

Potential roles of gut microbiota and microbial metabolites in chronic inflammatory pain and the mechanisms of therapy drugs

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Abstract: Observational findings achieved that gut microbes mediate human metabolic health and disease risk. The types of intestinal microorganisms depend on the intake of food and drugs and are also related to their metabolic level and genetic factors. Recent studies have shown that chronic inflammatory pain is closely related to intestinal microbial homeostasis. Compared with the normal intestinal flora, the composition of intestinal flora in patients with chronic inflammatory pain had significant changes in *Actinomycetes*, *Firmicutes*, *Bacteroidetes*, etc. At the same time, short-chain fatty acids and amino acids, the metabolites of intestinal microorganisms, can regulate neural signal molecules and signaling pathways, thus affecting the development trend of chronic inflammatory pain. Glucocorticoids and non-steroidal anti-inflammatory drugs in the treatment of chronic inflammatory pain, the main mechanism is to affect the secretion of inflammatory factors and the abundance of intestinal bacteria. This article reviews the relationship between intestinal microorganisms and their metabolites on chronic inflammatory pain and the possible mechanism.

Keywords: arthritis, chronic inflammatory pain, glucocorticoids, intestinal microflora, nonsteroidal anti-inflammatory drugs

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Introduction

Chronic pain (CP) has always been a public medical problem in the world. Usually, the duration of pain lasting more than 3 months is defined as CP. It is not only a high incidence rate but also a relapse after recovery, which brings great obstacles to the physiology and psychology of patients and seriously affects the quality of life of patients. CP is divided into seven categories in the international classification of diseases. This article is divided into one kind of chronic primary pain and six kinds of secondary chronic cancer-related pain, chronic neuropathic pain, chronic secondary visceral pain, chronic posttraumatic and post-operative pain, chronic secondary headache, and orofacial pain, and chronic secondary musculoskeletal pain.¹ The above factors lead to the occurrence of CP, resulting in the pathogenesis of CP is not clear, more difficult to cure, higher treatment costs and most of the vulnerable groups

are middle-aged and elderly, and the economic situation is not optimistic.

Chronic inflammatory pain refers to local or systemic pain caused by long-term infiltration of an organ or joint by inflammatory factors, which is an important part of CP. Here are a few examples of chronic inflammatory pain. Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a long-term urinary system pain or discomfort in the pelvic region, accompanied by reproductive system disorders. Inflammatory CP/CPPS (NIH category III a) is the cause of abnormal leukocytes in the prostate.² Inflammation and autoimmunity are thought to be major contributors to CP/CPPS. TNF- α , IL-6, COX-2, and other factors were abnormally increased in the blood and semen of patients.³ The incidence of rheumatoid arthritis (RA) in Europe and North America ranges from 0.5% to 1% but is likely to decline in

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the coming years.⁴ The pathogenesis of RA is related to immune protein G and citrulline.⁵ It is characterized by inflammatory and destructive reactions in synovial tissue, and pain is a key problem in RA. Peripheral sensitization of nociceptors is caused by cytokines (IL-1 β , IL-6, and TNF), chemokines, and growth factors in synovial membrane and synovial fluid.⁶ The prevalence of gout ranged from <1% to 6.8% and the incidence ranged from 0.58 to 2.89 per thousand people per year.⁷ The pathogenesis of gout is the activation of the NLRP3 receptor and inflammatory IL-1 and IL-18. Urate crystals also induce microglia to secrete inflammatory factors. It occurs when high levels of uric acid (supersaturation) in the body cause sodium urate to deposit in joints and cause pain.⁸ The pathogenesis of knee osteoarthritis (OA) is the production and release of inflammatory factors, such as IL-6, IL-1 β , TNF- α , and IL-8 in serum, synovial fluid, and synovial tissue. In addition, some pain-related neurotransmitters, such as substance P and nerve growth factor, are released from osteoarthritic joints.⁹

There are many kinds and inducements of chronic inflammatory pain. And more and more evidence shows the role of intestinal microorganisms in chronic inflammatory pain. In this article, we explain the pathogenesis mechanisms of CP based on the relationship between gut microbes and their metabolites and CP.¹⁰ In addition, the progress of the regulation and mechanism of intestinal microorganisms of chronic inflammatory pain drugs were discussed to provide a scientific basis for the pathogenesis of CP and its effective drug research and development.

Gut-brain axis and chronic inflammatory pain

The human gut is a large, diverse, and dynamic intestinal microbiota with more than 100 trillion microorganisms, including at least 1000 different species.¹¹ The microorganisms in the human intestine can be divided into bacteria, archaea, acellular phages, and eukaryotes. *Bacteroides* and *Firmicutes* accounted for more than 90% of the gastrointestinal bacteria.^{12,13} Different intestinal microorganisms cause functional differences. Through the current popular genomics, high-throughput sequencing technology, 16SrDNA, and polymerase chain reaction (PCR) technology, it is found that the sources of differences in

intestinal microorganisms *in vivo* may be related to genetics, environment, diet, stress, age, infection, drugs (antibiotics), etc.¹⁴ Intestinal microorganisms can participate in host metabolism, have digestion and absorption function, and are also an important component of the human immune system. Intestinal bacterial disturbance can lead to disorder of the immune system, leading to obesity, diabetes, cardiovascular and cerebrovascular diseases, and other diseases.^{15,16}

With the development of the 'gut-brain axis' and 'microbe-gut-brain axis', the research on gut and central nervous system has become a hot topic. Low-fat and low-sugar diet can reduce oxidative stress and prevent the activation of microglia cells after digestion and absorption.¹⁷ Immune cells produced by intestinal flora can cross the blood-brain barrier and are activated by dendritic cells of the central nervous system, which can change cytokines through nerve signaling pathways, such as Toll-like receptors.¹⁸ Mast cells may be the mediators that lead to the association between intestinal flora and the neuroimmune system, thus generating sensory signals.¹⁹ Recent studies have shown a strong link between gut bacteria and CP. The differences in the levels of intestinal flora in patients with CP/CPPS were reflected in that the relative abundance of *Actinomycetes* was lower than that in normal people.²⁰ At the class level, the proportion of γ -Proteobacteria increased and that of β -Proteobacteria decreased. At the genus level, the relative abundance of *Clostridium* and *Escherichia* was significantly higher than that of the normal human body, while the relative abundance of *Dorea*, *Hallella Moore and Moore*, *Alistipes*, and *Dialister* was significantly lower than that of the normal human body. At the species level, the relative abundance of *Bacteroides* and *Escherichia coli* was higher than that of a normal human body, while the relative abundance of *Eucobacteria nitpicks* and *Eucobacteria rectum* was lower than that of a normal human body.²¹ The intestinal bacteria of patients with RA were lower than those of normal people and showed a negative correlation with inflammatory indicators C-reactive protein (CRP), TNF- α , and IL-6, and the levels of inflammatory factors were significantly increased, and the diversity of intestinal flora in RA patients was lower than that in normal people.²² Gout belongs to a kind of arthritis and belongs to the category of metabolic rheumatism. During the attack, the joints will be accompanied by severe pain and changes in intestinal bacteria,

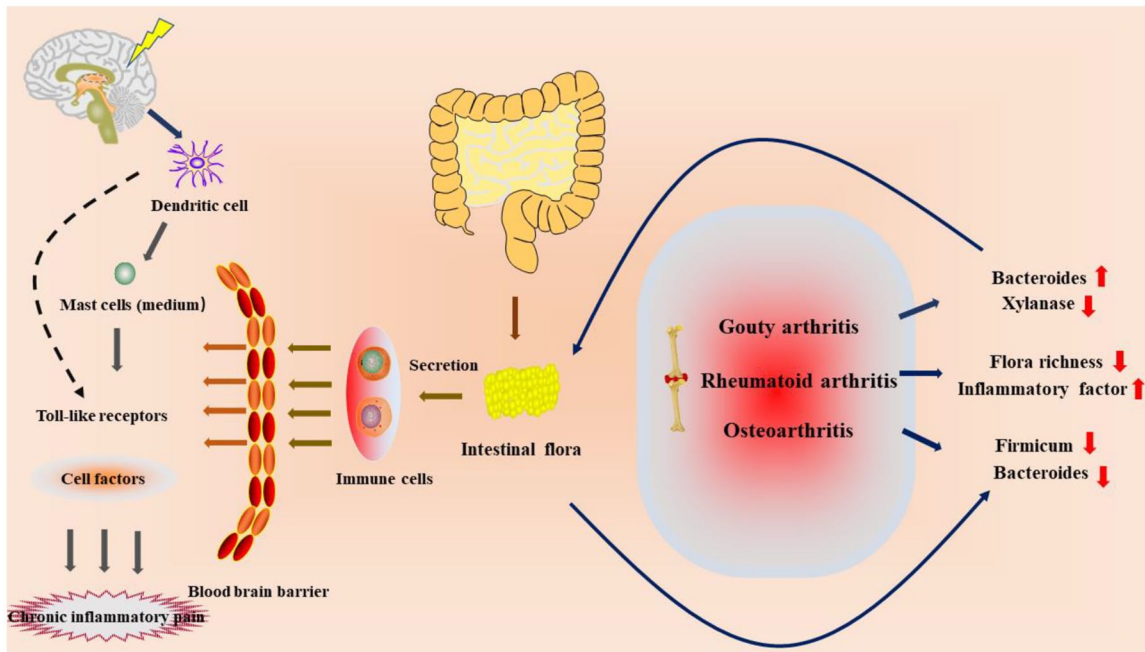


Figure 1. Relationship between intestinal flora and chronic inflammatory pain.

among which the contents of *Bacteroides* and *xylanase* are high, and the synthesis of butyric acid that protects intestinal mucosa in patients with gout is reduced.²³ OA is a degenerative disease that can lead to advanced pain and joint deformity. In patients with this disease, there is mild intestinal inflammation,²⁴ and the intestinal flora of the susceptible population, such as *Firmicutes* and *Bacteroidetes*, is significantly reduced compared with the normal population.²⁵ At the same time, vitamin D deficiency can lead to pain response and decreased microbial diversity in mice, characterized by an increase in *Firmicutes* and a decrease in microflora *Verrucomicrobium* and *Bacteroidetes*.²⁶

These studies suggest that chronic inflammatory pain may alter the intestinal microbiota, thereby negatively stimulating the chronic inflammatory response and generating metabolic resistance to promote CP, suggesting that intestinal bacteria are involved in many chronic inflammatory diseases.²⁷ It is believed that the changes of intestinal bacteria are related to the brain, affecting nerve signal transduction and inducing pain (Figure 1).

The changes of intestinal flora in patients with arthritis lead to the disorder of immune cells. Through the blood–brain barrier, immune cells

use dendritic cells located in the central nerve to conduct signal transduction and produce pain.

Relationship between intestinal microorganisms and their metabolites and chronic inflammatory pain

Short-chain fatty acid

Short-chain fatty acids (SCFAs) are natural metabolites with no more than six carbon chains produced by dietary fiber in the fermentation process of anaerobic bacteria, such as *Bacteroides*, *Bifidobacterium*, *Fusobacterium*, and *Streptococcus*, which are generally distributed in mammals and mainly consist of acetic acid, propionic acid, and butyric acid.²⁸ SCFAs in patients with inflammatory bowel disease activate downstream signaling pathways by binding specific G-protein-coupled receptors (GPR43, GPR109A, etc.), regulating T cell activation, increasing histone acetylation, decreasing NF- κ B activation, and regulating chronic inflammatory pain (Figure 2).^{29,30}

SCFAs can effectively alleviate osteoporosis by increasing calcium absorption and transport in mice, stimulating intestinal serotonin synthesis and directly inhibiting osteoclast differentiation and bone resorption.³¹ Meanwhile, at the same

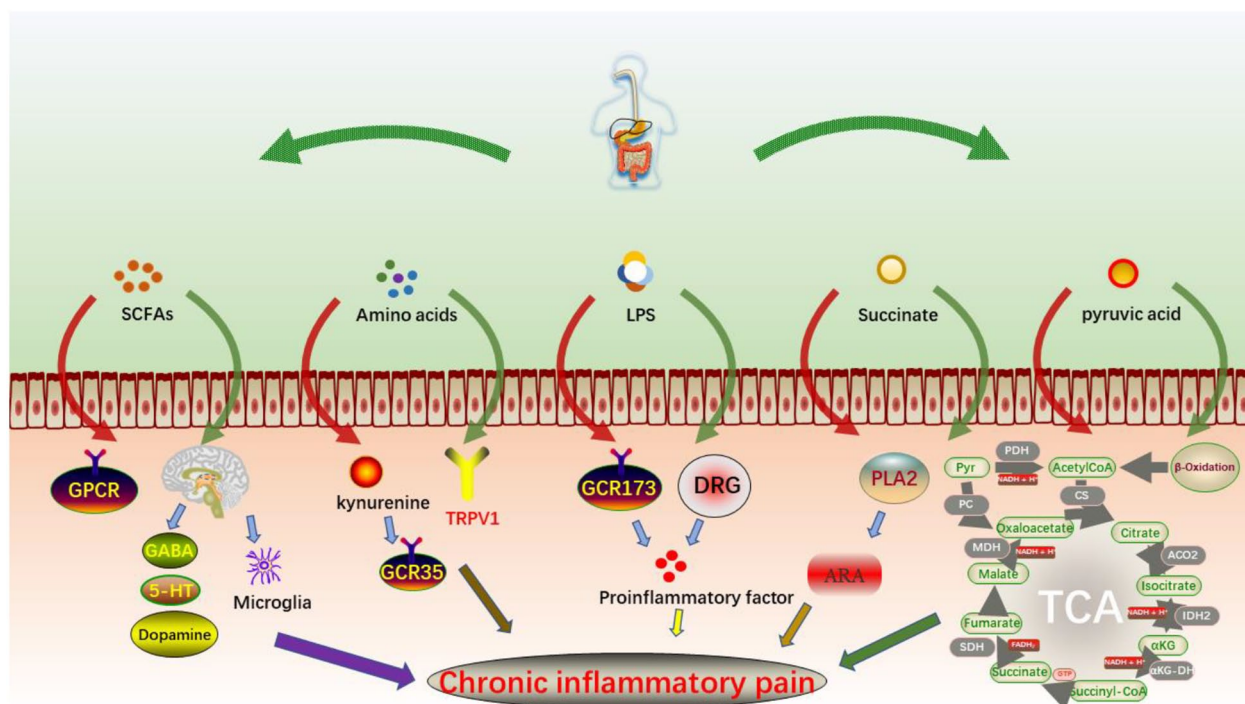


Figure 2. Regulation of intestinal metabolites on CP.

time, SCFAs play a role in regulating the maturation of mouse entero-brain axis and proximal microglia and regulate the expression of nerve molecules, such as GABA, serotonin, and dopamine, to influence inflammatory pain.³² The lack of fat in a high-fiber diet effectively alters SCFAs in the gut. High-fiber diet-induced G-protein-coupled protein activation of NLRP3 inflammasomes is directly associated with gout attacks.³³ The content of SCFAs in patients with chronic inflammatory pain may affect that not only acts on the intestinal tract to regulate the intestinal inflammatory balance but also maintains the overall balance through the blood–brain barrier, regulates the secretion of inflammatory factors, and effectively inhibits the occurrence of chronic inflammatory pain.^{28,30,32}

Amino acid metabolites

Significant differences in amino acid metabolism from normal levels have been observed in chronic critical patients with persistent inflammation.³⁴ Kynurenine is a tryptophan metabolite that activates G-protein-coupled receptor 35 (GPR35) and has anti-inflammatory pain effects in acetic acid writhing experiment mice.³⁵ In the serum

metabolism of 38 patients with angina, tryptophan degradation was found to produce serotonin, which affects the expression of nerve molecules, suggesting that tryptophan degradation inhibits pain.³⁶ Inflammation and pain are associated with the combined action of active metabolites p-benzoquinone and N-acetyl-p-benzoquinone imine on cysteine activation and sensitization of TRPV1 receptors.³⁷ The urine metabolomics of 74 patients with OA and 68 healthy subjects were compared. It was found that the expression levels of lysine metabolite aminophenediamine, serine metabolite L-methanesulfonate, and glycine metabolite 3-methylcrocodile glycine were lower than those of normal subjects (Figure 2).³⁸

Simultaneously, glutamate was found in the urine of 58 posttraumatic ankle arthritis patients as a major marker metabolite for posttraumatic ankle arthritis, helping to distinguish synovial fluid of patients from healthy subjects.³⁹ The recurrence of CP can greatly increase the risk of depression, which is often accompanied by the coexistence of two diseases. It was found that the tryptophan canine metabolic pathway was impaired in the urine metabolism of mice in both diseases, and the overall amino acid level in the high uric acid

group increased, the tryptophan level decreased, and the IL-1 receptor antagonist level decreased.⁴⁰ These results indicate that tryptophan metabolites have the potential to be the effective markers of chronic inflammatory pain.

Lipopolysaccharide

Intake of high-fat and high-sugar diet is prone to obesity, diabetes, hypertension and other diseases, joint inflammation, and painful degenerative disease OA, and other complications are also constantly occurring. It can also cause postoperative pain and delay wound growth in rats.⁴¹ Lipopolysaccharide (LPS) is the main component of the external membrane of most gram-negative bacteria, which often induces chronic inflammatory pain (Figure 2).

A model of inflammatory pain induced by injection of 0.4 ng/kg of *E. coli* LPS decreases pain threshold and increases serum levels of inflammatory cytokines IL-1 β , TNF- α , and IL-6 in patients aged 18–45 years. It also increased expression of dorsal root ganglion (DRG) neurons, TRPA1, and TRPV1 proteins.⁴² LPS-stimulated macrophage inflammatory cytokines in mice and increased exome of miRNAs mediate inflammation, thereby activating NF- κ B factor.⁴³ The levels of pro-inflammatory cytokines IL-1 β , COX-2, and PGE2 in the microglia of rats were increased.⁴⁴ LPS can reduce the activity of G-protein-coupled receptor GPR173 in human dental pulp, induce the secretion of pro-inflammatory factors, such as IL-6, activate toll-like receptor-4 (TLR-4), MyD88, NF- κ B pathway, and improve inflammatory response and pain.⁴⁵

Succinic acid

Succinic acid can be used as a food material and drug synthetic material, and an intermediate product of metabolism, which has analgesic, detoxification, and antibacterial effects.⁴⁶ In the agarose egg yolk experiment, it was found that succinic acid can control the synthesis of arachidonic acid and inhibit inflammation and pain by inhibiting the activity of phospholipase A2 (PLA2). The main way is that the active site of PLA2 can interact with histidine residues.⁴⁷ Metabolism of glutamate and succinate decreased in the serum of patients with chronic urticaria, suggesting decreased metabolic efficiency of butyric acid (Figure 2).⁴⁸

Notably, it was found that succinic acid could bind to the GRP91 receptor not only intracellular but also extracellular, promoting the release of inflammatory mediators, such as IL-1 β and NO, and promoting the inflammatory response by the initial neonatal rat cardiomyocytes experiment.⁴⁹ Its derivatives ammonia succinate and acetylsalicylic acid can be used in combination to regulate metabolic disorders in chronic inflammation of various joints and viscera.⁵⁰

According to human feces, *Prevotellaceae* and *Veillonellaceae* can produce succinic acid, while *Odoribacteraceae* and *Clostridiaceae* can consume succinic acid.⁵¹ An excessive amount of succinic acid in the human body can cause some intestinal diseases, such as inflammatory bowel disease and Crohn's disease.⁵²

Other metabolites

Many of the metabolites of patients with chronic inflammation are different from those of healthy people, such as elevated levels of acetone and pyruvate in patients with RA (Figure 2). In the redox environment, the transport and metabolism of iron, sulfur, zinc, and arginine are altered,⁵³ but the levels of taurine, urea, betaine, and hippuric acid are reduced.⁵⁴ The tricarboxylic acid cycle can regulate *Candida albicans*. Pyruvate participates in the tricarboxylic acid cycle and completes the transformation of three nutrients through acetyl CoA. Taurine is an essential amino acid in the body, but its synthesis in the human body is low, and it is related to nerve conduction and lipid metabolism. Probiotic therapy increased taurine in mice and significantly increased the abundance of *Firmicutes*, *Ruminobacteriaceae*, and an unidentified clostridium bacterium while decreasing the abundance of *Verruiciaceae* and *Erysipelaceae*.⁵⁵ In chronic kidney disease patients with acute gout, uric acid increases, urea and creatinine decrease in the same direction.⁵⁶ At the genus level, *E. coli* – *Shigella* numbers were significantly higher in patients with high uric acid. The intestinal flora of the high uric acid group was predicted to be rich in metabolism, human disease, and LPS biosynthesis.⁵⁷ Uric acid is the end product of purine metabolites, and gout arthritis is caused by the deposition of urate in the joints. Reducing intake of high-purine food, improving their metabolic function to prevent gout arthritis has a good effect (Table 1).

Table 1. Effects of intestinal microorganisms and metabolites on various indexes *in vivo*.

Metabolites	Targets	Biological effects (References)
SCFAs	Human	Bind-specific G protein-coupled receptor ^{29,30} Activate T cells ^{29,30} Reduce NF- κ B protein expression ^{29,30}
	Mice	Increase calcium absorption ³¹ Stimulate intestinal serotonin synthesis ^{31,32} Inhibition of osteoclast differentiation and bone resorption ³¹
Amino acid metabolites	Human	Serotonin production ³⁶ Activate the TRPV1 receptor ³⁷
	Mice	Activate G protein-coupled receptor 35 ³⁵ Impaired tryptophan canine metabolic pathway ^{35,40}
LPS	Human	Reduce pain threshold ⁴² Increase inflammatory factor IL-1 β , TNF- α , and IL-6 levels ⁴² Increase the expression of DRG neurons, TRPA1, and TRPV1 proteins ⁴²
	Rat	Increase postoperative pain and delay wound growth ⁴¹ Increase inflammatory factor IL-1 β , COX-2, and PGE2 levels ⁴⁴
Succinic acid	Yolk	Inhibit the activity of PLA2 ⁴⁷
	Rat	Bind to GRP91 receptor and promote IL-1 β and NO release ⁴⁹

DRG, dorsal root ganglion; LPS, Lipopolysaccharide; NF- κ B, nuclear factor kappa-B; SCFA, short-chain fatty acid

Intestinal microorganisms and their metabolites associated with chronic inflammatory pain include SCFAs, amino acids, LPSs, succinic acid, and pyruvate. SCFAs bind to some G-protein-coupled receptors to reduce NF- κ B activation. It can also regulate nerve molecules, such as GABA, 5-hydroxytryptamine, and dopamine to relieve pain. Kynurenine activates GPR35 to exert an analgesic effect. LPS can reduce the pain threshold, which is mainly used to induce the secretion of inflammatory factors, reduce the activity of G-protein-coupled receptor GPR173, and increase pain sensation. Succinic acid mainly reduces pain by inhibiting PLA2 activity. Pyruvate is involved in the tricarboxylic acid cycle mainly to enhance nerve conduction and lipid metabolism to regulate pain.

Mechanism of drugs intervention on chronic inflammatory pain and its effect on intestinal microflora

Patients with chronic inflammatory pain have a variety of options for treatment drugs, with the current use of non-steroidal anti-inflammatory drugs, glucocorticoids, traditional Chinese herbal plants, and other biological agents.^{58,59} The above

drugs affect intestinal flora through different channels *in vivo* and are closely related to glucose and lipid metabolism, protein metabolism, inflammatory response, and intercellular signal molecule transmission.⁶⁰ It is difficult to cure chronic inflammation and pain, while intestinal microorganism is a relatively stable environment. To clarify how drugs change intestinal microorganisms, find the correlation between the two, change intestinal microecology, to regulate the occurrence of an inflammatory response, reduce pain, and reduce recurrence. It is helpful for the radical treatment of chronic inflammatory pain (Figure 3).

Glucocorticoids

Dexamethasone. Dexamethasone is a synthetic substitute for cortisol, commonly used as an anti-inflammatory and also used to simulate stress state.⁶¹ Dexamethasone can alleviate joint swelling and pain by improving the expression of inflammatory cytokines and transcription factors, such as IL-1 β , IL-17, TNF- α , and MMP-3 in primary synovial tissue cells of CIA rats. Studies have shown that dexamethasone can downregulate the expression of the NF- κ B signaling pathway in

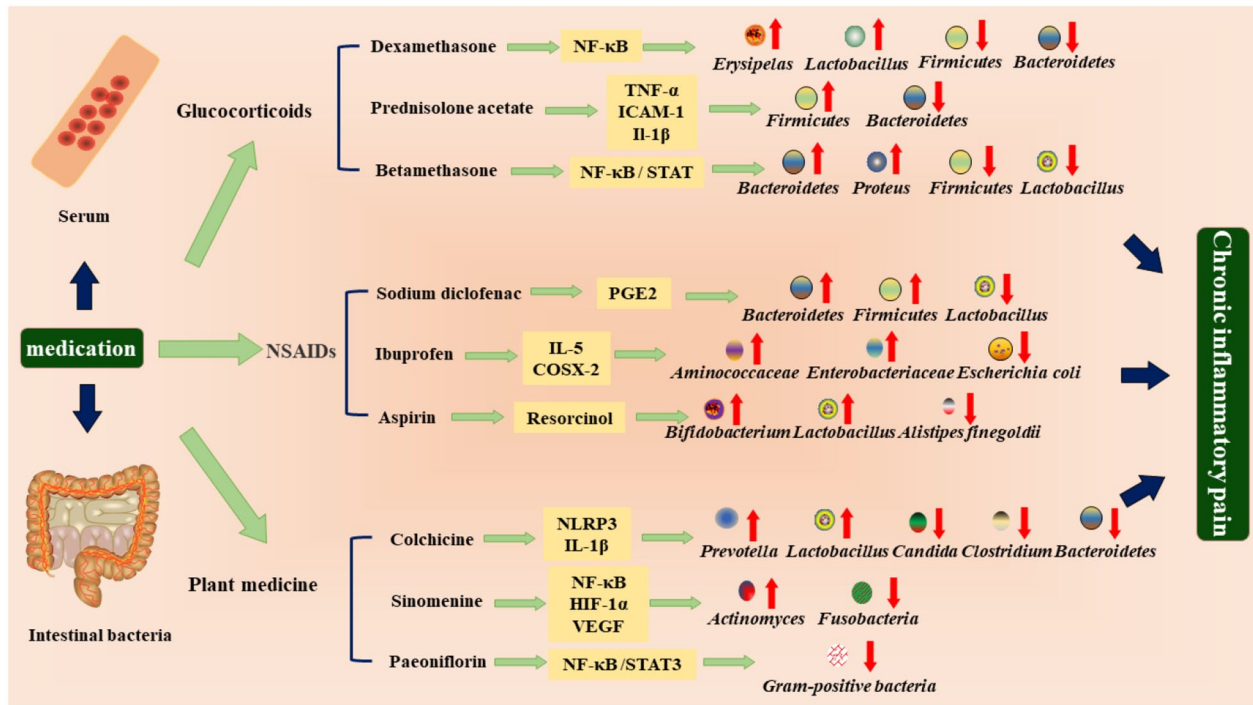


Figure 3. Improvement mechanisms of anti-inflammatory analgesic drugs based on the regulation of intestinal bacteria and inflammatory factors.

the serum of CIA rats, effectively treat knee OA, stabilize oxidative stress, and relieve pain.^{62,63} Dexamethasone protects glucocorticoid receptor knockout mice from TNF injection by promoting dimerization of glucocorticoid receptors.⁶⁴

After intraperitoneal injection of dexamethasone in 40 albino rats, it was found that a high concentration of 10 mg/kg dexamethasone regulated the intestinal flora, with total aerobic bacteria and lactic acid bacteria as the dominant flora, while a low concentration of 0.5 mg/kg dexamethasone regulated the number of anaerobic bacteria.⁶⁵ Dexamethasone also increased the abundance of *Erysipelas* and *Lactobacillus* in the feces of asthmatic rats,⁶⁶ while the relative abundance of *Firmicutes*, *Bacteroidetes*, α -*Proteobacteria*, γ -*Proteobacteria*, and *Actinobacteria* decreased in the feces of circadian rats.⁶⁷

Prednisolone acetate. Prednisolone acetate is mainly used in the clinical treatment of allergic and autoimmune inflammatory diseases, such as rheumatism and RA, to inhibit cellular immune response. However, it cannot repair articular cartilage tissue and even has the side effect of osteoblastic apoptosis. As a long-term but short-acting

drug, long-term use can lead to osteoporosis and bone loss, and adverse reactions increase after drug withdrawal.^{68,69} The levels of TNF- α , IL-1 β , and ICAM-1 in the serum of rats with RA were significantly decreased by intragastric administration of prednisolone.⁷⁰ Prednisolone destroyed the microbial community structure of immunosuppressed C57BL/6J mouse feces, decreased the *Bacteroidetes*, and increased the *Firmicutes* in feces. It also increased glutathione content and decreased catalase activity in the colon of Colitis rats.^{71,72}

Betamethasone. Betamethasone is widely used clinically as an anti-inflammatory and immunosuppressive agent. At present, the combination of betamethasone with some non-steroidal anti-inflammatory drugs and injectable Gellan Gel (GG) hydrogels has been widely used in clinical studies at home and abroad in the treatment of arthritis, and compared with the efficacy of single-use, it can effectively treat knee OA and gout arthritis.⁷³⁻⁷⁵ Betamethasone can downregulate signal transduction and transcriptional activators (STAT) 3 and nuclear factor κ B (nuclear factor- κ B) in CHON-002 human chondrocytes, inactivate the NF- κ B /STAT3 signaling pathway, and

significantly downregulate inflammatory cytokines IL-6 and IL-8.⁷⁶ One point of concern is that the CTX-II and COMP of the degradation products of betamethasone cartilage increased as the effect decreased in CIA rat models, suggesting that betamethasone can eliminate local inflammation but alter the cellular metabolic structure of its articular cartilage.⁷⁷

Looking at the gut microbes, betamethasone increased the fecal abundance of *Bacteroides* and *Proteus* but decreased the fecal abundance of *Lactobacillus* and *Firmicutes* in Balb/ C mice in an experiment to evaluate gut sensitivity to the colon.⁷⁸

Non-steroidal anti-inflammatory drugs

Sodium diclofenac. Diclofenac sodium has been found to inhibit prostaglandin synthesis in the plasma of 18- to 65-year-olds with RA, resulting in analgesic and anti-inflammatory effects and effective relief of joint pain and swelling.⁷⁹ It can inhibit glycolysis of fibroblast synoviocytes in human RA, and decrease the serum levels of rheumatoid factor (RF), high-sensitivity C-reactive protein (hs-CRP), erythrocyte sedimentation rate (ESR), disease activity score-28 (DAS-28), and joint symptom and sign the score.⁸⁰

Mice treated with diclofenac sodium increased β -glucuronidase (GUS) activity in fecal samples, while GUS was 60% from *Firmicutes* and 21% from *Bacteroidetes*.⁸¹ Sodium diclofenac may increase the intestinal flora of *Firmicutes* and *Bacteroidetes*. In rats, sodium diclofenac is mainly excreted into bile in the form of glucuronic acid conjugates to participate in the hepatointestinal circulation, which may affect the metabolic level of glutamate.^{82,83} Diclofenac sodium increased the abundance of *Proteobacteria* and *Bacteroidetes* in the fecal stool of enteric rats and eventually consumed *Lactobacillus*.⁸⁴

Ibuprofen. Ibuprofen has a strong anti-inflammatory and analgesic effect in clinical practice, which can mediate its therapeutic effect by inhibiting cyclooxygenase and subsequently by inhibiting the production of prostacyclin.⁸⁵ Ibuprofen improved joint inflammation induced by type II collagen in DBA/1 mice and increased the secretion of the typical Th2 cytokine IL-5 in their serum.⁸⁶ Ibuprofen can reduce the mRNA expressions of MMP-3, MMP-13, COX-2, ADAMTS-5,

IL-6, and TNF- α in synovial cells of OA rats stimulated by sodium iodoacetate through porous microspheres.⁸⁷

In an experiment on the effects of drugs on the composition of intestinal bacteria in 155 adults, 62 chose NSAIDs, in which ibuprofen increased the abundance of bacteria in the families of *Aminococcaceae*, *Enterobacteriaceae*, *Propioniaceae*, *Pseudomonas*, *Pomegranates*, and *Salicaceae*.⁸⁸ At the same time, ibuprofen and its degradation products were found to be toxic to *Lactobacillus acidophilus*, *E. coli*, and *Clostridium fisheri* by *in vitro* bacterial culture experiments, and inhibited their growth.⁸⁹

Aspirin. Aspirin has a good anti-inflammatory effect, but its specificity is not strong. It is not only used in the treatment of arthritis but also against inflammatory diseases, such as endometrium and digestive tract, and a cancer treatment. Aspirin irreversibly acetylates COX-1 and prevents arachidonic acid from entering the active site, thereby reducing the production of thromboxane A2 and resulting in thrombocytopenia.⁹⁰ Aspirin promotes the production of resorcinol, an anti-inflammatory and pro-decomposition lipid medium. Aspirin also acetylated the COX-2-activated pathway for enzymatic production and combined with choline had good effects on foot swelling induced by carrageenan in mice and inflammatory pain induced by LPS in mice.^{91,92} The expression of TNF- α , IL-6, IL-1 β , IL-10, and other inflammatory factors in synovial fluid of AIA rats was decreased by aspirin Elisa kit. Western blot results showed that it also contributed to the decrease in NF- κ B/p38MAPK signaling pathway-related proteins and phosphorylated proteins.⁹³

By using antibiotics to reduce some intestinal bacteria in mice, it was found that normal mice taking aspirin had fewer colon tumors than sterile mice taking aspirin. The results of the 16S rDNA technique showed that the feces samples of mice given aspirin were rich in *Bifidobacterium* and *Lactobacillus*, while *Alistipes finegoldii* and *Bacteroides fragilis* were decreased.^{94,95}

Plant medicine

Colchicine. Colchicine is one of the earliest drugs used to treat gouty arthritis. *In vitro* cell experiments, the micromolar dose of colchicine can

effectively relieve acute gout pain by inhibiting the crystal activation of NLRP3 induced by monosodium urate (MSU) and blocking the release of IL-1 β .^{96,97}

Colchicine has certain toxicity to the gastrointestinal tract, so it can regulate the composition of intestinal flora. It was found that colchicine could significantly increase the relative abundance of *Firmicutes* and reduce the relative abundance of *Bacteroidetes* at the concentration of 2.5 mg/kg. In general, with colchicine intervention, the abundance of *Bacteroidetes*, *Candida*, *Rickneria*, and *Clostridium* decreased significantly. However, the abundance of *Lactobacillus* and *Prevotella* increased significantly.⁹⁸

Sinomenine. Sinomenine is an alkaloid isolated from the root of *Sabia japonica*, which is a traditional Chinese medicine for the treatment of RA.⁹⁹ In Elisa's test of serum of adjuvant arthritis rats, 10 and 20 mg/kg oral dose of sinomenine can decrease TNF- α , IL-6, and IL-1 β in a dose-dependent manner. In terms of protein expression, the expression of p-NF- κ Bp65, P-I κ B α , and RIP140 was significantly downregulated by the above two doses.¹⁰⁰ In the same Elisa experiment, at the dose of 30, 100, and 300 mg/kg, the levels of HIF-1 α , VEGF, and ANG-1 in synovial membrane and peripheral blood of CIA mice were reduced in a dose-dependent manner, providing important theoretical support for the treatment of RA.¹⁰¹ Zhengqing Fengtongning is a proprietary Chinese medicine made from a sinomenine monomer, which reduces PGE2 synthesis by inhibiting mPGES-1 to treat RA.¹⁰² The use of leflunomide and methotrexate in combination with proprietary Chinese medicine effectively reduced side effects.¹⁰³

Sinomenine plays a broad role in the intestinal flora of zebrafish. After injection of 80 mg/kg sinomenine, the abundance of *Fusobacteria* in intestinal contents of zebrafish was decreased and the abundance of *Actinomyces* was increased. Meanwhile, the increase in *Bacteroidetes/Firmicutes* ratio was inhibited.¹⁰⁴

Paeoniflorin. It was found that paeoniflorin at a dose of 50 μ M could treat and prevent OA of the knee by inhibiting the activation of the NF- κ B pathway, chondrocyte inflammation and degeneration, and osteoclast differentiation in osteoclast cells of CIA mice.¹⁰⁵ The dose of 0.388 g/kg/d for 21 days can downregulate the inflammatory

factors IL-21, IL-6, and TNF- α in the serum of CIA mice. In terms of protein, it mainly inhibits the differentiation of SPLEEN TFH cells and the formation of germinal center response (GC) through the STAT3 signaling pathway.¹⁰⁶

At 25, 50, and 100 mg/kg/d for 5 days, paeoniflorin decreased the abundance of gram-positive bacteria in feces and infiltration of gram-positive bacteria in intestinal tissue of C57/BL/6 colitis mice, inhibited the MDP-NOD2 pathway dependent on gram-positive bacteria, and alleviated inflammation (Table 2).¹⁰⁷

Drug intervention changed the composition of intestinal bacteria. Most of the *Bacteroides* were decreased in CP, while most of the *Firmicutes* and *Lactobacillus* were increased. Drug therapy reduced the secretion of inflammatory factors, such as TNF- α , IL-1 β , and IL-6 in serum and reduced the inflammatory response through the corresponding pathways, so that the pain signal received by the brain was weakened.

Conclusion

Due to the unknown onset time and mechanism of chronic inflammatory pain and the rejuvenation of the disease, the research on chronic inflammatory pain has been carried out and deepened. The results show that the occurrence and regression of chronic inflammation cannot be separated from the balance of intestinal microecology, and the key factors to ensure the balance are the intake of diet and drugs, the good foundation of genetic metabolism, and a healthy lifestyle to restore the microecology balance. From the gut-brain axis, it is found that inflammatory pain is related to the brain nerve and the intestinal nerve, and the differences between the intestinal flora and metabolites in patients with chronic inflammatory pain and normal people, and the effects of metabolites on patients with CP are analyzed. The relationship between CP and intestinal flora and metabolites is proposed. From the aspect of CP treatment drugs, the commonly used drugs not only change the characteristics of chronic inflammatory pain but also change the intestinal microorganisms in the body.

It is still not realistic to fundamentally solve chronic inflammatory pain from the intestinal microbiological level. What we need is a large number of experimental studies and more precise instruments. This article aims to explore the

Table 2. Effects of different drugs on intestinal microflora of patients with chronic inflammatory pain and its therapeutic mechanism.

Drug type	Experimental model	Dosage of administration	Treatment mechanism (references)	Intestinal microbiota regulation (references)
Dexamethasone	Synovial cells of CIA rat fibroblasts	Administer Dex Intraperitoneally (1 mg/kg) three times a week for more than 2 weeks	Reduce IL-1 β , IL-17, TNF- α , MMP-3 inflammatory factors ⁶²	Increase the abundance of <i>Erysipelas</i> and <i>Lactobacillus</i> reduce the abundance of <i>Firmicutes</i> , <i>Bacteroidetes</i> , <i>α-proteobacteria</i> , <i>γ-Proteobacteria</i> , and <i>Actinobacteria</i> ^{66,67}
	Synovial tissue of CIA rat	The knee joint was injected 1 mg/kg twice a week for 3 weeks	Decrease NF- κ B pathway expression ⁶³	
	GR ^{mt/mt} , GR ^{dim/dim} mice	Intraperitoneal injection of 10 mg/kg	Promote glucocorticoid receptor synthesis ⁶⁴	
Prednisolone acetate	CIA rat serum	Intragastric administration of 0.1 mL/10g lasted for 10 days	Decrease the levels of TNF- α , IL-1 β , and ICAM-1 inflammatory factors ⁷⁰	Decrease the abundance of <i>Bacteroidetes</i> increased the abundance of <i>Firmicutes</i> ^{71,72}
Betamethasone	CHON-002 human chondrocyte cell	Treatment with 10 μ M for 48 h	Inhibit the expression of NF- κ B/STAT3 signaling pathway ⁷⁶ Downregulate inflammatory cytokines IL-6 and IL-8 ⁷⁶	Increase the abundance of <i>Bacteroides</i> and <i>Proteus</i> Decrease the abundance of <i>Lactobacillus</i> and <i>Firmicutes</i> ⁷⁸
Sodium diclofenac	45 patients (38 female, 7 male; mean age 47.88 years) with RA	Orally 50 mg tablets twice daily for 8 weeks	Inhibit prostaglandin synthesis ⁷⁹	Increase the abundance of <i>Firmicutes</i> , <i>Bacteroidetes</i> , and <i>Proteobacteria</i> Reduce the abundance of <i>Lactobacillus</i> ^{82,83}
Ibuprofen	Male DBA/1 mice	Ibuprofen was taken orally twice daily for 2 weeks	Promote IL-5 secretion ⁸⁶	Increase the abundance of <i>Aminococcaceae</i> , <i>Enterobacteriaceae</i> , <i>Propioniaceae</i> , <i>Pseudomonas</i> , <i>Pomegranates</i> , and <i>Salicaceae</i> consume <i>Lactobacillus Acidophilus</i> , <i>Escherichia coli</i> , and <i>Clostridium Fischer</i> ^{88,89}
	Rat synovial cells	Polylactic acid-glycolic acid copolymer was loaded with 300 μ g/mL, 900 μ g/mL, 1500 μ g/mL mixed medium for 72 h	Decrease mRNA expression of MMP-3, MMP-13, COX2, ADAMTS-5, and other factors ⁸⁷	

(Continued)

Table 2. (Continued)

Drug type	Experimental model	Dosage of administration	Treatment mechanism (references)	Intestinal microbiota regulation (references)
Aspirin	Synovial fluid of AIA rats	0.1 mmol/kg was administered orally once a day for 2 weeks	Decrease the expression of TNF- α , IL-6, IL-1 β , and IL-10 Reduce the protein expression of NF- κ B/p38MAPK signaling pathway ⁹³	Increase the abundance of <i>Bifidobacterium</i> and <i>Lactobacillus</i> Decrease the abundance of <i>Alistipes finegoldii</i> and <i>Bacteroides fragilis</i> ^{94,95}
Colchicine	J774 cells	5–15 μ M	Inhibit the activation of NLRP3 crystals Block IL-1 β release ^{96,97}	Increase the abundance of <i>Firmicutes</i> , <i>Lactobacillus</i> , and <i>Prevotella</i> Decrease the abundance of <i>Bacteroidetes</i> , <i>Candida</i> , <i>Ricknia</i> , and <i>Clostridium</i> ⁹⁸
Sinomenine	Arthritis induced by Freund's adjuvant in rats	Gavage of 10 and 20 mg/kg lasted for 1 week	Downregulate the protein expression of p-NF- κ Bp65, p-I κ B α , and RIP140 ¹⁰⁰	Increase the abundance of <i>Actinomyces</i> Decrease the abundance of <i>Fusobacteria</i> ¹⁰⁴
Paeoniflorin	Osteoporotic vertebral fractures in rats DBA/1 male mice and CIA rats	Zhengqing Fengtongning injection was injected at L3 Jiaji point in doses of 0.5 and 2.0 mg Daily gavage of 0.388 g/kg lasted for 3 weeks	Inhibition of mPGEs-1 reduces PGE2 synthesis ¹⁰² Downregulate inflammatory cytokines IL-21, IL-6, and TNF- α Inhibit the expression of STAT3 signaling pathway ¹⁰⁶	Decrease the richness of gram-negative bacteria ¹⁰⁷
NF- κ B, nuclear factor kappa-B; STAT-3, Signal Transducer and Activator of Transcription.				

relationship between chronic inflammatory pain and intestinal microorganisms, find out the potential targets of intestinal microorganisms and their metabolites and provide a theoretical basis for the development of more symptomatic and safer therapeutic drugs.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Author contributions

Jia-Shang Li: Conceptualization; Investigation; Visualization; Writing – original draft; Writing – review & editing.

Shu-Lan Su: Funding acquisition; Project administration; Resources; Supervision; Writing – review & editing.

Zhuo Xu: Formal analysis; Validation.

Li-Hui Zhao: Investigation; Methodology.

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Jian-Ming Guo: Resources; Supervision.

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Competing interests

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