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Review Article

IMMUNOMODULATOR ACTIVITY OF MANGIFERIN FROM MANGO (*MANGIFERA INDICA* L.) IN CANCER: A SYSTEMATIC REVIEW

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ABSTRACT

Cancer is a disease that is causing an increase in mortality all over the world. Cancer treatment is expensive and has a variety of side effects. Natural compound treatment is an attempt to reduce the side effects of cancer therapy. Mangiferin is a natural compound with anticancer and immunomodulatory activity. The immunomodulatory activity of mangiferin from mango (*Mangifera indica* L.) in cancer was discussed in this article.

The literature used in this review was obtained from several databases, including the Cochrane Library, Google Scholar, PubMed, ProQuest, ScienceDirect, and the Wiley Online Library, for articles published over the last ten years.

Mangiferin influenced anticancer activity by inhibiting NF-κB, affects the regulation of β-catenin, EMT, MMP2, MMP9, LDH, NO, ROS, and inhibits classical macrophages activation.

Mangiferin has an immunomodulatory effect that can be developed as a candidate drug for anticancer therapy.

Keywords: Cancer, Immune, Mangiferin, *Mango*

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INTRODUCTION

Cancer is a disease that has a high prevalence worldwide. Cancer treatment requires high costs and various side effects that can affect the quality of life [1, 2]. Cancer ranks first cause of death in every country. In 2019, cancer was the leading cause of death under the age of 70. Based on the WHO report, in 2020, there be 19.3 million cancer cases and almost 10 million cancer deaths [3].

Currently, cancer treatment is experiencing rapid development with the hope of decreasing cancer mortality. One of the cancer treatments is immunotherapy [4]. Food and Drug Administration (FDA) approved immunotherapy drugs for cancer, namely vemurafenib, and ipilimumab. Vemurafenib works by inhibiting the b-rapidly accelerated fibrosarcoma (BRAF) protein, and the ipilimumab activates the immune system [5]. Immunomodulators are natural and adaptive compounds that can modulate the immune response. Immunomodulators are classified as adjuvants, suppressants and stimulants [6]. Stimulant-type immunomodulators in cancer restore the damaged immune system by activating the body's defense mechanisms [7].

In cancer, various immune responses are activated to avoid damage to the immune system [8]. Cancer cells will detect immune cells likes T cells and macrophages, resulting in increased levels of proinflammatory cytokines that stimulate NF-κB activation and encourage proliferation and metastasis [9]. T cells play an essential role in immune and antitumor responses, while B cells help in producing antibodies [10]. T cell receptor (TCR) and CD3 gene increase TCR expression leading to faster tumor clearance [11, 12].

Many drugs derived from plants are sensitive and effective against tumor development, prolong patients' survival time, and prevent side effects of chemotherapy [13–15]. One of them is mango (*Mangifera indica* L.) which belongs to the Anacardiaceae family, widely used as food, cosmetics, and medicine (16]. It is found in tropical and subtropical regions and is one of the most popular fruits with low calories and high fiber [17, 18]. Mango contains polyphenol compounds (40-60%), a potentially therapeutic phytochemical compound (19]. Various studies had shown that polyphenols have anti-inflammatory and immunomodulatory [20, 21]. Polyphenol can also protect DNA from gamma-ray damage, which suggests that polyphenols act as radioprotection [22]. In mango, the most well-known compound is mangiferin [23].

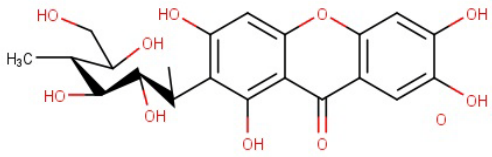

Fig. 1: Chemical structure of mangiferin

Mangiferin compounds (1,3,6,7-tetrahydroxyflavonoid-C2-β-D-glucoside) (fig. 1) are the compounds derived from the leaves and skin of mango [24, 25]. Several studies have shown that the natural compound mangiferin has an anticancer activity where this compound can increase the sensitivity of cancer cells to anticancer drugs [26, 27]. Mangiferin also showed anti-inflammatory, antidiabetic, antioxidants, hypolipidemic, antiviral, immunomodulators, analgesics, and hepatoprotective activity [28-30]. Studies show that mangiferin has an immunomodulatory on T-cells and B-cells [31]. So far, there is no clinical evidence of side effects of mangiferin. This compound could be a candidate in drug development [32]. This article aims to summarize the immunomodulatory activity of mangiferin compounds in cancer.

Method of collecting data

A comprehensive search was carried out by collecting publications from several databases, i.e., Cochrane Library, Google Scholar, PubMed, ProQuest, ScienceDirect, and the Wiley Online Library. The keywords used were "(cancer) AND (mangiferin) AND (immunomodulator)." The literature used is an article published in the last ten years. Fig. 2 showed the flow chart of this systematic review.

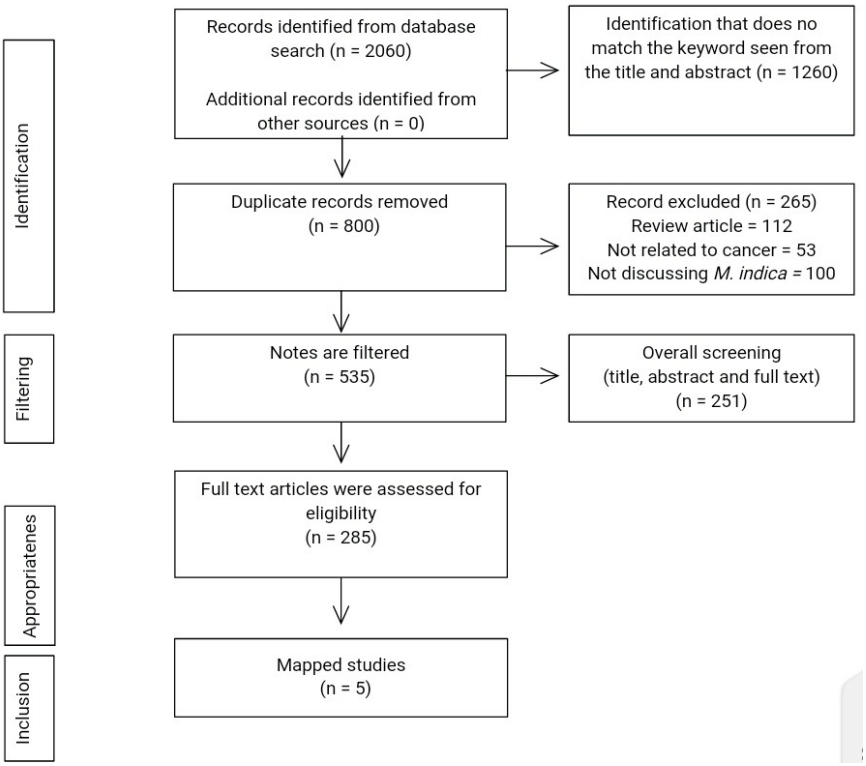

Fig. 2: Flow chart systematic review

Selection of articles

There are 2060 articles obtained from search results using keywords for articles published in the last ten years (0 articles from the Cochrane Library, 1416 articles from Google Scholar, two articles from PubMed, 555 articles from ProQuest, 32 articles from ScienceDirect, and 55 articles from the Wiley Online Library). After screening the title, abstract, and other variables, 285 articles met the inclusion criteria. After screening the full text, six articles meet the requirements, and it used in this review.

Mangiferin as NF-κB inhibitors

Natural compounds exhibit cytotoxic potential against cancer cells by causing apoptosis and suppressing Nuclear factor-kappa B (NF-κB) [33]. NF-κB is a transcription factor in the immune system with an anti-apoptotic effect, which works to increase the resistance of cancer cells [34]. Activation of NF-κB will increase the formation of TNF-α and IL-1β [35]. NF-κB is commonly used to promote tumor formation and regulate angiogenesis [36].

A study by du Plessis-Stoman *et al.* shows mangiferin act as NF-κB inhibitor and cause a reduction in NF-κB activation in cancer cells. Furthermore, the combination of oxaliplatin-mangiferin 10 µg mol/l increases IC_{50} in resistance cancer cells by modulating NF-κB. Mangiferin increased the percentage of dead cells with leakage of the cell membrane, with less necrosis occurred. These results suggest that mangiferin emphasizes cell death by apoptosis rather than necrosis [37,38] with oxaliplatin-mangiferin 10 µg mol/l [38]. Polyphenolic compounds such as mangiferin can affect signaling genes in the NF-κB pathway [39]. It inhibits not only NF-κB signaling but also inhibits phosphorylation of the mitogen-activated protein kinase signaling molecule (MAPK), including extracellular signal-regulated kinase (ERK1/2), jun-n terminal kinase (JNK), and p38 [40].

Mangiferin influences the regulation of β-catenin, EMT, MMP2, and MMP9

Administration of mangiferin 300 µM in ovarian clear cell endocervix (ES-2) produces an anti-MMP effect. It can inhibit the process of invasion, metastasis, angiogenesis in tumor cells. Mangiferin has also inhibited the β-catenin pathway, which plays an important role in anticancer activity [41]. β-catenin is a dual-function protein involved in regulating and coordinating cell adhesion and gene transcription, which plays an important role in the survival and regeneration of cells [42]. β-catenin modulates the proliferation of epithelial-mesenchymal transition cells (EMT) and matrix metalloproteinases (MMP). EMT is a process characterized by loss of adhesion with inhibition of closely related cell β-catenin, thereby leading to metastasis [43]. Meanwhile, MMP has the potential as a therapeutic target for cancer [44]. In the process of metastasis, MMP2 and MMP9 result in extracellular cleavage of matrix proteins in cancer cells by contributing to the epithelial to mesenchymal transition, which is the first step for cancer cells to become abnormal [45].

Mangiferin induces cytotoxicity by regulating LDH, NO, and ROS

The administration of 70 µM mangiferin toxic on rhabdomyosarcoma (RD) cells by using the MTT method. The mangiferin-induced cell death in RD cells is determined by lactate dehydrogenase and nitric oxide, generating reactive oxygen species in mitochondrial membranes [46]. Lactate dehydrogenase (LDH) is an enzyme produced by the cytosol. The increase in this enzyme occurred when the cell membrane was damaged by cytotoxicity. Nitric oxide (NO) plays a role in cellular signaling, and in high concentrations, NO has a cytotoxic effect [47]. NO can regulate many physiological processes that cause damage to DNA, proteins, and lipid molecules, leading to apoptosis [48]. One of the NO targets for maintaining thiol status and modulation of cell proliferation is glutathione (GSH) [49]. Research shows that NO induce GSH to make cells sensitive to cytotoxicity [50]. GSH forms oxidation products due to mangiferin, which leads to reactive oxygen species (ROS) generation. ROS plays a vital role in inducing cancer cell apoptosis [51]. Administration of 0.5 µM mangiferin to Mia-PaCa2 cells showed a significant increase in ROS levels so that it could induce apoptosis in cancer cells [52].

Mangiferin inhibits the activation of classic macrophages

Polarized macrophages release a large number of proinflammatory cytokines, including tumor necrosis factor-alpha (TNF-α),

interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and interleukin-8 (IL-8). Proinflammatory cytokines play an important role in the immune system response. Excessive production of cytokines will cause tissue and cell damage to induce cancer cell death through the proliferation process. Studies show that the levels of TNF-α, IL-1β, IL-6, and IL-8 in THP-1 cells can be reduced by stimulating lipopolysaccharides/interferon-gamma (LPS/IFN-γ) [53]. Administration of mangiferin 100 and 200 µmol/l to human THP-1 cells can significantly increase TNF-α, IL-1β, IL-6, and IL-8 [54]. Mangiferin also plays a role in reducing interferon regulatory factor 5 (IRF5), an important factor in regulating classical macrophage activation [55]. Classical macrophage activation is required for normal protection in the immune response. Thus, mangiferin produces beneficial disease-fighting effects that have potential in cancer therapy [56].

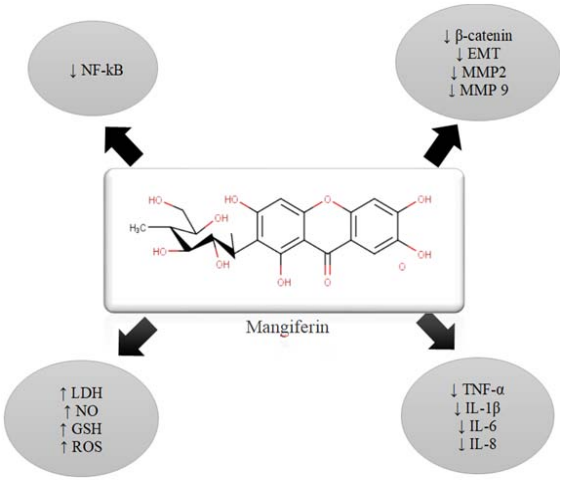

Fig. 3: Mangiferin mechanism to the immune system in cancer

CONCLUSION

Mangiferin in mango (Mangifera indica L.) potential as candidates drug in cancer. The effect of mangiferin on the immune system can treat cancer through various mechanisms. It works to inhibit NF-κB, anti-MMP, cytotoxic induction through LDH, NO, ROS regulation and inhibits the activation of classic macrophages. It can be developed in strategies for cancer therapy that threatens global public health.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally to the literature review, analysis, and interpretation part. The manuscript was written by Ms. Yachi Qurrata Ayuni L, reviewed and edited under the guidance and supervision of Mrs. Fitra Fauziah and Ms. Rezlie Bellatasie. The final version was approved for publication by Mrs. Fitra Fauziah.

CONFLICTS OF INTERESTS

The authors declare no conflicts of interest.

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