A review on the pharmacology and phytochemistry of traditional medicinal plant, *Glycosmis pentaphylla* (Retz.) Correa

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Received: 14-02-2012; Revised: 16-02-2012; Accepted: 21-04-2012

ABSTRACT

*Glycosmis pentaphylla* (Retz.) Correa belongs to Rutaceae family. It is commonly known as Orange berry (English). *G. pentaphylla* has a long history of usage in traditional medicine against various ailments around the world. It is commonly used as an Orange berry (English). *G. pentaphylla* has a long history of usage in traditional medicine against various ailments around the world. It is commonly used as an Orange berry (English). In Ayurveda and other traditional medicinal practices the plant has been used against diseases like bilious complaints, cough, worms, jaundice, fever, inflammation, rheumatism, anaemia and vermifuge. Phytochemicals like alkaloids, flavonoids, terpenes and sterols have been isolated. Important pharmacological activities such as hepatoprotective, anti-inflammatory, anti-tumour, antioxidant, antibacterial, anti-viral, anti-ulcer, chemo protective and antiseptic properties were shown by researchers. This review presents a detailed survey of the literature on various traditional uses, phytochemicals and pharmacological properties of *G. pentaphylla*.

Keywords: *Glycosmis pentaphylla*, traditional uses, phytochemicals, pharmacological activities.

INTRODUCTION

The herbal drugs have gained importance in the last few decades and their prevalence is continuously increasing in both developing and developed countries. Herbal drug are considered to be safer with lesser side effects. This is the most important factor for the wide acceptance of herbal medicine throughout the world. Plant based natural products have been the source of most of the medicines or ingredients of medicines. It has been reported that more than 80% of drug substances were natural products or their development was inspired by natural compounds [1]. The currently available technological advances and interdisciplinary research approach have speeded up the isolation and characterisation of pharmaceutically important molecules from natural sources. The traditional folk medicines of India use medicinal plant based drugs for preventing or suppressing various diseases [2].

*G. pentaphylla* is a common traditional/folklore medicinal plant used around the world against various ailments. Recent scientific publications support this traditional use. The plant is native to eastern, southern, and southeastern Asia and north-eastern Australia. *G. pentaphylla* is widely distributed from India, Malaysia and Southern China to the Philippine Islands where it occurs in tropical forests at low altitudes [3]. This plant is a small or medium sized evergreen shrub or small tree without thorns. It normally grows up to 4 m tall. The review will provide an outline of currently published research articles on the pharmacology and phytochemistry of *G. pentaphylla*.

Traditional Uses

Ayurveda, a traditional treatment system in India, have mentioned about the usage of this plant against various ailments. But a conventional scientific background to support this traditional knowledge is limited. The plant is used for cough, rheumatism, anaemia and jaundice [4-6]. Stems and roots of plant are used for treatment of ulcer. Paste of leaves, with a bit of ginger, applied over the navel for worms and other bowel disorders.

In parts of Asia the orange berry leaf is boiled down and used to reduce fever, liver complications and various intestinal parasites. The traditional healers in Gazipur district of Bangladesh utilize *G. pentaphylla* for prevention of all forms of cancer [7]. Stem and fruits of *G. pentaphylla* is used by medicinal practitioners in Bangladesh for the treatment of rheumatoid arthritis [9].

Roots were used in India against facial inflammation, rheumatism, jaundice and anaemia [10]. The root, stem and leaf of this plant are used in folklore medicine in Kerala and Tamil Nadu to cure fever, rheumatism etc [11]. Leaf juice is given with sugar in empty stomach in the morning to eradicate ascariasis. [12]. Crushed root piece mixed in water is administered in empty stomach in the morning to cure stomach pain. Juice of leaves is used in fever and liver complaints and as a vermifuge. Roots pounded and mixed with sugar are given in low fever and the wood of this plant has also traditionally been used to treat snakebite or to aid in appetite encouragement for women after childbirth [14].

In addition to these internal uses, orange berry has been utilized to help with excessive skin dryness. Folk medicinal practitioner in Jessore District, Bangladesh uses *G. pentaphylla* in combination with other plants to prevent bleeding from external wound as well as treatment of bone fracture and fracture induced pain [8]. Paste of leaves with ginger is used in eczema and skin affections. Leaves are considered as good antidote for eczema and other skin troubles and applied in the form of paste [13].

Chemical Constituents

recently a number of reports regarding the phytochemical analysis of *G. pentaphylla* have been published. Some of the major classes of compounds reported from *G. pentaphylla* include terpenoids [17], amides [18-24], imides [25], alkaloids [26-28], coumarins [29] and flavonoids [30]. Phytochemicals...
such as arborinine, glycozoline, 3-formyl carbazole, glycosinine, mupamine, varbazole, 3-methyl carbazole, glycolone, glycozolidol, glycozolinidol, glycozolylidine, glycozolidine, skimmianine, des-N-methylcrotonyline and des-N-methylroracronyline have been reported from this plant [31-40]. Air dried leaves yielded two furoquinoline bases, kokusaginine and skimmianine. Other alkaloids reported from the leaves include glycosine, arbinosine, arborinine (major), glycosamine, arborinone, arborinine, arbornine, skimmianine, glycorine, glycorine, glycozoline, glycozolidine, skimmianine, \( \gamma \)-fagarine and dictamine. Stems contain arborinine; other minor alkaloids also occur in this plant. The alkaloids arborinine, arbinosine, skimmianine, glycorine, glycozoline, glycozolidine and glycosicine have been isolated from the flowers. Glycolic acid has been isolated from the methanolic extract of the plant [41]. Six isoflavone glycosides like 3',7-dihydroxy-4',5,6-trimethoxyisoflavone 7-O-(5-O-trans-p-coumaroyl)-B-d-apiofuranosyl-(1\( \rightarrow \)6)-B-d-glucopyranoside, 2',7-dihydroxy-4',5,6-tetramethoxyisoflavone 7-O-(5-O-trans-p-coumaroyl)-B-d-apiofuranosyl-(1\( \rightarrow \)6)-B-d-glucopyranoside, 2',7-dihydroxy-4',5,6-tetramethoxyisoflavone 7-O-B-d-apiofuranosyl-(1\( \rightarrow \)6)-B-d-glucopyranoside, 2',7-dihydroxy-4',7-dimethoxyisoflavone 7-O-B-d-apiofuranosyl-(1\( \rightarrow \)6)-B-d-glucosepyranoside, 2',7-dihydroxy-4',7-dimethoxyisoflavone 7-O-B-d-apiofuranosyl-(1\( \rightarrow \)6)-B-d-glucosepyranoside, and 4',5-dihydroxy-3',7-dimethoxyisoflavone 4'-O-B-d-apiofuranosyl-(1\( \rightarrow \)6)-B-d-glucopyranoside have been reported [42-47]. Hydroquinone diglycoside acyl esters like, glypentosides and seguinonside, Glypentosides as methoxyquinoxilin 4-O-{(5-O-trans-p-coumaroyl)-B-d-apiofuranosyl-(1 \( \rightarrow \)2)-B-d-glucopyranoside} and 4-demethylantiroyl 4-O-{(3-methoxy-4-hydroxy-benzoyl)-B-d-apiofuranosyl-(1 \( \rightarrow \)2)-B-d-glucopyranoside} were reported from the stem of \( G. \) pentaphylla [48].

Pharmacological Properties
Recent pharmacological studies support the traditional medicinal use of \( G. \) pentaphylla. Several biological activities of \( G. \) pentaphylla have been reported. The major findings are given below.

Anti- hepatocellular carcinoma (HCC) activity
Recent study has showed that the alcohol extract of \( G. \) pentaphylla induces apoptosis on the hepatocellular carcinoma cell line (Hep3 B). The study has identified the major pharmacologically active molecule as is flavonoid which induces apoptosis by increasing the ratio of expression of apoptotic regulators Bax and Bcl2 in a time and dose dependent manner [49].

Hepatoprotective activity
Hepatoprotective activity of \( G. \) pentaphylla against paracetamol induced hepatic damage in Swiss albino mice has reported recently. The biochemical observations were supported by histopathological examination of liver sections from different experimental groups. The study has validated the hepatoprotective efficacy of methanol and petroleum ether extracts of \( G. \) pentaphylla. The results suggest that methanol extract of \( G. \) pentaphylla have higher hepatoprotective activity against paracetamol induced hepatotoxicity [50].

Wistar rats were treated with different concentrations of \( CCl_4 \) and proved the hepatoprotective effect of methanolic extracts of \( G. \) pentaphylla. The hepatoprotective effect of the extract was further confirmed by the histopathological examinations of the liver sections which revealed that the normal liver shape was disturbed by hepatotoxins intoxication and that was normalized after the extract treatment. It was concluded from the study that ethyl acetate and methanolic extracts of \( G. \) pentaphylla possess hepatoprotective activity against \( CCl_4 \) induced hepatotoxicity in rats [51]. Recent work suggested that the methanol extracts of \( G. \) pentaphylla significantly decrease the levels of serum markers after treating with different concentration \( CCl_4 \). The results are further supported by histopathological studies of liver tissue. Their results further confirmed that the methanol extracts offer significant dose dependent protection against carbon tetra chloride (\( CCl_4 \)) induced hepatic injury [52].

The hepatoprotective effect of stem bark of \( G. \) pentaphylla against the \( CCl_4 \) induced jaundice in rats has been reported early. The study showed that the crude extracts were administered orally for 7 days. On the 3rd and 6th day, the rats were given \( CCl_4 \) and olive oil subcutaneously in 50:50 ratios. The blood samples were taken on the 8th day and serum liver enzymes as alanine transaminase (ALT), aspartate aminotransferase (AST), glutamyl transpeptidase (GOT) and total bilirubin were analysed. The results of the study showed the crude extract of \( G. \) pentaphylla demonstrated the ability to prevent hepatic injury/liver necrosis in the preventive group and showed enhanced regeneration on the curative group [53].

The hepatoprotective efficacy of the butanol extract obtained from the aerial parts of \( G. \) arborea has been reported. Albino rats were prophylactically treated with the extract for 3 weeks. At the end of 3rd week all the groups were injected with hepatotoxic agents. After 48 h of injection liver function tests and histopathological studies were performed. They found that the \( G. \) arborea extract was able to overcome the toxic effects of hepatotoxic agents in terms of lowering the levels of serum glutamate pyruvate transaminase (GPT), alkaline phosphate (ALP) and increased level of super oxide dismutase (SOD) in serum. Thiobarbituric acid reactive substances (TBARS) generation in liver was also altered. Moreover, necrosis of liver produced by \( CCl_4 \) was reversed by the extract. All these results showed the hepatoprotective activity of butanol extract of \( G. \) arborea [54].

The hepatoprotective effect of leaf and stem bark extract of \( G. \) pentaphylla in albino rats were described after inducing hepatic injury with \( CCl_4 \). Parameters studied were includes plasma ALT, AST, ALP, total bilirubin and tissue histopathology. Recovery of hepatic tissue was indicated with the highest dose (750 mg/kg body wt.) of leaf extract. The therapeutic dose range was devoid of toxic effects. Toxicity of leaf extract was observed histopathologically and it was above 2.5 g/kg body weight [55].

Antibacterial activity
The anti-bacterial effect of different solvent extracts of stem and leaves of \( G. \) pentaphylla was described recently. The activities of the extracts were not significantly enough against most of the tested organisms. Chloroform extracts showed relatively better antimicrobial effect against the tested organisms. Whereas petroleum ether extracts were inactive against most of the tested organisms. Chloroform and methanol extracts of leaves exhibited higher activities against \( Staphylococcus aureus \). This study may be a lead for further ethnomedicinal investigation to identify new compounds with therapeutic promise [56].

Recently it has proved that the anti-bacterial activity of methanolic extracts of leaves and stems of \( G. \) pentaphylla against 12 test bacteria. The methanolic extracts of leaves and stems were found to inhibit the growth of several microbial species in agar media. Several bacteria were found to be insensitive to the extracts. However, the methanolic extract of stems showed significant antimicrobial activity against \( Escherichia coli \) and \( Salmonella paratyphi \). The antimicrobial activity could justify its traditional use as toothbrush [57].

The antimicrobial activity of leaf, stem and root extracts of \( G. \) pentaphylla were evaluated with different solvent extracts viz., petroleum ether, metha
anol and acetone. Bacteria like Bacillus subtilis and E. coli were used for study. The results of the study revealed that the methanolic extract of all parts of the plant showed effective antimicrobial activity against the tested organisms. However, the methanolic extract of stem part of this plant showed highest activity against the bacterium, Bacillus subtilis. Antibacterial effect of alkaloid especially graveolene and arborein from G. pentaphylla against Gram negative bacteria and its synergistic combination with suitable anti-bacterial chemotherapeutics also have reported [58].

The antibacterial activity of G. pentaphylla was estimated by disc diffusion method. The studies have evaluated different solvent extracts against a number of gram positive and negative microbes. It was identified that the methanol extract of G. pentaphylla exhibits a lower antibacterial activity against Staphylococcus aureus, Streptococcus beta haemolyticus, Bacillus cereus, B. proteus, Shigella sonnei, S. siga, Pseudomonas aeruginosa, Klebsiella sp. The high degree of antimicrobial activity seems to support the folk therapy for infectious and traditional therapeutic claims of this plant [52].

**Antifungal activity**

Compounds exhibiting antifungal activities have isolated and reported from several Glycosmis species [66, 67]. Recent findings evaluated the antifungal activity of chloroform, petroleum ether and methanol extracts from stem of G. pentaphylla against different fungal genus. Petroleum ether extract did not show any inhibitory effect against tested fungus. The fungus Aspergillus niger showed resistant against all the crude extracts. Of the three extracts, only chloroform and methanol extract was found to be active against all the tested fungi like Aspergillus flavus, Mucor sp and Candida sp [58].

**Anthelmintic activity**

Helminthic infections are now being recognized as cause of much chronic ill health and sluggishness amongst the tropical people. More than half of the population in the world suffers from worm infection of one or the other. The traditional knowledge related to anthelmintic activity of extract is well known. The recent study showed that G. pentaphylla roots showed potent anthelmintic activity on the earthworm, Pheretima posthumous. The study demonstrated that the methanol extract have greater activity than other extracts [65].

**Antioxidant activity**

Recently scientist has performed a survey of the antioxidant effect of different solvent extracts of G. pentaphylla by using 1,1-diphenyl-2-picylhydrazyl (DPPH) method. The results showed that the methanolic extract of G. pentaphylla stem showed moderate antioxidant property whereas the leaf extract showed very little activity. This antioxidant activity may be due to some polyphenolic compounds identified from this plant. The study results also indicated that G. pentaphylla contain a good source of medicinally important molecules [57].

Latest study has investigated the antioxidant effect of the ethanolic leaf extracts of G. pentaphylla. The antioxidant activity was evaluated by various antioxidant assays, including DPPH, 2,2’-azino-bis-(3-ethylbenzthiazoline-6-sulfonic acid) (ABTS), nitric oxide and hydrogen peroxide (H₂O₂) scavenging method. The antioxidant activities of extracts were compared with standard ascorbic acid. The findings suggested that this plant could be a potential natural source of antioxidants and could have greater importance as therapeutic agent in preventing or slowing oxidative stress related degenerative diseases. The overall antioxidant activity of these extracts might be attributed to its flavonoids, phenolic and other phytochemical constituents [59].

The antioxidant study with different crude extracts (petroleum ether, ethanolic and aqueous) of G. pentaphylla showed that extracts exhibits free radical scavenging activity and have hepatoprotective action also. The overall antioxidant and hepatoprotective activity of extract might be attributed to its triterpenoids and polyphenolic content and other phytochemical constituents. The findings of the study suggested that G. pentaphylla could be a potential natural source of antioxidants and could have greater importance as therapeutic agent [60].

**Antipyretic activity**

In recent a number of researchers have reported the antipyretic activity of G. pentaphylla in in vivo rat models. The study revealed that Ethanolic extracts of G. pentaphylla have good antipyretic activity in Brewer’s yeast induced pyrexia in rats. In general, non-steroideal anti-inflammatory drugs produce their antipyretic action through the inhibition of prostaglandin synthetase within the hypothalamus. Therefore, the antipyretic activity of G. pentaphylla is probably by inhibition of prostaglandin synthesis in hypothalamus [61, 62].

**Anti-tumor activity**

Brine shrimp lethality bioassay technique was applied for the determination of general toxic property of the stems and leaves extracts of G. pentaphylla. The in vitro lethality test has been carried out using brine shrimp nauplii eggs i.e. Artemia salina. The results suggested that the methanolic extracts prepared from stem of G. pentaphylla exhibits cytotoxic activity. Their findings clearly indicate the presence of potent anticancer bioactive principles in these extracts. Further studies regarding their isolation and characterisation are a need for tomorrow. This might be very useful as anti-proliferative, antitumor and other bioactive agents in future [57, 60].

The potential chemopreventive role of the hydro alcoholic leaf extract of G. pentaphylla was evaluated. The study found that specific activities of Cytb5, glutathione S-transferase (GST), Glutathione (GSH), Glutathione peroxidase (GPX), Glutathione reductase (GR), and SOD were significantly enhanced dose dependently by the extracts. The activity of CytP450 was observed to be increased only in the groups treated with a high dose of the extract. The findings indicate that the chemopreventive role of G. pentaphylla extract is through the synthesis of carcinogen metabolizing enzymes [63].

The antitumor activity of G. pentaphylla was recently attributed by many researchers. The results showed a potent inhibition of tumor produced by Agrobacterium tumefaciens on potato disc. Potato disc bioassay is a simple, convenient and inexpensive method for bioassay guided fractionation and isolation of active antitumor compounds. The final results Arborinine, an acridone alkaloid obtained from G. pentaphylla, exhibited significant inhibition of crown gall tumors produced by Agrobacterium tumefaciens in a potato disc bioassay [64].

**Wound healing activity**

Current findings suggest that the wound healing property shown by G. arborea syn. G. pentaphylla (Retz.) Correa (Rutaceae) is partly due to the increase in collagen synthesis, probably due to the presence of a mixture of phytoconstituents in the plant. The preliminary phytochemical screening of G. arborea leaf extract showed the presence of flavonoids, triterpenoids, alkaloids and polyphenols. Thus from this preliminary study it has established that the G. arborea leaf extract has a reproducible wound healing potential and hereby justifies its use for wound healing in folklore medicine in India [78].

**Anti-inflammatory activity**

The anti-inflammatory effect of methanolic and ethyl acetate extracts of roots of G. pentaphylla in carrageenan induced paw oedema in albino Wistar rats has already reported. The results show that the ethyl acetate extract
showing significant activity in reducing rat paw oedema [79]. The activity of extract may due to the presence of Undecan-X. Recently a group of researchers has isolated Undecan-2 from G. pentaphylla. Undecan-X ones are a well-known anti-inflammatory compound [80, 81].

Insecticidal and larvicidal activity

The larvicidal effect of G. pentaphylla have measured with larvae of Diaprepes abbreviatus L. (Coleoptera: Curculionidae) after rearing them on roots of rutaceous seedlings for 35 to 42 days. Growth inhibiting activity has been found in both live and milled roots of G. pentaphylla (orange berry) [68-70]. Milled root samples were incorporated into a standard semi defined diet at 5% concentrations (w/v), and growth of larval weevils was recorded following 32 day of feeding period. The results from these studies showed that the roots of G. pentaphylla having growth inhibiting activity against D. abbreviatus [71].

Another group reported the ethyl acetate fraction of G. pentaphylla leaf extract inhibits the juvenile hormone biosynthesis from the corpora allata of field cricket, Gryllus bimaculatus, in a dose dependent manner. The bioactive compound was identified as the alkaloid, arborine. This alkaloid was found to contain strong insecticidal activity against dipteran species as well as larvicidal activity against the mosquito, Culex quinquefasciatus. The results conclude that the partially purified ethyl acetate extract of G. pentaphylla root contains at least two compounds with high mosquito larvicidal activity [72]. Laboratory assays showed that the leaf extract of G. pentaphylla effectively inhibits first instar larvae stage of the citrus leaf miner, Phyllocnistis citrella (Stainton) [73].

In the course of search for insecticidal compound from plants a group of researchers found that the ethanol extracts of dried leaves of G. pentaphylla inhibit the larval growth of fruit fly, Drosophila melanogaster. They have also reported the isolation of the active compound, arborine, and its inhibitory activity against the fruit-fly [74].

Recent studies demonstrate that exposure to partially purified leaf extract of G. pentaphylla causes the duration of larval stage, inflicted very high larval mortality and induced developmental deformities in mosquito’s larvae, Culex quinquefasciatus, Anopheles stephensi and Aedes aegypti [75].

Alkaloids from the Rutaceae family are known to be quite effective as insecticide, antifeedants and insect growth regulator [76]. Previous studies show that oral administration of G. pentaphylla ethyl acetate extract to the penultimate and final instar larvae of the castor semiLooper, Achaea janata, decreased the weight gain and inhibited larval to pupal and pupal to adult metamorphosis, respectively [77]. The studies in future will lead to the discovery of possible juvenoids in ethyl acetate fraction of G. pentaphylla.

CONCLUSION

The medicinal properties of G. pentaphylla is available both in the written and non-written format as traditional knowledge since time immemorial. In traditional medicines the plant has been used as treatment option against cancer, inflammation, jaundice, fever, hematinic infection etc. Traditional knowledge regarding the usage of this plant is many but the scientific research available today to support this knowledge is limited. Here we have tried to compile all the available information from both traditional and published scientific literatures regarding the medicinal uses of G. pentaphylla. It will helpful for the future researchers to get the information in a nut shell. This will provide tremendous opportunities for planning and conduct research related to various aspects of this medicinal plant.

Acknowledgements

The authors express their gratitude to Dr. M. Radhakrishna Pillai director Rajiv Gandhi Centre for Biotechnology for their encouragement and support. Authors are also thankful to Dr. A. Subramoniam former director TBGRI for his critical suggestions. The University Grand Commission and Department of Biotechnology, Govt. of India is also acknowledged for providing Research Fellowship to Sreejith P.S. and Praseeja R.J.

REFERENCES

60. Gupta N, Bhatia, Jha, Dinesh I. In vitro antioxidant activity of crude extracts of the plant Glycosmis pentaphylla (Retz.) Correa. IJPSR. 06: 2011; 159-162.

Source of support: Nil, Conflict of interest: None Declared