

## ***Garcinia atroviridis* – A review on phytochemicals and pharmacological properties**

Hanisuhana HAMĪDON, Deny SUSANTĪ, Muhammad TAHER, Zainul Amiruddin ZAKARĪA

### **ABSTRACT**

*Garcinia atroviridis* or commonly named as 'Asam Gelugur' among locals is extensively used as flavouring agent to provide sour sensation. Apart from being used as flavouring agent, *G. atroviridis* is also used in many ways to promote health traditionally. Previous investigations of the plant reported many interesting potential of antioxidant, antimicrobial, antifungal, antiobesity and lipid metabolism, cytotoxicity, antiinflammatory, antimalarial and antinicotine stress activities

of *G. atroviridis*. This article discusses on *G. atroviridis* in aspect of its chemical constituents and bioactivities; *in vitro* and *in vivo* as well the clinical study made on this plant despite the limited data available. It is also an effort to update *G. atroviridis* data on its phytochemical and pharmacological data of the plant in the recent 15 years.

**Keywords:** *Garcinia atroviridis*, hydroxycitric acid, antioxidant, antimicrobial, antiinflammatory, cytotoxic, antihyperlipidaemia

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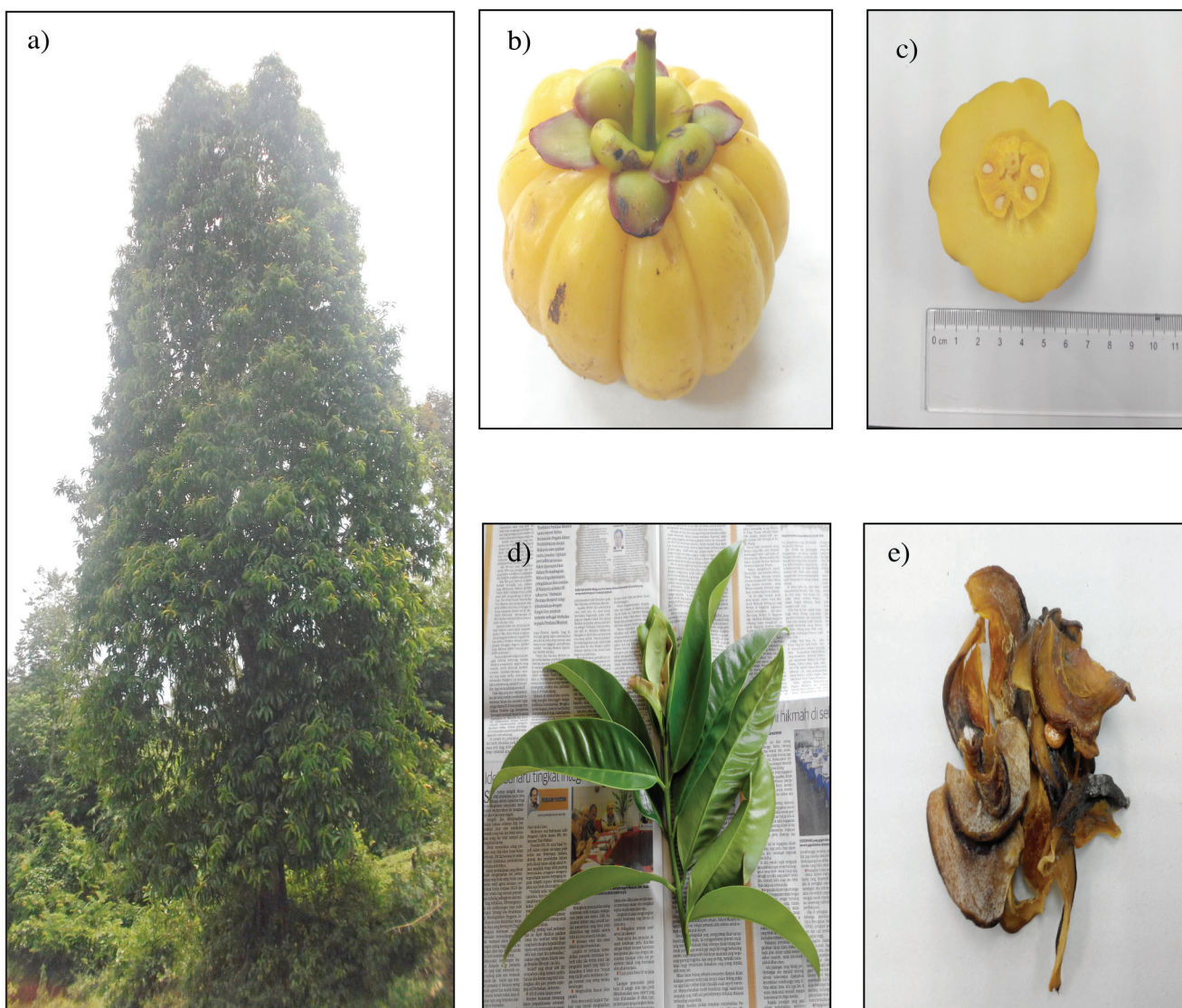
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### **INTRODUCTION**

Popular as 'Asam Gelugur' among locals, *Garcinia atroviridis* is commonly found in Peninsular Malaysia, Thailand and India (1). The tree can grow up to 20 m, with smooth grey long trunk and branches drooping. The plant leaves are dark green, shiny, long narrow with pointed tip while its flowers are dark red and round. The fruits, which are the most commonly utilised part, are large yellowish green to yellow in colour and globular in shape (2). Belongs to the family of Clusiaceae, *G. atroviridis* is commonly used as flavouring agent in cooking. The ripe fruits are sliced, dried and used to provide sour sensation in dishes to replace tamarind. Meanwhile, the young leafy shoots and leaves are consumed fresh or cooked as vegetable. In Thailand, the *G. atroviridis* is incorporated into their Tom-Yum soup mix, a famous hot and sour Thai soup. The plant parts also give some medicinal values in Asian folk medicine. It was used as pre and postpartum medication in treating stomach-ache due to pregnancy and as lotion to rub over abdomen after confinement. It also used to treat ear-ache, cough, throat irritation, dandruff, improving blood circulation and as laxative (1).



**Figure 1.** The various parts of *G. atroviridis*. (a) The tree of *G. atroviridis*. (b,c) The fruit of *G. atroviridis*. (d) The leaves of *G. atroviridis*. (e) The dried fruit of *G. atroviridis*.

## CHEMICAL COMPOSITION

The fruit part of *G. atroviridis* contains many organic acids such as citric acid [1], tartaric acid [2], malic acid [3], ascorbic acid [4], pentadecanoic acid [5], nonadecanoic acid [6] and dodecanoic acid [7] (3). Above all, the most interesting is the hydroxycitric acid [8], (-)-HCA has also been reported in the fruit and rind of *Garcinia* fruits. The (-)-HCA is the main acid in the fruits of *G. cambogia*, *G. indica*, *G. cowa* and *G. atroviridis* (4-6). The (-)-HCA originated from *G. cambogia* is commercialised as weight management product. It plays important roles in body weight and appetite; it prevents the hepatic enzyme production ATP citrate-lyase. This enzyme converts excess carbohydrates into fat. It also stimulates

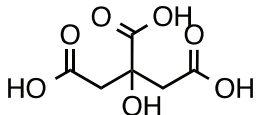
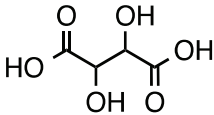
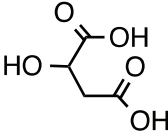
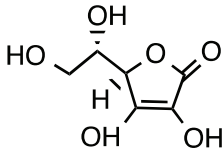



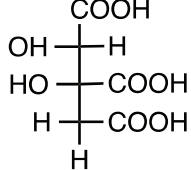
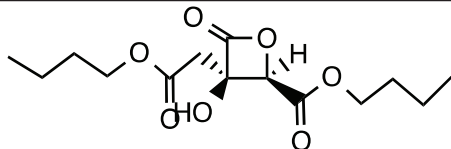
hepatic glycogen synthesis from the glucose (7). The (-)-HCA is available in calcium salt in the market. Among them are Citrimax<sup>®</sup>, HCA-500,7 GTF, Lipatrol, and Lapodex-2 that contains *G. cambogia* extract at different levels (8). Other compounds has also successfully isolated from fruit of *G. atroviridis* which were 2-(butoxycarbonylmethyl)-3-butoxycarbonyl-2-hydroxy-3-propanolide [9] and 1',1''-dibutyl methyl hydroxycitrate [10] (9).

Kosin *et al.* (10) elucidated a xanthone from stem bark of *G. atroviridis* namely atroviridin [11]. The atroviridin is a tetracyclic polyhydroxylated xanthone (11). Meanwhile Permana *et al.* (12) isolated new prenylated compounds, benzoquinone atrovirinone [12] and depsidone

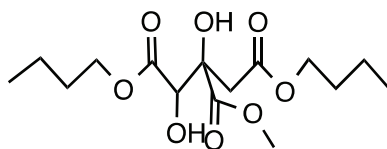
atrovirisidone [13] from *G. atroviridis* root. Another new prenylated hydroquinone, 4-methylhydroatrovirinone [14] and morelloflavone [15] and 7-O- $\beta$ -D-glucopyranoside, fukugiside, together with 14-*cis*-docosenoic acid was elucidated from root (13). Later, Permana *et al.* (14) isolated atrovirisidone B [16], together with naringenin [17] and 3,8''-binaringenin [18] from root of *G. atroviridis*. Dweck (3) also reported succinic acid [19], garcinol [20], camboginol

[21] and isogarcinol [22] present in *G. atroviridis*. Sesquiterpenoids dominated volatile constituents were also successfully obtained from *G. atroviridis* fruit which were (-)- $\beta$ -caryophyllene [23],  $\beta$ -caryophyllene alcohol [24] and  $\alpha$ -humulene [25] (15). Up to date, triflavone, garcineflavanone A [26] and a biflavonol, garcineflavonol A [27] had also been isolated from the stem bark (16).

**Table 1.** Chemical structures of compounds reported from *G. atroviridis*

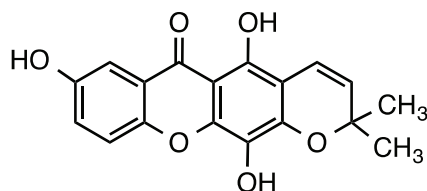
Compound Name	Structure	Compound No
Citric acid		1
Tartaric acid		2
Malic acid		3
Ascorbic acid		4
Pentadecanoic acid		5
Nonadecanoic acid		6
Dodecanoic acid		7
Hydroxycitric acid		8
2-(butoxycarbonylmethyl)-3-butoxycarbonyl-2-hydroxy-3-propanolide		9

1',1''-dibutyl methyl hydroxy-citrate



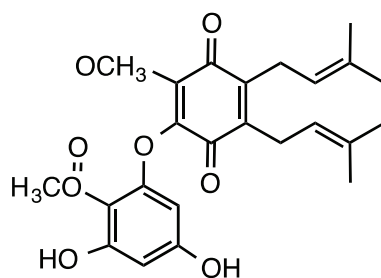
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Atroviridin



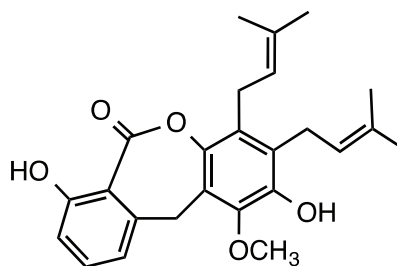
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Benzoquinone atrovirone



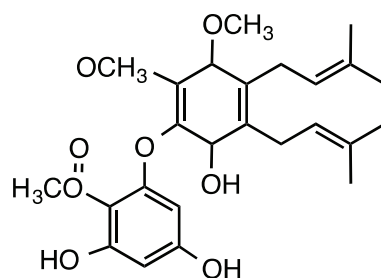
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Depsidone atroviridone



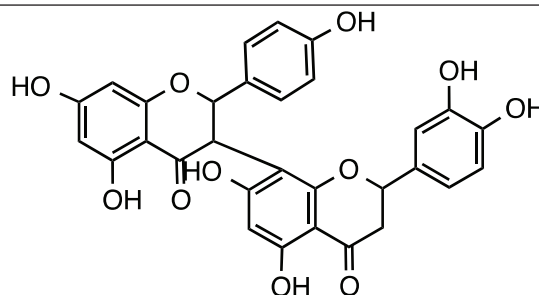
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4-methylhydroatrovirone and 14-cis-docosenoic acid



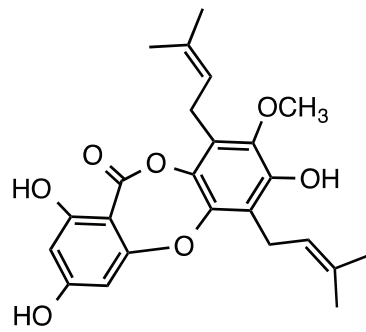
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Morelloflavone



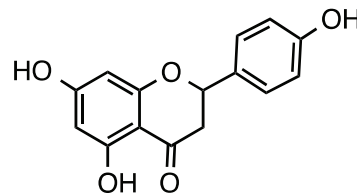
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Atrovirisdone B



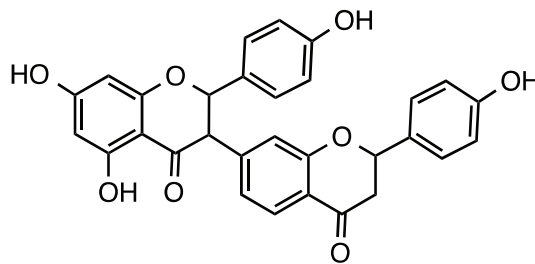
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Naringenin



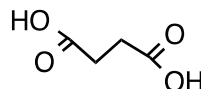
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3,8''-binaringenin



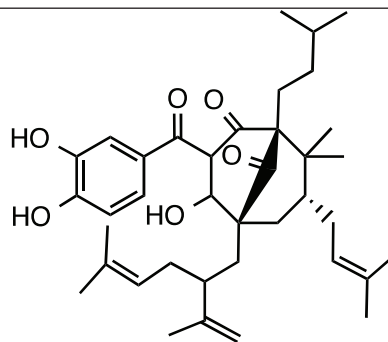
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Succinic acid



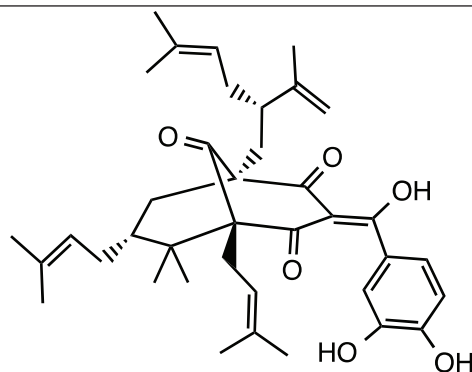
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Garcinol



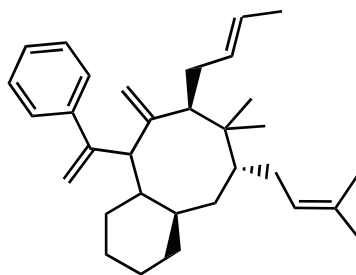
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Camboginol

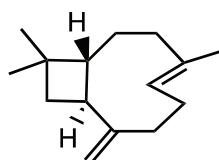


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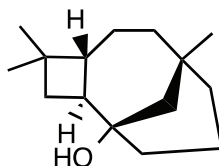
Isogarcinol



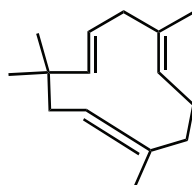
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(-)- $\beta$ -caryophyllene

23

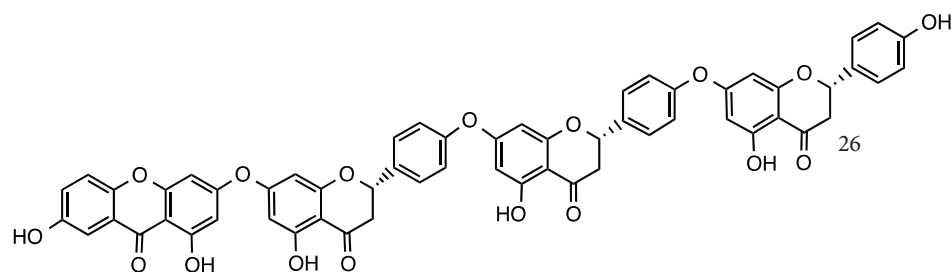
 $\beta$ -caryophyllene alcohol

24

 $\alpha$ -humulene

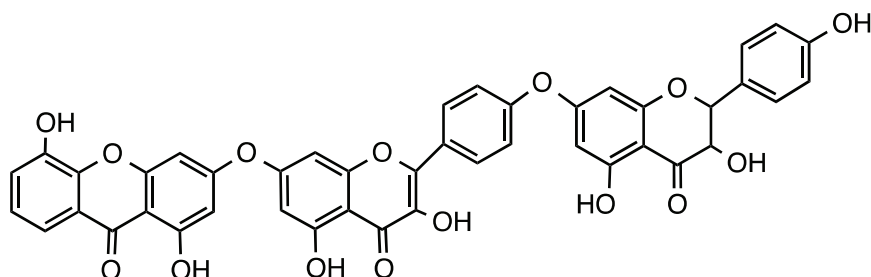
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Garcineflavanone A



26

Garcineflavonol A



27



## PRE-CLINICAL DATA

Data obtained mainly involved the *in vitro* investigation of various plant part of *G. atroviridis*. Antioxidant potential of this species was most commonly reported. Other bioactivities include antimicrobial, antifungal, antiobesity and lipid metabolism, cytotoxicity, antiinflammatory, antimalarial and antinicotine stress activities. This implies the various underexplored potential of *G. atroviridis* plant species.

### Antioxidant activity

Scientific investigations employ many types of assays to determine antioxidant capacity of *G. atroviridis* plant. This includes DPPH (1,1-diphenyl-2-picrylhydrazyl), ferric reducing anti-oxidant power (FRAP), ferric thiocyanate (FTC) and thiobarbituric acid (TBA) assay. All methods have different mechanism in assessing antioxidant capacity of plant extracts. Mackeen *et al.* (17) reported the antioxidant activity of parts of plant which were leaves, fruit, stem and trunk bark extracts. FTC and TBA methods were employed and all parts of plant except for fruit part exhibited strong antioxidant capacity with ranges of 64-90% for FTC and 87-93% for TBA method. The findings were found to be better than  $\alpha$ -tocopherol, a standard commercial antioxidant. Meanwhile, Nursakinah *et al.* (18) reported leaves and fruits extract antioxidant ability using DPPH and FRAP assays. Total phenolic content (TPC) was determined and leaves extract was found to have higher TPC than fruit extract. Antioxidant assays for leaves and fruits part were positively correlated to TPC. Report by Abdullah *et al.* (19) also in agreement with Nursakinah *et al.* (18) since TPC was found to be the highest in leaves extract. This followed by flavonoid and tannin content. The DPPH radical scavenging activity of leaves extract was in good correlation with TPC. However, Abdullah *et al.* (19) concluded that *G. atroviridis* extract have low potential as antioxidant agent since inhibition percentages was less than 60% which contradicts with previous findings. Other conclusion also include that leaves are better in antioxidant activity compared to stem part. Although such remarks made by previous author, interesting finding by Al-Mansoub *et al.* (20) stated that stem extract also have better antioxidant activity compared to leaves and fruit when extracted using methanol. Leaves part however, show better antioxidant capacity when extracted using water. Taken together, it can be concluded that the leaves and stem part of *G. atroviridis* exhibits antioxidant ability due to presence of phenolic content.

### Antimicrobial/antifungal activity

The extracts and isolated compounds originated from *G. atroviridis* were also screened for antimicrobial and antifungal activity. Root extract was found to be the most potent in antimicrobial assay against *Bacillus subtilis* B28 (mutant; Gram-positive), *B. subtilis* B29 (wild-type; Gram-positive), methicillin-resistant *Staphylococcus aureus* (Gram-positive), *Escherichia coli* (Gram-negative) that employed disc diffusion method (17). Meanwhile, only fruit extract exhibit antifungal against *Clasdosporium herbarum* in assay performed. Subsequently, the fruit extract was subjected to isolation and two compounds, compound **9** and **10** was found to be selective as antifungal against *C. herbarum* with the activity comparable to cycloheximide. However, both did not show any antibacterial activity against *B. subtilis*, methicillin-resistant *S. aureus*, *Pseudomonas aeruginosa* and *E. coli*, other fungi (*Alternaria sp.*, *Fusarium moniliforme* and *Aspergillus ochraceous*) including the yeast *Candida albicans* (9). Meanwhile, prenylated compounds isolated by Permana *et al.* (12) from roots of *G. atroviridis* which were compound **12** and **13** exhibit mild antimicrobial activity towards *B. cereus* and *S. aureus*. This was differed with previous study (17) that found that root extract was the most active against methicillin-resistant *S. aureus*. Hence it can be speculated that such findings might be due to synergistic action between compounds exist in the extract. It also may caused by difference in responsiveness towards treatment from wild type *S. aureus* and methicillin-resistant *S. aureus*. The ethyl acetate and ethanol extracts of fruit did also shows some antimicrobial properties according to investigation conducted by Basri *et al.* (21). The extracts were active towards gram-positive and gram-negative bacteria tested which were *S. aureus*, *S. epidermidis*, *B. subtilis*, *E. coli*, *Salmonella typhimurium*, *S. enteritidis* and *P. aeruginosa*. Later, the volatile constituent from the fruit showed antimicrobial activity in micro-dilution assay (15). Total volatile was active against gram-positive bacteria tested which were *B. subtilis* and *S. aureus*. Compound **24** exerts its antimicrobial towards gram-negative bacteria; *E. coli* and *S. typhimurium*. Unlike study performed by Mackeen *et al.* (9), compounds isolated from the fruit did not exert any antimicrobial effect. *In vitro* screening of fruit extract against several fungal strains proved that it showed fairly good antifungal activity towards *Candida albicans*, *Saccharomyces cerevisiae*, *Trichophyton mentagrophytes*, *Trichophyton rubrum*, *Trichophyton tonsurans*, *Epidermophyton floccosum*, *Microsporum canis*, *Microsporum gypseum*, *Aspergillus niger* and *Penicillium spp* (22). Unlike with previous finding (9),

compounds isolated from the fruit were found to be not active against tested fungi.

### Antiinflammatory activity

Compound **12** isolated from roots of *G. atroviridis* showed antiinflammatory activity in two cellular systems used in antiinflammatory analysis of bioactive compound (23). In the first cellular system which was RAW 264.7 macrophage cells, the compound inhibited nitric oxide and prostaglandin-E<sub>2</sub> production from lipopolysaccharides (LPS) and interferon- $\gamma$  (IFN- $\gamma$ ) stimulated cells. The generation of intracellular reactive oxygen species and tumour necrosis factor alpha (TNF- $\alpha$ ) from RAW 264.7 cells were also inhibited in dose-dependent manner when treated with the compound. Meanwhile in whole blood cellular system, the compound inhibits production of thromboxane-B<sub>2</sub> (TXB<sub>2</sub>) stimulated by cyclooxygenase-1 (COX-1) and COX-2 pathway but it favours COX-2 more in its inhibition. The lipoxygenase enzyme; enzyme which involved in synthesis of leukotrienes was also moderately inhibited. The authors concluded that such findings might be due to inhibition of nuclear factor-kappa B (NF- $\kappa$ B) pathway and COX/lipoxygenase enzyme activity that produced pro-inflammatory mediators. Subsequently, compound **12** demonstrated inhibitions towards IL-1 $\beta$  and IL-6 as well as enhances the secretion of IL-10 at the highest non-toxic dose used (24). The compound affects the NF- $\kappa$ B and MAPK signaling pathways which later result in reduction in pro-inflammatory mediators production. Investigation by Tan *et al.* (15) reported that volatile constituents of *G. atroviridis* fruit exhibit antiinflammatory potential through cyclooxygenase inhibitor screening assay. The constituents selectively inhibit COX-2 activity more as compared to COX-1. This trend of COX-2 inhibition was also showed by compound **12** (22) suggesting active constituents from *G. atroviridis* might be a potential antiinflammatory agent through its ability to disrupt COX-2 activity.

### Cytotoxic activity

Study on *G. atroviridis* crude extract of different parts of this plant previously did not show cytotoxic activity in human T-lymphoblastic leukaemia (CEM-SS) cell line and brine shrimp toxic assay. The root extract however cytotoxic towards human B-lymphoblastoid (Raji) cell (17). However, an active metabolites isolated, benzoquinone atrovirinone from roots exhibit cytotoxic activity towards cervix adenocarcinoma (HeLa) cell line by employing MTT assay (12). Later, the

same author and colleagues isolated compound **16**, **17** and compound **18** from roots as well (14). Compound **16** showed cytotoxic activity towards cell lines used which were human breast cancer (MCF-7), human prostate cancer (DU-145) and lung cancer (H-460). Meanwhile compound **17** only showed weak activity towards DU-145 cell line. This could imply that root part of *G. atroviridis* can be further explored for anticancer potential. Meanwhile, leaves extract of this species inhibit promyelocytic leukemia (HL60) cell line when tested in photodynamic therapy with combination of MTT assay (25). Compound **9** and **10** isolated from *G. atroviridis* fruit were also not cytotoxic against human T-lymphoblastic leukaemia (CEM-SS) and human B-lymphoblastoid (Raji) cell line as well as not toxic in brine shrimp lethality assay (26). The fruit extract was also tested on human skin fibroblast (HSF) cell and it was found not toxic towards it (22). In agreement with previous finding (17) it can be implied that fruit extract of *G. atroviridis* did not possess any cytotoxic effect.

### Antihyperlipidemic/antihypercholesteromic/antiobesity activities

Compound **8** was commonly reported to be originated from this plant genus and extensively used as weight management supplement. Various attempts have been done to investigate its effect in managing lipid metabolism *in vivo* and *in vitro*. The study (5) used potassium hydroxycitrate from fruit juice for body weight and cholesterol reduction ability in rats. The treatment was successfully reduced the LDL cholesterol level as well as body weight. In contrast, HDL cholesterol level was enhanced. Investigation by Amran *et al.* (27) used high-cholesterol diet guinea pig revealed that co-administration of methanolic fruit extract with high cholesterol diet lowered lipid profile in the serum as well as reduction in fat deposition in the aorta. The same co-administration treatment group of guinea pig did also reduce DNA damage as analysed using comet assay. As compared with high-cholesterol diet group, this group of treatment reduces the deposition of fat in the aorta and number of foam cell (28). Therefore, the results suggest the *G. atroviridis* fruit can lessen oxidative stress, which later contributes to lower possibility of developing atherosclerosis. Other study compares different plant part and extraction process in antihyperlipidemic activity in poloxamer 407-induced hyperlipid rat. It was found that aqueous extract of ripe fruit exhibit antihyperlipidaemic activity where total cholesterol and triglyceride was lowered at 34 hours (20). To sum up, the findings indicated and agreed that fruit extract of *G.*



*atroviridis* did exhibit lipid modulating properties regardless of different animal model used.

### Other bioactivities

Mackeen *et al.* (17) investigate antitumour promoting activity of various part extracts of the plant species and it was found that fruit, leaf, stem and trunk bark extracts inhibit the Epstein Barr Virus (EBV) activation. Mackeen *et al.* later reported the same activity of ester derivatives of garcinia acid [9] originated from the fruit (26). The leaves extract did also exhibits *in vivo* antimalarial activity when administered to *Plasmodium berghei* inoculated mice (29). Zaiton *et al.* (30) reported extract of *G. atroviridis* suppressed the nicotine-induced stress in *in vitro* embryo development. Leaves, twig and fruit extracts did also show *in vitro* platelet aggregation and low density lipoprotein (LDL) peroxidation activities and this was probably contributed by their phenolic content in the extracts (31). *In vitro* cholinesterase enzyme inhibition activity was also exhibited by compound 26 and 27 (16).

### CLINICAL DATA

There were limited data on the clinical uses of *G. atroviridis* in treating any kind of health condition. However, an interesting investigation conducted in Thailand using obese

women as subject results in promising HCA as effective weight management agent (32). Obese women that received HCA as *G. atroviridis* lost more weight as compared to control group. It was also proved by significant reduction in triceps skin fold thickness. Further clinical investigation may be proposed since such finding provides promising insight of HCA benefits in managing weight.

### CONCLUSION

*G. atroviridis* contains many active constituents that could provide promising source of treatment of various diseases. Even though the plants originated from genus of *Garcinia* become target of HCA for weight management agent, the potential of other constituents should not to be overlooked. Further exploration and investigation is anticipated to confirm the traditional medicinal value claimed of this plant and maximise the use of *G. atroviridis* in betterment of health status.

### ACKNOWLEDGEMENTS

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### *Garcinia atroviridis*'in fitokimyasal ve farmakolojik özellikleri

#### ÖZ

*Garcinia atroviridis* ya da yerel adıyla 'Asam Gelugor' ekşi tadı nedeniyle lezzet verici olarak kullanılmaktadır. Bu özelliğinin yanında *G. atroviridis*, geleneksel tedavide de insan sağlığına olumlu etkileri nedeniyle kullanılmaktadır. Yapılan araştırmalarda, bitkinin; antioksidan, antimikrobiyel, antifungal, anti-obezite ve lipid metabolizması düzenleyici, antienflamatuvar, antimalariyal, nikotin stresini ortadan

kaldırıcı ve sitotoksik özellikleri çalışılmıştır. Bu makale kapsamında *G. atroviridis*'in içerdiği kimyasal bileşenler ve biyolojik özellikleri incelenmiş, *in vitro* ve *in vivo* çalışmalara ek olarak sınırlı sayıdaki klinik çalışma hakkında da bilgi verilmiştir. Bu çalışmada, son 15 yılda *G. atroviridis*'in fitokimyasal ve farmakolojik özellikleri ile ilgili yapılan araştırmaların derlenmesi ile *G. atroviridis* hakkında güncel bir kaynak oluşturulması amaçlanmıştır.

**Anahtar kelimeler:** *Garcinia atroviridis*, hidroksisitrik asit, antioksidan, antimikrobiyel, antienflamatuvar, sitotoksik, antihiperlipidemik.

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