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# *Vitex madiensis Oliv*. (Lamiaceae): phytochemistry, pharmacology and future directions, a mini-review

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**Abstract**
The aim of this mini-review was to collect data obtained from various studies carried out by different authors concerning the phytochemistry and pharmacognosy of *Vitex madiensis* Oliv (Lamiaceae). This review has been compiled using references from major databases such as PubMed, PubMed Central, Science Direct and Google scholar. Plants and their active constituents play an important role in the prevention of various ailments. Most of species of Vitex genus are used as drugs in traditional medicine. *Vitex genus* contains between 270 and 300 species distributed around the world. These species contain a variety of potentially bioactive molecules suchas iridoids, flavonoids, terpenoids and essential oils. Most of these species possess analgesic, anti-inflammatory, hepatoprotective, anti-inflammatory, antimicrobial, antioxidant, antiplasmodial, anti-diarrhea and antiasthmatic properties. The results of this review make *Vitexmadiensis* Oliv.an interesting candidate for advanced anthelminthic properties.

**Keywords:** *Vitex madiensis* Oliv, Phytochemistry, Pharmacognosy, anthelminthic activity

## 1. Introduction
The World Health Organization (WHO) recognizes that traditional and complementary medicines (TCM) are a vital part of global health care system [1-2]. In Africa, it is estimated that over 80% of the population continues to rely on medicinal plant species to meet their basic health care needs [3-4]. The Traditional Medicine (TM) performed a good clinical practice and is displaying a bright future in the therapy of various ailments. *Vitex madiensis* Oliv. is a tropical and sub-tropical regions tree of ethno-pharmacological relevance in African TM. This plant species is traditionally used in Democratic Republic of the Congo to treat several diseases such as diabetes, anemia, diarrhea, dysentery, asthma and so on [5] and was reported to contain various secondary metabolites [6]. Fruits are important foods in human diet; they mainly provide vitamins, minerals and fibers [7]. Therefore, it can be hypothesizedthat this plant species could possess a broad spectrum of biological activities that could justify its use in ethno-medicine. The present literature survey was undertaken in order to make the state of research on this plant species with the aim of its integration in a future program of Tropical Plants Screening Research (TPSR) for anthelminthic properties mainly on animals.

## 2. Botanic description
In 1753, Linnaeus described the genus *Vitex* (Lamiaceae) before Verbenacea Nowadays, this genus includes between 250 and 300 specie softrees and bushes (rarely lianas). These plants are distributed over the tropical and sub-tropical regions [8-1] and sometimes it gives a shrub or small tree, often a suffrutex, less than 50 cm. Growing tips covered in long tawny hairs and having leaves which are digitated compound with five leaflets. These leaflets are obovate and the lower leaflets markedly smaller, dark green above, very rough to the tough; paler below with softer hairs; apex rounded to square, often with a short and abrupt point. Flowers in axillary heads, white with a pale blue to deep mauve lip; calyx lobes densely covered in tawny hairs. Fruit ellipsoid-oblong, fleshy, pendulous on long stalks, black, often spotted white, cupped in the persistent calyx. Figure1 shows *Vitex madiensis* tree with fruits of different sizes.

A B C

***Source*:** Google images collection

**Fig 1:** (a) *Vitex madiensis* tree with fruits of different sizes; (b) *Vitex madiensis* tree with fruits in different stages of fruiting; (c) fruits of *Vitex madiensis*.

## 3. Geographic Distribution

This species is found in tropical andsub-tropicalregionsnamely in Democratic Republic of the Congo, from Senegal to Somalia, Angola, Zambia, Zimbabwe and Mozambique.

## 4. Ethnobotany and pharmacology of *Vitex madiensis* Oliv

Historically, *Vitex spp*. have been widely used in traditional medicine; and up to date, they have a large number of ethnopharmacological applications such as treatment of premenstrual and gynecologic affections, bacterial infections, gastrointestinal problems and inflammation as well as insect repellent and against stings of venomous animals [11]. A large number of their medicinal properties are associated with their fruits; some of them are important as foods in highly marginated and low income areas. *Vitex spp*. fruits are small succulent drupes, globular or ovoid of 0.2-2 cm size (usually smaller than 2 cm); they possess a hardened endocarp that is divided in four pyrenes, each one with a seed [8-10]. Fruits of different *Vitex spp*. have similar morphology and sometimes they are difficult to differentiate. The ripe pulp of these fruits is characterized by dark-purple to brown colors [8, 10, 12, 13].

*Vitex mollis*, *Vitex piramidata*, *Vitexpubescens*, *Vitexagnus-castus* and *Vitexgaumeri* are reported topossess antidysentery, analgesic, anti-inflammatory, anti-tumor activities and are used in folksystems of medicine for the treatment of scorpion stings andgastrointestinal disorders. In the Ayurveda and Unani medicine, leaves [14] and seeds of*Vitexnegundo* are widely used for the treatment ofrheumatism and inflammatory joint conditions. In India, *Vitex glabrata*, *Vitex leucoxylon*, *Vitex penduncularis*, *Vitex pinnata*, and *Vitex trifolia* are found to have insecticidal properties.

The methanolic root extracts of *Vitex negundo* and *Emblica officinalis* significantly antagonized the lethal action induced by *Viper arussellii* and *Naja kaouthia* venom in both *in vitro* and *in vivo* studies. The petroleum ether extract of leaves has been evaluated for larvicidal activity against larval stages of *Culex tritaeniorhynchus* and the crude aqueous extract of *Vitex negundo* Linn. Leaves were investigated for the laxative activity. An ethanolic extract was tested for anthelminthic activity against the Indian earthworm *Pheritima posthuma* [15]. An ethanolic extract of leaves was found to reduce spontaneous motor activity. In addition the ethanolic extract produced significant inhibition of granulation tissue formation while a cold aqueous infusion reduced total serum cholesterol. In acute inflammation, a cold aqueous infusion as well as a mixture of flavonoids of *Vitexleucoxylon* Linn exhibited an anti-inflammatory activity without any effect on chronic inflammation [16].

In Democratic Republic of the Congo, *Vitex madiensis* fruits are soft, edible and refreshing. Decoction of young leaves is managed in case of cough, cold, diarrhea and dysentery. The roots cooked in water are used for the treatment of diabetes and anemia. Elsewhere in Africa, leaves, fruits, stem and root bark are used in the treatment of conjunctivitis, dysentery, diarrhea, fatigue, headaches, mental disorders, respiratory problems, evil back among women, leprosy, fever and jaundice [5].

## 5. Nutritional Characteristics of *Vitex* Fruits

Fruits are important foods in human diet; they mainly provide vitamins, minerals and fibers. Recently, functional and nutraceutical foods, which provide benefits for the prevention/treatment of diseases were incorporated in human nutrition. In addition, to their nutritional components, they have acquired an increased relevance; and within these food groups, fruits are highly represented (e.g. grapes, cranberries, blueberries, pomegranate) and their consumption were associated with a healthy condition and longevity of people [7]. Many of *Vitex* fruits are edible; about 70 species have been registered just in Africa, where they are known as “chocolate berries”. These wild berries have a significant contribution to food security and sustainable rural development for some African communities and many of them are valuable commercial products in those regions [6, 17]. The most representative chocolate berries are *V. doniana*, *V. payos*, *V. fischeri*, *V. grandifolia*, *V. simplicifolia*, *V. madiensis*, *V. mombassae*, *V. ferruginea* and *V. pooara* [6, 17]. *Vitex* fruits are consumed fresh, dried or in boiled preparations with sugar (e.g. jelly, marmalade) [6, 17]. Research groups have developed new products based on chocolate berry properties, for instance, the *V. doniana* pulp was used to prepare a syrup with sensorial characteristics and acceptability similar to those of honey [12]; a pasteurized juice of *V. mombassae* showed good acceptability and its physicochemical characteristics were preserved up to three months of storage [18]. In Mexico, *V. mollis* is used for sweet preparations that can be consumed alone or mixed with milk; however, the properties of such products have not been established [19]. Physico-chemical and proximate analysis of *Vitex spp.* fruits is presented in table 1 below.

**Table 1:** Physico-chemicalandproximate analysis of *Vitex* spp. Fruits [6].

| *Parameter* | *V. mollis* | *V. doniana* | *V. kenie- nsis* | *V. fis- cherii* | *V. mom- bassae* |
|---|---|---|---|---|---|
| **Proximate (percentf.w.)** | | | | | |
| Moisture | 87.00 | 39.42 | 40.56 | 37.74 | |
| Protein | 0.60 | 0.85 | 0.87 | 0.98 | – |
| Lipids | 0.38 | 2.44 | 2.35 | 2.66 | – |
| Ash | 0.66 | 3.41 | 3.40 | 3.66 | – |
| Fiber | 1.92 | 11.48 | 10.42 | 12.38 | – |
| Carbohydrates | 9.48 | 43.12 | 42.49 | 42.67 | – |

| *Parameter* | *V. mollis* | *V. doniana* | *V. kenie- nsis* | *V. fis- cherii* | *V. mom- bassae* |
|---|---|---|---|---|---|
| Minerals(mg/100gd.w.) | | | | | |
| Ca | 45 | 320 | – | – | 55 |
| Mg | – | 72 | – | – | 156 |
| Na | 300 | 100 | – | – | 43 |
| K | 1610 | 880 | – | – | 1757 |
| P | – | 200 | – | – | 309 |
| Fe | 4 | – | – | – | 2.69 |
| Zn | 4.4 | – | – | – | 1.53 |
| Cu | 0.38 | – | – | – | 0.27 |
| Ascorbicacid (mg/100gf.w.) | 5.8 | 81.6-100 | – | – | 40.4 |
| pH | 4.86 | 4.38 | – | – | 3.56 |
| Acidity (percent) | 0.13 | 0.36 | – | – | 0.14 |
| Solublesolids (°Brix) | 14 | 5.2 | – | – | 12.3 |

–: Non reported in the literature.
***Source*:** [1, 12, 19].

## 6. Essential Oils of *Vitex spp. Fruits*

*Vitex* fruits are an interesting source of essential oils and the best studied species is *Vitex agnuscastus* (Table 2). The main compounds of this essential oil are 1, 8-cineole, sabinene and α-pinene and its composition is almost the same at different maturity stages [19-41]. However, a clear variation between species has been registered and the essential oil composition can be used for species identification. Based on this consideration, pharmacological applications associated with essential oil composition must change within *Vitex sp*. On the other hand, contrasting the essential oil composition of fruits and leaves from *Vitexagnuscastus* were similar [19, 21, 41]. It was reported that adverse effects of treatment with *V. agnuscastus* essential oil depends on the source (leaf or fruit), but both have reduced the symptoms associated with gynecologic problems [28-29].

**Table 2:** Composition (%) of essential oils of *Vitex* spp. fruits

| *Compounds* | *V. agnuscastus (Ripe fruit)* | *V. agnuscastus (Unripefruits)* | *V. negundo* | *V. pseudone- gundo* |
|---|---|---|---|---|
| 1,8Cineole | 14-30.2 | 13.7-28.2 | | |
| Sabinene | 11.6-48.2 | 11.8-48.2 | | 2.9 |
| α-Pinene | 1.1-25.5 | 1.1-19.4 | | 31.7 |
| Limonene | tr-6.8 | tr-5.3 | | 11.5 |
| trans-β-Farnesene | 0-9.3 | 0-7.5 | | |
| α-Terpinylacetate | 0-6.6 | 0-6.5 | | 1.2 |
| Caryophylleneoxide | 0-4.6 | 0-3.8 | 3 | |
| trans-β-Caryophyllene | 0.6-6.7 | 1-6.4 | 5 | 1.8 |
| ô-Cadinol | 3.0 | 0.7 | | |
| Terpinen-4-ol | 0.3-3.6 | 0.4-3 | | |
| α-Terpineol | 0.6-3.6 | 0.6-4.5 | | |
| Sclarene | 0-2.0 | 0-1.7 | | |
| Geranyllinalool | 2.2-2.3 | 0.7 | | |
| Myrcene | 1.4-2.9 | 1.1-3 | | 1.7 |
| Abietatriene | 1.2 | 1 | | |
| trans-Sabinenehydrate | 0-0.9 | 0-0.9 | | |
| β-Pinene | 0-2.2 | 1.0-1.8 | | |
| cis-β-Farnesene | 0-0.7 | 0-0.5 | | 4.6 |
| Ledol | 0-1.8 | 0.3-1.6 | | |
| β-Selinene | – | – | 22 | |
| α-Cedrene | – | – | 14 | |
| GermacreneD | 0-2.1 | 0-1.4 | 8 | 4.3 |
| GermacreneB | | | | 2.0 |
| Aristolene | | | 8 | |
| Hexadecanoicacid | | | 8 | |
| α-Copaene | | | 5.4 | |
| α-Humulene | | | 4 | |
| Guaia-3,7-diene | | | 2 | |
| Bicyclogermacrene | 1.9-9.9 | 1.2-9.4 | | 14.5 |
| Citronellylacetate | | | | 1.4 |
| allo-Aromadendrene | | | | 2.7 |
| α-Phellandrene | | | | 1.2 |
| β-Sesquiphellandrene | | | | 1.2 |
| α-Gurjunene | | | | 1.1 |
| *trans*-α-Bergamotene | | | | 1.1 |

Different structures of various compounds found in *Vitex spp.* fruits are given in Figure 2 and their names are summarized in tables 3 and 4.

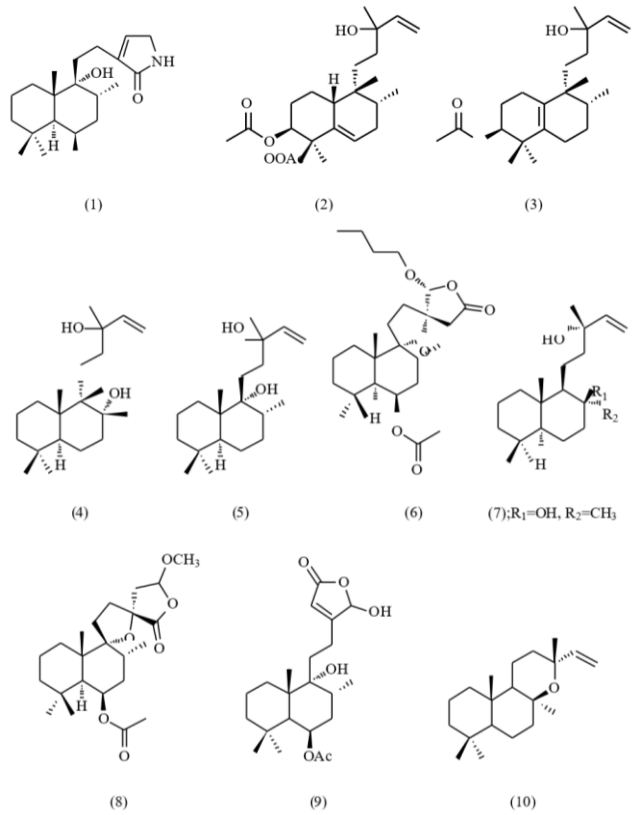



**Fig 2.1:** Chemical structures of compounds obtained from *Vitex spp*. fruits [6]

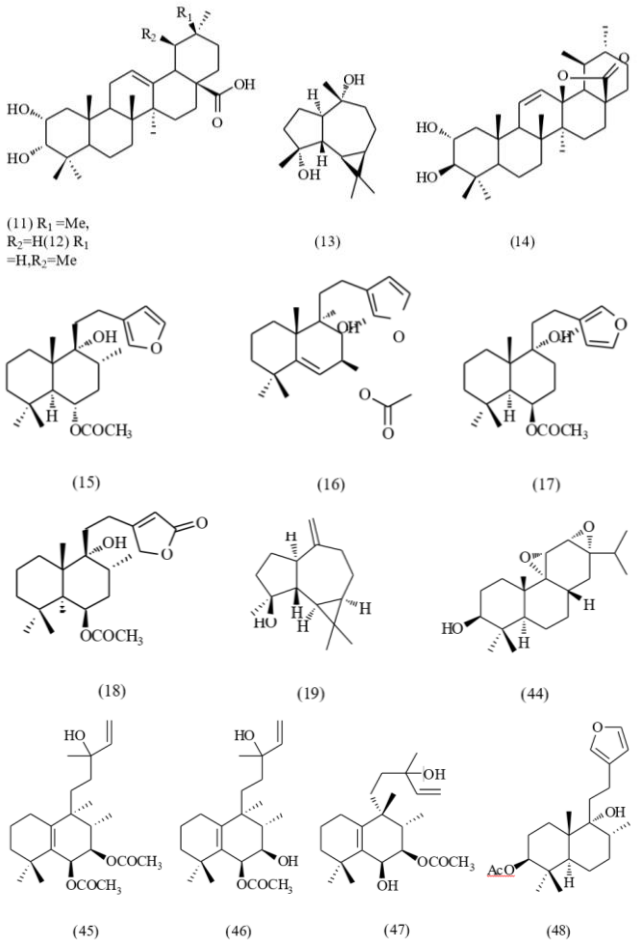



**Fig 2.2:** Terpenoids

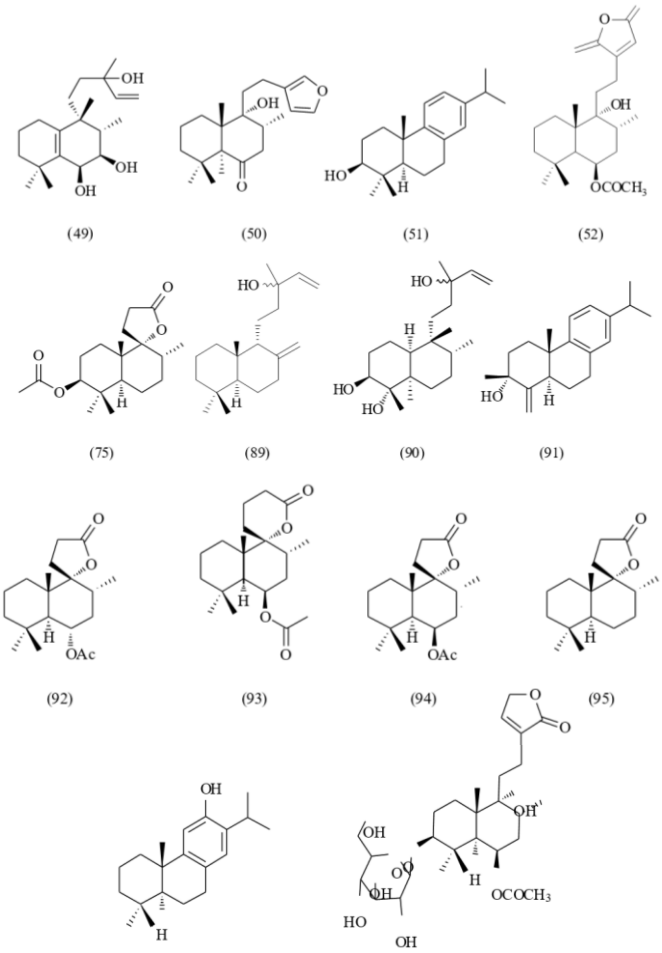
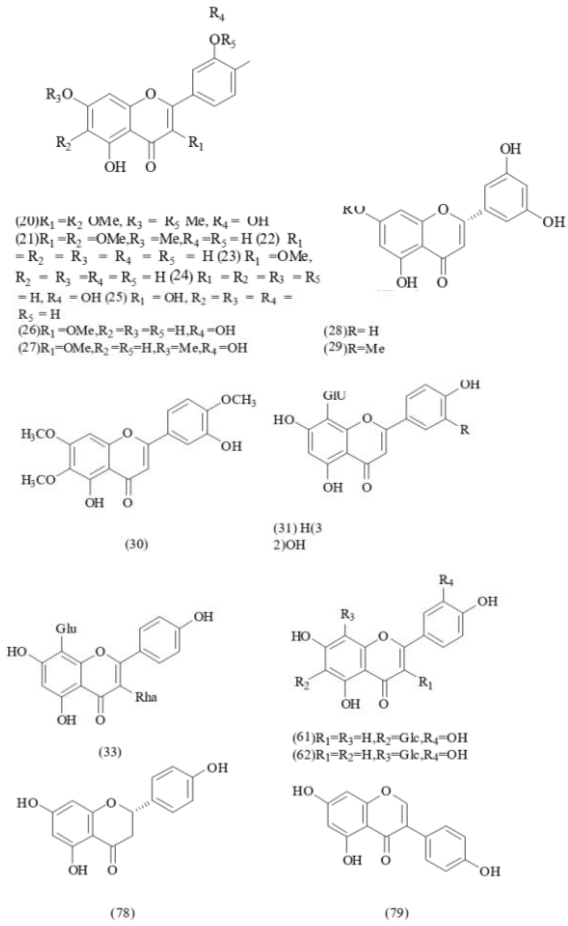



**Fig 2.3:** Terpenoids



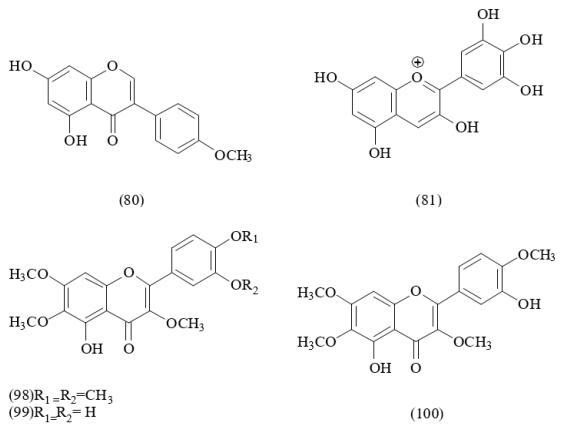



**Fig 2.4:** Flavonoids

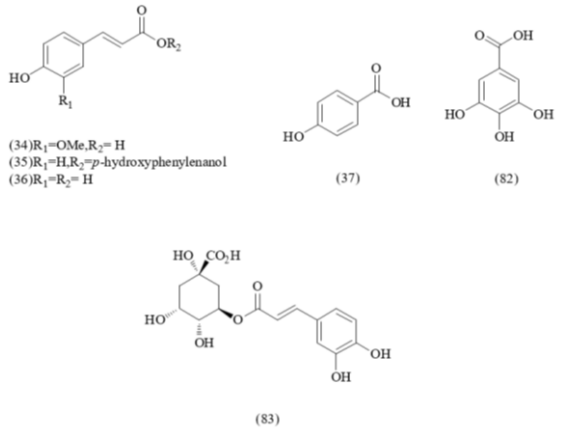



**Fig 2.5:** Simplephenolics

**Table 3:** Characterizedp hytochemicals obtained from *Vitex* spp. fruits.

| ***Vitex spp.*** | ***Family of Compounds: Identified Compounds*** | ***References*** |
|---|---|---|
| *Vitexagnus-castus* | Terpenoids:VitexlactamA(1) | [29] |
| Viteagnusin | A(2),viteagnusinB(3),viteagnusinC(4),viteagnusinD(5),viteagnusinE(6), 8-*epi*-sclareol(7),(*rel*5*S*,6*R*,8*R*,9*R*,10*S*,13*R*)-6-acetoxy-9,13-epoxy-15-methoxy-labdan-16,15-olide(8) | [26] |
| | ViteagnusinI(9),8-epi-manoyloxide(10),3-epi-maslinicacid(11),3-epi-corosolicacid(12),aromadendrane-4α,10α-diol(13),ilelatifolD(14) | [8] |
| | VitetrifolinB(15),vitetrifolinC(16),rotundifaran(17),vitexilactone(18),spathulenol(19) | [13,33] |
| | Flavonoids:Casticin(20),penduletin(21),apigenin(22),3-methylquercetin(23),luteolin(24),Kaempferol(25),3,7-dimethylquercetin(26),3-*O*-methylkaempferol(27),5,7,32,52-tetrahydroxyflavanon(28),5,32,52-trihydroxymethoxylflavanone(29),eupatorin(30),vitexin(31), orientin(32),apigenin3,8-di-C-glycosides(33) | [8,13,15,33] |
| | Phenolics:Ferulicacid(34),phydroxyphenylethanol-p-coumarate(35),p-Coumaricacid(36),4-hydroxybenzoicacid(37).Neolignans:Ficusal(38),vladirolF(39),balanophonin(40),Glycerides:Glyceryllinoleate(41). | [8] |
| | Iridoids:Agnuside(42) | [15] |
| | Aucubin(43) | [33] |
| *Vitextrifolia* | Terpenoids:VitetrifolinA(44),vitetrifolinB(15),vitetrifolinC(16),vitetrofilinD(45),vitetrofolinE(46), vitetrifolinF(47),vitetrifolinH(48),vitetrifolinI(49),rotundifaran(17),Dihydrosolidagenone(50),abietatriene3β-ol(51),vitexilactone(18),(rel5S,6R,8R,9R,10S)-6-acetoxy-9-hydroxy-13(14)-labden-16,15-olide(52). | [24,34] |
| | VitrifolA(53),dihydrodehydrodiconifenylalcohol(54),stigmast-4-en-6β-ol-3-one(55) | [11] |
| | Vitexoid(56),6-acetoxy-9-hydroxy-13(14)-labdane-16,15-olide(57),previtexilactone(58),6-acetoxy-9,13;15,16-diepoxy-15-methoxylabdane(59) | [34] |
| | Flavonoids:Casticin(20) | [35] |
| | Iridoids:Eucommiol(60) | [11] |

**Table 4:** Characterized phytochemicals obtained from *Vitex* spp. Fruits.

| ***Vitex spp.*** | ***Family of Compounds: Identified Compounds*** | ***References*** |
|---|---|---|
| *Vitexcannabifolia* | Flavonoids:5,4'-dihydroxy-3,6,7,8,3'-pentamethoxyflavone(61),isoorientin(62),orientin(32) Lignans:vitecannasideA(63),vitecannasideB(64),vitedoinA(65),6-hydroxy-4-(4-hydroxy-3-methoxyphenyl)-3-hydroxymethyl-7-methoxy-3,4-dihydro-2-naphthaldehyde(66),detetrahydro-conidendrin(67),vitrofolalE(68),vitrofolalF(69),pinoresinol(70). Iridoids:agnuside(42),10-*O*-vanilloylaucubin(71),nisindaside(72),geniposide(73). Phenylbutanoneglucoside:4-(3,4-dihydroxyphenyl)-butan-2-one-4*O*βD-glucoside(74). | [36] |
| *Vitexnegundo* | Terpenoids:vitedoinB(75).Lignans:VitedoinA(65),vitedoamineA(76),6-hydroxy-4-(4-hydroxy-3-methoxyphenyl)-3-hydroxymethyl-7-methoxy-3,4-dihydro-2-naphthaldehyde(66),detetrahydro-conidendrin(67),vitrofolalE(68),vitrofolalF(69),2α,3β-7-*O*-methylcedrusin(77). Flavonoids:naringenin(78),genistein(79),biochaninA(80),delphinidin(81).Phenolics: 4-Hydroxybenzoicacid(37),gallicacid(82),chlorogenicacid(83).Catechins:(-)-gallocatechin(84), epicatechin(85).Anthraquinones:alizarin(86),rhein(87).Others:Caffeine(88). | [12, 23] |
| *Vitexrotundifolia* | Diterpenoids:VitexifolinA(89),vitexifolinB(90),vitexifolinC(91),vitexifolinD(92),vitexifolinE(93), vitetrifolinD(45),trisnor-γ-lactone(94),*iso*-ambreinolide(95),ferruginol(96),abietatrien-3-ol(51), viteosideA(97) | [22, 25, 27] |
| | Rotundifaran(17) | [14] |
| | Flavonoids:Casticin(20),luteolin(26),artemetin(98),quercetagetin(99),5,3'-dihydroxy-6,7,4'–Kotrimethoxyflavanone(100). | |
| | Iridoid:agnuside(42) | [14] |

## 7. Pharmacological activities

### 7.1 Antioxidant and antimicrobial activities

Some Vitex fruits are characterized by their high antioxidant capacity. The antioxidant activity of methanol-acetone-water (6:3:1 v/v) extracts of three *Vitex spp.* (*V. doniana, V. keniensis* and *V. fischeri*) from Kenya were analyzed using three methods (DPPH, FRAP and NO scavenging) [20]. Ripe fruits showed a higher activity than green-ripe fruits and similar to that of the standards used (i.e., vitamin C, rutin and gallic acid). Moreover, total phenolics contents of three *Vitex* fruits were high and similar among them; phenolics content were also higher in ripe fruit (572-719 mg of gallic acid equivalents/100 g f.w.) than green-ripe fruit (290-371 mg of gallic acid equivalents/100g f.w.). Fruit ripening of Vitex fruits is accompanied by color changes from green to dark intense, which could be correlated with the phenolics content [6].

The essential oil of *V. agnuscastus* showed low antioxidant activity while evaluated in aqueous media (DPPH and ferric ion reducing power), but a high activity was obtained in an emulsion system (β-carotene bleaching). This essential oil of this species is a potent antimicrobial [30]. *V. agnuscastus* essential oil was effective against *Staphylococcus aureus* ATCC 6538, *Micrococcus flavus* ATCC 9341, *Bacillus subtilis* ATCC 10907, *Salmonella typhimurium* ATCC 13311 and *Escherichia coli* ATCC 35210 (minimal inhibitory concentration, MIC = 44.5- 445 µg/ mL), and also against fungi *Alternariaalternata* DSM 2006, *Aspergillus flavus* ATCC 9643, *Aspergillus niger* ATCC 6275, *Aspergillus ochraceus* ATCC 12066, *Fusarium tricinctum* CBS 514478, *Penicillium ochrochloron* ATCC 9112, *Penicilliumfuniculosum* ATCC 36839 and *Trichoderma viride* JCM 22452 (MIC = 44.5- 219 µg/mL). The active constituents of this essential oil were 1,8-cineole and α-pinene and their MIC values for bacteria and fungi (4-8 µg/mL) were better than those of streptomycin (MIC = 50-100 µg/mL) and bifonazole (MIC = 100-150 µg/mL). *V. doniana* essential oil inhibited the growth of *S. aureus, B. subtilis* and *E. coli*, in the disc diffusion assay; diameters were slightly smaller than those obtained with ciprofloxacin [30].

### 7.2 Antiplasmodial activity and cytotoxicity of *Vitex madiensis*

In Haut-Ogooue´, Gabon, *Vitex madiensis* Oliv. (Lamiaceae) is traditionally used to treat malaria symptoms. Leaves and stem barks extracts were obtained using dichloromethane ($CH_2Cl_2$), ethyl acetate (EtOAc) and methanol (MeOH) as extraction solvents and fractionated on silica gel column. The *in vitro* antiplasmodial activity of $CH_2Cl_2$, EtOAc and MeOH extracts and fractions was evaluated against the chloroquine-resistant FCB strain and field isolates of *Plasmodium falciparum* using the DELI test. The cytotoxicity of these extracts was tested on MRC-5 and THP1 cells using the tetrazolium salt MTT colorimetric assay, and the selectivity index (SI) of each extract was calculated. $CH_2Cl_2$ extract, the EA1 fraction from EtOAc extract of stem barks and cyclohexane (Lcycl), dichloromethane (LDM) and butanol (Lbut) fractions from MeOH⁄$H_2O$ extract of leaves exhibited the highest *in vitro*antiplasmodial activity on FCB strain and field isolates ($IC_{50}$ from 0.53 to 4.87 l g⁄mL) with high selectivity index (of 20.15–1800). The EA1, $C_6H_{12}$ and $CH_2C_{l2}$ fractions could be selected for future investigation or⁄and for the treatment of malaria symptoms [39].

### 7.3 Hypoglycemic and Antihyperglycemic Activities of *Vitex madiensis* Oliv.

The hypoglycemic and antihyperglycemic activities of nine plants used as antidiabetic treatments in Lubumbashi (Democratic Republic of the Congo)and its surroundings. Those are *Albizia adianthifolia, Azanza garckeana, Cassia occidentalis, Cassia sieberiana, Erythrina abyssinica, Gladiolus klattianus, Rauvolfia caffra, Strychnos spinosa, and Vitex madiensis*. Aqueous extracts, obtained by decoction and maceration, were administered (500 mg/kg) per os to guinea pigs (*Cavia porcellus*), both in glucose baseline conditions and in oral glucose tolerance test (OGTT) conditions (glucose, 2 g/kg; follow-up over 210 min). For OGTT experiments, area under the curve of blood glucose levels, maximum glucose concentration (Cmax), and time to reach Cmax (Tmax) were used to compare test groups with the control conditions (glucose group). In hypoglycemic tests, only three species induced significant ($p < 0.001$) lowering of normal glycemia: *A. adianthifolia* (33% reduction), *C. occidentalis* (32%), and *V. madiensis* (43%); in the same conditions, the positive control glibenclamide (6 mg/kg) induced a blood glucose lowering of 55%. In OGTT conditions, all tested herbs were active, with the highest inhibition of glycemia increases for *V. madiensis* (62%) and *A. adianthifolia* (57%), compared with the hyperglycemic inhibition rate of glibenclamide (50%). Oral glucose tolerance test conditions appear as essential to detect the extracts most interesting for clinical use [38].

## 8. Conclusion

The literature survey revealed that *Vitexmadiensis* Oliv. is a pharmacologically and chemically studied plant species. The diversity of secondary metabolites present in the plant species especially flavonoids, terpenoids, phenols and essential oils show that *Vitexmadiensis*Oliv.is a good candidate for Tropical Plants Screening Research program for the development of lead compounds against genetic and parasitic diseases such as the evaluation of antihelminthic activity.

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