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Formulation, Evaluation of Physical Properties, and *In Vitro* Antioxidant Activity Test of *Moringa* Leaf (*Moringa oleifera* L.) Ethanolic Extract Capsules

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Abstract

BACKGROUND: Supplements that contain antioxidants may enhance prevention and treatment effects of a wide range of diseases including COVID-19. Quercetin, a flavonoid compound, is a natural antioxidant that can neutralize free radicals.

AIM: The present study was conducted to formulate *Moringa* leaf (*Moringa oleifera* L.) ethanol extract capsules and to determine the quercetin antioxidant activity levels of Moringa ethanol extract capsule formulations.

MATERIALS AND METHODS: We tested the total flavonoid levels in solutions with concentrations of 20, 50, 60, 70, and 100 ppm using thin-layer chromatography densitometric method. Evaluation of physical properties of 96% *Moringa* leaf ethanol extract capsules included moisture content test, granule angle of repose test, granule flow property test, capsule weight uniformity test, and capsule disintegration time test. Antioxidant activity test using the 2,2-diphenyl-1-picryl-hydrazyl-hydrate method with two samples, namely, 96% *Moringa* leaf ethanol extract capsules with formulas I, II, and III, quercetin as a comparison.

RESULTS: The results of the evaluation of 96% *Moringa* leaf ethanol extract capsules showed that formula II (polyvinylpyrrolidone 50 mg) had good physical properties. Testing the antioxidant activity of capsules of the ethanol extract of *Moringa* leaves formulas I, II, and III, quercetin obtained IC50 values of 44.0 ppm, 40.2 ppm, 46.4 ppm, and 4.80 ppm, respectively.

CONCLUSION: The evaluation of the ethanol extract capsules of *Moringa* leaf formula II met the parameters of a good capsule evaluation test requirement and had very strong antioxidant activity seen from the acquisition of the IC50 value. The antioxidant properties of *Moringa* leaf extract capsules may be able to improve the immune system and clinical trials need to be carried out on patients to become candidates for prevention and therapeutic supplement for a range of diseases including COVID-19.

Introduction

Free radicals can cause oxidative stress and damage to our cells or tissues [1], [2] causing many diseases including type 2 diabetes mellitus, hypercholesterolemia, neurodegenerative diseases, and cancer [3], [4]. Free radicals are unstable due to their unpaired electrons. Free radicals or oxidants bind to other electrons by forming a new free radical in the oxidation reaction process [1]. Unpaired electrons react with other substances such as proteins, fats, and DNA in the human body [2]. Antioxidants can inhibit oxidation reactions with chemical structures that have a hydroxyl group on the flavone ring. Antioxidant compounds are essential for our body to neutralize and prevent the effects of free radical compounds [3], [4].

Flavonoid compounds are antioxidants [3]. Recent research states that flavonoids can improve the immune system in preventing degenerative diseases and infectious diseases by viruses, such as COVID-19 [5]. In addition to antioxidant activity, flavonoid compounds also have antiviral activity that can potentially prevent severe illnesses from viral diseases like COVID-19 [6]. The COVID-19 virus directly affects the immune system which can trigger various diseases, inflammatory, and infectious complications of the virus [7]. Inflammation occurs characterized by white blood cells that will respond to the production of cytokines. Cytokines will bind to cell receptors so that they can trigger inflammation [8]. According to recent research by Mrityunjaya *et al*. (2020), quercetin compounds have the potential to be protective against SARS-CoV-2 which may prevent severe illnesses from COVID-19 by reducing inflammation [9]. Furthermore, studies have suggested that quercetin compounds may be able to reduce inflammation caused by COVID-19 and help prevent hospitalization due to COVID-19.

Moringa (*Moringa oleifera* L.) contains compounds that act as antioxidants. The previous

research stated that phytochemical screening in *Moringa* leaf extract contains flavonoid compounds, tannins, terpenoids, alkaloids, and saponins [11]. *Moringa* leaves contain flavonoid compounds with marker compounds quercetin [12]. This compound can act as an antioxidant because it has a hydroxyl group with the working mechanism of donating a hydrogen atom to a hydroxyl group that can react with free radicals [13]. *Moringa* leaf ethanol extract has a stronger antioxidant power than n-hexane and ethyl acetate extracts because ethanol is the most effective solvent to attract flavonoid compounds [14]. The World Health Organization estimates that about 80% of the population in the developing countries use herbal plants as traditional medicine for basic needs for the treatment of diseases. The use of herbs as medicines is associated with their ability as antioxidants to be made into pharmaceutical preparations [15]. Dosage forms that can be considered for the formulation of herbal medicines from *Moringa* leaves are capsules. Capsules have an attractive shape, can mask the smell and even taste of the active substance or added ingredients, are easy to swallow, and disintegrate quickly in the stomach [16]. Our study aims to formulate *Moringa* leaf extract into capsules for the evaluation of physical properties, determination of total flavonoid content, and test of antioxidant activity using the 2,2-diphenyl-1-picryl-hydrazyl-hydrate (DPPH) method.

Methods

Materials

The ingredients used were *Moringa* leaf powder obtained from Beringharjo Market, Yogyakarta, 96% ethanol (Bratachem), capsule shell no.0, DPPH (Merck), quercetin (Merck), aerosil, polyvinylpyrrolidone (PVP-K30), avicel, lactose, formic acid, methanol pro analysis, toluene, ethyl acetate, and silica gel GF-254 (Merck). The equipment used is Pyrex glass, Oven (Memmert UN 55), Spectrophotometry (Thermo Scientific 201 UV-Vis), and Camag Thin-Layer Chromatography (TLC) Scanner.

Collection and extraction procedure

Moringa leaf powder (*M. oleifera* L.) was obtained from Beringharjo Market Yogyakarta in September 2020. *Moringa* leaf powder weighed 500 g dissolved using 96% ethanol 2.5 L (1: 5), maceration for 3 × 24 h, and remuneration 1 time. The filtrate was heated over a water bath or concentrated using a vacuum rotary evaporator 60°C and the thick extract formed will be calculated by calculating the percentage yield [12].

Formulation

Moringa leaf extract capsules (MLECs) were made by mixing *Moringa* leaf ethanol extract with powdered excipients into a mortar and pestle until homogeneous. Then dissolve the polyvinylpyrrolidone with 96% ethanol until it dissolves evenly and mix it into the powder containing the ethanol extract of *Moringa* leaves in a mortar. The wet granules were then sieved using a number 10 mesh sieve and dried at 40–60°C for 1 h in the oven. The granules were then sieved using a number 12 mesh sieve and then put into capsule shell number 0 [16]. The MLEC formulation is listed in Table 1. Furthermore, evaluation of physical properties includes moisture content (MC) (%), angle of rest (degrees), flow rate (g/s), weight uniformity (g), and breakdown time test (minutes) [17].

Table 1: Formulation capsule of *Moringa* leaf extract

Ingredients	Function	Formula		
		F I (mg)	F II (mg)	F III (mg)
Moringa extract	Active compound	250	250	250
Aerosil	Glidant	10	10	10
Polyvinylpyrrolidone	Binders	25	50	75
Avicel	Disintegrant	50	50	50
Lactose	Filler	165	140	115
Total		500	500	500

Information: FI (Formula I), FII (Formula II), and F III (Formula III).

Determination of total flavonoid levels in Moringa leaf capsules by TLC densitometry

The capsule sample of the best formula from the physical properties test weighed 50.0 mg and then dissolved in pro-analytical methanol (pa) in a 10 ml volumetric flask. The quercetin standard 25.0 mg of was dissolved in 25 ml of pro-analytical methanol solvent. Prepare a series of standard solutions of 20–100 ppm quercetin. The stationary phase using a 10 × 10 cm Silica Gel GF254 plate was heated in an oven at 100°C for 10 min. Samples and standards were spotted (0.5 ml) on the plate, at a distance of 10 mm. The elution distance used was 80 mm carried out at room temperature (28 ± 2°C), with toluene: ethyl acetate: formic acid, 5:4:0.2 (v/v/v) as mobile phase, in a glass Camag chamber previously was saturated with the mobile phase for 20 min. The stationary phase (plate) of TLC which has been dried in a fume hood is then inserted into the Densitometer (Camag TLC Scanner). This research was conducted at the Faculty of Pharmacy, Ahmad Dahlan University, Yogyakarta [18].

Test of antioxidant activity of MLEC with DPPH method

Preparation of 100 ppm DPPH solution was carried out by weighing 10 mg of DPPH powder then dissolved in 96% ethanol to the mark using a 100 mL volumetric flask and as a mother liquor placed in a dark glass bottle. The blank solution was made using 1.0 mL of 100 ppm DPPH solution then dissolved using 96%

ethanol in a 5.0 mL volumetric flask, adding solvent to the limit mark. Let stand for 30 min and measure the absorbance at a wavelength of 517 nm. The 100 ppm quercetin mother liquor was prepared by weighing 10 mg of quercetin powder then dissolved in 96% ethanol while stirring and homogenized in a 100 mL volumetric flask to make 100 ppm quercetin solution. Furthermore, variations in concentrations of 2 ppm, 4 ppm, 6 ppm, 8 ppm, and 10 ppm were made. Solutions of various concentrations as much as 1 ml, each added 1.0 mL of 100 ppm DPPH solution, vortexed, and incubated for 30 min in a dark room [19].

% Reduction = ((Abs control - Abs assay) / Abs Control) x 100%

Abs: Absorbance

Equation 1. The equation of DPPH reduction percentage.

The sample solution was made with a concentration of 1000 ppm by weighing the capsule powder according to the calculation of sample preparation and dissolved using 96% ethanol as solvent. Add 96% ethanol to the mark in a 25 mL volumetric flask, shake until homogeneous. Then make a series of sample solution concentrations, namely, 100; 200; 300; 400; and 500 ppm of the mother liquor sample of 1000 ppm. Solutions of various concentrations as much as 1 ml, each added 1.0 mL of 100 ppm DPPH solution, vortexed, and incubated for 30 min in the flask covered. The DPPH reduction percentage of MLEC (Moringa Leaf Ethanolic Capsule), wich was calculated by the Equation 1, that would be followed by the regression linier . The IC50 value is calculated by entering the number 50 as Y in the linear regression equation (Y= bx + a) [19].

Results

Evaluation of physical properties

The thick extract formed was calculated by calculating the percentage yield as 23.8%. Table 2 shows the results of the evaluation of *Moringa* leaf ethanol extract capsules through several tests such as the calculation of % MC, granule angle of repose, granule flow rate, capsule weight uniformity, and capsule disintegration time test with several formulas using different amounts of PVP [17].

Table 2: Results of evaluation of *Moringa* leaf ethanol extract capsules

Formula	MC (%)	AR (degrees)	FR (g/s)	WU (g)	BTT (min)
I	1.75 ± 0.06	35.17 ± 2.14	4.72 ± 0.16	0.4656 ± 0.5412	4.12 ± 0.15
II	3.62 ± 0.00	30.27 ± 2.67	5.93 ± 0.11	0.4678 ± 0.5436	2.42 ± 0.30
III	4.57 ± 0.00	38.07 ± 2.00	2.95 ± 0.03	0.4665 ± 0.5419	5.25 ± 0.20

Information: MC: Moisture content, AR: Angle of rest, FR: Flow rate, WU: Weight uniformity, BTT: Breakdown time test.

Total flavonoid levels in Moringa leaf capsules by TLC densitometry

Spectro-densitometric scanning quercetin was performed in fluorescence 389.0 nm (Figure 1), while at the theory mode at 380 nm [18]. Table 3 shows that MLECs contain a high flavonoid 8.97% (w/w), compared to a thick *Moringa* leaf extract containing a total flavonoid not <6.30% (w/w) calculated as quercetin. The results of linear regression calculations between the grade series and the area (Figure 2) are obtained with linear regression equations Y = 101.21x − 508.19 with R^2 = 0.9849. The linear regression equation can be used to calculate the total flavonoid content as quercetin.

Antioxidant activity of capsule

The standard DPPH experimental wavelength was 517.16 nm. The results of the antioxidant capsules of *Moringa* leaf extract compared with quercetin. Table 4 shows the antioxidant results in all MLEC formulas and quercetin standards including the category of very strong antioxidants (< 50 ppm) [13].

Discussion

Moringa leaf ethanol extract was obtained using the maceration or filtration method without heating, this method prevents decomposition of the compound due to heating. Immersion using ethanol solvent has better antioxidant activity than n-hexane and ethyl acetate solvent [14]. Maceration with ethanol is a suitable extraction method and solvent for extracting high-quality antioxidant raw materials from *Moringa* leaves for the development of pharmaceutical and nutraceutical products [20], [21]. The TLC densitometry method in the analysis of the total flavonoid content of *Moringa* leaf capsules was chosen because it is selective and sensitive when compared to the UV–visible spectrophotometric method. The high-performance liquid chromatography (HPLC) method is also an option in the analysis of flavonoid content, but this method has limited applications, such as extensive sample cleaning and the need for expensive solvents and a longer column stabilization period. High-performance TLC remains the choice of flavonoid content analysis because it is a versatile analytical technique that requires inexpensive instrumentation and expertise [18].

Moringa contains vitamins, minerals, proteins, essential phytochemicals, amino acids, carotenoids, and flavonoids that can be antioxidants [21]. Studies have examined the use of *Moringa* as a supplement in preventing infection with pathogens including SARS-CoV [22]. The immune modulator and immune stimulator activity of *Moringa* leaves makes it a suitable natural nutritional supplement and immune enhancer

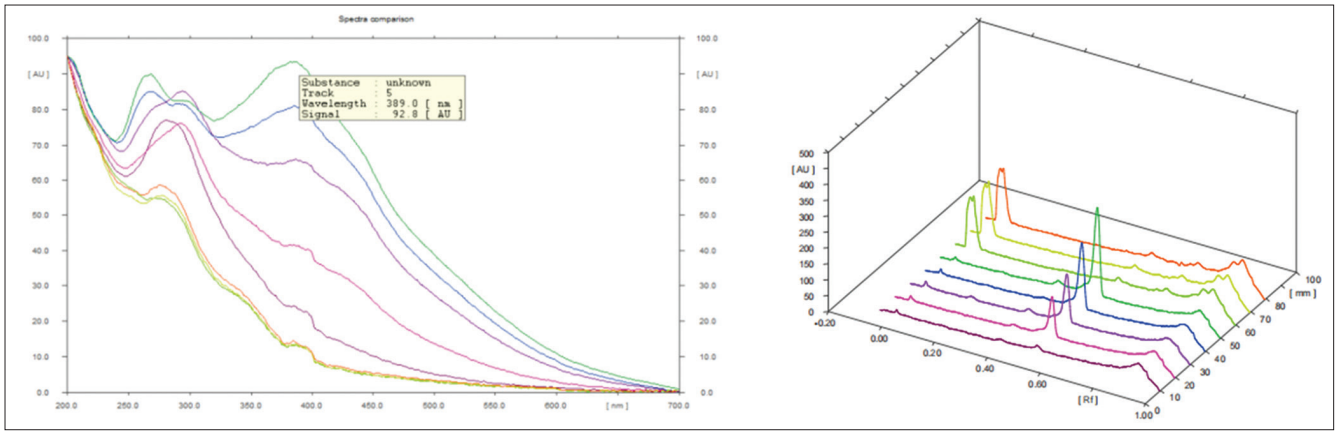

Figure 1: The wavelength of the quercetin compound in TLC densitometry

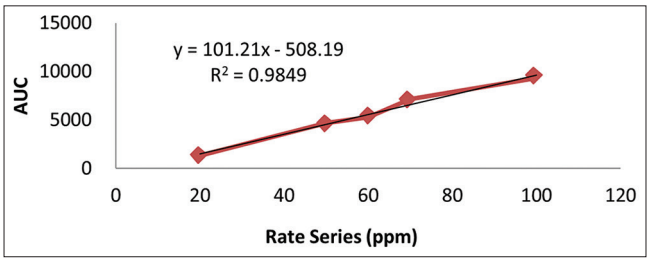

Figure 2: Standard curve of quercetin on TLC densitometry

against SARS-CoV-2 [23]. A study using an *in silico*-based approach showed the possibility of identifying a strong inhibitor of SARS-CoV-2 Mpro from plant sources, such as *Moringa*. The antioxidant properties of the *Moringa* extract may be able to enhance the immune system of secondary infections after COVID-19. Other components in *Moringa* leaves that may have beneficial impact on the immune system play a role include pterygospermin and apigenin [24].

Table 3: Total flavonoid capsule formula II

Sample replication	AUC	Quercetin levels % (w/w)	X ± SD
1	1618.30	8.49	8.97 ± 0.44
2	1835.77	9.35	
3	1761.90	9.06	

Das *et al*. (2020) showed that the total flavonoid content in *M. oleifera* leaves extract before synthesis was 23.0 ± 0.3% and in *M. oleifera* leaves extract after synthesis 17.0 ± 0.4%. While in this study, we made the MLEC formula, which had the flavonoid content of 8.97 ± 0.44%. This may be because this study used capsules as a sample so that the flavonoid content is reduced and further studies need to be carried out regarding the optimization of product manufacture on the total flavonoid content [25]. Studies have suggested that the content of flavonoids in *Moringa* leaves apart from being an antioxidant, may also be used as an antidiabetic, antibacterial, and dietary supplement [26], [27]. Nutraceutical products or supplements containing *Moringa* leaves may be able to contribute to prevention obesity and type 2 diabetes in Indonesian children and adolescents aged 10–18 years, many of whom lead unhealthy lifestyles with poor dietary choices [28], [29].

Quercetin is one of the bioactive compounds found in *Moringa* leaves, with strong antioxidant activity.

Table 4: Result of antioxidant activity of *Moringa* leaf capsule

Sample	Concentration (ppm)	Absorbance	% inhibition	IC_{50} (ppm)	Category
Formula I	100	0.365	56.17	44.0	Very strong
	200	0.354	57.49		
	300	0.349	58.09		
	400	0.254	69.43		
	500	0.194	76.72		
Formula II	100	0.365	56.17	40.2	Very strong
	200	0.346	58.45		
	300	0.333	59.98		
	400	0.215	74.20		
	500	0.185	77.76		
Formula III	100	0.368	55.77	46.4	Very strong
	200	0.352	57.73		
	300	0.345	58.49		
	400	0.213	74.40		
	500	0.200	75.96		
Quercetin	2	0.558	32.97	4.8	Very strong
	4	0.403	51.60		
	6	0.362	56.49		
	8	0.290	65.18		
	10	0.252	69.71		

In vitro, quercetin when reacted with DPPH, will be able to stabilize the unpaired electrons in DPPH. Chemical studies on quercetin compounds mainly focus on the antioxidant activity of metal ion complexes and their complex ions [30]. Pharmacologically, the antioxidant activity of quercetin compounds mainly its effects on enzymatic activity, glutathione, reactive oxygen species, and signal transduction pathways, which are caused by environmental exposure and toxicological conditions [29], [30]. The compound quercetin exhibits strong antioxidant activity by maintaining oxidative balance [30]. As an antioxidant, quercetin controls the effector mechanism of ROS production, with positive and negative effects of this antioxidant agent under conditions of oxidative stress [30]. Given the high concentration of quercetin in *Moringa*, the use of its supplements can inhibit the entry of the virus and have immunomodulatory properties. Oral supplementation doses with quercetin up to 1 g/day for 3 months did not produce significant side effects, so the consumption of *Moringa* leaf supplements was in accordance with this dose [6]. As an antioxidant, quercetin controls the effector mechanism of ROS production, with positive and negative effects of this antioxidant agent under conditions of oxidative stress [31], [32].

Medicinal plants since hundreds or even thousands of years ago have an important role in the treatment of various diseases by humans. The development of drugs from natural ingredients, especially medicinal plants, continues to be researched to provide alternative therapies and disease prevention efforts. *Moringa* capsules from *M. oleifera* leaf extract have the potential to be a supplement to maintain health with their flavonoid content. This is also known by the results of the antioxidant activity of *Moringa* leaf capsules *in vitro* (DPPH) which showed strong antioxidant activity. It is necessary to test the antioxidant activity of *Moringa* leaf capsule supplements in humans to determine its pharmacological effectiveness clinically.

Conclusion

All MLEC formulas met the evaluation parameters of physical properties and had very strong antioxidant activity category. Evaluation of the MLEC formula II is the best capsule evaluation parameters and had a very strong antioxidant activity IC50 of 40.2 ppm, and the total flavonoid content was 8.97 ± 0.44% (w/w). The antioxidant properties of MLEC may be useful for the prevention of obesity and type 2 diabetes as well as for improving the immune system. We suggest future studies to examine the effectiveness of *Moringa* supplements in preventing severe illnesses from viral diseases like COVID-19.

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