Bangladesh Pharmaceutical Journal ***29****(1): 99-106, 2026 (January)*

Exploring the Medicinal Potential of *Glycosmis cyanocarpa* (Rutaceae)

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(Received: August 23, 2025; Accepted: November 27, 2025; Published (web): January 28, 2026)

Abstract

Glycosmis cyanocarpa (Blume) Spreng., a member of the Rutaceae family, is a small shrub or tree distributed across South and Southeast Asia. Phytochemical investigations have identified 23 secondary metabolites, including quinolone alkaloids, phenolic compounds, sulfur-containing amides, terpenoids, and sterols, many of which exhibit significant antimicrobial, antioxidant, cytotoxic and thrombolytic activities. Notably, novel sulfur-containing amides have demonstrated antifungal activity, while other isolated compounds have shown antioxidant and antimicrobial properties. The crude extract and its fractions also exhibited pharmacological properties, further supporting the therapeutic potential of *G. cyanocarpa.* Despite these promising findings, systematic studies on its bioactive constituents and pharmacological mechanisms remain scarce. This review consolidates the current knowledge on the phytochemistry and therapeutic potential of *G. cyanocarpa*, emphasizing its role as a source of bioactive compounds for drug discovery. While findings highlight its potential in therapeutic applications, further research is required to elucidate its pharmacological mechanisms and assess its viability for drug development.

Key words: *Glycosmis cyanocarpa*, phytochemistry, secondary metabolites, pharmacological activity, antimicrobial, antioxidant.

Introduction

Nature has consistently served as a source of drug discovery, with an enormous quantity of bioactive chemicals produced by plants, microbes, and marine species (Cragg *et al*., 1997). These natural compounds have contributed to the development of many therapeutic agents due to their remarkable structural diversity and pharmacological activities. Notably, plants have long been considered vital sources of bioactive compounds, forming the basis for numerous therapeutic applications. These compounds, often secondary metabolites of plants, possess unparalleled chemical diversity and biological activity, making them invaluable for the development of safe and effective medicines (Bernhoft, 2010). The World Health Organization (WHO) reports that 80% of the global population continues to rely on traditional medicine for primary healthcare (World Health Organization, 2013). Plants are essential for developing safe and effective drugs because of their various secondary metabolites and capacity to combine traditional knowledge with contemporary research.

The Rutaceae family is remarkable among the diverse plant families, as it is an enriched source of pharmacologically active metabolites. The genus *Glycosmis*, belonging to this family, has been extensively studied for its phytochemical and biological properties. *Glycosmis* species are known for producing quinolone alkaloids, sulfur-containing amides, phenolic glycosides and terpenoids, many of which exhibit antimicrobial, antioxidant and anti-

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DOI: https://doi.org/10.3329/bpj.v29i1.87383

inflammatory activities (Teja *et al*., 2021). *Glycosmis cyanocarpa* (Blume) Spreng., a member of this genus, is a small shrub or tree widely distributed across South and Southeast Asia, including Nepal, India, Bangladesh, Sri Lanka, Thailand and Indonesia (Yasir *et al*., 2019). Its morphological features, including elongated fruits, four-merous flowers and eight stamens, distinguish it within the genus (Ashrafi *et al*., 2022; Taher *et al*., 2023). Phytochemical investigations of *G. cyanocarpa* have revealed the presence of enormous bioactive compounds, including quinolone alkaloids, phenolic glycosides, and sulfur-containing amides. These metabolites have demonstrated significant pharmacological activities, including anti-microbial, antioxidant, and thrombolytic effects. Additionally, extracts of related *Glycosmis* species have shown cytotoxicity against cancer cell lines, antioxidant activity and antidiabetic effects comparable to standard drugs (Ashrafi *et al*., 2022; Greger *et al*., 1996; Islam *et al*., 2023; Yasir *et al*., 2019).

Despite these promising findings, almost no systematic studies on *G. cyanocarpa* have been found yet. This review aims to summarize the existing knowledge on the phytochemistry and pharmacological activities of *G. cyanocarpa*, offering a comprehensive overview of its therapeutic applications by highlighting its potential as a source of bioactive compounds.

Review database search methodology

This review paper was carried out by collecting information from the published paper related to *G. cyanocarpa*. All information about this plant was gathered from books, journals, dissertations and electronic sources such as Google Scholar, Google Web, PubMed, Web of Science, Elsevier and Springer up to the year 2024. Keyword combinations such as ethnomedicinal, ethnobotanical, ethnopharmacology, Rutaceae, *Glycosmis*, chemistry, phytochemical, secondary metabolite, bioactive molecule, toxicity, clinical research and biological activity, antioxidant, antimicrobial and cytotoxicity were used in the search for *G. cyanocarpa.* To confirm the scientific name of the plant, the plant list (www.theplantlist.org) was used.

Taxonomic features and morphology of *G. cyanocarpa*

Taxonomy: Glycosmis is a distinct genus in the Clauseneae tribe of the Aurantioideae subfamily of the Rutaceae family, having approximately 40 species (Greger *et al*., 1996).

Figure 1. *G. cyanocarpa* (Rahim and Khan, 2024).

Taxonomical classification (POWO, 2025)

Kingdom: Plantae

Subkingdom: Tracheobionta

Division: Magnoliophyta

Class: Magnoliopsida

Order: Sapindales

Family: Rutaceae

Genus: *Glycosmis*

Species: *Glycosmis cyanocarpa*

Phytochemicals from *G. cyanocarpa*

Phytochemicals are the bioactive compounds found in plants and animals responsible for plants' defense mechanisms (Farnsworth, 1966). The *Glycosmis* genus belonging to Rutaceae family is a highly enriched source of biologically and pharmacologically active secondary metabolites including flavonoids, tannins, phenolic compounds, terpenoids, flavonoids, sulfur containing amides isolated from different parts of the plant (Yasir *et al*., 2019). *G. cyanocarpa*, a plant belonging to *Glycosmis* genus has been studied to a limited extent for its phytochemical composition. Different compounds have been isolated from various parts of the plant which indicates the possibility of the plant as a potent source of diverse bioactive compounds (Greger *et al*., 1996; Islam *et al*., 2023; Seger *et al*., 1998; Taher *et al*., 2023).

Alkaloids: Alkaloids are the most important secondary metabolites found in plants and possess potent therapeutic activities. They are classified into different types which include indole, imidazole, piperidine, pyrrolizidine, imidazole, tropane, quinolone, isoquinoline and purine alkaloids (Yang and Yue, 2012). Sarkar *et al.* (1978) reported a new minor alkaloid named glycarpine (**1**) and one more alkaloid named evolitrine (**2**) from the leaves of *G. cyanocarpa*. In another study, large quantities of the furoquinoline alkaloid kokusaginine (**3**), along with trace amounts of skimmianine (**4**) and the carbazole glycozolidol (**5**), were isolated from the crude methanolic leaf extract of *G. cyanocarpa* (Greger *et al*., 1992). Phenaglydon (**6**), a novel quinolone-derived alkaloid of the phenanthridine type was isolated together with schinifoline (**7**), a prenylated 2-quinolinone indicating their close biogenic connection from the lipophilic leaf extract of *G. cyanocarpa* (Rutaceae). The structure of the novel compound phenaglydon was further confirmed by synthesis (Wurz *et al.*, 1993). In another investigation, an alkaloid, 3-methyl-1H-indole (**8**) was isolated for the first time from the crude MeOH extract of the stem and leaf of this plant (Ashrafi *et al.*, 2022).

Terpenoids: Terpenoids are the most prominent compound isolated from the plant, *G. cyanocarpa*. Seger *et al.* (1998) isolated two new nor diterpenes from the chloroform fractions of the methanolic leaf extract of this plant. The compounds were identified as laipol ((4R, 7'S)-(1'E, 3'E)-4-(7-hydroxy-3-methylocta-1,3-dienyl)-3,5,5-trimethyl-2-cyclohexenone) (**9**), with the molecular formula $C_{18}H_{28}O_2$, characterized by a carbonyl function and a β-substituted α,β-unsaturated ketone fragment and isolaipol ((1'E, 3'Z)-4-(7-hydroxy-3-methylocta-1,3-dienyl)- 3,5,5-trimethyl-2-cyclohexenone) (**10**), by investigating the report of EI mass spectrometry, UV- and IR-spectra, ^{1}H NMR and ^{13}C NMR (Seger *et al.*, 1998). In another study, Ashrafi *et al.* (2022) reported the isolation of tri-transpoly-cis prenol-12 (**11**), a polyprenol derivative, from the crude methanol extract of the stem and leaf of this plant. Islam *et al*. (2023) investigated the EtOAc extract of the stem and leaf parts of *G. cyanocarpa* and found 3 terpenoids. A new phenyl acetate derivative (also a terpenoid ester), namely 3,7,11,15-tetramethylhexadec-2-en-1-yl 2-phenylacetate (**12**), was isolated as a colorless mass and was soluble in ethyl acetate and chloroform. Phytol (**13**), an acyclic diterpene, was also first isolated from this plant. A sesquiterpene oxide, named β-Caryophyllene oxide (**14**), was also isolated from the plant (Islam *et al.*, 2023).

Phenolic compounds: Phenolic compounds are diverse molecules that play a critical role in plant growth, development and defense mechanisms. They

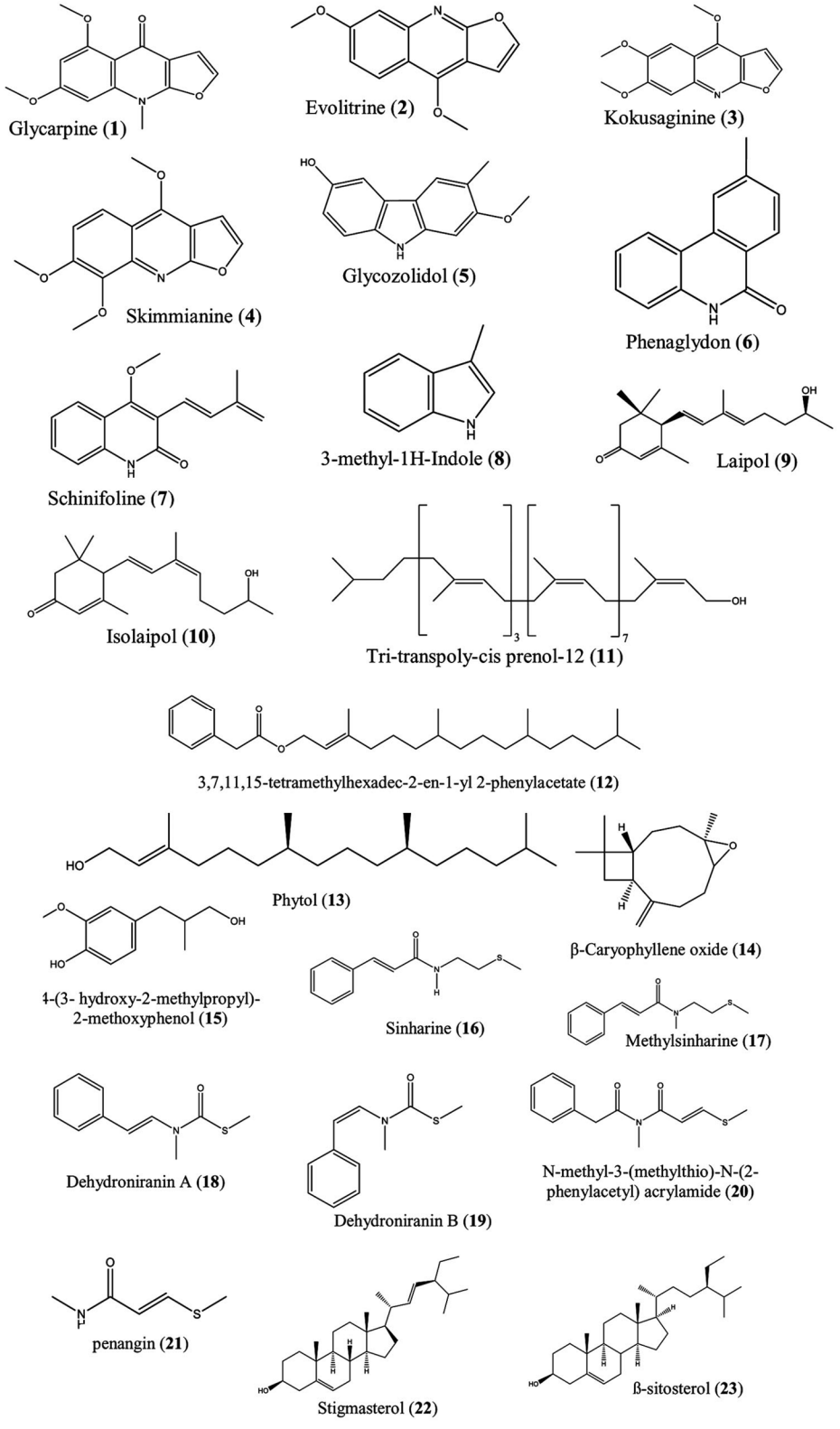

Figure 2. Structure of the isolated compounds from *G. cyanocarpa* .

contribute to various physiological processes, including cell wall formation, regulation of growth hormones and protection against environmental stresses, pathogens, and herbivores (Zepka *et al*., 2021). A new phenolic compound, 4-(3-hydroxy-2-methylpropyl)-2-methoxyphenol (**15**) has been isolated from the crude methanol extract of the stem and leaf of *G. cyanocarpa* (Ashrafi *et al*., 2022).

Amides: Amides are important phytochemicals that are present in *G. cyanocarpa* and contribute to a variety of its biological actions (Greger *et al*., 1996). Researchers investigating the bioactive compounds of *G. cyanocarpa* identified two antifungal amides, sinharine (cinnamic acid methylsulfidoethylamide) (**16**) and methylsinharine (**17**), from the chloroform fraction of its methanolic leaf extract (Greger *et al*., 1992). Greger *et al*. (1996) reported the isolation of two sulfur containing novel amides, designated as dehydroniranin A (**18**) and dehydroniranin B (**19**), from the chloroform fraction of methanolic leaf extract of this plant. In another study, Islam *et al*. (2023) isolated two known amides, N-methyl-3-(methylthio)-N-(2-phenylacetyl) acrylamide (**20**) and penangin ((E-N-methyl-3methylsulfanylprop-2-enamide) (**21**), for the first time from the EtOAc extract of the stem and leaf parts of this plant.

Sterols: Sterols are compounds characterized by their steroid structure and are essential for maintaining cell membrane integrity and fluidity in plants (Ahmed *et al*., 2014). In a recent study, two sterols stigmasterol (**22**) and β-sitosterol (**23**) has been isolated for the first time from the EtOAc extract of the stem and leaves of *G. cyanocarpa* (Ashrafi *et al*., 2022).

Table 1. Pharmacological activities of *G. cyanocarpa*

Test samples	Plant part	Activity	References
n-Hexane soluble fraction DCM soluble fraction Ethyl acetate soluble fraction Aqueous soluble fraction	Stem and leaf	Antioxidant activity	Islam *et al*. (2023)
4-(3-hydroxy-2-methylpropyl)-2-methoxyphenol (**15**)	Stem and leaf	Antioxidant activity	Ashrafi *et al*. (2022)
n-Hexane soluble fraction DCM soluble fraction Ethyl acetate soluble fraction Aqueous soluble fraction	Stem and leaf	Cytotoxic activity	Islam *et al*. (2023)
3-methyl-1H-indole (**8**) Tri-transpoly-cis prenol-12 (**11**) 4-(3-hydroxy-2-methylpropyl)-2-methoxyphenol (**15**) Stigmasterol (**22**) β-sitosterol (**23**)	Stem and leaf	Cytotoxic activity	Ashrafi *et al*. (2022)
Dichloromethane fraction	Stem and leaf	Thrombolytic activity	Islam *et al*. (2023)
Sinharine(**16**) Methylsinharine (**17**)	Leaf	Antifungal activity	Greger *et al.* (1992)
Tri-transpoly-cis prenol-12 (**11**) 4-(3-hydroxy-2-methylpropyl)-2-methoxyphenol (**15**)	Stem and leaf	Broad-spectrum antibacterial activity	Ashrafi *et al*. (2022)
3-methyl-1H-indole (**8**) Stigmasterol (**22**) β-sitosterol (**23**)	Stem and leaf	Antibacterial activity against Gram-positive bacteria	Ashrafi *et al*. (2022)

Pharmacological activities

G. cyanocarpa, though not widely studied, shows great promise in the field of pharmacology. Bioactive compounds isolated from this plant have shown significant antioxidant, antibacterial and cytotoxic activities. Its therapeutic potential remains largely untapped, making it a valuable subject for further pharmacological research and drug discovery (Ashrafi *et al*., 2022; Teja *et al.*, 2021).

Antioxidant activity: Antioxidant activity helps to protect the body from oxidative stress caused by free radicals. By preventing oxidative stress, they help prevent aging and chronic illnesses like diabetes, cardiovascular disease and cancer (Mo *et al*., 2021). The plant *G. cyanocarpa* with rich phytochemicals has shown strong antioxidant activity (Ashrafi *et al*., 2022; Islam *et al*., 2023). Islam *et al.* (2023) investigated the antioxidant activity of the n-hexane soluble fraction (GCH), DCM soluble fraction (GCD), ethyl acetate soluble fraction (GCE) and aqueous soluble fractions (GCA) of the crude extract of the *G. cyanocarpa* by DPPH free radical scavenging study. While compared with the standard ascorbic acid (ASA), the GCE had a remarkable scavenging activity of 92.96%, similar to that of the standard ASA at 200 µg/ml (Islam *et al*., 2023). Ashrafi *et al*. (2022) studied the antioxidant activity of five phytochemicals from *G. cyanocarpa* (Blume) Spreng., including a newly found phenolic compound (4-(3-hydroxy-2-methylpropyl)-2-methoxyphenol) (**15**), 3-methyl-1H-indole (**8**), Tri-transpoly-cis prenol-12 (**11**), stigmasterol (**22**) and β-sitosterol (**23**). In their DPPH free radical scavenging assay, the newly found phenolic compound **15** had the highest scavenging activity of 92.96%, at 200 µg/ml, which was very close to the standard butylated hydroxytoluene (BHT), having a scavenging activity of 96.48% (Ashrafi *et al*., 2022).

Cytotoxic activity: The term "cytotoxic activity" refers to a substance's ability to destroy or inhibit the proliferation of cells. This characteristic is important in cancer treatment because it targets and kills cancer cells (Feng *et al*., 2022). Cancer is one of the leading causes of death in the globe, after cardiovascular diseases (Kooti *et al*., 2017). Islam *et al.* (2023) investigated the cytotoxic activity of the n-hexane soluble fraction (GCH), DCM soluble fraction (GCD), ethyl acetate soluble fraction (GCE) and aqueous soluble fractions (GCA) of the crude extract by brine shrimp lethality bioassay. They compared the LC_{50} values of all the fractions to standard vincristine sulfate (VS) and found prominent cytotoxic activity (Islam *et al*., 2023). In their study, Ashrafi *et al.* (2022) reported that compound **8**, **11**, **15**, **22** and **23** isolated from *G. cyanocarpa* showed dose-dependent mortality in their assays. The compound **8** had the highest cytotoxicity, with an LC_{50} value of 1.02 µg/ml, compared to the standard's LC_{50} of 0.91 µg/ml. Overall, the LC_{50} values for the various compounds ranged from 1.02 µg/ml to 1.92 µg/ml (Ashrafi *et al.*, 2022).

Thrombolytic activity: Thrombolytic activity is vital in treating cardiovascular disorders, particularly in emergencies like heart attacks and strokes, because it dissolves blood clots, restoring blood flow and reducing tissue damage (Ali *et al*., 2014). Studies conducted on the plant suggest that it may possess thrombolytic properties due to its bioactive compounds. Islam *et al*. (2023) analyzed the different fractions of the crude extract to determine the thrombolytic effects. Among the fractions, the dichloromethane fraction (GCD) demonstrated the highest thrombolytic activity at around 16.42%, but the result was not significant compared to the standard streptokinase, which exhibited an activity of 65.98% (Islam *et al*., 2023).

Antimicrobial activity: The rise of antimicrobial resistance poses a significant challenge in treatment, rendering many conventional therapies ineffective (Walsh *et al*., 2023). *G. cyanocarpa* has demonstrated potential as a natural source of antimicrobial compounds, providing an alternate technique for combating resistant strains and improving treatment efficacy against infectious illnesses. Ashrafi *et al*. (2022) evaluated the antibacterial properties of isolated phytochemicals

against standard antibiotics, including vancomycin and tetracycline. The inhibition zones ranged from 15 to 21 mm, with compounds **15** and **11** showing broad-spectrum activity against both Gram-positive and Gram-negative bacteria, while compounds **8**, **22** and **23** targeted only Gram-positive bacteria. Gerger *et al*. (1992) reported that two compounds (**16, 17**) isolated from the $CHCl_3$ fraction of *G. cyanocarpa* methanolic leaf extract exhibited antifungal activity, assessed through bioassay-guided TLC using *Cladosporium cladosporioides*. Inhibition zones confirmed their fungitoxic properties, while no activity was detected in extracts from young stems, indicating the compounds' potential as antifungal agents (Greger *et al*., 1992).

Future perspective

Recent advances in natural product research have increasingly emphasized integrative and technology-driven approaches for drug discovery, which remain underutilized in the study of *G. cyanocarpa*. While preliminary phytochemical and pharmacological investigations have identified a range of bioactive compounds, including quinolone alkaloids and sulfur-containing amides, the molecular targets and mechanisms of action of these constituents remain largely uncharacterized. To align with emerging trends, future studies should incorporate computational tools such as molecular docking, molecular dynamics simulations and ADMET predictions to identify lead compounds and evaluate their drug-likeness. Additionally, network pharmacology and systems biology approaches can be employed to elucidate the multi-target interactions of complex phytochemical mixtures, offering insights into their therapeutic effects at the molecular and pathway levels. Techniques such as LC-MS/MS-based metabolomics and RNA-seq transcriptomics can further support the identification of active metabolites and their biosynthetic pathways. Moreover, the rising threat of antimicrobial resistance and chronic inflammatory diseases underscores the need to explore *G. cyanocarpa* as a sustainable source of novel pharmacophores. Establishing structure–activity relationships (SAR) of isolated compounds and semi-synthetic derivatives could accelerate the translation of traditional knowledge into clinically viable agents. These strategies, coupled with *in vitro, in vivo* and potentially clinical investigations, will pave the way for the rational development of *G. cyanocarpa* -derived therapeutics, ultimately enhancing its relevance in modern pharmacognosy and drug development.

Conclusion

This review aims to investigate the phytochemicals isolated from *G. cyanocarpa* and also their pharmacological activity. *G. cyanocarpa* has potential as a source of a variety of bioactive chemicals, including alkaloids, terpenoids, phenolic compounds, amides and sterols, all of which contribute to its remarkable pharmacology. Studies conducted on this plant have reported that the crude extract and the isolated compounds have antioxidant, cytotoxic, antibacterial and thrombolytic properties, emphasizing its medicinal use. More extensive research is needed to determine its pharmacological activities, understand its mechanisms of action and assess its potential for drug development.

Conflict of interest

There is no conflict of interest with respect to publication of this manuscript.

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