Electronic Supplementary Material (ESI) for RSC Advances.


Table S1. Transgenic arthritis animal model.

| **Model** | **Characteristics** | **Refs** |
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| TNF-α mice | Overexpression of the human TNF-α gene, synovial inflammatory vasospasm and bone erosion. | [26] |
| K/B×N mice | Glucose-6-phosphate isomerase is highly recognized, and its mechanism of action involves complement activation and mast cell degranulation, and is not only mediated by TNF but also mediated by IL-1. | [27] |
| SKG mice | A point mutation in ZAP-70 induces inflammatory arthritis in part reflecting altered thymic T-cell selection. | [28] |
| Human/SCID mosaic mice | Synovial-induced arthritis in RA patients, synovial damage and bone erosion. | [29] |
| Human DR4-CD4 mice | Contains four and human CD4 molecules, class II alleles associated with human leukocyte antigen, HLA-DR*0401 and human CD4 molecules, a RA-related human auto-antigenic protein (HCgp-39), and a TCR (TCR-ab) | [30] |
| HLA class II mice | Several HLA class II transgenic mice have been generated using different risk and protection associated loci – see. | [31] |
| PTPN22 polymorphisms murine | Polymorphisms by PTPN22 may ultimately affect homologous antigen T cell recognition. | [32] |
| IL-1RA−/− | Deficiency of IL-1 receptor antagonist results in spontaneous destructive arthritis. Disease is IL-17 and T cell dependent. | [33] |
| F759 | Direct joint damage and consequent microbleeding facilitate arthritis development in mice expressing a variant of the IL-6 signaling transducer gp130. | [34] |

Table S2. The mechanism of CHMs and prescription anti-RA.

| Formula | Extraction | Model | Mechanism | Effect | Refs |
|---|---|---|---|---|---|
| Wu-tou decoction | Water extraction | CIA rats, chicken embryos, HUVECs | Inhibition of VEGFR2 signaling pathway | Inhibition of vascular proliferation | [57] |
| Wu-tou formula | Concentrated after water extraction | AIA rats | Regulation of phenylalanine, tyrosine and tryptophan biosynthesis, taurine and hypotaurine metabolic pathways. | Improve synovial inflammation and hyperplasia, bone damage. | [58] |
| Danggui Sini decoction | Concentrated after water extraction | CIA rats | Regulation of taurine and hypotaurine, intestinal microbiota, pyruvate, glycolysis/gluconeogenesis, TCA circulating lipid metabolism. | Anti-inflammatory, improve bone erosion. | [59] |
| Huang-Lian-Jie-Du-Tang | The water is extracted and lyophilized | CIA rats | Improve energy metabolism. | Improve synovial hyperplasia, inflammatory cell infiltration, and partial bone destruction. | [60] |
| Kuan-Jin-Teng | The ethanol extract was extracted with an organic reagent and the EtOAc fraction was concentrated. | CIA rats, RAW264.7 cells | Inhibits the production of pro-inflammatory cytokines and down-regulates the MAPK signaling pathway. | Relieve inflammatory cell infiltration and bone destruction. | [61] |
| Simiao Pill | Extract and concentrate, granulate. (FDA's 2010 version of GMP) | CIA rats | Regulate the ATX-LPA and MAPK pathways. | Relieve synovial hyperplasia, vasospasm and bone erosion. | [55] |
| Wenjinghuoluo prescription | The water is extracted and lyophilized | CIA mice | The JAK2/STAT3 pathway and Th17 cells are specifically regulated. | Reduces proinflammatory cytokines and inhibits bone erosion and osteophyte formation. | [62] |
| Bi-Qi capsule | The water is extracted and lyophilized | CIA rats | Alleviates the levels of cartilage oligomeric matrix protein and osteopontin. | Reduce inflammation, synovial hyperplasia, and cartilage destruction. | [63] |
| Xitong Wan | The water is extracted and lyophilized | AIA rats | Inhibits the NF-κB inflammatory pathway. | Anti-inflammatory, inhibiting the number of osteoclasts. | [64] |
| Fu-Fang-Lu-Jiao-Shuang | Water extraction, drying under reduced pressure. | CIA mice | Decreased MMP-1, MMP3 but increased the expression of TIMP-1 and decreased the levels of TNF-α, IL-1 β, IL-17, PGE-2. | Relieve synovial hyperplasia, partial bone destruction and inflammatory cell infiltration. | [65] |
| Huo-Luo-Xiao-Ling Dan | A water-soluble suspension of raw herbs. | AIA rats | Inhibition of osteoclast function-related factor activity (NF-κB; RANKL and MMP). | Reduce bone damage. | [66] |
| Shuangtengbitong tincture | The filtrate was | CIA rats | Protein and mRNA expression levels of | Improve synovial | [67] |

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| | combined after ethanol extraction. | | TLR4, MyD88 and NF-κB were inhibited. | hyperplasia, excessive inflammation, cartilage and bone destruction. | |
| Xianfanghuomingyin | No mention was made in the text. | CIA mice | Down-regulation of abnormal differentiation of Th1 and Th17 cells, and up-regulation of Th2 and Treg cells. | Reduce cartilage damage and vasospasm formation. | [68] |
| Smilax glabra Roxb. (Tufuling) and Bolbostemmapaniculatum (Maxim.) Franquet (Tubeimu) | After ethanol extraction, it was rotary evaporated and extracted with n-butanol. | Carrageenan-induced arthritis rats | Reduce the levels of IL-1β, IL-6 and TNF-α. | Reduces obvious edema and massive inflammatory cell infiltration. | [69] |
| Eucommia ulmoidesOliv (Duzhong) | Ethanol, ethyl acetate and n-butanol were separately extracted. | CIA rats | Improve RANKL / OPG ratio and inhibit NF-κB pathway | Improve inflammatory cell infiltration, synovial hyperplasia, synovitis, vasospasm formation, cartilage degradation. | [70] |
| PeriplocaforrestiiSchltr | The ethanol was extracted, concentrated under reduced pressure, and the precipitate was collected after water-soluble, and the ethanol component of the macroporous resin was collected after acidifying the aqueous solution. | CIA rats, MH7A cells | Inhibition of the NF-κB and MAPK pathways. | Reduces severe necrosis of chondrocytes, proliferation of fibrous tissue and extensive inflammatory cell infiltration. | [71] |
| Silkworm excrement | Extracted separately with ethanol and water and concentrated in vacuo. | AIA rats | Regulation of niacin and nicotinamide, pentose and glucuronic acid conversion, TCA cycle, β-alanine metabolism, purine metabolism, glycolysis and gluconeogenesis. | Improve synovial hyperplasia, peripheral tissue mononuclear cell infiltration, cartilage erosion and joint cavity stenosis. | [72] |
| CircaeamollisSieb. &Zucc | The ethanol was extracted and concentrated by heating. | AIA mice | Down-regulation of TNF-α, IL-1β upregulates IL-10 levels. | Relieve synovial hyperplasia, inflammatory infiltration, cartilage destruction. | [73] |
| Caulophyllumrobustum Maxim | After the ethanol extraction, the macroporous resin was separated, and the ethanol eluate was dried. | CIA mice, RAW264.7 cells. | The levels of IL-1, IL-6, TNF-α and PGE-2 and the expression of NF-κBp65 were reduced. | Reduce synovial damage, inflammatory cell infiltration and telangiectasia. | [74] |
| AconitiSinomontani Radix | The aqueous solution | SW982 cells | Inhibition of Wnt5a-mediated JNK and | Targeting regulates | [75] |

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| | was decomposed, concentrated under reduced pressure, and concentrated under reduced pressure after ethanol precipitation. The pH was adjusted by NaOH and then separated by $CH_2CL_2$. | | NF-κB pathways. | proliferation and migration of SW982 cells. | |
| Urtica dentata Hand | The ethanol and water were separated and extracted, and the macroporous resin was separated and ethanol was eluted, and the ethanol component was lyophilized. | CIA mice | The production of IFN-γ and IL-2 was significantly reduced, the increase in IL-10 and TGF-β, and the inhibition of T-bet expression in DC, induced the production of CD4 + CD25 + Treg cells with the Treg phenotype Foxp3. Low expression of MHC class II and CD86 molecules, and reduction of IL-12p70. | Relieve vasospasm and bone erosion. | [76] |
| PeriplocaforrestiiSchltr | After ethanol extraction, it was dried under reduced pressure. | CIA rats | Inhibition of the Src/NF-κB signaling pathway. | Reduce synovial hyperplasia and massive mononuclear cell infiltration. | [77] |
| Clematidis Radix et Rhizoma | A series of HPLC extraction and separation[78] | CIA rats | Regulation of glycerophospholipids, sphingolipids, arachidonic acid metabolism, pantothenic acid and CoA biosynthesis. | Relieve articular cartilage swelling and narrowing of the gap, joint subluxation and stiffness. | [79] |
| Eucommia ulmoidesOliv | The ethanol was extracted and dried under vacuum. | CIA rats | Decreased RANKL mRNA expression and promoted OPG mRNA expression. | Inhibits synovial cell proliferation and reduces cartilage and bone degradation. | [80] |
| Gentiana macrophylla Pall | After ethanol extraction, it is dried under vacuum, and the organic reagent is separated after water dissolution and dried under vacuum. | CIA rats | Reduce levels of IL-1β, IL-6 and TNF-α and down-regulate levels of iNOS and COX-2. | Reduce synovial inflammatory cell infiltration and synovial hyperplasia. | [81] |
| Litseacubeba | After ethanol extraction, it was vacuum dried, dissolved in water, and then separated | RAW 264.7 cells | Inhibition of the NF-κB signaling pathway. | Anti-inflammatory. | [82] |

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| | and eluted. The eluate was dried under vacuum. | | | | |
| Clematis terniflora DC | After the ethanol extraction, the macroporous resin was separated, and the ethanol recovery liquid was collected. | Carrageenan-induced arthritis rats, RAW264.7 cells | Reduce NO and PGE2 levels. | Reduces inflammatory cell infiltration and improves tissue damage. | [83] |
| Celastrus aculeatus Merr | After ethanol extraction and concentration, the concentrate was combined in celite and extracted with ethyl acetate. | AIA rats | Apoptosis of CD4(+) CD25(+) FOXP3(+) T cells was induced. | Relieve synovial tissue hyperplasia and inflammatory cell infiltration. | [84] |
| SecuridacainappendiculataHassk | The ethanol was extracted and separated, and then rotary evaporated, and the crude product was extracted with an organic reagent. | Carrageenan-induced arthritis mice | Reduce PGE2 levels, inhibit carbon clearance, and block lymphocyte transformation and proliferation. | Anti-inflammatory, analgesic and immunosuppressive. | [85] |
| Vitex negundo L | After ethanol extraction, it was dried under reduced pressure. | AIA rats | Reduce levels of TNF-α, IL-1β, IL-6, COX-2, and 5-LOX, but increase IL-10. | Improve synovial lining hyperplasia and mononuclear cell infiltration of synovial tissue. | [86] |
| Bauhinia championii | The filtrate after ethanol extraction was concentrated in vacuo. | CIA rats | Down-regulation of protein and mRNA expression of TLR 4, MyD 88 and NF-κB. | Improve synovial hyperplasia, inflammatory cell infiltration, blood vessels, hyperplasia and bone erosion. | [87] |
| Litseacubeba (Lour.) Pers | The filtrate after ethanol extraction was dried under reduced pressure. | AIA rats | The levels of TNF-α, IL-1β and IL-6, COX-2 and 5-LOX are decreased, and IL-10 levels are elevated. | Relieve inflammatory cell infiltration and synovial hyperplasia. | [88] |
| Aconitum carmichaeli with Ampelopsis japonica | Concentrate after water extraction. | CIA rats | Regulates galactose, glycerolipid and inositol phosphate metabolism. | Reduce foot swelling. | [89] |
| Kadsuraheteroclita（Roxb）Craib | Concentrate after ethanol extraction. | AIA rats | Inhibition of TNF-α, IL-1β, IL-6, IL-17A and IL-17F production, inhibition of MMP-1 and MMP-3 and increase TIMP-1 protein expression. | Reduce inflammatory cell infiltration, synovial hyperplasia and vasospasm formation. | [90] |
| Vitex negundo | A series of HPLC extraction and | CIA rats | Decreased levels of IL-1β, IL-6, IL-8, IL-17A, TNF-α, MMP-3 and MMP-9 | Reduce infiltration of inflammatory cells, synovial | [91] |

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| | separation | | increased IL-10 levels. Decreased expression of COX-2, iNOS and p-IκB increased IκB expression. | hyperplasia and cartilage damage. | |
| Flemingiaphilippinensis | Concentrate after ethanol extraction. | CIA mice | Inhibition of NF-κB and MAPK signaling pathways. | Inhibition of osteoclast infiltration into the medullary cavity and angiogenesis. | [92] |
| Anoectochilusroxburghii | After the alcohol is lifted, the water is extracted and precipitated, and the organic reagent is eluted to collect the precipitate. | CIA rats, RAW264.7 cells | Inhibition of phosphorylation of IκB and p65 and activation of the NF-κB pathway down-regulate mRNA expression of IL-1β and IL-6. | Improve inflammatory cell infiltration and synovial tissue destruction. | [93] |
| CircaeamollisSieb. &Zucc. | Concentrate after ethanol extraction. | DMB-induced arthritis mice | The proinflammatory cytokine TNF-α, IL-1β and the anti-inflammatory factor IL-10 are regulated. | It relieves synovial hyperplasia, controls the infiltration of inflammation, and protects cartilage from damage. | [73] |

**Table S3.** Compounds of CHMs antagonize the mechanism of RA.

| Components | Classifications | Model | Mechanism | Effect | Refs |
|---|---|---|---|---|---|
| Celastrol | Triterpenoids | AIA rats | RANTES, MCP-1, MIP-1α and GRO/KC and the levels of TNF-α and IL-1β which induce them are decreased, and the level of CCR1 is increased. | Inhibits leukocyte migration. | [94] |
| Celastrol | Triterpenoids | CIA mice, RAW264.7 cells | RANKL-induced osteoclast gene and transcription factor expression, as well as phosphorylation of NF-kB and MAPK were reduced. | Relieve inflammatory cell infiltration and synovial hyperplasia. | [95] |
| Celastrol | Triterpenoids | AIA rats | Prevent STAT3 activation and reduce the levels of IL-6 and IL-1β, CCL3, and CCL5. | Th17 is reduced but Treg cells are increased. | [96] |
| Esculentic acid | Triterpenoids | Carrageenan-induced arthritis mice | Inhibition of TNF-α, IL-6 and PGE2 levels. | Anti-inflammatory and analgesic. | [97] |
| Betulinic acid | Triterpenoids | CIA mice, RA-FLSs | Block NF-κB signaling pathway activation. | Relieve synovial inflammation and joint destruction, inhibit cell proliferation and invasion. | [98] |
| Triptolide | Terpenoids | AIA rats | It inhibits the expression of neutrophils IL-6 and TNF-α, inhibits neutrophil migration, NETosis and autophagy, and promotes apoptosis. | Relieves multiple inflammatory cell infiltration, synovial fibrosis and bone erosion. | [99] |
| Astragaloside IV | Terpenoids | AIA rats | Reduce IL-1β, TNFα and NO levels, inhibit cartilage proteoglycan synthesis and chondrocyte proliferation. | Relieve bone damage. | [100] |
| Artesunate | Terpenoids | Human RA-FLSs | Inhibition of PDK1-induced phosphorylation of Akt and RSK2. | Inhibition of migration and invasion of RA-FLS. | [101] |
| Sinomenine | Alkaloids | MSCs and RAW264.7 cells. | Increase the ratio of OPG/RANKL. | Reduce the number of osteoclasts. | [102] |
| Sinomenine | Alkaloids | CIA rats | Regulate the expression of 79 proteins. | Improve inflammatory cell infiltration and synovial hyperplasia. | [103] |
| Sinomenine | Alkaloids | RA patients, CIA mice, RAW264.7 cells | Regulation of IL-6, GM-CSF, IL-12 p40, IL-1α, TNF-α, IL-1β, KC (CXCL1), Eotaxin-2, IL-10, M-CSF, RANTES, and MCP-1 secretion CD11b + F4 / 80 + CD64 + resident macrophages, CD11b + Ly6C + CD43 + macrophages and CD14 + CD16 + peripheral blood mononuclear cells. | Improve inflammatory cell infiltration and synovial hyperplasia. | [104] |
| Oxymatrine | Alkaloids | CIA rats | Decreased levels of TNF-α, IL-17A and RORγt, up-regulated FOXP3 levels, and regulated Treg/Th17 imbalance. | Relieve inflammatory cell infiltration and synovial hyperplasia. | [105] |
| Daphnetin | Coumarins | LPS-induced calvarial osteolysis mice | Inhibition of RANKL-ERK and NFATc1 signaling pathways. | Inhibits osteolysis. | [51] |
| 3R-(4'-hydroxyl-3'-O- | Coumarins | Rat FLS cells | Inhibition of NF-κB and JNK signaling | Anti-inflammatory. | [106] |

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| β-D-glucopyranosyl phenyl)-dihydro isocoumarin | | | pathways. | | |
| Scopoletin | Coumarins | AIA rats | Down-regulation of VEGF, overexpression of basic fibroblast growth factor and IL-6. | Inhibition of vascular proliferation in the synovium. | [107] |
| Prim-O-glucosylcimifugin | Saponins | AIA rats, SGC7901 GC cell | Reduce TNFα, IL-1β and IL-6 levels and down-regulate COX-2 expression. | Anti-inflammatory and analgesic. | [108] |
| Clematichinenoside AR | Saponins | CIA rats | Inhibition of SDH activity and hypoxia TGF-β1 induce and inhibit succinate-associated NLRP3 inflammasome activation. | Inhibition of synovial muscle fibrosis. | [109] |
| Dioscin | Saponins | CIA mice, Th17 cells | It inhibits the Th17 cell immune response and reduces the production of IL-17A. | Inhibits synovitis and bone erosion. | [110] |
| Polyphyllin I | Saponins | CIA mice, BMMs, PEMs | Reduces the production of inflammatory cytokines, inhibits phosphorylation of IKKα/β and p65, and prevents p65 nuclear localization. | Reduces bone erosion and synovitis. | [111] |
| 1,7-Dihydroxy-3,4-dimethoxyxanthone | Flavonoids | MH7A cells | P-p38p21 and cyclin D1, which regulate the MAPKs signaling pathway. | Inhibition of proliferation of MH7A cells. | [112] |
| Kaempferol | Flavonoids | CIA rats, Treg cells | Reduce PIM1-mediated FOXP3 phosphorylation in S422 and increase FOXP3 expression levels in Treg cells. | Inhibits inflammatory cell infiltration and bone erosion. | [113] |
| Eriodictyol | Flavonoids | Human RA-FLSs | Blocking the activation of AKT increases the expression of FOXO1. | Inhibition of cell survival and inflammatory responses in RA-FLS. | [114] |
| α-Mangostin | Flavonoids | CIA rats, HFLS-RA cells | Inhibition of iNAMPT expression inhibits NAD production, reduces ENAMPT secretion and inhibits NF-κB signaling. | Inhibition of synovial hyperplasia and bone erosion. | [115] |
| Astragalin | Flavonoids | CIA mice, MH7A cells | Inhibition of phosphorylation of MAPK and activation of c-Jun / AP-1. | Inhibition of synovial inflammation and bone destruction. | [116] |
| Total glucosides of paeony | Glycosides | CIA rats | TGP regulates VEGF levels, maintains a balance of T cell subsets, and inhibits levels of intestinal cytokines SIgA and IFN-γ. | Inhibition of synovial tissue proliferation and reduction of inflammatory cell infiltration. | [117] |
| Sweroside | Iridoids. | RAW264.7 cells | Activation of SIRT1, inhibition of NF-κB and activation of the FOXO1 signaling pathway. | Inhibition of RAW264.7cells proliferation. | [118] |
| Emodin | Anthraquinones | AIA mice, neutrophil | Inhibits autophagy and endotoxin in neutrophils. | Relieve leukocyte infiltration, cartilage erosion and synovial hyperplasia. | [119] |
| Cobrotoxin | Others | AIA rats | Inhibition of NF-κB signaling pathway and | Improve synovial | [120] |

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| | | regulation of abnormal proportion of CD4 + T cells / CD8 + T cells. | hyperplasia, inflammatory cell infiltration, cartilage destruction. |