Review Article
Food Science and Technology
ISSN 0101-2061 (Print)
ISSN 1678-457X (Online)
DOI: https://doi.org/10.1590/fst.100121


# A comprehensive review on nutritional contents and functional properties of *Gnetum gnemon* Linn.

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**Abstract**

This review article is focused on the nutritional constituents and functional properties of *Gnetum gnemon* Linn. Among the various plant parts, fruit or seed have been utilized and intensively investigated for food products in India and Indonesia. While the leaves may not be as popular as seeds, they protein sources with complete amino acids and high branched-chain amino acids (BCAAs). In addition, the plant has high contents of vitamin A, dietary fiber, minerals (potassium, calcium, iron, zinc, phosphorus) and high chlorophylls, which are related to chlorophyllin synthesis, antioxidant activity, anti-diabetes activity, and health benefits against various diseases. Therefore, *G. gnemon* is considered a candidate plant with high nutritional potential providing a wide range of essential nutrients and health benefits, and can be used safely as raw material for food, nutraceuticals, and medicinal products.

**Keywords:** *Gnetum gnemon* Linn.; nutritional value; functional properties.

**Practical Application:** *Gnetum* high nutritional value for use functional ingredient nutraceuticals medicinal products.

## 1 Introduction

*Gnemon* is a species of *Gnetum,* that are native plants to Southeast Asia and the western Pacific Ocean islands from Mizoram and Assam in India throughout southern Thailand, Malaysia, Indonesia, Philippines, Australia, and Fiji. *Gnetum* plants occur as woody shrubs, vines, or broad-leaved trees. They belong to Kingdom: *Plantae*, Division: *Gnetophyta*, Class: *Gnetopsida*, Order: *Gnetales*, Family: *Gnetaceae*, and Genus: *Gnetum*. With at least 30 species, the trees are mainly found in Africa, while most of the Asian varieties are woody vines, except for *G. Gnemon* that is a woody shrub or tree (Barua et al., 2015) (Figures 1-2).

Based on the literature review, *G. gnemon* has multiple names that vary by locality.

Common English names: Daeking Tree, *Gnetum* Nut, Gnemon Tree, Jointfir, Joint-Fir Spinach, Melinjo Nut, Paddy Oats, Spanish Jointfir, Tulip Tree, Two Leaf (Lim, 2012).

Local names of *G. gnemon*: (a) Borneo: Sabong; (b) Burmese: Hyinbyin, Tanyin-Ywe; (c) Chinese: Guan Zhuang Mai Ma Teng, Xian Zhou Mai Ma Teng; (d) Fiji: Bele Sukau, Bui No Vodre, Mosokau, Sikau, Sukau, Sukau Buli, Sukau Mata, Sukau Motu; (e) French: *Gnetum* À Feuilles Comestibles; (f) India: Ganemoe, Genemo (Assamese); (g) Indonesia: Melinjo, Emping Melinjo, Belinjo, Meninjo, Bagu, Bagoe, Blinjo, Eso, So, Trangkil, (Javanese), Ki-Trangkil,Maninjo, Tangkil Sake (Sundanese); (h) Khmer: Voë Khlaèt; (i) Malaysia: Belinjau, Belingar, Maninjau, Meninjau, Melinjau, Sejunteh, Sokat; (j) Papua New Guinea: Tulip (General), Ambiam, Ambiamtupee (Maring); (k) Philippines: Bago, Bago Banago, Banago (Bataan, Tayabas, and Camarines); (l) Solomon Islands: Dae, Daefasia, Daemalefo (Kwara'Ae), Zua, Dae Fasia, King Tree; (m) Thailand: Peesae, Miang, Liang; (n) Vietnamese: Bét, Rau Bép, Rau Danh, Gắm Cay (Lim, 2012).

## 2 Usage of the *Gnetum* plant parts

The usage of parts of *G. gnemon* parts starts from root, trunk, leaf, inflorescences, and seeds. In many countries, seeds (mainly *gnemon* variety) are the major part utilized, but leaves (*tenerum* variety) are used for human food in Thailand (Manner & Elevitch, 2006). *G. gnemon* leaves are dark green, shiny, smooth, acute at both ends, opposite, and variable in size and shape. Generally, a typical size of the leaves is 10-20 cm (4-8 in) in length and 4-7 cm (1.6-2.8 in) in width. *G. gnemon var. gnemon* variety has bigger and longer leaves compared to *G. gnemon var. tenerum*. Leaf shape is elliptic, lanceolate, and ovate oblong. Branches flush, and flowers are produced throughout the year (Manner & Elevitch, 2006). Young leaves are brownish red to light green, while old leaves are dark green with upper surface and lower surface full green (Figures 3-4). Although the *G. gnemon* leaves possess no tannin, they are usually not infected by diseases or insect pests due to a high content of fine crystals (Tomlinson & Fisher, 2005). In the *tenerum* variety leaves are a famous leafy vegetable consumed in Southern Thailand for more than a hundred years, but to date this is still not well documented. In Papua New Guinea, the leaves and inflorescences are cooked with meat or sauce made from the red pulp of *Pandanus conoideus* (Verheij & Sukendar, 2016). In addition, tender leaves are traded

*Received 04 Nov., 2021*
*Accepted 29 Mar., 2022*
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as vegetables by the local people in the entire North East India by Karbis, the Mongoloid race that is linguistically Kuki-Chin sub-group, considered themselves as the children of "Hanthu" (Barua et al., 2015). The young leaves, inflorescences, and fruits are cooked for vegetable dishes.

The edible rind of fruits and kernel of the seed can be eaten raw. However, the seed kernel is usually cooked or processed to flour for crisps making, which is found as a home industry in Java (Verheij & Sukendar, 2016). *G. gnemon* var. *gnemon*, a tree type, is a native plant found in Philippines, Sulawesi, and Sumba and eastwards to New Guinea and Fiji. The fruits or seeds of the *gnemon* variety are mainly utilized, while *G. gnemon* var. *tenerum* is a shrub that may reach 3-meter height with much smaller sized fruits. This variety is distributed in Thailand, Malay Peninsula, and some parts of Borneo, including Kalimantan, Brunei, Sabah, and Sarawak (Astuti et al., 2016). The main used part of *G. gnemon* var. *tenerum* is young leaves, and tender tip or apex is used as fresh vegetable and/or cooked; and recently even a commercial menu item has been launched in a modern supermarket in Thailand (Figure 5). The seed from *G. gnenom* var. *gnemon* of large size is normally processed to flour for making crisp snacks (emping) or in main dishes in Indonesia. In addition, seeds from the *gnemon* variety can be eaten raw, fried, or roasted, or as flour. In East Java, clips called "blinjo" made from the *Gnetum* seeds are quite popular.

**Figure 1**. *G. gnemon*: tree type (Harimutri, 2014).

Ethnobotanical uses *Gnetum* is among the oldest species of trees on Earth, dating back more than 200 million years, and is an arboreal dioecious plant. It is the sole genus in the family *Gnetaceae* with more than 30 species. Most of these species are lianas distributed in the tropical regions of Central Africa, South America, and particularly in Southeast Asia. In Africa, two different species of *Gnetum* are recorded as *G. africanum* and *G. bucholzianum,* which are distributed in the tropical rainforests from Nigeria through Cameroon, the Central African Republic, Gabon and the Democratic Republic of the Congo, and Angola. In the Central African Republic, Gabon, Congo, the Democratic Republic of the Congo, and Angola, both species are locally called KoKo (Bahuchet, 1990). However, it is hard to distinguish these two species without using their leaf shape and the characteristics of the male reproductive organs (Ali et al., 2011). About 19 species of Asian and Indomalesian region are lianas, include *G. arboreum*, *G. contractum*, *G. cuspidatum*, *G. diminutum*, *G. gnemonoides*, *G. hainanense*, *G. klossii*, *G. latifolium*, *G. leptostachyum*, *G. loerzingii*, *G. macrostachyum*, *G. microcarpum*, *G. montanum*, *G. neglectum*, *G. oxycarpum*, *G. ridleyi*, *G. ula*, and two other species. In addition, *G. gnemon* and one other Indomalesian species are trees. However, at this present time, *G. gnemon* is identified into four varieties; (1) *G. gnemon* var. *brunonianum* (Griff.) Markgr. and (2) *G. gnemon* var. *griffithii* (Parl.) Markgr., which occurs in Northeast India, while (3) *G. gnemon* var. *gnemon*

(2.1) Intercropping with rubber trees (2.2) Backyard garden

**Figure 2**. *G. gnemon*: shrub type. Source: photographed by authors.

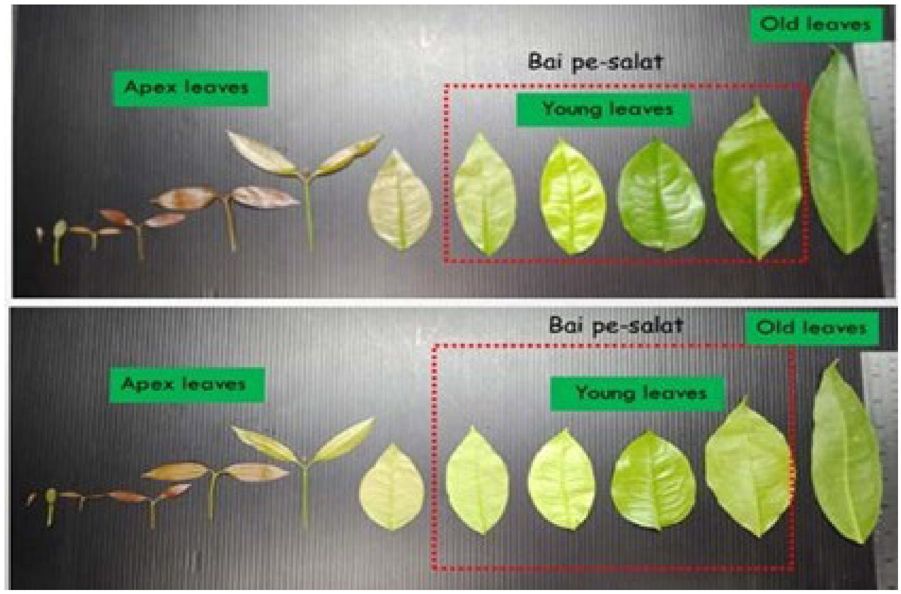


**Figure 3**. Appearance and characteristic of each stage of *Gnetum gnemon* var. *tenerum* Linn. leaves. Source: photographed by authors.

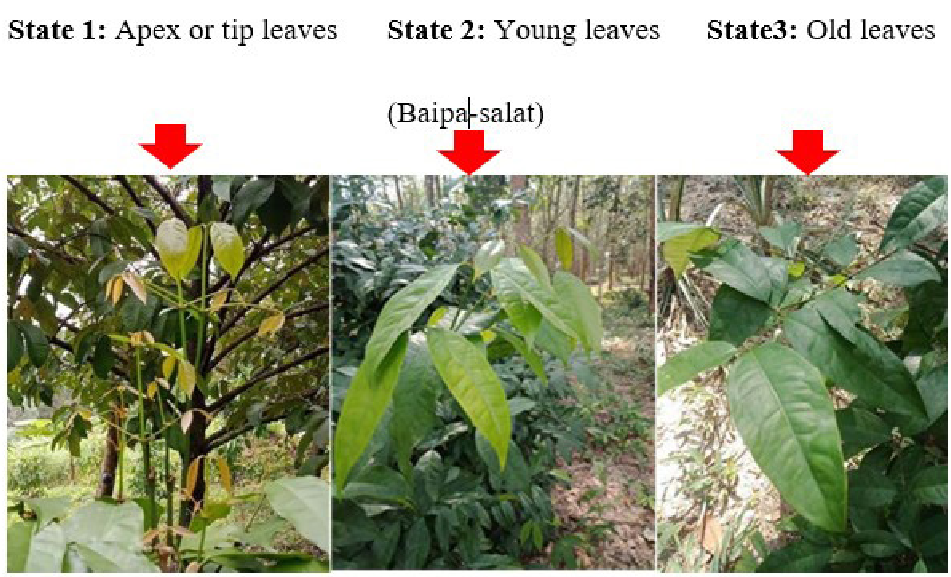


**Figure 4**. State of *Gnetum gnemon* var. *tenerum* leaves. Source: photographed by authors.

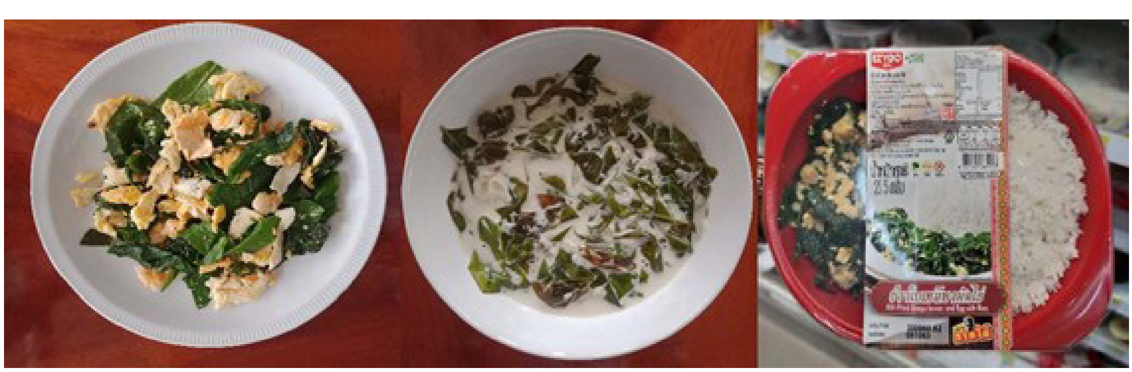

**Figure 5**. Popular recipes of *Gnetum gnemon* var. *tenerum* leaves, such as Liang leaf fried with egg, Liang leaf boiled in coconut milk, and a commercial product. Source: photographed by authors.

and (4) *G. gnemon* var. *tenerum* are mainly found in Indonesia and Thailand, respectively (Barua et al., 2015). Only *G. gnemon* var. *gnemon* is classified as a tree (Figure 6-6.1), while the other 3 varieties are woody shrubs (Figure 6.-6.2). *G. gnemon* is used for dry land improvement and rehabilitation, and reforestation because it can survive despite an annual rainfall of 750-5,000 mm. In Papua New Guinea these plants can be seen planted alongside breadfruit (*Artocarpus*.), (*Pandanus conoideus*) and other food crops. In Thailand, they are grown as an intercrop in rubber plantations (*Hevea brasiliensis*) or with durian (*Durio zibethinus* L.), mangosteen (*Garcinia mangostana* L.), rambutan (*Nephelium lappaceum* L.), and string *(Parkia a* Hassk) (survey data and personal information from interview). With intercropping, the shade-tolerant habit indicates potential for use as a ground cover crop. The growth of plants succeeds in a wide range of well-drained soils, preferably slightly acidic to neutral but tolerating calcareous rocks. The plant roots associate with ectomycorrhizal fungus *Scleroderma sinnamariense*, which improves nitrogen levels in the soil (Bechem & Alexander, 2012). Thai farmers in various plantations, particularly rubber plantations, noticed that *G. gnemon* var. *tenerum* can reduce the cost of fertilizer, pesticide, and irrigation. Recently, Thai government encourages farmers to grow this plant as intercrop and provided a large grant for interdisciplinary research. Generally, *G. gnemon* is used or planted for many beneficial aspects, including food and energy. For agroforestry purposes, *G. gnemon* is widely planted as a home garden tree or at field borders, for agroforestry and soil improvement purposes in many places of Southeast Asia. The young leaves, tender tips, and inflorescences of *G. gnemon* are edible and used as vegetables in aspects of Assam, mostly by the Karbi tribe. In ethnic markets of NE India, Karbis, the Mongoloid race linguistically of Kuki-Chin sub-group consider tender leaves commonly traded vegetables (Barua et al., 2015). In addition, the leaves are claimed as queen of local vegetables in southern Thailand. In the countryside, woody trees and shrubs or big vine can be used for charcoal or firewood.

## 3 Proximate composition and nutritional value of *G. gnemon*

### *3.1 Leaf*

Many phytochemical compounds, including alkaloids, phenolic compounds, saponins and vitamin C have been reported in *gnemon* leaves. However, no leucoanthocyanin or tannin are detected (Mollejon & Gabane, 2019). The preliminary testing of *G. gnemon* var. *tenerum* leaves showed these are slightly acidic with pH of approximately 6.0, and the dry leaves contain (in g/100 g) 27% protein, 56.8% carbohydrates, and 36.3% total dietary fiber, and vitamin A at 3,706 µg/100 g. Interestingly, complete essential amino acids with high branched-chain amino acids (BCAAs) that help build up muscles were also found (unpublished data, preliminary experiment). Bharali et al. (2018) stated that the moisture content, protein, crude fat, ash, carbohydrate, and crude fiber of the dried leaf of *G. gnemon* (Indonesia origin) are 4, 8, 1, 7, 5 and 22 g/100 g, respectively. Additionally, the mineral content is highest in N at 1.3 g/100 g, followed by K, P, Mg, Na, and Ca at 0.4 g, 0.3 g, 0.25 g, 0.2 g, and 0.16 g/100 g sample, respectively. Micronutrients including Zn, Mn, Cu, and Fe at 0.22, 0.21, 0.18, and 0.09 g/100 g sample were recorded in Indonesia from *G. gnemon* leaves. Consumption of fresh leaves will provide only 57 kcal/100 g from the edible portion, with moisture, protein, fat, carbohydrate, crude fiber, and ash contents of 81.7, 4.2, 1.5, 6.6, 4.7, and 1.3 g/100 g, respectively (Hoe & Siong, 1999). The anti-nutritional factors in leaves of *G. gnemon* (Sabong) include arsenic, phytic acid, and tannins (0.07, 1.52, and 1.52 µg/g, respectively) but no cyanide, lead, or alkaloids (Hoe & Siong, 1999). Among the 25 varieties, popular indigenous leafy vegetables consumed in Sarawak showed that malinjau or leaves of *G. gnemon* possessed high mineral contents (P, K, Ca, Mg, and Fe) of 68, 419, 94, 37, and 3.8 mg/100 g in edible portion, and 41, 1.5 and 12.1 ppm of Mn, Cu and Zn, respectively while the other species (Tengang: *Gnetum* spp.) had 21, 32, 42, 51 and 1.2 mg/100 g in edible portion, and

(6.1) (6.2)

**Figure 6**. Phenotype characteristic of (6.1) *gnemon* variety and (6.2) *tenerum* variety (Morad, 2011). (6.1) and photographed by authors (6.2).

29, 0, and 14.4 ppm, in the same order (Hoe & Siong, 1999). The above data on *G. gnemon* var. *tenerum* leaves in Thailand indicated that this variety seemed to have higher nutrition than *G. gnemon* var. *gnemon*.

### *3.2 Seeds*

Seed flour (g) of *G. gnemon* Linn. is a good source of protein (19.0 g/100), crude fiber (8.66 g/100), carbohydrates (64.1 g/100) and total dietary fiber (14.5 g/100) on a dry basis; and total phenols, tannins, flavonoids of 15.1 mg GAE (gallic acid equivalent)/100 g, 35.6 mg CE (catechin equivalent)/100, 709 mg CEQ (catechin equivalents)/100 g ethanol extraction, which are higher than with aqueous extraction that gave 12.6 mg GAE/100 g, 16.1 mg CE/100, 81.6 mg CEQ/100 g, respectively (Bhat & Yahya, 2014).

Supriyadi et al. (2019) reported the hydrolysated seed protein at different stages of seed maturation and indicated that the green stage provided higher free radical scavenging activities and inhibitory activity of α-amylase and α-glucosidase than the other stages. In addition, antioxidant and DNA damage protection of fermented melinjo (*G. gnemon*) flour seed were reported in the study of Siswoyo et al. (2017). Two protein fractions are isolated from *G. gnemon* seeds that exhibited antioxidant properties had molecular weights of approximately 30 kDa (Gg-AOPI) and 12 kDa (Gg-AOPII) assayed by SDS-PAGE (Siswoyo et al., 2011).

## 4 Phytochemicals and biological activities of *G. gnemon*

For more than 10 years, Japanese researchers have been intensively investigating phytochemical compounds of *G. gnemon*, particularly from seeds collected from Indonesia. An abundance of stilbenoids (namely resveratrol), saponins, flavonoids, and tannins were reported (Kato et al., 2009; Santoso et al., 2010). Several bioactive compounds are considered antioxidants, anti-DNA damage, anti-inflammatory, and anti-microbial agents. Unidentified or crude phytochemicals of mature fruits and young leaves or shoots have been reported to have anti-asthmatic and anti-inflammatory activity and help reduce constipation in vitro (Syahdi et al., 2019). In addition, aqueous extract of *G. gnemon* leaves provided a high antioxidant activity compared with other extracts by using methanol, ethanol, hexane or chloroform (Wazir et al., 2011). However, bark extracted with ethanol exhibited the highest antioxidant activity (Syahdi et al., 2019). Among 15 indigenous vegetables and fruits, young leaves without stem of *G. gnemon* are an excellent source of vitamin C at 109.43 mg/100 g. In addition, it provided various natural bioactive compounds including beta-carotene (404.52 ± 14.93 μg/100 g), lutein (6,731.17 ± 238.95 μg/100 g) and polyphenols (253.45 ± 5.68 mg GAE/100 g) as well as vitamin E (1.33 ± 0.04 g/100 g) (Kongkachuichai et al., 2015). The extract of *G. gnemon* leaves is dark green in color, density 0.93 g/mL, with pleasant odor, and pH 5.45, which is slightly acidic and is miscible in both ethanol and water but immiscible in toluene, indicating that the compounds in the sample are quite polar. Nutritionally the average ash content is about 3.03% as a good source of minerals, while 32.59 (g/100 g) of carbohydrates are a source of energy. Fat content is 13.101 g/100 g, which can provide enough energy, 69.54 g/100 g moisture, and protein 17.96 g/100 g (Mollejon & Gabane, 2019). Predominant amino acids in *G. gnemon* leaves are branched-chain amino acids (BCAA) having an aliphatic side-chain with a branch (a central carbon atom bound to three or more carbon atoms). Among the proteinogenic amino acids found in *G. gnemon* leaves were leucine (1,930 mg/100 g), isoleucine (916 mg/100 g), valine (1,320 mg/100 g), and glutamic acid (1,850 mg/100 g) as dominant (unpublished data, preliminary experiment). Vitamins are essential nutrients, although needed only in very small amounts to maintain human health. From preliminary test, concentrations of vitamins B1 and B2 in dried *G. gnemon* leaves were quite fair at 0.17 and 0.62 mg/100 g, respectively. In addition, vitamin A content was 3,706 μg/100 g (unpublished data). It is known that vitamins act as co-enzymes and are involved in the synthesis of new cells as well as in the metabolism of fat, protein and carbohydrates. Vitamin C may prevent various diseases by protecting the tissues from oxidative stress with its antioxidant activity. In addition, twelve antidepressant nutrients relate to the prevention and treatment of depressive disorders, including folate, long-chain omega-3 fatty acids (EPA and DHA), magnesium, potassium, selenium, thiamine, vitamin A, vitamin B6, and vitamin B12 (LaChance & Ramsey, 2018). A review of the literature shows that the highest-scoring plant foods having potential for antidepressant activity were leafy greens, lettuces, peppers, and cruciferous vegetables (LaChance & Ramsey, 2018). Based on the amounts of vitamin A, iron, zinc, vitamin C, magnesium and potassium, therefore, *Gnetum* leaves should have a high potential to prevent and treat depressive disorders, and further investigations of these aspects should be pursued. Beta-carotenes are the dominant carotenoids in *G. gnemon* leaves. On average, the total carotenoid content of dry leaves is 3,706 μg/100 g (unpublished data, preliminary experiment). Chlorophyll-rich vegetables are well known for their multiple bio functions as antioxidants, antiaging, anticancer, and antimutagenic compounds. Some scientists have suggested that chlorophyll-related compounds can reduce the formation of cytotoxic heme metabolites and decrease the risk of colon cancer (Vogel et al., 2005). Pheophorbide-related compounds originating from the breakdown of chlorophyll have demonstrated anticancer activities against human tumor cell lines, including lung carcinoma (A549), ileocecal carcinoma (HCT-8), kidney carcinoma (CAKI-1) and breast adenocarcinoma (MCF-7), which were mediated by direct photoirradiation (Wang et al., 2019). In addition, pheophorbide and pyropheophorbide are efflux pump inhibitors that affect antibiotic resistance in bacteria (Wang et al., 2019). Ethanol extract of *G. gnemon* leaves showed a high antioxidant activity even though not as high as ascorbic acid. Protein hydrolysates from *G. gnemon* seeds at different stages from green to yellow and red exhibited antioxidant and anti-diabetic properties. Furthermore, the results revealed antioxidant and anti-diabetic activity through α-amylase and α-glucosidase inhibitory pathways in hydrolyzed protein of green stage was significantly higher than when unhydrolyzed. In addition, radical reduction activities in hydrolysated case had EC50 at 0.03 μg/mL and in nonhydrolyzed case this was 0.33 μg/mL (Supriyadi et al., 2019). The higher anti-hydrophilic radical activity against ABTS and superoxide radicals were due to the formation of shorter peptides (tri-dipeptide) and free amino acids (Chen et al., 1998). Later Hafidz et al. (2017) reported that using dichloromethane as an extraction solvent gave the highest inhibitory activity against hypercholesterolemia through hydroxy-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitory activity with IC50 value of 0.40 μg/mL. In addition, the seed extract contained trans-resveratrol, piceid, gnetin C, gnetol, isorhapontigenin, ε-viniferin, gnemonol L, and gnemonol M when analyzed with UPLC-MS. The tested compounds showed that resveratrol dimer provided the main anti-cholesterol activity via enzyme HMG-CoA reductase inhibition. It pointed out that the melinjo seed extracts with dichloromethane could not only prevent HMG-CoA reductase, but also potentially acts with MAH (original ligand) substrate against HMG-CoA reductase receptor, which might play a key role in the treatment of hypercholesterolemia. Betaine-based (NADES) component containing betaine-lactic acid can be used as an alternative solvent for resveratrol extraction from the seeds with high effectiveness (Aryati et al., 2020). In addition, the rind of the fruit has been tested for inhibition of xanthine oxidase, which relates to antigout activity. The results indicate that flavonoids, saponins, polyphenols, and alkaloids detected in the rind extract could play key roles as xanthin oxidase inhibitors. Bioactivities of bioactive compounds in *G. gnemon*

1. Acetylcholinesterase inhibitory (AChEIs) properties

Acetylcholinesterase is an enzyme participating in cholinergic neurotransmission. It breaks down acetylcholine (Ach) which terminates the neurotransmission process of synaptic function. The leaves of G. gnemon var. tenerum containing various phytochemicals including polyphenolics and flavonoids exhibited %AChE inhibition of 22.29 ± 3.71 (Langyanai et al., 2017). Therefore *G. gnemon* var. *tenerum* may be used to treat Alzheimer' s disease by enhancing the ACh level in the brain using acetylcholinesterase inhibitory AChEIs (Langyanai et al., 2017); however, the identified bioactivity needs further study on the efficacy.

2. Anti-quorum sensing property (Anti-QS)

Quorum sensing is a cell-cell communication protocol that allows bacteria to share information about cell density and adjust gene expression of autoinducers (Als) accordingly (Rutherford & Bassler, 2012). Tan et al. (2013) studied anti-quorum sensing (anti-QS) properties of *Piper nigrum, Piper betle* and *G. gnemon* leaves, which are common Malaysian food sources. The results indicate that *G. gnemon* leaf extracts provided anti-quorum sensing (anti-QS) properties to *Escherichia coli* at a lower concentration than the others. In addition, *N*-acylhomoserine lactones (AHLs) are a major class of autoinducer signals of *E. coli* (pSB401, pSB1075) and *Pseudomonas aeruginosa* PA01. Therefore, reduction of AHLs leads to less communication, potentially retarding or postponing growth.

3. Antioxidant activities

Seal & Chaudhuri (2016) investigated the antioxidant activities of five wild leafy vegetables *G. gnemon, Prenanthes hookeri, Smilax perfoliata, Blumea lanceolaria* and *Pilea melastomoides* generally consumed in Meghalaya and India. The results showed that the *G. gnemon* leaves were the highest in phenolic compounds and antioxidant activity determined by DPPH assay, followed by *P. melastomoides,* when extracted with benzene, chloroform and acetone. Santoso et al. (2010) studied antioxidant properties and DNA damage prevention activities of the edible parts of *G. gnemon* (young and mature leaves, seed skin, and endosperm). The results showed that the mature leaves exhibited the greatest levels of antioxidant activity, followed by the young leaves. In addition, the endosperm showed significant antioxidant activity as determined by ORAC, peroxyl radical-scavenging assay, and DNA damage prevention activity. However, boiling with purified water for 10 min reduced antioxidant components (total phenolic content, total polyphenol, total gnemonoside, total ascorbic acid) and antioxidant activities in all edible parts, except for the seed peel (Santoso et al., 2010). Three phenolic derivatives were isolated from the stem bark of *G. gnemon,* namely 3,4-dimethoxychlorogenic acid, resveratrol, and 3-methoxyresveratrol. Two active antioxidant protein fractions, Gg-AOPI and Gg-AOPII, were isolated and characterized from *G. gnemon* seeds (Siswoyo et al., 2017). Besides the protein fraction, also four stilbene derivatives, gnemonols K and L (resveratrol trimers), M (isorhapontigenin dimer), and gnemonoside K (glucoside of resveratrol trimer) together with stilbenoids and a lignan were found from the root of *G. gnemon*. The occurrence of various stilbenoids in the roots was reported in *G. gnemon* and other *Gnetum* species, and these provide antioxidant activity against lipid peroxidation and super oxide scavenging activity. In addition, three new stilbenes, gnemonols D, E and F, were isolated from the roots of *G. gnemon*. These compounds provided lipid peroxide inhibition and scavenging of superoxides in a xanthine-xanthine oxidase system with a potent antioxidant activity based on DPPH assay. Four parts of *G. gnemon,* namely leaf, bark, twig, and seeds, were extracted using methanol, ethanol, hexane, chloroform, and hot water by reflux. The total phenolic contents of the plant extracts were determined by the Folin-Ciocalteu method. Expressed in gallic acid equivalents (GAE)/g freeze-dried weight (FDW), the hot water extracts from bark (3.25 to 10.71 mg GAE/FDW) and sticks (3.13 to 10.3 mg GAE/FDW) showed the highest total phenolics while the lowest level was found in chloroform extract of seed (1.15 to 6.49 mg GAE/FDW). Antioxidant activity based on superoxides in a xanthine-xanthine oxidase system showed that all plant extracts exhibited weak free radical scavenging activity when tested at the concentration of 300 μg/mL (Wazir et al., 2011). In contrast, the methanol twig extract showed a strong reducing power (FRAP) at 83.55 ± 1.05%, while the hot water seed extract showed the least activity of 41.86 ± 4.22% when tested at the concentration of 300 μg/mL. In addition, there was no correlation between total phenolics and the DPPH and FRAP scavenging activities (Wazir et al., 2011). It is known that low-density lipoproteins (LDL) are major transporters of beta-carotene and lycopene in circulation. At low oxygen tension (< 150 Torr) and in normal air conditions, beta-carotene expressed a scavenger of peroxyl radicals, especially at low oxygen tension; but at a high oxygen tension, it is turned to a pro-oxidant (Tapiero et al., 2004). This behavior may also occur in others carotenoids. The interaction of carotenoids with peroxyl radicals may proceed via an unstable beta-carotene radical adduct. Carotenoid adduct radicals have been shown to be highly resonance stabilized and are predicted to be relatively unreactive. In addition, they change to generate non-radical products and may limit radical reactions by binding to the attacking free radicals. Antioxidant carotenoids can react more rapidly with peroxyl radicals than other unsaturated acyl chains do, and carotenoids are destroyed in this process. Carotenoids could partially or completely protect intact cells (e. g., human liver cell line HepG2) against oxidant-induced lipid peroxidation, and the protective effect is independent of provitamin A activity. Further, in both normal and transformed T-cells (thymocytes), beta-carotene acted as an antioxidant at 150 mm Hg pO2, inhibiting radical-induced lipid peroxidation. However, upon increasing the pO2 to 760 mmHg, beta-carotene lost its antioxidant activity in normal thymocytes and actually exhibited a dose-dependent pro-oxidant effect in the tumor thymocytes. These data indicate a key role of the oxygen tension on the antioxidant/pro-oxidant effects of beta-carotene. In addition, high carotenoid concentrations may also result in a pro-oxidative effect, which may be modified by interactions with other nutrients (Eldahshan & Singab, 2013).

4. Anti-inflammatory activities

Kato et al. (2009) reported that the fruits and seeds of *G. gnemon* are consumed for them nutrition values and are also used in traditional medicines. Using T-helper (Th) cytokine production, i.e., interleukin-2 (IL-2), IL-4, IL-5, and interferon-gamma (IFN-γ), in cultured Peyer's Patch (PP) cells from mice, immune responses to *G. gnemon* fruits were examined. The results revealed that oral administration of 50% ethanol extract of *G. gnemon* fruit potentiated production of Th cytokines such as IL-2 and IFN-γ in PP cells irrespective of Con-A stimulation, but no effect on the production of the Th2 cytokines IL-4 and IL-5 was noticed. Two new stilbene glucosides compounds, gnemonoside L and gnemonoside M along with the previously identified stilbenoids resveratrol, isorhapontigenin, gnetin C, gnemonoside D, and gnetin E were found from the active EtOAc (ethyl acetate) fraction. Among these tested isolated compounds identified by NMR assay, only the new stilbenoid gnemonoside M strongly elevated Th1 cytokine production in cultured PP cells at 10 mg/kg/day. This finding suggested that gnemonoside M was an active constituent of *G. gnemon* fruit potentiating T cell-dependent immune responses in the ileal mucosa (Barua et al., 2015). Additionally, there is growing evidence from *in vitro* and *in vivo* laboratory animal studies that beta-carotene can protect phagocytic cells against auto-oxidative damage, enhance T and B lymphocyte proliferative responses, stimulate effector T cell functions, and enhance macrophage, cytotoxic T cell and natural killer cell tumoricidal capacities, as well as increase the production of certain interleukins (Eldahshan & Singab, 2013).

5. Antimicrobial properties

The chemical composition and antibacterial properties of the crude hexane, dichloromethane, and methanol extracts of the leaves and bark of *G. gnemon* were studied (Naksrikum, 2015). The major phytochemicals were fatty acids: linoleic acid, 9,12,15-octadecatrien-1-ol, and linoleic acid found in the leaves extracted with hexane, dichloromethane, and methanol, respectively. On the other hand, the major phytochemicals of the hexane, dichloromethane, and methanol extracts from bark was 9,12-octadecadien-1-ol, linoleic acid and gamma-sitosterol, respectively. In addition, the crude hexane, dichloromethane, and methanol extracts of the leaves and bark of *G. gnemon* were also examined for antibacterial activity against the two species of bacteria *E. coli* and *S. aureus* by agar disc diffusion method. The results showed that all crude extracts of bark as well as the crude methanol extract of leaves had no inhibitory effect on the growth of either *E. coli* or *S. aureus*. However, the crude hexane extract of leaves was a potent inhibitor of *S. aureus* growth. The crude dichloromethane extract of leaves demonstrated activity against the Gram-negative bacterium *E. coli* (Naksrikum, 2015). Up to now, *G. gnemon* has been used traditionally for treating malaria-related fever by indigenous people of North East India. The ethanol extract of *G. gnemon* leaves showed promising antiplasmodial activity against *Plasmodium falciparum* chloroquine-sensitive (3D7) strain *in vitro* with an IC50 value of 29.4 μg/mL. Thereafter, it was further investigated by a bioassay-guided approach. The (1) 2,3-dihydroxypropyl icosanoate (2) oleic acid, and (3) ursolic acid were firstly isolated from the leaves by Dutta et al. (2018). Ursolic acid showed the highest antiplasmodial activity with IC50 of 4.0, and 6.0 μg/mL against *P. Falciparum* in both chloroquine sensitive (3D7) and resistant (Dd2) strains, respectively. The antiplasmodial activity of 2,3-dihydroxypropyl icosanoate had IC50 9.5 and 11.4 μg/mL, and oleic acid had IC50 17.6 and 21.1 μg/mL as moderately active. In addition, the isolated constituents showed a low cytotoxicity against rat skeletal muscle (L6) and human cervical cancer (HeLa) cells (Dutta et al., 2018). Cyclopropene fatty acid relating to antimicrobial activity and having also other health benefits in *G. gnemon* leaves were reported as 37.87% of the total fatty acid (Berry, 1980). The dried *G. gnemon* leaf extracted with 96% ethanol demonstrated anti-acne properties. The result demonstrated that the *G. gnemon* leaf extract could inhibit the growth of the bacterium *Propionibacterium acnes* (Meinisasti et al., 2019). The extraction of dried leaf of *G. gnemon* with mixed acetone water (1 : 1) gave *C*-glycosylflavones (isovitexin, vicenin II, isoswertisin, swertisin, swertiajaponin, isoswertiajaponin). The ethyl acetate (EtOAC) soluble extract of the leaves of *G. gnemon* revealed a new phenylheptanoid, gnetumal *p*-coumaric acid, which has potent tyrosinase inhibitory activity. Melinjo (*G. gnemon* Linn.) seed extract (MSE) containing trans-resveratrol (3,5,4'-trihydroxy-trans-stilbene) reduced serum uric acid at 4 weeks and 8 weeks and increased high-density lipoprotein (HDL) cholesterol (Konno et al., 2013). Major fatty acid components of *G. gnemon* Linn. leaves extracted by using hexane, dichloromethane, and methanol were linoleic acid, 9,12,15-octadecatrien-1-ol, and linoleic acid, respectively. The crude extract of *G. gnemon* Linn. bark contained 9,12-octadecadien-1-ol, linoleic acid, and gamma-sitosterol, respectively (Naksrikum, 2015). In addition, the crude hexane extract of leaves showed anti *Staphylococcus aureus* activity, and when extracted with dichloromethane, it exhibited activity against the gram-negative bacterium *E. coli.* However, the crude extracts of bark provided no inhibitory effect against either bacteria (Naksrikum, 2015). It seemed to indicate that the leaves provide potentially more antibacterial activity compared to the bark. Anti-cancer properties *G. gnemon* seed extracts were found to be rich in polyphenols such as dimeric stilbenoids, including resveratrol dimers: gnetin C, gnemonosides A and D, and a small amount of trans-resveratrol. Resveratrol and its dimers and derivatives have been reported to have several health-promoting properties, including anti-tumor and anti-cancer activities (Uson-Lopez et al., 2018). Recent studies have reported various pharmacological activities of *G. gnemon* seed extracts, including anti-tumor activity and cytotoxicity against a panel of cancer cells. However, there is no study reporting its effects on human hepatocellular carcinoma cells (HepG2). This apoptotic effect of *G. gnemon* seed extracts was found to be associated with reactive oxygen species (ROS) generation, suggested by the dose-dependent depletion of intracellular free-SH levels. Western blot data showed the modulation of BCL-2 family of proteins, cytochrome c release, and cleavage of caspase 3, implying the induction of mitochondrial apoptotic pathway. Furthermore, *G. gnemon* seed extracts inhibited the activation of the prosurvival NF-κB pathway via induction of dephosphorylation and up-regulation of IkB-α, which ultimately led to the inhibition of the translocation of NF-κB p65 to the nucleus. NF-κB regulates the transcription of the genes of anti-apoptotic proteins like BCL-2, so inhibition of its translocation to the nucleus impacts cell survival and death. From these comprehensive studies, it can be concluded that *G. gnemon* seed extracts likely serve as an anti-cancer drug substantiated by its inhibition of NF-κB pathway (Uson-Lopez et al., 2018). Animal studies have indicated that beta carotene can retard or inhibit the induction of sarcomas and skin cancer in mice exposed to carcinogens. The inhibitory effects of the newly-developed forms of beta carotene, water soluble and liposomal, have been studied in rats and in mice bearing tumors, which were induced in 4 models of carcinogenesis. Water soluble beta-carotene failed to influence the carcinogenesis in the mammary gland and esophagus in rats; however, it significantly inhibited carcinoma development in the murine vagina and cervix uteri (47%). Liposomal beta-carotene significantly inhibited lung adenomas (46.4%) and mammary carcinomas (55.6%) in the urethane-treated mice. In a conducted double-blind placebo-controlled trial to evaluate the chemopreventive potential of either vitamin A or beta-carotene studied in the USA, Canada, and Italy, beta-carotene as a single agent completely or partially reduced oral leukoplakia in 44-71%of patients (Eldahshan & Singab, 2013). Numerous studies have shown that a high intake of carotenoid-rich fruit and vegetables is associated with decreased cancer risk. However, a large study examining the effects of beta-carotene and alpha-tocopherol on prostate cancer revealed that beta-carotene apparently increased the risk of clinically evident prostate cancer only in drinkers, when (for dose related to alcohol intake) treatment decreased the incidence by 32% in non-drinkers, but on the other hand showed an increased risk of 25%, 42% and 40% in quartiles (Eldahshan & Singab, 2013).Trans-resveratrol (tRV), a stilbenoid polyphenol, gnetin C (GC) from *G. gnemon* seed extract significantly inhibited the proliferation of pancreatic, prostate, breast, and colon cancer cell types ($P < 0.05$), without any effects on normal cells. Interestingly, GC enhanced antitumor activity was higher than that of tRV ($P < 0.05$). The increased apoptosis of cancer cells may be due to caspase 3/7-dependent and independent mechanisms. Additionally, GC might trigger both early and apoptosis in cancer cells, at least in part by activating caspase 3/7-dependent mechanisms (Narayanan et al., 2015). Furthermore, the antitumor efficacy of Malinjo seed extract (MSE) was also validated in a widely used colon-26 tumor-bearing mouse model. Oral administration of the seed extract at 50 and 100 mg/kg per day significantly inhibited tumor growth, intratumoral angiogenesis, and liver metastases in BALB/c mice bearing colon-26 tumors ($P < 0.05$) (Narayanan et al., 2015).

6. Antihypertensive properties

Mun'im et al. (2017) reported that the seed extracted with ethyl acetate of *G. gnemon* revealed the highest angiotensin-converting enzyme inhibitory activity (ACE) with the inhibitory concentration 50% (IC50) value of $9.77 \times 10^{8}$ μg/mL and with the highest content of total phenolic compounds (575.9 mg GAE/g sample). The stilbene constituents found in the extracted seed were resveratrol, gnetin C, ε-viniferin, and gnemonoside A/B, which had ACE inhibitory activity similar to lisinopril (ACE inhibitor). Inhibitory effects of gnetic C, resveratrol dimer from Melinjo (*G. gnemon*) seed, on tyrosinase activity and melanin were reported by Yanagihara et al. (2012). Tatefuji et al. (2014) reported that using melinjo seed powder, which has been consumed as a food and food ingredient for a long time in continental Asia (particularly in Indonesia), is safe without acute oral or subchronic toxicity when studied in rat model. A bone marrow micronucleus model indicated that MSE powder at level up to 4,000 mg/kg/day had no sign of genotoxicity. Gnetin C isolated from fruits (seeds), flowers, and leaves was used in the treatment and/or prevention of hypertension, affecting anti-angiotensin II type 1 (AT1) receptor as already patented in JP2013193997A. However, the plant part mostly used to produce gnetin C is the endosperm. The extract was applied in various ways, including food, nutraceuticals, pharmaceuticals, and antihypertensive agent. Gnetol (trans-2,6,3',5'tetrahydroxystilbene) is a stilbenoid found in various species of the genus *Gnetum*, which is a gymnospermous plant with more than 35 species that occur as trees, shrubs and lianas. Specifically, gnetol has been isolated from *Gnetum ula, G. gnemon, G. montanum, G. klossii* and *G. hainanese*. Gnetol is used in folk medicine for arthritis and asthma (Akinwumi et al., 2018). The ethanol extract of melinjo seed (MES) in preclinical testing exhibited antioxidant, anti-inflammatory properties and other health promoting activities based on its stilbenoids content (Espinoza et al., 2015). A summary of bioactivities of *G. Gnemon* is compiled in Table 1.

## 5 Microbiota dysbiosis

Thylakoid, a part of the chloroplast in all green vegetable tissues, is recently associated to promoting weight loss by increasing *Bacteriodes fragilis* and enhancing satiety in rats, induced byaltering appetite hormones. In addition, dietary fiber of vegetables could inhibit weight gain, and white adipose tissue accumulation through modulation of gut microbiota, including increases of *Bacteroidetes* to *Firmicutes* ratio and *Roseburia* abundance in high-fat-diet (HFD) induced fat mice. Vegetables and fruits could attenuate long-term weight gain with more abundance of *Ruminococcaceae*,which could improve energy metabolism (Meinisasti et al., 2019).In general,the anti-obesity effects of vegetables have been addressed. Dysbiosis, a

**Table 1**. Bioactivities of *G. gnemon* that may relate to direct and indirect health benefits.

| Bioactivity in *G. Gnemon* | Source | Activity | Reference |
|---|---|---|---|
| Treat Alzheimer's disease | *G. gnemon* leaves extracts | Exhibited acetylcholinesterase inhibitory (AChEIs) (% inhibition of 22.29 ± 3.71) | Langyanai et al., 2017 |
| Antiquorum sensing property (Anti-QS) | *G. gnemon* leaves extracts | Reduction of AHLs leads to less communication. *E. coli* (pSB401, pSB1075) and *P. aeruginosa* PA01. | Rutherford & Bassler (2012); Tan et al. (2013) |
| Anti inflammatory activities | *G.gnemon* leaves extracts | Beta-carotene protect phagocytic cells against auto-oxidative damage, enhance T and B lymphocyte proliferative responses, stimulate effector T cell functions, and enhance macrophage, cytotoxic T cell and natural killer cell tumoricidal | Eldahshan & Singab, 2013 |
| Antimicrobial properties | *G. gnemon* leaves extracts | -Antibacterial activity against the two species of bacteria *E. coli* and *S. aureus*<br>-Antiplasmodial activity against *Plasmodium falciparum* | Dutta et al., 2018 |
| Anticancer properties | Young leaves | Beta-carotene can retard or inhibit induction of sarcomas and skin cancer in mice | Eldahshan & Singab, 2013 |
| Antihypertensive properties | Flowers and leaves | Affecting anti-angiotensin II type 1 (AT1) receptor | Akinwumi et al., 2018 |

broad spectrum of imbalance of the gut microbiota, is one of the most crucial factors in gut dysfunctions related to many human diseases, including obesity, metabolic syndrome, inflammatory bowel diseases (IBDs), and non-alcoholic fatty liver diseases (NAFLD). The onset and development of gut dysbiosis are complex and may involve various mechanisms. Impaired IgA production and function exert vital roles in the initiation of the imbalance between an opportunistic bacterial pathogen (OBP) and commensal microbiota. Carotenoids such as beta-carotene in the metabolite form of retinoic acid (RA) may contribute to the gut immune homeostasis by directly regulating IgA production, thereby preventing of and/or delaying the development of dysbiosis even though the precise mechanisms are not yet well elucidated (Lyu et al., 2018). Since *G. gnemon* leaves are rich in phytochemicals including beta-carotene and fiber (Unpublished data, preliminary test), they should promote the growth of probiotics to deliver various beneficial compounds, such as vitamin A and short chain fatty acids etc., to the tissues of a mammalian host (Wassef et al., 2014).

## 6 Other properties

A recent study in HIV-infected women reported that there were lower serum concentrations of lycopene, alpha-carotene, and beta-carotene, especially in persons with low counts of CD-4 (Cluster of differentiation 4) helper cells. In addition, both beta-carotene and selenium were deficient in a significant percentage of both HIV and AIDS patients. The conclusion stated the roles of carotene and selenium as antioxidants in HIV/AIDS which are related to both direct immune modulation and inhibition of cytokine and NF-kB activation, inhibiting HIV replication. Beta-carotene has been shown to act directly as an immunomodulator by increasing natural killer cell function and improving CD4 count. As an antioxidant, beta-carotene, which was found at high level in *G. gnemon* leaves, supported enzymatic defense systems involved in minimizing oxidative damage (Patrick, 1999). In addition, *G. gnemon* seed extract consumption during lactation can be beneficial to the offspring of fructose-treated pregnant rats (Uson-Lopez et al., 2018), even though theactive compounds and mechanisms have not become clear yet.

## 7 Conclusions

In its unique nutritional composition, *G. gnemon* contains quite complete essential amino acids, and is high in beta-carotene and dietary fiber in plant parts from root to tip, including flowers and fruit. This plant deserves attention from the agricultural, pharmaceutical, and medical sectors. A literature review has shown that the fruit of *G. gnemon* var. *gnemon* are used as flour to make snack products. The main components in the fruit seeds (*G. gnemon*) are carbohydrate, protein, and fiber, while stilbenoids are the major active ingredients, and saponins, flavonoids, and tannins relate to various health benefits against diabetes and cardiovascular diseases. *G. gnemon* var. *gnemon* may get more attention, particularly for fruit and seeds, but recently *G. gnemon* var. *tenerum* has been co-planted on many plantations to supplement farmer income, reduce the use of pesticides, and to act as a soil fertilizer. *G. Gnemon,* particularly the *tenerum* variety, is native to and a signature vegetable in southern Thailand, with more attention to its leaves than to other plant parts. However, scientific information dealing with the leaves of *G. gnemon* var. *Gnemon,* which differs from *G. gnemon var. tenerum*, is still lacking both in vitro and in vivo.

There is no recent scientific study on various aspects, including agriculture management, harvesting technology, processing, and health impacts. Regarding the bioavailability of the compounds in leaves before and after digestion, future tests with a gut model system should provide more and deeper information. Therefore, further investigations of the *tenerum* variety are of interest in several aspects.

## Acknowledgements

This manuscript was proofread by Assoc. Prof. Dr. Seppo Karrila, for the Research and Development Office (RDO) of the Prince of Songkla University.

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