Comprehensive overview of alternative medicine in the treatment of ankylosing spondylitis: Symptoms, pathogenesis, diagnosis and treatments (Review)

SO YEON PARK*, MIN SEOK KWON*, SUNJU SO, LA YOON CHOI, DAE YONG KIM and MI HYE KIM

Department of Korean Medicine, College of Korean Medicine, Woosuk University, Jeonju, Jeollabuk-do 54986, Republic of Korea

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Abstract. Ankylosing spondylitis (AS) is an autoimmune disease characterized by chronic inflammation in the sacroiliac joints and cartilage, resulting in symptoms such as back pain, morning stiffness, sacroiliitis, and extra-articular manifestations. Several drugs reduce the inflammatory response, such as nonsteroidal anti-inflammatory drugs, and disease-modifying antirheumatic drugs. However, the adverse effects and high costs associated with drug therapy highlight the need for complementary treatments. In the present review, significant alternative and complementary remedies for the treatment of AS are examined to provide broader insight. PubMed and Google Scholar were searched for alternative and complementary treatments for AS, using the keywords 'ankylosing spondylitis', 'spondyloarthropathy', 'oriental medicine', 'herbs', and 'therapy'. The symptoms and underlying pathogenesis were described based on diagnostic methods, including principal criteria and radiographic findings. In addition, current remedies for AS, including exercise and pharmacological treatments, were reviewed alongside evidence indicating that alternative therapies, such as moxibustion, decoctions, herbal medicines, and plant-derived compounds, may regulate inflammation, oxidative stress, and abnormal osteogenesis in AS. Given the risks associated with drug use, herbal remedies, including decoctions, formulations, individual herbal extracts, and compounds isolated from herbs, may represent promising therapeutic options for managing the progression of AS. Further large-scale studies, building on cell- and animal-level research, are required to validate the efficacy of herbal medicines.

Correspondence to: Professor Dae Yong Kim or Professor Mi Hye Kim, Department of Korean Medicine, College of Korean Medicine, Woosuk University, 61 Seonneomeo 3-gil, Wansan-gu, Jeonju, Jeollabuk-do 54986, Republic of Korea
E-mail: dykim@woosuk.ac.kr
E-mail: kimmh526@woosuk.ac.kr

*Contributed equally

Abbreviations: AS, ankylosing spondylitis; HLA, human leukocyte antigen; NK cell, natural killer cell; SpA, spondyloarthropathy; TNF-α, tumor necrosis factor alpha

Key words: ankylosing spondylitis, alternative and complementary medicine, herbal medicine, HLA-B27, IL-23/IL-17 axis

Contents

1. Introduction

Ankylosing spondylitis (AS), one of the spondyloarthropathy (SpA) groups, is a type of autoimmune disease involved in sacroiliac joints and cartilage, eventually causing spine ankylosis (1,2). It commonly arises in the second decade of life and varies in symptom by geographic location and sex (3,4). The progression of inflammation in AS is associated with bone erosion, abnormal bone formation, and ankylosis, leading to pain and reduced mobility (5). Additionally, AS is reported to be accompanied by extra-articular manifestations, including anterior uveitis, psoriasis, and chronic inflammatory bowel disease (IBD) (6).

Although the pathological mechanisms of AS have not been fully elucidated, genetic background and environmental factors have been shown to influence its pathogenesis through complex interactions (7,8). Among them, human leukocyte antigen B27 (HLA-B27) was the first factor investigated and has the strongest association with AS (9,10), reflecting prevalence differences due to race-specific genetic variations (11). In addition, it has been reported that AS is a complex disease in which autoinflammatory and autoimmune systems are correlated (1). Aberrant HLA-B27, gut microbiota and biomechanical stress such as orthograde posture trigger inflammation in collaboration with natural killer (NK) cells and helper T (Th) 17 cells, resulting in inflammation of the spine joints and sacroiliac joints with their adjacent soft

tissues, tendons and ligaments (6). Through those responses, fibrosis and calcification ensue, subsequently leading to bone erosion and new bone formation (12). Consequently, patients with AS suffer from chronic back and spine pain (13).

Over the past few years, with the development of technology, there have been a variety of changes in pathology, diagnosis, and treatment. Especially, in terms of treatment, the therapy has been revolutionized due to the introduction of biotechnology medicine (14). Currently, nonsteroidal anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs (DMARDs), and tumor necrosis factor (TNF)-α inhibitors are used to relieve pain, restore physical function, and slow the progression of structural damage (15,16). Unfortunately, because the mechanism of AS pathogenesis has not been fully elucidated, the present treatment mainly focuses on the alleviation of symptoms (17). Moreover, these drugs can cause several adverse effects from long-term utilization (18). Thus, novel medicine with more advanced effectiveness and fewer side effects should be explored for treating AS. Considering the complexity of AS mechanisms, the multi-targeting traditional Chinese medicines may be promising alternative treatments for AS. In the present review, the pathology, symptoms, diagnosis, and current remedies of AS are described. In addition, recent herbal medicines with their effects and underlying mechanisms in the treatment of AS, are presented.

2. Symptoms

The main signs of AS involve back pain, sacroiliitis, morning stiffness, extra-articular manifestations such as acute anterior uveitis and IBD (19). Pain in the sacroiliac joint is a common symptom in the early phase of AS (16). As the disease progresses, patients with AS may experience mild discomfort or pain (15). At this stage, magnetic resonance imaging (MRI) can show modest alteration and mild inflammation (20). As it progresses further, patients develop severe inflammation and pain along with abnormalities at the sacroiliac joint, which could emerge in the imaging (21). The excessive inflammation causes back pain and morning stiffness, resulting in restriction of spinal mobility (22). Morning stiffness lasting longer than 30 min is also an important clinical feature of AS (23). Eventually, bone erosion and formation can lead to the development of syndesmophytes, which connect adjacent vertebrae (24). This process can result in fusion of the sacroiliac joints and spine, leading to loss of spinal mobility, alterations in lumbar lordosis, and kyphosis, which can be observed on radiographs as the characteristic 'bamboo spine' (24).

3. Pathogenesis

HLA-B27. Several factors are associated with the development and progression of AS, including genetic predisposition, immune responses and environmental influences (1). HLA-B27 is known as one of the most critical genes in AS. HLA is the human version of the major histocompatibility complex (MHC), which encodes cell surface proteins essential for adaptive immunity (10). HLA-B27 presents antigenic peptides to $CD8^+$ T cells, and has been strongly associated with inflammatory diseases affecting the cartilage and joints (25). The MHC class I encodes HLA-B27, providing epitopes to T cells and activating cytotoxic T lymphocytes (CTL) (26). Among the HLA-B27 subtypes, B*2702, B*2703, B*2704, B*2705 and B*2710 are associated with a significantly increased susceptibility to AS (27,28). There are four theories explaining the mechanism through which HLA influences the development of AS: The arthritogenic peptide theory, the misfolding theory, the homodimer theory, and the mimicry theory.

i) The arthritogenic peptide theory postulates that some microbial peptides similar to self-antigens induce AS (29). When HLA-B27 presents a microbial antigen resembling a self-peptide, T cells recognize the MHC-peptide complexes, leading to autoreactivity and auto-inflammatory disease (30). ii) The misfolding theory posits that the unfolded protein response (UPR) in the endoplasmic reticulum (ER) is a major factor in AS (31). The quaternary structure of HLA-B27, composed of three components needs proper folding in the ER for its correct function (32). If HLA-B27 misfolds due to abnormalities in its cysteine residues, it can accumulate in the ER, triggering ER stress (33,34). Additionally, it can activate the UPR and nuclear factor kappa B (NF-κB) which leads to the production of pro-inflammatory cytokines such as interleukin (IL)-23 (35). iii) The homodimer effect theory is also associated with the structure of HLA-B27. Disulfide bonds in the cysteine residues facilitate the formation of α heavy-chain homodimers following their dissociation from the β light chain (36). The homodimer exhibits a stronger affinity for killer cell immunoglobulin-like receptors (KIRs), which are expressed on NK cells and Th17 cells that release IL-17, compared with the heterodimer (37). iv) Finally, the mimicry theory suggests that the homologous amino acid structures between HLA and some bacterial antigens can stimulate CTL. CTL would recognize HLA itself or the peptide directly produced by HLA-B27 (38). Notably, certain components of *Klebsiella pneumoniae* exhibit genetic sequences similar to those found in humans, displaying mimicry in AS (39). Although HLA-B27 is regarded as a critical gene in AS, the pathogenesis of AS remains unclear. Research indicates that AS may develop in 1-2% of HLA-B27-positive individuals; however, 5-10% of patients with AS lack HLA-B27 positivity (1). This finding indicates that HLA-B27 is not directly linked to the manifestation of AS, suggesting that factors beyond HLA contribute to disease progression (40).

Endoplasmic reticulum aminopeptidase 1 (ERAP1). ERAP1 is considered to be the second relevant risk factor for AS (41). In order to bind to HLA class I molecules, peptides must be cleaved to an optimal length. In this process, ERAP1 is involved in trimming precursors to 8-9 amino acids (42). As regards its function, ERAP1 may be associated with the presentation of aberrant peptides, contributing to AS, as reported by the Australo-Anglo-American Spondyloarthritis Consortium (43). Additionally, loss of ERAP1 function affects HLA-B27 dimerization or misfolding, leading to the accumulation of abnormally formed HLA-B27 in the ER (44).

KIR. Immune cells, such as NK cells and Th17 cells, express killer-cell immunoglobulin-like receptor, three Ig domains and long cytoplasmic tail 2 (KIR3DL2) receptor that has a stronger affinity with the HLA-B27 homodimer (45). Interaction between KIR3DL2 and HLA-B27 homodimers leads to the

production of IL-17, which is known to have a crucial role in the cytokine network and contributes to the pathogenesis of AS (22,46). However, it can be challenging to demonstrate differences between specific groups, as KIR-mediated responses vary among individuals (47).

Immune response. AS is a chronic inflammatory SpA, mainly characterized by the inflammation of the spine and sacroiliac joint (48). In addition, the tendons and ligaments attached to the bones contribute to the pathogenesis of AS, as they are particularly susceptible to inflammatory responses (49). There are various complex immune cells and cytokines involved in the pathogenesis of AS (50). Th17 cells differentiated by IL-23 are major triggers of inflammation in numerous immune diseases (51). IL-17 can promote osteoclastogenesis directly or indirectly through receptor activator of nuclear factor kappa B (RANK) pathway in conjunction with TNF-α, thereby inhibiting bone regeneration in SpA (52-54). It can also stimulate immune cells to release IL-6, TNF-α, and other cytokines and produce IL-17 (55). Autoimmune diseases, including SpA, IBD, and rheumatoid arthritis, generally arise from dysregulation of the IL-23/IL-17 pathway (56). Research has shown that the serum levels of IL-17 and IL-23 are higher in patients with AS (57). Nevertheless, the role of IL-23 in AS remains controversial, as its inhibition has shown limited success (58).

Apart from the IL-23/IL-17 axis, IL-22, IL-32γ, and IL-37 are known to contribute to the initiation of AS development. IL-22 was reported to participate in osteogenesis, stimulating osteoproliferation when exposed to IL-23 in an inflammatory state (54,59). IL-32γ was shown to be increased in specific regions such as the joints and tissues in patients with AS, to generate osteoblast differentiation and abnormal new bone formation (60). Moreover, IL-37 was also demonstrated to be elevated in patients with AS, with its increase associated with disease severity and bone mineral density (61).

Gut microbiome. Recently, growing evidence suggests that the microbiome, a collection of microorganisms in specific organs of the body, contributes to the development of AS (62). The gut microbiome exists in intestinal mucosal surfaces acting as a safeguard against pathogens (63). Occurrence of gut dysbiosis may alter the permeability of the intestinal mucosa, inducing penetration of microbial components (64). This disruption leads to damage in the mucosal barrier, subsequently activating both innate immunity and adaptive immunity (65). As a result, bacterial antigens may enter sacroiliac joints and the spine through lymph nodes, inducing inflammatory responses (66). Research has shown that gut dysbiosis may increase the risk of AS, as nearly 70% of patients with AS exhibit gut inflammation (67).

4. Diagnosis

The Rome criteria was first established in 1961 by the Council for International Organizations of Medical Sciences (68). It included radiographic findings and clinical presentation. Later, the same council added the sacroiliitis grading system in the original criteria which is called the New York criteria. Although the New York criteria has been modified over the past two decades to be more inclusive, it still has limitations due to the low sensitivity of X-rays (69,70). The development of MRI has made it possible to detect inflammatory changes in the sacroiliac joints at early stages, as well as structural alterations associated with advanced AS, with high precision (70). Due to the advent of MRI technology, the new criteria can classify patients who exhibit active sacroiliitis on the MRI with one clinical feature as patients with SpA. This differs from the previous modified New York criteria which diagnosed patients based on bilateral moderate or unilateral severe sacroiliitis, which often led to a delay in diagnosis of approximately 7 to 10 years (70). The criteria are called Ankylosing Spondylitis Disease Activity Score (ASDAS) which was determined by the Assessment of Spondyloarthritis International Society (ASAS) in 2009. ASDAS is a measure of disease activity using patient global assessment, clinical pain, and morning stiffness duration (15). The ASDAS score can be categorized into various levels indicating the disease activity. Additionally, the Bath Ankylosing Disease Activity Index (BASDAI), a patient-reported questionnaire, was developed to assess fatigue, pain, and morning stiffness. It relies on patient self-reporting and is therefore considered less objective than the ASDAS (15). The ASDAS with the BASDAI now serve as the principal criteria in AS. However, ASDAS and BASDAI alone are insufficient for an accurate diagnosis of AS; therefore, radiographic evaluation and biomarker analysis should also be included (15).

5. Treatment

The treatment of AS focuses on alleviating back pain, morning stiffness, and loss of flexibility, as well as reducing inflammation and preventing complications (1). To date, anti-inflammatory drugs are the first-line treatment, according to the 2010 recommendations of the ASAS (71).

Physical therapy (exercise). Regarding daily activity and overall well-being, exercise is recommended in clinical guidelines for managing AS to alleviate pain, improve joint mobility, and maintain muscle strength (72). Research has shown that the combination of appropriate medication and physical activities could be effective (73). In this context, patient education and maintaining proper posture are important for achieving optimal treatment effectiveness (74).

Non-steroid anti-inflammatory drugs (NSAIDs). NSAIDs are the first-line treatment for patients with active AS (75). They block the formation of prostaglandin by inhibiting cyclooxygenase (COX) enzymes (76). Particularly, prostaglandin E2 (PGE-2) promotes the activation of Th17 cells, leading to the production of IL-23 and IL-17, which are strongly implicated in inflammation in AS (77). However, prescribing the appropriate NSAID can be challenging, as treatment response rates vary among individuals. Therefore, NSAIDs should be selected based on the prior response of the patient to these drugs, and their risk factors for adverse effects (78). In clinical practice, daily administration is more effective in slowing the progression of AS than on-demand use (79). Prolonged use of these medications can lead to gastrointestinal (GI) or cardiovascular events (18).

Disease-modifying antirheumatic drugs (DMARDs). DMARDs are prescribed for patients with AS who are unresponsive to NSAIDs (80). Sulfasalazine is a typical DMARD for acute anterior uveitis in AS by inhibiting the formation of prostaglandins. Additionally, methotrexate, which blocks dihydrofolate reductase and, subsequently inhibits deoxyribonucleic acid (DNA) synthesis, can be another solution (81). However, the efficacy of DMARDs on AS is unclear. Most studies have shown that DMARDs mainly target peripheral joints and certain extra-articular manifestations, but have limited efficacy for axial involvement, such as back pain (13,17).

TNF-α inhibitors. TNF-α is a cytokine that is produced by macrophages and lymphocytes (82). Patients with AS tend to have elevated levels of TNF-α, indicating its crucial role in the pathogenicity of AS (83). TNF-α inhibitors are an effective treatment option for patients with AS, particularly those with an inadequate response to NSAIDs (84). If the combination of more than 2 types of NSAIDs is ineffective even after 3 months of treatment, the ASAS guidelines recommend the use of TNF-α inhibitors (71). TNF-α inhibitors are beneficial for alleviating back pain, peripheral arthritis, morning stiffness, and inflammatory activity and improving overall daily functioning (85). Infliximab, the first developed TNF-α inhibitor, is a monoclonal immunoglobulin G1 antibody consisting of 75% human and 25% mouse sequence, which binds to the dissolved and receptor-bound forms of TNF-α (86,87). Adalimumab is a 100% human monoclonal antibody against TNF-α, blocking inflammatory processes (88). It is recommended to use it subcutaneously at 40 mg once every 2 weeks (89). Golimumab is also a fully human monoclonal antibody binding to TNF-α (90). The Food and Drug Administration (FDA) approved its use for patients with AS by subcutaneous injection of 50 mg once a month (91). Certolizumab pegol is a fragment crystallizable (Fc)-free monoclonal antibody that binds to TNF-α and neutralizes it. However, its long-term efficacy and potential adverse effects require further investigation (86). Etanercept is a recombinant protein fused with the Fc portion of immunoglobulin G1 and the TNF receptor. It has an affinity with the soluble form of TNF-α, thus blocking interaction with cell receptors. It is administered at 50 mg once or 25 mg twice per week subcutaneously (92). However, there are several challenges associated with the use of TNF-α inhibitors in the treatment of AS. Notably, ~40% of patients with AS have intolerance or inactivity to medications (93). In addition, recurrence of infections, such as tuberculosis (TB) and candidiasis, can appear by inhibiting immune responses (94). Furthermore, long-term use does not guarantee sustained remission (95).

IL-17 inhibitors. In recent years, research has found that the level of IL-17 is regularly higher in patients with AS, which means it has a key role in the onset of AS. Therefore, IL-17 has emerged as one of the important targets in developing drugs for treating AS (96). IL-17 inhibitors can serve as a second-line treatment in patients who fail to respond to TNF-α inhibitors (97). Secukinumab is the first accepted monoclonal antibody and it is effective in rapidly and sustainably relieving pain, as well as reducing bone marrow edema in the sacroiliac joints (98-100). It is considered to be advantageous in patients with TB, as there is no evidence of TB occurrence or reactivation associated with its use (101). Moreover, the efficacy of secukinumab is maintained long-term, reportedly up to ~5 years (100). Ixekizumab, an immunoglobulin G4 monoclonal antibody, was recently approved as an IL-17A inhibitor (102). It improves joint and skin symptoms but remains less effective for gastrointestinal manifestations, which may contribute to the development of IBD (103). Bimekizumab, another monoclonal antibody, can neutralize both cytokines, IL-17A and IL-17F, concurrently (104). It can reduce disease activity, C-reactive protein (CRP) levels, and bone marrow edema as observed on MRI, thereby improving scores on the ASDAS (105). Brodalumab is a monoclonal antibody targeting IL-17 receptor A, unlike bimekizumab. Its efficacy was validated for psoriatic arthritis, but adverse events were also reported, including infections, and GI disorders (106). However, a 3-year follow-up of patients with psoriasis treated with brodalumab revealed conflicting reports regarding suicidal ideation (107). Therefore, it needs to be further investigated with continuous monitoring.

Janus kinase (JAK) inhibitors. The JAK pathway involves the expression of cytokines, which are related to cell proliferation and inflammation, eventually leading to autoimmune disorders (108). The IL-23/IL-17 axis, a major regulator in the SpA immune system, could be partially controlled by the JAK signaling pathway (109). Tofacitinib is a first-in-class JAK inhibitor that targets JAK1, JAK3, and to a lesser degree JAK2 (110). It interferes with cytokine-induced signal transduction, leading to abnormal immune responses (111). Tofacitinib is generally effective in AS due to its targeting of other JAK proteins (112). Nevertheless, clinical trials for JAK2-specific inhibitors are also required (113). Upadacitinib is also a JAK inhibitor that targets JAK1 selectively (114). It has recently been studied in patients with AS who are unresponsive or intolerant to NSAIDs, as part of the SELECT-AXIS 1 clinical trial (115). However, there was a report that JAK inhibitors increase the possibility of thrombosis; therefore, further data to assess the risk is needed (116).

6. Alternative and complementary treatment

To date, drug therapy has been considered as a main treatment for AS; however, there have been several adverse effects and inconveniences to using these medications due to their long-term use and cost (18,117). In particular, long-term use of these drugs can lead to GI, cardiovascular, and renal complications (118,119). In addition, their high cost is a critical obstacle, as these treatments are generally unaffordable for most patients (117). For that reason, alternative and complementary therapies may represent a viable option due to their safety and cost-effectiveness in treating AS. However, they are not included in the official standard treatment guidelines (120). International articles regarding alternative and complementary treatments for AS were collected from the PubMed (https://pubmed.ncbi.nlm.nih.gov) and Google Scholar (https://scholar.google.com). The keywords included 'ankylosing spondylitis', 'spondyloarthropathy', 'oriental medicine', 'herbs' and 'therapy'. In this section, efficacious remedies for treating AS are introduced.

Moxibustion. Moxibustion is a heat therapy that puts burned 'moxa', dried *Artemisia* genus leaves (common name: mugwort), on acupoints of the skin stimulating thermal sensory receptors. When receptors are activated by stimulation, therapeutic effects occur when the nerve fibers transmit signals to the central nervous system (121). In clinical practice, patients treated with moxibustion, either in combination with Western medicine or alone, demonstrated greater clinical efficacy and lower CRP and erythrocyte sedimentation rate (ESR) levels compared with Western medicine treatment alone. CRP and ESR are two general indicators in monitoring the activity of inflammation. However, no significant differences were observed between the treatment with moxibustion alone and Western medicine alone, suggesting that the combination therapy with moxibustion and Western medicine may be an important approach in managing AS (121). In another study with a collagen-induced arthritis mouse model, the IL-6 level was lower in the moxibustion-treated group than the untreated group (122). Moxibustion may also be associated with regulating Treg cell numbers and altering NF-κB expression (123). Additionally, moxibustion can be used with warm acupuncture. After a sterilized needle is inserted at a specific point, a moxa stick is placed on the needle and ignited, delivering heat directly to the needle site. This treatment could control the blood circulation, and improve the immune system by reducing inflammatory cytokines (124). However, large-scale randomized controlled trials are needed to confirm the efficacy of moxibustion.

Herbal medicines. Herbal medicines are effective in alleviating clinical symptoms and improving the quality of life of patients (125). Because the constituents of herbal medicines are complex and variable, elucidating their exact mechanisms remains challenging (126). Currently, network pharmacology serves as an effective tool bridging the gap between modern science and traditional medicine, providing a foundation for further studies aimed at identifying active compounds and elucidating the mechanisms of herbal medicines (127). The present review summarizes the efficacy and underlying mechanisms of these therapies for the management of AS, as reported in experimental studies (Tables I-III).

Formulations

Bushen-Qiangdu-Zhilv (BQZ) decoction. BQZ decoction is a traditional Chinese medicine that is used in AS. It is composed of *Drynariae Rhizoma*, *Psoraleae Fructus*, *Rehmanniae Praeparata Radix*, *Epimedii Herba*, *Notopterygii Rhizoma et Radix*, *Cibotii Rhizoma*, *Angelicae Pubescentis Radix*, *Dipsaci Radix, Eucommiae Cortex*, *Cyathulae Radix*, *Lycopi Herba*, *Cinnamomi Ramulus*, *Anemarrhenae Rhizoma*, *Aconiti carmichaeli Radix*, *Ephedrae Herba*, *Zingiberis Rhizoma*, *Atractylodis Rhizoma Alba*, *Clematidis Radix*, *Saposhnikoviae Radix*, *Coicis Semen*, *Paeoniae Radix*, and *Paeoniae Radix Alba*. In a previous study, BQZ decoction was extracted with petroleum ether, ethyl acetate, n-butanol (BU) and water. BQZ was incubated in M1-polarized RAW264 cells that were first induced by interferon (IFN)-γ. The BQZ water extract significantly decreased the mRNA level of TNF-α, while the BQZ BU extracts suppressed that of IL-1. Moreover, neither the water nor the BU extracts induced cell death. These findings indicate that the BQZ decoction is beneficial in reducing inflammation and has low cytotoxicity (128).

Kunxian (KX) capsule. The KX capsule is used as an anti-inflammatory regulator in autoimmune diseases in China. KX has been reported to reduce back pain and morning stiffness in AS. It is composed of four main herbs, namely *Tripterygium wildfordii* Hook. f., *Epimedii Herba*, *Cuscutae Semen*, and *Lycii Fructus*. A previous randomized, double-blind, controlled trial involving 80 patients with AS was conducted to evaluate the efficacy of KX. The study used various indices to assess the effects of KX in patients with AS. The KX-treated group showed improvement in indicators, including the ASAS 20, BASDAI 50, ASDAS-CRP, serum CRP, and Bath Ankylosing Spondylitis Functional Index when compared to the placebo group. Moreover, 37% of the patients in the KX group achieved an ASAS 20 at week 12, and marked improvements in the BASDAI 50 were observed in 40% of the patients at week 6 (129).

Fengshi Gutong capsule (FSGTC). FSGTC is a traditional Chinese medicine used for patients suffering from joint pain in China. It contains seven herbs including *Aconiti Radix Cocta*, *Aconiti Kusnezoffii Radix Cocta*, *Carthami Flos*, *Glycyrrhizae Radix Et Rhizoma*, *Chaenomelis Fructus*, *Mume Fructus*, and *Ephedrae Herba*. A previous study recruited 180 patients with AS and randomized them into three groups by treatment type: The combination group, the FSGTC group, and the imrecoxib group. The ASAS20 response rate was measured as the primary endpoint. The results showed that the ASAS20 rate in the FSGTC group was higher than that in the imrecoxib group. Moreover, the other indicators, including the ASDAS-CRP, patient's global assessment of disease activity, morning stiffness, and BASDAI, were improved in the combination and FSGTC groups compared with the imrecoxib group. In the safety test, the FSGTC group exhibited the lowest adverse effects, especially in GI tolerability. The findings indicate that FSGTC alone or combined with NSAIDs may be another viable option for patients with GI intolerance (130).

Yun-Pi-Yi-Shen-Tong-Du-Tang (YYT). YYT is a traditional formula that consists of 11 medicinal herbs: *Dioscoreae Rhizoma*, *Atractylodis Rhizoma*, *Smilacis Glabrae Rhizoma*, *Lonicerae Japonicae Flos*, *Achyranthis Bidentatae Radix*, *Myrrha*, *Aconiti Praeparata Radix*, *Astragali Radix*, *Glycyrrhizae Radix et Rhizoma*, *Hirudo*, and *Coptidis Rhizoma*. A previous study used network pharmacology to compare YYT targets with those of FDA-approved drugs and AS-related proteins. A total of 34 proteins overlapped between YYT targets and drug targets, including TNF and COX-2. Additionally, YYT targets and AS-related proteins formed 3,732 protein-protein interaction (PPI) pairs, highlighting two key targets: JAK2 and signal transducer and activator of transcription 3 (STAT3). These results indicate the YYT might enhance the effects of western medicine and exert therapeutic effects on AS-related inflammation (131).

Xinfeng capsule (XFC). XFC has been used to treat AS for >10 years and is associated with fewer adverse effects (132). It primarily consists of four herbs: *Astragali Radix*,

Table I. List of formulations for AS.

First author, year	Formulation	Experimental design	Efficacy	(Refs.)
Huang *et al*, 2014	Bushen-Qiangdu-Zhilv decoction	M1-polarized Raw 264.7 macrophage-like cells with 100 ng/ml interferon-γ	Suppresses TNF-α and IL-1 mRNA expression levels	(128)
Li *et al*, 2016	Kunxian capsule	RCT	Decreases the disease activity of patients with AS assessed by international indicators ASAS 20, BASDAI 50, ASDAS-CRP, and serum CRP as well as by patient global assessment of the disease activity, total back pain, level of morning stiffness, tender joints, and BASFI score.	(129)
Xie *et al*, 2022	Fengshi Gutong capsule	RCT	Decreases disease activity of active patients with AS/ ASDAS-CRP, BASDAI, BASFI, BASMI, morning stiffness scores, PGA, nocturnal pain, total back pain, CRP	(130)
Xie *et al*, 2017	Yun-Pi-Yi-Shen-Tong-Du-Tang	Network analysis	Reduces the symptoms of morning stiffness, fatigue, pain and decreases the level of BASDAI, ASDAS-CRP and ASDAS-ESR Associated with the TLR signaling pathway, the AMPK signaling pathway, the T-cell receptor signaling pathway, and the TNF signaling pathway	(131)
Li *et al*, 2022	Xinfeng capsule	Network analysis	Improves PLT, ESR, and hs-CRP Associated with the NF-κB signaling pathway, the TNF signaling pathway, and the IL-17 signaling pathway	(133)
Zhang *et al*, 2024	Qiangji Jianpi decoction	Network analysis	Associated with lipids and atherosclerosis, the IL-17 signaling pathway, the TNF signaling pathway, chemical carcinogenesis-receptor activation, and the AGE RAGE signaling pathway	(134)

AMPK, AMP-activated protein kinase; AS, ankylosing spondylitis; ASAS, Assessment of Spondyloarthritis International Society; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IL, interleukins; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PGA, Patient Global Assessment; PLT, platelets; RCT, randomized controlled trial; TNF-α, tumor necrosis factor alpha; TLR, Toll-like receptor.

Table II. List of herbs for AS.

First author, year	Herb	Experimental design	Efficacy	(Refs.)
Wang *et al*, 2024	*Epimedium*	Network analysis	Modulates signaling pathways such as the AGE-RAGE, TNF, NF-κB/MAPK, and Toll-like receptor signaling pathways	(139)
Li *et al*, 2022	*Scutellaria baicalensis* Georgi	Network analysis	Involved in the IL-17 pathway, TNF pathway, and NF-κB pathway	(141)
Fang *et al*, 2022	*Salvia miltiorrhiza* Bunge	Network analysis and PBMCs from patients with AS	Inhibits the expression levels of PTGS2, IL-6, and TNF-α Reduces ESR and CRP Associated with the TNF, HIF-1, NF-κB, JAK-STAT, TLR, TGF-β, FoxO, cytokine receptor interaction, PI3K-Akt, and the MAPK signaling pathway	(143)
Dong *et al*, 2017	*Chrysanthemum indicum* Linne	2 mg Human proteoglycan extract dissolved in 2 mg DDA induced AS mice	Delays the progression of peripheral disease (paw swelling and stiffness of rear leg joints in mice) Alleviates the spondylitis score Decreases the serum levels of TNF-α, IL-1β, and IL-6 Upregulates the serum levels of SOD, CAT, and GSH-Px and downregulates the serum levels of MDA Decreases NF-κB p65 protein Increases the expression level of SOST and DKK-1 in AS tissues	(147)

AS, ankylosing spondylitis; CAT, catalase; CRP, C-reactive protein; DDA, deoxy-dihydro-aristeromycin; DKK-1, dickkopf-related protein 1; ESR, erythrocyte sedimentation rate; FoxO, forkhead box O; GSH-Px, glutathione peroxidase; HIF-1, hypoxia-inducible factor 1; IL, interleukin; JAK-STAT, Janus kinase-signal transducer and activator of transcription pathway; MAPK, mitogen-activated protein kinase pathway; MDA, malondialdehyde; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PBMCs, peripheral blood mononuclear cells; PI3K-Akt, phosphoinositide 3-kinase-protein kinase B; PTGS2, prostaglandin-endoperoxide synthase 2; SOD, superoxide dismutase; SOST, sclerostin; TGF-β, transforming growth factor beta; TNF-α, tumor necrosis factor alpha; TLR, Toll-like receptor.

Coicis Semen, *Tripterygium wilfordii* Hook. f., and *Scolopendra*. In a previous network analysis, the 103 active compounds and 212 potential targets of XFC were compared with 1,961 AS-related targets, resulting in 59 overlapping targets. PPI analysis and core target screening identified 13 key targets, including IL-4, IL-6, TNF, IL-1β, vascular endothelial growth factor A (VEGFA), IL-10, C-C motif chemokine ligand 2 (CCL2), COX-2, C-X-C motif chemokine ligand 8 (CXCL8), epidermal growth factor, STAT3, NF-κB inhibitor alpha, and IFN-γ. Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment identified 20 important pathways including the NF-κB, TNF, and IL-17 signaling pathways, which involve inflammatory responses. In addition, among the 103 active compounds analyzed, the top four active ingredients that have a strong connection to AS targets were as follows: Formononetin, triptolide, quercetin, and kaempferol. Molecular docking of the components with the core targets IL-6, CCL2, TNF, and IL-4 suggested that formononetin, triptolide, quercetin, and kaempferol may have important roles in the treatment of AS (133).

Qiangji Jianpi (QJJP) decoction. QJJP decoction is a modified traditional Chinese medicine which includes *Astragali Radix*, *Codonopsis Pilosulae Radix*, *Atractylodes Rhizome*, *Angelicae Sinensis Radix*, *Cimicifugae Rhizoma*, *Bupleuri Radix*, *Citri Reticulatae Pericarpium* and *Glycyrrhizae Radix et Rhizoma*. A previous study used network pharmacology, molecular docking, and Mendelian randomization to analyze the interactions among the decoction, IBD, and AS. The results showed that, among 105 targets of the QJJP decoction, 85 targets overlapped with targets associated with both AS and IBD. In the Gene Ontology (GO) and KEGG pathways, the targets were associated with oxidative stress, which is thought to be one of the main features of IBD.

Table III. List of compounds derived from herbs for AS.

First author, year	Compound	Experimental design	Efficacy	(Refs.)
Zou *et al*, 2016	Celastrol	Hip synovial fibroblasts from 6 patients with AS	Reduces the cell viability and EdU-positive AS fibroblasts Decreases ALP activity Inhibits PEG-2-induced osteogenesis Inhibits the mRNA expression of BMP2, type I collagen, RUNX2	(151)
Liu *et al*, 2016	Naringin	Zygotes from human chorionic gonadotropin hormone-injected mice and HLAB2704 gene fragment-injected pseudocyesis mice	Increases osteocalcin and ALP Decreases the concentration of triglycerides Attenuates the NF-κB p65, TNF-α, IL-1β and IL-6 activity values Downregulates the level of MDA and upregulates the expression of SOD, CAT and GSH-Px Decreases STAT3 and JAK2	(154)
Feng *et al*, 2020	Punicalagin	2 mg of Human proteoglycan extract dissolved in 2 mg DDA-induced AS mice	Reduces peripheral disease progression scored for signs and symptoms of arthritis Reduces IVD damage progression Downregulates the levels of ROS and MDA and upregulates the levels of SOD, CAT and GPx in the connective tissues excised from the vertebra Decreases the serum levels of IL-1β, IL-6, TNF-α, IL-17A, IL-23 and NO Downregulates the activation of NF-κB and the phosphorylation levels of JAK2 and STAT3	(155)
Dong, 2018	Sinomenine	2 mg Human proteoglycan extract dissolved in 2 mg DDA-induced AS mice	Decreases the levels of TNF-α, IL-1β, and IL-6 Increases the levels of SOD, CAT, and GSH-Px Decreases NF-κBp65 and p-p38 Increases the level of IκB Decreases the level of COX-2	(157)

ALP, alkaline phosphatase; AS, ankylosing spondylitis; BMP2, bone morphogenetic protein 2; CAT, catalase; COX-2, cyclooxygenase-2; DDA, deoxy-dihydro-aristeromycin; EdU, 5-ethynyl-2'-deoxyuridine; GPx, glutathione peroxidase; GSH-Px, glutathione peroxidase; IκB, inhibitor of kappa B; IL, interleukin; IVD, intervertebral disc; JAK2, Janus kinase 2; MDA, malondialdehyde; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NO, nitric oxide; PEG-2, prostaglandin E2; ROS, reactive oxygen species; RUNX2, Runt-related transcription factor 2; SOD, superoxide dismutase; STAT3, signal transducer and activator of transcription 3; TNF-α, tumor necrosis factor alpha.

Molecular docking indicated IL-1α, IFN-γ, TGF-β1, and endothelin-1 as important targets for the treatment of AS with IBD. IFN-γ is a cytokine that is released in the innate and adaptive immune systems (134). IFN-γ is known to be strongly produced in patients with AS following stimulation with Mycoplasma arthritis (135). Additionally, IFN-γ was revealed to be closely related to the HLA-B27-associated unfolded protein responses in SpA, indicating that IFN-γ could be one of the critical biomarkers for diagnosing and treating AS (136).

Herbs

Epimedium (EP). EP, the largest herbaceous genus of the Berberidaceae family, has various components including flavonoids, alkaloids, and other compounds (137). It has been used as an antirheumatic agent with its anti-inflammatory

effects (138). Using network pharmacology, 16 active compounds were identified in EP, and the corresponding EP targets were subsequently matched with disease targets, yielding 80 overlapping targets. The core active compounds were 8-(3-methylbut-2-enyl)-2-phenylchromone, anhydroicaritin, and luteolin, and the top-ranked overlapped targets were TNF, IL-6, IL-1β, matrix metalloproteinase-9, and COX-2. Through molecular docking and molecular dynamic simulation analysis, it was found that the core compounds of EP have a strong binding activity and stable interactions with five core targets. These findings indicated that EP has the potential to be used in the treatment of AS with the intersecting target genes (139).

Scutellaria baicalensis Georgi (SBG). SBG is a species of the Lamiaceae family, and its root is mainly used in various treatments. It is usually used in immune disorders and inflammatory diseases (140). The acquired active components and targets of SBG were analyzed by network analysis. The main components of SBG were baicalein, wogonin, and oroxylin A. Among them, 29 targets overlapped with AS targets. In the PPI analysis, TNF, IL-6, CXCL8, COX-2, and VEGFA were found to be associated with SBG in AS. Moreover, the core targets and main compounds exhibited strong connections in the molecular docking. As mentioned for NSAIDs, COX-2 mediates inflammatory pathways by inducing PG production. PG promotes the proliferation of synoviocytes and inflammation. Therefore, these findings indicated that SBG may have a therapeutic role in AS similar to that of NSAIDs (141).

Salvia miltiorrhiza Bunge. *Salvia miltiorrhiza Radix* (SMR) is from the root of *Salvia miltiorrhiza* Bunge, a plant of the Lamiaceae family. It has been used to treat various diseases, including cardiovascular and immune diseases (142). A previous study conducted data mining, network pharmacology, and *in vitro* assays. In clinical trials, immunology indices, including ESR, CRP, and complement component 3, were significantly reduced in 2,079 patients compared with baseline measurements. To identify the therapeutic targets against AS, the study used network pharmacology. The study identified COX-2, IL-6, TNF, STAT3, and VEGFA as key targets of SMR in the treatment of AS. Furthermore, the TNF signaling pathway appeared to be the most enriched pathway in the KEGG enrichment analysis. Moreover, cryptotanshinone and tanshinone IIA exhibited higher affinities with key targets, including TNF-α, IL-6, and COX-2 through molecular docking. In *in vitro* assays using peripheral blood mononuclear cells from patients with AS, it was demonstrated that cryptotanshinone and tanshinone IIA, the main compounds of SMR, significantly reduced the protein expression levels of COX-2, IL-6, and TNF-α. Consequently, the results indicated that SMR may inhibit the TNF signaling pathway by modulating the expression of COX-2, IL-6, and TNF-α (143).

Chrysanthemum indicum (C. indicum) Linne. *C. indicum* Linne has been commonly used in Korean, Chinese, and Japanese medicine for the treatment of autoimmune diseases. Various studies have concluded that *C. indicum* possesses antimicrobial, antioxidant, and immuneregulatory properties (144-146). A previous study assessed disease severity in the intervertebral joints by comparing the quantitative changes in the *C. indicum*-treated group with the control AS group. The treatment group that received the *C. indicum* extract exhibited decreased levels of TNF-α, IL-1β, IL-6, and NF-κB p65 protein. Antioxidant enzymes including catalase, superoxide dismutase, and glutathione peroxidase were regulated in the AS mice compared with the control group. Moreover, the levels of sclerostin and dickkopf-1, which inhibit the wingless and Int-1 (Wnt) pathway were increased in the AS mice. These findings indicated that *C. indicum* can inhibit the Wnt pathway, which plays a key role in the production, growth, and maturation of osteoblastic cells. Overall, *C. indicum* may have a beneficial role in oxidative stress, inflammation, and osteogenesis in the treatment of AS (147).

Compounds

Celastrol. Celastrol, (2R,4aS,6aS,12bR,14aS,14bR)-10-hydroxy-2,4a,6a,9,12b,14a-hexamethyl-11-oxo-1,2,3,4,4a,5,6,6a,11,12b,13,14,14a,14b-tetradecahydropicene-2-carboxylic acid), is one of the compounds in *T. wilfordii* Hook. f., revealed to have effects on decreasing inflammation and reducing arthritis (148). Fibroblasts obtained from hip synovial tissues of patients with AS were incubated with PGE-2, which promotes proliferation and osteogenesis, and celastrol. Notably, 1.0 μM celastrol had an inhibitory effect against alkaline phosphatase (ALP) and mineralization. In addition, it significantly reduced the gene expression levels of bone morphogenetic protein 2 (BMP2) and the regulation of runt-related transcription factor 2 (RUNX2) in the fibroblasts. BMP2, a key inducer of osteogenic activity in AS, upregulates RUNX2 expression, a transcription factor for ALP that promotes osteoblast differentiation (149,150). In further investigation with 1.0 μM celastrol, the levels of PGE-2, protein kinase B (AKT) and phosphatidylinositol 3-kinase (PI3K) were decreased, and the Wnt pathway was inhibited. Consequently, celastrol may inhibit the formation of abnormal new bone by blocking PGE-2 and the Wnt signaling pathway (151).

Naringin. Naringin is a natural flavonoid that can be found in citrus fruits. It has been suggested to affect oxidation and inflammation (152). Additionally, naringin has been reported to possess osteogenic effects (153). A study established an AS-induced mouse model and treated the mice with naringin at doses of 20, 40 and 80 mg/kg. Following treatment, the expression values of osteocalcin, ALP, and triglyceride activity became similar to those of the healthy group. The naringin-treated groups exhibited significant anti-inflammatory effects by modulating TNF-α, IL-1β, and IL-6, as well as improving oxidative stress markers. Furthermore, the JAK2/STAT3 signaling pathways were suppressed by naringin treatment (154).

Punicalagin. Punicalagin (2,3-hexahydroxydiphenoyl-gallagyl-D-glucose), a water-soluble compound usually present in *Punica granatum* Linné, is considered to have anti-inflammatory effects in AS. In a previous study, AS-induced mice injected with human proteoglycan extract were treated with punicalagin. As a result, the punicalagin treatment significantly improved antioxidant enzyme activities. It decreased the levels of reactive oxygen species and malondialdehyde, indicating

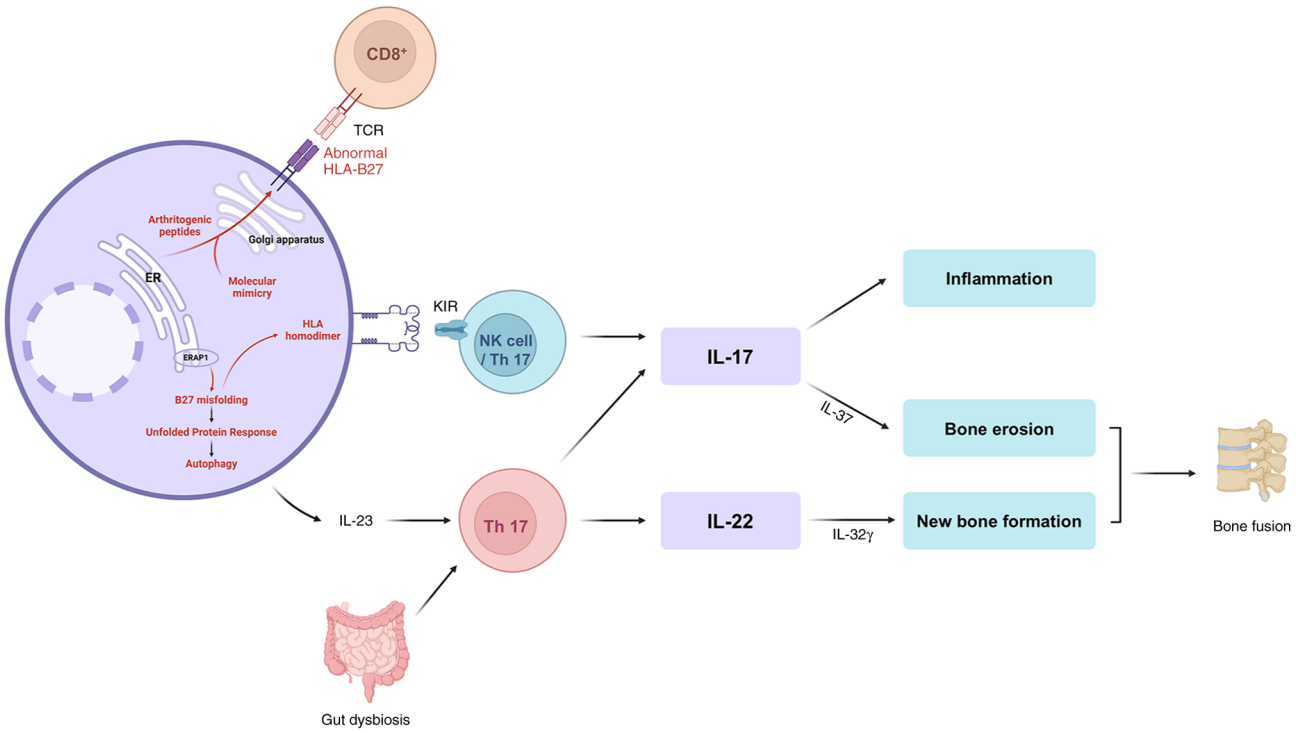

Figure 1. Diagram of possible pathogenesis of ankylosing spondylitis. The four hypotheses of HLA-related pathogenesis: The arthritogenic peptide theory, the misfolding theory, the homodimer theory, and the mimicry theory. The arthritogenic peptide theory suggests that presentation of abnormal or self-like peptides by HLA-B27 activates autoreactive $CD8^+$ T cells. The misfolding theory emphasizes that ERAP1 variants generate aberrant peptides that fail to stabilize HLA molecules, resulting in misfolded HLA accumulation in the ER. This induces ER stress and the UPR, subsequently activating autophagy and promoting IL-23 production. The homodimer theory suggests that dissociation of the β_2-microglobulin light chain allows HLA-B27 heavy chains to form homodimers, which strongly interact with KIRs on NK and Th17 cells. Th17 activation by IL-23 and homodimer signaling promotes release of IL-17 and IL-22, leading to inflammation, bone erosion, and new bone formation. The mimicry theory proposes that microbial peptides structurally resemble self-peptides, leading to cross-reactive immune responses when presented by HLA-B27. The interplay of bone erosion and aberrant new bone formation ultimately contributes to pathological bone fusion. HLA, human leukocyte antigen, ERAP1, endoplasmic reticulum aminopeptidase 1; ER, endoplasmic reticulum; UPR, unfolded protein response; IL, interleukin; KIRs, killer immunoglobulin-like receptors; NK, natural killer.

that punicalagin may have a direct effect on oxidative stress. Regarding the anti-inflammatory effects of punicalagin, serum levels of cytokines, including IL-1β, IL-6, TNF-α, IL-17A, and IL-23, were reduced. The reduction of IL-1β, IL-6, and TNF-α suggests that punicalagin may inhibit the NF-κB pathway, which is generally associated with oxidative stress. Moreover, the JAK2 and STAT3 phosphorylation levels were decreased in the punicalagin-treated groups (155).

Sinomenine. Sinomenine (7,8-didehydro-4-hydroxy3,7-dimethoxy-17-methyl-9a, 13a, 14a-morphinan-6-one) is derived from *Sinomenium acutum* Rehder et Wilson, and widely used for rheumatoid arthritis in China (156). Previous research has focused on the NF-κB pathway, the mitogen-activated protein kinase (MAPK) p38 pathway, and COX-2, as these have been reported to modulate inflammatory cytokines and oxidative stress. In this study, AS mice were treated with different doses of sinomenine (10, 30, and 50 mg/kg), and in the sinomenine-treated AS mouse groups, the levels of TNF-α, IL-1β, and IL-6 were dose-dependently reduced. Moreover, antioxidant enzymes such as catalase, glutathione peroxidase and superoxide dismutase were increased compared with the control AS group. Furthermore, the mRNA expression levels of NF-κBp65 and COX-2 were decreased, while the sinomenine treatment increased the expression level of the inhibitor of NF-κB. Overall, sinomenine ameliorated AS via inhibition of the MAPKp38 and NF-κB pathways, and COX-2 expression (157).

7. Conclusion

AS is a progressive chronic disease that typically occurs around the second decade of life. Patients with AS experience pain in the sacroiliac joint, morning stiffness, bone erosion, and bone formation, which can lead to bone fusion known as syndesmophytes. In diagnosing AS, criteria from the ASAS, patient-reported questionnaires such as the BASDAI, and radiographs are used to assess disease progression. Although the pathogenesis of AS has yet to be fully elucidated, HLA-B27 is considered to be an important factor. There are four hypotheses regarding HLA-related pathogenesis in AS: The arthritogenic peptide theory, the misfolding theory, the homodimer theory, and the mimicry theory. The arthritogenic peptide and mimicry theories suggest that the presentation of an abnormal peptide to HLA activates $CD8^+$ T cells. The misfolding theory and ERAP1, a secondary risk factor, are associated. When ERAP1 dysfunction leads to abnormal peptide trimming, HLA molecules fail to fold properly and accumulate in the ER, causing ER stress and UPR. This in turn activates autophagy, promoting IL-23 production. The homodimer theory suggests that dissociation of the β light chain in HLA enhances its affinity for KIRs, which are expressed on

the surface of NK cells and Th17 cells. Th17 cells activated by IL-23 and the homodimer promote the release of IL-17 and IL-22. IL-17 induces inflammation and bone erosion. IL-22 stimulates new bone formation. Thus, the bone erosion and new bone formation develop into bone fusion (Fig. 1).

Treatment for AS includes physical exercise and pharmacological approaches. The main drugs currently in use are NSAIDs, DMARDs, and TNF-α inhibitors, and IL-17 inhibitors and JAK inhibitors are currently in development. These drugs primarily target the control of inflammation. However, Western medicine can cause side effects depending on treatment duration and is associated with a significant cost burden. Therefore, alternative and complementary therapies may be another option for treating AS. Commonly used alternative remedies include moxibustion and herbal medicines. Moxibustion is a heat therapy that transmits signals by stimulating acupoints. Herbal medicines encompass various forms, including decoctions, formulations, herbal extracts, and isolated compounds, demonstrating a multi-targeted approach.

In the present review, potential natural medicines for the treatment of AS, along with their efficacy and underlying mechanisms were discussed. The underlying mechanisms of herbal medicines, including formulations, herbs, and compounds derived from herbs, have been identified as the reduction of inflammation, oxidative stress, and abnormal osteogenesis in AS. Given that most known drugs for AS exert anti-inflammatory effects, particularly through the Th17 cell-mediated IL-23/IL-17 axis and TNF-α, various responses to herbal medicines may contribute to inhibiting AS progression. Furthermore, as identified in the present review, the fact that most herbal medicines have a multi-targeting mechanism suggests that this could be a key factor in treating AS, a disease characterized by complex pathogenic mechanisms. In addition, investigating the functional mechanisms of herbal medicines in preclinical and clinical research is crucial for the development of novel treatments for AS. Although numerous studies have explored effective herbal medicines for AS, most are based on network analyses, which only provide predictive results. One of the difficulties in investigating AS is that it is not easy to collect spinal specimens from patients. For this reason, AS animal models are considered critical in research aimed at developing novel treatments. Future studies are expected to focus on the discovery of new herbal medicines for AS through large-scale preclinical research, followed by clinical trials to validate their efficacy.

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Authors' contributions

DYK and MHK conceived the study and supervised the review. SYP, MSK, SS and LYC performed the literature search and data collection. SYP and MSK wrote the first draft of the manuscript, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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