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A Systematic Review of Terpenoids in *Azadirachta indica*: Classes, Structures and Medicinal Uses

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Authors' contributions

This work was carried out in collaboration among all authors. Author MMA designed the study, wrote the protocol, and wrote the first draft of the manuscript. Authors MMS and HMK managed the literature searches and writing formats. Author JMK proof-read and prepared the final draft of the manuscript. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Azadirachta indica (neem) can be considered as "Nature's Chemist" due to its therapeutic, pharmaceutical, agro and medicinal properties. Neem tree is the most researched tree so far and has proven to be the most prospect target for the future drug discoveries. Its bioactivity has been associated with vast richness in phytochemicals whereas the terpenoids are the major medicinal components. Terpenoids are classified into different categories which display a wide range of biological activities. This article reviews the terpenoids reported in different parts of neem tree, classes, structures, their usage and application in modern medicine.

Keywords: Terpenoids; Azadirachta indica; phytochemicals; antimalarial; triterpenoids.

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1. INTRODUCTION

Azadirachta indica (neem), a versatile tree of immense value, has attained a pride of place in international scientific research and literature because of its diverse utility in pharmaceuticals, cosmetics, agriculture, veterinary, toiletries and as potential biomass [1]. Various pharmacological attributes such as antifungal [2], antiviral [3], antibacterial [4], anti-inflammatory [5], antifeedant pesticides [6], sterilant, antiscabic, antiulcer [7], antiallergenic [8], analgesic [9], prominent biopesticide [10] and nematicidal are ascribed to various parts of the tree that has long been revered by ancient Indian people and is entitled "village drugstore" [11]. Fruits, seeds, leaves, bark and roots have extensively been used in treatment of various ailments. Different parts of this miraculous tree are used to treat pyrexia, headache, ulcer, respiratory disorders, cancer, diabetes, leprosy, malaria, dengue, chicken pox, and dermal complications [12].

Medicinal potential of the tree can be attributed to various diverse nature of secondary metabolites/bioactives, that is, terpenes [13], limonoids [14], flavonoids [15], alkaloids [16], and saponins [17], which mediated their role by affecting various biological processes.

Terpenes are a class of natural products consisting of compounds made up of isoprene molecules with the formula $(C_5H_8)n$. Based on the number of isoprene units they have, they are classified as mono, di, tri, tetra, and sesquiterpenes [18]. Terpenes are the largest and most diverse group of naturally occurring compounds. They are mostly found in plants and form the major constituent of essential oils from plants. T*erpenoids* are modified class of terpenes with different functional groups and oxidized methyl group. Terpenoids display a wide range of biological activities against cancer, malaria, inflammation, tuberculosis and a variety of infectious diseases including viral as well as bacterial [19]. Fig. 1 gives the basic skeleton for different classes of terpenes.

2. CLASSES AND STRUCTURES OF TERPENOIDS

Terpenoids, also known as isoprenoids, are a large and diverse class of naturally occurring organic chemicals derived from the 5-carbon compound isoprene, and the isoprene polymers called terpenes. Terpenoids are usually cyclic unsaturated hydrocarbons, with the altered number of oxygen moieties in the constituent groups attached to the basic isoprene skeleton. They are divided into monoterpenes, sesquiterpenes, diterpenes, sesterpenes, and triterpenes depending on its carbon units [18]. Most of the terpenoids with the variation in their structures are biologically active and are used worldwide for the treatment of many diseases.

3. MONOTERPENES

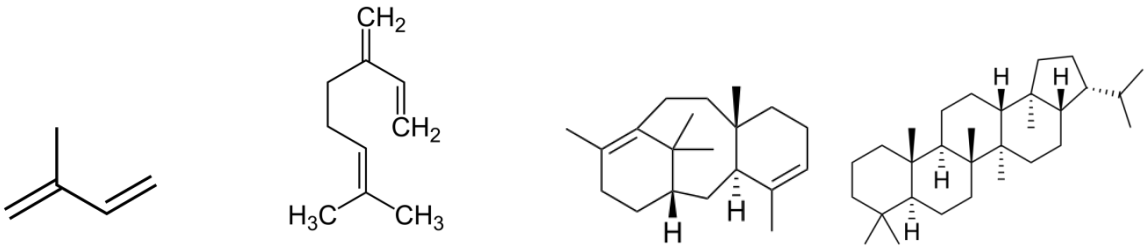
Monoterpenes ($C_{10}H_{16}$) are dimers of isoprene and can be divided into acyclic, monocyclic, bicyclic, and tricyclic compounds [20]. Monoterpene derivatives typically containing oxygen or nitrogen atoms are known as *monoterpenoids*. Monoterpenes and their derivatives are valuable renewable raw materials in organic chemistry. Their unique structure is often combined with high chemical lability and optical activity. Many monoterpenoids and products of their transformation are of practical importance in the pharmaceutical and cosmetic industries, for production of flavor additives and pesticides [21]. Monoterpenes are the main components of essential oils and fragrances [18] and are responsible to attract pollinators or to serve the purpose of repelling other organisms from feeding off of plants [22]. Fig. 2 gives examples of monoterpenoids isolated from neem tree.

4. SESQUITERPENES

Sesquiterpenes are the class of secondary metabolites consisting of three isoprene units ($C_{15}H_{24}$) and found in linear, cyclic, bicyclic, and tricyclic forms. Sesquiterpenes are also found in the form of lactone ring. many of the latex in latex-producing plants contain sesquiterpene, and these are potent antimicrobial and anti-insecticidal agent [23]. Sesquiterpenes are naturally occurring and found in plants, fungi, and insects and act as a defensive mechanism or attract mates with pheromones in insects [24]. Fig. 3 shows some of the sesquipetenes isolated from neem tree.

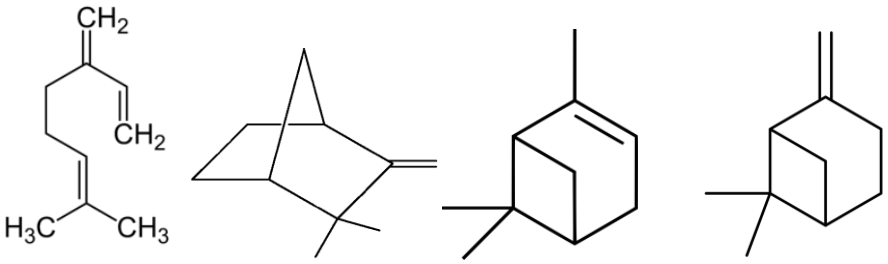
5. DITERPENOIDS

Diterpenoids are chemical compounds with 20 carbon atoms. They are made up of four isoprene units and are derived from geranylgeraniol, a C_{20} precursor. They have a $C_{20}H_{32}$ basic structure. these characteristics distinguish diterpenoids from simple terpenes, which have just 10 carbon atoms [25].



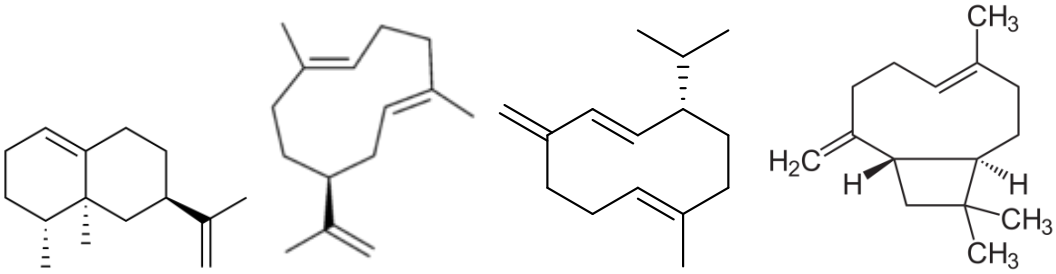
Isoprene unit **Monoterpene** **Sesquiterpene** **Diterpene**

Fig. 1. Basic skeleton for different classes of terpenes

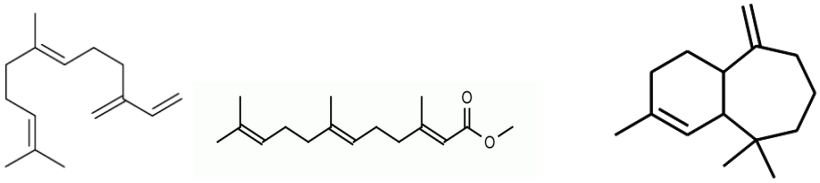


Myrcene **Camphene** **α-Pinene** **β-Pinene**

Fig. 2. Monoterpenoids isolated from *Azadirachta indica*



Valencene **Germacrene B** **Germacrene D** **Caryophyllene**



β-farnesene **methyl (2E, 6E)-farnesoate** **α-Himachalene**

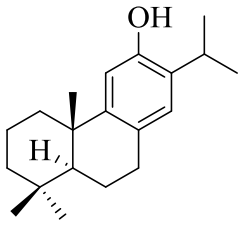
Fig. 3. Sesquiterpenes isolated from neem tree

Diterpenes have physiologically dynamic compounds, for example, plant development chemicals that manage germination, blooming, switch regenerative cycles (from abiogenetic to sexual multiplication) of plants, and vitamin A activity [26]. Fig. 4 shows some diterpenoids extracted from neem tree.

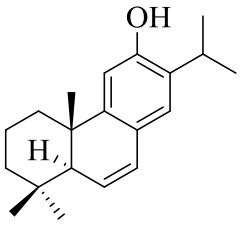
6. TRITERPENOIDS

Triterpenoids are composed of 30 carbon atoms, polymerized to form six isoprene units. triterpenoids are biosynthesized by the cyclization of its precursor squalene, a hydrocarbon composed of two molecules of

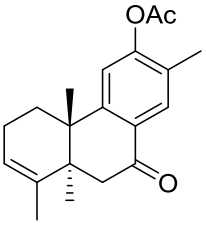
farnesyl pyrophosphates joined tail to tail [27]. Based on their chemical structures, triterpenoids can be grouped into linear, monocyclic, dicyclic, up through pentacyclic compounds.



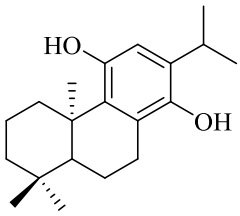
Ferruginol



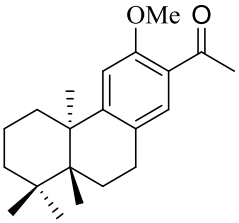
6,7-dehydroferruginol



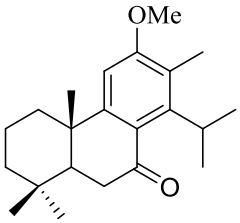
Nimbilicin



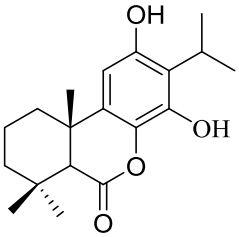
Nimbocidin



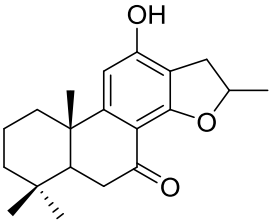
Nimbosone



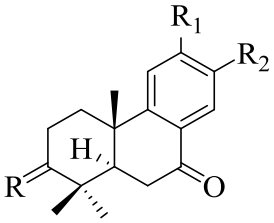
Margosone



Nimbocinin



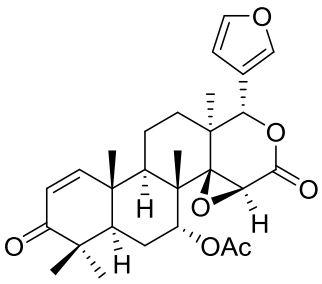
Azadirilin



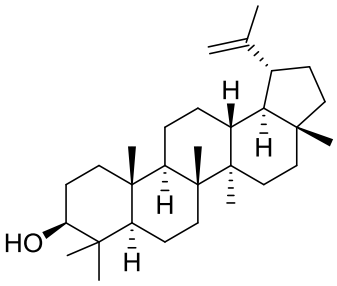
Azadirone Class Diterpenoids

Name	R	R1	R2
Azadirin A	H	Me	$(CH_2)_2OH$
Azadirin B	H	$(CH_2)_2OH$	Me
Margocilin	β-OH, H	OH	i-Pr
Maegocin	O	H	i-Pr
Margocinin	O	OH	$MeCHCH_2OH$
Nimbidiol	H_2	OH	OH
Nimolinin	H_2	OH	Ac
Nimbisonol	β-OH, H	OH	Me
Demethylnimbionol	β-OH, H	OH	OH
isomargolonone	O	COOH	Me
Margolone	H_2	Me	COOH
Margolonone	O	Me	COOH
Methylnimbiol	H_2	OMe	i-Pr
Nimosone	O	OH	i-Pr
Methylnimbionone	O	OMe	OMe
Nimbione	O	Me	OH
Nimbinone	O	OH	Me
Nimbionol	β-OH, H	OH	OMe
Nimbionone	O	OH	OMe
Nimbonone	H_2	Et	OMe
Nimbiol	H_2	OH	i-Pr
Sugiol	H_2	OH	Me

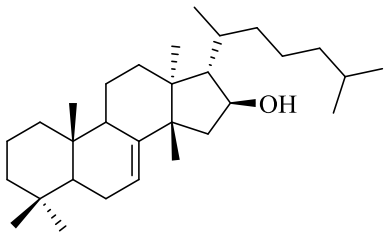
Fig. 4. Examples of diterpenoids from neem plant



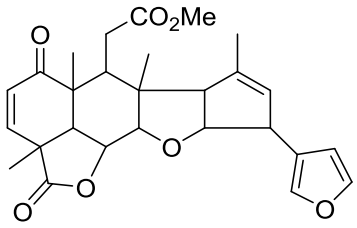
Gedunin



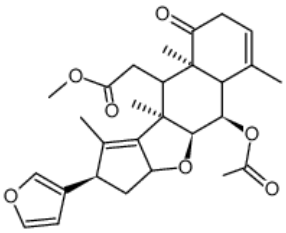
Lupeol



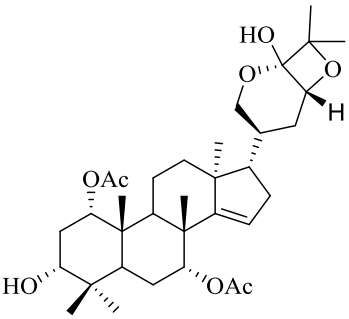
Limocinol



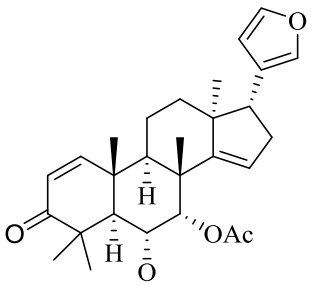
Nimbolide



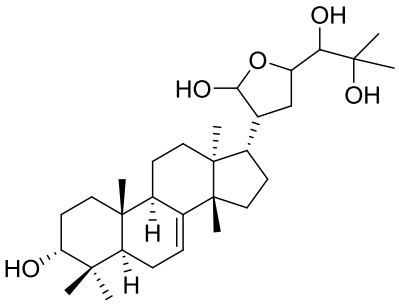
Nimbinene



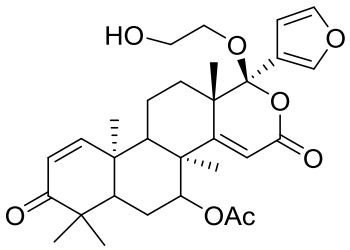
Azadirahemiacetyl



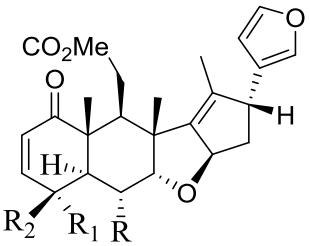
Nimocinol



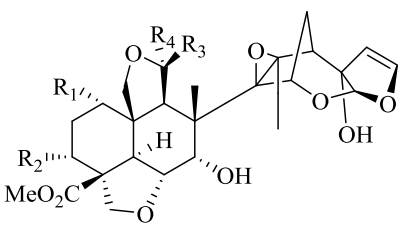
Meliantriol



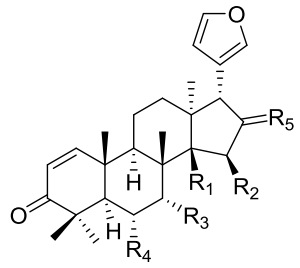
Mahmoodin



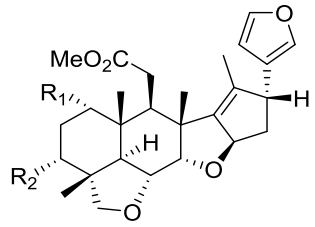
Name	R	R1	R2
Nimbin	OAc	CO_2Me	Me
6-deacetylnimbin	OH	CO_2Me	Me
Nimbanal	OAc	CHO	Me
Nimbinene	OAc	Me	H
6-deacetylnimbinene	OH	Me	H



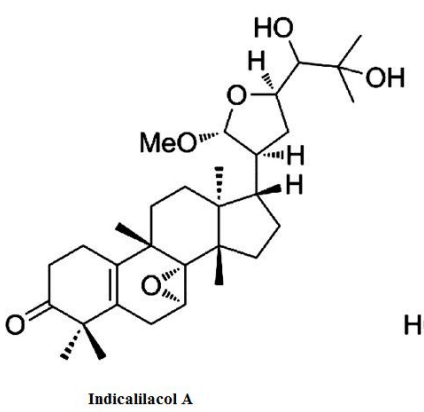
Name	R1	R2	R3	R4
Azadirachtin A	Tiglate	OAc	OH	CO_2Me
3-deactylazadirachtin A	Tiglate	OAc	OH	CO_2Me
Azadirachtin B	OH	Tiglate	H	CO_2Me

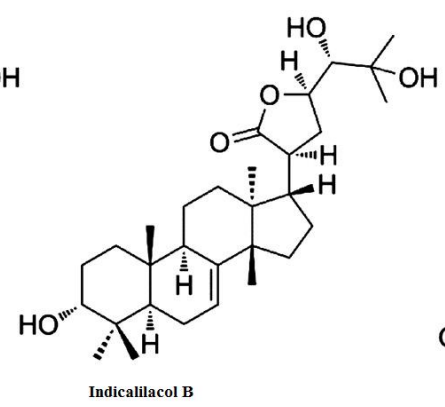


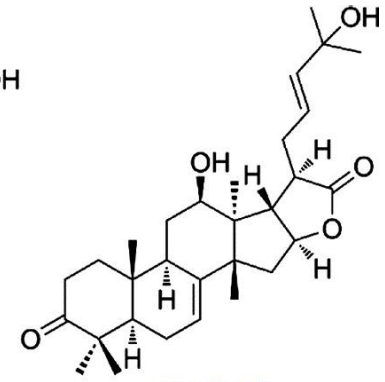
Name	R1, R2	R3	R4	R5
Azadiradione	double bond	OAc	H	O
Epoxyazadiradione	epoxy	OAc	H	O
Azadirarone	double bond	OAc	H	H_2
Nimocinol	double bond	OAc	OH	H_2



Name	R1	R2
Salannon acetate	isovalerate	OAc
Salannin	Tiglate	OAc
3-Deacetylsalannin	Tiglate	OH



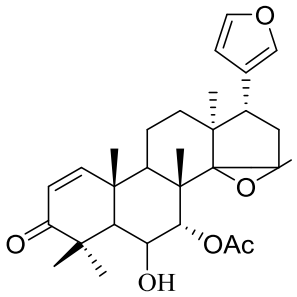




Indicalilacol A **Indicalilacol B** **Indicalilacol D**

Fig. 5. Triterpenoids from neem plants

triterpenes are produced by animals, plants, and fungi. They play a role as precursors to steroids in animal and plant organisms [28]. Some triterpenoids from neem tree are shown in Fig. 5.



14,15-Epoxynimonol

Tetraterpenes are mainly responsible for red, yellow, or orange fat-soluble plant and animal pigments [29]. 14,15-Epoxynimonol was obtained from the fresh green whole leaves of neem.

7. MEDICINAL USES OF TERPENOIDS

Leaves of *Azadirachta indica* have been used to treat eye problems, earache, rheumatism, anorexia, wounds, skin infections, blood contaminations, nose troubles and gastro-intestinal (GIT) worms among others [12]. A study by Arumugan et al. in 2014 confirmed that ethanolic fraction of neem leaf treatment significantly increased the expression of pTEN, which could inhibit mammary tumourigenesis through its inhibitory effect on Akt [30]. Other results showed that leave extracts promote wound healing activity through increased inflammatory response and neovascularization [31]. Dried leaves are pulverized into fine powder using an industrial blender and the powdered leaves is added to boiling water with additives for

taste or improves efficiency. The fresh leaves are chewed and swallowed directly after thorough washing. In India, leaf juice is administered by intravenous infusion for chronic skin diseases, and is taken orally as an anthelmintic. In Nigeria, hot water extract of the fresh leaf and bark is taken orally to treat jaundice, malaria and as a cathartic [41]. Young neem leaves are boiled with tamarind fruit to soften its bitterness and eaten as a vegetable. Pickled neem leaves are also eaten with tomato and fish paste sauce [42]. In a more recent study, the leaves extract was involved in the fabrication of nanoparticles of various metal oxides. These were then evaluated further for antibacterial and photocatalytic activity. The results reported by patil et al. in 2022 showed that metal oxides nanoparticles have better antibacterial activity and photocatalytic potential over aqueous leaves extract [43]. The leaves mostly contain triterpenoids as shown in Table 1 which include nimbin and its derivatives, gedunin and its derivatives, salannin and its derivatives, zafaral, nimbolides, nimocinol, nimonol, lupeo, isomeldenin. gedunin possesses potential antitumor, antimalarial, and anti-diabetic activities [34]. azadiradione confers anti-inflammatory and anti-diabetic effects [44]. 14,15-epoxynimonol, a tetraterpenoid obtained from the fresh green whole leaves, has been reported to inhibit covid-19 main protease [32, 33]. Nimbiol is a diterpenoid extracted from leaves, and is used as antiacne [37, 45].

Neem fruits have been generally used for treatment of piles, intestinal worms, urinary disorder, epistaxis, phlegm, eye problem, diabetes, wounds and leprosy [46]. Neem fruits are eaten fresh or cooked or prepared as a dessert or lemonade-type drink [42]. In India, the fresh fruit is used externally for leprosy. In Thailand, hot water extract of the dried fruit is taken orally as an anthelmintic, laxative, bitter tonic and for fever; while the dried unripe fruit is taken orally as a bitter tonic and for fever [41]. Fruits contain monoterpenes (myrcene, α- and β-pinene, camphene), sesquiterpenes (valencene, α-himachalene, β-farnesene, methyl (2E, 6E)-farnesoate, germacrene B and D, caryophyllene) and triterpenoids (indicalilacols A-D, neemfruitins A-B, meliantrol, azadirone and its derivatives, gedunin and its derivatives) as indicated in Table 2. Myrcene and α-Pinene, monoterpenes from neem fruits both were reported to possess antitumor properties [47, 48]. α-Pinene can also counteract THC-induced anxiety and short-term memory loss [48]. Camphene is proven for its ability to fight bacterial and fungal infections while reducing inflammation and stress [49]. Valencene is a sesquiterpene which offers anti-inflammatory, skin protectant and anti-allergic benefits [50]. Inhaling germacrene B, a sesquiterpene, can help clear the sinuses and relieve congestion. It can also act as an expectorant, helping clear out mucus. These properties make this terpene helpful for relief from both cold and allergy symptoms [46]. Sharma et al. reported in 2022 that Germacrene D showed anticancer properties [51].

Seeds have generally been used to treat urinary tract disorders, bloody nose, phlegm, eye disorders, leprosy, cancer, malaria and intestinal worms [52]. The seeds are the primary source of insecticides. They can be used in the form of simple aqueous extracts or as a basic raw material for formulated pesticides. The seeds are crushed and steeped in water, alcohol, or other solvents. For some purposes, the resulting extracts can be used without further refinement. Ground neem seeds or neem kernel powder (before or after oil extraction) is used as a soil amendment, and it is effective for control of nematodes. It is also used for control of stalk borers, and to prepare water extracts, which are then sprayed onto plants [42]. Some people apply neem directly to the skin to treat head lice [53], skin diseases, wounds, and skin ulcers; as a mosquito repellent; and as a skin softener. Seeds contain triterpenoids (azadirahemiacetal, deacetylazadirachtonil, geducin, meliacin, nimbin, nimbicin, saladucin, valassene), tetracyclictriterpenoids (azadiradione, nimocinol) and tetranortriterpenoids (azadirachtins A-N, nimbidin and its derivatives, gedunin and its derivatives, meliantiol) as indicated in Table 3. Some of the first isolated terpenes include nimbin and nimbolide [54]. Azadirachtin, a tetranortriterpenoid and its derivatives, derived from the neem seed, is one of the prominent biopesticides commercialized and remains the most successful botanical pesticide in agricultural use worldwide. Azadirachtin is a powerful antifeedant and insect growth disruptor with exceptional low residual power and low toxicity to biocontrol agents, predators, and parasitoids [82]. Nimbolide, a triterpenoid, has shown anti-angiogenic, anti-proliferative. It was also reported by Chitta et al. in 2014 to possess anticancer and anticancer preventive effects [83]. Geducin, a triterpenoid from seeds, has been observed to have anticancer properties [52, 72].

Table 1. Terpenoids isolated from the neem leaves

SR/No	Terpenoid	Class	Solvent	Medicinal uses	References
1	14,15-epoxynimonol	tetraterpenoid	MeOH	COVID19 Main Protease inhibitor	[32] [33]
2	23,23-dihydronimocinol	triterpenoid	MeOH	COVID19 Main Protease inhibitor	[32]
3	Gedunin	tetranortriterpenoid	hexane	anti-inflammatory, anticancer	[34]
4	isomeldenine	tetranortriterpenoid	ethanol	anti-inflammatory, anticancer	[34]
5	Lupeo	pentacyclictriterpene	hexane	anti-inflammatory, anticancer	[34]
6	meliacinanhydride	tetracyclic triterpenoid	ethanol	COVID19 Main Protease inhibitor	[32]
7	meliatetraolenone	tetranortriterpenoid	MeOH	antibacterial, insecticidal	[35]
8	Nimbanene	triterpenoid	MeOH	antibacterial, antifungal	[36]
9	nimbin	triterpenoid	MeOH	spermacidal, bactericidal, antihistamine	[36]
10	Nimbiol	diterpenoid	MeOH	antiacne, antimalarial	[37]
11	nimbolide	triterpenoid	MeOH	anti-angiogenic, anti-proliferative	[38,39]
12	nimocinol	tetranortriterpenoid	hexane	anti-inflammatory, anticancer	[34]
13	nimonol	tetranortriterpenoid	MeOH	COVID19 Main Protease inhibitor	[32]
14	salannin	triterpenoid	MeOH	spermacidal, antigastric lesions	[40]
15	Zafaral	tetracyclic triterpenoid	ethanol	COVID19 Main Protease inhibitor	[32]

Table 2.Terpenoids isolated from the neem fruits

SR/No	Terpenoid	Class	Solvent	Medicinal uses	References
1	17-hydroxyazadiradione	tetranortriterpenoids	MeOH	antidiabetic, antifeedant	[55]
2	Azadinorol	tetranortriterpenoids	ethanol	not reported	[56]
3	Azadirachtol	tetranortriterpenoids	MeOH	potent antifeedant	[57, 58]
4	Azadiradinol	tetranortriterpenoids	ethanol	not reported	[56]
5	azadiradione	tetranortriterpenoids	MeOH	anticancer, antidiabetic	[44]
6	Azadirolic acid	tetranortriterpenoids	ethanol	antidiabetic	[59]
7	azadirone	tetranortriterpenoids	MeOH	antiplasmodial	[60]
8	Camphene	monoterpene	pet-ether	antinociceptive, antibiotic	[49]
9	Caryophyllene	sesquiterpenoid	ethanol	antiplasmodial, antibacterial	[12]
10	deacetylnimbin	tetranortriterpenoids	MeOH	antifeedant	[57, 61]
11	dihydromyrcenol	monoterpene	pet-ether	metabolite, flavour, fragrance	[62]
12	epoxyazadiradione	tetranortriterpenoids	MeOH	anti-inflammatory, anticancer	[61, 63]
13	Gedunin	tetranortriterpenoids	MeOH	antiplasmodial, antitumor, antifungal	[60, 64]

SR/No	Terpenoid	Class	Solvent	Medicinal uses	References
14	Germacrene B	sesquiterpenoid	ethanol	expectorant, relieve congestion	[65]
15	indicalilacols A	triterpenoid	MeOH	anticancer	[66]
16	indicalilacols B	triterpenoid	MeOH	anticancer	[67]
17	indicalilacols C	triterpenoid	MeOH	anticancer	[67]
18	indicalilacols D	triterpenoid	MeOH	anticancer	[66]
19	Mahmoodin	triterpenoid	ethanol	insecticide, pesticide, antibacterial	[57]
20	Meliantrol	tetracyclic triterpenoid	ethanol	potent antifeedant, anticancer property	[66]
21	methyl (2E, 6E)-farnesoate	sesquiterpenoid	ethanol	morphogenesis, osmoregulation	[68]
22	Myrcene	monoterpene	ethanol	anti-inflammatory, antitumor	[47]
23	Naheedin	protolimonoid	ethanol	antibacterial	[57]
24	neemfruitins A	triterpenoid	MeOH	antiplasmodial	[60]
25	neemfruitins B	triterpenoid	MeOH	antiplasmodial	[60]
26	Nimocin	tetranortriterpenoids	ethanol	insecticide, pesticide	[36]
27	Nimocinol	triterpenoid	ethanol	antimicrobial	[69]
28	Nimolicinol	triterpenoid	ethanol	antifeedant	[69]
29	Salimuzzalin	triterpenoid	ethanol	antidiabetic	[56]
30	Valencene	sesquiterpenoid	ethanol	anti-inflammatory, antiallergic, antiacne	[50]
31	α-Himachalene	sesquiterpenoid	ethanol	anti-inflammatory	[65]
32	α-Pinene	monoterpene	ethanol	anticancer	[70]
33	β-farnesene	sesquiterpenoid	ethanol	anti-inflammatory and antimicrobial	[71]
34	β-Pinene	monoterpene	ethanol	anti-inflammatory, bronchodilator	[70]

Table 3. Terpenoids isolated from neem seeds

SR/No	Terpenoid	Class	Solvent	Medicinal uses	References
1	Azadirachtin A	tetranortriterpenoids	ethanol	antibacterial, antifungal,	[61, 72-74]
2	Azadirachtin B	tetranortriterpenoids	ethanol	anticancer, anti-inflammatory	[61, 75]
3	Azadirachtin C	tetranortriterpenoids	ethanol	anticancer, anti-inflammatory	[61, 75]
4	Azadirachtin H	tetranortriterpenoids	ethanol	antimalarial, anti-inflammatory	[61, 73]
5	Azadirachtin I	tetranortriterpenoids	ethanol	COVID19 Main Protease inhibitor	[32, 61]
6	Azadirachtin M	tetranortriterpenoids	ethanol	antimalarial, anti-inflammatory	[61, 73]
7	Azadirachtin N	tetranortriterpenoids	ethanol	antimalarial, anti-inflammatory	[61, 73]
8	Azadiradione	tetracyclictriterpenoid	Methanol	antibacterial, anti-inflammatory,	[44, 61]
9	Azadirahemiacetal	triterpenoid	Methanol	antimicrobial	[76]

SR/No	Terpenoid	Class	Solvent	Medicinal uses	References
10	Deacetylazadirachtonil	triterpenoid	Methanol	insect ecdysis inhibitor	[77]
11	Deacetylgedunin	tetranortriterpenoids	Methanol	antifeedent activity	[78]
12	geducin	triterpenoid	Methanol	anticancer	[52, 72]
13	meliacin	triterpenoid	Methanol	anticancer	[52]
14	Meliantriol	tetranortriterpenoids	Methanol	antifeedent activity	[78]
15	nimbicin	triterpenoid	Methanol	anticancer	[52]
16	Nimbidic acid	tetranortriterpenoids	Methanol	anti-inflammatory, antimicrobial	[61]
17	Nimbidin	tetranortriterpenoids	Methanol	anti-inflammatory, antiarthritis	[79]
18	Nimbidinin	tetranortriterpenoids	Methanol	anti-inflammatory, antimicrobial	[79]
19	Nimbin	triterpenoid	Methanol	insecticide, pesticide, antipyretic	[36, 61, 74]
20	Nimocinol	tetracyclictriterpenoid	Methanol	antimicrobial, antimalarial	[80]
21	saladucin	triterpenoid	Methanol	antifungal	[81]
22	valassin	triterpenoid	Methanol	anticancer	[52]

Table 4. Terpenoids isolated from bark of neem tree

SR/No	Terpenoid	Class	Solvent	Medicinal uses	References
1	Demethyl nimbionol	tricyclic Diterpene	ethanol	fever	[90]
2	Isonimbinolide	tetranortriterpenoid	ethanol	anti-inflammatory	[35]
3	Margosolone	tricyclic Diterpene	ethanol	antifungal, antibacterial	[91]
4	Margosone	tricyclic Diterpene	ethanol	antifungal, antibacterial	[91]
5	Methyl nimbiol	tricyclic Diterpene	ethanol	anti-inflammatory	[87]
6	Methyl nimbionone	tricyclic Diterpene	ethanol	anti-inflammatory	[87]
7	Nimbinone	tricyclic Diterpene	ethanol	anti-inflammatory	[35]
8	Nimbionol	tricyclic Diterpene	ethanol	anti-inflammatory	[35]
9	Nimbionone	tricyclic Diterpene	ethanol	antivirus	[35]
10	Nimbisonol	tricyclic Diterpene	ethanol	cosmeceutical industry	[92]
11	Nimbosodione	tricyclic Diterpene	ethanol	immune booster	[35]
12	Nimbosone	tricyclic Diterpene	ethanol	anti-inflammatory	[35]
13	Nimosone	tricyclic Diterpene	ethanol	anti-inflammatory	[35]
14	Sugiol	tricyclic Diterpene	ethanol	antimicrobial	[87]

Table 5. Terpenoids isolated from neem flowers

SR/No	Terpenoid	Class	Solvent	Medicinal uses	Reference
1	azadirone	tetranortriterpenoids	MeOH	antiplasmodial	[60]
2	Caryophyllene	sesquiterpenoid	ethanol	antiplasmodial, antibacterial	[12]
3	Diepoxyazadinol	triterpenoid	MeOH	larvicidal	[12]
4	Isoazadinorolide	triterpenoid	MeOH	antiplasmodial	[12]
5	nimbolide	triterpenoid	MeOH	anti-angiogenic, anti-proliferative	[89]
6	O-methylazadironolide	triterpenoid	MeOH	larvicidal	[12]
7	Trichilenone acetate	triterpenoid	MeOH	antimutagenic	[36]

Table 6. Terpenoids isolated from the neem roots

SR/No	Terpenoid	Class	Solvent	Medicinal uses	References
1	6,7-dehydroferruginol	Diterpenes	MeOH	anti-inflammatory, antimycobacterial	[78, 93]
2	Azadirilin	Diterpene	MeOH	venom detoxification	[94]
3	Azadricin	Diterpene	MeOH	antiplasmodial	[95]
4	ferruginol	Diterpenes	MeOH	anti-inflammatory, antimycobacterial	[78, 93]
5	morenolide	triterpenoid	MeOH	anti-inflammatory, antimycobacterial	[78, 93]
6	nimbandiol	triterpenoid	MeOH	COVID19 Main Protease inhibitor	[32]
7	nimbidiol	Diterpenes	MeOH	intestinal carbohydrases inhibitor	[96]
8	Nimbilicin	Diterpenes	petrol ether	not reported	[97]
9	Nimbilin	tetranortriterpenoid	DCM	antibacterial	[45]
10	nimbinal	triterpenoid	MeOH	anti-inflammatory, antimycobacterial	[78, 93]
11	Nimbinene	Diterpenes	MeOH	anti-inflammatory, antimycobacterial	[78, 93]
12	Nimbocidin	Diterpene	petrol ether	insecticidal	[97]
13	Nimbocinin	Diterpene	methanol	not reported	[86, 98]
14	Nimolinin	tricyclic diterpene	DCM	not reported	[97]
15	salannin	triterpenoid	MeOH	antimycobacterial, spermicidal	[78, 93]

The bark is used as analgesic and as an alternative and curative of fever [52]. It is also used as antivirus and antimicrobial [84]. The bark extract also showed therapeutic potential for controlling gastric hypersecretion and gastroesophageal and gastroduodenal ulcers [85]. In India, Hot water extract of the bark is taken with water, orally before breakfast for leprosy. The extract is also taken for fever and diabetes, and as a tonic, refrigerant, anti-helmintic and antiperiodic. The extract is also taken for fever and diabetes. In China, Hot water extract of the bark and the leaf are taken orally as a treatment of malaria. In Senegal, Hot water extract of the dried bark is taken orally for gingivitis, and for the healing of wounds [41]. A neem twig is what people used as a make-do toothbrush. It fights germs, maintains the alkaline levels in your saliva, keeps bacteria at bay, treats swollen gums and also gives you whiter teeth. The twig also shreds into threads, almost like bristles that also destroy and prevent plaque [42]. Twigs are used for cough, asthma, piles, phantom tumor, intestinal worms, spermatorrhoea, obstinate urinary disorder, diabetes [52]. The twigs are normally used as a tooth-brush and also mixed with other vegetables and eaten as a salad [86]. Gum is used for scabies, wounds, ulcers and acne [52]. Neem gum is used as a bulking agent and for preparation of special purpose food like diabetic cases and has potential as food additives due to its high protein material. An exudate can be tapped from the trunk by wounding the bark [84]. In Thailand, the dried gum is used as a bitter tonic [41]. Bark contains diterpenoids (margosone and its derivatives) and cyclicditerpenoids (margosolone, nimbinol, nimbionol, nimbionone, nimbisonol, nimbisodione, nimbosone, nimosone, methyl nimbiol, methyl nimbionone, isonimbinolide, dimethyl nimbionol, sugiol) as in Table 4. Sugiol, nimbosone and nimbilicin are diterpenoids extracted from neem bark or root, and are used as antimicrobial [45, 87], anti-inflammatory [35, 45] and antimalarial, respectively [45].

Flowers are very good tonic used for bile suppression, elimination of intestinal worms, phlegm [46]. White and delicate, neem flowers with their off-white buds are edible and therapeutic. The flowers have a sweet scent. They are eaten raw with other vegetable as salad. They can be used fresh, dried or in a powdered form. They are used commonly in the South Asia to cook a number of dishes: flower rice, pachadi, rasam, lentils and more. They are often dry roasted and sprinkled on top of the dish to garnish as well [42]. In Thailand, Extract of the dried flower is taken orally as a bitter tonic [41]. Flowers contain sesquiterpenoid (caryophyllene) and triterpenoids (diepoxyazadinol, O-methylazadironolide, trichilenone acetate) as shown in Table 5. Caryophyllene is reported to be antiplasmodial and antibacterial [12]. Table 6 summarizes triterpenoids isolated from neem roots.

Neem oil contains triterpenoids (azadirachtin, meliantriol, nimbin, nimbidin, nimbinin, nimbolides, fatty acids (oleic, stearic, and palmitic), and salannin). Oil is generally used in the treatment of leprosy and elimination of intestinal worms [52]. The oil also is reported to be spermicidal [88]. Meliantriol, a tetracyclic triterpenoid from the oil, has been reported to possess anticancer property [66]. Nimbin, a triterpenoid has shown to be antipyretic [36, 61, 74]. Nimbidin, a tetranortriterpenoid, has shown anti-inflammatory and antiarthritis [79]. Nimbolide, a triterpenoid, is reported to be anti-angiogenic and anti-proliferative [89]; while salannin has spermicidal and antigastric lesions [40].

In Sri Lanka, Hot water extract of the entire plant is used externally for wounds and ulcers, skin diseases, leprosy and rheumatic disorders; and the extract is taken orally for fevers, malaria, jaundice, and syphilis [41].

8. CONCLUSION

Neem tree has proven to be the Nature's Chemist due to the natural drugs isolated from its different parts. Traditional herbalists do not only use the drugs in the informal sector but also find wide application in pharmaceuticals and agro chemistry. The neem plant is actually a store house for terpenoids, which are the most active compounds and associated with its various medicinal properties.

The drugs from neem have been used for health and medical purposes. They are safe, efficient with minimal side effects. Neem terpenoids have shown to be quite effective in treating diseases as well as for preventive measures. From this, neem products are growing faster and popular over the counter-drugs.

9. RECOMMENDATIONS

From the growing interest of health care companies in the neem products, more efforts is

needed to tap the hidden drug treasures of the neem tree through appropriate extraction processes and better isolation methods.

The already isolated compounds should be subjected more to analysis against various chronic diseases like cancer, hypertension and COVID-19 among others. This will help in to establish the broad spectrum of the isolates.

Better methods should be devised to produce the drugs in large-scale without depleting the neem tree population.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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