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The Molecular Mechanisms and Current Clinical Applications of Paeoniflorin in Rheumatoid Arthritis

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Abstract:

Rheumatoid arthritis (RA) is an autoimmune disease and a debilitating condition that significantly impacts patients' lives, placing a considerable burden on healthcare systems and society as a whole. At the same time, natural medicinal compounds are gradually emerging as a key area of research due to their notable advantage of holistic regulation. Therefore, this paper concentrate data from a wide range of literature sources. To offers a more comprehensive perspective on the role and recent developments regarding paeoniflorin in the treatment of RA. Paeoniflorin is the principal constituent of white peony root. Research find that, the paeoniflorin exerts anti-inflammatory and antioxidant effects by modulating multiple signalling pathways and regulating relevant lncRNA. Furthermore, a highly selective inhibitor from paeoniflorin, Ritlecitinib, is currently in Phase II clinal trials. The paper according to the limitations of paeoniflorin, put forward to the prospects for its use in the treatment of RA. And it is expect that this will bring about higher therapeutic effects, reducing the economic burden.

Keywords: Paeoniflorin; rheumatoid arthritis; molecular mechanism.

1. Introduction

Rheumatoid arthritis (RA) is an autoimmune disease, it main attack sites involving the joints, but can also damage the heart, digestive system, nervous system, etc. [1]. The exact aetiology of RA remains unclear, but most studies suggest that it may be influenced by variety of factors, including environmental, genetic and immunological factors. It main pathological features include symmetrical, persistent swelling and pain in the small joints, as well as damage to cartilage and bone [2]. RA is no longer a notable disease, but a global condition charaterised by uncertainly. According to data from 1990 to 2019, the incidence of RA was 12. 21 cases per 100, 000 people in 1990, rising to 13 cases per 100, 000 people in 2019. Meanwhile, over the course of 20 years, the DALY rate rose from 39. 12 per 100, 000 to 39. 57 per 100, 000, indicating that the burden of RA remains significant [3].

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Paeoniflorin (PF) is a monoterpene bicyclic glycoside derived from total paeoniflorin (TGP) found in peony root. It is also a important component of TGP. As a traditional medicinal herb, white peony root has been highly valued by medical experts throughout the ages. And is featured in ancient texts on Chinese medicine such as the Shennong Bencao Jing and Tang Bencao. Modern research has demonstrated that PF possesses a variety of role,such as anti-inflammatory [4]. Nowadays, PF is widely used in the treatment of conditions such as diabetes. It's high safety profile and low toxicity score both underscore the value of developing PF [5]. As a natural medicine, PF may serve as a substitute for certain synthetic drugs. Due to its excellent anti-inflammatory and immunomodulatory effects, it is also one of the new natural medicines currently used to treat RA. Products already on the market include Paeoniae Albus Glycosides Capsules. This article aims to provide an overview of PF therapy for RA and to highlight recent developments of PF-based therapeutic agents, with a view to supporting the discovery and research efforts of drug developers. And broaden the scope and applications of natural medicinal compounds in drug research, development and disease treatment, to promote their development. Actually,given the poor fat-solubility of PF and the difference in its behaviour under acidic and alkine conditions。 Existing research has largely focused on drug delivery using PF-based nanocomposite systems.This paper suggets that a 'probiotic-PF' hydrogel delivery system could be utilised to achieve targeted delivery to the gut and enhance bioavaliability.Furthermore,drawing inspiration from the traditional Chinese madicine(TCM) formula 'Peony and Licorice Decoction',future research could explore the combined delivery of PF with other TCM ingredients. To mitigate the adverse effects,such as reduced efficacy causing by a deficiency of PF.

2. The Pathogenesis of RA

RA is influenced by many factors, the first stage is primarily influenced by genetic and environmental factors. Because the human body harbours two RA susceptibility genes, HLA-DR1 and PTPN22, their presence significantly increases the risk of developing RA. At the same time, environmental factors such as smoking and air pollution may induce citrullination of proteins in respiratory tract [2,6,7]. In the second stages, the immune system id influenced by susceptibility genes,and such proteins are not recognized. Consequently, they are taken up by antigen-presenting cells and transported to the lymph nodes as complexes [2]. The activation of CD4+T cells, T helper cells (Th) and B cells in the lymph nodes. Furthermore, B cells differentiate into plasma cells, producing large quantities of autoantibodies. These two types may have been present in the patient's joints several years ago, exerting a significant influence on the onset of the disease [2]. An upregulation in the levels of inflammatory cytokines secreted by Th17 cells (T helper cell type 17, Th17)-such as TNF-α (tumour necrosis factor alpha) and IL-6 (interleukin-6)-disrupts the balance between these cells and Treg cells, thereby exacerbating the inflammatory response. At the same time, the upregulation of IL-2, IFN-γ (Interferon-gamma γ). TNF-a secreted by Th2 cells, thereby exacerbating the inflammatory response in RA. B cells continuously stimulate T cells activation and the production of Pro-inflammatory cytokines, amongst other functions. Furthermore, B cells are the 'main force behind the formation of Immune Complexes (ICs).

In the third stage, once inflammatory medicators reach the joints and trigger inflammation, the fibroblast-like synoviocytes (FLS) in the synovial tissue which come into direct contact with these medicators, are stimulated by IC. The quality of FLS surges, and they secrete large amounts of inflammatory cytokines such as ILs, which further exacerbate RA and synovial fluid within the tissues. FLS produce Matrix Metalloproteinase (MMP) after stimulations. At the same time they stimulate the receptor activator of nuclear factor κB (NF- κB) ligand, enabling T cells to bind to proteins on the surface of osteoclasts [8]. The osteoclasts actived and matured, combined with the action of T cells, leads to increased bone resorption. However, the production of MMPs and reactive oxygen species (ROS) by neutrophils in the synovial fluid can also lead to bone erosion [2].

In the fourth stage, after attacking the joints, inflammatory factors are carried by the bloodstream to other parts of the body. This can lead to a variety of complications throughout the body, such as osteoporosis and atherosclerosis. Now RA progresses to a systemic autoimmune disease.

3. The Molecular Mechanisms of PF

3.1 The Nature and Function of PF

PF have distinct physical and biological properties. It has highly hydrophilic of its physical properties. Its molecules contain multiple hydroxyl groups and are readily soluble in water. However, this also means that it less fat-soluble and finds it difficult to penetrate cell membranes. PF has great safety of its biological properties. Current research indicates that it is of minimal toxicity and poses no harm to humans. Peony glycoside-based medicines take effect quickly but have a short duration of action。 They are characterized by widespread distribution, rapid metabolism and renal excretion. However, due to its poor fat-sol-

ubility, it exhibits low intestinal permeability and has very low oral bioavailability. The stability of PF also influenced by pH. environment. Research by Huo Xiaoguang and colleagues has shown that, in vitro, paeoniflorin is stable under acidic conditions but unstable under alkaline conditions, where its molecular structure is disrupted and it exists in ionic form [9].

3.2 The Anti-inflammatory Mechanism of PF

As mentioned earlier, PF is used to treat RA primarily for its anti-inflammatory and immunomodulatory effects. Aim to the anti-inflammatory role of PF, its mainly through the regulation of signaling pathways and the modulation of the long non-coding RNA (lncRNA) MALAT1.

PF exerts its anti-inflammatory effects by modulating intracellular signal transduction. The signaling pathways include JAK (Janus kinase) , STAT (Signal Transducer and Activator of Transcription), MAPK (Mitogen-Activated Protein Kinase) [10]. This blocks the transcriptions of inflammatory cytokines and reduces P38 MAPK expression, thereby preventing the symptoms from worsening. At the same time, PF is also increasing RNA MALAT1 to inhibit Wnt1 (Wingless/Integrated 1) /β-catenin (Beta-catenin) pathway, thereby inducing apoptpsis in FLS.

Yang Fan and colleagues established an RA-FLS group and an NC-FLS group, treated the cells with PF, and analyzed They found that the apoptosis rate between the two groups differed significantly [11]. The subject was further divided into a control group, an si-MALA1 group, and an observation group of si-MALA1 treated with PF. The mRNA and protein expression of molecules involved in the regulation of apoptosis, such as Wnt1, β-catenin, caspase-3, were analysed using qRT-PCR and western blot techniques, respectively. Finally, it was found that the expression levels of these molecules, at both the mRNA and protein levels, differed significantly from hose of the control group. this result was stastically significant (P<0. 01). This demonstrates that PF promotes apoptosis in FLS by upregulating the expression of caspase-3/9, thereby inhibiting the formation of pathological blood vessels. Reducing the risk of the inflammatory factors enter the bloodstream or even spreading throughout the body [2].

3.3 The Immunoregulatory Mechanisms of PF

The mechanism by which PF regulates immune cells primarily involves exerting an anti-inflammatory effect by modulating the expression of factors associated with T cells and macrophages.

Research by Chunling Liang et al. found that B6/gld mice susceptible to lupus nephritis, following PF treatment, the expression levels of mTNF-α in some M2 macrophages in the spleen showed a slight increase [12]. But M1 are the opposite. And the expression of TNFR2 also increased accordingly. Further analysis of Treg cells in the BMDM/T-cell system revealed that the addition of PF significantly increased the number of CD4+FoxP3+Treg. The study demonstrated that PF enhances TNFR2 expression to expand Treg cells, restoring the Treg/Th17 balance in the body. To promte the healing of inflammation. In addition, PF is capable of suppressing the Th1 response, thereby upregulating Th2, reducing the levels of pro-inflammatory cytokines such as IL-2 and IL-17, and increasing the levels of anti-inflammatory cytokines such as IL-4 and IL-5.

3.4 The Antioxidant Machanisms of PF

ROS is also an important factor in exacerbating the aetiology and pathological manifestations of RA in its later stages. PF can reduce the concentration of Malondialdehyde (MDA) in the body and enhance relevant antioxidant enzymes. This indicates the antioxidant capacity increasing and an improvement in its ability to scavenge ROS [7]. Jia et al. divided the RA rats into a control group and a study group. The rats in the control group were injected with sodium pentobarbital, whilst those in the study group were injected with PF [13]. Following a three-week course of treatment, clinical arthritis scores were assessed in both groups. The result showed a significant reduction in scores in the PF study group compared with the control group(P<0. 01), which was statistically significant. In addition,measurements were taken of various parameters, including MDA concentrations in both groups. The results showed that antioxidant enzyme activity had increased in the PF study groups.

It can enhance the secretion of anti-inflammatory factors and the body's antioxidant capacity by inducing Collagen-Induced Arthritis (CIA). Huang et al. established a CIA model in rats and set up a control group and several treatment groups [14]. The control group of rats received no treatment, whilst the treatment groups were divided according to the medication administered: the COR group, the PF group and the COR&PF combination group. Inflammation scores, bone damage scores and levels of oxidative stress in synovial tissue were measured in the rats 34 days after the onset of disease in the control group and 20 days after the start of treatment in the treatment group. The result showed that the inflammatory response was alleviated in all rats in the treatment group, with inflammation scores lower than those in the control group. These differences were statistically significant. Furthermore, with regard to measurements of oxidative stress levels, the COR group and the PF group exhibited stronger antioxidant activity than the combination group.

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From the perspective of mitochondrial function, PF activates the AMPK pathway, thereby promoting the abnormal mitochondrial fission induced by CIA, which in turn alleviates oxidative stress and promotes synovial cell apoptosis [2]. At the same time, activation of AMPK pathway can also induce the expression of antioxidant enzymes, thereby enhance the body's antioxidant capacity and maximize the drug's efficacy.

4. The Clinical Use of PF in the Treatment of RA

4.1 Current Pharmacological Treatments for RA

There are three main categories of drug therapy for RA: non-steroidal anti-inflammatory drugs (NSAIDs), disease modifying management (DMARDs) and Glucocorticoids (GCs). NSAIDs mainly used to relieve pain, they cannot prevent joint damage. It works by inhibiting Cyclooxygenase (COX) to provide rapid relief from swelling and pain.

DMARDs mainly alleviate symptoms and control flare-ups by suppressing the body's immune response. Based on their mechanism of action and time of introduction, they can be divided into three groups. Among these, CsDMARDs are the first drug to treat RA, it can delay or prevent joints damage. Commonly used CsDMARDs include methotrexate (MTX), leflunomide (LEF). According to the 2021 American College of Rheumatology (ACR) guidelines on the treatment of RA, MTX is the first-line core medicine for RA. However, as CsDMARDs have the disadvantage of being slow to take effect, doctors will predescribe bDMARDS or tsDMARDs depending on the individual patient's circumstance.

bDMARDs are protein molecules produced by biotechnology and can be divided into several categories, including TNF inhibitors and B cells depletors. According to an analysis by Anton Matsson et al. of data from the US CorEvitas RA registry for the period 2012-2021, TNF inhibitors were the most commonly used treatment regimen [15]. But meanwhile, due to the suppressed by immune system, bDMARDs can increase susceptibility to infection. Especially, TNF-αraise the risk of developing tuberculosis.

The third are GCs. GCs treat RA in several aspects, one of which is their ability to block various pro-inflammatory factors. In the treatment of RA, GCs are often used to provide rapid relief from patient's pain symptoms. According to the 2025 newest guidelines from European League Against Rheumatism (EULAR), they still recommended to use MTX in combination with GCs to compensate for the slow onset of action associated with CsDMARDs. So, GCs always use to support DMARDs. However, GCs have strong side effects. The research by Mahamadou Sagara and other people showed that patients with RA who are exposed to GCs over the long term, the efficacy of targeted therapies is reduced. And these patients have a significantly higher relative risk of developing conditions such as diabetes, hypertension and osteoporosis compared with others.

In summary, now treatment options for RA fairly comprehensive and well established. But limited by the adverse effects of certain drugs. So, researchers still need to find higher safety drugs [16].

4.2 The Benefits and Limitations of PF Treatment

As mentioned earlier, many of the drugs currently used to treat RA have the drawback of being slow to take effect and causing severe side effects. Among the current treatments for RA, PF-06651600 (Ritlecitinib), a drug currently in Phase II clinical trials, is attracting considerable attention.

PF-06651600 (Ritlecitinib) is an orally administered, irreversible JAK3/TEC (Thymic Epithelial Cells , TEC) inhibitor that exhibits high selectivity. According to an experiment conducted by Jean-Baptiste Telliez et al. in which a rat AIA (Adjuvant-Induced Arthritis) model was established, the rats were divided into three treatment groups (3 mg/kg, 10 mg/kg, 30 mg/kg)and one negative control group, and were administered the treatment orally for a period of seven days. The consequence showed that all three doses significantly reduced paw swelling, with the effect being significant($P<0.05$) [17].

This trials directly demonstrates that Ritlecitinib as a JAK3 inhibitor, has a significant disease-mpdifying effect in RA model. At the same time, it also serves to preserve anti-inflammatory signalling in macrophages, without blocking IL-10 signalling or interfering with IL-27. Consequently, this not affect IL-10's suppression of pro-inflammatory cytokines, nor does it affect IL-27's induction of TNF- α or its suppression of IL-8. Ritlecitinib also can inhibit the function of Th1 and Th27, thereby restoring the balance between Th1/Th2 and Th17/Tregs. According to the study made by Michael F Robinson, Ritlecitinib has advantages of rapid onset of action and significant efficacy. At the week 8 efficacy endpoint, the SDAI score was higher than that of the placebo group, and so serious adverse events or deaths were reported during the study [18].

The PF series of drugs offer a number of advantages, including high selectivity, consistent efficacy, rapid onset of action and a high safety profile. But as mentioned earlier,

PF has the drawbacks of being poorly fat-soluble and susceptible to alkaline environment. Moet oral formulations of PF currently suffer from a number of issues related to poor bioavailability.

5. Conclusion

This review summarises the current mechanisms underlying the treatment of Ra with PF and the relevant drugs available for this purpose. PF is a multi-targeted drug component that uses its therapeutic effects by regulating pathways and IncRNA.In terms of drug development, Ritlecitinib, a member of the PF series currently in Phase II clinical trials, has demonstrated highly selective inhibitory activity. It is expected to play a better role in the future treatment of RA. However, the poor fat solubility of PF suggests that researchers should focus on developing novel formulations of PF-based drugs and exploring their combination with CsDMARDs. PF also could be developed in combination with novel delivery systems to enhance its utilization rate. The optimization to exist formulations be utilized and innovated upon to enhance the targeting of PF and improve its efficacy in the treatment of RA.

Existing research on PF remains limited and is largely confined to the laboratory stage,having not yet progressed to clinical trials.Most studies have demonstrated that PF exerts anti-inflammatory and antioxidant effects by modulating multiple signaling pathways.The specific targets of PF'direct action have not been verified.At the same time,there is a lack of research data on PF in specific populations,such as pregnant women.Furthermore,existing innovative drug delivery systems,such ass PF-based composite nanostructures,pften involve various excipients,including polymers.In particular,the potential toxicity has not been adequately assessed.Overall,research into PF remains incomplete.This paper argues that future researchers should not only focus on innovations in drug delivery systems,but also investigate the as yet undiscovered targets of PF and its potential for combination therapy with other drugs.Research into the target population should be continued and the scope of the study expanded to ensure that PF can be used to treat a wider range of patients.To capitalise on its strengths.

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