Systematic review: andrographolide as a potential Anti-inflammatory treatment for psoriasis

Indira Dharmasamitha¹, Ni Kadek Warditiani², Luh Mas Rusyati¹, DK Wati¹, Made Agus Gelgel Wirasuta²

ABSTRACT

A chronic inflammatory skin condition called psoriasis affects 1-3% of people worldwide. It will lead to other psychological, endocrine, and cardiovascular issues. It mainly affects the elbows, knees, scalp, back, umbilicus, and lumbar regions and is distinguished by well-defined crimson plaques and thick silvery white scales. Topical corticosteroid cream has been the main therapy in treating inflammatory skin in psoriasis vulgaris until now. Nowadays, andrographolide is an active compound of Andrographis paniculate, or the name in Indonesia is Sambiloto, which has been reported as a potential anti-inflammatory. Therefore, this study aimed to systematically review the published efficacy of andrographolide as an anti-inflammatory in an in vivo study and synthesize the available data. This study was a literature review searched using PubMed/ Medline, Science Direct, and Cochrane up to September 2022. The following search terms were used: (andrographolide or Andrographis paniculate) AND (anti-inflammatory) AND (animal study or in vivo). The bias in the research using the Newcastle-Ottawa quality assessment score was rated as low risk, of some concern, or high risk. A total of six in vivo studies were included in our analysis. Methotrexate and biologic agents are used for the systemic treatment of psoriasis. Topical corticosteroid therapy remains the first line of topical therapy but has some side effects. Specific reporting of andrographolide as a potential anti-inflammatory in other inflammatory diseases is necessary to support the possible treatment for psoriasis. There still needs to be further studies regarding the use of andrographolide as a topical psoriasis treatment.

Keywords: andrographolide, Andrographis paniculate, anti-inflammatory, psoriasis.

INTRODUCTION

Psoriasis is a chronic inflammatory skin disease resulting in excessive epidermal proliferation.¹ The incidence of psoriasis is reported to affect 1-3% of the world’s population.² In Sanglah Hospital, Bali, the prevalence of psoriasis in 2018 was 0.708%, with cases dominated by men at 63.4%.³ Psoriasis is a serious problem because if it is not treated right, it will cause other comorbid diseases such as cardiovascular, endocrine, and psychiatric.⁴

This disease can affect all ages and is characterized by well-defined reddish plaques covered with thick silvery white scales with locations mainly on the elbows, knees, scalp, back, umbilicus, and lumbar—topical corticosteroid cream has become the main therapy for treating inflammatory skin in psoriasis vulgaris until now. Topical corticosteroids have a mechanism of action against psoriasis if anti-inflammatory, antiproliferative, immunosuppressive, and vasoconstriction.⁵ However, long-term use of corticosteroids must be monitored because it can cause tachyphylaxis, skin atrophy, telangiectasia, striae, hirsutism, rebound flare phenomena, and adrenal suppression.⁶ Therefore, clinicians and researchers seek non-corticosteroid anti-inflammatory potential from herbs with fewer side effects than steroids.

Nowadays, andrographolide is an active compound of Andrographis paniculate, or the name in Indonesia is Sambiloto, which has been reported as a potential anti-inflammatory. It produces a secondary metabolism named andrographolide. It may have anti-inflammatory properties by activating the NF-B pathway.⁷ Andrographolide had a stronger bond when compared to dexamethasone in a silico simulation of the strongest effect.⁸ This could be the foundation for comparing the potency of andrographolide's anti-inflammatory effects to corticosteroids.⁹

The anti-inflammatory properties of the pure substance Andrographis paniculate can lower the 1 TNF-, IL-6, and IL-1β gene expression levels, increase the activity of proinflammatory cytokines including TNF-, IL-6, IL-1, and IL-23 directly associated to the pathogenesis of psoriasis, which is related to this.¹⁰ The proinflammatory cytokines interleukin 23 (IL-23), IL-6, IL-1, and tumor necrosis factor alpha (TNF-alpha) are associated with the pathophysiology of psoriasis.¹¹ Studies on the use of andrographolide in diseases that have anti-inflammatory effects both pre and clinically have been reported, for example in asthma, rheumatoid arthritis, osteoarthritis, and Chron’s disease but not so many in dermatology field.¹² Thus, this study aims to review the anti-inflammatory effect of andrographolide as a promising potential anti-inflammatory drug for psoriasis treatment.

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METHODS

Literature search
A literature review was searched using PubMed/ Medline, Science Direct, and Cochrane to find articles related to the efficacy of andrographolide as an anti-inflammatory drug. The following search terms were used: (((andrographolide) OR andrographis paniculate) AND anti-inflammatory) AND animal study) OR in vivo) OR in vitro study)))

Inclusion and exclusion criteria
The inclusion criteria in this study are that the journal is in English, the experimental research is either in vivo or in vitro, and it is an open-access journal that specifically discusses psoriasis related to the Andrographis paniculate effect. Meanwhile, the manuscript over the last ten years, the journal published above 2022 and has no complete variable, was excluded.

Data extraction
Two writers independently screened and examined the titles and abstracts found in the electronic databases to determine eligibility. The same two authors then independently assessed the full-text studies using the inclusion and exclusion criteria for records determined to be pertinent. A third independent author settled any differences. Data extraction was done after all patient studies had been incorporated.

Methodological quality assessment
Each study’s risk of bias has been evaluated using the SYRCLE tool for in vivo study (animals study) and QUIN for in vitro study. The manuscript that fulfills the inclusion and exclusion criteria will be assessed by these tools before being extracted.

RESULTS

Risk Of Bias Analysis
Regarding each of the specific interest categories in the risk of bias tool from SYRCLE. Our analysis indicates that no study from the whole body of research explains sequence creation, allocation concealment, blinding result, or intervention. All of those groups thus have a high probability of bias. While the remainder of the domain, including the baseline characteristics, random housing, random outcome assessment, incomplete outcome data, selective outcome reporting, and our sources of bias, were at low risk of bias (Table 1), the rest of the domain was at high risk of bias. In the meanwhile, we employed QUIN tools analysis for the in vitro investigation. Our investigation found that the majority of the twelve domains in a single in vitro study had minimal bias risk. The domains involved in low risk of bias were clearly stated aims, detailed explanation of sample size, methodology, method of measurement of outcome, outcome assessor details, statistical analysis, and presentation results (Table 2).

Extracted Data
From 647 studies, we found 632 for assessing the eligibility study. After that, the manuscript was screened according to our inclusion and exclusion criteria. Thus, the final manuscript that will be extracted is 7. Our results showed several potencies of andrographolide, particularly in psoriasis. Meanwhile, we also found a similar effect with different mechanisms in different diseases.

Anti-inflammatory effects
According to a detailed study, the major effect of andrographolide was as an anti-inflammatory agent. It is beneficial for psoriasis disease because it activates many inflammatory pathways. Numerous studies that we discovered have supported this mechanism. According to Gupta et al’s study, andrographolide decreased inflammatory factors more effectively than dexamethasone in mice with RA illness when 100 mg/kg was administered into each animal on days 1, 3, and 5. In this study, the inflammatory variables COX-2, NF-B, CD40, TNF-, IL-1, and IL-6 were decreased. MCP-1, hs-CRP, and IL-1 are other inflammatory pathways that andrographolide has the ability to suppress. This mechanism has been proven by Shu et al. in vivo study. Our finding study also found several interleukin families inhibited by andrographolide, namely IL-23, IL-1β, IL-6, IL-17A, and IL-1. Lie et al., in assessing andrographolide effects in Wistar mice with RA disease, found that in comparison to monotherapies, concurrent andrographolide and methotrexate therapy produced a more favorable therapeutic outcome with decreased hepatotoxicity and improved anti-arthritis benefits.

In addition, we found two studies discussing the effect of andrographolide on psoriasis. Shao et al. did the research in an animal study. However, Jindal et al. did the study survey vivo design study. Reducing psoriasis, andrographolide 10

![Figure 1. The flow diagram of searching procedures.](image-url)
mg/kg was equivalent to etanercept 10 mg/kg. In the skin of mice with psoriasis, andrographolide at doses of 5 or 10 mg/kg dramatically decreased the mRNA expressions of IL-23 and IL-1β. When psoriasis was developing, andrographolide did not suppress the downstream of IL-23. Andrographolide’s ability to treat psoriasis may be mediated via MAP1LC3B. By causing the autophagic proteolysis of MyD88, andrographolide blocked LPS/IMQ pathway transmission.

In Jindal et al. study, an andrographolide showed a strong inhibitory impact on human HaCaT keratinocyte growth in cell culture, which is a characteristic of psoriatic illness, at 31.25 g/mL (90 M). According to this study, andrographolide, which was isolated from A. paniculate, has anti-proliferative properties.

### Immune system effects

As an autoimmune disease, our antibody’s reaction determines psoriasis patients’ prognosis. Several studies found the effect of andrographolide on the immune system. In the immune system effects, andrographolide had an autophagy effect, lowering CD4+T cell and macrophage infiltration. According to Ahmed et al., they were found to encourage the creation of autophagic flux, which will lead to the clearance of damaged mitochondria and stop the death of dopaminergic neurons. Another benefit of Gao et al. in C5BL/6 mice was lowering CD4+T cell and macrophage infiltration, suppressing the subset of pathogenic CD4+T cells. In addition, andrographolide’s ability to treat psoriasis may be mediated via MAP1LC3B by causing the autophagic proteolysis of MyD88. Andrographolide blocked LPS/IMQ pathway transmission.

### DISCUSSION

Andrographolide has been studied for decades and has a strong anti-inflammatory impact. It has anti-inflammatory actions by blocking several intracellular pathways that various pro-inflammatory drugs have triggered. By increasing matrix metalloproteinases and pro-inflammatory cytokines like TNF-, IL-1, IL-6, and IL-8 (e.g., MMP-1, MMP-3, and MMP-9), HIF-1 is an important mediator of inflammation in rheumatoid arthritis. Andrographolide may be a beneficial therapy for rheumatoid arthritis since it reduced cell cytotoxicity more effectively than dexamethasone. It blocks several different molecules, such as COX-2, NF-B, CD40, TNF-, IL-1, and IL-6.14,15 This mechanism is similar to several journals in this study.

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**Table 1. Risk of Bias Analysis in Animal Study.**

<table>
<thead>
<tr>
<th>References</th>
<th>Sequence Generation</th>
<th>Baseline Characteristic</th>
<th>Allocation Concealment</th>
<th>Random Housing</th>
<th>Binding (Intervention)</th>
<th>Random Outcome Assessment</th>
<th>Blinding (Outcome)</th>
<th>Incomplete Outcome Data</th>
<th>Selective Outcome Reporting</th>
<th>Out Sources of Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahmed, Kwatra, Ranjan Panda, Murty, and Naidu (2021)</td>
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<td>Gupta, Mishra, Kumar, Singh, and Ganju (2020)</td>
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<td>Shu et al. (2020)</td>
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<td>Gao et al. (2020)</td>
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<td>Li et al. (2018)</td>
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<tr>
<td>Shao et al. (2016)</td>
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**Table 2. Risk of Bias Analysis in In Vitro Study.**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Stated Aims</th>
<th>Detailed Explanation Of Sample Size</th>
<th>Detailed Explanation Of Sampling Technique</th>
<th>Details Of Comparison Group</th>
<th>Detailed Explanation Of Methodology</th>
<th>Operator Details</th>
<th>Randomization</th>
<th>Method Of Measurement Of Outcome</th>
<th>Outcome Assessor Details</th>
<th>Blinding</th>
<th>Statistical Analysis</th>
<th>Presentation of Results</th>
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<tbody>
<tr>
<td>Jindal et al., (2021).</td>
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## Table 3. Andrographolide as anti-inflammatory

<table>
<thead>
<tr>
<th>References</th>
<th>Disease</th>
<th>Models</th>
<th>Dosage</th>
<th>Regimen</th>
<th>Application</th>
<th>Detail Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahmed, Kwatra, Ranjan Panda, Murty, and Naidu (2021)</td>
<td>Parkinson</td>
<td>C57BL/6 mice</td>
<td>5, 10 mg/kg daily intraoral for 14 days</td>
<td>Andrographolide 98% purity, cat no 365645</td>
<td>In vivo</td>
<td>Encourage the creation of autophagic flux, which will lead to the clearance of damaged mitochondria and stop the death of dopaminergic neurons.</td>
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<tr>
<td>Gupta, Mishra, Kumar, Singh, and Ganju (2020)</td>
<td>Rheumatoid Arthritis (RA)</td>
<td>BALB/C mice</td>
<td>On days 1, 3, and 5, each animal received about 250 l of andrographolide at a dose of 100 mg/kg.</td>
<td>Andrographolide 98% purity, cat no 365645</td>
<td>In vivo</td>
<td>Better than dexamethasone at suppressing a variety of molecules, including COX-2, NF-κB, CD40, TNF-α, IL-1, and IL-6.</td>
</tr>
<tr>
<td>Shu et al. (2020)</td>
<td>Coronary heart disease</td>
<td>C57BL/6 mice</td>
<td>10, 50 mg/kg by intraperitoneal injection</td>
<td>Andrographolide (molecular formula: C20H30O5, molecular weight: 350.45)</td>
<td>In vivo</td>
<td>Reduce TC, TG, and LDL-C and increase HDL-C while reducing TNF-, MCP-1, hs-CRP, and IL-1; lessen endothelial dysfunction; cut down on NO and PGI2; and avoid cardiac apoptosis.</td>
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<tr>
<td>Gao et al. (2020)</td>
<td>Chron’s disease</td>
<td>C57BL/6 mice</td>
<td>3 days of intraperitoneal administration of 1.25–10 mg/kg</td>
<td>Sulfonated andrographolide (Xi-Yan-Ping Injection, commercial name)</td>
<td>In vivo</td>
<td>By lowering IL-6, IL-17A, TNF, and IFN; decreasing CD4+T cell and macrophage infiltration; and inhibiting the fraction of pathogenic CD4+T cells, one can lessen the damage and fibrosis induced by TNBS to the colonic epithelium.</td>
</tr>
<tr>
<td>Li et al. (2018)</td>
<td>Rheumatoid Arthritis</td>
<td>Wistar rats</td>
<td>50 mg/kg per day by intragastric administration for 35 days.</td>
<td>Andrographolide, 98% purity, was suspended in a 1% carboxymethyl cellulose sodium (CMC-Na) solution.</td>
<td>In vivo</td>
<td>Lower serum levels of IL-6, IL-1β, and TNF-α. Concurrent andrographolide and methotrexate therapy led to a better therapeutic result than monotherapies, with less hepatotoxicity and enhanced anti-arthritic effects.</td>
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<tr>
<td>Shao et al. (2016)</td>
<td>Psoriasis</td>
<td>C57BL/6 mice</td>
<td>2.5 mg/kg, 5 mg/kg, and 10 mg/kg daily intragastric</td>
<td>Andrographolide sulfonate</td>
<td>In vivo</td>
<td>Reducing psoriasis, andrographolide 10 mg/kg was equivalent to etanercept 10 mg/kg. In the skin of mice with psoriasis, andrographolide at doses of 5 or 10 mg/kg dramatically decreased the mRNA expressions of IL-23 and IL-1β. When psoriasis developed, andrographolide did not suppress the downstream of IL-23. Andrographolide’s ability to treat psoriasis may be mediated via MAP1LC3B. By causing the autophagic proteolysis of MyD88, andrographolide blocked LPS/IMQ transmission.</td>
</tr>
<tr>
<td>Jindal et al., (2021)</td>
<td>Psoriasis</td>
<td>cultivated human HaCaT keratinocyte cell model</td>
<td>Separately, the herbal extract sample (10 mg) was dissolved in DMEM-HG (Dulbecco’s Modified Eagle Medium-High Glucose) supplemented with 2% inactivated fetal bovine serum (FBS) to create a stock solution at a concentration of 1 mg/ml.</td>
<td>200 g of A. paniculata leaves were macerated for 12 hours in 500 ml of 90% ethanol.</td>
<td>In vitro</td>
<td>As a hallmark of psoriatic illness, andrographolide at 31.25 g/mL (90 M) significantly inhibited the growth of human HaCaT keratinocytes in cell culture. According to this study, andrographolide, which was isolated from A. paniculata, has anti-proliferative properties.</td>
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An essential regulator of inflammation, the NLRP3 inflammasome is activated in a number of neurodegenerative diseases. It was activated by a variety of factors, such as PAMPs and DAMPs, and it released mature IL-1 and IL-18 to breach the immune system’s protection. Andrographolide, intimately linked to the NLRP3 pathway and microglial activation in neurodegenerative disorders, may reduce neuroinflammation by blocking this pathway. One of the most typical symptoms in people with acute coronary heart disease is inflammation (CHD). Treatment with andrographolide reduced endothelial dysfunction, cardiac apoptosis, serum levels of TNF-, MCP-1, hs-CRP, and L-1, and these conditions in CHD animals. Treatment with andrographolide enhances mice model CHD processes via regulating PPAR and NF-B. Psoriasis has a very complicated etiology. The existence and growth of Th17 and Th22 cells depend on IL-23. Interferon-gamma (IFN-γ) and TNF- cells are secreted by Th1 cells; IL-22 and IL-17 are produced by Th22 cells; and IFN- and TNF- are produced by Th17 cells. It is believed that the Th17 route, which IL-23 activates, is the most important of these pathways. The transcription of important inflammatory mediators is triggered by IL-23 pathway, which is intracellularly mediated by Tyk2-Jak2 and STAT3. These cytokines cause the infiltration of immune cells into skin lesions, the proliferation of keratinocytes in the downstream pathway, and an increase in the production of angiogenic mediators and endothelial adhesion molecules.

Andrographolide has anti-inflammatory actions by blocking several intracellular pathways triggered by various pro-inflammatory substances. Pure substance Andrographis paniculata has anti-inflammatory properties that can lower the expression of TNF-a, IL-6, and IL-1β genes. This is related to the pathogenesis of psoriasis, which is closely related to the increased activity of proinflammatory cytokines, including TNF-a, IL-6, IL-1β, and IL-23. In our review, either in vivo or in vitro study, andrographolide is potentially treating psoriasis in various pathway. In the Invitro study, it could inhibit the proliferation of keratinocytes which also has a pivotal role in the n disease development of psoriasis. On the other hand, the in vivo study found an effect of Andrographolide by decreasing the mRNA expressions of IL-23 and IL-1β. Psoriasis causes erythematos skin rash, scaling, keratinocyte hyperproliferation, and plaque formation. Thus, in this condition, corticosteroids as a common treatment for the patient. The transcription factors NF-B and AP-1, which control the expression of these inflammatory genes, may be inhibited by corticosteroids. Inhibition of the production of adhesion molecules, enzymes, pro-inflammatory cytokines, and chemokines (such as eotaxin, macrophage inflammatory protein, and regulated and normal T cell expressed and secreted, or RANTES), as well as nitric oxide and cyclooxygenase 2, is a phenomenon of immune regulation caused by these transcription factors. The similar mechanism also found in Andrographolide with a different pathway (Table 4), as explained before. Unfortunately, while writing this article, research on the outcome of giving andrographolide to psoriasis was very limited. This is also a limitation in this study, so comparative analyses that can be carried out are also limited. For this reason, research related to similar matters needs to be developed with various modifications and research designs.

CONCLUSION

Management of patients with psoriasis involves more than choosing and prescribing recommended medications. Andrographolide is potentially treating psoriasis in various pathways, such as inhibiting keratinocyte proliferation and decreasing the mRNA expressions of IL-23 and IL-1β. Both mechanisms belong to the inflammation and proliferation mechanism of psoriasis. That mechanism is also found in topical corticosteroids as a common psoriasis treatment. Thus, this biological compound is potential in the future for psoriasis disease.

DISCLOSURE

Author Contribution

All of the authors contributed to making this article

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None

Conflict of interest

None

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