Anti-inflammatory Effect of Gambier Catechin (*Uncaria gambir* Roxb) on Rheumatoid Arthritis: A Review

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Abstract

BACKGROUND: Rheumatoid arthritis (RA) is a chronic inflammatory disease of the joints and varies in severity in patients. Inflammation in the joints causes high levels of systemic pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) which have an impact on permanent damage to the joints. Until now, the treatment of RA is only symptomatic, without being able to prevent the progression of damage to the joints, and this treatment also causes side effects such as gastrointestinal and cardiovascular toxicity. Therefore, many patients are looking for alternative medicine to complement their treatment.

METHODS: This research was a narrative review that was performed using PubMed, Science Direct, and Google Scholar using pre-clinical and clinical studies which aim to determine whether the therapeutic mechanism of gambier catechin (*Uncaria gambir* Roxb) on RA. A literature review is carried out to formulate a scientific basis for innovation.

RESULTS: The gambier plant is a typical plant of West Sumatra, which is rich in phytochemicals. The active compounds in gambier are catechins which are classified as flavans/flavonoids. Catechins are compounds that are well-known as antioxidant, anti-inflammatory compounds, the highest found in gambier plants. Catechins affect the expression of inflammation-related genes and proteins such as TNF-α, IL-1, and show their anti-inflammatory roles. This research is a literature review using secondary data from original research based on in vitro, in vivo, and clinical trials. The results showed that catechins can inhibit the production of IL-1, TNF-α, prostaglandin and increase levels of cyclic adenosine monophosphate in rats. On histological findings, peri-synovial inflammation and cartilage damage decreased in the group given epigallocatechin-3-gallate which showed anti-rheumatic activity and increased CD4+ and CD25+ regulatory T cells, thereby inhibiting the B cell population effectively suppresses inflammation and arthritis pain and shows its therapeutic potential in the treatment of RA.

CONCLUSION: It can be concluded that gambier catechins have the potential as a candidate for RA therapy. This, if developed, can certainly improve the health status of the community locally and globally.

Introduction

The 2030 Sustainable Development Goals (SDGs) or which are translated as the SDGs are a comprehensive vision issued by the United Nations to achieve a better world by 2030. The health sector is one of the main sectors in the future development of the world based on the SDGs, this is firmly stated in the third goal of the SDGs, namely good health and welfare. In the details, there are 13 main targets in the SDGs goals at this point, where target 3.4 states that by 2030, reduce one-third of premature deaths caused by non-communicable diseases (NCDs), through prevention and treatment [1].

NCDs have recently become the leading cause of death worldwide. NCDs are responsible for 71% of global deaths or the equivalent of 41 million people every year. As many as 15 million people aged 30–69 years died from NCDs, 85% of which occurred in lower-middle-income countries. Poverty, the damaging effects of globalization on product trade, rapid urbanization, and aging are the main causes of the global epidemic of premature death from NCDs [2]. As stated in the global action plan for the prevention and control of NCDs 2013–2020, poor diet and lifestyle are the main risk factors contributing to this global burden of disease [3].

NCDs not only cause pain, physical disability, and even death but also often carry a financial burden on families. Special attention needs to be given to sufferers, especially during a pandemic like today. This is because this disease can be a comorbidity that increases a person’s chances of contracting and getting sick from COVID-19. Health conditions deteriorate rapidly, treatment failures and treatment cannot be given perfectly due to access or other limitations due to the pandemic. One disease that needs attention is rheumatoid arthritis (RA), which is an autoimmune disease with a high risk of experiencing severe COVID-19 symptoms [4].

RA is a chronic disease that occurs more often in women than men. This disease is mostly found in the
RA disease primarily affects the lining of the synovial joint and can cause progressive disability, premature death, and socioeconomic burden. Clinical manifestations of symmetric joint involvement include arthralgia, swelling, redness, and even a limited range of motion caused by inflammation [6]. Inflammation in the joints causes high levels of systemic pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) which have an impact on permanent damage to the joints [7].

Early diagnosis is the main improvement index for a better prognosis, namely reduced joint damage, less radiological development, no functional disability, anti-rheumatic drug-free remission (DMARD), and cost-effectiveness as the first 12 weeks after initial symptoms occur are considered as optimal therapy window [8]. Until now, the treatment of RA is symptomatic. Drug therapy commonly used is non-steroidal anti-inflammatory drugs to reduce pain and swelling, steroid drugs to suppress inflammation and as immunosuppressants, to DMARDs that can reduce joint damage, control inflammation, and protect joint structure and function. However, many patients still cannot achieve disease remission. Some therapeutic agents show good potency but cause various side effects, such as gastrointestinal and cardiovascular toxicity [9], [10]. Therefore, many patients are looking for alternative medicine to complement their treatment so that further research and scientific review are needed regarding the potential of herbal medicines, especially medicinal plants that are effective with minimal side effects for patients.

Indonesia ranks third in the world in terms of biodiversity and has at least 10% of the world’s plant species [11]. One of the biological treasures is the gambier plant which is commonly found in the tropics, especially in West Sumatra, Indonesia. Gambir is a special superior commodity in this province with an annual export supply of 95%, which continues to increase every year [12]. Gambier (U. gambir roxb) is a plant that is commonly used for various uses, including as traditional medicine. The biologically active ingredients of this plant are mainly catechins which account for 73.3%, followed by tanners, and some alkaloids [13].

Catechins are flavonoid compounds with very high antioxidant activity, even exceeding synthetic antioxidants. Catechins are gaining attention for the treatment of RA due to their anti-proliferative and anti-inflammatory activities. Catechins induce apoptosis of fibroblast-like synoviocytes (FLS) which is the synovial intima layer of joints and osteoclasts that are important for bone matrix synthesis. Catechins affect the expression of inflammation-related genes and proteins such as TNF-α, IL-1, and show their anti-inflammatory roles. Catechins also inhibit the production of IL-6, matrix metalloproteinase (MMP)-1, and MMP-3 in the inflammatory mechanism as a cause of RA [14].

Administration of catechins reduces the incidence and severity of arthritis in experimental animals. Catechins have a better radical scavenging ability than synthetic antioxidants and are non-toxic [15]. Antioxidants are commonly used for supplementation and have been studied for the prevention of non-communicable and degenerative diseases. Supplementation aims to add nutrients to food products to maintain or increase their nutritional value [16].

Therefore, the idea of an alternative therapy for RA using gambier catechins is very urgent to be realized. This innovation has great potential to be developed through anti-proliferative and anti-inflammatory activities in RA. It is hoped that this can be realized to encourage the achievement of the 2030 SDGs, especially in the management of NCDs and health quality assurance in Indonesia.

Methods

The research design used is a literature study. Literature study is a form of research conducted through search by extracting original articles in national and international journals obtained through the Pubmed electronic database using Google Scholar. The literature reviewed is about the anti-inflammatory roles of gambier catechin in RA, both literature with in vitro and in vivo research designs (Figure 1).

![Figure 1: Gambier plant (Uncaria gambir Roxb)](image)

The inclusion criteria of this study were primary literature or journals (original research), full text, in English and Indonesian, period 2011–2021, researching the role of catechins in RA with in vitro and in vivo studies. The exclusion criteria are if the research group is mixed with other compounds, does not have a
control group, the discussion about the mechanism is not explained, and the journal is not indexed. The search was limited to articles written in English. The search process was carried out using the following keywords: Anti-inflammatory, catechin, gambier, inflammation, RA. Data collection is done by taking data from the source, reading, synthesizing, and extracting the required data.

Results and Discussion

**Literature review matrix**

This section contains a literature review matrix (Table 1), possibly because the document format does not match the subchapter, please help to adjust it.

![Figure 2: Inhibitory mechanism of catechin on IL-6][26]

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**Table 1: Literature review matrix of study**

<table>
<thead>
<tr>
<th>No.</th>
<th>Author, Year</th>
<th>Research design</th>
<th>Research objective</th>
<th>Sample</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Pitrityah, 2016</td>
<td>Experimental (in vivo study)</td>
<td>To determine the anti-inflammatory activity of gambier catechin isolates and to find the optimal dose as anti-inflammatory in terms of decreasing the volume of edema in the soles of male white rats induced by carragenan.</td>
<td>Dawley’s sparague male rat</td>
<td>The effect of edema inhibition of gambier catechin isolates from all dosage variations showed a significant difference (p ≤ 0.05) with the negative control. The dose of 10 mg/kg BW is the optimal dose.</td>
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<tr>
<td>2.</td>
<td>Fechtner et al., 2017</td>
<td>Experimental (in vitro study)</td>
<td>To assay EGC (epigallocatechin-3-gallate), EGC (epigallocatechin), and EC (epicatechin) alone and in combination to study the impact on anti-inflammatory outcomes in human RA SF and the underlying molecular mechanisms.</td>
<td>Human RA synovial tissue.</td>
<td>All types of catechins tested can inhibit TAK1 activity. EGC, EGC, and EC all occupy the active site of the TAK1 kinase domain. However, EGC occupies most of the active site of TAK1. In addition to TAK1 inhibition, EGC can also inhibit nuclear P38 and NF-kB expression whereas EC and EGC are not effective inhibitors.</td>
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<tr>
<td>3.</td>
<td>Liu et al., 2016</td>
<td>Experimental (in vitro study)</td>
<td>Assaying EGCG would promote osteogenic differentiation in bone marrow isolated hMSCs (BM-hMSCs) and to identify potential interactions between EGCG and TNF-α in this setting.</td>
<td>EGCG promoted osteogenic differentiation even at lower doses (50 and 10 mg/mL), with no effect at higher doses (20 and 40 mg/mL). In the presence of low-dose EGCG (5 mg/mL), TNFs could no longer block osteogenic differentiation of BM-hMSCs, indicated by ALP activity, mineralized nodule formation, Runx2 expression, and OsteX.</td>
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<tr>
<td>4.</td>
<td>Goncalves et al., 2015</td>
<td>Experimental (in vivo study)</td>
<td>Evaluating the possible effects of administration of green tea extract on the oxidative state of the liver and brain of adjuvant-induced rheumatic rats, a model for human rheumatoid arthritis.</td>
<td>Male Holtzman rats</td>
<td>This treatment significantly reduced damage to liver, brain and plasma, reduced tissue ROS and increased plasma antioxidant capacity. Antioxidant defense, which is reduced by arthritis, activity of glucose 6-phosphate dehydrogenase, which is increased by arthritis in the liver, is also almost normalized.</td>
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<tr>
<td>5.</td>
<td>Singh et al., 2016</td>
<td>Experimental (in vitro study)</td>
<td>To assess post-translational modification of T1 and therapeutic regulation of epigallocatechin-3-gallate (EGCG) in rheumatoid arthritis (RA).</td>
<td>FLS isolated from human RA synovium</td>
<td>Administration of EGCG (50 mg/kg/day) for 10 days improved AIA by reducing TAK1 phosphorylation and K48 polyubiquilination.</td>
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<tr>
<td>6.</td>
<td>Lee et al., 2021</td>
<td>Experimental (in vitro and in vivo study)</td>
<td>To examine the hyaluronic acid-EGCG conjugate (HA-EGCG) as an anti-rheumatic agent capable of targeting synoviocytes such as fibroblasts through the HA-C44 interaction.</td>
<td>Human fibroblast-like synoviocytes (FLS) and mice as experimental animals</td>
<td>The conjugates exhibit superior anti-proliferative and anti-inflammatory activities compared to EGCG under simulated physiological conditions. Near-infrared fluorescence imaging revealed preferential accumulation of conjugates in inflamed joints in a mouse model of collagen-induced arthritis, and anti-rheumatic efficacy was investigated by measuring edema changes and histopathological scores.</td>
</tr>
</tbody>
</table>

**Catechin targets on cytokine IL-1β**

*U. gambir* Roxb is a plant native to Indonesia that contains high levels of catechins. The purity of the catechin isolates obtained 99.80% ± 0.132% using the chromatographic method [17]. Catechins are flavonoid compounds found in gambier, green tea, and several other plants and have been known to exhibit strong anti-inflammatory properties [18], [19]. I+−n RA there is an increase in the expression of IL-1β, TNF-α, and IL-6 in the synovial microenvironment contributing to joint pain, inflammation, and tissue damage. However, among these cytokines, the most important in the pathogenesis of RA is IL-1β [20].

Of the various types of catechins found in gambier plants, one of which is epigallocatechin-3-gallate (EGCG) has been known as a potent anti-inflammatory molecule in regulating IL-1β. Activation of these cytokines increases the production of IL-6 and chemokines as well as the activation of MMP-2 which plays a role in the activation of synovial fibroblasts (RA-FLS). Inhibition of IL-1β by EGCG through the Janus kinase (JNK) inhibitor pathway, p38, and nuclear factor-κB (NF-κB) [21]. IL-1β will induce the production of IL-6 and IL-8 which will stimulate osteoclasts, as well as MMP-2 which underlies the RA patho-mechanism. The results of the analysis showed that administration of EGCG even at nanomolar concentrations was effective in inhibiting IL-6-induced IL-1β (20–35%) and IL-8 (15–20%) [22].
Preclinical study of catechin for RA

Elevated levels of inflammatory cytokines, especially IL-6 and IL-8, TNF-α are pathways that underlie bone erosion. In vitro stem cell studies demonstrated that the viability and osteoblast differentiation of human bone marrow-derived mesenchymal stem cells were significantly inhibited by TNF-α. Moreover, the effect of low-dose EGCG was able to increase cell viability and osteoblast differentiation of mesenchymal stem cells and was able to reverse TNF-α-induced inhibition. The mechanism of TNF-α inhibition by EGCG occurs through inhibition of NF-κB signaling stimulated by TNF-α. So that these data can be used as a clinical basis for the use of EGCG in stem cell-based bone regeneration due to bone erosion in RA disease [27].

The protective role of EGCG on bone has been demonstrated in previous studies that there is a relationship between EGCG consumption and reduced fracture risk and improved bone health. Therefore, these data support the positive effect of EGCG on osteoblastic differentiation in general by increasing osteoblast differentiation and inhibiting the cytokine TNF-α which is expected to prevent bone damage in RA patients [28] (Figure 2 & Figure 3).

The chronic inflammatory process in patients with RA can cause signs of inflammation, especially in the joint area. The administration of catechin extract from gambir which was carried out on male white rats of the Sparague–Dawley strain showed satisfactory results, where it was found that there was a decrease in signs of inflammation in experimental animals. From an in vivo study, the administration of gambir catechin isolate could reduce the percentage of edema by 33.57% at the 6th h at a dose of 10 mg/kg BW. Inhibition of inflammation at a dose of 10 mg/kg BW is the best dose used for anti-inflammatory because its activity in reducing edema is comparable to the use of dichlorophenac sodium [29]. RA is a chronic inflammatory process and disease progression is also associated with an increase in reactive oxygen species (ROS) and oxidative stress in inflamed body parts. Because RA is a multisystem disease, this potentially damaging compound can damage other organs such as the liver, lungs, and blood vessels [30].

The flavonoid compounds from the catechin gambier extract will inhibit the lipooxygenase and cyclooxygenase pathways. By decreasing the synthesis of prostaglandins, it will reduce pain. Through this mechanism, it can increase cell viability and have an effect in reducing erythema when the inflammatory mechanism occurs [32]. A Catechin dose of 250 mg/kg (59.8 mg catechin per kg) for 23 days has been shown to reduce tissue ROS content and increase plasma antioxidant capacity. Arthritis increased the production of protein carbonyl (74%), ROS (72%), and TBARS (59.5%). The administration of catechins reduced these parameters to 56.9%, 44%, and 59%. So that the administration of catechins is able to stop the process of

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**Figure 3: Composition of isolates on Gambier [31]**

Recent studies on intracellular signaling pathways have identified the transforming growth factor-activated kinase 1 (TAK1) as a therapeutic target for inflammatory disease and cancer [23]. TAK1 is a mitogen-activated-protein-kinase-kinase-kinase that mediates the activation of MAPK (JNK and p38) and NF-kB pathways in response to IL-1β, TNF-α, or Toll-like receptors. TAK1 has been implicated in the regulation of various physiological and pathological processes. TAK1 functions through assembly with binding partners of TAK1-binding protein (TAB1, TAB2, and TAB3) and can be activated by various stimuli such as TNF-α, IL-1β, and toll-like receptor ligands, and they play an important role in NF-B and MAPKs activation [24]. It is known that by inhibiting TAK1 can completely inhibit the production of IL-6 and IL-8 cytokines induced by IL-β. Moreover, the results of the study found that EGCG can regulate TAK1 at therapeutic levels. The mechanism of EGCG in regulating TAK1 through inhibition of the p38, JNK, and NF-B pathways in RA-FLS was observed in many previous studies. Therefore, catechins in Gambier can be an alternative treatment of RA disease as an anti-inflammatory through the inhibition of IL-β cytokines [21].

Previous studies examining the effect of each of the catechins EGCG, EGC, and EC have different ways of inhibiting the cytokine IL-1β which regulates the expression of pro-inflammatory mediators (IL-6 and IL-8) and Cox-2 in humans. EGCG and EGC inhibited the production of IL-6, IL-8, and MMP-2 and selectively inhibited Cox-2 expression. EC showed no inhibitory effect. Meanwhile, all tested catechins can inhibit TAK-1 activity. Therefore, consumption of catechins has been shown to provide an overall anti-inflammatory effect [25]. The results of the study showed that EGCG was the most effective catechin in inhibiting the production of IL-6 and IL-8 by 59% and 57%, respectively (p < 0.05). Surprisingly, EC showed no inhibitory effect on IL-1β-induced IL-6 and IL-8 production, suggesting its limited role in anti-inflammatory effects [19], [25].
damage to other organs, especially the brain and liver due to chronic inflammation in RA [33]. According to the research of Saad et al. (2020), there are no reports on gambier toxicity studies, either in vitro studies or in vivo studies. So by considering this, the selection of gambier extract can be used as a candidate for palliative therapy in RA patients [31].

Conclusion

_U. gambier_ Roxb is a plant native to West Sumatra, Indonesia, and is widely used as an alternative medicine with various applications. Phytochemical and pharmacological studies have proven several functions of the gambier plant, especially on the role of catechin compounds. Through inhibition of various pathways, especially by suppressing the IL-1β cytokine and the role of catechins as anti-inflammatory and antiproliferative in both in vitro and in vivo studies, catechin extract from gambier can be used as an alternative therapy candidate in RA.

Meanwhile, by looking at the shortcomings of the unfavorable results of gambier processing, making gambier catechin for any medicinal purposes can increase the consumption of gambier so that it can be used as an applicable therapeutic in the community and further developed as a finished product in the industry.

References


