Review

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Antimalarial plants with potential male-factor antifertility properties

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Abstract:
Malaria, caused mainly by *Plasmodium falciparum* among other *Plasmodium* species, is one of the main causes of death from parasitic diseases. Malaria is still a health problem mainly because of the cost of effective antimalarial drugs and the growing parasite resistance to conventional antimalarial drugs, making a great proportion of the people in malaria endemic countries dependent on plants for its treatment. Corollary, a large number of the rural populations consume antimalarial herbal preparations in large or excessive quantities despite the fact that it has been reported that some of them could cause male-factor infertility, a growing global health concern. Few studies have compiled information on the scientifically validated male-factor antifertility effects of these antimalarial plant remedies. The aim of this review therefore is to compile information on commonly used antimalarial plant remedies that have been experimentally validated as having male-factor antifertility effects. Thus, antimalarial plant remedies with experimentally confirmed male-factor antifertility potentials and compounds isolated from them are identified and discussed. The male-factor antifertility effects of these plants include reduction of sperm quality, regulation of reproductive hormone levels and induction of lipid peroxidation. Indiscriminate use of such antimalarial plants is discouraged when male contraception is not desired.

Keywords: antimalarial, malaria, male-factor infertility, medicinal plants
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Introduction

Malaria is caused by the *Plasmodium* species. It is one of the main causes of global morbidity and mortality from parasitic diseases [1]. The following five *Plasmodium* species have been identified to cause malaria in humans: *Plasmodium falciparum*, *P. vivax*, *P. malariae*, *P. ovale* and *P. knowlesi*. Out of these, *P. falciparum* is the most dangerous; it is transmitted to humans by the biting of female *Anopheles* mosquito to feed on blood [2]. In 2015, about 212 million clinical malaria cases were reported, leading to about 429,000 deaths [3]. Although efforts to eradicate malaria have been relatively successful, the rate of decline has reduced since 2015. For instance, in 2016, a total of 216 million cases of malaria was reported, an increase of 5 million cases over 2015 [3]. Malaria continues to be a public health problem mainly because of the resistance of the malaria parasite to antimalarial drugs, the resistance of mosquito to insecticides and the high cost of effective antimalarials drugs. Corollary, a large percentage of the population in malaria prone countries depends on medicinal plants for the treatment of the disease. Thus, majority of the population use antimalarial plants indiscriminately, giving no thought about their toxic implications. However, some of these antimalarial medicinal plants have deleterious side effects that may be as a result of toxic constituents, the quantity consumed, the part consumed, the species, the soil and climate, the time of exposure and individual susceptibility. Data on toxicities of most African antimalarial medicinal plants are not readily available, especially their male-factor antifertility implications because herbal medicines are not subjected to the same regulatory scrutiny as conventional drugs. Also, most users of antimalarial herbal remedies believe that "anything herbal medicine is safe" even though several phytoremedies have been found to be potentially toxic. While poisonous plants are known, based on folkloric knowledge, it is those plants with subacute or chronic toxic implications that constitute major sources of danger for people who are heavily dependent on them [4]. A large number of the rural population consumes antimalarial herbal

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medicines in large or excessive quantities, making them vulnerable to any male-factor antifertility effects of such plant remedies.

Infertility is described as the inability of a woman to conceive after a year of rightly timed unprotected vaginal sex [5]. Globally, male factor is responsible for more than 50% of infertility, although the prevailing rate is different from country to country. For example, it is 15.7% in Denmark, about 6% in the United Kingdom and 10% in the United States of America [6]. The infertility rate in Nigeria and some other countries in Africa (where we have countries mostly affected by malaria) was estimated to be as high as 30% [7]. Could heavy dependence on antimalarial plant remedies be a contributing factor?

However, few studies have consolidated information on the male antifertility effects of such antimalarial plant remedies. Therefore, the aim of this review is to compile information on commonly used antimalarial plant remedies that have been experimentally validated as having potential male-factor antifertility effects. The corresponding active phytochemicals isolated from the parts of the plants eliciting the antifertility effects are also compiled to uncover gaps and future research opportunities about the chemistry and pharmacy of these plants. This information can assist the general populace in making informed decision on the use of such plants.

Materials and methods

A search for relevant data was done using scientific databases (Google Scholar, Mendeley, ScienceDirect, PubMed and other web sources, such as The Plant List and PROTA), books and other literatures using the key terms: antimalarial plant, medicinal plants, male fertility, testis, sperm and testosterone.

Findings and discussion

This review compiled the data of 28 plants having potential male-factor antifertility activity along with their major phytoconstituents. Table 1 lists the antimalarial medicinal plants with male-factor antifertility activities, the parts eliciting male antifertility effect, type of extract, the bioactive effects and the experimental model used. The isolated phytochemicals from the part(s) exhibiting male-factor antifertility effects are listed in Table 2. The 28 antimalarial plants exhibiting male-factor antifertility activity are now discussed.

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Table 1: Antimalarial medicinal plants with male-factor antifertility activities.

S. no.	Plant species	Parts used	Type of extract	Bioactive effect	Experimental model	References
1	*Abrus precatorius* Linn. (Leguminosae-Caesalpinioideae)	Leaf	Aqueous	Testicular degeneration characterised by decreased numbers of lining cells of the epithelium as well as reduction in sperm cells with presence of scattered Sertoli cells.	Wistar rat	[8]
2	*Allium sativum* Linn. (Liliaceae)	Bulb	Crushed galic (mixed with standard feed)	Induction of apoptosis in testicular germ cells, antispermatogenic and antiandrogenic activities,	Wistar rat	[9]
		Bulb	Aqueous extract	Reduced sperm count, reduced sperm motility, reduction in morphologically normal spermatozoa	Wistar rat	[10]
		Bulb	methanol	Antifertility effect (no pregnancy after mating with fertile female mice)	Albinomice	[11]
		Bulb	Crude galic as part of daily food (20%)	Decreased testosterone, histological and ultra-structural changes in testicular cells, testicular apoptosis and disruption of spermatogenesis	Wistar rat	[12]
		Bulb	Powdered bulb	Spermatogenic arrest and histological alteration of somatic cells	Wistar rat	[13]
		Bulb	Aqueous extract	Spermicidal activity and spermatozoa immobilizing effect	*In vitro*	[14]
3	*Alstonia boonei* De Wild. (Apocynaceae)	Stem bark	Methanol	Reduction of sperm viability sperm count and sperm motility	Wistar rat	[15]
		Stem	Ethanol	Decreased sperm count, motility, viability. Adversely changed morphology of the sperm.	Wistar rat	[16]
4	*Annona senegalensis* Pers. (Annonaceae)	Leaf	aqueous	Decrease in testis-body weight ratio, increased testicular concentration of malondialdehyde and marked degeneration of seminiferous tubules.	Wistar rat	[17]
5	*Aspilia Africana* (P. Beauv.) C.D. Adams (Asteraceae)	Leaf	methanol	Decreased weight of testis, epididymis, seminal vesicle and prostate gland	Wistar rat	[18]
6	*Azadirachta indica* A. Juss. (Meliaceae)	Leaf	Powdered leaf	Antiandrogenic and antispermatogenic	Wistar rat	[19]
		Stem bark	ethanol	Arrest of spermatogenesis, reduction in sperm motility and density, reduction in the diameter of seminiferous tubule, Leydig cell nucleus and epithelial heights of epididymis. Depletion of androgen level	Wistar rat	[20]

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		Stem bark	Methanol	Decreased weights of testis, seminal vesicle and epididymis. Alters sperm count, morphology and viability. Reduction in serum testosterone and luteinising hormone. Inability to impregnate female rats	Wistar rat	[21]
		Seed	Neem oil	Infertility in male rats by arrest of spermatogenesis	Wistar rat	[22]
7	*Bridelia ferruginea* Benth. (Euphorbiaceae)	Stem bark	Aqueous	Decreased sperm count and motility, as well as increase in morphological aberration	Wistar rat	[23]
8	*Cajanus cajan* (Linn.) Millsp. (Leguminosae-Caesalpinioideae)	Leaf	Ethanol	Decreased weight of testes and epididymis	Wistar rat	[24]
9	*Carica papaya* Linn. (Caricaceae)	Root	Methanol	Decreased sperm counts, increased percentage of defective sperm cells and severe necrosis of the germinal epithelium	Wistar rat	[25]
		Leaf	Aqueous	Reduction in sperm count, motility and viability, serum testosterone concentration as well as marked degeneration of the seminiferous tubule epithelium and disruption of interstitial cells of the testis	Wistar rat	[26]
		Leaf	Methanol	dose dependent reduction in sperm count, increased percentage of defective sperm cells and severe necrosis of the germinal epithelium of the testis	Wistar rat	[27]
		Leaf	Aqueous	Reduction in sperm count, sperm motility, sperm viability and testosterone with transverse sections of testes exhibiting mild to moderate atrophy	Wistar rat	[28]
10	*Chromolaena odorata* Linn. King & Robinson (Compositae)	Leaf	Aqueous	Reduction in testicular body weight ratio, and testosterone concentrations. Reduction in the number of spermatozoa. Disruption in the arrangement of seminiferous tubules.	Wistar rat	[29]
		Leaf	Crude alkaloid extract	Decreased testes-body weight ratio, significant decrease in serum luteinizing hormone and follicle stimulating hormone levels, testicular and serum testosterone levels, sperm count, motility, and density, morphological changes in the sperm cells	Wistar rat	[30]
11	*Crossopteryx febrifuga* (Afzel. ex G. Don) Benth. (Rubiaceae)	Stem bark	Methanol	Reduction of spermatogenesis	Albino mice	[31]
12	*Cryptolepis sanguinolenta* (Lindl.) Schltr. (Asclepiadaceae)	Leaf	Ethanol	Testosterone suppression, rise in luteinizing hormone and decrease in sperm count.	Wistar rat	[32]

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		Root	Aqueous	Reduction in the mean weight of the left caudal epididymis and the testes. Significant reduction in sperm numbers.	Albino mice	[33]
13	*Curcuma longa* Linn. (Zingiberaceae)	Rhizome	Aqueous	Reduction in sperm motility and density	Wistar rat	[34]
		Rhizome	Aqueous	Adverse effects on sperm motility, viability, morphology and number, serum level of testosterone and on fertility and litter size	Albino mice	[35]
14	*Cylicodiscus gabunensis* (Taub.) Harms (Leguminosae-Mimosoideae)	Stem bark	Ethanol	Reduced levels of testosterone, prolactin, luteinising and follicle stimulating hormone. Significant difference in percentage sperm motility and viability.	Wistar rat	[36]
15	*Ficus thonningii* Blume (Moraceae)	Stem bark	Ethanol	Caused degeneration in the testes	Wistar rat	[37]
16	*Khaya senegalensis* (Desr.) A. Juss. (Meliaceae)	Stem bark	Ethanol	Decrease in testicular weight, total sperm count and sperm motility. Increase in non-motile spermatozoa and sperm abnormalities. Depletion of spermatogenic cells and loss of architecture of the semineferous tubules.	Wistar rat	[38]
17	*Lippia multiflora* Moldenke (Verbanaceae)	Leaf	Aqueous	Reduction in sperm motility, sperm count. Increased morphological abnormalities of the spermatozoa. Degeneration and necrosis of the germinal epithelia cell of the seminiferous tubules, spermiostasis and complete epididymal aspermia	Wistar rat	[39]
18	*Morinda lucida* Benth. (Rubiaceae)	Leaf	Methanol	Reduced sperm motility and viability, epididymal sperm counts. Increased sperm morphological abnormalities, damage to the seminiferous tubules. Reduced fertility by reducing litter size.	Wistar rat	[40]
19	*Nauclea latifolia* Sm. (Rubiaceae)	Stem bark	Ethanol	Reduced sperm motility, sperm viability and sex hormone	Rat	[36]
20	*Ocimum gratissimum* Linn. (Labiatae)	Leaf	Aqueous	Decreased sperm count and motility. Increased abnormal sperm cells, sperm debris and primordial cells	Albino mice	[41, 42]
21	*Phyllanthus amarus* Schum. & Thonn. (Euphorbiaceae)	Leaf	Ethanol	Inhibition of fertility potential with a decline in epididymal sperm profiles	Albino mice	[43]

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		Leaf	Aqueous	Testicular degeneration, reduction in the mean seminiferous tubular diameter	Wistar rat	[44]
22	*Picralima nitida* (Staph) Th. & H. Dur. (Apocynaceae)	Seed	Ethanol	Degeneration of nuclear content of spermatogenic lining cell, Leydig cells, myoid cell and sertolic cell and interstitial and tubular constriction.	Wistar rat	[45]
		Seed	Ethanol	Reduced sperm count and progressive degenerative changes in the seminiferous tubules.	Wistar rat	[46]
23	*Quassia amara* Linn. (Simaroubaceae)	Stem wood	Methanol	Inhibited both the basal and luteinizing hormone-stimulated testosterone secretion of Leydig cells	Wistar rat	[47]
		Stem wood	Methanol	Reduction in the weight of the testis, epididymis and seminal vesicle. Reduction in epididymal sperm counts, serum levels of testosterone, luteinizing hormone and follicle stimulating hormone.	Wistar rat	[48]
		Bark	Chloroform	Reduction in the weight of testis and epididymis. A marked decrease in the sperm count, motility and viability. A number of abnormalities like double heads, double tails, detached heads and fragile tails were observed. Epididymal alpha-glucosidase activity was drastically reduced	Wistar rat	[49]
		Bark	Methanol	Abnormal sperm morphology, in the coiling of tail around an apparently malformed head	Albino mice	[50]
24	*Solenostemon monostachyus* (P. Beauv.) Briq. (Labiatae)	Leaf	Hydro-ethanol	Distortion of the shape of the seminiferous tubules, increased population of leydig cell and deranged spermatogenic cells.	Albino mice	[51]
25	*Sphenocentrum jollyanum* Pierre. (Menispermaceae)	Root	Methanol	Reduction in sperm motility, viability and counts.	Wistar rat	[52]
26	*Tithonia diversifolia* (Hemsl.) A. Gray (Compositae)	Leaf	Aqueous	Decrease sperm count and sperm motility. sperm abnormalities; headless tail, tailless head and bent tail. Degeneration and necrosis of the germinal epithelia cell of the seminiferous tubules. Spermiostasis and complete epididymal aspermia.	Wistar rat	[53]
		Leaf	Aqueous	Decrease width, length of the testes. Reduced weight of the right epididymidis. Decreased plasma testosterone, sperm count, motility and viability.	Wistar rat	[54]
27	*Vernonia amygdalina* Del. (Compositae)	Leaf	Ethanol	Dose-dependent poor testes histo-morphometric profiles	Wistar rat	[55]

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	Leaf	Aqueous	Decreased spermatozoa mobility and percentage livability. Hypoplasia of the seminiferous tubule.	Wistar rat	[56]

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Table 2: Isolated active phytochemicals from antimalarial plants having male-factor antifertility activities.

S. no.	Plant species	Bioactive compounds	References
1	*Abrus precatorius* Linn. (Leguminosae-Caesalpinioideae)	Leaf: Glycyrrhizin, abrusoside A, abrusoside B, abrusoside C, abrusoside D, abrusoside E, (20S,22S)-3β,22-dihydroxycucurbita-5(10),24-diene-26,29-dioic acid δ-lactone, 3-O-[60-methyl-β-D-glucuronopyranosyl]-3β,22β-dihydroxyolean-12-en-29-oic acid methyl ester, 3-O-β-D-glucuronopyranosylsophoradiol methyl ester, sophoradiol, abrusogenin, abrine, trigonelline, abruslactone A, hemiphloin, hypaphorine, precatorine, choline, trigonelline and pinitol.	[57–60]
2	*Allium sativum* Linn. (Liliaceae)	Bulb: Allicin, allyl methyl thiosulphonate, 1-propenyl allyl thiosulphonate, L-glutamyl-S- alkyl-L-cysteine, lignin and quercetin	[61]
3	*Alstonia boonei* De Wild. (Apocynaceae)	Stem Bark: echitamine, echitamidine voacangine, akuammidine, Nα-formylechitami dine, Nα-formyl-12-methoxyechitamidine, boonein and loganin, lupeol, ursolic acid, and β-amyrin.	[62]
4	*Annona senegalensis* Pers. (Annonaceae)	Leaf: Limonene, α-pinene, myrcene, sabinene, (-)-Roemerine, β–pinene, linalool, citronellal, citronellol, linalyl acetate, geranial, thymol, carvacrol, β–caryophyllene, γ-cadinene, α-humu lene, germacrene D, p-cymene, 1,8 cineole, α-copaene, E-β-caryophyllene, β-selinene, α-selinene, germacrene A, β-eudesmol, δ-cadinene, γ-eudesmol, elemol and caryophyllene oxide	[63]
5	*Aspilia Africana* (P. Beauv.) C.D. Adams (Asteraceae)	Leaf: 3β-O-[α-rhamnopyranosyl-(1→6)-β-gluco pyransyl-(1→3)-ursan-12-ene, 3β- hydroxyolean -12-ene and 3β-acetoxyolean-12-ene, kaurenoic acid and grandiflorenic acids. Leaf oil: α-cubebene, α-copaene, β-caryophyllene, germacrene B, patchoulene, β-elemene, cedrene, isocaryophyllene, α-guaiene, germacrene D, β-santalol, α-pinene, α-thujene, car-3-ene, limonene, α-myrcene, β-ocimene and α-phellandrene.	[64, 65]

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6	*Azadirachta indica* A. Juss. (Meliaceae)	Leaf and seed: Isomeldenin, nimbin, nimbinene, 6-desacetyllnimbinene, nimbandiol, nimbobide, nimocinol, quercetin, beta-sitosterol, 24,25,26,27-tetranorapotirucalla-(apoeupha)-6a-methoxy-7a-acetoxy-1,14-dien-3,16- dione-21-al, meliacinanhydride, 24,25,26,27-tetranorapo- tirucalla-(apoeupha)-6a-hydroxy,11a-methoxy-7a,12a-diacet-oxy,1,14,20(22)-trien-3-one. Stem: gedunin and azadirachtin, azadirone, azadiradione	[66–70]
7	*Bridelia ferruginea* Benth. (Euphorbiaceae)	Stem bark: gallocatechin-(4 -O-7) epigallocatechin, quercetin, 3,5-dicaffeoylquinic acid, 1,3,4,5-tetracaffeoylquinic acid, quercetin 3-methyl ether, quercetin 3,7,3 ,4 -tetramethyl ether, myricetin 3,3 ,4 ,5 -tetramethyl ether, myricetin, quercetin3-O-glucoside, 3-O-methylquercetin, 3,7,3 ,4 -tetra-O-methylquercetin (rutisin) and 3 ,4 ,5 -tri-O-methylmyricetin (ferrugin).	[71, 72]
8	*Cajanus cajan* (Linn.) Millsp. (Leguminosae-Caesalpinioideae)	Leaf: Logistylin A, logistylin C, betulinic acid, 1-dodecene, 2-tridecene, γ-elemene, bisabolene, 2,4-di-tert-butylphenol, 1,11-hexadecadiyne, nerolidol, 1-hexadecene, 8-methyl-6-nonenoic acid, 2,3-epoxydecahydronaphthalene, caryophyllene oxide, 2-isopropyl-5-methylhexyl acetate, 3,7,11-trimethyl-1-dodecanol, 1-octadecyne, 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionic acid, 2-undecenoic acid, N-(2-oxo-5-hexenyl)acetamide, M-diphenylmethane carboxylic acid methyl ester, 2′,6′-dihydroxy-4′-methoxy chalcone, cyclotrisiloxane, trans-3-methoxy-4-propoxy-β-methyl-β-nitrostyrene, 3H-cycloocta[c]pyran-3-one, 5,6,7,8,9,10-hexahydro-4-phenyl-1- (trifluoromethyl), methylidene]-2-pyridinecarbohydrazon amide, hexasiloxane, 1,2-bis(trimethylsilyl)benzene, urs-12-ene, 2-nitro-4-trimethylsilyl-benzaldehyde, lupeol	[73, 74]

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9	*Carica papaya* Linn. (Caricaceae)	Leaf: 2,4-dimethyl-2-nitropentane, 1-nonanol, cis-3-tetradecene, 3-methylbutanal, 3,5-di-tert-butylphenol, 2-(tert-butylperoxy)-2-ethylbutyl butyrate, 1-tetradecene, 3-octadecene, 1-octadecyne, 3,7,11,15-tetramethyl-2-hexadecen-1-ol, cyclopentaneundecanoic acid, methyl ester, methyl 3-(3,5-di-tert-butyl-4 hydroxyphenyl) propanoate, propan-2-yl decanoate, heptadecanoic acid (15-ethyl-, methyl ester), 3,5-bis(trimethylsilyl)-2,4,6-cycloheptatrien-1-one, ethyl 2-(3-methoxy-4-trimethyl silyloxyphenyl)acetate, 1-trimethylsilyl-4-(1-methyl-1-silacyclobutyl)benzene, decamethylpentasiloxane, undec-10-enyl 6-bromohexanoate, tricyclo[3.2.1.1(3,6)] nonane-5-methanol (3-bromo-2,2-ethylenedioxy-), 1,3,5-cycloheptatriene (7,7-dimethyl-2,4-bis(trimethylsilyl)-), mandelic acid, 1,2,3,5-tetramethyl-4,6-dinitrobezene, diethyl bis(trimethylsilyl) orthosilicate, 4-(4-chlorophenyl)-1-methyl -3,6-dihydro-2H-pyridine, pentamethylcy clopentadienyl-(N,N,N′-trimethyl)-o-phenylenediamine-N′-o-nickel, (p-trime thyl silyloxyphenyl)-1-trimethylsilyloxy propane, 2,2,4,4,6,6-hexamethyl-1,3,5,2, 4,6-trioxatrisilinane, silicic acid and carposide Root: carposide and myrosin	[74–76]
10	*Chromolaena odorata* Linn. King & Robinson (Compositae)	Leaf: quercetin, sinensetin, sakuranetin, padmatin, kaempferol and salvagenin.	[77, 78]
11	*Crossopteryx febrifuga* (Afzel. ex G. Don) Benth. (Rubiaceae)	Stem bark: crossoptines A and B, 3β-urs-12,20(30)-diene-27,28-dioic acid, 18-epi-3β-urs-12,20(30)-diene-27,28-dioic acid, 3β-D-glucopyranosylurs-12,20(30)-diene-27,28-dioic acid, 18-epi-3β-D-glucopyranosylurs-12,20(30)-diene-27,28-dioic acid, monoglyceride of palmitic acid, β-sitosterol and its glucoside.	[79, 80]

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12	*Cryptolepis sanguinolenta* (Lindl.) Schltr. (Asclepiadaceae)	Leaf: methyl cryptolepinoate, cryptolepinoic acid, hydroxycryptolepine, cryptolepine, quidoline. Root: Cryptolepine, cryptosanguinolentine, cryptotackieine, isocryptolepine, neocryptolepine, quindoline, cryptomisrine, cryptospirolepine, cryptolepicarboline, 11-isopropylcryptolepine, cryptoheptine, cryptoquindoline and cryptolepinone, biscryptolepine,	[32, 81–83]
13	*Curcuma longa* Linn. (Zingiberaceae)	Bulb: curcumin, desmethoxycurcumin, bisdesmethoxycurcumin, o-cymene, L-trans-chrysanthenyl acetate, DL-2,3-butanediol, 5-isopropenyl-1,2-dimethylcyclohexan-2-enol, p-cymene, (2,4,6-triethylcyclohexyl)methanol, α-thujone, 2-ethenyl-1,1-dimenthyl-3-methylene-cyclohexane, cis-sabinol, cis-p-menth-2,8-dienol, 2-isopropylidene-3-methylhexa-3,5-dienal, thymol, 2-methoxy-4-vinyl phenol, m-eugenol, hemellitol, benzene-2-methyl-1,4-bis(1-methylethyl), β-curcumene, α-cedrene, γ-curcumene, β-caryophyllene, ar-curcumene, β-himachalene, α-curcumene, β-elemene, α-cubebene, β-cedrene, β-bisabolene, β-sesquiphellandrene, cis-Z-α-bisabolene epoxide, β-vatirenene, agarospirol, β-turmerone, curlone, germacrone, α-turmerone, curzerene, dihydrocostunolide, furanodiene, Ar-turmerone, isocurcumenol, curdione, curcumenol, 7-epi-cis-sesquisabinene hydrate, (–)-isolongifolol, geranyl-p-cumene, cis-β-elemenone, isoshyobunone, dihydrocostunolide, dehydrosaussurea lactone and corymbolone.	[84]
14	*Cylicodiscus gabunensis* (Taub.) Harms (Leguminosae-Mimosoideae	Stem bark: Cylicodiscus acid, cyclodione, gabunoside, cylicodiscoside, 3-O-[α-L-arabinopyranosyl -(1-3)-b-D-glucopyranosyl] cylicodiscic acid, coumestoside C and coumestoside D.	[85, 86]
15	*Ficus thonningii* Blume (Moraceae)	Stem bark: β-sitosterol, lupeolacetate, taraxerol, β-sitosterol glucoside, aromadendrin, thonnigiiflavanonol B, dihydroquercetin, 5,7,3′-trihydroxy-isoflavone	[87]

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16	*Gossyium spp*	Leaf: Gossypol Leaf volatiles: 3-methyl-l-butanol 3-methyl-2-butanol, 2-boten-l-ol, 2-butoxy alcohol, 1-pentanol, 4-penten-l-ol, cis-2-hexene-l-o1 cis-3-hexene-l-ol, 1-heptanol, 3-hepten-1-o1, 1-nonanol, 1 –decanol, hexanal, trans-2-hexenal, 2, 4hexadienal, 2-hexenal, diethylacetal, heptanal, trans-2-heptenal, octanal, trans-2-octenal, nonyl aldehyde, trans-2-nonenal, N-decyl aldehyde, dodecyl aldehyde, 2-pentanone, 3-pentanone, cyclohexanone, 2-heptanone, 3-heptanone, 3-octanone, 2-nonanone, myrcene, ocimene, limonene, camphene, α-pinene, ß-pinene, caryophyllene, 4-pentenoic acid and ethyl acetate.	[88, 89]
17	*Khaya senegalensis* (Desr.) A. Juss. (Meliaceae)	Stem bark: khayanolides A, khayanolides B, khayanolides C, methyl angolensate, khayasin, 7-deacetoxy-7-oxokhivorin, methyl 6-hydroxyangolensate, 7-deacetoxy-7-oxogedunin, 12β-hydroxy-6-de, oxydestigloylswietenine diacetate, methyl 3β,12β-diacetoxy-l- oxomeliac-S(30)-enate, 2,6-dihydroxyfissinolide, fissinolide, methyl 3β-acetoxy-6-hydroxyl-oxomeliac-14-enoate, seneganolide, methyl angolensate, khayanolide E,1-O-deacetylkhayanolide E, 6-dehydroxylkhayanolide E, 1-O-acetylkhayanolide B and 3α,7α–dideacetylkhivorin.	[90–96]
18	*Lippia multiflora* Moldenke (Verbanaceae)	Leaf: Nuomioside A, isonuomiside A, samioside, verbascoside, isoverbascoside, alyssonoside and leucoseptoside A, geniposide, luteolin-7-O-glucuronide Leaf oil: 1,8-cineole, abinene, α-pinene, β-pinene, linalool, α-terpineol, terpinolene, thymol, (Z)- tagetone, (E)-tagetone, myrcene, epoxymyrcene, myrtenol, limonene, γ-terpinene, carvacrol, trans-caryophylene, (Z)-ocimenone, (E)-ocimenone, ipsdienone, geranial, neral, thymyl acetate, ρ-cymene, α-phellandrene, ipsenone, nerolidol, geraniol, (E)-caryophyllene, β-caryophyllene, Caryophyllene oxide β- farnesene, farnesol, germacrene D, γ-muurolene, elemol, 3-methyl-6-(1-methylethylidene)-cyclohex-2-en-1-one, 2 phenyl-ethyl propionate, elemene, ethyl cinnamate, amorphene, carvone, α-thujone, verbascoside, isoverbascoside, α-humulene, trans-α-bergamotene, α-alaskene	[97–99]

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19	*Morinda lucida* Benth. (Rubiaceae)	Leaf: Ursolic acid oleanolic acids, oruwacin, molucidin, ML-2-3, ML-F52, phytol and cysteine-stabilised peptides. Leaf oil: Component α-Thujene, Tricyclene, Camphene, Sabinene, β-Pinene, Myrcene, α-phellandrene, δ-3-Carene, α-Terpinene o-Cymene ρ-Cymene, Limonene, 1,8-Cineole, (E) β-Ocimene, g-Terpinene, Cis-Sabinene hydrate, Terpinolene, Linalool, Cis-ρ-Menth-2-en-1-ol, α-Campholenal, Trans-ρ-Menth-2-en-1-ol, Camphor, β-Pinene oxide, Pinocarvone, Borneol, δ-Terpineol, Terpinene-4-ol, ρ-Cymen-8-ol, Trans-ρ-Mentha-1(7),8-dien-2-ol, α-Terpineol, Myrtenal, Trans-Piperitol, Trans-Carveol, Nerol, Cuminaldehyde Carvone, Cis-Verbenyl acetate, Isobornyl acetate, Trans-Sabinyl acetate, Trans-Pinocarvyl acetate, Neo-verbanol acetate, α-Terpinyl acetate, Eugenol, Cis-Carvyl acetate, Neryl acetate, Geranyl acetate, β-Elemene, Methyl eugenol, β-Caryophyllene, ρ-Cymen-7-ol-acetate, (E)-Cinnamyl acetate, (E)-Methyl isoeugenol, Bicyclogermacrene, α-Bulnesene, Sesquiphellandrene, Elemol, Elemicin, Spathulenol, Caryophyllene oxide, g-Eudesmol, β-Eudesmol, α-Eudesmol and Intermedeol	[100–105]
20	*Nauclea latifolia* Sm. (Rubiaceae)	Stem bark: 19-O-Ethyl-angustoline, angustidine, angustine, angustoline, latifoliamide A, latifoliamide B, latifoliamide C, latifoliamide D, latifoliamide E and nauclefine.	[106]
21	*Ocimum gratissimum* Linn. (Labiatae)	Leaf: α-pinene, β-pinene, 1,8-cineole, ocimene, α-terpineol, eugenol, β-caryophyllene, α-humulene γ-muurolene, β-selinene, α-selinene, sabinene, myrcene, linalool, trans-caryophyllene, germacrene D, germacrene A, methyl eugenol, cis-ocimene, trans-ocimene, pinene, camphor, farnesene, l-bisabolene, bisaboline and thymol, citral, ethyl cinnamate, γ-terpinene, p-cymene, limonene, terpinolene, oleanolic acid, methyl isoeugeneol, geraniol, α-copaene, bisabolol, fenchone, cubenene, camphene, T-cadinol, γ-eudesmol, β-bisoboline and β-elemene.	[107]

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22	*Phyllanthus amarus* Schum. & Thonn. (Euphorbiaceae)	Leaf: Phyllanthin, hypophyllanthin, niranthin, phyltetralin, nirtetralin, isonirtetralin, hinokinin, lintetralin, isolintetralin, demethylenedioxy-niranthin, 5-demethoxy-niranthin, (3-(3,4-dimethoxy-benzyl)-4-(7-methoxy-benzo[1,3]dioxol-5-yl-methyl)-dihydrofuran-2-one, 4-(3,4-dimethoxy-phenyl)-1-(7-methoxy-benzo[1,3]dioxol-5-yl)-2,3-bis-methoxymethyl -butan-1-ol, rutin, astragalin, kaempferol, quercetin-3-O-glucoside, quercetin, quercitrin Gallic acid, ellagic acid, gallocatechin 1,6-digalloylglucopyranose, 4-O-galloylquinic acid, geraniin, amariin, furosin, geraniinic acid B, amariinic acid, amarulone, repandusinic acid A, corilagin, isocorilagin, elaeocarpusin, phyllanthusiin A, B, C and D, melatonin Securinine, dihydrosecurinine, tetrahydrosecurinine, securinol, phyllanthine, allo-securine, nor-securinine, epibubbialine, isobubbialine, 4-methoxy-nor-securinine, 4-methoxy dihydrosecurinine, 4-methoxytetrahydro securinine, hydrosecurinine Phenazine and phenazine derivatives 2Z, 6Z, 10Z, 14E, 18E, 22E-farnesylfarnesol, lupeol, phyllanthenol, phyllanthenone, phyllantheol, Oleanolic acid, ursolic acid Amarosterol A, amarosterol B Linalool, phytol	[108]
23	*Picralima nitida* (Staph) Th. & H. Dur. (Apocynaceae)	Seed: picratidine, akuammine, akuammidine, akuammine, akuammidine, pseudoakuammigine, picraphylline, picracine, picraline, picralicine, picratidine, picranitine, burnamine, pericalline and pericine.	[109]
24	*Quassia amara* Linn. (Simaroubaceae)	Stem wood/bark: 11-α-O-(β-D-glucopyranosyl)-16-α-O-methylneoquassin, 1-α-O-methylneoquassin, 12-α-hydroxy-13,18-dehydroparain, amarastelline A, 1-ethyl-b-carboline, pavettine, crenatine, 1-vinyl-4-methoxy-b-carboline, picrasidine, 1-acethyl-b-carboline, ethyl-9-methoxy-b-carboline, 1-vinyl-9-methoxy-b-carboline, canthin-6-one, 5,6-dihydro-4H-indolo[3,2,1,de][1,5]naphthyridin-4-one, simalikalactone C and picrasinoside B, quassin, neoquassin, paraine, nigakilactone A, 18-hydroxyquassin and quassialactol	[110–112]

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25	*Solenostemon monostachyus* (P. Beauv.) Briq. (Labiatae)	Leaf: coleons C, coleons H, 2α-formoxy-coleon C, 12β-O-acetyl-coleon Z, 12β-O-acetyl-7-O-formyl 7 O-desacetyl-coleon Z, 17-acetoxy-12β-O-acetyl-coleon Z, 12β-O-acetyl- 17-formoxy-coleon Z, 1-Octen-3-ol, β-Pinene, δ-3-Carene, (E)-2-Octen-1-ol, β-Linalool, Dodecane, Myrtenyl acetate, α-Copaene, β-Caryophyllene, Germacrene D, δ-Cadinene, α-Caryophyllene, Caryophyllene oxide, Globulol, δ-Cadinol, hesperedin, rosmarinic acid, myricetin, chicoric acid, chlorogenic acid, genistein, caffeic acid, kaempferol, daidzein. apigenin, lutein and luteolin	[113–115]
26	*Sphenocentrum jollyanum* Pierre (Menispermaceae)	Root and root oil: Palmatine, jatrorrhizine, α-pinene, α-ylangene, guaia-6,9-diene-4α-ol, globulol, guaiene-11-ol, α-eudesmol, isocaryophyllene, aromadendrene, selina-4(15),6-dien E-β-isocaryophyllene, γ-terpinene, γ-humulene, epi-zonarene, δ-amorphene, 1,8-cineol,camphene, B-pinene, p-cymene, d3-carene.	[116, 117]
27	*Tithonia diversifolia* (Hemsl.) A. Gray (Compositae)	Leaf: Tagitinin C 2-methylbutyrate, 1β,2α-Epoxytagitinin C, Tagitinin C, 1-Acetyltagitinin A, 3-O-Methyltirotundin 2α-Hydroxytirotundin, Tagitinin A, 1α-Hydroxy-3-O-methyltirotundin, Tagitinin D, 11,13-Dihydro-8b-hydroxytagitinin D, Diversifolin, 3-O-Methyldiversifolin, 1β-Methoxydiversifolin, 3β,10β-Epoxy-1,3-dihydroxy-8-[(2-methylpro-panoyl)oxy] germacra-4,11(13)-dien-12,6α-olide, 3β,10β-Epoxy-1,3-dimethoxy-8-[(2-methylpro-panoyl)oxy]germacra-,11(13)-dien-12,6α-olide, 3β,10β-Epoxy-1b-hydroxy-3-methoxy-8-[(2-methyl-propanoyl)oxy]germacra-4,11(13)-dien-12,6α-olide, orizabin, 2-O-Methyltagitinin B, tagitinin F, Tithofolinolide, 3β-Acetoxy-8β-(isobutyroyloxy)reynosin, 3α-Acetoxydiversifolol, 4α-Hydroxyeudesm-11(13)-en-12-oate, diversifolol, 8β-(Isobutyroyloxy)cumambranolide, 4α,10α-Dihydroxy-8β-(isobutyroyloxy)-3-oxoguai-11(13)-en-12,6a-olide, 3-Hydroxy-8β-(isobutyroyloxy)leucodin-11(13)-ene-8b-(Isobutyroyloxy)-4-oxo-3,4-secoguai-11(13)-ene-12,6a;3,10a-diolide, 6-Acetyl-7-hydroxy-2,2-dimethyl-2H-chromene, ent-Kaur-16-en-19-oic acid, hispidulin, luteolin, nepetin, tithoniaquinone A, tithoniamide B, tithoniamarin	[118]

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28	*Vernonia amygdalina* Del. (Compositae)	Leaf: luteolin, luteolin-7-O-glucosides, luteolin 7-O-glucuronide, vernonioside A, B, A1, A2, A3, B2, B3, A4, vernodalin, vernodalol and 11, 13-dihydrovernodalin, eucalyptol, 1, 8 cineole, α-pinene and α-muurolol, vernolide, 11β, 13-dihydrovernolide and vernomygdin.	[119–121]

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Abrus precatorius Linn (Leguminosae-Caesalpinioideae)

Abrus precatorius Linn. is one of the medicinal plants used for the treatment of malaria. In addition to being used as an antimalarial, *A. precatorius* has also been shown to have other pharmacological activities including anti-spermatogenic and antifertility effects. For example, the aqueous extract of *A. precatorius* leaf has been reported to cause degeneration of the testis and reduction of sperm cells in experimental rats after 18-day administration [8].

Allium sativum Linn. (Liliaceae)

This popular plant commonly called garlic has been listed as one of the medicinal plants used for the treatment of malaria. There are contradictory reports on the potential effects of *Allium sativum* on male fertility factors. It was reported that *A. sativum* extract is spermicidal *in vitro* [14], while it was also reported that ingestion of garlic for 1 month negatively affected testosterone secretion and spermatogenesis [122]. Furthermore, garlic powder consumption has been shown cause arrest of spermatogenesis in rat following 70-day administration [13]. However, another study reported that administration of *A. sativum* extract has positive effect in the recovery of these functions of in rats [123].

Alstonia boonei De Wild. (Apocynaceae)

Alstonia boonei is a tropical plant popular in folklore medicine for its antimalarial and other medicinal. When administered to rats, the methanolic extract of *A. boonei* stem bark altered sperm viability, motility and counts [15]. The ethanolic extract of *A. boonei* stem bark has also been reported to reduce sperm viability, count and motility and also caused changes in the morphology of sperm cells [16].

Annona senegalensis Pers. (Annonaceae)

Ethnomedicinal studies have indicated that *Annona senegalensis* is used as an antimalarial remedy. On the male antifertility effects, it was reported that administration aqueous extract of *A. senegalensis* leaf for 21 days led to a significant decrease in the testis-body weight ratio and total protein content in the testes, an increase in testicular concentration of cholesterol, glycogen and malondialdehyde and degeneration of seminiferous tubules in rats [17]. However, an earlier study [124] showed that aqueous leaf extract of *A. senegalensis* enhances male fertility in rats. The result of the 15-day study revealed that the weights of the testes and epididymis and sperm motility and sperm concentration increased significantly compared to control animals. Further research is recommended to determine the actual effect of this plant on male fertility.

Aspilia Africana (P. Beauv.) C.D. Adams (Asteraceae)

The traditional use of different parts of *A. Africana* for treating malaria has been reported. It has been reported that methanolic leaf extract of *A. africana* adversely affected male fertility parameters in Wistar rats. After a 52-day administration, the extract caused a significant reduction of the weight of testis, epididymis, seminal vesicle, prostate gland and serum testosterone while the histology of the testis was also distorted [18].

Azadirachta indica A. Juss. (Meliaceae)

Azadirachta indica commonly called neem is a popular antimalarial remedy in many countries. The male antifertility potential of various parts of *A. indica* has been reported extensively. For example, it was reported that the ethanolic extract of the stem back administered subcutaneously for 30 days led to arrest of spermatogenesis, reduction in sperm motility and density, the diameter of seminiferous tubule, Leydig cell nucleus and epithelial heights of epididymis and also the diminution of androgen level [20]. It has also been reported that only one administration of neem oil in the vas caused infertility in male rats, although libido and the level of testosterone were not affected [22]. In another study, the powdered leaf of *A. indica* orally administered was reported to significantly affect androgenic and spermatogenic parameters in rats [19]. The aqueous wood ash extract of the whole plant administered orally significantly reduced sperm motility, sperm count, live/dead

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sperm as well as increase in abnormal sperm cells [125]. Furthermore, it has been reported that intraperitoneal administration of ethanolic extract of *A. indica* stem bark for 10 weeks caused decrease in weights of testis, seminal vesicle and epididymis in experimental rats. The extract altered sperm count, morphology and viability and caused reduction in serum testosterone and luteinising hormone in rats such that the animals were unable to impregnate female rats during the experimental period [21].

Bridelia ferruginea Benth. (Euphorbiaceae)

Bridelia ferruginea Benth (Euphorbiaceae) is one of the plants used to treat malaria and other diseases like diabetes. The ability of *B. ferruginea* stem bark aqueous extract to disrupt male reproductive indices in rat has been reported. Administration of the extract led to reduced sperm count and motility and significant morphological abnormality [23].

Cajanus cajan (Linn.) Millsp. (Leguminosae-Caesalpinioideae)

Studies have reported the antimalarial activities of *C. cajan* leaf, while compounds such as stilbenes (longistylin A and C) and betulinic acid extracted from *C. cajan* have also been reported to exhibit *in vitro* antiplasmodial activity [73]. The capacity of ethanolic extract of *C. cajan* leaves to negatively affect the weight of testes and epididymis has also been reported [24].

Carica papaya Linn. (Caricaceae)

The decoction of *Carica papaya* leaf and root is used to treat malaria, while its antifertility effects have also been reported by various studies. For instance, the ability of the methanolic root extract of *C. papaya* to negatively affect sperm parameters has been reported, the extract caused decreased number of sperm, damage sperm cells and cause necrosis of the germinal epithelium in rats has been reported [25]. Reduction in sperm viability, motility and count, degeneration of the seminiferous tubule epithelium are some of the deleterious effects observed following administration of aqueous leaf extract of *C. papaya* to Wistar rats [26]. A similar study also revealed that 4-week treatment of rats with methanolic extract of *C. papaya* leaf caused reduction in sperm count, leading to production of defective sperm cells and severe necrosis of the germinal epithelium of the testes [27].

Chromolaena odorata Linn. King and Robinson (Compositae)

Although ethnobotanical study on *Chromolaena odorata* indicated that it is used in the enhancement of libido and boosting of sperm count [126], experimental evidence has indicated that *C. odorata* exhibits male antifertility potentials. For example, the aqueous extract of *C. odoratum* leaves has the ability to reduce the weight of the testes and number of spermatozoa alter biochemical parameters as well as arrangement of seminiferous tubules [29]. In another study, it was reported that alkaloids from *C. odorata* negatively affected testes-body weight ratio, sperm parameters, testicular and serum biochemical parameters after a 60-day oral administration [30].

Crossopteryx febrifuga (Afzel. ex G. Don) Benth. (Rubiaceae)

Crossopteryx febrifuga (Afzel.) Benth. is one of the medicinal plants used in the treatment of malaria. The potential of the methanolic stem bark extract of *C. febrifuga* to cause reduction in spermatogenesis in mice after 28-day administration has been reported, indicating that the extract may elicit toxic effects on the male reproductive system [31].

Cryptolepis sanguinolenta (Lindl.) Schltr. (Asclepiadaceae)

Cryptolepis sanguinolenta is one of the commonly used plants for the treatment of malarial in West Africa. The possible male-antifertility effect of the ethanolic leaf extract of *C. sanguinolenta* following 21 days oral administration has been reported. This was evidenced by suppression of testosterone and decreased sperm count following administration of the extract [32]. In another study that employed male mice, aqueous root extract of *C. sanguinolenta* was shown to adversely affect sperm count and the weight of the testes and epididymis [33].

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Curcuma longa Linn. (Zingiberaceae)

Decoction of the rhizome is used to treat malaria in Nigeria, while *in vitro* and *in vivo* antiplasmodial activity of curcumin has also been reported. Numerous studies have established the potential male antifertility activity of *C. longa*. For example, a study has shown that aqueous extracts and 70% alcoholic extract of *C. longa* caused reduction in sperm motility and sperm density in albino rats [34]. The aqueous extract of *C. longa* has also been reported to cause degeneration of testicular tissue of treated mice. Moreover, the extract adversely affected motility, viability, morphology and number of spermatozoa, levels of sialic acid and fructose, serum level of testosterone as well as litter size [35]. Various other studies have also validated the male antifertility potential of this plant product.

Cylicodiscus gabunensis (Taub.) Harms (Leguminosae-Mimosoideae)

The use of extract of *Cylicodiscus gabunensis* for the treatment of malaria has been reported [36]. It has however been reported that the ethanolic extracts of the stem bark of *C. gabunensis* severely affected sperm parameters and caused reduction of testosterone, luteinizing hormone and follicle stimulating hormone in experimental albino rats [36].

Ficus thonningii Blume (Moraceae)

Ficus thonningii Blume is used in traditional medicine in parts of Africa for the treatment of malaria. Experimental evidence showed that ethanolic extract of the stem bark of *F. thonningii* adversely affected the structural integrity of the testes of Wistar rat following a 42-day oral administration [37]. This suggests that extract of *F. thonningii* of the stem bark might have male antifertility effect.

Gossypium barbadense Linn./*Gossypium hirsutum* Linn. (Malvaceae)

Gossypium barbadense and *G. hirsutum* Linn leaves are used for the treatment of malaria. The male contraceptive ability of gossypol isolated from leaves and seed of plants belonging to *Gossypium L.* (cotton genus) has been experimentally confirmed [127].

Khaya senegalensis (Desr.) A. Juss. (Meliaceae)

The leaves and stem bark of *Khaya senegalensis* is well known in Ethnomedicine for the treatment of malaria. The adverse effect of the ethanolic stem bark extract of *K. senegalensis* on testicular weight, sperm count and motility, sperm structures and structural integrity of the seminiferous tubules of rats has been reported [38].

Lippia multiflora Moldenke (Verbanaceae)

The aerial part of *Lippia multiflora* Moldenke has been documented as an antimalarial remedy. The deleterious effect of the aqueous leaf extract of *L. multiflora* on sperm indices has been reported; this manifested in the form of reduction in sperm motility, sperm count and structural deformity of the spermatozoa in Wistar rats. Results from histology evaluation indicated deterioration and damage of the seminiferous tubules and inhibition of sperm production **[39]**.

Morinda lucida Benth. (Rubiaceae)

Morinda lucida Benth (Rubiaceae) is used in folkloric medicine as a remedy for various ailments including malaria. The antispermatogenic properties *M. lucida* leaf methanolic extract has been reported [40]. Administration of the extract led to reduced sperm motility, viability, sperm counts, increased sperm morphological distortions, damaged seminiferous tubules and reduced fertility typified by reduced litter size in albino rats [40].

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Nauclea latifolia Sm. (Rubiaceae)

Nauclea latifolia Sm is a popular antimalarial remedy in parts of Africa. The negative effect of *N. latifolia* stem bark ethanolic extract on sex hormones and male reproductive organs in rat has been reported [36]. Oral administration of the extract for 65 days adversely affected sperm motility, sperm viability and sex hormones [36].

Ocimum gratissimum Linn. (Labiatae)

Although oral administration of the ethanolic leaf extract of *O. gratissimum* was reported to elicit increased sexual activity in male mice [128]. Other studies have revealed that aqueous extract of *O. gratissimum* leaf caused decreased sperm count and motility and increased sperm cells abnormality in mice as well as in rats after 4 weeks of administration [41].

Phyllanthus amarus Schum. & Thonn. (Euphorbiaceae)

It was reported that the methanolic extracts of *P. amarus* leaf caused increase in the level of testosterone in Guinea pigs just like Vitamin E, supporting the traditional claim as an aphrodisiac [129]. The male antifertility potential of the alcohol leaf extract of *P. amarus* has been reported manifesting its effect in diminished epididymal sperm profiles [43]. Also, Adedapo et al. [44] reported that the aqueous extract of *P. amarus* leaf caused varying degrees of degeneration in the morphology of the seminiferous tubule and testes of rats.

Picralima nitida (Staph) Th. & H. Dur. (Apocynaceae)

Picralima nitida is widely used in the traditional management of several ailments including malaria. The ethanolic extract of *P. nitida* seed has been reported to cause degeneration in structure of sperm cells, Leydig cells, myoid cell and sertolic cell of rat following oral administration of the extract for 21 days. These results indicate that *P. nitida* seeds could adversely affect male fertility [45]. In another study, the ethanolic extract of *P. nitida* seed was shown to cause reduced sperm count and progressive degeneration of the seminiferous tubules after 14-day administration. However, the study also indicated that the extract enhances sexual behaviours but the male antifertility effect was obvious [46].

Quassia amara Linn. (Simaroubaceae)

Quassia amara Linn is a tropical plant whose leaf and stem are popular in Ethnomedicine for the treatment of various diseases including malaria. Several experimental reports have shown that *Q. Amara* displayed male antifertility potentials. For example, the crude methanolic extract of stem wood of *Q. amara* was shown to inhibit testosterone secretion of rat Leydig cells [47]. Also in another study, the adverse effect of the methanolic extract of *Q. amara* stem wood on the weight of epididymis, testis and seminal vesicle, sperm count, testosterone level, follicle stimulating hormone and luteinizing hormone has been reported [48]. It has also been reported that intramuscular injections chloroform extract of *Q. amara* stem bark caused a significant reduction in the weight of epididymis and testis. An obvious reduction in sperm count, motility and viability was also recorded [49]. Faisal et al. [50] also reported that the methanolic extract of the bark of this plant caused the coiling of tail around a malformed sperm head following a 35-day intraperitoneal administration in mice [50].

Solenostemon monostachyus (P. Beauv.) Briq. (Labiatae)

The leaf of *S. monostachyus* is used in Nigeria as an antimalarial remedy. It was reported that 49 days oral administration of the hydro-ethanolic extract of *S. monostachyus* leaf led to distortion in the shape of the seminiferous tubules, marked increase in the population deranged sperm cells inexperimental albino rats [51].

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Sphenocentrum jollyanum Pierre. (Menispermaceae)

The root of *Sphenocentrum jollyanum* is used to treat malaria. The root is also reported to be used as sexual stimulant in Ghanaian traditional medicine [130], while the stem bark is valued as an aphrodisiac and general tonic, especially in Igboland of Southern Nigeria [131]. It has also been shown that the methanolic root extract of *S. jollyanum* enhanced libido and increased the levels of testosterone in male experimental animals, supporting the claims for its traditional use as a sexual stimulant [130]. However, the male antifertility property of the methanolic root extract in male albino rats has been reported. Administration of the extract caused reduction in sperm motility, viability and counts, increased serum testosterone levels. Degeneration of seminiferous tubules was also observed, suggesting that methanol extract of the *S. jollyanum* root may adversely affect reproductive functions in male albino rats [52].

Tithonia diversifolia (Hemsl.) A. Gray (Compositae)

Tithonia diversifolia leaf is widely used as a traditional antimalarial remedy with confirmed *in vitro* and *in vivo* antiplasmodial activities. Experimental evidences have shown that extracts of *T. diversifolia* leaves have male antifertility potential. For example, the aqueous extract of *T. diversifolia* leaf was reported to cause reduced sperm count, sperm motility in Wistar rats. The extract also caused sperm abnormalities as well as degeneration and necrosis of the germinal epithelia cell of the seminiferous tubules [53]. It has also been reported that the male reproductive organ characteristics of broiler cocks could be negatively affected by *T. diversifolia forage in the meal* [132]. Moreover, administration of aqueous extract of *T. diversifolia* leaf for 28 days caused a significant decrease in the width, length and weight of the epididymis, plasma testosterone, sperm count, motility and viability in male Wistar rats [54].

Vernonia amygdalina Del. (Compositae)

Vernonia amygdalina is an important plant widely used in traditional medicine for treating malaria and other ailments [133]. Oral administration of ethanolic leaf extract of *V. amygdalina* for 56 days has been shown to cause testicular toxicity in rats [55]. The aqueous extract of *V. amygdalina* leaf for 15 days was reported to have adverse effects on sperm parameters and caused degeneration of testicular tissues [56].

Potential male antifertility compounds isolated from ethnomedicinal antimalarial plants

Numerous compounds have been isolated from ethnomedicinal antimalarial plants; however, only few have been evaluated for their male antifertility effects. Such isolated phytochemicals from the part(s) exhibiting male-factor antifertility effects are listed in Table 2, while those compounds with confirmed male antifertility potentials are now discussed with their chemical structures shown in Figure 1.

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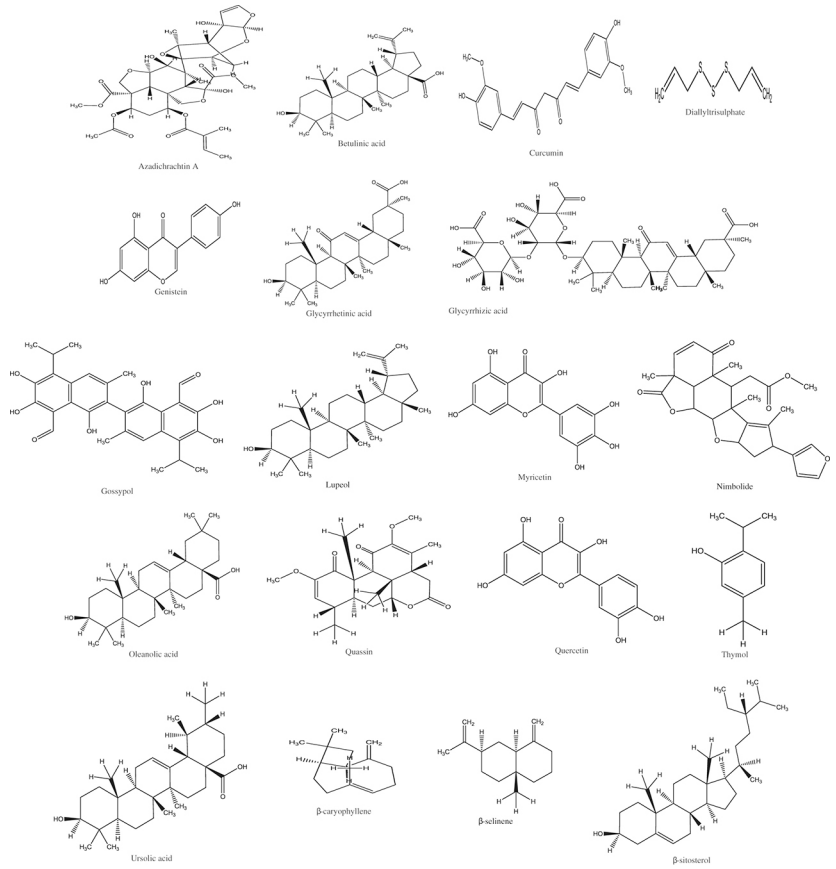


Figure 1: Potential male antifertility compounds isolated from ethnomedicinal antimalarial plants.

Azadirachtin A: Azadirachtin A is a major component of *A. indica* leaf. The effect of azadirachtin A has been shown to cause general decrease in weight of reproductive organs, alteration in biochemical parameters and reduction in the sperm functional parameters with increased sperms abnormalities, with the conclusion that azadirachtin A may be an effective contraceptive agent for the induction of infertility in humans [134].

Betulinic acid: Results from an *in vitro* study on human sperm revealed that betulinic acid disrupted the mitochondrial transmembrane potential, activation of caspase 3 and caspase 9 and caused significant reduction of sperm motility. In another study that evaluated the effects of betulinic acid on the reproductive system of diabetic mice, results revealed that streptozotocin-nicotinic acid induced diabetic alterations in the male reproductive system; however, co-administration of betulinic acid in diabetic mice aggravated the alterations on the male reproductive system [135].

Curcumin: Curcumin, responsible for the yellow colour of turmeric, has been found to affect the weight of reproductive organs in hamsters and inhibit the motility of human sperm [77, 136]. The mechanism of action has been indicated to be the inhibition of 5α-reductase, which converts testosterone to 5α-dihydrotestosterone, thus inhibiting the growth of flank organs [77].

Diallyl trisulfide (Attridium): Diallyl trisulfide from garlic (*A. sativum*) has been reported to have spermicidal activity *in vitro*, causing total immobilization of all spermatozoa within 20 s at 7.5 mg/mL and within 3 min at 1.5 mg/mL [137].

Genistein: Genistein has been reported to affect the production steroids, although intake of genistein may have anticancer property and protects against osteoporosis [138]. In another *in vitro* study to examine the influence of genistein on testosterone production, genistein was shown to inhibit testosterone secretion by Leydig cells relative to dose [139]. In another study using organ culture of foetal testes from genetically engineered mice, it was also reported that genistein interferes with testosterone secretion in early foetal development [140].

Glycyrrhizin: The use of glycyrrhizin (glycyrrhizic acid), the active component of licorice, is popular in the food industry as well as in herbal medicine [141]. The antiandrogenic effect of licorice, which may precipitate erectile dysfunction, has been reported. This was because licorice inhibits the enzymes catalysing the production of androstenedione [142–144]. This activity is attributed to glycyrrhetinic acid, the active metabolite of glycyrrhizin from licorice. *In vitro* evaluation has also revealed that incubating Leydig cells with glycyrrhetinic acid led to decreased testosterone production and accumulation of 17α-hydroxyprogesterone [145].

Gossypol: The male antifertility effects of gossypol have been validated by several studies. For example, gossypol has been reported to elicit male antifertility effects including decrease in the sperm number and

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weight of the epididymis, changes in the histological structure of the testis [146], spermicidal activity [147], antispermatogenic effect and muscular paralysis [148]. The mechanism of action involves the ability of gossypol to inhibit adenyl cyclase that is essential for maintaining high levels of cAMP necessary for normal sperm motility [149].

Lupeol: The ability of lupeol to compete with progesterone and pregnenolone sulfate and significantly reduced activation of calcium channel of sperm thereby inhibiting the hyperactivation of sperm is a mechanism by which lupeol can prevent fertilisation. This report indicates the potential of lupeol as a male antifertility agent, since it can prevent sperm hyperactivation, which in turn will prevent fertilization [150].

Myricetin: Myricetin, a flavonoid found mainly in red wines, occurs widely among plants. Myricetin has been shown to enhance sperm function at low concentrations, whereas this effect was not seen at higher doses; the sperm potentiation by lower doses was reduced or even abolished at higher doses [151]. Myricetin has also been reported to cause atrophy of the testes of rats as well precipitate formation of germinal cell debris in the epididymis [152].

Nimbolide: The administration of nimbolide, a major constituent of *A. indica* leaves, to rats has been reported to cause increased number of abnormal sperms, decrease in the weights of reproductive organs, with adverse effect on sperm functional parameters and reduction in number of pregnant female rats mated with treated male animals [153]. Studies have shown that nimbolide elicit antifertility effect by depleting sperm antioxidant defense system as evidenced by reducing the activities of superoxide dismutase, catalase, glutathione reductase, glutathione peroxidase, α-glucosidase, as well as increasing the generation of hydrogen peroxide and lipid peroxidation in rat spermatozoa *in vitro* [154]. **Oleanolic acid and ursolic acid:** These two isomeric triterpeneshave been reported to affect the fertility indices of livestock, such as suppressing progression to puberty and sperm production [155]. The mechanism of antifertility action of oleanolic acid has been shown to involve induction of premature hyperactivity in sperm cells, indicating that oleanolic acid possibly altered the protein coat of the sperm and thus exposed the receptors leading to a cascade of events involving stimulation of G protein and adenylate cyclase, activation of Ca^{2+} influx, and transient increase in intracellular cyclic adenosine monophosphate [156].

Quassin: The inhibitory effect of Quassin on testosterone production by Leydig cells, an indication that quassin could affect male fertility, has been reported [47]. Quassin was shown to cause reduction in the levels of serum follicle stimulating hormone, luteinising hormone and testosterone, as well as causing coiling epididymal tubules, significant reduction in total epididymal protein and suppression of epididymal HongrES1 protein expression [157].

Quercetin: Garlic was reported to contain two phyto-oestrogens, lignin and quercetin (also found in *A. indica*, *B. ferruginea*, *C. odorata* and *Phyllanthus amarus*). The irreversible and dose-dependent reductive effect of quercetin on human sperm motility, viability and lipid peroxidation has been reported [158].

Thymol: It has been reported that exposure of freshly ejaculated sperm exposed to various doses of thymol hinder motility and hyperphosphorylation of sperm cell [159]. These observations revealed that thymol could be a potent sperm-immobilizing and spermicidal agent.

β-caryophyllene: β-caryophyllene, a natural antioxidant, is found in many plant sources including *Annona senegalensis, Cajanus cajan* and *Lippia multiflora*. It has been reported that β-caryophyllene caused a significant disruption of sperm functionalities and morphology when administered to rats. However, β-caryophyllene did not affect the histology and the cytostructure of the testes and cauda epididymides of the subject rats [160].

β-selinene: The antifertility effect of β-selinene has been reported by [161] who suggested that β-selinene and other sesquiterpenes could be explored further for male antifertility activity.

β-sitosterol: The antifertility potential of β-sitosterol in albino rat has been reported; for example, β-sitosterol administration led to diminution of number of sperm, weight of testis and other associated sex tissues, although these antifertility effects were abrogated upon withdrawal of treatment [162]. In another study, it was shown that administration of β-sitosterol caused a significant reduction in the weight of reproductive organs, serum levels male hormones and sperm motility [163].

Conclusion

Plants are long-standing reliable source of therapeutics and industrial materials in different civilisations. The popularity of plants as remedy for various diseases notwithstanding, plant resources could also elicit various unwanted effects including male antifertility activity. In this review, 28 antimalarial plant remedies with experimentally confirmed male-factor antifertility potentials have been identified and discussed. The male-factor antifertility effects of these plants include reduction of sperm quality, regulation of reproductive hormone levels and induction of lipid peroxidation. Among the isolated compounds from these plants, azadichrachtin A,

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betulinic acid, curcumin, diallyltrisulphate, genistein, glycyrrhizic acid, gossypol, lupeol, myricetin, nimbolide, oleanolic acid, ursolic acid, quassin, quercetin, thymol, β-caryophyllene, β-selinene and β-sitosterol have shown male antifertility potential. However, the male-factor antifertility potentials of several compounds identified are yet to be reported, while some plants or isolated compounds have been shown to have both antifertility and fertility enhancing effects, thus requiring clarification by further experimental studies. Considering the male antifertility effect that could result from the use of some of these antimalarial plant remedies, their indiscriminate use is discouraged when male contraception is not desired.

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