

# Probiotics in Ankylosing Spondylitis: A Possible Potency

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## ABSTRACT

Ankylosing Spondylitis (AS) is a common autoimmune arthritis which prevalence ranging from 0.1% up to 1.4% globally. Furthermore, in Asian population the prevalence of AS was increasing overtime. Up until now, there were several treatment options available in treating AS in Indonesia. However, there was still some limitations in complete remission achievement and some have limitation in potential adverse drug reaction. Eventually, these affect both patients's daily activity and their quality of life.

There were studies demonstrated the association between intestinal dysbiosis and inflammatory rheumatic disorders. Previous studies also presented there was an altered composition of gut microbiota in AS patients. Probiotic in the other hand, has been known previously for its efficacy in treating intestinal dysbiosis. Hence, this review aimed to identify potencies, efficacy and safety of probiotics as AS treatment options.

**Keywords:** ankylosing spondylitis, gut microbiota, dysbiosis, spondyloarthritis, probiotic

## ABSTRAK

Spondilitis ankilosa (SA) adalah penyakit arthritis autoimun yang cukup banyak ditemukan, memiliki prevalensi beragam secara global (0,1%-1,4%). Pada populasi Asia, prevalensi SA terus mengalami peningkatan. Hingga saat ini, terdapat beberapa pilihan terapi yang tersedia di Indonesia. Namun, masih terdapat beberapa keterbatasan pada pasien untuk mencapai remisi secara komplit dan keterbatasan pada potensi efek samping obat. Akhirnya, hal-hal ini yang mempengaruhi baik aktivitas sehari-hari maupun kualitas hidup pasien.

Beberapa penelitian menunjukkan hubungan antara disbiosis usus dengan penyakit rematik inflamasi. Terdapat adanya perubahan pada komposisi mikrobiota usus pada pasien SA. Sedangkan, probiotik telah diketahui efektif mengatasi disbiosis usus. Maka, review ini bertujuan untuk mengidentifikasi potensi, efektivitas dan keamanan probiotik sebagai salah satu pilihan terapi SA.

**Kata kunci:** spondylitis ankilosa, mikrobiota usus, disbiosis, spondiloarthritis, probiotik

## INTRODUCTION

Ankylosing Spondylitis (AS) is a common autoimmune inflammatory arthritis, which affects both patient's daily activity and quality of life. Ankylosing Spondylitis (AS) is the most prevalence subtype among Spondyloarthritis (SpA). Prevalence of AS was ranging from 0.1% up to 1.4% globally, the mean AS prevalence was 16.7 cases per 10,000 persons in Asian population.<sup>1</sup> Similarly, another study in Asian population showed the prevalence of AS in 2015 was 52.30 per 100,000 persons, which increased linearly from 2010 to 2015 at a rate of 7.7% per year.<sup>2</sup> In 2017, data from Rheumatology Clinic, Dr. Hasan Sadikin General Hospital, Bandung presented 4% patients had spondyloarthritis. Ankylosing spondylitis was dominating among the spondyloarthritis group (45%).<sup>3</sup> Up until now, there were several treatment options available. However, some have limitation in complete remission achievement and some have limitation in potential adverse drug reaction. Hence, additional supplementary treatment modality is still needed.<sup>4</sup>

Intestinal dysbiosis was found to be associated with several autoimmune disease, including inflammatory rheumatic disorders. There were several mechanisms proposed in the etiology of AS, such as alterations of intestinal permeability, stimulation of immune responses, molecular mimicry, and so on.<sup>5</sup> While previous study presented that probiotics affected including the mesenteric lymph nodes that communicate with the systemic immune system. Probiotics produced critical metabolites (short-chain fatty acids, dietary tryptophan and probiotic-produced indole derivatives) which have anti-inflammatory effects.<sup>6</sup>

Previous studies also showed different microbial composition was found in patients with AS. "Healthy" microbiota was considered as an interesting therapeutic strategy in order to restore intestinal homeostasis and manage autoimmune disease eventually.<sup>7, 8</sup> Probiotic has been known previously for its clinical potential in treating diseases related with intestinal dysbiosis. The purpose of the review is to identify potencies, efficacy and safety of probiotics as AS treatment options.

### Human Microbiota and Autoimmune Diseases

Normal flora or microbiota colonizes human body as defense mechanism from many diseases. They can be found on skin, oral cavity, nasal mucosa, gut, genital and urinary tracts. Aging, geography and many external factors (diet, infection, medication)

change the intestinal epithelial cells and microbiota composition.<sup>9-12</sup> Human intestinal tract has up to  $10^{14}$  microorganisms, with more than 1 kg biomass. Microbiota composition varies at different anatomic locations along the gut, ranging from  $10^{11}$  cells/g content in the ascending colon to  $10^{7-8}$  in the distal ileum and  $10^{2-3}$  in the proximal ileum and jejunum. Both anaerobes and aerobes were found in the bacterial community; majority of the population (60–90%) are *Bacteroidetes* and *Firmicutes*. Moreover, there were some fungal species in the components of microbiota.<sup>13-16</sup>

Intestinal microbiota affects both innate and adaptive immunity, locally as well as systemically.<sup>7, 10, 16</sup> Dysbiosis or alteration of its function and composition, are associated with autoimmune disease. The mechanism is by promoting T cells regulatory by cross reactivity between its metabolites and host immune system.<sup>17, 18</sup> Dysbiosis affects proinflammatory and anti-inflammatory processes at the epithelial level, including at remote sites such as the joints.<sup>7, 8</sup>

### ANKYLOSING SPONDYLITIS (AS)

Ankylosing Spondylitis (AS) is an autoimmune disease that often diagnosed in early adulthood and associated with significant disability and eventually reduces patient's quality of life.<sup>19</sup> Several therapeutic options are limited to nonsteroidal anti-inflammatory drugs (NSAIDs), DMARDs, tumor necrosis factor inhibitor (TNFi), physical therapy, or combinations of them. No data comparison of direct treatment responses to non-TNFi biologic agents or slow-acting anti rheumatic drugs (SAARDs) in patients with active AS who have contraindications to TNFi. Rituximab showed little benefit in patients who had not responded to prior treatment with TNFi. Furthermore, overall level of evidence supporting the use of non-TNFi biologic agents was very low.<sup>20</sup> Despite the development of biologic agent therapy in AS, there are drawbacks in the high cost of biologic therapy and associated risk of serious infection such as tuberculosis. Therefore, investigation of additional cheaper and safer therapies is still worth to be performed.<sup>21, 22</sup>

### Probiotics for Ankylosing Spondylitis

Spondyloarthritis (SpAs) is a condition associated with MHC class 1 gene HLA-B27. AS is one the SpAs and associated with inflammatory bowel disease (IBD). AS and IBD are also considered as inter-related diseases which include arthritis and ileocolonic disease.

Early life exposure to pathogen was thought to reduce the risk of IBD.<sup>23</sup> Stebbings et al presented that fecal samples from AS patients had higher sulphate-reducing bacteria ( $p = 0.0004$ ), which was also had a role in the pathogenesis of inflammatory bowel disease.<sup>24</sup> Altered intestinal microbiota has been proposed to have a role in AS pathogenesis. Study from Costello et al utilized 16S rRNA sequencing to determine that the microbial profile from terminal ileal biopsies differed significantly between patients with AS and healthy controls ( $p < 0.001$ ), predominantly consisted of five families of bacteria *Lachnospiraceae* ( $p = 0.001$ ), *Veillonellaceae* ( $p = 0.01$ ), *Prevotellaceae* ( $p = 0.004$ ), *Porphyromonadaceae* ( $p = 0.001$ ), and *Bacteroidaceae* ( $p = 0.001$ ).<sup>25</sup> Yeoh et al also presented that increase *Klebsiella* species in AS patients intestinal has been proposed to be involved in pathogenesis of AS and IBD, however a proposed mechanism of molecular mimicry between *Klebsiella* and HLA B-27 was not strong enough to prove their pathogenic role in AS.<sup>23</sup> Interestingly, Tito et al demonstrated intestinal biopsy result from SpA patients showed strong association between intestinal inflammation and profile of mucosal microbiota. Furthermore, the microbiota genus *Dialister* was positively correlated with the Ankylosing Spondylitis Disease Activity Score (Spearman's  $\rho = 0.62$ , false discovery rate-corrected  $q < 0.01$ ).<sup>26</sup>

Many considerations of which mechanisms were involved in the pathogenesis autoimmune rheumatic diseases. Molecular mimicry was thought to be an initiating factor for autoimmunity. Previous studies proposed that the mechanisms between intestinal dysbiosis and rheumatic diseases (including AS) may be caused by altered intestinal permeability or loss of immune tolerance which leads to induce or activate Th17 T helper cells and Treg cells. Eventually this will increase the expression of regulatory cytokines, both T cells and antigenic material invasion to the joints.<sup>23,27</sup> However, dysbiosis was considered to exacerbate immune disorder in genetic susceptible individual rather than accentuate an initial autoimmune disease attack.<sup>28</sup>

### From Antibiotics to Probiotics

There were several studies targeting this intestinal dysbiosis in AS management. Antibiotic utilization such as moxifloxacin, was significant change in the mean of bath ankylosing spondylitis disease activity index (BASDAI) ( $p < 0.001$ ), bath ankylosing spondylitis functional index (BASFI) ( $p < 0.001$ ), physician's global assessment of disease activity

( $p < 0.001$ ), patient's global assessment of disease activity ( $p < 0.001$ ), and nocturnal spinal pain ( $p < 0.001$ ) after 12 weeks. There was significant change in the mean of ESR and CRP after 12 weeks ( $p < 0.001$ ). However, several adverse events were found such as nausea, headache and dizziness.<sup>29</sup> Sulfasalazine altered bowel flora by decreasing the numbers of nonspring anaerobes and reduced enterobacteria antibody titrations during treatment for AS. Chen et al demonstrated a meta-analysis study regarding sulfasalazine, an antibiotic which was previously known as DMARDs in AS treatment. The study showed sulfasalazine significantly reduced spinal stiffness and ESR among the subjects (Chi-square = 11.25,  $I^2 = 64.4\%$ ,  $p = 0.02$  and Chi-square = 22.11,  $I^2 = 68.3\%$ ,  $p = 0.002$ , respectively). Among the studies, only one severe adverse event was reported, a generalized, erythematous, raised, pruritic eruption that was associated with nausea, anorexia, and insomnia. However, this study was limited to AS patients with early-stage disease, higher ESR (active disease), and peripheral arthritis.<sup>29,30</sup> Minocycline, an antibiotic group was previously known as disease-modifying antirheumatic drugs in rheumatoid arthritis treatment. Combination of immunomodulatory and anti-microbial properties of minocycline had been known for its efficacy in the treatment of multifactorial condition such as inflammatory bowel disease which has been linked with AS.<sup>31</sup> Minocycline also altered gut microbiome by significantly decreased microbiome KEGG orthologous (KO) group proportion in fecal samples immediately after exposure to minocycline compared to placebo group ( $p < 0.05$ ).<sup>32</sup> However, no study presented minocycline effect on AS yet.

Restoring balance of intestinal microbiota should improve patient's symptom, therefore instead of using antimicrobial therapy, probiotic were proposed to alter intestinal dysbiosis. Up to now, there were only three clinical trial published regarding probiotics in AS. A small uncontrolled intervention study showed supplementation of *Lactobacillus acidophilus* and *Lactobacillus salivarius* daily for 4 weeks to 18 patients gave significant improvements in BASDAI ( $5.8 \pm 1.5$  vs  $4 \pm 1.8$ ,  $p < 0.05$ ) and pain symptom (VAS) ( $33.6 \pm 10$  vs  $28.6 \pm 6.3$ ,  $p < 0.05$ ).<sup>33</sup> In contrary, another studies presented that probiotic had no significant improvement in BASDAI and BASFI. Randomized controlled trials (RCT) of probiotic treatment in AS were limited by short duration and showed inconsistent results. Consumption of probiotic containing *Streptococcus salivarius*,

*Bifidobacterium lactis* and *Lactobacillus acidophilus* for period of 12 weeks did not improve quality of life and disease activity in AS patients<sup>34</sup> Likewise, in another RCT by Brophy et al, of same duration, the use of probiotics containing *Lactobacillus salivarius*, *Lactobacillus paracasei*, *Bifidobacterium infantis* and *Bifidobacterium bifidum* did not give significant clinical and statistical improvement of in AS over the placebo.<sup>35</sup> There were no serious adverse events reported in these studies. The most common adverse events were change in bowel habit, nausea, flatus, and abdominal pain.<sup>33-35</sup>

## CONCLUSION

Despite inconclusive results from the review, there were some evidences pointing to the benefit of using probiotic in AS patients. More research with larger number subjects, homogen and specific type of probiotic strain and dosage, specific duration of therapy are required to be conducted to verify the benefit of probiotics for AS.

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