Research Article

Towards Rigorous Safety Standards for Indonesian Jamu: A Review and Rationale for Non-Human Primate Toxicology Models

Tiza W. Mawaddah[1,2], Elisa D. Pratiwi[1,2], Astria N. Nidom[2,4], Jonny[4,5], Zakiyyan I. Ayyuba[1,2], Irma Y. Rosytania[1,2], Setyarina Indrasari[2,6], Reviany V. Nidom[2,6*], Chairul A. Nidom[1,2,3*]

[1]Faculty of Veterinary Medicine, Universitas Airlangga, Surabaya, Indonesia; [2]Professor Nidom Foundation, Surabaya, Indonesia; [3]Global Biosains Teknologi, Malang, Indonesia; [4]Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia; [5]Indonesia Army Cellcure Center, Gatot Soebroto Central Army Hospital, Jakarta, Indonesia; [6]Riset AIRC Indonesia, Surabaya, Indonesia.

Tiza W. Mawaddah and Elisa D. Pratiwi contributed equally for this study.

Abstract | *Jamu* is a traditional Indonesian herbal drink that was officially recognized as an Intangible Cultural Heritage (ICH) by UNESCO on December 6, 2023. It has long been consumed for the prevention and treatment of various diseases and is composed of multiple herbal ingredients, including Curcuma longa, Curcuma xanthorrhiza, Zingiber officinale (ginger), and Kaempferia galanga. While these plants contain bioactive compounds with established pharmacological benefits, their complex combinations may also pose toxicological risks, particularly with long-term or improper use. To enhance the quality, safety, and global acceptance of jamu, rigorous toxicity evaluation comparable to modern pharmaceuticals is required. As direct toxicity testing in humans is ethically limited, preclinical testing using experimental animal models is essential. This review employs a structured narrative literature review approach to analyze existing studies on jamu toxicology, with particular emphasis on comparative animal models. Scientific articles were retrieved from PubMed, Scopus, and Google Scholar using predefined keywords related to jamu, herbal toxicology, and animal models, and were selected based on their relevance to safety, toxicity endpoints, and translational value. Special attention is given to non-human primates, particularly Macaca fascicularis, due to their close genetic, physiological, and biochemical similarities to humans. Compared to rodent models, this species offers improved translational relevance for assessing systemic toxicity, organ-specific effects, and potential efficacy. By aligning jamu safety assessment with internationally accepted preclinical standards, this review aims to support the scientific validation and broader national and international recognition of *jamu*.

Keywords | UNESCO, Jamu, Spices, Efficacy, Toxicology, *Macaca fascicularis*

Received | December 27, 2025; **Accepted** | January 11, 2026; **Published** | February 04, 2026
***Correspondence** | Reviany V. Nidom and Chairul A. Nidom, Professor Nidom Foundation, Surabaya, Indonesia; **Email:** reviany@pnfinstitute.org, nidomca@fkh.unair.ac.id
Citation | Mawaddah TW, Pratiwi ED, Nidom AN, Jonny, Ayyuba ZI, Rosytania IY, Indrasari S, Nidom RV, Nidom CA (2026). Towards rigorous safety standards for Indonesian Jamu: A review and rationale for non-human primate toxicology models. Adv. Anim. Vet. Sci., 14(2):342-355.
DOI | https://dx.doi.org/10.17582/journal.aavs/2026/14.2.342.355
ISSN (Online) | 2307-8316

INTRODUCTION

Indonesia has a very abundant biodiversity, especially with regard to plants. Many plants that grow in Indonesia are utilized by the local community, and are generally processed into herbal medicines such as *jamu*. Jamu is a traditional medicine consumed in developing countries, especially in Indonesia, for the treatment of various ailments. There is

also a traditional medicine from another country, namely Ayurveda medicine from India. Ayurveda is an ancient Indian medical system that literally means knowledge of healthy longevity (Sebastian, 2022). It is a holistic approach to health that emphasizes the balance of body, mind, and soul that aims to treat disease and improve overall well-being and longevity. Ayurvedic treatment primarily uses herbal formulations, which are believed to have therapeutic properties. These formulations often include various plant materials, and in some cases, minerals and animal products are also added (Prakash *et al*., 2014). Herbs are not only used because of their efficacy as medicines, but also because of their ability to enhance the body's natural healing processes. For example, the herbal combination known as Triphala, which includes *Emblica officinalis, Terminalia chebula*, and *Terminalia bellirica*, is widely known for its digestive and detoxifying benefits (Gordon *et al*., 2019). Despite its ancient roots, Ayurveda has gained renewed interest in modern times, especially as a complementary approach to conventional medicine. Several studies have shown that Ayurvedic practices can have beneficial effects on a variety of chronic conditions, such as diabetes, cardiovascular disease, and cognitive impairment (Kumar *et al*., 2016). One study highlighted the efficacy of integrated yoga and Ayurveda in improving cognitive function in elderly patients with mild cognitive impairment (Kumar *et al*., 2016; Chobe *et al*., 2022). In addition, there is the Traditional Chinese Medicine (TCM) originating from China, which plays a major role in maintaining health for the Chinese people. It was the only medical practice in China before the early nineteenth century in the Qing dynasty. TCM is characterized by its unique holistic multi-target efficacy against chronic or complex diseases (Chobe *et al*., 2022). The basic ingredients for making *jamu* are natural ingredients from Indonesian cultural heritage that have been passed down from generation to generation, aimed at improving health (Muliasari *et al*., 2019). *Jamu* formulations generally come from selected plants and their mixtures come from whole plants, cut plants, or fragmented plants. It offers ease of accessibility of products that can be purchased without the need to show a doctor's prescription. Consumers can purchase *jamu* in drug stores, supermarkets, health stores, herbal medicine shops, and via the internet, making the number of *jamu* enthusiasts continue to increase and providing noticeable economic benefits (Suparmi *et al*., 2021). In 2023, *jamu* has officially been included in the intangible cultural heritage recognized by UNESCO (Waluyo, 2023). The benefits contained in *jamu* are increasing body immunity, antioxidants, helping the metabolism process, and curing inflammation (Kusumo *et al*., 2020). *Jamu* production is currently being developed on an industrial scale. The government, industry, and academics in Indonesia have realized that in order to advance the scientific development of *jamu*, research is needed to ensure the safety of *jamu* ingredients (Woerdenbag and Kayser, 2014).

Jamu primarily focuses on maintaining health in healthy individuals with the aim of preventing disease and improving immune health. For example, turmeric and tamarind *jamu*, which is known for its anti-inflammatory and antioxidant benefits, is very popular for maintaining hormonal balance and improving the immune system. *Jamu* is an important tool in maintaining overall health, especially in the context of increasing awareness of healthy lifestyle among modern society today. This review examines the current state of knowledge on these hazards and risks based on case reports of adulteration and the actual detection of genotoxic and carcinogenic constituents of concern in *jamu*. It is important to distinguish between hazards arising from deliberate drug adulteration and those associated with the intrinsic toxicological properties of herbal constituents. Adulteration with synthetic pharmaceuticals represents a quality control and regulatory issue that cannot be directly identified through conventional animal toxicity testing. In contrast, preclinical toxicity studies are essential for evaluating the safety, dose-related effects, and organ-specific toxicity of authentic herbal formulations.. The potential hazards of exposure to APIs are mainly related to the presence of constituents that may cause liver damage, renal impairment, renal failure, steroid dependence, or genotoxicity and carcinogenicity (Suparmi *et al*., 2021; Tjen, 2024). The purpose of this review is to analyze and synthesize existing literature on the toxicological safety of jamu and to evaluate the scientific rationale for the use of *Macaca fascicularis* as a translational preclinical model for safety and risk assessment, rather than to present new experimental toxicity data.

While non-human primates such as *Macaca fascicularis* offer improved translational relevance compared to rodent models, interspecies differences in metabolism, lifespan, and disease progression remain important limitations. Therefore, findings from non-human primate studies should be interpreted as supportive preclinical evidence rather than direct predictors of long-term human outcomes. Their primary value lies in bridging the gap between rodent data and carefully designed clinical and post-marketing surveillance studies.

MATERIALS AND METHODS

Literature review methodology

This study employed a structured narrative literature review methodology with qualitative thematic synthesis. Literature searches were conducted using PubMed, Scopus, and Google Scholar up to November 7, 2024. Search terms included combinations of keywords related to jamu and herbal medicine ("jamu", "Indonesian herbal medicine"),

toxicology ("toxicity", "safety", "genotoxicity", "organ toxicity"), and experimental models ("animal models", "rodent", "non-human primates", "*Macaca fascicularis*").

Study selection was performed in two stages: Initial screening of titles and abstracts followed by full-text assessment. Inclusion criteria comprised peer-reviewed articles published in English that reported pharmacological, toxicological, or safety-related data on jamu or its major herbal constituents, including *Curcuma longa*, *Zingiber officinale*, and *Kaempferia galanga*. Both in vivo and relevant in vitro studies were considered, with emphasis placed on studies employing animal models for toxicity assessment. Studies focusing on chronic or subchronic exposure and reporting toxicological endpoints such as hematological parameters, blood biochemistry, and histopathological changes in major organ systems (including hepatic, renal, cardiovascular, and lymphoid organs) were prioritized.

To reflect recent scientific developments while maintaining foundational context, the majority of included studies were published within the last five years. Older studies dating back to 2002 were included when they provided essential baseline toxicological data, historical relevance, or early evidence pertinent to long-term safety evaluation and translational modeling. Given the heterogeneity of study designs, no formal quantitative risk-of-bias assessment was applied. Instead, study quality was considered qualitatively based on clarity of experimental design, reporting of dosage and exposure duration, relevance of toxicological endpoints, and appropriateness of the animal model used. Data were synthesized using a qualitative thematic analysis approach. Studies were grouped according to (1) type of herbal constituent, (2) animal model employed, and (3) reported toxicological outcomes, allowing for comparative evaluation of translational relevance, limitations, and research gaps, particularly concerning the use of non-human primates.

Research question and objectives

This literature review was guided by the following primary research question:

How appropriate are current preclinical animal models for assessing the safety and toxicology of Indonesian jamu, and what is the potential role of *Macaca fascicularis* as a translational model?

The secondary objectives of this review were:

1. To summarize the pharmacological benefits and toxicological risks of major jamu herbal constituents.
2. To compare commonly used animal models in jamu toxicology studies.
3. To evaluate the scientific rationale for the use of *Macaca fascicularis* in herbal safety assessment.
4. To propose a framework for improving national and international safety standards for jamu.

RESULTS

Main composition of herbal medicine (*JAMU*)

While the pharmacological benefits of jamu constituents have been widely reported, this section prioritizes toxicological findings relevant to safety assessment, including dose-related adverse effects, organ-specific toxicity, and potential implications for long-term use. Jamu formulations generally consist of combinations of spices such as ginger, turmeric, lemongrass, and palm sugar (Sidik *et al*., 1992). In addition, several plant species commonly used in jamu are traditionally consumed to support immune function, including turmeric, curcuma, and ginger.

Curcuma xanthorrhiza Roxb. is an abundant Indonesian medicinal plant belonging to the Zingiberaceae family and is widely used as a raw material in traditional medicine (Rosidi *et al*., 2014; Nursuprianah *et al*., 2022). It contains a diverse range of chemical constituents, with starch representing the most abundant component (Sidik *et al*., 1992). The essential oil fraction of curcuma includes phellandrene, camphor, borneol, cineole, and xanthorrhizol, which have been associated with bile secretion, cholesterol reduction, and antimicrobial activity (Syamsuddin *et al*., 2019). Curcuma has traditionally been used for the management of hepatic disorders, digestive disturbances, vaginal discharge, and dermatological conditions (Ata *et al*., 2015). Experimental studies have reported antimicrobial and antiviral activities, including inhibition of Simian Retrovirus Serotype-2 (SRV-2) replication in vitro using combined *Phyllanthus niruri* and curcuma extracts at concentrations of 100–500 ppm in A549 cell cultures (Hernani and Raharjo, 2005). Given the broad tissue tropism of SRV-2 in macaques, these findings highlight the biological activity of curcuma-derived compounds but also underscore the importance of evaluating dose-dependent systemic effects and potential toxicity under prolonged exposure. Curcumin, the major curcuminoid in curcuma, exhibits antioxidant and detoxifying properties through modulation of glutathione S-transferase (GST) activity and inhibition of nitric oxide synthase in macrophages (Aldizal *et al*., 2019). Although these mechanisms may confer protective effects, their relevance to safety assessment depends on exposure level, duration of use, and potential interactions with hepatic and renal function.

The rhizome of *Boesenbergia rotunda* is another traditional medicinal plant widely used in Indonesian herbal preparations (Handayani *et al*., 2018). Bioactive compounds identified in this species include boesenbergin, cardamonin, pinostrobin, pinocembrin, panduratin A,

and 4-hydroxypanduratin A, which have been reported to possess antioxidant, antibacterial, antifungal, anti-inflammatory, and anticancer activities (Erlyn, 2016). Fingerroot has been extensively studied for its antibacterial properties, particularly against *Streptococcus mutans*, a primary etiological agent of dental caries (Yanti *et al*., 2009; Handayani *et al*., 2018). Flavonoid-rich extracts from fingerroot have demonstrated inhibitory effects on *S. mutans* growth, supporting its traditional use in oral health applications (Yuan and Iskandar, 2018). However, the widespread use of antibacterial herbal agents also necessitates toxicological evaluation, as inappropriate dosing or prolonged exposure may contribute to unintended tissue effects or microbial imbalance.

Zingiber officinale is one of the most commonly used herbal ingredients in jamu formulations. Ginger contains essential oils and bioactive compounds such as gingerol, beta-carotene, capsaicin, caffeic acid, curcumin, and salicylates, which are primarily associated with anti-inflammatory and antioxidant activities (Ballester *et al*., 2022). While these properties contribute to its therapeutic popularity, the presence of multiple active compounds highlights the need for safety assessment, particularly with respect to dose-dependent gastrointestinal effects and potential interactions during chronic consumption (Ballester *et al*., 2022).

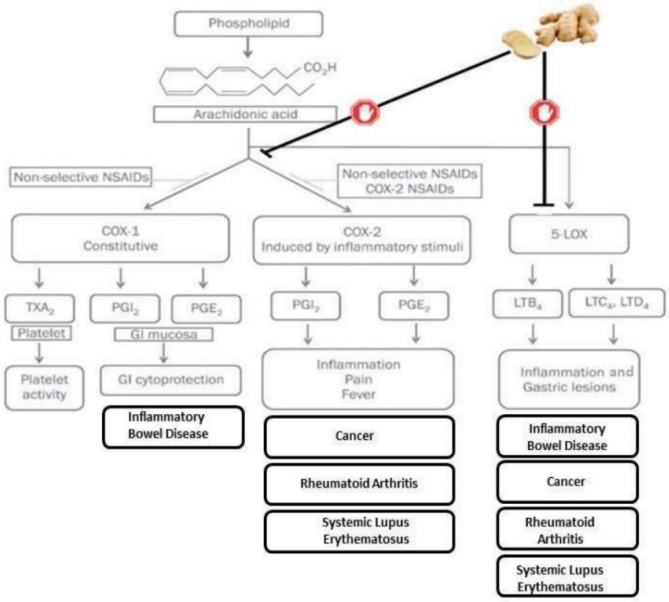

Figure 1: Inflammation, ginger action, and its relationship to disease etiology and symptoms (Aryanta, 2019)

Turmeric (*Curcuma longa* L) contains curcumin, which has antioxidant, antibacterial, anti-inflammatory, and antiviral properties. It is highly suitable for improving the immune system (Srivastava and Srimal, 1985). The Food and Drug Supervisory Agency in Indonesia has classified it as a priority plant for medicinal use as a treatment for headaches, nausea, vomiting, influenza, coughs, and vertigo. Curcumin is a powerful anti-inflammatory agent effective in treating acute and chronic inflammation (Antony *et al*., 1999). Curcumin encapsulated by liposomes has been shown to increase the total number of white blood cells and the number of bone marrow cells. This is associated with the production of cytokines that regulate the proliferation and differentiation of bone marrow cells or directly work on these cells. Treatment with curcumin significantly increased leukocyte esterase positive cells, which showed its effect on stem cell proliferation. Administration of curcumin increases humoral immunity as seen from the increase in antibody titers and antibody-forming cells. Macrophage phagocytosis activity also increases when given treatment with curcumin (Widowati, 2008). This means that the body's response to infection or inflammation will be faster and more effective, particularly in dealing with pathogens or foreign objects entering the body.

Available evidence suggests that curcumin is generally well tolerated at low to moderate doses; however, adverse effects have been reported, particularly at high doses or during prolonged use. Curcumin has been shown to inhibit platelet aggregation and may potentiate the effects of anticoagulant and antiplatelet drugs, thereby increasing the risk of bleeding (Vaughn *et al*., 2016). In addition, curcumin can stimulate gallbladder contraction, which may exacerbate symptoms in individuals with gallstones or biliary obstruction (Majeed *et al*., 1995). These findings indicate clinically relevant herb–drug and herb–disease interactions that should be considered in jamu safety assessment. From a toxicokinetic perspective, curcumin exhibits poor oral bioavailability due to rapid metabolism and systemic elimination, resulting in low plasma concentrations following oral administration (Devassy *et al*., 2015). Consequently, many reported pharmacological effects particularly anticancer activities are derived from in vitro studies employing concentrations that are unlikely to be achieved through traditional jamu consumption. This discrepancy between experimental exposure levels and achievable systemic concentrations raises an important safety concern, as consumers may increase dosage or frequency in an attempt to obtain perceived therapeutic benefits, thereby increasing the risk of adverse effects and drug interactions (Chainani-Wu, 2003).

Animal studies evaluating curcumin toxicity have generally reported no severe acute hepatotoxicity at conventional doses; however, alterations in liver enzyme activity and modulation of drug-metabolizing enzymes have been observed at higher doses (Shah *et al*., 1999). Curcumin has also been reported to influence cytochrome P450 enzyme activity, suggesting a potential for interaction with concomitantly administered drugs that undergo hepatic metabolism. Animal studies evaluating curcumin toxicity

have generally reported no severe acute hepatotoxicity at conventional doses; however, alterations in liver enzyme activity and modulation of drug-metabolizing enzymes have been observed at higher doses. Curcumin has also been reported to influence cytochrome P450 enzyme activity, suggesting a potential for interaction with concomitantly administered drugs that undergo hepatic metabolism (Deogade and Ghate, 2015)

Although curcumin demonstrates extensive biological activity in vitro, its oral bioavailability in humans is low due to rapid metabolism and elimination. This discrepancy between experimental concentrations and achievable systemic exposure raises a potential safety concern, as consumers may increase dosage or frequency to obtain perceived therapeutic effects, thereby increasing the risk of adverse reactions and herb–drug interactions, particularly with anticoagulants.

Kaempferia galanga

Jamu formulations containing *Kaempferia galanga* commonly consist of rice and sand ginger rhizomes, which are rich in phenolic compounds known to exert antioxidant activity. Polyphenolic compounds can mitigate cellular damage by scavenging free radicals, reducing oxidative stress, and downregulating tumor necrosis factor-α (TNF-α), a mediator associated with inflammatory and oxidative tissue injury (Latifah, 2014). Experimental evidence suggests that the antioxidant content of *Kaempferia galanga* jamu may attenuate chemically induced abnormalities in the islets of Langerhans, indicating potential effects on pancreatic tissue integrity (Melliani *et al*., 2011).

Several bioactive constituents in *Kaempferia galanga* jamu including saponins, flavonoids, phenolics, terpenoids, and polysaccharides (amylose) have been associated with antihyperglycemic activity. Saponins have been reported to lower blood glucose levels by inhibiting intestinal glucose transport and stimulating insulin secretion in pancreatic β-cells (Pinent *et al*., 2008). Flavonoid compounds such as kaempferol and apigenin, as well as phenolic constituents, may enhance insulin secretion and increase glucose uptake in peripheral tissues (Hsiech *et al*., 2010). Additional mechanisms include inhibition of glucose absorption through competitive inhibition of α-glucosidase, β-glucosidase, and α-mannosidase in the digestive tract, as well as reduced glucose reabsorption in the renal proximal tubule (Arjita *et al*., 2002). These compounds have also been reported to improve glucose tolerance, inhibit gluconeogenesis (Coskun *et al*., 2005), and protect pancreatic β-cells from oxidative damage induced by free radicals (Lakshmanan *et al*., 2011). Furthermore, polysaccharides derived from rice components in the formulation exhibit antihyperglycemic effects by increasing serum insulin levels, reducing blood glucose concentrations, and enhancing glucose tolerance.

Beyond metabolic effects, active components of *Kaempferia galanga* have demonstrated inhibitory activity against various tumor types, including gastric, colorectal, oral cancers, and multiple myeloma. Isolated constituents such as trans- and cis-ethyl-p-methoxycinnamate have shown anticarcinogenic activity in Epstein–Barr virus (EBV) assays, with reported IC_{50} values of 5.5 and 9.5 μM, respectively (Xue and Chen, 2002). Trans-p-methoxycinnamic acid has also been reported to suppress colon carcinogenesis in induced rat models by modulating pathways related to invasion, proliferation, apoptosis, and inflammation (Gunasekaran *et al*., 2019). While these findings highlight biological activity, many such effects are derived from experimental models employing defined concentrations, underscoring the need to contextualize these data within safety and exposure assessments. *Kaempferia galanga* also exhibits anti-inflammatory properties relevant to traditional use in the treatment of stomachache and toothache associated with inflammatory conditions. Trans-ethyl-p-methoxycinnamate has been reported to inhibit granuloma formation in mice and suppress the release of pro-inflammatory cytokines, including IL-1 and TNF-α. In vitro studies using HMC-1 mast cells stimulated with lipopolysaccharide (LPS) demonstrated that *Kaempferia galanga* extracts significantly reduced the release of IL-6, IL-8, IL-1β, and TNF-α at a concentration of 40 μmol/L, as assessed by MTT assay (Zhou *et al*., 2015). These findings indicate anti-inflammatory potential while also emphasizing the importance of dose-dependent evaluation for toxicological safety.

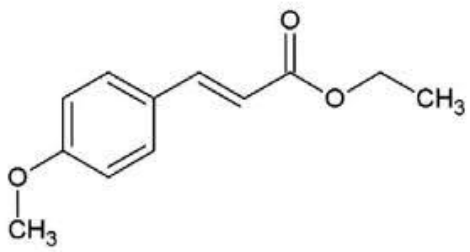

Figure 2: Chemical structure of *Kaempferia galanga* (Wardani *et al*., 2023).

Chemical composition of herbal formulations

Experimental studies have demonstrated various pharmacological properties of ginger (*Zingiber officinale*), particularly its anti-inflammatory activity. Shogaol compounds derived from ginger have been reported to inhibit cyclooxygenase and lipoxygenase enzymes, which play central roles in the metabolism of prostaglandin E_2 and leukotriene B_4 key mediators of inflammatory responses. In addition, ginger exerts anti-inflammatory effects through inhibition of thromboxane synthase, increased prostacyclin levels, and suppression of nitric

oxide release (Shandy *et al*., 2023). These mechanisms contribute to the reported efficacy of ginger in alleviating nausea, vomiting, inflammation, and pain associated with conditions such as arthritis and muscle pain. The anti-inflammatory properties of ginger are primarily attributed to gingerol, the main bioactive compound found in fresh ginger rhizomes (Anggraeni *et al*., 2024). Gingerol inhibits the synthesis of prostaglandins and leukotrienes, thereby reducing inflammatory signaling. Gingerol and shogaol have also been reported to inhibit cancer cell growth and induce apoptosis, supporting their investigation as complementary agents in cancer therapy (Nagabhushan *et al*., 1987; Semwal *et al*., 2015). In addition, ginger exhibits antimicrobial activity, with ginger essential oil demonstrating efficacy against bacteria, fungi, and viruses, contributing to immune modulation and potential benefits in oral health and periodontal disease prevention.

From a toxicological perspective, adverse effects associated with ginger consumption have been reported, particularly at high doses. Oral intake of approximately 35 g of ginger has been associated with heartburn, while doses exceeding 6 g may cause gastric irritation. Inhalation of ginger powder has also been reported to induce IgE-mediated allergic reactions (Muliaty *et al*., 2018). However, developmental toxicity studies administering ginger at a dose of 1000 mg/kg body weight to pregnant mice during the organogenesis period did not reveal maternal toxicity or developmental abnormalities (Santos *et al*., 2017), suggesting a relatively wide safety margin under controlled exposure conditions. Pharmacokinetic studies have shown that gingerol undergoes enzymatic metabolism to gingerdiol in rat liver cells. Investigations administering ginger at doses ranging from 100 mg to 2 g reported no detectable levels of gingerol or shogaol in rat serum, although conjugated metabolites were detected in the bile of mice following oral administration (Zick *et al*., 2008, cited in Semwal *et al*., 2015). Gingerol derived from natural ginger extracts has been shown to exhibit higher bioavailability and greater stability compared to synthetic gingerol mixtures, with only 30% degradation after 21 days of incubation, compared to approximately 80% degradation of shogaol. During drying or thermal processing, gingerol due to its thermolabile β-hydroxy group may undergo dehydration to form shogaol or degradation via retro-aldol reactions to produce zingerone and corresponding aldehydes (Ding *et al*., 1991).

At the cellular level, ginger extracts rich in gingerol or shogaol have demonstrated strong inhibitory effects on lipopolysaccharide (LPS)-induced prostaglandin E_2 production through suppression of cyclooxygenase-2 (COX-2) expression in U937 cells (Mohd, 2016). Similar inhibitory effects on prostaglandin and leukotriene synthesis have been observed in RBL-1 cells (Kiuchi *et al*., 1982) and intact human leukocytes in vitro, where ginger extracts exhibited mechanisms comparable to nonsteroidal anti-inflammatory drugs (NSAIDs) (Flynn *et al*., 1968). While these findings underscore the biological activity of ginger constituents, they also highlight the importance of dose-dependent evaluation and consideration of metabolic and toxicological profiles when assessing long-term safety.

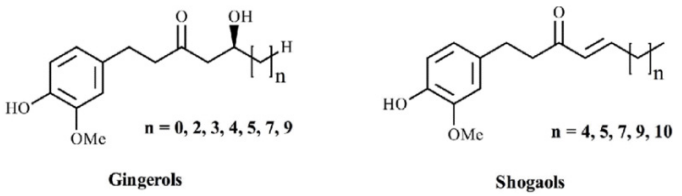

Figure 3: Ginger active compounds (Rahmat *et al*., 2021).

Turmenic (*Curcuma longa*) is a spice with a strong yellow pigment that has been used for cosmetics, dye, and for medical remedies in all over the world. Curcumin is the active component of Turmenic and was first isolated and characterized in 1910. Since then, it has been shown to exhibit antiinflammatory, antimucrobial, antioxidant, antineoplastic properties, and even potential to improve mental illnesses (Vaughn *et al*., 2016). Curcuma contains antioxidants that work synergistically in capturing free radicals by inhibiting oxidation reactions. Aerobic metabolism in humans can produce free radicals (nitric oxide, superoxide, and hydroxyl radicals). Free radical reactions can cause dangerous degenerative diseases, such as dementia, asthma, diabetes, atherosclerosis, cancer, and inflammation. The antioxidant ability of curcuma has been proven and evaluated using various methods (Chainani-Wu, 2003). The curcumin content in turmeric has been proven safe and does not cause significant side effects in high doses (Shah *et al*., 1999). Curcumin has inhibitory effects on platelet aggregation and can interact with anticoagulant and antiplatelet drugs (Rasyid and Lelo, 1999). The compounds contained in turmeric include 69.4% carbohydrates, 5.1% fat, 6.3% protein, 3.5% minerals, and 13.1% water (Prasad *et al*., 2014). Dried turmeric root extract also contains curcuminoids, which include the component curcumin. Curcuminoids consist of 77% curcumin, 17% demethoxycurcumin, and 3% bidemethoxycurcumin. Other components of turmeric, including curcuminoids, have biological activity. The chemical notation for curcumin is 1,7-bis-(4-hydroxy-3-methoxyphenyl)-hepta-1,6-diene-3,5-dione or diferuloylmethane (Deogade and Ghate, 2015). The body cannot absorb curcumin completely due to its high metabolic rate and rapid elimination from the body, resulting in limited bioavailability of curcumin in the body. The low bioavailability of curcumin significantly limits its therapeutic effects (Devassy *et al*., 2015). In ancient times, curcumin was used in Ayurvedic medicine in India to treat injuries, skin diseases, eye infections, burns, and acne (Hatcher *et al*., 2008). Over

the past 30 years, curcumin has been shown to have therapeutic effects in the treatment of cancer, metabolic disorders, autoimmune diseases, neurological diseases, cardiovascular diseases, respiratory diseases, liver diseases, and various other inflammatory diseases (Kannappan *et al*., 2011). Curcumin may have an inhibitory effect on platelet aggregation and could interact with anticoagulation and antiplatelet medications. Curcumin can stimulate gallbladder contractions, exacerbating symptoms in patiens gallstones (Vaughn *et al*., 2016).

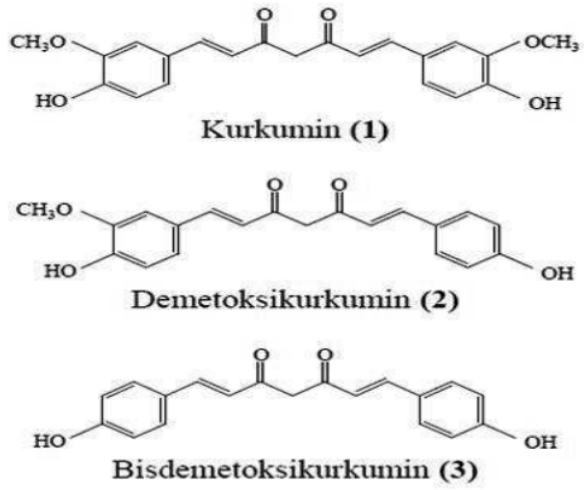

Figure 4: Curcuminoid chemical structure (Nawawi *et al*., 1999).

Methanol extracts of plants used in herbal medicine, such as *A. paniculata, Swietinia mahagoni*, and *C. Aeruginosa* have shown anti-HIV activity by inhibiting HIV-protease activity in MT4 cells infected with HIV-I . Methanol extract of *Melaleuca leucadendron* fruit significantly prolonged the development of herpes-related skin lesions in HSV-1 infection tests in mice and also reduced mortality caused by this herpes virus (Calabrese *et al*., 2000). *A. Paniculata* has also been clinically tested for its antiviral activity. In a phase I clinical trial of andrographolide isolated from *A. Paniculata*, it was tested on 13 HIV-positive patients and five healthy volunteers who were not infected with HIV. The results obtained were that andrographolide could inhibit cell cycle deregulation induced by HIV which causes an increase in CD 4 (+) lymphocyte levels in HIV-1 infected individuals (Calabrase *et al*., 2000). Curcumin can also stimulate gallbladder contractions, worsening symptoms in patients with gallstones (Majeed *et al*., 1995).

Goodarzi *et al*. (2019) reported promising hepatoprotective activity, as indicated by as indicated by a decrease in AST (aspartate aminotransferase) and ALT (alanine aminotransferase) enzyme levels (Goodarzi *et al*., 2019). Studies have been conducted on the hepatoprotective activity of curcumin in relation with nonalcoholic fatty liver disease (NAPLD), which is a cause of liver-related morbidity. They stated that curcumin significantly reduces body mass index (BMI) and waist circumference (WC) (Baziar *et al*., 2020; Akaberi *et al*., 2021).

Toxicology study process

International regulations related to human health require that all traditional medicines undergo toxicity tests on animals before being distributed to the public. acute and subchronic toxicity tests can provide preliminary information about the toxic properties of ingredients contained in traditional medicine formulations that previously had no information (Sasmito *et al*., 2015). Toxicity testing is carried out to estimate the degree of damage caused by a compound contained in herbal medicine to biological and non-biological materials. Toxicity testing is intended to determine the unwanted effects of a drug. This test is carried out by giving a single dose to test animals (rodents and non-rodents). The herbal medicine to be tested is given in different doses to the test animals and then observed for 14 days, after which end-point is carried out. Testing is conducted morphologically, biochemically, pathologically, and histopathologically (Sundari *et al*., 2015). Acute toxicity testing is carried out to determine the acute toxicity value (LD50), which will provide an idea of the toxicity level of a herbal drink. The smaller the LD50 value, the greater the toxicity of the substance. Subchronic toxicity testing is carried out to assess blood chemistry by measuring the number of red blood cells, white blood cells, hemoglobin levels, hematocrit, and also the biochemical overview of the blood by measuring the levels of SGPT, SGOT, creatinine, urea, and seeing the shape of the organs using histopathology methods (Winarno, 2015). While the majority of existing toxicological studies on jamu rely on rodent models, these studies primarily serve as a comparative foundation. The inclusion of multiple animal models in this review is intentional, as it highlights the translational limitations of rodents and provides a scientific basis for proposing *Macaca fascicularis* as a more predictive preclinical model for human safety assessment.

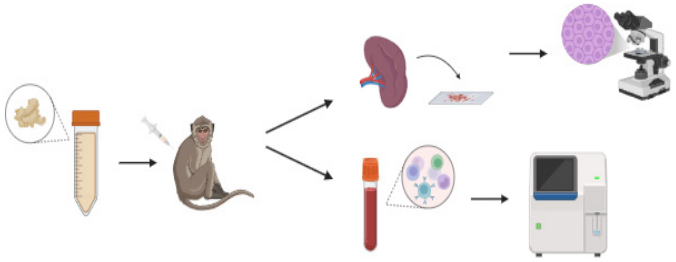

Figure 5: Herbal medicine toxicity tests on *Macaca fascicularis.*

Table 1: The animal models that have been widely used for toxicity study.

Model animal	Toxicity test	Major compound[s]	Dose	Key toxicological findings	Target Organ
Rat	Acute	Herbal medicine for hyperuricemia: Catappa leaves, sappan wood, *Stelechocarpus burahol* leaves, curcuma rhizome, turmeric rhizome, and leafflower (total 19 g) Herbal	~54,720 mg/kg BW	No mortality; LD_{50} > 54,720 mg/kg BW	
	Acute	hypertension medicine: celery herb, gotu kola (centella) herb, cat's whiskers, curcuma temulawa rhizome, turmeric rhizome, leafflower (total 22g)	~50,190 mg/kg BW.	No mortality; LD_{50} > 54,720 mg/kg BW	
	Sub-chronic	Herbal medicine for hyperuricemia	~15,390 mg/kg BW.	No abnormalities in blood, liver, or kidney	Liver, kidney
	Sub-chronic	Herbal medicine for hypertension	~17,820 mg/kg BW	No abnormalities in blood, liver, or kidney (Saryanto and Ardiyanto, 2017)	Liver, kidney
Rat	Acute and sub-chronic	Zedoary rhizome, benzoin tea leaves, mango ginger rhizome, Strychnine tree tuber	>5,000 mg/kg BW	No significant changes in SGOT, urea, creatinine (p>0.05) (Huda *et al*., 2017).	Liver, kidney
Mice	Sub-chronic	*Zingiber officinale*, *Piper nigrum*, *Orthosiphon stamineus*, *Cinnamomum sintoc*, *Abrus precatorius,* and *Massoia aromatica*	800 mg/kg BW	Lymphocytic infiltration in portal vein	Liver
		Cinnamomum sintoc	1,000 mg/kg BW	Fatty liver changes, disrupted hepatocyte architecture (Esti and Novita, 2002).	Liver
Mice	Sub-chronic	Noni fruit extract (*Morinda citrifolia Linn*)	0,2 ml; 0,4 ml; 0,6 ml; and 0,8 ml	No toxic effects observed (Rahmawati and Hulukiti, 2016).	Pancreas
Artemia salina Shrimp larvae	Acute	*Zingiberis rhizomeyang, Phyllanthus niruri L, Achilleae folium, Piperis nigri Fructus, Curcuma domesticeae Rhizoma. Ginger*-based menstrual stimulant herbs	2,000–6,000 ppm	LC_{50} = 3,131 ppm; low acute toxicity (Pehlivanovic *et al*., 2019)	

Across the rodent studies summarized in Table 1, most multi-component jamu formulations exhibited a relatively wide safety margin in acute and sub-chronic exposure, with no mortality or clinically relevant changes in hepatic or renal biomarkers at doses exceeding 5,000 mg/kg BW. However, herb-specific toxicological signals were consistently observed at lower doses in certain plant constituents. Notably, sub-chronic administration of *Abrus precatorius* at 800 mg/kg BW was associated with lymphocytic infiltration in the hepatic portal area, indicating inflammatory liver injury. Similarly, *Cinnamomum sintoc* at 1,000 mg/kg BW produced histopathological alterations consistent with fatty liver degeneration and disrupted hepatocyte architecture. These findings identify the liver as the primary target organ of toxicity across rodent models.

Based on available evidence, the lowest observed adverse effect level (LOAEL) among jamu-related components in rodent studies appears to occur in the range of 800–1,000 mg/kg BW, particularly for formulations containing *Abrus precatorius* and *Cinnamomum sintoc*. In contrast, ginger-based formulations and several commonly used jamu components (*Zingiber officinale*, *Piper nigrum*, *Orthosiphon stamineus*) demonstrated comparatively cleaner safety profiles within the tested dose ranges. This qualitative synthesis highlights that while many jamu formulations show low acute toxicity, component-specific risks exist, emphasizing the need for ingredient-level safety evaluation rather than reliance on formulation-level outcomes alone.

Studies employing macaques as experimental models for herbal medicine research remain relatively limited but demonstrate important scientific value. Available investigations involving *Macaca fascicularis* and other macaque species have examined the effects of plant-derived compounds on lipid metabolism, bile acid balance, antiparasitic activity, and antiviral properties, highlighting the physiological relevance of non-human primates in evaluating complex herbal formulations. Although the number of toxicological studies on jamu specifically using *Macaca fascicularis* is still scarce, the existing non-human primate data provide critical insights that are not readily attainable through rodent models. These include closer similarities to humans in hepatic metabolism, cytochrome

Table 2: Macaques as model animals for herbal medicine study.

Model animal	Study of herbal medicine	Relevance to jamu toxicology
Macaca fascicularis	Cholesterol and Bile Acid Balance in *Macaca fascicularis* Effects of Alfalfa Saponins (Malinow *et al.,* 1981)	Demonstrates similarity to humans in hepatic and bile acid regulation
Macaca fuscata yakui	Antiprotozoal and antihelminthic properties of plants ingested by wild Japanese macaques [Macaca fuscata yakui] in Yakushima Island (Tasdemir *et al*., 2019)	Illustrates physiological tolerance and metabolic handling of plant secondary metabolites

Table 3: *In vitro* studies relevant to *jamu* toxicology

Cell line/ *In vitro* system	Study of herbal medicine	Relevance to jamu toxicology
A549 cells	*Phyllanthus niruri* and curcuma extracts at concentrations of 100 ppm, 250 ppm, and 500 ppm can inhibit the growth of SRV-2 virus grown on A549 cells (human lung cancer cells) (Hernani and Rahardjo, 2005)	Indicates biological responsiveness to jamu-related compounds, though not *in vivo* toxicity

P450 enzyme profiles, endocrine regulation, and long-term toxicity responses. Importantly, the limited availability of primate-based studies should not be interpreted as a lack of scientific relevance; rather, it underscores the need for ethically designed, hypothesis-driven, and targeted non-human primate research to strengthen the translational assessment of jamu safety and efficacy.

DISCUSION

Laboratory animals are widely used as experimental models in biomedical research, including drug development, toxicity assessment, and pharmacokinetic studies. Commonly used experimental animals include mice, rats, ferrets, and non-human primates. The selection of appropriate animal models is a critical step in preclinical testing, as these models serve as the primary biological systems for evaluating therapeutic efficacy and safety prior to human exposure (Mukherjee *et al*., 2022). Beyond drug development, animal models also play essential roles in the preclinical evaluation of medical devices and tissue engineering applications intended for human use (Stone *et al*., 1987).

In herbal toxicology studies, commonly used in vivo models include mice (*Mus musculus*) and rats (*Rattus norvegicus*), which offer advantages in terms of cost, availability, and ethical feasibility. However, these models may not fully capture complex human-relevant biological processes. In contrast, the long-tailed macaque (*Macaca fascicularis*) has been proposed as a potentially more translationally relevant model due to its closer genetic, physiological, and behavioral similarities to humans. Immunological studies have demonstrated that *M. fascicularis* exhibits standardized immune parameters relevant to toxicity research, supporting its value in studies where immune-mediated effects are a concern (Ignatova *et al*., 2014). Furthermore, the genome of *M. fascicularis* has been fully sequenced, revealing a high degree of similarity to human transcripts, which enhances its relevance for studying drug metabolism and toxicological responses compared to rodents, which exhibit greater genetic divergence (Mutai *et al*., 2018; Amato *et al*., 2022). Despite these advantages, the use of non-human primates in research is highly constrained. Primate studies account for less than 1% of all laboratory animal use due to stringent ethical oversight, high financial costs, limited availability, and societal concern (Ernita *et al*., 2021). Consequently, *M. fascicularis* cannot be justified as a routine model for jamu safety screening. Instead, its potential role should be considered selectively, particularly for addressing complex toxicological questions that cannot be adequately resolved using rodent models or emerging human-relevant in vitro systems.

The growing global consumption of jamu has prompted increased interest in its safety and biological effects in animal models, including non-human primates. Jamu formulations typically contain multiple plant extracts rich in bioactive compounds, such as those derived from the Zingiberaceae family, which are known to contain essential oils and oleoresins with anti-inflammatory, antioxidant, and immunomodulatory properties (Phillips *et al*., 2014). Experimental evidence suggests that combinations of ginger, turmeric, and temulawak (*Curcuma xanthorrhiza* Roxb) can improve growth performance and health parameters in broiler chickens, indicating potential biological activity that may also be relevant in higher-order species (Widyowati and Agil, 2018). However, extrapolation of such benefits to primates or humans requires careful toxicological evaluation. Curcumin, one of the most extensively studied constituents of jamu, has been reported to interfere with multiple stages of cancer development by suppressing angiogenesis, metastasis, and tumor cell proliferation through diverse molecular pathways, including cyclin D1, c-myc, Bcl-2 family proteins, caspase activation, p53 signaling, and death receptor pathways (Ravindran *et al*., 2009). These mechanisms underpin its reported efficacy against multiple cancer types, including

multiple myeloma, colon, breast, prostate, lung, and pancreatic cancers (Anand *et al*., 2008). Nevertheless, the translation of such findings to safety assessment remains challenging, particularly given the low bioavailability of curcumin and the risk of dose escalation during long-term consumption (Kocaadam and Sanlier, 2017).

Safety concerns associated with herbal medicine use must therefore be carefully evaluated, especially in non-human primates. Certain herbal formulations have been reported to alter plasma uric acid levels and induce histopathological changes in animal models, raising concerns regarding chronic exposure (Xiang *et al*., 2023). Additionally, the adulteration of herbal products with synthetic pharmaceuticals has been associated with severe adverse effects, including seizures and coma, underscoring the need for rigorous quality control and regulatory oversight (Mustika *et al*., 2022). These issues are particularly relevant for *M. fascicularis*, as its physiological responses may differ substantially from those of rodents. Examples of non-human primate research involving purified compounds, such as triptonide and Shi-Bi-Man, further illustrate both the strengths and limitations of primate models. Studies on triptonide derived from *Tripterygium wilfordii* F demonstrated its efficacy as a reversible, non-hormonal male contraceptive in mice and cynomolgus monkeys by selectively disrupting sperm motility without systemic toxicity (Chang *et al*., 2021; Diarti *et al*., 2020). Similarly, Shi-Bi-Man was shown to promote hair follicle stem cell activation through metabolic modulation in cynomolgus monkeys (Du *et al*., 2023). While these studies highlight the translational relevance of primate models for targeted pharmaceutical development, they do not directly address the safety evaluation of complex, multi-herb jamu formulations, where synergistic or antagonistic interactions may further complicate interpretation.

Advances in alternative research technologies, including in vitro systems and computational modeling, offer promising complementary approaches to animal experimentation. Nevertheless, for certain high-priority toxicological questions such as chronic low-dose exposure, immune endocrine interactions, and complex metabolic responses animal models remain indispensable (Mikail *et al*., 2023). In this context, the value of *Macaca fascicularis* lies not in routine testing, but as a targeted, confirmatory model applied selectively when rodent and in vitro data are insufficient to address critical human-relevant safety concerns.

CONCLUSION

Long-term evaluation is essential for assessing the chronic toxicity and pharmacokinetic behavior of herbal medicines, particularly due to the complex interactions among multiple bioactive constituents and host metabolic pathways. Herbal formulations typically consist of heterogeneous compounds that may influence drug-metabolizing enzymes and transporters, thereby altering bioavailability and systemic exposure. Interactions between herbal medicines and conventional drugs have been shown to modify metabolic profiles and, in some cases, increase the risk of adverse effects. Consequently, a detailed understanding of herb–metabolism interactions is critical for robust safety assessment. In principle, non-human primates such as *Macaca fascicularis* offer advantages for pharmacokinetic and long-term toxicity studies because of their closer physiological, genetic, and metabolic similarity to humans. Long-duration studies in primates may provide insights into compound accumulation, delayed toxicity, and regulatory-system effects that are not readily detectable in short-term studies or in rodent models. However, the feasibility of such studies must be carefully weighed against substantial ethical, financial, and logistical constraints. As discussed earlier, these considerations largely explain the very limited proportion of primate use in toxicological research and preclude their routine application for broadly consumed traditional medicines.

Accordingly, the sustainability of herbal medicine safety assessment should primarily rely on rodent-based in vivo studies using mice (*Mus musculus*) and rats (*Rattus norvegicus*), complemented by advanced analytical approaches to characterize dose–response relationships, organ-specific toxicity, and metabolic pathways. Non-rodent species, including *Macaca fascicularis*, should be considered only at a later stage and for specific, high-priority questions particularly when rodent and human-relevant in vitro systems yield inconclusive results due to interspecies metabolic differences. In contrast, the use of phylogenetically distant organisms such as *Artemia salina* shrimp larvae should be interpreted cautiously, as their genetic, biochemical, and physiological dissimilarities from humans limit their translational relevance beyond preliminary toxicity screening. The application of the 3R principles replacement, reduction, and refinement is therefore central to any proposed use of *Macaca fascicularis* in herbal toxicology. Rather than justifying increased primate use, adherence to the 3Rs necessitates that primate studies be hypothesis-driven, minimized in number, and employed only when alternative models cannot adequately address critical safety concerns. Implemented in this manner, the 3R framework not only reduces animal use but also promotes the development of complementary non-animal methodologies and more refined experimental designs. This balanced approach supports ethical responsibility while ensuring that toxicity assessments generate reliable and human-relevant data for the long-term safety evaluation of herbal medicines.

ACKNOWLEDGMENT

The authors are thankful for supporting via the PMDSU Grant (Batch VIII), provided by the Ministry of Education and Culture, Republic of Indonesia. This study was additionally supported by the Professor Nidom Foundation, Indonesia.

NOVELTY STATEMENT

The novelty of this review lies in its integrative discussion of Macaca spp. as an advanced preclinical model for the evaluation of traditional herbal medicines (jamu). While most existing reviews focus on rodent-based preclinical studies, this article highlights the physiological, immunological, and genetic proximity of Macaca to humans as a critical advantage for translational research. Importantly, the review extends beyond conventional efficacy and toxicity assessments by synthesizing evidence on the potential role of pathogen challenge models in non-human primates, offering a comprehensive framework for improving the predictive value of preclinical jamu research.

AUTHOR'S CONTRIBUTION

Methodology: TWM, EDP, and CAN. Software: ANN, ZIA, IYR, and JJ. Validation: SI and RVN. Formal analysis: ANN, ZIA, IYR, and JJ. Investigation: ANN, ZIA, IYR and JJ. Resources: TWM, EDP, and CAN. Data curation: TWM, EDP, and CAN. Writing original draft: TWM and EDP. Writing review and editing: RVN and SI. Visualization: ANN, ZIA, IYR, and JJ. Supervision: SI, RVN, and CAN. Project administration: TWM, EDP, and CAN. All authors have read and agreed to the published version of the manuscript.

Generative AI and AI-assisted technology statement

The authors declare that generative AI was used solely for language editing and grammar improvement. The authors take full responsibility for the content of the manuscript.

Conflict of interest

The authors have declared no conflict of interest.

REFERENCES

Ahnafani MN, Nasiroh N, Aulia N, Lestari NLM, Ngongo M, Hakim AR (2024). Jahe (*Zingiber officinale*): Tinjauan fitokimia, farmakologi, dan toksikologi. J. Ilmu Kedokteran Kesehatan, 11(10): 1992–1998. https://doi.org/10.33024/jikk.v11i10.15945

Akaberi M, Sahebkar A, Emami SA (2021). Turmeric and curcumin: From traditional to modern medicine. Adv. Exp. Med. Biol., 1291: 15–39. Springer. https://doi.org/10.1007/978-3-030-56153-6_2

Aldizal R, Rizkio M, Perdana F, Suci F, Galuh V, Putri A, Rina A, Cahyani ND, Yanti R, Khendri F (2019). Review: Temulawak plant (*Curcuma xanthorrhiza* Roxb) as traditional medicine. Sci. J. Pharma. Bahari.

Amato R, Gardin JF, Tooze JA, Cline JM (2022). Organ weights in relation to age and sex in cynomolgus monkeys (*Macaca fascicularis*). Toxicol. Pathol., 50(5): 574–590. https://doi.org/10.1177/01926233221088283

Anand P, Sundaram C, Jhurani S, Kunnumakkara AB, Aggarwal BB (2008). Curcumin and cancer: An "old-age" disease with an "age-old" solution. Cancer Lett., 267(1): 133–164. https://doi.org/10.1016/j.canlet.2008.03.025

Antony S, Kuttan R, Kuttan G (1999). Immunomodulatory activity of curcumin. Immunol. Invest., 28(5–6): 291–303. https://doi.org/10.3109/08820139909062263

Anggraeni L, Anggraheni EN, Deima HUH, Thohar IYQ, Marwa KO, Satya MA, Suhada RA, Pascafitra A, Wulandari G, Hutabarat LG, Saputra MR (2024). Pengembangan Ekonomi Masyarakat Desa Genengan melalui Produksi Ginger Oil sebagai Unit Usaha "Gemati" dalam Upaya Pemanfaatan Limbah Jahe. In Prosiding Seminar Nasional Pengabdian Masyarakat & CSR Fakultas Pertanian UNS (Vol. 4, No. 1, pp. 72-80).

Arjita IPD, Widodo MA, Widjajanto E (2002). Pengaruh kadar glukosa tinggi terhadap sintesis nitric oxide dari human umbilical vein endothelial cells (HUVEs) culture dengan tehnik bioassay. Biosain.

Aryanta IWR (2019). Manfaat Jahe untuk Kesehatan. Widya Kesehatan, 1(2): 39–43. https://doi.org/10.32795/widyakesehatan.v1i2.463

Ata N, Yusuf NA, Tan BC, Husaini A, Yusuf YM, Majid NA, Khalid N (2015). Expression profiles of flavonoid-related gene, 4-coumarate: Coenzyme A ligase, and optimization of culturing conditions for the selected flavonoid production in *Boesenbergia rotunda*. Plant Cell, Tissue Organ Cult., 123(1): 47–55. https://doi.org/10.1007/s11240-015-0813-4

Ballester P, Cerdá B, Arcusa R, Marhuenda J, Yamedjeu K, Zafrilla P (2022). Effect of ginger on inflammatory diseases. Molecules, 27(21): 7223. https://doi.org/10.3390/molecules27217223

Baziar N, Parohan M (2020). The effects of curcumin supplementation on body mass index, body weight, and waist circumference in patients with nonalcoholic fatty liver disease: A systematic review and dose-response meta-analysis of randomized controlled trials. Phytother. Res., 34(3): 464–474. https://doi.org/10.1002/ptr.6542

Bolton ID (2015). Basic physiology of Macaca fascicularis. In: The nonhuman primate in nonclinical drug development and safety assessment. pp. 67–86. https://doi.org/10.1016/B978-0-12-417144-2.00005-6

Calabrese C, Berman SH, Babish JG, Ma X, Shinto L, Dorr M, Wells K, Wenner CA, Standish LJ (2000). A phase I trial of andrographolide in HIV positive patients and normal volunteers. Phytother. Res., 14(5): 333–338. https://doi.org/10.1002/1099-1573(200008)14:5<333::AID-PTR584>3.0.CO;2-D

Carlsson HE, Schapiro SJ, Farah I, Hau J (2004). Use of primates in research: A global overview. Am. J. Primatol., 63(4): 225–237. https://doi.org/10.1002/ajp.20054

Chainani-Wu N (2003). Safety and anti-inflammatory activity of curcumin: A component of turmeric (*Curcuma longa*). J. Altern. Complement. Med., 9(1): 161–168. https://doi.

org/10.1089/107555303321223035
Chang Z, Qin W, Zheng H, Schegg K, Han L, Liu X, Wang Y, Wang Z, McSwiggin H, Peng H, Zhang Z, Yu Y, Gao F, Cao J, Zhang Y, Mao J, Wang X, Han C, Li N, Cheng CY (2021). Triptonide is a reversible non-hormonal male contraceptive agent in mice and non-human primates. Nat. Commun., 12: 1253. https://doi.org/10.1038/s41467-021-21517-5
Chobe S, Patra SK, Chobe M, Metri K (2022). Efficacy of integrated yoga and ayurveda rasayana on cognitive functions in elderly with mild cognitive impairment: Non-randomized three-arm clinical trial. J. Ayurveda Integr. Med., 13(1): 100373. https://doi.org/10.1016/j.jaim.2020.11.003
Coskun O, Kanter M, Korkmaz A, Oter S (2005). Quercetin, a flavonoid antioxidant, prevents and protects streptozotocin-induced oxidative stress and β-cell damage in rat pancreas. Pharmacol. Res., 51(2): 117–123. https://doi.org/10.1016/j.phrs.2004.06.002
Deogade S, Ghate S (2015). Curcumin: Therapeutic applications in systemic and oral health. Int. J. Biol. Pharma. Res., 6(4): 281–290.
Devassy JG, Nwachukwu ID, Jones PJH (2015). Curcumin and cancer: Barriers to obtaining a health claim. Nutr. Rev., 73(3): 155–165. https://doi.org/10.1093/nutrit/nuu064
Diarti M, Rohmi R, Jiwintarum Y (2020). The preparation of rajalom (herb of chili herbs) on plasma uric acid levels and histopathological features of the aorta of rattus novergicus. Poltekita J. Health Sci., 14(2): 141-148. https://doi.org/10.33860/jik.v14i2.222
Ding GH, Naora K, Hayashibara M, Katagiri Y, Kano Y, Iwamoto K (1991). Pharmacokinetics of [6]-gingerol after intravenous administration in rats. Chem. Pharma. Bull. (Tokyo), 39(6): 1612–1614. https://doi.org/10.1248/cpb.39.1612
Du H, Zhang T, Wang Q, Cao X, Zheng H, Li J, Zhu J, Qu J, Guo L, Sun Y (2023). Traditional Chinese medicine Shi-Bi-Man regulates lactic acid metabolism and drives hair follicle stem cell activation to promote hair regeneration. Chinese Med., 18: 84. https://doi.org/10.1186/s13020-023-00791-z
Erlyn P (2016). Efektivitas antibakteri fraksi aktif serai (*Cymbopogon citratus*) terhadap bakteri *Streptococcus mutans*. Syifa' MEDIKA: J. Kedokteran Kesehatan, 6(2): 111–125. https://doi.org/10.32502/sm.v6i2.1387
Ernita R, Setia TM, Dewi FNA, Darusman HS (2021). Long-tailed monkeys (*Macaca fascicularis*) as model animals and the ethics of their use. Gunung Djati Conf. Ser., 6: 308–315.
ESTI, Dwi Ery Novita (2002). Subchronic toxicity test of Jamu X on the pancreas of male mice (Musculus) Microscopically.
Flynn DL, Rafferty MF, Boctor AM (1968). Inhibition of human neutrophil 5-lipoxygenase activity by gingerdione, shogaol, capsaicin and related pungent compounds. Prostaglandins Leukot Med., 24: 195–198. https://doi.org/10.1016/0262-1746(86)90126-5
Goodarzi R, Sabzian K, Shishehbor F, Mansoori A (2019). Does turmeric/curcumin supplementation improve serum alanine aminotransferase and aspartate aminotransferase levels in patients with nonalcoholic fatty liver disease? A systematic review and meta-analysis of randomized controlled trials. Phytother. Res., 33(3): 561–570. https://doi.org/10.1002/ptr.6270
Gordon A, Buch Z, Baute V, Coeytaux R (2019). Use of Ayurveda in the treatment of type 2 diabetes mellitus. Glob. Adv. Health Med., 8: 2164956119861094. https://doi.org/10.1177/2164956119861094
Gunasekaran S, Venkatachalam K, Namasivayam N (2019). Anti-inflammatory and anticancer effects of p-methoxycinnamic acid, an active phenylpropanoid, against 1,2-dimethylhydrazine-induced rat colon carcinogenesis. Mol. Cel. Biochem., 451(1-2): 117–129. https://doi.org/10.1007/s11010-018-3398-5
Hadipoentyanti E, Syahid SF (2007). Respons temulawak (*Curcuma xanthorrhiza* Roxb.) hasil rimpang kultur jaringan generasi kedua terhadap pemupukan. J. Penelitian Tanaman Industri, 13(3): 106–110. https://doi.org/10.21082/jlittri.v13n3.2007.106-110
Handayani R, Anggraeni E, Handayani Y, Sari MP (2024). Edukasi kesehatan: Pelatihan pembuatan air rebusan jahe sebagai terapi herbal non-farmakologi untuk mengatasi dismenore. Indones. J. Commun. Dedicat. Health, 4(1): 13–19. https://doi.org/10.38165/jk.v15i1.422
Handayani S, Mursiti S, Wijayati N (2018). Uji Aktivitas Antibakteri Senyawa Flavonoid dari Rimpang Temu Kunci (*Kaempferia pandurata* Roxb.) terhadap *Streptococcus mutans*. Indones. J. Chem. Sci.,
Hatcher H, Planalp R, Cho J, Torti FM, Torti SV (2008). Curcumin: From ancient medicine to current clinical trials. Cell Mol. Life Sci., 65: 1631–1652. https://doi.org/10.1007/s00018-008-7452-4
Hernani RM, Rahardjo M (2005). Plants with antioxidant properties. Jakarta: Penebar Swadaya.
Hsieh PC, Huang GJ, Ho YL, Lin YH, Huang SS, Chiang YC, Tseng MC, Chang YS (2010). Activities of antioxidants, α-Glucosidase inhibitors and aldose reductase inhibitors of the aqueous extracts of four Flemingia species in Taiwan. Botanical Stud., 51: 293–302.
Huda MN, Holidah D, Fajrin FA (2017). Uji toksisitas subkronik jamu asam urat pada hati mencit galur balb-C. Pustaka Kesehatan, 5(1): 65–70.
Ignatova IE, Agrba VZ, Karal-Ogly DD (2014). Cellular immunity standard values in *Macaca fascicularis*. Bull. Exp. Biol. Med., 157(2): 265–267. https://doi.org/10.1007/s10517-014-2541-x
Kannappan R, Gupta SC, Kim JH, Reuter S. and Aggarwal, BB, (2011). Neuroprotection by spice-derived nutraceuticals: you are what you eat!. Molecular neurobiology, 44(2), pp.142-159
Kiuchi F, Shibuya M, Sankawa U (1982). Inhibitors of prostaglandin biosynthesis from ginger. Chem. Pharm. Bull. (Tokyo), 30: 754–757. https://doi.org/10.1248/cpb.30.754
Kocaadam B, Şanlier N (2017). Curcumin, an active component of turmeric (Curcuma longa), and its effects on health. Critical reviews in food science and nutrition, 57(13), pp.2889-2895.
Kumar S, Dobos GJ, Rampp T (2017). The significance of ayurvedic medicinal plants. J. Evid. Based Complement. Altern. Med., 22(3): 494–501. https://doi.org/10.1177/2156587216671392
Kusumo AR, Wiyoga FY, Perdana HP, Khairunnisa I, Suhandi RI, Prastika SS (2020). Traditional Indonesian herbs: Boost immunity naturally during pandemic [Jamu tradisional Indonesia: Tingkatkan imunitas tubuh secara alami selama pandemi]. J. Publ. Ser., 4(2): 465–471. https://doi.org/10.20473/jlm.v4i2.2020.465-471
Lakshmanan D, Werngren J, Jose L, Suja KP, Nair MS, Varma RL, Mundayoor S, Hoffner S, Kumar RA (2011). Ethyl p-methoxycinnamate isolated from a traditional anti-

tuberculosis medicinal herb inhibits drug resistant strains of *Mycobacterium tuberculosis in vitro*. Fitoterapia, 82(5): 757–761. https://doi.org/10.1016/j.fitote.2011.03.006

Latifah NJ (2014). Uji Aktivitas Jamu Gendong Beras Kencur (*Oryza sativa* L.; *Kaempferia galanga* L.) sebagai Antidiabetes pada Tikus Putih Jantan Galur Wistar yang Diinduksi Streptozotocin. J. Mahasiswa Farmasi Fakultas Kedokteran UNTAN, 1(1).

Majeed M, Badmaev V, Shivakumar U, Rajendran R (1995). Curcuminoids: Antioxidant phytonutrients. Nutr. Sci., 2: 1–8.

Malinow MR, Connor WE, McLaughlin P, Stafford C, Lin DS, Livingston AL, Kohler GO, McNulty WP (1981). Cholesterol and bile acid balance in Macaca fascicularis. Effects of alfalfa saponins. J. Clin. Invest., 67(1): 156–162. https://doi.org/10.1172/JCI110008

Meliani N, Dib MEA, Allali H, Tabti B (2011). Hypoglycaemic effect of *Berberis vulgaris* L. in normal and streptozotocin-induced diabetic rats. Asian Pac. J. Trop. Biomed., 1(6): 468-471. https://doi.org/10.1016/S2221-1691(11)60102-0

Mikail M, Azizan TRPT, Noor MHM, Hassim HA, Che'Amat A, Latip MQA (2023). Long-tailed macaque (*Macaca fascicularis*) contraception methods: A systematic review. Biology, 12(6): 848. https://doi.org/10.3390/biology12060848

Mohd-Yusof YA (2016). Gingerol and its role in chronic diseases. Adv. Exp. Med. Biol., 929: 177–207. Springer. https://doi.org/10.1007/978-3-319-41342-6_8

Mukherjee P, Roy S, Ghosh D, Nandi SK (2022). Role of animal models in biomedical research: A review. Lab. Anim. Res., 38(1): 18. https://doi.org/10.1186/s42826-022-00128-1

Muliasari H, Ananto AD, Andayani Y (2019). Innovation and quality improvement of jamu products in jamu gendong crafters in Mataram city. ProsidinG Pepadu, 1: 72-77.

Muliaty S, Indrawati L, Ikawati Z (2018). Efek Jahe (*Zingiber officinale*) terhadap Kadar Gula dan Kadar Kolesterol Darah: Tinjauan Sistematik. Majalah Kedokteran UKI, 34(1): 26-40.

Mustika A, Mohamad K, Sutardi L, Rabi'ah S, Pangesti U, Leluala S (2022). Performa broiler dengan pemberian jamu kombinasi jahe, kunyit, dan temulawak. Acta Vet. Indones., 10(3): 253–261. https://doi.org/10.29244/avi.10.3.253-261

Mutai H, Miya F, Shibata H, Yasutomi Y, Tsunoda T, Matsunaga T (2018). Gene expression dataset for whole cochlea of *Macaca fascicularis*. Sci. Rep., 8(1): 15554. https://doi.org/10.1038/s41598-018-33985-9

Nagabhushan M, Bhide SV. (1987). Antimutagenicity and anticarcinogenicity of ginger (*Zingiber officinale*). Nutrition and Cancer, 8(3), 201–210. https://doi.org/10.1080/01635588709513935

Nawawi A, Nakamura N, Hattori M, Kurokawa M, Shiraki K (1999). Inhibitory effects of Indonesian medicinal plants on the infection of herpes simplex virus type 1. Phytother. Res., 13(1): 37–41. https://doi.org/10.1002/(SICI)1099-1573(199902)13:1<37::AID-PTR382>3.0.CO;2-S

Nursuprianah I, Heryandi Y, Risdianto R (2022). Manfaat jamu empon-empon untuk peningkatan imunitas tubuh pada masa pandemi Covid-19. Dimasejati: Jurnal Pengabdian Kepada Masyarakat, 4(1): 107–117. https://doi.org/10.24235/dimasejati.v4i1.10846

Organisation for Economic Co-operation and Development (OECD). (2001). Test No. 420: Acute oral toxicity. Fixed dose procedure. OECD Publishing.

Pehlivanović B, Fetahović D, Aruković E, Žiga Smajić N, Bečić F (2019). Animal models in modern biomedical research. Eur. J. Pharma. Med. Res., 6(7): 35–38.

Phillips KA, Bales KL, Capitanio JP, Conley A, Czoty PW, 't Hart BA, Hopkins WD, Hu SL, Miller LA, Nader MA, Nathanielsz PW, Rogers J, Shively CA, Voytko ML (2014). Why primate models matter. Am. J. Primatol., 76(8): 801–827. https://doi.org/10.1002/ajp.22281

Pinent M, Castell A, Baiges I, Montagut G, Arola L (2008). Bioactivity of flavonoids on insulin-secreting cells. Comprehens. Rev. Food Sci. Food Saf., 7(4): 299–308. https://doi.org/10.1111/j.1541-4337.2008.00048.x

Prakash S, Shelke AU (2014). Role of Triphala in dentistry. J. Indian Soc. Periodontol., 18(2): 132–135. https://doi.org/10.4103/0972-124X.131299

Prasad S, Gupta S, Tyagi A, Aggarwal B (2014). Curcumin, a component of golden spice: From bedside to bench and back. Biotechnology Advances. Advance online publication. https://doi.org/10.1016/j.biotechadv.2014.04.004

Qin F, Huang X, Zhang HM, Ren P (2009). Pharmacokinetic comparison of puerarin after oral administration of Jiawei-Xiaoyao San to healthy volunteers and patients with functional dyspepsia: Influence of disease state. J. Pharma. Pharmacol., 61(1): 125–129. https://doi.org/10.1211/jpp/61.01.0018

Rahmat E, Lee J, Kang Y (2021). Javanese turmeric (*Curcuma xanthorrhiza* Roxb.): Ethnobotany, phytochemistry, biotechnology, and pharmacological activities. Evid. Based Complement. Altern. Med., 2021: 9960813. https://doi.org/10.1155/2021/9960813

Rahmawati F, Ignatia H (2016). Toxicity and phytochemical test of menstrual relief herbs made from ginger (*Zingiberis rhizome*). UKI Med. Mag., 32(3): 126–129.

Rasyid A, Lelo A (1999). The effect of curcumin and placebo on human gall-bladder function: An ultrasound study. Aliment. Pharmacol. Therap., 13(2): 245–249. https://doi.org/10.1046/j.1365-2036.1999.00464.x

Ravindran J, Prasad S, Aggarwal BB, (2009). Curcumin and cancer cells: how many ways can curry kill tumor cells selectively?. The AAPS journal, 11(3), pp.495-510. Aliment. Pharmacol. Therap., 13(2): 245–249. https://doi. org/10.1046/j.1365-2036.1999.00464.x

Rosidi A, Khomsan A, Setiawan B, Riyadi H, Briawan D (2014). Potential of temulawak (*Curcuma xanthorrhiza* Roxb) as antioxidant. In: Proceedings of National and International Seminar.

Rukmana R (2004). Living pharmacy discoveries in the garden. Kanisius.

Rusmalina S, Khasanah K, Nugroho DK (2020). Deteksi asam mefenamat pada jamu pegel linu yang beredar di wilayah Pekalongan. Pharmacon J. Farmasi Indones., pp. 51–60. https://doi.org/10.23917/pharmacon.v0i0.10111

Santos-Sánchez NF, Salas-Coronado R, Valadez-Blanco R, Hernández-Carlos B, Guadarrama-Mendoza PC (2017). Natural antioxidant extracts as food preservatives. Acta Sci. Polon. Technol. Aliment., 16(4): 361–370. https://doi.org/10.17306/J.AFS.0530

Saryanto S, Ardiyanto D (2017). Uji toksisitas akut dan subkronis ramuan jamu untuk fibro adenoma mammae (FAM). Jurnal Ilmu Farmasi dan Farmasi Klinik, 2(8): 42–50.

Sasmito WA, Wijayanti AD, Fitriana I, Sari PW (2015). Pengujian toksisitas akut obat herbal pada mencit berdasarkan organization for economic co-operation and

development (OECD). J. Sain Vet., 33(2): 234–239. https://doi.org/10.22146/jsv.17924

Sebastian CD (2022). Ayurveda and the medical knowledge in ancient India: Shadows and realities. Indian J. Med. Ethics, 8(1): 8–15. https://doi.org/10.20529/IJME.2021.085

Semwal RB, Semwal DK, Combrinck S, Viljoen AM (2015). Gingerols and shogaols: Important nutraceutical principles from ginger. Phytochemistry, 117: 554–568. https://doi.org/10.1016/j.phytochem.2015.07.012

Shah BH, Nawaz Z, Pertani SA, Roomi A, Mahmood H, Saeed SA, Gilani AH (1999). Inhibitory effect of curcumin, a food spice from turmeric, on platelet-activating factor- and arachidonic acid-mediated platelet aggregation through inhibition of thromboxane formation and Ca^{2+} signaling. Biochem. Pharmacol., 58(7): 1167–1172. https://doi.org/10.1016/S0006-2952(99)00206-3

Shandy AD, Fauziah F, Azzahro NH, Siregar WT (2023). Literature study: Effectiveness of indonesian rhizomes as anti-inflammatory. J. Adapt. Health Innov., 5(5).

Sidik M, Mulyono MW, Muhtadi A (1992). Temulawak (*Curcuma xanthorrhiza* Roxb.). Phytomedic medicine development foundation.

Srivastava R, Srimal RC (1985). Modification of certain inflammation-induced biochemical changes by curcumin. Indian J. Med. Res., pp. 215-223.

Stone WH, Treichel RCS, VandeBerg JL (1987). Genetic significance of some common primate models in biomedical research. Prog. Clin. Biol. Res., 229: 73–93.

Sundari D, Widowati L, Winarno MW (2015). Studi keamanan ramuan jamu untuk hiperurisemia dan hipertensi. Bull. Penel. Kesehatan, 43(3): 137–146. https://doi.org/10.22435/bpk.v43i3.4341.137-146

Suparmi S, Wahidin D, Rietjens IM (2021). Risk characterisation of constituents present in jamu to promote its safe use. Crit. Rev. Toxicol., 51(2): 183–191. https://doi.org/10.1080/10408444.2021.1912708

Syamsudin RAMR, Perdana F, Mutiaz FS (2019). Curcuma longa plant (*Curcuma xanthorrhiza* Roxb) as a traditional medicine. Sci. J. Pharmacol. Bahari, 10(1): 51–65. https://doi.org/10.52434/jfb.v10i1.648

Tasdemir D, MacIntosh AJJ, Stergiou P, Kaiser M, Mansour NR, Bickle Q, Huffman MA (2020). Antiprotozoal and antihelminthic properties of plants ingested by wild Japanese macaques (*Macaca fuscata yakui*) in Yakushima Island. J. Ethnopharmacol., 247: 112270. https://doi.org/10.1016/j.jep.2019.112270

Tjen D (2024). From jamu to biodefense: Navigating global health in a changing world. Elex Media Komputindo.

Vaughn AR, Branum A, Sivamani RK (2016). Effects of turmeric (*Curcuma longa*) on skin health: A systematic review of the clinical evidence. Phytother. Res., 30(8): 1243–1264. https://doi.org/10.1002/ptr.5640

Waluyo Dwitri. Jamu Officially Entered UNESCO Intangible Cultural Heritage. https://indonesia.go.id/kategori/budaya/7831/jamu-resmi-masuk-warisan-budaya-takbenda-unesco?lang=1

Winarno FG. (2015). Toksikologi pangan. Jakarta: Gramedia Pustaka Utama

Wardani RS, Schellack N, Govender T, Dhulap AN, Utami P, Malve V, Wong YC (2023). Treatment of the common cold with herbs used in Ayurveda and Jamu: Monograph review and the science of ginger, liquorice, turmeric and peppermint. Drugs Context, 12: 2023-2-12. https://doi.org/10.7573/dic.2023-2-12

Widowati W (2008). Potensi antioksidan sebagai antidiabetes. Jkm, 7(2): 1-11.

Widyowati R, Agil M (2018). Chemical constituents and bioactivities of several Indonesian plants typically used in jamu. Chem. Pharma. Bull., 66(5): 506–518. https://doi.org/10.1248/cpb.c17-00983

Woerdenbag HJ, Kayser O (2014). Jamu: Indonesian traditional herbal medicine towards rational phytopharmacological use. J. Herb. Med., 4(2): 51–73. https://doi.org/10.1016/j.hermed.2014.01.002

Xiang L, Liu Z, Liao J, Qian C, Lu X, Fan X (2023). Network pharmacology approaches for research of traditional chinese medicines. Chinese J. Natl. Med., 21(5): 323–332. https://doi.org/10.1016/S1875-5364(23)60429-7

Xue Y, Chen H (2002). Study on the anti-carcinogenic effects of three compounds in *Kaempferia galanga* L. Wei Sheng Yan Jiu, 31(4): 247–251.

Yanti R, Rukayadi Y, Lee KH, Hwang JK (2009). Activity of panduratin a isolated from *Kaempferia pandurata* Roxb. Against multi-species oral biofilms *in vitro*. J. Oral Sci., 51(1): 87–95. https://doi.org/10.2334/josnusd.51.87

Yuan SC, Iskandar Y (2018). Study of chemical content and pharmacological activity of turmeric plants (*Curcuma longa* L.). Pharmacia.

Zhou YJ, Wang H, Li L, Sui HH, Huang JJ. (2015). Inhibitory effect of kaempferol on inflammatory response of lipopolysaccharide-stimulated human mast cells. Yao Xue Xue Bao (Acta Pharmaceutica Sinica), 50(10), 1332–1337.

Zick SM, Djuric Z, Ruffin MT, Litzinger AJ, Normolle DP, Alrawi S, Feng MR, Brenner DE (2008). Pharmacokinetics of 6-, 8-, 10-gingerols and 6-shogaol and conjugate metabolites in healthy human subjects. Cancer Epidemiol. Biomark. Prevent., 17(8): 1930–1936. https://doi.org/10.1158/1055-9965.EPI-07-2934