Antibacterial activity of Turmeric longa (Curcuma longa L.)

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SUMMARY

Long turmeric (Curcuma longa L.) and its biologically active substances curcuminoids have pleiotropic activity, including antibacterial activity. Numerous studies have shown that the antibacterial activity of turmeric and curcuminoid extracts has a wide range of biological and pharmacological properties against various pathogenic and opportunistic microbes. The mechanisms of antibacterial action of curcumin consist either in direct interference with the reproduction of bacteria or in the suppression of cellular signaling pathways required for their replication. This review summarizes current data and prospects for the use of the antibacterial activity of curcumin.

Key words: long turmeric, curcumin, antibacterial action, bacteria.

RESUME

Curcuma longa L. and its compound curcuminoids have pleiotropic activity, including antimicrobial activity. Numerous studies have shown that antimicrobial activities for extracts of Curcuma longa and curcuminoids possesses a wide spectrum of biological and pharmacological properties against different microbes. Mechanisms of antimicrobial activity of curcuminoids involve either a direct interference of microbial replication machinery or suppression of cellular signaling pathways essential for microbial replication. This review summarizes the current knowledge and future perspectives of the use of the antimicrobial effects of curcumin.

Keywords: curcuma, curcumin, antimicrobial properties, microbes.

INTRODUCTION

On our planet, there is a huge number of microbes that inhabit nature (soil, plants, water bodies, atmosphere) and live in the human body, animals, birds and insects. The human body contains at least 1014 bacteria. Many microbes are pathogenic and opportunistic. Antibiotics are used to combat them. However, the use of antibiotics is complicated by the emergence and spread of antibiotic-resistant strains. Bacteria in biofilms, which protect them from biocides, are also a problem in the treatment of infectious diseases. The stability of biofilm microbes is also associated with a slowdown in their growth rate [14].

Due to the insufficient effectiveness of traditional medicines - antibiotics, it is proposed to use herbal medicines [11]. It has been shown that herbal antimicrobial agents, the biological activity of which is due to the presence of certain chemical compounds, can serve as an alternative to antibiotics. [54]. Medicinal plant preparations are officially considered as natural antibiotics that can replace existing ones. For widespread implementation in practice, a comprehensive study of their properties is necessary. There is an extensive literature that provides data on numerous medicinal plants. One of them is Curcuma longa. This review focuses on the antimicrobial potential of curcumin, which is found in Curcuma longa.

1. Turmeric and Curcuminoids

The history of using Curcuma longa in traditional medicine in different countries goes back several centuries. Turmeric, which belongs to the ginger family (Zingiberaceae), is native to India and Southeast Asia. It is a plant with a fleshy rhizome, the numerous branches of which are tuberous. Tubers with a bright yellow color are raw materials for the production of medicines and spices. There are various types of turmeric. Turmeric long - Curcuma longa, (turmeric) is used in pharmacology.

Turmeric rhizome contains a complex complex of biologically active substances, among which the most pharmacologically important is curcuminoids. Curcumin is the main curcuminoid. Chemically, curcumin belongs to the class of natural polyphenols [1]. The immunomodulatory, antibacterial, antiviral and antifungal properties of curcumin are being intensively investigated. Experimental data show that curcumin has the ability to interact with a variety of target molecules. This property is responsible for the broad spectrum of action of curcumin. The great value of curcumin lies in its synergism with other antimicrobial drugs that are active against antibiotic-resistant strains and biofilms. The antibacterial activity of curcumin is combined with its good tolerance for the body. Shown that drugs from Curcuma longa have an inhibitory effect on various types of bacteria. They are candidates for a modern defense system against infectious diseases. [29, 42].

2. SPECTRUM OF ANTIBACTERIAL ACTION OF CURCUMIN

It has now been established that curcumin is characterized by antibacterial, antiviral, antifungal properties [5, 32]. Reviewed by Moghadamtousi et al. [32] reported that methanol and hexane extracts of Curcuma longa are active against 13 species of gram-positive and gram-negative bacteria: Vibrio harveyi, V. alginolyticus, V. Vulnificus, V. parahaemolyticus, V. cholerae, Bacillus subtilis, Bacillus cereus, Aeromonas hydrophila agalactiae, Staphylococcus aureus, S. intermedius, S. epidermidis. The antibacterial effect of curcumin has been shown in a number of other studies. In an article by Adamczak et al. for 2020 summarized the latest results on the study of the antibacterial action of curcumin. [7]. The authors include gram-positive bacteria as sensitive to curcumin microbes: Streptococcus pyogenes, S. agalactiae, S. aureus, S. haemolyticus, S. epidermidis, Enterococcus faecalis, methicillin-resistant S. aureus, S. haemolyticus, and gram-negative Acinetobacter lwoffii, A. baumannii, Escherichia coli, Klebsiella oxytoca, K. pneumoniae, Pseudomonas aerugilis, Proteins Table 1 provides a summary of the antibacterial activity of Curcuma longa and curcumin, as well as their mechanisms of action underlying the inhibitory effect.

Table 1

Antibacterial activity of curcumin

Microorganism	Mechanism of action	Links
Staphylococcus aureus	Bacterial growth inhibitor, sortase A inhibitor	38, 45, 48
Staphylococcus epidermidis	Inhibition of bacterial growth and biofilm formation	7, 10
Streptococcus mutans	Inhibition of adhesion, biofilm formation, grade A inhibitor	23, 30
Streptococcus pyogenes	Inhibition of bacterial growth	7
Bacillus subtilis	Growth inhibition due to effects on FtsZ protein and biofilm formation	24, 38, 39, 49
Bacillus cereus	Inhibition of bacterial growth and biofilm formation	24, 38, 49
Listeria innocua	Inhibition of bacterial growth	8, 16
Escherichia coli	Inhibition of bacterial growth, FtsZ protein and biofilm formation	7, 24, 27
Salmonella enteritica serotype Typhimurium	Growth retardation and decreased motility of bacteria	7, 33
Helicobacter pylori	Inhibition of bacterial growth, inhibition of (NF) kB, shikomat dehydrogenase and biofilm formation	15, 19, 22, 47
Pseudomonas aeruginosa	Inhibition of growth and biofilm formation	7, 24
Clostridium difficile	Inhibition of bacterial growth	37
Vibrio vulnificus	Inhibition of bacterial growth	40

Peculiarities actions curcumin on representatives of gram-positive and gram-negative bacteria have been identified using electron microscopy. The morphology of E. coli (gram) and S. aureus (gram +) after exposure to curcumin was analyzed by transmission electron microscopy (TEM). In E. coli, the appearance of filaments on the cell surface was found. In S. aureus, destruction of the cell wall and impaired division were revealed [35].

Gram-positive bacteria were found to be more sensitive to curcumin than gram-negative ones, in which the outer lipopolysaccharide membrane of the cell wall is a barrier that protects the cell from external antimicrobial agents [53]. It has been found that curcumin acts against clinically significant pathogens. The activity of curcumin against Helicobacter pylori bacteria, which is the cause of the development of diseases of the gastrointestinal tract (GIT), such as gastritis, peptic ulcer and stomach cancer, has been shown. To combat H. pylori, various plant extracts are used, including those from Curcuma longa [32]. Currently, curcumin is considered as a treatment for diseases due to H. pylori infection [52, 59]. Curcumin is active against staphylococci, which cause purulent inflammatory processes, furunculosis, abscesses, septicemia, etc.in vitro action Curcuma longa on laboratory strains and clinical isolates of S. aureus. Clinical isolates were the most sensitive. Scanning electron microscopy (SEM) revealed morphological deformation, partial disappearance of the cytoplasmic membrane, and destruction of cells in bacteria treated with curcumin [20]. In vitro experiments have shown the antibacterial activity of curcumin against methicillin-susceptible S. aureus (MSSA) and methicillin-resistant S. aureus (MRSA) strains [18, 57]. Curcumin also has an antimicrobial effect on listeria, salmonella, staphylococcus, E. coli that infect food [8, 16]. An important property of cucumin is activity against spore-forming bacteria, bacilli and clostridia. Curcumin has been shown to be active

against B. subtilis, B. cereus, Bacillus macerans, and Bacillus licheniformis [41]. Recently, the group of authors Mody et al. [37] found the antibacterial activity of curcumin against Clostridium difficile. At the same time, a decrease in the toxin-forming ability of clostridia and a violation of sporulation were found.

Antimicrobial activity of curcumin against Vibrio vulnificus, which causes septicemia and necrotic wound infection, was found [40]. It has been shown experimentally that curcumin inhibits motility, adhesion, and toxin formation in V. vulnificus and protects mice from septicemia.

3. MECHANISMS OF ANTIMICROBIAL ACTION OF CURCUMIN

Currently, a search for new drugs is being carried out, including drugs from medicinal plants, with a different mechanism of antibacterial action [9]. A 2020 review by Chinese scientists presents various aspects of the action of curcumin on bacteria: membrane destruction in gram-negative and gram-positive bacteria; inhibition of the drain pump (efflux pump); suppression of the division of bacteria by disrupting the assembly of the FtsZ protein; inhibition of the synthesis of polysaccharides and a decrease in adhesive activity [25]. There are other mechanisms of curcumin's antimicrobial action. These include inhibition of chicomat dehydrogenase and inactivation of the transcription factor NFkB [15.46]. Shikomatdehydrogenase is considered as a potential target for drug therapy [12]. Shikimic acid (shikomat) is a precursor of the aromatic amino acids phenylalanine, tyrosine, tryptophan. The action of curcumin against H. pylori is associated with inhibition of the enzyme shikomat dehydrogenase, which leads to disruption of the synthesis of aromatic amino acids [22]. The shikimate pathway of biosynthesis of aromatic compounds is found in plants, fungi, algae, protozoa, microorganisms and is absent in humans and animals [31]. Enzymes of the shikomat pathway attract attention as targets of antimicrobial and antiparasitic agents, as well as herbicides [17]. Another target for the action of curcumin is the transcription factor NFkB. The nuclear factor NFkB (kappa B - "kappabi") is one of the main transcription factors important for such cellular processes as immune response, proliferation, apoptosis and inflammation. One of the causes of gastrointestinal diseases caused by H. pylori bacteria, is the activation of NFkB in the epithelial cells of the stomach, leading to inflammation. [28, 55]. Curcumin prevents disease from H. pylori infection by inhibiting the nuclear transcription factor (NF) kB. [19].

The next mechanism of antimicrobial action of curcumin is the suppression of cell proliferation. The process of bacterial cell division is considered in detail in the review by A.D. Vedyaykin. and others [2]. Bacterial division is controlled by the tubulin homologue, the FtsZ protein, which forms a ring structure (Z-ring) at the site of division. FtsZ, like tubulin, has GTPase activity. Hydrolysis of GTP provides polymerization of FtsZ with the formation of linear protofilaments. FtsZ is found in almost all bacteria. FtsZ assembles the scaffold of the Z-ring cytoskeleton, which, together with additional proteins, shrinks to divide the cell in two. Ftz is considered an important target for antibacterial drugs. Rai et al. [49] showed that curcumin inhibits the assembly of the bacterial protofilament FtsZ. Shows the effect of curcumin on B. subtilis, associated with a violation of cell division. Curcumin induces the formation of filamentous forms in B. subtilis. The suppression of E. coli growth by curcumin is also explained by the inhibition of polymerization of the FtsZ protein [27]. It has also been shown that curcumin disrupts the division of B. subtilis due to its effect on membrane permeability and integrity, which is necessary for intracellular localization of FtsZ [39].

Curcumin has a similar effect on pathogenic bacteria, disrupting the assembly of FtsZ, which inhibits the proliferation of H. pylori [46]. The effect of curcumin on staphylococci has been studied in detail [58]. It was shown using fluorescence microscopy and SEM that

curcumin increases membrane permeability and damages its structure. Information on the action of curcumin at St. aureus are summarized in a review by Teow et al. [57]. The authors came to the following conclusions: curcumin can bind to the FtsZ protein, suppressing the assembly of protofilaments, which suppresses the formation of the Z-ring leading to inhibition of cytokenesis and bacterial proliferation; in the case of MRSA, curcumin can inhibit the mecA transcription gene, reducing the expression of the PBP2a protein, as a result of which MRSA becomes sensitive to the antibacterial effect of β-lactam antibiotics; the binding of curcumin to cell wall peptidoglycan can trigger cell wall and membrane damage, leading to cell lysis. Subsequently, a study was made of the effect of curcumin in combination with tetracycline on S. aureus and E. coli cells. TEM and SEM have shown that curcumin, together with an antibiotic, destroy the bacterial cell wall [56]. Thus, curcumin acts on the outer structures of the bacterial cell - the cell wall and the cytoplasmic membrane. To this should be added information about the effect of curcumin on external organelles - flagella. It turned out that curcumin reduces the motility of Salmonella enterica serotype Typhimurium due to the shortening of the flagellum (from 8 μm to 5 μm) and reduces the number of flagella per cell (from 8 to 4–5). The total number of flagellated bacteria is reduced from 84% to 59%. However, the expression of the flagellin gene is not disturbed. It is possible that the flagellum becomes more fragile and fragmented [33]. curcumin acts on the outer structures of the bacterial cell - the cell wall and cytoplasmic membrane. To this should be added information about the effect of curcumin on external organelles - flagella. It turned out that curcumin reduces the motility of Salmonella enterica serotype Typhimurium due to the shortening of the flagellum (from 8 μm to 5 μm) and reduces the number of flagella per cell (from 8 to 4–5). The total number of flagellated bacteria is reduced from 84% to 59%. However, the expression of the flagellin gene is not disturbed. It is possible that the flagellum becomes more fragile and fragmented [33]. curcumin acts on the outer structures of the bacterial cell - the cell wall and cytoplasmic membrane. To this should be added information about the effect of curcumin on external organelles - flagella. It turned out that curcumin reduces the motility of Salmonella enterica serotype Typhimurium due to the shortening of the flagellum (from 8 μm to 5 μm) and reduces the number of flagella per cell (from 8 to 4–5). The total number of flagellated bacteria is reduced from 84% to 59%. However, the expression of the flagellin gene is not disturbed. It is possible that the flagellum becomes more fragile and fragmented [33]. that curcumin reduces the motility of Salmonella enterica serotype Typhimurium due to the shortening of the flagellum (from 8 μm to 5 μm) and reduces the number of flagella per cell (from 8 to 4–5). The total number of flagellated bacteria is reduced from 84% to 59%. However, the expression of the flagellin gene is not disturbed. It is possible that the flagellum becomes more fragile and fragmented [33]. that curcumin reduces the motility of Salmonella enterica serotype Typhimurium due to the shortening of the flagellum (from 8 μm to 5 μm) and reduces the number of flagella per cell (from 8 to 4–5). The total number of flagellated bacteria is reduced from 84% to 59%. However, the expression of the flagellin gene is not disturbed. It is possible that the flagellum becomes more fragile and fragmented [33].

4. ANTI-BIOFILM ACTIVITY OF CURCUMIN

Curcumin has been shown to be active against bacteria existing in the form of biofilms. Biofilms are a continuous layer of bacteria attached to each other, to various surfaces and enclosed in a biopolymer matrix [4]. Intercellular communication in the biofilm is carried out with the participation of a regulatory mechanism, “quorum sensing” (QS) [36]. At the initial stage, bacteria adhere to the surface and form a monolayer. Then they move along the surface, aggregating and forming microcolonies. In the process of biofilm formation, the extracellular matrix is synthesized. The matrix contains exopolysaccharides (EPS), proteins, lipopolysaccharides, nucleic acids, lectins and minerals. The matrix protects biofilm bacteria from antibacterial factors and stabilizes its structure. Biofilm matrix B. subtilis contains three structural proteins TasA, TapA, and BslA [60]. The TasA protein assembles into long amyloid-like fibrils attached to the cell wall by the TapA protein. The process of biofilm formation in H. pylori has been studied in detail. SEM reveals bacterial aggregates surrounded by an exopolymer matrix. [13]. In the biofilm, the H. pylori bacteria change shape, turning from rod-shaped to coccoid, and pass into an uncultivated state, becoming inaccessible to antibiotics. Currently, preparations from medicinal plants are being studied that act at various stages of biofilm formation. It was found that biologically active substances of plants can participate in antiadhesive therapy [3]. Plant extracts prevent biofilm formation by suppressing the sense of quorum. Herbal preparations with antibiofilm properties include curcumin. Data on the inhibitory effect of curcumin on pathogen biofilms are summarized by Pravin Charles et al. [48]. The authors demonstrated the antibiofilm activity of curcumin against clinical isolates. E. coli, K. pneumoniae, S. aureus, C. freundii, Ps. aeruginosa, Enterococcus faecalis by biofilm testing on Congo red agar. The antibiofilm activity of curcumin was also revealed against H. pylori [47]. A decrease in H. pylori adhesion to Hep2 cells was found. SEM has shown that curcumin reduces the amount of extracellular polymer matrix by inhibiting biofilm formation. At the same time, a less pronounced ability to form coccoid forms was observed. It also turned out that curcumin suppresses the sense of quorum (QS). Similar data were obtained when working with the uropathogens E. coli, Ps. aeruginosa PAO1, Pr. mirabilis and Serratia marcescens. Curcumin treatment depleted the QS dependent factors,

such as the synthesis of EPS, alginate, and bacterial motility [43]. Curcumin has been shown to be effective against Ps. aeruginosa PAO1, which was shown using plant and animal models. It was found that curcumin inhibits biofilm formation, pyocyanin biosynthesis, elastase and protease activity, and affects the QS system. The presence of Ps. aeruginosa PAO1 multiple targets for the action of curcumin shows the possibility of its use in the fight against pseudomonas infection [51]. One of the ways to combat biofilm is to influence its structural components. Thus, an amyloid-like protein can be considered as a target for antibioplenon drugs [34].

Curcumin has been shown to be active against Streptococcus mutans, the main etiological agent of dental caries that colonizes the oral cavity and forms a biofilm. It turned out that curcumin reduces the production of EPS and the adhesion of S. mutans, which leads to an antibiofilm effect comparable to that of chlorhexidine [30].

An important property of curcumin is its synergism with antibiotics against biofilm clinical isolates [26].

The fight against polymicrobial biofilms on catheters is an urgent task, the solution of which can be facilitated by the use of curcumin. It has multiple anti-biofilm activity against catheter-colonizing microorganisms S. aureus, Ps. aeruginosa, E. coli and C. albicans. It was found that curcumin damages the matrix of the polymicrobial biofilm and disrupts its structure [21].

Another way to combat biofilm is to inhibit sortase A, a transpeptidase that fixes a protein on the cell surface. Curcumin, a variety A inhibitor, inhibits the adhesion of S. aureus cells to the extracellular matrix glycoprotein (fibronectin). These data indicate that curcumin can be used to combat S. aureus infections by inhibiting the activity of sort A [45]. It has also been shown that cultivar A plays a role in S. mutans biofilm formation. Curcumin exhibited antimicrobial properties against S. mutans and inhibited the activity of sortase A [23].

5. BIOAVAILABILITY OF CURCUMIN

Curcumin, by its nature as a polyphenol, is poorly absorbed when taken orally. It has poor bioavailability, partly due to a low rate of absorption in the intestine and partly due to its rapid metabolism (glucuronidation), which limits its clinical use. One of the important challenges is the development of effective forms of curcumin in order to increase the bioavailability of this compound. This is achieved through the incorporation of curcumin into systems such as liposomes, nanoparticles, micelles, etc., the formation of complexes with cyclodextrins, and the use of bio-enhancers. In particular, the use of a complex of curcumin with piperine, a known inhibitor of the glucuronidation process in the liver and intestines, increased the bioavailability of curcumin several times. Curcumin in the form of nanoparticles had a pharmacological effect lower - 15 times

- concentration than regular curcumin. Curcumin nanoparticles are used - nanocurcumin. The particle size is 2–40 nm. Unlike curcumin, nanocurcumin is water dispersible. It was found that aqueous solutions of nanocurcumin are effective against S. aureus, B. subtilis, E. coli, Ps.aeruginosa, Penicillium notatum, and Aspergillus niger. The mechanism of action of curcumin nanoparticles was studied using TEM. It was shown that nanoparticles penetrate into bacterial cells, destroying the cell wall, which leads to their death [10, 50]. Curcumin nanoparticles based on silver [24] and other metals are also used. The problem of bioavailability of curcumin and methods of its increase are discussed in detail in the review by Solovieva et al. [6]. Thus, the use of modified curcumin is considered as an alternative therapy for bacterial infections,

CONCLUSION

Curcumin has shown high antibacterial activity and other pharmacological properties over the past 50 years. Curcumin is used worldwide as a dietary supplement for its antioxidant and anti-inflammatory properties. The research results presented in the review show that curcumin has high potential for future use as an antibiotic against pathogens. Further research is needed to fully understand the effects of curcumin and improve its formulation for use as a medicinal antimicrobial agent.

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