



Systematic Literature Review: Side Effect of *Moringa oleifera* Lam.

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ABSTRACT

Moringa oleifera Lam. (Drumstick tree) is a herbal plant commonly found in subtropical and tropical areas such as Indonesia. Moringa plants have been widely used because they have many pharmacological effects. In addition, due to the high consumption of Moringa, there still needs to be monitoring regarding the safety of Moringa. This study aimed to Identify and analyze the side effects of using Moringa based on the results of a systematic literature review. A systematic literature review using articles with a case report study design (collected from 2011 to 2021). The search databases used are PubMed, Google Scholar, and Science Direct. Journal quality is assessed by JBI (Joanna Briggs Institute) Critical Appraisal. 10 articles met the criteria and were of good quality. Based on the results, the side effects that occur in the use of Moringa are in the respiratory tract, dermal, and rhabdomyolysis. The incidence of side effects in Moringa is associated with chemical compounds contained in Moringa which can trigger hypersensitivity reactions and structural similarities to other synthetic drug compounds so that they can cause the same side effect reactions. Moringa in both leaves and seeds can cause side effects, the manifestations of which are respiratory, dermal, and rhabdomyolysis disorders.

Keywords: *Moringa oleifera* Lam., side effects, atopic dermatitis, rhabdomyolysis.

1. INTRODUCTION

Adverse drug reactions (ADR) are the body's response to an unwanted drug, usually occurring at doses of common drugs used to prevent, diagnose, or treat disease [1]. Of the cases of ADR that occur in the use of pharmaceutical products, about 7.9% are cases of ADR due to the use of herbs. Side effects are any unintended effect of a pharmaceutical product occurring at doses normally used in humans related to the drug's pharmacological properties. Reactions to side effects of using herbs do not always occur in every individual and are often unpredictable, but the factors that cause these side effects will increase a person's chances of experiencing side effects from using herbs. The main factors that cause side effects in the use of herbs are the use of herbs that are not following the indications, the

dosage of herbs is not right, or the consumption of herbs for a long time [2].

Moringa oleifera Lam. (drumstick tree) is a herbal plant that grows in subtropical and tropical climates such as Indonesia and belongs to the Moringaceae family [3]. Moringa is easy to grow and easy to obtain by the community and its use has long been known in the community. Moringa has many benefits and has been widely used by the community both as an herb and as food because Moringa contains many nutritious compounds as well as complex nutritional values [4][5]. Although Moringa herbs are often considered safer than synthetic drugs, in reality, Moringa herbs can cause side effects, either due to side effects from the use of Moringa itself or the interaction of Moringa with other herbs or other synthetic drugs [6]. Monitoring related to

safety in the use of Moringa herbs then becomes important, in addition to the efficacy of Moringa herbs which has long been known in the community [7].

Monitoring is important not only for therapeutic effects but also for side effects. Indications for the use of Moringa that are not appropriate, the period of consumption of Moringa is too long, and the dose of Moringa that is too much can not provide good efficacy and can even trigger unwanted side effects for the user [7][8]. The side effects of using Moringa in patients can be observed from physical examination and laboratory examinations related to the clinical manifestations of the side effects of Moringa experienced by patients.

This study reviews the literature systematically on the side effects that occur due to the use of *Moringa oleifera* Lam. (Moringa). This systematic literature review contains a description of the theory and findings from reference materials to be used as a basis for research activities on the risk of side effects using Moringa (*Moringa oleifera* Lam.). As previously described, the use of Moringa herbs is considered safe by the public, but it is also possible to cause side effects in its use. This study aimed to identify and analyze the side effects of using Moringa based on the results of a literature review. Research related to the evaluation of the side effects of herbal medicine is one part of the pharmacovigilance system of herbal medicines that the WHO has regulated [8]. The most crucial part is that it is hoped that awareness will arise so that people are more aware of the use of herbs, especially moringa, and can detect if signs of side effects appear after consuming moringa so that they can be prevented from causing more severe problems.

2. METHODS

2.1 Literature Search

The literature search aims to find articles with case report study designs that report cases related to side effects after using Moringa. This literature search used the publication year limitation on the search database with the search limitation for the last 10 years. The case reports collected are case reports of side effects of using Moringa from 2011 to 2021.

The literature search database sources used include PubMed, Google Scholar, and Science Direct. Search the database using the keywords "moringa", "moringa oleifera", "adverse drug reaction", "case report", "asthma", "allergy", and "skin irritation". All searches in the database used Boolean Logic, on PubMed, Google Scholar, and Science Direct were used ((moringa OR "moringa oleifera") AND "adverse drug reaction" OR "case report"); "moringa oleifera" AND "asthma" AND "allergy"; "moringa oleifera" AND "skin irritation" AND "allergy". The article search process was carried out using the PubMed, Google Scholar, and Science Direct search databases.

2.2 Article Selection

The articles selected for review have met the inclusion and exclusion criteria. The inclusion criteria in this study included articles from the last 10 years; article using English or Indonesian; articles in the form of case reports or case study; articles that meet the critical assessment criteria using the JBI Critical Appraisal Tools.

Exclusion criteria include duplication of journals; the article does not match the topic of Moringa oleifera natural side effects.; articles in the form of reviews; the plant presented in the article is not *Moringa oleifera* Lam.; drug interactions cause the incidence of side effects related to the use of Moringa; the identity of the library source is incomplete; there are no full-text articles.

2.3 Article Quality Criteria

In determining the quality criteria of the article, an article review is carried out using critical appraisal tools that follow the article research design. This critical assessment aims to assess the quality, credibility, and clinical practice value of a study and to avoid possible bias in a study design.

The article research design used is a case report, for and the appropriate critical appraisal tools are JBI Critical Appraisal tools. The answers in each of the available question checklists will affect the quality of the article. There are four answer columns related to the questions in the checklist, namely "yes", "no", "unclear", and "not applicable". From the results of critical appraisal using JBI Critical Appraisal Tools, articles are considered to have good quality if the article has a "yes" answer >75% of the total answers to questions on JBI Critical Appraisal Tools.

Articles that have been collected are then reviewed or studied by 3 different reviewers. If there are differences in perception, then they are discussed with 3 other reviewers. The article tracing diagram refers to the PRISMA 2020 flow diagram, which is presented in Figure 1.

2.4 Data Analysis

All selected articles found in the search database using keywords that have been designed and have met the inclusion and exclusion criteria will be further examined using the JBI Critical Appraisal Tools. The subjects in this study were all patients who had experienced adverse reactions while using Moringa. Manifestations of side effects have been assessed by physical examinations and laboratory test results of the patient that are relevant to the clinical. Further data analysis was carried out descriptively.

The side effects on the respiratory tract can be seen from the results of physical examination in the form of symptoms of shortness of breath, tachypnea (rapid breathing frequency), and the patient's blood pressure; as well as the results of laboratory tests, namely the value of the Forced Expiratory Volume in one second / Forced Vital Capacity (FEV1/FVC) as well as the value of the FeNO (Fractional Exhaled Nitric Oxide) test,

serum tryptase level, and skin prick test. The side effects on the dermal side can be seen from the results of physical examination in the form of erythema (redness of the skin), vesicles on skin rashes, and itching. Rhabdomyolysis can be seen from the results of laboratory tests in the form of creatine kinase (CK) levels and the results of physical examinations in the form of pain in certain body parts.

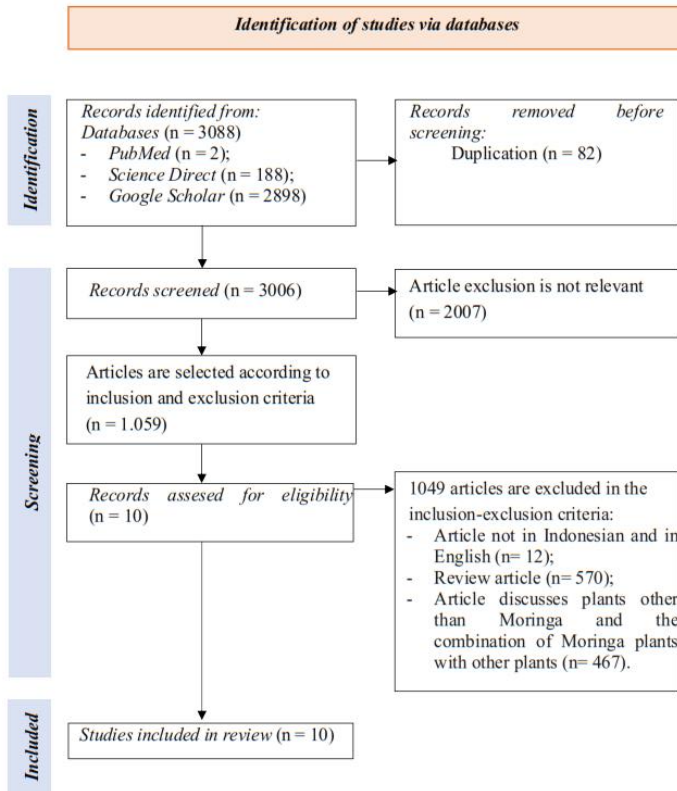


Figure 1. PRISMA 2020 flow diagram search

3. RESULTS AND DISCUSSION

The search in the database was performed using keywords combined with Boolean operators. Search the PubMed, Google Scholar, and Science Direct databases from November 2021, to February 2022, using the keywords ((Moringa OR “moringa oleifera”) AND “adverse drug reaction” OR “case report”); “moringa oleifera” AND “asthma” AND “allergy”; “moringa oleifera” AND “skin irritation” AND “allergy”. Then the articles in the PubMed, Google Scholar, and Science Direct databases were obtained, each with 2 articles; 2,898 articles; and 188 articles. The articles that have

been obtained from the search database are then screened based on their language, title, and abstract. After screening, duplicate articles were eliminated for further analysis. The analysis results based on the inclusion and exclusion criteria obtained 10 articles that are relevant to the topic to be studied and can be used to answer the research topic. Table 1. Shows quality of case report articles with JBI Critical Appraisal Tools.

The ten relevant articles were then checked for quality using the JBI Critical Appraisal Tools as shown

in Table 2. All articles with good quality in the JBI Critical Appraisal Tools assessment will be analyzed further. After the quality assessment was carried out, 10 articles of good quality were obtained which would then be used in research. Of the 10 case reports that have been collected, 2 articles that are side effects of using Moringa seeds where the clinical manifestations of these side effects are disorders of the respiratory tract, while 8 other articles are side effects of using Moringa leaves where 5 articles report disturbances in the parts of the body, dermal and 3 other articles reported muscle disturbances in the form of rhabdomyolysis.

Clinical manifestations of the respiratory tract disorders can be in the form of asthma or anaphylactic reactions that occur in a fast time, caused using Moringa seeds. The side effect reaction of using Moringa leaves on the dermal clinical manifestations can be in the form of skin redness (erythema) with the presence or absence of lesions or prominent skin areas accompanied by

itching, even skin redness in some patients can leave hyperpigmentation. Skin redness can be a clustered maculopapular rash or a morbilliform rash that spreads throughout the body. The side effects of rhabdomyolysis due to the use of Moringa leaves manifest as pain in certain body parts, especially the limbs. Clinical manifestations of side effects of Moringa leaves or seeds, can then be classified based on the dose and duration of exposure. Chronic types classification when Moringa used for six months or up to years [9]. Chronic types side effect classification in case reports of Poussel *et al.* [10] and Olanrewaju *et al.* [11] due to Moringa is consumed for a long time, about 1-2 years. The case reports of Berglund [12]; Adegbidi *et al.* [13]; Witharana *et al.* [14]; Sagrera *et al.* [15]; Deogade *et al.* [16]; Acharya *et al.* [17]; Treidler *et al.* [18] can be classified into the bizarre types of side effects because of the appearance of side effects in the patient unpredictable and the use of Moringa in less than six months.

Table 1. Checklist the quality of case report articles with JBI Critical Appraisal Tools [19]

No.	Author	Subject	Question							
			1	2	3	4	5	6	7	8
1	Poussel <i>et al.</i> (2015)	Human	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2	Berglund, L. (2018)	Human	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3	Olanrewaju <i>et al.</i> (2017)	Human	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes
4	Adegbidi <i>et al.</i> (2019)	Human	Yes	Unclear	Yes	No	Yes	Yes	Yes	Yes
5	Witharana <i>et al.</i> (2018)	Human	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6	Sagrera <i>et al.</i> (2021)	Human	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
7	Deogade <i>et al.</i> (2019)	Human	Yes	Unclear	Yes	Yes	Yes	No	Yes	Yes
8	Acharya <i>et al.</i> (2020)	Human	Yes	Yes	Yes	Unclear	Yes	Unclear	Yes	Yes
9	Treidler <i>et al.</i> (2017)	Human	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes
10	Treidler <i>et al.</i> (2017)	Human	Yes	Unclear	Yes	Yes	Yes	No	Yes	Yes

The presence of side effect reactions due to the use of Moringa leaves or seeds can be seen from the physical examination results and the results of the patient's laboratory tests presented in Table 2. Disorders of the respiratory tract due to the use of Moringa seeds can be seen from the symptoms of coughing, shortness of breath, and wheezing, patients, as well as the results of the measurement of the FEV1/FVC value where if there is a decrease of more than 20% from the normal value (normal value FEV1/FVC > 75-80%) indicates an obstruction in the airways whose manifestations can be shortness of breath and wheezing such as as well as asthma symptoms complained of by patients in case

reports [20]. In addition to asthma, respiratory disorders due to the use of Moringa seeds can be in the form of an anaphylactic reaction that occurs rapidly, characterized by symptoms of hypotension, high respiratory rate (tachypnea), and angioedema. Investigations for anaphylaxis are a measurement of serum tryptase levels. This serum tryptase level will indicate when a patient has an anaphylactic reaction. Elevated serum tryptase levels were associated with mast cell degranulation due to the anaphylaxis reaction that occurred in the patient. Mast cells contain mature -tryptase so that when mast cells degranulate, β-tryptase will be released into the blood, increasing serum tryptase levels [21]. Disorders

of the dermal part seen from the results of the patient's physical examination in the form of skin redness (erythema) with prominent skin parts (the presence of lesions) or not and accompanied by itching, even redness of the skin which can leave persistent hyperpigmentation [22]. Muscle disorders in the form of rhabdomyolysis can be seen from the symptoms of

muscle pain in certain body parts, as well as the results of laboratory tests in the form of creatine kinase (CK) levels. An increase in CK levels >40 times (normal CK value in men: 55-170 IU/L and women: 30-135 IU/L) indicates the presence of muscle cell necrosis which is a manifestation of ongoing muscle pain and progresses to rhabdomyolysis [23].

Table 2. Manifestation of *Moringa oleifera* Side Effects

No	Part of <i>Moringa</i>	Dosage and duration of exposure	Administration route	<i>Moringa</i> side effects manifestations	Parameters affected	Author
1	Pods of <i>Moringa oleifera</i> (MO)	Dosage: - Duration of exposure: 2 years where the patient was exposed 3 hours/day; 3 days/week	Inhaled	Respiratory tract (shortness of breath and wheezing such as well as asthma symptoms)	<ul style="list-style-type: none"> • FEV1/FVC= 81%. • FeNO test= 91.21 ppb; • Methacholine test of 1280 g showed a decrease in the value of FEV1/FVC by 22% from the normal value. • Skin prick test, the diameter of the reddish spots on the skin is 10 mm. 	[10]
2	Pods of MO	Dosage: - Exposure time: 20 minutes after eating MO seed cooking	Oral (Food)	Respiratory tract (anaphylactic reaction)	<ul style="list-style-type: none"> • Blood pressure= 85/51 mmHg. • Tachypnea (+) • Serum tryptase levels were 39.6 g/L; • Skin prick test, the diameter of the reddish spots on the skin is 4 mm. 	[12]
3	Leaves of MO	Dosage: - Exposure time: 1 year after consuming MO leaf aqueous extract	Oral (Water extract)	Dermatitis	<ul style="list-style-type: none"> • Physical examination: <ul style="list-style-type: none"> a) red macules with the presence or absence of vesicles; b) Lesions in the form of black spots on the upper and lower arms, and thighs. 	[11]
4	Leaves of MO	Dosage: - Exposure time: 24 hours after eating MO leaf cooking	Oral (Food)	Dermatitis	<ul style="list-style-type: none"> • Physical examination: Grayish patches, not scaly, oval with clear boundaries, and scattered around the neck, back, legs, chest, and abdomen. 	[13]
5	Leaves of MO	Dosage: - Exposure time: 14 hours after eating MO leaf cooking	Oral (Food)	Steven Johnson Syndrome	<ul style="list-style-type: none"> • Fever (+). • Skin redness (macular popular rash) (+); • Canker sores (mouth ulcers) to difficulty swallowing. • Blood pressure= 130/80 mmHg. • Heart rate = 82 x/minute. 	[14]

					<ul style="list-style-type: none"> • Neutrophil content = 90%. • Platelet level= 260,000×10¹²/L.
6	Leaves of MO	Dosage: - Exposure time: 3 days after consuming MO leaf powder	Oral (Food)	Dermatitis	<ul style="list-style-type: none"> • Mild shortness of breath. [15] • Swollen tongue. • Morbilliform rash (red spots) on the face, trunk, and upper arms accompanied by papules. • Biopsy data revealed the presence of necrotic keratinocytes.
7	Leaves of MO	Dosage: - Exposure time: 3 days after consuming MO leaves	Oral (Food)	Dermatitis	<ul style="list-style-type: none"> • Skin rash that spreads all over the patient's back. [16] • Blood pressure 110/80. • Heart rate 82 beats/minute.
8	Leaves of MO	Dosage: - Exposure time: Immediately after ingestion of MO leaves	Oral (Food)	Rhabdomyolysis	<ul style="list-style-type: none"> • Severe pain in both thighs. [17] • Nausea. • The creatinine kinase level was increased, but the creatinine kinase value was not attached.
9	Leaves of MO	Dosage: - Exposure time: Immediately after ingestion of MO leaves	Oral (Food)	Rhabdomyolysis	<ul style="list-style-type: none"> • Pain in the hands. [18] • Creatine Kinase (CK) 19.210 U/L.
10	Leaves of MO	Dosage: - Exposure time: Immediately after ingestion of MO leaves	Oral (Food)	Rhabdomyolysis	<ul style="list-style-type: none"> • Pain in the hands. [18] • Creatine Kinase (CK) 22.000 U/L.

Asthma that occurs after 2 years of exposure to Moringa leaf powder is associated with the content of niazirin, marumosiide A, and sitosterol-3-O-β-D-glucoside contained in the seeds which can increase the overexpression of Th2 T Cells [24]. The increase in T cells will induce the mechanism of a type IV hypersensitivity reaction. Type IV hypersensitivity reaction is a delayed hypersensitivity reaction that takes 24-72 hours or even a long time to show the onset of symptoms [25]. The mechanism of the type IV hypersensitivity reaction is associated with an asthmatic

reaction (Figure 2) which begins with an epitope on an antigen recognized by T cells memory. The antigens in this case were niazirin, marumosiide A, and sitosterol-3-O-β-D-glucoside. Th2 T-cells secrete IL-4, IL-13, and IL-5 cytokines, which promote B cell production of IgE and IgG4, macrophage deactivation and mast cell and eosinophil responses. The high production of IL-5 leads to eosinophilic inflammation, the characteristic inflammatory cell type in many drug hypersensitivity reactions. The inflammatory mediators that can cause asthma reactions [26][27].

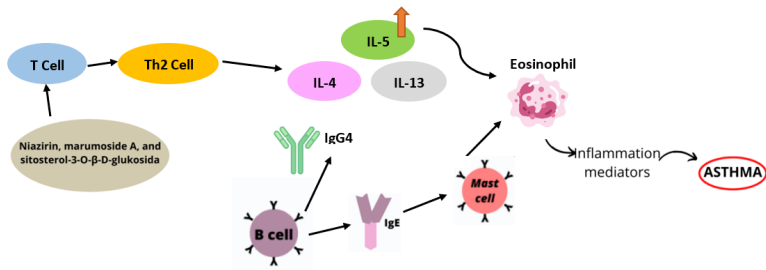


Figure 2. Mechanism of type IV hypersensitivity reaction when exposed to Moringa seeds

The anaphylactic reaction that only lasted 20 minutes after ingestion of Moringa seeds was associated with the protein contained in Moringa seeds capable of binding to IgE which then proved the occurrence of a type I hypersensitivity reaction as shown in Figure 3 [28][29]. Type I hypersensitivity reactions occur rapidly within seconds to 2 hours. The mechanism of the type I hypersensitivity reaction starts from Moringa seed protein which is recognized by bronchial epithelial cells and then triggers the formation of IL-25 and IL-33 which will trigger the action of dendritic cells, as well as basophil cells and Natural Killer (NK) cells which

will trigger IL-4. Dendritic cells will carry allergens (proteins) to be processed in the lymph and after those allergens will be recognized by CD4+ T cells together with MHC class II which can then cause T cells to differentiate into Th2 cells [30]. IL-4 will then amplify th2 cells to produce B cells. B cells will then produce IgE. IgE will bind to high-affinity IgE receptors (FcεRI) causing mast cells to degranulate and release inflammatory mediators that can cause vasoconstriction and excessive mucus secretion which can cause shortness of breath reactions in patients [31][32].

Innate immunity

Adaptive immunity

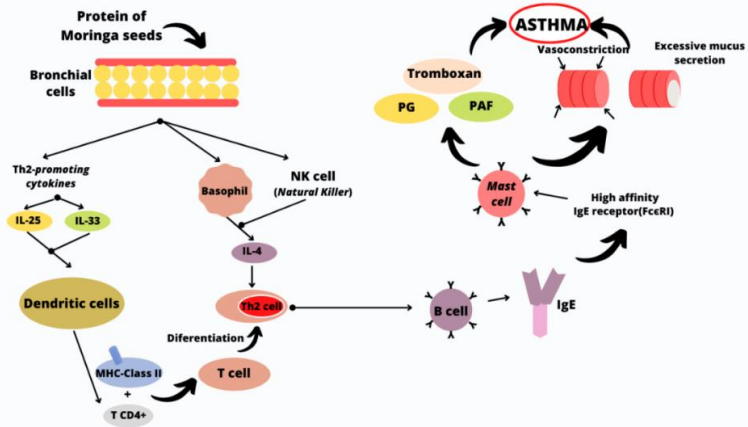


Figure 3. Mechanism of type I hypersensitivity reaction when exposed to Moringa seed protein

Dermal disorders due to the use of Moringa leaves are associated with the alkaloid content, namely moringin contained in Moringa leaves shown in Figure 4. Moringin has a similar mechanism of action with ephedrine, a sympathomimetic drug [33][34]. This sympathomimetic drug then triggers the formation of a T cell complex with MHC, triggering a type IVa hypersensitivity reaction mediated by T cells. The

mechanism of the type IVa hypersensitivity reaction begins with the epitope on moringin recognized by T cells memory. T cells memory then together with MHC class II will trigger T cells to differentiate into Th1 cells and Th2 cells. Th1 cells with Th17 cells then stimulate macrophage activation and strengthen the work of CD8+ Tc cells. Activation of these macrophages can release IL-12, which can then stimulate ThCD4+ cells

to produce IL-2 and IFN- γ which are inflammatory mediators whose manifestations are dermatitis [35]. In addition, the epitope on the antigen will be on the surface of the APC (Antigen-presenting cells) which can then be directly recognized by Tc CD8+ cells which

will induce apoptosis or cell death occupied by the antigen from Moringa. Apoptosis then induces activation of macrophage cells which causes the release of IL-12 cells which will then stimulate ThCD4+ cells to produce IL-2 and Interferon gamma (IFN- γ) [32][36].

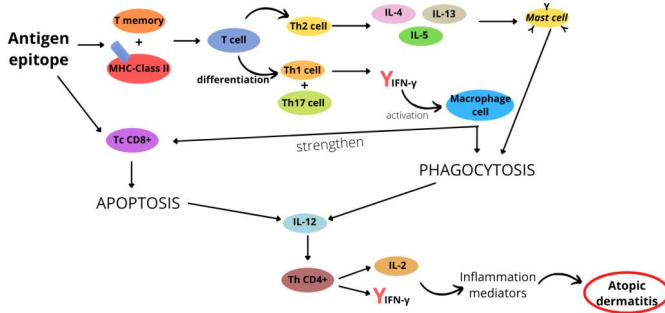


Figure 4. Type IV hypersensitivity reaction causing atopic dermatitis

Rhabdomyolysis disorders are associated with the content of flavonoids in Moringa leaves, namely quercetin and kaempferol which have a similar structure to the statin class of drugs shown in Figure 5 [37]. The flavonoids in Moringa leaves can inhibit HMG-CoA reductase thereby inhibiting the formation of farnesyl-PP which is the basic ingredient in the formation of ubiquinone (CoQ10) so that CoQ10 levels decrease in the body as depicted in Figure 6. The absence or low levels of ubiquinone (coenzyme Q10) can further cause damage to the mitochondria so that they cannot produce ATP or energy for the muscles so that the manifestation is experiencing muscle pain or myalgia. ATP that is not produced sustainably can result in the death of mitochondrial cells which will lead to muscle tissue damage because the muscles do not get ATP as energy to be used by the muscles, which manifests in the form of rhabdomyolysis which is characterized by a significant increase in creatine kinase levels up to >40 times the normal value limit [23][38].

In addition, the mechanism of action of flavonoids in inhibiting cholesterol synthesis can also result in cholesterol depletion in the plasma membrane of muscle fibers (sarcolemma) which is thought to cause myopathy because the sarcolemma is depleted so that the stability of the sarcolemma can be disturbed and the ion balance in the sarcolemma can change [23].

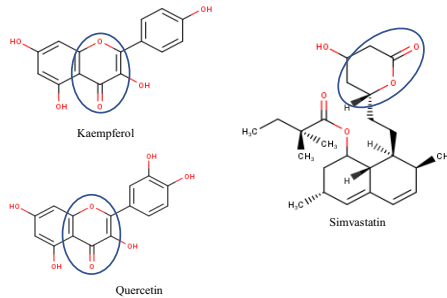


Figure 5. The structural similarity of kaempferol and quercetin with simvastatin

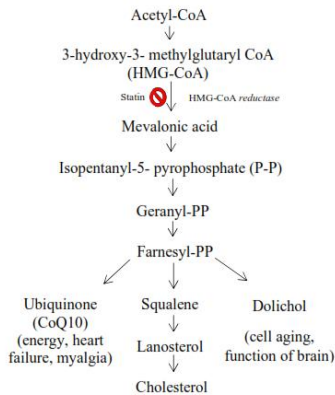


Figure 6. Mechanism of Action of Statins

CONCLUSION

From the results of case reports collected from 2011 to 2021, it was found that the Moringa plant used for its leaves and seeds can cause side effects with clinical manifestations in the respiratory tract, dermatology, and rhabdomyolysis. The side effects of these herbs can arise depending on the method of consuming the herbs, both the dose consumed and the duration of herbal consumption. Reports related to side effects of using herbs in case reports should be accompanied by complete patient laboratory examination data to identify side effect reactions correctly. If side effects are found in the use of herbs in the community, they should be reported to the Pusat Pharmacovigilant / MESO Nasional Badan Pengawasan Obat dan Makanan RI.

AUTHOR'S CONTRIBUTIONS

Deborah Felinda Hari Wijaya contribute for conducting research and preparing the data, contribute for writing original article. Alfian Hendra Krisnawan, Oeke Yunita, Krisyanti Budipramana, contribute for reviewing the article, Karina Citra Rani contribute for writing original article and reviewing the article. Nikmatul Ikhrom Eka Jayani contribute for the conceptualization and writing original article, reviewing the article.

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