

# TERPENOIDS IN AZADIRACHTA INDICA: CLASSES, STRUCTURES AND MEDICINAL USES: A Systematic REVIEW

## 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.

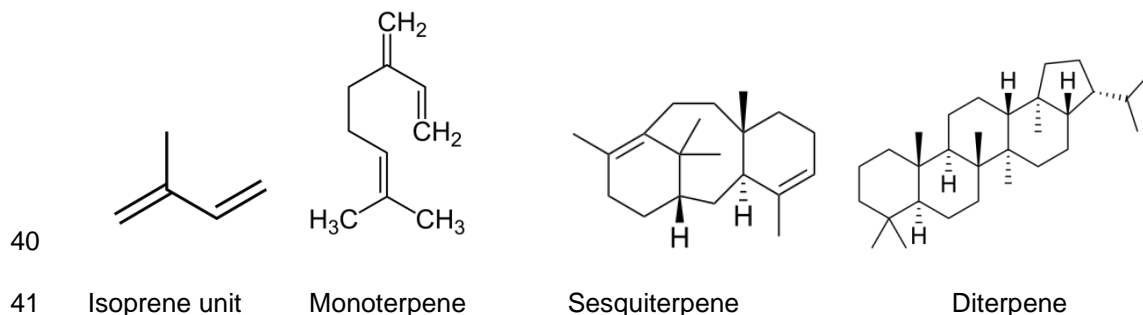
**Keywords:** *Terpenoids, Azadirachta indica, Phytochemicals, antimalarial, triterpenoids*

## 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. *Terpenoids* 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]. **Figure 1** below gives the basic skeleton for different classes of terpenes.



42 **Figure 1:** Basic skeleton for different classes of terpenes.

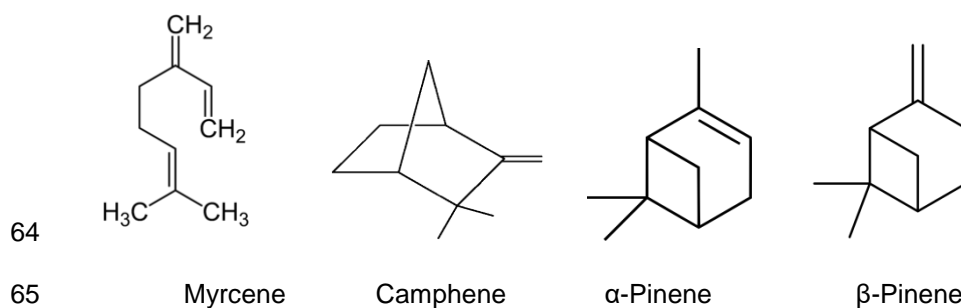
43 **Classes and Structures of Terpenoids**

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

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53 **Monoterpenes**

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



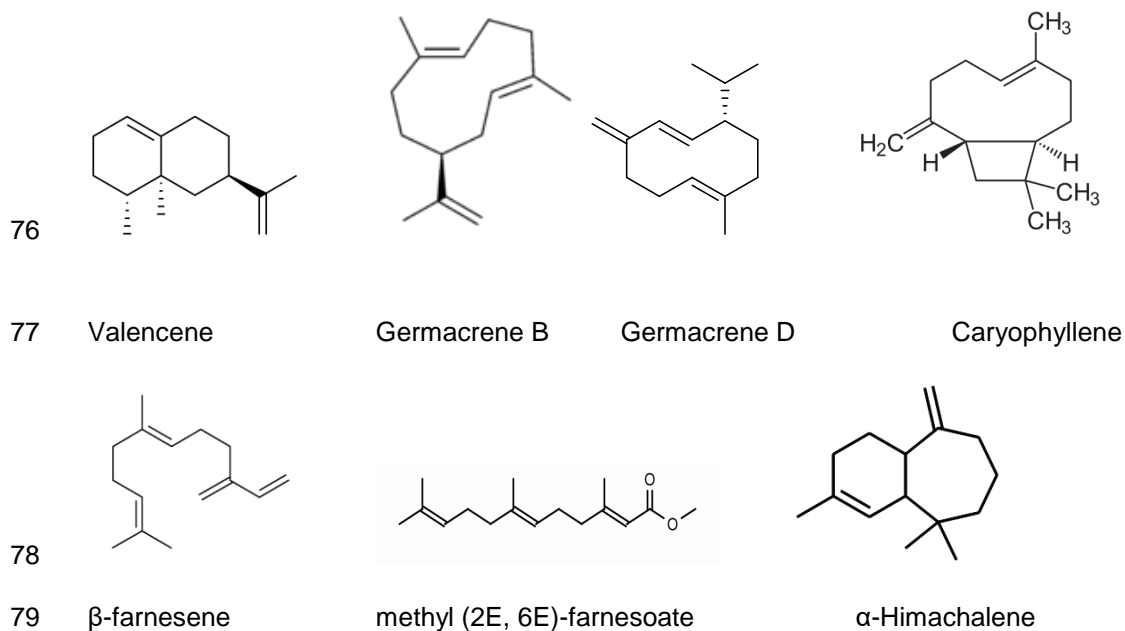
65 **Figure 2:** monoterpenoids isolated from *Azadirachta indica*

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67 **Sesquiterpenes**

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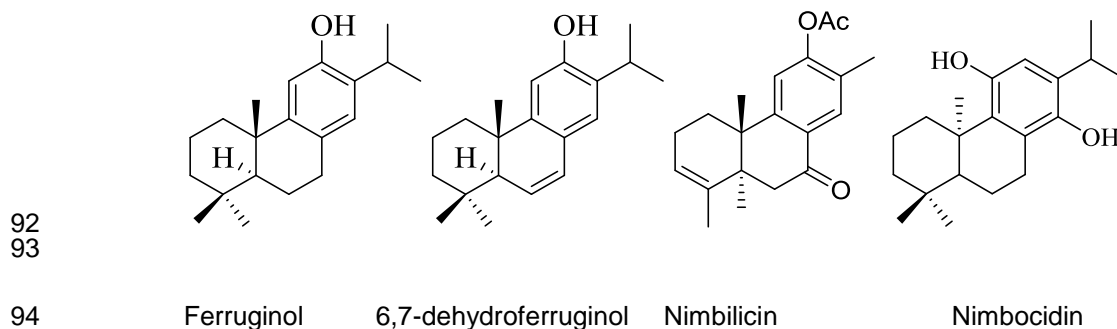
73 "Sesquiterpenes are naturally occurring and found in plants, fungi, and insects and act as a  
 74 defensive mechanism or attract mates with pheromones in insects"[24]. **Figure 3** shows  
 75 some of the sesquiterpenes isolated from neem tree.

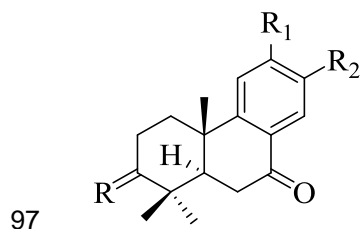
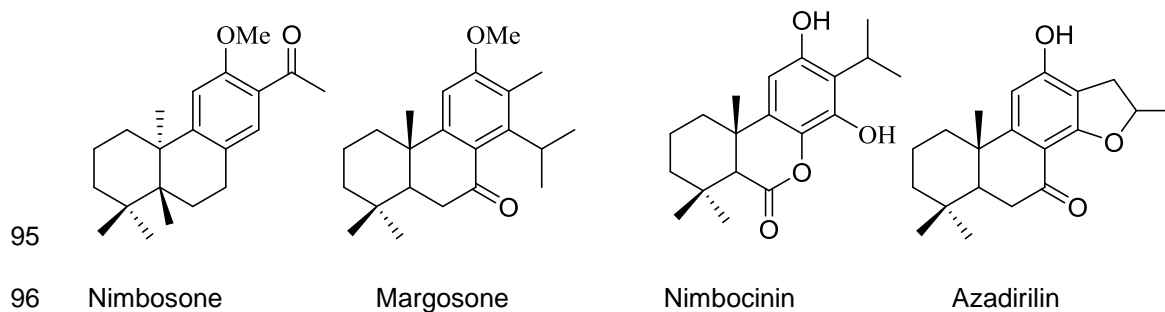


80  
 81 **Figure 3:** Sesquiterpenes isolated from neem tree.  
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84 **Diterpenoids**

85 "Diterpenoids are chemical compounds with 20 carbon atoms. They are made up of four  
 86 isoprene units and are derived from geranylgeraniol, a  $C_{20}$  precursor. They have a  
 87  $C_{20}H_{32}$  basic structure. these characteristics distinguish diterpenoids from simple terpenes,  
 88 which have just 10 carbon atoms"[25]. "Diterpenes have physiologically dynamic  
 89 compounds, for example, plant development chemicals that manage germination, blooming,  
 90 switch regenerative cycles (from abiogenetic to sexual multiplication) of plants, and vitamin A  
 91 activity"[26]. **Figure 4** shows some diterpenoids extracted from neem tree.





98 Azadirone Class Diterpenoids

NAME	R	R1	R2
Azadirin A	H	Me	(CH <sub>2</sub> ) <sub>2</sub> OH
Azadirin B	H	(CH <sub>2</sub> ) <sub>2</sub> OH	Me
Margocilin	β-OH, H	OH	i-Pr
Maegocin	O	H	i-Pr
Margocinin	O	OH	MeCHCH <sub>2</sub> OH
Nimbidiol	H <sub>2</sub>	OH	OH
Nimolinin	H <sub>2</sub>	OH	Ac
Nimbisonol	β-OH, H	OH	Me
Demethylnimbionol	β-OH, H	OH	OH
isomargolonone	O	COOH	Me
Margolone	H <sub>2</sub>	Me	COOH
Margolonone	O	Me	COOH
Methylnimbiol	H <sub>2</sub>	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 <sub>2</sub>	Et	OMe
Nimbiol	H <sub>2</sub>	OH	i-Pr

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**Figure 4:** Examples of diterpenoids from neem plant

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**Triterpenoids**

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"Triterpenoids are composed of 30 carbon atoms, polymerized to form six isoprene units.

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triterpenoids are biosynthesized by the cyclization of its precursor squalene, a hydrocarbon

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composed of two molecules of farnesyl pyrophosphates joined tail to tail"[27]. "Based on

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their chemical structures, triterpenoids can be grouped into linear, monocyclic, dicyclic, up

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through pentacyclic compounds. triterpenes are produced by animals, plants, and fungi.

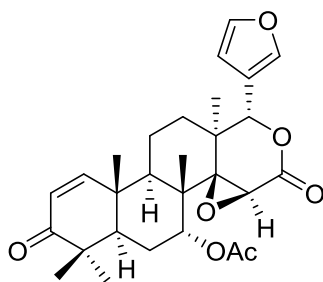
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They play a role as precursors to steroids in animal and plant organisms"[28]. Some

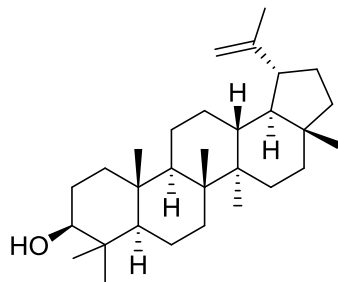
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triterpenoids from neem tree are shown in **Figure 5**.

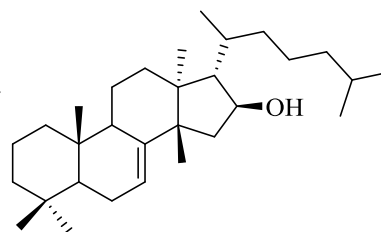
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Gedunin

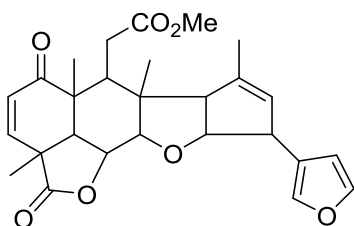


Lupeol

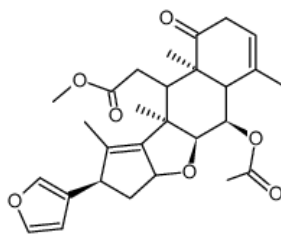


Limocinol

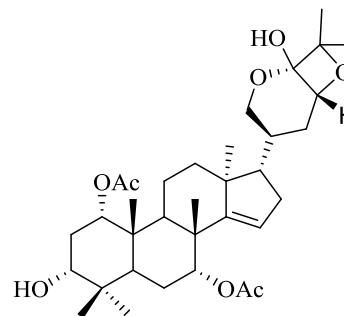
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Nimbolide

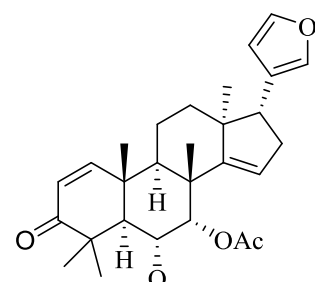


Nimbinene

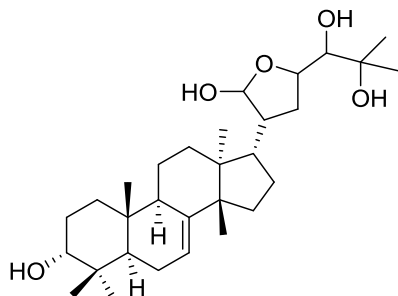


Azadirahemiacyl

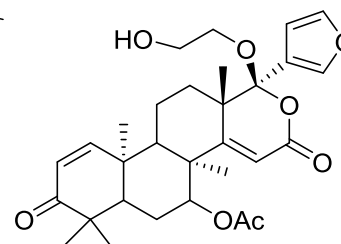
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Nimocinol



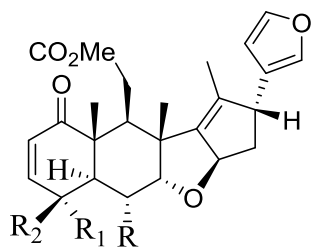
Meliantriol



Mahmoodin

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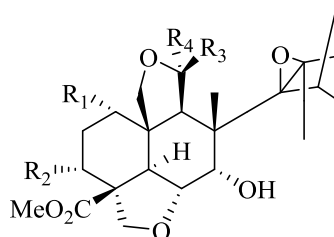


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NAME	R	R1	R2
Nimbin	OAc	CO <sub>2</sub> Me	Me
6-deacetylnimbin	OH	CO <sub>2</sub> Me	Me
Nimbanal	OAc	CHO	Me
Nimbinene	OAc	Me	H
6-deacetylnimbinene	OH	Me	H

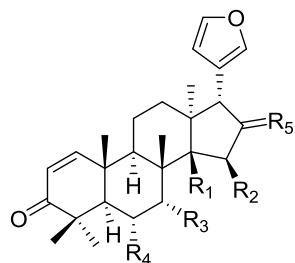
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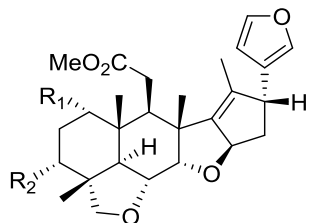
NAME	R1	R2	R3	R4
Azadirachtin A	Tiglate	OAc	OH	CO <sub>2</sub> Me
3-deacetylazadirachtin A	Tiglate	OAc	OH	CO <sub>2</sub> Me
Azadirachtin B	OH	Tiglate	H	CO <sub>2</sub> Me

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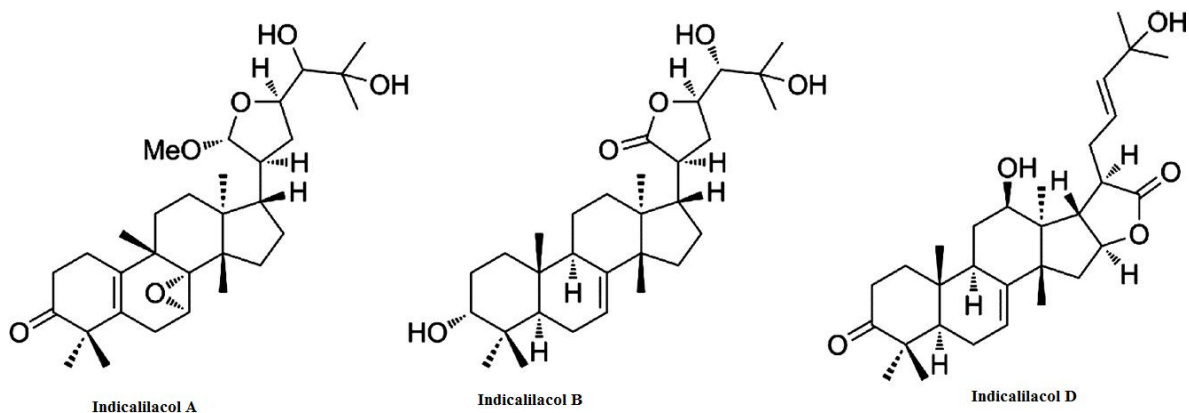
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NAME	R1, R2	R3	R4	R5
Azadiradione	double bond	OAc	H	O
Epoxyazadiradione	epoxy	OAc	H	O
Azadirarone	double bond	OAc	H	H <sub>2</sub>
Nimocinol	double bond	OAc	OH	H <sub>2</sub>

126



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



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Indicalilacol A

Indicalilacol B

Indicalilacol D

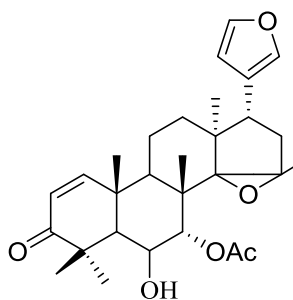
**Figure 5:** triterpenoids from neem plants

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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.



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**Figure 6:** 14,15-Epoxynimonol

### 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 leaf 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.**

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**Table 1: Terpenoids isolated from the neem leaves**

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SR/No	Terpenoid	Class	Solvent	Medicinal uses	Reference
1	14,15-epoxynimonol	tetraterpenoid	MeOH	COVID19 Main Protease inhibitor	[32][33]
2	23,23-dihydrnimocinol	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	pentacyclitriterpene	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	spermicidal, 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	spermicidal, antigastric lesions	[40]
15	Zafaral	tetracyclic triterpenoid	ethanol	COVID19 Main Protease inhibitor	[32]

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148 or improves efficiency. The fresh leaves are chewed and swallowed directly after thorough  
149 washing. "In India, leaf juice is administered by intravenous infusion for chronic skin  
150 diseases,  
151 and is taken orally as an anthelmintic. In Nigeria, hot water extract of the fresh leaf and bark  
152 is taken orally to treat jaundice, malaria and as a cathartic"[41]. "Young neem leaves are  
153 boiled with tamarind fruit to soften its bitterness and eaten as a vegetable. Pickled neem  
154 leaves are also eaten with tomato and fish paste sauce"[42]. In a more recent study, the  
155 leaves extract was involved in the fabrication of nanoparticles of various metal oxides. These  
156 were then evaluated further for antibacterial and photocatalytic activity. The results reported  
157 by patil *et al.*, in 2022 showed that metal oxides nanoparticles have better antibacterial  
158 activity and photocatalytic potential over aqueous leaves extract[43]. The leaves mostly  
159 contain triterpenoids as shown in **Table 1** which include nimbin and its derivatives, gedunin  
160 and its derivatives, salannin and its derivatives, zafaral, nimbolides, nimocinol, nimonol,  
161 lupeo, isomeldenin. gedunin possesses potential antitumor, antimalarial, and anti-diabetic  
162 activities[34]. azadiradione confers anti-inflammatory and anti-diabetic effects[44]. 14,15-  
163 epoxyimonol, a tetraterpenoid obtained from the fresh green whole leaves, has been  
164 reported to inhibit covid-19 main protease [32, 33]. Nimbiol is a diterpenoid extracted from  
165 leaves, and is used as antiacne [37, 45].  
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167 Neem fruits have been generally used for treatment of piles, intestinal worms, urinary  
168 disorder, epistaxis, phlegm, eye problem, diabetes, wounds and leprosy[46]. Neem fruits are  
169 eaten fresh or cooked or prepared as a dessert or lemonade-type drink[42]. In India, the  
170 fresh fruit is used externally for leprosy. In Thailand, hot water extract of the dried fruit is  
171 taken orally as an anthelmintic, laxative, bitter tonic and for fever; while the dried unripe fruit  
172 is taken orally as a bitter tonic and for fever[41]. Fruits contain monoterpenes (myrcene,  $\alpha$ -  
173 and  $\beta$ -pinene, camphene), sesquiterpenes (valencene,  $\alpha$ -himachalene,  $\beta$ -farnesene, methyl  
174 (2E, 6E)-farnesoate, germacrene B and D, caryophyllene) and triterpenoids (indicalilacols A-  
175 D, neemfruitins A-B, meliantrol, azadirone and its derivatives, gedunin and its derivatives) as  
176 indicated in **Table 2**. Myrcene and  $\alpha$ -Pinene, monoterpenes from neem fruits both were  
177 reported to possess antitumor properties [47, 48].  $\alpha$ -Pinene can also counteract THC-  
178 induced anxiety and short-term memory loss[48]. Camphene is proven for its ability to fight  
179 bacterial and fungal infections while reducing inflammation and stress[49]. Valencene is a  
180 sesquiterpene which offers anti-inflammatory, skin protectant and anti-allergic benefits[50].  
181 Inhaling germacrene B, a sesquiterpene, can help clear the sinuses and relieve congestion.  
182 It can also act as an expectorant, helping clear out mucus. These properties make this  
183 terpene helpful for relief from both cold and allergy symptoms[46]. Sharma *et al.* reported in  
184 2022 that Germacrene D showed anticancer properties[51].  
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186 Seeds have generally been used to treat urinary tract disorders, bloody nose, phlegm, eye  
187 disorders, leprosy, cancer, malaria and intestinal worms[52]. The seeds are the primary  
188 source of insecticides. They can be used in the form of simple aqueous extracts or as a  
189 basic raw material for formulated pesticides. The seeds are crushed and steeped in water,  
190 alcohol, or other solvents. For some purposes, the resulting extracts can be used without  
191 further refinement. Ground neem seeds or neem kernel powder (before or after oil  
192 extraction) is used as a soil amendment, and it is effective for control of nematodes. It is also  
193 used for control of stalk borers, and to prepare water extracts, which are then sprayed onto  
194 plants[42]. Some people apply neem directly to the skin to treat head lice[53], skin diseases,  
195 wounds, and skin ulcers; as a mosquito repellent; and as a skin softener. Seeds contain  
196 triterpenoids (azadirahemiacetal, deacetylazadirachtin, geducin, meliacin, nimbin, nimbicin,  
197 saladucin, valassene), tetracyclitriterpenoids (azadiradione, nimocinol) and  
198 tetranortriterpenoids (azadirachtins A-N, nimbidin and its derivatives, gedunin and its  
199 derivatives, meliantiol) as indicated in **Table 3**. Some of the first isolated terpenes include  
200 nimbin and nimbolide[54]. Azadirachtin, a tetranortriterpenoid and its derivatives, derived

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**Table 2: Terpenoids isolated from the neem fruits.**

SR/No	Terpenoid	Class	Solvent	Medicinal uses	Reference
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]
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	Melianrol	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	Naheedidin	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	$\alpha$ -Himachalene	sesquiterpenoid	ethanol	anti-inflammatory	[65]
32	$\alpha$ -Pinene	monoterpene	ethanol	anticancer	[70]
33	$\beta$ -farnesene	sesquiterpenoid	ethanol	anti-inflammatory and antimicrobial	[71]
34	$\beta$ -Pinene	monoterpene	ethanol	anti-inflammatory, bronchodilator	[70]

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**Table 3: Terpenoids isolated from neem seeds**

SR/No	Terpenoid	Class	Solvent	Medicinal uses	Reference
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	tetracyclitriterpenoid	Methanol	antibacterial, anti-inflammatory,	[44, 61]
9	Azadirahemiacetal	triterpenoid	Methanol	antimicrobial	[76]
10	Deacetylazadirachtin	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	tetracyclitriterpenoid	Methanol	antimicrobial, antimalarial	[80]
21	saladucin	triterpenoid	Methanol	antifungal	[81]
22	valassin	triterpenoid	Methanol	anticancer	[52]

208 from the neem seed, is one of the prominent biopesticides commercialized and remains the  
209 most successful botanical pesticide in agricultural use worldwide. Azadirachtin is a powerful  
210 antifeedant and insect growth disruptor with exceptional low residual power and low toxicity  
211 to biocontrol agents, predators, and parasitoids[82]. Nimbolide, a triterpenoid, has shown  
212 anti-angiogenic, anti-proliferative. It was also reported by Chitta *et al.* in 2014 to possess  
213 anticancer and anticancer preventive effects[83]. Geducin, a triterpenoid from seeds, has  
214 been observed to have anticancer properties [52, 72].  
215

216 The bark is used as analgesic and as an alternative and curative of fever[52]. It is also used  
217 as antiviral and antimicrobial[84]. The bark extract also showed therapeutic potential for  
218 controlling gastric hypersecretion and gastroesophageal and gastroduodenal ulcers[85]. In  
219 India, Hot water extract of the bark is taken with water, orally before breakfast, for leprosy.  
220 The extract is also taken for fever and diabetes, and as a tonic, refrigerant, **anti-helmintic**  
221 and antiperiodic. The extract is also taken for fever and diabetes. In China, Hot water extract  
222 of the bark and the leaf are taken orally as a treatment of malaria. In Senegal, Hot water  
223 extract of the dried bark is taken orally for gingivitis, and for the healing of wounds[41]. A  
224 neem twig is what people used as a make-do toothbrush. It fights germs, maintains the  
225 alkaline levels in your saliva, keeps bacteria at bay, treats swollen gums and also gives you  
226 whiter teeth. The twig also shreds into threads, almost like bristles that also destroy and  
227 prevent plaque[42]. Twigs are used for cough, asthma, piles, phantom tumor, intestinal  
228 worms, spermatorrhoea, obstinate urinary disorder, diabetes[52]. The twigs are normally  
229 used as a tooth-brush and also mixed with other vegetables and eaten as a salad[86]. Gum  
230 is used for scabies, wounds, ulcers and acne[52]. Neem gum is used as a bulking agent and  
231 for preparation of special purpose food like **diabetic cases** and has potential as food  
232 additives due to its high protein material. An exudate can be tapped from the trunk by  
233 wounding the bark[84]. In Thailand, the dried gum is used as a bitter tonic[41]. Bark contains  
234 diterpenoids (margosone and its derivatives) and cyclicditerpenoids (margosolone, nimbinol,  
235 nimbionol, nimbionone, nimbisonol, nimbisodione, nimbose, nimosone, methyl nimbiol,  
236 methyl nimbionone, isonimbinolide, dimethyl nimbionol, sugiol) as in **Table 4**. Sugiol,  
237 nimbose and nimbilicin are diterpenoids extracted from neem bark or root, and are used  
238 as antimicrobial [45, 87], **anti-inflammatory** [35, 45] and antimalarial, respectively[45].  
239

240 Flowers are very good tonic used for bile suppression, elimination of intestinal worms,  
241 phlegm [46]. White and delicate, neem flowers with their off-white buds are edible and  
242 therapeutic. The flowers have a sweet scent. They are eaten raw with other vegetable as  
243 salad. They can be used fresh, dried or in a powdered form. **They are** used commonly in the  
244 South Asia to cook a number of dishes: flower rice, pachadi, rasam, lentils and more. **They**  
245 **are** often dry roasted and sprinkled on top of the dish to garnish as well[42]. In Thailand,  
246 Extract of the dried flower is taken orally as a bitter tonic[41]. Flowers contain  
247 sesquiterpenoid (caryophyllene) and triterpenoids (diepoxyazadinol, O-methylazadironolide,  
248 trichilenone acetate) as shown in **Table 5**. Caryophyllene is reported to be antiplasmodial  
249 and antibacterial[12]. **Table 6** summarizes triterpenoids isolated from neem roots.  
250

251 Neem oil contains triterpenoids (azadirachtin, meliantriol, nimbin, nimbidin, nimbinin,  
252 nimbolides, fatty acids (oleic, stearic, and palmitic), and salannin). Oil is generally used in  
253 the treatment of leprosy and elimination of intestinal worms[52]. The oil also is reported to be  
254 spermicidal[88]. Meliantriol, a tetracyclic triterpenoid from the oil, has been reported to  
255 possess anticancer property[66]. Nimbin, a triterpenoid has shown to be antipyretic [36, 61,  
256 74]. Nimbidin, a tetranortriterpenoid, has shown **anti-inflammatory** and antiarthritis[79].  
257 Nimbolide, a triterpenoid, is reported to be anti-angiogenic and anti-proliferative[89]; while  
258 salannin has spermicidal and antigastric lesions[40].

259

**Table 4: Terpenoids isolated from bark of neem tree.**

SR/No	Terpenoid	Class	Solvent	Medicinal uses	Reference
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]

260

261

262

**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	Diepoxызadinol	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]

263  
264  
265  
266

**Table 6: Terpenoids isolated from the neem roots.**

SR/No	Terpenoid	Class	Solvent	Medicinal uses	Reference
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	Nimbinin	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]

267 In Sri Lanka, Hot water extract of the entire plant is used externally for wounds and ulcers,  
268 skin diseases, leprosy and rheumatic disorders; and the extract is taken orally for fevers,  
269 malaria, jaundice, and syphilis[41].  
270

## 271 **CONCLUSION**

272 Neem tree has proven to be the Nature's Chemist due to the natural drugs isolated from its  
273 different parts. Traditional herbalists do not only use the drugs in the informal sector but also  
274 find wide application in pharmaceuticals and agro chemistry. The neem plant is actually a  
275 store house for terpenoids, which are the most active compounds and associated with its  
276 various medicinal properties.  
277

278 The drugs from neem have been used for health and medical purposes. They are safe,  
279 efficient with minimal side effects. Neem terpenoids have shown to be quite effective in  
280 treating diseases as well as for preventive measures. From this, neem products are growing  
281 faster and popular over the counter-drugs.  
282

## 283 **RECOMMENDATIONS**

284 From the growing interest of health care companies in the neem products, more efforts is  
285 needed to tap the hidden drug treasures of the neem tree through appropriate extraction  
286 processes and better isolation methods.

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

290 Better methods should be devised to produce the drugs in large-scale without depleting the  
291 neem tree population.  
292

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## 297 **COMPETING INTERESTS**

298 Authors have declared that no competing interests exist.  
299

## 300 **AUTHORS' CONTRIBUTIONS**

301 Awadh designed the study, wrote the protocol, and wrote the first draft of the manuscript.  
302 Swaleh and Kiti managed the literature searches and writing formats. Kahindo proof-read  
303 and prepared the final draft of the manuscript. All authors read and approved the final  
304 manuscript.  
305

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