Mangosteen Peel Extract (*Garcinia mangostana* L.) and its Constituents to Lower Lipid Content on Adipogenesis Cells Model (3T3-L1)

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**Abstract**

Obesity is one of the risk factor for dyslipidemia incident, cancer, diabetes mellitus, and cardiovascular disease. Treatment of obesity using common commercial drugs shows low rate of success, hence natural products may provide better or more efficient therapeutic approach. Mangosteen (*Garcinia mangostana* L.) (Clusiaceae) peel extract contains xanthones and it is potentially used as alternative medicine for obesity. This research was done to determine the anti-obesity characteristics of Mangosteen Peel Extract (MPE) and its xanthones α-Mangostin (AM) and γ-Mangostin (GM) on 3T3L1 cell line. Anti-obesity effects of MPE and xanthones were investigated using differentiated-3T3L1 preadipocyte cells. Inhibitory activity of the extract and compounds on the production of Triglyceride (TG), Cholesterol (CHOL), Glucose-6-Phosphate Dehydrogenase (G6PDH) activity, and lipid droplets were examined. MPE and its compound were capable to inhibit the production of TG, CHOL, G6PDH, lipid droplets. MPE 50 μg/mL and GM 75 μM were the most active to lower TG 57.95% and 59.72%, CHOL 33.33% and 31.68%, G6PDH 52.90%, 41.95%, lipid droplets 72.99% and 70.07% respectively. In conclusion mangosteen peel extract and γ-Mangostin are the most active antiobesity compared to α-Mangostin.

**Keywords:** Glucose-6-Phosphate Dehydrogenase, Mangosteen, Obesity, Xanthones, 3T3-L1 Cells

1. **Introduction**

Obesity is a complex disorder that has effects on the normal functions of the body. Obesity is a worldwide threat for public health, as it is involved in various diseases, such as hypertension, coronary heart disease, osteoarthritis, cancer, type 2 diabetes, and many more¹. In the first half of 21st century, obesity became one of a great challenge in public health². Many studies to prevent and treat obesity have been conducted³. There are many strategies known for effective obesity therapy, some of them are inhibiton of adipocyte differentiation, stimulation of energy expenditure, suppression of food intake, regulation on lipid metabolism, and lipase inhibition⁴.

Plants and their active chemical constituents are known to posses activity that can be used in the treatment of obesity. This approach is considered effective as herbal medicine has less toxicity and side effect compared to synthetic drugs⁵–⁹. Mangosteen (*Garcinia mangostana* L.) of the family clusiaceae is a tropical tree and mostly found in India, Malaysia, Myanmar, Philippines, Thailand, and other tropical countries. The fruit hull has been used for treatment of many medical conditions and diseases such as skin infection,
wounds, and amoebic dysentery in Southeast Asia for hundreds of years. The bioactive metabolites that are mostly found in G. mangostana are xanthone derivatives including γ-Mangostin, α-Mangostin, Garcinone-D (Gar-D), Garcinone-C (Gar-C), 8-deoxygartanin, cudraxanthone G, garcimangosone B, gartanin, 1-isomangostin, garcinone E, smearthxanthone A, tovophyllin A, and mangostinone. Xanthones have been reported for their numerous and varied pharmacological effects, such as antioxidant, antibacterial, antifungal, anti-inflammatory, antihistamine, cytotoxic, Central Nervous System (CNS) depressant or stimulant, anti-HIV, anticancer, antihypertensive, antidiabetic, hepatoprotective, immunomodulation properties, antioxidant, antimicrobial and other activities. The dominant xanthone found from the G. mangostana fruit hull is α-Mangostin, which has been demonstrated by previous pharmacological studies to possess antibacterial, antioxidant, anti-inflammatory, renoprotective and antitumor activities. Therefore, this study was aimed to evaluate the inhibitory potential of Mangosteen Peel Extract (MPE), α-Mangostin (AM), γ-Mangostin (GM) in adipogenesis cells model (3T3-L1) by analyzing the level of Cholesterol (CHOL), Tryglyceride (TG), lipid, and Glucose-6-Phosphate Dehydrogenase (G6PDH) which plays a major role in lipid metabolism.

2. Materials and Methods

2.1 Mangosteen Peel Extraction

The mangosteen (G. mangostana L.) fruit were obtained from farms in Cisalak-Subang, West Java, Indonesia. The plant was identified by a herbarium staff from Department of Biology in School of Life Science and Technology, Bandung Institute of Technology, Bandung, Indonesia. The peel was collected from mangosteen fruit, then dried and then extracted by maceration with distilled ethanol (70%). The filtrate was collected after 24 hours this procedure was repeated until the filtrate was colorless. The filtrate was then evaporated with a rotatory evaporator at 40°C to yield Mangosteen Peel Extract (MPE). It was stored in -20°C until further used.

2.2 Cell Cultures and Adipogenesis Induction

The 3T3-L1 cells (ATCC®CL173) were obtained from Aretha Medika Utama, Bimolecular and Biomedical Research Center, Bandung, Indonesia. The cells were grown and then maintained in Dulbecco’s Modified Eagle Medium (DMEM) (Gibco, 11995065) which was supplemented with 10% of Fetal Bovine Serum (FBS) (Gibco, 26140079) and 1% Antibiotic/Antimycotic (ABAM) (Gibco, 15240-062) then incubated for 24 hours at 37°C and 5% CO2. After cells confluence reached 60-70%, cells differentiation was induced using Millipore ECM 950 kit. The medium was replaced by initiation medium (DMEM containing Fetal Calf Serum (FCS) 10%, IBMX (1:1000), dexamethasone (1:10000), 1% ABAM), and then incubated for 48 hours. The initiation medium was then replaced with progression medium (DMEM supplemented with FBS 10% and insulin (1:1000), 1% ABAM and again incubated for 48 hours. The medium used was replaced again with the maintenance medium DMEM supplemented with 10% FCS (Biowest, S0400-500) and then incubated for 4-5 days in 37°C incubator. On the fifth day after differentiation induction, medium was refreshed with DMEM containing 10% FBS and 1% ABAM.

2.3 Measurement of Lipid Accumulation

Measurement of lipid accumulation was done with Adipogenesis Assay Kit (Merck, ECM950). Differentiated cells were treated with MPE (25 and 50 μg/ml), AM (25 and 50 μM), and GM (50 and 75 μM), and incubated for as long as 24 hours. The medium was discarded, washed with PBS, then added with Oil-red O (Merck, 90358) 500 μl, incubated for 15-30 minutes. Oil-red O was removed, and cells were washed with Wash Solution (Merck, 90360). The cells were observed with the inverted light Olympus microscope (Olympus Inverted Microscope CKX41-F32FL). Cells were extracted with Dye Extraction (Merck, 90359) 500 μl, incubated in orbital shaker (Labnet, S0600) for 15-30 minutes. Dye extraction was transferred into 96-well plate, and absorbance was read at 490 nm (Multiskan™ GO Microplate Spectrophotometer).
2.4 Triglyceride (TG) Assay

The 3T3-L1 adipocytes were harvested 5 days after the initiation of differentiation. The cells were washed twice with cold PBS, collected, and lysed in lysis buffer (1% Triton X-100 in PBS). The total TG content in the cells was determined with a colorimetric enzymatic test using Glycerol-3-Phosphate-Oxidase (GPO) (DiaSys 1 5760 99 10 023). 500 μl mixed reaction contained 450 μl reagent with five microlitre sample (cell lysate) was incubated in 37 °C for 5 minutes. The absorbance was measured at 500 nm15,22.

2.5 Cholesterol (CHOL) Assay

The cholesterol level of lysed differentiated cells was measured with enzymatic photometric test (DiaSys 1 1300 99 10 021). Briefly, 5 μl sample (cell lysate after MPE, AM, GM treatment) was introduced into the sample well which contained 450 μl reagent, while 5 μl of ddH2O was used as blank sample, incubated at temperature 37 ºC for 10 minutes. The absorbance was measured at 500 nm15,22.

2.6 Glucose-6-Phosphate Dehydrogenase Activity Assay

The differentiated cells were added in 96 well plates (5 x 10^3 cells/well) in 100 μl medium (DMEM containing 10% FBS and 1% ABAM) for 24 hours at 37°C and 5% CO2, then assayed using G6PDH kit (Abcam, AB102529). Briefly 50 μl reaction mix were added into positive control and sample wells (MPE, AM, GM treatment), while background mix was added into background control wells. Samples were incubated at 37°C in dark room. The absorbance of samples was read at 450 nm after 30 minutes22,24.

2.7 Statistical Data Analysis

Statistical analysis of the data was evaluated using Statistical Package for the Social Sciences statistics version 17.0 software. Statistical analysis was evaluated by One-way Analysis of Variance (ANOVA). And then analysis was followed by Duncan post-hoc test and was considered to be significant (p<0.05). Data are presented as mean±Standard Deviation.

3. Results

3.1 Effect of MPE, AM, GM on Lipid Accumulation in 3T3-L1 Adipocytes

Obesity is a disorder of lipid metabolism25. To measure the lipid accumulation in obesity model in 3T3-L1, quantified by measuring the Optical Density (OD) at 490 nm26. Lipid accumulation is associated with the development and occurrence of obesity. Lipid accumulation in the adipocytes is a result of a hyperplasia and hypertrophy of adipocyte cells. Inhibition and prevention of accumulation of cytoplasmic lipid droplets and adipogenesis in 3T3-L1 cells that were treated at the differentiation and maintenance stages are shown to reduce lipid accumulation24 (Figure 1).

As shown in the Figure 1, treatment of MPE, AM, and GM reduced the lipid accumulation as indicated by lipid droplet compared to differentiated cells (0.7968). MPE of 50 μg/ml showed highest decrease among treated groups. This was also supported with the results of quantitative lipid measurement in which treatment of MPE 50 μg/ml showed the lowest lipid level (0.2153) among treatments (Table 1). Negative control (without treatment) showed no differentiation as indicated by the lipid droplet formation (Figure 1) and lowest of absorbance value (Table 1).

Table 1. Level of lipid in adipocytes (3T3-L1) treated with MPE, AMP, GMP

| Samples                        | Level of lipid     |
|--------------------------------|--------------------|
| Positive control (Differentiated) | 0.7968±0.0368e    |
| Negative control (Undifferentiated) | 0.1326±0.0182e   |
| MPE 25 μg/ml                   | 0.3172±0.0009abc  |
| MPE 50 μg/ml                   | 0.2153±0.0549ab   |
| AM 25 μM                       | 0.5704±0.09820d   |
| AM 50 μM                       | 0.4316±0.0682cd   |
| GM 50 μM                       | 0.3951±0.0770bcd  |
| GM 75 μM                       | 0.2385±0.0103abc  |

*Data are presented as Means±Standard Deviation. Different superscript letters (a,a,b,b,c,c,d,d,e) show significant difference (p<0.05) among treatments (undifferentiated, differentiated cells, MPE, AM, GM treatment) the data was analyzed with Anova and Duncan post hoc test.
3.2 Effect of MPE, AM, GM on Cholesterol Level in 3T3-L1 Adipocytes

Consumption of long-chain saturated fatty acids increases cholesterol level\(^{25}\). High level of cholesterol is associated with both degree and distribution of obesity\(^{27}\). Induced expression of Lipo-Protein Lipase (LPL) and leptin also play roles in cholesterol reduction\(^{28}\). Effect of MPE and xanthones treatment on CHOL level of adipocytes (3T3-L1) is presented in Table 2.

MPE of 50 \(\mu g/ml\) showed the highest inhibitory activity among treatments (33.33\%) with cholesterol level of 177.42 mg/dl. The inhibition activity of MPE was comparable with negative control (29.43\%). However, MPE 50 \(\mu g/ml\) and GM 75 \(\mu M\), have antiobesity potency due to higher CHOL inhibitory activity (Table 2).

Table 2. Level of cholesterol in adipocytes (3T3-L1) treated with MPE, AM, GM

| Samples                      | CHOL (mg/dl) | Inhibition of CHOL level over positive control (%) |
|-----------------------------|-------------|--------------------------------------------------|
| Positive control             | 266.12±37.95\(^{b}\) | 0.00±14.26\(^{a}\) |
| (Differentiated)            |             |                                                  |
| Negative control             | 187.80±37.38\(^{a}\) | 29.43±14.05\(^{b}\) |
| (Un-differentiated)         |             |                                                  |
| MPE 25 \(\mu g/ml\)        | 220.17±8.67\(^{ab}\) | 17.27±3.26\(^{ab}\) |
| MPE 50 \(\mu g/ml\)        | 177.42±32.75\(^{a}\) | 33.33±12.31\(^{b}\) |
| AM 25 \(\mu M\)            | 245.34±34.79\(^{ab}\) | 7.81±13.07\(^{ab}\) |
| AM 50 \(\mu M\)            | 218.57±19.95\(^{ab}\) | 17.87±7.50\(^{ab}\) |
| GM 50 \(\mu M\)            | 222.97±15.27\(^{ab}\) | 16.22±5.74\(^{ab}\) |
| GM 75 \(\mu M\)            | 181.81±9.08\(^{a}\) | 31.68±3.41\(^{b}\) |

*Data are presented as Mean±Standard Deviation. Different superscript letters (\(a,ab,b\)) show significant difference (\(p<0.05\)) among treatments (un-differentiated, differentiated cells, MPE, AM, GM treatment) in CHOL level and inhibition CHOL level over positive control show significant difference, the data was analyzed with Anova and Duncan pos hoc test.
3.3 Effect of MPE, AM, GM on Triglyceride Level in 3T3-L1 Adipocytes

Obesity is correlated with high level of TG\textsuperscript{29}. TG in adipose tissue acts as a major energy storage form. Obesity that is associated with adipocyte hypertrophy occurs when TG synthesis exceeds TG breakdown and resulting in elevated TG storage\textsuperscript{30}. It was also stated that 3T3-L1 adipocyte cells that is treated with lypolitic substance at differentiation stage\textsuperscript{24}. Effect MPE and xanthones treatment on TG level of adipocytes (3T3-L1) can be seen in Table 3.

Based on Table 3, GM 75 μM showed the lowest TG level (201.90 mg/dl) than GM 50 μM (227.55 mg/dl), MPE 50 μg/ml (210.76 mg/dl) and were also comparable with negative control (195.37 mg/dl). This data is in line with inhibitory activity of TG of GM 75 μM (59.72%), GM 50 μM (54.60 %), MPE 50 μg/ml (57.95 %). However, MPE 50 μg/ml, GM 75 μM, GM 50 μM has antiobesity potency due to higher TG inhibitory activity (Table 3).

![Table 3](image.png)

**Table 3.** Level of triglyceride in adipocytes (3T3-L1) treated with MPE, AM, GM

| Samples                  | TG (mg/dl) | Inhibition of TG level over positive control (%) |
|--------------------------|------------|-------------------------------------------------|
| Positive control (Differentiated) | 501.26±35.69\textsuperscript{c} | 0.00±7.12\textsuperscript{a} |
| Negative control (Undifferentiated) | 195.37±15.41\textsuperscript{a} | 61.02±3.07\textsuperscript{c} |
| MPE 25 μg/ml             | 286.30±10.68\textsuperscript{b} | 42.88±2.13\textsuperscript{b} |
| MPE 50 μg/ml             | 210.76±24.12\textsuperscript{a} | 57.95±4.81\textsuperscript{c} |
| AM 25 μM                 | 316.14±17.27\textsuperscript{b} | 36.93±3.44\textsuperscript{b} |
| AM 50 μM                 | 296.09±14.56\textsuperscript{b} | 40.93±2.90\textsuperscript{b} |
| GM 50 μM                 | 227.55±24.64\textsuperscript{a} | 54.60±4.92\textsuperscript{c} |
| GM 75 μM                 | 201.90±4.85\textsuperscript{a} | 59.72±0.97\textsuperscript{c} |

*Data are presented as Mean±Standard Deviation. Different superscript letters (a,b,c) show significant difference (p<0.05) among treatments (un-differentiated, differentiated cells, MPE, AM, GM treatment) in TG level and inhibition TG level over positive control show significant difference, the data was analyzed with Anova and Duncan pos hoc test.

3.4 Effect MPE, AM, GM on G6PDH Level in 3T3-L1 Adipocytes

G6PDH is responsible in adipogenesis by generating ligand Peroxisome Proliferator-Activated Receptor γ (PPARγ) activating adipocyte-specific gene expression and differentiation, as well as regulating adipose tissue mass which is associated with obesity development\textsuperscript{31}. Effect MPE and xanthones treatment on G6PDH level of adipocytes (3T3-L1) can be seen Table 4.

![Table 4](image.png)

**Table 4.** Level of G6PDH in adipocytes (3T3-L1) treated with MPE, AM, GM

| Samples                  | G6PDH level (nmol/min/ml) | Inhibition of G6PDH over positive control (%) |
|--------------------------|---------------------------|---------------------------------------------|
| Positive control (Differentiated) | 0.79±0.03\textsuperscript{f} | 0.00±4.41\textsuperscript{a} |
| Negative control (Undifferentiated) | 0.33±0.02\textsuperscript{a} | 57.84±2.00\textsuperscript{f} |
| MPE 25 μg/ml             | 0.53±0.03\textsuperscript{cde} | 32.69±3.45\textsuperscript{bcd} |
| MPE 50 μg/ml             | 0.37±0.06\textsuperscript{ab} | 52.90±8.09\textsuperscript{de} |
| AM 25 μM                 | 0.63±0.02\textsuperscript{a} | 20.28±3.10\textsuperscript{b} |
| AM 50 μM                 | 0.52±0.01\textsuperscript{cd} | 34.46±1.83\textsuperscript{cd} |
| GM 50 μM                 | 0.59±0.06\textsuperscript{de} | 25.24±7.10\textsuperscript{bc} |
| GM 75 μM                 | 0.46±0.05\textsuperscript{bc} | 41.95±5.71\textsuperscript{de} |

*Data are presented as Mean±Standard Deviation. Different superscript letters (a,ab,bc,cd,de,ef) show significant difference (p<0.05) among treatments (un-differentiated, differentiated cells, MPE, AM, GM treatment) in G6PDH level and inhibition G6PDH level over positive control show significant difference, the data was analyzed with Anova and Duncan pos hoc test.

In G6PDH level, MPE 50 μg/ml showed the lowest level (0.37 nmol/min/ml), this result was comparable with negative control (0.33 nmol/min/ml). MPE 50 μg/ml also showed the highest inhibitory activity of G6PDH among treatments (52.90%), and this data was comparable with negative control (57.84%). However, MPE of 50 μg/ml has antiobesity potency due to higher G6PDH inhibitory activity (Table 4).

4. Discussion

Obesity is a disorder which involves lipid metabolism and the enzymes that are involved in this process can be targeted to develop various antiobesity drugs. Xanthones from *G. mangostana* have antiobesity activity through anti-adipogenic, anti-inflammatory, antioxidant activities\textsuperscript{29}. α-Mangostin attenuated TNF-α and IL-8 secretion by the various cell lines activated macrophage including THP-1, hepatic HepG2, enterocyte-like Caco-2, and colon HT-29 primary human Monocyte-Derived Macrophages (MDM)\textsuperscript{32}, mangosteen peel extract and its constituents α-Mangostin, and γ-Mangostin possess...
Mangosteen peel extract and its constituents reduced the levels of lipid, cholesterol, triglyceride, and G6PDH which makes it as a promising antiobesity agent.

5. Conclusion
6. References

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