monocytogenes* MTCC 657 | 6 – 22 | ND | 42 |
| *Mimusops elengi* (Bakul) | Seed | Ethanol | **Gram negative:** *E. coli, Pr. vulgaris, K. pneumonia, E. coli ATCC 25922, K. pneumonia MTCC 7407 and Ps. aeruginosa ATCC 27853* | 7 – 17 | ND | 25 |
| *Syzygium cumini* (Jamun) | Seed | Ethanol | **Gram negative:** *E. coli, K. pneumonia* and *E. coli ATCC 25922*<br>**Gram positive:** *S. aureus* and *S. aureus ATCC 29213* | 8 – 15 | ND | 43 |
| *Mangifera indica* (Mango) | Seed | Ethanol | | 10 – 20 | ND | |
| *Punica granatum* (Pomegranate) | Fruit Peel | Ethanol and aqueous | **Gram negative:** *E. coli, Proteus spp., K. pneumoniae, P. aeruginosa, A. baumannii* | 6 – 28 | 2500 – 20000 | 44 |
| **Spices** | | | | | | |
| *Piper nigrum* (Black pepper) | Corn | Ethanol and chloroform | **Gram negative:** *E. coli, Ps. aeruginosa, Klebsiella Sp, Proteus Sp.*<br>**Gram positive:** *Streptococcus mutans,* Coagulase negative *Staphylococci* and *S. aureus* | 6 – 29 | ND | 45, 46 |

KOH: potassium hydroxide, MIC: minimum inhibitory concentration, ND: not done, ZDI: zone diameter of inhibition

### 2.3. Probiotics

Probiotics, in the form of lactic acid bacteria (LAB), generally the lactobacilli, might be crucial in controlling the emerging antibiotic resistant pathogenic bacteria. Probiotics have the inhibition property against bacterial pathogens, including the antibiotic resistant individuals: spoilage, food-borne and pathogenic bacteria, by producing $H_2O_2$, lactic acid and bacteriocin[47]. Sheep and goat milks and their derivatives (cheese and yoghurt) are commercially available as functional foods, which are with nutritional as well as medicinal importance, and can be selected as valid candidates having microbiological and technological qualities[48]. Current studies revealed that some lactic acid bacteria isolated from non-milk fermented foods act as potential probiotics with huge nutritional as well as medicinal values that might be due to the production of bacteriocins[49,50]. In the intestine, probiotic microorganisms compete with pathogenic bacteria in terms of nutrients and cell-surface for colonization, and can create inhibition against biofilm formation and quorum sensing properties of many pathogens[51 – 53].

The milk and non-milk food-based probiotics, being isolated and characterised by the scientists from around the world, are summarized, in terms of the effectiveness against bacteria, in Table 3.

**Table 3: Antibacterial activity of probiotics**

| Source | Geographical location | Probiotic strain | Activity against bacteria | Antibacterial activity | | Ref |
|---|---|---|---|---|---|---|
| | | | | ZDI (mm) | MIC | |
| **Milk-based products** | | | | | | |
| Local fermented milk products | Bangkok region of Thailand | *Lactococcus lactis subsp. lactis* | **Gram negative:** *E. coli, Ps. aeruginosa and S typhimurium*<br>**Gram positive:** *B. cereus* and *S. aureus* | 11 – 27 | ND | 54 |
| Toraja Belang buffalo milk | Indonesia | *Enterococcus faecalis* | **Gram negative:** Enteropathogenic *E. coli* ATCC 25922*, and S. typhi* ATCC 58105535<br>**Gram positive:** *S. aureus* 134-P | 6 – 13 | ND | 55 |
| Home-made cow milk curd, commercial curd | Malda district, India | *Lactobacillus animalis* LMEM6, *Lactobacillus plantarum* LMEM7, *Lactobacillus acidophilus* LMEM8 and *Lactobacillus rhamnosus* LMEM9 | **Gram negative:** *S. enterica serovar* Typhi, *E. coli, P. vulgaris* and *A. baumannii* | 11 – 35 | ND | 56 |
| Commercially available curd | Malda district, India | *Lactobacillus fermentum* | **Gram negative:** *A. baumannii,*<br>*Ps. aeruginosa, E. coli, Pr. vulgaris, K. pneumoniae, S. enterica serovar* Typhi<br>**Gram positive:** *S. aureus, B. cereus, E. faecalis, L. monocytogenes* | 10 – 20 | ND | 57 |
| Sheep and goat raw milk | Tunisia | *L. plantarum* and *L. pentosus* | **Gram negative:** *S. thyphimirium* ATCC 25922 and *E. coli*<br>**Gram positive:** *S. aureus* ATCC 25923, *L. monocytogenes* ATCC 070 101 121 | 6 – 12 | ND | 48 |
| **Non milk-based products** | | | | | | |
| Home-made fermented vegetables | Malaysia | *Lactobacillus sp* | **Gram negative:** *Yersinia enterocolitica* and *E. coli*<br>**Gram positive:** *S. aureus* ATCC 25923, *B. cereus* | 6 – 20 | ND | 49 |
| Fermented plant beverages and pickles | Thailand | *Lactobacillus casei* and *L. plantarum* | **Gram negative:** *S. thyphimirium* PSSCM10035, *S. typhi* PSSCM10034, *E. coli* O157:H7, *E. coli ATCC 25922*, *Shigella sonnei PSSCM10032, Shigella flexneri PSSCM10035, Pr. vulgaris PSSCM10041, Providencia rettgeri* psscm10044, *Enterobacter cloacae* PSSCM10040, *Enterobacter aerogenes* PSSCM10039, *Vibrio parahaemolyticus* VP4<br>**Gram positive:** *S. aureus* ATCC 25923, *B. cereus* ATCC11778 | 7 – 10 | ND | 50 |
| Vegetables and traditional Indian fermented foods | India | *L. fermentum, L. plantarum Weissella confusa, Weissella cibaria* and *Pediococcus parvulus* | **Gram negative:**<br>*E. coli* K12 | 14 – 23 | ND | 58 |

MIC: minimum inhibitory concentration, ND: not done, ZDI: zone diameter of inhibition

**2.4. Antimicrobial peptides**

Several authors reported that antimicrobial peptides (AMPs) can be administered as typical candidates effective against different MDR bacterial strains. Biofilms formation by the bacterial cells causes more resistant to antibiotic managements than the planktonic forms of the same bacterial strains[59]. Food protein hydrolysates and fermented food products serves as promising source of bioactive AMPs. The caseins and whey proteins are major milk precursors proteins found in cow milk. Caseins derived bioactive peptides consists of about thirty different constituents comprising with genomic variations, mainly of αs- (αs1-, αs2-), β, and κ-casein[60]. Most of the potential AMPs are cationic as well as amphipathic in nature consisting of a minimum five to maximum hundred amino acids. Current studies have shown that some probiotics can synthesise AMPs that contribute significantly to host survivability, exclusively against pathogenic bacteria. Although scientists are facing some difficulties in obtaining significant and economically sustainable quantities of AMPs, and thus they are trying to manufacture heterologous endogenous AMPs using cloning technique[61].

Recently, a number of anionic antimicrobial peptides have been identified in vertebrates, invertebrates and plants[62]. The vast source of antimicrobial peptides is marine organisms because of their close contact with microbes[59]. Some antimicrobial peptides derived from plants are mostly composed of cystine-rich peptides. Insects is one of the major sources of antimicrobial peptides that show inhibition against bacteria, fungi, viruses as well as some parasites. These can be classified into four families: the α-helical peptides (cecropin and moricin), glycine-rich peptides (gloverin and attacin), proline-rich peptides (drosocin, apidaecin and lebocin) and cysteine-rich peptides (insect drosomycin and defensin)[63].

Recent studies showed antimicrobial peptides can potentially serve as novel antimicrobial agents. Different AMPs can be utilized by innate immune cells and proteins to counterbalance microbial infections, and contribute more to other cellular and/or biomolecular pathways[64]. Table 4 summarizes the antibacterial activities of AMPs with molecular weight ranging from 1.55 to 41.44 kDa.

**Table 4: Antibacterial activity of different bioactive peptides**

| Source | Amino acid number in peptides | Molecular weight (kDa) | Activity against bacteria | Antibacterial activity | | | Ref |
|---|---|---|---|---|---|---|---|
| | | | | ZDI (mm) | MIC (µg/ml) | AU/ml | |
| Sea Cucumber, *Holothuria tubulosa* | 14 – 36 | 1.55 – 4.09 | **Gram positive:** *Listeria monocytogenes* | ND | 1200 – 5000 | ND | 59 |
| Bacteriocin from *Lactococcus lactis* MMFII (from a Tunisian dairy product) | ~40 | 25 – 41.44 | **Gram positive:** *Enterococcus faecalis* JH22 *E. faecalis* V583 *Listeria ivanovi* BUG 496 | ND | 0.05 – 0.1 | 20 – 60 | 65 |
| Bacteriocin produced by *Lactobacillus plantarum* KLDS1.0391 (from fermented cream from China) | ND | 21.80 – 29.70 | **Gram negative:** *Salmonella typhimurium* | ND | ND | 80 | 66 |
| Marine Ascidian *Didemnum* sp. | ND | < 40 | **Gram negative:** *Ps. aeruginosa* ATCC 27853, *Salmonella typhimurium* ATCC 202165 **Gram positive:** *Staphylococcus aureus* ATCC 6538, *Serratia marcescens* ATCC 14756 and *E. faecalis* ATCC 29212 | 7 – 11 | 1.83 – 2.30 | ND | 67 |
| Soybean, *Glycine max* | ND | <10 | **Gram negative:** *Acinetobacter genomospecies, Aeromonas hydrophila FDA110-36, A. hydrophila ATCC7966, Escherichia coli DH5alf, E. coli ATCC43895, E. coli NCTC8959, Salmonella enterica ATCC12325, S. enterica ATCC29934, Vibrio parahaemolyticus ATCC17802* **Gram positive:** *S. aureus ATCC14458, coagulase-negative S. saprophyticus KT955005, S. aureus ATCC13150* | ND | 72 – 1050 | ND | 68 |

**Table 4:** (*Continued*)

| Source | Amino acid number in peptide | Molecular weight (kDa) | Activity against bacteria | Antibacterial activity | | | Ref |
|---|---|---|---|---|---|---|---|
| | | | | ZDI (mm) | MIC (µg/ml) | AU/ml | |
| Laba garlic | 5 – 6 | 4 – 6 | **Gram negative:** *E. coli,* ATCC 25922*, S. enteritidis* BNCC103134, **Gram positive:** *B. subtilis* ATCC 6633*, and S. aureus* ATCC 25923 | 9 – 27 | 100 – 450 | ND | 69 |
| Skin Secretion of the Fujian Large Headed Frog, *Limnonectes fujianensi* | 33 | ND | **Gram negative:** *E. coli* NCTC 10418 **Gram positive:** *S. aureus* NCTC 10788 | ND | 16 – 32 | ND | 70 |
| Moss *Physcomitrella patens* | 14 – 18 | ND | **Gram negative:** *E. coli* K-12 substr. MG1655 **Gram positive:** *B. subtilis* 168HT | ND | 16 – 128 | ND | 71 |
| *Trianthema portulacastrum* Leaves | ND | 5.57 – 23.44 | **Gram negative:** *E. coli* **Gram positive:** *B. subtilis and S. aureus* | 6 - 14 | ND | ND | 72 |
| Rumen microbiome | <25 | ND | **Gram negative:** *A. baumannii* | ND | 64 – 128 | ND | 73 |
| *Rana arvalis* | 13 – 32 | ND | **Gram negative:** *E. coli* ATCC 25922*, Acinetobacter baumannii* ATCC 19606 **Gram positive:** *S. aureus* ATCC 29213 *and En. faecalis* ATCC 29212 | ND | 16 - >64 µM | ND | 74 |

AU/ml: arbitrary unit per millilitre, MIC: Minimum inhibitory concentration, ND: not done, ZDI: zone diameter of inhibition

## 3. Concluding remarks

Due to the problem of antibiotic inactivity, exploration of alternative new antibacterial agents is needed to combat several life-threatening infections caused by MDR bacteria. Honey, plant extracts, probiotics and AMPs can inhibit the growth of infectious bacterial pathogens, as non-antibiotic antibacterials. Although, more specific experiments are required to know the effective dose dependent pharmacokinetic nature of the explored agents.

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