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Review Article

Phytoconstituents and pharmacological activities of *Mitrephora* species (Annonaceae): a review

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Abstract

This study reviewed the phytoconstituents and pharmacological properties of 13 Mitrephora species, namely, Mitrephora alba Ridl., Mitrephora celebica Scheff., Mitrephora diversifolia (Span.) Miq., Mitrephora glabra Scheff., Mitrephora heyneana (Hook. f. and Thomson) Thwaites, Mitrephora maingayi Hook. f. and Thomson, Mitrephora sirikitiae Weeras., Chalermglin and RMK Saunders, Mitrephora teysmannii Scheff., Mitrephora thorelii Pierre, Mitrephora tomentosa Hook.f. and Thomson, Mitrephora vulpina CEC. Fisch., Mitrephora wangii Hu, and Mitrephora winitii Craib. The data retrieved from key databases revealed the presence of 85 phytoconstituents derived from the genus Mitrephora, and were categorized based on their chemical composition (alkaloids, terpenoids, polyacetylene acids, lignans, and lignanamides). This review highlights the promising uses of these phytoconstituents in cancer therapeutics, microbial infections, malaria, and inflammation, and in modulating platelet activity.

Keywords: *Mitrephora, Annonaceae, Phytoconstituents, Phytochemicals, Cancer therapeutics, Malaria, Platelet activity*

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INTRODUCTION

The word *phyto* is a Greek term that refers to plants. Phytoconstituents or phytochemicals are a unique class of organic compounds found abundantly in plants. These phytoconstituents consist of primary and secondary metabolites. Primary metabolites are crucial for essential plant functions, while secondary metabolites are vital for plant defense, adaptation, and growth [1]. Secondary metabolites are synthesized through diverse biochemical pathways, producing various organic compounds such as alkaloids, terpenoids, and phenolics. These compounds vary in chemical structure and functional groups, contributing to their diverse pharmacological properties and application in traditional and folkloric medicine [1]. Plants were the primary means of maintaining health and treating various diseases before the establishment and advancement of pharmaceutical technology.

World Health Organization (WHO) reported that 80 % of the global population relies on herbal medicine and traditional practitioners for healthcare. Today, numerous plant extracts and isolated compounds have been utilized to develop modern medication, demonstrating the essential role of plant-derived products in drug discovery and development. Nevertheless, there is a lack of scientific evidence and clinical studies using these plant extracts in traditional practices [2]. As a result, there is an urgent need to

address the knowledge gap on the phytoconstituents and pharmacological properties of *Mitrephora* species.

Mitrephora is a genus within the Annonaceae family and consists of approximately 50 species. Native to tropical and temperate regions, the plant leaves, bark, and roots of specific *Mitrephora* species have been widely utilized in traditional medicine [3]. These plants contain phytoconstituents such as alkaloids, terpenoids, polyacetylene acids, and lignans, demonstrating anti-microbial [4], anti-cancer [5], anti-malarial [6], and platelet-activating factor (PAF) antagonism [7]. Therefore, this narrative review discussed the phytoconstituents and pharmacological effects of *Mitrephora* species and highlighted their potential ethnopharmacological relevance.

METHODS

Search strategy

A detailed literature search on phytoconstituents and pharmacological effects of *Mitrephora* species was performed in key research databases, including Google Scholar, PubMed, Ovid, and Taylor & Francis. The keywords used in this process were *Mitrephora*, pharmacological effects, phytoconstituents, anti-microbial, anti-cancer, platelet-activating factors, and anti-inflammatory. Based on the findings, 13 *Mitrephora* species were identified for this review: *Mitrephora alba* Ridl., *Mitrephora celebica* Scheff., *Mitrephora diversifolia* (Span.) Miq., *Mitrephora glabra* Scheff., *Mitrephora heyneana* (Hook. f. and Thomson) Thwaites, *Mitrephora maingayi* Hook. f. and Thomson, *Mitrephora sirikitiae* Weeras., Chalermglin and R.M.K. Saunders, *Mitrephora teysmannii* Scheff., *Mitrephora thorelii* Pierre, *Mitrephora tomentosa* Hook.f. and Thomson, *Mitrephora vulpina* C.E.C. Fisch., *Mitrephora wangii* Hu, and *Mitrephora winitii* Craib.

RESULTS

Phytoconstituents of *mitrephora* species

Extensive studies have revealed the phytoconstituents present in *Mitrephora* species, namely alkaloids, terpenoids, polyacetylene acids, lignans, and lignanamides derived from plant leaves, bark, root, and twigs. Other miscellaneous compounds found in these plants include cyclitols and megastigmenes which enhance the pharmacological profile.

Alkaloids

Alkaloids found in *Mitrephora* species vary in structure (**1–13**) and are classified as aporphine, azafluorenone, and miscellaneous alkaloids. These alkaloids are distributed in the leaves, stems, twigs, and bark. Liriodenine (**1**; a well-known aporphine alkaloid) is present in *M. glabra* [4], *M. vulpine* [7], *M. maingayi* [8], and *M. sirikitae* [9]. Oxostephanine (**4**) has been reported in *M. maingayi* [8], dicentrinone (**9**) in *M. sirikitae* [9] and *M. Maingayi* [10]; oxoputerine (**5**) in *M. vulpine* [7] and *M. Sirikitae* [9]. Studies have also isolated two 5-oxonoraporphine alkaloids, 1,2,3-trimethoxy-5-oxonoraporphine (**11**) and 1,2-dimethoxy-3-hydroxy-5-oxonoraporphine (**12**) from *M. maingayi* [11]. Azafluorenone alkaloids such as 5,8-dihydroxy-6-methoxyonychine (**2**) and 5-hydroxy-6-methoxyonychine (**3**) have been reported in *M. diversifolia* [6]. Maingayinine (**10**) was identified from the twigs of *M. maingayi* [10], while stephranine (**6**), 6-methoxymarcanine A (**7**), and N-trans-feruloyl tyramine (**8**) have been isolated from *M. sirikitae* [9] (Table 1 and Table 2).

Terpenoids

Terpenoids were primarily isolated from the leaves, stems, bark, and twigs of *Mitrephora* species and classified into monoterpenoids, sesquiterpenoids, diterpenoids, and triterpenoids. Currently, 30 terpenoids have been reported from *Mitrephora* species, with diterpenoids as the most common. Diterpenoid variants include kauranes, pimaranes, trachylobanes, and clerodanes. Kaurenes are mainly found in *M. celebica* (**14**) [12], *M. maingayi* (**15** and **16**) [8], and *M. tomentosa* (**15**) [13]. Compound **15** in *M. maingayi* has been identified as a chemomarker [8]. Furthermore, investigation on *M. glabra* stem bark revealed three kaurane-type diterpenoids (**17** – **19**) [4], while kaurenoic acid (**20**) has been isolated from *M. sirikitae* [9].

Pimaranes have been identified in *M. alba*, *M. celebica, M. maingayi*, *M. tomentosa*, and *M. sirikitae*. A pimarane-type diterpenoid (**21**) has been isolated from *M. maingayi* [8]. Meanwhile, two pimarane-type diterpenoids were present in *M. celebica* (**21** and **22**) [12], and *M. alba* (**23** and **24**) [14], and one pimarane compound (**25**) was identified in *M. tomentosa* [13]. Trachylobane-type diterpenoids were isolated from *M. alba*, *M. celebica*, *M. glabra*, and *M. sirikitae.* One trachylobane-type diterpenoid (**26**) was found in *M. celebica* [12], three (**27** – **29**) in *M. glabra* [5], seven (**30** – **36**) in *M. alba* [14], and two (**26** and **37**) in *M. sirikitae* [9].

Table 1: Alkaloids extracted from various *Mitrephora* species

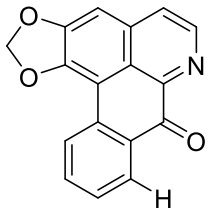
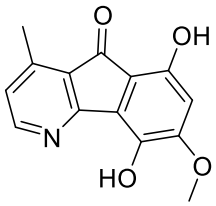
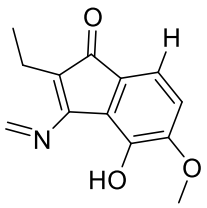
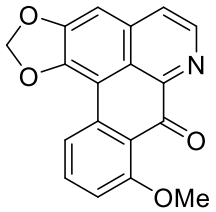
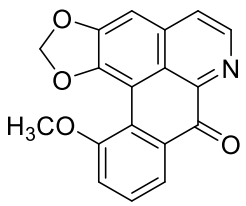
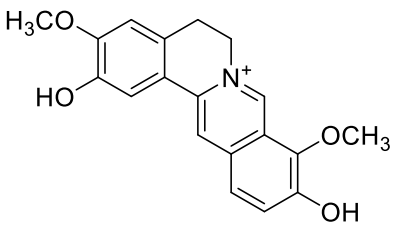
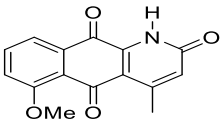
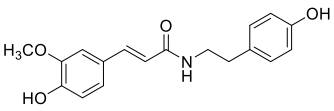
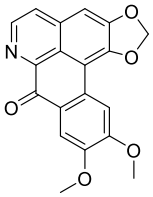
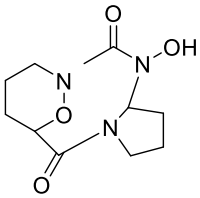
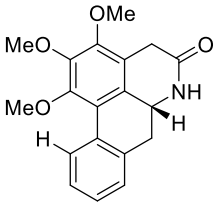
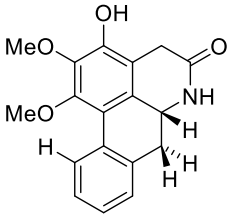
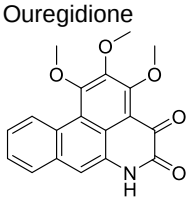
Structure Number	Compound	Species	Plant part	Reference
1	Liriodenine 	*Mitrephora glabra*	Bark	[4]
		Mitrephora vulpina	Twigs	[7]
		Mitrephora maingayi	Stem	[8]
		Mitrephora sirikitae	Leaves and stem	[9]
2	5,8-Dihydroxy-6-methoxyonychine 	*Mitrephora diversifolia*	Root	[6]
3	5-Hydroxy-6-methoxyonychine 	*Mitrephora diversifolia*	Root	[6]
4	Oxostephanine 	*Mitrephora maingayi*	Stem	[8]
5	Oxoputerine 	*Mitrephora vulpina*	Twigs	[7]
		Mitrephora sirikitae	Leaves and stem	[9]
6	Stephranine 	*Mitrephora sirikitae*	Stem	[9]

Table 2: Alkaloids extracted from various *Mitrephora* species *(continued)*

Structure Number	Compound	Species	Plant part	Reference
7	6-Methoxymarcanine A 	*Mitrephora sirikitae*	Stem	[9]
8	N-*trans*-feruloyl tyramine 	*Mitrephora sirikitae*	Leaves	[9]
9	Dicentrinone 	*Mitrephora sirikitae* *Mitrephora maingayi*	Leaves Twigs	[9] [10]
10	Maingayinine 	*Mitrephora maingayi*	Twigs	[10]
11	1,2,3-Trimethoxy-5-oxonoraporphine 	*Mitrephora maingayi*	Bark	[11]
12	1,2-Dimethoxy-3-hydroxy-5-oxonoraporphine 	*Mitrephora maingayi*	Bark	[11]
13	Ouregidione 	*Mitrephora maingayi*	Bark	[11]

Clerodane-type diterpenoids (38 and 39) have been reported in *M. thorelii.* Compound 39 had been isolated from *Polyalthia longifolia* but later published as a new compound within the *Mitrephora* genus in 2007 [15]. Other terpenoids, such as monoterpenoids and triterpenoids, were reported in *M. zippeliana* [16] and *M. heyneana* [17], respectively. Furthermore, sesquiterpenoids are present in several *Mitrephora* species, including thorelinin (40) from *M. thorelii* [18] (Tables 3 - 6).

Table 3: Terpenoids isolated from *Mitrephora* species

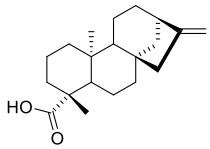
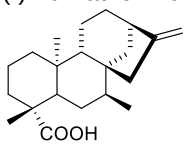
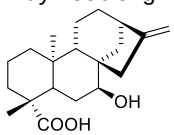
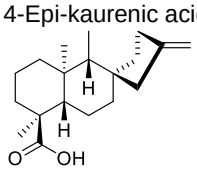
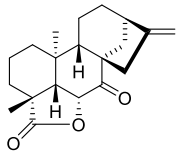
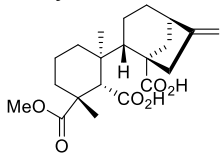
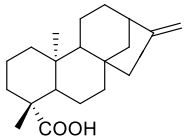
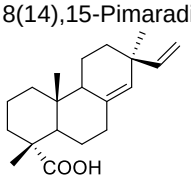
Structure Number	Compound	Species	Plant part	Reference
14	*Ent*-kaur-16-en-19-oic acid 	*Mitrephora celebica*	Stem bark	[12]
15	(-)-16-Kauren-19-oic acid 	*Mitrephora maingayi*	Leaves	[8]
		Mitrephora tomentosa	Bark	[13]
16	Didymooblongin 	*Mitrephora maingayi*	Leaves	[8]
17	4-Epi-kaurenic acid 	*Mitrephora glabra*	Stem bark	[4]
18	Mitrekaurenone 	*Mitrephora glabra*	Stem bark	[4]
19	Methylmitrekaurenate 	*Mitrephora glabra*	Stem bark	[4]
20	Kaurenoic acid 	*Mitrephora sirikitae*	Stem	[9]
21	8(14),15-Pimaradien-18-oic acid 	*Mitrephora maingayi*	Stem	[8]
		Mitrephora celebica	Stem bark	[12]

Table 4: Terpenoids isolated from *Mitrephora* species *(continued A)*

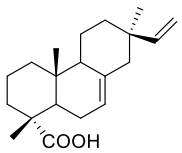
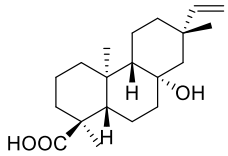
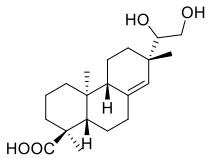
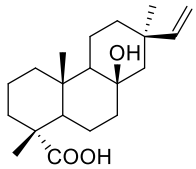
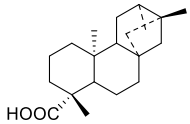
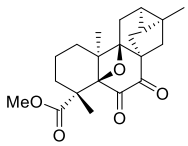
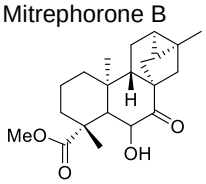
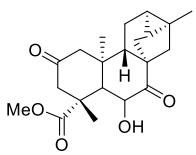
Structure Number	Compound	Species	Plant part	Reference
22	7,15-Pimaradien-18-oic acid 	*Mitrephora celebica*	Stem bark	[12]
23	*Ent*-8β-hydroxypimar-15-en-18-oic acid 	*Mitrephora alba*	Twigs	[14]
24	*Ent*-15,16-dihydroxypimar-8(14)-en-18-oic acid 	*Mitrephora alba*	Twigs	[14]
25	(-)-8β-hydroxypimar-15-en-18-oic acid 	*Mitrephora tomentosa*	Bark	[13]
26	*Ent*-trachyloban-19-oic acid 	*Mitrephora celebica* *Mitrephora sirikitae*	Stem bark Stem	[12] [9]
27	Mitrephorone A 	*Mitrephora glabra*	Twigs	[5]
28	Mitrephorone B 	*Mitrephora glabra*	Twigs	[5]
29	Mitrephorone C 	*Mitrephora glabra*	Twigs	[5]

Table 5: Terpenoids isolated from *Mitrephora* species *(continued B)*

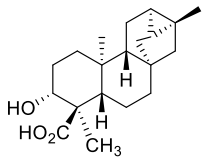
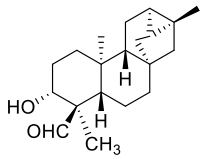
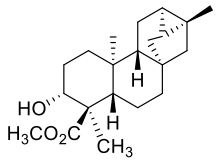
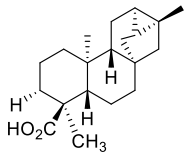
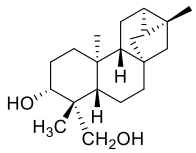
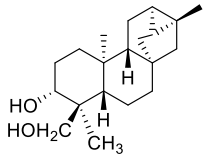
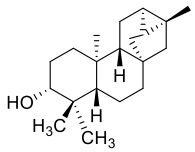
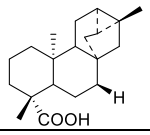
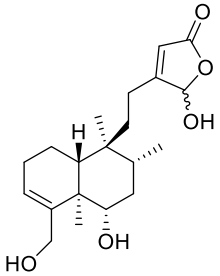
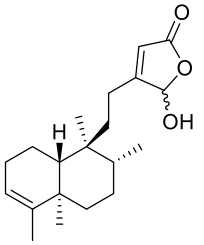
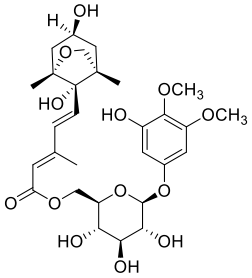
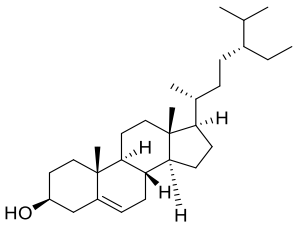
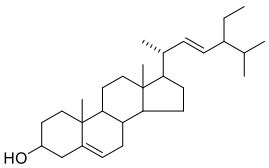
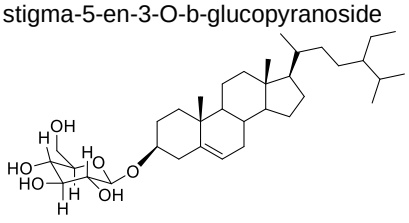
Structure Number	Compound	Species	Plant part	Reference
30	*Ent*-3β-hydroxytrachyloban-18-oic acid 	*Mitrephora alba*	Twigs	[14]
31	*Ent*-3β-hydroxytrachyloban-18-al 	*Mitrephora alba*	Twigs	[14]
32	Methyl-*ent*-3β-hydroxytrachyloban-18-oate 	*Mitrephora alba*	Twigs	[14]
33	*Ent*-trachyloban-18-oic acid 	*Mitrephora alba*	Twigs	[14]
34	*Ent*-trachyloban-3β,19-diol 	*Mitrephora alba*	Twigs	[14]
35	*Ent*-trachyloban-3β,18-diol 	*Mitrephora alba*	Twigs	[14]
36	*Ent*-trachyloban-3β-ol 	*Mitrephora alba*	Twigs	[14]
37	Ciliaric acid 	*Mitrephora sirikitae*	Stem	[9]

Table 6: Terpenoids isolated from *Mitrephora* species *(continued C)*

Structure Number	Compound	Species	Plant part	Reference
38	6α,16,18-Trihydroxycleroda-3(4),13(14)-dien-15,16-olide	*Mitrephora thorelii*	Aerial	[15]
				
39	16-Hydro-xycleroda-3(4),13(14)-dien-15,16-olide	*Mitrephora thorelii*	Aerial	[15]
				
40	Thorelinin	*Mitrephora thorelii*	Stem	[18]
				
41	β-Sitosterol	*Mitrephora tomentosa*	Bark	[13]
		Mitrephora heyneana	Bark	[17]
				
42	Stigmasterol	*Mitrephora vulpina*	Twigs	[7]
				
43	stigma-5-en-3-O-b-glucopyranoside	*Mitrephora sirikitae*	Leaves	[9]
				

Polyacetylenic acids and esters

Mitrephora species contain polyacetylenic acids and esters as phytoconstituents. Studies had identified nine polyacetylene acid structures (44–52) from selected *Mitrephora* species. Two polyacetylene acids (44 and 45) are present in *M. celebica* [19], five (45–49) in *M. glabra* [4], and four (44, 47, 50 and 51) in *M. teysmannii* [20]. Meanwhile, the polyacetylenic ester mitregenin (52) was isolated from *M. maingayi* along with compound 45 [21] (Table 7).

Lignans and lignanamides

A total of 25 different lignans have been identified in *M. maingayi*, *M. vulpina*, *M. teysmannii*, *M. sirikitiae, M. winitii,* and *M. wangii. M. wangii* contains the most lignans with 10 distinct structures (53–62) [22]. In 2016, two new lignans (63 and 64) and five known lignans were isolated from *M. teysmannii* (65–69) [20]. The lignan phylligenin (70) was identified in *M. vulpina* [7].

Two lignans (71 and 72) were reported in *M. maingayi* [8], while six lignans (66-68, 73-75) were found in *M. sirikitiae* [9,23]. Furthermore, *M. thorelii* contains three lignanamides (thoreliamide A (78), thoreliamide B (79), and thoreliamide C (80)) [18] (Tables 8 - 12).

Miscellaneous compounds

Apart from alkaloids, terpenoids, polyacetylene acids, lignans, and lignanamides, other phytoconstituents such as cyclitol, megastigmenes, and benzaldehyde have also been reported in *Mitrephora* species. Quebrachitol (81) was found in *M. maingayi*, *M. vulpina,* and *M. winitii* [7,10,24]. Furthermore, two megastigmanes (82 and 83) had been identified in *M. teysmannii* [20]. Terepthalic acid (84) and 4-hydroxy-benzaldehyde (85) were isolated from *M. maingayi* [10] and *Mitrephora wangii* [22], respectively (Table 13).

Pharmacological properties of *Mitrephora* species

Numerous studies have assessed the pharmacological activities of *Mitrephora* species, particularly *M. alba, M. celebica*, *M. diversifolia*, *M. glabra*, *M. sirikitiae, M. teysmannii, M. vulpina*, and *M. winitii.* The following sections discuss the anti-microbial, anti-cancer, α-glucosidase inhibition, anti-malarial, PAF inhibition, and anti-inflammatory exhibited by several *Mitrephora* species.

Pharmacological activity

Anti-microbial effects

Alkaloids, diterpenoids, and polyacetylene acids contribute to the anti-microbial activity of *M. glabra* and *M. celebica*. Two polyacetylene acids (44 and 45) from *M. celebica* were tested against methicillin-resistant *Staphylococcus aureus* (MRSA) and *Mycobacterium smegmatis*. Compound 45 demonstrated higher potency against MRSA than compound 44 at a minimum inhibitory concentration (MIC) of 12.5 µg/mL and 25 µg/mL, respectively, however, higher than vancomycin (MIC of 0.8 µg/mL). In the same study, both compounds were equipotent when tested against *M. smegmatis* (MIC of 12.5 µg/mL), however, higher than isoniazid (0.8-1.6 µg/mL) [19]. Furthermore, a diterpenoid (26) isolated from *M. celebica* exhibited moderate resistance against MRSA and *M. smegmatis* (MIC of 6.5 µg/mL) [12]. Three diterpenoids identified in *M. glabra* (27–29) demonstrated anti-microbial activity against *Micrococcus luteus*, *M. smegmatis*, *Saccharomyces cerevisiae*, and *Aspergillus niger*. Compound 29 exhibited the highest potency against yeast (MIC = 31 µg/mL) compared to amphotericin B (MIC = 25 µg/mL) [5]. In another study, compounds 46 and 49 were demonstrated to exhibit anti-microbial effect.

Anti-cancer properties

Previous study reported that *M. glabra* contains two diterpenoids (27 and 28) with anti-cancer activities against human cancer cells [5]. However, compound 27 (IC_{50} = 8–31 µg/mL) exhibited significantly stronger cytotoxic potential compared to compound 28 against human oral epidermoid carcinoma (KB), human breast carcinoma (MCF-7), human large cell lung carcinoma (NCI-H460), and human astrocytoma (SF-268) cell lines. Cytotoxic potential of polyacetylene acids (45, 47–49) (IC_{50} ranging from 10 to 40 µM) had been demonstrated [4] with liriodenine alkaloid emerging as the most potent (IC_{50} = 5 µM) in *M. glabra* [4]. Also, trachylobane diterpenoids in *M. alba* demonstrated anti-cytotoxic activity compared to doxorubicin [14]. Lignan (3,4-dimethoxyphenyl)(5-(3,4-dimethoxyphenyl)-4-(hydroxymethyl) tetrahydrofuran-3-yl) methanol (77) isolated from *M. winitii* demonstrated anti-proliferative activity against KB and MCF-7 cell lines (ED_{50} of 13.07 and 11.77 µg/mL) respectively [24].

Table 7: Polyacetylenic acids and esters isolated from *Mitrephora* species

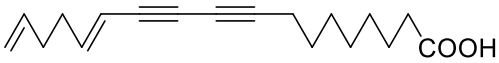
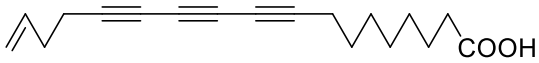
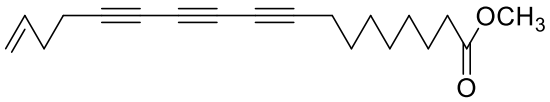
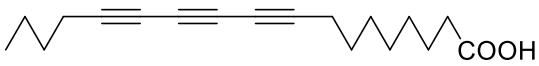
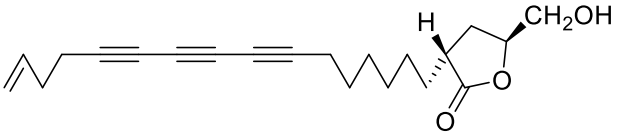
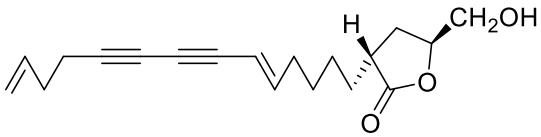
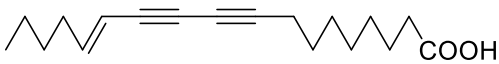
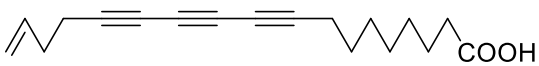
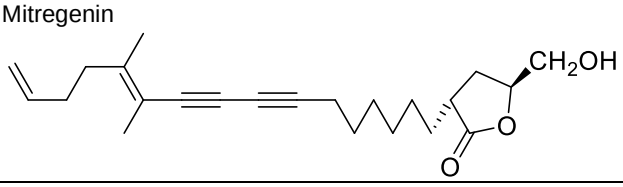
Structure Number	Compound	Species	Plant part	Reference
44	13(E),17-Octadecadiene-9,11-diynoic acid 	*Mitrephora tomentosa*	Stem bark	[13]
		Mitrephora celebica	Stem bark Leaves	[19]
		Mitrephora teysmannii		[20]
45	17-Octadecene-9,11,13-triynoic acid (oropheic acid) 	*Mitrephora glabra*	Stem bark	[4]
		Mitrephora celebica	Stem bark Twigs and leaves	[19]
		Mitrephora maingayi		[21]
46	Methyloropheate 	*Mitrephora glabra*	Stem bark	[4]
47	Octadeca-9,11,13-triynoic acid 	*Mitrephora glabra*	Stem bark	[4]
		Mitrephora teysmannii	Leaves	[20]
48	Oropheolide 	*Mitrephora glabra*	Stem bark	[4]
49	9,10-Dihydrooropheolide 	*Mitrephora glabra*	Stem bark	[4]
50	13(E)-Octadecene-9,11-diynoic acid 	*Mitrephora teysmannii*	Leaves	[20]
51	Octadeca-17-en-9,11,13- triynoic acid 	*Mitrephora teysmannii*	Leaves	[20]
52	Mitregenin 	*Mitrephora maingayi*	Twigs and leaves	[21]

Table 8: Lignans isolated from *Mitrephora* species

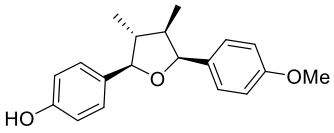
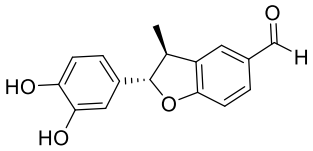
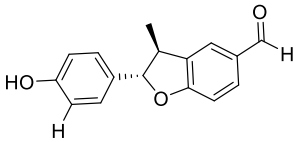
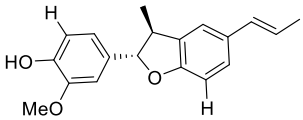
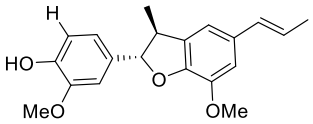
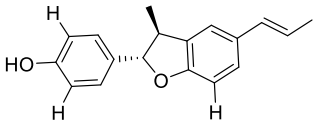
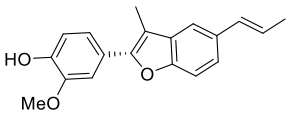
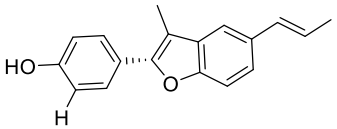
Structure Number	Compound	Species	Plant part	Reference
53	(7S,8R,7'R,8'R)-4'-Hydroxy-4-methoxy-7,7'-epoxylignan 	*Mitrephora wangii*	Leaves	[22]
54	(2S,3S)-2,3-Dihydro-2-(3',4'-dihydroxyphenyl)-3-methyl-5-benzofurancarboxaldehyde 	*Mitrephora wangii*	Leaves	[22]
55	Decurrenal 	*Mitrephora wangii*	Twigs	[22]
56	Parakmerin A 	*Mitrephora wangii*	Twigs	[22]
57	(−)-Licarin A 	*Mitrephora wangii*	Twigs	[22]
58	(+)-Conocarpan 	*Mitrephora wangii*	Twigs	[22]
59	Eupomatenoid-5 	*Mitrephora wangii*	Twigs	[22]
60	Eupomatenoid-6 	*Mitrephora wangii*	Twigs	[22]

Table 9: Lignans isolated from *Mitrephora* species *(continued)*

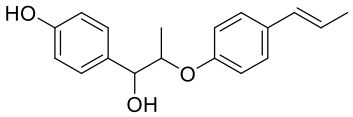
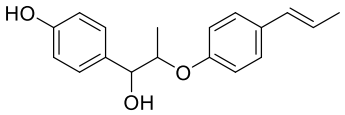
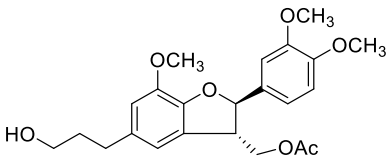
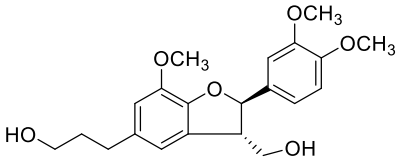
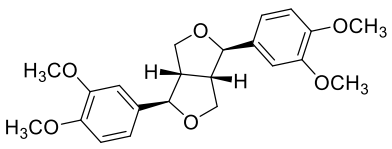
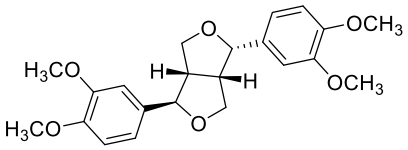
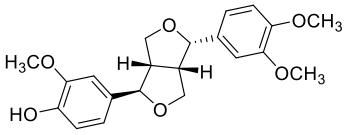
Structure Number	Compound	Species	Plant part	Reference
61	Threo-1-(4-hydroxyphenyl)-2-(4-(E)-propenyl phenoxy)-propan-1-ol 	*Mitrephora wangii*	Leaves	[22]
62	Erythro-1-(4-hydroxyphenyl)-2-(4-(E)-propenyl phenoxy)-propan-1-ol 	*Mitrephora wangii*	Twigs	[22]
63	(2R,3S)-2-(3',4'-Dimethoxyphenyl)-5-(3-hydroxypropyl)-7-methoxy-2,3-dihydrobenzofuran-3-methyl acetate 	*Mitrephora teysmannii*	Leaves	[20]
64	(−)-3',4-Di-*O*-methylcedrusin 	*Mitrephora teysmannii*	Leaves	[20]
65	(−)-Eudesmin 	*Mitrephora teysmannii*	Leaves	[20]
66	(−)-Epieudesmin 	*Mitrephora teysmannii*	Leaves	[20]
		Mitrephora sirikitiae	Leaves and stem	[9]
			Leaves	[23]
67	(−)-Phillygenin 	*Mitrephora teysmannii*	Leaves	[20]
		Mitrephora sirikitiae	Leaves	[9, 23]

Table 10: Lignans isolated from *Mitrephora* species *(continued B)*

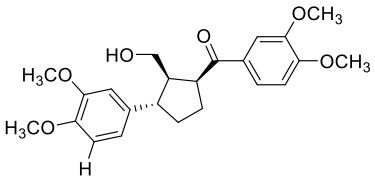
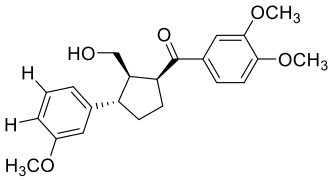
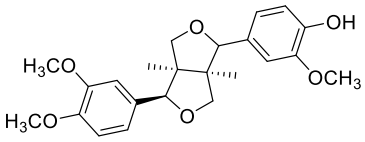
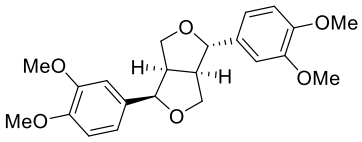
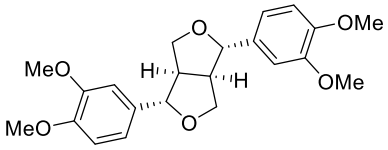
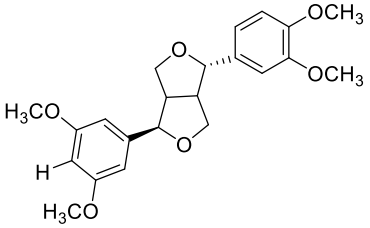
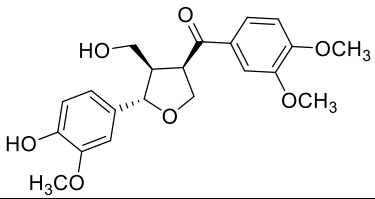
Structure Number	Compound	Species	Plant part	Reference
68	Magnone A 	*Mitrephora teysmannii*	Leaves	[8]
		Mitrephora maingayi	Leaves	[20]
		Mitrephora sirikitiae	Leaves	[9, 23]
69	Forsythialan B 	*Mitrephora teysmannii*	Leaves	[20]
70	Phylligenin 	*Mitrephora vulpina*	Twigs	[7]
71	(+)-Epieudesmin 	*Mitrephora maingayi*	Leaves and stem	[8]
72	Eudesmin 	*Mitrephora maingayi*	Leaves and stem	[8]
73	2-(3,4-Methylene-dioxyphenyl)-6-(3,5-dimethoxyphenyl)-3,7-dioxabicyclo(3.3.0)octane 	*Mitrephora sirikitiae*	Leaves	[9, 23]
74	Mitrephoran 	*Mitrephora sirikitiae*	Leaves	[9, 23]

Table 11: Lignans isolated from *Mitrephora* species *(continued)*

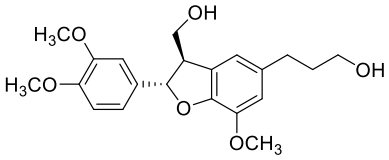
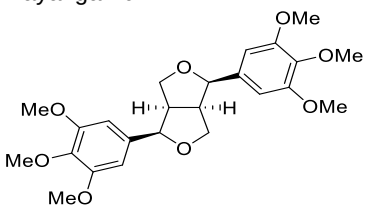
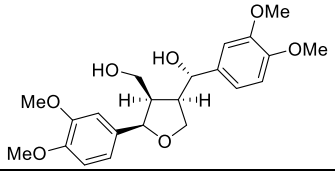
Structure Number	Compound	Species	Plant part	Reference
75	3',4-*O*-Dimethylcedrusin 	*Mitrephora sirikitiae*	Leaves	[9, 23]
76	Diayangambin 	*Mitrephora winitii*	Leaves and twigs	[24]
77	(3,4-Dimethoxyphenyl)(5-(3,4-dimethoxyphenyl)-4-(hydroxymethyl)tetrahydrofuran-3-yl)methanol 	*Mitrephora winitii*	Leaves and twigs	[24]

Table 12: Lignanamides isolated from *Mitrephora* species

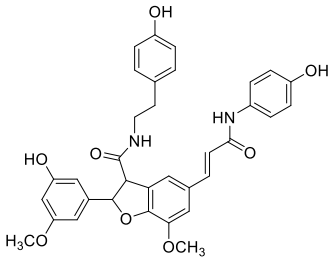
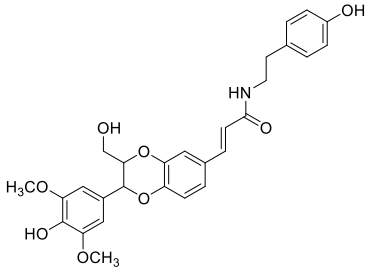
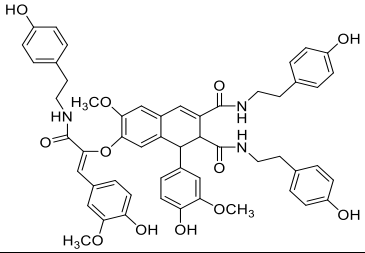
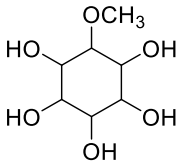
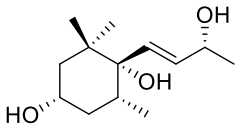
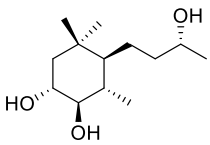
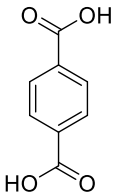
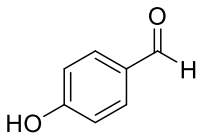
Structure Number	Compound	Species	Plant part	Reference
78	Thoreliamide A 	*Mitrephora thorelii*	Stem	[18]
79	Thoreliamide B 	*Mitrephora thorelii*	Stem	[18]
80	Thoreliamide C 	*Mitrephora thorelii*	Stem	[18]

Table 13: Miscellaneous compounds isolated from *Mitrephora* species

Structure Number	Compound	Species	Plant part	Reference
81	Quebrachitol 	*Mitrephora maingayi*	Twigs	[7]
		Mitrephora vulpina	Twigs	[10]
		Mitrephora winitii	Leaves and twigs	[24]
82	(3S,5R,6S,7E,9R)-7-Megastigmene-3,6,9-triol 	*Mitrephora teysmannii*	Leaves	[20]
83	Annoionol A 	*Mitrephora teysmannii*	Leaves	[20]
84	Terepthalic acid 	*Mitrephora maingayi*	Twigs	[10]
85	4-Hydroxy-benzaldehyde 	*Mitrephora wangii*	Twigs	[22]

In another study, the alkaloids liriodenine (**1**) and oxoputerine (**5**) from *M. sirikitiae* exhibited potent cytotoxicity (IC_{50} = 6.59 – 11.02 µM) against murine lymphocytic leukemia (P-388), KB, human colon carcinoma (Col-2 and HT-29), MCF-7, human lung carcinoma (Lu-1 and A549), and rat glioma (ASK) [9]. Another alkaloid, 6-methoxymarcanine A (**7**), selectively inhibited the growth of P-388, HT-29, MCF-7, and A549 cells (IC_{50}: 8.33 – 12.30 µM), while displaying lower cytotoxicity against KB, ASK, and non-cancerous human embryonic kidney cells (HEK-293). Among the lignans, magnone A (**68**) exhibited selective cytotoxicity against P-388 (IC_{50}: 8.96 µM) and MCF-7 cells (IC_{50}: 4.40 µM). Given the selective inhibitory effects and lower toxicity toward normal cells, magnone A (**68**) and 6-methoxymarcanine A (**7**) are promising candidates for further anti-cancer studies [9].

Alpha-glucosidase inhibition

Four polyacetylenic acids (**44, 47, 50** and **51**) from *M. teysmannii* were potential α-glucosidase inhibitors [14]. The study demonstrated that compounds **44** (IC_{50} = 59 µM) and **50** (IC_{50} = 53 µM) exhibited α-glucosidase inhibitory activity superior to acarbose (IC_{50} = 1457 µM). Also, previous study has demonstrated α-glucosidase inhibitory activity of compound **47** (IC_{50} = 128 µM) and **51** (IC_{50} = 274 µM) [20].

Anti-malarial effects

Azafluorenone alkaloids (compounds **2** and **3**) from *M. diversifolia* demonstrated anti-malarial activity against chloroquine-sensitive (3D7) and chloroquine-resistant (Dd2) strains of *Plasmodium falciparum* without any signs of kidney toxicity. Conversely, compound 3 was highly effective against strains 3D7 (IC_{50} = 9.9 µM) and Dd2 (IC_{50} = 11.4 µM), however, signs of kidney toxicity were detected at 120 µM [6].

Platelet-activating factor (PAF) inhibitor

Phylligenin (**70**) and quebrachitol (**81**) isolated from *M. vulpina* significantly inhibited PAF receptor binding at 18.2 µg/mL (IC_{50} = 13.1 and 42.2 µM, respectively) compared to cedrol (positive control used in the assay). Also, compound **70** exhibited anti-platelet activity in arachidonic acid (AA)- and adenosine diphosphate (ADP)-induced aggregation in a dose-dependent manner (IC_{50} = 230.6 and 121.8 µM, respectively) [7].

Anti-inflammatory activity

Lignans isolated from *M. sirikitiae* have demonstrated significant anti-inflammatory activity in LPS-induced RAW 264.7 macrophages by modulating key inflammatory mediators. Phylligenin (**70**) and 3',4-O-dimethylcedrusin (**75**) significantly suppressed prostaglandin E_2 (PGE_2) and nitric oxide (NO) production through the downregulation of cyclooxygenase 2 (COX-2) and inducible nitric oxide synthase (iNOS) expression. Meanwhile, 2-(3,4-dimethoxyphenyl)-6-(3,5-dimethoxyphenyl)-3,7-dioxabicyclo (3.3.0) octane (**73**) and mitrephoran (**74**) inhibited tumor necrosis factor-alpha (TNF-α) secretion and mRNA expression, indicating their role in modulating inflammatory cytokines. These findings suggest that lignans from *M. sirikitiae* are potential anti-inflammatory agents, targeting multiple inflammation pathways [23].

Limitations of the study

Despite the promising findings, there are knowledge gaps that need to be addressed. Advanced molecular studies should be conducted to elucidate the mechanisms of action of the bioactive compounds of *Mitrephora* species, particularly for anti-cancer and anti-microbial applications. Exploring drug delivery systems for *Mitrephora*-derived compounds may also optimize their therapeutic potential. Furthermore, existing studies are primarily conducted *in vitro*, thus lacking comprehensive clinical validations. Therefore, clinical trials are needed to confirm the safety, efficacy, and pharmacokinetics of bioactive compounds derived from *Mitrephora* species. Therefore, the genus *Mitrephora* may significantly contribute to the development of novel therapeutic agents.

CONCLUDING REMARKS

This review has highlighted the diversity of phytoconstituents (alkaloids, terpenoids, lignans, and polyacetylene acids) across *Mitrephora species* and their corresponding pharmacological effect. The literature presents evidence of these compounds in combating human cancer cells, microbial infections, malaria, inflammation, and PAF inhibition. Notably, aporphine alkaloids and diterpenoids have emerged as key bioactive agents, underlining the therapeutic potential of this genus in modern drug development.

DECLARATIONS

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Ethical approval

Not applicable.

Use of Artificial intelligence/Large language models

We declare also that we did not use Generative artificial intelligence (AI) and AI-assisted technologies in writing the manuscript.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the author(s) named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

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