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Natural polyphenols as potential antibacterial agents and their delivery systems of nanosized level

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ABSTRACT Bacterial infections associated with multidrug-resistant pathogens are a serious danger to both humans and farm animals. For this reason, natural biologically active agents (BAA), in particular, polyphenols, with a wide range of biological activity could become promising molecules for effective antibacterial therapy. Despite the potentially high antibacterial activity and other beneficial biological effects, the use of such BAA is hindered due to their low water solubility. To overcome this problem, various approaches are used, for example, loading BAA into nanosized delivery systems (nanoparticles, nanocapsules, micelles, etc.). Such approaches allow not only to increase the effectiveness of natural BAA, but also to ensure their targeted (local) effect, which is important in the treatment of bacterial diseases, and in some cases result in synergic action. This review describes the antibacterial properties of the most promising polyphenols and key approaches for their delivery at the nanoscale level, as well as the methods for their development.

KEYWORDS polyphenolic agents, antibacterial activity, natural biologically active agents, carnosic acid, curcumin, mangiferin, rosmarinic acid, drug resistance, nanoparticles, analysis methods.

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1. Introduction

In recent years, there has been a significant spread of resistant bacterial infections; therefore, antibiotic resistance has become a major public health problem [1]. To address this problem, numerous studies are being conducted worldwide to find alternative treatment options. One such option is the use of natural biologically active agents (BAA) derived from plants with unique antibacterial properties and low side effects.

Plants have long been used by humans as therapeutic agents and their secondary metabolites show promising antimicrobial activity. The effectiveness of these natural compounds is determined by their chemical structure, which allows them to affect bacterial cells and disrupt their essential biological processes. In addition, due to their diverse mechanisms of action, plant secondary metabolites are less likely to lead to the development of resistance in pathogens. Importantly, natural agents have fewer side effects and less environmental impact than traditional antibiotics.

However, most natural BAA have a hydrophobic nature, which limits their use as highly effective antibacterial agents. To increase the activity of such agents and ensure their targeted action, various approaches are used, in particular, "loading" (encapsulation) of BAA into polymer matrices with subsequent production of various dosage forms: films, fibers, nanoparticles, etc.

In this work, natural polyphenols, namely mangiferin, curcumin, rosmarinic and carnosic acids, were selected as natural biologically active agents with pronounced antibacterial activity. The aim of this review is to conduct a comparative analysis of the antibacterial properties of these natural agents in order to determine the potential for their use in the composition of new effective drugs to combat resistant bacterial infections, including those based on nanoscale polymeric carriers.

2. Antibacterial activity of natural biologically active agents

A unique feature of plants is the ability to produce not only primary metabolites necessary for the vital activity of all cells, but also secondary metabolites that do not participate in the main metabolism. These agents allow plants to adapt to various abiotic and biotic environmental conditions [2]. Secondary metabolites determine the unique properties of plants such as colour, odour and taste and also possess biological activity, thereby affecting other plants, microorganisms, animals and humans [3].

As a result of the microbial evolution, namely the continuous expansion of the spectrum of antibiotic resistance genes, the development of new antibacterial drugs has become necessary in the last decade [4]. Currently, natural BAA are of particular interest as antimicrobial agents due to their easy availability and therapeutic potential [5].

The antibacterial activity is mainly mediated to two mechanisms. The first is by affecting the synthesis or function of vital components of bacteria. For example, bacterial protein biosynthesis or bacterial DNA replication and repair can serve as targets for antibacterial drugs. The second way is alternative mechanisms for the development of antibiotic resistance, for example, through antibiotic modification [6].

Based on the structure of the cell wall, there are two main groups of bacteria: Gram-negative and Gram-positive. Their main difference is the structure of cell walls (Fig. 1). Gram-negative bacteria have a thinner layer of peptidoglycan in their walls than Gram-positive bacteria, and also acquire a red color when stained by Gram staining, in contrast to Gram-positive bacteria, which stain purple [7].

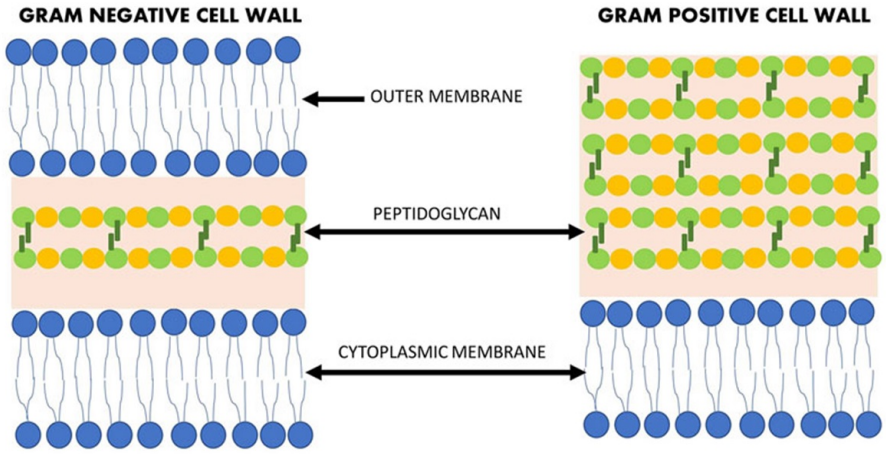


FIG. 1. Structural differences between the cell wall of gram-negative and gram-positive bacteria. Reproduced under the terms of the CC-BY 4.0 license. [8] Copyright 2021, Collective authors. Published by Frontiers Media S.A. (Frontiers in Pharmacology)

Antibacterial activity of secondary metabolites of plants has been confirmed in numerous studies. These compounds can be classified into three main groups: phenolic compounds, terpenoids and alkaloids [9]. Depending on the structural characteristics of bacteria, the efficacy of antibacterial agents may greatly vary [8]. In this paper, the antibacterial properties of a subgroup of phenolic BAA, namely polyphenols, have been considered.

3. Polyphenols

Polyphenols are natural compounds synthesized exclusively by plants and have at least two phenolic groups and one or more hydroxyl substituents in the molecule. These agents are mainly present in fruits, vegetables, green tea and whole grains, and are widely recognized for their antioxidant properties [10].

Polyphenols can be classified into two large groups: flavonoids and non-flavonoids. All flavonoids have a basic structure of diphenylpropanes, where the phenolic rings are usually linked by a heterocyclic ring [11]. Nonflavonoid compounds include phenolic acids, stilbenes (Fig. 2) and lignans (Fig. 3) [10–13].

Polyphenolic BAA have a huge range of biological properties such as antioxidant, anti-oncological, anti-inflammatory and antidiabetic. In addition, numerous studies have shown that polyphenols also possess antiviral, antifungal and antibacterial properties [14]. Thus, polyphenols can be considered as an alternative or complementary treatment for infectious diseases.

3.1. Mangiferin

The fruits and leaves of the mango tree contain a unique xanthone derivative, mangiferin. This compound is present in different plant families in varying concentrations and is usually found as a glycoside [15]. However, one of the major sources of mangiferin is *Mangifera indica*. Mangiferin is a secondary metabolite of this plant and its presence has been

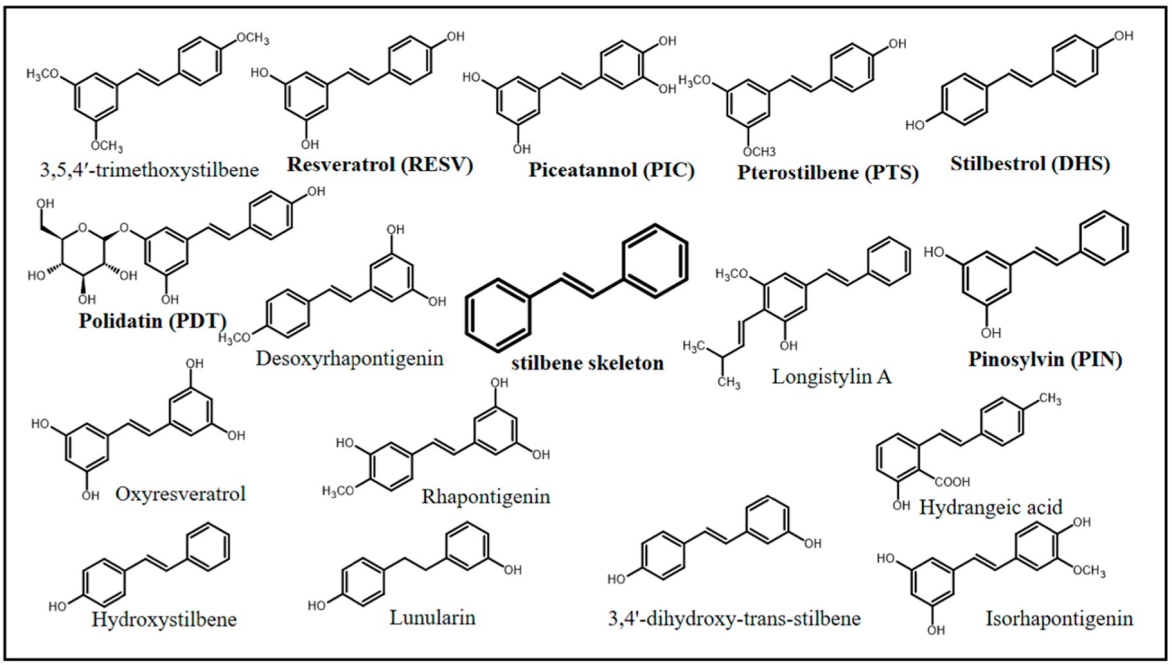


FIG. 2. Chemical structures of stilbenes with documented biological activity. Reproduced under the terms of the CC-BY 4.0 license.[12] Copyright 2024, Collective authors. Published by MDPI

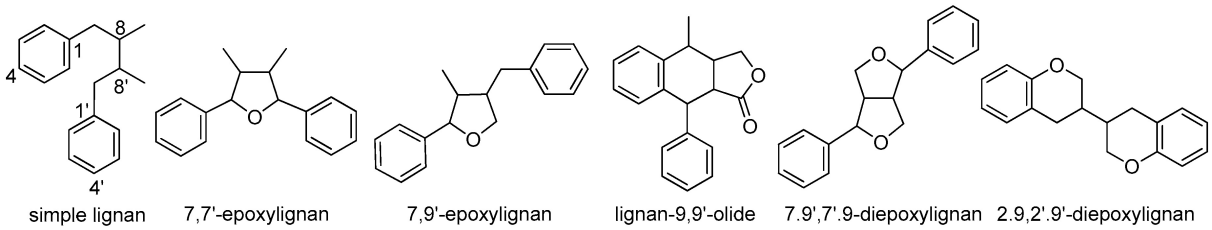


FIG. 3. Subtypes of classical lignans. Reproduced under the terms of the CC-BY 4.0 license.[13] Copyright 2018, Collective authors. Published by MDPI

detected in extracts of bark, peel and pips but the highest amount is found in the leaves [16]. Mangiferin isolated from mango leaves, for example, is a light-yellow crystalline powder [17].

Since the 1960s studies of the structure of mangiferin [18] confirmed that this molecule is 2-C-β-D-glucopyranosyl-1,3,6,7-tetrahydroxyxanthone (Fig. 4).

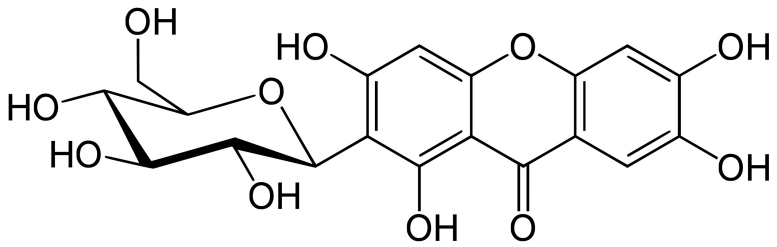


FIG. 4. Mangiferin structure

Besides antibacterial properties, mangiferin has numerous biological properties, including antioxidant, antiviral, antidiabetic, anticancer, immunomodulatory, hepatoprotective, analgesic and anti-aging [19].

Contact dermatitis is the most common inflammatory skin disease characterized by pruritus, immune dysregulation and epidermal barrier dysfunction [20]. Mangiferin also demonstrated anti-inflammatory activity in animal models (mice with oxazolone-induced contact dermatitis). The active ingredient reduced the levels of inflammatory mediators, namely interleukin-1-beta, interleukin-6 and inducible nitric oxide synthase, through the inhibition of the NF-kB signalling pathway, thereby reducing epithelial thickness [21]. In addition, mangiferin is able to inhibit collagenase and elastase activity

and penetrate through the stratum corneum into the epidermis and dermis [22]. It is the stratum corneum of the skin that is the main barrier to transdermal penetration of drugs.

3.2. Curcumin

The plant *Curcuma longa*, belonging to the ginger family, is widely cultivated in southern and south-eastern tropical Asia. The rhizome of this plant is the most useful part of the plant for culinary and medicinal purposes. The most active component of turmeric is curcumin, which makes up 2-5 % of the spice. The characteristic yellow color of turmeric is due to curcuminoids, first isolated by Vogel in 1842. Curcumin is an orange-yellow crystalline powder that is insoluble in water. The structure of curcumin was first described in 1910 and is diferuloylmethane (Fig. 5) [23].

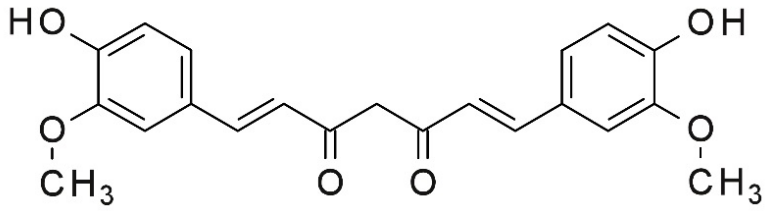


FIG. 5. Curcumin structure

Curcumin has a number of unique properties, which makes it possible to use this substance in various fields of medicine. For example, it has antioxidant, antibacterial, anti-inflammatory, anticancer, antidiabetic, antiviral, cardioprotective properties and is also active against dementia [24].

In addition, curcumin has been shown to be effective against various skin diseases including skin cancer, psoriasis, scleroderma, and dermatitis [25]. Numerous evidences suggest that curcumin accelerates wound healing, also prevents scarring and plays an important role in muscle regeneration after the injury.

3.3. Natural phenolic acids

Although the position of hydroxyl groups in aromatic rings play an important role in biological properties possessing, phenolic acids can be divided according to the skeleton structure into two main groups: hydroxycinnamic acids and hydroxybenzoic acids. Hydroxybenzoic acids occur as free acids or in conjugated forms, namely as glycosides or esters. The most common compounds belonging to this group are gallic, syringic and vanillic acids [26]. Hydroxycinnamic acids have a three-carbon side chain at the aromatic ring, and the most commonly found representatives are caffeic acid, ferulic acid and sinapic acid [27].

Rosmarinic acid is classified as hydroxycinnamic acid. This compound is an ester of caffeic acid (Fig. 6) [28]. It was first isolated from *Rosmarinus officinalis* and named after this plant. Rosmarinic acid has also been found in other plant families such as *Boraginaceae*, *Apiaceae* and *Cucurbitaceae* [29].

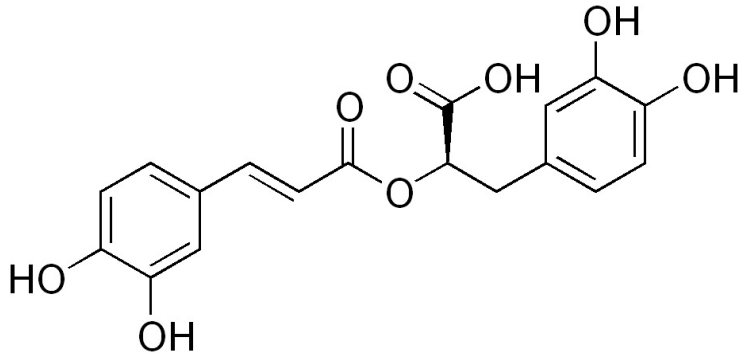


FIG. 6. Rosmarinic acid structure

Rosmarinic acid has a wide range of pharmacological properties such as antibacterial, anti-inflammatory, anti-oncological, anti-aging, anti-diabetic, hepatoprotective, antiviral and nephroprotective [30].

Carnosic acid belongs to hydroxybenzoic acids. This compound has been found in the family Lamiaceae, which includes plants such as *Salvia*, *Rosmarinus*, *Rosmarinus*, *Lepechinia*, *Oreganum* and *Thymus* [31]. The structural formula of carnosic acid is shown in Fig. 7.

Carnosic acid has antibacterial, anti-inflammatory, antioxidant and anti-oncological properties [32].

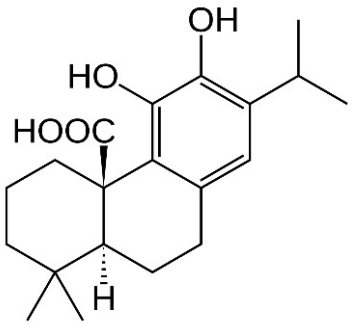


FIG. 7. Carnosic acid structure

4. Analysis of antibacterial activity of polyphenols

In 2017, the World Health Organization (WHO) published the list of 12 families of bacteria that pose the greatest threat to human health. The focus was on Gram-negative bacteria, which have a greater ability to develop resistance to antibiotics through the transfer of genetic material, allowing other bacteria to also develop resistance to the drugs. This list has been divided into three categories according to the urgency of the need for new antibiotics: critical, high priority and medium priority. The top priority is the fight against bacteria with the highest developed resistance, such as *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacteriaceae*. These pathogens are capable of causing pneumonia and infection in the bloodstream. Bacteria capable of causing gonorrhea and food poisoning were categorized as high and medium priority. Examples of these groups are *Entorococcus faecium*, *Staphylococcus aureus*, *Salmonella*, *Streptococcus pneumoniae* and *Haemophilus influenza* [33].

There is also another classification of bacteria with the increasing multidrug resistance and virulence consisting of 6 pathogens. This group is called ESKAPE, and this abbreviation is made from the first letters of bacterial names: *Enterococcus faecium* (Gram-positive), *Staphylococcus aureus* (Gram-positive), *Klebsiella pneumoniae* (Gram-negative), *Acinetobacter baumannii* (Gram-negative), *Pseudomonas aeruginosa* (Gram-negative) and *Enterobacter spp* (Gram-negative). It is these pathogens that cause the majority of hospital-acquired infections [34]. In this analytical review, the antibacterial activity of polyphenols against ESKAPE group was considered.

The specificity of the diseases caused by *Enterococcus faecium* is the formation of a bacterial film. In one study, *Enterococcus faecium* was cultured on dentin biofilm to evaluate the bacterial activity of mangiferin. It was shown that after three weeks, methanolic mango seed extract with the concentration of 5 mg/ml killed 99.8 % of the bacterial colonies on the biofilm [35]. A similar study on dentin biofilm was carried out with 10.2 % aqueous curcumin extract. After three weeks, the significant reduction in *Enterococcus faecium* colonies (approximately 53 %) was found [36].

Staphylococcus aureus is capable to cause a large number of diseases ranging from skin infections to pneumonia and meningitis. Mangiferin has antibacterial activity against this pathogen. For example, disc diffusion method showed that 4 mg/disc of xanthone derivative was able to inhibit about 12.3 mm of *Staphylococcus aureus*, while the antibiotic ampicillin inhibited about 19.7 mm [37]. The same method of study showed that an organic solution (isopropyl alcohol/hexane) of curcumin (1 g / 10 ml) was able to inhibit about 22.3 mm *Staphylococcus aureus* [38].

Klebsiella pneumoniae was first isolated from the person who died of pneumonia, but this pathogen is also capable to cause diseases such as pyelonephritis, septicemia and meningitis. In one study, a methanolic extract of mango fruit containing mangiferin showed inhibitory activity against the growth of *Klebsiella pneumoniae*. The inhibitory zone was 12 mm (100 mg/disc) while the antibiotic kanamycin inhibited 18 mm (30 mg/disc) [39]. Another study showed that curcumin was able to inhibit the growth of *Klebsiella pneumoniae*. Curcumin dissolved in 2 % dimethyl sulfoxide had the minimum inhibitory concentration of 128 μg/ml, the antibiotic meropenem had an identical value [40].

Acinetobacter baumannii is responsible for the development of infections in the bloodstream, respiratory tract, skin and soft tissues. Mangiferin and curcumin have no pronounced antibacterial activity against this microorganism; however, when used in combination with antibiotics, these polyphenols show a synergistic effect [41, 42].

Pyocyanic infection caused by *Pseudomonas aeruginosa* is a leading nosocomial infection. Ethanol solution of mangiferin exhibits an inhibitory effect against this pathogen at the minimum concentration of 62.5 μg/ml [43]. Curcumin dissolved in ethanol showed the minimum inhibitory concentration of 175 μg/ml in an antibacterial study against *Pseudomonas aeruginosa* [44].

Enterobacter spp is also one of the most frequent causes of nosocomial infections, this pathogen causes urinary and respiratory tract, skin and soft tissue infections. Acetone extract of mango peel containing mangiferin was able to inhibit the growth of *Enterobacter spp* (the zone of inhibition was 16 mm) [45]. Acetone solution of curcumin (10 mmol/L) also has antibacterial activity against this microorganism, but its zone of inhibition was only 9 mm [46].

The study of antibacterial activity against *Enterococcus faecium* and *Staphylococcus aureus* of methanol solutions of rosmarinic and carnosic acids showed that the minimum inhibitory concentration against strains of these pathogens for carnosic acid was 60 μg/ml, and rosmarinic acid was inactive even at high concentrations (480 μg/ml) [47]. In addition, the methanolic solution of carnosic acid has the minimum inhibitory concentration of 30 μg/ml against *Klebsiella pneumoniae*, while rosmarinic acid was unable to inhibit the growth of this bacterium [48]. Also, the methanolic extract of *Rosmarinus officinalis* leaves, with high content of rosmarinic and carnosic acids, is able to inhibit the growth of *Acinetobacter baumannii*. The best result was obtained using the solution with the concentration of 100 μg/ml, which had the inhibitory zone of 33 mm [49]. Another study on the antibacterial properties against *Pseudomonas aeruginosa* showed that ethanolic extract of *Rosmarinus officinalis* leaves, achieved the minimum inhibitory concentration at 128 μg/ml [50]. Despite this, neither aqueous nor ethanolic extracts of the same plant (2000 μg/ml) had antibacterial activity against *Enterobacter spp* [51].

The antibacterial activity of the considered polyphenols depends on many factors such as extraction method, degree of purification, solution composition and concentration of bioactive agent. Table 1 summarizes the ability of mangiferin, curcumin, rosmarinic acid and carnosic acid to inhibit the growth of ESKAPE bacteria.

TABLE 1. Comparative analysis of polyphenols antibacterial activity

Pathogen	Polyphenol			
	Mangiferin	Curcumin	Rosmarinic acid	Carnosic acid
Enterococcus faecium	+	+	-	+
Staphylococcus aureus	+	+	-	+
Klebsiella pneumoniae	+	+	-	+
Acinetobacter baumannii	-	-	+	+
Pseudomonas aeruginosa	+	+	+	+
Enterobacter spp	+	+	-	-

Table 1 shows that polyphenols such as curcumin and mangiferin have antibacterial activity against ESKAPE group of pathogens except *Acinetobacter baumannii* strain.

Phenolic acids are also capable of inhibiting the growth of multidrug resistant microorganisms. However, rosmarinic acid is not active against this group of pathogens, while *Rosmarinus officinalis* leaf extracts are likely to have antibacterial properties due to the carnosic acid included in the extract, which has good inhibitory ability against the ESKAPE group of bacteria except *Enterobacter spp*.

Thus, polyphenols are potential candidates for the control of infectious diseases caused by pathogens with high antimicrobial resistance. Their relevance for the use against highly resistant bacteria is due to their synergistic effect when used with existing antibiotics, as well as their different mechanisms of action on microorganisms than conventional drugs [52]. In addition, there is an opportunity to improve the antibacterial properties of polyphenols using various methods, including their introduction into delivery systems based on polymer matrices [53].

5. Nanoscale delivery systems for natural compounds with antibacterial action

Currently there are a lot of carriers which could be used for the incorporation of biologically active agent into nanoscale delivery systems. Schematic representation of the most promising nanocarriers is demonstrated in Fig. 8. More detailed information was published earlier [54, 55]. Summarized information of various nanocarriers is shown in Table 2.

5.1. Mangiferin

Mangiferin-loaded delivery systems are described in the recently published review [56].

It was many times documented that mangiferin have antioxidant, anti-infection, anti-cancer, anti-diabetic, cardiovascular, neuroprotective properties and this molecule also enhance immunity, without demonstrating any toxicity even at high doses. To improve the solubility, increase the biological effects and bioavailability, mangiferin was integrated into polymer systems. This review summarizes molecular mechanisms of anti-cancer action and also a number of designed polymer-mangiferin systems.

TABLE 2. Summarized information of various nanocarriers Reproduced under the terms of the CC-BY 4.0 license.[54] Copyright 2020, Collective authors. Published by MDPI

Nanosystems	Advantages	Limitations
Liposomes	Biodegradability Biocompatibility Reduced systemic toxicity Improved stability and circulation time of the drugs	Low drug loading Lack of colloidal stability Difficulties in sterilization Some leakage of the encapsulated agent
SLNs	Suitable for a variety of routes of administration Good physiological compatibility A wide range of drug adaptability Improve the stability of drugs	Requires organic solvent during preparation Low loading capacity compared with other nanocarriers Possibly containing other colloidal structures and complex physical state
NLCs	Stability Good biocompatibility High drug-loading capacity Targeting and controlled release Improved bioavailability of drugs	No data
Micelles	Suitable for water-insoluble drugs due to hydrophobic core	Poor chemical versatility and structural instability
PMs	Good stability Allow drugs to avoid mononuclear macrophages phagocytosis Water-insoluble drugs can be easily incorporated into PMs by the simple act of mixing	Premature drug leakage Toxicity of materials, fixed functionality after synthesis Response mechanism in the human body unknown
Polymeric NPs	Targeted, controlled drug release Easy surface functionalization	The polymer cytotoxicity Difficulty in large-scale industrial production The residual organic solvent in the preparation process
Dendrimers	Structural symmetry and stable nature Has a strong EPR Enhancement in the blood circulation time Multiple functional groups in its surface Customize the drug release profiles	Time-consuming synthesis and increased production costs Difficulties in mass production Cytotoxic and hemolytic properties
Niosomes	Overcome phospholipid oxidation	No data
Nanoemulsions	Improve drug stability To avoid drug inactivation in the gastrointestinal tract Increase drug solubility and improve bioavailability With lymphatic targeting and sustained release to reduce the side effects of drugs	No data

Nanocrystals	Free of organic solvents or other solubilizing chemicals Carrier-free delivery system High-drug loading efficiency Steady dissolution rates Great structural stability	Difficulty in large-scale industrial production
Bio-NPs	Overcome various biological barriers Lower immunogenicity and toxicity Biocompatibility and biodegradability	Limited drug loading capacity
Exosomes	High capacity to pass through various biological barriers High stability Less immunogenity Natural targeting capacity	Specific approaches to load the desired additional drugs without disturbing the exosomes
Metal NPs	Simple synthesis procedures Modifiable (control of pore size) Multifunctional surface functionalization	Poor biocompatibility Low stability Poor water solubility
Inorganic non-metallic NPs	Simple synthesis procedures	Low loading capacities
Hybrid nanomedicines	Targeted delivery of drugs Has high structural integrity Stable storage of drugs and the controlled release of drugs Increased drug encapsulation efficiency and biocompatibility	Potential material toxicity

5.2. Curcumin

Curcumin-loaded delivery systems are extremely numerous and are presented in main reviews [57–59]. However, its clinical use is extremely difficult due to the pH-dependent structure transformations of curcumin [60].

Commercially available curcumin, commonly used *in vitro* and *in vivo* studies, is the mixture of curcuminoids derived from the rhizome of *Curcuma longa Linn*, it is a mixture of three main diarylheptanoids: 75-77% is curcumin (C) (diferuloyl methane; MW $C_{21}H_{20}O_6$; log P = 3.29; MM = 368.38), 15-18% – demethoxycurcumin (DMC) (p-Hydroxycinnamoyl feruloyl methane; $C_{20}H_{18}O_5$; log P = 2.792; MM= 338.35), 5-7% –bis-demethoxycurcumin (BDMC) (di-p-hydroxycinnamoylmethane; $C_{19}H_{16}O_4$; log P = 2,649; MM = 308,33) [61–63].

According to the chemical structure, the main component of the curcuminoid mixture, curcumin is bis-α, β, an unsaturated β-diketone formed as the result of the conjugation of two ferulic acid molecules connected by a methylene bridge [64]. In the solution curcuminoid molecules are in keto-enol form stabilized by hydrogen bonds. The direction of the equilibrium shift in keto-enol tautomerism depends from the polarity of the solvent and the pH value of the solution. In nonpolar solvents, curcumin is mainly represented in the enol form, which is maintained by the formation of an intramolecular hydrogen bond, and in polar solvents curcumin passes into the diketo form [62–64]. Fig. 9 shows the structural formulas of the main diarylheptanoids and structural transitions in keto-enol tautomerism of the curcumin molecules [65].

There are three proton-donating groups in the curcumin molecule that dissociate at different pH values of the medium: a proton of the enol group (pKa=8.5) and two phenolic OH groups (pKa=10–10.5). Fig. 10 shows the ionization scheme of the hydroxyl groups of curcumin.

5.3. Rosmarinic acid

Rosmarinic acid (RA) is an important antitumour phytochemical due to its multi-targeted anti-oncological mechanisms. However, its bioavailability when ingested is limited due to poor solubility and permeability. In recent years, tremendous efforts have been made to develop nanoforms of rosmarinic acid for the treatment of cancer. However, these

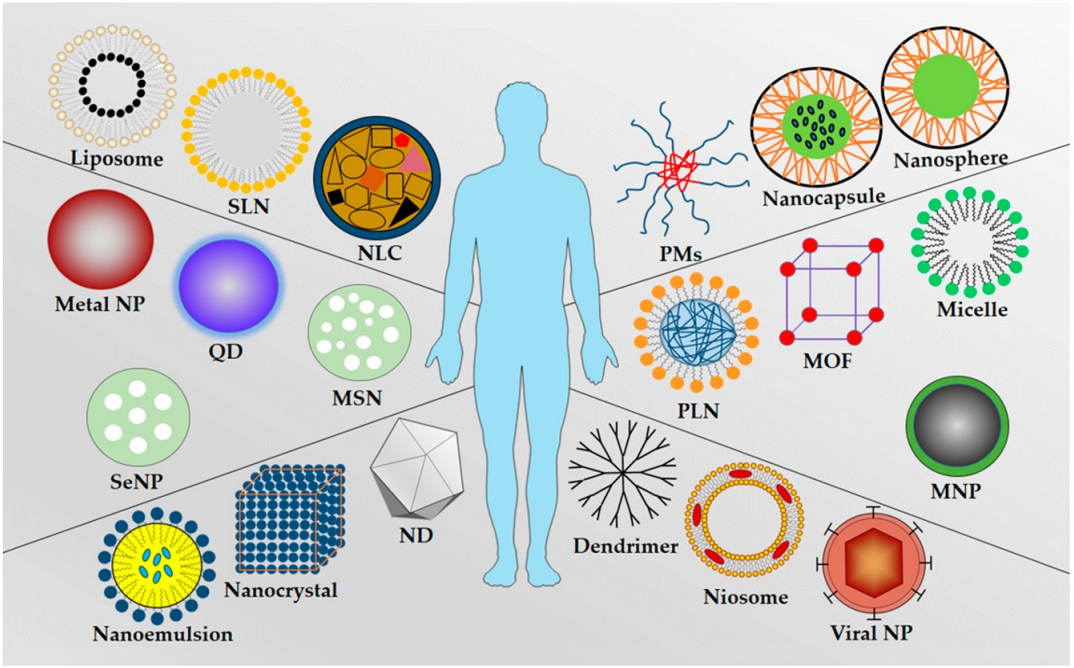


FIG. 8. Typical nanocarriers used for the loading (incorporation) of biologically active agents: dendrimer, liposome, magnetic nanoparticle (MNP), mesoporous silica nanoparticle (MSN), metal nanoparticle, metal–organic framework (MOF), micelle, nanocapsule, nanodiamond (ND), nanoemulsion, nanocrystal, nanosphere, nanostructured lipid carrier (NLC), niosome, polymer–lipid hybrid nanoparticle (PLN), polymeric micelles (PMs), selenium nanoparticle (SeNP), quantum dot (QD), solid lipid nanoparticle (SLN), viral nanoparticle. Reproduced under the terms of the CC-BY 4.0 license.[54] Copyright 2020, Collective authors. Published by MDPI

studies are at an early stage as bringing nanoparticles to the market is itself associated with numerous challenges such as stability, toxicity and scalability of the synthesis process [66].

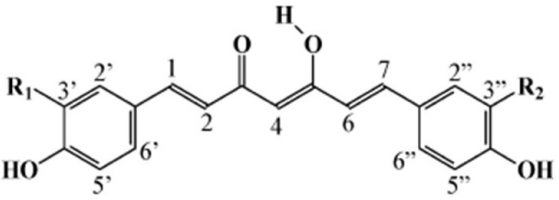
Xue et al. developed liposomes with RA and doxorubicin, named rososomes (RS). RS were synthesized by the classical thin film hydration method. Phospholipid choline and 1-polmitoyl-2-hydroxy-sn-glycero-3-phosphocholine were taken as lipid matrix (RA-L). RA-L was obtained through the conjugation of an amphiphilic lipid to RA by the esterification method. RA-L was combined with polyethylene glycol and phosphotidylcholine to obtain RS. RS was found to have the diameter of 198.9 nm and the polydispersity index (PDI) of 0.194, indicating a rather narrow size distribution of the rhososomes. Cross-linking was carried out with trivalent iron to stabilize the structure of liposomes. *In vivo* experiments on mice with breast cancer showed that RS cross-linked with iron exhibited significant activity in cancer treatment [67].

Subongkot et al. developed ultra-deformable liposomes (ULS) of RA with fatty acids such as oleic, linoleic and linolenic acids to improve the skin penetration of RA in skin cancer. The size, zeta potential, size distribution, shape, encapsulation efficiency (% EE) and polymer matrix capacity (% DL) of the prepared ULSs were evaluated. The obtained ULSs with fatty acids had negative zeta potential and average particle size ranging from 50.37 ± 0.3 to 59.82 ± 17.3 nm. The average EE and DL were 9 % and 24 %, respectively. RA has been shown to penetrate the skin much more easily with ULS containing oleic acid than ULS without added fatty acids [68].

Fuster et al. developed silk fibroin nanoparticles containing RA (RA-SFN) and investigated their activity against breast cancer cells (MCF-7) and human cervical cancer cells (HeLa). The characteristics of the synthesized nanoparticles were determined: the average particle diameter was 255 nm, zeta potential was -17 mV, and PDI was 0.187. About 50 % of the total drug content was released in 0.5 h, indicating rapid release under physiological conditions. Studies on cell lines showed that concentration-dependent cancer cell death was observed after the treatment by RA-SNs. MCF-7 and HeLa cell death was observed at IC_{50} values of 1.568 and 1.377 mg/ml, respectively. In addition, the inhibition of cell proliferation was observed in cancer cell lines following cell cycle and apoptosis studies [69].

Tabatabaeian et al. developed a unique conjugate of NH_2-UiO-66 with nitrogen-doped carbon nanodots (N-CND) with embedded rosmarinic acid to target adenocarcinoma. The size range of the obtained particles was 35 ± 10 nm and the zeta potential was -03.6 mV. To study the apoptotic effect, MTT assay was performed on cell line A549: apoptosis increased with the increasing nanoparticle concentration from 25 to 150 μg/ml. Thus, a new carrier of rosmarinic acid was found to be promising and cost-effective for drug delivery systems for cancer treatment [70].

Chung et al. developed PEGylated rosmarinic acid nanoparticles, (RA-NPs), for the treatment of inflammatory bowel disease and colorectal cancer. Particles with the diameter of 63.5 ± 4.0 nm were prepared from PEG-containing



C: R^1=OCH_3, R^2=OCH_3; DMC: R^1=OCH_3, R^2=H; BDMC: R^1=H, R^2=H

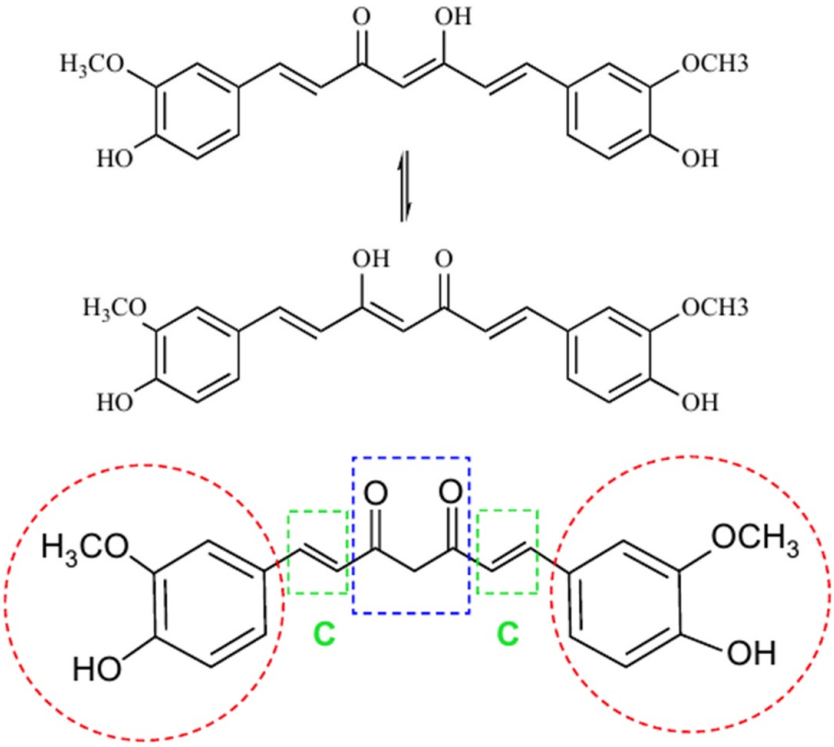


FIG. 9. Structural formulas of the main diarylheptanoids [60]

amine and rosmarinic acid in a single step followed by self-assembly in the buffer solution. In physiological media, the obtained RA-NPs exhibited good colloidal stability for a fortnight. RA-NPs could efficiently absorb hydrogen peroxide, preventing cell damage due to the oxidative stress. In inflamed colon, RA-NPs reduced the expression and production of pro-inflammatory cytokines [71].

Campos et al. developed lipid nanoparticles with rosmarinic acid. Witepsol H15 was used as a lipid shell and Tween 80 was used as the surfactant. The hot melt ultrasonication method was used. The authors used different formulations: 1 %, 2 % and 3 % vol/vol of lipid and 0.5 %, 1 % and 1.5 % wt/vol of surfactant. The results showed that nanoparticles with an average diameter ranging from 270 to 1000 nm could be obtained using Witepsol H15. The obtained particles were found to be extremely stable: during 28 days in aqueous solution at 5°C, they maintained their morphological characteristics and had no tendency to aggregate. The encapsulation efficiency of rosmarinic acid was 99 %, and rosmarinic acid was not washed out from the matrix during the storage [72].

Interestingly, rosmarinic acid in the composition of nanoparticles can be used not only as an antibacterial agent, but also as a modifier. Thus, Bhatt et al. proposed silver nanoparticles whose surface was modified with rosmarinic acid (Ro-AgNPs). Such particles can be used to create sensitive colorimetric probe sensors for the rapid determination of cyanide (CN-) and chromium (VI) [Camr(VI)] in aqueous solutions, including waste water [73].

In addition to nanoparticles, other types of nanomaterials, such as nanofibers, can be fabricated with rosmarinic acid. One of the possible methods to produce such fibers is the electroforming method of polymer solutions [74]. Thus, nanofibers based on cellulose acetate with rosmarinic acid were prepared and investigated. To evaluate the biological activity of nanofibers containing BAS, their ability to inhibit protein denaturation was analyzed as an indicator of anti-inflammatory properties, and their antioxidant activity was determined by free radical capture method. Homogeneous distribution of the drug throughout the volume of nanofibers provided high loading efficiency, absence of explosive release at the initial stages, and prolonged release for 64 h by the mechanism of diffusion according to Fick's law. The nanofibers

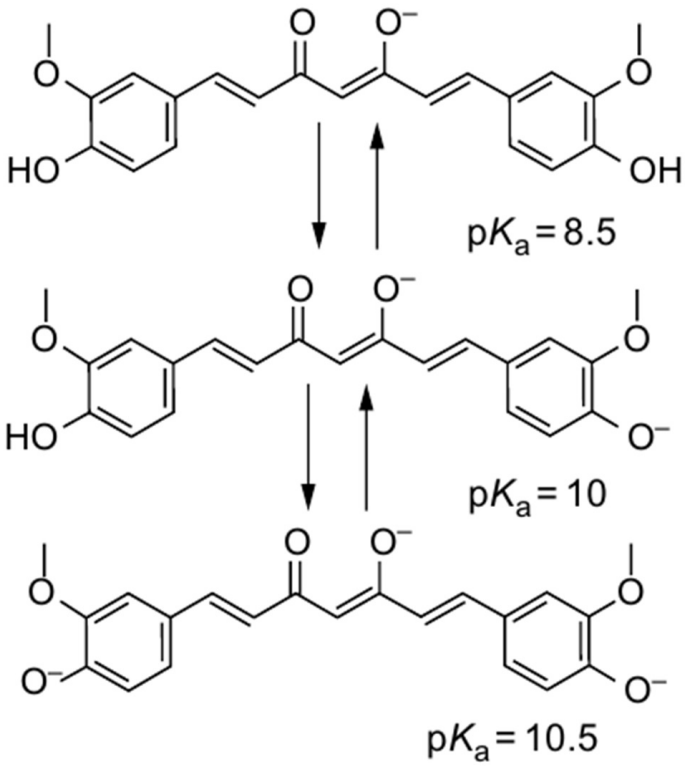


FIG. 10. Scheme of ionization of hydroxyl groups of curcumin at pH values of medium >8 [60]

with higher RA content exhibited anti-inflammatory activity comparable to ibuprofen and higher antioxidant activity compared to nanofibers with low bioactive agent content. In addition, the nanofibers did not have any significant cytotoxic effects on cells. The delayed release of RA and the biological activity of RA-containing nanofibers confirmed the potential of the obtained matrix as a drug delivery system [75].

5.4. Carnosic acid

Chitosan nanoparticles containing carnosic acid were prepared by ionotropic gelation method. The effect of factors such as chitosan concentration (0.1–1.0 % by weight), tripolyphosphate concentration (0.1–1.0 % by weight) and ultrasonic treatment time (2–10 min) on key particle parameters such as size and morphology, zeta potential, drug encapsulation efficiency and drug release kinetics were evaluated. The protein level of neurotrophins in rat brain during intranasal administration of optimized dose of carnosic acid nanoparticles was determined. The experimental values of the drug doses correlated well with those predicted by mathematical models. A single intranasal administration of carnosic acid nanoparticles was sufficient to achieve the required level of endogenous neurotrophins in the brain, which was almost the same as when chitosan solution with carnosic acid was intranasally administered to rats once a day for four days. The results clearly demonstrated the fact that the nanoparticle drug delivery system for intranasal administration of carnosic acid requires fewer injections to achieve the required pharmacological activity due to its ability to localize on the nasal mucosa and provide controlled delivery of carnosic acid over a long period of time [76].

A lecithin-based nanoemulsion (CA-NE) was developed to enhance the bioavailability and biological activity of carnosic acid (CA). The investigated material was found to have high capacity (2.80 $\pm$ 0.15 %), small particle size (172.0 $\pm$ 3.5 nm) with homogeneous particle distribution (PDI index is 0.231 $\pm$ 0.025) and zeta potential value of -57.2 ± 0.24 mV. More importantly, the bioavailability of CA-NE was improved 2.8-fold compared to the CA content of MCT oil. In addition, cellular antioxidant assay (CAA) and cellular uptake study of CA-NE in HepG2 cell model demonstrate a longer endocytosis process, indicating a controlled release of CA from CA-NE. In addition, improved anti-inflammatory activity was assessed by inhibition of the production of pro-inflammatory cytokines, nitric oxide (NO) and TNF-α in lipopolysaccharide-stimulated RAW 264.7 macrophage cells [77].

Carnosic acid was encapsulated in bovine serum albumin (BSA), chitosan (CH) and cellulose (CL) nanoparticles to enhance its activity against breast cancer (MCF-7) and colon cancer (Caco-2) cells. CA-enriched BSA nanoparticles (CA-BSA-NPs) showed good drug encapsulation efficiency and best release profile as the drug concentration reached 80 % after 10 hours. The antitumour activity of CA-BSA-NPs was evaluated by the measuring of cell viability, apoptosis rate and gene expression of GCLC, COX-2 and BCL-2 in MCF-7 and Caco-2. Cytotoxicity (MTT) assay showed enhanced antitumour activity of CA-BSA-NPs against MCF-7 and Caco-2 compared to free CA and BSA-NPs. Moreover, apoptosis

test data showed growth arrest of Caco-2 cells at G2/M (10.84 %) and MCF-7 cells at G2/M (4.73 %) when treated with CA-BSA-NPs. Gene expression analysis based on OT-PCR showed the increased activity of GCLC gene and the decreased activity of BCL-2 and COX-2 genes in cells treated with CA-BSA-NPs compared to the untreated cells. In conclusion, CA-BSA-NPs have been presented as a promising formula for the treatment of breast cancer and colorectal cancer [78].

6. Conclusion

In this paper, an analytical review of natural biologically active agents exhibiting antibacterial activity, namely such polyphenols as mangiferin, curcumin, rosmarinic acid and carnosic acid has been carried out. A comparative analysis of the antibacterial properties of these natural substances against a group of microorganisms possessing multidrug resistance and virulence was also carried out.

Comparative analysis of antimicrobial activity showed that mangiferin, curcumin and carnosic acid are potential candidates to address the problem of multidrug resistance to antibacterial drugs. These natural agents can be recommended for the incorporation into advanced drug delivery systems such as nanoparticles, nanomicelles, nanocapsules, etc.

Analysis of data on delivery systems for these natural molecules has shown that for rosmarinic and carnosic acids, the number of delivery systems is extremely limited and require development based on biocompatible and biodegradable matrices with targeted action. Equally important is the review of methods used to characterize nanoscale delivery systems.

Thus, this review not only highlights the known data on natural agents with antibacterial action, but also points to new directions in the development of nanosystems and nanoscale materials for the delivery of potential drugs to combat multidrug resistance.

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