Systematic Review: Mechanism of Ginger (Zingiber offinale) as Anti-inflammatory

Dwi Monika Ningrum[1*], Denih Agus Setia Permana[2], Atri Sri Ulandari[3]

[1]Department of Pharmacy, Faculty of Pharmachy, Sultan Agung Islamic University, Semarang, Indonesia
[2]Department of Pharmacy, Faculty of Pharmachy, Al Irsyad University Cilacap, Cilacap, Indonesia
[3]Department of Pharmacy, Faculty of Medicine, University of Lampung, Lampung, Indonesia

*Corresponding Author: dwiheliosika@gmail.com

ABSTRACT

The appearance of inflammation is a hallmark of a large number of human diseases, ranging from infection to neurodegeneration. In the treatment of inflammation, a group of drugs that are widely given are non-steroidal anti-inflammatory drugs (NSAIDs). Long-term use of NSAIDs can result in various side effects, namely gastrointestinal disorders, damage to the kidneys, and cardiovascular disorders. Given the side effects that can be caused by the use of NSAIDs, other alternatives are needed to overcome and reduce inflammation. One of the plants that can be used to treat inflammation is ginger. This journal review was conducted by reviewing electronic journals related to the use of ginger as an anti-inflammatory mechanism with the study report method. The inclusion criteria used include ginger as an anti-inflammatory, journals from 2008-2012, journals are scientific journals, in vitro and in vivo, free full text, while the exclusion criteria are the benefits of ginger not as an anti-inflammatory.Ginger as an anti-inflammatory has several mechanisms including inhibiting macrophage activation, increasing endogenous antioxidant activity, inhibiting the production of PGE2, tumor necrosis factor α (TNFα), and cyclooxygenase. Inhibition of cyclooxygenase is selective only for COX-2 activity. COX-1 inhibition is associated with gastrointestinal irritation, selective inhibition of COX-2 will help minimize side effects.

Keywords: Anti-inflammatory; Ginger; Mechanism.

INTRODUCTION

Inflammatory phenomena include microvascular damage, increased capillary permeability and leukocyte migration to inflamed tissues. Common symptoms of the inflammatory process are kolor, rubor, tumor, dolor, and function laesa. During the inflammatory process many chemical mediators are released locally including histamine, 5-hydroxytryptamine (5-HT), chemotatic factors, bradykinin, leukotrienes, and PG (Pázmándi, Ágics, et al., 2024).

The appearance of inflammation is characteristic of a large number of human diseases, ranging from infection to neurodegeneration. In compromised tissues, the chemical equilibrium can result in the accumulation of reactive oxygen species (ROS) such as peroxides of hydrogen, which in turn can lead to oxidative stress and its associated toxic effects. Although some ROS have important roles in cell signaling and defense mechanisms, these chemical compounds also contribute to and are indicators of various diseases (Tripathi et al., 2008).

In the treatment of inflammation, a widely administered group of drugs are non-steroidal anti-inflammatory drugs (NSAIDs). These are synthetic drugs with heterogeneous chemical structures. The therapeutic effect of AINS is related to the mechanism of action of inhibition of the enzyme cyclooxygenase-1 (COX-1) which can cause gastrointestinal side effects and inhibition of the enzyme cyclooxygenase-2 (COX-2) which can cause side effects on the cardiovascular system. Both enzymes are required in the biosynthesis of prostaglandins. Long-term use of NSAIDs can result in various side effects, namely gastrointestinal disorders, kidney damage, and cardiovascular disorders (Tripathi et al., 2007).

Considering the side effects that can be caused by the use of NSAIDs, other alternatives are needed to overcome and reduce inflammation. One plant that can be used to treat inflammation is ginger. The various benefits of ginger that have been known so far include indigestion, analgesic, antipyretic, anti-inflammatory, antiemetic, antirheumatic, increase body resistance, treat diarrhea, and also have antioxidant properties whose activity is higher than vitamin E. (Astuti & Murbawani, 2011).

Recently, ginger has gained widespread attention as a botanical dietary supplement in the United States and Europe due to its antioxidant, anti-inflammatory, and anti-tumor activities. The anti-inflammatory effect of ginger is supported by various research and studies that have been conducted both in vivo and in vitro. The anti-inflammatory effect of ginger is due to its active components, namely gingerol, gingerdione, and zingeron. These effects are similar to the anti-inflammatory effects of mefenamic acid and ibuprofen, which are NSAIDs (Maryam et al., 2023).

METHODS

The writing of this journal review was done by reviewing electronic journals related to the use of ginger as an anti-inflammatory mechanism. The method used is a study report, which is to analyze and report back the results of research, in this case regarding the use of ginger as an anti-inflammatory mechanism.

The PICO used is P = Anti-inflammatory; I = Ginger; C = Placebo; O = Mechanism. The inclusion criteria used include the sample is ginger as an anti-inflammatory, journals from 2008-2012, journals are scientific journals, in vitro and in vivo, free full text, while the exclusion criteria are the benefits of ginger is not as an anti-inflammatory.

Data were retrieved from several scientific websites (such as www.pubmed.com; www.biomedcentral.com) that provide journals related to the mechanism of ginger as an anti-inflammatory by entering keywords: anti-inflammatory, ginger, placebo, mechanism.

RESULTS AND DISCUSSION

In macrophages stimulated with LPS after administration of ginger extract showed inhibition of macrophage activity. Ginger extract inhibited IL-12, TNF-α, IL-1β (proinflammatory cytokines) and RANTES, MCP-1 (proinflammatory chemokines) produced by LPS-induced macrophages. The production of TNF-α decreased tenfold in the administration of ginger extract compared to those who were not given ginger extract (Yohanes Bare et al., 2021).

The COX-2 inhibitor was 10-shogaol with an IC50 of 7.5 ± 0.6 pM, followed by 8-shogaol (IC50 17.5 ± 2.2 pM) and 10-gingerol (IC50 32.0 ± 1.5 pM). In addition, gingerols and shogaols are selective COX-2 inhibitors as they were shown not to inhibit COX-1. Ginger extract can inhibit COX-2 approximately three-fold higher than COX-1 (Morakinyo et al., 2011).

Another study mentioned that Zingiber officinale extract inhibits oxidative stress and inflammation by increasing antioxidant enzymes and TNF-α activity in STZ-induced rats. The effect of Z. officinale on oxidative stress using MDA, SOD, CAT and GSH activity levels, and inflammation using TNF-α. The tested Z. officinale extracts increased the intracellular activities of SOD, CAT and GSH (Wresdiyati et al., 2003). Data from the study showed that ginger extract inhibited lipid peroxidation and cytokine TNF-α, increasing endogenous antioxidant activity. This suggests that the mechanism of ginger's antidiabetic effect may be partly due to inhibition of oxidative stress and inflammatory activity (Susila et al., 2014).

Table 1. Review of several articles on the mechanism of ginger as an anti-inflammatory.

No.	Journal Title, Researcher	Year	Method	Result
1	Ginger extract inhibits LPS induced macrophage activation and Function	2008	Cell culture assay	Ginger extract inhibited IL-12, TNF-α, IL-1β (proinflammatory cytokines) and RANTES, MCP-1 (proinflammatory chemokines) produced by LPS-induced macrophages.
2	Modulation of Antioxidant enzymes and Inflammatory Cytokines: Possible Mechanism of Anti-diabetic Effect of Ginger Extracts	2011	Preclinical test	Ginger extract inhibited lipid peroxidation and cytokine TNF-α, increasing endogenous antioxidant activity. This suggests the mechanism of anti-diabetic effect of ginger may be due to inhibition of oxidative stress and inflammatory activity in beta cells.
3	Cyclooxygenase-2 inhibitors in ginger (*Zingiber officinale*)	2011	In vitro test	Ginger extract has activity to inhibit COX-2 but not COX-1. This means that ginger extract can function as a selective COX-2 inhibitor.

Cellular injury triggers the release of a range of mediators that originate either from plasma or from within the affected cells. Among these are histamine, prostaglandins, and leukotrienes. These mediators initiate a localized vasodilatory response, enhancing blood flow and increasing the permeability of blood vessels. This physiological response leads to the classic signs of inflammation: redness, warmth, and swelling. The fluid that escapes from capillaries, known as exudate, not only carries these chemical mediators but also includes fragments of foreign proteins or pathogens. These components are transported to the spleen, where they stimulate the production of antibodies. Circulating immune cells, such as neutrophils and monocytes, are drawn to the site of injury by chemotactic signals, some of which originate from the invading organisms. Additionally, certain inflammatory mediators activate sensory nerve endings, contributing to the sensation of pain (Wresdiyati et al., 2005).

In addition to this innate response, the body also mounts an acquired immune defense, which is a highly specific mechanism that generates new immune cells tailored to target invading pathogens or foreign proteins. This adaptive process relies on the recognition of antigens—foreign protein markers—by specialized immune cells called lymphocytes. Within the cell-mediated branch of this system, T lymphocytes play distinct roles: cytotoxic T cells directly destroy infected cells, while helper T cells release cytokines that can stimulate antibody production by B lymphocytes or activate macrophages. B lymphocytes are responsible for generating antibodies, which bind to antigens and activate the complement system, leading to the destruction or neutralization of the foreign

substance. One particular antibody class, immunoglobulin E (IgE), is involved in promoting inflammation by triggering mast cells to release additional mediators (Pázmándi, Szöllősi, et al., 2024).

Inhibition of macrophage activation is one approach that may modulate inflammation. In macrophages stimulated with LPS after administration of ginger extract showed inhibition of macrophage activity. Ginger extract inhibited IL-12, TNF-α, IL-1β (proinflammatory cytokines) and RANTES, MCP-1 (proinflammatory chemokines) produced by LPS-induced macrophages. The production of TNF-α decreased tenfold when ginger extract was administered compared to those without ginger extract (Antoniewicz (Kałduńska) et al., 2021).

The anti-inflammatory effect of ginger is due to its active components, namely gingerol, gingerdione, and zingeron, which inhibit prostaglandins by inhibiting the enzyme cyclooxygenase. In addition, ginger can also inhibit the enzyme lipoxygenase. Red ginger oleoresin components are effective in inhibiting the production of PGE2, tumor necrosis factor α (TNFα), and cyclooxygenase released in synoviocytes by regulating nuclear factor κB (NFκB) activation and degrading the inhibitory subunit IκBα. The assay of cyclooxygenase enzyme inhibitory activity was determined by IC50. Ginger extract can inhibit COX-2 approximately three-fold higher than COX-1 and this makes a favorable contribution to the anti-inflammatory activity of ginger (Devi & Singh, 2023).

Another study mentioned that Zingiber officinale extract inhibits oxidative stress and inflammation by increasing antioxidant enzymes and TNF-α activity in STZ-induced rats. The effect of Z. officinale on oxidative stress using MDA, SOD, CAT and GSH activity levels, and inflammation using TNF-α. The tested Z. officinale extracts increased the intracellular activities of SOD, CAT and GSH. Ginger extract inhibited lipid peroxidation and cytokine TNF-α, increasing endogenous antioxidant activity (Pournaderi et al., 2019).

Zingeron found in ginger is a phenol compound, which is an organic compound that has at least one aromatic ring with one or more hydroxyl groups. Phenolic compounds can function as antioxidants because of their ability to stabilize free radicals, namely by providing hydrogen atoms quickly to free radicals, while radicals derived from phenol compound antioxidants are more stable than free radicals. One of the mechanisms in reducing inflammation is by stabilizing or neutralizing free radicals. The inflammatory process will release macrophages as an inflammatory response. The released macrophages will produce ROS that will increase tissue damage and increase pain. ROS can be neutralized with antioxidants. Antioxidant properties possessed by phenolic compounds, one of which is gingerol, can neutralize ROS. ROS neutralization will reduce tissue damage and reduce pain due to inflammation (Breemen et al., 2013).

CONCLUSION

Ginger as an anti-inflammatory has several mechanisms including inhibiting macrophage activation, increasing endogenous antioxidant activity, inhibiting the production of PGE2, tumor necrosis factor α (TNFα), and cyclooxygenase. Inhibition of cyclooxygenase is selective only for COX-2 activity. COX-1 inhibition is associated with gastrointestinal irritation, selective inhibition of COX-2 will help minimize side effects.

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