Based on the provided sources, here is a list of herbs and phytochemicals tested for the treatment of rheumatoid arthritis (RA), sorted by their theoretical efficacy level—ranging from human clinical trials to preclinical animal models and in vitro studies.

Level 1: Evaluated in Human Clinical Trials

These compounds have reached the stage of testing in humans, providing the strongest evidence of potential efficacy, though results may vary.

- **Curcumin (*Curcuma longa*):**
    - **Efficacy:** A meta-analysis of seven randomized controlled trials (RCTs) indicated that curcumin supplementation statistically reduced disease activity (DAS28), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) levels. However, a separate systematic review noted substantial heterogeneity and suggested that curcumin had limited and inconsistent effects on these same biomarkers.
    - **Mechanism:** Curcumin is believed to inhibit the NLRP3 inflammasome, reduce mitochondrial ROS generation, and suppress NF-κB signaling.
    - **Delivery:** Novel formulations like ethosomal gels have been developed to enhance transdermal delivery and synergistic effects with drugs like cyclosporine.
- **Astaxanthin:**
    - **Efficacy:** In a triple-blind, randomized placebo-controlled trial, patients receiving 20 mg/day of astaxanthin for 8 weeks showed significantly reduced DAS-28 scores, pain intensity, and inflammatory markers (ESR, CRP) compared to the control group.
- **Tripterygium Glycosides (TGT):**
    - **Efficacy:** Extracts from *Tripterygium wilfordii* (such as Tripterygium glycoside tablets) are widely used in clinical practice in China for autoimmune diseases, including RA.
    - **Mechanism:** TGT exerts anti-inflammatory and demyelination-improving effects, potentially via the PACAP/cAMP signaling axis.
- **Cannabidiol (CBD):**
    - **Status:** A Phase I clinical trial has assessed the pharmacokinetics and tolerability of a fixed-dose combination of CBD and hydroxychloroquine (IHL-675A) for inflammatory conditions like RA.
    - **Mechanism:** In animal models, CBD regulated L-carnitine and butyric acid metabolism by modulating gut microbiota, thereby inhibiting inflammation. It also selectively suppressed IL-1β production in human monocytes.

Level 2: Validated in Animal Models (Systematic Reviews & Meta-Analyses)

These compounds have substantial preclinical evidence supported by quantitative synthesis of multiple animal studies.

- **Celastrol (*Tripterygium wilfordii*):**
    - **Efficacy:** A meta-analysis of 21 in vivo studies confirmed that celastrol significantly reduces paw swelling, arthritis scores, and pro-inflammatory cytokines (TNF-α, IL-6) in animal models.
    - **Mechanism:** It regulates the Hsp90-NLRP3 interaction, inhibiting inflammasome activation. It also targets multiple pathways including NF-κB and autophagy. Novel delivery systems, such as liposomes and biomimetic nanoparticles, are being developed to mitigate its toxicity and poor solubility.
- **Geniposide (*Gardenia jasminoides*):**
    - **Efficacy:** A meta-analysis of 14 preclinical studies showed geniposide significantly reduced arthritis scores and joint damage.
    - **Mechanism:** It inhibits angiogenesis by reducing the extracellular release of HSP70 and improves glycolysis-driven angiogenesis by inhibiting the SphK1-PI3K-Akt-PFKFB3 signal. It also suppresses pyroptosis via the miR-223-3p/NLRP3 axis.
- **Triptolide (*Tripterygium wilfordii*):**
    - **Efficacy:** A systematic review of 32 animal studies found that triptolide extracts significantly reduced joint manifestations, histopathological changes, and cytokine levels.
    - **Mechanism:** It suppresses IGF1-mediated epithelial-mesenchymal transition and regulates key cells like macrophages and osteoclasts. Due to hepatotoxicity, macrophage depletion strategies and targeted nanoplatforms have been explored to improve safety.

Level 3: Demonstrated Efficacy in In Vivo Studies (Single Studies)

These compounds have shown positive results in specific animal experiments (e.g., Collagen-Induced Arthritis in rats/mice).

Alkaloids

- **Sinomenine:** Used in advanced delivery systems like microneedles and nanopolymers to reduce joint swelling and cartilage damage by inhibiting M1 macrophage polarization and scavenging ROS.
- **Berbamine:** Alleviated RA in mice by promoting ROS production and DNA damage in fibroblast-like synoviocytes (FLS).
- **Berberine:** Used in a microneedle patch; promoted M2 macrophage polarization and suppressed angiogenesis.
- **Higenamine:** Promoted M1 to M2 macrophage transition and inhibited osteoclast differentiation via the THBS-1/TGF-β pathway.
- **Polyschistine D:** A diterpenoid alkaloid that reduced cartilage degradation and bone erosion via JAK/STAT and PI3K/Akt/mTOR pathways.

Flavonoids & Polyphenols

- **Resveratrol:** Inhibited NLRP3 inflammasome activation via SIRT1 and ITGB α5β1. Nanocrystal-based microneedles showed high efficiency in RA treatment.
- **Emodin:** Promoted recovery by regulating the crosstalk between macrophage subsets and synovial fibroblast subsets and inhibiting the ROS/TXNIP/NLRP3 pathway.
- **Fucoxanthin:** Mitigated inflammation and angiogenesis by regulating the PPAR-γ/CTGF pathway and the JAK-STAT pathway.
- **Fisetin:** Combined with Nicorandil, it suppressed oxidative stress and downregulated synovial TLR4/NF-κB signaling.
- **Myricetin:** Identified as the active component in *Wuwei Ganlu*; inhibited M1 macrophage polarization via the SHBG/SREBP1 axis.
- **Lutein:** Attenuated RA progression by suppressing MAPK/NF-κB signaling and MMP expression.
- **Astragalin:** Relieved inflammatory pain and negative mood in arthritic mice by down-regulating the mGluR5 signaling pathway.
- **Amentoflavone:** Induced ferroptosis in FLS to alleviate proliferation and inflammation.
- **Vanillic Acid:** Ameliorated arthritis by suppressing inflammation via MAPK and NF-κB pathways.

Terpenoids & Saponins

- **Ginsenoside Compound K:** Inhibited Wnt/β-catenin signaling and anti-angiogenesis. Also decreased citrullinated peptide presentation by regulating autophagy.
- **Ginsenoside AD-1:** Suppressed pathogenic phenotypes of FLS by modulating the PI3K/Akt pathway.
- **Catalpol:** An iridoid glycoside that reduced arthritis severity and bone-metabolizing cytokine gene expression.
- **Paeoniflorin:** Delivered via pH-responsive nanoparticles to target macrophages and inhibit joint inflammation.
- **Ursolic Acid:** Inhibited the TNF signaling pathway to reduce joint swelling and articular erosion.
- **Marrubiin:** Identified as a Cathepsin C inhibitor that reduced neutrophil serine protease activity and exerted therapeutic effects in arthritis models.
- **Pulegone:** Demonstrated dose-dependent anti-arthritic activity and antioxidant effects.
- **Linalool:** Exhibited dose-dependent anti-arthritic effects and membrane-stabilizing activity.
- **Bakuchiol:** Showed anti-inflammatory effects and protection against bone necrosis.
- **Cucurbitacin B & E:** Inhibited Th17 cell differentiation via JAK/STAT and M1 macrophage polarization, respectively.
- **Farnesol:** Downregulated pro-inflammatory mediators via IL-17 and TNF signaling pathways.

Herbal Extracts & Formulas

- **Er Miao San:** Reduced inflammation and neutrophil extracellular trap (NET) formation. Modulated gut microbiota and metabolites (butyrate).

- **Fengshining Decoction:** Alleviated RA by modulating gut microbiota (increasing SCFA-producing bacteria) and inhibiting the HDAC/NF-κB pathway.
- **Wu-Teng Decoction:** Network pharmacology indicated it treats RA via PI3K-Akt and MAPK pathways.
- **Ammopiptanthus nanus:** Stem extract inhibited PI3K/AKT/NF-κB mediated macrophage infiltration. Contains active flavonoids like lupiwighteone.
- **Caragana acanthophylla:** Ethanol extract attenuated paw swelling and downregulated inflammatory cytokines.
- **Kodo Millet (*Paspalum scorbiculatum*):** Dietary supplementation enhanced antioxidant status and attenuated inflammation in arthritic rats.
- **Dischidia bengalensis:** Methanolic extract suppressed paw edema and showed thrombolytic activity.
- **Plumbago zeylanica:** Methanolic extract of processed roots reduced paw volume and inflammatory markers.

Level 4: In Vitro / In Silico Evidence (Early Stage)

These agents have shown potential in cell lines or computer modeling but lack extensive in vivo validation in the provided sources.

- **Isoliquiritigenin Derivatives:** Shown to reduce inflammatory factors and activate the PI3K/AKT pathway in LPS-induced FLS cells.
- **Tracheloside:** Inhibited IL-6 and IL-17 release and migration in MH7A cells.
- **Vitedoamine A:** A lignan alkaloid that targets IKKβ to suppress NF-κB and osteoclastogenesis in vitro.
- **Bacopaside I:** Acts as an Aquaporin 1 inhibitor to suppress autophagy and proliferation in RA FLS.
- **Total Flavonoids from *Artemisia argyi*:** Compounds like hispidulin and jaceosidin were screened for anti-RA synovitis activity via spectrum-effect relationships.
- **Lupane-type Triterpenoids:** Identified as inverse agonists of RORγ, a target for autoimmune diseases including RA.
- **Torreya nucifera Phenolics:** Network pharmacology and docking suggested inhibition of the NF-κB pathway.