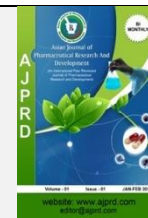


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Review Article

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, spiroxylopropane rings, proanthocyanidins, alkaloids, epicatechins, and caffeic acid, which were distributed in leaves, trunk, bark, shoots, stems, and gambir.

Keywords: Anti-inflammatory, uncaria, pharmacology, phytochemistry

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INTRODUCTION

Inflammation was a protective response after infection or injury¹. This inflammatory process was characterized by redness, heat, swelling, and pain². 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-18³. 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 bleeding⁴⁻⁶. 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^{7,8}.

Previous studies found different plants have different therapeutic activities, including anti-inflammatory⁹⁻¹². *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 coughs¹³⁻¹⁵. 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/mg. It was proven that it did not contain epigallocatechin. This ultrasonic immersion method can be practical, environmentally friendly, and avoid harmful chemicals¹⁶.

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 was *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 Dreagendorff 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 extract, while the chloroform extract did not show the presence of catechin compounds. The total phenolic content of ethanol 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 sample¹⁹.

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 spectrophotometer²⁰. 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 spectroscopy²¹.

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 stem²². 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 method²⁴.

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 (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 compounds²⁵.

Likewise, Kassim *et al.* analyzed total phenol levels, condensed tannins, flavonoids, and antioxidant activity

using three kinds of solvent extracts from *U. gambir*. The quantitative analysis methods used are Fourier Transform Infra-Red (FTIR) and High-Performance Liquid Chromatography (HPLC). This study reported that there were differences in the total phenolic content of each solvent where ethyl acetate extract solvent had the highest total phenolic content (113.43 mg/g) followed by methanol extract (99.25 mg/g) and aqueous extract (76.75 mg/g). The total flavonoid content in the three solvents is as follows: ethyl acetate extract solvent contained (93.31 mg) followed by methanol extract (70.94 mg) and aqueous extract (60.85 mg). Ethyl acetate extract in *gambir* obtained the highest catechin content (87.33% wt), followed by methanol extract (59.47% wt) and aqueous extract (47.75% wt). Characteristic tests using FTIR revealed that most functional groups were almost identical to standard catechins²⁶.

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

Compounds	Parts	Country	References
Catechins, polyphenols	Gambir	Indonesia	16
Flavonoids, phenolic	Trunk Bark	Indonesia	17
Alkaloids, flavonoids, catechins	Leaves	Indonesia	19
Catechins, flavonoids, saponins	Gambir	Indonesia	20
Prenyl resorcinol derivatives (spiroxyloropropane ring)	Gambir	Japan	21
Catechins	Leaves, stems	Malaysia	22
Tannins	Leaves	Germany	23
Flavonoids, alkaloids, phenolics	Leaves, shoots	India	24
Polyphenols, catechins, epicatechins, caffeic acid	Stems	Indonesia	25
Flavonoids	Gambir	Indonesia	26

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 IC₅₀ values of 12.4 µg/mL, 39.8 µg/mL, and 13.6 µg/mL²⁷.

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)²⁸.

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%²⁷.

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.
<i>In Vitro Study</i>							
Ethanol extract	Leaves	20 µl (COX-1,COX-2) 10 µl (5-LOX)	The COX/5-LOX Colorimetric Inhibitor Screening Assay	-	Extract of <i>Uncaria gambir</i> and root bark of <i>Morus alba</i> showed anti-inflammatory activity mainly through inhibition of cyclooxygenase-1 (COX-1), COX-2, and lipoxigenase (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 <i>Uncaria gambir</i> at all doses has an anti-inflammatory effect by inhibiting the enzymes COX-2 and iNOS expression.	Indonesia	²⁸
<i>In Vivo Study</i>							
Ethanol extract	Leaves	100, 200, 300 mg/kg BW	Carrageenan induced paw edema	Female Lewis rats	Extract of <i>Uncaria gambir</i> and root bark of <i>Morus alba</i> 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 <i>Uncaria gambir</i> showed an anti-inflammatory effect through decreased paw edema	Indonesia	²⁹
Ethyl acetate fraction	Leaves	5, 10, 20 mg/kg BW	Carrageenan induced paw edema	White wistar strain rats	Ethyl acetate fraction in <i>Uncaria gambir</i> at all doses exhibit an anti-inflammatory effect through reducing inflammation, COX-2, and iNOS expression.	Indonesia	²⁸

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 33.57% had a lower anti-inflammatory effect in inhibiting edema in rat feet ²⁹.

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 ²⁸.

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, spiroxylopropane 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.

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