J Prima Med Sains (2025) 7(1):54-60
doi.org/10.34012/jpms.v7i1.6581

REVIEW

Medicinal potential of gambier extract for recurrent aphthous stomatitis treatment

Nurfitri Amaliah[1]*, Muhammad Yamin Saud[2]

ABSTRACT

Recurrent aphthous stomatitis (RAS) remains as one of the most common disorders in the oral cavity. Various treatment options for RAS conditions include topical, systemic, and the use of traditional ingredients that have pharmacological content. One of the plants known to have good pharmacological content for RAS treatment is gambier (Uncaria Gambier). Gambir plant extract is known to have various benefits for health, including in the management of RAS due to the active ingredient compounds in the form of anti-inflammatory, antioxidant and antibacterial properties. One of the active compounds possessed by gambier plant extract in the form of catechine is proven to have the ability to reduce inflammation and help to accelerate the healing process in RAS cases.

Keywords: gambier plant, recurrent aphthous stomatitis, treatment

INTRODUCTION

The global interest in plant-derived alternative medicine continues to grow, particularly for its potential in complementing conventional therapies.[1,2] Many medicinal plants contain bioactive secondary metabolites with antimicrobial, anti-inflammatory, and wound-healing properties.[3,4] One such plant is *Uncaria gambir* Roxb., or gambier, indigenous to Southeast Asia, especially Indonesia and Malaysia.[5,6] Traditionally used to treat wounds, ulcers, respiratory conditions, and oral diseases, gambier is rich in catechins and tannins compounds with well-documented antimicrobial and anti-inflammatory effects.[5,6,8] Recurrent aphthous stomatitis (RAS) is a common inflammatory condition of the oral mucosa marked by painful, recurring ulcers.[9,10] Current treatment strategies aim to reduce pain, accelerate healing, and prevent recurrence, often through the use of antimicrobial agents.[11] While chlorhexidine gluconate is commonly employed, its use can lead to adverse effects such as mucosal irritation and tooth staining.[10,13] These limitations underscore the need for safer, effective alternatives. Given its bioactive profile, gambier extract presents a promising natural candidate for RAS treatment. By combining efficacy with reduced risk of irritation, gambier may address key limitations of existing therapies. This review explores its pharmacological basis and potential application in the treatment of RAS.

DISCUSSION

Clinical features of RAS

Recurrent aphthous stomatitis (RAS) is the most common disease affecting the oral mucosa, characterized by multiple, round or ovoid canker sores with erythematous halos and grey or yellow floors. These lesions reoccur periodically and are often painful, especially during the initial 4–5 days, interfering with speech and eating. The condition commonly begins in adolescence or early adulthood and affects up to 25% of the global population.[12-13]

RAS manifests in three clinical forms: minor RAS (MiRAS), major RAS (MaRAS), and herpetiform RAS (HeRAS). MiRAS, which accounts for 80% of cases, presents as small (<5 mm), round ulcers on non-keratinized mucosa and resolves without scarring in 10–14 days.[12] MaRAS affects about 10% of patients

Affiliation
[1]School of Dental Medicine, Universitas Ciputra, Surabaya, Indonesia
[2]Program of Development Study, Graduate School, Universitas Hasanuddin, Makassar, Indonesia

Correspondence
nurfitri.amaliah@ciputra.ac.id

and is characterized by larger lesions that may persist for weeks and heal with scarring.[13] HeRAS, the rarest form (1.1%), typically presents with multiple, small (2–3 mm), painful ulcers on the floor of the mouth and tongue, with a female predominance.[12-15]

Although the exact etiology remains unclear, the role of oral microbiota including *Streptococcus*, *Helicobacter pylori*, and viruses like cytomegalovirus is strongly suspected.[10-17] Additionally, systemic diseases may present with similar ulcers, complicating diagnosis.[16] Due to this ambiguity, no definitive treatment exists, and current approaches focus on symptom management.

Limitations of conventional RAS therapy

Current RAS management strategies aim to alleviate pain, reduce inflammation, and shorten the healing period.[11] Chlorhexidine gluconate is a commonly prescribed antiseptic; however, its use is limited by adverse effects such as mucosal irritation and tooth staining.[13] These limitations highlight the need for alternative agents with improved safety profiles and comparable efficacy.

Phytochemical composition and traditional uses of gambier

Uncaria gambir Roxb., or gambier, is a plant native to Southeast Asia, especially Indonesia and Malaysia, and has traditionally been used to treat wounds, ulcers, digestive disorders, and oral lesions.[7,18] It is rich in catechins and tannins, bioactive compounds with known antimicrobial, antioxidant, and anti-inflammatory effects.[5-8]

Indonesia ranks among the top global exporters of gambier, particularly from Sumatra. Two varieties are commonly used: commercial and raw gambier. Studies have shown high catechin content in commercial samples from Payakumbuh (93.94%), Lampung (91.97%), and Padang Panjang (97.99%), identified using Thin Layer Chromatography.[20] In contrast, raw gambier extracted from leaves and stems in Riau demonstrated antioxidant activity and catechin content varying with solvent type: 62.18% (ethanol) and 44.85% (ethyl acetate).[18]

Preclinical and clinical evidence of gambier's efficacy

Several studies support the potential of gambier extract in promoting wound healing. A study by Thaib et al. (2021) showed that 10% gambier leaf extract cream significantly accelerated burn healing in rabbits within 17 days.[21] Similarly, Arif et al. (2023) found that 15% extract concentrations were more effective in wound healing on mice compared to lower concentrations.[22] These findings indicate dose-dependent efficacy, although differences between 7.5% and 15% were relatively minor—suggesting a potential therapeutic threshold. Clinical research by Dewi et al. (2023) revealed that gambier mucobiadhesive significantly reduced both pain (VAS score) and lesion size in RAS patients.[23] This supports its use in oral ulcer management, although further studies with larger samples and randomized designs are needed for confirmation.

Critical appraisal of current studies

While the existing data are promising, the methodological limitations of several studies warrant attention: a) Small sample sizes (e.g., animal models with limited subjects or short follow-up periods); b) Lack of human trials for wound healing beyond preliminary mucobiadhesive studies; c) Variability in extraction methods, leading to inconsistent catechin concentrations and outcomes; and 4) Limited placebo-controlled or blinded trials, which raises concerns about bias.

Future research should employ standardized extraction protocols, involve larger, multi-centered human clinical trials, and compare gambier formulations directly with established agents like chlorhexidine to determine real-world applicability.

Antioxidant

Antioxidants are substances that prevent oxidative damage caused by free radicals, playing a protective role against diseases such as cancer, cardiovascular disorders, and premature aging.[27] Increased free radical formation can overwhelm endogenous defenses, necessitating external antioxidant sources, which may be synthetic or natural.[28] Due to potential side effects of synthetic antioxidants, natural antioxidants are preferred. Gambier (Uncaria gambir) is a notable natural antioxidant source, primarily due to its high phenolic compound content, with catechins being the most significant antioxidant constituents.[29,30] The antioxidant activity of gambier correlates strongly with its catechin levels.

The main chemical constituents of gambier include catechu tannic acid (20–50%), catechin (7–33%), and pyrocatechol (20–30%).[22] Catechins act as natural antioxidants by delaying, attenuating, and inhibiting lipid oxidation.[31] Generally, natural antioxidants are phenolic or polyphenolic compounds, often flavonoids, which neutralize oxidative stress.[32] Widiyarti (2020) evaluated the antioxidant activity of ethyl acetate extracts from dried gambier leaves, reporting significant phenolic content and free radical scavenging capacity.[20] Similarly, Nur Sazwi et al. (2015) found gambier exhibited strong antioxidant activity (IC50 6.4 ± 0.8 ppm via DPPH assay), outperforming other traditional plants, with quinic acid identified as a major bioactive compound.[33]

These antioxidant properties are clinically relevant in conditions like Recurrent Aphthous Stomatitis (RAS), where oxidative stress contributes to mucosal damage and inflammation.[9,10] By neutralizing free radicals, gambier's antioxidants could help mitigate oxidative injury, potentially reducing lesion severity and accelerating healing. However, further clinical studies are needed to confirm these benefits in RAS management.

Antibacterial

Gambier (*Uncaria gambir*) contains abundant flavonoids and alkaloids, bioactive compounds known for their potent antibacterial properties, particularly against oral pathogens involved in recurrent aphthous stomatitis (RAS) pathogenesis. Flavonoids, alkaloids, and terpenoids have been reported to inhibit *Streptococcus mutans*, a key bacteria contributing to oral microbial imbalance and inflammation in RAS.[34] Kresnawaty (2020) demonstrated that Gambier ethanol extracts exhibit significant antimicrobial activity, including inhibition of *Escherichia coli* O157:H7, suggesting that ethanol extraction effectively concentrates these antibacterial constituents, unlike water extracts which showed minimal activity.[35,36]

Further investigations confirmed that ethanol extracts of Gambier possess antibacterial effects against *E. coli* and other Gram-positive and Gram-negative bacteria relevant to oral infections.[35,37] For instance, microwave-assisted extraction yielded inhibition zones ranging from 12.07 mm to 14.38 mm against *E. coli*, *Salmonella typhimurium*, *Staphylococcus aureus*, and *Bacillus cereus*.[37] Musdja (2017) assessed the minimum inhibitory concentrations (MICs) of (+)-catechin, a major Gambier catechin, showing MICs of 5.5 mg/mL, 8 mg/mL, and 8 mg/mL against *Staphylococcus epidermidis*, *S. mutans*, and *S. viridans*, respectively, highlighting its potential to reduce oral bacterial colonization contributing to RAS lesions.[28,41]

These antibacterial activities suggest that Gambier extracts could play a dual role in RAS management by reducing microbial triggers and modulating local inflammation, which are central to the pathogenesis of RAS ulcers.[9,10] The ability of Gambier's bioactive compounds to inhibit key oral pathogens may help restore microbial balance, thereby accelerating lesion healing and reducing recurrence.[43] Hence, incorporating Gambier-derived antibacterial agents into therapeutic strategies could offer a complementary approach to managing RAS by targeting both microbial and inflammatory components.

Anti-inflammatory

Inflammation is a defensive response of the microcirculation that develops in tissues following trauma, infection, toxic exposure, or autoimmune injury.[38] It is a hallmark of several chronic diseases, including rheumatoid arthritis, atherosclerosis, and asthma, all of which are prevalent globally [39]. During inflammation, reactive oxygen species (ROS) and free radicals are released, leading to tissue damage and upregulation of arachidonic acid metabolism into prostaglandins and leukotrienes via cyclooxygenase (COX) and lipoxygenase (LOX) pathways.[40]

In vivo research by Yimam et al. demonstrated that a 1:1 mixture of *Uncaria gambir* leaf and *Morus alba* root bark extracts exhibited significant anti-inflammatory effects, reducing inflammation by 53.7%, 55.3%, and 48.8% at 1, 3, and 5 hours, respectively, at a dose of 300 mg/kg. Moreover, the same extracts exhibited COX-2 and LOX enzyme inhibitory activity in vitro, with IC_{50} values of 12.4 µg/mL and 13.6 µg/mL, respectively.[40] However, while promising, these results are based on animal models, and translation to human clinical outcomes—particularly in diseases such as recurrent aphthous stomatitis (RAS) requires caution. The COX-2/LOX pathways are relevant to RAS pathology, but differences in immune regulation and epithelial healing in humans may limit direct extrapolation.

Similarly, Musdja et al. investigated catechin isolates from *Uncaria gambir* using ethyl acetate via the paw edema method, noting that the optimal dose was 100 mg/kg body weight, which inhibited edema by 59.19%.[41] Another study by Yunarto et al. confirmed the anti-inflammatory properties in Wistar rats at doses as low as 5 mg/kg.[42] These findings reinforce the potential of catechins as anti-inflammatory agents,

but again, a more critical evaluation of dosing, delivery, and metabolic stability in humans is needed. No current trials have assessed catechin bioavailability or mucosal healing in RAS patients.

Expanding on this, polyphenol-rich plant extracts such as those from *Annona muricata*—have been shown to modulate inflammatory responses in macrophages and neutrophils, and improve outcomes in experimental lung injury models by downregulating NF-κB and oxidative stress pathways.[2] This suggests a plausible mechanism whereby similar compounds from *Uncaria gambir* may influence innate immune responses in RAS. Furthermore, Ginovyan et al. demonstrated broad-spectrum antimicrobial activity in traditional medicinal plants, reinforcing the dual anti-inflammatory and antimicrobial role that *Uncaria gambir* may play in oral lesions like RAS.[1]

Despite encouraging preclinical data, these studies often suffer from limited sample sizes, lack of standardization in extract composition, and absence of human trial validation. Translational research into standardized topical formulations for RAS that target both microbial colonization and mucosal inflammation is warranted. Given the multifactorial nature of RAS—including nutritional, immune, and microbial components monotherapies may be insufficient. Thus, future investigations should emphasize randomized controlled trials, pharmacokinetics, and biomarker-driven efficacy endpoints to determine clinical relevance.

Effect of gambier extract for RAS treatment

The primary goals in managing recurrent aphthous stomatitis (RAS) are to alleviate inflammation and pain, shorten ulcer duration, and prevent recurrences.[15] Medicinal plants have long been employed in traditional medicine for treating a variety of diseases due to their bioactive compounds and relatively low incidence of adverse effects.[43,44] One such agent is *Uncaria gambir* (gambier), a traditional plant rich in catechins and oxindole alkaloids known for their anti-inflammatory, antimicrobial, and wound-healing activities.[46,47,55] The pathophysiology of RAS involves mucosal inflammation, with tissue injury triggering the release of inflammatory mediators like prostaglandin E2 (PGE2), histamine, and leukotrienes. These mediators induce vasodilation and increase vascular permeability, leading to classic signs of inflammation redness, swelling, and pain.[45] Clinical management often includes topical agents due to their localized effect and reduced systemic side effects.[15]

Gambier extract has demonstrated promising results in managing RAS symptoms. It reduces pain intensity and promotes ulcer healing.[15,46] This therapeutic effect is largely attributed to the high concentration of catechins, which exhibit immunomodulatory, antioxidant, and anti-inflammatory properties.[47,48] Catechins modulate inflammatory pathways by downregulating cytokines such as interleukin-6 (IL-6) and interleukin-8 (IL-8), and suppressing COX-1 and COX-2 enzyme activity.[48]

In addition to its anti-inflammatory effects, gambier extract has shown potent antimicrobial activity. In vitro studies have demonstrated that catechins disrupt bacterial membranes, leading to cell lysis and death, particularly against *Streptococcus mutans* a key pathogen in the oral cavity.[51,52] These properties are beneficial, as secondary bacterial infections can delay mucosal healing in RAS.[50] Several experimental and clinical studies have confirmed the wound-healing potential of gambier. In animal models, topical application of gambier significantly enhanced angiogenesis, fibroblast proliferation, and collagen deposition, thereby accelerating wound closure.[53-55] Clinical data suggest that topical gambier reduces the healing time of oral ulcers and gingival wounds through these mechanisms.[6,56]

Moreover, the antimicrobial potential of gambier aligns with broader literature on traditional medicinal plants. For instance, Ginovyan et al. (2017) found that various plant extracts used in Armenian traditional medicine, including polyphenolic-rich substances, exhibited broad-spectrum antimicrobial activity, further supporting the ethnopharmacological value of gambier.[1] Similarly, Saraiva et al. (2022) confirmed that polyphenols attenuate inflammatory responses in immune cells, adding mechanistic support to their use in inflammatory conditions like RAS.[2]

Regarding practical application, gambier is most commonly prepared as an ethanolic extract or mucobioadhesive gel for topical use. Dewi et al. (2023) formulated a mucoadhesive gel that significantly reduced pain scores and shortened ulcer healing duration in RAS patients.[23] Safety evaluations have shown that topical formulations are well tolerated, with minimal risk of adverse reactions when used locally.[6,23] Although human clinical trials are limited, existing in vivo and in vitro evidence suggest gambier is safe and effective when used topically in doses ranging from 1–3% extract concentrations. No significant systemic toxicity has been reported, although further studies are warranted to assess long-term safety, standardization of dosage, and potential drug interactions.

RAS is generally a self-limiting condition, with ulcer healing occurring within 8 to 14 days. The wound healing process encompasses an inflammatory phase (4–6 days), a proliferative phase with re-epithelialization and angiogenesis (4–14 days), and a maturation phase.[57,58] Gambier extract expedites this process by enhancing re-epithelialization, reducing inflammatory infiltration, and promoting tissue regeneration through angiogenesis and granulation.[59-61]

CONCLUSION

This literature review suggests that gambier extract has considerable potential in the treatment of RAS. Nevertheless, further research and development are required to ascertain its safety and efficacy in order to ensure that the product is safe for public use.

REFERENCES

1. Ginovyan M, Petrosyan M, Trchounian A. Antimicrobial activity of some plant materials used in Armenian traditional medicine. *BMC Complement Altern Med*. 2017;17(1):1-9. doi:10.1186/s12906-017-1573-y
2. Saraiva AL, Justino AB, Franco RR, et al. Polyphenols-Rich Fraction from Annona muricata Linn. Leaves Attenuates Oxidative and Inflammatory Responses in Neutrophils, Macrophages, and Experimental Lung Injury. *Pharmaceutics*. 2022;14(6). doi:10.3390/pharmaceutics14061182
3. Ahmad R, Salim F. *Oxindole Alkaloids of Uncaria (Rubiaceae, Subfamily Cinchonoideae): A Review on Its Structure, Properties, and Bioactivities*. Vol 45. Elsevier; 2015. doi:10.1016/B978-0-444-63473-3.00012-5
4. Gonelimali FD, Lin J, Miao W, et al. Antimicrobial properties and mechanism of action of some plant extracts against food pathogens and spoilage microorganisms. *Front Microbiol*. 2018;9(JUL):1-9. doi:10.3389/fmicb.2018.01639
5. Dewi SRP, Handayani P, Anastasia D, Maulina ST. Antimicrobial potency of toothpaste containing gambir (Uncaria gambir) extract. *Padjadjaran J Dent*. 2023;35(2):98. doi:10.24198/pjd.vol35no2.47130
6. Rusdiana Puspa Dewi S, Pratiwi A. the Effect of Gambier Extracts (Uncaria Gambir [Roxb.]) As Antiseptic on Gingival Wound in Rats. *ODONTO Dent J*. 2018;5(1):80-88.
7. Rauf A, Rahmawaty, Siregar AZ. The Condition of Uncaria Gambir Roxb. as One of Important Medicinal Plants in North Sumatra Indonesia. *Procedia Chem*. 2015;14:3-10. doi:10.1016/j.proche.2015.03.002
8. Andre N. A Review of the Occurrence of Non-Alkaloid Constituents in Uncaria Species and Their Structure-Activity Relationships. *Am J Biomed Life Sci*. 2013;1(4):79. doi:10.11648/j.ajbls.20130104.13
9. Gasmi Benahmed A, Noor S, Menzel A, Gasmi A. Oral Aphthous: Pathophysiology, Clinical Aspects and Medical Treatment. *Arch Razi Inst*. 2021;76(5):1155-1163. doi:10.22092/ari.2021.356055.1767
10. Sánchez-Bernal J, Conejero C, Conejero R. Recurrent Aphthous Stomatitis. *Actas Dermosifiliogr*. 2020;111(6):471-480. doi:10.1016/j.ad.2019.09.004
11. Liu H, Tan L, Fu G, Chen L, Tan H. Efficacy of Topical Intervention for Recurrent Aphthous Stomatitis: A Network Meta-Analysis. *Med*. 2022;58(6). doi:10.3390/medicina58060771
12. Giannetti L, Murri Dello Diago A, Lo Muzio L. Recurrent aphtous stomatitis. *Minerva Stomatol*. 2018;67(3):125-128. doi:10.23736/S0026-4970.18.04137-7
13. Parra-Moreno FJ, Egido-Moreno S, Schemel-Suárez M, González-Navarro B, Estrugo-Devesa A, López-López J. Treatment of recurrent aphtous stomatitis: A systematic review. *Med Oral Patol Oral y Cir Bucal*. 2023;28(1):e87-e98. doi:10.4317/medoral.25604
14. Tappuni AR, Kovacevic T, Shirlaw PJ, Challacombe SJ. Clinical assessment of disease severity in recurrent aphthous stomatitis. *J Oral Pathol Med*. 2015;42(8):635-641. doi:10.1111/jop.12059
15. Sridevi Anjuga EP, Aravindha Babu N. Guidelines for diagnosis and treatment of recurrent aphthous stomatitis for dental practitioners. *Indian J Forensic Med Toxicol*. 2020;14(4):1099-1104. doi:10.37506/ijfmt.v14i4.11657
16. Chiang CP, Yu-Fong Chang J, Wang YP, Wu YH, Wu YC, Sun A. Recurrent aphthous stomatitis – Etiology, serum autoantibodies, anemia, hematinic deficiencies, and management. *J Formos Med Assoc*. 2019;118(9):1279-1289. doi:10.1016/j.jfma.2018.10.023
17. Sympli HD. *Estimation of Drug-Likeness Properties of GC–MS Separated Bioactive Compounds in Rare Medicinal Pleione Maculata Using Molecular Docking Technique and SwissADME in Silico Tools*. Vol 10. Springer Vienna; 2021. doi:10.1007/s13721-020-00276-1
18. Gani M, Cuaca Y, Ayucitra A, Indraswati N. Daun Dan Tangkai Gambir. 2015;11(5):250-256.
19. Mahendra I, Azhar M. EKSTRAKSI DAN KARAKTERISASI KATEKIN DARI GAMBIR (Uncaria gambir roxb). *J Period Jur Kim UNP*. 2022;11(1):5. doi:10.24036/p.v11i1.113262
20. Widiyarti G, Sundowo A, Filailla E, Laksmono A. The Mechanically Extraction Process of Gambier (Uncaria gambier Roxb.) from Limapuluh Kota, West Sumatera and Its Antioxidant activity. *J Pure Appl Chem Res*. 2020;9(1):8-15. doi:10.21776/ub.jpacr.2020.009.01.509
21. Thaib CM, Sinaga TR, Manurung K. FORMULASI KRIM EKSTRAK DAUN GAMBIR (Uncaria gambir Roxb.) SEBAGAI PENYEMBUH LUKA BAKAR. *J Farmanesia*. 2021;8(1):76-82. doi:10.51544/jf.v8i1.3419
22. Arief S, Nasution FW, Zulhadjri, Labanni A. High antibacterial properties of green synthesized gold nanoparticles using Uncaria gambir Roxb. leaf extract and triethanolamine. *J Appl Pharm Sci*. 2020;10(8):124-130. doi:10.7324/JAPS.2020.10814
23. Dewi SRP, Handayani P, Hestiningsih T, Destriarum D, Sari AP. POTENSI MUKOBIOADHESIF EKSTRAK GAMBIR (Uncaria gambir) TERHADAP PENURUNAN RASA NYERI DAN DURASI PENYEMBUHAN LESI ULSERASI RONGGA MULUT. *Cakradonya Dent J*. 2023;13(2):129-136. doi:10.24815/cdj.v13i2.23534

24. Sabarni. Teknik Pembuatan Gambir (Uncaria gambir Roxb) Secara Tradisional. *J Islam Sci Technol*. 2015;1(1):105-112. www.jurnal.ar-raniry.com/index.php/elkawnie
25. Pambayun R, Program DS. Journal of International Dental and Medical Research ISSN 1309-100X http://www.jidmr.com Antiseptic Effect of Betel Quid Extract Rindit Pambayun, et al. Published online 2018:621-627.
26. V E, P R, W TW, S B, Puspa D SR. Antibacterial Activity toward Streptococcus mutans and Antioxidant from Traditional Betel Chew Formulation of Indonesia. *J Microb Biochem Technol*. 2017;09(06):316-320. doi:10.4172/1948-5948.1000384
27. Firdausni F, Wilsa H, Yulia DH. Aplikasi gambir (Uncaria gambir Roxb) melalui proses pencucian berulang sebagai antioksidan pada pangan berminyak. *J Litbang Ind*. 2022;2014(2):73-81.
28. Musdja MY, Rahman HA, Hasan D. Antioxidant Activity of Catechins Isolate of Uncaria Gambier Roxb in Male Rats. *LIFE Int J Heal Life-Sciences*. 2018;4(2):34-46. doi:10.20319/lijhls.2018.42.3446
29. Malrianti Y, Kasim A, Asben A, Syafri E, Yeni G, Fudholi A. Catechin extracted from uncaria gambier roxb for nanocatechin production: Physical and chemical properties. *Int J Des Nat Ecodynamics*. 2021;16(4):393-399. doi:10.18280/ijdne.160406
30. Herlina, Syamsuardi, Syawaluddin A, Suhade. The Effect of Demonstration Methods to Improve Science Thinking Skills In Children Aged 5-6 Years. *J Educ Sci Technol*. 2023;9(1):77-85.
31. Ismail AS, Rizal Y, Armenia, Kasim A. Identification of bioactive compounds in gambier (Uncaria gambir) liquid by-product in west Sumatra, Indonesia. *Biodiversitas*. 2021;22(3):1474-1480. doi:10.13057/BIODIV/D220351
32. Rizk FH, Soliman NA, Abo-Elnasr SE, et al. Fisetin ameliorates oxidative glutamate testicular toxicity in rats via central and peripheral mechanisms involving SIRT1 activation. *Redox Rep*. 2022;27(1):177-185. doi:10.1080/13510002.2022.2116551
33. Nur Sazwi N, Nalina T, Rahim ZHA. Antioxidant and cytoprotective activities of Piper betle, Areca catechu, Uncaria gambir and betel quid with and without calcium hydroxide. *BMC Complement Altern Med*. 2015;13. doi:10.1186/1472-6882-13-351
34. Lanchoti Fiori GM, Fachin AL, Correa VSC, et al. Antimicrobial Activity and Rates of Tannins in *Stryphnodendron adstringens* Mart. Accessions Collected in the Brazilian Cerrado. *Am J Plant Sci*. 2015;04(11):2193-2198. doi:10.4236/ajps.2013.411272
35. KRESNAWATY I, ZAINUDDIN A. AKTIVITAS ANTIOKSIDAN DAN ANTIBAKTERI DARI DERIVAT METIL EKSTRAK ETANOL DAUN GAMBIR (Uncaria gambir). *J Penelit Tanam Ind*. 2020;15(4):145. doi:10.21082/jlittri.v15n4.2009.145-151
36. Rahmawati N, Bakhtiar A, Putra P. Isolasi Katekin dari Gambir (Uncaria gambir (Hunter). Roxb) untuk Sediaan Farmasi dan Kosmetik. *J Penelit Farm Indones*. 2019;1(1):6-10.
37. Magdalena NV, Kusnadi J. Antibakteri dari Ekstrak Kasar Daun Gambir (Uncaria gambir Var Cubadak) Metode Microwave-Assisted Extraction Terhadap Bakteri Patogen. *J Pangan dan Agroindustri*. 2015;3(1):124-135.
38. Fullerton JN, Gilroy DW. Resolution of inflammation: A new therapeutic frontier. *Nat Rev Drug Discov*. 2016;15(8):551-567. doi:10.1038/nrd.2016.39
39. Auliana FR, Ifora I, Fauziah F. Phytochemical and Anti-Inflammatory of Uncaria gambir: A Review. *Asian J Pharm Res Dev*. 2022;10(1):79-83. doi:10.22270/ajprd.v10i1.1077
40. Yimam M, Lee YC, Kim TW, et al. Analgesic and anti-inflammatory effect of UP3005, a botanical composition Containing two standardized extracts of Uncaria gambir and Morus alba. *Pharmacognosy Res*. 2015;7:S39-S46. doi:10.4103/0974-8490.157995
41. Musdja MY, Hapsari MA, Agusta A. Comparison of Activity and Inhibitory Mechanism between (+) - Catechin and Water Extract of Gambier (Uncaria Gambir Roxb.) Against some Bacteria. *Sci J PPI-UKM Sci Eng*. 2017;4(2):55-60. doi:10.27512/sjppi-ukm/se/a29012018
42. 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. *Adv Heal Sci Res*. 2020;22(Ishr 2019):108-112. doi:10.2991/ahsr.k.200215.021
43. Puspa Dewi SR, Karina Ginting MP, Anggraini NR, Parisa N, Handayani P, Chairani S. EVALUATION OF THE EFFECT OF GAMBIER (Uncaria gambier) EXTRACT FOR TREATMENT OF RECURRENT APHTHOUS STOMATITIS. *Int Res J Pharm*. 2020;11(1):27-31. doi:10.7897/2230-8407.11015
44. Ekor M. The growing use of herbal medicines: Issues relating to adverse reactions and challenges in monitoring safety. *Front Neurol*. 2014;4 JAN(January):1-10. doi:10.3389/fphar.2013.00177
45. Teshome N, Degu A, Ashenafi E, Ayele E, Abebe A. Evaluation of Wound Healing and Anti-Inflammatory Activity of Hydroalcoholic Leaf Extract of Clematis simensis Fresen (Ranunculaceae). *Clin Cosmet Investig Dermatol*. 2022;15(September):1883-1897. doi:10.2147/CCID.S384419
46. Dita Septiani, Euis Reni Yuslianti, Saskia Lenggogeni Nasroen. Pengaruh Ekstrak Etanol Daun Gambir (Uncaria Gambir) Dibandingkan Dengan Chlorhexidine Gluconate 0,2% Topikal Terhadap Penyembuhan Luka Mukosa Palatum Tikus Galur Wistar. *Dentika Dent J*. 2015;18(3):262-267. doi:10.32734/dentika.v18i3.1973
47. Fan FY, Sang LX, Jiang M, McPhee DJ. Catechins and their therapeutic benefits to inflammatory bowel disease. *Molecules*. 2017;22(3). doi:10.3390/molecules22030484
48. Crespy V, Williamson G. A review of the health effects of green tea catechins in in vivo animal models. *J Nutr*. 2018;134(12 SUPPL.). doi:10.1093/jn/134.12.3431s
49. Rismana E, Ningsih S, Fachrudin F. In vitro study of xanthine oxidase inhibitory of gambir (Uncaria gambir) hunter roxb extracts. *Pharmacogn J*. 2014;9(6):862-865. doi:10.5530/pj.2017.6.135
50. Negut I, Grumezescu V, Grumezescu AM. Treatment strategies for infected wounds. *Molecules*. 2018;23(9):1-23. doi:10.3390/molecules23092392
51. Tsuchiya H. Membrane interactions of phytochemicals as their molecular mechanism applicable to the discovery of drug leads from plants. *Molecules*. 2015;20(10):18923-18966. doi:10.3390/molecules201018923
52. Rusdiana Puspa Dewi S, Totong Kamaluddin M, Pambayun R, Author C. Anticariogenic Effect of Gambir (Uncaria Gambir [Roxb.]) Extract on Enamel Tooth Surface Exposed by Streptococcus mutans. *Int J Heal Sci Res*. 2016;6(8):171. www.ijhsr.org
53. Sumoza NS, Rahayu R. Pengaruh Gambir (Uncaria gambir R.) Terhadap Penyembuhan Luka Bakar Pada Mencit Putih (Mus musculus L.). *J Biol Univ Andalas*. 2015;3(4):283-288.

54. Musdja MY, Elvita L, Rahayu N. Effects of Gambir (Uncaria gambir Roxb) Catechins on Burn Wound Healing in Male Rats. 2019;(Bromo):261-271. doi:10.5220/0008361002610271
55. Handayani FF, Pangesti LAT, Siswanto E. Penyembuhan Luka Bakar Pada Kulit Punggung Mencit Putih Jantan (Mus musculus). *J Ilm Manuntung*. 2019;1(December 2015):133-139.
56. Tan BC, Mahyuddin A, Sockalingam SNMP, Zakaria ASI. Preliminary in vitro cytotoxic evaluation of Uncaria gambier (Hunt) Roxb extract as a potential herbal-based pulpotomy medicament. *BMC Complement Med Ther*. 2023;23(1):1-16. doi:10.1186/s12906-023-04163-w
57. Suragimath G, Krishnaprasad KR, Moogla S, Sridhara SU, Raju S. Effect of carbonated drink on excisional palatal wound healing: A study on Wistar rats. *Indian J Dent Res*. 2020;21(3):330-333. doi:10.4103/0970-9290.70789
58. Politis C, Schoenaers J, Jacobs R, Agbaje JO. Wound healing problems in the mouth. *Front Physiol*. 2016;7(NOV):1-13. doi:10.3389/fphys.2016.00507
59. Kong X, Fu J, Shao K, Wang L, Lan X, Shi J. Biomimetic hydrogel for rapid and scar-free healing of skin wounds inspired by the healing process of oral mucosa. *Acta Biomater*. 2019;100:255-269. doi:10.1016/j.actbio.2019.10.011
60. Griffin MF, Fahy EJ, King M, et al. Understanding Scarring in the Oral Mucosa. *Adv Wound Care*. 2022;11(10):537-547. doi:10.1089/wound.2021.0038
61. Desjardins-Park HE, Gurtner GC, Wan DC, Longaker MT. From Chronic Wounds to Scarring: The Growing Health Care Burden of Under-and Over-Healing Wounds. *Adv Wound Care*. 2022;11(9):496-510. doi:10.1089/wound.2021.0039