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Clinical Research

# Hypolipidemic Effect and Antioxidant Activity of Tamarind Leaves Extract in Hypercholesterol-Fed Rats

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**Background:** Higher cost and side effects made of some anticholesterol drugs used in long time are the reasons why some people change to herbal therapies. Tamarind (*Tamarindus indica*) leaves is one of the herbal therapies. This research aims to determine hypolipidemic effect and antioxidant activity of extract of tamarind leaves (ETL).
**Methods:** We used 25 rats as samples, divided into five groups of negative control (CMC 0.5%), positive control (Ezetimibe 1.26 g/kgBW)), first, second and third dose of ETL consequently are 0.93, 1.86 and 3.73 g/kgBW.
**Results:** Paired-samples T-test showed ETL significantly decreased total cholesterol (TC), triglyceride (TG) level, and high-density lipoprotein cholesterol (HDL-C) level significantly increased compared with negative control groups ($p \leq 0.05$). Low-density lipoprotein cholesterol (LDL-C) level had significant difference only at second dose of ETL ($p < 0.05$). Furthermore, the data's difference between pre- and post-intervention were analyzed with one-way ANOVA test in TC, TG, and HDL-C level, ETL had a significant difference ($p \leq 0.05$), while there was no significant difference in LDL -C between groups ($p > 0.05$). Data were also analyzed by Post Hoc test. TC, TG, and HDL-C level had a significant difference between all variance ETL's doses and positive control compared with negative control group ($p \leq 0.05$). For antioxidant activity, ETL exhibited the significant reduction in the levels of malondialdehyde (MDA) by paired-samples T-test ($p \leq 0.05$) but there was no significant difference in both of MDA and superoxide dismutase (SOD) level ($p > 0.05$) analyzed by One-way ANOVA test.
**Conclusion:** All variant of ETL's doses have hypolipidemic effect and antioxidant activity. ETL also has similar effect with Ezetimibe. Saponin, flavonoid, epicatechin, tanin, and polyphenol that is contained likely contribute to these pharmacologic effects.

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**Keywords**: extract of tamarind leaves (ETL), hypolipidemic effect, antioxidant activity

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Penelitian Klinis

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# Efek Hipolipidemik dan Aktivitas Antioksidan Ekstrak Daun Asam pada Tikus yang Diinduksi Pakan Hiperkolesterol

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**Latar Belakang**: Tingginya biaya dan efek samping yang ditimbulkan dari beberapa obat antikolesterol yang digunakan dalam jangka waktu lama menjadi faktor pendorong meningkatnya penggunaan obat herbal. Salah satu obat herbal yang digunakan adalah daun asam jawa (*Tamarindus indica*). Tujuan penelitian adalah menilai efek hipolipidemik dan aktivitas antioksidan ekstrak daun asam jawa (EDAJ).
**Metode**: Sampel yang digunakan berjumlah 25 ekor tikus yang dibagi ke dalam lima kelompok yakni kontrol negatif (CMC 0,1%), kontrol positif (Ezetemibe), EDAJ dosis-1, dosis-2, dan dosis-3 berturut-turut 0,93 g/kgBB,1,86 g/kgBB), dan 3,73 g/kgBB).
**Hasil**: Paired-samples T-test menunjukkan EDAJ menurunkan kadar total kolesterol (TC) dan trigliserida (TG) sementara kadar *high-density lipoprotein cholesterol* (HDL-C) meningkat secara signifikan ($p \leq 0,05$). Dan kadar *low-density lipoprotein cholesterol* (LDL-C) menunjukkan adanya perbedaan secara signifikan hanya pada EDAJ dosis-2 ($p \leq 0,05$). Selanjutnya, selisih data intervensi dianalisis menggunakan uji One-way ANOVA. Dari kadar TC, TG, dan HDL-C, EDAJ memiliki perbedaan signifikan di antara kelompok tersebut ($p \leq 0,05$), sementara tidak ada perbedaan signifikan ($p > 0,05$) pada kadar LDL-C. Selisih data intervensi TC, TG, dan HDL dianalisis dengan Post-Hoc Test dan didapatkan adanya perbedaan yang signifikan di antara kelompok kontrol negatif dengan kontrol positif dan seluruh variasi dosis EDAJ ($p \leq 0,05$). Dalam hal aktivitas antioksidan, dengan Paired-Samples T-Test diketahui bahwa EDAJ memiliki perbedaan penurunan kadar malondialdehida (MDA) secara signifikan ($p \leq 0,05$), namun baik kadar MDA dan superoksida dismutase (SOD) tidak memiliki perbedaan yang signifikan jika dianalisis dengan uji One-way ANOVA ($p > 0,05$).
**Kesimpulan**: Seluruh variasi dosis EDAJ memiliki efek hipolipidemik dan aktivitas antioksidan. EDAJ memilki efek yang sama dengan Ezetimibe. Saponin, flavonoid, epicatechin, tanin, dan polifenol yang dimiliki berkontribusi terhadap timbulnya efek farmakologi.

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**Kata kunci**: ekstrak daun asam jawa (EDAJ), efek hipolipidemik, aktivitas antioksidan

## Introduction

According to World Health Organization, there are around 58 million deaths in the world in 2005, with 17.5 million of them (30%) due to cardiovascular diseases and specifically by heart attacks caused 7.6 million deaths (13%).[1,2] Riskesdas 2007 showed that the prevalence for cardiovascular disease in Indonesia is 7.2% while the percentage for ischemic heart disease at all age was

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around 5.1% from the total percentage of cardiovascular disease.[1]

Ischemic heart disease or better known as coronary heart disease (CHD) is caused by the formation of plaque, vascular remodeling, both acute and chronic luminal obstruction, blood flow abnormality and decline oxygen supply to target organs.[3]

According to the study of Framingham in Atherosclerosis Risk in Communities, and the study of Honolulu there are risk factors in the occurrence of CHD, i.e.: age, family history, dyslipidemia, cigarette smoking, hypertension, and diabetes.[4] The continuity of dyslipidemia formation is correlated with the incident of CHD i.e. increase triglyceride level and decrease cholesterol HDL level will indirectly increase the level of total cholesterol.[5]

Pharmacologic therapy usually aimed to lower cholesterol-LDL level, triglyceride, or increase HDL.[6] Drugs from statin groups in Indonesia are the best cholesterol-lowering drugs. Despite statin, there also another group from hypocholesterol agent called Ezetemibe. Ezetemibe therefore has an important role in pharmacological lipid modification.[7] However, Ezetemibe having lesser adverse effect than statin.[8] Gastrointestinal disruption and other complaint like headache is the most adverse effect from Ezetemibe,[9] meanwhile statin groups adverse effects are gastrointestinal disruption and hepatotoxic effect.[10] Ezetemibe has less number of research for hypocholesterol agent as a control group done than statin in Indonesia. Higher cost and side effects after used in long time are the reasons why some people change to herbal therapy.[11,12]

One of the herbal therapy that has been used empirically in lowering blood cholesterol level is Tamarind (*Tamarindus indica*). Tamarind leaves has been known to contain compound like tannin, alkaloid, saponin, sesquiterpenes, and tannin through phytochemical tests.[12] Extract of Tamarind Leaves (ETL) in controlling lipid profile levels is the effect of saponin action to inhibit lipid absorption in intestine.[13,14] Saponin levels in ETL (in ethanol 70%) are higher than flavonoid levels.[15] Thus, ETL which contained more saponin has a mechanism similar to Ezetemibe as a positive control. Meanwhile, statin inhibit HMG-CoA reductase and has no effect in inhibition of lipid absorption in intestine.[16] This research is to compare it with a positive control group which has no difference in their mechanism of action. We aimed at learning more on the hypolipidemic effect and antioxidant activity of ETL in hyper cholesterol-fed rats compared to Ezetimibe.

## Methods

The materials used for this study are tamarind leaves obtained from Balai Penelitian Tanaman Rempah dan Obat-Bogor which turned into ETL. This extract is divided into three doses: 1st dose=0.93 g/KgBW; 2nd dose=1.86 g/KgBW, and 3rd dose=3.73 g/KgBW.

Samples used in this study are albino rats (*Rattus norvegicus*), wistar strain, male, age 8 weeks, 200-250 gram in weight. Male albino rats obtained from Bogor Agricultural University, matching the inclusion criteria. This study has been approved by the ethics committee of Universitas Pembangunan Nasional "Veteran", Jakarta.

On day 8 through day 22, rats were induced with hypercholesterol feeds and distilled water as their drinking water. Hypercholesterol feeds were done by mixing standard feeds as much as 8 kg added with boiled duck egg yolk (400 g), goat fats (800 g; thawed by boiling), and sufficient amount of hot water for 7 days. One rat was given 50 g of hypercholesterol diet, once per day (modified from Gani, et al's research).[17]

On day 24, rats were given hypercholesterol feeds and intervention for 2 weeks according to its group, which are: (1) group I: CMC solution; (2) group II: Ezetimibe 1.26 g/KgBW/day; (3) group III/1st dose ETL 0.83 g/KgBW/day; (4) group IV/2nd ETL: 1.86 g/KgBW/day; (5) group V/3rd ETL 3.73 g/KgBW/day.

On day 33 blood examination were tested as post intervention data.

### *Biochemical analysis*

Biochemical analysis was tested on day 7 (pre-hypercholesterol feed) and day 21 (post-hypercholesterol feed/pre-intervention) by taking 3 cc of blood from caudal vein rats. On day 35 (post-intervention) by taking 6 cc of blood from the heart without anticoagulant for lipid profile test and with anti-coagulant for antioxidant test. Sample then centrifuged with the speed of 1000 rpm for 10 minutes.

### *Assessment of hypolipidemic effect from ETL*

Lipid profile were measured by using automatic analyzer standard kit.[17] Standard serum used for calibration before each parameter was analyzed.[18] For the biochemical analysis, the plasma was separated from the blood by centrifugation at room temperature for

15 min.[19] Level of every examination declared in milligram per deciliter (mg/dL).[20]

### *Assessment of antioxidant activities from ETL*

Assessment of the antioxidant activities collected from MDA level measurement and SOD. MDA level determine lipid per oxidation level.

Principal measurement using Thiobarbituric Acid-Reacting Substances (TBARS) method on wave length of 532 nm. MDA blood concentration declared as nmol/mL serum.[20] SOD level according to the rate of inhibition from ferri- (Fe3+) cytochrome c reductase by superoxide anion produced by xanthine/xanthine oxidase. Xanthine oxidized to uric acid, while superoxide anion which later formed will reduce ferri- (Fe3+) cytochrome c. Reduction of ferri- (Fe3+) cytochrome c was observed according to the increase absorbance on wave length of 550 nm.[21]

### *Statistical analysis*

First, the data was analyzed with Shapiro Wilk Test as normally distributed test. If the data is normally distributed then Analysis of Variance (ANOVA) test is proceed to show the significant differences between groups. Furthermore, the data was tested using Post-Hoc Test to show exactly how significant the differences between two groups in a row (confidence degree 95% with score p ≤0.05).[22]

## Results

All groups were given hypercholesterol feeds for 2 weeks. Mean value lipid profile for 2 weeks shown in **Table 1**. According to Paired Samples T-Test, there were significant increase of TC, TG, LDL-C level and decrease of HDL-C level in all groups (p≤0.05). The intervention is started by giving hypercholesterol feeds and Ezetimibe 1.26 g/KgBW as positive control and three ETL dose variations for 2 weeks. After 2 weeks, lipid profile examination was repeated. The lipid profile data before and after intervention is shown in **Figure 1** and **Table 2**.

Hypercholesterolemics rats treated with ETL exhibited significant decrease of TC level (p≤0.05) in all group except negative control group (by Paired-samples Test). Furthermore by One-way ANOVA test also resulted in significant difference between groups compared with negative control groups (p≤0.05). The highest decline was seen in the 1st dose ETL (0.93 g/KgBW) as much as 43.3 mg/dL.

There were significant decreases of TG level (p≤0.05) in all groups except negative control group (by Paired-samples Test). One-way ANOVA test also had resulted in significant difference between groups compared with negative control group (p≤0.05). The highest decline was seen in the 1st dose ETL (0.93 g/KgBW) as much as 51.6 mg/dL.

Mean value of LDL-C level significantly decreased only in the 2nd dose ETL group (p≤0.05)

**Table 1**. Lipid profile after hypercholesterol feeds for 2 weeks.

| Parameter | TC (mg/dl) | | TG (mg/dl) | | LDL-C (mg/dl) | | HDL-C (mg/dl) | |
|---|---|---|---|---|---|---|---|---|
| | Before | After | Before | After | Before | After | Before | After |
| Negative Control (CMC 0.5 %) | 58.00 ± 10.20 | 96.60 ± 8.59* | 98.60 ± 16.21 | 105.80 ± 5.68 | 17.12 ± 11.35 | 17.32 ± 10.35 | 59.20 ± 4.97 | 55.60 ± 6.91* |
| Positive Control (Ezetimibe 1.26 g/KgBW) | 59.00 ± 3.54 | 96.00 ± 3.94* | 105.60 ± 8.26 | 110.40 ± 5.46 * | 16.20 ± 6.43 | 29.32 ± 10.71* | 54.00 ± 6.17 | 44.60 ± 8.35* |
| 1st dose ETL (0.93 g/KgBW) | 58.00 ± 6.87 | 97.80 ± 6.87* | 91.60 ± 16.37 | 107.20 ± 8.63 | 13.92 ± 13.67 | 26.56 ± 7.77* | 52.80 ± 7.76 | 46.40 ± 13.72* |
| 2nd dose ETL (1.86 g/KgBW) | 55.00 ± 2.92 | 89.60 ± 6.58* | 90.20 ± 12.47 | 90.80 ± 7.12* | 18.69 ± 9.18 | 25.64 ± 4.90* | 55.80 ± 8.17 | 45.80 ± 8.17* |
| 3rd dose ETL (3.73 g/KgBW) | 55.20 ± 4.50 | 89.40 ± 10.43* | 97.80 ± 13.47 | 109.40 ± 10.47* | 16.12 ± 14.51 | 35.64 ± 3.03* | 51.40 ± 8.23 | 47.60 ± 8.01* |

TC=total cholesterol; TG=triglyceride; LDL-C=low density lipoprotein-cholesterol; HDL C=high density lipoprotein-cholesterol; ETL=extract of tamarind leaves; a=significance (p≤0.05) in comparison to the negative control group; b=significance (p≤0.05) in comparison to the positive control group.

*Significance (p≤0.05) before and after intervention.

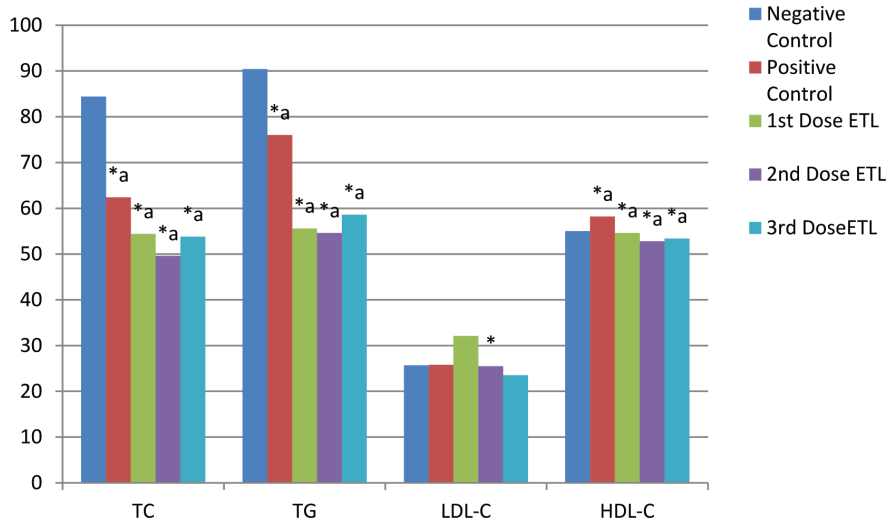


**Figure 1.** The effects of extract of tamarind leaves (ETL) on lipid profile after hypercholesterol feeds induction.
TC=total cholesterol; TG=triglyceride; LDL-C=low density lipoprotein-cholesterol; HDL-C=high density lipoprotein-cholesterol; negative control=CMC 0.5%; Positive Control=Ezetimibe 1.26g/KgBW; ETL=extract of tamarind leaves; 1st dose=0.93 g/KgBW, 2nd dose=1.86 g/KgBW; 3rd dose=3.73 g/KgBW; a=significance ($p \leq 0.05$) in comparison to the negative control groups; b=significance ($p \leq 0.05$) in comparison to the positive control groups.
*Significance ($p \leq 0.05$) before and after intervention (Paired-samples test).

**Table 2.** Mean of the lipid profile level after intervention

| Parameter | TC (mg/dl) | | | TG (mg/dl) | | | LDL-C (mg/dl) | | | HDL-C (mg/dl) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Before | After | Diff. | Before | After | Diff. | Before | After | Diff. | Before | After | Diff. |
| Negative Control (CMC 0.5 %) | 96.60 ± 8.59 | 86.40 ± 3.29 | 10.2 | 105.80 ± 5.68 | 90.40 ± 11.86 | 15.4 | 26.32 ± 5.37 | 25.68 ±8.71 | 0.64 | 54.00 ± 5.87 | 55.00 ± 5.29 | 1 |
| Positive Control (Ezetimibe 1.26 g/KgBW) | 96.00 ± 3.94 | 62.40 ± 8.38 *a | 33.6 a | 110.40 ± 5.46 | 76.00 ± 6.51 *a | 34.4 a | 34.84 ± 10.02 | 25.8± 5.82 | 9.04 | 39.00 ± 8.60 | 58.20 ± 5.80*a | 19.2a |
| 1st dose ETL (0.93 g/KgBW) | 97.80 ± 6.87 | 54.40 ± 6.11*a | 43.4 a | 107.20 ± 8.63 | 55.60 ± 2.87 *a | 51.6 a | 40.92 ± 5.09 | 32.08 ± 8.02 | 8.84 | 35.40 ± 6.16 | 54.60 ± 3.04*a | 19.2 a |

TC=total cholesterol; TG=triglyceride; LDL-C=low density lipoprotein-cholesterol; HDL C=high density lipoprotein-cholesterol; ETL=extract of tamarind leaves; a= significance ($p \leq 0.05$) in comparison to the negative control group; b= significance ($p \leq 0.05$) in comparison to the positive control group; Diff = difference.
*Significance ($p \leq 0.05$) before and after intervention.

**Table 3.** Antioxidant activities of ETL

| Parameter | MDA (µMolar) | | | SOD (Unit/ml) |
|---|---|---|---|---|
| | Pre-intervention | Post-intervention | Diff. | Post-intervention |
| Negative control (CMC 0.5 %) | 10.70 ± 3.24 | 8.82 ± 7.14 | 1.88 | 133.58 ± 18.09 |
| Positive control (Ezetimibe 1.26 g/KgBW) | 13.65 ± 2.28 | 6.61 ± 1.44* | 7.04 | 175.84 ± 19.33 |
| 1st dose ETL (0.93 g/KgBW) | 13.06 ± 1.95 | 6.93 ± 1.17* | 6.13 | 183.90 ± 18.02 |
| 2nd dose ETL (1.86 g/KgBW) | 12.79 ± 1.50 | 5.96 ± 0.89* | 6.83 | 143.51 ± 12.65 |
| 3rd dose ETL (3.73 g/KgBW) | 17.42 ± 9.94 | 6.08 ± 3.24* | 11.34 | 166.57 ± 22.80 |

MDA=malondialdehyde; SOD=superoxide dismutase; ETL=extract of tamarind leaves; a=significance ($p \leq 0.05$) in comparison to the negative control group; b=significance ($p \leq 0.05$) in comparison to the positive control group.
*Significance ($p \leq 0.05$) before and after intervention.

(by Paired-samples Test). Further One-way ANOVA test did not found significant difference between groups (p>0.05). And the highest decline was found in 2nd dose ETL (1.86 g/KgBW) group as much as 11.76 mg/dL.

There were significant increases of HDL-C level in all groups (p≤0.05) except negative control groups (by Paired-samples Test). Further One-way ANOVA test also shown significant difference between groups compared with negative control group (p≤0.05). The highest increase was found in the 3rd dose ETL (3.73 g/KgBW) group as much as 20 mg/dL.

Antioxidant activities showed by MDA and SOD level. MDA level marked the occurence oxidative stress, higher level of MDA similar with higher oxidative stress in the cell. Based on the mean of MDA level before and after intervention, there were significant decrease in MDA level on every groups (p≤0.05) except negative groups and there was no significant difference in all groups (p≥0.05). The lowest MDA decline was found in the 3rd dose of ETL (3.73 g/KgBW), as much as 11.34 µMolar (**Table 3**).

While for the purpose to fight against advanced oxidation is shown by the presence of activity from SOD. Higher level of SOD simil ar with higher antioxidant activity in the cell. Based on the results of this studies, the highest SOD level was found in the 1st dose of ETL (0.93 g/KgBW) as much as 183.90 ± 18.02 unit/ml. And there was no significant difference in all groups (p>0.05) (**Table 3**).

## Discussions

### *Hypolipidemic effect*

There were significant TC and TG level decreases, and HDL-C increases in all groups except negative group. Saponin, flavonoid, epicatechin contained in ETL are likely contributed to hypolipidemic effect. Saponin in tamarind leaves will bind with bile acid and form a large mixed-micelle resulting in failure of absorption of cholesterol in the micelle by the microvilli on the surface of epithelial intestine, resulting in the decrease of total plasma cholesterol level.[12,13.14] Flavonoid will increase activation of LDL-C receptor in liver and makes the clearance of LDL-C faster therefore the TC level will decrease because of this mechanism.[26] Epicatechin in tamarind leaves will decrease TG level and also increase the clearance of free fatty acid and sterol acid through feces.[27] Meanwhile Ezetimibe specifically works as competitive inhibitor in cholesterol absorbtion with cholesterol carrier (protein Niemann-Pick C1 like 1) in epithelial cells of small intestines.[8,10]

In our study, there was no significant difference between LDL-C level. For the 1st dose of ETL, the difference between LDL-C levels was lower than the 2nd dose of ETL. This is because the relationship between pharmacological responses and drug doses can be explained as follows: Increase doses in logarithmic scale followed by increased pharmacological responses.[23] Linear relationships also occur between drug doses and active concentrations of drugs in serum.[24]

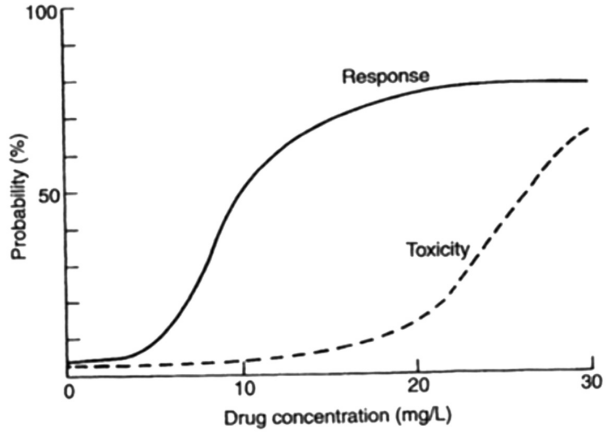


**Figure 2.** The relationship between drug concentration in serum and probability response or toxicity.[23,24]

Pharmacological activity of natural medicinal ingredients (herbal medicines), just like synthetic drugs, is determined by the presence of such drug bonds with receptors. The magnitude of the pharmacological intensity depends on the concentration/number of drugs reaching the receptor and the type of drug-receptor bond, which can be both specific and non-specific. The duration of pharmacological effects depends on the length of the drug remains in the receptor. For natural remedies with large clearances, duration time in the body is shorter than that of natural remedies that have small clearances. It is used as one of the basic doses of natural medicine. The relationship between hypothetical drug concentrations in serum with probability of response and toxicity.[23]

For the 3rd dose of ETL, there was no difference in LDL-C reduction with the 2nd dose of ETL. This may

be due to an interaction of a chemical compound in the form of an antagonist mechanism, in which one compounds neutralize the other compound by producing the opposite effect on the same physiological conditions.[25]

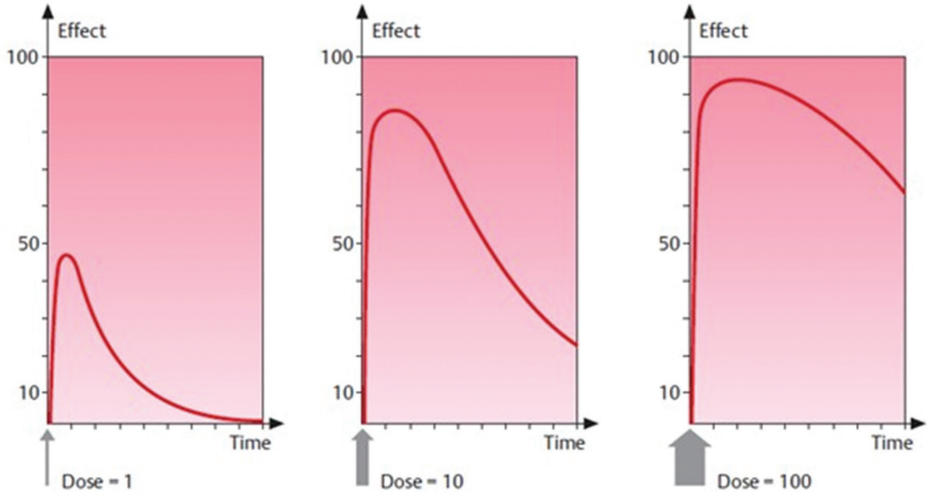


**Figure 3.** The relationship of dose to effect.[25]

### *Antioxidant activity*

Flavonoid, polyphenol, and tannin contained in ETL plays a role as antioxidant. These agents work by increasing antioxidant enzymes activity such as glutathione peroxidase (GPx), catalase (CAT), and SOD making lipid difficult to oxidize and prevent the formation atherogenic plaque.[28] MDA level will decrease and SOD level will increase because of this mechansim. These facts were supported by RuiLi Yang, M.S et al whom mentions that atherosclerosis decrease by antioxidant correlates with the decrease MDA level in blood.[29]

This study also found that ezetimibe can decrease oxidative stress as seen on the significant decrease of MDA level before and after intervention. In contrast, Pandaya et al said that Ezetimibe does not significantly decrease the MDA level but increases SOD significantly. [30]

## Conclusion

All ETL dose variants have hypolipidemic effect and antioxidant activity which play role against hypercholesterolemic condition. ETL also have the same effect with Ezetimibe. Saponin, flavonoid and tannin are the contents suspected to have pharmacological effect in improving lipid profile. Ezetimibe may play a role as antioxidant.

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## Abbreviations

ANOVA: analysis of variance
CAT: catalase
CHD: coronary heart disease
ETL: tamarind leaves/*ekstrak daun asam jawa (EDAJ)*
GPx: glutathione peroxidase
HDL-C: high-density lipoprotein cholesterol
LDL-C: low-density lipoprotein cholesterol
MDA: malondialdehyde/*malondialdehida*
SOD: superoxide dismutase
TBARS: thiobarbituric acid-reacting substances
TC: total cholesterol/*total kolesterol*
TG: triglyceride/*trigliserida*

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## Ethical Clearance

All experimental procedures were approved by Health Research Committee Universitas Pembangunan Nasional "Veteran" Jakarta, Ethical Clearance No. B/001/XI/2014/KEPK.

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The authors indicate no conflict of interest.

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