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Therapeutic effect and mechanism of action of geniposide in rheumatoid arthritis

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Abstract. Rheumatoid arthritis is a systemic autoimmune disease with persistent, symmetric and polyarthritis as the main clinical manifestations, which can improve the risk of cardiovascular disease and lymphoma. Untimely or inadequate treatment will result in a high rate of disability. In the context of the development of Chinese medicine modernisation, in order to explore the therapeutic effects and mechanisms of the diseases, researchers have extracted the active ingredients of Chinese herbal medicine for experiments. Geniposide through modern research found that it has anti-inflammatory analgesic and other effects, and has therapeutic effect on rheumatoid arthritis. But at present for geniposide's action mechanism and the pathogenesis of rheumatoid arthritis are not completely clear. This paper analyses the geniposide anti-inflammatory effect and analgesic effect aspect research, finds that geniposide can have a therapeutic effect on rheumatoid arthritis through anti-inflammatory analgesic effect. At present, the mechanism of action of geniposide against rheumatoid arthritis has not been fully defined, and geniposide has hepatotoxicity and many uncertainties in high concentrations, so it is of great significance to explore its action mechanism and provide theoretical reference for the new drugs' development to treat rheumatoid arthritis. The future research can pay more attention to explore the geniposide anti-inflammatory effect on the cell signalling pathway mainly embodied in a specific target, as well as geniposide development as a new drug possible direction.

Keywords: Geniposide, Rheumatoid arthritis, anti-inflammatory effect, analgesic effect.

1. Introduction

Synovial inflammation is the biological foundation of rheumatoid arthritis (RA), a chronic systemic autoimmune disease defined by the infiltration and erosion of inflammatory cells [1]. As RA is associated with a wide range of factors, including a series of immune responses, antigens, macrophages, and cytokines, it causes degradation of cartilage and bone in patients, ultimately leading to joint deformity and dysfunction [1]. Although its pathogenesis is not yet clear, current studies have shown that the interaction between genetics and environment is closely related to the initiation of RA [2]. At this time, both T and B cells are activated, and T cells activate B cells to produce autoantibodies like rheumatoid factor (RF) at this point. Activated T cells are recruited to the synovial membrane to activate macrophages and stimulate them to produce a substantial amount of inflammatory factors, such as tumor necrosis factor (TNF)-alpha, interleukin (IL)-6, and IL-1b, which make Fibroblast-like synoviocytes (FLS) in the synovial membrane excessive proliferation and causes osteoarticular injuries [2].

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Chinese medicine gardeniae-fructus is the dried mature fruit of Gardenia jasminoides Ellis in the family of Rubiaceae, which has the efficacy of clearing heat and relieving fidgetness, removing pattogenic heat from the blood and toxic material from the body, and relieving swelling and pain for external use [3]. As shown in Figure 1, geniposide (GE), is an iridoid glycoside compound, with the development of modern pharmacology, research shows that geniposide has hepatoprotective, choleretic, anti-inflammatory, analgesic, hypoglycemic, neuroprotective and other pharmacological effects [3]. It has been found that geniposide have the effect of improving RA through research [1].

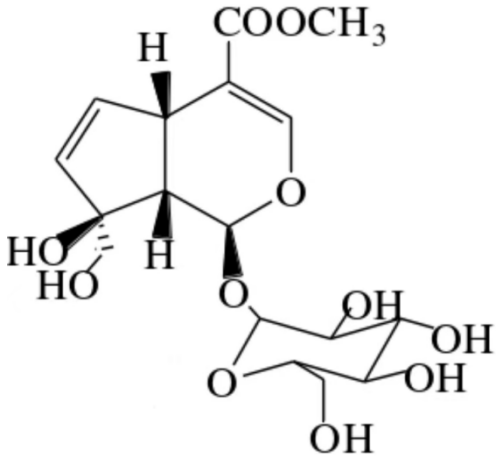

Figure 1. GE structural formula [3].

Although the existing research have proved that GE has therapeutic efficacy on RA, the mechanism of action of GE against RA is still not perfect, some molecular mechanisms have not been clarified, and a complete summary of the mechanism of action of GE against RA has not appeared. By summarizing the therapeutic effects of GE on RA under current research, the author found that GE mainly treats RA through anti-inflammatory and analgesic effects. Therefore, this paper will summarize and deeply explore the mechanisms of GE's anti-inflammatory and analgesic action.

In terms of scientific research, scientists have found that naturally occurring chemicals hold good promise in the development of new medicines, and as a result, naturally occurring chemicals have become an important source or precursor for the treatment of different diseases. This study can provide theoretical support for the development of new drugs for the treatment of RA using GE as a biopharmaceutical. This study allows researchers of GE to refine the mechanism of action of their anti-inflammatory and analgesic effects.

2. Anti-inflammatory effects of gardenia geniposide

2.1. Effects of geniposide on T cells

$CD4^+$T cells can be categorized into four subpopulations like pro-inflammatory Th1 cells, anti-inflammatory Th2 cells, Th17 cells and regulatory T (Treg) cells [4]. It has been found that Th17 cells are a type of $CD4^+$T cells characterized by the secretion of IL-17, which induces many pro-inflammatory cytokines, chemokines also produce other inflammatory cytokines involved, which in turn leads to the clinical symptoms of RA [4]. Additionally, Tregs can inhibit the immune response in order to exert anti-inflammatory effects, mainly through the expression of Forkhead box protein 3 (Foxp3) [4].

In the treatment of rats with adjuvant arthritis, GE was found to decrease the influence of Th17 cytokines and increase the expression of Treg cytokines by raising the number of Treg cells, thus GE exerts anti inflammatory action by regulating T cells [4]. Studies have shown that ulcerative colitis (UC) in animals can be treated by GE. In the treatment of UC mice with GE, it was found that the levels of IL-1βand TNF-αin the colon and serum of mice with UC were reduced and the expression of FOXP3, which can inhibit the immune response to alleviate inflammation, was found to be increased in the colon,

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so it was found that GE could alleviate the UC intestinal inflammation and barrier damage through the increase of the Treg cell differentiation of splenocytes [5].

2.2. Geniposide ameliorates inflammatory cytokines

When the body has an inflammatory reaction, it will induce the release of cellular inflammatory cytokines or chemokines, like TNF-α, IL-8,IL-6,IL-1β, etc., and the production of much inflammatory cytokines will induce the inflammatory reaction; Meanwhile the release of certain factors (such as IL-8) accelerates endothelial cell damage, causing stagnation of microcirculatory blood flow, resulting in organ function damage and even leading to tissue necrosis [6].

TNF-αis involved in normal inflammatory and immune responses. The massive expression of TNF-α at the onset of RA leads to a series of clinical symptoms and destruction of local joint tissues, and is due to the fact that overexpressed TNF-α promotes the massive expression of other inflammatory factors (e.g., IL-6, IL-17, etc.) [1]. It was found that GE can effectively inhibit peripheral blood inflammatory factors and significantly reduce the serum levels of TNF-αand IL-6 in rats with RA, and GE plays an anti-inflammatory role by improving inflammatory factors [1]. Asthma is an inflammatory process characterized and associated with Th2 cytokines [7]. The Th2 response is associated with a range of inflammatory cytokines and chemokines, particularly IL-4, IL-5 and IL-13 [7]. Yanhong Deng et al. found that GE reduced the increase of IL-4, IL-13 and IL-5 and the expression of vascular cell adhesion molecule-1 (VCAM-1) in mice with ovalbumin-induced allergic airway inflammation treated with GE [7].

2.2.1. The NF-κB signalling pathway

NF-κB is a transcriptional factor that can regulate inflammatory genes and has a crucial role in inflammation [8]. When the organism is in an inflammatory state, NF-κB is activated and NF-κB p65 is transferred to the nucleus to regulate the expression of inflammatory genes [8].

Bin Yu et al. found that NF-κB is activated in a mouse model of Staphylococcus aureus-induced pneumonia [8]. By establishing an animal model and designing a control group, a Staphylococcus aureus group, and GE group, the NF-κB expression was detected by western blotting, and found that GE's protective effect against Staphylococcus aureus-induced pneumonia was attributed to its ability to weaken NF-κB activation and inhibit inflammatory cytokines expression [8]. A20, a negative regulator of inflammation that plays a key role in activating NF-κB, mainly through the TNF receptor and toll-like receptors (TLR) pathway, has been shown to exert neuroprotective effects through anti-inflammatory actions. [9]. Qian Sun et al. found that GE could improve the ischemia-induced upregulation of TRAF-6 and p-NF-κB and increase the expression of A20, thus exerting anti-inflammatory effects through the NF-κB signaling pathway [9].

2.2.2. MAPK signaling pathway

Mitogen-activated protein kinase (MAPK), a member of intracellular serine-threonine protein kinase superfamily members, is a central node of several signal transduction pathways [10]. Extracellular signal-regulated kinase (ERK), p38 and c-Jun N-terminal kinase (jnk) together form the MAPKs pathway [10].

MAPK/ERK is a protein kinase, and this signaling pathway has been implicated in diseases such as tumors, inflammation, and diabetes [6]. During the experiments exploring the anti-inflammatory effects of brain microvascular endothelial cells, it was found that GE could activate the $P2Y_{14}$ receptor and thus inhibit the expression of the downstream ERK1/2 signaling pathway, which down-regulated the overexpression of pro-inflammatory cytokines (IL-8, MCP-1, and IL-1β) to play an anti-inflammatory role [11].

Activation of the p38-MAPK signal pathway increases the production of downstream inflammatory cytokines, and blocking this signaling pathway reduces cytokine production, prevents chondrocyte apoptosis, and has anti-inflammatory effects [10]. Yuan Chen et al. [10] found that GE could attenuate

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the phosphorylation of p38 and synergize with p38 MAPKs inhibitors to inhibit the p38-MAPK signaling pathway and achieve anti-inflammatory effects.

The anti-inflammatory effect of GE and its mechanism of are described above, from the outside to the inside to the deep.GE plays a role in alleviating inflammation through regulation of T cells and amelioration of inflammatory factors. The improvement of inflammatory factors is mainly achieved by affecting the biological molecules in the signaling pathway to achieve anti-inflammatory effects, such as affecting the NF-κB to cause changes in the signaling pathway to achieve anti-inflammatory effects, affecting the $P2Y_{14}$ receptor to inhibit the expression of ERK1/2 signaling pathway to achieve anti-inflammatory effects, as well as affecting the phosphorylation of p38 to inhibit the role of the p38-MAPK signaling pathway to achieve the effect of anti-inflammatory effects.

3. The analgesic effect of geniposide

It was found that geniposide dose-dependently reduced acetic acid induced twisting in mice and increased the pain threshold of mice in the hot-plate experiment, and the analgesic effect of GE could be partially inhibited by naloxone with L-Arg, so the analgesic mechanism of GE is related to the synthesis and release of opioid receptors and NO [12]. In addition, GE can alleviate the mechanical nociceptive response in diabetic rats by inhibiting the activation of Spinal dorsal horn microglia, decreasing the level of cytokines in the spinal cord, and lowering blood glucose [12].

The EGFR/PI3K/AKT signaling pathway exerts important effects on proliferation, growth, cell migration, metabolism and survival [13]. In the sciatic nerve chronic crush injury model (CCI) experiment, it was found that GE relieved neuropathic pain, while the addition of an EGFR agonist reduced the analgesic effect of GE [13]. Dan-Dan Zhang et al. found that GE reduced EGFR/PI3K/AKT pathway activity to improve CCI symptoms, attenuate mechanical pain threshold, and relieve pain after in-depth analysis [13].

4. Current status of geniposide in RA

It has been shown through many studies [7,13] that GE has good anti-inflammatory and analgesic effects to relieve inflammation and pain. The mechanism of action of GE anti-inflammatory concerns the p38-MAPK signaling pathway [14]. Research has shown [14] that the p38-MAPK signaling pathway is a popular target for anti-inflammatory drug design, and that it is by inhibiting the p38-MAPK-induced stress response that will block the production of pro-inflammatory cytokines thereby ameliorating RA. However, the regulatory and feedback mechanisms involved in p38-MAPK have led to different intracellular pathways crosstalking each other, interacting, inhibiting or regulating p38-MAPK through phosphorylation or dephosphorylation thereby limiting its clinical potential and leading to the discontinuation of many clinical trials [14]. The anti-inflammatory effects of MSK1/MSK2 may also be inhibited, for example, by inhibiting p38-MAPK [14]. GE has been found to have a variety of pharmacologic effects through modern research, but clinical trials have found GE to be hepatotoxic [15]. In an experiment, the hepatotoxicity of geniposide in SD rats and Wistar rats and ICR mice was found that GE could cause toxic responses at high doses [15]. Wang Bo et al. experimented with different concentration grades of aqueous extracts, alcoholic extracts, and GE of gardeniae-fructus, and confirmed that too much concentration of gardeniae-fructus can cause obvious hepatotoxic reactions [15].

The anti-inflammatory effects of GE are broad, involving many different cellular pathways, but there are no relevant clinical studies to demonstrate whether GE also produces a lack of anti-RA efficacy resulting from different intracellular pathways crosstalking each other. Therefore, in the future development, the research of GE needs to consider not only its toxic response, but also whether it has better efficacy within the dose range, due to the fact that GE has too many unpredictable results in the treatment of RA, with a certain degree of risk leading to the fact that at present there is no new drug research and development with GE as the main drug.

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5. Conclusion

The anti-inflammatory and analgesic effects of the Chinese medicine gardeniae-fructus extract GE are remarkable, with multi-system and multi-target therapeutic effects on RA.GE has a broad spectrum of anti-inflammatory effects involving many intracellular signaling pathways, indicating a broad spectrum of targets that bind to GE as well as a broad spectrum of anti-inflammatory therapeutic effects upon binding. Meanwhile, the analgesic effect of GE can reduce the mechanical pain threshold and relieve the pain. Although the anti-inflammatory effect of GE has been widely recognized, however, the molecular mechanism of its regulation of inflammatory response for the treatment of RA has not been completely clarified, and GE has hepatotoxicity and uncertainty in high concentration, so it is meaningful to explore its mechanism of action and provide theoretical references for new drugs development for the treatment of rheumatoid arthritis with GE as the raw drug. This article focuses mostly on the mechanism of action of the therapeutic effects of GE on RA, and its modern applications have not been carefully expanded and explored. The author believes that future studies could focus more on exploring the effects of GE's anti-inflammatory effects on cell signaling pathways mainly on a specific target, as well as on the direction of the possibility of developing GE as a new drug.

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