

## SYSTEMATIC REVIEW

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# Utilization of *Garcinia mangostana* L. Peel as an Immunomodulator to Improve the Quality of Human Resources: A Systematic Review

## Pemanfaatan Kulit *Garcinia mangostana* L. sebagai Immunomodulator untuk Meningkatkan Kualitas Sumber Daya Manusia: Sebuah Tinjauan Sistematis

Yunita Satya Pratiwi<sup>1\*</sup>, Dina Mustika Rini<sup>2</sup>, Ifwarisan Defri<sup>3</sup>, Tawaffani Qubra<sup>4</sup>, Nadien Mutia Intan Maulidi<sup>5</sup><sup>1</sup>Department of Food Technology, Faculty of Engineering, Universitas Pembangunan Nasional "Veteran" Jawa Timur, Surabaya, Indonesia<sup>2</sup>Graduate School of Integrated Sciences for Life, Hiroshima University, Higashi-Hiroshima, Japan<sup>3</sup>Department of Food Industry, School of Agricultural Technology and Food Industry, Walailak University, Nakhon Si Thammarat, Thailand<sup>4</sup>Department of Biotechnology, Graduate School, Universitas Andalas, Padang, Indonesia<sup>5</sup>Department of Nutrition, Faculty of Public Health, Universitas Jember, Jember, Indonesia

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**\*Correspondent:**

Yunita Satya Pratiwi

[yunita.satya.tp@upnjatim.ac.id](mailto:yunita.satya.tp@upnjatim.ac.id)

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### ABSTRACT

**Background:** Mangosteen (*Garcinia mangostana* L.) is recognized for its immunomodulatory properties, which can rejuvenate, regulate, and modulate immune system function. As a rich source of antioxidants, mangosteen peel has the potential to enhance immune responses and improve overall health status. However, further investigation into the biological mechanisms underlying its immunomodulatory effects remains limited.

**Objectives:** This review aimed to explore the various biological functions of mangosteen peel related to immunomodulation and examine its therapeutic potential in improving human health.

**Methods:** A Systematic Literature Review (SLR) was conducted, focusing on articles published between 2013 and 2023. From a total of 132 articles identified, ten were selected based on relevance and research quality.

**Discussions:** The review reveals significant associations between the properties of mangosteen peel, such as its anti-diabetic, anti-obesity, antidepressant, anti-inflammatory, anticancer, and antioxidant activities, and the complex network of immune cell responses. Nevertheless, most studies have not clearly identified the specific compounds responsible for these immunomodulatory effects, and the underlying mechanisms remain unclear. Further comprehensive studies are necessary to isolate and identify the bioactive compounds in mangosteen peel extract, beyond xanthenes, to better understand their diverse therapeutic effects and mechanisms. Well-designed clinical trials involving diverse populations, including vulnerable groups, are essential to validate the efficacy and safety of the extract in various therapeutic contexts.

**Conclusions:** This review provides valuable insights into the potential of mangosteen peel as an immunomodulator and lays the groundwork for future research aimed at utilizing its therapeutic properties to improve human health.

### INTRODUCTION

Mangosteen (*Garcinia mangostana* L.) is a naturalized plant native to Southeast Asia, including Indonesia, Peninsular Malaysia, Myanmar, Thailand, Cambodia, Vietnam, and the Maluku Islands. The genus *Garcinia* comprises approximately 400 to 800 species and belongs to the family Clusiaceae (formerly Guttiferae). Over the past two centuries, mangosteen has also been cultivated in other tropical regions such as India, Australia, Brazil, and Honduras<sup>1</sup>.

Often referred to as the "Queen of Fruits," mangosteen is well known both locally and

internationally for its unique taste. Almost all parts of the plant, skin, fruit, seeds, bark, and leaves, can be utilized as natural remedies for various diseases. Mangosteen exhibits significant antioxidant activity due to its high xanthone content<sup>2</sup>. Xanthenes, extracted from different parts of the plant, possess antioxidant properties that help mitigate the accumulation of free radicals generated through respiration during fruit storage<sup>3</sup>. Both xanthenes and anthocyanins demonstrate strong antioxidant activity by counteracting the harmful effects of reactive oxygen species and inhibiting cellular degeneration<sup>4</sup>.

Beyond its antioxidant properties, mangosteen has also been recognized for its pharmacological potential as an immunomodulator. These properties include anti-inflammatory, anti-tumor, antidepressant, antimicrobial, anticancer, antiparasitic, antiparasitoid, and antidiabetic effects<sup>5</sup>. According to the International Diabetes Federation (IDF), approximately 537 million adults aged 20 to 79 years were affected by diabetes globally in 2021. Consequently, the antidiabetic effects of mangosteen may contribute to the prevention and management of diabetes mellitus. Furthermore, the regular consumption of mangosteen may help protect organs and enhance immune function, thereby defending against viruses, bacteria, metabolic disorders, and infectious diseases associated with antioxidant deficiency.

The immune system plays a crucial role in defending the body against infectious agents and maintaining overall health<sup>6</sup>. Mangosteen is a promising source of antioxidants that can be incorporated into various food and health products such as teas, instant powders, tablets, capsules, and functional foods. Several studies have demonstrated that consuming antioxidant-rich products can significantly enhance immune responses and improve individuals' subjective health assessments<sup>4</sup>. Both *in vivo* and *in vitro* studies have shown that flavonoid compounds present in mangosteen stimulate immune activity. In particular, mangosteen peel has been reported to exert anti-inflammatory effects against various degenerative and infectious diseases<sup>7</sup>. However, the specific biological function of mangosteen peel in modulating immune responses remains poorly understood.

Although numerous studies have explored the general health benefits of mangosteen, comprehensive reviews that specifically highlight the

immunomodulatory properties of active compounds in the peel are lacking. Therefore, this study aimed to provide an in-depth overview of the biological functions of mangosteen peel related to immunomodulation and to explore its therapeutic potential in enhancing immune function and improving public health outcomes.

## METHODS

This review focuses on elaborating recent findings regarding the immunomodulatory potential of mangosteen (*Garcinia mangostana*) peel. The writing process employed a Systematic Literature Review (SLR) method, following the procedures outlined by established academic standards<sup>8</sup>.

The review process involved several key stages: conducting a literature search, selecting relevant studies, presenting the data, analyzing findings, and drawing conclusions. These steps are illustrated in Figure 1.

A comprehensive literature search was conducted using four academic databases: Google Scholar, ScienceDirect, MDPI, and NCBI. The search employed the following keywords: "mangosteen", "mangosteen AND utilization", "immunomodulator", "immune AND system", and "health AND quality of human resources". Articles published between 2013 and 2023 were included in the search.

A total of 132 articles were initially identified. These articles were screened based on their relevance to the review's objectives. After applying the inclusion criteria, 10 articles were selected for further analysis. These selected articles were summarized in tabular form, analyzed qualitatively, and reviewed to synthesize the findings related to the immunomodulatory properties of mangosteen peel.

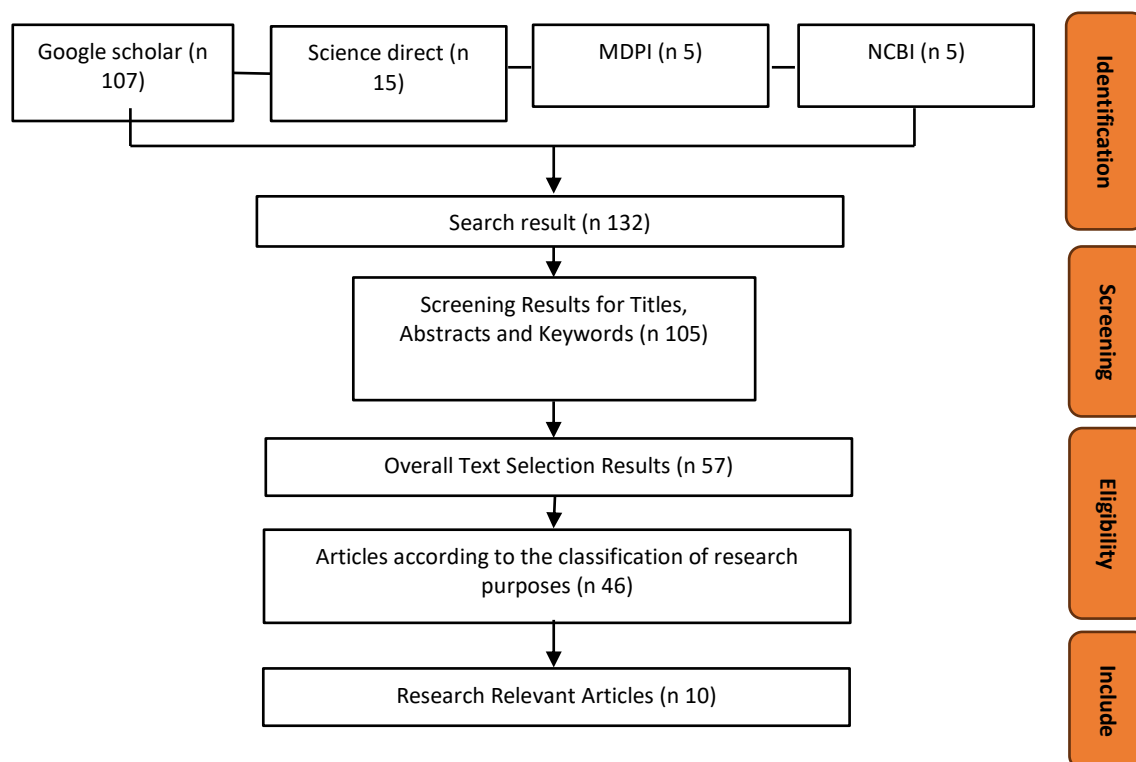


Figure 1. Systematic literature screening and selection method used

## DISCUSSIONS

*Garcinia mangostana* L.

*Garcinia mangostana* L., commonly known as mangosteen, is an herbal medicine increasingly cultivated for its therapeutic potential. The mangosteen tree can grow up to 25 m in height, with a stem diameter of approximately 45 cm. It thrives at altitudes ranging from 0–600 m above sea level, in areas with average air temperatures of 20–30°C, and in soils with a pH of 5–7<sup>9</sup>. Over 70 different xanthone compounds have been isolated from the mangosteen plant. Among them,  $\alpha$ -mangostin has been identified for its anti-cancer

properties<sup>10</sup>. The safety of extracts and compounds derived from *Garcinia mangostana* L. has been confirmed in animal models, where their cytotoxic effects were observed to specifically target tumor cells while sparing normal cells. However, as xanthone toxicity is dose-dependent, novel delivery systems have been developed to enhance its efficacy against cancer cells while minimizing adverse effects on healthy tissue<sup>9</sup>.

The bioactive compounds present in mangosteen peel have shown potential as immunomodulators. Recent studies exploring the immunomodulatory potential of mangosteen peel are summarized in Tables 1 and 2 based on the selected articles.

**Table 1.** Summary of articles on the immunomodulatory activity of mangosteen peel

Specific Factor	Experimental Method	Immunomodulatory Activity	Reference
Xanthone	<i>In vivo</i> : alloxan-induced diabetic rats	Anti-diabetic	Maliangkay <i>et al.</i> , 2018 <sup>11</sup>
$\alpha$ -mangostin, procyanidin, anthocyanin, hydroxycitric acid	<i>In vivo</i> : diet-induced metabolic syndrome	Anti-obesity	John <i>et al.</i> , 2021 <sup>12</sup>
$\alpha$ - and $\gamma$ -mangostin	<i>In vivo</i> : FSL rat depression model	Anti-depression	Oberholzer <i>et al.</i> , 2018 <sup>13</sup>
-	<i>In vivo</i> : egg white-induced inflammation in mice	Anti-inflammation	Megawati, 2019 <sup>14</sup>
-	<i>In vitro</i> : MCF-7 cell	Anti-cancer, antioxidant	Geetha <i>et al.</i> , 2020 <sup>15</sup>
-	<i>In vitro</i> : H357 and HeLa cell	Anti-cancer, antioxidant	Janardhanan <i>et al.</i> , 2020 <sup>16</sup>

Abbreviations: FSL – Flinders Sensitive Line; MCF-7 – Breast Cancer Cells; HeLa – Cervical Cancer Cells; H357 – Tongue Squamous Cell Carcinoma

**Anti-Diabetic**

According to the World Health Organization, diabetes mellitus is projected to become the seventh leading cause of death by 2030. A previous study reported that administration of mangosteen peel decoction, rich in antioxidants such as anthocyanins, xanthenes, tannins, and phenolic acids, significantly reduced blood glucose levels in respondents when combined with healthy lifestyle practices and dietary modifications<sup>17</sup>. Diabetes mellitus is characterized by elevated blood glucose levels due to pancreatic beta-cell dysfunction. Recent evidence suggests that mangosteen's antioxidant properties may help regulate insulin secretion<sup>1</sup>. Antioxidants in mangosteen may also protect pancreatic beta cells from free radical damage, supporting immune function and reducing glucose levels in diabetic patients.

As illustrated in Figure 2, although there is no direct comparison of immunological changes between individuals with different blood glucose levels, various studies suggest that glycemic states influence immune responses<sup>18</sup>. Hypoglycemia is associated with reduced immune surveillance, including diminished T cell and Natural Killer (NK) cell function and increased anti-inflammatory cytokines. Conversely, hyperglycemia tends to cause chronic inflammation, characterized by increased M1 macrophage and monocyte activity, Th1/Th17 polarization, decreased Treg function, and elevated proinflammatory cytokines and adipokines. These findings underscore the role of metabolic states in modulating immune cell function and immune response dynamics.

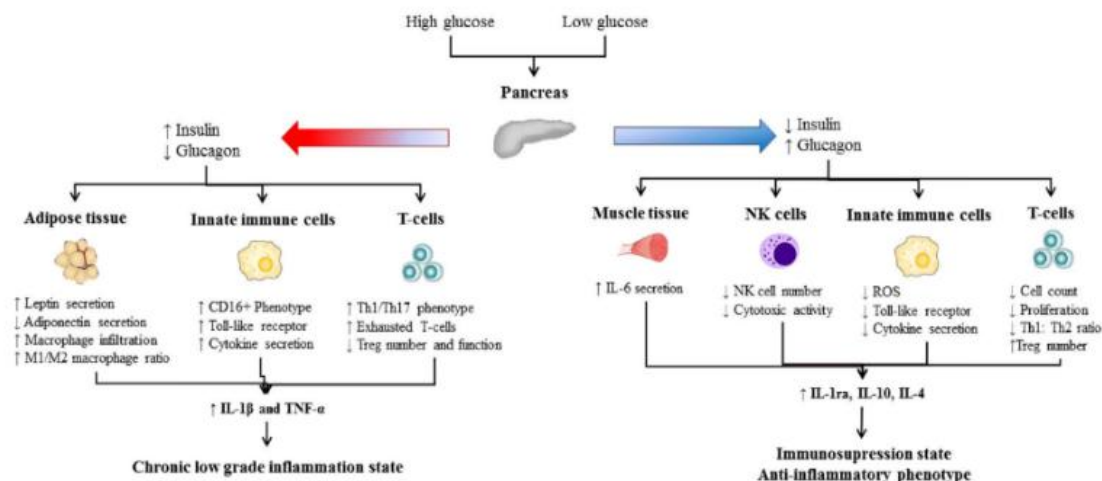


Figure 2. Effects of blood glucose levels on the immune system<sup>18</sup>

A previous study revealed that the ethanol extract of mangosteen peel can suppress blood glucose levels in alloxan-induced diabetic rats<sup>11,12</sup>. A dose of 150 mg/kg body weight of the extract had a more pronounced effect in reducing hyperglycaemia symptoms than a dose of 300 mg/kg body weight. In relation to the present study, this finding highlights the potential of mangosteen peel, which contains bioactive compounds, particularly xanthenes, in exerting antidiabetic effects. This is evident from trials conducted on white rats (*Rattus norvegicus*) that were induced with alloxan to evaluate blood glucose reduction. The observed antidiabetic activity suggests that the antioxidants in mangosteen peel contribute to lowering blood glucose levels<sup>11,12</sup>. However, the precise molecular and cellular mechanisms by which these bioactive compounds alleviate diabetic symptoms remain unclear. Further *in vitro* studies involving cell cultures related to insulin production, glucose uptake, and inflammation, as well as *in vivo* investigations, are necessary to elucidate the underlying mechanisms.

### Anti-Obesity

There is limited research on the immune response in the body during obesity. However, multiple studies suggest that obesity can lead to inflammation and related diseases, with potential implications for the immune response. Obesity can result in the presence of newly polarized M1 macrophages with a proinflammatory phenotype and cytokine secretion (e.g., TNF- $\alpha$ ), leading to an increase in macrophages that act as effectors in complex immune programs. Consequently, the immune response triggers a chronic inflammatory reaction in adipose tissue, involving various effector T cells, B cells, NK cells, and others, which produce cytokines that regulate the accumulation and activity of proinflammatory M1 macrophages, as shown in Figure 3<sup>19</sup>. Therefore, obesity initiates an immune response that causes inflammation.

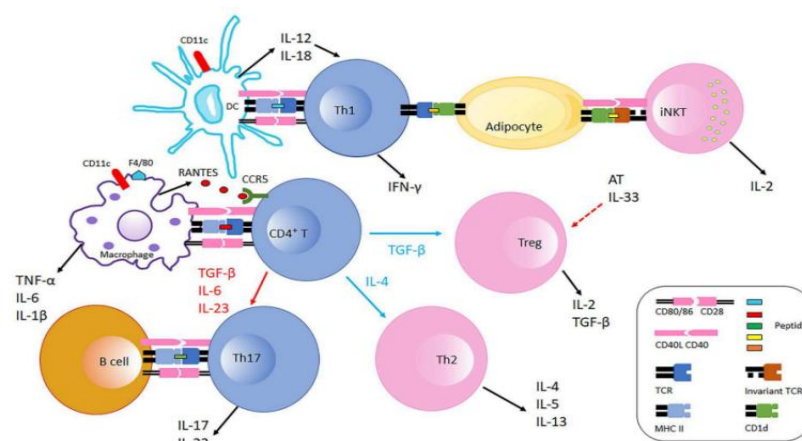


Figure 3. Interaction of the immune system in obesity<sup>20</sup>

Figure 3 shows immune cell interactions in adipose tissue during obesity. As obesity shifts macrophage polarization toward the M1 phenotype (F4/80+), macrophages recruit CD4+ T cells by producing RANTES, a CCR5 ligand expressed on T cells. Upon

stimulation with fate-determining cytokines, CD4+ T cells differentiate into various effector types, including Th1, Th2, Th17, and Treg cells. CD11c+ DCs secrete IL-12 and IL-18, further polarizing CD4+ T cells into Th1 cells in the adipose tissue (AT). Th1 cells interact with adipocytes via

MHC class II molecules, suppressing AT IL-33 production from unspecified cellular sources, which promotes Treg proliferation. Adipocytes also communicate with iNKT cells via CD1d molecules expressed on adipocytes, which induce iNKT cells to produce IL-2 and other cytokines that counteract AT inflammation. B and Th17 cell interactions are likely mediated by MHC class II molecules and costimulatory receptors that facilitate the production of IL-17 and IL-22. During obesity, AT Th2 and Treg populations decrease, and the balance shifts toward proinflammatory responses with an increase in Th1 and Th17 populations. Typical proinflammatory T cells in AT are depicted in blue, while anti-inflammatory T cells in AT are shown in pink<sup>20</sup>.

Obese female patients experienced weight loss when their arm circumference was monitored over an extended period, with higher doses of mangosteen administered. The results showed a reduction in fat or lipogenesis through multiple mechanisms, one of which involved monitoring C-reactive protein (CRP) levels. A decrease in CRP was found to be effective in reducing and controlling chronic inflammation in obese patients<sup>21</sup>. John *et al.* (2021)<sup>12</sup> demonstrated that an 8-week supplementation of mangosteen peel components, such as  $\alpha$ -mangosteen, procyanidins, anthocyanins, and hydroxycitric acid, ameliorates obesity by decreasing the infiltration of inflammatory cells, curtailing the expansion of adipocytes, and mitigating age- and inflammation-related adipose tissue changes. Mangosteen peel improves physiological, metabolic, hepatic, and cardiovascular symptoms in rats with metabolic syndrome<sup>12</sup>. A previous study showed that  $\alpha$ -mangosteen has been reported to reduce macrophage quantities,

modify proinflammatory macrophage polarization, and attenuate proinflammatory cytokines, including IL-1 $\beta$ , iNOS, and TNF, in adipose tissue related to aging<sup>22</sup>. However, the precise role of procyanidins, anthocyanins, and hydroxycitric acid from mangosteen peel in reducing obesity is not yet fully understood. Although animal studies offer valuable insights, well-designed human clinical trials are essential to validate the potential of mangosteen peel.

### Anti-Depression

Numerous studies have demonstrated a link between the state of the immune system and the occurrence of depression, or vice versa. The Central Nervous System (CNS) can modulate the immune system through mechanisms involving the nervous and endocrine systems. When one of these systems is in a state of anger or negative emotions, it activates the HPA-axis and the sympathetic adrenal-medullary axis, leading to decreased immunity and a positive correlation between aggression and peripheral cytokine levels<sup>21</sup>. The formation of inflammation is known to stimulate an immune response. Chronic stress can suppress or regulate both innate and adaptive immune responses by altering type 1 and type 2 cytokines, inducing low-level inflammation, which can result in an increase in immunosuppressive mechanisms<sup>23</sup>. Mangosteen peel, which has procognitive antioxidant activity, had a positive effect on Flinders Sensitive Line (FSL) mice, a genetic model of depression, after both acute and chronic treatment, compared to the antidepressant imipramine (IMI).

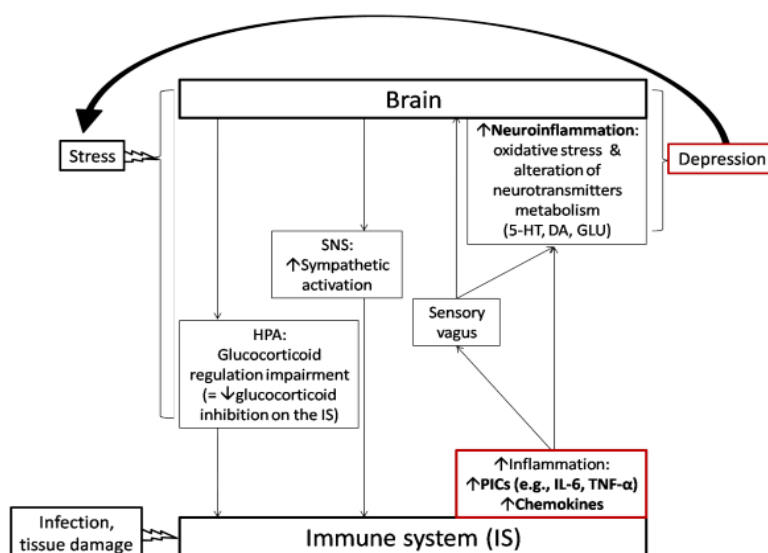


Figure 2. Immune system interaction and depression<sup>24</sup>

Figure 4 illustrates the interaction between the immune system and proinflammatory cytokines (PICs) (e.g., IL-6, TNF- $\alpha$ ) and brain function. In response to infection or tissue damage, the immune system is automatically activated. Similarly, stress and anxiety lead to activation of the immune system, primarily through the sympathetic nervous system (SNS) and by disruption of the hypothalamic-pituitary-adrenal (HPA) axis.

Activation of the immune system results in increased inflammation, characterized by elevated levels of PICs and chemokines, which, indirectly through the vagus nerve and directly through the bloodstream, cause neuroinflammation with oxidative stress and alterations in neurotransmitter metabolism (5-HT: serotonin, DA: dopamine, GLU: glutamate), contributing to depressive symptoms. Conversely, depression can put individuals at



higher risk for physical or psychological stress. Increased irritation signals the CNS to induce or intensify "illness behaviors," which consist of poor mood, fatigue, anhedonia, heightened sensitivity to pain, loss of appetite, and cognitive deficits, a cluster of signs and symptoms reminiscent of human hopelessness<sup>24</sup>.

A previous study revealed that the use of mangosteen peel powder contributed to several positive effects related to brain health and function. Specifically, the treatment resulted in decreased lipid peroxidation, as shown by a reduction in MDA levels, and improved conditions related to the hippocampal region of the brain. These improvements were seen in memory recognition and serotonergic effects, suggesting a potential impact on mood regulation. In addition, ethanol-extracted mangosteen peel showed significant antioxidant effects in subjects with traumatic brain injury. It increased the levels of the antioxidant enzyme SOD while concurrently reducing neuronal apoptosis, a process of cell death in neurons. This reduction was associated with the downregulation of various factors involved in apoptosis, including apoptosis-inducing factor (AIF), caspase-8, and caspase-9, along with decreased levels of MDA, a marker of oxidative stress. The observed improvements in memory recognition, serotonergic effects, and the protective effects against neuronal damage and oxidative stress are relevant factors in the context of depression and brain health<sup>22</sup>. This phenomenon has been previously documented in scientific literature, highlighting the association between stress and the potential antidepressant properties of mangosteen peel juice. Administration of mangosteen peel juice has been observed to diminish cortisol levels in mice subjected to stress induced by factors such as weight gain and

exposure to noise. This effect is believed to occur through the inhibition of noradrenaline and serotonin reuptake into presynaptic neurons, thereby modulating neurotransmitter levels and fostering a more favorable emotional state<sup>23,25</sup>. Hence, the findings suggest that mangosteen peel, particularly in its powdered or ethanol-extracted form, may play a beneficial role in ameliorating factors associated with depression or depressive symptoms by influencing brain health, oxidative stress levels, and neuronal protection. Further research could explore the direct effects on depressive symptoms and mood regulation to better understand the potential role of mangosteen peel as an antidepressant.

### Anti-Inflammation

Inflammation consists of three phases: acute inflammation, immune response, and chronic inflammation. It is typically a protective response of the immune or defense system aimed at preventing, limiting, and repairing cellular damage caused by pathogens or endogenous biomolecules<sup>26</sup>. This response may not occur effectively in the absence of nutrients that support the immune system in combating inflammation. Among the antioxidant compounds, flavonoids found in mangosteen have demonstrated potential as anti-inflammatory agents by inhibiting pro-inflammatory cytokines, particularly tumor necrosis factor-alpha (TNF- $\alpha$ ). These flavonoids reduce the activation of TNF- $\alpha$  signaling pathways<sup>7</sup>. Although several pathophysiological mechanisms exist within the immune system to suppress pro-inflammation, this paper focuses on the most significant mechanisms involved in the inflammatory process.

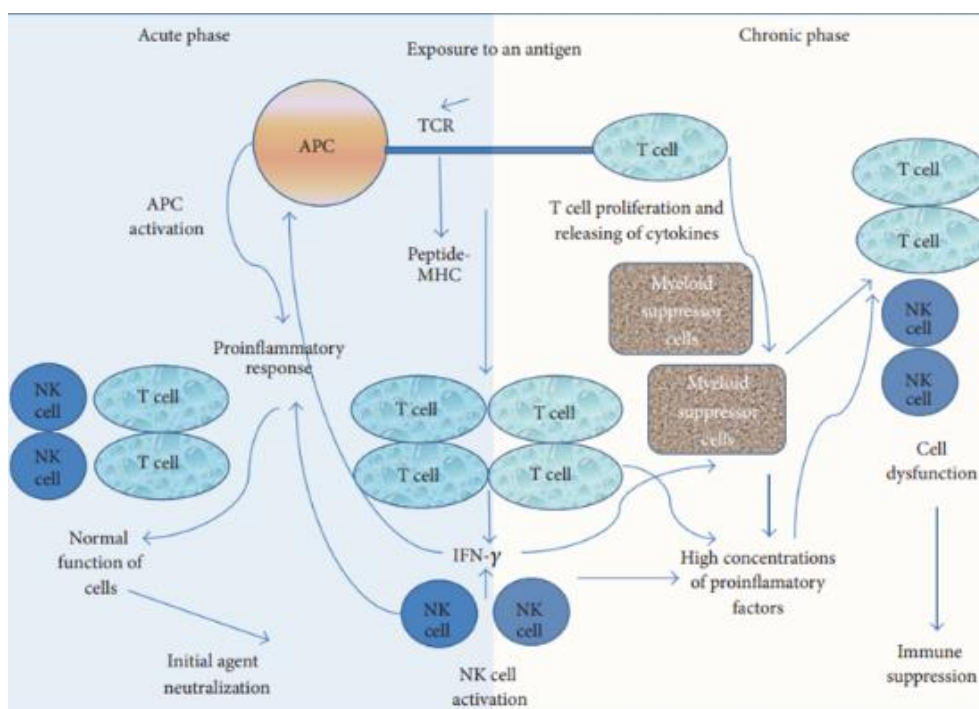


Figure 3. The occurrence of inflammation and its effect on the immune system<sup>26</sup>

Figure 5 illustrates the process of inflammation and the immune response (IIR). The primary defense

mechanism of the immune system involves the activation of various cell phenotypes and intercellular signaling

pathways. Among the cytokines, interleukins (IL-1 and IL-6) and TNF- $\alpha$  play central roles in inducing IIR through the regulation of monocytes. Immunocompetent cells such as macrophages, neutrophils, fibroblasts, and endothelial cells are essential for the optimal functioning of the immune system<sup>27</sup>.

An alternative approach to managing inflammation with minimal side effects involves the use of plant-derived remedies, with mangosteen showing promising potential. A previous study demonstrated that the administration of mangosteen peel extract significantly reduced average edema volume, indicating its effectiveness as an anti-inflammatory agent<sup>14</sup>. Megawati (2019)<sup>14</sup> showed that mangosteen peel extract concentrations of 1%, 2%, and 3% b/v produced anti-inflammatory effects in mice. The active compounds responsible for these effects are flavonoids.

Another study highlighted the roles of  $\gamma$ -mangostin and flavonoid compounds, key constituents of xanthenes, in inhibiting cyclooxygenase (COX) enzyme production, which is a major contributor to the inflammatory response<sup>28</sup>. Flavonoids exert irreversible inhibition on the release of the COX enzyme (prostaglandin synthetase), which catalyzes the conversion of arachidonic acid into endoperoxide compounds. This process ultimately reduces prostaglandin formation and suppresses the inflammatory cascade. As a result of this suppression, a reduction in neutrophil count is observed. Accordingly, mangosteen peel extract has proven effective in treating gingival inflammation<sup>29</sup>.

While  $\gamma$ -mangostin and flavonoids have been identified as key active compounds, a comprehensive

analysis of the full spectrum of bioactive constituents in mangosteen peel extract is warranted. Isolating and identifying the specific bioactive molecules responsible for the observed anti-inflammatory effects would facilitate the development of targeted therapies. Additionally, further elucidation of the molecular mechanisms underlying these effects is necessary.

### Anti-Cancer

Cancer is a systemic disease characterized by prolonged inflammation that begins during tumorigenesis, facilitating tumor growth in conjunction with external factors that accelerate the progression from tumor to cancer<sup>30</sup>. Another contributing factor to cancer incidence is the relationship between lifestyle and the presence of free radicals, which can be mitigated by consuming adequate amounts of antioxidants, such as those found in mangosteen fruit.

The process of cancer formation and its impact on the immune system has been extensively studied. Technical abbreviations are explained upon first mention. A previous study demonstrated that during the elimination phase, there is an inflammatory response and initiation of danger signals linked to tumor cells. Moreover, the secretion of pro-inflammatory cytokines such as interleukin-12 (IL-12) and interferon-gamma (IFN- $\gamma$ ), along with the death of innate immune cells (e.g., natural killer (NK) cells, dendritic cells (DC), and macrophages), are observed. In some cases, newly formed cancer cells evade immune surveillance, leading to further clinical symptoms<sup>30</sup>.

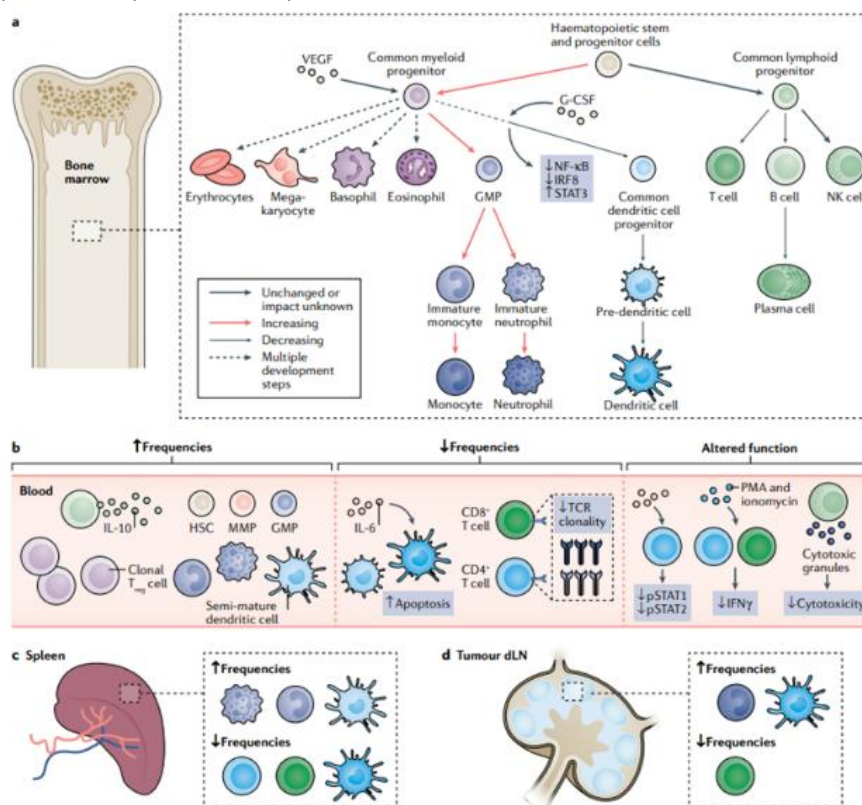


Figure 4. Immune system and cancer work<sup>28</sup>

Figure 6 illustrates that systemic immune dysregulation results from the presence of tumor cells. The peripheral immune system is impaired in numerous tumor types. During tumor progression, the bone marrow, blood, spleen, and lymph nodes form an immunological network that remains in constant communication. Collectively, studies conducted on various human and mouse tumors indicate that peripheral immunity transitions into a suppressive state. This state is marked by the proliferation of anti-inflammatory cell types, a decrease in key factors of anti-tumor immunity, and alterations in matrix metalloproteinases (MMPs) and other multipotent sources<sup>30</sup>.

Mangosteen has the potential to function as an immunomodulatory agent, promoting equilibrium within the immune system, particularly as an anti-cancer agent. A prior study found that mangosteen peel extract exhibited significant anticancer activity when tested on MCF-7 cells, as evidenced by distinct morphological changes indicative of apoptotic cell death. This effect was attributed to the presence of polyphenolic compounds in the extract, known for their ability to scavenge free radicals produced by reactive oxygen and nitrogen species (ROS/RNS). These compounds demonstrated a capacity to induce apoptosis specifically in cancer cells, thereby highlighting the potential of mangosteen pericarp extract as an effective anticancer agent through its apoptosis-inducing properties<sup>15</sup>.

On the other hand, a previous study revealed that the xanthone content, particularly  $\alpha$ -mangostin, exhibited anti-proliferative and apoptotic activities. The compound was found to activate the apoptotic enzymes caspase-3 and caspase-9, but not caspase-8, indicating that  $\alpha$ -mangostin mediates apoptosis via the mitochondrial pathway<sup>31</sup>. Additionally, a separate study focused on examining the ethanol extract of mangosteen peel, highlighting its cytotoxic activity and its capacity to induce apoptosis in oral and cervical cancer cells. The findings underscore the potential of mangosteen peel extract as a therapeutic agent for cancer. The observed cytotoxicity and induction of apoptosis in cancer cells further support its effectiveness in treating oral and cervical cancers. These findings reaffirm its role as a potential anticancer therapeutic agent<sup>16</sup>. However, both studies primarily investigated the anticancer potential of mangosteen peel extract through in vitro experiments, which do not account for the complexities of the human physiological response. A more comprehensive understanding of the effects of mangosteen peel extract as an anticancer agent would require in vivo studies using animal models or, ideally, clinical trials involving human subjects.

#### Antioxidant

A previous study investigated the immunomodulatory effects of ethanol extract from mangosteen leaves in male white mice. The mice were administered varying doses of the extract over six days,

followed by assessments of the phagocyte index and leukocyte cell count on the seventh day. Mangosteen peel extract, at doses of 100 mg/kg BW, 300 mg/kg BW, and 900 mg/kg BW, increased the phagocyte index ( $>1$ ) and elevated leukocyte cell counts, suggesting its potential immunostimulatory properties<sup>3</sup>. Xanthones have demonstrated the ability to protect the body from free radicals, combat aging, enhance the immune system, and manage various degenerative diseases<sup>30,32</sup>. This supports earlier findings indicating that, with respect to phagocytic capacity, the number of bacteria phagocytosed by 50 macrophages not only remains consistent but also shows an increasing trend when exposed to a 70% concentration. This reinforces its immunomodulatory activity, supported by comparative analysis with more potent positive controls<sup>31,33</sup>.

The immunomodulatory effects attributed to mangosteen peel are primarily due to its potent antioxidant activity. Mangosteen peel aids in regulating immune system function and mitigating oxidative damage. The modulation of oxidative stress levels has been linked to enhanced immune cell activity, fostering a more efficient immune response. While other mechanisms may contribute to its immunomodulatory properties, antioxidant activity remains a significant factor influencing the observed effects on the immune system. For instance, as previously mentioned, mangosteen peel extract was shown to reduce blood glucose levels in alloxan-induced diabetic rats<sup>11</sup>, partly by exerting its antioxidant effects through  $\alpha$ - and  $\gamma$ -mangostin. Previous research has demonstrated that antioxidants can reduce reactive oxygen species (ROS) levels, which otherwise damage pancreatic beta islets and interfere with insulin production<sup>32,34</sup>. Additionally, mangosteen extract has shown potential anti-cancer, anti-inflammatory, and anti-depressive effects<sup>35</sup>.

#### Mangosteen Peel Potentials in Improving the Quality of Human Resources

The consumption of mangosteen is expected to offer protection to vital organs and enhance immunity against a wide range of viruses, bacteria, and metabolic disorders due to the immunomodulatory role of its antioxidant constituents. Studies exploring the immunomodulatory properties of mangosteen often focus on its active constituent profile, particularly the antioxidant content that plays a critical role in this function. Consequently, mangosteen has the potential to serve as an alternative treatment for conditions associated with metabolic or neurological factors. It presents therapeutic possibilities free from complications, including anti-diabetic, anti-obesity, anti-cancer, anti-inflammatory, and anti-depressant effects. The complex interplay between diseases and the immune system underscores the potential of mangosteen as a therapeutic agent. Its intrinsic properties and link to immune-related disorders make it a promising candidate for the development of new treatments.

**Table 2.** Article selection results: utilization of mangosteen peel in various products

Plant Parts	Utilization	Reference
Mangosteen peel	Ice cream	Yani et al., 2021 <sup>34</sup>



Plant Parts	Utilization	Reference
Mangosteen peel - Xanthone	Antiseptic, yoghurt, <i>pempek</i> (savory Indonesian fishcake delicacy), <i>wedang</i>	Wathoni et al., 2021 <sup>36</sup>
Mangosteen peel - Antioxidant	Tea, bread, and cake	Rahmawati et al., 2022 <sup>37</sup>
Mangosteen peel - Antioxidant, $\alpha$ -mangosteen, and xanthone	Tablet for cancer treatment	Banjarnahor, 2023 <sup>32</sup>

*Wedang*: Indonesia's signature spice drink

The diverse applications of the mangosteen plant, including in anti-cancer tablets, herbal teas, crystal sugar powder, antiseptic products, soap, natural food colorants, and as a composite ingredient in processed foods such as cakes, ice cream, bread, and yogurt, highlight its versatility in both topical and oral forms, as shown in Table 2. A previous study focusing on organoleptic assessments found that ice cream containing mangosteen peel exhibited a neutral to slightly favorable taste, color, aroma, texture, and aftertaste<sup>38</sup>. These results suggest that incorporating mangosteen peel does not produce an acrid or unpleasant taste, making it widely acceptable across various communities.

The increasing public interest in and utilization of mangosteen validate its multifunctionality, demonstrating that every part of the fruit has value beyond being discarded as waste. Another study emphasized the potential of mangosteen peel as a functional food ingredient, particularly in processed *pempek*, due to its antioxidant content, which supports immune cell optimization and enhances immune system performance<sup>18,36</sup>. This further demonstrates the mangosteen fruit's wide-ranging applications in the food industry, contributing to waste reduction and diversified usage.

In addition, a separate study noted the effectiveness of mangosteen peel in tablet form for consistent cancer treatment, citing its cost-efficiency and high community acceptance<sup>32</sup>. The use of mangosteen peel in herbal medicine is well-established and supported by numerous previous studies, with no reported adverse effects, making it a long-standing alternative therapy.

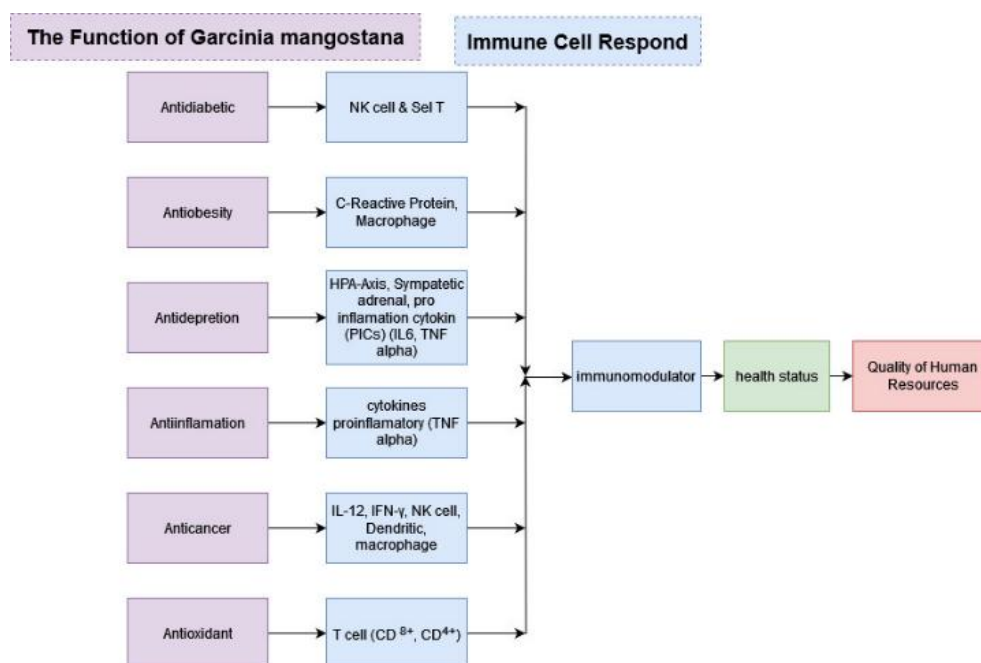
Earlier research has shown that mangosteen peel is a rich source of antioxidants, suitable for developing food and health-related products such as teas, instant powders, tablets/capsules, and various food formulations. Its secondary metabolites, such as xanthenes, mangostin, garcinones, tannins, and saponins, serve as antioxidants that help neutralize free radicals, thereby reducing health risks. However, further studies are necessary to establish safe dosage guidelines for vulnerable groups, including the elderly, pregnant individuals, and those with compromised immune systems.

According to the World Health Organization (WHO), the increasing prevalence of metabolic disorders and infectious diseases threatens to reduce the quality of human capital. Multiple studies have reported, for instance, that diabetes mellitus is associated with a reduced quality of life, often linked to unhealthy lifestyle choices<sup>39</sup>. Individuals with impaired immune systems and deficient in antioxidants are more susceptible to illness and health complications, which significantly disrupt their daily routines, work productivity, and interpersonal interactions.

Over recent decades, poor nutritional awareness and dietary habits, particularly in Western societies, have contributed to rising rates of obesity and chronic diseases such as cardiovascular conditions, diabetes, and cancer<sup>40</sup>. Maintaining quality of life requires both physical and psychological well-being, essential for performing daily activities. A healthy lifestyle, including a balanced diet and good habits, is crucial for minimizing organ damage and delaying the onset of systemic diseases<sup>41</sup>.

Figure 7 illustrates the potential effects of mangosteen peel on immune cells. Mangosteen peel exhibits a variety of biological activities that modulate immune cell function. These include antidiabetic properties that reduce the activity of NK cells and T cells, anti-obesity effects that lower C-reactive protein levels and macrophage activity, and antidepressant effects that suppress the hypothalamic-pituitary-adrenal (HPA) axis, sympathetic adrenal activity, and proinflammatory cytokines (e.g., IL-6, TNF- $\alpha$ ). Specifically, it demonstrates anti-inflammatory effects, notably through the reduction of proinflammatory cytokines such as TNF- $\alpha$ .

Furthermore, mangosteen peel displays anticancer properties, as evidenced by the downregulation of IL-12, IFN- $\gamma$ , NK cells, dendritic cells, and macrophages. The antioxidant compounds found in mangosteen peel have also been shown to contribute to the decline of T cell populations (CD8+, CD4+). These immunomodulatory effects of mangosteen peel suggest its potential role in promoting better health and reducing the risk of illness by regulating immune responses. Consequently, regular consumption of mangosteen peel may lead to improved individual health outcomes and contribute to the overall quality of human resources.



**Figure 5.** The potential effect of mangosteen peel function on immune cells

While most studies attribute these effects to the xanthone content of mangosteen peel, comprehensive research is necessary to isolate and identify the specific bioactive compounds responsible for its therapeutic potential and to elucidate the underlying mechanisms. One limitation of this study is the selection of references, which were constrained by the availability of sources and the publication years matching the keywords used in this research.

## CONCLUSIONS

The research demonstrates the effectiveness of mangosteen peel in managing diabetes by lowering blood glucose levels and mitigating inflammation associated with obesity. Its neuroprotective properties help reduce depressive symptoms by decreasing oxidative stress and neuronal apoptosis, thereby enhancing brain health. Additionally, mangosteen peel exhibits anti-inflammatory effects through inhibition of cyclooxygenase (COX) enzymes and shows anticancer potential by inducing apoptosis in cancer cells. Although many effects are attributed to xanthones, further comprehensive research is warranted to identify the specific bioactive constituents responsible for these diverse therapeutic actions and to clarify the underlying mechanisms involved.

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## CONFLICT OF INTEREST AND FUNDING DISCLOSURE

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## AUTHOR CONTRIBUTIONS

YSP: Conceived and designed the experiments; analyzed the data; contributed reagents/materials/analysis tools; wrote and revised the manuscript. TQ: Conceived and designed the experiments; analyzed the data; contributed reagents/materials/analysis tools. DMR: Performed the experiments; analyzed the data; wrote and revised the manuscript. ID: Performed the experiments; analyzed the data; wrote and revised the manuscript. NMIM: Analyzed the data; wrote and revised the manuscript.

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