Scientific Foundation SPIROSKI, Skopje, Republic of North Macedonia
South East European Journal of Immunology. 2023 Apr 05; 6(1):92-97.
https://doi.org/10.3889/seejim.2023.6055
eISSN: 1857-9388
Category: *Review article*
Section: *Clinical Immunology*

OPEN ACCESS

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

Refa Rahmaddiansyah[1]*, Wahida Rahmi[2], Rauza Sukma Rita[3]

[1]*Medical Doctor Study Program, Department of Medicine, Faculty of Medicine, Universitas Andalas, Padang, Indonesia;* [2]*Medical Doctor Study Program, Department of Medicine, Faculty of Medicine, Universitas Andalas, Padang, Indonesia;* [3]*Department of Biochemistry, Faculty of Medicine, Universitas Andalas, Padang, Indonesia*

Edited by: Slavica Hristomanova-Mitkovska
Citation: Rahmaddiansyah R, Rahmi W, Rita RS. SEE J Immunol. 2023 Oct 21; 6(1):92-97. https://doi.org/10.3889/seejim.2023.6055
Keyword: Anti-inflammatory; Catechin; Gambier; Inflammation; Rheumatoid arthritis
***Correspondence:** Refa Rahmaddiansyah, Medical Doctor Study Program Department of Medicine, Faculty of Medicine, Universitas Andalas, 25175, Padang, Indonesia.
E-mail: refarahmad@gmail.com
Received: 30-Jul-2023
Revised: 17-Aug-2023
Accepted: 27-Sep-2023
Copyright: © 2023 Refa Rahmaddiansyah, Wahida Rahmi, Rauza Sukma Rita
Funding: This research did not receive any financial support
Competing Interests: The authors have declared that no competing interests exist
Open Access: This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (CC BY-NC 4.0)

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 flavanols/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

elderly. The prevalence rates reported in 2002 ranged from 0.5% to 1% of the population and have regional variations. This figure continues to grow, reports until 2020 it is known that the average prevalence of RA is 56/10,000. The prevalence of RA is higher in urban areas than in rural areas, indicating the impact of environmental differences [5].

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)

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

Table 1: Literature review matrix of study

No.	Author, Year	Research design	Research objective	Sample	Result
1.	Pitrityah, 2016	Experimental (*in vivo* study)	To determine the anti-inflammatory activity of gambir 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 carrageenan.	Dawley's sparague male rat	The effect of edema inhibition of gambier catechin isolates from all dosage variations showed a significant difference ($p \leq 0.05$) with the negative control. The dose of 10 mg/kg BW is the optimal dose.
2.	Fechtner *et al*., 2017	Experimental (*in vitro* study)	To assay EGCG (epigallocatechin-3-gallate), EGC (epigallocatechin), and EC (epicatechin) alone and in combination to study the impact on anti-inflammatory outcomes in human RASF and the underlying molecular mechanisms.	Human RA synovial tissue.	All types of catechins tested can inhibit TAK-1 activity. EGCG, EGC, and EC all occupy the active site of the TAK1 kinase domain. However, EGCG occupies most of the active site of TAK1. In addition to TAK1 inhibition, EGCG can also inhibit nuclear P38 and NF-κB expression whereas EC and EGC are not effective inhibitors.
3.	Liu *et al*., 2016	Experimental (*in vitro* study)	Assaying EGCG would promote osteogenic differentiation in bone marrow isolated human MSCs (BM-hMSCs) and to identify potential interactions between EGCG and TNF-α in this setting.	Human MSCs isolated from bone marrow (BM-hMSCs)	EGCG promoted osteogenic differentiation only at lower doses (5 and 10 mM), with no effect at higher doses (20 and 40 mM). In the presence of low-dose EGCG (5 mM), TNFa could no longer block osteogenic differentiation of BM-hMSCs, indicated by ALP activity, mineralized nodule formation, Run×2 expression, and Osterix.
4.	Goncalves *et al*., 2015	Experimental (*in vivo* study)	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.	Male Holtzman rats	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.
5.	Singh *et al*., 2016	Experimental (*in vitro* study)	To assess post-translational modification of T1 and therapeutic regulation of epigallocatechin-3-gallate (EGCG) in rheumatoid arthritis (RA).	FLS isolated from human RA synovium	Administration of EGCG (50 mg/kg/day) for 10 days improved AIA by reducing TAK1 phosphorylation and K48 polyubiquitination.
6.	Lee *et al*., 2021	Experimental (*in vitro* and *in vivo* study)	To examine the hyaluronic acid-EGCG conjugate (HA-EGCG) as an anti-rheumatic agent capable of targeting synoviocytes such as fibroblasts through the HA-CD44 interaction.	Human fibroblast-like synoviocytes (FLS) and mice as experimental animals	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.

TAK1: Transforming growth factor-activated kinase.

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.

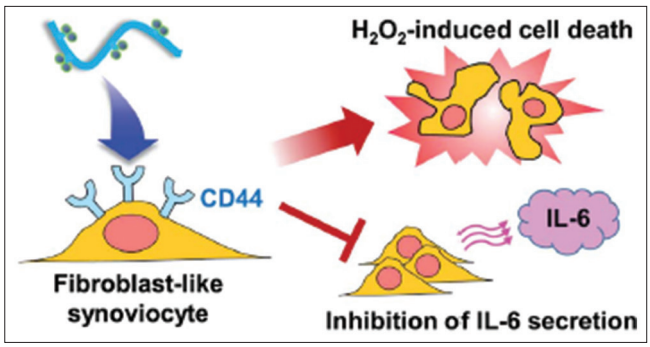

Figure 2: Inhibitory mechanism of catechin on IL-6 [26]

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-kB) [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].

Compound	Class	Extract	Plant part
(+)-Catechin	Flavonoid	Aqueous	Leaf and young twig
		Aqueous	Leaf and young twig
		Aqueous	Leaf
		Aqueous	Leaf
		Methanol	Leaf
(-)-epicatechin	Flavonoid	Aqueous	Leaf and young twig
		Aqueous	Leaf and young twig
Gambiriin A_1, A_2, A3, B1, B_2, B_3	Flavonoid	Aqueous	Leaf and young twig
Gambiirin C	Flavonoid	Aqueous	Leaf and young twig
		Aqueous	Leaf and young twig
Gambiriin A_1, A_2, B_1, B_2	Flavonoid	Aqueous	Leaf and young twig
Procyanidin B1, B3			
Gambirine	Flavonoid	Aqueous	Leaf and young twig
		Aqueous	Leaf
		Ethanol	Leaf
		Methanol	Leaf
Isogambirine	Flavonoid	Aqueous	Leaf and young twig
		Aqueous	Leaf
		Ethanol	Leaf
		Methanol	Leaf
		Methanol	Leaf
Quercetin	Flavonoid	Aqueous	Leaf
		Aqueous	Leaf
Roxburghine A, B, C, D, E	Alkaloid	Aqueous	Leaf
Gambirtannine	Alkaloid	Methanol	Powdered gambir
Dihydrogambirtannine			
Oxogambirtannine			
Neooxygambirtannine			

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].

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-kB 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 gambier 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 dichlorofenac 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

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

1. Hák T, Janoušková S, Moldan B. Sustainable development goals: A need for relevant indicators. Ecol Indic. 2016;60:565-73.
2. World Health Organization. Noncommunicable Diseases. World Health Organization; 2021. Available from: https://www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases [Last accessed on 2022 Mar 25].
3. Grabowski D, Aagaard-Hansen J, Willaing I, Jensen BB. Global Action Plan for the Prevention and Control of non Communicable Diseases. Vol. 1. Geneva: WHO Press, World Health Organization; 2013.
4. England BR, Roul P, Yang Y, Kalil AC, Michaud K, Thiele GM, *et al*. Risk of COVID-19 in rheumatoid arthritis: A national veterans affairs matched cohort study in at-risk individuals. Arthritis Rheumatol. 2021;73(12):2179-88. https://doi.org/10.1002/art.41800
   PMid:33955209
5. Almutairi KB, Nossent JC, Preen DB, Keen HI, Inderjeeth CA. The prevalence of rheumatoid arthritis: A systematic review of population-based studies. Ann Rheum Dis. 2020;79(Suppl 1):1246-73.
6. Guo Q, Wang Y, Xu D, Nossent J, Pavlos NJ, Xu J. Rheumatoid arthritis: Pathological mechanisms and modern pharmacologic therapies. Bone Res. 2018;6:15. https://doi.org/10.1038/s41413-018-0016-9
   PMid:29736302
7. Bykerk VP, Akhavan P, Hazlewood GS, Schieir O, Dooley A, Haraoui B, *et al*. Canadian rheumatology association recommendations for pharmacological management of rheumatoid arthritis with traditional and biologic disease-modifying antirheumatic drugs. J Rheumatol. 2012;39(8):1559-82. https://doi.org/10.3899/jrheum.110207
   PMid:21921096
8. Cho SK, Kim D, Won S, Lee J, Choi CB, Choe JY, *et al*. Factors associated with time to diagnosis from symptom onset in patients with early rheumatoid arthritis. Korean J Intern Med. 2019;34(4):910-6. https://doi.org/10.3904/kjim.2017.113
   PMid:29232938
9. Bakker MF, Jacobs JW, Welsing PM, Verstappen SM, Tekstra J, Ton E, *et al*. Low-dose prednisone inclusion in a methotrexate-based, tight control strategy for early rheumatoid arthritis: A randomized trial. Ann Intern Med. 2012;156(5):329-39. https://doi.org/10.7326/0003-4819-156-5-201203060-00004
   PMid:22393128
10. Heimans L, Wevers-de Boer KV, Visser K, Goekoop RJ, van Oosterhout M, Harbers JB, *et al*. A two-step treatment strategy trial in patients with early arthritis aimed at achieving remission: The IMPROVED study. Ann Rheum Dis. 2014;73(7):1356-61. https://doi.org/10.1136/annrheumdis-2013-203243
    PMid:23716067
11. Tobing IS, Sukara E. Biodiversity based industry, the future of Indonesia. Vis Vitalis. 2008;1(2):1-12.
12. Hosen N, Pengkajian B, Pertanian T, Barat BS. Gambir Agricultural Business System Profile in West Sumatra. J Penelit Pertan Terap. 2017;17(2):124-31. https://doi.org/10.25181/jppt.v17i2.291
13. Haryanto S. Encyclopedia of Indonesian Medicinal Plants. Vol. 2. Yogyakarta: Pallmall; 2009.
14. Karatas A, Dagli AF, Orhan C, Gencoglu H, Ozgen M, Sahin N, *et al*. Epigallocatechin 3-gallate attenuates arthritis by regulating Nrf2, HO-1, and cytokine levels in an experimental arthritis model. Biotechnol Appl Biochem. 2020;67(3):317-22. https://doi.org/10.1002/bab.1860
    PMid:31746064
15. Aditya M, Ariyanti PR. Benefits of gambir (*Uncaria gambir* Roxb) as an antioxidant. J Kedok Univ Lampung Majority. 2016;5(3):129-33.
16. Abner EL, Schmitt FA, Mendiondo MS, Marcum JL, Kryscio RJ. Vitamin E and All-cause mortality: A meta-analysis. Curr Aging Sci. 2012;4(2):158-70. https://doi.org/10.2174/1874609811104020158
    PMid:21235492
17. Yunarto N, Intan PR, Kurniatri AA, Sulistyowati I, Aini N. Anti-inflammatory activities of ethyl acetate fraction from *Uncaria gambir* leaves through the inhibition of edema, COX-2 and iNOS Expression. 2020;22(Ishr 2019):108-12.
18. Fan FY, Sang LX, Jiang M. Catechins and their therapeutic benefits to inflammatory bowel disease. Molecules. 2017;22(3):484. https://doi.org/10.3390/molecules22030484
    PMid:28335502
19. Nakanishi T, Mukai K, Yumoto H, Hirao K, Hosokawa Y, Matsuo T. Anti-inflammatory effect of catechin on cultured human dental pulp cells affected by bacteria-derived factors. Eur J Oral Sci. 2010;118(2):145-50. http://doi.org/10.1111/j.1600-0722.2010.00714.x
    PMid:20487003
20. Dinarello CA, van der Meer JW. Treating inflammation by blocking interleukin-1 in humans. Semin Immunol. 2013;25(6):469-84. https://doi.org/10.1016/j.smim.2013.10.008
    PMid:24275598
21. Singh AK, Umar S, Riegsecker S, Chourasia M, Ahmed S, Egcg B. Regulation of transforming growth factor β-Activated kinase activation by epigallocatechin-3-gallate in rheumatoid

arthritis synovial fibroblasts: Suppression of K63-Linked autoubiquitination of tumor necrosis factor receptor-associated factor 6. Arthritis Rheumatol. 2016;68(2):347-58.

22. Zheng Y, Xiao L, Yu C, Jin P, Qin D, Xu Y, *et al*. Enhanced antiarthritic efficacy by nanoparticles of (-)-epigallocatechin gallate-glucosamine-Casein. J Agric Food Chem. 2019;67(23):6476-86. https://doi.org/10.1021/acs.jafc.9b02075
PMid:31117504
23. Iriondo O, Liu Y, Lee G, Elhodaky M, Jimenez C, Li L, *et al*. TAK1 mediates microenvironment-triggered autocrine signals and promotes triple-negative breast cancer lung metastasis. Nat Commun. 2018;9(1):1994. https://doi.org/10.1038/s41467-018-04460-w
PMid:29777109
24. Xu YR, Lei CQ. TAK1-TABs complex: A central signalosome in inflammatory responses. Front Immunol. 2021;11:608976. https://doi.org/10.3389/fimmu.2020.608976
PMid:33469458
25. Fechtner S, Singh A, Chourasia M, Ahmed S. Molecular insights into the differences in anti-inflammatory activities of green tea catechins on IL-1β signaling in rheumatoid arthritis synovial fibroblasts. Toxicol Appl Pharmacol. 2017;329:112-20. https://doi.org/10.1016/j.taap.2017.05.016
PMid:28532672
26. Lee F, Bae KH, Ng S, Yamashita A, Kurisawa M. Hyaluronic acid-green tea catechin conjugates as a potential therapeutic agent for rheumatoid arthritis. RSC Adv. 2021;11(24):14285-94. https://doi.org/10.1039/d1ra01491a
PMid:35423998
27. Liu W, Fan JB, Xu DW, Zhang J, Cui ZM. Epigallocatechin-3-gallate protects against tumor necrosis factor alpha induced inhibition of osteogenesis of mesenchymal stem cells. Exp Biol Med (Maywood). 2016;241(6):658-66. https://doi.org/10.1177/1535370215624020
PMid:26748399
28. Chen CH, Ho ML, Chang JK, Hung SH, Wang GJ. Green tea catechin enhances osteogenesis in a bone marrow mesenchymal stem cell line. Osteoporos Int. 2005;16(12):2039-45. https://doi.org/10.1007/s00198-005-1995-0
PMid:16170444
29. Pitrityah P. Activity Test of Gambier Catechin Isolate (*Uncaria gambir* Roxb) Against Carrageenan-Induced Sparague-Dawley Strain Male White Rat Leg Edema. Fakultas Kedokteran dan Ilmu Kesehatan Program Studi Farmasi. Vol. 1. Jakarta: Universitas Islam Negeri; 2016. Available from: https://repository.uinjkt.ac.id/dspace/handle/123456789/34197 [Last accessed on 2023 Feb 22].
30. Mateen S, Moin S, Khan AQ, Zafar A, Fatima N. Increased reactive oxygen species formation and oxidative stress in rheumatoid arthritis. PLoS One. 2016;11(4):e0152925. https://doi.org/10.1371/journal.pone.0152925
PMid:27043143
31. Mat Saad MF, Goh HH, Rajikan R, Tuan Yusof TR, Baharum SN, Bunawan H. *Uncaria gambir* (W. Hunter) Roxb: From phytochemical composition to pharmacological importance. Trop J Pharm Res. 2020;19(8):1767-73.
32. Maleki SJ, Crespo JF, Cabanillas B. Anti-inflammatory effects of flavonoids. Food Chem. 2019;299:125124. https://doi.org/10.1016/j.foodchem.2019.125124
PMid:31288163
33. de Almeida Gonçalves G, de Sá-Nakanishi AB, Wendt MM, Comar JF, Bersani Amado CA, Bracht A, *et al*. Green tea extract improves the oxidative state of the liver and brain in rats with adjuvant-induced arthritis. Food Funct. 2015;6(8):2701-11. https://doi.org/10.1039/c5fo00548e
PMid:26146010