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Anti-inflammatory Effects of Topical *Hypericum perforatum*: A Systematic Review

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Abstract

Introduction: *Many inflammatory conditions directly impact the skin through different pathways, the understanding of which should be a priority to develop new medications to treat patients suffering from these conditions. Some studies have demonstrated the anti-inflammatory properties of Hypericum perforatum (HP), but no previous systematic reviews have described all the mechanisms by which topical HP may act on inflammation. Therefore, the purpose of this review was to assess the effects of topical HP on inflammatory markers in inflammatory skin conditions or models involving epithelial cells that have been described so far.*

Methods: *The databases PubMed, Scopus, Research4Life (HINARI), and SciELO were used to retrieve experimental and observational studies, from inception to September 25, 2022, reporting the effects of HP on inflammatory markers in inflammatory skin conditions or models involving epithelial cells. We used the following keywords: Hypericum perforatum, H. perforatum, Saint John's wort, hypericin, hyperforin, inflammation, pro-inflammatory, inflammatory, inflammatory biomarkers, chemokine, prostaglandin, inflammation mediators, TNF, and tumor necrosis factor.*

Results: *From 348 articles screened, 11 were selected based on inclusion and exclusion criteria: two in vitro studies, eight animal studies, and one human pilot trial. A reduction in proliferation and proinflammatory pathways, IL-8 modulation, and a decrease in TNF expression were the main findings reported in the included studies.*

Discussion: *HP has shown promising effects in reducing inflammatory biomarkers in inflammatory skin diseases and experimental models of epithelial cells. Further studies should confirm this herb's clinical significance and future applications.*

Introduction

The skin is the largest organ in the body and an immune organ involving innate and acquired immune systems. It responds to internal and external stimuli by secreting proinflammatory cytokines (Yamanaka, 2021; Hay, 2015). Skin diseases represent the fourth most common type of human disease, affecting approximately 1.9 billion people, roughly one-third of the world's population (Hay, 2010). Skin disorders can be inflammatory, such as psoriasis (Ghazizadeh, 2010). Despite inflammation being a protective mechanism, it can have deleterious effects when unregulated. At the same time, it plays a prominent role in acute conditions, such as infection and tissue injury; it is also important in chronic conditions, such as autoimmune diseases, diabetes, obesity, and cancer

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(Arulselvan, 2016).

It is thus of great relevance to explore new medications and interventions, including natural products, that act on the different stages of the inflammatory process (Arulselvan, 2016). *Hypericum perforatum* (HP), also known as St. John's wort (SJW), is a medicinal herb containing naphthodianthrones, such as hypericin, and phloroglucinols, such as hyperforin (Russo, 2014). Antiseptic, antibiotic, anti-viral, analgesic, and anti-inflammatory activities are some of the effects of HP, and the most well-known are antidepressant and anxiolytic properties (Ng, 2017; Shrivastava, 2015). Various preparations of this herb, including oils, can be applied topically (Wölfle, 2014). This has allowed for extending its safe use in skin conditions, and literature shows that this herb is a promising therapeutic alternative for skin diseases.

Several clinical trials have investigated the topical use of HP (Sosa, 2007) by mechanisms described in various in vitro and in vivo studies (Nafee, 2013). These studies have shown that the mechanism underlying the favorable effects of HP in inflammatory skin conditions is related to the modulation of inflammatory biomarkers (Sosa, 2007).

Although there is extensive information on the effects of HP as a topical anti-inflammatory agent, no study collects and assesses this information. In addition, HP is still under investigation, so there are no conclusions regarding its potential clinical use. Therefore, a systematic review was conducted to answer the question, "What are the effects of topical *Hypericum perforatum* on inflammation?". The purpose of the study was to examine the available literature regarding the effects of topical HP on inflammatory biomarkers in models using epithelial cells and on inflammatory skin conditions. This study provides a comprehensive assessment of the current evidence for the effect of HP and its potential use as a topical anti-inflammatory agent. It can serve as the basis for future studies evaluating HP's possible clinical use.

Materials and Methods

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA) guidelines (Page, 2021).

Search strategy

PubMed, Scopus, Research4Life (HINARI), and SciELO databases were used to retrieve experimental and observational studies reporting the effects of HP on inflammation, searched from the database's inception to September 25, 2022. This included English, Spanish, Portuguese, German, Italian, and French scientific articles.

The terms used to identify the articles were *Hypericum perforatum*, *H. perforatum*, Saint John's wort, hypericin, hyperforin, inflammation, proinflammatory, inflammatory, inflammatory biomarkers, chemokines, prostaglandins, inflammation mediators, TNF, and tumor necrosis factor. The search was performed through the Boolean operators "AND" and "OR" with a combination of descriptors. The entire search strategy is described in Supplementary Table 1. Citations for each article were downloaded and uploaded to Rayyan (a systematic review web software). The initial selection was based on titles and abstracts, and the final piece was based on full text. Two authors independently evaluated the articles according to the inclusion criteria, and a third party resolved disagreements.

Study criteria

Experimental or observational studies that used topical HP treatment were included. This involved in vivo (human or animal) models with inflammatory conditions and in vitro models of epithelial cells.

The intervention could be an extract of HP, hypericin, or hyperforin. Topical application was defined as medication applied to the skin or mucous membranes (InformedHealth.org, 2022). Inflammatory conditions are acute or chronic diseases characterized by a biological response from the immune system caused by pathogens, toxins, or damaged cells, leading to tissue damage (Chen, 2018). The control group could be other interventions or placebo. Outcome measures were measures of inflammation, such as inflammatory biomarkers (e.g., cytokines, growth factors), changes in inflammatory signaling pathways, or inflammatory cells.

Studies without primary data repeated reports of the same setting, or papers without appropriate reporting of the main features of the population, exposure/intervention, and the outcome, were excluded from the analysis.

Data extraction

Data were extracted using a standard form. Title, language, authors, country, year of publication, journal, aims, study design, sample size, type of subjects (humans, animal models, experimental model), and type of inflammatory disease were retrieved for study characteristics. For intervention features, information was retrieved on the dose and route of treatment and the type of control (placebo or other intervention).

In terms of outcomes, types of inflammatory biomarkers were collected. After data extraction, studies that fulfilled the inclusion criteria were in-

cluded in the qualitative analysis. Then, data were extracted from the main text and the tables of included articles. Finally, a third investigator resolved any conflicts.

Results

Study selection

A total of 348 articles were retrieved using the search strategy. First, the studies were screened for duplicates, and 105 articles were eliminated. Next, 243 articles were independently reviewed by two collaborators. After analysis of titles and abstracts, fifteen titles were selected for full-text analysis based on the inclusion criteria. Eleven articles were chosen as the final sample and included for detailed analysis. Four articles were excluded: two because they involved inadequate outcomes, one because they applied the wrong drug, and one had non-topical administration. The articles included were: two in vitro model studies and nine in vivo (eight animal studies and one clinical trial). Most studies investigated HP's effects on wounds in animal subjects. A flowchart of the article selection process is presented in Figure 1.

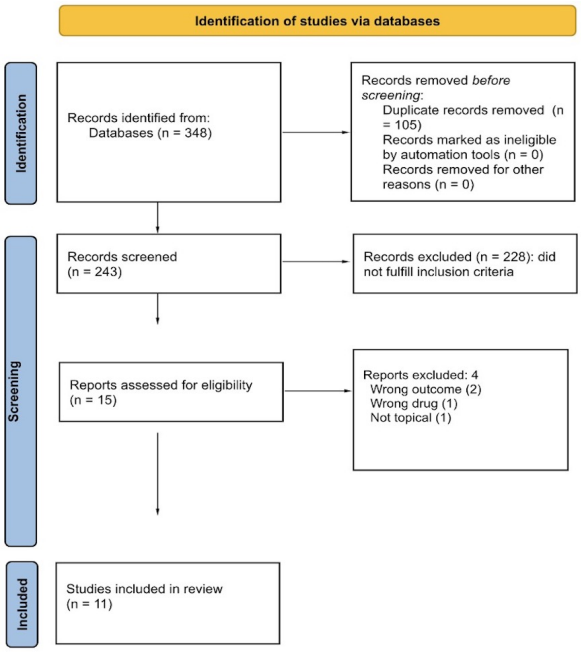

Figure 1: *Prisma Flow Diagram.*

Study characteristics

1. In vitro model studies

Two in vitro model studies were reviewed. The first study showed that in human psoriatic-like keratinocytes, HP compounds reduced gene expression involved in cell proliferation and pro-inflammatory pathways, namely DEFB4A, KRT17, GLUT1, IL-6, and IL-8 genes (Gendrisch, 2021). Another study showed that an HP-derived compound induced and modulated IL-8 expression in human intestinal epithelial cells (Zhou, 2004).

2. In vivo model studies

2.1. Animal studies

2.1.1. Wounds

Four animal studies evaluated the effects of HP on wounds. The first study explored the antibacterial wound healing effect of hypericin (HY) nanoparticles and HY free compared to the untreated control group, analyzing the gene expression of PDGF, VEGF, COX-2, and TNF-α using RT-PCR. This study showed that the groups treated with HY had an increased expression of growth factors and COX-2 and an inhibited expression of TNF-α in wounds treated with HY nanoparticles (Nafee, 2013). Another study produced nanofibers damage dressing patches with Aloe vera and HP, and the effect of these nanofibers dressing was determined by biochemical methods (TAS, TOS, TNF-α, and FTIR spectroscopy). It showed that rats with diabetic wounds treated with HP and Aloe vera had a higher antioxidant status and a significant reduction in TNF-α levels (Guleken, 2021). A similar study in a diabetic rat model with full-thickness excision wounds showed that HP led to faster wound closure; the rate in the treated group's HP 5% and 10% were 8.61%/day and 6.80%/day respectively, while the rate of wound closure in the gel base and control group were 4.92%/day and 4.42%/day respectively (Yadollah-Damavandi, 2015).

In a more recent study, the authors investigated various combinations of HP, Liquidambar Orientalis (OL), and propolis and their effects on wound healing. Their findings showed that angiogenesis and epithelialization rates were higher, and inflammation was lower in the treatment groups compared with the control. However, they did not find differences between treatment groups (Altiparmak, 2019).

2.1.2. Burns

Three animal studies evaluated the effects of HP on burns. The first study showed that SJW oil treatment led to a significantly smaller average wound area and lesser epidermal thickness than chitosan treatment in rats with second-degree burns. The treatments were first administered 4 hours after the burn was created. And then, every day, morning and evening,

for three weeks, no therapy was issued in the fourth week. The wounds were evaluated weekly. The rats were sacrificed at the end of the fourth week, and histopathological examinations were performed (Güler, 2021). Another study showed that HP oil extract induced anti-inflammatory, anti-fibroblastic, and an-ti-angiogenic effects in rats with corneal alkali-burn (Yılmaz, 2019). Similarly, endoscopically administered HP extract significantly reduced inflammation, fibrosis, and necrosis in rats with corrosive esophageal burns (Sümeli, 2022).

2.1.3. Other

One of the analyzed studies evaluated the effects of HP on the prevention of experimentally induced myringosclerosis (MS) in a rat model using otomicroscopy and histopathology. This study showed that oral and topical HP extracts reduced inflammation and fibrosis and inhibited the development of MS in white albino rats with tympanic membrane perforations (Eğilmez, 2015).

2.2. Clinical trials

A double-blind, placebo-controlled clinical trial evaluated the effect of HP in patients with mild to moderate plaque-type psoriasis, an immune-mediated inflammatory disease characterized by elevated levels of TNF-α. This study showed that topical HP decreased endothelial and dendritic cells and TNF-α concentrations compared with placebo. Moreover, treated lesions significantly improved clinical and histological characteristics (Mansouri, 2017).

Discussion

This systematic review summarizes the current evidence on the effects of HP on inflammatory biomarkers in inflammatory skin conditions or epithelial cell models of inflammation. To the best of our knowledge, this is the first systematic review that comprehensively investigates the English, Spanish, Portuguese, German, Italian, and French literature to evaluate topical HP's effects on inflammation and includes both human and animal model studies with promising results. In addition, eleven articles encompassed in vitro and animal studies, and a clinical trial was identified.

Most of the studies were of animal models. Wounds were the primary condition assessed, followed by burns and psoriasis. A single clinical trial was evaluated and focused on patients with psoriasis (Mansouri, 2017). These studies demonstrate that HP is anti-inflammatory when used topically and directly in epithelial cell models. Studies have shown that HP reduces inflammatory marker levels, especially TNF-α, and inflammatory cell infiltration. In vitro and animal models have shown that HP is a promising therapeutic agent for diseases affecting the epithelium.

However, additional clinical trials are needed to confirm the efficacy of HP and determine its effectiveness in human subjects.

It is also essential to recognize the limitations of this study. These include publication bias, language restrictions, and limited available clinical trials. For the former, it is well-known that articles with negative results face more barriers to publication. Hence, they will be automatically excluded from being analyzed and compared in this study's analysis. To acknowledge language restrictions, there was an effort to include English publications from non-English-speaking countries and journals in other languages. Similarly, despite utilizing several databases to broaden the amount of literature available for analysis, there was still the limitation of analyzing only a single clinical trial that met the inclusion criteria. It is recommended that future studies include well-designed randomized clinical trials to investigate the applications of these findings, especially in treating wounds and burns.

Conclusions

This systematic review suggests HP has encouraging anti-inflammatory effects in inflammatory skin conditions and experimental epithelial cell models of inflammation. Reduced concentrations of inflammatory and proliferative biomarkers characterize these effects. Additionally, due to fewer side effects and a less invasive route of administration, HP could be a valuable alternative to conventional drugs for treating inflammatory diseases. Mainly, HP displays promising potential in managing epithelial inflammatory conditions. However, further studies should be performed to confirm this herb's clinical significance and applications.

Author Contributions

All authors contributed equally to the conceptualization, methodology, software, validation, investigation, writing, reviewing, and editing of this article. Additionally, all the authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors have no conflicts of interest to declare.

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