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The role of traditional medicine in the comprehensive treatment of patients with rheumatoid arthritis (Literature review)

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Annotation

Rheumatoid arthritis (RA) is a complex autoimmune disorder characterized by joint pain, swelling, and significant healthcare costs. Despite advancements in treatment, many patients experience uncontrolled disease activity, highlighting the need for personalized management strategies. Current approaches, including pharmacological therapies, have limitations, such as variable efficacy and potential adverse effects. This underscores the importance of exploring alternative treatment modalities.

Traditional medicine, particularly folk remedies and practices rooted in cultural contexts, may offer unique benefits when integrated into the treatment of RA. For instance, Tibetan medicine regards RA as a form of "Grum bu disease" and emphasizes dietary regulation and holistic interventions. Similarly, Chinese herbal medicine harnesses botanical resources like Tripterygium wilfordii and Curcuma longa to alleviate symptoms and potentially modify disease progression. The combination of Traditional Chinese Medicine (TCM) and Western medicine (WM) has shown promise in improving treatment outcomes and reducing side effects.

In addition to cultural practices, recent advancements in machine learning and deep learning models offer new opportunities to predict RA disease activity and tailor treatments to individual patients. The integration of these advanced technologies with holistic approaches may enhance disease management and improve patient quality of life.

In conclusion, the complex treatment of RA could benefit significantly from a multifaceted approach that incorporates traditional medicine, dietary modifications, and state-of-the-art predictive modeling to address the unique needs of each patient, providing a comprehensive framework for improving therapeutic outcomes in RA management.

Keywords: arthritis, osteoarthritis, rheumatoid arthritis, septic arthritis, electronic health records, artificial intelligence, deep learning, traditional Chinese medicine, Tibetan medicine, CTLA4Ig, disease activity prediction, therapeutic approaches, cardiovascular health, immune modulation, joint health, pharmacologic interventions, clinical management, treatment outcomes, herbal medicine.

Randomized controlled trials (RCTs) are often seen as the gold standard for evaluation; however, they come with several significant limitations that impacted the formulation of final recommendations. These include potential publication bias (which favors the release of positive findings), insufficient blinding, and the lack of necessary active comparators and appropriate sham controls. Moreover, short-term RCTs fall short in delivering adequate prognostic information for complex diseases like osteoarthritis (OA), where pathophysiological processes develop gradually over many years. Our focus was on management options available in the United States, particularly on pharmacological therapies using agents in pharmaceutical-grade formulations, thereby excluding most nutraceuticals. We confined our review to literature published in English and utilized the website

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THE MULTIDISCIPLINARY JOURNAL OF SCIENCE AND TECHNOLOGY

VOLUME-5, ISSUE-1

www.clinicaltrials.gov to find phase 2 and 3 trials that could be at an advanced stage enough to receive approval from the US Food and Drug Administration (FDA) by the time this guideline was released (1).

Rheumatoid arthritis (RA) is a complex systemic inflammatory disease characterized by joint pain and swelling that affects approximately 1 in 100 people worldwide (1). A chronic autoimmune disease, RA is associated with significant morbidity and high costs of care. Disease progression varies greatly among people, and although numerous treatment options exist, individual responses to treatment vary widely. Although advances in therapeutics and clinical disease management have greatly reduced the proportion of treated patients living with uncontrolled disease activity, remission and durable response are less common. Data from the American College of Rheumatology's (ACR's) Rheumatology Informatics System for Effectiveness (RISE) registry indicate that 42% of patients nationwide had moderate or high disease activity at their most recent visit. These data suggest that additional tools to facilitate and personalize disease management are needed. Given the volume of data available in electronic health records (EHRs), the number of possible treatment and outcome trajectories associated with heterogeneous patient comorbidities, medications, and other factors is greater than a human, even an experienced physician, can use. Many machine learning methods have been applied to clinical data, such as Cox proportional hazards regression, random forests, and LASSO (least absolute shrinkage and selection operator). However, these methods are often not well-suited to forecast outcomes based on EHR data because of the unequal numbers of data points among patients, large amounts of missing data, and highly variable dimensions with time-dependent interactions (eTable 1 and eTable 2 in the Supplement). Deep learning, a subdiscipline of artificial intelligence, has redefined computer vision and demonstrated multiple successes in clinical applications that involve image data for melanoma , retinopathy , metastatic breast cancer , and other biomedical and healthcare domains. Deep learning is being applied to a rapidly increasing number of EHR-related data sets, and like the application of technology to any new field, there are numerous opportunities and challenges. A subfamily of deep learning called recurrent neural networks has become state-of-the-art in longitudinal predictions, solving complex problems in sequence-modeling fields, such as language translation and self-driving cars. Longitudinal deep learning models have previously been applied to EHR data, classifying cardiovascular arrhythmias and predicting inpatient mortality and emergency department readmissions. To our knowledge, there has been no attempt to forecast RA disease activity in future clinic visits using any deep or machine learning approach. In the current study, we aimed to use structured data from the EHR to build a model that would most accurately predict RA disease activity. If successful, the ability to forecast disease activity could be clinically used to inform the aggressiveness of treatment on an individualized basis at each clinical visit. Models developed for predicting RA disease activity may be informative for other health conditions with quantifiable outcomes in the outpatient setting (2).

In the theoretical system of Tibetan medicine, RA is regarded as a kind of "Grum bu disease," which belongs to the category of joint disease and is similar to the "arthralgia disease" of traditional Chinese medicine (Zhijia and Ciren, 2021). According to the Tibetan medical classic "blue glaze," the occurrence and development of the disease are related to three factors (r-lung, mKhris-pa, and Bad-kan). Tibetan medicine states that the disease is due to living in a humid place for a long time and the excessive consumption of fatty, hot, sour, and spicy food, which disrupts the balance of the internal and external environments of the human body and causes stomach fire and dysfunction, as well as the gradual transformation of Bad-kan into mKhris-pa. Moreover, "yellow water" in the body

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THE MULTIDISCIPLINARY JOURNAL OF SCIENCE AND TECHNOLOGY

VOLUME-5, ISSUE-1

causes lesions in the meridians, muscles, and joints, resulting in restricted joint movement, stiffness, redness, swelling, and other pathological manifestations of difficult diseases (Ge and Nima, 2021). "Yellow water" is scattered in the skin, bones, and internal and external organs, exerting nourishing, lubricating, and other physiological effects, nourishing internal organs, and ensuring that the joints move freely. Under the influence of various internal and external pathogenic factors, the human body has three factors of imbalance, resulting in the abnormal quality and quantity of "yellow water," inducing "yellow water" disease (Bian et al., 2019). In modern medicine, the "yellow water" disease is mainly manifested in RA and skin diseases (Grum bu disease). Owing to the geographical environment, people's living habits, and other factors in plateau areas, "Grum bu disease" is a common disease. Thus, its treatment has been systematically researched in Tibetan medicine. It is recorded that the treatment of RA mainly focuses on combinations of internal and external treatment and begins with the regulation of diet and living. The combination of Tibetan medicine with medicinal baths, fire moxibustion, and other characteristic external treatment methods has achieved a unique clinical effect for the treatment of the "Grum bu disease" (Zhijia et al., 2021) (3).

China has abundant botanical resources, which have been widely used in RA treatment (13–15). **Tripterygium wilfordii** Hook. f., **Aconitum carmichaelii** Debx., and **Curcuma longa** L. represent a few of the many medicines of botanical origin for RA in traditional Chinese medicine (TCM), which may have a positive effect not only on the symptoms but also on disease progression (16–18). Formula is the main category of herbal remedies. Guizhi Shaoyao-Zhimu Decoction is a representative prescribed formula to treat RA. A synthetic approach (19) that combined drug target prediction, network analysis, and experimental validation indicated that Guizhi-Shaoyao-Zhimu Decoction may partially attenuate RA by reversing inflammation-immune system disequilibrium and regulating the HDAC1-HSP90AA1-NFKB2-IKBKB-TNF-α signaling axis. As one of the novel Chinese patent medicines, Xinfeng capsule shows benefits in alleviating joint pain, swelling, and early morning stiffness, and it could also ameliorate extra-articular manifestations such as anemia, platelet disorder, lipid metabolism disturbance, abnormal cardiopulmonary function, depression, and quality of life with few adverse reactions. Many effective ingredients of antirheumatic Chinese herbs have been found to inhibit RA development, and some of the effective extracts have been verified. Luo et al. summarized evidence on the efficacy and safety of the clinical application of tripterygium glycosides and total glucosides of paeony, suggesting that they might be potential beneficial complementary and alternative medicines for RA patients. **Artemisia asiatica** has a long history of ethnopharmacological use in Asian countries such as China, Korea, and Japan, and a novel antioxidative and anti-inflammatory formulation prepared from the ethanol extracts of **Artemisia asiatica** named DA-9601 is now on sale in South Korea. A recent study has shown that DA-9601 injection reduced arthritis scores in collagen-induced arthritis mice; moreover, eupatilin, the main active component of DA-9601, could markedly downregulate the expression of inflammatory cytokines and suppress the differentiation of osteoclasts, indicating that DA-9601 and eupatilin are candidate anti-inflammatory agents. TCM has special advantages in reducing the adverse reactions of WM and improving its curative effect. Therefore, the combination of TCM and conventional WM provides a new approach for improving the quality of life and disease control of RA patients. Many studies have shown that the integrated TCM-WM therapy has a positive effect on the treatment of RA. However, due to the small sizes of multi-samples and uneven quality of articles, it is difficult to draw reliable conclusions based on small-sample randomized controlled trials (RCTs). Therefore, we conducted this meta-analysis aiming to systematically evaluate the efficacy and safety of integrated

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THE MULTIDISCIPLINARY JOURNAL OF SCIENCE AND TECHNOLOGY

VOLUME-5, ISSUE-1

TCM-WM versus WM monotherapy for the treatment of RA. We suppose that this research could provide evidence for the superiority of treating RA with integrative medicine (4).

Rheumatoid arthritis (RA) is an autoimmune disorder that causes inflammatory arthritis, as well as extra-articular manifestations, and mostly affects synovial joints. It often begins in small peripheral joints, and it is commonly symmetric. If left untreated, it continues to affect proximal joints. Over time, joint inflammation causes cartilage and bone degradation, resulting in joint degeneration. Early RA is described as having symptoms for less than six months, while established RA is defined as having symptoms for more than six months. Most clinical signs of RA show that the wrists, metacarpophalangeal joints, proximal interphalangeal joints, and metatarsophalangeal joints in the foot are always painful and swollen. The cause of RA is still unclear. It is hypothesized to be caused by the interplay of a patient's genetics and environment. Rheumatoid disease has a heritability of 40–65% for seropositive rheumatoid arthritis and 20% for seronegative rheumatoid arthritis. Genetic studies showed that HLA-DRB1 alleles (HLA-DRB1*04, *01, and *10) have been linked to an increased chance of developing rheumatoid arthritis. Cigarette smoking is the most significant environmental risk factor for rheumatoid arthritis. There is an association between genes and smoking that raises the incidence of RA in ACPA (anti-citrullinated protein antibody)-positive persons. On the other hand, the diversity of the gut microbiome changes in RA patients (dysbiosis) shows a lower gut microbiome diversity compared with healthy individuals. **Collinsella** has been linked to increased RA disease severity by altering the gut mucosal permeability. RA generally appears between the ages of 35 and 60, with periods of remission and aggravation. It can also affect young children before the age of 16, which is known as juvenile RA (JRA), which is identical to RA except that no rheumatoid factor is present. JRA is divided into five subtypes: oligoarticular, polyarticular arthritis, systemic arthritis, enthesitis-related arthritis, and psoriatic arthritis. The previous subtypes are seronegative except for polyarticular arthritis, which may be seropositive like adults or seronegative. The prevalence of RA in the West is estimated to be 1–2%, with a global incidence of 1% . The interplay of genetic and environmental variables might cause RA in the potential trigger sites (lung, oral, and gut), which is defined by the initiation of self-protein citrullination and the development of autoantibodies against citrullinated peptides (5).

Rheumatoid arthritis (RA) is a chronic autoimmune disease with symmetric and erosive arthritis as the principal clinical manifestations. The primary pathological changes are persistent synovial hyperplasia and pannus formation. The gradual articular cartilage and bone destruction would eventually lead to joint deformities and loss of function. With the development of biological agents, the disease process of RA patients is effectively controlled, and the joint and bone damage caused by it is significantly reduced. However, in addition to joint damage, complications of other systems also significantly affect RA patients, such as severe infections, cancer, osteoporosis, cardiovascular, and respiratory diseases. Cardiovascular disease (CVD) is the leading cause of mortality. Previous studies demonstrated that people with RA had a 1.5-fold higher risk of CVD than healthy controls. Traditional risk factors for CVD include obesity, hyperlipidemia, hypertension, and diabetes. These factors have a higher prevalence and incidence among patients with RA. Apart from this, the interaction between inflammation and traditional CVD risk factors can exacerbate the risk of CVD, such as higher disease activity and autoantibodies formed after post-translational modifications of proteins in patients with RA can help promote local/systemic inflammation and ultimately lead to endothelial dysfunction. Therefore, it is necessary to monitor the cardiovascular risk factors of RA

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THE MULTIDISCIPLINARY JOURNAL OF SCIENCE AND TECHNOLOGY

VOLUME-5, ISSUE-1

patients in clinical practice. How to improve the awareness and treatment strategies of CVD in RA patients is an issue that should concern rheumatologists and cardiologists (6).

Rheumatoid arthritis is a systemic disease that causes progressive joint damage and disability. The macrophage is an important pathogenic mediator in rheumatoid arthritis, and cytokines such as tumor necrosis factor alpha (TNF-α) and interleukin-1 are therapeutic targets. Drugs that block TNF-α decrease joint inflammation and slow radiographic progression. However, since only approximately 40 percent of patients have an improvement of 50 percent, according to the criteria of the American College of Rheumatology (ACR), during treatment with TNF-α inhibitors, effective therapies directed against novel targets are needed. Class II major-histocompatibility-complex (MHC) phenotype confers susceptibility to rheumatoid arthritis. HLA-DR1 and DR4 are expressed in over 80 percent of white patients with rheumatoid arthritis. Class II MHC molecules present antigens to CD4+ T cells, suggesting an important role of T cells in the pathogenesis of rheumatoid arthritis. The rheumatoid synovium contains activated T cells, providing further support for the theory that T cells have an important role in rheumatoid arthritis. Cells resembling monocytes and macrophages and dendritic cells are also present in the rheumatoid synovium. These antigen-presenting cells are activated and express both class II MHC and costimulatory molecules such as CD80 (B7-1) and CD86 (B7-2). These observations suggest that synovial T cells, macrophages, dendritic cells, and B cells may have a direct role in the disease process. T cells require at least two signals to become fully activated. Signal 1 is antigen-specific and is delivered by engagement of the T-cell receptor with an MHC–peptide complex on an antigen-presenting cell. Signal 2 is delivered by the binding of a costimulatory receptor on T cells to a ligand on the antigen-presenting cell. A key costimulatory signal is provided by the interaction of CD28 on T cells with CD80 or CD86 on antigen-presenting cells. In the presence of optimal T-cell–receptor and CD28 signals, T cells proliferate and produce cytokines that can activate other inflammatory cells, such as macrophages. With only a T-cell–receptor signal and no CD28 signal, T-cell activation is not optimal, and T cells may be rendered poorly responsive to otherwise optimal subsequent stimulation, or they may undergo apoptosis. Cytotoxic T-lymphocyte–associated antigen 4 (CTLA4) is expressed on the surface of T cells hours or days after they become activated. CTLA4 is the high-avidity receptor for both CD80 and CD86, binding approximately 500 to 2500 times as avidly to these ligands as to CD28. CTLA4Ig is constructed by genetically fusing the external domain of human CTLA4 to the heavy-chain constant region of human IgG1. CTLA4Ig binds both CD80 and CD86 on antigen-presenting cells, thereby preventing these molecules from engaging CD28 on T cells. By blocking the engagement of CD28, CTLA4Ig prevents the delivery of the second costimulatory signal that is required for optimal activation of T cells. Blocking the second signal is a novel therapeutic concept. Preclinical studies demonstrated the efficacy of CTLA4Ig in many animal models of autoimmune disease (26, 27) and allograft rejection (28). In a three-month pilot study in which patients with rheumatoid arthritis were given 0.5, 2, or 10 mg of CTLA4Ig per kilogram of body weight as monotherapy on days 1, 15, 29, and 57, 53 percent of patients who received the dose of 10 mg per kilogram had a 20 percent improvement (an ACR 20 response) after 85 days, and 16 percent had a 50 percent improvement (an ACR 50 response), according to the ACR criteria (29). Here, we report the results of a six-month, double-blind, randomized, placebo-controlled investigation of the effectiveness of CTLA4Ig therapy in patients with rheumatoid arthritis who had an inadequate response to methotrexate (7).

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THE MULTIDISCIPLINARY JOURNAL OF SCIENCE AND TECHNOLOGY

VOLUME-5, ISSUE-1

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