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Momordica cochinchinensis Spreng (Gac fruit): An abundant source of nutrient, phytochemicals and its pharmacological activities

Priscilla Jayanthi Thavamany[1], Hong Lim Chew[2], Sreeramanan S.[2,3,4], Bee Lynn Chew[2], Ming-Thong Ong[1*]

[1]Institute for Research in Molecular Medicine (INFORMM), Universiti Sains Malaysia, 11800 USM, Penang, Malaysia
[2]School of Biological Sciences, Universiti Sains Malaysia, 11800 USM, Penang, Malaysia
[3]Centre for Chemical Biology, Universiti Sains Malaysia, 11900, Bayan Lepas, Penang, Malaysia
[4]School of Bioprocess Engineering, Universiti Malaysia Perlis (UNIMAP), 02600 Arau, Perlis, Malaysia

***Corresponding author: omt@usm.my (also ong.mt1@gmail.com) (Ming-Thong Ong)**

Abstract

Gac fruit (*Momordica cochinchinensis* Spreng) is an exploitable perennial dioecious fruit found commonly in Southeast Asian countries (SA). Gac fruit has been traditionally used in folk medicine due to its high medicinal and nutritive value. Generally, the aril of the fruit is used as a red colourant for cuisines and supplement for healthier vision. Gac fruit is highly rich in lycopene and β-carotene, fatty acids, vitamin E, polyphenols like phenolic acids, flavonoids and trypsin inhibitors. These compounds are linked with many important bioactivities such as provitamin A, antioxidant, antimicrobial, antiulcer and anticancer activities. This paper reviews the findings on nutritional properties, phytochemical composition and the biological activities of Gac fruit. The review has also briefly discussed the suitable conditions for the storage and utilisation of the fruit in food, beverage, nutraceutical, pharmaceutical and cosmeceutical industries.

Keywords: Gac fruit; Lycopene; β-carotene; Phytochemical; Healthcare.
Abbreviations: Southeast Asian countries_SA; mg_miligram; g_gram; FW_fresh weight, µg_microgram; mL_microlitre; MW_molecular weight, TIs_trypsin inhibitors, KDa_kilodaltons; DNA_ deoxyribonucleic acid; LLC-PK1_ pig kidney epithelial cells; A549, H1264, H1299, Calu-6_ lung cancer cells; µmol _ micromole; DPPH_ 2,2-diphenyl-1-picrylhydrazyl; FRAP_ ferric reducing antioxidant power; ABTS_ 2,2'-azino-bis-3-ethylbenzthiazoline-6-sulphonic acid; AAE_ ascorbic acid equivalents; ASE_ accelerated solvent extraction; TE_Trolox; mm_ millimeter; MIC_minimmum inhibitory concentration; MBC_ minimum bactericidal concentration; SP_ screw press; SC_ supercritical; MCF_*Momordica cochinchinensis* fruits; kg_kilogram; AE_aril extract; DAPI_ 4',6-diamidino-2-phenylindole; MCF7_breast cancer cell, JNK_ c-Jun N-terminal kinases; AKT_protein kinase B; SGC7901 and MKN-28_ gastric cancer cell; PARP_ Poly (ADP-ribose) polymerase; ECMS_ ethanolic extract of seeds; ECM_ extracellular matrix, MMP-2 _ matrix metallopeptidase 2; MMP-9_ Matrix Metallopeptidase 9.

Introduction

Momordica cochinchinensis Spreng is widespread in Southeast Asian countries (SA), especifically in Vietnam, China, Thailand, India, Indonesia and Malaysia. The fruit is commonly known as Gac, Chinese bitter cucumber and cochinchin gourd (Lim, 2012). This fruit comes from the melon family of Cucurbitaceae inclusive of cucumbers, squash and bitter melon (Kubola et al., 2013). The botanical classification of the fruit is as follows: *Plantae* (Kingdom); *Cucurbitales* (Order); *Cucurbitaceae* (Family); *Cucurbitoideae* (Subfamily); *Momordica* (Genus); *Momordica cochinchinensis* (Species).

Tepurang is the vernacular name given to this fruit in Malaysia and Indonesia. However, names of the fruit vary in different countries (Table 1). The vines of Gac plant can grow up to 6 metre long over a fence. Gac is a perennial dioecious plant with separate male and female plants (Parks et al., 2013). The plant contains leaves of 3-5 palmately lobed, along with white to ivory yellow flowers (Bharathi and John, 2013). Gac plants usually flowers two months after being planted. Female flowers have an unformed fruit forming a bulge at the base whereas male flowers have paled coloured petals that results in an open bloom (Parks et al., 2013). Hand pollination through dusting the pollen on receptive stigma by paint brush is crucial in order to obtain higher fruit setting and yield, especially when the native pollinators are absent (Parks et al., 2013). A Gac plant can yield up to 60 fruits on average in one season (Burke et al., 2005). The fruits become ripe in around 9 to 10 weeks after pollination. The ripe fruit can be harvested when its fruit skin colouration changes from green to yellow, dark orange and finally to red as shown in Figure 1 (Tran et al., 2016). The fruit is hard at harvest but turns soft quickly after harvesting. leading to problems in transportation of the fruit and in its shelf-life (Win et al., 2015). The cultivation of the fruit is mainly from the seeds, branches, and roots (Chuyen et al., 2015).

Gac fruit is value-added due to its importance in health benefits as it contains an exceptional source of lycopene and beta-carotene. The content of lycopene in the fruit has been reported to be five times higher than tomatoes (Aoki et al., 2002), and that of beta-carotene to be 8 times more than the amount found in carrots (Aoki et al., 2002 ; Kandlakunta et al., 2008). It was also reported that the fruit contained an astounding amount (60 times) of vitamin C compared to that from oranges, and 40 times more zeaxanthin than that found in yellow corn (Aoki et al., 2002). In addition to many recent studies on its traditional uses and biological activities, this review will also focus on the emerging benefits of Gac fruit as therapeutic food.

Gac fruit anatomy

Typically, Gac fruits are round or ovoid in shape. However, one Gac cultivar grown in India has been reported to have oblong shape (Gopalakrishnan, 2007). The fruit comprises of two main parts, namely mesocarp and endocarp. The mesocarp includes orange/yellow spines that cover the skin, and thick, spongy orange layer called pulp as shown in Figure 2. Fruit spines distribution is ranged from smooth and dense to hard and far apart. The endocarp contains red, soft and sticky arils that cover the black seeds (Vuong, 2000). Each fruit comes with an average of 15 to 20 seeds. The seeds are mainly round, compressed and have a sculptured seed coat covered with red aril as shown in Figure 2. The yellow pulp covers 50% of the total weight while the aril, the highest amounted carotenoids, forms 10 – 25% of the fruit's weight. The skin and seeds are 17 % and 16 % of the fruit's total weight, respectively (Vuong, 2000; Kha et al., 2013; Chuyen et al., 2015). Parks et al. (2013) have shown a correlation between the size of fruit, weight, and portion of aril. The increment of the fruits weight and size would results in higher aril production. However, lighter fruit weight may occur due to loss of water during the storage (Nhung et al., 2010 ; Win et al., 2015).

Traditional uses

Gac fruit has been consumed in numerous ways amongst various cultures around the world (Tuyen et al., 2013). The pleasant taste of ripened Gac aril is commonly used as a colourant for the preparation of red glutinous rice or *xoi Gac* (Ishida et al., 2004). This dish is usually served at occasions during new year celebration and weddings in Vietnam (Zheng et al., 2015). On the other hand, the young green fruit can be cooked with chili paste or boiled for food. It is also used to cook curry in Thailand (Kubola and Siriamornpun, 2011). Stir-fried meals and soups reported to be scrumptious with the addition of aril leading to lustrous appearance and distinct flavour of the dish (Chuyen et al., 2015). *Xerophthalmia* also known as dry eyes and night blindness caused mainly by provitamin A deficiency. It was reported that *xerophthalmia* could be prevented by the intake of aril oil of Gac fruit as supplement (Chuyen et al., 2015). The seeds of the fruit, called *mubiezhi* (in Chinese: 木鳖子), play a vital role in traditional Chinese medicine for treatment of breast cancer (Zheng et al., 2015). It has been shown that the ethyl acetate seed extract inhibited the proliferation of MDA-MB231 cells and induced cell cycle arrest and apoptosis (Zheng et al., 2015). Traditonally, the seeds are used to treat skin problems such as boils, pyodermatitis, ringworm infections, freckles, sebaceous and medical conditions such mastitis, tuberculous cervical lymphadenitis, hemorrhoids and hemangiomas (Zheng et al., 2015). The grounded Gac seeds are used both orally and externally for the treatment of inflammatory scrofula, swelling, and tinea. It can also be used to treat diarrhea and suppurative skin infections such as sore, carbuncles, furuncles and boils in both human and animals (Xiao et al., 2007). In Vietnam, the roots of the plant is believed to promote blood circulation and urination by eliminating the damp heat (Tran et al.,2016). The roots are also used to treat rheumatism, inflammation, swelling of legs and edema (Tuyen et al., 2013, Tran et al., 2016).

Phytochemical composition of Gac fruit

Gac fruit gained the name "super fruit" or "heaven's fruit" because of its phytonutrients composition like carotenoids, essential fatty acids and other compounds such as fat-soluble vitamins like α-tocopherol (vitamin E), phenolic compounds, flavonoids and Vitamin C (Ishida et al., 2004; Kubola and Siriamornpun, 2011). Regular intake of this fruit that contains significant amounts of bioactive components improves basic nutrition and play a significant role in prevention of diseases (Tinrat et al., 2014; Chuyen et al., 2015).

Carotenoids

Gac fruit holds high levels of carotenoids specially lycopene and β-carotene in all parts (aril, pulp and peel) up to 500 mg/ 100 g each compared to lycopene rich fruit and vegetable like tomato (3.1 mg / 100 g), watermelon (4.1 mg / 100 g) and pink grapefruit (3. 36 mg / 100 g) (Aoki et al., 2002). The discrepant results of total carotenoid content (lycopene and β-carotene) in aril contents was determined as 48.1 mg/ 100 g fresh weight (FW) (Aoki et al., 2002) as indicated in Table 2. Further studies on Gac fruit showed varied results of total carotenoid content reported such as 294.5 mg/100 g FW (Ishida et al., 2004), 49.7 mg/ 100 g FW (Vuong et al., 2006), and 410.7 mg/ 100g FW (Nhung et al., 2010), 1502 mg/100 g (Kubola and Siriamornpun 2011), and 78 mg/100 g FW (Tran et al., 2016). The total carotenoid contents showed highest in aril >pulp > peel (Aoki et al., 2002). In one study investigated by Nhung et al. (2010), the total carotenoid content showed highest in ripe fruits compared to green or medium ripe fruit. Thus, the fruit maturity is one of factors to be considered to obtain highest yield of carotenoids. Apart from that, transportation and storage conditions above -20°C may cause isomerization and degradation of carotenoids as most are sensitive to heat and light (Vuong et al., 2006). Gac fruit also contains other carotenoids such as lutein, zeaxanthin, and β-cryptoxanthin Lutein and zeaxanthin are derived from xantophylls which has been extensively utilized to treat eye-related diseases such as cataracts (Vuong and King, 2003, Giordano and Quadro, 2018). Although lutein is present in all parts of the fruit, its content in the peel and pulp were found to be in higher concentrations at 12 48 and 144.8 mg/ 100 g FW, respectively. The analysis of Gac fruit conducted by Aoki et al. (2002) showed the presence of 0.9 mg / 100 g FW zeaxanthin and 0.2 mg/ 100 g FW β-cryptoxanthin in seed membrane (Gac aril), whereas 0.16 mg/ 100 g zeaxanthin and 0.35 mg/ 100 g FW β- cryptoxanthin were found in fruit meat (Gac pulp) (Aoki et al., 2002). Hence, it can be deduced that apart from the aril, the yellow pulp and skin form a huge potential source of carotenoids.

Vitamins

The mean concentration of Vitamin E (α-tocopherol) found in Gac aril was 7.6 mg/ 100 g of fresh weight, higher when compared to Gac pulp or even other *Momordica* genus such as *M.Charantia* (bitter melon) (Vuong et al., 2006). In a later study, the α-tocopherol content in peel, pulp and seed membrane extract were 1.46, 1.53 and 1.30 mg/100g, respectively (Reungpatthanaphong et al., 2018). Consuming vitamin E rich Gac fruit significantly contribute to the daily intake of vitamin E (15 mg/ day) as recommended (Vuong et., 2006 ; Institute of Medicine, 2000). Apart from that, vitamin E also plays an important role in preventing the polyunsaturated oil in the fruit from oxidation (Vuong and King, 2003). Water soluble Vitamin C (ascorbic acid) content was detected in Gac fruit at 42.57 mg/100 under wild growing condition in India (Sarmah et al., 2018). The investigation suggests that presence of vitamin C correlated to its antioxidant activity. Thus, these fruits can be consumed as dietary food for its high nutraceutical activity.

Polyphenolics and flavonoids

Both phenolic and flavonoids compounds are widely distributed in many plants and have gained much attention as primary antioxidants through their free-radical scavenging abilities by reacting with hydroxyl, superoxide anion and lipid peroxy radicals (Chandra et al., 2014). They also protect DNA from oxidative damage, inhibit growth of tumor cells and posses anti-inflammatory, anticancer and antimicrobial properties (Lee et al., 2017). The total phenolic content (TPC) values have been reported as: aril > peel > pulp > seed while the total flavonoid content (TFC) were peel > aril> pulp> seed (Kubola and Siriamornpun 2011). Kubola and and Siriamornpun (2011) reported a positive correlation for the antioxidant activity and the contents of total flavonoids phenolics of Gac fruit. In another study by Tinrat et al. (2014), they obtained highest TPC in the flesh acetone extract (41.6 ± 0.246 mg GAE / 100 g FW) and aril's methanolic extract (73.7 ± 0.00 mg RE/ 100g FW) (Tinrat 2014). The total antioxidant activities of Gac fruit accordingly to the following order of aril> peel > flesh.

Fatty acids

Gac fruit contains mixture of unsaturated, saturated, poly- and mono-unsaturated fatty acids. Vuong et al. (2002) reported seventy percent of the total fatty acids from 102 mg/g fresh weight comprised of unsaturated and 50 % were polyunsaturated. The fatty acid composition of the Gac aril is listed in Table 3. Major fatty acids present in aril are oleic, palmitic and linoleic as shown in Table 3. On the other hand, stearic, linoleic, oleic and palmitic are the main fatty acids in Gac seeds (Ishida et al., 2004). Percentage reported by other authors are also listed for comparison (Kha et al., 2014, Bruno et al., 2018).

Interestingly, the study conducted by Bruno et al. (2018) showed that Gac fuit contained higher concentration of oleic acid, 44.5 % of total fatty acids, when compared to tomato and watermelon at 2.5 % and 20.7 % respectively. Hence, it can be used as a source of oleic acid in addition to other sources such as soya, palm and coconut (Vuong and Kind 2003). These fatty acids from aril play a vital role in the uptake of fat-soluble nutrients like carotenoids through low-fat diet (Vuong et al., 2002 ; Kuhnlein, 2004 ; Muller-Maatsch et al., 2017). It has been shown that Vietnamese households use Gac fruit oil as a substitution for pork fat (Vuong and King, 2003). The consumption of Gac fruit oil (2 mL/day) increases the intake of β-carotene and essential fatty acids as well as reduces the intake of saturated fatty acids (Vuong and King, 2003). Several authors reported intake of saturated fatty acids increases the risk of contracting cardiovascular disease. However, usage of Gac fruit oil containing , mono- or poly- unsaturated fatty acids over coconut oil and fat of animal origin may prevent from long-term effect on health (Rodriguez Levya et al., 2010 ; Poudyal et al., 2011). Thus, the composition of fatty acids and high carotenoids in Gac oil suggests that Gac fruit is a fruit with high nutritional value (Vuong and King, 2003).

Trypsin inhibitors

Trypsin inbitors (Tis) are low molecular weight peptides and inhibits the hydrolase activity of serine proteases (Le et al., 2018). The seeds of Gac fruit are known to contain trypsin inhibitors also known as *Momordica cochinchinensis* trypsin inhibitors (MCoTIs) (Liu et al., 2012). MCoTIs contains 28-34 amino acid residues, 6 cysteine residues which forms 3 disulfide bonds structurally (Le et al., 2018). A total of nine tryspin inhibitors have been isolated and sequenced from the seeds of Gac fruit. Huang et al. (1999) isolated a trypsin inhibitor from Gac seed with molecular weight (MW) of 3.479 kDa, belonging to the squash family inhibitors. Furthermore, three other trypsin inhibitors (TIs) were segregated from the seeds of the squash *Momordica cochinchinensis* (Hernandez et al., 2000).

In addition, five trypsin inhibitors with MW of 5.1, 4.8, 4.4, 4.1, and 3.9 kDa were reported to be present in Gac seeds (Wong et al., 2004). Due to their low molecular weight, they are compact and very stable (Hernandez et al., 2000). This enables them to penetrate into cells. In the study conducted by Le et al. (2018) was highlighted on protease inhibitors which have various biochemical functions such as acting as anticancer agents by inhibiting the growth of two melanoma cells (MM418C1 and D24) compared to control.

Others saponins

Several studies on ethanolic extract of Gac seed have reported that chemical compounds such as saponins from the seed have renoprotective effects against cisplatin-induced damage to LLC-PK1 pig kidney epithelial cells *in vitro* via blocking of mitogen-activated protein kinase (MAPKs) signaling cascade (Jung et al., 2016). The three major saponins that have been isolated are tabulated in Table 4 as gysogenin (compound 1), quillaic acid (compound 2) and gypsoside (compound 3). In another study conducted by Yu et al. (2017) on four lung cancer cell lines, namely A549, H1264, H1299, Calu-6 and primary lung endothelial cells from human confirmed that cell proliferation was inhibited for all the cell lines with two major saponins identified previously as gysogenin and quillaic acid (Yu et al., 2017).

Pharmacological activities of Gac fruit

New developments associated with Gac fruit have led to keen interest in many biological activities including the synthesis of provitamin A in the fruit and antioxidant properties of the fruit (Vuong et al., 2002, Barathi et al., 2014). Moreover, the anticancer and antimicrobial properties of the fruit have also been extensively investigated (Liu et al., 2012, Innum 2013, Tinrat and Asna 2016).

Provitamin A activity

Momordica cochinchinensis is a reservoir for vitamin A due to the presence of β-carotene, which provide vitamin A after enzymatic cleavage. β-carotene is converted to retinal and

Table 1. Vernacular names of *Momordica cochinchinensis* based on the different Asian countries. Adopted from (Lim, 2012).

Countries	Vernacular names
Bangladesh	Kakrol
China	Da Ye Mu Bie Zi, Mu Bie, Mù-Biē Guǒ , Mu Bie Zi, Teng Tong, Tu Mu Bie
India	Bhat Kerala, Golkara, Kakrol, Gangerua, Gulkakra, Kakur, Kakrol, Kantola, Kathaamla
Indonesia	Pupia, Torobok, Toropu
Laos	Khaawz
Malaysia	Teruah, Terupang
Philippines	Tabog-Ok, Tabog- Uak
Thailand	Bai- Khai- Du, Fak-khao, Phak-Khao
	Khika-Khrua Yawd-Fak-Kao
Vietnam	Red Gac, Mộc Miết Tử
Cambodia	Makkao

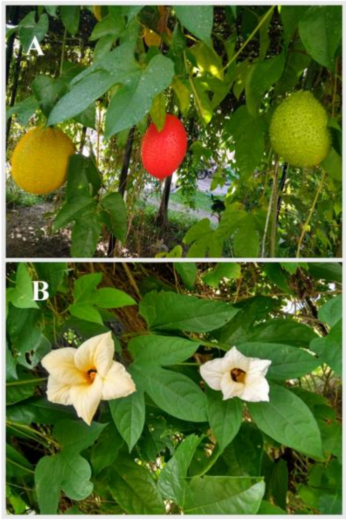


Fig 1. (A) Leaves and fruits of Gac plant; (B) Female (right) and male (left) flowers of Gac plant.

Table 2. Carotenoid contents of Gac aril [mg/ 100 g FW].

β - carotene	Lycopene	Total carotenoids	References
10.1	38.0	48.1	Aoki et al., 2002
71.8	222.7	294.5	Ishida et al., 2004
8.3	40.8	49.7	Vuong et al., 2006
37.9	372.8	410.7	Nhung et al., 2010
800	702	1502	Kubola and Siriamornpun 2011
33	45	78	Tran et al., 2016

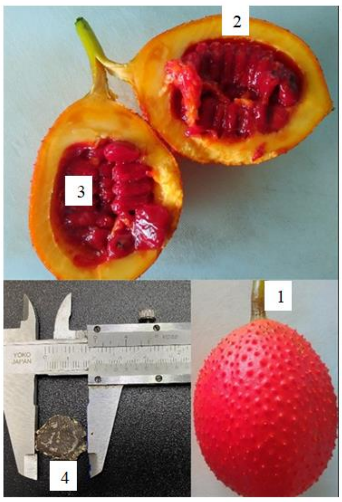


Fig 2. Anatomical parts of Gac fruit (1. Peel with spines, 2. Pulp, 3. Aril, 4. Seed).

Table 3. Composition of fatty acids in aril of Gac fruit (% total fatty acid)

`		References				
		(Vuong et al., 2002)	(Ishida et al., 2004)	(Mai et al., 2013)	Kha et al., 2014)	(Bruno et al., 2018)
Saturated Fatty Acids (SUFAs)	Palmitic (16:0)	22.04	29.2	17.31	24.76	30.1
	Stearic (18:0)	7.20	7.7	7.45	6.72	5.1
	Myristic (14:0)	0.89	0.5	0.22	0.42	0.8
	Arachidic (20:0)	0.40	0.5	0.32	-	-
Monounsaturated Fatty Acids MUFAs)	Oleic (18:1Δ^{9})	34.76	32.3	59.50	49.18	44.5
	Palmitoleic (16:1 Δ^{9})	0.27	0.3	0.18	0.43	-
Polyunsaturated Fatty Acids (PUFAs)	Linoleic (18:2 $\Delta^{9,12}$)	32.06	28.1	13.98	17.65	19.6
	α-linoleic (18:3 $\Delta^{9,12,15}$)	2.18	0.5	0.52	0.84	-

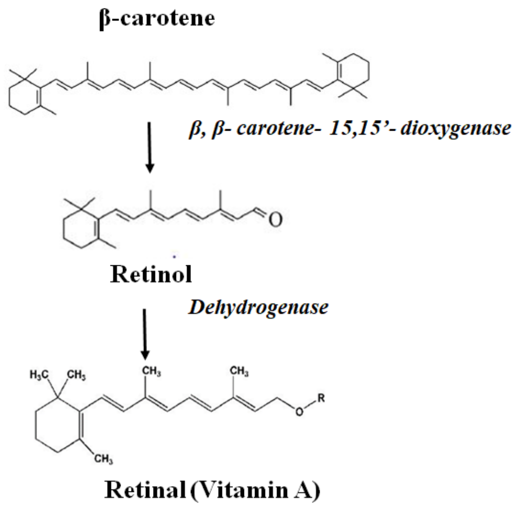
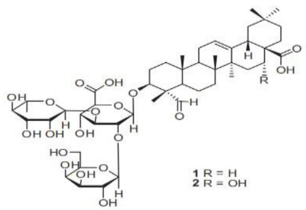
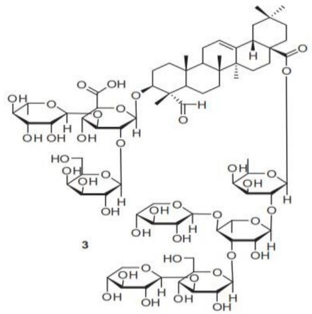


Fig 3. Chemical structure of β- carotene and its derivatives.

Table 4. Saponins in Gac seeds.

Name	Structure	Reference
Gypsogenin (1) **3-O-β-Dgalactopyranosyl (1→2)[α-L-rhamnopyranosyl (1→3)]β-D-glucuronopyranoside**		Jung et al., 2016
Quillaic acid (2) **3-O-β-Dgalactopyranosyl (1→2)[α-L-rhamnopyranosyl (1→3)]β-D-glucuronopyranoside**		
Momordica Saponin I **(Gypsoside) (3)** **3-O-β-Dgalactopyranosyl(1->2)[α-L-rhamnopyranosyl(1>3)]-β-Dglucuronopyranosido-28O-β-D-xylopyranosyl(1>3)-β-Dglucopyranosyl(1->3)-[βD-xylopyranosyl(1->4)]-α-L-rhamnopyranosyl(1->2)β-Dfucopyranosylgypsogenin**	 3	Jung et al., 2016

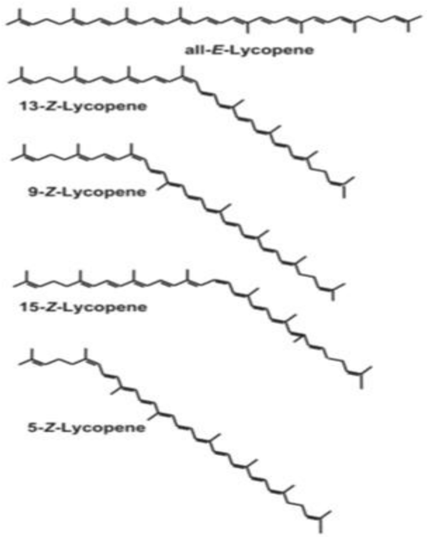


Fig 4. Geometric isomers of lycopene (Rodriguez-Amaya, 2015).

Table 5. Antioxidant activity of various extract from different parts of Gac fruits.

Extracts	Antioxidant Assay	Results	References
Extracts obtained by accelerated solvent extraction (ASE)	DPPH ABTS FRAP	Peel: EC_{50}= 11.78±0.45mg/ml ABTS: EC_{50}= 81.27 ± 1.26 mg/ml FRAP= 252.06±31.68 µm Pulp: EC_{50}= 8.65±0.15 mg/ml ABTS: EC_{50}= 82.48 ± 4.04 mg/ml FRAP= 112.11±5.3 µm Seed: EC_{50}= 71.25±1.22 mg/ml ABTS: EC_{50}= 77.44 ± 2.65 mg/ml FRAP= 57.06±13.88 µm	(Reungpatthanaphong et al., 2018)
Ethanolic extract (peel, pulp and aril)	DPPH& FRAP	Peel= 4.56 mg AAE/g FW FRAP=0.012 mg AAE/g FW Pulp= 2.41 mg AAE/g FW FRAP= 0.012 mg AAE/g FW Aril= 4.87 mg AAE/g FW FRAP= 0.016 mg AAE/g FW	(Tinrat et al., 2014)
Ethanolic extracts of Gac peel, pulp, aril and seed	DPPH& FRAP	Peel: IC_{50}= 2.56 mg g^{-1} FRAP: 472µmol $FeS0_4$ g^{-1} Pulp: IC_{50}= 2.53 mg g^{-1} FRAP: 466 µmol $FeS0_4$ g^{-1} Aril: IC_{50}= 3.66 mg g^{-1} FRAP: 531 µmol $FeS0_4$ g^{-1} Seed : IC_{50}= 6.66 mg g^{-1} FRAP: 36.3 µmol $FeS0_4$ g^{-1}	(Kubola and Siriamornpun, 2011)
Methanol extract of immature Gac fruit (green)	DPPH FRAP	45.1 mg AAE/ 100g 5.9 mg AEAC/ 100g	(Bharathi et al., 2014)
Gac aril Lycopene in *cis*-isomers	ABTS	3.7µmol TE	(Phan-Thi and Wache, 2014)
Spray dried Gac aril powder	ABTS	1.4 mm TE g^{-1}	(Kha et al., 2010)
Vacuum dried Gac aril	ABTS DPPH	162 mm TE g^{-1} DW 124 mm TE g^{-1} DW	(Mai et al., 2013a; Mai et al., 2013b)

retinol by β-carotene 15, 15’ monooxygenase enzyme (BCMO1 gene) (Figure 3). This enzyme not only plays an important role in converting vitamin A but also decreases the amount of β-carotene by converting this latter into retinal via feedback loop when higher level of retinoic acid is detected in the body (Seino et al., 2008).

An *in vivo* (human) study among 185 Vietnamese preschoolers conducted by Vuong et al. (2002), confirms the β-carotene in Gac fruit is highly bioavailable. The author suggests that the readily bioavailable β-carotene in Gac is presumably due to its fatty acids (Vuong et al., 2002). The existence of fatty acids stimulates the intestinal uptake of β-carotene in the body by forming micelle, which can be easily absorbed in the intestines by passive diffusion through the border of enterocytes (Yeum and Rusell, 2002 ; Failla et al., 2008; Reboul, 2019). Hence, it can be concluded that Gac fruit has highly potential and bioaccessible source of provitamin A.

Antioxidant activity

The diphenyl-picrylhydrazyl (DPPH) radical scavenging, ferric reducing antioxidant power (FRAP), and 2’2’-azino-bis 3-ethylbenzothiazoline-6-sulphonic acid (ABTS) were used in determining various antioxidant activities. Numerous studies were conducted on the antioxidant properties of Gac fruit (Table 5). Investigation on the aril, peel, pulp and seed showed that the antioxidant capacity was highest in aril fraction. A decrease was reported in the antioxidant capacity from immature to ripe stage for pulp and peel, whereas the seed increased from mature to ripe stage. The decrease observed in the antioxidant capacity in DPPH and FRAP were correlated to the decrease in the total phenolic content and total flavonoid levels during the fruit development stage (Kubola and Siriamornpun, 2011). Bharathi et al. (2014) reported that immature Gac fruit (25 days after pollination) contained 45.06 and 5.84 mg AAE / 100 g ascorbic acid for DPPH and FRAP, respectively.

In another study, Tinrat et al. (2014) reported that the ripe ethanolic aril extract had the highest antioxidant activities at 4.87 and 0.016 mg ascorbic acid equivalents in FRAP and DPPH as compared to peel and pulp, respectively. Thus, it can be concluded from these studies that the antioxidant capacity of Gac fruit is influenced by its fraction parts and maturation. Several authors suggested suitable drying method with optimal drying temperature could improve antioxidant properties from the aril (Kha et al., 2010 ; Mai et al., 2013 a,b). The Gac aril powder prepared in a concentration ranging from 10-20% of maltodextrin using spray drying method and increasing drying temperature from 120 to 200ºC showed significant loss of antioxidant activity from 0.14 to 0.08 mmol Trolox (TE)/ g of powder components (Kha et al., 2010). These effects in the antioxidant activity may be due to the thermal treatment that destroys the antioxidant components (Kha et al., 2010). In 2013, Mai et al. (2013) highlighted that moisture content (15-18%) of Gac aril was retained by semi-drying via vacuum dryer at optimal temperature of 60ºC to improve the retention of the carotenoids. This method has helped to retain up between 81 to 87% of the total antioxidant from the fresh Gac aril (Mai et al., 2013a,b).

Isomerization by heat treatment made Gac’s lycopene more antioxidant. The all-*trans*-form lycopene isomerized to the 13- and 9-*cis* isomers at 80 °C (Figure 4).The increase of this *cis*-isomers results in higher antioxidant activity in the extract related to higher solubility compared to *trans*-isomers (Phan-Thi and Wache, 2014). However, caution must also be taken as isomerization is the first step of degradation since *cis* -isomers are less stable and easily cleaved than *trans*-isomers (Phan-Thi and Wache, 2014). The antioxidant values and carotenoid level for the Gac fruit were higher when extracted using ultrasonic-assisted extraction (UAE) at 75°C for 15 min (Natnoi & Pirak, 2019). UAE extraction changed the lycopene isomerization from all-*trans* to *cis*-isomers giving rise to high antioxidant activity without degradation (Natnoi & Pirak, 2019).

Antimicrobial activity

Antibiotic resistance has emerged as global problem and possesses a threat to human health. This situation can be overcomed with the presence of antimicrobials (secondary metabolites) in plants. These antimicrobials can inhibit the growth of microorganisms effectively with minimum side effects and low cost (Putta et al., 2014). Gac fruit has abundance of bioactive phytochemicals, particularly carotenoids like lycopene, β-carotene, lutein, phenolic compounds that may exert antimicrobial capacity (Putta et al., 2014). The antimicrobial activity of Gac aril and pulp extracts extracted with aqueous, 95% ethanol and ether was investigated against different strains of Gram positive and negative bacteria. The ethanolic pulp extract showed the highest antimicrobial activity against *Micrococcus luteus* 745 (20mm) and 884 (15.5mm).

Nevertheless, the ether extract using both pulp and aril showed no antimicrobial activity (Innum , 2013). In another study, the ethanolic extract from peel and pulp showed significant inhibitory effects with minimum inhibitory concentration (MIC) value of 1.562 mg/mL for *E.coli* while the aril extract inhibited *P.euroginosa* with MIC value of 3.125 mg/mL (Tinrat et al., 2014) . These results prove that the ethanolic extract showed antimicrobial activity against both Gram positive and negative bacteria. Tinrat and Asna (2016) highlighted that crude aril oil obtained through screw press and supercritical CO_2 fluid technique extraction showed prominent inhibition against Gram positive and negative bacteria. MIC and MBC values of crude extracts and oils varies between 0.78 and 400.0 mg/mL (Tinrat and Asna, 2016).

Anti-ulcer

In the findings of Kang et al. (2010) reported that the treatment with Gac seed (SK-MS10) hasten the healing of acetic acid induced gastric ulcers by enhancing angiogenesis and the expression of angiogenic factor,VEGF. Gac seed extract showed promising anti-gastritis effect in ethanol- and diclofenac-induced gastritis when compared to standard rebamipide treatment (Jung et al., 2013). The results obtained suggested that Momordica saponin 1 from seed could be used as an active biomarker compound. Moreover, the seed extract demonstrated comparable wound healing effect to positive control drug, CGS-21680 (Jung et al., 2013a).

In another study, anti-ulcer properties of methanolic extract of *Momordica cochinchinensis* fruits (MCF) was tested on ethanol-induced ulcer models in experimental rats at 50 and 300 mg/kg and pylorus ligation (Sowjanya et al., 2015). Both these concentrations showed a significant reduction in gastric volume, free acidity, total acidity based on the ulcer index as compared to control (Sowjanya et al., 2015). Thus, it can be concluded that the extract possesses anti-ulcerogenic properties as well as ulcer healing properties, which could be due to its anti-secretory activity (Sowjanya et al., 2015).

Anti-inflammatory

The Gac seed contains rich source of triterpenoids and saponins. The triterpenoidal saponins, among the isolated momordica saponin 1 inhibited the production of nitric oxide (NO) production and transcriptional activation of inhibitory genes further suppress the activation of inflammatory signaling proteins linked to the activation of NFκB (Yu et al., 2017). Another saponin, quillaic acid glycoside, demonstrated anti-inflammatory effects in lipopolysacharride (LPS)- activated RAW 264.7 cells by blocking the expression of nitric oxide (NO), IL-6 and downregulating iNos expression and cyclooxygenase (COX)-2 via NF-kB pathway (Jung et al., 2013b). Wang et al. (2019) investigated five new lignans mubiesins and twenty-seven known compounds (including lignans, sterols) for cytotoxic and anti-inflammatory activities. The results indicated that seventeen compounds could inhibit the release of NO and TNF-α in LPS-induced RAW 264. 7 cells. Thus, Gac seed could be a promising tool in treating inflammatory disease.

Anti-cancer activity

Herbs have been broadly used as a substitute remedy for cancer treatment (Shukla and George, 2011). The presence of high carotenoids such as lycopene, β-carotene and phenolic compounds in the Gac fruit has drawn numerous studies to be conducted on anticancer activity as these compounds are being extensively studied for their abilities to inhibit or supress cancer related oxygen radicals based on various mechanisms via *in vitro* and *in vivo* conditions.

The gac seed ethanol extracts inhibited the proliferation of human SGC7901 and MKN-28 gastric cancer cells (Liu et al., 2012). In addition , the extract induces apoptosis by increasing the caspase 3, 9 and 8 activities through poly (ADP-ribose) polymerase (PARP) and p53 signalling pathways. Likewise, Shen et al. (2015) found that Gac seed suppressed the proliferation of human lung cancer cell line, A549 by inducing apoptosis via p53 activation and inactivation of PI-3K/ AKT signaling pathways. The migration and invasion was inhibited by seed extracts via reduction in the expression of STAT-3, MMP-2 and increased the expression of E-cadherin. However, no effects were seen in the expression of VEGF (Shen et al., 2015).

Similarly, Zheng et al. (2014) discovered strong inhibitory effects of seed extract against human breast cancer ZR-75-30 cell line. The enzymatic activity of MMP-2 and MMP-9 were repressed by seed extract leading to inhibition of metastasis in breast cancer treatment Gac seed showed good anticancer potential against two melanoma cell lines (MM418C1 and D24), effect of which was higly associated with trypsin inbitors extracted efficiently with water (Le et al., 2018). In a recent study, few lignans namely Mubiesins showed cytotoxicity against growth of tumor cell lines Hepg2, B16, SGC-790 with IC50 value less than 10 μM (Wang et al., 2019).

Gac aril water extract inhibited the proliferation of colon 26-20 and HepG2 cell lines transplanted in Balb/c mice via inducing necrosis rather than apoptosis. This was evidenced by the downregulation of cyclin A, Cdk2, p27waf1/ Kip 1 (Tein et al., 2005). It has also been shown that a protein with 35 kDa molecular weight, highly water soluble is responsible for the antitumor activity. In addition, lycopene-enriched aril extract (AE) demonstrated cytotoxicity and antiestrogenicity on human MCF-7 breast cancer cell line with cell shrinkage and chromatin condensation,leading to intrinsic and extrinsic apoptosis pathways (Petchsak and Sripanidkulchai, 2015). Cytotoxicity with 60 and 70% mortality on breast and melanoma cells using aril's water extract was obtained and it was suggested that the reduction in cell viability could be through necrotic phase of apoptotic pathways (Wimalasiri et al., 2016). Abdulqader et al. (2018) demonstrated a remarkable effect of Gac fruit (peel, pulp , seed and aril) on human retinal pigment epithelial cells ARPE-19 cell viability. They found that the introduction of Gac fruit extracts to ARPE19 cells in high glucose condition (30 mmol/L) led to inhibition of cell viability which was evidenced by morphological changes of the cells. The fruit showed decreased level of reactive oxygen (ROS) and vascular endothelilal growth factor (VEGF) secretions, and increases the amount of pigment epithelium-derived factor (PEDF) levels which is a pre-requiresitive for angiogenesis process.

Other properties of Gac fruit

Reductions of sperm concentration and seminiferous tubule diameters are the adverse effects of valproic acid (VPA) treatment. The aril water extract showed protective effect against adverse male reproductive parameters and testicular damage induced by VPA with an increase in sperm concentration and seminiferouls tubule diameters. The extract also protects the decrease of the weights of the epididymis and seminal vesicle (Sukhorum et al., 2016).

The Gac seed extract showed neutrotrophic effects by mimicking the effects of NGF through early pERK signalling pathways and their morphological changes in structural protein is associated with neutrite branching and outgrowth (Mazio et al., 2015). It was reported that a protein with 17 kDa obtained from the Gac seed extract induced the neutrite outgrowth in PC-12 cells (Mazio et al., 2018). A clinical study on Gac-containing antiwrinkle cream formulation showed that the cream effectively worked to increase the cutaneous hydration (moisture) and smoothness, also reduced skin wrinkles (Leevutinum et al., 2015). In addition, the presence of carotenoids (lycopene, β-carotene) in Gac fruit contributes to substantial free radical scavenging activity evident in DPPH and ABTS assay (Leevutinun et al., 2015). Gac fruit is also safe for human consumption making it an effective antiwrinkle cream product.

Storage of Gac fruit

Long term storage management requires a intensive study in changes in postharvest quality of Gac fruit and shelf life in order to minimize the losses in commercialization of Gac fruit. Proper maturity index, growing and optimized storage conditions plays a great impact on the nutritional value of the fruit. Gac fruit harvested prior to full maturity (fully ripe) can increase their nutritional qualities, lycopene and β-carotene contents in aril (Kubola and Siriamornpun, 2011, Tran et al., 2017). Gac fruit at fully ripe stage reported the highest amount of carotenoids (3.852 and 0.409 mg/g aril FW) for lycopene and β-carotene which decreases after 14 days of storage (Nhung et al., 2010). Thus, these authors concluded that fruit firmness and maturity index are important factors for quality management (Nhung et al. 2010). The fruit stored at low temperature (10-13°C) lasted for 30 days when compared to that at high temperature (25°C) (Win et al., 2015). This latter only lasted half shelf life of the fruits kept at low temperature. Thus, it was concluded that storage at low temperatures was the best way to maintain the quality of the fruit and its products. However, fruit exhibited chilling injury symptoms both internally and externally at 4°C (Win et al., 2015).

Gac powder stored in vacuum storage below 25°C retained the best quality of total carotenoids over 4 months after pretreatment and dehydration with various drying process (Tran et al., 2008). The addition of antioxidant agents during drying significantly prevented the loss of total carotenoid in the powder due to precipititation of β-carotene at 5°C (Minh and Dao, 2013). Gac aril powder supplemented with Vitamin C at 2000ppm and mixing carrier maintained 70% carotene content for three months at 10°C or five months at 5°C in the absence of oxygen and light (Minh and Dao et al., 2013). Further studies on storage and preservation of carotenoids in Gac should be carried out.

Products of Gac fruit

Apart from its traditional uses by the locals as natural colourant, Gac is also used in commercially marketed food as food additives in medicine and cosmetics industries. Gac is used in the form of nutritional supplements such as Gac extracts in soft capsules. Fresh ripe aril is used forjuice and ice cream processing in Thailand (Kubola and Siriamornpun, 2011, Innun, 2013). Fresh gac's fruit blend consisting of honey, lemon and fresh aril are consumed in Malaysia, Indonesia, and Philipines. Commercial Gac products such as aril puree, oil, dried aril powder and juice, fruit enzyme, skin balm, soap, seed alcohol are in domestic and international markets in countries like Vietnam, China and Thailand. Gac oil and dried gac powder are marketed due to its high content of lycopene, β-carotene, and lutein. Gac aril contains oil component that plays a crucial role in the absorption of carotenes, vitamin E and other fat-soluble nutrients needed by the body (Chuyen et al., 2015).

Conclusions

Gac fruit (*Momordica cochinchinensis* Spreng.) is highly valued for its high amounts of lycopene and β-carotene, α-tocopherol and fatty acids which has been extensively used in both nutritional and medicinal purposes. The antioxidant, antimicrobial and anticancer properties conducted in the studies evidenced the presence of bioactive compounds in Gac fruit. Although many biological properties have been reported for Gac fruit, the underlying mechanisms of action of the bioactive compounds are still lacking. Through in depth studies on this aspect of the fruit, it is hoped that it could be used as a health supplement. Currently, research are mostly focused on bioactive compounds residing in the aril and seed of Gac fruit whereas large amount of pulp and peel are discarded as waste after processing. There are enormous potential for Gac fruit pulp and peel which contained valuable sources of phytochemical which can be used in medicinal, agricultural and pharmaceutical industries.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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