

Review article A Comprehensive Review of the Systemic Evidence on the Immunomodulatory Properties of *Zingiber officinale* (Ginger)

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Abstract: Synthetic medications used to treat immune-related disorders have recently been discovered to have a variety of negative effects on patients. Corticosteroids, for example, are used to control inflammation during infections, but they may have negative consequences, including bruising, muscular weakness, pathologic fractures, weight gain, and sleep difficulties. The ginger plant, *Zingiber officinale*, also known as "Halia" in Malaysia, has a promising future as a safer option for preventative and therapeutic agents with minimal risk of adverse effects. This is because this plant is utilized in traditional medicine by the local population to treat various illnesses, including immunological and infectious disorders. Numerous investigations have shown that the bioactive substances and crude extracts of *Z. officinale* have a range of pharmacological effects, including anticancer, anti-inflammatory, antibacterial, antioxidant, and immunomodulatory. The goal of this study is to determine how *Z. Officinale* affects immunomodulatory activities based on a few carefully chosen prior studies conducted between 2000 and 2021. 12 randomized controlled trials (RCTs) were used in this investigation to investigate *Z. officinale*'s immunomodulatory properties. Systematic investigation revealed that *Z. officinale* has immunomodulatory properties for both in vitro and in vivo assessments. However, there are some restrictions on the thorough reporting of the controls employed in the included research. To show the effects of *Z. officinale* on the immunomodulatory system as well as the safety data of ingesting this plant, future well-designed RCTs with thorough reporting on the controls are necessary.

Keywords: Immunomodulatory, ginger, comprehensive review, *Zingiber officinale*, properties.

Introduction: The human immune system is an organization of cells responsible for protecting from infection. The immune system protects the human body with two different types of responses, innate and acquired. Innate immunity is a non-specific defence mechanism that provides immediate action or within hours of infection(1). Meanwhile, the acquired immunity creates an immunological memory during the first infection that leads to an enhanced response for the next similar infection. The innate immune system mainly consists of physical barriers such as skin and mucous membranes, chemical barriers, antimicrobial peptides, innate cells, and oxygen-reactive species(2). Instead of that, innate immunity contains soluble mediator systems such as the complement system and cytokines. The major roles of the adaptive immune system are to recognize specific "non-self" antigens through pathways of pathogen-based immune effectors to get rid of specific infections(3). Besides, the acquired immunity creates an immunological memory that is able to remove a certain pathogen quickly if an infection occurs subsequently.

Immune imbalance is able to cause numerous disorders, such as allergies, autoimmune disorders, immunosuppression, and acquired immunodeficiency syndrome (AIDS)(4). The epidemiological evidence currently shows an increasing pattern of immunological diseases. This problem has led to the development of a specific molecular class, generally termed "immunomodulators," which are able to improve or suppress the immune response to treat or prevent immune-mediated diseases(5). The immunomodulators have a potential application as immunostimulatory agents for treating infection, immunodeficiency, and cancer, while they are also useful as immunosuppressive agents in organ transplantation and the treatment of autoimmune diseases(6). An example of an immunomodulator agent is methotrexate, which is a type of disease-modifying anti-rheumatic drug that helps to reduce the growth of cancer cells and treat rheumatoid arthritis by decreasing the activity of the immune system(7).

The balance of the human immune system is very important to protect against many diseases. There are many available chemically produced drugs to treat immune-related and infectious diseases, but they can also cause many side effects to the consumer(8). For example, corticosteroids are used to suppress inflammation by reducing the activation of several inflammatory mediators during infection and inflammation. The consumption of the drug promotes several side effects that include bruising, muscle weakness, weight gain, skin changes, sleep disturbances, cataracts, and pathologic fractures(9). Based on previous research, natural products contain numerous bioactive constituents and provide a wide range of pharmacological activities. Medicinal plants are among those that have been shown to have immunomodulatory activities(10). *Zingiber officinale* Roscoe is well-known in the community for its safe treatment and prevention and low risk of side effects. It is traditionally used to boost immunity, treat fever, and prevent infectious diseases. *Z. officinale*, or known as ginger, from the Zingiberaceae family and genus *Zingiber*, has been a medicinal herbal and spice product for a long time(11). The taxonomy of *Z. officinale* and the picture of *Z. officinale* are exhibited in **Table 1** and **Picture 1**, respectively. Ginger root has a broad variety of uses, including treating headaches, colds, nausea, and emesis. Ginger

is an herb that contains numerous bioactive phytochemicals and is scented, sparkling, and spicy(12). This plant species is used as a flavouring agent and is now at the top of the list of popular treatments for colds and sore throats. A significant explanation for its use as a medicinal agent is related to its phytochemicals, which contain nutritional values and have significant antioxidant effects. Due to this, its active phytochemicals have a good prospect as a potential future drug(13).

Z. officinale is an herbaceous perennial plant whose rhizome part is used as a spice and folk medicine to treat many illnesses in the community. The herb grows false stems made up of rolled leaves about one meter tall. The Zingiberaceae family, which originated in Maritime Southeast Asia, has been linked to antimicrobial, antioxidant, anti-inflammatory, and anti-cancer properties(14). For centuries, ginger has been known as a routine spice that was used by many regions all around the world. Ginger has also been used in traditional medicine to treat common gastrointestinal system ailments as well as part of therapeutic procedures for the treatment of many other disorders, including cancer(15). Ginger contains many natural organic materials (6-gingerol, 6-shogaol, and 6-paradol), and its main compounds show a variety of pharmacological effects that boost the host's immunity against infectious diseases by enhancing non-specific and specific immunological responses(16). However, there are only a few papers that make a systematic compilation of the immunomodulatory activities of *Z. officinale*. The pharmacological validation of the immunomodulatory effects of *Z. officinale* is quite limited, and several existing review publications on this plant haven't focused on this activity(17). Therefore, this study aimed to conduct a systematic assessment of all available data (from 2000 to 2020) to determine the effects of *Z. officinale* on immunomodulatory activity. Hence, it is also crucial to proving the community statement related to *Z. officinale*'s immunomodulatory activity(18). This review aims to combine the existing literature to offer fundamental knowledge for researchers involved in the confirmation of the traditional claims and immunomodulatory activities of this plant(19). Hopefully, this study will also provide facts for an idea of an advanced study to produce a new option for the immunomodulatory agent to prevent and treat immune-related diseases(20).

Table 1. Morphological category of Ginger

Classification	Name
Kingdom	Plantae
Division	Magnoliophyte
Class	Liliopsid
Order	Zingiberales
Family	Zingiberaceae
Genus	Zingiber
Species	Zingiber officinale var. Roscoe



Figure 1: Picture of Ginger

METHODOLOGY:

Systematic review:

To represent the conclusions, a systematic review compiles information from various studies on related research issues. This approach gathers all pertinent research on a certain subject and style. The best method for locating, gathering, analysing, and summarising data on preclinical and clinical topics is a systematic review(21). The results of systematic reviews provide the most trustworthy evidence foundation for creating trustworthy evidence-based guidelines (and their recommendations) and medical decisions(22). They use a systematic research methodology that demands the application of exacting standards to guarantee that the findings are reliable and relevant to the target audience. The foundation of evidence-based medicine is thus seen to be systematic reviews. This comprehensive review was carried out using the Cochrane Collaboration methodology(23).

Research approaches and study selection:

Two different internet databases, Science Direct and PubMed were used to conduct an online search for original publications between the years 2000 and 2021. *Z. officinale* or ginger along with "immunomodulatory activities" or "impact of *Z. officinale* or ginger on immunomodulatory activities" were used as strategic search phrases. The investigations that were cited in the articles concern earlier studies that used *Z. officinale* extract or a bioactive component that has immunomodulatory effects (in vivo, in vitro, or clinical studies). The article that does not meet the aforementioned requirements will be disqualified(24).

RESULTS:

Study selection:

There were 136 items found when the database search was completed. There were no items deleted because of redundancy. Upon screening for titles, abstracts, and keywords, 24 publications were found to be relevant. All of the studies were included in the comprehensive study, which looked at eleven full-text research articles from the titles, abstracts, and keywords that had been prescreened. Figure 2 shows the procedure for choosing studies to investigate the immunomodulatory activity. Table 2 provides a summary of all the data pertaining to this plant's immunomodulatory activity (model and technique used, compounds tested, outcomes, and dosage tested).

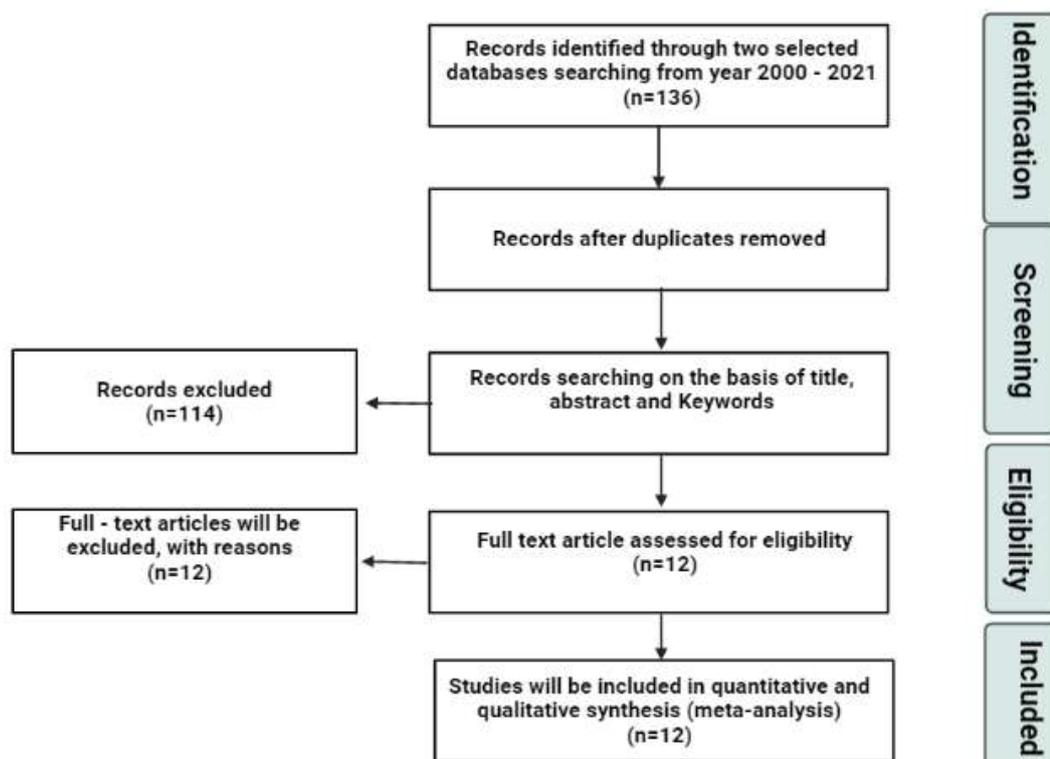


Figure 2: Diagram showing the selection process for studies on immunomodulatory activity.

Table 2. Immunomodulatory properties of ginger-derived substances, bioactive fractions, and crude extracts

S.No.	Tested substances	Model used	Tested dose	Results (using tested substances)	References
1.	Lipophilic extract	Human peripheral blood mononuclear cells (PBMCs)	6-gingerol: 2.75 mg 6-shogaol: 0.75 mg	↑ mRNA expression (PPM1B and RORA). ↓ gene expression (ALDOA, DEFA1/DEFA3, PRDX2, PRDX3 and SDCBP).	(24)
2.	Ginger crude aqueous extract and [6]-gingerol	<i>In-vitro</i> : PBMCs carrying hydatid cyst (cystic echinococcosis)	Ginger extract: 1, 10, and 100 mg/mL [6]-gingerol: 100 mg/mL	Ginger extract: 1mg/mL: kill 51.80% parasite after 24 hours of culture. 100mg/mL: kill 89.72% parasite after 24 hours of culture. [6]-gingerol: 100mg/mL: ↓ cell viability and nitric oxide (NO) production.	(25)
3.	Aqueous extract	Heparinized blood of broiler chicks	5g/kg diet daily for 21 days	↑ phagocytic cells capacity to engulf <i>Candida albicans</i> yeast particles. ↓ NO production.	(26)
4.	Ethanol and aqueous extracts	BALB/c mice (male) 6–8 weeks old	Ethanol extract: 500 mg/kg aqueous extract: 720 mg/kg	Both extracts: ↓ inflammatory cell infiltration around the airways. ↓ elevated levels of IL-4 and IL-5 in lung and BALF.	(27)

5.	[6]-gingerol	Female C57BL/6 mice (8 weeks) induced experimental autoimmune encephalomyelitis (EAE)	10mg/kg	↓ inflammatory cell infiltration from the peripheral blood into the central nervous system. ↓ neuroinflammation and demyelination.	(28)
6.	Dried, ground of fresh herbs	Spleen cells of C57 mice	0.15mg/mL	↓ thymidine incorporation in alloantigen activated lymphocytes by 56.2%. ↓ thymidine incorporation in mitogen-activated lymphocytes by 68.9%.	(29)
7.	Ethanol extract	Cardiac muscle tissue of male Wistar rats, weighing 250±30g.	100, 200 and 400mg/kg	↓ inflammatory cells in a dose-dependent manner.	(30)
8.	[6]-gingerol	CD ⁴⁺ and CD ⁸⁺ T cells of female C57BL/6 (6–8 weeks of age) and Thy1.1 ⁺ mice infected with H37Rv	[6]-Gingerol: 10 mg/kg	↑ host protective Th1 and Th17. ↑ IFN-γ and IL-17 expression. Activation of p38 MAPK signalling pathway.	(31)
9.	Zingerone (ZGR)	Serum and portion of the liver male C57BL/6 mice (aged 6 weeks, weighing 27 g) exposed to lipopolysaccharides (LPS)	0.18mg/kg, 0.36mg/kg and 0.72 mg/kg	0.72 mg/kg: ↓ TLR4 expression. ↓ MyD88-dependent signalling. ↓ MAPK activation. ↓ expression of inflammatory genes in LPS-induced hepatic failure.	(32)
10.	[6]-gingerol	Tissue colon of male C57BL/6 mice aged seven to eight weeks old, macrophages (RAW 264.7) and bone marrow-derived macrophages (BMDMs) cells.	20mg/kg	↓ serum IL-1β expression in septic mice. ↓ LPS/ATP-induced HMGB1, activate caspase-1p20 and mature IL-1β secretion in both RAW264.7 and BMDMs cells. ↓ NLRP3 inflammasome by inhibiting phosphorylation of MAPK.	(33)
11.	Aqueous extract of the whole plant	Proximal colon and ileum of newborn pups of <i>Wistar albino rats</i> induced with necrotizing enterocolitis.	1000 mg/kg/day	↓ levels of TNF-α, IL-1β and IL-6. ↑ antioxidant system.	(25)
12.		In vitro C2812 human Chondrocyte cell	5 to 25 µg/mL	↑ increasing antioxidant enzyme gene expression; decreasing ROS and	

	Ginger extract			lipid peroxidation levels	(16)
		In vitro HT1080 human Fibrosarcoma cell	200 to 400 µg/mL	↓ decreasing the amount of ROS produced	
		In vitro Rat heat homogenates	78-313 µg/mL	↓ decreasing the MDA levels	

The property of investigations that were included in a comprehensive examination of outcomes linked to immunomodulation. (↑= increase, ↓=decrease).

DISCUSSION:

According to early research, several chemicals from the lipophilic extract considerably upregulate the mRNA expression of RORA and PPM1B and dramatically reduce the expression of PRDX2, ALDOA, PRDX3, DEFA1/DEFA3, and SDCBP in human PBMCs. These genes are all necessary for the suppression of inflammation. A study found a whole ginger aqueous extract (1000 mg/kg/day) to reduce IL-1, TNF-, and IL-6 levels. Albino rats with necrotizing enterocolitis have less inflammation when their IL-1, TNF-, and IL-6 levels are reduced. Additionally, the albino rat's antioxidant system may be stimulated by the use of an aqueous extract. The results of the other investigation demonstrated that ginger crude extract and [6]-gingerol substantially killed 89.72% of *Echinococcus granulosus* after 24 hours of culture. They also demonstrated a dose-dependent reduction in the cell viability and NO secretion of human PBMCs. numerous in vivo studies were also carried out to look at the immunomodulatory abilities of ginger. According to prior research using the heparinized blood of broiler chickens as a model, ginger's aqueous extract may inhibit *C. Albicans* at a dosage of 5 g/kg of food per day for 21 days. This research showed a considerable reduction in NO generation and an increase in the ability of phagocytic cells to swallow *C. Albicans* yeast particles. In addition, the study stated that ethanol and aqueous extracts decrease the inflammatory cell infiltration around the airways and also decrease the elevated levels of IL-4 and IL-5 in the lung and BALF of BALB/c mice when compared to methylprednisolone as a control group. The other in vivo investigation revealed that [6]-gingerol in phosphate-buffered saline (PBS) at a dose of 10 mg/kg decreased the inflammatory cell infiltration from the peripheral blood into the central nervous system and decreased neuroinflammation and demyelination.

Moreover, the in vitro study by those who were using the spleen cells of C57 mice as a model discovered that the dried, ground fresh ginger (0.15 mg/mL) decreased the thymidine incorporation in alloantigen activated lymphocytes to 56.2% and also decreased the thymidine incorporation in mitogen-activated lymphocytes to 68.9%. Another study found that ethanol extract at concentrations ranging from 100 to 400 mg/kg reduced inflammatory cells in the cardiac muscle tissue of male Wistar rats in a dose-dependent manner when compared to a control group given metformin (200 mg/kg) 46. In another study, [6]-gingerol at 10 mg/kg increased host protective T helper 1 (Th1) and T helper 17 (Th17) expression, as well as IFN- and IL-17 expression, and activated the p38 MAPK signaling pathway in mice.

Additionally, zingerone (ZGR) in 0.5% dimethyl sulfoxide (DMSO) at a dose of 0.72 mg/kg inhibits the expression of the inflammatory gene and the toll-like receptor 4 (TLR-4) protein in lipopolysaccharide (LPS)-induced liver failure in C57BL/6 mice. Myeloid differentiation signaling pathway gene 88 (MyD88)-dependent signaling and mitogen-activated protein kinase (MAPK) because the TLR-4 protein is involved in the activation of immune cells, ZGR has a hepatoprotective function to stop the overexpression of TLR-4. In accordance with the prior report, 20 mg/kg of in septic mice, gingerol reduced the expression of IL-1 in their blood. It also reduced the production of HMGB1 caused by LPS/ATP, triggered caspase-1 p20 and mature IL-1 secretion in RAW 264.7 and BMDM cells, and inhibited the NLRP3 inflammasome by preventing MAPK activation.

Conclusion:

The ginger plant, *Zingiber officinale*, also known as "Halia" in Malaysia, has a promising future as a safer option for preventative and therapeutic agents with minimal risk of adverse effects. Corticosteroids, for example, are used to control inflammation during infections, but they may have negative consequences, including bruising, muscular weakness, pathologic fractures, weight gain, and sleep difficulties. Numerous investigations have shown that the bioactive substances and crude extracts of *Z. officinale* have a range of pharmacological effects, including anticancer, anti-inflammatory, antibacterial, antioxidant, and immunomodulatory properties.

Conflict of Interest

None

Reference:

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