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Literature Review

CIPLUKAN'S ANTI-INFLAMMATORY EFFECTS: MECHANISMS UNCOVERED

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ABSTRACT

Background: Ciplukan (*Physalis angulata* Linn) is a native American plant widely distributed in tropical regions including Indonesia. This herb has been used as a traditional ingredient to treat inflammation as well as other diseases. Ciplukan's anti-inflammatory effects are thought to be triggered by the active compounds in the various parts of the herb.

Objective: This review aims to describe the herb's anti-inflammatory effects and its mechanisms.

Methods: PubMed and Google Scholar databases were searched for articles using Boolean operations with keywords related to *Physalis angulata* and inflammatory components. We included literature in English and Indonesian without limiting the publication time range.

Results: Ciplukan has an anti-inflammatory effect by regulating inflammatory mediators, inhibiting immune signaling pathways, and the genes associated with the immune system.

Keywords: Ciplukan, anti-inflammatory effect, immune signaling pathways

INTRODUCTION

Inflammation is a biological response that occurs after tissue damage, characterized by edema (swelling), erythema (redness), warmth, pain, and loss of function in the affected tissues. The tissue damage can be caused by infection, trauma, toxic effects, or overuse of organs. Inflammation serves as the human body's second line of defense against damage and involves both the cellular and humoral immune systems. Acute inflammation allows for the regeneration and repair of damaged tissue making it a beneficial defense mechanism. However, excessive and prolonged inflammation can disrupt homeostasis and cell signaling pathways in the body, potentially leading to detrimental effects even after the etiologic agent has been cleared. Therefore, immunomodulatory agents have been developed to control inflammation.

Studies of immunomodulatory agents have usually focused on examining the inflammatory response after administering the modulator candidates to subjects. Subsequently, specific cellular or humoral immune markers are studied. Examples of cellular markers include macrophages, neutrophils, basophils, eosinophils, NK cells, dendritic cells, and various types of lymphocytes. On the other hand, humoral markers comprise inflammatory mediators and secreted immune substances, such as the complement system, reactive oxygen species (ROS), reactive nitrogen oxide species (RNOS), cytokines, chemokines (such as IL-1β, IL-6, TNF-α), and acute phase proteins. Additionally, other markers such as COX activity and its metabolites, as well as growth factors or inflammation-associated transcription factors (NFκB), are typically investigated.

Ciplukan (*Physalis angulata* Linn) is a native American plant from the Solanaceae tribe that has been widely distributed in tropical regions of the world including Asia and Africa. In Indonesia, the herb is known by many names such as ceplukan, ceplokan, ciciplukan (Java), cecendet (Sunda), leletep (Sumatera), karuhux (Borneo), leletopan (Sulawesi), lapironat (Maluku), gekatomato (Papua), nyornyoran (Madura), telak (Flores), and dedes (Lombok). Morphologically, Ciplukan has a height of 10-100 cm, purplish-green stems, pinnate leaves, single star-shaped flowers, and fleshy oval fruit covered with bell-shaped petals. The fruit is shown in Picture 1. It grows wild in gardens, fields, roadsides, shrubs, and forests, and is commonly considered a weed by the community. An altitude of 1-1550 m above sea level is ideal for Ciplukan to grow.[1]

Ciplukan has been used as a traditional ingredient to treat ulcers, fever, hypertension, diabetes mellitus, fractures, sprains, abdominal pain, gonorrhea, epilepsy, urinary incontinence, and jaundice.[1] These various benefits are thought to be generated by the active compounds in the herb. It contains saponins in the shoots, flavonoids in the

leaves, polyphenols and physalin in the fruit, angulatin-A in the fruit and stems, palmitic and stearic acids in the seeds, and alkaloids in the roots. In addition, there is chlorogenic acid in the stems and leaves, cryptoxanthin, and vitamin C in the fruit. The most abundant contents are flavonoids, alkaloids, and saponins.[3]

Picture 1. Fruits of Ciplukan inside petals[2] (adapted from Setiawan (2021)).

The potential of Ciplukan herb as an anti-inflammatory agent has been studied, so a review of the literature is necessary to summarize its various anti-inflammatory effects. This review aims to describe the anti-inflammatory effects of Ciplukan and the mechanisms that might underlie these effects.

METHODS

This review was conducted on a literature search of PubMed and Google Scholar databases of journals. Keywords used were "*Physalis angulata*" and its equivalents, "inflammation" and its equivalents including inflammatory cells such as macrophages and neutrophils, inflammatory cytokines such as IL-1β, IL-6, TNF-α, nitric oxide, and prostaglandins, as well as other factors involved in the inflammatory response such as COX-2 and LPS. The keywords were combined using Boolean operations and the literature found was not limited by year of publication. Inclusion criteria included original or review literature related to the anti-inflammatory effects of the Ciplukan herb and its molecular mechanisms, inflammation including inflammatory responses in general, autoimmune conditions, and organ transplants, in both cultured cells, experimental animals, and humans.

Exclusion criteria included literature in languages other than English and Indonesian, abstracts or full text not accessible to researchers, gray literature (unpublished theses, dissertations, reports, guides, seminar papers, and symposiums), and literature discussing the effect of *P. angulata* only on agents of infection such as parasites, bacteria, viruses, or direct inhibitory effects on neoplasms without involvement of the immune system. Analysis and synthesis were carried out in a narrative manner by summarizing the collected literature and subsequently grouping it according to the anti-inflammatory mechanism.

RESULTS AND DISCUSSIONS

ANTI-INFLAMMATORY EFFECTS OF CIPLUKAN (*P. angulata* L.)

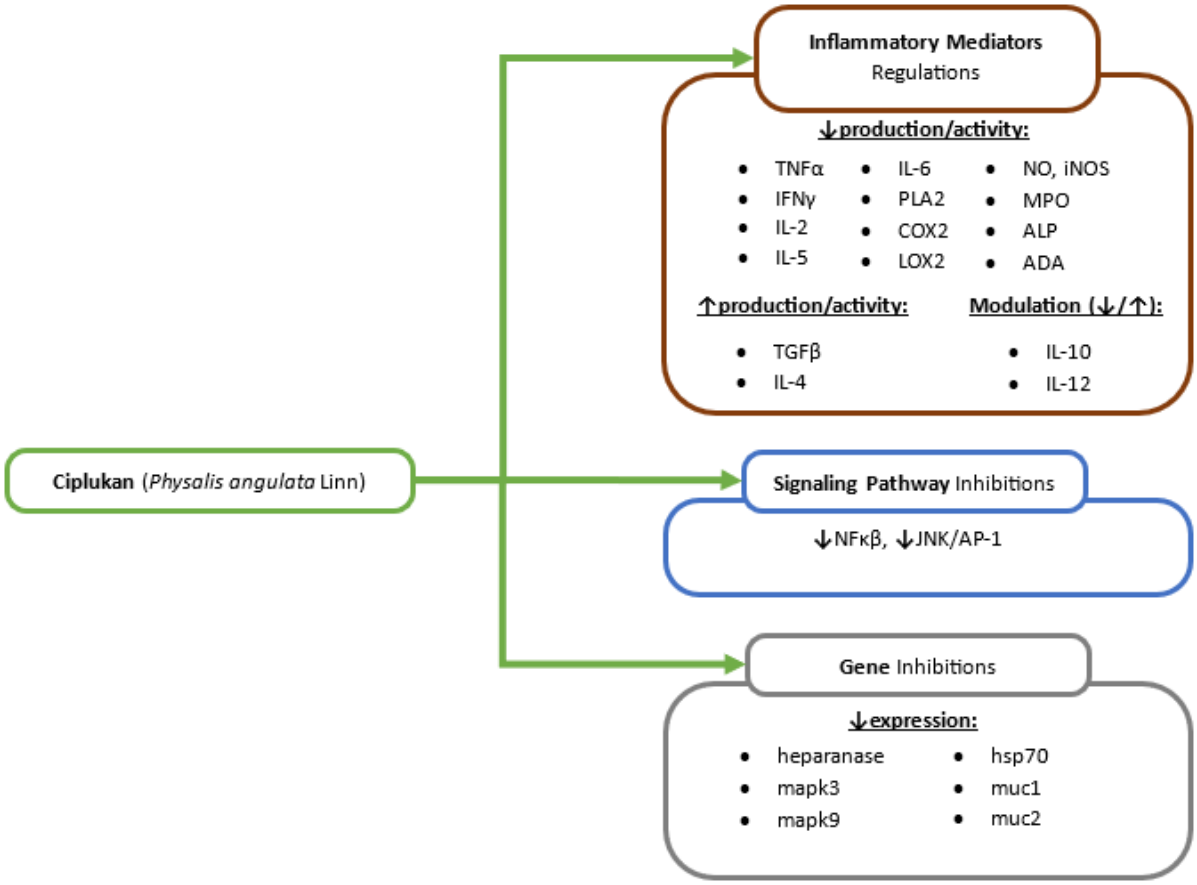
Ciplukan herb has been reported to have an analgesic and antirheumatic effect.[4] In the carrageenan-induced arthritis and edema mice model, administration of 200 mg/kg oral *P. angulata* flower extract was found to inhibit acute and subacute inflammatory processes. Analgesic effects were reported in the administration of *P. angulata* ethanolic extract. The extract contained Physalin B, D, F, and G which were able to reduce pain in mice subjects.[5]

A standardized supercritical CO_2 extract of Ciplukan herb given orally to rat models of colitis was studied to prevent worsening of the inflammation processes. Inflammation could be minimized by injecting the extract before exposure to the colitis inducer (trinitrobenzoic acid/TNBS) and increasing the dose of the extract would increase the anti-inflammatory effect. This extract modulated oxidative stress and immune response including immune cells such as neutrophils and inflammatory cytokines.[6] Another inflammatory modulation was demonstrated in a study using roots of *P. angulata*. In the carrageenan-induced mice model, Ciplukan root aqueous extracts administered intraperitoneally at 1 and 5 mg/kg were able to reduce inflammatory exudate volume by about 50% and 84% less than no treatment.[7]

Topical preparations of *P.angulata* isolates showed potential results when administered to 12-0-tetradecanoul phorbol-13-acetate (TPA) and oxazolone-induced dermatitis mouse models. Physalin E, a secosteroid isolated from *P. angulata*, was able to inhibit the course of dermatitis characterized by greatly reduced edema, confirmed by histopathological examination. This effect was confirmed by a reversal challenge test through the administration of mifepristone, a steroid antagonist.[8]

Physalin F, another secosteroid, was also reported to have immunosuppressive activity. In peripheral blood samples of patients with tropical spastic paraparesis, a virus-associated progressive myelopathy, physalin F elicited an immunosuppressive effect by increasing apoptosis of the peripheral blood mononuclear cells (PBMC).[9]

A controlled double-blind randomized clinical trial was conducted to examine the effect of Ciplukan herb extract as an adjuvant therapy in stable scleroderma patients in the hospital. Among the 59 subjects who completed the research, a significant improvement in skin fibrosis was found in the test group compared to the no treatment group.[10]



Picture 2. Summary of anti-inflammatory mechanisms of Ciplukan.

UNDERLYING MECHANISMS OF CIPLUKAN INFLAMMATORY EFFECT

Inflammatory effects of Ciplukan could be summarized into regulation of inflammatory mediators, inhibition of inflammatory signaling pathway, and inhibition of the genes involved. These mechanisms are resumed in Picture 2.

1. Regulation of Inflammatory Mediators.

P. angulata has regulatory effects on inflammatory modulators in the form of cytokines and other inflammatory markers such as TNF α, IFN γ, TGF-β, IL-1α, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-10, IL-12, IgM, PGE2, NO and iNOS, myeloperoxidase (MPO), alanine phosphatase (ALP), adenosine deaminase (ADA), cyclooxygenase (COX2), lipooxygenase (LOX) and its products leukotriene B4, and phospholipase A2 (PLA2). A Research by Pinto et al showed that topical administration of Physalin E was able to reduce TNF-α and IFN-γ levels and reduce MPO expression in a dermatitis model in mice.[8] Another research showed that physalin in the ethanol extract of P. angulata was able to reduce levels of TNF-α, IL-1β, COX-2, mRNA iNOS, and PGE2 in subject mice.[5] In research using an ischemia reperfusion injury model, administration of physalin supressed TNF-α production and provided a similar effect to dexamethasone as a positive control.[11] Inhibition of TNF-α production by administration of physalin A also occurred in LPS-induced RAW 264.7 cells. In this study, Lin et al demonstrated inhibition of IL-1β, IL-6, NO and PGE2 secretion, downregulated COX2 and iNOS mRNA expression, and increased levels of antioxidant factors SOD, CAT, GPx.[12] In an irritable bowel disease (IBD) model in rats, *P. angulata* extract was able to inhibit colonic IFN-γ and IL-6 production, as well as decrease MPO and ALP expression, although no differences in TNF-α, IL-1β, and IL-10 levels were found compared to controls that were not given the extract.[6] Research by Bastos et al showed a decrease in ADA activity, NO and PGE2 levels by 20%, 60%, and 41% in rats given *P. angulata* root water extract. Interestingly, the study also showed higher levels of TGF-β in the extract group than the positive control.[7] Withanolide, wiphysalin, and physalin X isolated from P. angulata were also studied for their ability to reduce NO levels.[13-16]

a. Regulations of TNF-α, IFN-γ, TGF-β and their effectors.

TNF-α is a cytokine produced by macrophages and monocytes and has a proinflammatory effect. TNF-α acts locally on endothelial cells by stimulating the expression of adhesion molecules and extravasation of monocytes and neutrophils. In addition, this cytokine can stimulate endothelial cells to initiate blood clotting in small blood vessels to stop bleeding. Therefore, the infectious agent that triggers inflammation will usually be isolated at the site of TNF-α secretion. If TNF-α is released into the circulation, it can trigger systemic reactions

including disseminated intravascular coagulation (DIC), sepsis, hypotension, as well as extensive tissue damage thereby increasing the risk of death. Blockade of TNF-α or its receptors would be beneficial in keeping the inflammatory response under control. Physalin in *P. angulata* can inhibit and reduce TNF-α production.[4,5,8,11,12,17–22]

IFN-γ is produced by NK cells, neutrophils, T cells, and intraepithelial lymphocytes (ILCs). These cytokines are useful for activating macrophages. IFN γ also plays a role in increasing the expression of MHC molecules as well as antigen processing. IFN-γ triggers class-switching in B cells. This cytokine suppresses differentiation towards Th17 and Th2 cells thereby increasing the differentiation of CD4+ T cells towards Th1. Thus, it triggers a type 1 immune response that focuses on eliminating intracellular pathogens and activates macrophages. IFN-γ is known to be elevated in IBD patients, and higher levels are associated with more severe IBD.[6] Ciplukan herbs had the effect of suppressing IFN-γ production.[6,8,17,21,23]

TGF-β is a cytokine that was first discovered in tumors, which works to reduce the immune system and inflammatory response. TGF-β regulates the immune system by suppressing T-cell responses and cell-mediated immunity. These cytokines induce T cell differentiation towards regulatory T cells. Research showed an increase in TGF-β levels and its anti-inflammatory effect after administration of *P. angulata* extract.[7]

b. Regulations of Interleukins and their effectors.

Interleukins (ILs) are cytokines that regulate immune system function. ILs consist of more than 60 molecules. *P. angulata* has a modulating effect on several ILs, namely IL-1α, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-10, and IL-12. IL-1α and β are secreted by macrophages and epithelial cells. Both can trigger the activation of macrophages and T cells. An increase in IL-1α or β can cause fever in patients. *P. angulata* was able to reduce IL-1α[21] and IL-1β[5,12] levels and therefore suppress the inflammatory effects of both ILs.

IL-2 is also called T cell growth factor which is useful in the maintenance of regulatory T cells as well as T cell proliferation and differentiation in general. IL-2 is secreted by T cells in response to inflammatory stimuli. Studies showed that Ciplukan could reduce IL-2 levels.[22-24]

IL-4 functions as a B cell activator, triggering immunoglobulin switching towards IgE, and inducing the differentiation of T cells into Th2 cells. IL-4 is secreted by T cells, mast cells, and ILC2. There was an increase in splenocyte IL-4 with the administration of *P. angulata* extract. This indicates that there is indeed a modulation of the immune system, specificically the inhibition of the type 1 immune response.[17]

IL-5 plays a role in eosinophil growth and differentiation. These interleukins are produced by T cells, mast cells, and ILC2. Research shows a decrease in IL-5 secretion with the administration of *P. angulata*.[12]

IL-6 is produced by T cells, B cells, macrophages, and endothelial cells. IL-6 functions to stimulate the growth and differentiation of T and B cells and triggers the production of acute phase proteins. IL-6 plays a role in various immune responses because it can recruit CD4+ Th17 cells, which themselves are neutrophil recruiters.[6] *P. angulata* has the effect of reducing IL-6 levels.[4,6,17,19–22,25] These decreased levels of IL-6 would lead to a reduction of neutrophil infiltration into the inflamed tissue.[6]

IL-10 is a potent suppressant of macrophage function. IL-10 is secreted by macrophages, dendritic cells, T cells and B cells as a controller of the ongoing inflammatory response. Research by Viera showed that *P. angulata* was able to increase IL-10 levels and regulate the immune system.[11] In contrast, Suciady et al reported that IL-10 levels decreased when physalin was given. IL-10 is reported to still have an immunostimulant effect so the inhibition of the IL-10 seems to indicate inhibition of type 1 immune response, and differentiation of T cells towards Th2. IL-10 inhibition also seems to be associated with increased IgM production in *P. angulata* administration[22], even though *P. angulata* also decreased the expression of BAFF and its receptors which function as regulators of B cells in systemic lupus erythematosus mice.[25]

IL-12 is secreted by macrophages and dendritic cells and has the function of stimulating NK cells and inducing T cell differentiation towards Th1. Administration of *P. angulata* was able to reduce IL-12 levels.[4,17,21]

c. Regulations of PLA2, COX2, and LOX pathways mediators.

Physalis angulata had a modulating effect on PLA2, COX, LOX, as well as PGE2 and Leukotriene B4. Damage to cell membranes (including chemical and physical stimuli) will trigger the enzyme phospholipase A2 (PLA2) to hydrolyze phospholipids in the cell membrane which then produces arachidonic acid (AA). AA is then immediately released and quickly metabolized into oxygenated products by enzymes such as cyclooxygenase (COX), lipoxygenase (LOX), and cytochrome (CYP). Kurniasih and Yuniaswan reported a decrease in PLA2 expression after *P. angulata* administration, resulting in a decreased expression of COX2, LOX and leukotriene B4.[21]

Various AA metabolites are inflammatory mediators such as prostaglandins, lipoxins, and leukotrienes. These mediators also play a role in the body's normal homeostasis in the absence of inflammation. In general, anti-inflammatory drugs can act on this pathway of AA metabolism and are divided into steroidal and non-steroidal anti-inflammatory drugs (NSAIDs). Steroids can inhibit PLA2 thereby inhibiting the formation of AA and its metabolites. In addition, steroids can inhibit transcription factors in immune cells, namely NFκB, resulting in the inhibition of their function. NSAIDs inhibit COX-1 and/or COX-2. Other agents are capable of inhibiting LOX, such as anti-asthmatic drugs. Inhibition of the AA pathway has the side effect of normal protective function resulting from impaired metabolites. In the digestive tract, for example, prostaglandins function as protection from stomach acid, thromboxane A2 functions in platelet aggregation. Inhibition of both can increase the risk of bleeding in the stomach. Steroids have systemic side effects in chronic use, such as Cushing's syndrome in addition to side effects of gastrointestinal bleeding such as NSAIDs. Several studies reported lower COX2 expression in the administration of *P. angulata* although no effect was reported on the PLA2 or LOX pathways[5,12,23]. PGE2 was also reported to have decreased due to the inhibition of COX.[5,7,12,19]

d. Regulations of NO and iNOS.

Nitric oxide (NO) is a reactive gas molecule produced by macrophages during infection and is toxic to bacteria and intracellular microbes. The enzyme-inducible NO synthase (iNOS) produces NO from L-arginine. iNOS activity and excessive NO production are studied as pathological causes of various diseases such as sepsis, neurodegeneration, cancer, and various types of pain. *Physalis angulata* had an anti-inflammatory effect by reducing the expression of iNOS and NO which could also be associated with the antioxidant effect of this herb.[5,7,12,14–17,19,21]

e. Regulations of other inflammatory mediators.

The Ciplukan herb influences several inflammatory marker enzymes such as MPO, ALP, and ADA. MPO is an enzyme that produces reactive mediators in inflammatory conditions, which then trigger immune cell infiltration. MPO is closely related to inflammation and oxidative stress because it can cause oxidative damage to lipids and proteins. ALP is another enzyme that can be elevated in inflammatory conditions. ALP increases because of the influx of inflammatory cells into the tissue and peroxidation of membrane lipids that occur when inflammation occurs.[6] ADA is a product of activated lymphocytes. ADA catalyzes the conversion of adenosine to inosine which is important for lymphocyte differentiation. ADA deficiency can lead to an immunodeficiency condition. Administration of *P. angulata* decreased MPO[6,8], ALP[6], and ADA[7] levels.

2. Inhibition of immune signaling pathway.

The mechanism of inhibition of immune cell signaling has been investigated through the NFκB pathway[19-21,23] and JNK/AP-1[12]. Inhibition of this pathway is accompanied by blockade of IκB degradation and NFκB/p65 translocation.[19] NFκB inhibition will be able to reduce COX-2 expression as shown by L. Sun et al., who studied a group of mice exposed to Withangulatin A. In this study, COX-2 inhibition was found via the MAPK pathway.[23] On the other hand, research by Wang did not show changes in the protein expression of the MAPK pathway (ERK, JNK, and p38) so there is still the possibility of inhibition not from this pathway.[19]

3. Inhibition of genes associated with immune system.

Physalis angulata affects the expression of genes that play a role in IBD pathology, namely heparanase, hsp70, mapk3, mapk9, muc1, and muc2. Heparanase and hsp70 will be synthesized after exposure to triggering agents in IBD conditions. Mapk3 is a gene that plays a role in signaling neutrophil adhesion. Increased gene expression triggers neutrophil infiltration into damaged tissue. Mapk9 encodes the JNK2 protein and participates in signaling during the development of inflammation. Mapk9 regulates cytokine release and neutrophil response. The muc gene, especially MUC2, plays a role in the synthesis of mucus in the digestive tract including the colon. In IBD, increased expression of the Muc gene can occur as a response to maintaining mucus integrity against inflammation. In research by Almeida Junior et al, rats that were given *P. angulata* extract orally 25-100 mg/kg once a day for 5 days before being induced by TNBS were able to express these genes lower than control, so they seemed able to act as agents preventing the development of inflammation.[6]

CONCLUSION

Ciplukan can be used as an anti-inflammatory agent. These herbs can regulate inflammatory mediators, inhibit immune system signaling pathways, and inhibit gene expressions involved in the immune system. Further research is needed to ensure the most appropriate dose for anti-inflammatory effects, pharmacokinetic and pharmacodynamic profiles, the most suitable dosage forms, and confirm the safety of the Ciplukan herb and its respective potential isolates.

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CONFLICT OF INTEREST AND FUNDING RESOURCES

We declare no conflict of interests. No funding was received for conducting this review.

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