Chapter

Phytochemistry and Ethnopharmacology of *Vebris nobilis* Delile (Rutaceae)

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Abstract

Vepris nobilis Mziray (formerly *Teclea noblis* Delile) is an ever-green plant in the tropical climate. The different parts (leaves, stem bark, roots and fruits) of this plant are popular for treatment of various diseases including; malaria, rheumatism, arthritis, pneumonia, cough, fever, measles, asthma, common cold, headache, join and chest pains and as antithelmintic. Several phytochemical compounds including quinoline and furoquinoline alkaloids, terpenoids and flavonoids have been isolated from the different plant. Pharmacological investigations on the different crude extracts and isolated compounds covering antipyretic, analgesic, anti-inflammatory, antimicrobial, antimalarial, antileishmanial and ant-trypanosomal have been conducted.

Keywords: *Vepris nobilis*, Teclea noblis, Phytochemistry, Ethnopharmacology

1. Introduction

The genus Teclea Delile subsumed into Vepris Mziray (Rutaceae-Toddalieae) were merged because of their similarity in morphological characteristics [1]. Currently, there are about 86 species in the genus vepris comprising of evergreen shrubs and trees, predominantly of tropical lowland evergreen forest, but with some species extending into submontane forests and some into drier forests and woodland distributed in Africa, Saudi Arabia and India. In Africa, the species in the genus vepris are widely distributed in countries like Ethiopia, Sudan, Somalia, Cameroon, South Africa, Kenya, Uganda and Tanzania [2].

Vepris nobilis Mziray, formerly *Teclea noblis* Delile (family Rutaceae) is about 2-12 m high but can be much taller in rain forests. Its bark is smooth and gray and has branchlets glabrous. The leaves are trifoliolate, occasionally 2-or 1 foliolate; petiole 1.5–6 cm long, sometimes slightly grooved at the apex usually glabrous. The leaflets are subsessile or with a petiolulate up to 10 mm long, oblong-elliptic, 5–15 cm long, 1.5–4 cm broad, acute to acuminate at the apex, narrowly cuneate at the base, glabrous, but sometimes puberulous on the midrib; lateral nerves numerous. The inflorescence of terminal and axillary panicles 4–15 cm long, glabrous. The flowers are polygamous with four Sepals united into a cupuliform calyx 0.6–0.8 mm long; lobes small, ovate, ciliate., narrowly elliptic, 3.5–4 mm long, 1.5–1.7 mm broad. The male flowers are with 4–5 stamens 3–5.5 mm long; anthers basifixed; rudimentary ovary slender and glabrous while the female flower are with 4 or 5

staminodes 0.5–1.2 mm long. The ovary are subglobose, 1–1.4 mm in diameter, glabrous unilocular, 2-ovulate; style up to 0.5 mm long. The stigma are disk-shaped and peltate, 1 mm in diameter, red, glabrous, barely foveolate, wrinkled when dry and one seeded. Its fruit are yellow, orange or red in color, round or ellipsoid becoming wrinkled 6–8 x 5–6 mm. The seed are ovoid 5.5–6.0 mm long. *Vepris nobilis* is native to Uganda, Kenya, Tanzania and Ethiopia [3].

2. Ethnomedicinal uses

Vepris nobilis is used in folk or traditional medicine to treat several diseases or illnesses. A decoction of the arial parts of the plant has been reported to treat malaria [4]; stem bark as a remedy for gonorrhea and pain; a mixture of the bark and leaves as analgesics and antipyretic [5, 6]; leaves as a cure for fever [2, 7], pneumonia [3] and malaria [8]; roots for treating rheumatism, arthritis, pneumonia [9, 10], as an anthelminthic [11], weight loss and chronic cough [12]. A decoction of stem bark and root in treating asthma, common cold, headache, join and chest pains [11, 13]. Steam inhalation of the leaves was reported to cures fever [3] and stem bark as a chewing stick for brushing teeth [14].

3. Chemistry

3.1 Extraction yield

The percentage extraction yield of the leaves of *V. nobilis* with methanol, hexane, dichloromethane and ethyl acetate was found to be 10.95, 2.73, 2.48 and 1.57%, respectively [15]. However, extraction yields for roots with methanol, and a mixture of dichloromethane (DCM) and methanol in the ratio of 1: 1 was found to be 2.12 and 2.36% [16]. Hydro distillation of the leaves of *V. nobilis* resulted in 0.23% essential oil yield [7].

3.2 Phytochemicals

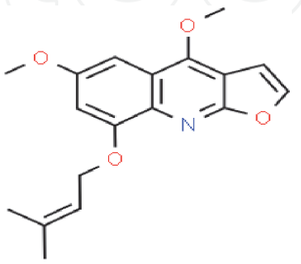
Phytochemical analyses of the leaves, fruits, roots and stem bark have indicated presence of several phytochemicals. For instance, ethanol extract *V. nobilis* root bark and the leaves were found to contain tannins, reducing compounds, alkaloids, steroid glycosides, polyuronides, glucides, starch, coumarin derivatives and flavonoids [16, 17]. The fractionation of the different plant part extract has resulted in the identification of several quinoline and furoquinoline alkaloids, terpenoids and flavonoids.

3.2.1 Alkaloids

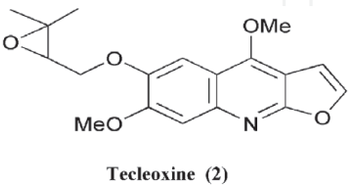
Alkaloids are organic heterocyclic nitrogen compounds that are weak bases. They form a bicyclic system in which benzene and a pyridine ring are fused together. There are several quinoline, furoquinoline and acridone alkaloids identified in the different plant parts. For instance, furoquinoline alkaloids; tecleabine [18], tecleoxine [7], isotecleoxine [19], methylnkolbisine [5], chlorodesnkolbisine [20], pteleine [21], isohaplopine-3,3-dimethylallylether [22], nobiline [23] haplopine-3,3-dimethylallylether [24] anhydroevoxine [9], kokusaginine [12] and

8-methoxyflindersine [25]; and acridone alkaloid, arborinine [26] were isolated from the aerial parts of *V. nobilis* [4, 5].

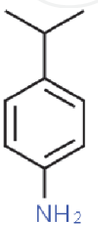
Similarly, furoquinoline alkaloids including nobiline [23], montrifoline [8], skimmiamine [4], flindersiamine [6] and maculine [11] were isolated from the leaves; and isoplatydesmine [2], ribalinine [27] and edilinine [1] isolated from both the leaves and fruits [8]. The fruits of *V nobilis* fruit were found to contain furoquinoline alkaloids; acetylmontrifoline [10], montrifoline [8], maculine [11], kokusaginine [12] and skimmiamine [4, 8]. The stem bark was found to contain furoquinoline alkaloids, Nkolbisine [28] while the root contained tecleabine [18], N -methylflindersine [29], flindersiamine [6], skimmianine [4] and desloratadine [13, 17].



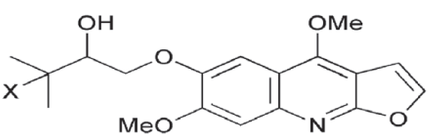
Tecleabine (1)



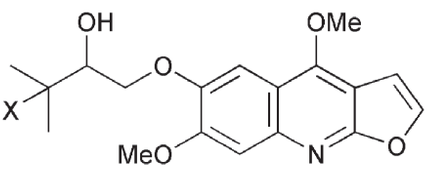
Tecleoxine (2)



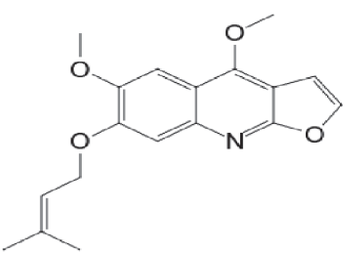
Iso-tecleoxin (3)



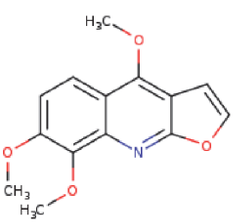
Methylnkolbisine (4), X=OMe



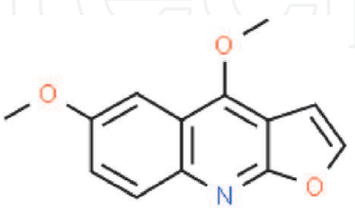
chlorodesnkolbisine (5) , X=Cl



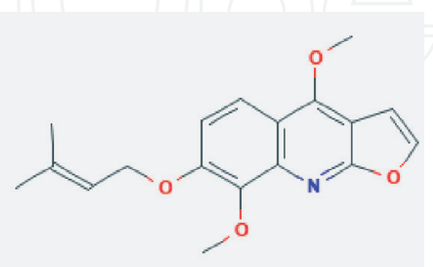
Pteleine (6)



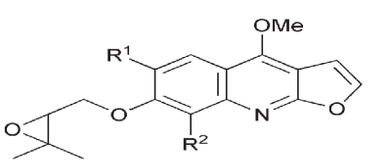
isohaplopine-3,3-dimethylallylether (7),



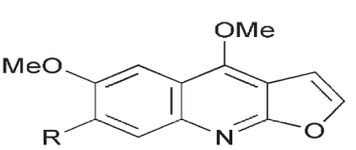
Nobiline (8)



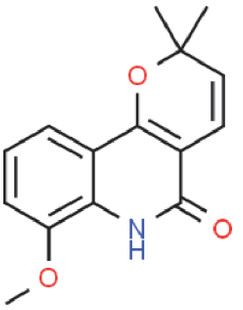
haplopine-3,3-dimethylallylether (9)



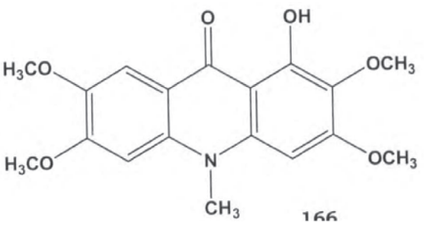
Anhydroevoxine R[1]=H, R[2]=OMe (10)



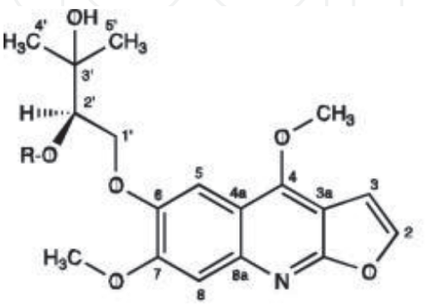
kokusaginine R= OMe (11)



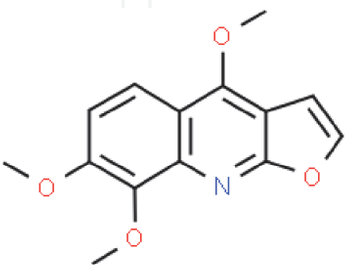
8-methoxyflindersine (12)



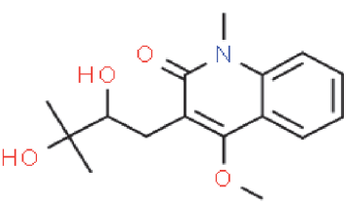
Arborinine (13)



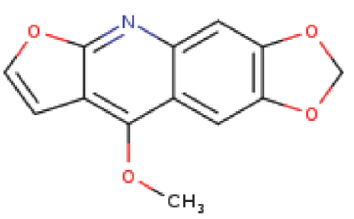
Montrifoline (R=H) (14)



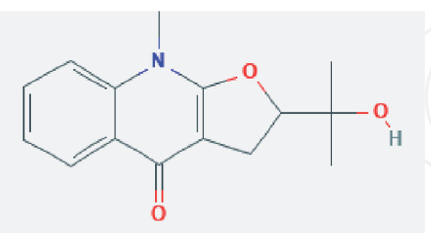
Skimmianine (15)



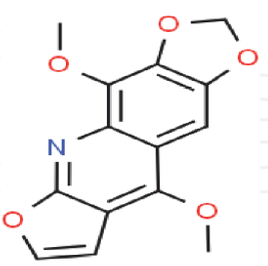
Flindersiamine (16)



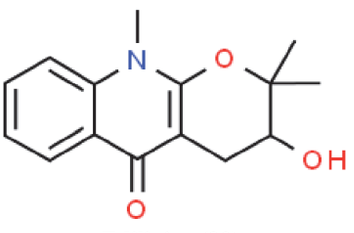
Maculine (17)



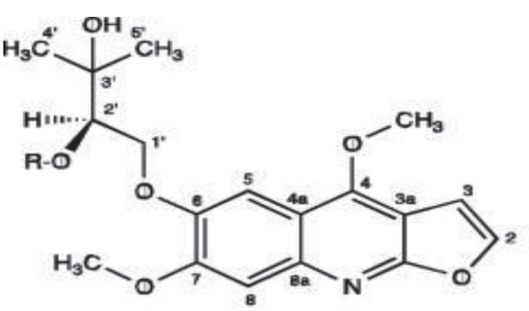
isoplatydesmine (18)



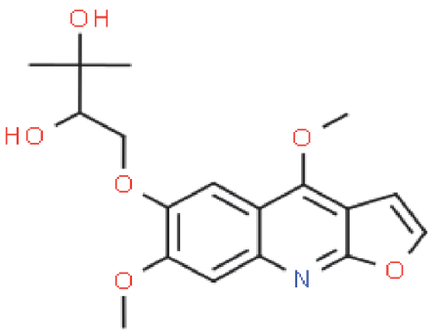
Ribalinine (19)



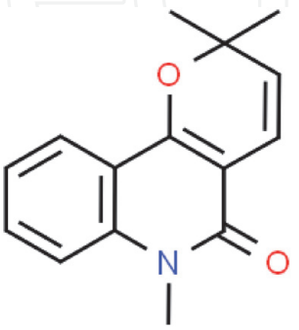
Edilinine (20)



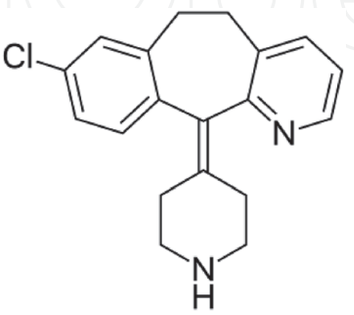
Acetylmontrifoline R= CH3-CO-(21)



Nkolbisine (22)



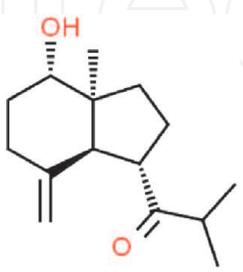
N -methylflindersine (23)



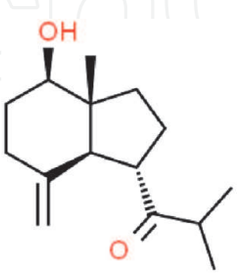
Desloratadine (24)

3.2.2 Terpenoids

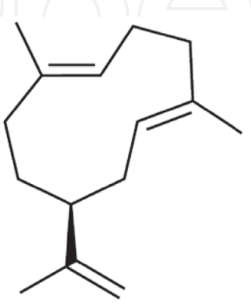
Terpenes form the largest group of natural compounds and they are usually identified on the basis of the number of isoprene units they possess. For instance, terpenes with one, two and three isoprene unit are called hemiterpene, monoterpenes and sesquiterpene, respectively. Essential oils mainly comprise of monoterpenes or/and sesquiterpenes. Ocheng et al. [14] and Al-Rehaily [7] evaluated essential oil profile of the roots and leaves respectively. In both studies, Germacrene-D [14] and Ocimene [17] were the major sesquiterpene and monoterpene hydrocarbon (**Table 1**). A study by Al-Rehaily et al., [19] also isolated sesquiterpenes, teclenone A [30] and teclenone B [31] from the aerial parts while a study by Al-Rehaily et al., [5] isolated lupeol from the leaves of V. nobilis. β-sitosterol was one of the setroids isolated from the aerial parts of *V. nobilis* [15, 19].



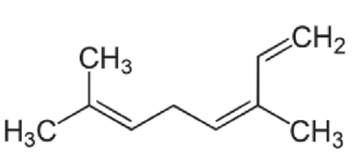
Teclenone A (25)



Teclenone B (26)



Garmacrene D (27)



Ocimene (28)

Compound	% Area	
	Root [29]	**Leaves [7]**
trans-β-Ocimene	8.5	
Ocimene isomer		22.3
Epoxyocimene		0.2
α-Copaene-11-ol		0.7
δ-Cadinene	7.3	1.9
γ-Elemene	2.4	
Elemol		2.9
Spathulenol		0.2
Guaiol		3.9
Bulnesol		2.5
Benzyl benzoate		0.3
Elemene		1.5
Germacrene D	54.4	19.0
α-Gurjunene	4.9	
α-Cardinol	9.1	
Tau-Cardinol	2.0	
Nerolidol	1.9	
Muurolol	3.4	
Phytol	1.2	
Methyl isoeugenol	1.7	
Palmitic acid	2.1	
β-Myrcene		0.1
Linalool		1.6
Dihydroedulan II		1.0
Dihydroedulan I		0.5
α-Copaene		0.6
β-Bourbonene		0.4
Cyperene		0.2
Methyl-N-methyl		0.3
β-Caryophyllene		0.9
α-Humulene		1.3
Other compounds less than 1% in the oil.	1.1	

Table 1.
Essential oils from the leaves and roots of V. nobilis.

3.2.3 Flavonoids

Flavonoids are a class of polyphenol phytochemicals made up of a skeleton of 15-carbon atoms which consists of two benzene rings (ring A and B) linked via a heterocyclic pyrane ring [26]. Depending on the chemical structures, flavonoids are divided into clases like anthocyanins, flavones, flavonols, flavanones,

dihydroflavonols, chalcones, aurones, flavonons, flavan and proanthocyanidins, isoflavonoids, isoflavones, isoflavonones, isoflavons, isoflavene, biflavonoids, neoflavonoids and flavonoid alkaloids. A study conducted by Al-Rehaily et al. [5] isolated flavanone 4,5-dihydroxy-7- prenyloxyflavanone from aerial parts of *V. nobilis* [5]. Phytochemical quantification of flavonoids in the roots resulted in 33.5 and 20.6 mg/g. Quercetin Equivalent while quantification of phenolic compounds resulted in 168.4 mg/g Garlic Acid Equivalent.

4. Pharmacological activity

Vepris nobilis has been reported to poses analgesic, antipyretic, anti-malarial, anti-plasmodial, antimicrobial, anti-inflammatory, anti-caseinolytic, anti-leishmanial and anti-trypanosomal activities.

4.1 Antipyretic and analgesic activities

Pyrexia or fever is the increase in body temperature above normal physiological range, which may result due to physiological stress such as during microbial infections as natural defense system of the body is activated [32]. Usually, at the elevated body temperature, there is increased production of proinflammatory mediators' cytokines such as interleukin 1β, β, α and TNF-α which enhance the formation of prostaglandin E2 (PGE2) near the peptic hypothalamus area and the prostaglandin in turn act on the hypothalamus. To lower the elevated body temperature, antipyretic drugs administered usually inhibit COX-2 expression thereby inhibiting prostaglandin synthesis.

Since *V. nobilis* is used to treat fevers, a study on the antipyretic and analgesic activity of ethyl acetate fraction from the residue of the 85% ethanol extract of *V. nobilis* was found to exhibit a significant antipyretic effect in hyperthermic rats and rabbits [32]. Similarly, essential oils of the leaves of *V nobilis* showed significant analgesic and antipyretic activity recorded in both writhing and tail flick test in mice [7]. Analgesic and antipyretic activity in this study was attributed to Central nervous system depression as observed in the behavioral studies on the animals.

A study conducted by Mascolo et al. [2] by intravenous administration of 50 mg/kg of dried leaf extract of *V. nobilis* resulted in antipyretic and analgesic activity, and thereby causing decrease in body temperature, with the effect being equipotent to acetylsalicylic acid. The same extract also demonstrated antinociceptive activity as judged by its ability to increase the thermal response latencies of mice kept on heated surface with IC_{25} of 26.1 mg/kg compared to acetylsalicylic acid with IC_{25} of 32.5 mg/kg. In a study conducted on antipyretic and analgesic activities of ethanolic extract of *V. nobilis*, a compound 4,6-dimethoxy-7-((3-methylbuta-1,3-dien-1-yl) oxy)furo [2,3-b]quinolone was found as a good lead compound to be developed into a drug for managing pain.

4.2 Anti inflammatory activity

Inflammation is a normal, protective response to tissue injury caused by physical trauma, noxious chemicals, or microbiologic agents with the aim to inactivate or destroy the invading organism, remove irritants and set the stage for tissue repair. In the process, proinflammatory cytokines like TNF-α, IL-6, and IL-1β are produced in large quantities by macrophages and monocytes that stimulate the cellular responses via increasing prostaglandins (PGs) and reactive oxygen species [33]***. In laboratory animal experiments, inflammatory pain can be induced by acetic acid

due it is ability to induce capillary permeability and liberating endogenous substances that excite pain nerve endings [34].

A study conducted on ethanol extract dose-related effect of *V. nobilis* extract on carrageenin-induced oedema at high doses of 200-300 mg/kg significantly modified carageenin oedema with IC_{25} of 157.5 mg/kg compared to acetylsalicylic acid with 22.5 mg/kg [2]. This biological effect was attributed to phytochemicals present in the extract because of their potential to inhibit the cyclooxygenase enzyme in peripheral tissues and interfere with the transduction mechanism of primary afferent nociceptors.

A similar study conducted by Omujal et al. [17] found that 400 and 600 mg ethanolic root bark extract / kg of body weight on formalin induced paw oedema in mice was inhibited much better than by 25 mg of Diclofenac sodium /kg body weight, and indicated that compounds including, *N*-methylflindersine, Skimmianine, Germacrene-D, α-Cubebene, α-Cardinol and lupeol could be responsible for the anti-inflammatory activity.

4.3 Antimicrobial activity

Microbial infection is the process of invasion of infectious agents into the organism. These infectious agents mainly include bacteria, virus, parasite and fungi naturally occurring in the environment [24]. Antimicrobial activity can be defined as a collective term for all active principles (agents) that inhibit the growth of bacteria, viruses and fungi. Although antibiotics play an essential role in treating microbial infections, extracts of plants have also been attributed to contribute significantly to antibiotic activity. Currently, some of the antimicrobial drugs on the market have been isolated from natural sources.

Studies on the antimicrobial activity of the leaves; stem bark and roots of *V. nobilis* on gram-negative bacteria (like *Escherichia coli*), gram-positive bacteria (e.g., *Staphylococcus aureus* and *Bacillus subtilis*) and fungi (e.g. *Candida albican*) has been conducted. For instance, the inhibition zones (in mm) of DCM, hexane, ethyl acetate and methanol crude extracts of the air-dried leaf extracts of *V. nobilis* showed activity against *S. aureus* with DCM exhibiting the highest activity among the solvent, though its activity was lower than that of ampicilin or gentamycin. In these solvents, DCM and methanol also registered some activity against *S. pneumoniae* and *B. subtilis.*

A study conducted by Kisangau et al. [12] also determined the antimicrobial activity of petroleum ether extract of the leaves of *V. nobilis* and found activity against *B. subtilis* and *E. coli*, though there activities were lower than ampicillin and gentamicin, respectively. Furthermore, antimicrobial activity against *S. typhi* and *E. coli* were only realized in DCM and methanol extract. A similar study conducted by Nuru et al. [16] found that methanol root extract of *V. nobilis* showed promising activity against *S. aureus* and *P.aeruginosa,* but not for *Klebsiella pneumania* and *E. coli.* When an extract of a mixture of solvents (DCM and methanol in the ratio of 1:1) on the same microorganism was evaluated, the results were contrary. In another study conducted on fractionated furoquinoline alkaloids e.g. maculine and benzoylbetulin isolated from its roots showed antimicrobial activity against *S. aureus* and *P. aeruginosa* [16].

Although Onyacha et al. [15] and Kuete et al. [25] found that kokusaginine, dictamine, 8-Dimethoxy-7-(3-methyl-but-2-enyloxy)-furo [2, 3-*b*] quinoline, and β-Sitosterol isolated from *V. nobilis* showed activity towards *S. aureus* and *S. pneumonia,* Michael [27] had indicated earlier that kokusaginine and dictamine had not exhibited antimicrobial activity towards a range of microorganisms at concentrations even up to 100 g/mL But a study by Kuete et al. [25] also found that that

kokusaginine, kolbisine, maculine and lupeol had promising antimicrobial activity on bacteria and fungi. A similar study by Adamska-Szewczyk et al. [18] indicated that dictamine alkaloid possed anti-fungal properties while that of Onyancha et al. [13] indicated that skimmianine alkaloid showed antimicrobial sensitivity to *B. subtilis*, *B. cereus*, *S. aureus*, *S. epidermidis*, *S. pyogenes*, *Enterobacter aerogenes*, *Enterococcus* spp., *E.coli*, *Klebsiella pneumonia*, *P. aeruginosa*, *E. cloacae*, *Shigella sonnei*, *Salmonella typhimurium*, *Burkholderia cepacia*, *Morganella morganii* and *Candida albicans*, *C. tropicali*, *C. krusei*, *C. parapslosis*, *Sacharomyces cerevisae*, *Cryptococcus neoformans* and *C. gatti* [15].

Although a study by Al-Rehaily [7] indicated no microbiological potential of the essential oil from the leaves against a number of micro-organism, a study by Ocheng et al. [29] reported that essential oils from the root possessed antimicrobial sensitivity to periodontopathic and cariogenic bacteria clinically present in the dental plaque including A*ggregatibacter. Actinomycetemcomitans (*HK 1519) and *Porphyromonas gingivalis* (ATCC 33277), *Bacillus megaterium* (BM11), *Streptococcus mutans* but not to *Lactobacillus acidophilus* (NCTC 1723) at concentrations of 0.01%, 0.1 and 1%. An invitro antibacterial study of teclenone A (**1**) and teclenone B conducted against *S. aureus, P. aeruginosa*, *C. albicans* and *Cryptococcus neoformans* were found to be inactive [19].

4.4 Anti-malarial and antiplasmodial activity

Malaria is one of the major parasitic infection in many tropical and subtropical regions that has contributed the largest burden on public health of most developing countries with global estimates of 600 million new infections annually and at least 1 million of these infections being fatal [35]. *Vepris nobilis* is one of the medicinal plants used in traditional medicine to treat malaria in rural areas where malaria is the major cause of death. A study conducted by Lacroix et al. [8] on the antiplasmodial activity of ethyl acetate extracts of the fruits and leaves showed that leaves had more activity than the fruits with 98% instead of 55% growth inhibition of *Plasmodium falciparum* FcB1 strain at 10 mg/ml, respectively [8]. In another study conducted on the stem bark extract of *V. nobilis* against *P. falciparum* FcB1 strain (10 μg/mL), 54.7% inhibition was obtained compared to chloroquine with 98.1% Inhibition, and this showed a promising anti-plasmodial activity against *P. falciparum.* In terms of toxicity on two cell lines, the stem bark extract showed low cyto-toxicity of 36.0% and 22.0% with inhibition of KB cells (10 μg/mL) and MRC5 cells (10 μg/ml), respectively [4].

Further investigation of anti-plasmodial activity of skimmianine alkaloid from the arial parts and leaves of *V. nobilis* show a weak activity against *P. falciparum* with cytotoxicity being exhibited towards L-6 cells [18]. A study on the antimalarial activity of kokusaginine and maculine against chloroquine sensitive (CQS) strain of *P. falciparum* NF54 *in vitro* with concentrations ranging from 2 to 8 μM showed partial suppression of parasitic growth with significantly different from untreated control group after four days. Montrifoline alkaloid from the fruits of *V. nobilis* also showed a weak activity against chloroquine- resistant FcB1/Colombia strain of *P. falciparum* with IC_{50} of 56 mg/ml compared to chloroquine 0.1 mg/ml, and its cytotoxicity was found to be weak with IC_{50} with greater than 50 mg/ml. Arborinine alkaloid isolated from arial parts of *V. nobilis* was found to have moderate antimalarial activity against CQS D10 strain of *P.falciparum* with IC_{50} values of 12.3 and 24.5 mM respectively [6].

In another study by Waffo et al. [36] there was antimalarial activity of 12.3 μM of arborinine alkaloid against a Nigerian CQS strain. Similarly, Mwangi et al. [29]

found anti-plasmodial activities of arborinine and skimmianine alkaloids from *Teclea trichocarpa* against chloroquine-resistance strain K1 to be mild with IC_{50} of 1.61 and 5.60, respectively compared to chloroquine with IC_{50} of 0.0665 μg/ml.

However, furaquinoline alkaloids including teclealbine, −tecleoxine, isotecleoxine, methylnkolbisine, chlorodesnkolbisine, anhydroevoxine and pteleine were reported to be ineffective in antimalarial tests [4]. Similarly, in vitro antimalarial activity of teclenone A and teclenone B against *P. falciparum* D6 and W2 clones registered no activity [19].

4.5 Anti-leishmanial and anti-trypanosomal activity

Leishmaniasis is a disease caused by a protozoa parasite from over *20* Leishmania *species*. Over 90 sandfly species are known to transmit Leishmania *parasite*s through the bites of infected female phlebotomine sandflies which feed on blood to produce eggs [37]. Globally, leishmaniasis disease affects over 350 million people. Although chemotherapeutic therapies including pentavalent antimonials, miltefosine, stibogluconate, amphotericin B and paromomycin are used against leishmaniasis, medicinal plants are also potential sources of lead compounds. A study conducted by Lacroix et al. [4] on the anti-leishmanial activity of montrifoline alkaloid from the leaves of *V. nobilis* found moderate activity against *Leishmania donovani* with EC_{50} of 31.2 mg/ml and no activity against *Trypanosoma brucei* when compared with pentamidine with EC_{50} of 3.1 mg/ml. Even Adamska-Szewczyk et al. [18] indicated anti-leishmanial activity of skimmianine activity. Most alkaloids extracted from the fruits and leaves were found not to show *Trypanosoma brucei* activity with their EC_{50} being ≥125 mg/ml when compared with that of pentamidine with EC_{50} of 1.8 mg/ml [4]. *N*-methyl-8-methoxyflindersin, isolated from the leaves of *Raputia heptaphylla* was found to show antiparasitic activity against *Leishmania* promastigotes and amastigotes [38].

4.6 Anti-caseinolytic activity

Snakebite envenomations continue to be a threat to public health in some parts of the world. At least 1,841,000 snakebites resulting in about 94,000 deaths are recorded annually. Venomous snakebites have been traditionally treated with medicinal plants. Pharmacological invitro evaluation of aqueous methanol crude plant extract of *V. nobilis* demonstrated significant abilities to inhibit the caseinolytic effect of crude *Bitis arietans* venom and this was related to the higher composition of flavonoids, flavonols and phenolics [20]. Caseinolytic activity is the ratio of the absorbance of casein relative to the absorbance of the venom-casein mixture.

4.6.1 Anthelmintic activity

Helminth infections cause major morbidity and mortality in both human and animals. In developing countries, helminth infections pose a major threat to public health and contribute to the prevalence of malnutrition, anemia, eosinophilia and pneumonia [21]. Anthelmintics can be defined as drugs that either kill or expel infesting helminths or their larvae from the gastrointestinal tract or that live in tissue. Natural products have been found as potential sources for new, effective and safe anthelmintic drug. Although *V. nobilis* is ethnomedicinally reported to be anthelmintic, a study by Muema et al. [2] on lupeol terpenoid isolated from *V. nobiis* was found not to show anthelmintic activity.

4.7 Anti-depression activity

Depression is an illness which involves not only mood or emotion disorder but also the physical body and thought process disorder including loss of interest, reduced energy and concentration. This disease is estimated to affect about 21% of the world population. Although there are existing drugs for treatment of depression, they are associated with side effects like dry mouth, fatigue, gastrointestinal or respiratory problems, anxiety, agitation, drowsiness, and cardiac arrhythmias. There are several phytochemicals with antidepressant activity. Adamska-Szewczyk et al. [18] has indicated that alkaloids like kokusaginine and skimmianine in *V. nobilis* inhibit 5-HT2 receptor activity, thus suggesting their significance in the treatment of various diseases related to serotonin neurotransmission including depression [18].

4.8 Toxicity of *V. nobilis*

Assessing the safety of medicinal plants has been regarded to be essential even if it has been used for decades. A study by Mailu et al., [11] on toxicity of dichloromethane and ethanol extracts of aerial parts of *V. nobilis* found mild toxicity and no toxicity to brine shrimp as showed by their LC_{50} of 75.5 μg/mL and 156.6 μg/mL respectively [10]. In another study using brine shrimp lethality tests conducted on various solvent leaf extracts of *V. nobilis* including hexane, dichromethane, ethyl acetate and methanol against *Artemia salina* found LD_{50} of 235, 165, 557 and 268 respectively [15]. It was concluded that *V. nobilis* leaf extracts were non-toxic. Brine shrimp results of LC_{50} < 1.0, 10–30, 30–100 and > 100 μg/mL are regarded highly toxic, toxic, moderately toxic, mildly toxic and none toxic respectively [10].
Even an alkaloid, 6-dimethoxy-7-((3-methylbuta-1,3-dien-1-yl) oxy) furo[2,3- b] quinolone isolated from *V. nobilis* was predicted with median lethal dose (LD_{50}) of 1600 mg/kg, suggesting its toxicity to be of class 4, which has LD_{50} between 300 and 2000.

5. Conclusion

Vepris noblis is a rich source of furoquinoline alkaloids, terpenoids and flavonoids. The extracts and phytochemical compounds extracted from the different parts have shown promising pharmacological antimalarial, analgesic, anti-inflammatory and antipyretic activities. Toxicity studies also indicate that *V. nobilis* is generally safe.

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