Review Article

Ethnomedicinal uses, phytochemistry, pharmacological activities and toxicological profile of *Glycosmis pentaphylla* (Retz.) DC.: A review

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ABSTRACT

Ethnopharmacological relevance: *Glycosmis pentaphylla* (Retz.) DC. is a perennial shrub indigenous to the tropical and subtropical regions of India, China, Sri Lanka, Myanmar, Bangladesh, Indonesia, Malaysia, Thailand, Vietnam, Philippine, Java, Sumatra, Borneo and Australia. The plant is used extensively within these regions as a traditional medicine for the treatment of a variety of ailments including cough, fever, chest pain, anemia, jaundice, liver disorders, inflammation, bronchitis, rheumatism, urinary tract infections, pain, bone fractures, toothache, gonorrhea, diabetes, cancer and other chronic diseases.

Aim of the review: This review aims to present up-to-date information regarding the taxonomy, botany, distribution, ethnomedicinal uses, phytochemistry, pharmacology and toxicological profile of *G. pentaphylla*. The presented information was analyzed critically to understand current work undertaken on this species and explore possible future prospects for this plant in pharmaceutical research.

Materials & methods: Bibliographic databases, including Google Scholar, PubMed, Web of Science, ScienceDirect, SpringerLink, Wiley Online Library, Semantic Scholar, Europe PMC, Scopus, and MEDLINE, were explored thoroughly for the collection of relevant information. The structures of phytoconstituents were confirmed with PubChem and SciFinder databases. Taxonomical information on the plant was presented in accordance with The Plant List (version 1.1).

Results: Extensive phytochemical investigations into different parts of *G. pentaphylla* have revealed the presence of at least 354 secondary metabolites belonging to structurally diverse classes including alkaloids, amides, phenolic compounds, flavonoids, glycosides, aromatic compounds, steroids, terpenoids, and fatty derivatives. A large number of *in vitro* and *in vivo* experiments have demonstrated that *G. pentaphylla* had anticancer, antimutagenic, antibacterial, antifungal, anthelmintic, mosquitocidal, antidiabetic, antihyperlipidemic, anti-oxidant, anti-inflammatory, analgesic, antipyretic, anti-arsenicosis, and wound healing properties. Toxicological studies have established the absence of any significant adverse reactions and showed that the plant had a moderate safety profile.

Conclusions: *G. pentaphylla* can be suggested as a source of inspiration for the development of novel drugs, especially anticancer, antimicrobial, anthelmintic, and mosquitocidal agents.

Moreover, bioassay-guided investigations into its diverse classes of secondary metabolites, especially the large pool of nitrogen-containing alkaloids and amides, promises the development of novel drug candidates. Future pharmacological studies into this species are also warranted as many of its traditional uses are yet to be validated scientifically.

Keywords: *Glycosmis pentaphylla*; ethnomedicinal uses; phytoconstituents; pharmacological activities; toxicological profile

1. Introduction

Over the past two decades, there has been an increasing interest among countries in South-East Asia (India, Indonesia, Sri Lanka, Bangladesh, Thailand) and the Western Pacific region (Australia, China, Cambodia, Malaysia, Philippines, Vietnam) to recognize ethnomedicinal systems as part of their healthcare strategies and include herbal medicinal products either as over-the-counter or essential prescription drugs. A lack of adequate research data to support the use of such products, however, still undermines their true potential in global healthcare management (World Health Organization, 2019).

Glycosmis pentaphylla (Retz.) DC. is an evergreen shrub that has a rich history of ethnomedicinal applications in the aforementioned countries (Babu and Radhamany, 2020). The word "*Glycosmis*" originates from two Greek words viz. "Glykys" and "Osme" which mean sweet and smell, respectively, as indicative of the characteristic sweet-scented flowers common within the genus (Babu and Radhamany, 2019). The twigs are employed as a toothbrush, hence the name Toothbrush plant (also Orange/Gin berry) in English. The plant is known as Ashshoura, Ban Jamir, Daton, Kawatuti, Motali and Motmoti (Bengali), Ashvashakota and Vananimbuka (Sanskrit), Bannimbu (Hindi), Tejmoyee (Assamese), Anam and Kula pannai (Tamil), Gongi pandu (Telegu), Paanal (Malayalam), Manikyan (Kannda) and Som chuen (Thai) (Bulbul and Jahan, 2016; Nayak et al., 2011; Sivakumar et al., 2014; Sreejith et al., 2012a; Sripisut et al., 2012; Yasir et al., 2015). In traditional ethnomedicinal systems, especially in India, Bangladesh, and China, different parts of *G. pentaphylla,* including its leaves, stems, barks, fruits, and roots are employed for the treatment of cough, fever, bronchitis, chest pain, anemia, jaundice, liver disorders, inflammation, rheumatism, fractures, pain, urinary tract infections, gonorrhea, diabetes, cancer and other chronic diseases. The plant has been recorded to alleviate diarrhea, dysentery and helminthic infestations. Topical preparations are used for boils, eczema and other skin disorders and inflammatory conditions (Azad et al., 2008; Babu and Radhamany, 2020; Bulbul and Jahan, 2016; Nayak et al., 2011; Ramkumar et al., 2016; Sarkar et al., 2013; Shoja et al., 2015; Sivakumar et al., 2014). *G. pentaphylla* has demonstrated a wide range of biological effects including anti-oxidant, anti-inflammatory, analgesic, antidiabetic, antihyperlipidemic, cytotoxic, antibacterial, antifungal, anticancer, anthelmintic, mosquitocidal, antipyretic, wound healing and anti-arsenicosis properties. A significant number of phytochemical and biological investigations have been carried out on this plant since it was last reviewed (Sreejith et al., 2012b). The present review endeavors to provide an updated and comprehensive description of the taxonomy, botany, distribution,

ethnomedicinal uses, phytoconstituents, pharmacological activities, and safety profile of *G. pentaphylla*.

2. Methodology

Electronic versions of different bibliographic databases, including Google Scholar, PubMed, Web of Science, ScienceDirect, SpringerLink, Wiley Online Library, Semantic Scholar, Europe PMC, Scopus, and MEDLINE were explored thoroughly to identify, collect and curate any information relevant to *Glycosmis pentaphylla*. The search was primarily conducted using several keywords such as "*Glycosmis pentaphylla"*, "distribution", "ethnopharmacology", "ethnomedicinal uses", "traditional uses", "phytoconstituents", "chemical constituents", "secondary metabolites", "pharmacological activity", "biological activity" and "toxicological study". A total of 73 articles (published between 1952 and September 2020) have been included in this review. Among them, 27 articles focused on phytochemical investigations of different parts of *G. pentaphylla*, 30 articles described single or multiple *in vitro* or *in vivo* pharmacological studies on *G. pentaphylla* extracts, 5 articles described both phytochemical and pharmacological studies, and 11 articles focused on the pharmacological activities of individual secondary metabolite(s) isolated from *G. pentaphylla*. The articles were scrutinized extensively for authenticity, validity, and relevance prior to including them in the present review. Proper recognition of these research endeavors was ensured wherever possible by stating the names of the authors and respective years of publication. The accepted name of the plant and its established synonyms was confirmed from The Plant List (version 1.1, 2013) (http://www.theplantlist.org/). The chemical structures of all the secondary metabolites were validated through SciFinder and PubChem databases and drawn with the help of ChemDraw Ultra 15.0 following standard ACS guidelines.

3. Taxonomy

The genus *Glycosmis* belongs to the Rutaceae family and includes at least 51 species as accepted names. *Glycosmis pentaphylla* (Retz.) DC. (Figure 1), a prominent member of this genus, is a perennial shrub that grows between 1.5 and 5 m high. The accepted synonyms of *G. pentaphylla* includes *Bursera nitida* Fern.-Vill., *Chionotria monogyna* Walp., *Chionotria rigida* Jack, *G. arborea* (Roxb.) DC., *G. arborea* var. *linearifoliolata* V. Naray., *G. chylocarpa* Wight & Arn., *G. madagascariensis* Corrêa ex Risso, *G. pentaphylla* var. *linearifoliolis* Tanaka, *G. quinquefolia* Griff., *G. retzii* M.Roem., *G. rigida* (Jack) Merr., *Limonia arborea* Roxb., *Limonia pentaphylla* Retz. and *Myxospermum chylocarpum* (Wight & Arn.) M. Roem.

The rachis of the plant is usually 6-10 cm long and the petioles are around 2 mm in length. Leaflets are arranged imparipinnately and sub-oppositely, with the leaves being dark green on the adaxial surface and light green on the abaxial surface. The leaves are elliptic to lanceolate, with the tips being acute to round and the base being cuneate. Reticulate venation as well as glandular distribution can be observed on the glabrous surfaces of the leaves. Flowers are small, fragrant, greenish-white in color, and arranged in axillary or terminal panicles. Both the petals and sepals are 5 in number while the stamens are 8-10 in number. The berry-type fruits are pulpy and round to ovoid in shape. The fruits contain 1-3 seeds with the color turning from white to reddish as they ripen (Prakasia and Nair, 2016; Sasidharan, 2004; The Plant List, 2013). The complete taxonomical classification of *G. pentaphylla* is given below (Sasidharan, 2004):

- Kingdom: Plantae
- Division: Tracheophyta
- Class: Magnoliopsida
- Order: Sapindales
- Family: Rutaceae
- Genus: *Glycosmis*
- Species: *Glycosmis pentaphylla* (Retz.) DC.
- Synonyms: *Bursera nitida* Fern.-Vill.

4. Distribution

Glycosmis pentaphylla is indigenous to the tropical and subtropical regions of mainland China, South and Southeast Asia, the Malay Archipelago and Northwest Australia. Within South and Southeast Asia, the plant is extensively distributed in India, Sri Lanka, Myanmar, Bangladesh, Indonesia, Malaysia, Thailand, Vietnam and the Philippines. In the Malay or Indo-Australian Archipelago, the plant has been recorded in Java, Sumatra and Borneo (Babu and Radhamany, 2020; Shams-Ud-Doha et al., 2012). Within China, the most prominent distribution of the plant has been reported in the Gengma, Mengding, Shuangjiang and Xishuangbanna regions of the Yunnan Province (Wang et al., 2016). The plant is also widespread in the tropical and subtropical regions of northeastern India, including the Assam, Arunachal, Meghalaya, Mizoram, Nagaland and Sikkim states as well as the Himalayan peninsula where the plant has been recorded to grow as high as 2300 m above sea level (Sarkar

et al., 2013; Vignesh et al., 2014). In Bangladesh, the plant grows in the low altitude forest regions of Madhupur and Tangail (Rahmatullah et al., 2011).

5. Ethnomedicinal uses

G. pentaphylla has extensive medicinal applications in different traditional practices throughout the Indian subcontinent. In India, the plant has been recorded to be useful in the treatment of cough, anemia, jaundice, inflammation, bronchitis and rheumatism. It is also employed as astringent, expectorant and for counteracting the effects of snakebites (Azad et al., 2008; Sivakumar et al., 2014). Both the plant and the juice of its leaves have been found to be effective in the treatment of fever as well as different forms of liver disorders and worm infestations (Nayak et al., 2011; Ramkumar et al., 2016; Sivakumar et al., 2014). Topical application of the plant has been recorded to promote wound healing and to alleviate eczema, erysipelas and other skin conditions. Decoctions prepared from the root and leaf pastes have been employed to treat skin inflammatory conditions and eczema, respectively (Ramkumar et al., 2016; Sarkar et al., 2013; Sivakumar et al., 2014). The stem bark of *G. pentaphylla* has been found to beneficial in the management of diabetes and gonorrhea, whereas the roots and fruits have been used to treat fever and dysentery, respectively (Sarkar et al., 2013). In Indian homeopathy, the leaves have been employed for diarrhea, dysentery, and to alleviate abdominal pain resulting from biliary obstruction as well as worm infestations. A tincture prepared from the leaves has been part of the treatment of throat cancer while a one-to-one aqueous ethanol extract of the aerial parts has been used as a diuretic and spasmolytic agent (Nayak et al., 2011).

In Bangladesh, juice and paste prepared from the leaves have been employed traditionally in the treatment of cough, fever, anemia, jaundice, hepatic disorders, rheumatism, ascariasis, bone fractures and pain associated with fractures. Topical administration of both the juice and the paste has been employed to alleviate eczema and other skin disorders (Bulbul and Jahan, 2016). In some areas of the Tangail district, the juice prepared from *G. pentaphylla* roots is used to alleviate toothache and pyorrhea (Rahmatullah et al., 2011). In the Gazipur district, traditional medicinal practitioners have employed the plant in the treatment of different forms of cancer (Sreejith and Asha, 2015). In other areas of the country, the plant is used for gastritis, rheumatoid arthritis, migraine and leucorrhea (Hossan et al., 2010).

Within the south and southwest regions of the Yunnan province of China, *G. pentaphylla* is used to treat cough, fever, anemia, liver disorders, rheumatism and other chronic

diseases. In those regions, the plant is also employed to improve muscular soreness and numbness (Wang et al., 2016; Yang et al., 2012). In southwest China, traditional Dai practitioners have used the plant to maintain body homeostasis, regulate blood circulation and alleviate pain (Zhang et al., 2016).

The plant also has noteworthy ethnomedicinal applications in other parts of the World. In many countries, the juice of the leaves has found its application in the treatment of fever, cough, bronchitis, anemia, jaundice, urinary tract infections, rheumatism, diarrhea, and boils (Babu and Radhamany, 2020; Ramkumar et al., 2016; Shoja et al., 2015). The ethnomedicinal uses of *G. pentaphylla* are summarized in Table 1.

6. Phytochemistry

Around 354 secondary metabolites have been isolated and characterized from different extracts and fractions of *G. pentaphylla*. Phytochemical investigations have been conducted on the whole plant, the aerial parts, and other individual plant parts, including the stem, bark, leaves, twigs, roots, and fruits. *G. pentaphylla* has developed diverse and elaborate metabolic mechanisms to incorporate nitrogen into its secondary metabolites, resulting in the characterization of a large number of alkaloids and amides from this plant. Other classes of phytoconstituents reported widely from this plant include phenolic compounds, flavonoids, aromatic constituents, steroids and terpenoids. All these phytoconstituents are summarized in Table 2 and their structures are presented in Figure 2-10.

6.1. Alkaloids

Seventy structurally-diverse alkaloids (**1**-**70**) categorized under at least eleven structural sub-classes have been reported from different parts of *G. pentaphylla* (Figure 2 and 3). These included nineteen monomeric (**1**-**19**) and four dimeric (**20**-**23**) carbazole, eight acridone (**24**-**31**), ten quinolone (**32**-**41**), five quinazolone (**42**-**46**), four furanopyridine (**47**-**50**), seven furoquinoline (**51**-**57**), one pyrrole (**58**), two pyrrolidinone (**59**-**60**), two indole (**61**-**62**), two pyrazole (**63**-**64**) and one piperidine (**65**) alkaloids. The acridone alkaloids arborinine (**24**) and skimmianine (**55**) have been reported in almost all parts (stems, leaves, twigs, roots and fruits) of *G. pentaphylla* and may serve as potential marker compounds for the plant (Ahmed et al., 2014; Chatterjee and Majumdar, 1954; Choi et al., 2019; Chokchaisiria et al., 2020; Das and Deka, 2017; Govindachari et al., 1966; Ito et al., 1999; Kumar et al., 2018;

McKenzie and Price, 1952; Murugan et al., 2020; Sivakumar and Chamundeeswari, 2016; Sripisut et al., 2012; Yang et al., 2012; Zhang et al., 2016).

6.2. Amides

Twenty eight amides (**71**-**98**) have been isolated from *G. pentaphylla* (Figure 4). A large number of these amides (**78**-**98**) are characterized by the presence of sulfur atoms within their structures. Twenty of these sulfur-containing amides (**79**-**98**) are prenylated, further contributing to the diversification of these compounds and their potential antiproliferative and anti-inflammatory activities *in vivo* (Nian et al., 2020). Although the sulfur-containing amides have been found to be localized predominantly in the leaves, other amides have also been isolated from the roots and flower heads (Sarkar and Chakraborty, 1977; Shapiro et al., 2000; Sivakumar and Chamundeeswari, 2016).

6.3. Phenolic constituents

Thirty one phenolic constituents and derivatives (**99**-**129**) as well as eighteen phenolic glycosides (**130**-**147**) have been reported from *G. pentaphylla* (Figure 5 and 6), especially in the aerial parts (stem, leaves and twigs). A wide variety of phenolic aglycones, including six hydroxybenzoic acid derivatives (**99**-**104**), five cinnamic acid derivatives (**105**-**109**), five coumarins (**115**-**117**, **128**, **129**), three naphthoquinones (**125**-**127**), one cinnamyl alcohol derivative (**111**), one stilbene (**119**) and one quinic acid derivative (**122**) have been reported. Although the majority of the phenolic compounds in *G. pentaphylla* are present in the aerial parts (mainly stem and leaves), four of these compounds (**112**, **113**, **128**, **129**) have been identified from the roots (Sivakumar and Chamundeeswari, 2016). All the phenolic glycosides reported to date have been found in the stems, including ten compounds (**130**-**139**) with a single sugar moiety and eight compounds (**140**-**147**) with two sugar moieties (Chen et al., 2015b; Tian et al., 2014; Wang et al., 2006a).

6.4. Flavonoids

At least thirty flavonoids (**148**-**177**) have been isolated from the stems and leaves of *G. pentaphylla* (Figure 7). These included three flavones (**148**-**150**), seven flavonols (**151**-**157**), two flavanones (**158**-**159**), two flavanonols (**160**-**161**), six flavanols (**162**-**167**) and ten isoflavones (**168**-**177**). Mono- and di-glycosidic flavonoid derivatives have also been recorded. This included two flavones (**149**, **150**) and two flavonols (**152**, **154**) isolated as monoglycosides, and one flavonol (**155**) and ten isoflavones (**168**-**177**) isolated as diglycosides. The glycosides were primarily constituted of D-glucose, D-apiose and L-

rhamnose moieties (Ali et al., 2020; Chen et al., 2016; Choi et al., 2019; Wang et al., 2006b). In two of the isoflavone diglycosides (**175**, **177**), the glycosidic parts were further extended with one *para*-coumaroyl terminal group.

6.5. Aromatic constituents

Eleven non-phenolic aromatic derivatives (**178-188**) have been characterized from the leaves, roots and seeds of *G. pentaphylla* (Figure 8). This included four ester derivatives of benzoic acid (**185**, **186**) and phthalic acid (**187**, **188**) (Prakasia and Nair, 2015; Sivakumar and Chamundeeswari, 2016; Vignesh et al., 2014; Vignesh et al., 2016).

6.6. Steroidal constituents

Six steroidal compounds (**189-194**) have been reported from *G. pentaphylla* (Figure 9). Four of them (**189**, **191-193**) have been isolated from the roots, whereas the other two (**190**, **194**) were characterized from the stems and leaves, respectively (Ahmed et al., 2014; Sivakumar et al., 2014; Wu et al., 2012).

6.7. Non-volatile terpenoids

Three ent-abietane type diterpene lactones (**195-197**) and three pentacyclic oleanane type triterpenes (**198-200**) have been isolated from the leaves, twigs and roots of *G. pentaphylla* (Figure 10) (Ahmed et al., 2014; Chokchaisiria et al., 2020; Sivakumar and Chamundeeswari, 2016).

6.8. Volatile constituents

As many as one hundred and fifty four volatile constituents (**201-354**) have been reported from the bark, leaves, roots and seeds of *G. pentaphylla* (Figure 11). These comprised of terpenoids, fatty acids and their esters, fatty alcohols, fatty aldehydes, ketones and other long chain hydrocarbons. A wide range of structurally-diverse volatile terpenoids, with varying degrees of cyclization and oxygenation, have been identified. This included eleven acyclic (**200-211**), twenty two monocyclic (**212-233**), fourteen bicyclic (**234-247**) and two tricyclic (**288**, **289**) monoterpenes. Among the sesquiterpenes, two acyclic (**250**, **251**), thirteen monocyclic (**252-264**), sixteen bicyclic (**265-280**), sixteen tricyclic (**281-296**) and two tetracyclic derivatives (**297**, **298**) have been characterized. Three acyclic diterpene alcohols (**299-301**) and one acyclic triterpene (**302**) have also been isolated from this plant. Among the long chain volatile compounds, five were fatty acids (**303-307**), eight were fatty acid esters (**308-315**), eight were fatty alcohols (**316-323**), three were fatty aldehydes (**324-326**), seven

were aliphatic ketones (**327**-**333**), sixteen were aliphatic hydrocarbons (**334**-**349**) and two were cyclic hydrocarbons (**350**, **351**) while the remaining three (**352**-**354**) were heterocycles in nature (Ahmed et al., 2000; Murugan & Natarajan, 2016; Prakasia and Nair, 2015; Ramkumar et al., 2016; Sivakumar et al., 2014; Sivakumar and Chamundeeswari, 2016; Vignesh et al., 2014; Vignesh et al., 2016).

7. Pharmacological activities

Various *in vitro* and *in vivo* studies on extracts and individual phytoconstituents isolated from *G. pentaphylla* have demonstrated prominent anticancer, antimutagenic, antimicrobial, anthelmintic and mosquitocidal activities owing to selective and non-selective cytotoxic effects on vital biological targets. Extract and individual compounds have also showed antidiabetic, antihyperlipidemic, anti-oxidant, anti-inflammatory, analgesic, antipyretic, wound healing and anti-arsenicosis properties. Wherever possible, the pharmacological investigations have been described in terms of the type(s) of plant extract investigated, the type(s) of experiments employed, the dose/concentration at which the extract(s) were administered and the name(s) of the standard(s) against which the extract/phytochemical(s) were evaluated. The pharmacological properties of extracts and individual phytoconstituents of *G. pentaphylla* are summarized in Table 3 and Figure 12.

7.1. Cytotoxic and anticancer activity

The methanol extract of *G. pentaphylla* demonstrated significant dose-dependent but moderate cytotoxicity in the brine shrimp lethality bioassay (LC_{50} value of 22.55 µg/mL) versus vincristine sulfate (LC_{50} value of 0.451 µg/mL) (Rahman et al., 2018). The ethanol extract of the plant showed promising anticancer potential and dose-dependent cytotoxicity when tested in the concentration range of 10 to 200 µg/mL against RAW 264.7 cells in a Dalton's lymphoma ascites (DLA) cell assay. The extract exhibited maximum cellular mortality (98.4%) at the dose of 200 µg/mL with an IC_{50} value of 78.39 µg/mL (Babu and Radhamany, 2019).

Different fractions of *G. pentaphylla* exhibited moderate anticancer activity when tested using a sulforhodamine B (SRB) assay. One fraction derived from the petroleum ether extract showed IC_{50} values of 40.66 ± 1.89 and 38.5 ± 0.9 µg/mL against MCF-7 and MDA-MB-231 breast adenocarcinoma cell lines, respectively. One ethyl acetate fraction (designated as EF1) and one dichloromethane fraction (designated as DCM2) exerted prominent

cytotoxicity against the MDA-MB-231 cell line (IC_{50} values of 31.1 ± 0.82 and 27.7 ± 1.5 µg/mL, respectively). Although to a slightly lesser extent, EF1 and DCM2 also exhibited cytotoxic properties against the MCF-7 cell line with IC_{50} values of 40.4 ± 1.75 and 46.04 ± 2.11 µg/mL, respectively. Further investigation at the cellular level revealed that the fractions were able to cause extensive DNA fragmentation and lead to apoptosis (Shoja et al., 2015). The standard doxorubicin in comparison had IC_{50} values of 4.32 ± 1.22 and 5.4 ± 1.16 µg/mL against MCF-7 and MDA-MB-231 breast adenocarcinoma cell lines, respectively.

The acridone alkaloid arborinine (**24**) showed promising cytotoxic activity in the potato disc assay. This compound at a dose of 18.75 µg/disc inhibited *Agrobacterium tumefaciens*-induced crown gall tumor by a margin of 25%, whereas the standard vincristine sulfate (3.13 µg/disc) exerted 100% inhibition (Quader et al., 1999). A recent study involving an *in vitro* SRB assay further demonstrated that arborinine (**24**) was capable of exhibiting comparable anticancer activity as the standard adriamycin against the human colon cancer cell line COLO-205, the human ovarian cancer cell line OVCAR-3 and the human breast cancer cell lines T-47D (Das and Deka, 2017).

The carbazole alkaloid glycoborinine (**18**) showed potent dose- and time-dependent cytotoxicity against HepG2 human liver cancer cells. Over a time period of 48 hours, glycoborinine (**18**) had an IC_{50} value of 39.7 µM and showed maximum inhibition (78%) at the dose of 100 µM. Further cellular and biochemical analyses revealed that this alkaloid led to apoptosis by activating caspase-3 via the mitochondrial pathway followed by cleavage of poly ADP-ribose polymerase (PARP). This was associated with strong radical oxygen scavenging activity and an increased cytoplasmic level of cytochrome C, mediated by upregulation of the pro-apoptotic Bax protein and downregulation of the anti-apoptotic Bcl-2 protein (Yang et al., 2014). Other carbazole-derived dimeric alkaloids from *G. pentaphylla* stems, namely biscarbalexine A (**20**), glycosmisine A (**22**) and glycosmisine B (**23**), showed dose-dependent anticancer activity against HepG2, Huh-7 human liver cancer and A549 alveolar adenocarcinoma cells. Over the 48 hours observation period, glycosmisine A (**22**) was found to exert the most prominent antiproliferative effect against Huh-7 cells (IC_{50} of 30.6 µM). A moderate degree of antitumor activity was demonstrated for all three alkaloids against A549 cells (IC_{50} values of 43.68, 57.10 and 56.06 µM, respectively) (Chen et al., 2015a). With phytochemical studies having characterised at least nineteen monomeric and four dimeric carbazole alkaloids from *G. pentaphylla*, further efforts should be directed towards screening

such molecules for their anticancer potential, including quantitative structure-activity relationship (QSAR) modelling and identification of the pharmacophore(s).

The ethanol extract of *G. pentaphylla* has demonstrated apoptosis-mediated cytotoxicity against Hep3 B hepatocarcinoma cells. Glycopentalone (**58**) was identified as the major cytotoxic constituent of this extract with 68% growth inhibition at a dose of 3 µg/mL. This compound did not show any significant cytotoxicity neither against RAW264.7 macrophages nor against LX2 hepatic stellate cells (only 28 and 13% inhibition, respectively) (Sreejith et al., 2012a; Sreejith and Asha, 2015). Another study revealed that glycopentalone (**58**) exhibited prominent antiproliferative activity against Hep3 B cells comparable to the standards doxorubicin and sorafenib with IC_{50} values of 8, 0.75 and 1.5 µM, respectively. The anticancer effect of glycopentalone (**58**) was further attributed to its ability to arrest the cell cycle at the G1 stage as it caused 72% cell arrest at the dose of 10.488 µM compared to sorafenib which exhibited 74% cell arrest at 1 µM concentration. Glycopentalone (**58**) also reduced the invasiveness of cancer cells through down-regulation of tumor growth factor β (TGF β) expression at the cellular level (Sasidharan and Vasumathi, 2017). Two bioactive flavanols (**165**, **167**) from the stems of *G. pentaphylla* exhibited potent antiproliferative activity against HL-60 leukemia and A549 cells. The compounds demonstrated IC_{50} values of 14.4 and 15.2 µM, respectively, against HL-60 cells and IC_{50} values of 22.4 and 21.1 µM, respectively, against A549 cells (Wang et al., 2016).

A recent study identified fourteen bioactive amides from the ethanol extract of *G. pentaphylla* with potent activity against cancerous HepG2 hepatocytes. In comparison to the standard cisplatin (IC_{50} value 5.96 ± 0.40 µM), the highest antiproliferative effects were observed for methylgerambullin (**79**), glycopentamide J (**90**) and glycopentamide H (**88**) with IC_{50} values of 7.47 ± 0.91, 8.01 ± 3.79 and 9.22 ± 0.06 µM, respectively. Ten other sulfur-containing glycopentamide derivatives viz. glycopentamide B, C, E, G, K, M, N, O, P and R (**82**, **83**, **85**, **87**, **91**, **93-96**, **98**) with IC_{50} values ranging from 11.46 ± 4.13 µM to 16.23 ± 0.80 µM were also recorded for their potent anticancer activity (Nian et al., 2020). Although the study presented a preliminary estimation of structure-activity relationships, further investigations, especially in animal models, may lead to the development of an efficient QSAR model for the design of novel anticancer molecules.

Although a good number of phytoconstituents from *G. pentaphylla* have displayed promising anticancer activity, all findings to date have been based entirely on *in vitro* assays

against different cell lines. The anticancer activity of molecules is often known to be associated with general toxicity rather than target specificity (Chari, 2008). In order to consider these molecules as future drug templates, it is therefore important to extend further research on their anticancer effect by using experimental animal models and investigate their specific biochemical interactions with biological targets at the cellular level.

7.2. Antimutagenic activity

The effect of *G. pentaphylla* on intrinsic mutagenicity was investigated in *Salmonella typhimurium* strains TA98 and TA100, in the presence and absence of the Ames S9 metabolic activation factor. The methanol extract administered at five different concentrations between 10 to 10000 μg/plate, showed no mutagenic effects in any of the strains. The extract exhibited noticeable antimutagenic properties in both strains against known mutagens including 4-nitro-*O*-phenylenediamine, sodium azide and 2-aminofluorene, especially in the presence of the Ames S9 factor (Kumar et al., 2018).

A recent study explored the antimutagenic potential of the methanol extract of *G. pentaphylla* against silver nanoparticle-induced genetic and biomolecular alterations in Swiss albino mice. The mice were administered with 20 and 100 nM of silver nanoparticles at doses of 100 mg/kg for one month. Subsequent histological studies revealed significant DNA damage as well as chromosomal aberrations in bone marrow cells and spermatocytes. The extract at a dose of 500 mg/kg suppressed these changes to a remarkable extent, indicating potent antimutagenic activity *in vivo*. Further biochemical characterization of the hepatic tissues from silver nanoparticle-administered mice, revealed prominent increase in the activities of aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP) enzymes as well as an enhanced level of pro-inflammatory C-reactive protein (CRP). The nanoparticles also diminished the activities of antioxidative enzymes including superoxide dismutase (SOD), glutathione-S-transferase (GST) and glutathione peroxidase (GPx). The methanol extract of *G. pentaphylla* exerted powerful attenuation against these adverse changes and reversed all the enzymatic changes to significant extents (Ali et al., 2020).

Cancer pathogenesis is always secondary to mutagenic changes in regulatory genes which might be either congenital or acquired (Black, 1994). Thus, the antimutagenic properties of *G. pentaphylla* can be considered complementary to its anticancer potential. The phytoconstituents showing anticancer activity should be considered as prime candidates for the evaluation of their antimutagenic properties.

7.3. Antimicrobial activity

In a disc diffusion assay, the ethanol extract of *G. pentaphylla* (500 µg per disc) revealed moderate dose-dependent antibacterial activity against *Staphylococcus aureus*, *Escherichia coli*, *Salmonella typhi* and antifungal activity against *Candida albicans* with zones of inhibition of 15.67 ± 1.155, 17.67 ± 3.786, 16.25 ± 1.258 and 15.50 ± 0.577 mm, respectively (Ansari et al., 2015b). Standard kanamycin (30 µg per disc) produced zones of inhibition of 33.33 ± 3.055, 30.33 ± 3.512, 26 ± 4.0 and 29 ± 3.606 mm, respectively. The methanol extract of *G. pentaphylla* (500 µg per disc) moderately inhibited the growth of *Salmonella paratyphi* and *Escherichia coli* with zones of inhibition of 22 and 20 mm, respectively, compared to kanamycin (30 µg per disc) which exhibited zones of inhibition of 42 and 40 mm, respectively (Bulbul and Jahan, 2016).

The aqueous alcoholic extract of *G. pentaphylla* exhibited potent activity against *C. albicans* as indicated by a minimum inhibitory concentration (MIC) of 50 µg/mL, compared to those of the standards nystatin and griseofulvin (100 and 50 µg/mL, respectively). Noteworthy antifungal activity was also recorded against *C. tropicalis* and *C. krusei,* with MIC values of 250 µg/mL in both cases (Yasir et al., 2015).

The antibacterial and antifungal activity improved drastically when the methanol extract was administered in the form of zinc nanoparticles. The latter at the dose of 100 µg/mL generated zones of inhibition of 41 ± 2.18, 36 ± 1.93, 42 ± 2.24 and 40 ± 2.16 mm against *Bacillus cereus*, *S. aureus*, *Shigella dysenteriae* and *S. paratyphi*, respectively, compared to the standard ciprofloxacin (5 µg/disc) with zones of inhibition of 40 ± 2.12, 35 ± 1.71, 30 ± 1.91 and 25 ± 1.26 mm, respectively. The nanoparticles (100 µg/mL) showed powerful antifungal activity inhibiting the growth of *C. albicans* and *Aspergillus niger* (34 ± 1.28 and 30 ± 3.11 mm, respectively) while standard nystatin (50 µg/disc) showed zones of inhibition of 30 ± 0.93 and 12 ± 0.79 mm, respectively, (Vijayakumar et al., 2018).

The acridone alkaloid arborinine (**24**) (100 µg per disc) exhibited moderate antibacterial activity against *B. subtilis* and *Klebsiella pneumoniae* with zones of inhibition of 15 ± 0.01 and 19 ± 0.006 mm, respectively, compared to that of the standard tetracycline (25 and 38 mm, respectively at 100 µg/disc) (Das and Deka, 2017).

The quinazolone alkaloid arborine (**45**) and the furoquinoline alkaloid skimmianine (**55**), isolated through a process of bioactivity-guided fractionation from the ethyl acetate

extract of *G. pentaphylla*, demonstrated potent activity against multidrug-resistant *S. aureus* strains 101, 270, 315, 319 and 410. Both alkaloids generated zones of inhibition in the range of 25-28 mm, comparable to the standard amoxicillin (zones of inhibition in the range of 23-29 mm at 10 μg/mL).

Arborine (**45**) exhibited a minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of 0.2 μg/mL against *S. aureus* strains 101 and 410, compared to those of amoxicillin (≥ 2 μg/mL). Skimmianine (**55**) exhibited MIC and MBC of 0.2 and 1 μg/mL against strains 315 and 319. In a time-killing kinetic assay, both arborine (**45**) and skimmianine (**55**) at their MBC killed the microbial population completely over an incubation period of 12 hours. Microscopic examination of the cells confirmed membrane and cellular damage as well as cellular size reduction. Further in-depth analysis at the biomolecular level revealed that arborine (75 μg/mL) and skimmianine (100 μg/mL) induced protein leakage up to an extent of 54 and 55%, respectively, which in turn compromised the cellular integrity of the bacterial population (Murugan et al., 2020).

Since a wide range of structurally-related alkaloids has been isolated from *G. pentaphylla*, further screening of molecules such as acridone, furoquinoline and quinazolone alkaloids for antimicrobial activity might be advantageous in the development of QSAR models and help with the design and synthesis of novel antimicrobial agents. Future replications of such investigations using *in vivo* experimental animal models, along with the characterization of the exact cellular mode(s) of action of active phytoconstituents, are warranted in order to ascertain the suitability of these molecules for clinical application.

7.4. Anthelmintic activity

A noticeable and dose-dependent antihelmintic effect was recorded when the methanol extract of *G. pentaphylla* (doses of 10, 20, 40 and 80 mg/mL) was tested on the earthworm *Pheretima posthuma*. The extract at 80 mg/mL completely killed the worms in an average time of 67 ± 2.60 minutes compared to that of the standard piperazine hydrate (83 ± 4.15 minutes at 20 mg/mL) (Gangarao and Jayaraju, 2009). This was observed in another study with the methanol extract and the standard albendazole, administered at 15, 30 and 60 mg/mL, exerting comparable dose-dependent anthelmintic properties. The average death times for the extract and the standard at the dose of 60 mg/mL, were recorded to be 30.52 ± 0.02 and 36.12 ± 0.02 minutes, respectively (Arora et al., 2011). These results, however, require further confirmation using in-depth *in vivo* investigations and biochemical studies in appropriate animal models.

The evaluation of the efficacy of *G. pentaphylla* extracts in treating epithelial ringworm rashes might be a simple and suitable approach for prospective research in this area.

7.5. Mosquitocidal activity

The potential mosquitocidal activity of *G. pentaphylla* extracts were explored against three malarial vectors, namely *Culex quinquefasciatus*, *Anopheles stephensi* and *Aedes aegypti*, both in their larval and adult stages of life. Dose-dependent larvicidal and adulticidal effects were observed for *G. pentaphylla* chloroform, ethyl acetate, acetone and methanol extracts. The most prominent larvicidal activity against all three species was observed for the acetone extract (LC_{50} values of 0.00045, 0.267 and 0.0585 mg/mL, respectively). The ethyl acetate extract also suppressed the larval population to a significant extent (LC_{90} values of 2.458, 14.314 and 22.687 mg/mL, respectively). In the case of adult mosquitoes, the most potent inhibitory effect was observed for the chloroform extract (LC_{50} values of 2.957, 2.708, 3.449 mg/mL, respectively and LC_{90} values of 5.458, 4.777, 6.676 mg/mL, respectively) (Ramkumar et al., 2016). Another study investigated the larvicidal activity of the essential oil of *G. pentaphylla* against the aforementioned mosquito species. A significant dose-dependent suppression of the larval population was reported after 48 hours of extract administration (LC_{50} values of 19.405, 5.855, 21.451 ppm, respectively and LC_{90} values of 42.7, 30.513, 53.371 ppm, respectively) (Vignesh et al., 2016). Bioactivity-guided fractionation of the methanol extract of *G. pentaphylla* led to the characterization of arborine (**45**) as a potent larvicidal component. Exposure of the fourth instar larvae of *C. quinquefasciatus* to arborine (**45**) at concentrations of 10^{-5} and 10^{-4} M for a time period of 240 hours (10 days) resulted in 88 and 100% mortalities, respectively (Muthukrishnan et al., 1999). Further investigations should aim to discover other mosquitocidal molecules from *G. pentaphylla* extracts and compare this isolated alkaloid with known mosquitocidal agents. Being natural in origin, *G. pentaphylla* extracts and isolated phytoconstituents may offer safer and eco-friendlier mosquitocidal alternatives to current molecules.

7.6. Antidiabetic activity

The antidiabetic activity of the methanol extract of *G. pentaphylla* was explored in alloxan-induced diabetic rats over a period of three weeks. The standard glibenclamide administered at a dose of 5 mg/kg body weight suppressed blood glucose level by a margin of 65% in 14 days. Compared to that, the methanol extract (250 mg/kg body weight) reduced plasma glucose level by 33.82 and 24.38% after 7 and 14 days of regular administration,

543 respectively (Rahman et al., 2018). It should be noted, however, that in that study, a larger dose
544 of the extract (e.g. 400 mg/kg) could have been administrated since the maximum non-lethal
545 dose for the methanol extract had previously been established as 4 g/kg body weight (Nayak et
546 al. 2011). The administration of a larger doe of extract might have led to a higher antidiabetic
547 effect.

548 Another study involving large doses of the ethanol extract of *G. pentaphylla* (400 and
549 800 mg/kg body weight) given to streptozotocin-induced diabetic rats over the same time
550 period showed superior antidiabetic properties. The extract, at both doses, improved serum
551 insulin concentrations by 47.4 and 68.4%, respectively, whereas the standard glibenclamide
552 (0.25 mg/kg) enhanced the same by 73.7%. Plasma glucose concentrations were lowered by
553 48.8, 53.3 and 61.9% by the extract (400 and 800 mg/kg) and the standard, respectively.
554 Furthermore, over a period of four weeks, the plant extract at both doses reduced total
555 cholesterol, triglyceride and low-density lipoprotein (LDL) levels as well as AST and ALT
556 concentrations in plasma. A similar effect on lipid metabolism and hepatic performance was
557 also observed for glibenclamide (Ramesh Petchi and Vijaya, 2012). Another study
558 investigating the effect of the ethanol extract of *G. pentaphylla* on oral glucose tolerance
559 revealed that the extract (250 and 500 mg/kg body weight) improved post-prandial glucose
560 tolerance by 50.7 and 66%, respectively, after 120 minutes of administration (Khatun et al.,
561 2012).

562 Although noteworthy antidiabetic properties have been attributed to *G. pentaphylla*
563 extracts, there has been an overall lack of efforts towards the identification of the
564 phytoconstituents responsible for such activity. This warrants further research work in the
565 future.

566 **7.7. Antihyperlipidemic activity**

567 One study reported the effect of the ethanol extract of *G. pentaphylla* administered to
568 Wistar albino rats following intraperitoneal injection of the hyperlipidemia-inducing Triton X
569 (100 mg/kg body weight) over a period of 7 days. The lipid profiles, recorded on the 8th day,
570 revealed that the standard atorvastatin (10 mg/kg body weight) reduced the serum
571 concentrations of triglycerides, total cholesterol, low density lipoprotein-cholesterol (LDL-C),
572 very low density lipoprotein-cholesterol (VLDL-C) and glucose in hyperlipidemic rats by 32.0,
573 33.1, 69.1, 32.0 and 31.5%, respectively. Comparably, the ethanol extract at the doses of 200
574 and 400 mg/kg body weight, suppressed triglyceride (25.9 and 29.3%, respectively), total

cholesterol (25.8 and 34.6%, respectively), VLDL-C (26 and 29.3%, respectively) and glucose (28.8 and 30.4%, respectively), but failed to diminish the serum levels of LDL-C. Atorvastatin as well as the extract at both doses elevated high density lipoprotein-cholesterol (HDL-C) by 30.2, 10.3 and 26.6%, respectively. Statistical significance was established for all these changes, indicating prominent anti-hyperlipidemic activity for the ethanol extract of the plant. A similar trend of lipid-lowering activity was also demonstrated for the extract in high fat diet-induced hyperlipidemic rats over a longer time period of 28 days. On the 28th day, the ethanol extract at both doses greatly reduced the serum triglyceride level (77.2 and 78.0%, respectively) compared to that of atorvastatin (43.6%). The administration of the extract over a longer time period also resulted in a significant decline in LDL-C concentration (serum levels reduced by 15.5 and 36.1%, respectively), compared to 46.8% reduction with atorvastatin. Further histopathological studies showed that the extract (400 mg/kg body weight) reversed the high fat diet-induced deposition of fatty tissues on the aortic wall and maintained a normal vascular architecture in a similar way as the standard (Ghori et al., 2015). A thorough bioassay-guided phytochemical investigation into the plant with the screening of purified phytoconstituents for anti-hyperlipidemic activity is warranted in the future in order to identify bioactive secondary metabolites.

7.8. Anti-oxidant activity

The anti-oxidative potential of different extracts of *G. pentaphylla* using multiple *in vitro* assays, including 1,1-diphenyl-2-picrylhydrazyl (DPPH), 2,2'-azino-bis (3 ethylbenzthiazoline-6-sulfonic acid) (ABTS), nitric oxide and hydrogen peroxide (H_2O_2) scavenging methods, showed remarkable anti-oxidant potential for the petroleum ether, the ethanol and the aqueous extracts of the plant. Compared to the standard ascorbic acid (IC_{50} values of 23, 22.8, 24, and 18.3 µg/mL in the aforementioned assays, respectively), the ethanol extract demonstrated the highest anti-oxidative effect (IC_{50} values of 28.5, 26.2, 31 and 26.2 µg/mL, respectively). The petroleum ether extract also exhibited noteworthy anti-oxidant activity (IC_{50} values of 30.0, 29.8, 36.5, and 38.1 µg/mL, respectively) (Gupta et al., 2011a).

Another study confirmed the prominent free radical stabilizing activity of the ethanol extract in the DPPH and ABTS assays (IC_{50} values of 18.14 ± 2.08 and 12.04 ± 1.71 µg/mL, respectively). More powerful anti-oxidative properties were demonstrated for the dichloromethane extract with IC_{50} values of 16.70 ± 0.77 and 6.11 ± 0.7 µg/mL, respectively, compared to those of ascorbic acid (8.46 ± 0.34 and 12.04 ± 1.71 µg/mL, respectively). Such

activities were linked to the high contents in phenolic and flavonoids observed for both the ethanol and dichloromethane extracts. The phenolic contents for the extracts were 83.7 ± 0.98 and 54.7 ± 1.11 mg gallic acid equivalents/g, respectively. The flavonoid contents were 23.05 ± 0.31 and 18.24 ± 0.54 mg naringenin equivalents/g, respectively (Shoja et al., 2015).

The methanol extract of *G. pentaphylla* also significantly inhibited DPPH free radicals with an IC_{50} value of 46.75 µg/mL, compared to that of ascorbic acid (IC_{50} value of 21.16 µg/mL) (Rahman et al., 2018). Another study showed high phenolic and flavonoid contents for the methanol and aqueous extracts of the plant. The phenolic contents were measured at 22.45 ± 1.49 and 5.23 ± 1.11 µg gallic acid equivalents per mg of samples, respectively, whereas the flavonoid contents were measured at 98.312 ± 1.21 and 59.52 ± 0.33 µg rutin equivalents per mg of samples, respectively (Yasir et al., 2015).

The volatile content of *G. pentaphylla* was investigated for anti-oxidant activity using the DPPH free radical scavenging and the ferric ion reducing assays. The essential oil at a concentration of 200 µg/mL showed 70.71% inhibition in the DPPH assay, compared to 83.82% inhibition exerted by gallic acid at the same concentration. The reducing capacities of the essential oil and of ascorbic acid were determined at 1.372 and 1.834, respectively, indicating significant anti-oxidative activity for the volatile constituents of the plant (Vignesh et al., 2014).

A recent study, which attempted to determine the plant parts showing the highest concentration of anti-oxidant constituents, evaluated the activity of *G. pentaphylla* leaves, stems and roots separately. The significant anti-oxidative activity was recorded for the ethanol extract of the leaves in both the DPPH and the ABTS scavenging assays (IC_{50} values of 29.04 and 49.02 µg/mL, respectively) compared to those of ascorbic acid (22.33 and 26.03 µg/mL, respectively) (Babu and Radhamany, 2020).

As prominent anti-oxidative properties have been attributed to different extracts of *G. pentaphylla*, it seems logical to assume the plant is a rich source of anti-oxidant molecules. Further studies should aim to fractionate the active extracts, screen subsequent fractions for anti-oxidative activity, and purify and characterize active phytoconstituents.

7.9. Anti-inflammatory activity

The ethanol extract of *G. pentaphylla*, administered in multiple doses ranging from 62.5 µg/mL to 1000 µg/mL, exhibited potent dose-dependent anti-hemolytic activity in a membrane-stabilizing assay involving human red blood cells. At the maximum dose of 1000 µg/mL, the extract and the standard diclofenac suppressed hemolysis by 75.34 and 55.16%, respectively. Based on the structural similarities between the red blood cell plasma membrane and the intracellular lysosomal membrane, such activity can be extrapolated to estimate the capacity of the extract to stabilize the lysosomal membrane. Stabilization of the lysosome minimizes the intracellular release of cyclooxygenase (COX) which, in turn, can be translated into prominent anti-inflammatory activity (Ansari et al., 2015a).

Another study showed dose-dependent anti-inflammatory activity for the methanol extract of *G. pentaphylla* roots (administered at doses of 50, 100, 200 and 400 mg/kg body weight) in multiple *in vivo* models. The extract (200 mg/kg body weight) inhibited the carrageenan- and formaldehyde-induced paw edema in rats by up to 68.92 and 37.76%, respectively. The standard indomethacin (10 mg/kg body weight) exhibited 71.17 and 47.34% inhibition, respectively. In the egg albumin-induced paw edema in rats, the methanol extract (200 mg/kg) exerted anti-inflammatory activity equivalent to that of the standard chlorpheniramine (60 mg/kg) (51.04 and 53.65%, respectively). The plant extract (400 mg/kg body weight) and the standard dexamethasone (1 mg/kg) suppressed the xylene-induced ear edema in mice to an extent of 59.09 and 63.64%, respectively (Arora and Arora, 2016).

The ethanol extract of *G. pentaphylla* (800 mg/kg body weight) and the standard indomethacin (10 mg/kg) suppressed the paw swelling induced by Frenaud's complete adjuvant (FCA) in arthritic mice by 39.1 and 43.5%, respectively, indicating significant anti-arthritic and anti-inflammatory activity (Ramesh Petchi and Vijaya, 2012).

A recent phytochemical investigation of the ethanol extract of *G. pentaphylla* identified potent anti-inflammatory amides by analyzing the extent of inhibition of nitric oxide (NO) in lipopolysaccharides (LPS)-stimulated RAW 264.7 cells. Eight sulfur-containing amides, namely glycopentamide H (**88**), methylgerambullin (**79**), glycopentamide M (**93**), glycopentamide C (**83**), glycopentamide A (**81**), glycopentamide P (**96**), glycopentamide D (**84**) and methylgerambullone (**80**) exhibited significantly stronger anti-inflammatory activity than the standard dexamethasone (IC_{50} value of 9.24 ± 0.94 µM), as indicated by IC_{50} values of 0.16 ± 0.10, 0.25 ± 0.02, 0.41 ± 0.08, 0.76 ± 0.08, 1.85 ± 0.94, 2.42 ± 1.23, 2.82 ± 2.62 and

668 7.80 ± 1.51 μM, respectively (Nian et al., 2020). It remains to be seen if these phytoconstituents
669 interact with the COX enzymes and whether they show selectivity towards COX-2. If future
670 studies fail to associate these phytoconstituents with significant COX-2 inhibition, further
671 comparative studies are warranted to compare the effects of NO inhibition against that of COX
672 inhibition, in the management of inflammation.

673 Another study investigated the anti-inflammatory potential of glycopentalone (**58**)
674 isolated from the ethanol extract of *G. pentaphylla*. This compound at doses of 3.499, 10.488
675 and 17.466 μM was capable of suppressing the expression of pro-inflammatory modulators
676 viz. tumor necrosis factor α (TNFα) and cyclooxygenase 2 (COX2) in macrophages leading to
677 lower inflammatory responses (Sasidharan and Vasumathi, 2017). Further work using
678 experimental animal models is required to ascertain the efficacy of *G. pentaphylla*
679 phytoconstituents within the physiological condition.

680 **7.10. Analgesic activity**

681 The methanol extract of *G. pentaphylla* administered at doses of 200 and 400 mg/kg
682 body weight inhibited the acetic acid-induced writhing in mice by 31.97 and 44.21%,
683 respectively, compared to the standard diclofenac (50 mg/kg dose) which reduced writhes by
684 65.31% (Shams-Ud-Doha et al., 2012). Another similarly designed study reported 36.54 and
685 57.70% reductions in writhing counts for the methanol extract at doses of 250 and 500 mg/kg
686 body weight, indicating prominent dose-dependent analgesic property for the extract (Sarkar
687 et al., 2013). The ethanol extract (500 mg/kg body weight) inhibited the nociceptive response
688 in mice by 75.51%, suggesting that the plant was a potential source of antinociceptive
689 phytoconstituents (Khatun et al., 2012). Further efforts are warranted to identify the underlying
690 mechanism(s) of action of these extracts and screen individual phytoconstituents for
691 antinociceptive activity. Future works may also include *in silico* docking studies on *G.*
692 *pentaphylla* phytoconstituents at the opioid receptor sites to design new analgesic drug
693 templates.

694 **7.11. Antipyretic activity**

695 When tested against Brewer's yeast-induced pyrexia in rats over an observation period
696 of 6 hours, the ethanol extract of *G. pentaphylla* (200 mg/kg body weight) was found to reduce
697 the average rectal temperature by 0.58 °C while paracetamol (150 mg/kg body weight)
698 diminished the average rectal temperature by 0.77°C, indicating noteworthy antipyretic activity
699 (Gupta et al., 2011b). Further investigations are required to evaluate the antipyretic effect of

the ethanol extract of *G. pentaphylla* over a longer period of time, as is the case in the clinical management of fever.

7.12. Anti-arsenicosis activity

The methanol extract of *G. pentaphylla* was investigated for its potential role in reversing the adverse effects of arsenicosis in rats. The animals were given sodium arsenite through drinking water at the dose of 4 mg/kg body weight per day over a period of 90 days. Thirty days after the discontinuation of sodium arsenite (i.e. after a total of 120 days), a marked increase in the concentrations of arsenite/arsenate ions in hair, liver and feces was observed in untreated animals. In the group treated with the methanol extract of *G. pentaphylla*, the organic arsenic level declined dramatically, especially in the feces, resulting in a reduced rate of arsenic excretion from the body. The methanol extract (160 and 320 mg/kg body weight) was found to minimize the severity of arsenicosis. A larger dose of extract (320 mg/kg body weight) diminished arsenite concentrations in hair and liver (by 27.1 and 44.4%, respectively) and arsenate concentrations (by 59.0 and 63.6%, respectively). The extract (160 and 320 mg/kg body weight) also enhanced fecal excretion of organic arsenic by 267.2 and 272.2%, respectively, which eventually led to decreased arsenic accumulation within the body (De et al., 2016). This study, however, lacked in the utilization of a suitable standard, providing limited scope for comparisons. Further investigations, including a standard such as the arsenic-chelating agent dimercaprol (Hall, 2002), into the anti-arsenicosis activity of *G. pentaphylla* extracts and constituents may provide alternative options to the treatment of arsenic poisoning.

7.13. Wound healing activity

The methanol extract of *G. pentaphylla* was investigated for its wound-healing properties in male albino Wistar rats. The standard nitrofurazone administered as an ointment (0.2% w/w) improved the epithelialization of a surgically-excised wound (500 mm^2 area, 2 mm depth) and completely healed the wound within 16.15 ± 0.21 days. The methanol extract employed as a 10 and 15% w/w ointment healed the wound entirely within 19.03 ± 0.59 and 17.86 ± 0.19 days, respectively (Jha et al., 2009).

8. Toxicological profile

Administration of the ethanol extract of *G. pentaphylla* at doses of 125 and 250 mg/kg body weight for a period of 7 and 14 days demonstrated the absence of adverse hepatic toxicity.

Both doses improved hepatic functions through augmentation of the anti-oxidative activities of several hepatic enzymes. After 14 days of the administration, the extract (250 mg/kg body weight) increased the enzymatic activities of SOD, GST, GPx, glutathione reductase (GR) and reduced glutathione (GSH) by 54, 178, 332, 301 and 253%, respectively. The standard butylated hydroxyanisole (BHA) enhanced the enzymatic activities of SOD, GST, GPx, GR and reduced glutathione (GSH) by 45, 73, 163, 146 and 172%, respectively (Azad et al., 2008). Another study illustrated the protective effects of the methanol extract of *G. pentaphylla* against carbon tetrachloride-induced hepatotoxicity. The extract (500 mg/kg body weight) suppressed the carbon tetrachloride-mediated increase in ALT, AST, bilirubin and cholesterol levels by 37.07, 39.04, 21.15 and 37.47%, respectively (Ahsan et al., 2009).

A similar trend of hepatoprotective activity was demonstrated for the methanol and the petroleum ether extracts of *G. pentaphylla* against paracetamol-induced hepatotoxicity. Acute liver toxicity resulting from paracetamol administration (250 mg/kg) was characterized by an enlarged liver along with enhanced levels of AST, ALT, ALP and bilirubin. The methanol extract of *G. pentaphylla* (400 mg/kg) inhibited the elevations of these markers by 55.8, 38.8, 58.0 and 39.1%, respectively. This was compared with the standard silymarin (50 mg/kg body weight), which reversed the elevation of these markers by 60.4, 45.7, 56.1 and 32.3%, respectively. The methanol extract (200 and 400 mg/kg) also inhibited liver enlargement by 27.4 and 297%, respectively. The petroleum ether extract demonstrated a similar, though less prominent, hepatoprotective effect to the methanol extract (Nayak et al., 2011).

One study investigated the methanol and the petroleum ether extract of *G. pentaphylla* for acute toxicity and determined the maximum non-lethal dose to be 4g/ kg body weight (Nayak et al., 2011). Another study investigated the acute toxicological effect of the ethanol extract of *G. pentaphylla* administered orally at large doses (0.5, 1, 2 and 4 g/kg of body weight) to Wistar rats. The absence of any noticeable adverse responses observed in various behavioral, neurological and autonomic models indicates that this extract has a relatively safe profile for oral administration (Ramesh Petchi and Vijaya, 2012).

A phytochemical investigation of the ethanol extract of *G. pentaphylla* yielded glycopentalone (**58**) as a phytoconstituent with remarkable anti-inflammatory, anticancer and anti-fibrotic properties *in vitro*. When assessed for acute toxicity in rats, this compound (administered at 2 g/kg body weight) led to no morphological changes in hepatocytes and

762 relatively unchanged levels of ALT, AST and lactate dehydrogenase (LDH). This suggested a
763 lack of any adverse effects for this compound (Sasidharan and Vasumathi, 2017).

764 ## 9. Conclusion and future prospects

765 *G. pentaphylla* extracts and their individual phytoconstituents have demonstrated a
766 wide variety of biological properties to date. Several avenues can be considered for future
767 research on this plant. This includes focussing on its antimicrobial potentials in the search for
768 novel antibiotics against the ever-increasing threat of drug-resistant pathogens. The
769 antibacterial activities of the alkaloids arborine (**45**) and skimmianine (**55**) against selective
770 multidrug-resistant strains of *S. aureus* may act as a good starting point for such prospective
771 endeavors in antibacterial drug discovery. A similar line of investigation can also be considered
772 in terms of the anthelmintic activities of the plant. *In vivo* assessment of the plant extracts for
773 their vermifuge properties, followed by bioactivity-guided phytochemical analysis, may
774 culminate into the generation of novel anthelmintic drug candidates with better efficacy and
775 safety. Moreover, the anticancer and its supplementary anti-mutagenic properties of the plant
776 make it an ideal target for exploration towards generating newer anticancer drug candidates.
777 Already a total of six different alkaloids from three structural sub-classes have been
778 characterized with promising cytotoxic potentials. These classes, especially the carbazole one,
779 can be suggested as a prime target for future investigations in anticancer drug research. The
780 mosquitocidal activity of *G. pentaphylla* also warrants further attention as current synthetic
781 mosquitocidal agents pose a significant environmental burden and mosquitoes have developed
782 significant resistance mechanisms against them.

783 Significant anti-inflammatory property has been attributed to different extracts of *G.*
784 *pentaphylla* through several *in vitro* and *in vivo* experimentations thus validating its
785 ethnomedicinal uses in the treatment of various inflammatory conditions. Multiple amides and
786 a single alkaloid from this plant have also been demonstrated to exert remarkable anti-
787 inflammatory activities in different cell lines. Replication of such findings in appropriate
788 animal models can lead to the development of newer drug molecules. Extensive
789 pharmacological studies into different extracts of *G. pentaphylla* have also characterised the
790 plant with noteworthy antidiabetic, antihyperlipidemic, anti-oxidant, analgesic, antipyretic and
791 wound healing properties. However, identifying the responsible phytoconstituents is yet to be
792 achieved in these avenues and requires future in-depth bioassay-guided phytochemical
793 investigations. Furthermore, the potential of *G. pentaphylla* to counteract the effects of

arsenicosis should also be explored further as it may provide a more effective and economical solution for the arsenic-affected population mostly located in rural areas of developing and under-developed countries.

Ethnomedicinal records of *G. pentaphylla* have successfully guided the scientific community to establish and consolidate many pharmacological potentials of the plant and its individual constituents. Many of the discussed biological activities of the plant can be traced back to its traditional uses in the treatment of cancer, infection, inflammation, diabetes, helminthiasis, fever, pain and wounds. However, a number of major ethnomedicinal applications of *G. pentaphylla,* including its use in the treatment of cough, anemia, jaundice, liver disorders, and diarrhea, are yet to be rationalized on the basis of valid scientific evidence. Therefore, future work should endeavor to evaluate the aforementioned biological potentials of this plant using appropriate experimental models.

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TABLES

Table 1. Ethnomedicinal uses of *G. pentaphylla*

Geographical location	Local name	Plant part used	Traditional uses	References
Xishuangbanna, Gengma, Shuangjiang, Mengding of Yunnan Province, China		Whole plant	Used to treat fever, cough, rheumatism, anemia, sourness, numbness, liver disorders and other long-term conditions.	(Wang et al., 2016; Yang et al., 2012)
Southwest China		Leaves	Used traditionally by the Dai ethnic group to strengthen body, improve systemic circulation and suppress pain.	(Zhang et al., 2016)
Assam, Arunachal, Meghalaya, Mizoram Nagaland and Sikkim of India	Ashvashakota and Vananimbuka (Sanskrit), Bannimbu (Hindi), Tejmoyee (Assam), Anam and Kula pannai (Tamil), Gongi pandu	Whole plant	Employed traditionally to treat cough, fever, bronchitis, anemia, jaundice, liver disorders, inflammation, rheumatism, intestinal worm infestations, snakebite, wounds, eczema, erysipelas and other skin afflictions.	(Azad et al., 2008; Sarkar et al., 2013; Sivakumar et al., 2014)
		Bark	To alleviate diabetes and gonorrhea.	(Sarkar et al., 2013)
		Leaves juice	Used in the treatment of fever, liver disorders and helminthiasis.	(Nayak et al., 2011; Ramkumar et al., 2016)
		Leaves as paste	Applied topically to treat eczema and other skin diseases.	(Sarkar et al., 2013)
		Leaves as homeopathic formulation	Utilized in alleviating diarrhea, dysentery and pain associated with gallstone as well as worm infestations.	(Nayak et al., 2011)

	(Telegu), Paanal (Malayalam) and Manikyan (Kannda).	Leaves as homeopathic tincture	Employed to treat throat cancer.	(Nayak et al., 2011)
		Aerial parts as 50% ethanol extract	Applied for its diuretic and spasmolytic properties.	(Nayak et al., 2011)
		Roots	As a febrifuge.	(Sarkar et al., 2013)
		Roots in the form of decoction	Applied topically to treat facial inflammations.	(Ramkumar et al., 2016)
		Fruits	Effective in the treatment of dysentery.	(Sarkar et al., 2013)
Bangladesh (Gazipur, Tangail, Madhupur)	Bengali – Ashshoura, Ban Jamir, Daton, Kawatuti, Motali, Motmoti	Whole plant	Used traditionally to treat toothache, gastritis, rheumatoid arthritis, jaundice, migraine, leucorrhea, and cancer.	(Hossan et al., 2010; Sreejith and Asha, 2015)
		Leaves in the form of juice and paste	Employed in the treatment of cough, fever, rheumatism, anemia, jaundice, liver abnormalities, ascariasis, bone fracture, pain, eczema and other skin diseases.	(Bulbul and Jahan, 2016)
		Root juice	Applied in the treatment of toothache and periodontitis.	(Rahmatullah et al., 2011)
Sri Lanka, Myanmar, Indonesia, Malaysia, Thailand, Vietnam, Philippines, Java, Sumatra, Borneo and Australia	Toothbrush plant (English), Orange berry, Gin berry	Leaves juice	Used traditionally around the globe to treat cough, fever, bronchitis, anemia, jaundice, rheumatism, boils, urinary tract infections and diarrhea.	(Babu and Radhamany, 2020; Ramkumar et al., 2016; Shoja et al., 2015)

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1098 **Table 2.** Phytoconstituents isolated from *G. pentaphylla*

No.	Compounds	Type of compound	Plant parts	References
Alkaloids				
1	Carbazole	Carbazole alkaloid	Root barks	Bhattacharyya et al., 1987
2	3-Methylcarbazole	Carbazole alkaloid	Leaves and twigs	Chokchaisiria et al., 2020
			Root barks	Bhattacharyya et al., 1987
3	3-formyl carbazole	Carbazole alkaloid	Roots	Chakraborty et al., 1992
4	Glycosinine	Carbazole alkaloid	Roots	Chakraborty et al., 1992
5	Methyl carbazole-3-carboxylate	Carbazole alkaloid	Root barks	Kumar et al., 2018
6	Glycozolinine	Carbazole alkaloid	Seeds	Mukherjee et al., 1983
7	Glycozoline	Carbazole alkaloid	Root barks	Chakraborty, 1969; Kumar et al., 2018
8	2-Hydroxy-3 methylcarbazole	Carbazole alkaloid	Leaves	Pacher et al., 2001
9	Glycozolidol	Carbazole alkaloid	Leaves	Pacher et al., 2001
			Roots	Bhattacharyya et al., 1985
10	Carbalexin C	Carbazole alkaloid	Leaves	Pacher et al., 2001
11	Glycozolidine	Carbazole alkaloid	Root barks	Kumar et al., 2018
12	Glycozolidal	Carbazole alkaloid	Roots	Bhaitacharyya and Chowdhury, 1985a
13	Glycozolicine	Carbazole alkaloid	Roots	Chakraborty et al., 1992
14	Carbalexin A	Carbazole alkaloid	Stem	Yang et al., 2012
			Aerial parts	Chen et al., 2012
			Leaves	Pacher et al., 2001
15	Carbalexin B	Carbazole alkaloid	Leaves	Pacher et al., 2001

			Leaves and twigs	Chokchaisiria et al., 2020
16	Glybomine B	Carbazole alkaloid	Stem	Yang et al., 2012
			Aerial parts	Chen et al., 2012
17	4-(7-hydroxy-3-methoxy-6-methyl-9H-carbazol-4-yl)but-3-en-2-one	Carbazole alkaloid	Stem	Yang et al., 2012
18	Glycoborinine	Carbazole alkaloid	Stem	Yang et al., 2012
			Aerial parts	Chen et al., 2012
			Leaves	Pacher et al., 2001
			Leaves and twigs	Chokchaisiria et al., 2020
19	Mupamine	Carbazole alkaloid	Leaves	Chakraborty et al., 1989
20	Biscarbalexine A	Carbazole-type dimeric alkaloid	Stem	Yang et al., 2012
				Chen et al., 2015a
21	Bisglybomine B	Carbazole-type dimeric alkaloid	Stem	Yang et al., 2012
22	*Glycosmis*ine A	Carbazole–indole-type dimeric alkaloid	Stem	Chen et al., 2015a
23	*Glycosmis*ine B	Carbazole–indole-type dimeric alkaloid	Stem	Chen et al., 2015a
24	Arborinine	Acridone alkaloid	Whole plants	Quader et al., 1999
			Stem	Ito et al., 1999; Yang et al., 2012
				Choi et al., 2019
			Leaves	Ahmed et al., 2014
				Das & Deka, 2017

			Leaves and twigs	Chokchaisiria et al., 2020
			Root barks	Kumar et al., 2018
			Fruits	Sripisut et al., 2012
25	5-hydroxyarborinine	Acridone alkaloid	Stem	Ito et al., 1999
26	1-hydroxy-3,4- dimethoxy-10-methylacridan-9-one	Acridone alkaloid	Fruits	Sripisut et al., 2012
27	Noracronycine	Acridone alkaloid	Stem	Ito et al., 1999
			Root barks	Govindachari et al., 1966
28	Des-N-methylacronycine	Acridone alkaloid	Stem	Ito et al., 1999
			Roots	Sivakumar and Chamundeeswari, 2016
			Root barks	Govindachari et al., 1966
29	Des-N-methylnoracronycine	Acridone alkaloid	Stem	Ito et al., 1999
			Root barks	Govindachari et al., 1966
30	Citracridone-I	Acridone alkaloid	Stem	Ito et al., 1999
31	Glycocitrine-III	Acridone alkaloid	Stems	Ito et al., 1999
32	Glycosolone	Quinolone alkaloid	Leaves	Bhaitacharyya and Chowdhury, 1985b
33	Glycolone	Quinolone alkaloid	Leaves	Bhaitacharyya and Chowdhury, 1985b
34	4,8-dimethoxy-1-methyl-3-(3-methylbut-2-en-1-yl)quinolin-2(1H)-one/ O-methylglycosolone	Quinolone alkaloid	Stem	Yang et al., 2012
			Fruits	Sripisut et al., 2012
35	Acutifolin	Quinolone alkaloid	Fruits	Sripisut et al., 2012
36	Glycopentaphyllone	Quinolone alkaloid	Fruits	Sripisut et al., 2012

37	Glycocitlone C	Quinolone alkaloid	Fruits	Sripisut et al., 2012
38	Glycopentanolones A	Quinolone alkaloid	Stem	Choi et al., 2019
39	Glycopentanolones B	Quinolone alkaloid	Stem	Choi et al., 2019
40	Glycopentanolones C	Quinolone alkaloid	Stem	Choi et al., 2019
41	Glycopentanolones D	Quinolone alkaloid	Stem	Choi et al., 2019
42	Glycosmicine	Quinazolone alkaloid	Stem	Choi et al., 2019
43	Glycophymine	Quinazolone alkaloid	Stem	Choi et al., 2019
			Flower heads	Sarkar and Chakraborty, 1977
44	Glycosminine	Quinazolone alkaloid	Leaves	Chatterjee and Majumdar, 1954
45	Arborine	Quinazolone alkaloid	Leaves	Murugan et al; 2020
46	Glycosine	Quinazolone alkaloid	Stem	Choi et al., 2019
			Leaves	Chatterjee and Majumdar, 1954
47	Glypenfurans A	Furanopyridine alkaloid	Leaves	Zhang et al., 2016
48	Glypenfurans B	Furanopyridine alkaloid	Leaves	Zhang et al., 2016
49	Glypenfurans C	Furanopyridine alkaloid	Leaves	Zhang et al., 2016
50	Melicarpine	Furanopyridine alkaloid	Leaves	Zhang et al., 2016
51	Dictamine	Furoquinoline alkaloid	Roots	Sivakumar and Chamundeeswari, 2016
			Root barks	Kumar et al., 2018
			Fruits	Sripisut et al., 2012
52	Robustine	Furoquinoline alkaloid	Leaves	Zhang et al., 2016
53	γ-Fagarine	Furoquinoline alkaloid	Stem	Yang et al., 2012
			Leaves	Zhang et al., 2016
			Fruits	Sripisut et al., 2012

54	Haplopine	Furoquinoline alkaloid	Leaves	Zhang et al., 2016
55	Skimmianine	Furoquinoline alkaloid	Leaves and twigs	McKenzie and Price, 1952
			Stems	Ito et al., 1999
			Leaves	Chatterjee and Majumdar, 1954; Murugan et al., 2020; Zhang et al., 2016
			Roots	Sivakumar and Chamundeeswari, 2016
			Root barks	Govindachari et al., 1966; Kumar et al., 2018
			Fruits	Sripisut et al., 2012
56	Kokusaginine	Furoquinoline alkaloid	Leaves and twigs	McKenzie and Price, 1952
			Stems	Ito et al., 1999
57	Platydesmine	Furoquinoline alkaloid	Leaves	Zhang et al., 2016
58	Glycopentalone	Pyrrole alkaloid	Whole plant	Sasidharan & Vasumathi, 2017; Sreejith & Asha, 2015
59	1-Methyl-2-pyrrolidinone	Pyrrolidinone alkaloid	Leaves	Prakasia and Nair, 2015
60	5-(3-Hydroxybutyl)-2-pyrrolidinone	Pyrrolidinone alkaloid	Leaves	Prakasia and Nair, 2015
61	N,N-Dimethyltryptamine	Indole alkaloid	Roots	Sivakumar et al., 2014
62	5- Methoxy-N,1-dimethyl-1H-Indole-3-Ethanamine	Indole alkaloid	Roots	Sivakumar et al., 2014
63	5-Amino-1-phenylpyrazole	Pyrazole alkaloid	Leaves	Prakasia and Nair, 2015
64	5-(2,5-dimethoxy-phenyl)-2H-pyrazol-3-ol	Pyrazole alkaloid	Leaves	Ramkumar et al., 2016
65	5-hydroxypipecolic acid	Piperidine alkaloid	Roots	Sivakumar et al., 2014
66	2-(methylamine)-methylbenzoate	Miscellaneous alkaloid	Leaves and twigs	Chokchaisiria et al., 2020

67	Thioanthranilic Acid, N-Methyl-, S-Butyl Ester	Miscellaneous alkaloid	Leaves	Murugan & Natarajan, 2016
68	Cyclopenta[c][1]benzopyran-4(1H)-one, 7-(dimethylamino)-2,3-dihydro	Miscellaneous alkaloid	Roots	Sivakumar and Chamundeeswari, 2016
69	1-Methoxybenzene,-4-(2-hydroxybenzylideneamino)	Miscellaneous alkaloid	Roots	Sivakumar and Chamundeeswari, 2016
70	2-Methoxy-3H-azepine	Miscellaneous alkaloid	Leaves	Vignesh et al., 2014; Vignesh et al., 2016
Amides				
71	Isoprocarb/ Carbamic acid, methyl-, o-cumenyl ester	Amide	Roots	Sivakumar and Chamundeeswari, 2016
72	Glycomide	Amide	Flower heads	Sarkar and Chakraborty, 1977
73	Dehydrothalebanin B	Amide	Roots	Shapiro et al., 2000
74	Glycoamide A	Amide	Leaves and twigs	Chokchaisiria et al., 2020
75	Glycoamide B	Amide	Leaves and twigs	Chokchaisiria et al., 2020
76	2-(N-methyl-2-phenylacetamido) benzoic acid	Amide	Leaves and twigs	Chokchaisiria et al., 2020
77	N-*p*-coumaroyltyramine	Amide	Aerial parts	Chen et al., 2012
78	N-(p-hydroxyphenethyl)-3-(methylsulfonyl)-propenamide	Sulphur containing amide	Leaves	Nian et al., 2020
79	Methylgerambullin	Prenylated sulphur containing amide	Leaves	Nian et al., 2020
80	Methylgerambullone	Prenylated sulphur containing amide	Leaves	Nian et al., 2020

81	Glycopentamide A	Prenylated sulphur containing amide	Leaves	Nian et al., 2020
82	Glycopentamide B	Prenylated sulphur containing amide	Leaves	Nian et al., 2020
83	Glycopentamide C	Prenylated sulphur containing amide	Leaves	Nian et al., 2020
84	Glycopentamide D	Prenylated sulphur containing amide	Leaves	Nian et al., 2020
85	Glycopentamide E	Prenylated sulphur containing amide	Leaves	Nian et al., 2020
86	Glycopentamide F	Prenylated sulphur containing amide	Leaves	Nian et al., 2020
87	Glycopentamide G	Prenylated sulphur containing amide	Leaves	Nian et al., 2020
88	Glycopentamide H	Prenylated sulphur containing amide	Leaves	Nian et al., 2020
89	Glycopentamide I	Prenylated sulphur containing amide	Leaves	Nian et al., 2020
90	Glycopentamide J	Prenylated sulphur containing amide	Leaves	Nian et al., 2020
91	Glycopentamide K	Prenylated sulphur containing amide	Leaves	Nian et al., 2020

92	Glycopentamide L	Prenylated sulphur containing amide	Leaves	Nian et al., 2020
93	Glycopentamide M	Prenylated sulphur containing amide	Leaves	Nian et al., 2020
			Leaves	Nian et al., 2020
94	Glycopentamide N	Prenylated sulphur containing amide	Leaves	Nian et al., 2020
95	Glycopentamide O	Prenylated sulphur containing amide	Leaves	Nian et al., 2020
96	Glycopentamide P	Prenylated sulphur containing amide	Leaves	Nian et al., 2020
97	Glycopentamide Q	Prenylated sulphur containing amide	Leaves	Nian et al., 2020
98	Glycopentamide R	Prenylated sulphur containing amide	Leaves	Nian et al., 2020
Phenolic constituents				
99	Salicylic acid	Hydroxy benzoic acid	Stem	Choi et al., 2019
100	4-hydroxybenzoic acid/ *p*-hydroxybenzoic acid	Hydroxy benzoic acid	Stem	Choi et al., 2019
			Leaves	Ali et al., 2020
101	Protocatechuic acid	Hydroxy benzoic acid	Stem	Choi et al., 2019
			Leaves	Ali et al., 2020
102	Vanillic acid	Hydroxy benzoic acid	Stem	Choi et al., 2019
			Leaves	Ali et al., 2020
103	Gallic acid	Hydroxy benzoic acid	Leaves	Ali et al., 2020

104	Syringic acid	Hydroxy benzoic acid	Leaves	Ali et al., 2020
105	Cinnamic acid	Phenolic	Leaves	Ali et al., 2020
106	*p*-Coumaric acid	Cinnamic acid derivative	Stem	Choi et al., 2019
			Leaves	Ali et al., 2020
107	Caffeic acid	Cinnamic acid derivative	Leaves	Ali et al., 2020
108	Ferulic acid	Cinnamic acid derivative	Leaves	Ali et al., 2020
			Leaves and twigs	Chokchaisiria et al., 2020
109	Sinapic acid	Cinnamic acid derivative	Leaves	Ali et al., 2020
110	Alphitol	Polyphenol	Stem	Wu et al., 2012
111	3,4-dimethoxy-5-hydroxy-trans-cinnamyl alcohol	Cinnamyl alcohol derivative	Stem	Wu et al., 2012
112	Phenol, 2,4-bis(1,1-dimethylethyl)-	Phenolic	Roots	Sivakumar and Chamundeeswari, 2016
113	3-tert-butyl-4-hydroxyanisole	Phenolic	Roots	Sivakumar et al., 2014
114	Cyclopropanecarboxylic acid, 2-methyl-, 2,6-di-t-butyl-4-methylphenyl ester	Substituted phenolic	Leaves	Ramkumar et al., 2016
115	Scopoletin	Coumarin	Leaves and twigs	Chokchaisiria et al., 2020
116	Fraxidin	Coumarin	Leaves and twigs	Chokchaisiria et al., 2020
117	2H-1-Benzopyran-2-One, 6-(1-Hydroxy-3-Methylbutyl)-7-Methoxy	Coumarin	Leaves	Ramkumar et al., 2016
118	1,1'-Biphenyl, 2-Formyl-4',5',6'-Trimethoxy	Substituted phenolic	Leaves	Ramkumar et al., 2016
119	Oxyresveratrol	Stilbene	Stem	Wu et al., 2012
120	4,4'-ethylenebis(2,6-di-tert-butylphenol)	Polyphenol	Leaves	Ramkumar et al., 2016
121	Rosmarinic acid	Polyphenol	Leaves	Ali et al., 2020

122	Chlorogenic acid	Quinic acid derivative	Leaves	Ali et al., 2020
123	(-)-Syringaresinol	Polyphenol	Leaves and twigs	Chokchaisiria et al., 2020
124	α-Tocopherol	Phenol	Leaves	Murugan & Natarajan, 2016
125	Avicenol-B	Naphthoquinone	Stem	Ito et al., 1999
126	Avicequinone-C	Naphthoquinone	Stem	Ito et al., 1999
127	Glycoquinone	Naphthoquinone	Stem	Ito et al., 1999
128	Marmesin/ 7H-Furo[3,2-g][1]benzopyran-7-one, 2,3-dihydro-2-(1-hydroxy-1-methylethyl)-,(s)-	Coumarin	Roots	Sivakumar and Chamundeeswari, 2016
129	Xanthyletin/ 8,8-Dimethyl-2H,8H-pyrano[3,2-g]chromen-2-one	Coumarin	Roots	Sivakumar and Chamundeeswari, 2016
130	Arbutin	Phenolic glycoside	Stem	Tian et al., 2014
131	Tachioside	Phenolic glycoside	Stem	Tian et al., 2014
132	2,6-dimethoxy-4-hydroxyphenyl-1-*O*-β-D-glucopyranoside	Phenolic glycoside	Stem	Tian et al., 2014
133	3-Methoxyphenethyl alcohol 4-O-β-D-glucopyranoside	Phenolic glycoside	Stem	Tian et al., 2014
134	Syringin	Phenolic glycoside	Stem	Tian et al., 2014
135	Icariside E_5	Phenolic glycoside	Stem	Tian et al., 2014
136	*threo*-1-C-syringylglycerol 4-*O*-β-D-glucopyranoside	Phenolic glycoside	Stem	Tian et al., 2014
137	Glycopentosides A	Phenolic glycoside	Stem	Tian et al., 2014
138	Glycopentosides B	Phenolic glycoside	Stem	Tian et al., 2014

139	Glycopentosides C	Phenolic glycoside	Stem	Tian et al., 2014
140	Markhamioside F	Phenolic glycoside	Stem	Tian et al., 2014
141	Seguinoside K	Phenolic glycoside	Stem	Tian et al., 2014
142	Glypentosides A	Hydroquinone diglycoside acyl esters	Stem	Wang et al., 2006a
143	Glypentosides B	Hydroquinone diglycoside acyl esters	Stem	Wang et al., 2006a
144	Glypentosides C	Hydroquinone diglycoside acyl esters	Stem	Wang et al., 2006a
145	Glycopentosides D	Phenolic glycosides	Stem	Chen et al., 2015b
146	Glycopentosides E	Phenolic glycosides	Stem	Chen et al., 2015b
147	Glycopentosides F	Phenolic glycosides	Stem	Chen et al., 2015b
Flavonoids				
148	Apigenin	Flavone	Leaves	Ali et al., 2020
149	Apigenin-7-O-glucoside	Flavone	Leaves	Ali et al., 2020
150	Vitexin	Flavone	Stem	Choi et al., 2019
151	Kaempferol	Flavonol	Aerial parts	Chen et al., 2016
152	5,7,4'-trihydroxyflavonol-3-O-α-L-rhamnopyranoside	Flavonol	Aerial parts	Chen et al., 2016
153	Quercetin	Flavonol	Aerial parts	Chen et al., 2016
			Leaves	Ali et al., 2020
154	Quercetin-3-O-α-L-rhamnopyranoside	Flavonol	Aerial parts	Chen et al., 2016
155	Rutin	Flavonol	Leaves	Ali et al., 2020

156	Myricetin	Flavonol	Leaves	Ali et al., 2020
157	Hexamethylquercetagetin/ 3,5,6,7,3',4'-Hexamethoxyflavone	Flavonol	Leaves	Ramkumar et al., 2016
158	Naringenin	Flavanone	Leaves	Ali et al., 2020
159	Hesperidin	Flavanone	Leaves	Ali et al., 2020
160	Aromadendrin/ Dihydrokaempferol	Flavanonol	Aerial parts	Chen et al., 2016
161	Taxifolin/ Dihydroquercetin	Flavanonol	Aerial parts	Chen et al., 2016
162	Catechin	Flavanol	Leaves	Ali et al., 2020
163	4'-O-methylgallocatechin	Flavanol	Stem	Wu et al., 2012
164	Glycoflavanones A	Flavanol	Stem	Wu et al., 2012
165	(8S,9R)-9,10-dihydro-5,9-dihydroxy-8-(3,4,5-trimethoxyphenyl)-2H,8H-benzo[1,2-b:3,4-b']dipyran-2-one	Flavanol	Stem	Wang et al., 2016
166	Glycoflavanones B	Flavanol	Stem	Wu et al., 2012
167	(2S,3R)-3,4-dihydro-3,5-dihydroxy-2-(3,4,5-trimethoxyphenyl)-2H,8H-benzo[1,2-b:3,4-b']dipyran-8-one	Flavanol	Stem	Wang et al., 2016
168	7-hydroxy-4′-methoxyisoflavone 7-O-α-D-apiofuranosyl-(1→6)-α-D-glucopyranoside	Isoflavone diglycosides	Stem	Wang et al., 2006b
169	7-hydroxy-4′,6-dimethoxyisoflavone 7-O-α-D-apiofuranosyl-(1→6)-α-D-glucopyranoside	Isoflavone diglycosides	Stem	Wang et al., 2006b

170	7-hydroxy-4′,8-dimethoxyisoflavone 7-O-α-D-apiofuranosyl- (1→6)-α-D-glucopyranoside	Isoflavone diglycosides	Stem	Wang et al., 2006b
171	Coromandelin/ 5,4'-dihydroxy-7-methoxyisoflavone 4'-O-α-D-apiofuranosyl-(1→6)-α-D-glucopyranoside	Isoflavone diglycosides	Stem	Wang et al., 2006b
172	Tectorigenin 7-O-α-D-apiofuranosyl-(1→6)-α-D-glucopyranoside	Isoflavone diglycosides	Stem	Wang et al., 2006b
173	4′,5-dihydroxy-6,7-dimethoxyisoflavone 4′-O-α-D-apiofuranosyl-(1→6)-α-D-glucopyranoside	Isoflavone diglycosides	Stem	Wang et al., 2006b
174	4′,5-dihydroxy-3′,7-dimethoxyisoflavone 4′-O-α-D-apiofuranosyl-(1→6)-α-D-glucopyranoside	Isoflavone diglycosides	Stem	Wang et al., 2006b
175	3′,7-dihydroxy-4′,5,6-trimethoxyisoflavone 7-O-(5-O-trans-*p*-coumaroyl)-α-D-apiofuranosyl-(1→6)-α-D-glucopyranoside	Isoflavone diglycosides	Stem	Wang et al., 2006b
176	2′,7-dihydroxy-4′,5′,5,6-tetramethoxyisoflavone 7-O-α-D-apiofuranosyl-(1→6)-α-D-glucopyranoside	Isoflavone diglycosides	Stem	Wang et al., 2006b
177	2′,7-dihydroxy-4′,5′,5,6-tetramethoxyisoflavone 7-O- (5-O-trans-p-	Isoflavone diglycosides	Stem	Wang et al., 2006b

	coumaroyl)-α-D-apiofuranosyl-(1→6)-α-D-glucopyranoside			
Aromatic constituents				
178	Toluene	Aromatic constituent	Leaves	Prakasia and Nair, 2015
179	*p*-Cymene	Aromatic constituent	Seeds	Ahmed et al., 2000
180	1-(1,5-dimethyl-4-hexenyl)-4-methylbenzene	Aromatic constituent	Leaves	Ramkumar et al., 2016
181	Benzaldehyde oxime	Aromatic constituent	Leaves	Vignesh et al., 2014; Vignesh et al., 2016
182	3- Benzyloxy-1,2-diacetyl-1,2-propanediol	Aromatic constituent	Roots	Sivakumar et al., 2014
183	(+)-Calamenene/ 4-Isopropyl-1,6-dimethyl-1, 2, 3, 4- tetrahydronaphthalene	Aromatic constituent	Leaves	Vignesh et al., 2014; Vignesh et al., 2016
184	Dehydroabietic acid	Aromatic constituent	Roots	Sivakumar et al., 2014
185	Benzoic acid, 2-propenyl ester	Benzoic acid ester	Leaves	Vignesh et al., 2014; Vignesh et al., 2016
186	3-Hexen-1-ol, benzoate, (Z)	Benzoic acid ester	Leaves	Prakasia and Nair, 2015
187	Mono(2-ethylhexyl) phthalate	Phthalic acid ester	Roots	Sivakumar and Chamundeeswari, 2016
188	1,2-Benzenedicarboxylic acid, bis(2-methylpropyl) ester	Phthalic acid ester	Roots	Sivakumar and Chamundeeswari, 2016
Steroidal constituents				
189	Campesterol/ Ergost-5-en-3-ol, (3.beta.24R)-	Sterol	Roots	Sivakumar et al., 2014
190	β-sitosterol	Sterol	Stem	Wu et al., 2012
191	γ-Sitosterol/ Stigmast-5-en-3-ol	Sterol	Roots	Sivakumar et al., 2014; Sivakumar and Chamundeeswari, 2016

192	Sitostenone/ 4-Stigmasten-3-one	Sterol	Roots	Sivakumar et al., 2014
193	Stigmasterol	Sterol	Roots	Sivakumar et al., 2014; Sivakumar and Chamundeeswari, 2016
194	Spinasterol	Sterol	Leaves	Ahmed et al., 2014
Non-volatile terpenes				
195	Helioscopinolide A	Diterpene	Leaves and twigs	Chokchaisiria et al., 2020
196	Helioscopinolide E	Diterpene	Leaves and twigs	Chokchaisiria et al., 2020
197	3-oxojolkinolide A	Diterpene	Leaves and twigs	Chokchaisiria et al., 2020
198	β-amyrin	Triterpene	Leaves	Ahmed et al., 2014
199	3-Epi-oleanolic acid	Triterpene	Leaves	Ahmed et al., 2014
200	Canophyllal	Triterpene	Roots	Sivakumar and Chamundeeswari, 2016
Volatile constituents				
201	β-Myrcene	Acyclic monoterpene	Seeds	Ahmed et al., 2000
202	β-Ocimene	Acyclic monoterpene	Leaves	Prakasia and Nair, 2015
203	2,4,6-octatriene,2,6-Dimethyl	Acyclic monoterpene	Leaves	Vignesh et al., 2014; Vignesh et al., 2016
204	3,7-Dimethyl-1,6-octadien-3-ol	Acyclic monoterpene	Leaves	Vignesh et al., 2014; Vignesh et al., 2016
205	Nerol	Acyclic monoterpene	Seeds	Ahmed et al., 2000
206	Geraniol	Acyclic monoterpene	Seeds	Ahmed et al., 2000
207	Linalool	Acyclic monoterpene	Seeds	Ahmed et al., 2000; Prakasia and Nair, 2015
208	Hotrienol	Acyclic monoterpene	Leaves	Prakasia and Nair, 2015
209	3,7-Dimethyl-1-octene-3,7-diol	Acyclic monoterpene	Seeds	Ahmed et al., 2000
210	3,7-dimethyl-l,5-octadiene-3,7-diol	Acyclic monoterpene	Seeds	Ahmed et al., 2000
211	6,10-Dimethyl-9-undecen-2-one	Acyclic monoterpene	Leaves	Prakasia and Nair, 2015

212	*o*-Menth-8-ene	Monocyclic monoterpene	Leaves	Vignesh et al., 2014; Vignesh et al., 2016
213	1,5,5-Trimethyl-6-methylene-cyclohexene	Monocyclic monoterpene	Leaves	Prakasia and Nair, 2015
214	Isophorone/ 3,5,5-Trimethyl-2-cyclohexen-1-one	Monocyclic monoterpene	Roots	Sivakumar and Chamundeeswari, 2016
215	P-Menth-4(8)-ene	Monocyclic monoterpene	Leaves	Vignesh et al., 2016
216	α-Terpinene	Monocyclic monoterpene	Leaves	Vignesh et al., 2014; Vignesh et al., 2016
217	β-Terpinene	Monocyclic monoterpene	Leaves	Vignesh et al., 2014; Vignesh et al., 2016
218	γ-Terpinene	Monocyclic monoterpene	Leaves	Vignesh et al., 2014; Vignesh et al., 2016
			Seeds	Ahmed et al., 2000
219	Terpinolene	Monocyclic monoterpene	Leaves	Vignesh et al., 2014
220	Limonene	Monocyclic monoterpene	Seeds	Ahmed et al., 2000
221	β-Phellandrene	Monocyclic monoterpene	Seeds	Ahmed et al., 2000
222	α-Terpineol	Monocyclic monoterpene	Leaves	Prakasia and Nair, 2015
			Seeds	Ahmed et al., 2000
223	Terpinen-4-ol	Monocyclic monoterpene	Leaves	Prakasia and Nair, 2015
			Leaves and barks and seeds	Ahmed et al., 2000
			Seeds	Ahmed et al., 2000
224	*p*-Menth-2-en-1 -ol	Monocyclic monoterpene	Seeds	Ahmed et al., 2000
225	2-Cyclohexen-1-ol, 1-methyl-4-(1-methylethenyl)-, trans	Monocyclic monoterpene	Leaves	Vignesh et al., 2014; Vignesh et al., 2016
226	1,2,4-Trihydroxy-*p*-menthane	Monocyclic monoterpene	Seeds	Ahmed et al., 2000
227	*cis*-Linalool oxide (furanoid)	Monocyclic monoterpene	Seeds	Ahmed et al., 2000

228	*trans*-Linalool oxide (furanoid)	Monocyclic monoterpene	Seeds	Ahmed et al., 2000
229	*cis*-Linalool oxide (pyranoid)	Monocyclic monoterpene	Seeds	Ahmed et al., 2000
230	*trans*-Linalool oxide (pyranoid)	Monocyclic monoterpene	Seeds	Ahmed et al., 2000
231	1-(3,3-dimethyl-1-yl)-2,2-dimethylcyclopropene-3-carboxylic acid	Monocyclic monoterpene	Leaves	Vignesh et al., 2014; Vignesh et al., 2016
232	*trans*-β-Ionone	Monocyclic monoterpene	Leaves	Prakasia and Nair, 2015
233	Cyclooctanemethanol	Monocyclic monoterpene	Leaves	Vignesh et al., 2014
234	Bicyclo [6.1.0] non-1-ene	Bicyclic monoterpene	Leaves	Vignesh et al., 2014; Vignesh et al., 2016
235	Bicyclo[5.1.0]octane, 8-methylene	Bicyclic monoterpene	Leaves	Vignesh et al., 2014; Vignesh et al., 2016
236	Sabinene	Bicyclic monoterpene	Seeds	Ahmed et al., 2000
237	Dehydrosabinene/ 2,4(10)-Thujadiene	Bicyclic monoterpene	Leaves	Vignesh et al., 2014; Vignesh et al., 2016
238	α-Pinene	Bicyclic monoterpene	Seeds	Ahmed et al., 2000
239	β-Pinene	Bicyclic monoterpene	Leaves	Prakasia and Nair, 2015; Vignesh et al., 2014; Vignesh et al., 2016
			Seeds	Ahmed et al., 2000
240	6-Methylenebicyclo[3.2.0]heptane	Bicyclic monoterpene	Leaves	Vignesh et al., 2014; Vignesh et al., 2016
241	Bicyclo[4.1.0]heptane, 7-(1-methylethylidene)	Bicyclic monoterpene	Leaves	Vignesh et al., 2014; Vignesh et al., 2016
242	2-Carene	Bicyclic monoterpene	Leaves	Prakasia and Nair, 2015
243	3-Carene	Bicyclic monoterpene	Leaves	Vignesh et al., 2014; Vignesh et al., 2016
244	Trans-2-Caren-4-ol	Bicyclic monoterpene	Leaves	Vignesh et al., 2014; Vignesh et al., 2016
245	Camphene	Bicyclic monoterpene	Leaves	Vignesh et al., 2014; Vignesh et al., 2016
246	Borneol	Bicyclic monoterpene	Seeds	Ahmed et al., 2000

247	1,8-Cineole/ Eucalyptol	Bicyclic monoterpene	Seeds	Ahmed et al., 2000
248	Tricyclo[4.1.0.0(2,7)]heptane	Tricyclic monoterpene	Leaves	Vignesh et al., 2014; Vignesh et al., 2016
249	Adamantane	Tricyclic monoterpene	Leaves	Vignesh et al., 2014; Vignesh et al., 2016
250	Nerodilol/ 3,7,11-Trimethyl-1,6,10-dodecatrien-3-ol	Acyclic sesquiterpene	Leaves	Vignesh et al., 2014; Vignesh et al., 2016
251	6,10,14-trimethyl-2-pentadecanone	Acyclic sesquiterpene	Leaves and barks	Ahmed et al., 2000; Prakasia and Nair, 2015
252	Cyclohexane, 1,5-diethenyl-3- methyl-2-methylene-, (1.alpha., 3.alpha.,5.alpha)-	Monocyclic sesquiterpene	Leaves	Vignesh et al., 2014; Vignesh et al., 2016
253	1,5,5-Trimethyl-6-(2-Propenylidene)-1-Cyclohexene	Monocyclic sesquiterpene	Leaves	Ramkumar et al., 2016
254	β-elemene	Monocyclic sesquiterpene	Leaves	Sivakumar and Chamundeeswari, 2016
255	γ-Elemene	Monocyclic sesquiterpene	Leaves	Prakasia and Nair, 2015
256	δ-Elemene/ Cyclohexene,4-ethenyl-4-methyl-3-(1-methylethenyl)-1-(1-methylethyl)-, (3r-trans)-	Monocyclic sesquiterpene	Roots	Sivakumar and Chamundeeswari, 2016
257	Isoshyobunone	Monocyclic sesquiterpene	Leaves	Prakasia and Nair, 2015
258	Nerolidol oxide	Monocyclic sesquiterpene	Leaves and barks	Ahmed et al., 2000
259	2R-acetoxymethyl-1,3,3-trimethyl-4t-(3-methyl-2-buten-1-yl)-1t-cyclohexanol	Monocyclic sesquiterpene	Leaves	Ramkumar et al., 2016
260	1-Methylene-2b-Hydroxymethyl-3,3-Dimethyl-4b-(3-Methylbut-2- Enyl)-Cyclohexane	Monocyclic sesquiterpene	Leaves	Murugan & Natarajan, 2016

261	Hedycaryol/ 2-(4,8-Dimethyl-3,7-cyclodecadien-1-yl)-2-propanol	Monocyclic sesquiterpene	Roots	Sivakumar and Chamundeeswari, 2016
262	Germacrene D/ 1,6-Cyclodecadiene, 1-methyl-5-methylene-8-(1- methylethyl)-,[S(E,E)]-	Monocyclic sesquiterpene	Leaves	Prakasia and Nair, 2015
263	α-Humulene/ α-Caryophyllene	Monocyclic sesquiterpene	Leaves	Prakasia and Nair, 2015
			Roots	Sivakumar and Chamundeeswari, 2016
264	β-Humulene	Monocyclic sesquiterpene	Leaves	Prakasia and Nair, 2015
265	Bicyclogermacrene	Bicyclic sesquiterpene	Leaves	Prakasia and Nair, 2015
266	Bicyclo[4.4.0]dec-1-ene, 2-isopropyl-5-methyl-9-methylene-	Bicyclic sesquiterpene	Leaves	Prakasia and Nair, 2015
267	δ-Amorphene	Bicyclic sesquiterpene	Leaves	Prakasia and Nair, 2015
268	γ-Muurolene	Bicyclic sesquiterpene	Leaves	Prakasia and Nair, 2015
269	α-Cadinol	Bicyclic sesquiterpene	Leaves and barks	Ahmed et al., 2000
270	1-*Epi*-cubenol	Bicyclic sesquiterpene	Leaves and barks	Ahmed et al., 2000
271	T-muurolol	Bicyclic sesquiterpene	Leaves and barks	Ahmed et al., 2000
272	Rosifoliol	Bicyclic sesquiterpene	Roots	Sivakumar et al., 2014; Sivakumar and Chamundeeswari, 2016
273	γ-Eudesmol	Bicyclic sesquiterpene	Roots	Sivakumar and Chamundeeswari, 2016
274	Cedrene-V6	Bicyclic sesquiterpene	Leaves	Vignesh et al., 2014; Vignesh et al., 2016
275	1H-Indene, 1-ethylideneoctahydro-7a-methyl-(1E, 3a.alpha.,7a.beta.)	Bicyclic sesquiterpene	Leaves	Prakasia and Nair, 2015

276	4,8,8-trimethyl -2-methylene--4-vinylbicyclo[5.2.0]nonane	Bicyclic sesquiterpene	Leaves	Prakasia and Nair, 2015
277	Guaiol/ Champaca camphor	Bicyclic sesquiterpene	Roots	Sivakumar et al., 2014; Sivakumar and Chamundeeswari, 2016
278	Glaucyl alcohol	Bicyclic sesquiterpene	Leaves	Ramkumar et al., 2016
279	β-Caryophyllene	Bicyclic sesquiterpene	Leaves	Murugan & Natarajan, 2016; Prakasia and Nair, 2015; Vignesh et al., 2014; Vignesh et al., 2016
			Roots	Sivakumar and Chamundeeswari, 2016
280	*trans*-Z-α-Bisabolene epoxide	Bicyclic sesquiterpene	Leaves	Prakasia and Nair, 2015
281	β-Panasinsene	Triicyclic sesquiterpene	Leaves	Vignesh et al., 2014; Vignesh et al., 2016
282	*cis*-Thujopsene	Tricyclic sesquiterpene	Leaves	Prakasia and Nair, 2015
283	α-Copaene	Tricyclic sesquiterpene	Leaves	Prakasia and Nair, 2015; Vignesh et al., 2014; Vignesh et al., 2016
			Leaves and barks	Ahmed et al., 2000
			Roots	Sivakumar and Chamundeeswari, 2016
284	β-copaene	Tricyclic sesquiterpene	Leaves	Prakasia and Nair, 2015
285	α-Copaene-8-ol	Tricyclic sesquiterpene	Leaves	Ramkumar et al., 2016
286	α-Cubebene	Tricyclic sesquiterpene	Leaves	Prakasia and Nair, 2015; Vignesh et al., 2014; Vignesh et al., 2016
287	β-Patchoulene	Tricyclic sesquiterpene	Leaves	Prakasia and Nair, 2015
288	Aromadendrene	Tricyclic sesquiterpene	Leaves	Prakasia and Nair, 2015; Vignesh et al., 2014; Vignesh et al., 2016

289	Globulol	Tricyclic sesquiterpene	Leaves and barks	Ahmed et al., 2000
290	Viridiflorol	Tricyclic sesquiterpene	Leaves and barks	Ahmed et al., 2000
291	Ledol	Tricyclic sesquiterpene	Leaves	Prakasia and Nair, 2015; Vignesh et al., 2014; Vignesh et al., 2016
292	Isoaromadendrene epoxide	Tricyclic sesquiterpene	Leaves	Prakasia and Nair, 2015
293	Spathulenol	Tricyclic sesquiterpene	Leaves and barks	Ahmed et al., 2000
294	(-)-Spathulenol	Tricyclic sesquiterpene	Leaves	Prakasia and Nair, 2015
295	1H-Cycloprop[e]azulene	Tricyclic sesquiterpene	Leaves	Prakasia and Nair, 2015
296	Caryophyllene oxide	Tricyclic sesquiterpene	Leaves	Prakasia and Nair, 2015
297	1,4-dimethyl-8- isopropylidenetricyclo [5.3.0.0 (4, 10)]decane	Tetracyclic sesquiterpene	Leaves	Vignesh et al., 2014; Vignesh et al., 2016
298	Cycloisolongifolene	Tetracyclic sesquiterpene	Leaves	Vignesh et al., 2014; Vignesh et al., 2016
299	Phytol	Acyclic diterpene	Leaves	Prakasia and Nair, 2015
300	Isophytol	Acyclic diterpene	Leaves	Prakasia and Nair, 2015
301	trans-Geranylgeraniol	Acyclic diterpene	Leaves	Prakasia and Nair, 2015
302	Squalene	Acyclic triterpene	Leaves	Murugan & Natarajan, 2016
			Roots	Sivakumar and Chamundeeswari, 2016
303	Dodecanoic (lauric) acid	Fatty acid	Leaves and barks	Ahmed et al., 2000
304	Tetradecanoic (myristic) acid	Fatty acid	Leaves and barks	Ahmed et al., 2000
305	Pentadecanoic acid	Fatty acid	Leaves and barks	Ahmed et al., 2000
306	Hexadecanoic (palmitic) acid	Fatty acid	Leaves and barks	Ahmed et al., 2000
307	Oleic acid	Fatty acid	Leaves and barks	Ahmed et al., 2000
308	2,3-dihydroxypropyl acetate	Fatty acid ester	Roots	Sivakumar and Chamundeeswari, 2016

309	cis-3-Hexenyl isovalerate	Fatty acid ester	Leaves	Prakasia and Nair, 2015
310	3-Hexenyl butyrate	Fatty acid ester	Leaves	Vignesh et al., 2014; Vignesh et al., 2016
311	Ethenyl dodecanoate	Fatty acid ester	Leaves and barks	Ahmed et al., 2000
312	Ethyl hexadecanoate	Fatty acid ester	Leaves and barks	Ahmed et al., 2000
313	Butyl hexadecanoate	Fatty acid ester	Roots	Sivakumar et al., 2014
314	Methyl octadecanoate	Fatty acid ester	Roots	Sivakumar et al., 2014
315	Butyl-11-eicosenoate	Fatty acid ester	Roots	Sivakumar et al., 2014
316	3- Hexen-1-ol	Fatty alcohol	Leaves	Prakasia and Nair, 2015
317	4-Hexyn-3-ol	Fatty alcohol	Leaves	Vignesh et al., 2014; Vignesh et al., 2016
318	Octanol	Fatty alcohol	Seeds	Ahmed et al., 2000
319	Undecanol	Fatty alcohol	Leaves and barks	Ahmed et al., 2000
320	2-Undecanol	Fatty alcohol	Leaves and barks	Ahmed et al., 2000
321	Tridecanol	Fatty alcohol	Leaves and barks	Ahmed et al., 2000
322	2-Tridecanol	Fatty alcohol	Leaves and barks	Ahmed et al., 2000
323	1-Tetracosanol	Fatty alcohol	Roots	Sivakumar and Chamundeeswari, 2016
324	Octanal	Fatty aldehyde	Seeds	Ahmed et al., 2000
325	Decanal	Fatty aldehyde	Seeds	Ahmed et al., 2000
326	Tetradecanal	Fatty aldehyde	Leaves and barks	Ahmed et al., 2000
327	2-Undecanone	Aliphatic ketone	Leaves and barks	Ahmed et al., 2000
328	3-Undecanone	Aliphatic ketone	Leaves	Vignesh et al., 2014; Vignesh et al., 2016
329	2-Dodecanone	Aliphatic ketone	Leaves and barks	Ahmed et al., 2000
330	2-Tridecanone	Aliphatic ketone	Leaves and barks	Ahmed et al., 2000
331	2-Pentadecanone	Aliphatic ketone	Leaves and barks	Ahmed et al., 2000

332	Z,Z-6,27-Hexatriactontadien-2-One	Aliphatic ketone	Leaves	Murugan & Natarajan, 2016
333	Z,Z-6,28-Heptatriactontadien-2-One	Aliphatic ketone	Leaves	Murugan & Natarajan, 2016
334	4-Methyl-1,3-pentadiene	Aliphatic hydrocarbon	Leaves	Vignesh et al., 2014; Vignesh et al., 2016
335	1-Hepten-3-yne	Aliphatic hydrocarbon	Leaves	Vignesh et al., 2014; Vignesh et al., 2016
336	3,3,5-Trimethyl-1,4-hexadiene	Aliphatic hydrocarbon	Leaves	Vignesh et al., 2014; Vignesh et al., 2016
337	3-Undecyne	Aliphatic hydrocarbon	Leaves	Vignesh et al., 2016
338	1-Tetradecene	Aliphatic hydrocarbon	Roots	Sivakumar and Chamundeeswari, 2016
339	(Z)-2-Petadecen-4-yne	Aliphatic hydrocarbon	Leaves	Vignesh et al., 2014; Vignesh et al., 2016
340	(Z)-3-Hexadecen-7-yne	Aliphatic hydrocarbon	Leaves	Vignesh et al., 2014; Vignesh et al., 2016
341	1-Heptadecene	Aliphatic hydrocarbon	Roots	Sivakumar and Chamundeeswari, 2016
342	1-Nonadecene	Aliphatic hydrocarbon	Roots	Sivakumar and Chamundeeswari, 2016
343	3-Eicosene	Aliphatic hydrocarbon	Leaves	Prakasia and Nair, 2015
344	1,19- Eicosadiene	Aliphatic hydrocarbon	Leaves	Prakasia and Nair, 2015
345	1-tricosene	Aliphatic hydrocarbon	Roots	Sivakumar et al., 2014
346	Nonacosane	Aliphatic hydrocarbon	Roots	Sivakumar et al., 2014
347	Hentriacontane	Aliphatic hydrocarbon	Leaves	Murugan & Natarajan, 2016
348	Hexatriacontane	Aliphatic hydrocarbon	Roots	Sivakumar et al., 2014
349	n-Tetracontane	Aliphatic hydrocarbon	Roots	Sivakumar et al., 2014
350	1,1,3-Trimethylcyclopentane	Cyclic hydrocarbon	Leaves	Prakasia and Nair, 2015
351	1,2,3,4,5-Pentamethylcyclopentane	Cyclic hydrocarbon	Leaves	Prakasia and Nair, 2015
352	3-Methyl-2-(2-oxopropyl)furan	Miscellaneous heterocycle	Leaves	Ramkumar et al., 2016
353	3,4-Dimethyl-2-prop-2-enyl-2,5-dihydrothiophene 1,1-dioxide	Miscellaneous heterocycle	Leaves	Vignesh et al., 2014; Vignesh et al., 2016

354	3,5-Dihydroxy-6-methyl-2,3-dihydro-4H-pyran-4-one	Miscellaneous heterocycle	Roots	Sivakumar et al., 2014

1101 **Table 3.** Pharmacological activities of different extracts and phytoconstituents of *G. pentaphylla*

Activity	**Preparation type**	**Type of study**	**Testing subjects/ methods**	**Administered Dose**	**Effects**	**References**
Antioxidant activity	Ethanol extract	*In vitro*	DPPH, ABTS, NO and H_2O_2 scavenging assays	IC_{50} values of 28.5, 26.2, 31 and 26.2 µg/mL, respectively	Prominent antioxidant activity compared to the standard ascorbic acid.	Gupta et al., 2011a
	Ethanol extract	*In vitro*	DPPH and ABTS scavenging assays	IC_{50} values of 18.14 and 12.04 µg/mL, respectively	Powerful antioxidant activity compared to the standard ascorbic acid.	Shoja et al., 2015
	Petroleum ether extract	*In vitro*	DPPH, ABTS, NO and H_2O_2 scavenging assays	IC_{50} values of 30.0, 29.8, 36.5 and 38.1 µg/mL, respectively	Moderate anti-oxidative effect compared to the standard ascorbic acid.	Gupta et al., 2011a
	Dichloromethane extract	*In vitro*	DPPH and ABTS scavenging assays	IC_{50} values of 16.70 and 6.11 µg/mL, respectively	Powerful antioxidant activity compared to the standard ascorbic acid.	Shoja et al., 2015

	Methanol extract	*In vitro*	DPPH scavenging assays	IC_{50} value of 46.75 µg/mL	Moderate anti-oxidative property comparable to that of ascorbic acid.	Rahman et al., 2018
	Volatile contents	*In vitro*	DPPH scavenging assays	200 µg/mL	Moderately inhibited DPPH free radicals to an extent of 70.71%.	Vignesh et al., 2014
Antidiabetic activity	Methanol extract	*In vivo*	Wister albino rats	250 mg/kg body weight	Reduced plasma glucose concentration to a moderate extent over a time period of 14 days.	Rahman et al., 2018
	Ethanol extract	*In vivo*	Male Wister rats	400 & 800 mg/kg body weight	Exhibited significant antidiabetic activity by elevating serum insulin and attenuating plasma glucose concentration compared to the standard glibenclamide.	Ramesh Petchi and Vijaya, 2012
	Ethanol extract	*In vivo*	Swiss albino mice	250 & 500 mg/kg body weight	Significantly reduced blood glucose concentration after 120 minutes of oral administration of the extract.	Khatun et al., 2012
Anti-hyperlipidemic activity	Ethanol extract	*In vivo*	Wistar albino rats	200 & 400 mg/kg body weight	Diminishing TC , TG , LDL-C, VLDL-C, glucose and elevating HDL levels after inducing hyperlipidemia in rats	Ghori et al., 2015
Antimicrobial activity	Methanol extract	*In vitro*	Disk diffusion assay	500 µg per disc	Potent activity against gram-positive *Staphylococcus aureus*, gram-negative *Escherichia coli* and *Salmonella typhi* as well as the yeast *Candida albicans*.	Ansari et al., 2015b; Bulbul and Jahan, 2016

	Aqueous alcoholic extract	*In vitro*	Disk diffusion assay	MIC of 50 & 250 µg/mL	Prominent activity against the yeasts *C. albicans C. tropicalis* and *C. krusei.*	Yasir et al., 2015
	Methanol extract	*In vitro*	Disk diffusion assay	100 µg/mL (In Zinc nanoparticle form)	Showed significant zone of inhibition against the gram-positive *Bacillus cereus* and *S. aureus* as well as the gram-negative *Shigella dysenteriae* and *S. paratyphi,* and the fungi *C. albicans* and *Aspergillus niger*	Vijayakumar et al., 2018
	Arborinine	*In vitro*	Disk diffusion assay	100 µg per disc	Moderately inhibited the growth of the gram-positive *B. subtilis* and the gram-negative *Klebsiella pneumonia*	Das and Deka, 2017
	Skimmianine	*In vitro*	Kinetic and protein leakage assay	0.2 µg/mL	Strong antibacterial activity against different strains of multidrug resistant *S. aureus*.	Murugan et al; 2020
	Arborine	*In vitro*	Kinetic and protein leakage assay	0.2 µg/mL	Strong antibacterial activity against different strains of multidrug resistant *S. aureus*.	Murugan et al; 2020
Anthelmintic activity	Methanol extract	*In vitro*	*Pheretima posthuma* (earthworm)	80 mg/mL	Potent activity on experimental populations.	Gangarao and Jayaraju, 2009

	Methanol extract	*In vitro*	*Pheretima posthuma* (earthworm)	60 mg/mL	Potent activity on experimental populations.	Arora et al., 2011
Mosquitocidal effect	Chloroform, ethyl acetate, acetone and methanol extracts	*In vitro*			Acetone and ethyl acetate extracts showed notable larvicidal property, and chloroform extract exerted adulticidal activity against *Culex quinquefasciatus*, *Anopheles stephensi* and *Aedes aegypti* malarial vectors.	(Ramkumar et al., 2016
	Essential oils	*In vitro*			Significant larvicidal action in a dose dependent manner.	Vignesh et al., 2016
	Arborine	*In vitro*		10^{-5} and 10^{-4} M	Prominent larvicidal potential.	Muthukrishnan et al., 1999
Cytotoxicity	Methanol extract	*In vitro*	Brine shrimp lethality bioassay	LC_{50} values of 22.55 µg/mL	Moderate anticancer activity.	Rahman et al., 2018
	Ethanol extract	*In vitro*	Dalton's lymphoma ascites (DLA) cells assay	10 - 200 µg/mL	Prominent inhibitory action on RAW 264.7 cells.	Babu and Radhamany, 2019
	Petroleum ether, dichloromethan	*In vitro*	Sulforhodamine B (SRB) assay		Significant cytotoxicity against MCF-7 and MDA-MB-231 breast adenocarcinoma cell lines	Shoja et al., 2015

	e and ethyl acetate fractions					
	Arborinine	*In vitro*	Potato disc bioassay	18.75 µg/disc	Showed moderate anticancer potential.	Quader et al., 1999
	Glycoborinine	*In vitro*		39.7 µM -100 µM	Exhibited strong activity against HepG2 human liver cancer cell line in a dose-dependent manner.	Yang et al., 2014
	Glycopentalone	*In vitro*		3 µg/mL	Strong anticancer potential against Hep3 B cells.	Sreejith et al., 2012a; Sreejith and Asha, 2015
		In vitro		10.488 µM	Arrested the cell cycle at the G1 stage and diminished the expression of the tumor growth factor β (TGF β).	Sasidharan and Vasumathi, 2017
	*Glycosmis*ine A, *Glycosmis*ine B and Biscarbalexine A	*In vitro*		30.6 – 57.10 µM	Exhibited prominent antiproliferative activity against HepG2 and Huh-7 human liver cancer cell lines as well as A549 alveolar adenocarcinoma cell lines	Chen et al., 2015
	(8S,9R)-9,10-dihydro-5,9-	*In vitro*		IC_{50} values of 14.4 and 15.2	Exhibited remarkable cytotoxicity against HL-60 cell lines.	Wang et al., 2016

	dihydroxy-8-(3,4,5-trimethoxyphenyl)-2H,8H-benzo[1,2-b:3,4-b']dipyran-2-one and (2S,3R)-3,4-dihydro-3,5-dihydroxy-2-(3,4,5-trimethoxyphenyl)-2H,8H-benzo[1,2-b:3,4-b']dipyran-8-one			µM, respectively		
				IC_{50} values of 22.4 and 21.1 µM, respectively	Potent cytotoxic against A549 cell lines.	Wang et al., 2016
	N-(p-hydroxyphenethyl)-3-(methylsulfonyl)-propenamide, Methylgerambullin, Glycopentamide derivatives (B, C, E, G, J, H, K, M, N, O, P and R)	*In vitro*	CCK-8 method	7.47 ± 0.91 to 16.23 ± 0.80 µM	Remarkable anticancer potential through antiproliferative activity against HepG2 cell line.	Nian et al., 2020

Antimutagenic activity	Methanol extract	*In vivo*	Swiss albino mice	500 mg/kg	Increased the action of anti-oxidative enzymes and attenuated the pro-inflammatory C-reactive protein (CRP) levels.	Ali et al., 2020
Wound-healing property	Methanol extract	*In vivo*	Male albino Wistar rats	10 and 15% w/w ointment	Recovered wound entirely within a short period of time.	Jha et al., 2009
Anti-inflammatory activity	Ethanol extract	*In vitro*		62.5 µg/mL to 1000 µg/mL	Excellent anti-inflammatory property by minimizing the release of intracellular cyclooxygenase.	Ansari et al., 2015a
	Methanol extract	*In vivo*		50, 100, 200 and 400 mg/kg body weight	Suppressed egg albumin-as well as carrageenan- and formaldehyde-induced paw edema in rats and xylene induced ear edema in mice.	Arora and Arora, 2016
	Ethanol extract	*In vivo*		800 mg/kg body weight	Significant anti-arthritic as well as anti-inflammatory property	Ramesh Petchi and Vijaya, 2012
	Glycopentamide derivatives (A, C, D,H, M, P), methylgerambullin and methylgerambullone	*In vitro*		0.16 ± 0.10 to 7.80 ± 1.51 µM	Exerted prominent anti-inflammatory activity by inhibition of NO production in lipopolysaccharides-stimulated RAW 264.7 cells	Nian et al., 2020

	Glycopentalone	*In vitro*		3.499, 10.488 and 17.466 µM	Anti-inflammatory activity through diminishing the expression of tumor necrosis factor α and cyclooxygenase 2 enzyme.	Sasidharan and Vasumathi, 2017.
Analgesic activity	Methanol extract	*In vivo*		200 and 400 mg/kg body weight	Reducing the writhing count notably.	Shams-Ud-Doha et al., 2012
	Methanol extract	*In vivo*		250 and 500 mg/kg body weight	Showed prominent dose-dependent analgesic activity.	Sarkar et al., 2013
	Ethanol extract	*In vivo*		500 mg/kg body weight	Inhibited the nociceptive response.	Khatun et al., 2012
Antipyretic activity	Ethanol extract	*In vivo*	Male albino Wistar rats	200 mg/kg body weight	Significant attenuation of rectal temperature	Gupta et al., 2011b
Anti-arsenicosis activity	Methanol extract	*In vivo*		160 and 320 mg/kg body weight	Reduced arsenic accumulation within the body	De et al., 2016
Hepatoprotective effect	Ethanol extract	*In vivo*		125 and 250 mg/kg body weight	Increased the anti-oxidative property of hepatic enzymes.	Azad et al., 2008
	Methanol extract	*In vivo*		500 mg/kg body weight	Showed protective function by decreasing the elevated level of ALT, AST, bilirubin and cholesterol.	Ahsan et al., 2009

	Methanol extract	*In vivo*		400 mg/kg body weight	Significantly improved paracetamol-induced hepatotoxicity	Nayak et al., 2011

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FIGURES LEGENDS

Figure 1. *Glycosmis pentaphylla* (Retz.) DC. A) Whole plant, B) Leaves, C) Flowers and D) Ripe fruits.

Figure 2. Carbazole and acridone alkaloids from *G. pentaphylla*.

Figure 3. Quinolone, quinazolone, furanopyridine, furoquinoline and other alkaloids from *G. pentaphylla*.

Figure 4. Amides from *G. pentaphylla*.

Figure 5. Phenolic constituents from *G. pentaphylla*.

Figure 6. Phenolic glycosides from *G. pentaphylla*.

Figure 7. Flavonoids from *G. pentaphylla*.

Figure 8. Aromatic constituents from *G. pentaphylla*.

Figure 9. Steroidal constituents from *G. pentaphylla*.

Figure 10. Non-volatile terpenes from *G. pentaphylla*.

Figure 11. Volatile constituents from *G. pentaphylla*.

Figure 12. Pharmacological activities of different extracts of *G. pentaphylla*; AcE: Acetone extract, AqE: Aqueous extract, CE: Chloroform extract, DCME: Dichloromethane extract, EAE: Ethyl acetate extract, EE: Ethanol extract, ME: Methanol extract and PEE: Petroleum ether extract.