



## PHARMACOLOGICAL ACTIVITY OF GELUGUR ACID PLANT (GARCINIA ATROVIRIDIS GRIFF.): A STUDY

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### ABSTRACT

Traditional medicine is still one of the most preferred alternatives by the society as it proves to have several health benefits and can treat many diseases. One of the plants that can be used to treat disease is the *AsamGelugur* fruit (*Garciniaatroviridis*). *AsamGelugur* widely used as a flavoring dish by the Malaysians but also proved useful to lower cholesterol. This plant has many scientific benefits as anti-hyperlipidemia, anti-microbial, antioxidant, anticancer, anti-inflammatory, anti-atherosclerosis, antimalarial, antibacterial, and pre clinical trials and clinical trials. This paper aims to determine the pharmacological activity of *Garciniaatroviridis* plants based on scientific data. The method used for this research is literature study. Print scientific online data through PubMed, Science Direct and Google Scholar databases. There is 9 pharmacological activities are presented in this article. So it has the potential to be developed as a toxicity test of *Garciniaatroviridis*.

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## INTRODUCTION

Traditional medicine is still one of efficacious medicine that are proven to have some health benefits and can treat many diseases. About 80% of the population in Asia and Africa still depend on treatment with traditional medicine as a primary treatment. The driving factor that increase the use of traditional medicine is because traditional medicine has a cheap price, is easy to obtain (Muchlisah, 2001), and has less side effects than treatment with chemical drugs or through surgery (Mahendra, 2006).

Mangosteen and *asamgelugur* is a tropical fruit plant that is also used as a traditional medicine since a long time ago. Both of these trees have dark brown stem skin color and have a height of about 6-12 m. Indonesia, Malaysia, Thailand, and Filipina are countries that have cultivated this plant as consumption of functional foods. Each ripe fruit contains 6-8 seeds, and has a sweet and sour taste (Pedraza *et al*, 2008). *Garciniaatroviridis* tree can grow up to 20 m, with a soft gray rod. The leaves are dark green plants, shiny, long with pointed tips while the flowers are dark red and round. The fruit is a most used part with a

yellowish to yellowish green color and round shape (Tandon *et al*, 2007).

One of the plants that can be used to treat disease is the fruit of *asamgelugur*(*Garciniaatroviridis*). *asamgelugur* is widely used as a flavoring dish by the malaysians, but it also proved beneficial for reducing cholesterol. It is also an antioxidant and able to reduce body weight and cholesterol. *Garciniaatroviridis*Griff. et Anders proved to contain  $\gamma$ -lactone compounds, atroviridine, atrovirisdone, atrovirinone, vitamin C, pentadecanoat, octadecanoate, nonodo-canoate, dodecanoic acid, some organic acids (Mackeen *et al*, 2002).

*Asamgelugur* has antioxidant activity based on FRAP and DPPH testing (Nursakinah *et al*, 2012). *Asamgelugur*proves to contain  $\gamma$ -lactone compound, atroviridin, atrovirsidon, atrovirinon, vitamin C, pentadecanoat, octadecanoate, nonodecanoate, dodecanoic acid and some organic acids (Mackeen *et al*, 2012). Several studies have been published on the activity of hydroxysitic acid, such as weight loss (Gogoi *et al*, 2015; Chuah *et al*, 2013).

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The plant of *asamgelugur*fruit (*Garciniaatroviridis*) has many benefits that can be developed into a standardized herbal medicine. This paper aims to examine the pharmacological activities of *Garciniaatroviridis* based on scientific data collected.

## METHODOLOGY

The method used is literature study related to *AsamGelugur* it's genus. The literature study search using online-based and search on various books. The online literature sources was on Abstract, PubMed, Science Direct and Google Scholar databases using the keywords "*GarciniaAtroviridis*", " pharmacology activity". There is no language limitation and publication time for articles to be cited. Scientific articles obtained from the online database which included in the inclusion criteria are abstarct, original research and pre clinical studies. The book searches were conducted on the Indonesian Herbal Pharmacopoeia (official literature) and Plant Resources of South-East Asia (PROSEA)

### *Nutrition of Garcinia Atroviridis*

The nutrient composition of young leaves which contained in each 100 g of consumable parts are: has a energy of 73 kcal, 79.1 gr of water, 1.8 gr protein, 0.4 g fat, 15.5 gr of carbohydrate, 2,6 gr fiber, 0.6 gr ash, Ca 63 mg, P 19 mg, Fe 1.6 mg, Na 2 mg, K 83 mg, carotenes 459 mg, vitamin A 77 mg RE, vitamin B1 0,06 mg, vitamin B2 0.13 mg, niacin 0 mg, and vitamin C 37.2 mg (Tee *et al*, 1997).

### *Activity of Garcinia atroviridis Pharmacology*

#### *Antihyperlipidemia activity*

The first study consisted of a high-fat group given a high-fat diet (0.375ml chicken lard, 1.5ml quail egg and 1ml PTU) and a nonfat group given standard diet and PTU, and administered 3 groups of extract (10 mg, 20 mg , 30 mg). Then the results can be tested with the parametric test t-test to test the induction method, and one way anova to test the effectiveness of the extract. The results showed that high-fat diet for 21 days was not enough to induce an increase in triglyceride levels in the blood of rats, while consumption of 42 days was able to provide higher triglyceride levels. Can be seen for the average triglyceride levels in the 21-day group get a value of 36.4 g / dL, while in the 42-day group get a value of 125.8 g / dL. Extracts of *AsamGelugur* can give effect in reducing triglyceride levels with the most effective dose of 30 mg (Rico and Idris, 2013). Increased doses of the extract given were not proportional to the decrease of LDL in mice. Optimal doses which show the lowest LDL levels at the first dose of 10 mg (Dwi and Idris, 2013). The content of hydroxysitic acid in *AsamGelugur* able to inhibit ATP-citrate liaseand support the formation of fatty acids and cholesterol. In this study, LDL levels decreased with a dose of 10 mg as an inhibitory effect of ATP-citrate liase. The ATP-citrate liase is capable of catalyzing the extramitochondrial separation from citrate to acetyl-CoA and oxaloacetate (Downs *et al*, 2005;Hayamizu *et al*, 2003; Murray and Bender, 2009).

*G. atroviridis* extract of 1000 mg / kgBW was given orally to *polazamer 407* to induce acute hyperlipidemia in male

rats for three consecutive days. The extract reduced the low density lipoproteins (LDL) ( $3.15 \pm 0.34$  mmol / L) and very low-density lipoprotein (VLDL) ( $2.15 \pm 0.46$  mmol / L) compared with the hyperlipidemic control group for LDL dab VLDL was  $4.24 \pm 0.17$  mmol / L and  $4.91 \pm 1.17$  mmol / L. The atherogenic index (AI) extract showed a significant decrease ( $p < 0.05$ ) ( $10.22 \pm 1.87$  mmol / L) than the hyperlipidemic control group ( $20.62 \pm 2.64$  mmol / L) (Mansoub *et al*, 2014).

#### *Antimicrobials*

The antimicrobial activity of *AsamGelugur* extract at the root portion showed the strongest result for 15.6 µg / disc MIB (Minimum Inhibition Dose) / disc on *E. coli* and *P. aeruginosa* bacteria compared to the other parts. For extracts of fruits, leaves, and roots have antibacterial inhibition on the broad spectrum, both positive gram (*B.subtilis* b28 & B29, MRSA (methicillin-resistant Saureus), *s.aureus*) and negative gram (*E.coli* and *P.aeruginosa*) (Mackeen *et al*, 2000). Another plant is *Garciniacelebica L* leaf plant which made an extract to get extracts of chloroform and methanol extract. The medium used for the antimicrobial assay is Mueller Hinton Agar. Concentrations of test solutions were used for antimicrobial tests of 1000, 500, 250 and 125 µg / ml. The results obtained are chloroform extract and methanol from *Garciniacelebica L*. leaves have antimicrobial activity against *Staphylococcus aureus* bacteria, *Shigelladysenteriae* and *Candida albicans* fungi at a minimum resistance concentration of 500 µg / ml. The chemical content of this plant is terpenoids, flavonoids, and tannins (Retno and Abdul, 2010).

#### *Antioxidants*

*AsamGelugur* has antioxidant activity on the leaves and fruit. A study of antioxidant activity of leaf and fruit section using DPPH method and FRAP testing (Ferric Reducing Antioxidant Power). The results obtained, *AsamGelugur* leaf at extraction 100 ° C / 15 minutes showed a high TPC value of  $21.21 \pm 0.28$  mg GAE / mg and significantly different ( $p < 0.05$ ) than extracted at 60 ° C / 6 hours and 40 ° C / 12 hours. While on *AsamGelugur* extracted at 60 ° C / 6 hours showed the highest TPC value of  $16.23 \pm 0.18$  mg GAE / mg ( $p < 0.05$ ) compared with that extracted at 40 ° C / 12 hours and 100 ° C / 15 hours. *AsamGelugur* leaf contains much higher protein, carbohydrate and ash with each value that is 2,16% ± 0,08; 15.98% ± 0.12 and 0.72% ± 0.07 compared with fruit extract 0.46% ± 0.08, 8.64% ± 0.06 and 0.15% ± 0.06. Energy content was found to be higher in leaf extract than fruit extracts with values of  $73.64\% \pm 2.15$  and  $38.38\% \pm 1.72$  (Nursakinah *et al*, 2012).

The presence of phenolic compounds, flavanoids and tannins in methane extract *Garciniaatroviridis* that can find the relationship between chemical content with antioxidant activity. *Garciniaatroviridis* has the highest phenolic content followed by flavonoids and tannins. The antioxidant activity of dry *Garciniaatroviridis* sample performed by using 2,2-diphenyl-1-picrylhydrazyl (DPPH) test showed low antioxidant activity. Furthermore, garcinia leaves from ethyl acetate extract showed the highest antioxidant activity (59.18%) followed

by *Garcinia* leaves from methanol extract (57.97%), and then *Garcinia* leaves from hexane extract (55.67%). Total of phenolic content showed good correlation with antioxidant activity but not with total of flavonoid and tannin content (Abdullah *et al*, 2013).

A comparative study was conducted to determine the effect of extraction solvents and plant parts used in the reduction of lipid and antioxidant activity of *Garcinia atroviridis*. The water extract showed better antihyperlipidemic activity than methanol extract. Water extract *Garcinia atroviridis* fruit showed the most potent antihyperlipidemic activity, comparable to atorvastatin. Significantly reduced total cholesterol ( $P < 0.05$ ), triglycerides ( $P < 0.01$ ), low-density lipoprotein ( $P < 0.01$ ) and atherogenic index ( $P < 0.01$ ). In contrast, the antioxidant activity of methanol extract from all parts of *G. atroviridis*, where stem and leaf extracts show better antioxidant activity than fruit (Mansoub *et al*, 2014).

Water extract and methanol from *G. atroviridis* fruit showed antioxidant activity with total of phenolic content of  $32.53 \pm 0.56$  mg equivalent gastric acid (GAE) / 100 g and  $62.34 \pm 3.07$  mg GAE / 100 g. *G. atroviridis* also demonstrated the ability to reduce Fe<sup>2+</sup> + capability, for each water and methanol extracts are  $434.17 \pm 28.34$   $\mu$ M / g and  $624.17 \pm 12.58$   $\mu$ M / g by using ferrous reduction antioxidant power (FRAP) (Rabeta and Faraniza, 2013).

#### Anticancer

Compounds from the results of root isolation of *garciniaatroviridis* are benzoquinone atrovirinone and atrovirisidone, based on the analysis of spectroscopic data showed the presence of Hela cells. Metabolites isolated from *G. atroviridis* roots which is benzoquinone atrovirinone showed cytotoxic activity against cervical cell adenocarcinoma (HeLa) using an MTT test (Permana *et al*, 2001). Studies of *G. atroviridis* extracts from various parts of previous crops did not show cytotoxic activity in human lymphoblastic leukemia (CeM-SS) T-cell and shrimp toxic test. *G. atroviridis* root extract has cytotoxic properties of human B-lymphoblastoid cells (Mackeen *et al*, 2000). In another study there were 4 compounds to be tested for its cytotoxic activity such as atrovirisidone (1), atrovirisidone B (2), together with naringenin (3) and 3,8"-binaringenin (4). Atrovirisidone compounds show cytotoxic activity against human breast cells (MCF-7), prostate (DU-145) and human lung cancer cells (H-460). The result is the compounds (1) and (2) show the cytotoxic activity of all the cells tested in a row (MCF-7 =  $11.02 \pm 6.4$ , DU-145 =  $24.78 \pm 13.4$ , H-460 =  $16.11 \pm 1.2$ ) and (MCF-7 =  $22.93 \pm 6.8$ , DU-145 =  $9.34 \pm 7.4$ , H-460 =  $16.47 \pm 1.2$ ). Compound (3) showed weak activity against DU-145 cells ( $IC_{50} = 30.9 \pm 1.9$ ), whereas compound (4) showed no activity against all tested cells (Permana *et al*, 2005).

Meanwhile, leaf extracts of this species were able to inhibit leukemia promyelocytic leukemia (HL60) leukemia cell lines when tested in photodynamic therapy with a combination of MTT test (Ong *et al*, 2009). Compounds 9 and 10 are isolated from the *G. atroviridis* fruit also not cytotoxic to human T-lymphoblastic leukemia (CeM-SS) and human B-lymphoblastoid cells

and also non-toxic in a deadly test of brine shrimp (Mackeen, 2012). Fruit extracts were also tested on human skin fibroblast cells (HSF) and apparently had no cytotoxic effects (Suwanmanee *et al*, 2014).

#### Anti-inflammatory

In this study showed that atrovirinone and 1.4 benzoquinone that have been isolated from the roots of *Garciniaatroviridis*, able to inhibit some mediators of inflammation. This is indicated by atrovirinone inhibiting the synthesis of NO and PGE<sub>2</sub> by inhibition of iNOS and Expression of COX-2. *Garciniaatroviridis* also showed that atrovirinone inhibits the secretion of IL-1  $\beta$  and IL-6 in certain doses, whereas in IL-10 secretion, the anti-inflammatory dose cytokine needs to be increased. In addition, atrovirinone also prevents the phosphorylation of I- $\kappa$ B $\alpha$  which results in a decrease of p65NF- $\kappa$ B. Atrovirinone has a strong potential as an anti-inflammatory drug that targets the MAPK and NF- $\kappa$ B pathways (Israf *et al*, 2010).

Many natural compounds from plant are reported to inhibit the production of pro-inflammatory mediators such as nitric oxide, prostaglandin E<sub>2</sub>, TNF- $\alpha$  and reactive oxygen by suppressing the expression of inducible enzymes through inhibition of the path of activated mitogen kinase protein. This study was conducted to evaluate the effect of atrovirinone [2-(1-methoxycarbonyl-4,6-dihydroxyphenoxy)-3-methoxy-5,6-di-(3-methyl-2-butenyl)-1.4 benzoquinone], a benzoquinone which had previously been isolated from *Garciniaatroviridis* using an analysis of anti-inflammatory bioactive compounds which are RAW 264.7 macrophage cells and whole blood. Atrovirinone is reported to inhibit the production of nitric oxide and prostaglandin E<sub>2</sub> from induced LPS and IFN- $\gamma$  RAW 264.7 Full macrophage and blood cells, with an inhibitory concentration (IC) of 50 each of  $4.62 \pm 0.65$  and  $9.33 \pm 1.47$  mmol / L. The analysis of thromboxane B<sub>2</sub> (TXB<sub>2</sub>) secretion from all blood stimulated by either cyclooxygenase (COX) -1 or COX-2 pathway showed that atrovirinone was able to inhibit the growth of both TXB<sub>2</sub> from both paths, with value (IC) respectively  $7.41 \pm 0.92$  and  $2.10 \pm 0.48$  mmol / L. IC<sub>50</sub> analysis showed that more atrovirinone with COX-2 was more selective in TXB<sub>2</sub> inhibition with a ratio of 0.32. Atrovirinone also inhibits the formation of intracellular oxygen reactive species and TNF- $\alpha$  secretion from RAW 264.7 cells with each values of IC<sub>50</sub> which are  $5.99 \pm 0.62$  and  $11.56 \pm 0.04$  mmol / L (Syahida *et al*, 2006).

#### Anti-atherosclerosis

Another study, 24 males Dunkin Hartley rabbits divided randomly into four groups. The first group as control and fed a commercial rabbit. The second group was orally given only *G. atroviridis* (50 mg / body weight). The third group is fed one percent diet of cholesterol in the pellet in sequence to induce atherosclerosis. The fourth group was given *G. atroviridis* with cholesterol. All groups were given daily for eight weeks and then their blood was taken for analysis. Supplementation of *G. atroviridis* with cholesterol diet may decrease serum lipid profile level. Histological studies showed a decrease in fat deposition in

the aorta of high cholesterol given *G. atroviridis* compared with the high cholesterol diet group. Supplementation of *G. atroviridis* extract has a tendency to lower total cholesterol and LDL-C levels in serum, as well as lipid deposition in the high aorta. Therefore, *G. atroviridis* is useful for preventing atherosclerosis or decreasing the relative risk of atherosclerosis. (Amran *et al*, 2009)

#### Antimalarials

*AsamGelugur* (*Garciniaatroviridis* Griff T Anders) is one of the traditional medicines possessed has been recognized as an effective antimalarial drug. Thirty rats were inoculated by *Plasmodium berghei* and then randomly divided into 6 groups of 5 mice treated with dosage of *Garciniaatroviridis* leaf extracts ranging from 90 mg / kgBW, 180mg / kgBW, 360mg / kgBW, 720mg / kgBB and other control groups were administered by 0.9% NaCl solution and fanidar with a dose of 5mg / kgBW / day. Each group was kept for 4 days after the inoculation of *Plasmodium berghei*. Levels of parasitemia are checked daily by applying thin blood up to 4 days from inoculation which is then analyzed by log-probit method. This proves that with a dose of 360mg / kgBB*Garciniaatroviridis* leaf extract has a statistically significant inhibitory effect (Syamsudin and Hernita, 2004).

#### Antibacterial

Test of antibacterial activity using solid dilution method. The parameters used are Minimum Inhibitory (KHM) and Minimum Kills (KBM). The concentration series used was 0.72%; 0.56%; 0.4%; 0.24%; 0.08%; 0.064%; 0.048% and 0.032%. The extract of ethanol *Asamgelugur*fruit showed KHM to *Staphylococcus aureus* by 0,08% and *Shigelladysenteriae* 0,24%, while KBM to *Staphylococcus aureus* was 0,56% and *Shigelladysenteriae* 0,72%. Bioautographic results on *Staphylococcus aureus* showed clear zones in hRf 88 and *Shigelladysenteriae* indicating clear zones on hRf 67 and 83 (Miss and Rima, 2014). Total volatile compounds from fresh fruit *G. atroviridis* showed antibacterial activity in Gram-positive bacteria with minimum inhibitory concentration (4.8 µg / mL for *Bacillus subtilis* and 4.8 µg / mL for *Staphylococcus aureus*) compared with gentamicin sulfate as a positive control (Minimum Inhibition Concentration value of 0.4 µg / mL for *B. subtilis* and 0.1 µg / mL for *S. aureus*) using a micro solvent test (Tan *et al*, 2013).

#### Pre-clinical & Clinical data

Dilute extract of 2000 mg / kg *G. atroviridis* given orally as a single dose for female Sprague Dawley rats (aged between 8 to 12 weeks) showed no toxic effects on observed parameters including behavioral changes, weight, food. All mice were observed for 14 days and no deaths were found during the study (lethal dose (LD50)> 2000 mg / kg) (The *et al*, 2012).

Fifty obese women with a body mass index (BMI) more than 25 kg / m<sup>2</sup> were randomly divided into two groups of 25 each in each group. In Group 1, an average (± SEM) of age of 40.0 ± 2 years was obtained, which was calcium hydroxentrate (HCA) soluble in *Garciniaatroviridis* water. Group 2 with an average age of 35.6 ± 1.8 years

received a placebo. All subjects are advised to diet similar to 1000 Kcal / day. This test lasts for 2 months. Basically means IMT groups 1 and group 2 respectively are 27.5 ± 0.2 kg.m<sup>-2</sup> and 26.7 ± 0.5 kg.m<sup>-2</sup>. Group 1 lost weight significantly (2.8 vs 1.4 kg, p <0.05) compared with Group 2 during the study. Their weight loss was due to a loss of fat storage as proved by a significant decrease in triceps skin folds. In the short term, HCA in *Garciniaatroviridis* is effective for weight management (Roongpisuthipong *et al*, 2007).

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