

Efficacy of *Garcinia mangostana* L. (mangosteen rind extract) to reduce acne severity

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Abstrak

Latar belakang: Penelitian *in vitro* ekstrak kulit buah manggis (*Garcinia mangostana* L.) (EKBM) yang mengandung xanthone terbukti bersifat antibakteri terhadap kuman penyebab jerawat *Propionibacterium acnes* dan mempunyai efek anti-inflamasi. Tujuan penelitian ini adalah menilai secara klinis efektifitas EKBM untuk mengobati jerawat (akne vulgaris).

Metode: Uji klinis dilakukan secara acak, berpembanding plasebo, tersamar ganda pada 94 subjek berjerawat ringan dan sedang, berumur 18-30 tahun. Kelompok perlakuan diberi 400 mg EKBM 3 kali sehari per oral selama 3 minggu, dan kelompok kontrol diberi plasebo. Semua subjek diberi terapi standar berupa krim topikal asam retinoat 0,025% dioleskan pada lesi jerawat pada malam hari. Parameter penelitian adalah pengurangan jumlah lesi (*t-test*), proporsi subjek yang mengalami pengurangan jumlah lesi $\geq 20\%$ dan penurunan kadar malondialdehid (MDA) dalam darah (*t-test*).

Hasil: Sesudah perlakuan, terjadi pengurangan secara bermakna jumlah lesi jerawat pada kedua kelompok. Sebanyak 37% pada kelompok perlakuan (934 menjadi 584 lesi, $p < 0,001$) dan 27% pada kelompok kontrol (832 menjadi 608 lesi, $p < 0,001$). Perbandingan antara kedua kelompok tidak signifikan ($p > 0,55$). Proporsi subjek dengan pengurangan lesi $\geq 20\%$ lebih besar pada kelompok perlakuan [33 dari 45 orang (73%)] dibandingkan kelompok kontrol [27 dari 41 orang (66%)] pada kelompok kontrol ($p > 0,2$). Kadar MDA menurun lebih besar pada kelompok kontrol (1,32 menjadi 1,02 nmol/mL) dibanding kelompok perlakuan (1,16 menjadi 1,02 nmol/mL), namun secara statistik tidak bermakna.

Kesimpulan: Pemberian per oral kapsul EKBM selama 3 minggu meredakan jerawat lebih besar dibanding plasebo, tetapi secara statistik tidak bermakna. Efek antioksidan EKBM nampaknya tidak berperan spesifik untuk mengurangi lesi jerawat. (*Med J Indones.* 2013;22:167-72. doi: 10.13181/mji.v22i3.586)

Abstract

Background: *In vitro* studies showed that extract of mangosteen rind (EMR) (*Garcinia mangostana* L.) containing xanthones has antibacterial effect against *Propionibacterium acnes* and also anti-inflammatory effect. The aim of this study is to determine the efficacy of EMR in reducing acne vulgaris (AV).

Methods: A randomized, double-blind, placebo controlled clinical trial was done on 94 subjects (18-30 years) with mild and moderate AV. The treatment group was given 400 mg EMR 3 times daily orally, for 3 weeks and control group was given placebo capsules. As a standard therapy, all subjects were given a topical cream of 0.025% retinoic acid applied on acne lesions during night time. Efficacy was assessed by counting the acne lesion number as well as proportion of subjects with more than 20% decrease in lesion. The decrease of plasma malondialdehyde (MDA) levels were also measured.

Results: After 3 weeks of treatment, acne lesion counts was significantly reduced in both groups [from 934 to 584 lesion (37%) in treatment group, $p < 0.001$ and from 832 to 608 lesion (27%) in control group, $p < 0.001$]. Comparison between the two groups revealed a non significant difference ($p > 0.55$). The proportion of subjects whose acne lesion reduced $\geq 20\%$ was 73% (33 of 45 subjects) in treatment group vs 66% (27 of 41 subjects) in control ($p > 0.2$). The level MDA was reduced from 1.16 to 1.02 nmol/mL in treatment group and from 1.32 become 1.02 nmol/mL in control ($p > 0.48$).

Conclusion: Extract of mangosteen rind given orally for 3 weeks clinically reduced acne severity better than placebo, although statistically was not significant. Antioxidant effect of EMR seem to be unspecific in reducing acne severity. (*Med J Indones.* 2013;22:167-72. doi: 10.13181/mji.v22i3.586)

Keywords: *Acne vulgaris*, malondialdehyde, mangosteen rind extract, retinoid acid

Acne vulgaris (AV) is a dermatologic major problem especially in adolescence, since this disease is mainly manifest on the face and concerns with esthetical appearance. AV may manifest as transient dermatologic lesion which elapse within several days, but in some patients it becomes chronic. The average prevalence of AV is 75-85% in adults.¹ At the age of 20 to 30 years, the prevalence of AV in women is 50.9% and 42.5% in men,² and then decreases with age.³ Etiopathology of AV is multifactorial. Infection

of *Propionibacterium acnes* is considered as the main etiology of AV, but the roles of oxidative stress and hormonal influences seem to be important.

AV is characterized by excessive sebum production,⁴ follicular hyperkeratinisation, and increased release of inflammatory chemical substances. Oxidative stress presumably plays an important role in the pathogenesis of AV, because oxidative stress alters the condition of the pilosebaceous unit which originally

is not suitable for the growth of anaerobic bacteria, especially *Propionibacterium acnes*.⁵ Exposure of pilosebaceous keratinocyte cells to surface protein of *Propionibacterium acnes* induces formation of free radicals superoxide O₂ leading to lipid peroxidation of sebum. Neutrophils kill propionibacterium by producing hydrogen peroxide (H₂O₂) resulted in inflammation and further tissue damage.⁶

Polyunsaturated fatty acid, the component of membrane cells damaged by oxidative stress, will form malondialdehyde (MDA) which has been recognized as an important lipid peroxidation indicator.⁷ This can be used as a marker for diagnosis and follow up the progress of AV. The level of MDA in AV patient has been shown higher than healthy person.⁸ Endogenous and exogenous antioxidants may play a role in scavenging free radicals influencing the severity of AV. Extensive laboratory research has suggested a strong link between the mechanisms by which oxidative stress leads to chronic inflammation, which in turn may mediate a wide array of chronic diseases including acne vulgaris.⁹

Garcinia mangostana L (mangosteen) is a natural raw materials of exogenous sources of antioxidants has been investigated *in vitro*. Amongst colorful fruits rich in anthocyanins (phenolic compounds), mangosteen rind is known to contain the family of bioactive xanthenes that can inhibit the activities of unpaired electrons in free radicals by donating H (hydrogen) atoms.¹⁰ *In vitro* study showed that xanthone compounds, α -mangostin, promote strong antimicrobial activity against *Propionibacterium acnes*¹¹ and other study showed its anti-inflammatory effect.¹²

This study was aimed to evaluate the efficacy of mangosteen rind extract given orally in term of clinical effectiveness as well as its influence on oxidative stress parameter.

METHODS

Subjects

This was a randomized, phase-3, placebo controlled clinical trial on subjects with mild to moderate acne vulgaris, conducted between July-September 2012. Subjects were students of Nurse Academy in Jakarta (18-30 years old), living in the dorm and suffering from mild to moderate AV, not pregnant and no allergic history to the extract. Written informed consent was obtained from each volunteer participating in this study. All procedures of the protocol have been approved by Health Research

Ethics Committee, Faculty of Medicine, Universitas Indonesia (Approval letter no. 329/PT02.FK/ETIK/2012 on May 28, 2012).

The sample size was calculated based on the formula of two independent proportion, and 42 subjects in each group was needed. With additional anticipated 10% drop out, 94 subjects were finally recruited.

Study drug

The subjects were randomly allocated to receive either extract of mangosteen rind (EMR) containing 400 mg extracts of mangosteen rind or placebo capsules with the same appearance. EMR capsules are produced by PT Sido Muncul and marketed under BPOM (Indonesian National Agency on Food and Drug Administration and Control) registration number of TR. 112 325 671.

The capsules were given three times daily for 3 weeks. Numbers of AV lesions is calculated at the beginning and at the end of the study and classified as inflamed (papules, pustules) and non-inflamed lesion (comedos). Photography in the face, upper chest and back were obtained by permission from the subjects.

Standard therapy

As an ethical reason, topical cream containing retinoic acid 0.025% have been given to all subjects (in control and treatment group) to be applied on AV lesions in the face only, during night time. Before (in the evening before sleep) and after (in the morning) applying topical cream, all subject should wash his/her face with soft soap which was also provided.

Blood specimens

For evaluating the levels of MDA we randomized 20 subjects in each group, calculated based on previous study by Surlinia.⁸ After randomization of the subjects, 2 subjects in control group were dropped out, hence there were 18 subjects in control group and 20 subjects in treatment group whose blood specimen were taken.

Blood specimen was taken from fore arm vein and kept with heparin anti-coagulant in refrigerator at -20°C until analysis. Level of plasma MDA was measured by TBARS assay.¹³ The analysis is done at the laboratory of Department of Biochemistry and Oxidative Stress Centre, Faculty of Medicine, Universitas Indonesia.

Study parameters and data analysis

Acne severity

Number of AV lesions in photos of the face, upper chest and back were calculated, classified as inflamed (papules & pustules) and non-inflamed (comedos) lesions. To evaluate the efficacy of the treatment, we define the success as 20% reduction in numbers of AV lesion. The changes in acne severity (mild, moderate or severe AV) were assessed according to Lehman's criteria with a scoring system to measure the severity of AV¹⁴ in accordance with photographic technique scores.¹⁵

The change of numbers of AV lesions before and after treatment within the same group was analyzed by paired t-test and the comparison between group at the end of study was performed with unpaired t-test. In accordance with predilection of acne, the number of lesions was divided into 3 different areas that are face, upper chest and back. The proportions of subjects, who met the success rate definition in each group, were analyzed by chi-square test.

Plasma MDA level

The results of MDA level in each group, before and after treatment, were analyzed by paired-t-test. The results of MDA level, after treatment, were analyzed by unpaired-t-test. A p-value of < 0.05 was taken as the limit of statistical significance.

RESULTS

Demography of the subjects

The demographic characteristics of the subjects are shown in Table 1. It is seen that subjects' characteristics are equally distributed in both groups.

AV severity assessed by number of acne lesions

The numbers of AV lesions before and after treatment are showed in Table 2. Overall, reduction of total lesion was higher in treated compared to control group, 37 vs 27% ($p < 0.05$). The reduction of non-inflamed lesions (comedos) was higher (63%) than inflamed (papules + pustules) lesions (35%) after three weeks treatment with mangosteen extracts ($p < 0.05$). Whereas in control group, the reduction of numbers of lesions was higher in inflamed lesions (32%) than non-inflamed (23%).

AV severity remission

The proportion of subjects who met the criteria of success tend to be higher in treatment group compared to control group. This occurred for total lesion, as well as separately on the face, back, and neck. The difference was more discrete in non-inflamed lesions (comedo). However, statistical analysis did not show any significant difference (Figure 1).

Level of MDA

The change of plasma MDA level, before and after treatment was shown in Figure 2. After 3 weeks of

Table 1. Demographic characteristic of the subjects

Parameter	Control group (n = 41)	Treatment group (n = 45)
Male	5 (12.2%)	6 (13.3%)
Female	36 (87.8%)	39 (86.7%)
Age (year)*	22.19 ± 5.046	22.74 ± 5.322
Height (cm)*	155.64 ± 5.929	156.74 ± 6.989
Weight (kg)*	56.15 ± 11.288	56.71 ± 11.366

*Results were given in means ± SD

Table 2. Number and type of acne lesions in treatment and control groups, before and after treatment

Group	Type of lesions	Before (B)	After (A)	Difference (B - A)
Treatment (n = 45)	Non-inflamed	629	386	243 (63%)
	Inflamed	305	198	107 (35%)
	Total lesions	934	584	350 (37%)
Control (n = 41)	Non-inflamed	492	378	114 (23%)
	Inflamed	340	230	110 (32%)
	Total lesions	832	608	224 (27%)

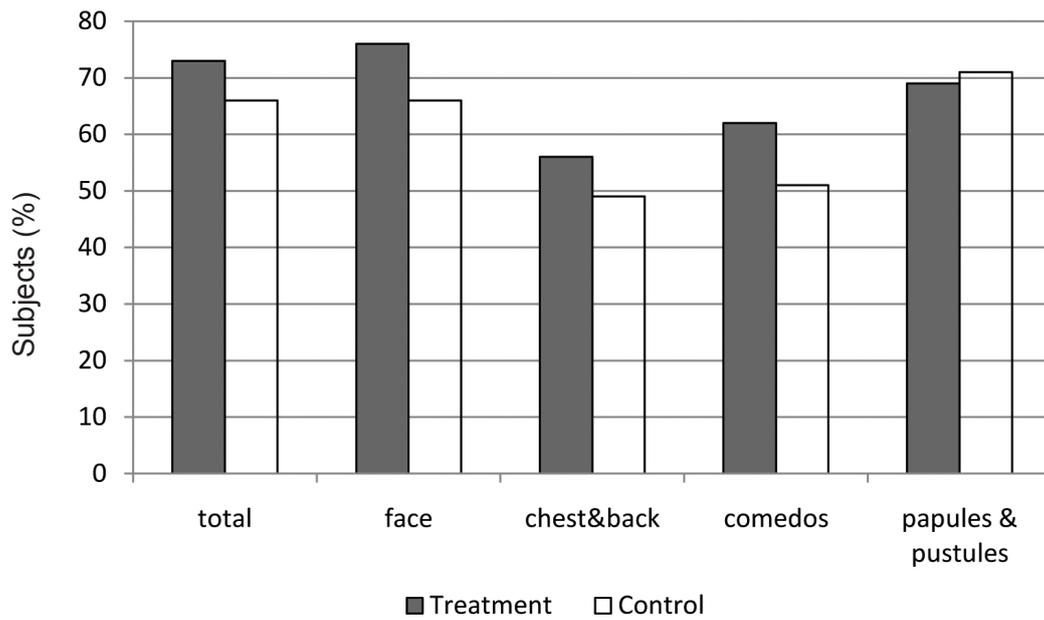


Figure 1. Proportion of subjects with number of acne lesion decreased more than 20% after treatment

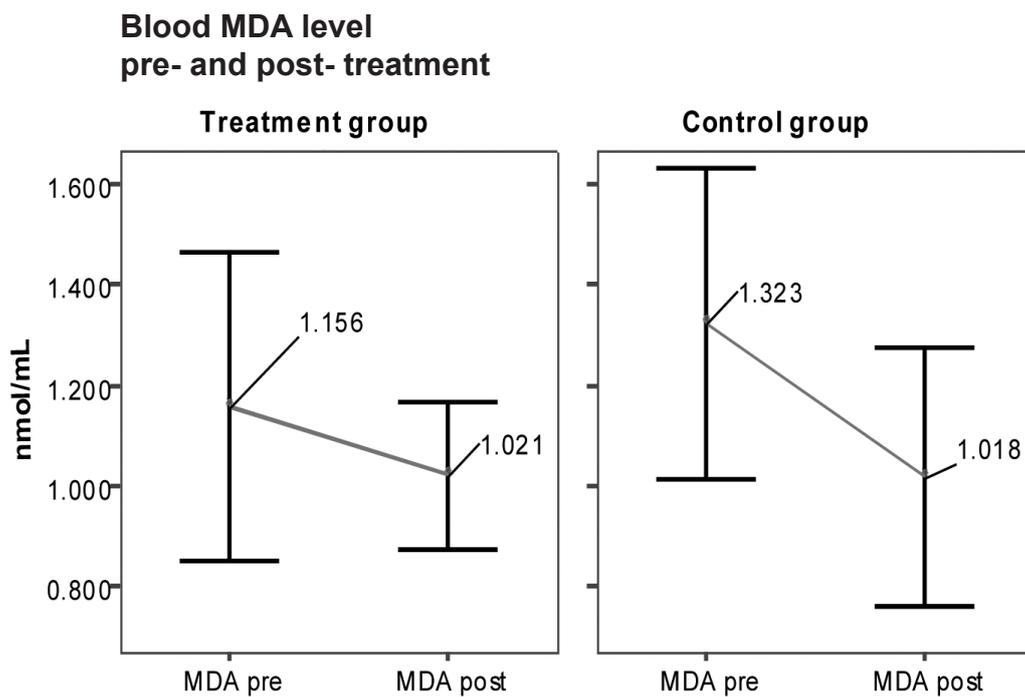


Figure 2. Means of MDA level (nmol/mL) in control & treatment groups, pre- and post-treatment

treatment, means of MDA level decreased in both groups, however, the difference were not statistically significant.

DISCUSSION

The results of this study showed that the extract of mangosteen rind was effective in reducing number

of acne lesions. These results are consistent with *in vitro* study by Chomnawang, et al^{11,12} demonstrating that EMR has anti-bacterial properties against *Propionibacterium acnes* and anti-inflammatory activity.^{11,12} Based on the success rate criteria (reduction of number of acne lesion $\geq 20\%$), the benefit of EMR on non-inflamed lesions (comedos) was higher (63%) than inflamed lesions (papules &

pustules) (35%), although statistically the difference was not significant. In contrast, the response of inflamed-lesion (papules and pustules) was equal between groups receiving EMR and control group.

It seems that antioxidant activities of EMR does not cause anti-inflammatory effect on acne, which is contradictive to the finding from an *in vitro* study.¹² The reasons behind this phenomenon might be related to the fact that all patient also received topical retinoic acid on the face. As already known, retinoic acid has become a standard treatment for acne and has a stronger anti-inflammatory effect. This might mask anti-inflammatory effect of EMR, thus rendering a more inferior effect on the area of chest and back. Pharmacokinetic factors of EMR should also be considered as the determinant of the efficacy of EMR, e.g. dosages, duration, and route of administration.

Capsule containing EMR was given orally and the possibility of enzymatic degradation in alimentary tract and hepatic metabolism could not be excluded. Bioactive xanthone will theoretically circulate systemically throughout the body, but we do not have enough data concerning the fate of this substance in the body.

Other possible explanation, might be due to the short duration of treatment. Three weeks application might be too short for natural source of antioxidant to come out with significant results, compared to synthetic (chemical) antioxidant. The remission of a chronic skin disease such as acne will need, about 1½ up to 2 months. Multifactorial etiology of AV certainly affect the healing process.

A study by Surlinia⁸ showed that the level of MDA in the blood of patients with moderate to severe acne vulgaris was significantly higher than that in healthy persons.

Our study recruited participants with mild to moderate AV. The results showed that level of MDA was decreased in both groups, the decrease being slightly but not significantly higher than that in control group. Although the MDA level was approaching the condition of healthy person, but still higher than that in healthy persons, since at the end of the study the subjects were still suffering from AV. Further study is needed to confirm whether the extension of study periode to 6-8 weeks or the increase of the dosage of EMR would normalize the MDA levels.

During this study, no adverse events were found. The dose of EMR used for human in this study was based

on bioavailability and toxicity studies in rats. Although liver and kidney function were not explored to confirm any organ damage related to EMR administration, there were no subjects reported any sign and symptom of organ dysfunction during 3 weeks of study and one month afterward.

EMR capsules have been marketed for years and so far we do not find any reports from Indonesian National Agency of Drug and Food Control regarding to its side effects.

From the present study, it is concluded that oral administration of extract of mangosteen rind decreases acne severity in patients with mild and moderate acne vulgaris better than placebo. Antioxidant effect of EMR seem to be unspecific in reducing acne severity which might be related to masking effect of topical retinoic acid.

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REFERENCES

1. Collier CN, Harper JC, Cafardi JA, et al. Prevalence of acne in adults 20 years and older. *J Am Acad Dermatol*. 2008;58(1):56-9.
2. Shen Y, Wang T, Zhou C et al. Prevalence of acne vulgaris in chinese adolescents and adults. A community-based study of 17,345 subjects in six cities. *Acta Derm Venereol*. 2012;92(1):40-4.
3. Perkins AC, Maglione J, Hillebrand GG, Miyamoto K, Kimball AB. Acne vulgaris in women: prevalence across the life span. *J Womens Health*. 2002;21(2):223-30.
4. Pappas A, Johnsen S, Liu JC, Eisinger M. Sebum analysis of individuals with and without acne. *Dermato-Endocrinology*. 2009;1(3):157-61.
5. Sarici G, Cinar S, Armutcu F, Altnayaza C, Koca R, Tekin NS. Oxidative stress in acne vulgaris. *J Euro Acad Dermatol Venereol*. 2010;24(7):763-7.
6. Bowe WP, Logan AC. Clinical implications of lipid peroxidation in acne vulgaris: old wine in new bottles. *Lipids Health Dis*. 2010;9:141.
7. Grotto D, Maria LS, Valentini J, et al. Importance of the lipid peroxidation biomarkers and methodological aspects for malondialdehyde quantification. *Quimica Nova*. (Sociedade Brasileira de Quimica). 2009;32(1):169-74.
8. Surlinia N. Perbandingan nilai aktivitas glutation peroksidase eritrosit dan kadar malondialdehid darah pasien akne inflammasi dengan individu sehat [Thesis]. Mount Pleasant (MI): Universitas Indonesia; 2002. Indonesian.
9. Pinto, Sausa ME, Nascimento MSJ. Xanthone derivatives: new insight in biological activities. *Curr Med Chem*. 2005;12(21):2517-38.

10. Fang YZ, Yang S, Wu GY. Free radicals, antioxidants, and nutrition. *Nutrition*. 2002;18(10):872-9.
11. Chomnawang MT, Surassmo S, Nukoolkarn VS, Gritsanapan W. Antimicrobial effect of Thai medicinal plants against acne-inducing bacteria. *J Ethnopharmacol*. 2005;101(1-3):330-3.
12. Chomnawang MT, Surassmo S, Nukoolkarn VS, Gritsanapan W. Effect of *Garcinia mangostana* on inflammation caused by *Propionibacterium acnes*. *Fitoterapia*. 2007;78(6):401-8.
13. Tug T, Karatas F, Terzi SM, Ozdemir N. Comparison of serum Malondialdehyde levels determined by two different methods in patients with COPD: HPLC or TBARS Methods. *Labmedicine*. 2005;36(1):41-4.
14. Adityan B, Kumari R, Thappa DM. Scoring system in acne vulgaris. *Indian J Dermatol Venereol Leprol*. 2009;75(3):323-6.
15. Hayashi N, Akamatsu H, Kawashima M; Acne Study Group. Establishment of grading criteria for acne severity. *J Dermatol*. 2008;35(5):255-60.