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Clinical Efficacy of Modified Yanghe Decoction in Ankylosing Spondylitis: A Randomized Controlled Trial

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: This study evaluated the effects of Modified Yanghe Decoction on pain, disease activity, and functional capacity, and its safety in subjects with ankylosing spondylitis (AS).

Material/Methods: A randomized, controlled study of subjects with AS was conducted over 8 weeks to compare the efficacy of the Modified Yanghe Decoction to celecoxib-sulfasalazine therapy. Subjects were evaluated at visit 1, and at weeks 4 and 8 of the trial. The Bath ankylosing spondylitis disease activity index (BASDAI), nocturnal back pain (NBP), total back pain (TBP), patient global disease activity (PGDA), the Bath ankylosing spondylitis functional index (BASFI), and the Bath ankylosing spondylitis metrology index (BASMI) were measured at each time point. Safety was monitored throughout the study through blood, urine, and stool samples, along with heart, liver, and kidney function tests. The ASAS 20 improvement criteria were used as efficacy criteria.

Results: A total of 80 subjects were included. Both treatment groups were effective: 32 subjects (80%) in the Modified Yanghe Decoction group and 34 (85%) in celecoxib-sulfasalazine group met ASAS 20 improvement criteria; no statistically significant difference between groups was observed (P>0.05). Two subjects in the Modified Yanghe Decoction group reported mild diarrhea during the trial. In the celecoxib-sulfasalazine group, 8 subjects experienced upper-abdominal pain; in 3 subjects this was combined with lowered white blood cell count and in 1 subject it was combined with mild proteinuria. This represents a statistically significant difference in safety (P<0.05) between the 2 treatments.

Conclusions: This study demonstrates the efficacy and safety of the Modified Yanghe Decoction in AS treatment, especially for patients who have poor clinical responses, severe adverse reactions, or for patients unable to afford the standard clinical options.

MeSH Keywords: Ankylosing Spondylitis • Modified Yanghe Decoction • Traditional Chinese Medicine

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Background

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease that affects the axial skeleton, causes characteristic inflammatory back pain, and can lead to structural and functional impairments and a decreased quality of life [1]. In China, the prevalence of AS is approximately 0.3%, with a male: female ratio of (2–3): 1 and a peak age of onset between 20 and 30 years [2]. Several common treatments exist. Non-steroidal anti-inflammatory agents (NSAIDs), which are recommended as first-line therapy by the Assessment of SpondyloArthritis International Society (ASAS) [3], the European League Against Rheumatism (EULAR) [4], and the American College of Rheumatology (ACR) [5], increase gastrointestinal and cardiovascular risks. Disease-modifying anti-rheumatic drugs (DMARDs), including sulfasalazine and methotrexate, can be considered for AS with peripheral arthritis, but no definitive evidence of their benefit for the treatment of axial disease exists [3]. Biologic therapies have recently become prevalent as treatments for AS, providing significant improvements in reducing inflammation and increasing functionality, but they create a large financial burden on patients lacking health insurance that covers biologic therapy.

Based on efficacy, adverse effects, and cost, Traditional Chinese Medicine (TCM) seems to be a suitable replacement treatment for AS patients in China. Modified Yanghe Decoction is based on the classical prescription Yanghe formula recorded in the *Life-saving Manual of Diagnosis and Treatment of External Diseases* from the Qing dynasty, to warm the kidneys, dissipate cold, and dispel dampness, thereby freeing the collateral vessels, which, according to the disease mechanism of AS, is a deficiency of kidney-yang and obstruction of cold-dampness; it has been used clinically for years with efficacy and safety.

This study was designed to further assess the efficacy and safety of a modified Yanghe Decoction in subjects with AS by comparing its effects with celecoxib (200 mg *qd*) and sulfasalazine (start from 0.5 g *bid* for 1 week, then 0.5 g *tid* for another 1 week, maintaining at 0.75 g *tid* after 2 weeks) over an 8-week period [2].

Material and Methods

Twenty subjects were recruited from February 2013 until December 2013 at Jiangsu Province of Traditional Chinese Medicine and another 20 were recruited from January 2017 until February 2018 at Shanghai Municipal Hospital of Traditional Chinese Medicine. Subjects provided informed consent prior to participation in the study.

Subjects

Subjects included males and females, 18–60 years of age, with a diagnosis of AS according to the Modified New York criteria [6], as well as the syndrome of kidney-yang deficiency and cold-dampness obstruction [7], a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) >4 [8] (as assessed at Visit 1), and either no history of treatment or a history of taking NSAIDs for over 1 month or DMARDs or biologic therapies for over 3 months with uncontrolled disease activity.

Subjects were excluded from the study if they had conditions that would confound study results, including cardiovascular disease, respiratory disease, cerebrovascular disease, hepatopathy, nephropathy, hemopathy or malignant tumor. Additional conditions leading to exclusion were pregnancy, lactation, and mental disorders.

Subjects who could not follow the instructions of the therapy or who had severe adverse effects were dropped from the study.

Study design

A randomized, controlled study took place over a period of 8 weeks to compare the efficacy of the Modified Yanghe Decoction *vs.* celecoxib-sulfasalazine therapy in subjects with AS. All subjects were evaluated at Visit 1 and then randomized to either the Modified Yanghe Decoction or celecoxib-sulfasalazine groups at Visit 2.

The Modified Yanghe Decoction group subjects were given a Modified Yanghe Decoction containing Lujiaopian (*Cornu cervi*), Shudihuang (*Rehmannia glutinosa*), Mahuang (*Herba ephedrae*), Guizhi (*Ramulus cinnamomi*), Fangfeng (*Radix saposhnikoviae*), Qingjiao (*Radix gentianae macrophyllae*), Cangzhu (*Rhizoma atractylodis*), Baizhu (*Rhizoma atractylodis macrocephalae*), Baijiezi (*Semen sinapis albae*), Sangjisheng (*Herba taxilli*), Chuanniuxi (*Radix cyathulae*), and Zhigancao (*Radix glycyrrhizae*) at a dose of 200 ml *bid*.

The celecoxib-sulfasalazine group was given celecoxib 200 mg *qd* with sulfasalazine. Sulfasalazine dose was started at 0.5 g *bid* for 1 week, then increased to 0.5 g *tid* for week 2, and after 2 weeks it was maintained at 0.75 g *tid*.

Subjects were re-evaluated at 4 and 8 weeks after Visit 2. A numerical rating scale (NRS) was applied for each evaluation form. The Bath ankylosing spondylitis disease activity index (BASDAI), nocturnal back pain (NBP), total back pain (TBP), patient global disease activity (PGDA), the Bath ankylosing spondylitis metrology index (BASMI), and the Bath ankylosing spondylitis functional index (BASFI) [8] were measured at each time point.

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Safety was monitored throughout the study by: physical examination (temperature, respiration, heart rate, blood pressure, height, and weight); blood, urine, and stool tests; heart, liver, and kidney function tests; Human leukocyte antigen B27 (HLA-B27); erythrocyte sedimentation rate (ESR); and C-reactive protein (CRP).

The ASAS 20 improvement criteria were used as the measure of treatment efficacy [8].

Primary outcome

The primary outcome in this study was BASDAI, which is a standardized questionnaire used by professionals to evaluate the disease activity of AS patients, including fatigue, spinal pain, peripheral arthritis, enthesitis, and intensity and duration of morning stiffness. The index uses a NRS from 0 to 10.

Secondary outcomes

The secondary outcomes in the study were NBP, TBP, PGDA, BASMI, and BASFI. NBP and TBP are 2 questionnaires aimed at measuring nocturnal and total pain, respectively, of AS patients. PGDA is an assessment of the total spondylitis activity from the patient's view. BASMI is used for the assessment of spinal mobility and BASFI is used for the assessment of functional ability in daily life. All use an NRS from 0 to 10.

Sample size

Sample size was based on a preliminary study assessing the short-term efficacy of the Modified Yanghe Decoction. The effective rates of the preliminary study were 80% in the Modified Yanghe Decoction group and 75% in the celecoxib-sulfasalazine group, with α set at 0.05, β at 0.2, and δ at 1.34. Treatment and control groups had equal sample sizes. Based on mean values and standard deviation of measurements at week 8 from the preliminary study, 23 cases were required for each group. With a 15% withdrawal rate, 28 subjects need to be recruited for each group. Based on clinical practice, study design, and the preliminary study results, a total of 80 subjects were recruited, with 40 each.

Statistical analysis

Subjects were randomly assigned to 1 of the 2 groups in a 1: 1 ratio using a computer-generated random allocation sequence through the block randomization method. Evaluations before and after treatment within groups were tested with a paired *t* test with a hypothesis of decreased scores of each measure, while comparisons between the 2 groups was tested using a two-sample *t* test. Fisher's exact test was used to estimate efficacy and safety measures. All analyses were done using SPSS v. 22.0 (IBM Corp. 2013, IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY, USA) and $P<0.05$ set as the significance level, with $P<0.01$ considered highly significant.

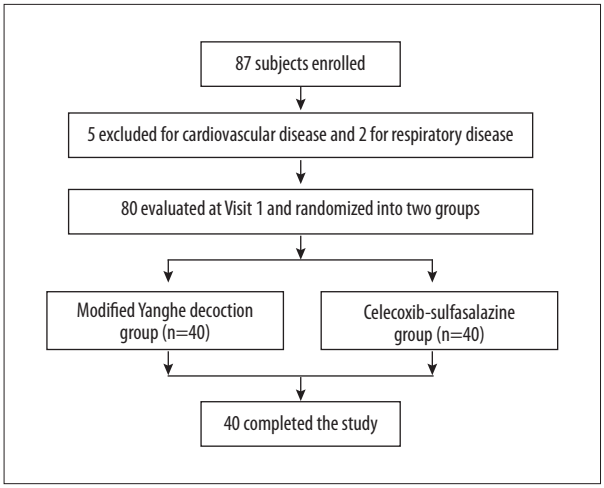

Figure 1. Study flow chart. AS – ankylosing spondylitis; NBP – nocturnal back pain; TBP – total back pain; PGDA – patient global disease activity' BASDAI – bath ankylosing spondylitis disease activity index; BASFI – bath ankylosing spondylitis. functional index; BASMI – Bath ankylosing spondylitis metrology index.

Results

A total of 87 subjects began the experiment, and 7 were excluded because of cardiovascular or respiratory diseases, leaving 80 subjects randomly assigned to the Modified Yanghe Decoction or celecoxib-sulfasalazine groups, with the intention-to-treat number of each group equal to 40 (Figure 1).

The majority of subjects were male (n=24 in the Modified Yanghe Decoction group; n=25 in the celecoxib-sulfasalazine group), subject ages varied from 18 to 60 years in the Modified Yanghe Decoction group (mean ± standard deviation (SD): 32.03±8.67 years) and 19 to 59 years in the celecoxib-sulfasalazine group at enrollment (mean ±SD: 31.50±8.54 years). AS course in subjects varied from 3 months to 15 years in the Modified Yanghe Decoction group (mean ±SD: 3.00±4.76 years) and 3 months to 14 years in the celecoxib-sulfasalazine group at enrollment (mean ±SD: 2.60±3.71).

At Visit 1, the 2 groups showed no significant difference in BASDAI, NBP, TBP, PGDA, BASMI, or BASFI (Figures 2, 3). In both groups, BASDAI was statistically significantly different at week 4 compared to Visit 1, but at week 8 it was not significantly different from week 4 (Figure 2). The Modified Yanghe Decoction group at week 4 showed significant improvement in NBP, TBP, PGDA, and BASFI scores, but not in BASMI. At week 8, NBP, PGDA, and BASMI were statistically significantly

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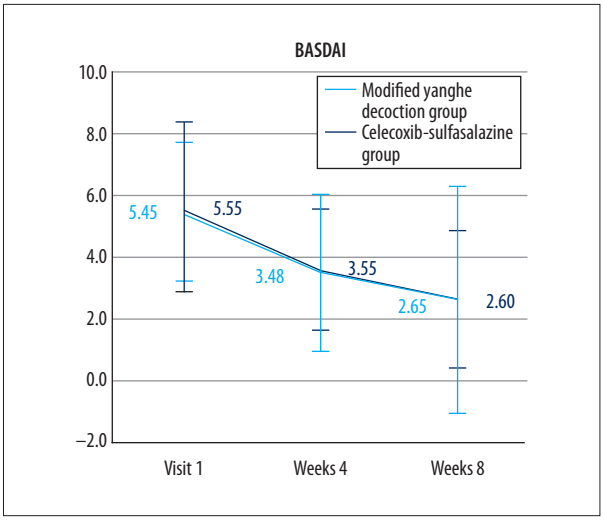

Figure 2. BASDAI in modified Yanghe Decoction group and Celecoxib-Sulfasalazine group. Comparison within groups: Modified Yanghe Decoction Group: at Week 8 (compared to Week 4), BASDAI showed no statistical significance. Celecoxib-Sulfasalazine group: At Week 8 (compared to Weeks 4), BASDAI showed no statistical significance. Comparison between groups: the measurements at each time point showed no statistical significance. BASDAI – bath ankylosing spondylitis disease activity index.

different when compared to week 4; all measurements were significantly decreased compared to Visit 1 (Figure 3). In the celecoxib-sulfasalazine group, by week 4, similar to the Modified Yanghe Decoction group, NBP, TBP, PGDA, and BASFI were significantly decreased, but not in BASMI, and at week 8 only NBP was statistically significantly improved compared to week 4. However, at the end of 8 weeks, all measurements were statistically significantly lower than at Visit 1 (Figure 3).

In comparisons between groups, no statistically significant differences were found between groups for any time point (Figures 2, 3). Thirty-two subjects (80%) in the Modified Yanghe Decoction group and 34 (85%) in the celecoxib-sulfasalazine group met the ASAS 20 improvement criteria; this difference was not statistically significant (Table 1). Until week 8, only 2 subjects in the Modified Yanghe Decoction group reported mild diarrhea, while in the celecoxib-sulfasalazine group, 8 subjects experienced upper abdominal pain, and this was combined with a lowered white blood cell count in 3 subjects and with mild proteinuria in 1 subject; thus, statistically significant differences occurred in safety ($P<0.05$; Table 2).

Discussion

In this study, both treatments effectively relieved inflammation and improved joint function of AS patients within 8 weeks, with no significant differences in outcome between the 2 groups at week 8.

In the Modified Yanghe Decoction group, after 4 weeks all evaluations (except BASMI) decreased significantly, especially BASDAI, NBP, and PGDA, showing that the Modified Yanghe Decoction can reduce local inflammation to relieve pain and disease activity in the short term. Over the next 4 weeks, BASMI also started to improve and was significantly reduced after 8 weeks compared to Visit 1. This result can be explained as axial mobility improving with time, after inflammation is controlled. Similar results occurred in the celecoxib-sulfasalazine group. At each time point, outcomes and efficacy rates (ASAS 20) were not significantly different between the 2 groups.

Previous studies have focused on the efficacy of TCM combined with common therapies compared to the common therapies alone[9]. In this study, the 2 types of treatments were separated, showing that the efficacy of TCM treatment is equal to that of common Western therapies for AS. In the clinic, patients using the Modified Yanghe Decoction reported remission of pain and reduced muscle stiffness after 1 month, while patients in the celecoxib-sulfasalazine group still felt muscle stiffness. However, because no recognized criteria for assessing muscle stiffness exist, it was not measured in this study. Only 2 subjects in the Modified Yanghe Decoction group experience any adverse effects (mild diarrhea), suggesting it is safe. However, this study was very short compared to the course of AS; a long-term evaluation is necessary to ascertain safety.

There are multiple herbs in the Modified Yanghe Decoction. Lujiaopian (*Cornu cervi*) and Shudihuang (*Rehmannia glutinosa*) are sovereign ingredients to tonify the kidney yin and yang, to replenish blood and essence, and to strengthen bones and muscles. Mahuang (*Herba ephedrae*), Guizhi (*Ramulus cinnamomi*), Fangfeng (*Radix saposhnikoviae*), Qingjiao (*Radix gentianae macrophyllae*) and Sangjisheng (*Herba taxilli*) are minister ingredients to harmonize nutrient and defense Qi and to expel wind and cold. Cangzhu (*Rhizoma atractylodis*), Baizhu (*Rhizoma atractylodis macrocephalae*) and Baijiezi (*Semen sinapis albae*) are assistant ingredients used to fortify the spleen, to dry dampness, and to resolve phlegm. Chuanniuxi (*Radix cyathulae)* and Zhigancao (*Radix glycyrrhizae*) are courier ingredients to lead all the ingredients to location and to harmonize them.

Lujiaopian has anti-fatigue, anti-inflammation, and analgesic functions [9]. Pilose antler peptide (PAP) is the major effective component isolated from Lujiaopian. In osteoblast cells, it blocks tumor necrosis factor-α (TNF-α)-mediated suppression of osteoblastogenesis via the nuclear factor kappa B (NF-κB)/p65 pathway and also inhibits osteoclastogenesis [10]. In addition, PAP decreases interleukin-1β (IL-1β) and interleukin-6 (IL-6),

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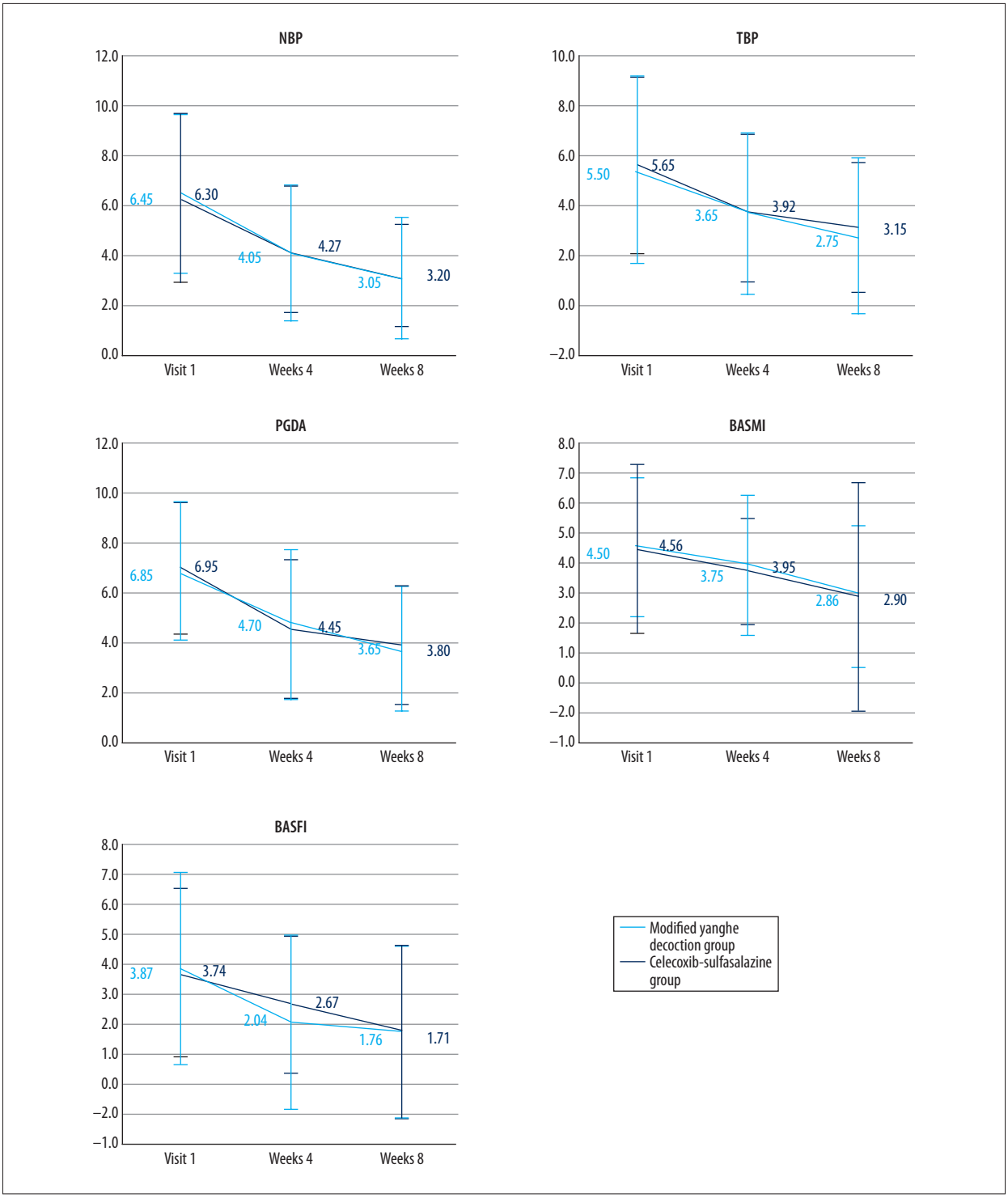

Figure 3. Other measurements in Modified Yanghe Decoction Group and Celecoxib-Sulfasalazine Group. Comparison within groups: Modified Yanghe Decoction Group: BASMI at Week 4 (compared to Visit 1), TBP, BASFI at Week 8 (compared to Week 4) showed no statistically significant difference. Celecoxib-Sulfasalazine group: BASMI at Week 4 (compared to Visit 1), TBP, PGDA, BASMI, BASFI at Week 8 (compared to Week 4) showed no statistically significant difference. Comparison between groups: the measurements at each time points showed no statistically significant difference. NBP – nocturnal back pain; TBP – total back pain; PGDA – patient global disease activity; BASMI – bath ankylosing spondylitis metrology index; BASFI – bath ankylosing spondylitis functional index.

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Table 1. Effective rates in modified Yanghe Decoction group and Celecoxib-Sulfasalazine group.

n=40	Modified Yanghe Decoction group	Celecoxib-Sulfasalazine group	P Value
ASAS 20	32	34	
Effective Rate	80%	85%	
			>0.05

Table 2. Adverse effects in modified Yanghe Decoction group and Celecoxib-Sulfasalazine group.

	Modified Yanghe Decoction group	Celecoxib-Sulfasalazine group	P Value
Diarrhea	2	–	
Upper abdominal pain	–	8	
Lowered white blood cell	–	3	
Proteinuria	–	1	
Total	2	8	<0.05

The 3 subjects with lowered white blood cell and 1 with proteinuria were complicated with the symptom of upper abdominal pain.

Table 3. Herbs from modified Yanghe Decoction and their possible mechanisms.

Names	Functions	Effective components	Signaling pathways
Lujiaopian (*Cornu cervi*)	Anti-fatigue, anti-inflammation analgesic, modulation of bone metabolism, anti-oxidation	Pilose antler peptide (PAP)	NF-κB/p65, EGF/EGFR
Shudihuang (*Rehmannia glutinosa*)	Anti-inflammation, bone-protection	Catalpol	PPAR-γ
Mahuang (*Herba ephedrae*)	Anti-inflammation, analgesic	Ephedra polysaccharide	TLR4
Guizhi (*Ramulus cinnamomi*)	Anti-inflammation, analgesic, inhibition of Mahuang's neurotoxicity	Guizhi extract	TLR4/MyD88
Fangfeng (*Radix saposhnikoviae*)	Anti-inflammation, anti-nociception	Prim-o-glucosylcimifugin (POG)	COX-2
Qingjiao (*Radix gentianae macrophyllae*)	Osteoclastogenesis suppression	Gentiopicroside	NF-κB

along with oxidative responses by increased activity of catalase (SOD) and decreased levels of malondialdehyde (MDA). It protects osteoblasts from inflammatory and oxidative injury through EGF/EGFR signaling by stimulating the nuclear (erythroid factor 2)-related factor 2 (Nrf2)/heme oxygenase-1 (HO-1) signaling and inhibiting activation of the NF-κB pathway [11]. Similar results have been demonstrated in nucleus pulpous cells from intervertebral discs [12]. PAP can also inhibit lipopolysaccharides (LPS)-induced IL-1β, IL-6, and TNF-α, and reverse the increased expression of MARK/NF-κB protein levels. The ingredient Shudihuang showed bone-protecting features in osteoporosis models [13]. Catalpol is a major iridoid glycoside from Shudihuang; it can reduce the production of inflammatory mediators, including IL-6, IL-8, and monocyte chemotactic protein 1 (MCP-1), playing a role similar to the effect of troglitazone via PPAR-γ activation in intestinal cells [14]. Ephedra polysaccharide from Mahuang decreases the production of cytokines in LPS-induced THP-1 pro-monocytic cells *in vitro*, and all parameters of inflammation on adjuvant-induced arthritis in Wistar rats *in vivo* by inhibiting the Toll-like receptor 4 (TLR4) signaling pathway [15]. Guizhi and Fangfeng have potential as anti-inflammatories and analgesics. *Guizhi* extract inhibits IL-1β, IL-6, TNF-α, and protein expression levels of cyclooxygenase-2, TLR4, and myeloid differentiation factor 88

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in LPS-induced BV2 microglial cells, suggesting it alleviates neuroinflammation by downregulating the TLR4/MyD88 signaling pathway [16]. Moreover, it inhibits the neurotoxicity of ephedrine from Mahuang in rats [17]; these 2 herbs are widely used together to enhance their effects and reduce toxicity clinically. Prim-o-glucosylcimifugin (POG) is a molecule from Fangfeng that leads to a dose-dependent decrease of spinal COX-2 content in arthritic rats and *in vitro*; it produces antinociceptive activity by downregulating spinal COX-2 expression [18]. The main active component in Qingjiao is gentiopicroside; it suppresses receptor activation of nuclear factor-κB ligand (RANKL)-induced osteoclastogenesis through the inactivation of c-Jun N-terminal kinase (JNK) and NF-κB signaling pathways in bone marrow macrophages (BMMs) [19] (Table 3). Other ingredients show multiple effects, including anti-inflammation [20], immunoregulation [21], and gastrointestinal protection [22]; however, they remain to be tested for their mechanism and their interactions with each other. In summary, Modified Yanghe Decoction can restrict inflammation and osteoclasia via multiple signaling pathways, thus relieving symptoms and improving joint function of AS patients, and this needs further study.

Conclusions

This study demonstrates the efficacy and safety of the Modified Yanghe Decoction for AS treatment, especially for patients who have poor clinical responses, experience severe adverse reactions, or for patients who cannot afford clinical treatments. Thus, the Modified Yanghe Decoction might be a viable clinical treatment option.

Acknowledgement

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Conflict of interest

None.

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