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Indonesian Anti-Inflammation Herbs Mechanism: Mini Review

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Abstract
This mini-review aims to provide an overview of some commonly used anti-inflammatory herbs in Indonesia. Inflammation is a complex physiological response that plays a role in various diseases, and herbal remedies have been used traditionally in Indonesian culture for their potential anti-inflammatory properties. We utilize Portal Garuda as the primary database for searching herbs with anti-inflammatory activity using the keyword "anti-inflamasi". The selected herbs discussed in this review include turmeric (Curcuma longa), ginger (Zingiber officinale), clove (Syzygium aromaticum), and cinnamon (Cinnamomum sp.). These herbs have been reported to possess anti-inflammatory effects through various mechanisms, such as inhibition of pro-inflammatory enzymes and cytokines, antioxidant activity, and modulation of immune responses. Moreover, these herbs have also demonstrated safety profiles in traditional use. However, further scientific research is needed to elucidate the specific bioactive compounds responsible for their anti-inflammatory effects and to determine the optimal dosages and formulations for therapeutic use. The exploration of Indonesian anti-inflammatory herbs could contribute to the development of natural and affordable options for managing inflammatory conditions, complementing conventional treatments, and promoting overall health and well-being.

Keywords: inflamasi, herbal, inflammation pathway, traditional medicine, peradangan

Abstrak
Tinjauan mini ini bertujuan untuk memberikan gambaran tentang beberapa herba antiinflamasi yang umum digunakan di Indonesia. Peradangan adalah respons fisiologis kompleks yang memainkan peran dalam berbagai penyakit, dan ramuan herbal telah lama digunakan secara tradisional dalam budaya Indonesia karena potensi sifat antiinflamasinya. Kami menggunakan Portal Garuda sebagai basis data utama untuk mencari herba dengan aktivitas antiinflamasi menggunakan kata kunci "anti-inflamasi". Herba yang dipilih yang dibahas dalam tinjauan ini meliputi kunyit (Curcuma longa), jahe (Zingiber officinale), cengkeh (Syzygium aromaticum), dan kayu manis (Cinnamomum sp.). Herba-herba ini dilaporkan memiliki efek antiinflamasi melalui berbagai mekanisme, seperti penghambatan enzim dan sitokin proinflamasi, aktivitas antioksidan, dan modulasi respons imun. Selain itu, herba-herba ini juga telah menunjukkan profil keamanan dalam penggunaan tradisional. Namun, penelitian ilmiah lebih lanjut diperlukan untuk mengungkapkan senyawa bioaktif spesifik yang bertanggung jawab atas efek antiinflamasi mereka dan untuk menentukan dosis dan formulasi optimal untuk penggunaan terapeutik. Eksplorasi herba antiinflamasi Indonesia dapat berkontribusi pada pengembangan pilihan alami dan terjangkau untuk mengelola kondisi inflamasi, melengkapi pengobatan konvensional, serta meningkatkan kesehatan dan kesejahteraan secara keseluruhan..

Kata kunci: inflamasi, herbal, inflammation pathway, traditional medicine

1. Introduction

Inflammation is a fundamental biological response that plays a critical role in the body's defense mechanisms [1]. It is a complex process involving various cells, mediators, and signaling pathways, and serves as a protective mechanism against infections, injuries, and tissue damage [2]. However, when inflammation becomes chronic or dysregulated, it can contribute to the pathogenesis of numerous diseases, including cardiovascular disorders, neurodegenerative conditions, and autoimmune disorders [3]. In recent years, there has been growing interest in natural alternatives for managing inflammation, and traditional herbal medicine has emerged as a valuable resource. Indonesia, with its diverse flora and rich traditional knowledge, offers a wealth of medicinal plants that have been used for centuries to address inflammatory ailments. Exploring the anti-inflammatory potential of Indonesian herbs not only holds promise for developing new therapeutic interventions but also provides an opportunity to preserve traditional knowledge and cultural heritage.

Indonesian traditional medicine, known as Jamu, has a long history of utilizing herbal remedies to promote health and well-being. These traditional practices are deeply rooted in Indonesian culture and have been passed down through generations [4]. Traditional healers and herbalists have identified specific plants and herbal preparations that possess anti-inflammatory properties based on their observations and empirical evidence. The use of these herbal remedies is often guided by traditional knowledge systems, which have been refined over time and are ingrained in the local communities. However, as scientific research advances, there is a growing need to bridge the gap between traditional practices and modern evidence-based medicine, to validate the efficacy and safety of these herbal remedies and understand the mechanisms underlying their anti-inflammatory effects.

Indonesian traditional medicine offers a treasure trove of herbal remedies that have been utilized for their anti-inflammatory properties. Turmeric and ginger are just a few examples of the rich botanical resources that Indonesia has to offer [5]. These herbs have demonstrated promising anti-inflammatory effects through various mechanisms, making them valuable candidates for further scientific investigation. By combining traditional knowledge with modern scientific research, we can unlock the full potential of Indonesian anti-inflammatory herbs and contribute to the development of natural and affordable interventions for managing inflammation-related disorders. Additionally, the preservation and integration of traditional knowledge into modern healthcare practices can help to ensure the sustainability of these herbal resources and promote cultural heritage.

2. Methodes

The study design was adopted from previous report form Fajriyah, et al. with slight modification [6]. We searched in Portal Garuda database using the terms "anti-inflamasi", "ekstrak," and "herbal medicine". From a chronological perspective, all of the references used to write this review article were written in Indonesia and covered the years 1980 to the present. The whole body of research pertaining to our objective was compiled and categorized according to the strength of the evidence. Subsequently, an analysis was conducted to determine the inflammatory mechanism in which the herbal substance is involved. Additionally, inflammation is a complex physiological response triggered by the immune system to protect the body from harmful stimuli, such as pathogens, tissue injury, or irritants.

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It involves a series of intricate cellular and molecular events that contribute to the initiation, progression, and resolution of the inflammatory process [7]. Further, the analysis focused on identifying the specific mechanisms through which the herbal substance exerted its anti-inflammatory effects. One approach employed was the examination of key inflammatory mediators, including cytokines, chemokines, and inflammatory enzymes. These molecules play crucial roles in orchestrating the inflammatory response by promoting immune cell recruitment, activation, and the release of additional inflammatory mediators.

3. Result and Discussions

Mechanism of inflammation

The vast array of plants that have been claimed to possess anti-inflammatory effects is extensive, making it impractical to evaluate each one within the confines of this paper. Consequently, we have chosen to focus on the herbs that are supported by a substantial body of evidence. By doing so, we aim to provide a concise overview of some of the most well-researched herbs known for their anti-inflammatory properties. Further, the diverse mechanisms of the inflammation process lead to a wide range of therapeutic approaches. Numerous cytokines assist in tissue damage, which is commonly referred to as inflammation, as well as enzyme activation (including phospholipase A2 release), mediator release, fluid extravasation and vasodilation, cell migration, and fluid extravasation (figure 1) [8].

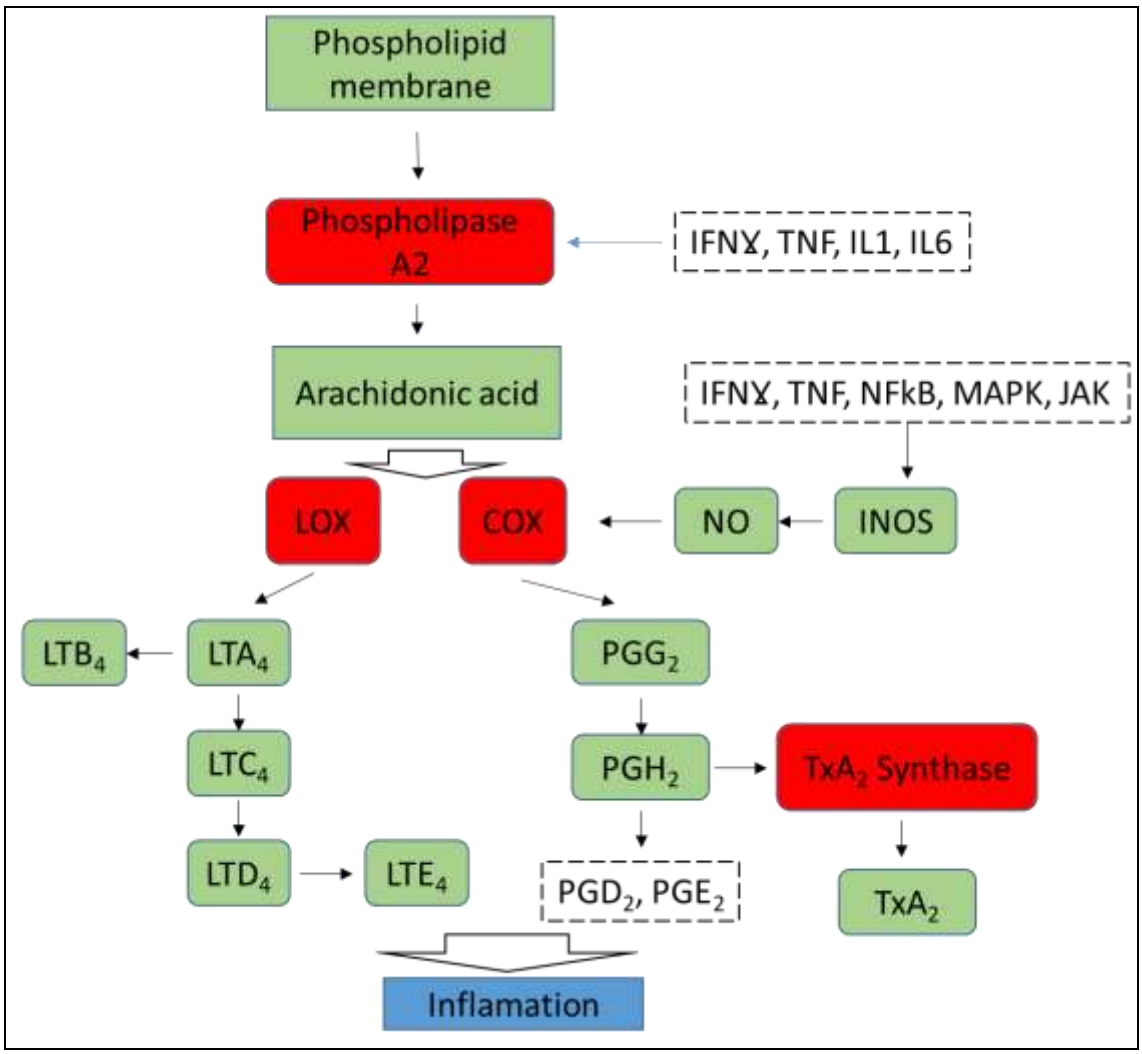

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Figure 1. Bimolecule involved in Inflamation pathway
COX, cyclooxygenase; LOX, lipoxygenase; PG, prostaglandin; LT, leukotriene; TX, thromboxane; NO, nitric oxide; iNOS, inducible NO synthase; IFN, interferon; TNF, tumor necrosis factor; NF-κB, nuclear factor-κB; MAPK, mitogen activated protein kinase; JAK, janus kinase; IL, interleukin.

Kunyit (*Curcuma longa* Linn.)

The perennial herb turmeric, *Curcuma longa* Linn., is farmed primarily in south and southeast tropical Asia. It is a member of the Zingiberaceae family, which also includes ginger. The most beneficial component of this plant is its rhizome, which is also known as its root and has been used as a spice in food for generations. To treat a number of illnesses, it has been applied topically and orally. It is frequently used to treat hepatic problems, anorexia, cough, diabetic wounds, rheumatoid arthritis, and sinusitis in conventional Indian Ayurvedic medicine [9]. In addition, two to five percent of turmeric is made up of curcumin, the spice's most potent ingredient. The curcumin component gives turmeric its characteristic yellow hue. Curcumin (C21H20O6) was first identified as a diferuloylmethane, 1,7-bis (4-hydroxy-3-methoxyphenyl) by Lampe and Milobedeska in 1910.-1,6-heptadiene-3,5-dione [10].

Curcumin's ability to reduce inflammation has not yet been fully understood. Peroxisome proliferator-activated receptor gamma (PPAR-) has been linked to anti-inflammatory properties, according to studies [11]. PPARs are a member of the nuclear receptor superfamily, which consists of three genes that produce the PPARα, PPARβ, and PPARɣ subtypes [12]. Studies conducted both in vivo and in vitro have demonstrated that thiazolidinediones can activate PPARɣ [11]. These positive effects of PPAR-ligands were linked to decreased JNK activation, decreased NF-B and AP-1 pathway activity, and decreased IB kinase complex activity . Akt, NF-B, AP-1, or JNK signaling pathway blockage has been suggested as the method by which curcumin induces apoptosis [13].

Jahe (*Zingiber officinale* Ros)

The Zingiberaceae family includes ginger (*Zingiber officinale* Ros). It is a spice and condiment that has its roots in South-East Asia and is used to flavor dishes in many different nations [14]. In addition to this, traditional herbal therapy has also employed ginger's rhizome. The rich phytochemistry of ginger is thought to be responsible for its health-promoting properties [15]. Fresh ginger was divided into two broad categories by Jolad et al., namely volatiles and non-volatiles. Sesquiterpene and monoterpenoid hydrocarbons, which give ginger its distinctive flavor and scent, are examples of volatiles. The non-volatile pungent substances, however, include zingerone, paradols, shogaols, and gingerols [16].

Through the inhibition of 5-lipoxygenase or prostaglandin synthetase, gingerol, shogaol, and other structurally similar compounds in ginger prevent the formation of prostaglandins and leukotrienes. They can also prevent the production of pro-inflammatory cytokines such IL-1, TNF-, and IL-8 [17]. In a different study, Pan et al. demonstrated that shogaol can suppress the production of the inflammatory genes iNOS and COX-2 in macrophages [18]. According to Jung et [19], Z. officinale's rhizome hexane fraction extract reduced the overproduction of NO, PGE [20], TNF-alpha, and IL-1beta. Ginger rhizome's strong anti-allergic properties make it a potential treatment and preventative measure for allergic illnesses [21].

Cengkeh (*Syzygium aromaticum* (L.) Merr.)

Eugenia cariophylata, also known as *Syzygium aromaticum* (L.) Merr. Et Perry, is the common name for this medium-sized tree from the Myrtaceae family, which is native to the Maluku islands in eastern Indonesia and is grown all over the world. *Syzygium aromaticum*(L.)'s dried flower buds are what are known as cloves [22]. The parts of the clove tree that are sold the most are the leaves and buds. Four years after planting, the flower bud production phase starts. Then, at the pre-flowering period, these clove buds are plucked by

hand or using natural phytohormones [23]. *S. aromaticum* includes Eugenol, a phenylpropanoid substance. Cloves' primary chemical, eugenol, has a concentration of roughly 50%. Eugenyl acetate, -humulene, and -caryophyllene make up the final 10–40%. Less than 10% of minor ingredients such chavicol, karyophyllene oxide, 4-(2-propenyl)-phenol, -copaene, cadinene, and -cubebene. Eugenol is a volatile substance that ranges in color from colorless to light yellow. It has a low water solubility (about 2460 mg/L at 25 °C), a potent aroma, and a potent flavor. Insecticidal, antibacterial, anti-inflammatory, wound-healing, antiviral, antioxidant, and anticancer activity are only a few of the biological effects of eugenol that have been noted [24].

It is believed that cellular eugenol controls the nuclear factor-B (NF-B), ERK/MAPK, nitric oxide (NO), suppression of pro-inflammatory interleukins, and endogenous antioxidant defense mechanisms that cause inflammation in macrophages in response to LPS. The levels of several pro-inflammatory biomarkers, including vascular cell adhesion molecule-1 (VCAM-1), interferon-induced protein 10 (IP-10), interferon-inducible T-cell chemoattractant (I-TAC), and monokine induced by interferon (MIG)-induced monokines, were significantly reduced by clove essential oil (CEO). Additionally, CEO dramatically reduced tissue inhibitor metalloproteinase 2 (TIMP-2), macrophage colony-stimulating factor (M-CSF), and the tissue remodeling protein components collagen-I and collagen-III. Global gene expression is regulated by CEO, which also modifies important signaling pathways involved in inflammatory response, tissue remodeling, and cancer signaling. Clove hydroalcoholic extract's water-soluble components have an anti-inflammatory impact by preventing BALB/c mice's macrophages from producing the pro-inflammatory cytokines (IL-1 and IL-6) [25].

Sirsak (*Annona muricata* L.)

Annona muricata is commonly known as graviola or Soursop, belongs to the family. It is a typical tropical tree with heart-shaped fruit which are edible and widely distributed in most tropical countries. Based on previous years reports have shown that the leaves, bark, roots, stems, and Annona muricata seed extract has antibacterial, antifungal and antimalarial properties Annonaceae [26]. However, it was recently reported that Annona muricata can exhibit anti-inflammatory and analgesic effects. Furthermore, phytochemicals such as alkaloids, terpenoids, polysaccharides, lactones, flavonoids, carotenoids, and glycosides as well as essential oils isolated from several plants have also been shown to exhibit potential anti-inflammatory [27].

An in vitro study conducted by Laksmitawati et al. (2016) revealed that A. muricata leaf extract has anti-inflammatory activity because it inhibits inflammatory mediators, namely TNF-α, IL-1β, IL-6 and nitric oxide (NO) [27]. A. muricata leaf extract showed remarkable differences in TNF-α levels in the LPS-induced RAW264.7 cell line compared to the positive control (LPS stimulated cells without the extract) and showed decent inhibitory activity with 46.8% inhibition. They suggested that the anti-inflammatory action of the plant extract was related to inhibition of one or more intracellular signaling pathways involved with the mediators (e.g., histamine, serotonin, bradykinin, substance P, and a platelet activating factor and prostaglandin) [28].

Kayu manis (*Cinnamomum sp.*)

Cinnamon (*Cinnamomum sp.*) is a spice plant belonging to the Lauraceae family, which includes several species. This plant is widely distributed in subtropical and tropical regions. It grows to a height of 5-15 meters, with its bark being dark gray and possessing a unique aroma, while the wood itself is light brown to reddish [29]. Cinnamon bark is used for a variety of things, including flavoring foods and pastries, and has a distinct scent. the main chemical components of cinnamon include cinnamyl alcohol, coumarin, cinnamic acid, cinnamaldehyde, anthocyanin, as well as sugar, protein, sweet fat, and pectin [30]. Explains how Cinnamomum burmannii's bark extract is thought to include important antioxidants

such polyphenols (tannins, flavonoids), which have antidiabetic properties, and phenolic essential oils [31].

Cinnamomum, specifically certain species within the Cinnamomum genus, has been found to exhibit COX1 and COX2 enzyme inhibitory activity. Research studies have shown that certain compounds present in cinnamon, such as cinnamaldehyde and cinnamic acid, possess anti-inflammatory properties and can effectively inhibit the activity of these enzymes [32]. Furthermore, The combination of Cinnamomum and Zingiber (ginger) has been found to effectively reduce the expression of mRNA of pro-inflammatory cytokines, including IL-6, TNF-α, and IL1β. Studies have demonstrated that the bioactive compounds present in cinnamon and ginger, such as cinnamaldehyde and gingerol, possess anti-inflammatory properties. When used in combination, these compounds synergistically target the inflammatory pathways, leading to a decrease in the expression of these specific pro-inflammatory cytokines at the mRNA level. IL-6, TNF-α, and IL1β are key players in the immune response and have been implicated in various inflammatory disorder [33].

Binahong (*Anredera cordifolia* (Tenore).Steenis)

Binahong, scientifically known as *Anredera cordifolia* (Tenore).Steenis, is a plant that is widely recognized in Indonesia for its medicinal properties in treating various diseases [34]. The leaves of this plant contain several secondary metabolite compounds such as flavonoids, saponins, alkaloids, phenols, and steroids. Among these compounds, one that has been identified is Vitexin [35]. Binahong extract is known to possess high levels of flavonoids, which contribute to its antioxidant capabilities. Antioxidants play a crucial role in stabilizing free radicals that can otherwise lead to various diseases, including diabetes, antihyperlipidemia, analgesic effects, anti-inflammatory properties, and antipyretic activities [34]. The presence of these beneficial compounds in Binahong highlights its potential as a natural remedy for promoting health and treating various ailments.

In a previous study, the anti-inflammatory potential of *A. cordifolia* (Tenore) leaf extract was demonstrated in a pure macrophage cell line induced by lipopolysaccharide (RAW 264.7) [36]. To assess cell viability, the MTS test was performed. Various parameters were measured to evaluate the anti-inflammatory activity, including interleukin-1β (IL-1β), tumor necrosis factor (TNF)-α, nitric oxide (NO), and IL-6. The results showed that A. cordifolia (Tenore) plants at a concentration of 50g/ml significantly reduced the levels of TNF-α (250.3 pg/ml), IL-1β (50 g/ml), IL-6 (10 g/ml), and NO (50 g/ml)(1) [36]. Further, Binahong, known for its vitexin content, possesses the remarkable ability to stabilize Red Blood Cells (RBCs) in a manner similar to lysosomal membranes. In the inflammatory process, lysosomal enzymes are released and can damage cell membranes, resulting in inflammation [37]. However, binahong extract demonstrates another valuable property as a Cataract inhibitor. It has the ability to inhibit the production of malondialdehyde (MDA), a mutagenic product of lipid peroxidation that is associated with cataract formation. This inhibition of MDA production showcases the potential of binahong extract as a natural remedy for preventing and managing cataract-related conditions. Its multifaceted properties, including RBC stabilization and the inhibition of MDA production, further emphasize the beneficial effects of binahong in maintaining cellular health and combating oxidative stress-related diseases.

Mengkudu (*Morinda citrifolia* L.)

Morinda citrifolia L. has been recognized as an important herb for treating various hysiological disorders worldwide. M. citrifoliais commonly known as Indian mulberry or Noni in India. According to reports, *M. citrifolia* has a wide range of medicinal applications for treating conditions like arthritis, burns, headaches, wounds, and skin infections. Noni has been grown in Polynesia for more than a millennium and is utilized there as food, medicine, and a coloring agent. Australians and Indians have used the root as dyeing chemicals for various shades of red, purple, and yellow. Ailments like cough, cold, pain, liver diseases, hypertension, blood pressure, tuberculosis, malaria, intestinal worms, diabetes, loss of

appetite, hernias, urinary tract infections, menstrual disorders, cancer, cardiovascular diseases, arthritis, etc. are treated with various parts of the Noni plant, including the stem, bark, root, leaf, and fruits [38].

Various bioactive substances, such as fatty acids, flavonoids, polysaccharides, and sterols, have been extracted from noni fruits [39]. An experimental model of Helicobacter pylori infection using ethanol and ethyl acetate extracts has shown the anti-inflammatory efficacy of noni fruit components. These extracts were able to lessen neutrophil chemotaxis as well as the generation of COX-2 and induced nitric oxide (iNOS) [40]. Further, the ability of *Morinda citrifolia* leaf extract to reduce TNF-, IL-1, and NO levels in macrophages after lipopolysaccharide activation further demonstrated the plant's anti-inflammatory properties [41].

Manggis (*Garcinia mangostana* Linn.)

The *Garcinia mangostana* Linn., commonly referred to as Mangosteen or GM, is a highly regarded fruit recognized as the preeminent of its kind, and is indigenous to the Southeast Asian region. The consumption of this particular fruit is prevalent, and its pericarp has been extensively researched due to the presence of active compounds that exhibit diverse pharmacological properties. The mangosteen pericarp is primarily composed of xanthones, with a total of 50 distinct xanthones having been identified and isolated from this source. According to reports, xanthones exhibits antioxidant, antiproliferative, wound healing, and anti-inflammatory properties. Numerous publications have documented the biological properties of the underutilized component of mangosteen, which include anti-obesity and lipid metabolism disorder, antihypertensive, antidiabetic, and anticancer activities [42].

Alpha- and gamma-mangostins are compounds found in Garcinia, which exhibit inhibitory activity against nitric oxide (NO) and inducible nitric oxide synthase (iNOS). These compounds, derived from Garcinia, have been shown to effectively inhibit the production of NO and suppress the activity of iNOS. Their presence in Garcinia highlights the potential of these natural compounds in modulating inflammatory responses and may hold promise for the development of therapeutics targeting NO and iNOS-related disorders [43].

Dadap (*Erythrina lithosperma*)

Different parts of *Erythrina lithosperma* have been used as nervine sedatives, febrifuges, anti-asthmatics, and anti-epileptics in traditional medicine. It also has potential effects for treating some diseases, including convulsion, fever, inflammation, bacterial infection, insomnia, helminthiasis, cough, cuts and wounds [44]. In an in vitro study conducted by Nagaraj et al., it was demonstrated that the plant known as "dadap" exhibits inhibitory activity against glucosidase and glycosylation. The findings of this study suggest that dadap possesses the ability to hinder the enzymatic activity involved in the breakdown of complex carbohydrates into simpler sugars (glucosidase inhibition) as well as the process of attaching sugar molecules to proteins or lipids (glycosylation inhibition). These activities are of interest due to their potential implications in managing conditions related to glucose metabolism, such as diabetes [45]. Further, the phytochemical analysis of Dadap (Erythrina variegata) revealed the presence of over 50 chemical compounds, highlighting its complex chemical composition. Among these compounds, two notable ones are Palmitic acid and Octadecadienoic acid [45].

The ethanolic extract derived from *Erythrina lithosperma* exhibited significant anti-inflammatory properties in research findings. It effectively inhibited the production of prostaglandins, a key component of inflammation, by targeting the enzyme COX-2. Additionally, the extract demonstrated inhibitory activity against the production of nitric oxide induced by lipopolysaccharide in RAW 264.7 cell lines, with IC50 values of 9.27±0.72 and 47.1±0.21 µg/ml, respectively. These results highlight the potential of the extract to attenuate inflammatory processes. However, it is important to note that the extract did not

exhibit effectiveness in suppressing the release of TNF-α, another pro-inflammatory cytokine [46].

Summary

The biochemical results from experimental studies provide clear evidence regarding the potential impact of herbs on the activation or inhibition of pro-inflammatory cytokines (as shown in **Table 1**). However, to address any conflicting findings, it is crucial to conduct further clinical studies with larger sample sizes and perform meta-analyses. Considering the extensive number of plants that have been claimed to possess anti-inflammatory effects, it is beyond the scope of this paper to evaluate all of them comprehensively.

Table 1. Mechanisms by which the medicinal plants listed in this review article have an anti-inflammatory effect.

Herbals	Mechanism of action by inhibiting of						
	TNF-α	COX-2	iNOS	NF-κB	PGE2	NO	IL fam
Kunyit (*Curcuma longa* Linn)				√			
Jahe (*Zingiber officinale* Ros)	√	√	√		√	√	
Cengkeh *Syzygium aromaticum* (L.)				√			√
Sirsak (Annona muricata)	√					√	√
Kayu manis (*Cinnamomum sp*.)	√	√					√
Binahong (*Anredera cordifolia* (Tenore))	√					√	√
Mengkudu (Morinda citrifolia L.)	√	√	√		√		√
Manggis (*Garcinia mangostana* Linn)			√			√	
Dadap (*Erythrina lithosperma*)	√	√					

4. Conclusion

This mini-review provides an overview of commonly used anti-inflammatory herbs in Indonesia. Traditional Indonesian culture has long recognized the potential of herbal remedies for their anti-inflammatory properties, which are now being supported by scientific research. Through the utilization of the primary database, Portal Garuda, several herbs were identified as having anti-inflammatory activity, including turmeric, ginger, clove, and cinnamon. These herbs have shown promising anti-inflammatory effects through various mechanisms. However, further scientific investigations are necessary to identify the specific bioactive compounds responsible for their anti-inflammatory effects, determine optimal dosages, and develop appropriate formulations for therapeutic use.

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