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Immunomodulator Activity of Bitter Melon (*Momordica charantia*) Fruit Extract as an Antimalarial in Patients with Uncomplicated *Plasmodium Falsifarum* Malaria Mediated by Cytokine IFN-γ, in Southwest Sumba Regency : a Case Report

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ABSTRACT: Cytokines are peptides or proteins secreted by body cells as a medium for intercellular communication and function as a body defense due to foreign substances, bacteria, viruses or parasites that enter the body. One of the cytokines that plays an important role in the regulation of Plasmodium falsiparum malaria parasite elimination is IFN-γ cytokine. IFN-γ cytokine is a cytokine that plays a role in the elimination of malaria parasites in patients with uncomplicated malaria. Case report **a** young man aged 18 years, weighing 36 kg, had a fever, a physical examination was carried out, parasitology was diagnosed by the doctor as having uncomplicated Plasmodium falsiparum malaria with an asexual parasite count of 4211/µL. The young man was given bitter melon extract 1x a day for 3 days. IFN-γ cytokine examination was performed on D0 (31.27 pg/mL) and D1 (6.42 pg/mL). Parasite examination in D1 was 826/µL), D2 was 123/µL, and D3, D4, D7, D14, D21, D28 had no asexual parasites and gametocytes. Haematology, clinical chemistry, blood fat and blood glucose examinations were carried out on D0, D14 and D28 with results still within normal limits. Clinical symptoms reported were weakness, headache, dizziness, chills, nausea, abdominal pain, muscle pain and fever and these clinical symptoms had disappeared by D4**.** Conclusion bitter melon extract has antimalarial activity through the mechanism of reducing IFN-γ cytokine which is one of the immunomodulatory markers.

KEYWORDS: Clinical symptoms reduction; IFN-γ reduction; *Momordica charantia*; Parasite reduction.

1. INTRODUCTION

Cure in patients infected with malaria occurs if the parasite can be eliminated without causing significant pathological conditions. The current situation of research in Africa reveals that malaria treatments such as kinins, chloroquine, amodiaquine, artesunate, artemisinin, mefloquine, halofantrine, lumefantrine, pyrimethamine, cycloguanil, chlorsicloguanil, atovaquone, sulphonamide and sulfone combinations, artemisinin and its derivatives have developed resistance to P. falciparum. Pyrimethamine and chloroquine are reported to be resistant to P. vivax. Currently, malaria treatment in Indonesia uses combination therapy, namely the combination of dihydroartemisinic piperaquine-primaquine [1,2,3]. One of the antimalarial developments from natural materials is the use of Momordica charantia extract plants. Momordica charantia extract plants have been widely used by developing countries such as Brazil, Columbia, China, Cuba, Mexico, Panama, Peru which are used as antidiabetic, antiviral, antitumor, antibacterial, antioxidant, anti-inflammatory, anticancer, anthelmintic, immunomodulatory and antimalarial treatments[4]. Previous research conducted by Syamsudin et al proved that bitter melon fruit extract has antimalarial activity in

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reducing asexual parasites and gametocytes against P. Falciparum parasites [5,6,7,8,9]. Almost all malaria treatment with pathological conditions occurs through immunological mechanisms and parasite elimination mechanisms that can be mediated by the body's immunity so that the immune response must be well regulated. The immune response to malaria begins with a natural immune response which is then followed by an adaptive immune response that plays a protective role. Regulation of the body's immune response involves effector molecular components (monocytes, macrophages, neutrophils, NK cells, T lymphocytes, T cells), antibodies and various cytokines, both pro-inflammatory cytokines and anti-inflammatory cytokines. The body's immune response at the cellular level, responds against the parasite through the activity of T lymphocyte cells. Elimination of parasites by immune cells occurs through phagocytosis, pinocytosis and lysis of infected red blood cells, production of small molecules such as nitric oxide, formation of free radicals in infected cells, production of cytokines, antibodies that are toxic to the body [10,11]. Cytokines are peptides or proteins secreted by body cells as a medium for intercellular communication and function as a body defense due to foreign substances, bacteria, viruses or parasites that enter the body [12]. One of the cytokines that plays an important role in the regulation of Plasmodium falsiparum malaria parasite elimination is IFN-γ cytokine. IFN-γ cytokine is a cytokine that plays a role in the elimination of malaria parasites in patients with uncomplicated malaria [12,13]. In patients with uncomplicated Plasmodium falsiparum malaria, IFN-γ is produced by T lymphocytes that play a role in stimulating macrophages and neutrophils that have phagocytosis and pinocytosis activities on parasites [14]. One of the plants that has antimalarial activity is bitter melon (Momordica charantia) [5]. Bitter melon extract contains alkaloids, flavonoids, saponins, tannins, quinone, steroids, triterpenoids, cumarine which plays a role in reducing Plasmodium falsiparum parasites through increased macrophage activity [6,15].

2. Case Report

A young man aged 18 years, weighing 36 kg, had a fever, conducted a physical examination, parasitologically diagnosed by the doctor as having uncomplicated Plasmodium falsiparum malaria with an asexual parasite count of 4211/µL. The young man was given bitter melon (Momordica charantia) fruit extract capsules containing 325 mg in 500 mg capsules for 3 days. The young man had not taken other antimalarials in the last 2 weeks. The patient was followed up for 28 days and parasite examination was carried out on D1 (826/µL), D2 (123/µL), and D3, D4, D7, D14, D21, D28 no asexual parasites and gametocytes were found. IFN-γ cytokine examination was performed on D0 (31.27 pg/mL) and D1 (6.42 pg/mL). Hematologic examination, liver function test examination, kidney function test examination, blood fat and blood glucose were performed on D0, D14 and D28 with results within normal limits. Clinical symptoms reported were weakness, headache, dizziness, chills, nausea, abdominal pain, muscle pain and fever and these clinical symptoms had disappeared by D4.

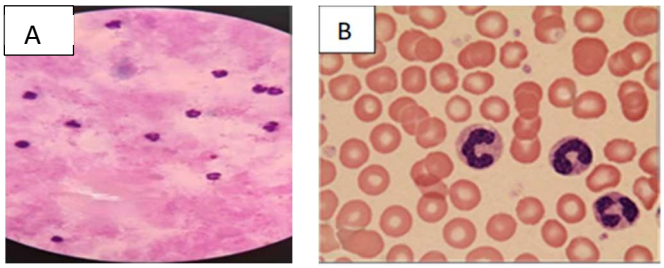

Figure 1 Observation of red blood cells with *Plasmodium falsiparum* parasites on thick blood smear under microscope at D0 (A), observation of red blood cells on thick blood smear at D3 without *Plasmodium falsiparum* parasites (B).

Table 1. Examination Value IFN γ

Descriptive	D0	D1
Value IFNγ Pg/mL	31,27	6,42

Table 2. Examination Value Parasites

Descriptive	D0	D1	D2	D3	D4	D7	D14	D21	D28
Value parasites/µL	4211	826	123	0	0	0	0	0	0

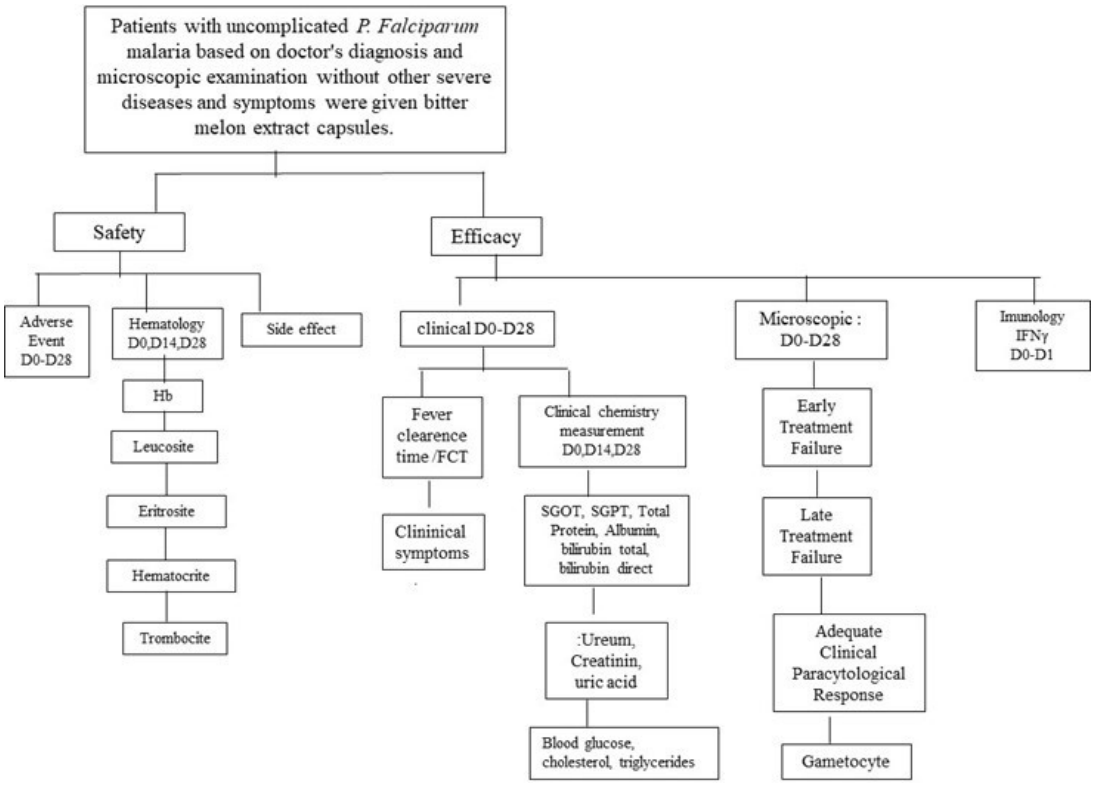

Figure 2. Flowchart of Treatment and Examination of Malaria Patients *P. Falciparum* without Complications

Table 3. Examination Value Haematology, Clinical Chemical, Blood Lipids and Blood Sugar

Descriptive	D0	D14	D28
value Haemoglobin g/dl	13.2	13.8	14.5
value Erythrocytes 10^6/mm^3	5.63x10^6	5.10x10^6	5.21x10^6
value Haematocrits %	40,6	41,5	45,1
value Thrombocytes 10^3/mm^3	112 x 10^3	299 x 10^3	245 x 10^3
value Leucocytes /µL	3.63x10^3	11.89x10^3	5.94x10^3
value Albumin mg%	4.7	4.7	5.1
value AST/SGOT µ/mL	27	16	28
value ALT/SGPT µ/mL	18	11	18
value total bilirubin mg %	0.6	0.5	0.5
value Direct bilirubin mg %	0.3	0.2	0.2
value Total protein mg %	6.9	6.9	7.5
value Creatinine mg %	1.1	0.9	1.2
value Urea mg %	58.9	13.6	30
value uric acid mg %	3.6	4.2	5
value Total Cholesterol mg/dL	156	150	145
value Triglycerides mg/dL	83	124	99
value Glucose mg/dl	85	112	132

Table 4. Clinical Symptoms Reported during Follow-up D0 until D28

No	Symptoms	H0	H1	H2	H3	H4	H7	H14	H21	H28	Total
1	Weak	1	1	1	0	0	0	0	0	0	3
2	Headache	1	1	1	1	0	0	0	0	0	4
3	dizzy	1	1	1	0	0	0	0	0	0	3
4	sleep disorder	0	0	0	0	0	0	0	0	0	0
5	chills	1	0	0	0	0	0	0	0	0	1
6	sweating	0	0	0	0	0	0	0	0	0	0
7	cough	0	0	0	0	0	0	0	0	0	0
8	no appetite	0	0	0	0	0	0	0	0	0	0
9	pounding	0	0	0	0	0	0	0	0	0	0
10	nausea	1	0	0	0	0	0	0	0	0	1
11	vomit	0	0	0	0	0	0	0	0	0	0
12	stomach ache	1	0	0	0	0	0	0	0	0	1
13	diarrhea	0	0	0	0	0	0	0	0	0	0
14	muscle pain	1	1	0	0	0	0	0	0	0	2
15	fever	1	1	0	0	0	0	0	0	0	2
	Total	8	5	3	1	0	0	0	0	0	

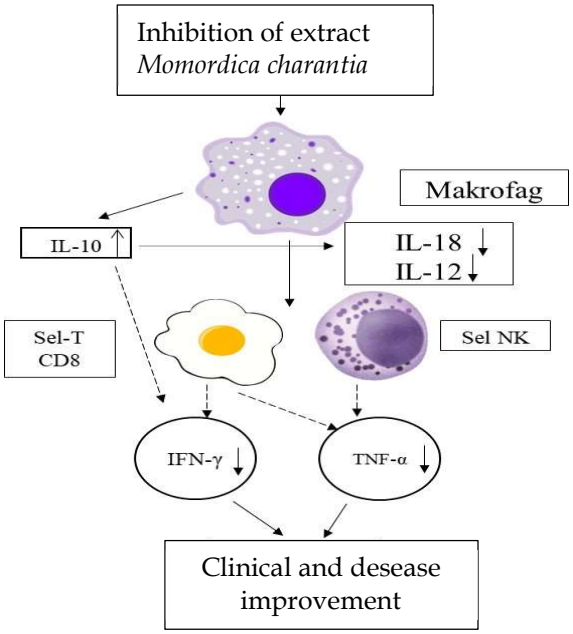

Figure 3. Mechanism of Action of Parasite Elimination from Bitter Melon Extract through Immunological Pathway [16][12][17][18]

Adverse events symptoms felt by patients after taking bitter melon extract capsules are mild, namely nausea and vomiting. During the treatment of extract capsules, there was no early treatment failure where there was no parasitemia in D1, D2, D3. In addition, bitter melon extract treatment did not occur late Treatment failure or no asexual parasites were found again on D7 to D28. In the patient, no gametocytes were found from D0 to D28.

3. DISCUSSION

Cytokines are small peptides or proteins secreted by body cells that play an important role in regulating immunity in the body and are a way for cells to communicate with each other. Cytokines are a cell signaling category of extracellular polypeptides/glycoproteins produced by various immune cells, especially T cells, neutrophils, and macrophages, and are important for the regulation and promotion of immune responses. In addition to acting on major lymphocyte growth and other biological processes, these polypeptides stimulate cells and signaling molecules to head towards wounds, infections and inflammatory areas.[12][19] In malaria, cytokines are critical for controlling disease magnitude, parasite load, and disease symptoms. TNF-α, IFN-γ, interleukin (IL-6), IL-8, IL-18, and MCP-1 are examples of pro-inflammatory cytokines that have been associated with deadly malaria, while regulatory cytokines, namely anti-inflammatory cytokines such as TGF and IL-10, play a role in maintaining balance in the immune system[20][21]. IFN-γ cytokine is one of the cytokines that plays an important role in cellular immune regulation to reduce parasites in patients with uncomplicated malaria [12][17]. Research conducted by Syamsudin et al invitro and invivo bitter melon extract reduces Plasmodium falsiparum and Plasmodium berghei parasites. Bitter melon extract contains alkaloids, flavonoids, saponins, tannins, quinone, steroids, triterpenoids, cumarine which have activity in reducing Plasmodium falsiparum parasites.[6] The alkaloid content in bitter melon extract is effective in reducing Plasmodium falsiparum parasites invitro and invivo.[7] Bitter melon extract works as an immunomodulator through the activation of macrophages and neutrophils in increasing phagocytosis activity. [22] In patients with uncomplicated Plasmodium falciparum malaria parasites, stimulation of macrophage activation increases cytokines IL18 +, IL12, NK cells (producing cytokine IFN-γ, reducing cytokine TNF-α), stimulating CD8 T cells (producing cytokine IFN-γ, reducing cytokine TNF-α) which has an impact on disease resolution. [12] The activity of bitter melon extract eliminates Plasmodium falsiparum malaria parasites through immunological pathways has an impact on improving clinical symptoms that disappear in patients with uncomplicated Plasmodium falsiparum parasites. [23] IFN-γ cytokines play an important role in the regulation of the immune system in the body and are one of the effective treatment strategies. [19] The results of this case report are in line with previous research that in uncomplicated falsiparum malaria the role of IFN-γ is very important in parasite elimination. The presence of one of the proinflammatory cytokines (IFN-γ) needs to be balanced with the formation of anti-inflammatory cytokines (IL-10, TGFβ). Regulation of the presence of anti-inflammatory cytokines to prevent organ damage at the cellular level[12].

Table 2 shows that the hemoglobin value is still within normal values. In line with the research of Syamsudin et al invivo in acute and subchronic toxicity tests there were no changes in the hispatological condition of the liver and kidneys of rats and the value of liver function tests ALT, AST, urem and creatinine in rats given bitter melon extract (Momordica charantia). In the toxicity test with the highest level of bitter melon extract of 5000 mg/kg bw given to rats did not experience death.[9] In the research of Hasan Ali et al that there is a relationship between bilirubin values with increased parasitemia in patients with falsiparum malaria. There is a relationship between bilirubin levels with levels of SGOT, SGPT and alkaline phosphatase. Bitter melon extract may have a hepatoprotector effect that has an impact on preventing jaundice. The mechanism of action as an antioxidant and maintaining the cellular integrity of the liver from pathogenic substances or organisms.[24][25] The involvement of bitter melon extract in stimulating macrophages which has an impact on the regulation of the decrease in IFN-γ cytokines plays a role in inhibiting the progression of uncomplicated malaria to severe malaria.[17].

In Figure 3 Inhibition of MC extract compounds against macrophages will increase the production of anti-inflammatory cytokine IL-10 to reduce pro-inflammatory cytokines IL-18 and IL12. Macrophages through a complex mechanism will stimulate natural cell killer (NK), CD8 T cells to reduce the production of pro-inflammatory cytokines IFN-γ and TNF-α so that it is associated with decreased parasites, improved clinical symptoms and impact on the healing of malaria patients [16][12][17][18]. Immunity to malaria infection involves cellular and humoral immune responses. Cellular immune response mediated by T lymphocytes, especially cytotoxic T cells, plays an important role against intra-cellular sporozoite infection (erythrocytic schizogony). The defense effect of cytotoxic T cells is mediated by direct lysis with IFNγ secretion and activation of macrophages to produce NO or other compounds to kill parasites. Increased activity of cytotoxic T cells is expected to increase the body's defense reaction against malaria, especially against sporozoites in the extra-erythrocytic schizogony phase [26][12].

4. CONCLUSION

Bitter melon (Momordica charantia) extract has antimalarial activity through the mechanism of decreasing IFN-γ cytokine which is one of the immunomodulatory markers that has an impact on the elimination of Plasmodium falciparum malaria parasites and clinical symptoms that disappear on day 4. Unwanted symptoms felt by patients after being treated using bitter melon extract are mild, namely nausea and vomiting.

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REFERENCES

[1] N. J. White, "Review series Antimalarial drug resistance," *J. Clin. Invest.*, vol. 113, no. 8, pp. 1084–1092, 2004 ,

[2] A. Samson, "Resistance to Antimalarial Monotherapy is Cyclic," *J. Clin. Med.*, pp. 1–8, 2022 .

[3] World Health Organization, "WHO Guidelines for malaria - 2021," *World Heal. Organ.*, vol. 1, p. 210, 2021 .

[4] J. K. Grover and S. P. Yadav, "Pharmacological actions and potential uses of Momordica charantia: A review," *J. Ethnopharmacol.*, vol. 93, no. 1, pp. 123–132, 2004 ,

[5] S. Abdillah, R. M. Tambunan, Y. M. Sinaga, and Y. Farida, "Ethno-botanical survey of plants used in the traditional treatment of malaria in Sei Kepayang, Asahan of North Sumatera," *Asian Pac. J. Trop. Med.*, vol. 7, no. S1, pp. S104–S107, 2014 ,

[6] S. Abdillah, R. M. Tambunan, Y. Farida, N. M. D. Sandhiutami, and R. M. Dewi, "Phytochemical screening and antimalarial activity of some plants traditionally used in Indonesia," *Asian Pacific J. Trop. Dis.*, vol. 5, no. 6, pp. 454–457, 2015 ,

[7] S. Abdillah, Y. Farida, N. Made Dwi Sandhiutami, and K. Mohamad, "Antimalarial activity and toxycity evaluation of the alkaloid rich fraction of Momordica charantia fruits," *Int. J. Pharm. Sci. Res.*, vol. 10, no. 5, p. 2516, 2019 ,

[8] mitra wynne Timburas, D. Hasan, and S. Abdillah, "Efikasi dan Keamanan Kombinasi Kapsul Pare-Primakuin sebagai Antimalaria pada Pasien Malaria Falsiparum Tanpa Komplikasi Di RSUD Manokwari Mitra," *J. Sains dan Kesehat.*, 2020 .

[9] S. Abdillah, B. Inayah, A. Balqis Febrianti, and S. Nafisa, "Acute and Subchronic Toxicity of Momordica Charantia L Fruits Ethanolic Extract in Liver and Kidney," *Syst. Rev. Pharm.*, vol. 11, no. 12, pp. 2249–2255, 2020 .

[10] Nugroho Agung ; Gunawan Carta ; Harijanto Paul N, *Malaria Tata Laksana Klinis dan Terapi*, Edisi 3. Jakarta: EGC Penerbit buku kedokteran, 2019.

[11] B. Forte *et al.*, "Prioritization of Molecular Targets for Antimalarial Drug Discovery," *ACS Infect. Dis.*, vol. 7, no. 10, pp. 2764–2776, 2021 ,

[12] C. A. Azike, C. U. Nyenke, N. Agi, C. U. Okoye, and C. Fyneface, "Assessment of Cytokines Levels In Malaria And Their Respective Roles In The Pathological Severity," *J. Appl. Heal. Sci. Med.*, vol. 3, no. 9, pp. 1–11, 2023 .

[13] D. Prakash, C. Fesel, R. Jain, P. A. Cazenave, G. C. Mishra, and S. Pied, "Clusters of cytokines determine malaria severity in Plasmodium falciparum-infected patients from endemic areas of central India," *J. Infect. Dis.*, vol. 194, no. 2, pp. 198–207, 2006 ,

[14] A. Cruz Cubas, M. Gentilini, and L. Monjour, "Cytokines and T-cell response in malaria," *Biomed. Pharmacother.*, 1994 .

[15] Parawansah, T. Nurtamin, S. A. Mulyawati, Nuralifah, and W. O. A. Misnaeni, "Immunomodulatory effect of pare (Momordica charantia L.) fruit ethanol extract on phagocytic activity and capacity of mice peritoneal macrophages," *Indones. Biomed. J.*, vol. 10, no. 2, pp. 144–147, 2018 ,

[16] M. H. Ali, I. Ibrahim, M. Jasamai, N. Embi, and H. Sidek, "Anti-malarial Effect of Momordica charantia Involved Modulation of Cytokine Mediated via GSK3β Inhibition in Plasmodium berghei- Infected Mice," *Jordan J. Biol. Sci.*, vol. 15, no. 3, pp. 523–529, 2022 ,

[17] D. Torre, F. Speranza, M. Giola, A. Matteelli, R. Tambini, and G. Biondi, "Role of Th1 and Th2 cytokines in immune response to uncomplicated Plasmodium falciparum malaria," *Clin. Diagn. Lab. Immunol.*, vol. 9, no. 2, pp. 348–351, 2002 ,

[18] D. Yudianto, S. Abdillah, H. U. Ramadaniaty, E. J. Nelwan, and D. Yudianto, "Effects of Momordica charantia (MC) Extract on Clinical Symptoms, Parasite Account, Thrombocytes, Total Bilirubin and Direct Bilirubin in Patients with Uncomplicated Plasmodium falciparum Malaria: A Case Report," *Arch. Med. Case Reports*, vol. 5, no. 1, pp. 492–496, 2023 .

[19] V. L. Ferreira, H. H.L. Borba, A. de F. Bonetti, L. P. Leonart, and R. Pontarolo, "Cytokines and Interferons: Types and Functions," *Autoantibodies and Cytokines*, 2019 ,

[20] K. E. Lyke *et al.*, "Serum levels of the proinflammatory cytokines interleukin-1 beta (IL-1β), IL-6, IL-8, IL-10, tumor necrosis factor alpha, and IL-12(p70) in Malian children with severe Plasmodium falciparum malaria and matched uncomplicated malaria or healthy controls," *Infect. Immun.*, vol. 72, no. 10, pp. 5630–5637, 2004 ,

[21] L. Farrington *et al.*, "Both inflammatory and regulatory cytokine responses to malaria are blunted with increasing age in highly exposed children," *Malar. J.*, vol. 16, no. 1, pp. 1–11, 2017 ,

[22] O. Mahamat, H. Flora, C. Tume, and A. Kamanyi, "Immunomodulatory Activity of Momordica charantia L. (Cucurbitaceae) Leaf Diethyl Ether and Methanol Extracts on Salmonella typhi -Infected Mice and LPS-Induced Phagocytic Activities of Macrophages and Neutrophils," *Evidence-based Complement. Altern. Med.*, vol. 2020, 2020 ,

[23] M. W. T. D. H. S. A. Tjiokonegoro, "Efikasi dan keamanan kombinasi kapsul pare-primakuin sebagai antimalaria pada pasien malaria malaria falsiparum tanpa komplikasi di rsud manokwari," *Med. Med. Prof.*, vol. 3, no. 3, pp. 256–262, 2019 .

[24] V. Janghel, P. Patel, and S. S. Chandel, "Plants used for the treatment of icterus (jaundice) in Central India: A review," *Ann. Hepatol.*, vol. 18, no. 5, pp. 658–672, 2019 ,

[25] A. J. Thenmozhi and P. Subramanian, "Antioxidant potential of momordica charantia in ammonium chloride-induced hyperammonemic rats," *Evidence-based Complement. Altern. Med.*, vol. 2011, 2011 ,

[26] L. A. Abbas AK, *Cellular and molecular immunology*, 9 th editi. Elseveir Saunders, Philadelphia, 2018.