FEATURE ARTICLE

Action Mechanisms of Complementary and Alternative Medicine Therapies for Rheumatoid Arthritis

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ABSTRACT Rheumatoid arthritis (RA) is characterized as a chronic inflammatory disease in joints and concomitant destruction of cartilage and bone. Cartilage extracellular matrix components, such as type Ⅱ collagen and aggrecan are enzymatically degraded by matrix metalloproteinases (MMPs) and aggrecanases in RA. Currently, treatments targeting cytokines, including anti-tumor necrosis factor (TNF) α antibodies, soluble TNF receptor, anti-interleukin (IL)-6 receptor antibody, and IL-1 receptor antagonist, are widely used for treating RA in addition to anti-inflammatory agents and disease-modifying antirheumatic drugs (DMARDs), such as methotrexate, but these treatments have some problems, especially in terms of cost and the increased susceptibility of patients to infection in addition to the existence of low-responders to these treatments. Therefore, therapeutics that can be safely used for an extended period of time would be preferable. Complementary and alternative medicines including traditional Chinese medicines (TCM) have been used for the arthritic diseases through the ages. Recently, there are many reports concerning the anti-arthritic action mechanisms of TCM-based herbal formulas and crude herbal extracts or isolated ingredients. These natural herbal medicines are thought to moderately improve RA, but they exert various actions for the treatment of RA. In this review, the current status of the mechanism exploration of natural compounds and TCM-based herbal formulas are summarized, focusing on the protection of cartilage destruction in arthritic diseases including RA and osteoarthritis.

KEYWORDS rheumatoid arthritis, extracellular matrix, aggrecanase, matrix metalloproteinase, complementary and alternative medicine

Rheumatoid arthritis (RA) is an immune-related disease that is well characterized by persistent synovitis followed by the destruction of the cartilage and bone in joints.[1,2] RA affects 0.5%–1% of people in the world.[1] Currently, disease-modifying antirheumatic drugs (DMARDs) and the biological agents targeting tumor necrosis factor (TNF)-α, interleukin (IL)-1, and IL-6 are mainly used for the treatment of RA in addition to steroidal anti-inflammatory agents and immunosuppressive drugs.[1-3] However, these treatments still have many problems, especially in terms of cost and the increased susceptibility of patients to infection in addition to the existence of the low responders in the RA patients.[3] Therefore, therapeutics that can be safely used for an extended period of time at a reasonably low cost would be preferable. Complementary and alternative medicines including traditional Chinese medicines (TCM) have also been used for treating arthritic diseases throughout the ages. Recently, there are a number of reports concerning anti-arthritic action mechanisms of TCM-based herbal formulas and the extracts or the ingredients of herbs.[4,5] In this review, we have summarized the current status of the mechanism exploration of natural compounds and TCM-based herbal formulas focusing on the cartilage destruction in arthritic diseases including RA and osteoarthritis (OA).

Degradation by Matrix Metalloproteinases and Aggrecanases of Cartilage Extracellular Matrix

Cartilage is composed of small amounts of chondrocytes and specialized extracellular matrix (ECM) including type Ⅱ collagen, hyaluronan (HA),

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and aggrecan.[6,7] Type Ⅱ collagen forms a fibrillar meshwork that provides the tissue with tensile strength. Aggrecan is present in cartilage as large aggregates interacting with HA and link protein, and they are highly hydrated due to the negatively charged polysaccharide chains attached to the core proteins. This provides the cartilage with its ability to resist compressive load. Therefore, the destruction of the cartilage ECM leads to a loss of its ability to resist compressive and tensile forces, resulting in a dysfunction of the joints.

In RA, the degradation of cartilage ECM exceeds its synthesis due to the elevated activity of proteolytic enzymes, of which matrix metalloproteinases (MMPs) and aggrecanases are considered to be the major effectors (Figure 1).[8-10] A number of MMPs are elevated in the joints of patients with RA, including collagenases (MMPs-1, -8, and -13) that can cleave type Ⅱ collagen α1 chain at a specific site located at about three-fourths the distance from the N-terminal.[8-10] In particular, stromelysin-1 (MMP-3) has been reported to be extremely increased in both the synovial fluid and serum of RA patients, thereby serum MMP-3 is routinely monitored as a clinical marker for RA diagnosis.[11]

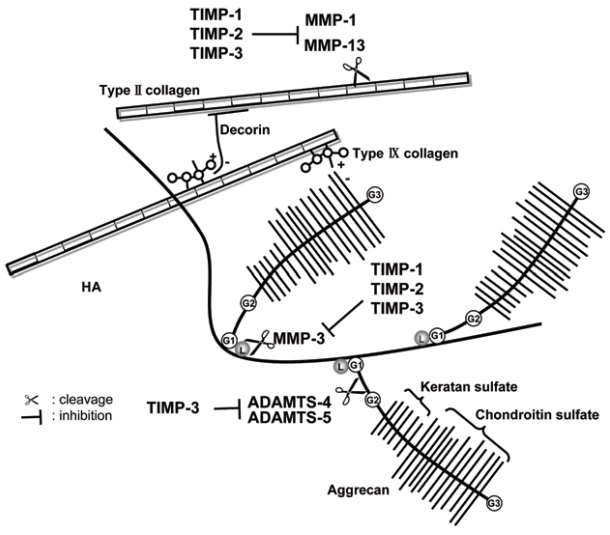

Figure 1. Schematic Structure of Cartilage Extracellular Matrix

Notes: G1, G2, and G3: globular domains-1, -2, and -3, respectively; L: link protein; TIMPs: metalloproteinases; ADAMTS: a disintegrin and metalloprotease with thrombospondin-like motifs; the same below

Many MMPs, including MMPs-1 and -3, can also cleave the aggrecan at the site of ^{341}asparagine (N)-^{342}phenylalanine (F)[12] (Figure 2). However, aggrecan fragments that are generated by the cleavage at the site of ^{373}glutamic acid (E)-^{374}alanine (A) (Figure 2) are increased rather than MMP-dependent aggrecan fragments in synovial fluid of arthritic diseases including RA and OA.[12-15] Two kinds of aggrecanases, a disintegrin and metalloproteinase with thrombospondin-like motifs (ADAMTS)-4 and ADAMTS-5, have been identified as principle enzymes that contribute to cartilage degradation in arthritic diseases.[16,17] The deletion of active ADAMTS-5 in mice protected their joints from destruction occurring in the antigen-induced RA model and in the meniscus destabilization model of OA, suggesting that aggrecan degradation by ADAMTS-5 is crucial for the development of arthritis at least in those animal models.[18,19] Aggrecanase-mediated aggrecan cleavage is followed by the degradation of the other ECM components, such as type Ⅱ collagen by MMPs, and thus, aggrecanases are thought to be pivotal enzymes as a trigger of cartilage destruction.[12] Therefore, both MMPs and aggrecanases are likely to be molecular targets for the treatment of RA as well as OA.

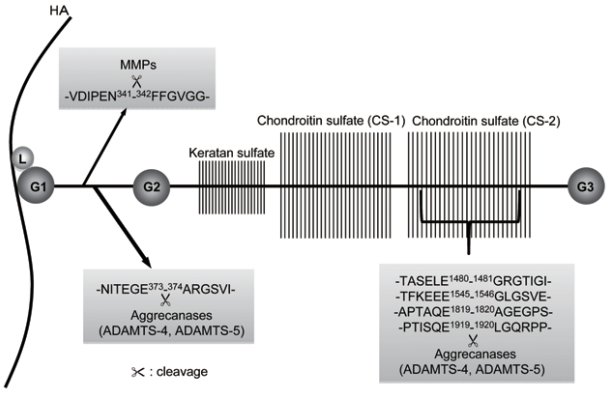

Figure 2. Sites of Aggrecan Core Protein Cleavage by MMPs and Aggrecanases

Tripterygium wilfordii Hook. F

In the ancient past of China, formulae consisting of a number of Chinese herbs are commonly used for the treatment of arthritic diseases including RA based on TCM. Among a number of herbs used in China, *Tripterygium wilfordii* Hook. F (TWHF) is the most popular herb for the treatment of RA.[4] Indeed, the extract of TWHF has been clinically shown to be more effective for the cure of RA than sulfasalazine.[20] Triptolide, a diterpenoid triepoxide purified from TWHF, has been identified as a major component of TWHF and accounts for its therapeutic effects.[21] Previous studies have shown that triptolide possesses both immunosuppressive and anti-inflammatory activities, including the inhibition of cytokine gene

expression in T cells.[22-24] We have also reported on the biological activity of triptolide *in vitro* and shown novel evidence that triptolide at the concentration of 28 to 140 nmol/L suppresses the production of proMMPs-1 and -3 and augments those of the inhibitors of MMPs, tissue inhibitors of metalloproteinases (TIMPs)-1 and -2 in human synovial fibroblasts.[25] We have also shown that daily oral administration of triptolide exerts a therapeutic effect on collagen-induced arthritis (CIA) in mice.[26] The therapeutic effects were resulted in part from the direct suppression of the production of MMPs-3 and -13 and the simultaneous up-regulation of TIMPs-1 and -2 production in the joints.[26] Interference by triptolide with the production of inflammatory mediators, IL-1β, TNFα, IL-6, and prostaglandin E_2 (PGE_2) has also been observed in CIA mice[26] as well as in cultured mouse macrophages.[25] Inhibition by triptolide of PGE_2 production is attributed to the selective suppression of cyclooxygenase (COX)-2 expression.[26] The suppression of MMPs and cytokines production is due to the inhibition of activity of nuclear factor (NF)-κB.[26] In addition to our reports, Liacini, et al[27] have reported that triptolide suppresses IL-1β-, TNFα-, and IL-17-induced gene expression of ADAMTS-4 in bovine cartilage explants. Besides these actions, triptolide has been found to suppress the expression of intercellular adhesion molecule (ICAM)-1 and monocyte chemotactic protein (MCP)-1.[28] Thus, triptolide interferes with the cartilage ECM breakdown in RA in addition to the suppression of inflammatory responses in a comprehensive manner.

Polyphenols

Some polyphenols including catechins, flavonoids, and curcuminoids have been shown to exert possible therapeutic effects on arthritic diseases both *in vitro* and *in vivo*. Green tea is one of the most commonly consumed beverages in the world and contains rich polyphenols including catechins. Epigallocatechin-3-gallate (EGCG) is a major catechin in green tea polyphenols, and there are a number of reports concerning the biological activities of EGCG.[29,30] In addition, EGCG has been shown to inhibit the enzymatic activities of ADAMTSs-4 and -5 with 100 to 150 nmol/L of inhibitory concentration (IC_{50}).[31,32] Furthermore, it has been reported that EGCG inhibits the production of chemokines including MCP-1, regulated upon activation of normal T-cell expressed and secreted (RANTES), growth-regulated oncogene (Gro)-α, and epitherial neutrophil-activating peptide (ENA)-78 based on the selective suppression of the IL-1β-induced protein kinase Cδ and NF-κB pathways in RA synovial fibroblasts.[33,34] EGCG also effectively inhibits TNFα-mediated production of MMPs-1 and -3 by interference with activator protein-1 (AP-1) activity. Moreover, EGCG has been shown to reduce osteoclast differentiation through the inhibition of receptor activator of NF-κB ligand (RANKL)-induced activation of c-Jun N-terminal kinase (JNK) and NF-κB pathways.[35] Thus, EGCG is likely to be useful to protect cartilage and bone from pathological degeneration in RA.

Nobiletin (5,6,7,8,3',4'-hexamethoxyflavone), a polymethoxylated flavon specifically found in citrus fruits, has been reported to exhibit pharmacological actions including anti-inflammation, anti-tumor proliferation, and anti-tumor invasion and metastasis *in vitro* and *in vivo*.[36-38] We have previously reported that nobiletin (16–64 μmol/L) suppresses the production of proMMPs-1 and -3 and augments their inhibitor of TIMP-1 production in human and rabbit synovial fibroblasts.[39,40] Nobiletin also effectively suppresses the production of progelatinase B/proMMP-9 in rabbit synovial fibroblasts[39] and IL-1α, IL-1β, TNFα, and IL-6 in mouse macrophage cell line, J774A.1.[40] We have also demonstrated that nobiletin effectively interferes with cartilage destruction based on the inhibition of ADAMTSs-4 and -5 gene expression as well as MMPs-3 and -13 in CIA mice.[41] In addition to our studies, Murakami, et al[42] have been reported that nobiletin suppresses bone loss via interference with RANKL-induced osteoclastogenesis in ovariectomized mice and CIA mice. Therefore, nobiletin may exert a preventive effect on synovial inflammation and the destruction of cartilage and bone in RA.

Curcumin, diferuloylmethane, is the major curcuminoid component in turmeric, which is a spice from *Curcuma longa*. Curcumin is well known as a potent anti-oxidant and exerts various biological actions including anti-tumor and anti-inflammatory properties.[43,44] There are many studies concerning the biological actions of curcumin on articular chondrocytes.[45] Curcumin has also been shown to suppress IL-1β- and oncostatin M (OSM)-induced gene expression of MMPs-1, -3, -9, and -13 via the inhibition of NF-κB activation in human chondrocytes.[46-48] In addition, curcumin has been reported to block the IL-17 and IL-18 signaling pathways that activate AP-1 and NF-κB, resulting

in the suppression of MMPs, cytokines, and vascular endothelial growth factor (VEGF) production.[49,50] Furthermore, curcumin inhibits COX-2-induced PGE_2 production, inducible nitric oxide synthase (iNOS)-mediated production of nitrix oxide (NO), and proinflammatory cytokine production including IL-6 and IL-8.[51-53] Thus, curcumin is thought to act as an inhibitor of cartilage catabolism in articular cartilage in RA and OA. However, an *in vivo* experiment to examine the effect of curcumin on an arthritic animal model has yet to be conducted, and there is no clinical or epidemiological evidence for the anti-arthritic effects of curcumin. Further studies are required for the relevance of curcumin as a potent inhibitor of arthritic diseases, such as RA.

Other polyphenols including resveratrol,[54] luteolin,[55,56] genistein,[57] and quercetin[58] have also been shown to have bioactivity, such as anti-inflammatory and anti-oxidative actions, and to be candidates for the treatment of arthritic diseases. The anti-arthritic potency of these polyphenols will be elucidated by further studies both *in vitro* and *in vivo*.

Polysaccharides

Since cartilage is composed of a variety of polysaccharides including HA and chondroitin sulfate, some polysaccharides have been used for the treatment of arthritic disease. Intra-articular administration of HA with a high molecular weight (>800 kDa) has been applied for protection from cartilage erosion in OA and RA.[59,60] The chondroprotective effects of HA are thought to be due to not only its viscosity but also its specific biological activities. HA has also been shown to inhibit the production of TNF α, IL-8, and iNOS in human synovial fibroblasts and also suppress IL-1 β-stimulated MMPs-1, -3, and -13 production in human osteoarthritic chondrocytes.[61-63] Furthermore, Yatabe, et al[64] revealed that the high molecular weight of HA suppresses IL-1 β-mediated ADAMTS-4 production through the interference with the IL-1-mediated intracellular signaling via CD44, a cell surface receptor for HA, and the inhibition of ICAM-1 signaling in human chondrocytes at a physiological concentration in synovial fluid (2.5 mg/mL). These observations suggest that HA in synovial fluids physiologically protects cartilage from degradation through the inhibition of gene expression of catabolic factors, and thereby, the supplementation of HA is effective for the treatment of arthritic diseases.

On the other hand, chondroitin sulfate (CS) is also used as a medication for the treatment of arthritic diseases around the world. CS extracted from shark fins or porcine cartilage is well recognized as a symptomatic slow-acting drug for OA (SySADOA) in a few European countries.[65] In North America, CS is popular as a dietary supplement expected to alleviate joint pain.[66] We have previously demonstrated that CS suppresses the IL-1 β-enhanced gene expression of ADAMTSs-4 and -5 both in human articular chondrocytes and synovial fibroblasts at concentrations of 1 to 10 μg/mL.[67] CS has also been reported to suppress the gene expression of MMP-13 in IL-1 β-stimulated articular chondrocytes.[67] Furthermore, CS interfered with the IL-1 β-mediated decrease of gene expression of aggrecan core protein and TIMP-3 in articular chondrocytes.[67] These effects of CS on MMP and ADAMTS expression have also been observed in some previous reports.[68,69] Thus, CS also exerts a chondroprotective effect on articular chondrocytes and synovial fibroblasts. However, CS has yet to be applied for the treatment of RA.

Calcium pentsan polysulfate (CaPPS), a chemically sulfated xylanopyranose from beechwood, has been shown to inhibit arthritic diseases in various animal models and in some human OA trials.[70,71] Troeberg, et al[72] have reported that CaPPS interacted with the noncatalytic spacer domain of ADAMTS-4 and the cystein-rich domain of ADAMTS-5, blocking their enzymatic activities with IC_{50} values of 10–40 nmol/L. Takizawa, et al[73] have also shown that CaPPS effectively inhibited aggrecanolysis based on the interaction with ADAMTS-4 in IL-1 α-stimulated human osteoarthritic chondrocytes. In addition, CaPPS increased the cartilage levels of TIMP-3, which is an endogenous inhibitor of ADAMTSs-4 and -5.[72] Therefore, CaPPS, as a chondroprotective agent, may be a candidate as a cure of arthritic diseases.

TCM-Based Formulae as Multicomponent Medicines

Most complementary and alternative medicines are multicomponent, such as the crude herbal extracts and TCM-based Chinese herbal formulae. Multicomponent medicines have advantages in that they possess a variety of action points, and thus, they are more effective by their synergistic actions.

RA is a complicated chronic disease accompanying cartilage and bone destruction. Thereby, therapeutics that moderately exerts various actions may be more effective than molecular, targeting strong medicines for long-term treatment of RA. There are many reports concerning TCM-based Chinese herbal formulae for the treatment of RA.[4,5] Huo-Luo-Xiao-Ling Dan (活络效灵丹), which is composed of 11 herbs, has been shown to suppress arthritis in antigen-induced arthritic rats accompanying the inhibition of the activation and proliferation of antigen-reactive effecter T-cells and proinflammatory cytokines production including IL-1 and IL-17 as well as decreasing disease-regulating cytokines, such as IL-10 and interferon-γ.[74] The Yangqixue Qufengshi (养气血祛风湿, YQXQFS) Recipe has also been reported to mildly affect total pathological scores and bone erosion but not the onset of arthritis in CIA mice.[75] The YQXQFS Recipe is composed of four Chinese herbal formulae, Siwu Decoction (四物汤), Simiao Powder (四妙散), Siteng Decoction (四藤汤), and Sichong Decoction (四虫汤). In Japan, Da Fang Feng Tang (大防风汤, DFFT) has been used for the treatment of RA, and Wang, et al[76] have reported that DFFT suppresses both cartilage and bone erosion. Thus, TCM-based formulae composed of many herbal medicines are used or expected for the cure of RA. Yang, et al[77] have shown that the Sanshui Baihu Decoction (三水白虎汤) inhibited synovial inflammation based on the suppression of NF-κB and p38 mitogen-activated protein kinase (MAPK)α in CIA rats. These TCM-based formulae include a great number of ingredients, and their anti-arthritic mechanisms are thought to be more complicated than those from single herbal extracts. To explore their exact mechanisms, combination experiments with isolated principal compounds are fundamental in addition to elucidate the principle ingredients in the formulae.

Concluding Remarks and Future Perspective

Currently, available DMARDs and biological agents targeting cytokines, such as TNFα antibodies, demand a basic remedy for RA via modifying the immune system. In addition, DMARDs and biological agents could improve the therapeutic performance to a large extent. However, these medicines have some problems, especially in increased susceptibility to infection and the existence of low-responders against these medicines. Moreover, biological agents have economic problems in terms of cost. Complementary and alternative medicines, such as TCM, are not so strong when compared with DMARDs and biological agents, but they mildly exert a variety of actions to cure arthritic diseases. Therefore, complementary and alternative medicines can be safely used for a long time at a reasonably low cost. In the future, more advanced research concerning the mechanisms of the anti-arthritic effects of each natural ingredient, and their combinations are necessary to generate ideal novel formulas for RA treatment. Further investigations are expected to broaden the choices for the treatment of RA.

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