Phytochemical and Anti-Inflammatory of *Uncaria gambir*: A Review

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**ABSTRACT**

Inflammation occurs because of a response to tissue injury, cell death, cancer, ischemia, and degeneration. *Uncaria gambir* is one of the pharmacological solutions in overcoming inflammation. *U. gambir* has traditionally been used as a febrifuge, pain reliever, anti-inflammatory, antioxidant, and burn wound healing. The purpose of this paper is to present knowledge of the phytochemical and anti-inflammatory properties of *U. gambir*. This review provides literature evidence from 2011 to 2021. Three search sources were used as literature review sources (Pub Med, Science Direct, and Google Scholar). 13 articles in this review were based on our eligibility criteria. Pharmacological studies reported that *U. gambir* had been shown to have anti-inflammatory activity by reducing the volume of edema, inhibiting the enzymes COX-1, COX-2, 5-LOX, and iNOS. The phytochemical compounds contained in *U. gambir* were flavonoids, phenolics, polyphenols, catechins, spirooxylopropane rings, proanthocyanidins, alkaloids, epicatechins, and caffeic acid, which were distributed in leaves, trunk, bark, shoots, stems, and gambir.

**Keywords:** Anti-inflammatory, uncaria, pharmacology, phytochemistry

**ARTICLE INFO:** Received: 14 Sept. 2021 Review Complete: 20 Jan. 2022 Accepted: 11 Feb. 2022 Available online: 15 Feb. 2022

**Cite this article as:** Fia Rizka Auliana, Ifora Ifora, Fitra Fauziah, Phytochemical and Anti-Inflammatory of *Uncaria gambir*: A Review, Asian Journal of Pharmaceutical Research and Development. 2022; 10(1):75-78. DOI: [http://dx.doi.org/10.22270/ajprd.v10i1077](http://dx.doi.org/10.22270/ajprd.v10i1077)

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**INTRODUCTION**

Inflammation was a protective response after infection or injury. This inflammatory process was characterized by redness, heat, swelling, and pain. In inflammation, free radical compounds are produced, which can cause tissue damage and trigger the biosynthesis of arachidonic acid into prostaglandins as mediators of inflammation. The inflammatory response that occurs in the body was characterized by the release of various inflammatory mediators, such as pro-inflammatory cytokines such as Interleukin-1 (IL-1), Tumor Necrosis Factor-α (TNF-α), Interferon (INF)-γ, IL-6, IL-12, and IL-18. The drugs commonly used to treat anti-inflammatory drugs are non-steroidal anti-inflammatory drugs (NSAIDs). Long-term use of NSAIDs causes side effects such as gastrointestinal (GI), kidney toxicity, luminal ulceration, intestinal disorders, mucosal and cardiovascular bleeding. Because clinical use in the long term can be dangerous, it is urgently needed to search for safer compounds that can act as anti-inflammatory agents without causing adverse side effects. The community is increasingly using traditional medicine to fight inflammation and minimize treatment’s side effects using synthetic drugs. Previous studies found different plants have different therapeutic activities, including anti-inflammatory. *Uncaria gambir* comes from the family of Rubiaceae. Indonesia is the largest producer of *gambir* globally, but it has not been developed optimally. The community has widely used *U. gambir* as a traditional medicine to treat various diseases such as gout, fever, diabetes, diarrhea, headaches, colds, and coughs. The main content of *U. gambir*, which has many benefits, is catechin, a flavonoid group.

However, only a tiny part of *U. gambir* has been investigated and confirmed as an anti-inflammatory. This paper aims to provide recent studies on phytochemicals and the anti-inflammatory properties of *U. gambir*.
METHODS
The method used by researchers in this paper is a literature review study. Plant names were verified using www.theplantist.org. This study was conducted to find evidence in the literature on phytochemical and anti-inflammatory activity in vitro or in vivo in U. gambir from 2011 to 2021. In making this review, data search using online media was done with the following keywords: “Phytochemistry”, “Phytochemical”, “Bioactive Compound”, “Anti-inflammatory”, and “Uncaria gambir”. The most recent information on U. gambir is collected from scientific journals accepted worldwide through the electronic search of PubMed, ScienceDirect, and Google Scholar. The articles reviewed in this study are original articles or research articles published in Indonesian and English. Articles in the form of books, review articles, systematic reviews, meta-analysis, short communication, newsletters, and expert opinions are not included in this review. Complete articles were collected, examined, summarized, and concluded.

RESULT AND DISCUSSION
The literature study on phytochemicals and anti-inflammatory U. gambir used 13 articles, of which 10 articles about the phytochemicals and 3 articles about anti-inflammatory of U. gambir.

Phytochemical
The chemical compounds in U. gambir have a high usefulness value because they have natural and potential phytochemical compounds in all parts, like leaves, trunk, bark, shoots, stems, and gambir. Potential phytochemical components found and proven include flavonoids, phenolics, polyphenols, catechins, spiroxylopropane rings, proanthocyanidins, alkaloids, epicatechins, and caffeic acid. Therefore U. gambir has many health benefits. Anggraini et al. investigated the effect of extraction of gambir catechins using the Ultrasonic Assisted Extraction (UAE) method/ultrasonic extraction with water solvent as seen at the extraction time for 30, 60, 90, and 120 minutes. This study proved that the extract of U. gambir, which was extracted for 90 minutes, produced the best polyphenol content 5.077 mg/ml, the levels of catechin compounds in the extract of U. gambir obtained were 933.45 µg/g. It was proven that it did not contain epigallocatechin. This ultrasonic immersion method can be practical, environmentally friendly, and avoid harmful chemicals. 16.

The identification of phytochemical compounds in the wood and bark of the bajakah was carried out by Paramita et al., using the GC-MS pyrolysis method and the folin-ciocalteu method to identify flavonoid compounds and total phenols. Bajakah is a wood-liana for traditional medicine by the Dayak and Banjar in Central Kalimantan. Three bajakah, which were identified were Salacia sp, Uncaria acida and Uncaria gambir. The results showed that U. acida had the highest total phenol and flavonoid content (0.013% and 0.028%), followed by U. gambir (0.0126% and 0.0275%) and Salacia sp (0.0123 and 0.0271) 17.

The study by Sakti et al. carried out a phytochemical screening to see the content of alkaloids and flavonoids in the ethanol extract and chloroform extract from the leaves of U. gambir and Uncaria sclerophylla. Qualitative tests were carried out using the Dregendorff method to identify alkaloids and the Shinoda test to identify flavonoids. Quinine was used as a positive control of alkaloids and catechin as a positive control of flavonoids. The total phenolic content of ethanolic extracts and chloroform extracts from the leaves of U. gambir and U. sclerophylla were determined using Folin-Ciocalteu reagent following Pratami et al. 18.

The results of screening both U. gambir and U. sclerophylla leaves were proven to contain alkaloids. The chloroform extract showed the presence of alkaloids, while the ethanol extract showed negative results. The KLT profile revealed the presence of catechin compounds in the ethanolic extracts, while the chloroform extract did not show the presence of catechin compounds. The total phenolic content of ethanolic extract and chloroform extract in U. gambir and U. sclerophylla leaves was 7.309: 5.734 and 0.437: 0.161 mg gallic acid equivalent for each sample. 19.

A study conducted by Musdja et al. reported that the extract of Uncaria gambir contains catechins (85.3%), flavonoids, phenolics, and saponins as measured using a UV-VIS spectrophotometer. 20. In a study, Kim et al. did isolation of a new derivative of prenyl resorcinol with seven known compounds, namely two flavone glycosides, three analog catechins, and two simple phenolics. The structure of the isolated compounds was determined by data analysis and spectroscopy. 21.

The determination of catechin levels in the leaves and stems of U. gambir carried out by Ibrahim et al. in hexane, dichloromethane, and methanol solvents using the HPLC-DAD method reported that higher catechin content was obtained in the methanol extract of the leaves, namely 8.64% and the stems, which was 5.12%. However, the dichloromethane extract was 0.77% in the leaves and 0.92% in the stem 22. Kardel et al. investigated the tannin content in U. gambir determined by the butanol/HCL method and the Folin-Ciocalteu method. The tannin levels found in U. gambir were thick tannins (43.1 g/kg) and total phenol (675.1 g/kg) 23.

In addition, Amir et al. also reported that the results of the initial phytochemical screening of the methanol extract of U. gambir were the most prominent, namely the flavonoids and tannins. The overall components of the phytochemical screening results of U. gambir methanol extract are alkaloids, sterols, carbohydrates, phenolics, flavonoids, resins, proteins, and amino acids. The total phenolic content of U. gambir extract (18.37+2.79) mg was equivalent to gallic acid (GAE)/G dry weight using the Folin-Ciocalteu colorimetric method. The total flavonoid content found in the extract of U. gambir was (5.82+2.23) using aluminium in the chlorimetric method. 24.

In a research conducted by Anggraini et al reported a comparison of the polyphenol content and catechin content of the four types of U. gambir from siguntur, West Sumatra, namely Gambir cubadak (GC), Gambir udang (GU), Gambir riau mancik (GRm), and Gambir riau gadang (GRg). The total polyphenol content of the four types of U. gambir, is as follows Gambir cubadak (13.86 g/100g), Gambir udang (13.60 g/100g), Gambir riau mancik (13.58 g/100g), and Gambir riau gadang (12.60 g/100g).
g/100g), and Gambir riau gadang (13.90 g/100g). The catechin content of the four types of U. gambir is as follows: Gambir cubadak (104.5 µg/mL), Gambir udang (101.2 µg/mL), Gambir riau mancik (99.4 µg/mL) and Gambir riau gadang (108 µg/mL). The epicatechin content of the four types of U. gambir is as follows: Gambir cubadak (0.80 µg/mL), Gambir udang (0.62 µg/mL), Gambir riau mancik (0.49 µg/mL) and Gambir riau gadang (0.74 µg/mL). Of the four types of Uncaria gambir containing caffeic acid, only Gambir cubadak (0.99 µg/mL) and Gambir riau mancik (0.98 µg/mL) were not detected, while in Gambir udang and Gambir riau gadang were not detected. Among the four types of U. gambir, it showed the presence of catechin, epicatechin and caffeic acid compounds.

Likewise, Kassim et al. analyzed total phenol levels, condensed tannins, flavonoids, and antioxidant activity of UP3005, which is a combination of two extracts, leaves U. gambir and root bark Morus alba (1:1). In vitro study showed the enzymatic inhibitory activity of UP3005 on the activity of cyclooxygenase-1 (COX-1), COX-2, and lipoxygenase (5-LOX) enzymes with IC\textsubscript{50} values of 12.4 µg/mL, 39.8 µg/mL, and 13.6 µg/mL. Similarly, the study conducted by Yunarto et al. in this study, the researcher observed the expression of COX-2 and iNOS in vitro. Inhibition COX-2 and iNOS expression were determined by enzyme-linked immunosorbent assay. The most significant inhibition of the COX-2 and iNOS enzyme activity of gambir leaf extract was at dose III (20 mg/kg BW fraction), which was able to inhibit the activity of COX-2 (64.49% ± 6.71%) and iNOS (37.95 ± 0.12%) compared to the control positive (sodium diclofenac 50 mg/kg bw).

### Table 1: Summary on Bioactive Compounds of Uncaria Gambir

| Compounds                        | Parts                  | Country   | References |
|----------------------------------|------------------------|-----------|------------|
| Catechins, polyphenols           | Gambir                 | Indonesia | 21         |
| Flavonoids, phenolic             | Trunk, bark            | Indonesia | 17         |
| Alkaloids, flavonoids, catechins | Leaves                 | Indonesia | 23         |
| Catechins, flavonoids, saponins  | Gambir                 | Indonesia | 20         |
| Prenyl resorcinol derivatives    | Gambir                 | Japan     | 24         |
| Catechins                        | Leaves, stems          | Malaysia  | 22         |
| Tannins                          | Leaves                 | Germany   | 24         |
| Flavonoids, alkaloids, phenolics | Leaves, shoots         | India     | 24         |
| Polyphenols, catechins, epicatechins, caffeic acid | Stems | Indonesia | 25         |
| Flavonoids                       | Gambir                 | Indonesia | 20         |

### Anti-Inflammatory Activity

U. gambir has many pharmacological activities, so it has many benefits for the body. The anti-inflammatory activity of U. gambir has been proven in vitro and in vivo studies. A total of 3 research studies have been conducted, and the results of these studies are summarized in table 2.

#### In vitro studies

Yimam et al. conducted a study on the anti-inflammatory effect of UP3005, which is a combination of two extracts, leaves U. gambir and root bark Morus alba (1:1). In vitro study showed the enzymatic inhibitory activity of UP3005 on the activity of cyclooxygenase-1 (COX-1), COX-2, and lipoxygenase (5-LOX) enzymes with IC\textsubscript{50} values of 12.4 µg/mL, 39.8 µg/mL, and 13.6 µg/mL.

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#### In vivo studies

A study by Yimam et al. reported the anti-inflammatory and analgesic effect of UP3005 containing a standard blend of two extracts from the leaves of U. gambir and the root bark of Morus alba in a ratio of 1:1 on the anti-inflammatory effect test by carrageenan-induced rat paw edema method. The highest dose of 300 mg reduced inflammation by 53.7%, 55.3%, and 48.8%, observed at 1 hour, 3 hours, and 5 hours. Thus, the anti-inflammatory activity at the highest dose of 300 mg was comparable to the positive control of ibuprofen with inhibition percentages of 52.5%, 62.9%, and 51.6%.
Table 2: Anti-Inflammatory Activities of Uncaria gambir

| Type of extract or Formulation | Plant part and source used for studies | Dose/ Concentration | Experimental Mode | Animal/ disease models/ cell/ specimen | Reported activity | Region | Ref. |
|--------------------------------|---------------------------------------|---------------------|-------------------|---------------------------------------|-------------------|--------|------|
| Ethanol extract               | Leaves                                | 20 µl (COX-1, COX-2) 10 µl (5-LOX) | The COX-5/LOX Colorimetric Inhibitor Screening Assay | Extract of Uncaria gambir and root bark of Morus alba showed anti-inflammatory activity mainly through inhibition of cyclooxygenase-1 (COX-1), COX-2, and lipooxygenase (5-LOX) enzymes | Korea | 27 |
| Ethyl acetate fraction        | Leaves                                | 5, 10, 20 mg/kg BW | COX2/iNOS inhibitor screening assay (enzyme-linked immunosorbent assay) | Ethyl acetate fraction in Uncaria gambir at all doses has an anti-inflammatory effect by inhibiting the enzymes COX-2 and iNOS expression | Indonesia | 26 |
| Ethanol extract               | Leaves                                | 100, 200, 300 mg/kg BW | Carrageenan induced paw edema | Extract of Uncaria gambir and root bark of Morus alba showed anti-inflammatory activity through reduction in paw edema | Korea | 27 |
| Ethyl acetate                 | Gambir                                | 1, 10, 100 mg/kg BW | Carrageenan induced paw edema | Wistar male rats | Ethyl acetate extract Uncaria gambir showed an anti-inflammatory effect through decreased paw edema | Indonesia | 27 |
| Ethyl acetate fraction        | Leaves                                | 5, 10, 20 mg/kg BW | Carrageenan induced paw edema | White wistar strain rats | Ethyl acetate fraction in Uncaria gambir at all doses exhibit an anti-inflammatory effect through reducing inflammation, COX-2, and iNOS expression | Indonesia | 26 |

Anti-inflammatory assays were carried out by Musdja et al. with catechin isolates in U. gambir with doses of 1, 10, and 100 mg/kg BW given orally to male Wistar rats. The catechin isolate in gambir was tested for anti-inflammatory activity in carrageenan-induced rat paw edema. This study reported that the best dose in inhibiting edema in the feet of rats was 100 mg/kg BW with a concentration of 59.19%, while for a dose of 1 mg/kg BW with a concentration of 13.98% and 10 mg/kg BW with a concentration of 3.57% had a lower anti-inflammatory effect in inhibiting edema in rat feet.

Similar to previous studies, Yunarto et al. tested the anti-inflammatory activity using 25 white Wistar rats, which were divided into five groups, i.e., negative group, the positive group (diclofenac sodium 50 mg/kg BW), the dose I (5 mg /kg BW), dose II (10 mg/kg BW) and dose group III (20 mg/kg BW). Each treatment animal was given orally for 30 minutes previously induced by 0.1 ml of 3% carrageenan. A plethysmometer measured foot volume for seven days after carrageenan injection. The dose with the highest potential anti-inflammatory activity is at dose III, with the most significant percentage inhibition of edema at 28.12% in the first hour and continues to increase until the fourth hour, which can inhibit edema 50.12%. Dose III also inhibited the activity of COX-2 (64.49 ± 6.71%) and iNOS (37.95 ± 0.12%); it has the highest potential for anti-inflammatory activity.

**CONCLUSIONS**

U. gambir has many benefits among the community as traditional medicine. Studies on the chemical components of U. gambir have shown that all parts of the plant contain many active substances, such as flavonoids, phenolics, polyphenols, catechins, spiroxylopropene rings, proanthocyanidins, alkaloids, epicatechins, and caffeic acid, which were the main compounds of U. gambir are catechins. All previous research studies on phytochemical compounds in U. gambir reported that U. gambir contained catechins with <50% levels found in plant parts such as leaves, trunk, bark, shoots, stems, and gambir.

The substances in U. gambir have played a role in anti-inflammatory activity. Through studies carried out in vivo and in vitro, U. gambir was reported to have the ability to regulate various inflammatory mediators such as inhibiting COX-1, COX-2, 5-LOX, & iNOS enzymes, which can reduce edema volume. This confirms that U. gambir has the potential as an anti-inflammatory.

However, further research needs to be done to ascertain its anti-inflammatory activity in the future by understanding metabolism in the body and receptor interactions associated with inflammation. Other studies of the activity of U. gambir should provide a clear source of the specifications for the ingredients used, especially when plant extracts were used.
ACKNOWLEDGMENTS

The authors would like to thank our colleagues at the Department of Pharmacology and Clinical Pharmacy, School of Pharmaceutical Sciences Padang for the useful discussion.

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