Jurnal Farmasi Galenika (*Galenika Journal of Pharmacy*) (e-Journal) 2023; 9 (2): 270 – 283
ISSN: 2442-8744 (electronic); 2442-7284 (printed)
Journal Homepage: https://bestjournal.untad.ac.id/index.php/Galenika
DOI: 10.22487/j24428744.2023.v9.i2.16265

Narrative Review: Potential of Flavonoids from Moringa (*Moringa oleifera* Lamk.) Leaves as Immunomodulators

(*Tinjauan Naratif: Potensi Flavonoid dari Daun Kelor (Moringa oleifera* Lamk.*) sebagai Imunomodulator)*

Jesica Carine Poluan[1*], Muhammad Sulaiman Zubair[2], Arba Pramundita Ramadani[3], Farida Hayati[3]

[1]*Student of Magister of Pharmacy, Department of Pharmacy, Faculty of Mathematics and Natural Sciences, Islamic University of Indonesia, Yogyakarta, Indonesia.*
[2]*Department of Pharmacy, Faculty of Mathematics and Natural Sciences, Tadulako University, Palu, Indonesia.*
[3]*Department of Pharmacy, Faculty of Mathematics and Natural Sciences, Islamic University of Indonesia, Yogyakarta, Indonesia*

Article Info:
Received: 15 January 2023
in revised form: 06 August 2023
Accepted: 02 October 2023
Available Online: 03 October 2023

Keywords:
Immunomodulator
Immunostimulant
Immunosuppressant
Flavonoids
Moringa oleifera

Corresponding Author:
Jesica Carine Poluan
Student of Magister of Pharmacy
Faculty of Mathematics and Natural Sciences
Islamic University of Indonesia
Yogyakarta
55584
Indonesia
email: carinepoluan5@gmail.com

ABSTRACT

Background: Moringa leaves (*Moringa oleifera* Lamk.) are plants from the *Moringaceae* family that have many properties and are often used empirically as traditional medicine. One of the benefits of *M. oleifera* leaves is immunomodulator, which functions to modulate the human immune system in both immunostimulants and immunosuppressants. **Objectives:** To provide information on the potential of flavonoids in *M. oleifera* leaves as immunomudulators developed as alternative therapies. **Methods:** Review of articles using original articles from national and international journals with the keywords "immunomodulator," "immunostimulant," "immunosuppressant," "Flavonoids," and "*Moringa oleifera* leaf or leaves". **Results:** Based on a search of various literature studies, *M. oleifera* leaf extract is proven as an immunomodulator with the most compounds found, namely flavonoids such as quercetin and kaempferol. This content can affect the immune response to trigger or inhibit the proliferation and activation of immune cells in the process of increasing or decreasing the immune system in the body. **Conclusions:** Moringa leaves have activity as immunomodulators that can help maintain the immune system in the body.

How to cite (APA 6th Style):
Poluan, J. C., Zubair, M. S., Ramadani, A. P., Hayati, F. (2023). *Narrative Review: Potential of Flavonoids from Moringa (Moringa oleifera* Lamk.*) Leaves as Immunomodulators*. *Jurnal Farmasi Galenika: Galenika Journal of Pharmacy (e-Journal)*, 9(2), 270-283. doi:10.22487/j24428744.2023.v9.i2.16265

INTRODUCTION

The immune system is an immunological response that can defend the body against pathogens, including bacteria, viruses, and fungi that can disturb the immune system and cause disease (Rachmawati & Rifa'i, 2014). The immune system is divided into two parts: the adaptive (specific) immune system and the innate (nonspecific) immune system. While the adaptive immune system, which develops after exposure to an antigen and is specific and includes memory cells, works by providing first-line defense and its immune system activity happens faster than the innate immune system, first-line defense is how the innate immune system works (Marshall et al., 2018).

A substance that can assist in protecting against pathogens, such as immunomodulators, is required in an effort to strengthen the body's defense mechanism. An immunomodulator is a drug or molecule that corrects the immune system's imbalance. Immune system upkeep is possible by using immunomodulators to stimulate (immunostimulants) or depress (immunosuppressants) (Nfambi et al., 2015). Immunomodulators stimulate the body, which then restores or corrects immune system abnormalities. Immunomodulators can boost the immune system's defenses, whether they are innate or adaptive (Wahyuni et al., 2019). The innate immune system is made up of a variety of cells, whereas the adaptive immune system is made up of T cells and B cells. These cells include macrophages, mast cells, dendritic cells, neutrophils, eosinophils, basophils, and Natural Killer (NK) cells. Antigen-Presenting Cells (APC) induce T cells to proliferate in order to create various types of lymphokines and activate macrophages as effectors, which in turn stimulates higher cytokine production from B cells or plasma cells. The body's innate and adaptive immune systems will work together to maintain homeostasis (Marshall et al., 2018).

The majority of immunostimulants and immunosuppressants are cytotoxic when used in clinical settings, thus people typically prefer to employ medicinal plants, which are thought to be safer because the side effects are minimal, available, and simply applied (Lotter et al., 2012). The immune system of the body has traditionally been strengthened by medicinal plants. In compounds with immunomodulatory action, flavonoids, saponins, glycosides, and alkaloids are typically present (Anywar et al., 2020; Jantan et al., 2015). Moringa leaves are one of the medicinal plants that may act as an immunomodulator (*Moringa oleifera* Lamk). Due to its ability to grow and develop in tropical climates, moringa is a plant that is empirically frequently utilized by most people. Flavonoids, tannins, saponins, alkaloids, glycosides, steroids, triterpenoids, and phenolic chemicals are said to be present in *M. oleifera* leaf extracts (Fathir et al., 2014; Sulastri et al., 2018).

It has been demonstrated that the flavonoid chemicals found in *M. oleifera* leaves function as immunostimulants by promoting the growth of lymphocyte cells made by T cells, which then stimulate phagocytic cells to launch phagocytic responses. In the meanwhile, using *M. oleifera* leaves in large doses can have immunosuppressive effects. This is believed to be caused by the substantial amount of chemicals found in *M. oleifera* leaves, which have been shown to inhibit the immune system in humans (Fathir et al., 2014; Wahyuni et al., 2019). The glycosylated flavonoids isoquercetin-3-O-glucoside (isoquercetin), quercetin-3-O-rutinoside (rutin), and kaempferol-3-O-glucoside (astragalin) are among the chemicals found mainly in *M. oleifera* leaves. These substances can quickly transform into aglycone substances like quercetin and kaempferol (Marrufo et al., 2013).

The bioactive elements in this plant are recognized to support the maintenance of the immune system in humans. Therefore, the aim of this review paper is to present information about the potential of flavonoid chemicals in *M. oleifera* leaves as immunomodulators so that they can be used as substitute medications for immune system maintenance.

MATERIAL AND METHODS

Please The process of preparing this article involved searching for relevant material using the terms "immunomodulator," "immunostimulant," "immunosuppressant," "flavonoids," and "*Moringa oleifera* leaf or leaves" on Google Scholar, PubMed, ScienceDirect, Research Gate, MDPI, and NCBI. The exclusion criteria are review publications, whereas the inclusion criteria are original articles that describe the immunomodulatory activity of *M. oleifera*, from compound identification to in vivo and in vitro testing, through national and international journals with publication years from 2012–2022.

RESULTS AND DISCUSSION

The following data was collected based on the appropriate literature study of the phytochemical screening and activity immunomodulatory of moringa leaves.

Table 1. Bioactive Compounds of *M. oleifera* Leaves

No	Solvents of Extraction	Analytical Method	Bioactive Compound	Reference
1	Aqueous extract	High performance liquid chromatography (HPLC) and mass spectrometry (MS/MS)	Flavonoids, isorhamnetin, myricetin, kaempferol, chlorogenic acid, gallic acid, ellagic acid, and ferulic acid.	(Singh et al., 2009)
2	Ethanol extract	Thin layer chromatography (TLC)	Flavonoids, steroids, triterpenoids, tannins, saponins, and phenolics	(Sulastri et al., 2018)
3	Ethanol extract	Liquid Chromatography with tandem mass spectrometry (LC-MS/MS)	Flavonoids, rutin, quercetin, and kaempferol	(Devaraj et al., 2011)
4	Ethanol extract	Colorimetric method	Polyphenol and flavonoids.	(Vongsak, Sithisarn, et al., 2013)
5	Ethanol extract	Spectrophotometer UV/Vis	Rutin and nicotiflorin (Kaempferol-3-O-rutinoside),	(Chigurupati et al., 2022)

			isoquercetin and astragalin, quercetin acetyl-glucoside, quercetin malonyl-glucoside, kaempferol acetyl-glycoside, coumaroylquinic acid and chlorogenic acid	
6	Methanol extract	HPLC-diode array detection (DAD)- electrospray ionization (ESI)-MS/MS	Isorhamnetin, kaempferol, quercetin, glucosinolate, isothiosianate, benzyl, 4-hydroxybenzyl (sinalbin), 4-(α-L-rhamnopyranosyloxy)-benzyl, then 4-O-(α-Lacetylrhamnopyranosyloxy)-benzyl	(Amaglo et al., 2010)
7	Methanol extract	LC-MS/MS	Flavonoid, isorhamnetin, and myricetin	(Coppin et al., 2013)
8	Ethanol, N-hexane, ethyl acetate extract	Chromatographic analysis	Flavonoid, alkaloid, phenol, tannin, saponin	(Ojiako, 2014)
9	Aquaeous, ethanol, and acetone extract	LC-MS/MS	Chlorogenic acid (3-caffeoylquinic acid and 4-caffeoylquinic acid) and quercetin glycosides (quercetin-3-O-glucoside, quercetin-3-O-galactoside and quercetin 3-O-(6-malonyl) glucoside)	(Braham et al., 2020)
10	N-hexane, diethyl ether and ethyl acetate fractions	TLC	Chlorogenic acid, ferulic acid, gallic acid, ellagic acid, β-sitosterol, hyperoside, oleanolic acid, rutoside, and terpenoids	(Marrufo et al., 2013)

Table 2. Immunomodulatory Effects of *M. oleifera* Leaves

No	Solvents of Extraction	Immunomodulator Method	Activity	Reference
1	Aqueous extract	In vitro, lymphocyte cell culture of male Babl/C strain mice	Increases lymphocyte proliferation	(Rachmawati & Rifa'i, 2014)
2	Aqueous extract	In vivo, blood of mice induced by *Chinese carbon ink* suspension	Increases the number of leukocytes	(Dillasamola et al., 2018)

3	Aqueous extract	In vitro, lymphocyte cell culture of female DDY strain mice induced with *Salmonella typhi*	Increase the number of CD4+, CD8+, B220, and nave T cells	(Fathir et al., 2014; Hefni et al., 2013)
4	Aqueous extract	In vitro, RAW 264.7 cell culture stimulated by *lipopolysaccharide* (LPS)	Inhibits IL-1 and IL-6 cytokine production	(Waterman et al., 2014)
5	Aqueous extract	In vitro, HSV-1 strain 7401H-induced vero cell and mouse organ cultures	Increases IFN-γ cytokine production	(Kurokawa et al., 2016)
6	Ethanol extract	In vivo, male rat blood induced with *Staphylococcus aureus* bacteria	It increases macrophage activity and capacity as well as the percentage number of neutrophils, eosinophils, and leukocytes.	(Husni et al., 2021)
7	Ethanol extract	In vivo, blood of melamine-induced rats	boosts the production of white blood cells (WBC).	(Abd-Elhakim et al., 2018)
8	Methanol extract	In vivo, blood of sheep red blood cells (SRBC)-induced rats	Increases the number of leukocytes, neutrophils, and lymphocytes	(Nfambi et al., 2015)
9	Polysaccharide extract	In vitro, RAW 264.7 cell culture	Increases macrophage activity and the production of cytokines	(Dong et al., 2018; Li et al., 2020)
10	Ethyl acetate extract	In vitro, LPS- and cigarette smoke-induced human monocyte-derived macrophages in cell culture (MDM)	Inhibits macrophage activation	(Kooltheat et al., 2014)
11	Ethyl acetate extract	In vitro, LPS-induced MDM cell culture	All IL-6, TNF-, and COX-2 synthesis is inhibited, as is NF-kB translocation.	(Luetragoon et al., 2020)

Moringa Plant (*Moringa oleifera* Lamk.)

Figure 1. Moringa leaves (*M. oleifera* Lamk.)

Plants in the *Moringaceae* family, which also includes species from India, Africa, Southeast Asia, Arabia, and South America, can grow and thrive in tropical and subtropical climates (Shah et al., 2015). This plant, which grows as tall as 12 meters, is called "Kelor" in Indonesia. The *M. oleifera* leaves in figure 1. are in compound form and are both light and dark green. Flat and pinnate leaf margins are grouped in small, ovoid leaves on *M. oleifera* leaves (Rianto et al., 2020).

Moringa, often known as the "drumstick tree" or "miracle tree," is a plant that was first discovered in the northwest Indian Himalayan foothills. Almost all parts of the plant have medicinal properties. One element of *M. oleifera* that offers a number of advantages is its leaves, which are nutrient-rich and include considerable amounts of calcium (Ca), iron (Fe), protein, and vitamins (Aslam et al., 2005; Misra & Misra, 2014; Oluduro, 2012). Figure 2 illustrates the abundance of flavonoid components in *M. oleifera* leaves. Quercetin, kaempferol, rutin, myricetin, and isoharmnetin are a few of them (Chigurupati et al., 2022; Devaraj et al., 2011). Furthermore, *M. oleifera* leaves are frequently used indiscriminately by the community as herbal medicine because this plant has demonstrated properties as an antimicrobial, anticancer, antihypertensive, antihyperlipidemia, antidiabetic, antidiarrheal, antioxidant, anti-inflammatory, analgesic, and immunomodulator (González et al., 2017; Husni et al., 2021; Ojiako, 2014; Vongsak, Gritsanapan, et al., 2013).

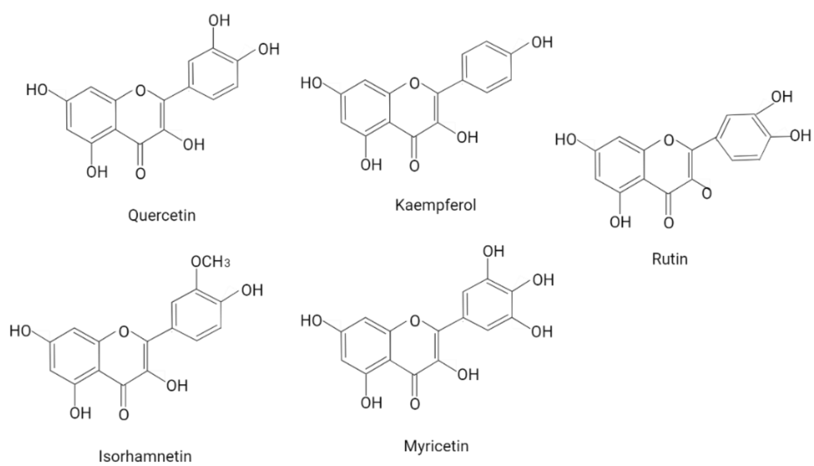

Figure 2. Chemical structure of flavonoids in *M. oleifera*

Phytochemicals as Immunomodulatory Agents

According to table 1. Alkaloids, saponins, tannins, terpenoids, glycosides, polyphenols, flavonoids, and phenolic acids are just a few of the bioactive substances found in *M. oleifera* leaves that can aid the immune system's functioning. By reducing the transcription of genes like Nuclear Factor Kappa β (NF-kβ) and the activity of T helper-2 (Th2) cells, alkaloids like piperine and papaverine can enhance T helper-1 (Th1) cells and cytokine production (Guan et al., 2020; Santos et al., 2018). Saponins have the ability to prevent the creation of nitric oxide (NO) and IL-1 (Zhou et al., 2017). Tannins can boost white blood cell counts while lowering inflammatory protein synthesis, including that of interleukin-2 (IL-2), tumor necrosis factor (TNF-α), and reactive oxygen species (ROS) (Behl et al., 2021). Terpenoids cause endotoxins' NO to be inhibited and IL-2 to be expressed more, which stimulates macrophages (Chahal & Jha, 2020). A cytokine imbalance can be resolved by glycosides. These chemicals have the ability to decrease the expression of Th2 molecules like TNF α -, IL-3, IL-4, and IL-5 while increasing the expression of Th1 molecules like IL-2, IL-10, and IL-12 (Guo et al., 2014). Polyphenols affect the Mitogen-Activated Protein Kinase (MAPK) pathway in addition to inhibiting NF-kB (Yahfoufi et al., 2018).

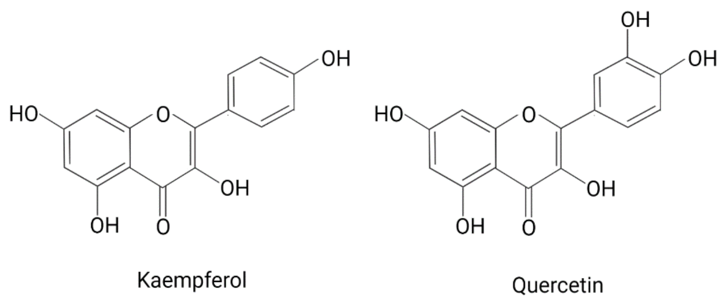

Figure 3**.** Chemical structure of immunomodulatory flavonoids from *M. oleifera*

According to the article in table 1. *M. oleifera* leaves contain chemicals from the flavonoid category most frequently. It is believed that this substance affects the immune system. Figure 3 illustrates how flavonoid substances, such as quercetin and kaempferol, influence neutrophils' ability to mount an immune response (Rabinovich & Croci, 2012). The proliferation of B220^{+} cells and lymphocytes can also be boosted by these flavonoids (Khumaidi et al., 2015; Rachmawati & Rifa'i, 2014).

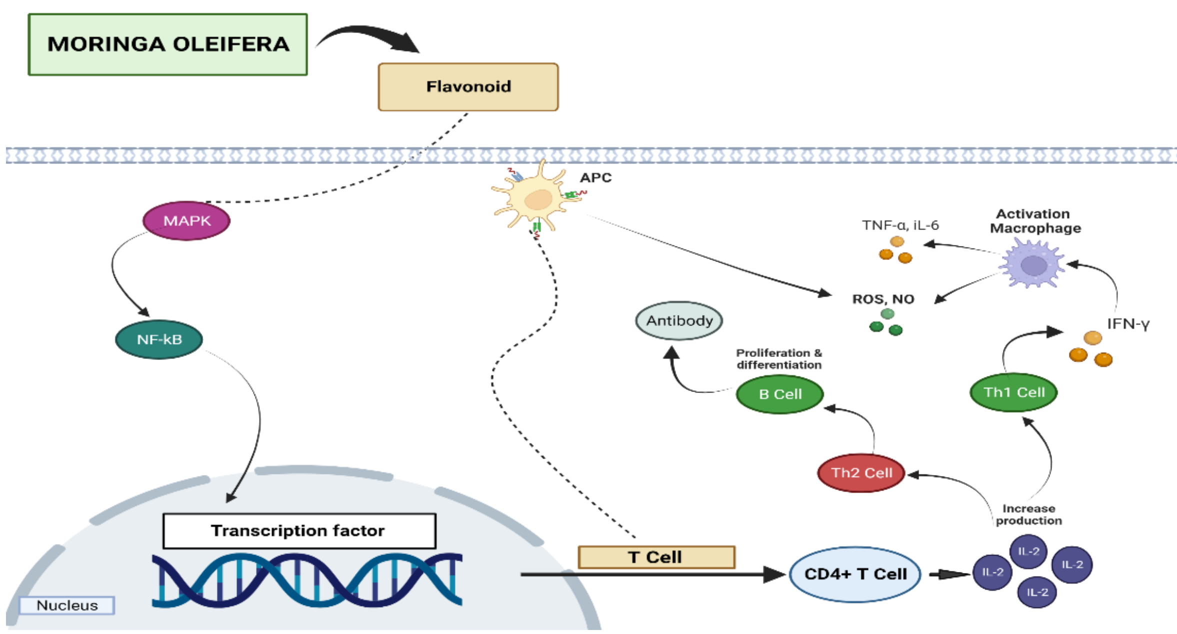

Figure 4. Mechanism of Flavonoids as Immunostimulants

Figure 4 illustrates the relationship between immunostimulants and protein tyrosine kinase activity. Moringa leaf flavonoid chemicals function as MAPK, which catalyzes the phosphorylation response of numerous proteins, including activating transcription factor proteins like NF-kβ, which stimulates T and B cell proliferation and differentiation by upregulating the expression of IL-2 (Hefni et al., 2013). With the use of this substance, $CD4^+$ T cells will be upregulated to differentiate into Th1 cell subsets and Th2 cells, which can boost the production of cytokines in $CD4^+$ T cell activity and cytotoxic T cells ($CD8^+$) (Fathir et al., 2014). The activity of CD4+ can be affected by these flavonoid compounds at high dosages, resulting in decreased NO generation and suppression of lymphocyte cell growth, for example (Gupta & Chaphalkar, 2016). This flavonoid molecule will prevent protein kinase from activating NF-kβ and restrict T and B cell proliferation and differentiation by IL-2 production, which will prevent the stimulation of cytokine secretion (Febryantono et al., 2020; Makiyah & Wardhani, 2017). This is demonstrated in figure 5.

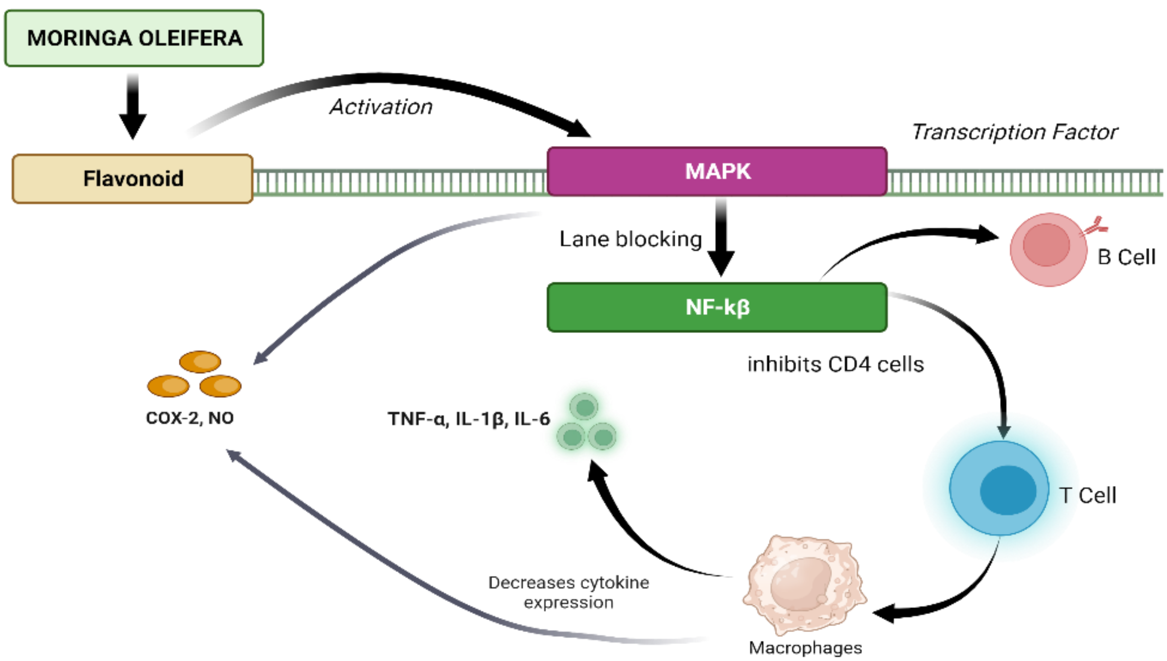

Figure 5. Mechanism of Flavonoids as Immunosuppressant

In Vivo Immunomodulatory Activity of Moringa Leaf

By raising leukocytes in male mice, *M. oleifera* aqueous extract demonstrated immunostimulant efficacy at dosages of 10 mg/kg, 30 mg/kg, and 100 mg/kg. The male mice were given test preparation for six days, and every minute after that, their blood's carbon absorbance decreased, indicating that the blood's carbon concentration was dropping. Male mice's constant value, phagocytosis index, and overall leukocyte count all increased as a result (Dillasamola et al., 2018).

Research by Husni et al (2021), showed that ethanol extract from *M. oleifera* leaves can affect phagocytic activity and macrophage cell capacity by increasing the percentage of leukocytes, neutrophils, and lymphocytes. The lowest to highest doses of 10 mg/kg BW, 30 mg/kg BW, and 100 mg/kg BW have different immunomodulatory activitiesThis shows that dose affects the immunomodulatory effects of *M. oleifera* leaf extract. The most effective dose is 100 mg/kg BW.

Research suggests that *M. oleifera* leaf ethanol extracts can prevent the loss of leukocytes, neutrophils, and lymphocytes (Abd-Elhakim et al., 2018). Nfambi et al (2015), this is corroborated by a study, which discovered that the maximum dose of methanol extract from M. oleifera leaves, 1000 mg/kg BW, significantly increased the number of leukocytes, neutrophils, and lymphocytes. This demonstrates that *M. oleifera* leaf extracts can encourage B cells to produce antibodies to restore weakened immunity.

In Vitro Immunomodulatory Activity of Moringa Leaf

In a study using lymphocyte cells from Balb/C mice, aqueous extracts from *M. oleifera* leaves increased the proportion of $CD4^+$, $CD8^+$, and $B220^+$ cells (Rachmawati & Rifa'i, 2014). Another study discovered that M. oleifera leaf aqueous extract may increase the quantity of CD4+, CD8+, B220+, and naive T cells in the spleen when administered at doses of 14 and 42 mg/kg BW (Fathir et al., 2014; Hefni et al., 2013). Moringa leaf aqueous extract can also increase NK cell-produced IFNγ-production and macrophage phagocytosis (Kurokawa et al., 2016). Polysaccharide extracts from *M. oleifera* leaves can stimulate macrophage pinocystosis and ROS release in RAW 264.7 cells, producing the same effect. Through the production of IL-6, TNF-α and inducible nitric oxide synthase (iNOS), mRNA genes, this extract can enhance the release of TNF-α, IL-6, and NO (Dong et al., 2018; Li et al., 2020).

Cytotoxic T cells and $CD4^+$ to produce antibodies and develop into Th1 and Th2 cells, T cells that have been activated by antigen infection can release a variety of cytokines, including IL-2, IFN, and TNF (Rachmawati & Rifa'i, 2014). When IFN-γ cytokines are released, macrophages may produce the pro-inflammatory cytokines IL-1, IL-6, and TNF-α. Also expelled by macrophages are reactive oxygen intermediates (ROI), reactive nitrogen intermediates (RNI), reactive oxygen species (ROS), and molecules of NO. Through this release, phagocytosis is carried out (Li et al., 2020; Qureshi et al., 2012). According to research, the ethyl acetate fraction of *M. oleifera* leaves reduces gene expression and Rel A (p65) of the NF-kβ activation pathway translocation, which inhibits macrophage activation and the production of IL-6, IL-8, and TNF-α (Kooltheat et al., 2014). The ethyl acetate fraction of *M. oleifera* leaves inhibits the activation of NF-kβ signaling and translocation into the nucleus, which suppresses the synthesis of IL-1, IL-6, TNF-α, iNOS, and cyclooxygenase (COX-2) (Luetragoon et al., 2020). Another investigation found that *M. oleifera* leaf extracts can reduce IL-1 and IL-6 cytokine production and gene expression (Waterman et al., 2014). As shown in table 2. Depending on the solvent and dose used, the cells stimulated or activated, and the body's immunological reaction, *M. oleifera* leaves have the capacity to change immune cells.

CONCLUSION

Moringa leaves have activity as immunomodulators that can affect the immune response. This is proven based on literature studies from previous studies that conducted tests on cell cultures or gave extracts to test animals in vivo and in vitro using various kinds of solvents. The most abundant compounds found in *M. oleifera* leaf extract are flavonoids such as quercetin and kaempferol, which have activity as immunomodulators. These compounds work by influencing the immune response to trigger or inhibit the proliferation and activation of immune cells such as lymphocytes, macrophages, CD4+ cells, and CD8+ cells, which are able to stimulate the release of various cytokines and other molecules involved in the immune process as immunostimulants and immunosuppressants.

ACKNOWLEDGEMENT

The authors acknowledge the Directorate General of Higher Education, Research, and Technology, Republic of Indonesia, for their financial support for this study under grant scheme of Penelitian Kerjasama Dalam Negeri 2023 (contract number: 1462.A/UN28.2/PL/2023).

CONFLICT OF INTEREST

The authors declare no conflict of interest

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