Plant Archives Volume 20 No. 1, 2020 pp. 2979-2986 **e-ISSN:2581-6063 (online), ISSN:0972-5210**

THE PHYTOCHEMICAL POTENTIAL OF GNETACEAE WITH PECULIAR REFERENCE TO *GNETUM ULA* AND TRADITIONAL USES OF *GNETACEAE* SPECIES

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Abstract

India is the home of numerous medicinally significant plants. These plants are used by people from over centuries. Among these plants, we have *Gnetum ula* (*G. ula*) which is found in India (Western Ghats). It belongs to the Gnetaceae family with one genus (*Gnetum*) and approximately 40 species. It is valued for its taxonomic distinctiveness and outstanding biological interest. Conventionally, it is extensively used to treat several ailments such as arthritis, jaundice, rheumatism, inflammation, etc. Initial phytochemicals analysis of *Gnetum ula* (*G. ula*) displayed the existence of saponins, tannins, resin and alkaloids, etc. Although, the plant has less economic significance. It has no official monograph and less scientific reports. These backdrops lead to lacking the attention for the plant during policy framing for conservation. Hence, the present article is an effort to compile and review the morphology, uses and importance in *Gnetum ula* and also explores the phytochemicals present in various species of *Gnetum*.

Key words: *Gnetum ula*, Gnetaceae, Phytochemicals, Western Ghats.

Introduction

Gnetum ula Brongn (2n=44) constitutes a precious group of plants where the plants have got unparalleled assembly of characters which are prevalent in both angiosperms as well as gymnosperms. This plant belongs to family Gnetaceae, which includes 40 species of *Gnetum* distributed globally. Five species (*G. contractum, G. gnemon, G. montanum, G. ula*having the synonym *G. scandens* Brandis Hook. f. (non-Roxb.) and *G. latifolium*) have been notified from India out of which *Gnetum ula* is most commonly occurs especially confined to Western Ghats, India. It is found in the Nilgiri and Palni hills of Tamil Nadu, a Godavari district in Andhra Pradesh, Orissa and South Andamans (Bharadwaja, 1957)

The flowering season of the plant is from March to April and fruits are sets April onwards (Guhabhakshi *et al*., 2001). Seeds, which are locally called as Kumti Beeja in Udupi, are used to eat either by roasting or boiling and the seed oil is also being used in rheumatism by folklore practitioners (Wealth of India, 1956). Leaf and Stem extracts are useful in treating both liver enlargement and jaundice (Pushpangadan and Atal, 1986), while leaf paste which can be applied externally can be used to curearthritis (Devi Prasad *et al*., 2014). The stem is notified to contain gnetol a stilbene, butanedione and gnetin. Seed kernel contains oil with sterculic, fatty acids and malavalic acids (Yoganarasimhaam, 1996)

It is a woody climber and the edible part is fruit. The fleshy sarcotesta is sweet and attracts flies, bats, rodents and several microorganisms that feed on it. Because of the unique characters which are a mixture of both angiosperms and gymnosperms; its taxonomic position has attracted the interest of many systematists and morphologists. It closely related to the genus *Ephedra* and *Welwitschia* based on phylogenetic analysis (Hou *et al*., 2015; Hsu *et al*., 2016)

Loss of habitat is the major threat to this plant. It is cut down along with the host plant and is useful as fuel (Baloch and Bachman, 2011). The seeds of *G. ula* are

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shed in June and germinate in approximately one year. Hence, this long seed dormancy is also a major problem for its propagation. To deal with this problem, the somatic embryogenesis technique employed and embryo callus obtained on the medium Murashige and Skoog with benzyl adenine (5mg/ml) hormone (Augustine and D'souza, 1997).

Morphology

G. ula is a woody liane straggling on tall trees. The plant body is distinguished into the roots, stem and leaves. The roots are taproot with profused branching, devoid of leaves in the lower portion. The stem articulated with prominent joints, which help the plant to climb on the host plant. The leaves are oval, entire with reticulate venation altogether like an angiosperm in general appearance.*G. ula* is a dioecious plant. Each one of the male flowers has a stalk bearing two unilocular anthers enclosed in a perianth. The female flower consists of the nucellus surrounded by three envelopes of which the outer most forms the micropylar tube to facilitate pollination. The pollens are shed during January and pollen grains become inhabitants in a pollination drop. When the drop dries the pollen is sucked in and germinates inside the pollen chamber. The pollen tubes reach the female gametophytes during the end of January. Fertilization happens during the 1st week of February. During fertilization, the gametophyte consists of a cellular endosperm at the base and free nuclei in the upper region. After fertilization, the walls get arranged in the free nuclear portion of the female gametophyte. With further growth, the bottom area of the endosperm becomes broader than the upper. Later the higher or upper area of the gametophyte is further consumed by the down growing suspensors. Finally, the gametophyte assumes an oval form with the upper part partially compressed and crushed. The zygote divides after a period of rest of approximately 15 days and the primary suspensor tubes are seen towards the end of February. During the next four months the suspensor tubes branch out and in June, are seen as a mass of coiled suspensors in the gametophyte. During June end or July, the seeds are shed. When the seeds are shed, the female gametophyte is packed with food reserves which enable the young undifferentiated embryo to continue its growth till germination. In August the seeds show a bundle of coiled suspensors with a few embryonal cells forming a small embryo head. During the 1st and 2nd weeks of September, a large multicelled secondary suspensor and the embryonal cells forming a well-defined head can be seen. Towards the ending time of the month, the stem apex and the initiation of the two cotyledons starts. The seeds have a three-layered seed coat, the outer sarcotesta is orange in color and fleshy, the middle one is stony and the inner is a thin and papery membrane. Within the seed coat is the fleshy nucellus in which is embedded the female gametophyte. The embryos lie in a cavity called the corrosion cavity which runs longitudinally through the female gametophyte (Markgraf, 1930)

Phytochemistry

Phytochemicals are a massive group of compounds that occur naturally in plants, endowing flavor, color, texture and aroma. These compounds have formulated from over thousands of years of evolution to provide protection to organisms from the effects of viruses, free radicals, fungi and bacteria. They are present in vegetables, fruits, whole grains, legumes, seeds, nuts, herbs fungi and spices and beverages such as tea and wine (Barbieri *et al*., 2017).

Phytochemicals are plant components that are widely used because of their ability for providing many health benefits. It is very crucial to set up the scientific rationale so as to defend the use of phytochemicals in foods, mainly as possible nutritionally active ingredients (Dillard and German, 2000).

Phytochemistry has become a distinct discipline in recent years, somewhere in between plant biochemistry and natural products of organic chemistry and is somewhere closely concerning both of these. It handles their natural distribution, their biosynthesis, their chemical structures, their biological function and turnover and metabolism, etc. In all of these operations, various methods are required for identification, separation and purification of the various constituents which are present in plants. Thus, greater and higher the advances in phytochemistry more will be the successful exploitation of notable techniques and the continuation of the evolution of new techniques which will help to resolve the problems which are outstanding. One of the priorchallenges of the branch of phytochemistry is to carry through all the above (Harborne, 1984).

Phytochemical screening of *G. ula* revealed the presence of phenols, flavonoids, alkaloids, tannin, phytosterols and carbohydrates from different extract prepared from stem (Preetham*et al*., 2015). However, only a few studies are available particularly with the phytochemistry of *G. ula*. Therefore, the whole *Gnetum* genus has been considered to reveal the phytochemicals' existence. The *Gnetum* species are rich in stilbenes and its derivatives and are responsible for various bioactivities. A list of phytochemicals isolated from *Gnetum* genus is given in the table 1.

Table 1: Phytochemicals from *Gnetum* species.

S. N.	Plant name	Compounds	References
1	*Gnetum ula*	Bergenin, 2-hydroxy-4-benzyloxyacetophenone 3,4-methylenedioxy-4'-methoxytrans-stilbene, 3,3',4-trihydroxy-2-methoxy-trans-stilbene, 2,3',5',6-tetrahydroxytrans-stilbene (gnetol), 3,4,5'-Trihydroxy-3'-methoxy-trans-stilbene, 1,4-Bis(2,4_dihydroxypkenyl)butanedione, 2-Methoxy-3,4,3'-trihydroxystilbene, Gnetulin, Gnetulin acetate,	(Prakash *et al*., 1985, Prakash *et al*., 1981, Siddiqui *et al*., 1993)
2	*Gnetum gnemon*	Isovitexin , Isovitexin -7-O-glucoside, vicenin II, 7-U- methyl-C-glucosylflavones, Swertisin, swertisin -X"-O-glucoside, isowertisin, Swertiajaponin, Isoswertiajaponin, Gnetifolin K, Gnemonoside A, B, F, Gnemonol A, B, D,E,F, G,, I,J,K,L, Gnetoflavanol E, F, (-)-e-viniferin, gnetol, isorhapontigenin, gnetifolin E, isorhapontigenin-3-O-β-d-glucopyranoside, resveratrol , latifolol, gnetifolin K, (+)-lirioresinol B	(Wallace and Morris, 1978, Iliya *et al*., 2003a, Iliya *et al*., 2002a, Iliya *et al*., 2003b, Iliya *et al*., 2003c)
3	*Gnetum cleistostachyum*	Gnetucleistol B, C, cis-Shegansu B, Bisisorhapontigenin A, gnetubainin P, Gnetulin, Gnetifolin F, GnetumontaninC, Lehmbachol D, Gnetucleistol F, Gnetifolin A, p-hydroxycinnamic acid, piceatannol, resveratrol, Gnetofuran A	(Yao *et al*., 2005, Yao and Lin , 2005, Yao *et al*., 2006)
4	*Gnetum parvifolium*	Gnetifolin K, Parvifolol A, B, C, D, gnetulin, resveratrol, isorhapontigenin, isorhapontigenin-4'-*O*-β-glucopyranoside, isorhapontigenin-3-*O*-β- glucopyranoside, (-)-*ε*-viniferin, 2b-hydroxyampelopsin F, pinosylvin, gnetol,	(Lin *et al*., 1992, Xu and Lin , 1997, Tanaka *et al*., 2001)
5	*Gnetum africanum*	Gnetifolin K, Gnemonoside A, B, H, I, J, Bisisorhapontigenin B, Gneafricanin A,B,C,D,E,F, Gnetoflavanol A,B,C,D	(Iliya *et al*., 2003c, Iliya *et al*., 2002b- Iliya *et al*., 2002c, Iliya *et al*., 2002d)
6	*Gnetum montanum*	Gnetifolin P, L, M, N,O,	(Xiang *et al*., 2002, Chen , 1996; Chen , 1998)
7	*Gnetum klossii*	Gnetofuran A, B, C	(Ali *et al*., 2003)
8	*Gnetum montanumf. Megalocarpum*	GnetumontaninA, C, D, Shegansu B, Gnetuhainin M	(Li *et al*., 2004)
9	*Gnetum pendulum*	Gnetupendin C, D, resveratrol, isorhapontigenin, shegansu B, b-daucosterol, 3-*O*-(13-hydroxy-9*Z*, 11*E*,15*E*-octadecatrienoyl) cycloeucalenol, 24'-hydroxy-tetracosyl ferulate, gnetupendin A , B	(Li *et al*., 2001a, Li *et al*., 2003, Xiang *et al*., 2008)
10	*Gnetum gnemonoides*	Gnemonoside A, B, C, D, E, H,G, Gnemonol B	(Iliya *et al*., 2002d, Iliya *et al*., 2001, Iliya *et al*, 2002e)
11	*Gnetum hainanense*	Gnetuhainin A, B, C, D,E,F,G,H,I,J,K,L,N,O,P,S, R Gnetuhainin M, gnetulin, rhapontigenin, isorhapontigenin, gnetol	(Huang *et al*., 2000a, Huang *et al*., 2000b, Wang *et al*., 2001)
12	*Gnetum latifolium*	Latifolol	(Iliya *et al*., 2002f)
13	*Gnetum cuspidatum*	Resveratrol, Cuspidan A and B	(Shimokawa *et al*., 2012)
14	*Gnetum brunonianum*	Gnetubrunol A, Shegansu B, Resveratrol, Isorhapontigenin, Gnetifolin E, Isorhapontigenin-11-O-b-D-glucopyranoside	(Yao *et al*., 2012)

India has a long term history of utilization of conventional and traditional herbal medicine for health care. India has an old-time tradition of employing and utilizing the medicinal plants and medicines made from herbs for the eradication of various diseases and relief from ailments, as well as for the indorsement and ennoblement of happiness and health. People look towards traditional medicines or systems because not only do they believe in the curative effects but also they consider that plants provide them youth and good health. Ethnomedicine is the system of medicine which is widely masteredin the tribal as well as aboriginal populations for the management and curing of ailments. Primitive societies weredependent on herbal remedies because these medicines they used for treating several disorders and diseases since old times (Singh *et al*., 2003).

Ethnomedicinal uses

Tribal and conventional medicines have been used for centuries with fundamental and important contributions made by various practitioners for the betterment of human health, specifically as basic providers of health care at the community level (Jain, 1967). Traditional medicine uses the skills, practices, knowledge, beliefs and experiences endemic for the cultures, for the well-being of the local people. It has a renowned inheritance, acceptance from communities and is based on the skill fullness gained by herbalists over time immemorial (Ved and Goraya, 2008).

Gnetum ula

In the era of developed medical science, still different parts of plants are used as medicine to cure various ailments in the remote areas. In an ethnobotanical survey, the stem of *G. ula* was reported to be used to cure jaundice in Tamil Nadu (Tirunelveli district), India (Mohan, 2008). Similar reports were found in the Vellore district of the state Tamil Nadu, India (Thirumalai*et al*., 2010). Fruits and oil extracted from the plant are used as a stimulant and anti-rheumatic agent in the Hassan district of Karnataka (Prashanth, 2016). The presence of glucosylflavones, stilbenes, malvalic acid, sterculic acid are the bioactive components responsible for the anti-rheumatic and antiperiodic activity (Sharma and Arya, 2016). Antifungal and Antibacterial activity was also reported by Kumar and Swamy, (2014). A part from these, ethanolic extract of *G. ula* also possess potent lethal larvicidal and ovicidal activity against malaria and dengue vector (Dhanasekaran *et al*., 2013).

Other plants of Gnetaceae are also traditionally used.some of the examples are *Gnetum gnemon*is majorly cultivated end to end in the region of Aceh and is considered as a vegetable belonging to high status. The female strobilus and male strobili leaves are mostly used as main constituents in their traditionalistic vegetable curry known as Kuahpliek which is served on various traditional occasions, like as khanduri and keureudja. In Java, the unpeeled seeds and young leaves are used as constituents in a dish called sayurasem.

Japanese scientists in the recent times found out that *Gnetum gnemon* does not cause of gout (uric acid disease) as believed earlier (Mori *et al*., 2008). The flour from the seeds of *Gnetum gnemon L.* (Belinjau) was evaluated for determination of antioxidant activity, functional properties and nutritional composition. It was found that the Seed flour was rich in crude fiber (8.66 g/ 100 g), protein (19.0 g/100 g), total dietary fiber (14.5%), carbohydrates (64.1%) and it contained adequate amounts of essential fatty acids, amino acids and minerals. The Antioxidant compounds like tannins (35.6 and 16.1 mg CE/100 g), flavonoids (709 and 81.6 mg CEQ/100 g) and total phenols (15.1 and 12.6 mg GAE/100 g), were high in ethanolic extracts over aqueous extracts. Inhibition of DPPH was found to be low in aqueous extracts (19.7%) in comparison to ethanol extracts (48.9%), while as aqueous extracts showed high FRAP value in comparison to ethanol extracts (0.98 and 0.61 mmol Fe(II)/100 g, respectively). Functional properties results showed the absorption capacities for oil and water (1.98 and 5.51 g/ g respectively), foaming capacity (5.78%) and stability and emulsion capacity (6.90% and 15.3% respectively). FTIR analysis revealed that the seed flour contained major functional groups such as carboxylic acids, amides, amino acids, polysaccharides, amines lipids and esters. Seed flour from belinjau possesses a rich value in terms of nutraceuticals, so this makes it as a high possibility to be used as a basic raw material for the development of new nutritious functional foods which are also low cost (Bhat and Yahya, 2014).

Also, this species of *Gnetum* has other benefits as well. The study was done on the molecular docking of stilbene contained in melinjo seeds and inhibitory activity of ACE *i.e* angiotensin-converting enzyme of melinjo (*Gnetumgnemon*) seed extract. The seed powders from Melinjo were extracted with dichloromethane, methanol, ethyl acetate, n-hexane and water successively. The evaluation of extracts was done with ACE kit-Wist for ACE inhibitory activities and with Folin–Ciocalteu method for phenolic content. The extract that showed the highest ACE inhibitory activity was taken for liquid chromatography-mass spectrometry (LC-MS) to get its stilbene constituent. Results revealed that the vitro analysis of ethyl acetate extract from melinjo seeds showed to

have the highest ACE inhibitory activity. Analysis of Molecular docking indicated that gnetin C, gnemonoside A and resveratrol dimers can be considered an ACE inhibitor (Abdul *et al*., 2017). Seed extract from *Gnetum gnemon* L. (Melinjo) (MSE) is considered as a potent entity as a skin-whitening agent because it consists of trans-resveratrol and derivatives of trans-resveratrol, which helps to inhibit tyrosinase in the melanogenesis process. Using MSE in cosmetic products will be difficult because of bioavailability in the skin and chemical instability of resveratrol. Lipid particle technology is used to develop many cosmetic products for bringing improvement in their limitations. So for testing, this experiment was carried out and the result showed the test product did not induce skin irritation effect. The skin melanin index was significantly decreased that too statistically ($P < 0.05$) after 28 days of application of the test product and the average was 3.50% and skin melanin index showed change by an increase of 0.75% in the control group (Sharma *et al*., 2019).

Gnetum as an economic crop has a crucial role in fighting rural poverty. It contributes to the generation of income for a vast majority of people in the villages who are otherwise left out from benefiting because of the exploitation of the forest. It paves way for providing jobs to the youths who are involved in the process at all stages - harvesting, then loading, followed by transportation, etc. It is the women of these places who dominate the marketing of *Gnetum* leaves in both cross-border markets and internal markets. For the rural woman, it paves a way for providing various opportunities to earn money that leads to contribution to the well being of her household. The leaves of *G. Buchholzianum and Gnetum africanum* are highly valued, traditional dishes are prepared with these leaves and it establishes the cultural identity for some tribal groups in this region. The exportation of *Gnetum* leaves from places to European countries has increased and Africans and Americans who reside there are the main consumers. The species have completely disappeared in some areas where it used to be commonly found. Fundamentally, thousands of people depend on the marketing and harvesting of *Gnetum* leaves for their living - women constitute more than 80 percent (Nkefor, 2000).

Leaves of *Gnetum* are considered as tasty vegetables after they are shredded and made into condiments or incorporated into them, stew or soup, or even taken raw. This leads to the suggestion about the potential role of these species in fighting malnutrition in rural areas which are poor with only limited or few sources of meat.

Gnetum is an affordable alternative for a local population where life depends on wildlife as a protein source. Today, in West Africa in many restaurants, dishes based on *Gnetum* leaves are prominent on the menu list and also in Central Africa and in special eating places that offer African dishes in the USA and Europe.

There cannot be over-emphasis of Socio-economic value. Dishes which are prepared from leaves of *Gnetum* provides the cultural identity to certain tribes belonging or present in the region (Tekwe *et al*., 2003).

Gnetum species are rich in oligostilbenes, especially gnetol oligomers and isorhapontigenin. Isorhapontigenin and its oligomers were found to show various bioactivities, like anti-inflammation, antioxidation and antitumor (Li *et al*., 2001b; Li *et al*., 2002). Gnetol (2, 32, 52, 6-tetrahydroxy-*trans*-stilbene), genus *Gnetum* consisted of a naturally occurring compound that showed a strong inhibitory effect on the activity of murine tyrosinase. kojic acid (IC50, 139 μM) was less stronger than Gnetol (IC_{50}, 4.5 μM) as a standard murine tyrosinase activity inhibitor. Moreover, *gnetol* significantly leads to the suppression of the biosynthesis of melanin in murine B16 melanoma cells (Ohguchi *et al*., 2003). Stilbene derivatives were also found to possess protein kinase C inhibitory (Kulanthaivel *et al*., 1995) and anti-inflammatory activity (Huang *et al*., 2001). The interesting biological activities recently found that *Gnetin* I and *Gnemonol* G has apoptotic activity because of the fragmentation and nuclear condensation of DNA in human leukemia HL60 cells (Iliya *et al*., 2006). All these activities revealed the importance of plants containing stilbenoids as resources for developing new drugs.

An acetone extract from lianas of *G. Parvifolium* showed a strong inhibitory activity (79%) in the Maillard reaction (Tanaka *et al*., 2001). Lehmbachol D, Gnetifolin F, Gnetofuran A, *Gnetum*ontanin C, Gnetucleistol F, isolated from *G. cleistostachyum* shows moderate inhibitory activities on TNF-α and Gnetucleistol F also show potent inhibitory activity on malondialdehyde (Yao *et al*., 2006). Similarly, Gnemonol D, E and F isolated from *G. gnemon* show considerable antioxidant activity (Iliya *et al*., 2003d).

The young leaves, inflorescences and the ripe and young fruits are cooked in vegetable dishes. Thefruit is not more important than a seed covered with a seed coat (tough husk) and an edible rind which is thin because the seed is the most crucial and valuable part. It can be consumed raw but can also be stored as flat cakes out of which crisps are cooked or made. In Java, this makes it an important home industry. After the eradication of the rind, the seed is carefully heated and the husk is separated and the hot kernel is pulverized into flat cakes. The cakes

are dried in sun, classified and placed in order and then packed up for selling them. Puffing and bloating up the cakes in the boiling oil forms a crisp snack ("emping").

High-quality fiber is extracted from the inner bark; it is used for the famous Sumba bowstring and fishing lines and nets because the fiber is durable in seawater. Leafy vegetable of *G. gnemon var. tenerum* is of great significance in the southern part of Thailand (Verheij, 1991).

Ngbolua *et al* studied the extract and evaluated the bioactivity of organic acids and anthocyanins from *Gnetum africanum* and *Grewia coriacea* against SCD and associated bacteria. The antibacterial activity was carried out using the microdilution method and antisickling bioassay was carried out by the Emmel method. The results showed that organic acids and anthocyanin extracts of these plants possess antibacterial and antisickling activities. The calculation showed the values of rates for sickle erythrocytes normalization and it was found as 82% and 78% respectively for organic acids and anthocyanins extracts of *Grewia coriacea* and for organic acids extract of *Gnetum africanum* it was found as 88% (Ngbolua *et al*., 2016)

The phytochemicals from these species have been isolated because they contain an abundance of phytochemicals are studied and demonstrated (Azmin and Fatini, 2018). Because of these phytochemicals, these plants have been a source of food for many places like Malaysia, where they consume these plants since ages (Mohd Noor *et al*., 2019). Taking the theoretical research into consideration, the evolution between angiosperms and gymnosperms is still under dispute although considerably vast amounts of studies have been executed and implemented on the anatomy, chemical constituents, morphology and molecular biology. In terms of applicable research, the various constituents for biological activities, alkaloid, stilbene or its derivatives and flavone, etc. are greatly available in large quantities in this family. However, some species have been Chinese traditional medicines in history. Moreover, the utilization and exploitation has been blocked because of its deficiency in the studies of domestication, cultivation and introduction (Shi and Jiang, 2011)

Conclusion

Gnetum ula is a taxonomically striking plant. Its leafy canopy, thick twiners and cones make it ideal for use as an exclusive ornamental for trellises, pergolas, bowers and sheltered pathways in parks and gardens. It has been the least concern species due to various human activities. The plant has potential ethnopharmacological applications but is not considered as a classical drug in the Ayurveda. Hence, it is required to propagate the plant through proper conservation policies and advanced biotechnological tools. Also, research must be undertaken to explore the bioactive components with their applications for it to be brought in use as herbal drug.

Other species of *Gnetum* are traditionally very important and have been used since times immemorial over the world for different purposes and ailments as well. What makes *Gnetum* different is that it has both the features of gymnosperms and angiosperms. Having the characteristics of both makes *Gnetum* very unique and useful.

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