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REVIEW ARTICLE **OPEN ACCESS**

Exploring Ethnomedicinal, Biological and Toxicological Aspects of The Genus Gnidia: A Comprehensive Review

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ABSTRACT
Gnidia (152 species) is the largest genus in the family thymelaeaceae comprising shrubs. Several species of Gnidia are known to be economically and medicinally useful. Members of this species are used in traditional medicines and extracts show antileukemic, antibacterial, antifungal, insecticidal and larvicidal properties. Several species are known to be toxic also. Hereby, we present an overview of the ethnomedicinal, biological and toxicological investigation on the Gnidia genus for future exploitation of species to create relevant herbal drugs.
Keywords: *antibacterial, gnidia, thymelaeaceae, traditional medicines.*

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INTRODUCTION

Plants, the backbone of life on Earth, are indispensable for human existence. Throughout ancient history, they have served various purposes. The bioactive compounds produced by plants have been harnessed for pharmacological applications. To bridge scientific knowledge and local wisdom, exploring the traditional applications of medicinal plants is imperative [1]. Ethnomedicinal practices are considered one of the potential sources for establishing safe and effective treatments [2]. According to the World Health Organization (WHO), traditional medicines, primarily derived from natural plant products, remain the primary healthcare resource for a significant portion of the population in developing nations [3]. However, the swift decline of traditional knowledge regarding plant resource usage is attributable to evolving mindsets, the impact of modern therapies, and socio-economic development [4]. Although there are an estimated 500,000 terrestrial plant species, including approximately 300-315 plant species that remain undiscovered and unreported by science [5], the genus Gnidia is an example of a relatively unexplored plant group. Within the family Thymelaeaceae, Gnidia is the largest genus. Plants within this genus are predominantly shrubby, encompassing trees and perennials as well [6]. The Gnidia genus comprises about 160 species, primarily distributed across southern and tropical Africa, Madagascar, and India [7]. In India, two species of Gnidia have been reported: *Gnidia glauca* (Fresen)Gilg (Fig.1) and *Gnidia sisparensis* Gardner [8]. *Gnidia sisparensis* has been reinstated and leptotypified by Prabhukumar [9]. Among the species, *Gnidia kraussiana* Meisn holds the distinction of being the most widely spread [10]. The objective of this article is to delve into the traditional, biological, and toxicological aspects (Fig.2) of the Gnidia plant genus. This review paper draws upon data sourced from research articles, electronic theses, and review papers.

Traditional Uses

The leaves of *Gnidia glauca* find use as pesticides and insecticides, while the stems of this plant are employed by herbal medicinal practitioners in Chikmagalore to alleviate dropsy by wrapping them around the stomach [11]. In regions like Embu and Mbeeru in Kenya, *Gnidia glauca* leaves are used for insecticides and to alleviate back and joint ache [12]. In Shimoga district, traditional veterinary healthcare practitioners grind the bark of *Gnidia glauca* along with the roots and leaves of Lobelia nicotianifolia to create a paste for wound treatment [13]. In Palakkad district, Kerala, tribal communities use tender shoots and fruits of *Gnidia glauca* to stupefy fish [14]. Additionally, the bark of *Gnidia glauca* is boiled in water for several hours, and the resulting residue is applied to arrow tips. In South Africa, Zulu women consume an herbal decoction known as Isihlambezo (which contains *Gnidia kraussiana*) as a preventive health tonic during pregnancy [15]. *Gnidia goetzeana* root is chewed as an antitussive agent [16]. In Tanzania, traditional healers utilize

the tubers of *Gnidia kraussiana* to address constipation and swollen stomach issues [17]. Crushed and boiled tuberous roots of *Gnidia kraussiana* are used for treating bone fractures and injuries [18], and in Zimbabwe, tuberous roots are used to treat measles, dropsy, anorexia, and ulcers [19]. The roots of Gnidia polycephala are mixed with milk and used for constipation [20]. In countries such as Congo, Nigeria, and Malawi, Gnidia species are used as fish poisons and molluscicides [21]. This plant is employed for psychoactive purposes in South Africa, and powdered tubers are mixed with porridge by the Shona people in Zimbabwe [22-23]. Similar plant extracts are even injected into fractured limbs of animals by the Sotho community [24-25]. The plant is also used to address chest complaints [26], and its roots are utilized against snake bites, bronchitis, and cancer [27]. *Gnidia polycephala*, along with *Ziziphus mucronata* and *Heliotropium ciliatum*, is incorporated into treatments for tumors and wounds [28]. The roots of *Gnidia stenophylla* serve as antimalarial agents in Ethiopia, and the root decoction of *Gnidia stenophylloides* is used as an antihemorrhagic agent [29]. Infusions prepared from the roots and leaves of *Gnidia stenophylla* are orally taken for indigestion, abdominal pain, and diarrhea [30]. The leaves and fruits of *Gnidia socotrana* are employed to alleviate constipation [31]. *Gnidia polycephala* is orally administered for tonsillitis, tuberculosis (TB), and heart problems stabilization [32]. In the eastern region of O.R Tambo district in South Africa, the root of Gnidia capitata is taken orally or as an infusion to treat tuberculosis [33]. The root decoction of Gnidia capitata is used to treat heartwater disease in cows [34], and in South Africa, it's used for treating anthrax. It is used as a diviniation tool to find thieves and bad guys. *Gnidia tomentosa* thought to cause disputes, if introduced into the household [35].The powdered root of *Gnidia involucrata* mixed with honey is used for treating leprosy, heart pain, syphilis, and gonorrhea [36-38]. The stalk of this plant serves as an expectorant [39]. It is also employed as a pesticide and insect repellent and used for treating TB, mental health issues, sexually transmitted diseases, and gastrointestinal pain [40]. In Somalia, the root of *Gnidia somalensis* is used to address tuberculosis, while the root of *Gnidia glabra* is mixed with camel milk as an effective laxative and emetic [29]. Additionally, the root and flower of *Gnidia carinata* are used as an emetic in Africa [41]. The root decoction of *Gnidia buchananii* was employed to address bronchitis [16]. Reports on the economic Importance of the Gnidia genus are listed in Table.1

Anticancerous activity

The methanolic and acetone root extracts of *Gnidia kraussiana* exhibited significant activity against P-388 lymphocytic leukemia [48]. The methanolic extract of *Gnidia kraussiana* demonstrated cytotoxic activity on the A431 cell line and displayed cytotoxicity, resulting in a reduction in cell proliferation ranging between 50% and 75% in HeLa and HT29 cell lines [27]. Mezerein, identified from Lasiosiphon burchelli, is toxic to cattle [49]. This compound exhibited excellent antileukemic properties against L-1210 and P-388 leukemia in mice [50]. In the case of Gnidia glauca, the in vitro cytotoxic assay conducted on its roots showed a dosage-dependent growth inhibitory effect on cell lines. The chloroform extracts exhibited significant cytotoxicity against the A-549 cancer cell line, while ethanolic extracts exhibited cytotoxic activity against the HT-29 cancer cell line [51]. Both n-hexane and ethanolic extracts of *Gnidia glauca* demonstrated significant cytotoxic activity against MCF-7 cancer cells [52]. The aqueous and methanolic extracts of Gnidia polycephala were found to be inactive against TK10 and MCF cancer cell lines, whereas the acetone extract showed weak activity against TK10, UACC62, and MCF-7 cell lines [53].

Antioxidant activity

Gnidia glauca is a rich source of phytochemicals such as coumarin, diterpenes, phenols, and phytosterols [54]. Kharat's investigation [55] supported the findings of various authors that *Gnidia glauca* contains phytochemical constituents like quinones, flavonoids, steroids, alkaloids, tannins, glycosides, anthraquinones, saponins, and terpenoids. Phenols, flavonoids, steroids, tannins, and saponins were detected in the roots of *Gnidia stenophylla* [56]. 80% methanolic extracts of *Gnidia stenophylla* exhibited excellent antioxidative properties [57]. Ethanolic extracts of *Gnidia glauca* were reported to have excellent activity in DPPH radical scavenging and nitric oxide scavenging assays [51]. Abundant flavonoid and phenolic content were observed in the leaf extracts of Gnidia glauca, while methanolic extracts of *Gnidia glauca* stem, leaf, and root contained higher amounts of antioxidants such as diphenyl sulfone and octadecanoic acid. Methanolic leaf extracts of *Gnidia glauca* showed the highest activity in scavenging DPPH, superoxide radicals, hydroxyl radicals, superoxide anions, and nitric oxide radicals. *Gnidia glauca* is highly recommended for wound healing and inflammation due to its ability to reduce nitric oxide levels. Both the leaf and stem of *Gnidia glauca* displayed remarkable reducing and free radical scavenging activity, suggesting its potential as a candidate for diseases caused by oxidative stress due to its strong antioxidative properties [58]. These study results align with the observations of Rao [59]. This study underscores Gnidia glauca's significant nitric oxide scavenging activity. The methanolic leaf extracts of *Gnidia glauca* are rich in phenolic content (203.3 mg GAE/g). At a concentration of 40 μg/ml, methanolic leaf extracts exhibited high ABTS radical inhibition.

Antimicrobial activity

Antibacterial activity of Gnidia species is listed in Table.2. The aqueous, chloroform, and methanol extracts of *Gnidia socotrana* did not show any antimicrobial activity against tested microorganisms such as Staphylococcus aureus, Micrococcus flavus, Pseudomonas aeruginosa, Candida maltosa, Staphylococcus epidermis 847, Staphylococcus haemolyticus 535, and Staphylococcus aureus North German reference strain [31]. In a study by Junaid [66], higher anticariogenic activity of methanolic leaf extracts of *Gnidia glauca* was observed against 13 clinical isolates of Streptococcus mutans than Pothos scandens and *Elaegnus kologa* using the Agar well diffusion technique. Marked antifungal activity of *Gnidia glauca* against *Aspergillus niger, Candida albicans, Chrysosporium keratinophilum, Chrysosporium indicum, Microsporum gypseum*, and *Trichophyton rubrum* was reported [67]. The presence of the antioxidant diphenyl sulfone contributes to the antifungal activity in *Gnidia glauca* [58]. Cow urine extracts of *Gnidia glauca* possess antibacterial and antifungal activity [68]. Extracts of Polyalthia longifolia and Anaphalis lawii exhibit significant inhibitory activity against Colletotrichum capsici and urinary tract pathogens compared to the extracts of *Gnidia glauca* [69]. The crude root extract of *Gnidia apiculata* and isolated compounds like 6-hydroxyflavone (4) and 6-O-acetylflavone (4a) showed antiplasmodial activity against chloroquine-sensitive (D6) and chloroquine-resistant (W2) strains of Plasmodium falciparum [70].

Insecticidal and Larvicidal activity

The petroleum ether root and stem extracts of *Gnidia kraussiana* were reported as the most potent against *Bulinus truncatus* adult snails, with LC50 values of 0.02 ppm and 0.07 ppm for LC100, respectively [71]. Sundararajan and Kumuthakalavalli [72] recorded 50% larval mortality using aqueous leaf extracts of *Gnidia glauca* against the sixth-instar larvae of *Helicoverpa armigera*. Four organic leaf extracts (methanol, ethyl acetate, dichloromethane and a blend) of *Gnidia glauca* exhibited active toxicity against Callosobruchus maculatus, the major pest of stored cowpea. These extracts showed repellency, oviposition deterrence, contact toxicity, and inhibition of progeny emergence [73]. Larvicidal mortality rates were observed in methanol, chloroform, ethyl acetate, acetone, and petroleum ether leaf extracts of *Gnidia glauca* at a concentration of 20 mg/ml against Aedes aegypti [74]. Javaregowda and Naik [75] reported the efficacy of *Gnidia glauca* leaf and bark extracts against the eggs of the teak defoliator Hyblaea purea cramer. The leaf and bark extracts exhibited 44.4% and 45.7% egg mortality, demonstrating their ovicidal property. Extracts of *Polyalthia longifolia* and *Anaphalis lawii* demonstrated more significant repressive activity compared to the extracts of *Gnidia glauca* (leaf, bark, and flower) against Colletotrichum capsici and urinary tract pathogens [69]. The dichloromethane stem extract of Gnidia cuneata exhibited mortality within 144 hours against the malaria vector Anopheles arabiensis [76]. *Gnidia kraussiana* appeared to be more effective than Neorautanenia mitis and can be utilized as a grain protectant against the large grain borer and maize weevil [77]. Acetone, methanol, and hexane root extracts of *Gnidia kraussiana* exhibited maximum repellent effects on Callosobruchum maculatus (coleoptera: chrysomelidae) [78].

Anti-inflammatory and Anti-viral effect

Hydromethanolic root extracts of *Gnidia kraussiana* have been found to possess anti-inflammatory effects in cases of gouty arthritis [79]. A recent study by Teklehaymanot and Giday [80], as well as Admasu and Mekonnen [81], reveals that the powdered root of *Gnidia glauca* has been traditionally taken orally with skimmed milk in various parts of Ethiopia as a folk remedy against rabies. In terms of virtual screening results, Gnidia lamprantha's gnidicin and gniditrin were found to exhibit a high binding affinity to RdRp (RNA-dependent RNA polymerase) and demonstrated potential inhibitory effects. This discovery was highlighted in a study by Wu et al. in 2020 (82). Nsp12, a conserved protein of coronaviruses, serves as an RNA-dependent RNA polymerase (RdRp), playing a crucial role in the replication/transcription complex of coronaviruses.

Antidiabetic activity

The initial documentation of Gnidia glauca's antidiabetic activity was presented by Ghosh [83]. The petroleum ether flower extracts of *Gnidia glauca* exhibited remarkable inhibitory properties against α-amylase (78.56%), thereby confirming its traditional use as a remedy for diabetes.

Cardio toxicity

During a medicinal plant test, hERG (human ether-a-go-go-related gene) channel blockage was shown by dichloromethane extract of *Gnidia polycephala* roots [84].

Nanobiotechnology

In today's world, plants are extensively employed in the field of nanobiotechnology due to their rapidity, cost-effectiveness, and potential for synthesizing gold, silver, and platinum nanoparticles. The first documented case of environmentally friendly AuNPs biosynthesis using *Gnidia glauca* leaf and stem extracts showcased a synthesis completion time of 20 minutes (85). The AuNPs produced from *Gnidia glauca* displayed strong chemocatalytic potential. Moreover, a recent report highlighted the swift synthesis of AgNPs using *Gnidia glauca* flower, leaf, and stem extracts, completed within just 5 hours (86).

Furthermore, CuNPs synthesized from Gnidia glauca-Plumbago zeylanica were considered promising candidates for antidiabetic medicine [87].

Toxic effects

Nonetheless, limited studies have been conducted regarding the toxic effects of Gnidia species. For instance, cattle poisoned by Gnidia latifolia exhibited an excessive accumulation of fluids in body cavities, along with lymphocytic necrosis and lymphocytopaenia in the spleen and lymph nodes [88]. Nwude and Parsons [89] observed that *Gnidia kraussianus* toxin can lead to the lysis of lymphocytes. In Northern Cameroon and Nigeria, the roots of Gnidia kraussiana, along with the seeds of Strophanthus hispidus, were boiled to create hunting poison, and young leaves were found to be poisonous to humans [90]. Lewis and Lewis [91] reported that in Africa, extracts of *Gnidia kraussiana* are utilized as homicidal criminal poison. The toxic principle known as mezereine, found in the flower tips and young leaves, was discovered to cause gastrointestinal irritation and ultimately lead to the death of livestock [92]. Consumption of large quantities of mature flowers and seeds of *Gnidia polycephala* by sheep and goats resulted in the formation of phytobezoars [93]. Ingestion of *Gnidia burchelli* and *Gnidia polycephala* caused diarrhea and emphysema [94]. Inhaling the dried powder had an irritant effect on the mucosa [95]. Consumption of *Gnidia ovalifolia* by animals led to anorexia, weakness, mucous discharge from nostrils, eyes, and vagina, as well as gastroenteritis, often resulting in death within 15 days [96]. Species like Gnidia latifolia and *Gnidia involucrata* caused nephritis, enteritis, and cardiomyopathy in humans [36]. In Ethiopia, some species of Gnidia were considered poisonous to both humans and animals [97]. Among the Muthuvan community in Idukki district, Kerala, *Gnidia glauca* fruit is employed as fish poison [98]. A study by Nigatu [99] in mice indicated that aqueous root extracts of *Gnidia stenophylla* had no adverse effects at a dose of 400 mg/kg body weight; however, at higher doses, the extract could lead to gastrointestinal irritation. The roots of Gnidia anthylloides contain hydrocyanic acid and volatile oils [100]. In another study by Muhammed [56], the roots of *Gnidia stenophylla* in southeastern Ethiopia were found to contain heavy metals (Co, Ni, Cr, Pb, Cu) and had total aerobic counts and fungal loads exceeding WHO limits. Hence, employing standardized quality parameters while utilizing medicinal plants becomes our responsibility.

Compounds isolated from Genus Gnidia

Photographs depicting crystal formations of Gnidia polycephala glucoside crystals were documented [101]. The initial ring compound, Gnidicoumarin, was isolated from the ethanolic extracts (95%) of Gnidia lampratha [102]. Gnididone was subsequently isolated from the same species by Kupchan [103]. The total synthesis of (±) Gnididione and (±) Isognididione was also documented [104]. From Gnidia lamprantha, compounds such as Gnididin, Gniditrin, Gnidicin, Gnidilatin and Gnidilatidin were isolated. Additionally, two diastereomers, GB-4 & GB-4a, were extracted from Gnidia involucrate [105]. Phenol propanoid glucosides were also found in the same species [106]. Gnidicin, Maltol, Mezerein, β-sitosterol, Gniditrin, Thymelea toxin,3-Hydroxy-2-methyl-4H-pyran-4-one, n-Octacosanol, 1-Glyceryl octacosanol, Gnilatmacrin, Odoracin, Yuanhuacine, Gnidilatin, Pimelea factor P2, Montanin, Excoecariatoxin, Gnidilatidin, kraussianin, Gnidicin, Daphnopsis factor R1, 7-epoxy-resinferonol- 9,13,14-orthobenzoate were isolated from *Gnidia kraussiana* [48]. 7,7'-dihydroxy-3,8'-biscoumarin,8-(6''-Umbelliferyll)-apigenin, 4',6'-Diacetyl-viburnolide A,4',6'-Diacetyl-12-coumaroyl-viburnolide A and Tetra acetyl viburnolide A were identified in the leaves and twigs of Gnidia socotrana [107]. Compounds such as Isovitexin, 6-C-β-D-glucopyranosylapigenin, Isoorientin, Yuankanin, Mangiferin, Mahkoside A, Vitexin, Gnidia biflavonoid, Astragalin, Manniflavanone, 2,3,4',5,6-pentahydroxybenzophenone-4-C-glucoside, and 2,4',6-trihydroxy-4methoxybenzophenone-2-O-glucoside were isolated from the aerial parts of Gnidia involucrate [108-111].

SL.NO	PLANT SPECIES	PART USED	ECONOMIC USES	REFERENCES
1	*Gnidia latifolia*	Stem and branches	used for traditional huts and fencing in Kenya, due to their resistance to termite attacks	[42]
2	*Gnidia anomala*		employed for thatching roofs and for textile and leather dyeing	[43]
3	*Gnidia daphnifolia*		used in the production of "Antaimoro" paper and for crafting stationary articles, photo albums, and gift bags	[44]
4	*Gnidia lamprantha*	Bark	employed for rope-making	[45]
6	*Gnidia subcordata*	Bark	For rope making. In Kenya, it is used as a base structure for plaster	[45]
7	*Gnidia species*	flower	Leather dyeing	[46]
8	*Gnidia glauca*	Stem and bark	Suitable for paper manufacturing	[47]
		Bark	employed for rope-making, igniting fires,	[45]

Table.1. Economic uses of plants reported from Gnidia genus

Table.2. Antibacterial activity reported from the Gnidia genus

Sl. No	Plant species	Plant part	Extract	Activity against	References
1	*Gnidia polycephala*	Stem, Leaf and Flower	Acetone and Methanol	*Staphylococcus aureus*	[53]
		Aerial Parts	Dichloromethane , Ethanol, Hexane	*Pseudomonas aeruginosa, Strptococcus aureus*	[60]
2	*Gnidia glauca*	Flower	Aqueous	*Bacillus cereus, Salmonella typhimurium, Pseudomonas aeruginosa, Staphylococcus aureus.*	[54]
		Leaf, Bark and Flower	Petroleum ether, Ethylacetate, Chloroform, Methanol	*Xanthomonas oryzae*	[61]
		Leaf	Saponin fraction	*Xanthomonas oryzae.pv.oryzae, Xantthomonas compestris.pv.punicae*	[62]
		Seed, Leaf and Bark	Aqueous	*Phytophthora parasitica*	[63]
3	*Gnidia capitata*	Bark	Ethyl acetae, Dichloromethane ,n-hexane	*Propionibacterium acnes*	[64]
4	*Gnidia kraussiana*	Whole Plant	Petroleum ether	*Staphylococcus aureus, Pseudomonas aeruginosa*	[65]

Fig.1. Image of *Gnidia glauca* (Fresen.)Gilg

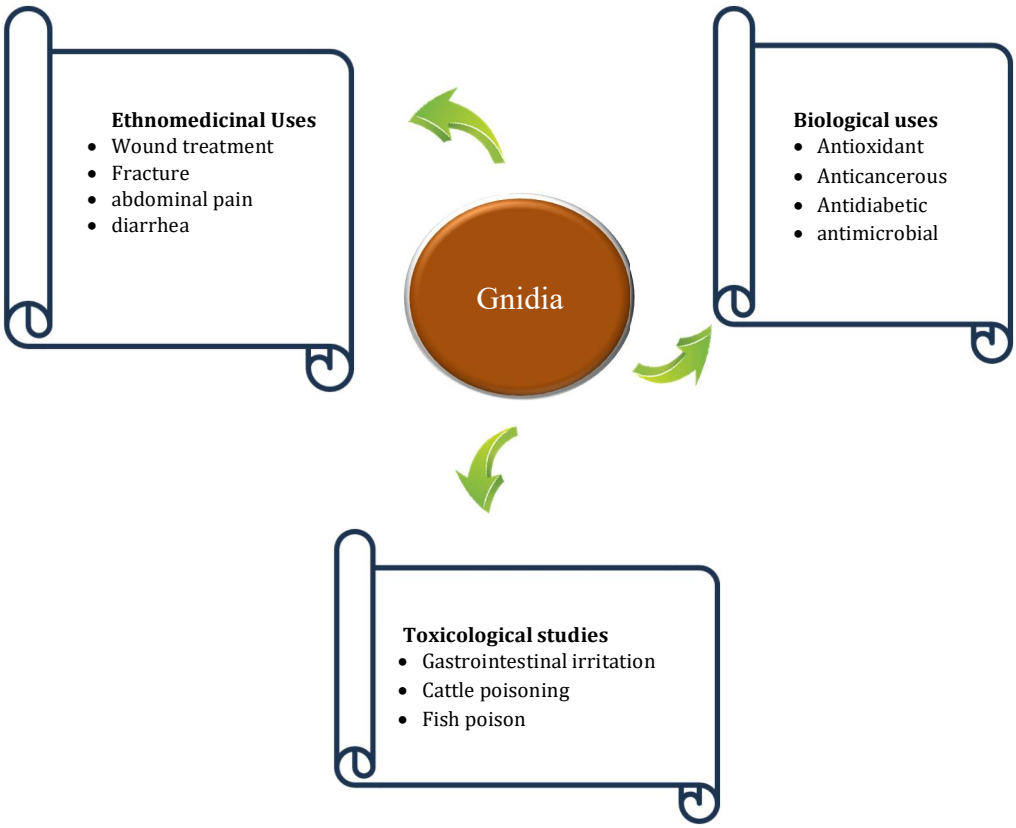

Fig.3. Studies reported in Genus Gnidia

CONCLUSION

This review article presents an overview of the phytochemical profiling and biological activities of the members of genus Gnidia so that this article may serve as a guideline for researchers for future study.

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