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CURCUMIN — PROSPECTS FOR USE IN THE TREATMENT OF DISEASES OF THE DIGESTIVE SYSTEM

© Andrey V. Nalyotov[1], Anatoly I. Khavkin[2, 3], Alexander N. Matsynin[1]

[1] Donetsk State Medical University named after M. Gorky. 16 Ilyich ave., Donetsk 283003 Russian Federation
[2] Research Clinical Institute of Childhood. 62 Bolshaya Serpukhovskaya str., Moscow 115093 Russian Federation
[3] Belgorod State National Research University. 85 Pobedy str., Belgorod 308015 Russian Federation

Contact information:
Anatoly I. Khavkin — Doctor of Medical Sciences, Professor, Head of the department of gastroenterology and dietology named after A.V. Mazurin, Head of the Moscow Regional Center of Pediatric Gastroenterology and Hepatology of the Research Clinical Institute of Childhood, Ministry of Health of the Moscow Region; Professor, Department of Pediatrics with a Course in Pediatric Surgical Diseases, Medical Institute, Belgorod National Research University. E-mail: gastropedclin@gmail.com ORCID: https://orcid.org/0000-0001-7308-7280 SPIN: 6070-9473

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Abstract. Inflammation underlies the development of most diseases. In recent years, more and more attention has been paid to curcumin, an active polyphenol found in turmeric root, which has numerous beneficial effects on the human body, including anti–inflammatory, anti-carcinogenic and antioxidant properties. Curcumin affects several cellular pathways and affects the composition of the gut microbiota. This review summarizes current information on the prospects of using curcumin in the treatment of inflammatory diseases of the digestive system.

Keywords*: curcumin, anti-inflammatory effect, therapy, intestinal microbiota, digestive system*

КУРКУМИН — ПЕРСПЕКТИВЫ ИСПОЛЬЗОВАНИЯ В ЛЕЧЕНИИ ЗАБОЛЕВАНИЙ ОРГАНОВ ПИЩЕВАРЕНИЯ

© Андрей Васильевич Налетов[1], Анатолий Ильич Хавкин[2, 3], Александр Николаевич Мацынин[1]

[1] Донецкий государственный медицинский университет имени М. Горького. 283003, г. Донецк, пр. Ильича, д. 16
[2] Научно-исследовательский клинический институт детства. 115093, г. Москва, ул. Большая Серпуховская, д. 62
[3] Белгородский государственный национальный исследовательский университет. 308015, г. Белгород, ул. Победы, д. 85

Контактная информация:
Анатолий Ильич Хавкин — д.м.н., профессор, заведующий кафедрой гастроэнтерологии и диетологии им. А.В. Мазурина, руководитель Московского областного центра детской гастроэнтерологии и гепатологии Научно-исследовательского клинического института детства Минздрава Московской области; профессор кафедры педиатрии с курсом детских хирургических болезней Медицинского института Белгородского государственного национального исследовательского университета. E-mail: gastropedclin@gmail.com ORCID: https://orcid.org/0000-0001-7308-7280 SPIN: 6070-9473

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Резюме. Воспаление лежит в основе развития большинства заболеваний. В последние годы все больше внимания уделяется куркумину — активному полифенолу, содержащемуся в корне куркумы, который обладает многочисленными благотворными воздействиями на организм человека, включая противовоспалительное, антиканцерогенное и антиоксидантное свойства. Куркумин воздействует на несколько клеточных путей и оказывает влияние на состав микробиоты кишечника. В данном обзоре обобщены современные сведения о перспективах использования куркумина в терапии заболеваний пищеварительной системы.

Ключевые слова: *куркумин, противовоспалительный эффект, терапия, кишечная микробиота, пищеварительная система*

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INTRODUCTION

Inflammation is a complex pathophysiologic process that is an adaptive response caused by exposure to a pathogenic stimulus, infection, or tissue damage to maintain the body's homeostasis. A long-lasting inflammatory process may participate in the pathogenesis of many chronic diseases, such as inflammatory bowel disease (IBD), obesity, diabetes mellitus, pancreatitis, cardiovascular pathology, metabolic disorders, arthritis, and others. The search for new effective compounds with anti-inflammatory effect without causing severe side effects from their use is an important task of current clinical researches.

This article will review the anti-inflammatory mechanisms of action of curcumin and the results of modern clinical studies devoted to its use in the therapy of diseases of the digestive system with emphasis on its effect on the state of the gut microbiome.

PHYSICAL AND CHEMICAL PROPERTIES OF CURCUMIN

Curcumin is a natural polyphenol which belongs to the curcuminoid family (compounds derived from *Curcuma longa L.*). Curcumin is known as the "golden spice of India". It has been used as an important medicinal herbal ingredient for thousands of years, and remains a popular dietary spice in many cuisines around the world. Nowadays, curcumin, an orange-yellow crystalline powder, is widely used in the food industry mainly as a coloring agent (E100) in food and beverage production.

Curcumin is considered to be one of the natural compounds with great potential in the treatment of various inflammatory diseases. This polyphenol has a beneficial effect on the composition of gut microbiota, antioxidant, antitumor and anti-inflammatory properties [1].

Curcumin is safe to take, as confirmed in human clinical trials. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) and the European Food Safety Authority (EFSA) have established an acceptable daily intake for curcumin at 0–3 mg/kg of weight [2].

Curcumin is a low molecular weight lipophilic compound that is almost insoluble in aqueous physiological media. Its molecules can accumulate in cell membranes and act as an antioxidant by absorbing reactive oxygen species. The polyphenol remains fairly stable at low acidic gastric pH. It is rapidly metabolized by reduction, sulfation and glucuronidation in the liver, kidney and intestinal mucosa with low intestinal absorption after oral intake [3, 4]. Current evidence suggests that despite low absorption, curcumin may have beneficial health effects by maintaining high mucosal concentrations, modulating intestinal barrier function, and reducing high concentrations of bacterial lipopolysaccharides (LPS) [5].

BIOLOGICAL EFFECTS AND PHARMACOKINETICS OF CURCUMIN

For many years, limitations to the use of curcumin as a drug have been its chemical instability and poor systemic bioavailability with very low or almost undetectable concentrations in blood and extraintestinal tissues, as well as its rapid metabolism and systemic elimination. Finding an effective method of curcumin delivery for its use as a treatment for inflammatory diseases has been a challenge for researchers [6].

The most common way to increase the low pharmacokinetic profile of curcumin is its combination with the natural alkaloid of black pepper — piperine (Piper nigrum), which is a strong inhibitor of its glucuronidation process. Curcumin dispersed with colloidal nanoparticles (preparation "Teracurmin") showed high absorption capacity in studies on healthy volunteers [7]. Another example of improved bioavailability of curcumin is its inclusion in a micellar system [8]. There are also other combinations of curcumin: formula of turmeric powder and turmeric essential oil, lipid-curcumin formulations, combination of curcumin with lecithin.

The pronounced anti-inflammatory properties of curcumin, described for many years, have attracted great interest of researchers in the context of the treatment of diseases with a chronic inflammatory genesis. The transcription factor NF-κB is a universal regulator of the expression of immune response genes, apoptosis and the cell cycle. Disruption of NF-κB regulation causes the development of inflammation and autoimmune diseases. The anti-inflammatory effect of curcumin is mainly mediated by its ability to inhibit the intracellular NF-κB signaling pathway by blocking IkappaB (IkB) kinase, which leads to the prevention of cytokine-mediated phosphorylation and degradation of IkB, which is an inhibitor of NF-κB [9].

Signal transducer and activator of transcription (STAT) proteins are one of the molecular pathways involved in various biological processes such as cell proliferation and apoptosis. Curcumin

is able to increase the levels of anti-inflammatory cytokines and reduce inflammatory disease activity by inhibiting the expression of the JAK/STAT signaling pathway. In addition, studies suggest that this mechanism of curcumin is involved in reducing cancer cell migration and invasion [10].

Curcumin reduced the levels of pro-inflammatory mediators such as IL-1, IL-1β, IL-6, IL-8, IL-17, IL-27, TNFα, inducible nitric oxide synthase (iNOS) in inflammatory cell and animal studies. Curcumin has also been reported to inhibit the activity of proinflammatory proteins (activator protein-1, mitogen-activated protein kinases, peroxisome proliferator-activated receptor gamma (PPAR-γ), β-catenin) [11].

The NOD-like receptor protein 3 (NLRP3) inflammasome is a protein complex that regulates innate immune responses through the activation of caspase-1 and the expression of inflammatory cytokines. Curcumin can directly restrain NLRP3 inflammasome assembly or inhibit its activation, which may be one of the mechanisms for its application in the therapy of inflammatory diseases [9].

Curcumin has a regulatory effect on immune cells such as dendritic cells, T helper 17 (Th17), and regulatory T lymphocytes (Treg). Th17 are important pro-inflammatory cells that synthesize pro-inflammatory IL-17, IL-22, and IL-23. In turn, Treg have an inhibitory effect on the development of the inflammatory response. Alterations in the number and function of Th17 and Treg can induce an abnormal immune response leading to inflammation. Maintaining Th17/Treg balance helps to maintain immune homeostasis and treat inflammatory diseases. Curcumin has been found to inhibit Th17 differentiation and regulate the restoration of Th17/Treg balance [12].

Accumulation of reactive oxygen species in tissues leads to the development of oxidative stress, which increases inflammation by activating inflammation-related transcription factors. Curcumin reduces the production of reactive oxygen species due to its effect on nicotinamidadenine dinucleotide phosphatoxidase (NADPH) and increased activity of antioxidant systems [13].

CLINICAL APPLICATIONS OF CURCUMIN

Clinical studies investigating the efficacy of curcumin in the treatment of inflammatory diseases remain few to date.

M. Kato et al. used curcumin dispersed in colloidal nanoparticles to stimulate glucagon-like peptide-1 (GLP-1) secretion, resulting in increased insulin synthesis and secretion and better glycemic control in mice. This finding suggests a potential role for curcumin in the treatment of diabetes mellitus. However, the use of native curcumin did not lead to therapeutic results and did not improve glucose tolerance in mice [14].

Oral intake of curcumin results in its high concentration in the gastrointestinal (GI) tract, which has aroused great interest of researchers to study the effect of the polyphenol on the gut microbiota and to determine its role in potential benefit in the treatment of digestive system pathology [4, 15].

Several studies have investigated the properties of curcumin with respect to regulatory effects on the intestinal microbiome. Bacteria are actively involved in the metabolism of curcumin, leading to its biotransformation with the formation of metabolites, exerting local and systemic effects [38]. In turn, curcumin supplements stimulate the growth of beneficial bacterial strains, improve intestinal barrier function and reduce the expression of proinflammatory mediators [5, 16].

A. Hassaninasab et al. identified microorganisms with high metabolic activity against curcumin (*Escherichia coli* strain) and capable of converting it into dihydrocurcumin and tetrahydrocurcumin due to the presence of NADPH-dependent enzyme (CurA) [17]. In turn, the results of a study by S.D. Jazayeri et al. revealed that microorganisms such as *Bifidobacteria pseudocatenulaum, Enterococcus faecalis, Bifidobacteria longum, Lactobacillus acidophilus* and *Lactobacillus casei* are also capable of reducing the original curcumin compound by more than 50% and thus can participate in the metabolism of polyphenol [18].

L. Shen et al. in a study conducted in a mouse model found statistically significant changes ($p < 0.05$) in the number of *Prevotellaceae, Bacterioidaceae* and *Rikenellaceae* in the gut microbiome between individuals that received curcumin supplementation as part of nutrient formulas and mice from the control group that received a similar diet but without curcumin supplementation. The abundance of *Prevotellaceae* decreased and *Bacterioidaceae* and *Rikenellaceae* increased in individuals receiving curcumin supplementation relative to the control group [19].

W. Feng et al. in their study found that curcumin reduced fat deposition in the liver, improved intestinal barrier integrity and alleviated systemic endotoxemia in rats fed a high-fat diet. Curcumin also dramatically altered the overall structure of

the gut microbiota disrupted by the high-fat diet toward an intestinal composition characteristic of rats with reduced weight. The authors conclude that curcumin administration partially reduces the severity of hepatic steatosis through specific effects on the phylotypes of gut microbiota associated with its development [20].

Results of a randomized, double-blind, placebo-controlled trial published in 2021 showed that 8-week administration of curcumin extract was associated with improvement in gastrointestinal symptoms (abdominal pain, diarrhea, and constipation) in adults. Patients also showed a greater reduction in anxiety scores on the Depression Anxiety and Stress Scale (DASS-21). At the same time, curcumin supplementation had no significant effect on the degree of microbial diversity and the development of intestinal bacterial overgrowth syndrome [21].

The studied properties of curcumin with respect to the correction of bacterial species involved in the pathogenesis of inflammatory GI diseases may expand the understanding of the therapeutic potential of this polyphenol.

In a study by S.T. Peterson et al. conducted with 30 healthy subjects evaluated changes in the gut microbiota using 16S RNA sequencing after oral administration of turmeric at a dose of 6000 mg/day with piperine extract, curcumin at a dose of 6000 mg/day with piperine extract, or placebo initially, after 4 and 8 weeks. Both turmeric and curcumin were found to alter the gut microbiota in similar ways. Participants taking turmeric supplements had a 7% increase in the number of microbial species studied after treatment, while subjects receiving curcumin had an average 69% increase in the number of bacterial species studied. The authors indicated that the response of the gut microbiota to the conducted saplementation was personalized. Subjects who responded to the conducted therapy showed uniform increases in most species of *Clostridium* spp., *Bacteroides* spp., *Citrobacter* spp., *Cronobacter* spp., *Enterobacter* spp., *Enterococcus* spp., *Klebsiella* spp., *Parabacteroides* spp. and *Pseudomonas* spp. with decreases in the relative abundance of a few species of Blautia spp. and most species of *Ruminococcus* spp. [5].

Two independent studies investigated the modulating effect of curcumin nanoparticle administration on the colonic microbiota during colitis [22, 23].

In one study, R.M. McFadden et al. evaluated the efficacy of dietary supplementation with curcumin in a colitis-associated colorectal cancer mouse model. Curcumin supplementation resulted in increased survival of individuals and completely eliminated tumor burden. Against the background of the observed diet, there was an increase in bacterial diversity in the intestinal microflora with an increase in the relative abundance of *Lactobacillales* and a decrease in *Coriobacteriales*. The authors concluded that the favorable effect of curcumin on oncogenesis was associated with the correction of the imbalance of the gut microbiota [22].

Another study by M. Ohno et al. examined the effect of curcumin nanoparticle supplementation on colitis induced by dextran sodium sulfate (DSS) in mice. Curcumin supplementation was found to reduce the mRNA expression of inflammatory mediators in the colonic mucosa and NF-κB activation in colonic epithelial cells, increase the abundance of butyrate-producing bacteria by increasing its level in the feces [23], and modulate the intestinal barrier function through the assembly of tight contact proteins, activation of bocaloid cells [24, 25].

Y.M. Chen et al. studied the effects of curcumin extract nanoparticle supplementation (NCE-5x) on gut microbiota, physical fatigue, and performance in mice. The researchers found that supplementation with curcumin extract nanoparticles for 6 weeks changed the composition of the gut microbiota and led to reduced physical fatigue and increased performance in mice. Animals receiving curcumin extract showed a decrease in *Bacteroidetes* and an increase in *Firmicutes*. The authors concluded that curcumin can affect the gut microbiome, increasing tolerance to exercise [26].

A large number of studies have shown that changes in the gut microbiome are associated with the development of various metabolic diseases such as metabolic syndrome, obesity, diabetes mellitus and non-alcoholic fatty liver disease [27, 28]. The first study reporting the association between curcumin intake and gut microbiome diversity in a menopausal rat model was published in 2017. Its results showed that curcumin could partially reverse changes in rat gut microbiota biodiversity by altering the distribution of gut microbiota due to ovariectomy-induced estrogen deficiency. Curcumin administration increased the number of *Serratia, Shewanella, Pseudomonas, Papillibacter* and *Exiguobacterium* species and decreased the number of Anaerotruncus and *Helicobacter pylori* [29].

PERSPECTIVES OF THE USE OF CURCUMIN IN THE TREATMENT OF ULCERATIVE COLITIS

An interest in studying the efficacy of curcumin for the treatment of ulcerative colitis (UC) has increased markedly since 2020, as evidenced by the increasing number of published systematic reviews. S. Chandan et al. reviewed and analyzed seven clinical trials involving 380 patients with UC. The authors concluded that combination therapy based on mesalamine and curcumin almost 3-fold increased the chances of clinical response in patients relative to the group receiving placebo [30]. T. Zheng et al. in the analysis of the results of six clinical trials involving 349 patients with UC showed that therapy with mesalazine with curcumin supplementation is safe and effective with regard to the induction of clinical and endoscopic remission of the disease [31]. M.R. Coelho et al. in their systematic review analyzed six clinical trials involving 372 patients with UC. They studied the efficacy of curcumin supplementation for remission induction in patients with mild to moderate disease activity. The studies showed good tolerability of curcumin supplementation in combination with standard therapies. In addition, five out of six studies demonstrated good results associated with the achievement of clinical and/or endoscopic remission [32]. R.A. Goulart et al. in their meta-analysis studied four clinical trials involving 238 patients with mild to moderate UC, where they evaluated the efficacy of oral curcumin administration in relation to the induction of disease remission [33]. The authors concluded that the addition of curcumin as an adjunct to standard therapy for UC had a beneficial effect on the development of clinical remission in patients. A recent systematic review by J. Yin et al. evaluated the efficacy and safety of curcumin therapy in patients with UC and included six clinical trials with a total of 385 patients. The authors reported that curcumin supplementation in addition to standard therapy for UC may be an effective strategy for achieving clinical remission of the disease without causing the development of serious side effects [34].

CONCLUSION

Nowadays, data on the anti-inflammatory properties of curcumin are accumulating. Features of its metabolism and its effect on the state of gut microbiota allow us to consider the use of this polyphenol as a promising tool in the treatment of chronic inflammatory diseases of the digestive system. Further studies are needed to determine the effective dosage of curcumin, its effect on inflammation and composition of gut microbiota in patients with various gastrointestinal pathologies.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

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