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QUERCETIN: A POTENTIAL NATURAL DRUG FOR ADJUVANT TREATMENT OF RHEUMATOID ARTHRITIS

Jian-Jun Ji [a] , Yuan Lin [a], Shan-Shan Huang [a] ,Hou-Li Zhang [a], Yun-Peng Diao [a]*,Kun Li [b]*

[a]College of Pharmacy, Dalian Medical University, Dalian 116044, China
[b]College of Chemistry and Chemical Engineering, Liaoning Normal University, Dalian 116029, China
*Email:diaoyiwen@126.com, doctordiaodiao@163.com

Abstract

Rheumatoid arthritis (RA) is the rheumatism mainly manifested as disabling joint disease and mainly involves hands, wrists, feet and other small joints. Recurrent arthritis attacks, synovial cell hypertrophy and hyperplasia and bone and cartilage damages eventually lead to joint dysfunction and other complications, and there is no cure. Quercetin (QU) is a kind of natural flavonoids, with lipid-lowering, anti-inflammatory and other pharmacological activities, and minor toxic side effects. Thus, we assume that QU may be an adjuvant natural drug for treatment of RA. The possible mechanism is through regulation of NF-κB, to inhibit the transcription of joint synovitis factors, hinder the generation of inflammatory factors, and inhibit the inflammatory reaction; through inhibiting the activities of VEGF, bFGF, MMP-2 and other cytokines, to inhibit angiogenesis in multiple links and inhibit synovial pannus formation. QU may be an adjuvant natural drug for treatment of RA.

Key Words: quercetin, natural drug, rheumatoid arthritis.

Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease mainly manifested as chronic, progressive and invasive arthritis. The prominent clinical manifestation is recurrent multiple symmetrical small arthritis, mostly involving hands, wrists, feet and other joints, joint redness, swelling, warmth, pain and dysfunction occur in early stage, and various degrees of stiffness and deformity may occur in late stage, complicated with bone and muscle atrophy, with extremely high disability rate. At the aspect of pathological changes, the main pathological changes of RA are that leukocytes infiltrate into articular cavity and cause recurrent synovitis (Cooles and Isaacs, 2011) and that invasive pannus forms to damage cartilage, bone and surrounding tissue. RA treatment has undergone a long process of exploration and development, and therapeutic drugs and methods are various. The treatment at the beginning can only ease pain, diminish inflammation and reduce symptoms and can not control the activities and progress of the disease, and drugs used are non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin, diclofenac and so on. Later, a kind of drugs able to prevent joint imaging damage was found, known as disease modifying anti-rheumatic drugs (DMARDs), such as sulfasalazine (SSZ), hydroxychloroquine (HCQ), methotrexate (MTX) and so on. Then, it developed to application of rheumatoid arthritis-related immunosuppressive agents, such as tumor necrosis factor antagonists (TNF-α) etanercept, infliximab, adalimumab and so on. Later, it developed to special inflammatory link-acting biological targeting agents, such as B-cell inhibitor rituximab, and new treatments, such as hematopoietic stem cell transplantation, gene therapy, RNA interference and other technology. The drugs are continuously updated, but adverse drug reactions are more and side effects are serious, affecting the therapeutic efficacy.

Quercetin (QU) (3, 3', 4', 5, 7-pentahydroxy flavone) is a natural flavonoid with various biological activities, and it is

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distributed in hundreds of herbs, vegetables and fruits. People in their daily diet can intake about 5-40 mg per day (Hertog et al.,1995), and some eating more fruits and vegetables rich in flavonoids (such as onions, apples, etc.) even can intake 200-500 mg per day(Harwood et al., 2007). QU has many pharmacological effects, such as expanding coronary arteries, lowering blood pressure, anti-inflammation, anti-allergy, anti-platelet aggregation, antitumor, etc (Hollman and Katan,1999; Sylwia et al., 2012). QU has very small side effects, and in phase-I human clinical trials, the resent recommended dose of quercetin is 1400 mg/m^2, which corresponds to about 2.5 g for a 70 kg individual (Ferry et al.,1996). For 4 g single-dose oral administration or 500 mg twice daily, no side effects were found after continuous administration for a month (Lamson and Brignall., 2000). Because of its small toxic side effects, it has become a research focus in disease prevention and treatment, especially those chronic diseases requiring long-term treatment. Teresita Guardia, et al (Teresita et al., 2001) found that QU and other flavonoids have anti-inflammatory effects on rat adjuvant arthritis. Mamani-Matsuda, et al (2006) found that when acting on adjuvant-induced arthritis in mice, QU can reduce the production of macrophage inflammatory mediators, thus have the anti-inflammatory effects.

Hypothesis

So far, there have been no reports on QU efficacy in clinical treatment of RA. However, considering QU pharmacological activity and its small side effects, we hypothesize that quercetin may be a potential natural drug for adjuvant RA treatment.

The possibility

The pathogenesis of RA is very complex, and domestic and foreign researchers have conducted a large number of studies, showing that it is related with heredity, microbial infection, endocrine, environment and other factors. Synovitis is one of the major pathological changes of RA Some studies (Sano et al.,1992;Miyasaka and Hirata,1997; Choy and Panayi,2001; Firestein, 2003) indicate that some pro-inflammatory cytokines, such as TNF-α, interleukin (IL)-1β and IL-6, chemokines, nitric oxide, etc; abnormal regulation of inflammatory enzymes, such as cyclooxygenase-2 (COX-2) and 5-lipoxygenase (5-LOX); abnormal expression of adhesion molecules are closely related to synovitis. That the regulation of these inflammatory cytokines is related to NF-kappaB (Nuclear factor-κB, NF-κB). NF-κB was firstly discovered by Sen and Baltimore in 1986 (Sen and Baltimore, 1986), it is an important factor to regulate gene transcription and involves in the regulation of gene expression of various inflammatory cytokines (Kumar et al., 2004). For example, cytokine TNF-α and IL-1β are agonists of NF-κB and also its target genes to induce transcription. Thus, NF-κB activation leads to TNF-α and IL-1β expression increase, and these substances are also agonists further acting on NF-κB, to make its activity more enhanced. QU can regulate NF-κB activity (Cho et al., 2003; MartI′et al., 2005; GarcI′et al., 2008), and through the regulation of NF-κB and inhibition of inflammatory cytokine expression, achieve the effects of preventing inflammation and reducing inflammatory reactions.

The other pathological change of RA is synovial pannus formation. Pannus is comprised of new capillaries, proliferated synovial cells, inflammatory cells and organized celluloses, with the similar characteristics of tumor tissues, and it is the main cause and pathological basis of joint disease and cartilage damage. The formation of new blood vessels include a series of processes of capillary endothelium basement membrane degradation, endothelial cell migration and proliferation, lumen formation and new basement membrane formation. Vascular endothelial growth factor (VEGF) can increase vascular permeability, is the strongest known vascular penetrant, is strongly expressed in various cells of RA synovial tissue (Yamada, 1998; Pfander et al., 2001), can promote blood vessel endothelial cell proliferation and migration and thus form new blood vessels, to provide micro-environment for synovial pannus, so synovial cells can maintain continuous proliferation and cause the damage of related joint tissues and functions. On the other hand, VEGF can promote the secretion of basic fibroblast

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growth factor (bFGF). bFGF can activate telomerase in synovial cells, and meanwhile promote blood vessel endothelial cell proliferation and migration, contributing to continuous proliferation of synovial cells and formation of pannus. A study (Tan et al., 2003) shows that QU can reduce the secretion of VEGF in endothelial cells. The decrease of VEGF level affects angiogenesis, thereby affecting synovial pannus formation. In addition, QU can inhibit protein kinase C (PKC) and receptor tyrosine kinase (TPK) activity, thereby inhibiting the activity of bFGF to produce anti-angiogenic effect.

Matrix metalloproteinase (MMP) family is a group of zinc-dependent proteolytic enzymes, present in normal human body, and the main regulator of tissue remodeling and extracellular matrix (ECM) degradation. It can degrade almost all the basement membrane skeleton components, such as various types of collagens, fibronectins, laminins, elastins, etc, it is closely related to the diseases with ECM degradation, and at least 26 members of the family have been found presently (Verma and Hansch,2007). The increase of activity of MMPs is closely related to RA cartilage and bone damage and angiogenesis. In which, collagenase (MMP-1), gelatinase A (MMP-2), gelatinase B (MMP-9) and others are particularly important in RA bone damage. MMPs involve in cartilage extracellular matrix degradation; promote osteoclasts for bone absorption; promote angiogenesis; also activate the proteins with potential activity, for example, MMP-2 can activate the potential activity of ECM structural proteins, and it plays an important role in attracting inflammatory cells (Li,2009). Quercetin (QU) can inhibit the activity of MMP-2 (Tan et al.,2003), thereby inhibiting the degradation of basement membrane and indirectly inhibiting angiogenesis and cartilage damage.

Conclusion

In summary, QU can regulate activation of NF-κB, inhibits the transcription of joint synovial inflammatory factors and affects the generation of inflammatory factors, thereby preventing or reducing inflammatory reactions. On the other hand, QU inhibits the activity of VEGF, bFGF, MMP-2 and other cytokines, inhibits angiogenesis in multiple links, and inhibits the formation of synovial pannus to certain extent. Thus, QU plays a certain role in relieving RA inflammation and preventing pannus formation, and it may become an adjuvant drug for RA treatment.

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