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Review

Natural products in drug discovery: meeting the urgency for new antimicrobials for human and veterinary use

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Abstract: The scenario of growing microbial resistance and of lack of interest of pharmaceutical companies in developing new antimicrobial drugs jeopardizes the present and the future of the treatment of infectious diseases. Different approaches such as antimicrobial peptides and CRISP-R have been explored to manage this situation, however, they have important limitations such as their high cost. Natural products comprise complex molecular structures for which reports of bacterial resistance are rare. They present specific and/or unspecific mechanisms of action that can be explored to provide safe and effective management of infectious diseases. In this review we assessed phytoextracts with evidence of their benefits for treating infectious diseases in humans and animals, towards the use of data for clinical and experimental purposes. Mechanisms of bacterial resistance to antimicrobials are also discussed.

Keywords: phytoextracts; antimicrobial; pharmacology; molecular targets; bacteria

1. Introduction

Drug therapy for infectious diseases is in a complex moment: therapeutic options are increasingly scarce, and new drugs are not available in the pharmaceutical market. The loss of efficacy of antimicrobials is explained by microbial resistance mechanisms, which are genetically

modulated to allow subpopulations of microorganisms to keep alive and grow on the presence of antimicrobials, due to selective pressure effect on the strains [1,2]. Resistance mechanisms are mostly studied in bacteria, given that several highly prevalent, life-threatening, hospitalizing and technically difficult to treat infectious diseases are frequently associated to pathogenic bacterial strains [2–4]. Unfortunately, conventional clinical solutions such as increasing antimicrobial doses and combination of drugs can result in side effects such as oto/nephro/neurotoxicity, and deep and permanent alterations of the indigenous microbiota, increasing the susceptibility to dysbiosis-related diseases [5,6].

Low (or no) efficacy of antimicrobials on minor infectious diseases is a phenomenon known as the post-antibiotic era [7]. Studies on this phenomenon started only around a decade ago, and thus, are very recent. The World Health Organization recognized the post-antibiotic era in 2014 [8], and its main causes are related to human and veterinary medicine practices such as the incorrect prescription and use of antimicrobials, especially as animal growth promoters [8,9]. Regarding human health, several studies provide data for laboratory evaluation of antimicrobial susceptibility. Conversely, studies on bacterial resistance in animals remain scarce, and tests on antimicrobial susceptibility are not frequent in clinical veterinary routines [10,11].

In this challenging scenario, what is left to be done? Combinations of antimicrobials are frequently explored and standardized in clinical settings. There are studies exploring CRISP-R technology to revert bacterial resistance on its very genetic core [12]. There are investigations on antimicrobial peptides, which are naturally present in humans, animals and plants [13]. Also, there are studies exploring bacteriophages that are not pathogenic to human and animal species [14]. These approaches are necessary, relevant and promising, but require expensive and robust technologies for most of the experiments.

Natural products (NP) have been successfully used in several ways to treat different conditions in humans and animals throughout the history of mankind, including infectious diseases. The golden age of antimicrobial therapy (after World War II) largely depended on NP-based molecules. In recent years, several advanced analytical and characterization equipment and methods have become more accessible and suitable to investigate NP, especially phytomolecules. Even preliminary experiments conducted in simple infrastructure might provide relevant results. The aim of the present is to review recent data on the use of NP of vegetable sources to treat infectious diseases in animals and humans. Plant extracts and their benefits will be discussed, considering molecular aspects such as targets and bioactive molecules, whenever properly described.

2. Overview of molecular aspects of bacterial resistance – and why NP are of interest as antimicrobials

It is important to differentiate antimicrobials from antibiotics. They are often used as synonyms, but antibiotics are bioactive substances naturally produced by microorganisms (such as bacteriocins), whereas antimicrobials are synthetic or semi-synthetic drugs (such as vancomycin), produced in large scale by pharmaceutical companies. Antimicrobials and antibiotics can be equally subdivided as antibacterial, antifungal, and antiviral substances, and may present these characteristics simultaneously [15].

Different mechanisms of bacterial resistance to antimicrobials have been described in a molecular level (Figure 1). They are classified as intrinsic or vertically transmitted when related to

chromosomal genes, whereas extrinsic or horizontal transfer of resistance genes happens through plasmids [16,17]. This extrachromosomal DNA harbors resistance genes that might be shared among bacteria of different species and genus, from live or dead strains [17]. Once plasmids reach the replication machinery, drug resistance genes are expressed, and the associated mechanisms become active in the strains – even if they were never exposed to antimicrobials before. Thus, horizontal dissemination of resistance genes is more frequent and faster than vertical [16–18].

The selective and highly specific behaviors of antimicrobial drugs are necessary to effectively reach bacterial targets (and thus, provide adequate pharmacotherapy), and to define the range of coverage of bacterial species (the spectrum of the drugs), classified as narrow or broad [17,18]. Thus, the pharmacodynamics of antimicrobials are a double-edged knife to some extension: the known resistance mechanisms work as a "counterintelligence", hampering or abrogating the activity of drugs of different molecular structures and mechanisms of action [17–19]. For instance, structural modification of microbial targets can prevent the activity of quinolones and antimetabolites, and efflux pumps may do the same for aminoglycosides and β-lactams [20]. This helps to explain the development of resistance mechanisms in bacteria.

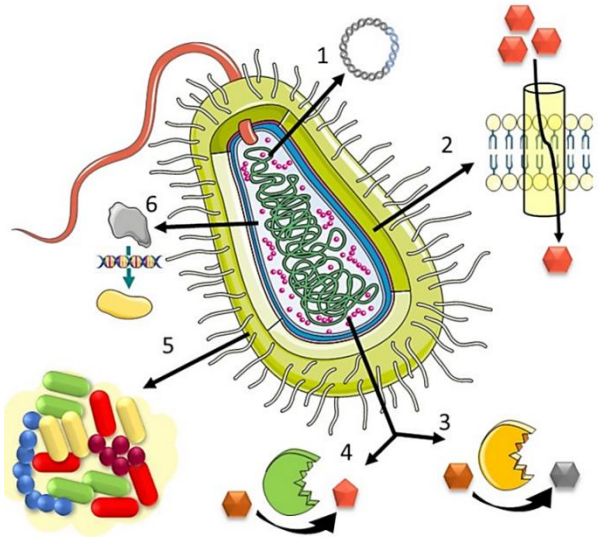

Figure 1. Bacterial resistance scheme. Rapid transfer of resistance genes happens horizontally through plasmids (1) from both live and dead bacteria. The main mechanisms include drug efflux pumps (2 – which are membrane proteins with ability to remove molecules from the cytoplasm), enzymatic inactivation (3 – partial degradation of the drug) or modification (4 – addition of functional moieties to the drugs), biofilm formation (5 – see more details in figure 2) and molecular modification of drug targets (6 – structural alterations of receptors or enzymes that hamper interactions with drugs). Parts of the figure were drawn by using pictures from Servier Medical Art.

Biofilm formation (Figure 2) is another important resistance mechanism that is also related to the pathogenicity of bacterial strains. Biofilms are microcolonies that grow in an extracellular polymeric matrix (EPM) made of biomolecules (carbohydrates, proteins, lipids and nucleic acids), being polymicrobial in the environment and in living organisms [21]. The diversity of microorganisms, the type of surface where it is being developed and the type of nutrients available are critical factors to define which types of biomolecules will be found in the biofilm EPM, as well

as the predominant microbial species [21,22]. Biofilms promote bacterial resistance in at least three ways: 1) by physically precluding drug diffusion to the bacteria adhered to the EPM; 2) by chemically inactivating antimicrobials due to interaction with substances in the EPM; and 3) by supporting plasmid DNA sharing [21–23]. Eradication of biofilms may require antimicrobial concentrations 1000 times higher than the used for planktonic (free) bacteria [23]. Curiously, few studies have investigated the antibiofilm potential of antimicrobial drugs and NP.

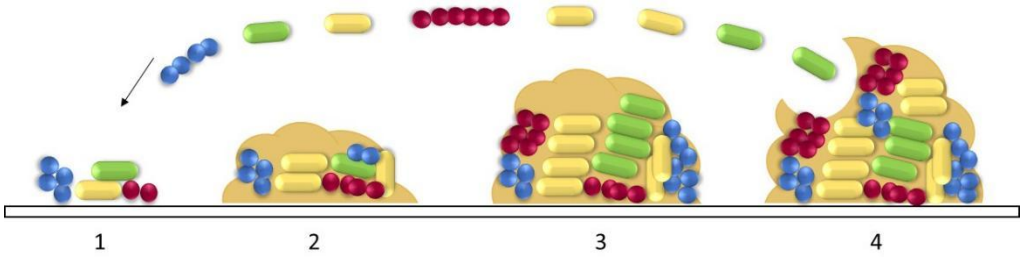

Figure 2. Schematic representation of polymicrobial biofilm formation. Following a primary attachment to a surface (1), bacteria start to grow and produce more EPM (2 – light brown background). As the biofilm reaches its microbial population limit (3), quorum-sensing peptides trigger detachment mechanisms that release microorganisms back to the environment (4), what may lead to more biofilm formation (1) at the same (or other) surface. Figure drawn by the authors.

NP can offer important advantages over antimicrobial drugs in clinical treatments of infectious diseases. In a scenario of bacterial resistance to antimicrobials, NP are being largely explored as to provide effective and accessible treatments. NP display both non-specific and specific mechanisms of antimicrobial activity, and present complex molecular structures, thus, reports on resistance of NP are extremely rare [24]. More recently, studies on combinations of NP to antimicrobial drugs have shed light on potential benefits of synergic interactions, activating different molecular pathways that can result in microbial death [17,24]. Recent research in this context will be discussed in the next sections.

3. NP for the treatment of infectious diseases in animals

The use of NP in food producing and companion animals is not a frequent object of scientific investigation, and studies on veterinary prescription of NP are scarce. The main causes include conflicts and missing results of efficacy, the inappropriate use NP by farmers, commercial interests, and the tasks of the authorities to ensure animal welfare and food safety in a context of scarce scientific evidence [25].

NP may be used against two or more infectious diseases in course simultaneously. Flowers and leaves of *Achillea millefolium*, a plant commonly found in Africa, Asia, Europe, and North America, are widely used for the treatment of gastrointestinal and respiratory system infections in humans. *In vitro* evidence suggests that it can offer the same benefits to calves, piglets, dogs and cats [26]. A blend of *Calendula officinalis* and *Hypericum perforatum* was investigated for the treatment of canine dermatitis associated to microbial infections in an ointment for topical use. Both plants presented wide spectrum antibacterial activity, and *C. officinalis* also displayed wound-healing

and anti-inflammatory effects. Commercial formulations of these plants are available in some countries to treat canine dermatitis [27]. Tea tree (*Melaleuca alternifolia*) oil is extracted from the leaves of the plant, and presents antimicrobial, antiparasitic and anti-inflammatory properties. To reach such benefits in dogs, it is necessary to have a minimum content of 30% terpinen-4-ol and a maximum content of 15% for 1,8-cineole [28]. A study compared the effects of a 10% tea tree oil emulsion and a common hydrating emulsion for 10 days on treatment of dogs with clinical manifestations of skin lesions. The treatment with tea tree oil emulsion reached 71% success rate, whilst the hydrating emulsion reached 41% [29]. It has been speculated that terpinen-4-ol inhibits penicillin-binding proteins (PBP), such as β -lactams drugs, and 1,8-cineole induces membrane disruption and leakage [28,29].

Curcumin is a naturally occurring anti-inflammatory and antioxidant polyphenol that is an active component of *Curcuma longa* (turmeric) roots. In rodent animal models of Parkinson's disease, curcumin reduce neural apoptosis and improved striatal dopamine levels [30]. Also, a recent study published by our group described the antimicrobial properties of *C. longa* extract against *Staphylococcus aureus* isolated from dogs with otitis externa, with a MIC value of 125 μg/mL [31]. It is possible that curcumin, its main flavonoid, alongside with flavonoids and tannins, induce membrane leakage in bacteria [31]. *Cymbopogon citratus* was also suggested to be effective to treat otitis externa caused by *Malassezia pachydermatis* in dogs. The plant is known as lemon grass in some countries and is originally from tropical regions of Asia [32].

NP are frequently associated to the improvement of immunologic response to infections. It is very likely that medicinal fungi, found as mushrooms, work similarly. Polysaccharide and sterol complexes appear to enhance cell-mediated immune responses and may also have antitumoral activity. Importantly, polysaccharide complexes found in medicinal fungi are more likely to be completely extracted in aqueous or dry preparations than in alcoholic extracts. Relevant species include *Ganoderma lucidum*, *Grifola frondosa*, *Lentinula edodes*, *Trametes versicolor*, *Cordyceps sinensis*, *Agaricus blazei* and *Inonotus obliquus* [33,34]. Furthermore, *Echinacea sp* leaf extracts have been shown to increase phagocytic activity in human peripheral monocytic cells, promote the production of various cytokines, and increase the function of natural killer cells, all of which involve the innate immune system as opposed to specific adaptive processes [33–35]. *Echinacea sp* is often recommended for treating chronic recurrent respiratory viral infection and retroviral infections in cats [35]. Finally, *Panax ginseng* polysaccharides and saponins are plants that have demonstrated immunostimulatory properties *in vitro* and *in vivo*: mice with chronic *Pseudomonas aeruginosa* lung infections were treated with *Panax ginseng* extracts and exhibited higher bacterial clearance and lower serum immunoglobulin levels than the untreated group [36,37].

The antiparasitic potential of NP has also been explored for veterinary purposes. *Azadirachta indica* is effective against helminthiasis and general weakness in livestock, poultry, sheep, pigs and goats [38]. Azadirachtin is the main active compound of the leaves and roots, which are usually prepared by decoction for therapeutic use. The antimicrobial mechanism of azadirachtin remains unclear, but it is possible that it affects the cell wall stability [38]. Parasitic diseases in fish have also been treated with NP. *Piper longum* has piperine as its main active compound, and it was effective against *Argulus spp* at a concentration of 9 mg/L following 48 h exposure. Its antimicrobial mechanism remains unknown. Similarly, *Fructus cnidii* and *Semen aesculiis* were effective against *Dactylogyrus intermedius* in a 48h treatment. Osthol and isopimpinellin are the main phytomolecules (coumarins) from *F. cnidii* extract, and are supposed to act by membrane lysis [39]. Osthol and

isopimpinellin were active at 1.6 mg/mL and 9.5 mg/mL respectively, whilst *S. aesculiis* methanolic extract was active at 10 mg/mL, and the aqueous extract was active at 12 mg/mL [39].

Paris polyphylla and *Dioscorea zingiberensis* extracts were more effective than mebendazole *in vitro* against *D. intermedius*. *P. polyphylla* has dioscin and polyphyllin D as its main active compounds, whereas *D. zingiberensis* main active compound is gracillin [39]. *Allium sativum* has the potential to cause Heinz body anemia in dogs and especially cats. However, its activity as anthelmintic and antiprotozoal has been demonstrated both *in vitro* and *in vivo*. Topical application of *A. savatium* has also shown some activity against chicken mites. The bulb is used as an antiparasitic product, insecticide and repellent on the back of livestock, in doses of around 3% [33,38].

4. NP for the treatment of infectious diseases in humans

The antimicrobial and antibiofilm activities of the hydroethanolic extract of cashew stem bark (*Annacardium occidentale*) was investigated for *Staphylococcus aureus and Staphylococcus epidermidis*. The extract was effective in the eradication of biofilms and planktonic cells of these species. Although the minimum bactericidal concentration for planktonic cells (15.2 mg/mL) and the minimal concentration for biofilm eradication (30.5 mg/mL) were considered high for natural products, the concentration was the lowest described at the time of the publication. The extract was also investigated for the possible effects of combining it to antimicrobial drugs to clinical isolates of *S. aureus* and *S. epidermidis*. The results of the combinations were mostly antagonistic. Tested drugs included neomycin, rifampicin and vancomycin [40,41]. Interestingly, cashew juice pulp extract also presented antagonistic results when combined to meropenem, ampicillin, chloramphenicol and gentamicin. Nevertheless, it presented antimicrobial activity against planktonic cells and biofilms of *Staphylococcus aureus,* in concentrations lower than the stem bark extract: the minimal inhibitory concentration was 15.6 μg/mL, whereas the minimal bactericidal concentration was 125 μg/mL and minimal biofilm eradication concentration was 500 μg/mL [42]. In both stem bark and juice pulp extracts, there were flavonoids, and tannins were also present in the stem bark extract, which are phytomolecules of known antimicrobial properties by membrane leakage and rupture [40,41].

Vaccinium myrtillus juice extract presented antimicrobial activity against *S. aureus*. Interestingly, when combined to antimicrobials such as levofloxacin, amoxicillin and gentamicin, no significant interference was detected. The minimal inhibitory concentration varied from 15.62 to 62.5 μg/mL. The minimum bactericidal concentration ranged from 125 to 250 μg/mL [43]. Methanolic extracts of fruit juice pulps of *Spondias tuberosa* (umbu), *Spondias purpurea* (seriguela), and *Theobroma grandiflorum* (cupuaçu) were effective against clinical isolates of *E. coli*. The minimal inhibitory concentration of the extracts was of 500 μg/mL, and the presence of flavonoids was confirmed by HPLC, which are expected to present antimicrobial activity by causing membrane leakage and possibly inhibition of enzymes critical to microbial metabolism [44].

Euterpe oleracea (açaí) pulp extract was effective against *Staphylococcus aureus,* presenting antimicrobial and antibiofilm activities. The minimum inhibitory concentration was 7.81 μg/mL, the minimum bactericidal concentration was 62.5 μg/mL and the minimum biofilm eradication concentration was 250 μg/mL. Non-anthocyanins flavonoids are possibly related to the antimicrobial effect, but the exact mechanism of action is not clear. The combination of the extract and antimicrobials resulted in synergic effect for ciprofloxacin, chloramphenicol and gentamicin. The presence of the

non-anthocyanin flavonoids with antimicrobial potential (orientin, protocatechuic acid and catechin) was suggested [45].

Black tea (*Camellia sinensis*) leaf extract presented antimicrobial activity against planktonic cells of *S.aureus*, *P. aeruginosa* and *E. coli* [46], but curiously, was not effective against biofilms of *P. aeruginosa* (Table 1). As the extract was combined to antimicrobial drugs, mixed results were obtained. Synergism was detected for azithromycin against *E. coli* and for clindamycin against *S. aureus*. Conversely, antagonism was detected for norfloxacin against *S. aureus,* and there was a tendency of antagonism for ciprofloxacin, ampicillin and nitrofurantoin against *P. aeruginosa.* Flavonoids were detected in the extract, and possibly act by membrane leakage [46].

Table 1. Antimicrobial susceptibility of bacterial pathogenic strains to black tea extract.

Parameter	*S. aureus*	*P. aeruginosa*	*E. coli*
MIC	3.9 μg/mL	15.62 μg/mL	31.25 μg/mL
MBC	15.62 μg/mL	125 μg/mL	62.5 μg/mL
MBEC	62.5 μg/mL	Not detected	250 μg/mL

Note: Data extracted and summarized from [46].

The antimicrobial potential of isolated carotenoids and flavonoids was investigated against *S. aureus, P. aeruginosa* and *E. coli*. Lycopene, β-carotene, rutin and resveratrol did not present antimicrobial activity against clinical isolates of these species, but the combinations of these molecules to antimicrobials resulted in abrogated activity of nitrofurantoin, penicillin, erythromycin, gentamicin, ciprofloxacin and oxacillin against *S. aureus* and *E. coli*. Conversely, the combination of lycopene and β-carotene to chloramphenicol and aztreonam resulted in a synergic effect against *P. aeruginosa*, as did curcumin and diosmin. Meropenem was tested in the study, but no interference was detected for any of the flavonoids or carotenoids [47,48].

The crisis on health systems and services caused by COVID-19 pandemic urged researchers worldwide to provide therapeutic options using NP. A study published in the very first months of the pandemic identified at least 10 blends comprising an average of 12 plants described in chinese traditional medicine guidelines, to treat mild to severe pediatric cases of COVID-19 [49]. A total of 56 plants were listed as potentially useful for these treatments, however, solid evidence of their efficacy is still lacking. A total of 20 bioactive compounds from *Ginkgo biloba* leaves such as ginkgolide A/B/C, ginkgetin and isoginkgetin were investigated for their potential to inhibit 3-chymotrypsin-like protease, an enzyme necessary for the replication of SARS-CoV-2 virus [50]. Ginkgolic acids were more effective *in vitro* and *in silico*, as well as sciadopitysin, a bioflavone which could interact with the catalytic site of the enzyme [50]. Finally, glycyrrhizic acid (obtained mainly from *Glycyrrhiza glabra* and other *Glycyrrhiza* species) has been investigated to treat COVID-19 by directly affecting the virus and by immunomodulation [51]. The virus could lose the stability of the lipid-bilayer membrane, and could be precluded to interact with ACE_2 enzyme; immunomodulation could be achieved by increasing the phagocytosis and nitric oxide production by macrophages [51].

5. Conclusion

NP are relevant sources of new antimicrobial molecules, especially flavonoids. Leaves and stem barks are largely explored. Fruit, seeds and roots have gained more attention in the latest years, mostly driven by nutritional benefits of edible parts. There is a need for more *in vivo* studies to assure the reproducibility of the methods, and to consider the effects of metabolism, immune system and nutritional status of humans for compounds that were effective *in vitro*. Clinical trials with plant extracts and/or isolated molecules in standardized formulations are very rare, and are necessary to support prescription and development of phytotherapics. The use of NP in veterinary medicine is very discrete, and thus, require more studies as to provide more solid evidence for clinical use in different species. This scenario open doors for research in NP and make them even more relevant and urgent for both humans and animals.

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Conflict of interest

The authors declare no conflict of interest.

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