

Effects of *Moringa oleifera* Leaf Extracts on Lipid Profile of Rats: A Meta-Analysis and Systematic Review

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ABSTRACT

Moringa oleifera (MO) has long been studied for its anti-obesity potential and its various effects on the lipid profile. However, the result of the basic researches done in rats appears to be imprecise, which may be due to the differences in the solvent extraction, dosing, and duration of administration of the extract. This paper evaluated the effects of different solvent extraction, dosing, and duration of administration of MO extracts on the lipid profile of rats, namely total cholesterol (TC), triglyceride (TG), low-density lipoproteins (LDL), and high-density lipoproteins (HDL). The articles used in this study were collected from various reputable indexing platforms. Meta-analysis was performed to compare the different treatments in the lipid profile of the rats through one-way analysis of variance (ANOVA) with Tukey's test, one-way ANOVA on ranks with Mann-Whitney test, and student t-test. Results show no significant difference ($p < 0.05$) in the rats' lipid profile after treatment of different MO extracts, suggesting that regardless of the MO solvent used results in a similar effect on the lipid profile of rats. However, the disparity of the effects on the lipid profile may be attributed to the dosing and duration of administration. We hypothesized that the level, bioavailability, and mechanism of action of certain phytochemicals present in MO extracts such as flavonoids, phenols, anthraquinones, terpenes, phenolic acids, flavones, terpenoids, and steroids might have also contributed to these differences. Hence, isolation of bioactive compounds from MO and testing their effects on different lipid-associated enzymes may elucidate the actual impact of MO in the lipid profile.

Key words: Leaf extract, Lipid profile, *Moringa oleifera*, Rats, Phytochemicals, Bioactive compounds.

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INTRODUCTION

On a global scale, the prevalence of obesity rapidly increases each year, making it the most extensive and fastest-growing public health concern.¹ Lipid profile is a blood test that serves as a diagnostic tool to measure lipid levels such as total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL), and high-density

lipoproteins (HDL). Abnormalities in lipid metabolism are commonly seen in people with lipid disorders and are correlated with abnormal lipid profiles.²

The pathophysiology of obesity involves several factors, including genetic, environmental, and behavioral.³ Out of these factors, environmental (e.g. lifestyle) and behavioral (e.g. high consumption of food and poor diet) are the common causes of obesity.³ Although a healthy diet and behavioral change are recommended, pharmacotherapy can be added to significant weight loss and maintenance.⁴

The use of plants with medicinal properties has gained the public's attention after several studies proved that they contain bioactive compounds that are beneficial to

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humans. Plants with medicinal properties play a vital role in various cultures, most significantly in Asian medicine⁵ since many are considered safe because it shows minimal to no side effects due to its organic origin.⁶ The most common source of active compounds in plants is leaves.⁷ An example of such a plant is *Moringa oleifera* (MO), locally known in the Philippines as “*malunggay*.” Aside from being easily accessible, its leaves are popular and well-acknowledged as a good source of nutritional and medicinal value.⁸

Bioactive compounds play a significant role in the efficacy of plant leaves as a form of medicine.⁹ Numerous studies about bioactive compounds present in various leaf extractions and their effects on lowering lipids involving rats. Among these studies, MO is one of the most explored leaves based on rats. Aqueous, ethanol and methanol are the commonly used solvents for extraction preparation. The bioactive components of these extracts are potentially valuable compounds such as polyphenols, vitamins, enzymes, and other phytochemicals that can be utilized for their natural lipid metabolism mechanism.¹⁰

In this study, we conducted a meta-analysis regarding the effect of various extracts (aqueous, ethanol, and methanol) of MO on the lipid profile of different lipid-associated disorder rat models. This way, we would determine whether the different MO extracts’ effect on the lipid profile varies.

METHODOLOGY

Literature Search Strategy

We collected the data from the articles indexed in PubMed, Google Scholar, and Scopus using the following keywords, (“*Moringa oleifera*” OR “*M. oleifera*”) AND (“leaf extract”) AND (“aqueous” OR “ethanolic” OR “methanolic”) AND (“lipid profile”) AND (“rats” OR “rat” OR “*Rattus sp.*”). We further streamlined the articles by assessing whether they satisfy the following criteria: (1) rats as the animal model with the induced lipid-associated disorder; (2) MO extracts were administered orally to the animal model without any additional chemicals or treatments; (3) the comparison group consisted of the experimental treatment and control treatment; (4) the lipid profile assessed were TC, TG, LDL, and HDL for both groups at the end of the experiment; and (5) solvent used in the extraction preparation of MO is either aqueous, ethanol, or methanol. We excluded the articles if they reflect the following conditions: (1) unavailability of full text; (2) unavailability of raw data; (3) review articles

and short communications; (4) preliminary results (5) included other plant parts; (6) duration of treatment administration lasted < 2 weeks.

Data Extraction

We extracted the following data from the included studies by the authors: (1) publication information: first author’s name, the title of the article, year of publication; (2) animal model information: animal used, number per group, disease model establishment; (3) administration information: dosage, duration of treatment, MO extract preparation (aqueous, ethanol, or methanol); (4) phytochemicals detected from the extract; (5) pathways and mechanisms involved in the lipidemic effect of the compounds. The outcome measurements extracted were the lipid profile results such as TC, TG, HDL, and LDL from both control and experimental groups of the studies. We presented the data as mean \pm standard deviation (SD) as shown in supplementary Table 4 and 5.

Meta-analysis

Statistical Package for the Social Sciences (SPSS) v. 17.0 and Microsoft Excel Spreadsheet were used to analyze the data. Levene’s and Shapiro-Wilk tests were used to determine the homogeneity and distribution of data. One-way analysis of variance (ANOVA) with Tukey’s test for post hoc analysis, Mann-Whitney test, and student t-test were performed to determinate the significance of the differences among the studies. We set the level of significance at $p < 0.05$.

RESULTS

General characteristics of included studies

A total of 15 studies were included for the meta-analysis and systematic review of this paper. The extract dosages administered to the animal models ranged from 150 to 1,000 mg/kg body weight, and the duration of the included studies ranged from 14 to 90 days. The rat disease models used in the studies can be divided into three: Types high-fat-diet (HFD)-induced models, diabetes-induced models, and chemical-induced models (alloxan, tamoxifen, and lead-acetate) as shown in Table 1. The phytochemical compounds present in MO extracts and their commonality is shown in Table 2 and Figure 1, respectively. MO aqueous extract (MOAE) showed the presence of polyphenols and other phenolic compounds. MO ethanolic extract (MOEE) and MO methanolic extract (MOME) also showed similar compounds with the addition of steroids and terpenoids.

Table 1: General characteristics of included studies.

Reference	Extract	Dose (mg/kg)	Duration (days)	Treatment (extract-dosage-duration)	No. of rats per group	Pathway involved	Major Findings			
							TC	TG	LDL	HDL
Abdelrazek <i>et al.</i> 2020 ¹¹	AE	200	14	AE200-14	6	TNF alpha	-	-	-	+
Luka <i>et al.</i> 2013 ¹²	AE	150	14	AE150-14	5	NS	-	+	-	+
Elmalt <i>et al.</i> 2018 ¹³	AE	200	90	AE200-90	15	Catabolic pathway	-	-	-	+
Abdel-wahhab <i>et al.</i> 2017 ¹⁴	AE	300	45	AE300-45	10	NS	-	-	-	+
Divi <i>et al.</i> 2011 ¹⁵	AE	200	60	AE200-60	22	Glycolytic pathway	-	-	-	+
Oyewo <i>et al.</i> 2013 ¹⁶	AE	1000	56	AE1000-56	6	Metabolic pathway	-	-	-	+
Oyedepo 2013 ¹⁷	AE	400	28	AE400-28	8	Lipid metabolic pathway	-	-	-	+
Ogbuehi <i>et al.</i> 2014 ¹⁸	AE	300	42	AE300-42	5	NS	-	-	-	+
Aborehab <i>et al.</i> 2020 ¹⁹	EE	400	30	EE400-30	7	Cholesterol synthesis pathway	-	-	-	+
Aborhyem <i>et al.</i> 2016 ²⁰	EE	400	28	EE400-28	10	NS	-	-	-	+
Ogbunugafor <i>et al.</i> 2012 ²¹	EE	200	21	EE200-21	5	NS	+	-	-	+
Jain <i>et al.</i> 2010 ²²	ME	300	30	ME300-30	6	Cholesterol synthesis pathway	-	-	-	+
Mabrouki <i>et al.</i> 2020 ²³	ME	200	84	ME400-84	6	NS	-	-	-	+
Madkhali <i>et al.</i> 2019 ²⁴	ME	400	21	ME400-21	6	Metabolic pathway	-	-	-	+
Bais <i>et al.</i> 2014 ²⁵	ME	200	21	ME200-21	10	NS	-	-	-	+

AE, aqueous extract; EE, ethanolic extract; ME, methanolic extract; TNF, Tumor Necrosis Factor; NS, not stated; (-) decrease; (+) increase

Table 2: Phytochemicals compounds present from extracts of *Moringa oleifera* (MO).

Treatment	Phytochemicals	Reference
AE200-14	Alkaloids, Flavonoids, Tannins, Saponins	Abdelrazek <i>et al.</i> 2020 ¹¹
AE150-14	Alkaloids, Flavonoids, Tannins, Saponins, Cardiac Glycosides, Terpenes, Phenols, Resins	Luka <i>et al.</i> 2013 ¹²
AE200-90	Polyphenols	Elmalt <i>et al.</i> 2018 ¹³
AE300-45	Polyphenols	Abdel-wahhab <i>et al.</i> 2017 ¹⁴
AE200-60	Phenolics, Flavonoids, Saponins	Divi <i>et al.</i> 2012 ¹⁵
AE1000-56	NS	Oyewo <i>et al.</i> 2013 ¹⁶
AE400-28	Flavonoids, Saponins, Alkaloids	Oyedepo 2013 ¹⁷
AE300-42	Phytochemicals-Alkaloids, Saponins, Glycosides, Tannins, Flavonoids, Anthraquinones	Ogbuehi <i>et al.</i> 2014 ¹⁸
EE400-30	Flavonoids, Flavones, Phenolic Acid	Aborehab <i>et al.</i> 2020 ¹⁹
EE400-28	Polyphenols, Flavonoids	Aborhyem <i>et al.</i> 2016 ²⁰
EE200-21	Phenolic, Flavonoid	Ogbunugafor <i>et al.</i> 2012 ²¹
ME300-30	Glycoside, Steroids, Flavonoids, Alkaloids	Jain <i>et al.</i> 2010 ^[22]
ME400-84	Phenols, Flavonoids, Tannins	Mabrouki <i>et al.</i> 2020 ²³
ME400-21	Flavonoids, Saponins	Madkhali <i>et al.</i> 2019 ²⁴
ME200-21	Alkaloids, Tannins, Flavonoids, Terpenoids, Steroids	Bais <i>et al.</i> 2014 ²⁵

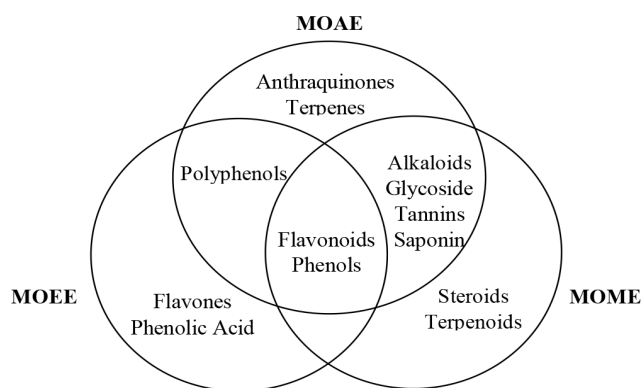


Figure 1: Venn diagram of phytochemicals present in various MO solvent extracts.

Effects of *Moringa oleifera* extracts on Total Cholesterol

The TC of the different solvents of MO extracts is comparable as shown in Figure 2A. Similarly, the normalized TC of the different solvent extracts is not significantly different ($p < 0.05$) as shown in supplementary Table 6. This suggests that the different solvents of MO have the same effects on TC.

The high dosage has significantly increased TC ($p < 0.05$), as exhibited by AE1000-56, AE400-28. Interestingly, a lower dosage than 400 mg/kg has significantly decreased TC ($p < 0.05$). Even though the rat was fed with a lower dose of MO extract (200 mg/kg), if it was given for 90 days, the TC becomes significantly higher ($p < 0.05$). This shows that a low dosage of MOAE given for an extended period exhibits increased TC comparable with those given with increased dosage for a shorter duration. Meanwhile, in MOEE, the same dosage (400 mg/kg) with different duration of exposure exhibited significantly different TC, wherein the extract given 30 days has significantly lower TC compared to the 28 days ($p < 0.05$). However, treatments with lower dosage (200 mg/kg) and shorter duration (21 days) demonstrated comparable TC with rats treated with 400 mg/kg ethanolic extract for 30 days.

In MOME, rats fed with the same dosage (400 mg/kg) for longer duration (84 days) have significantly lower TC ($p < 0.05$) than those of shorter period (21 days) as shown in Figure 2E. Moreover, a lower dosage (200 and 300 mg/kg) demonstrated significantly decreased TC compared to those given with 400 mg/kg MOME for 21 days. It suggests that increase in MOME dosage may directly affect the TC level; however, the longer feeding duration may have negated the increase in the TC level. Overall, the increase in dosage of MO extract shows an increase in TC level. However, the duration of the treatments varies on the solvent extract. Particularly

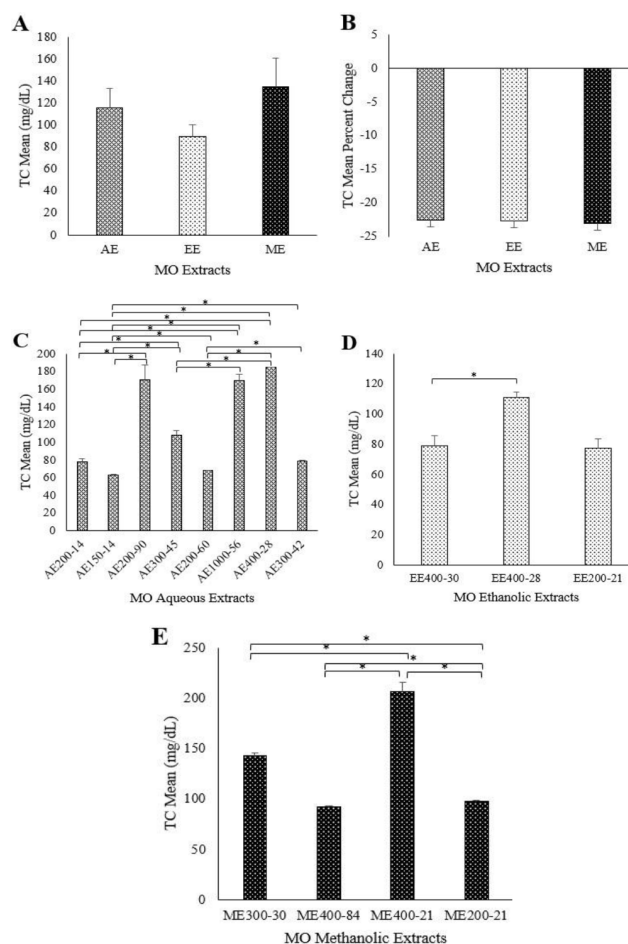


Figure 2: Effects of the MO aqueous, ethanolic, and methanolic extract on TC. A) Mean TC, B) Mean percent TC change, C) TC of different aqueous extract, D) TC of different ethanolic extract, E) TC of different methanolic extract. *significant difference ($p < 0.05$)

in AE, the longer period may have increased TC level, whereas, in ME, a longer duration may have decreased TC level.

Effects of *Moringa oleifera* extracts on Triglycerides

The TG of the different solvents of MO extracts is comparable with each other as shown in Figure 3A. Similarly, the normalized TG of the different solvent extracts is not significantly different from each other ($p < 0.05$) as shown in Table 6 which suggests that the solvents of MO have similar effects on the TG.

The MOAE with high dosage has significantly increased TG ($p < 0.05$), while there is significantly lower TG ($p < 0.05$) on rats fed with a dosage lower than 1000 mg/kg, treated with shorter durations. In addition, rats treated with similar dosages on more prolonged exposure have higher TG than those treated with shorter duration, as shown in Figure 3C. This shows

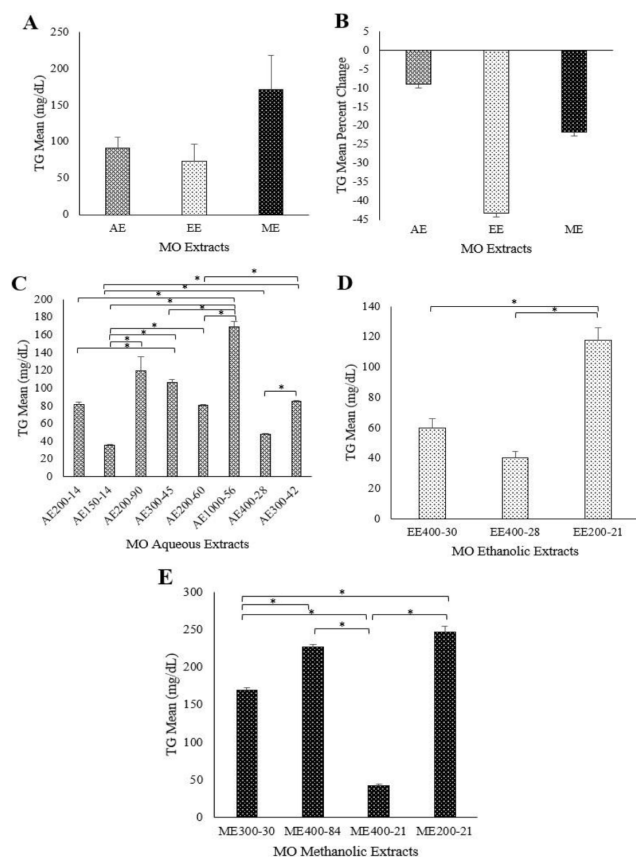


Figure 3: Effects of the MO aqueous, ethanolic, and methanolic extract on TG. A) Mean TG, B) Mean percent TG change, C) TG of different aqueous extract, D) TG of different ethanolic extract, E) TG of different methanolic extract. *significant difference ($p < 0.05$).

that varying dosages of MOAE given for shorter time shows decreased TG comparable to those treated with a longer duration.

On the other hand, in MOEE, rats treated with a lower dosage (200 mg/kg) and shorter duration (21 days) show significantly increased TG ($p < 0.05$). Notably, rats fed with a similar dosage (400 mg/kg) with a shorter duration (28 days) showed lower TG as compared to extended period (30 days). Rats treated with a higher dosage (400 mg/kg), demonstrated significantly decreased TG ($p < 0.05$) than those treated with lower dosages (200 mg/kg) and shorter duration (21 days), as shown in Figure 3D.

MOME-treated rats with high dosage on a short duration have significantly decreased TG ($p < 0.05$). However, there is an increase in TG ($p < 0.05$) with that same dosage with a longer duration. Interestingly, a lower dosage than 400 mg/kg with varying duration (21 and 30 days) exhibited significantly increased TG level ($p < 0.05$), as shown in Figure 3E.

Taken together, the dosage of MO extracts influences the level of TG; however, the effect of each solvent

differs according to their respective duration and their dosages. In ethanolic and methanolic extracts, high dosage (400 mg/kg) with shorter duration results to lower TG; compared to aqueous extract wherein high dosage and more prolonged duration show increased levels of TG.

Effects of *Moringa oleifera* extracts on Low-Density Lipoprotein

The LDL of the different solvents of MO extracts are comparable, as shown in Figure 4A. Similarly, the normalized LDL of the different solvent extracts are not significantly different ($p < 0.05$) as shown in supplementary Table 6. This suggests that the different solvents of MO have the same effects on the LDL.

In MOAE, high dosage shows significantly increased LDL ($p < 0.05$). Interestingly, a lower dosage than 400 mg/kg has significantly decreased LDL ($p < 0.05$). To add to that, rats treated with the same dosage (300mg/kg) with a longer duration (45 days) exhibited significantly decreased LDL ($p < 0.05$) than those treated with a shorter duration (42 days). Notably, rats treated with a lower dose (200mg/kg) on a shorter duration (14 and 60 days) show decreased LDL comparable to rats treated with MOAE on a longer duration (90 days), as shown in Figure 4C.

Meanwhile, in MOEE, rats treated with a high dosage (400 mg/kg) on a longer duration (30 days) show lower LDL comparable to those treated with a shorter period (28 days). Interestingly, low dosage (200 mg/kg) administered at a shorter duration (21 days) shows significantly decreased LDL levels ($p < 0.05$) than those of higher dosage (400 mg/kg) given at a longer duration (28 days) as shown in Figure 4D.

In MOME, rats treated with a high dosage (400mg/kg) with shorter durations (21 days) of treatment exhibited significantly increased LDL levels ($p < 0.05$). Interestingly, rats treated with that same dosage for a longer duration show decreased LDL comparable to lower dosages treated for a shorter time, as shown in Figure 4E. This instance shows that high dosages of MOME given for a shorter period showed increased levels of LDL.

Overall, administration of MOAE in high dosages shows high LDL levels while the opposite is true for lower dosages (below 400 mg/kg). As for the MOEE, lower dosages given on shorter duration will exhibit decreased LDL levels. Similarly, the course of treatment and the dose of MOME extracts and its relation to the reduced LDL levels can also be observed, as shown in Figure 4E.

Figure 4:

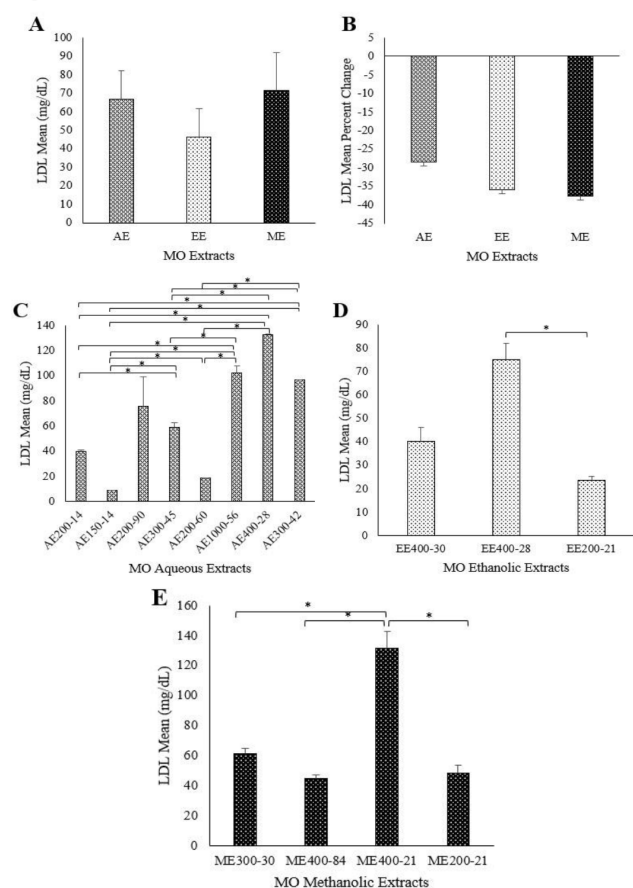


Figure 4: Effects of the MO aqueous, ethanolic, and methanolic extract on LDL. A) Mean LDL, B) Mean percent LDL change, C) LDL of different aqueous extract, D) LDL of different ethanolic extract, E) LDL of different methanolic extract. *significant difference ($p < 0.05$).

Effects of *Moringa oleifera* extracts on High-Density Lipoprotein

The HDL of the different solvents are comparable with each other as shown in Figure 5A, while the normalized HDL of the different solvents were not significantly different from each other ($p < 0.05$) as shown in Table 6, thus the different solvents of MO have the same effects on HDL.

In the aqueous extraction of MO, high dosages (400 and 1000 mg/kg) show significantly increased HDL levels ($p < 0.05$). Interestingly, lower dosage (200 mg/kg) treated with longer duration (60 and 90 days) has significantly higher HDL ($p < 0.05$) compared to rats treated with the same dosage but on a shorter period (14 days). In addition, rats treated with 300 mg/kg of MOAE with different duration shows a significant difference ($p < 0.05$). Evidently, a low dosage of MOAE given for an extended period has an increased HDL comparable to those provided with high dosage for a shorter duration, as shown in Figure 5C.

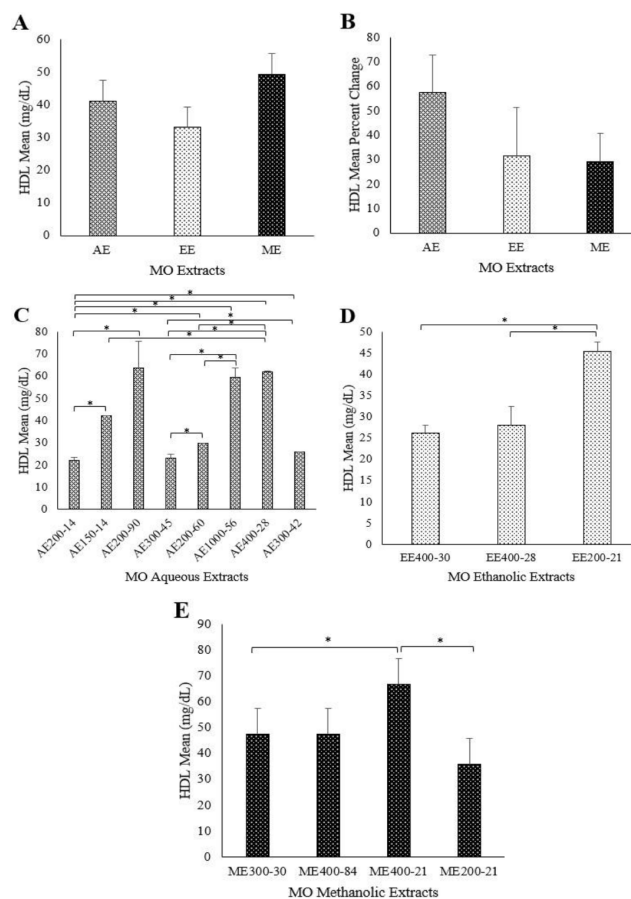


Figure 5: Effects of the MO aqueous, ethanolic, and methanolic extract on HDL. A) Mean HDL, B) Mean percent HDL change, C) HDL of different aqueous extract, D) HDL of different ethanolic extract, E) HDL of different methanolic extract. *significant difference ($p < 0.05$).

On the other hand, 200 mg/kg of MOEE treated on short duration (21 days) shows significantly increased HDL ($p < 0.05$). Notably, rats treated with a higher dosage (400 mg/kg) show decreased HDL comparable with each other. Lower dosage (200 mg/kg) and shorter duration (21 days) show significantly increased HDL ($p < 0.05$) compared to higher dosage (400 mg/kg) and longer-term (28 and 30 days), as shown in Figure 5D.

As for MOME, rats treated with a high dosage (400 mg/kg) for a short duration (21 days) shows significantly increased level of HDL ($p < 0.05$). Interestingly, with the same dosage but a more extended period (84 days), it shows comparable HDL levels to lower dosages (200 and 300 mg/kg) treated for a shorter duration, as shown in Figure 5E. This finding suggests that with higher dosage and shorter treatment time, a significant increase in HDL ($p < 0.05$).

To summarize, the elevation in HDL levels in MOAE varies on the amount of dosage given. However, this contrasts with MOEE, whose increase is observed

when a low dosage is provided for a short period. Similarly, MOME follows the same observation except for dosage, which is more effective in higher dosage and shorter duration.

Percent change of *Moringa oleifera* extracts on lipid profile

The percent change of TC, TG, LDL, and HDL is shown in Table 3. This evidence suggests that negative values exhibit decreased lipid profiles after the treatment of MO extracts. Otherwise, it may be attributed to an increased lipid profile.

The effects of MO extract on TC range from -48.96 to +5.75. It can be observed that AE300-42 exhibited the highest decrease in TC levels (-48.96), in contrast to EE200-21, where TC level was increased (+5.75). Interestingly, after treatment of MO extracts, there was a decrease in TC among all studies, except EE200-21.

On TG levels, the effects of MO extracts range from -69.13 to +3.33. Notably, EE400-28 exhibited the highest decrease in TG levels (-69.13) compared to AE150-14, where TG level was increased (+3.33). This observation suggests a reduction in TG level among all studies, except AE150-14 after treatment of MO extracts.

Meanwhile, in LDL, the effects of MO extracts range from -71.25 to -11.94. It was evident that AE150-14 exhibited the highest decrease in LDL level (-71.25), and AE300-45 exhibited the lowest decrease in LDL level (-11.94). There was a decrease in LDL levels among all studies after the treatment of MO extracts.

Conversely, the effects of MO extracts in HDL ranges from +117.99 to +2.74. Notably, AE150-14 exhibited the highest increase in HDL (+117.99), while EE200-21 exhibited the lowest increase in HDL level (+2.74). This finding shows an increase in HDL levels among all studies after treatment of MO extracts.

Based on the cumulative ranks among all studies, EE400-30 shows the most notable effect on lipid profile in terms of percent decrease in TC, TG, LDL, and percent increase in HDL. As shown in Table 3, EE400-30 has an effect of -48.96, -42.95, -65.84, and +69.48 respectively, and AE300-45 had the lowest ranking with lipid profile values of -12.19, -12.39, -11.94, and +15. Interestingly, the first three ranks had one of each extract, namely, EE400-30, AE300-42, and ME400-21, which may suggest that the efficiency of extract may be similar with each other.

DISCUSSION

Numerous studies suggest that MO leaf extracts improves lipid profile by having a negative effect on TC, TG, and LDL while having a positive effect on HDL.^{26,12} The extraction preparation of MO used are aqueous, ethanol, and methanol. In this discussion, doses less than 300 mg/kg are referred to as sub-median dose, and doses greater than 300 mg/kg are referred to as above-median dose. Moreover, sub-median duration is referred to as extract treatment given for less than 30 days, while the above-median period is referred to extract treatment given for more than 30 days.

The presence of flavonoids and phenols are common among the three MO extracts, which are widely associated with lipid-reduction.²⁷ Flavonoids improves HDL function through direct cellular antioxidative action. Preclinical studies indicate that flavonoids affect the function of reverse cholesterol transport (RCT) and HDL beyond the simple HDL cholesterol concentration. It was reported that flavonoids can inhibit HMG-CoA reductase. The main pathway involved is the cholesterol synthesis pathway, consisting of multiple reactions that lead to the production of cholesterol and HMG-CoA reductase, which in turn may cause a hypolipidemic effect on animal subjects.²⁸

Based on the meta-analysis results, it is shown that there is no significant difference ($p < 0.05$) in rats' lipid profile among MO extracts used; thus, different MO extracts may have the same effects on the lipid profile of rats. This can be explained by: (1) the efficacy of phytochemicals that is present on a specific extract; (2) the mechanism of these compounds on lipid metabolism/pathway; and

Table 3: Percent change of lipid profile values.

MO Extract	Percent Change				Rank
	TC	TG	LDL	HDL	
AE200-14	-14.61	-22.32	-25.29	+27.90	11
AE150-14	-25.46	+3.33	-71.25	+117.99	4
AE200-90	-23.12	-28.56	-26.29	+73.14	5
AE300-45	-12.19	-12.39	-11.94	+15.00	15
AE200-60	-18.00	-56.39	-13.93	+67.75	8
AE1000-56	-19.32	-22.67	-30.23	+13.59	9
AE400-28	-20.63	-26.46	-16.74	+27.98	10
AE300-42	-46.89	-40.74	-32.61	+116.19	2
EE400-30	-48.96	-42.95	-65.84	+69.48	1
EE400-28	-24.98	-69.13	-24.31	+22.17	6
EE200-21	+5.75	-17.83	-17.84	+2.74	14
ME300-30	-27.54	-15.48	-47.19	+16.74	7
ME400-84	-3.89	-14.20	-24.55	+56.58	12
ME400-21	-45.05	-51.21	-57.50	+39.13	3
ME200-21	-15.52	-6.27	-21.53	+3.62	13

(3) the duration and the amount of dosage administered during the treatment.

Sub-median doses at above-median duration treatment of MO extracts exhibited a decrease in the levels of TC. Various studies^{29,30} demonstrated that animal subjects treated with *Stevia rebaudia* and *Ocimum sanctum* aqueous extracts sub-median dosages at above-median duration decreased the TC levels and suggests that administration with above-median dosages at above-median durations resulted in lowered TC levels. This can be attributed to the presence of anthraquinones and terpenes which have an antioxidant property that helps in reducing TC levels.³¹ Bell *et al.*³² demonstrated that terpenes lower TC levels since it is involved in the cholesterol synthesis pathway by inhibiting HMG-CoA reductase.

In TG, administration of MOAE in sub-median dosage at sub-median duration shows a decrease in its level. Zhu *et al.*³³ treated aqueous extract of *Usnea* in HFD rats on sub-median dosage at a sub-median period where it exhibited decreased TG levels. Such effect might be due to the presence of anthraquinones and terpenes. Studies have shown that purpurin, an anthraquinone, reduces the serum TG levels in HFD rats due to its antioxidative properties.³⁴ Moreover, treatment of MOEE and MOME at an above-median dosage and sub-median duration resulted in decreased TG levels in rats. Ghauri *et al.*³⁵ experimented on rats using ethanolic extracts of *Citrullus colocynthis* at an above-median dosage and sub-median duration, resulting in decreased TG levels. Liao *et al.*³⁶ stated that the effect of flavones in ethanolic extract might be attributed to increasing the activity of G-6-P dehydrogenase, an enzyme that has decreased activity in diabetic rats. In addition, phenolic acids' hypotriglyceridemic effect might be due to the increased activity of lipolytic enzymes hepatic lipase and plasma lipoprotein lipase.³⁷

MOAE shows a decreased level of LDL when administered with sub-median dosages at sub-median durations. A study by Ezeigwe *et al.*³⁸ reported that rats treated with a sub-median dosage of *Ficus capensis* aqueous extract produced a significantly decreased LDL level within 14 days. On the other hand, MOME illustrates a decrease in LDL levels when treated with above-median dosages for above-median durations. Marrelli *et al.*³⁹ stated that the effects of steroids and steroidal components act as an effective inhibitor of adipogenesis and inhibit the accumulation of mature adipocytes. MOEE decreased LDL levels when treated with sub-median dosages and sub-median duration.

Studies that used the above-median dosage of MOAE presented an elevation on HDL levels. Adeneye and

Agbaje⁴⁰ conducted an experiment involving the administration of the plant's aqueous extract, and the results were as follows; as the dosage increases, the HDL levels increase. Sub-median dosage of MOEE administered at sub-median durations elevates HDL levels. This finding is similar to the study conducted by Muthu *et al.*⁴¹ administered two doses of methanolic extract to HFD rats, which resulted in an elevated HDL level when given higher dosages of the extract.

After the treatment of MO extracts, it is revealed that there is a negative effect in TC, TG, and LDL, while a positive effect can be observed on HDL. There was a notable reduction of TC in AE300-42, EE400-30, and ME400-21. According to various animal studies, flavanones exhibit significant biochemical reactions that reduce the model's TC levels. Moreover, it may increase the number of cholesterol receptors by inhibiting cholesterol acyltransferase in the liver, which lowers the plasma LDL levels by increasing the liver's LDL uptake.⁴² A notable reduction of TG after the administration of EE400-28 is present since MOEE contains phytochemicals, such as phenolic acid and flavones. Phenolic acid was proven to reduce TG and serum cholesterol by inhibiting enzyme activities such as α -glucosidase, α -amylase, lipase, and cholinesterases.²⁷ A sub-median dose of anthraquinones and terpenes in a sub-median duration notably decreases LDL levels. At the same time, administration of flavones and phenolic acid in the above-median dose and above-median duration decreases LDL levels. In a study conducted by Li *et al.*⁴³ on hyperlipidemic rats, anthraquinones significantly increase HDL levels.

CONCLUSION

This review reveals that treatment of various MO extracts in rats is comparable with its efficacy in improving lipid profiles by decreasing TC, TG, LDL levels and increasing HDL levels. Besides, 400 mg/kg of MO ethanolic extract given for 30 days best represent the ideal changes in the lipid profile of the rats. The ability of MO to affect the lipid profile may be attributed to the phytochemicals present in the different MO solvent extracts, such as flavonoids and phenols. Currently, numerous studies have supported that the phytochemicals present in MO but from other plant material demonstrated the same effects on the lipid profile of various organisms. However, there is little evidence on the effects of purified compounds from MO on the lipid profile, which warrants further investigations. Moreover, isolating the bioactive compound in MO and hypothesize its mechanism of

action with the different lipid-associated enzymes may illuminate understanding of the potential of MO in affecting the lipid profile in mammals.

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CONFLICT OF INTEREST

All authors declare no conflict of interest. The authors alone are responsible for the content of the paper.

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