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# Ethnopharmacological Importance of *Xylopia aethiopica* (DUNAL) A. RICH (Annonaceae) - A Review

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***Authors' contributions***

*This work was carried out in collaboration between all authors. Authors WK and RKA designed the study. Author JPF managed the literature searches and wrote the first draft of the manuscript. Authors WK and RKA proof read the manuscript. All authors read and approved the final manuscript.*

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## ABSTRACT

**Ethnopharmacological Relevance:** *Xylopia aethiopica* or Ethiopian pepper is a plant that thrives in most of the evergreen rain forests of tropical and subtropical Africa, and it is currently grown most prominently in Ghana as a crop. Almost all parts of *Xylopia aethiopica* possess great medicinal values in traditional medicine. In most parts of Africa, it is used in the treatment of cough, rheumatism, dysentery, malaria, uterine fibroid, boils, and wounds among others. This review summarizes published data on phytochemistry, toxicological properties, Ethnopharmacological and other uses of *Xylopia aethiopica*, and aims at providing an up-to-date detail that should constitute baseline information for future research on the plant.
**Materials and Methods:** Google Scholar, Scifinder® and PubMed were the electronic databases used to search for and filter published research on *Xylopia aethiopica*.
**Results:** The various parts of *Xylopia aethiopica* possess a wide diversity of phytochemicals. A detailed description of only a few of these phytochemicals i.e. essential oils, alkaloids and

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diterpenes is available in published research currently. Extracts and isolates from almost all parts of the plant tends to possess one bioactivity or another that confirms its traditional uses, and have largely shown to be of low toxicity.
**Conclusion:** *Xylopia aethiopica* has shown to possess potential pharmacological benefits; there is however, the need for further research to be conducted on various extracts and isolates of the plant that showed promise during *In vitro* and animal studies, to ascertain its potency, safety and efficacy in humans.

*Keywords: Xylopia aethiopica; xylopic acid; pharmacology; antimicrobial; essential oils; review.*

## 1. INTRODUCTION

Apart from serving as a source of food, plants invariably remain a major source of medicine in most parts of the world. This is particularly true about the people of Africa especially those in the tropical regions of the continent. This may be due to the fact that the tropical and subtropical regions of Africa alone contain about 45,000 species of plants with potential medicinal value. Despite the overabundance, only about 5,000 of these plant species have been exploited for medicinal use so far and even much less have been investigated for corroboration of the said therapeutic use and safety. For instance, Fetse et al. in 2014 [1], showed that total alkaloidal extract of *Alstonia boonei* root bark possess a good wound healing and antimicrobial activity and Hensel et al. [2] pointed out that the plant cell wall could possibly be a potential source of pharmacologically active compounds.

*Xylopia aethiopica* or Ethiopian pepper as it is usually called, is an angiosperm belonging to the family Annonaceae and is among the species that thrive in the evergreen rain forests of tropical and subtropical Africa. *Xylopia aethiopica* matures as a slim, tall tree of approximately 60 cm in diameter and up to 30 m high with a straight stem having a slightly stripped or smooth bark. It bears odoriferous fruits, which are slender pods slightly curved with about 15 carpels and are arranged in capitula to form bouquets of 12-20 bacciferous-like capsules [3]. *Xylopia* is a compression from the Greek words "*xylon pikron"* which mean "bitter wood". The second part of the plant's binomial name, *aethiopica*, refers to its origin, Ethiopia; however, currently it grows most prominently as a crop in Ghana [4]. The plant has several local names, in Ghana it is known as *'hwenteaa'* in Akan, *'etso'* in Ewe, *'so*' in Ga and '*samaamdabile'* by the Waala people in the Upper West Region. This plant has played a key role in African traditional medicine for several centuries owing to its wide array therapeutic indications. *Xylopia aethiopica* is used in the treatment of cough, biliousness, bronchitis, rheumatism, dysentery, malaria, uterine fibroid, amenorrhea [5], boils, sores, wounds and cuts among others [6].

Typically, studies on *Xylopia aethiopica*, like most medicinal plants have focused on the biological activities of its chemical constituents, ethnobotany, pharmacology, and taxonomy. However, a comprehensive or systematic review on the plant is generally lacking. That notwithstanding, it is worth mentioning that some attempts have been made in this regard. For instance, Juliani et al. [7] in a review, provided information on the composition of essential oils, antioxidant activity, quality control standards, and the pharmacological uses of the dried fruits of *Xylopia aethiopica* using the

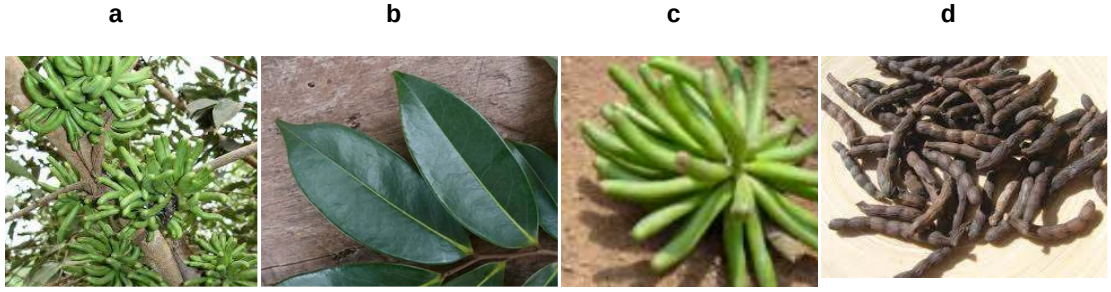


**Fig. 1. (a) Fruits of *Xylopia aethiopica* still attached to the tree (b) leaves of *Xylopia aethiopica* (c) a cluster of *Xylopia aethiopica* fruits and (d) dried fruits of *Xylopia aethiopica***

product of Ghana as an illustrative case study. Clearly, this study focuses mainly on *Xylopia aethiopica* fruits from Ghana and as such is barely comprehensive. Again, the study was conducted almost a decade ago and throughout this period, several studies have been carried out on the plant in various fields of science. Consequently, this paper presents information on but not limited to the morphology, ecology, ethnopharmacology, phytochemistry, biological activities and toxicological properties of *Xylopia aethiopica* and aims at providing an up-to-date detail that should constitute baseline information for future research and commercial exploitation of the plant.

## 2. TAXONOMY, CULTIVATION AND ETHNOBOTANICAL USES OF *Xylopia aethiopica*

### 2.1 Taxonomy

The genus *Xylopia* is consists of about 150 species which occur in tropical and subtropical Africa [8]. *Xylopia aethiopica*, also known as Negro pepper, is an angiosperm belonging to the custard apple family, Annonaceae [9].

| | |
|---|---|
| Kingdom: | Plantae |
| Subkingdom: | Viridiplantae |
| Infrakingdom: | Streptophyta (land plants) |
| Superdivision: | Embryophyta |
| Division: | Tracheophyta (vascular plants) |
| Subdivision: | Spermatophytina (seed plants) |
| Class: | Magnoliopsida |
| Superorder: | Magnolianae |
| Order: | Magnoliales |
| Family: | Annonaceae (custard apples) |
| Genus: | Xylopia |
| Species: | *Xylopia aethiopica* |

### 2.2 Cultivation

*Xylopia aethiopica* grows into a giant tree in most of the evergreen rain forests of tropical and subtropical Africa. The plant thrives in humid forest zones of West Africa. It can grow to as high as 20 m or even up to 45 m [10]. The stem is generally straight with a smooth or slightly striped bark and has a diameter of about 60 cm [3]. The leaves are elliptically shaped and can be longer than 15 cm at the offshoots with thick fringes and feel fatty to touch. They appear blue-green on the upper side, with a big clear green median nerve, while the secondary veins are much less pronounced. The trees also bear odoriferous greenish-white flowers with external petals up to 5 cm long [11]. *Xylopia aethiopica* is cultivated mainly for the fruits, made up of clusters of about 30 mericarps, *5* to 6 cm long and 0.5 to 0.8 cm wide. For each mericarp there are 1 to 9 seeds, which are *5* to 6 mm long and 2 to 3 mm wide, covered with a bright brown tegument [10]. In West Africa, the tree flowers twice every year (i.e. March-July and October-December) while fruiting occurs in December-March and June-September with harvesting time running from February to May and from August to October [4].

### 2.3 Ethnobotanical and Other Uses

*Xylopia aethiopica* possesses great nutritional and medicinal values in traditional medicine [12]. Almost all parts of *Xylopia aethiopica* are very useful medicinally, but the fruits are most commonly used for therapeutic purposes. Extracts of the fruits are used in the treatment of cough, biliousness, bronchitis, rheumatism, dysentery, malaria, uterine fibroid and amenorrhea [13,5,14]. The fruits can also be crushed and mixed with Shea butter and used as body creams, cosmetic products or perfumes [11]. It has also been showed that the essential oil from the seeds of *Xylopia aethiopica* can be used in the formulation of shampoos due to its high saponification value (207.2±8.0) [15]. Conversely, in a preliminary evaluation of the physical and chemical properties of essential oils from the seeds *Xylopia aethiopica,* Ogbonna and others [16] also determined the saponification value of the oil to be 130.18. This value is lower than that obtain in the instance described earlier. The geographical location of the plant and the time of harvest could all affect the nature and composition of essential oils in the plant thus resulting in the differences observed. In Benin, the dried fruits are commonly used as a constituent of extracts for bathing, and as a potion administered to new-borns [11]. The seeds are crushed and applied topically on the forehead in the treatment of headache and neuralgia. It can also be taken as a decoction, concoction or even chewed and swallowed for the management of various aches and pains [17]. It has also been shown experimentally, that the seeds possess good anthelminthic activity against *Nippostrongylus brasiliensis* and as such its use in man as an anthelminthic may be investigated [18]. Various extracts of *Xylopia aethiopica* have also demonstrated some promise in its employment as an adjunct therapy in the management of sickle cell disease [19]. An

oily extract of the seeds is used as a lotion for boils and eruptions, and as a liniment for lumbago. Traditional medical practitioners and birth attendants use a decoction of the seeds to induce placental discharge postpartum due to its abortificient effect [5,14].

The roots of *Xylopia aethiopica* are employed in tinctures, administered orally as an anthelminthic, or in teeth-rinsing and mouth-wash extracts against toothache [11]. They are also used as an antihemorrhagic agent. Aqueous concoction of the root is administered after child birth as an anti-infective agent [20]. The powdered root is also employed as a dressing and in the local treatment of cancer [12].

The leaves and bark are used in traditional medicine to manage boils, sores, wounds and cuts [6]. A decoction of the leaves is used as an anti-emetic. Powdered leaves are also taken as snuff for the treatment of headaches [21]. It was revealed in a survey conducted by Kadiri et al. [22] that the stem bark of *Xylopia aethiopica* is used in combination with other medicinal plants as an alcoholic decoction that is applied topically in the treatment of postpartum breast infections.

In some parts of Congo, the plant is used to manage asthmatic attacks, stomach aches and rheumatism. In the Ivory Coast, it is recommended as a postpartum tonic and also taken to promote fertility and ease of childbirth [5,23]. *Xylopia aethiopica* is also used locally as carminative, stimulant and adjunct to other remedies for the treatment of skin infections [24]. In a review, Ngo Van Hai [25] suggested that the seeds of *Xylopia aethiopica* could potentially be used to boost fishes' immunity against various infections. This is of particular interest to scientists in the field of aquaculture as these natural products, unlike antibiotics pose minimal risk to the fishes and also to the environment.

Aside its extensive use in traditional medicine, *Xylopia aethiopica* has other very important non medicinal uses. For instance, essential oils from various parts of the plant have been used as a pesticide to protect cereals against insect attack. Although this is effective, the relative high volatility and biodegradability of the essential oils, makes the method be of low persistence [26]. These essential oils have also been used as mosquito and housefly repellents, and termite antifeedants [13]. Again, extracts of *Xylopia aethiopica* have been shown to possess toxic and repellent activity against *Tribolium castaneum* Herbst and *Sitophilus zeamais* Motschulsky respectively and as such can potentially be used to protect various grains and cereals from such insect infestation on storage [27,28].

*Xylopia aethiopica* has also been investigated for its potential use as a preservative. Specifically, the applicability of both the aqueous and diethyl ether extracts of the dried fruits of *Xylopia aethiopica* as a fungicide has been investigated. Here, the aqueous extract showed a 23% reduction in lesion caused by the fungi, *Colletotrichum lindemuthianum* on cowpea after 21 days of application of the extract. The cowpea was infected with the above named fungi prior to application of the extract. Conversely, the ether extract showed a 29.6% lesion reduction when compared to the negative control while benomyl, a commercial fungicide serving as the positive control showed a 12.6% reduction in fungal lesion [29]. A hot water extract of the seeds of *Xylopia aethiopica* has also exhibited fungitoxic activity against *Fusarium oxysporum, Aspergillus niger* and *Aspergillus flavus* which are among the frequently occurring spoilage fungi that induce rot in yams. The extract was consequently shown to protect yam tubers from such fungi infection leading to rotting of yams [30]. Some extracts have also been shown to inhibit the growth of *Escherichia coli* and *Bacillus cereus* which are among the commonest microbes involved in food contamination [31]. These findings point out the fact that extracts of *Xylopia aethiopica* can potentially be used in food preservation and this is particularly advantageous because unlike the chemical preservatives, *Xylopia aethiopica* extracts are generally of low toxicity and environmentally safe.

*Xylopia aethiopica* has been investigated for its potential as an antioxidant in food. It was showed that an ethanolic extract of *Xylopia aethiopica* exhibited antioxidant effects on lard and groundnut oil [31]. At a storage temperature of 13℃, the influence of *Xylopia aethiopica* aqueous seed extract on the antioxidant properties of matured tomato fruits at red stage was investigated. It was reported that fruits treated with 5% aqueous seed extract after 5 days of storage had 21.0 mg of vitamin C in every 100 g of the fruits which was significantly ($p < 0.05$) higher than 18.2 mg/100 g obtained in the untreated control samples. On the 30th day of storage, ascorbic acid was 14.2 mg/100 g in tomato fruits treated with the extract and 10.1 mg/100g in the untreated control samples [32].

The potential of *Xylopia aethiopica* to retain the antioxidant properties of tomatoes creates opportunities for the investigation of its candidacy as a stabilizer in the food industry.

The wood from *Xylopia aethiopica* is resistant to termites' attacks and as such, is used in the construction of furniture, huts and boats. In some parts of Cameroon, Gabon and Togo, the wood was traditionally used to make bows and crossbows for hunters and warriors [5,13]. Furthermore, Okafor and Apebende [33] showed that ethanol extracts from the fruits of *Xylopia aethiopica* inhibit the corrosion of mild steel in sulphuric acid (5 M) solutions. The observed inhibitory effect was attributed mainly to the essential oil present in the extract. Essential oils of *Xylopia aethiopica* are known to predominantly contain large molecular weight compounds containing one or more heteroatoms. It was thus proposed in this study that, these compounds get adsorbed onto the metal surface *via* lone pair of electrons on the heteroatoms, creating a protective film of metal–inhibitor complex, leading to reduced metal-acid contact and thus a reduction in the corrosion rate. This suggests that extracts from the plant can potentially be used to protect various metals from corrosion. Therefore, further investigations can be conducted to identify the specific compounds responsible for the inhibition of corrosion and the feasibility of their application in the paint and other related industries assessed.

## 3. CHEMICAL COMPOSITION OF THE LEAF, BARK, FRUIT, SEED AND ESSENTIAL OIL

*Xylopia aethiopica* is known to have myriad chemical constituents with diverse therapeutic and pharmacological properties. These compounds, most of which have been isolated and characterized include saponins, sterols, carbohydrates, glycosides, mucilage, acidic compounds, tannins, balsams, cardiac glycosides, volatile aromatic oils, phenols [34-36], alkaloids, rutin and fixed oils [37,38]. The plant also contains vitamins A, B, C, D, and E, and proteins together with high amounts of minerals like copper, manganese and zinc [36,37].

### 3.1 Alkaloids

Alkaloids isolated from the methanolic extracts of the aerial parts of *Xylopia aethiopica* include the oxoaporphine alkaloids, oxophoebine and liriodenine. Also, the alkaloids oxoglaucine, O-methylmoschatoline and lysicamine have been isolated from ethyl acetate extracts of the plant. Most of these alkaloids have demonstrated some cytotoxic effects in various studies. The chemical structures of these alkaloids are as shown below [39].

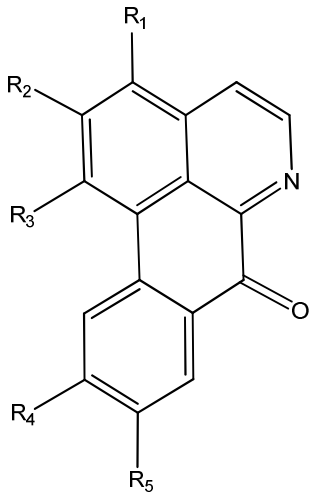


**Fig. 2. General structure of *Xylopia aethiopica* alkaloids**

**Table 1. Various alkaloids of *Xylopia aethiopica* and their respective substitution patterns in the parent structure**

| Alkaloid | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ |
|---|---|---|---|---|---|
| Oxophoebine | O-$CH_3$ | O-$CH_3$ | O-$CH_3$ | O-$CH_2$- | -O- |
| Liriodenine | H | O-$CH_2$- | -O- | H | H |
| Oxoglaucine | H | O-$CH_3$ | O-$CH_3$ | O-$CH_3$ | O-$CH_3$ |
| O-methylmoschatoline | O-$CH_3$ | O-$CH_3$ | O-$CH_3$ | H | H |
| Lysicamine | H | O-$CH_3$ | O-$CH_3$ | H | H |

### 3.2 Diterpenes

Most of the acidic compounds isolated from *Xylopia aethiopica* are the various kaurane, kolavane and trachylobane diterpenes which are reportedly present in the stem bark and fruit of the plant. Quite an extensive research has been conducted on most of these diterpenes leading to the elucidation of their structures. Typically, xylopic acid (Fig. 3), a kaurene diterpene has been taken through extensive research to the extent that several derivatives of it have been synthesized. Ekong and Ogan [40] isolated xylopic acid from the dried powdered fruits of *Xylopia aethiopica* by extracting the latter with light petroleum (b.p.60-80℃). The extract was subsequently concentrated and crystallised from ethyl acetate to obtain xylopic acid, its melting point was determined to be 259-260℃. Again, Soh et al. [13] also extracted xylopic acid using hexane where the extract was chromatographed over silica gel using hexane-ethyl acetate (95:5) mixtures to obtain xylopic acid as a white powder with melting point of 230-232℃. Although the two groups of researchers reported to have isolated xylopic acid, there was a vast difference in the melting point of the crystals obtained. This could possibly be attributed to the fact that a particular group isolated xylopic acid of low purity and as such the impurities might have altered the actual melting point of the compound. Better still, it could be that one group isolated a compound closely related to xylopic acid but not xylopic acid itself. Apart from the difference in melting point, Ekong and Ogan elucidated the structure of the compound isolated as 15β-acetoxy-(-)-kaur-16-en-l9-oic acid while Soh *et al* determined theirs to be 15α-acetoxy-ent-kaur-16-en-19-oic acid. Fiagbe et al. [41] also solved the structure of xylopic acid as 15β-acetoxy-(-)-kaur-16-en-l9-oic acid by use of crystallography. Elsewhere, Adosraku and Oppong Kyekyeku [42] isolated xylopic acid from the dried fruits of *Xylopia aethiopica* using petroleum ether (40-60℃) and recrystallized the former with distilled alcohol. The melting point obtained for these crystals was 261-262℃. In another research, Fahim et al. [43] determined the melting point of isolated xylopic acid as 265 – 266℃. The melting points obtained in these two separate studies for xylopic acid are in much agreement with that obtained by Ekong and Ogan (259-261℃) as compared to the melting point obtained by Soh et al. [13] (230-232℃). A major issue that requires further research is whether only one of these stereochemical forms of xylopic acid actually exists, or whether both do exist concurrently in the same plant or separately depending on the geographical location of the plant. And finally, the effects of the stereochemical difference if any on the melting point of the compound should be investigated.

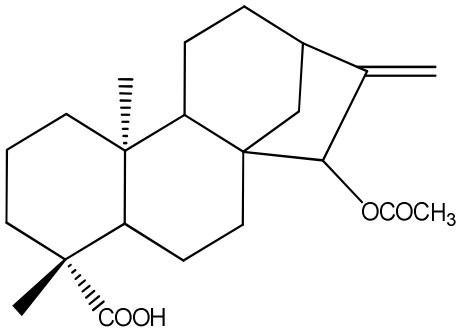


**Fig. 3. Chemical structure of xylopic acid**

Other kaurane diterpenes isolated from *Xylopia aethiopica* include xylopioxyde which has its nomenclature as 16, 17-epoxy-15-oxo-ent-kauran-19-oic acid, 15-oxo-ent-kaur-16-en-19-oic acid, ent-kaur-16-en-19-oic acid and (-) kaur-16-en-15-hydroxy-19-oic acid (melting point 204-206℃) among others. Xylopioxyde is obtained by column chromatographic separation (eluent: hexane-ethyl acetate 85:15, $^{v}/_{v}$) of hexane extract of *Xylopia aethiopica* fruits and exists as a white powder with melting point of 190-192℃. 15-oxo-ent-kaur-16-en-19-oic acid could also be obtained upon elution of hexane extract of *Xylopia aethiopica* fruits (eluent: hexane-ethyl acetate 90:10, $^{v}/_{v}$) and occurs as a white powder with melting point 192-194℃. Ent-kaur-16-en-19-oic acid is also obtained as a white powder having a melting point of 172-174℃ upon column chromatographic separation of the hexane extract of *Xylopia aethiopica* fruits on a silica gel column (eluent: hexane-ethyl acetate 80:20, $^{v}/_{v}$) [13,44]. Trachyloban-19-oic acid, 7β-hydroxytrachyloban-19-oic acid [45], 7α-hydroxytrachyloban-19-oic acid [46], 15-oxo-(-)-trachyloban-19-oic acid and 15β-hydroxy-(-)-trachyloban-19-oic acid [47] are among the trachylobane diterpenes while kolavenic acid [45] and 2-oxo-kolavenic acid [48] are typical kolavane diterpenes also present in *Xylopia aethiopica.*

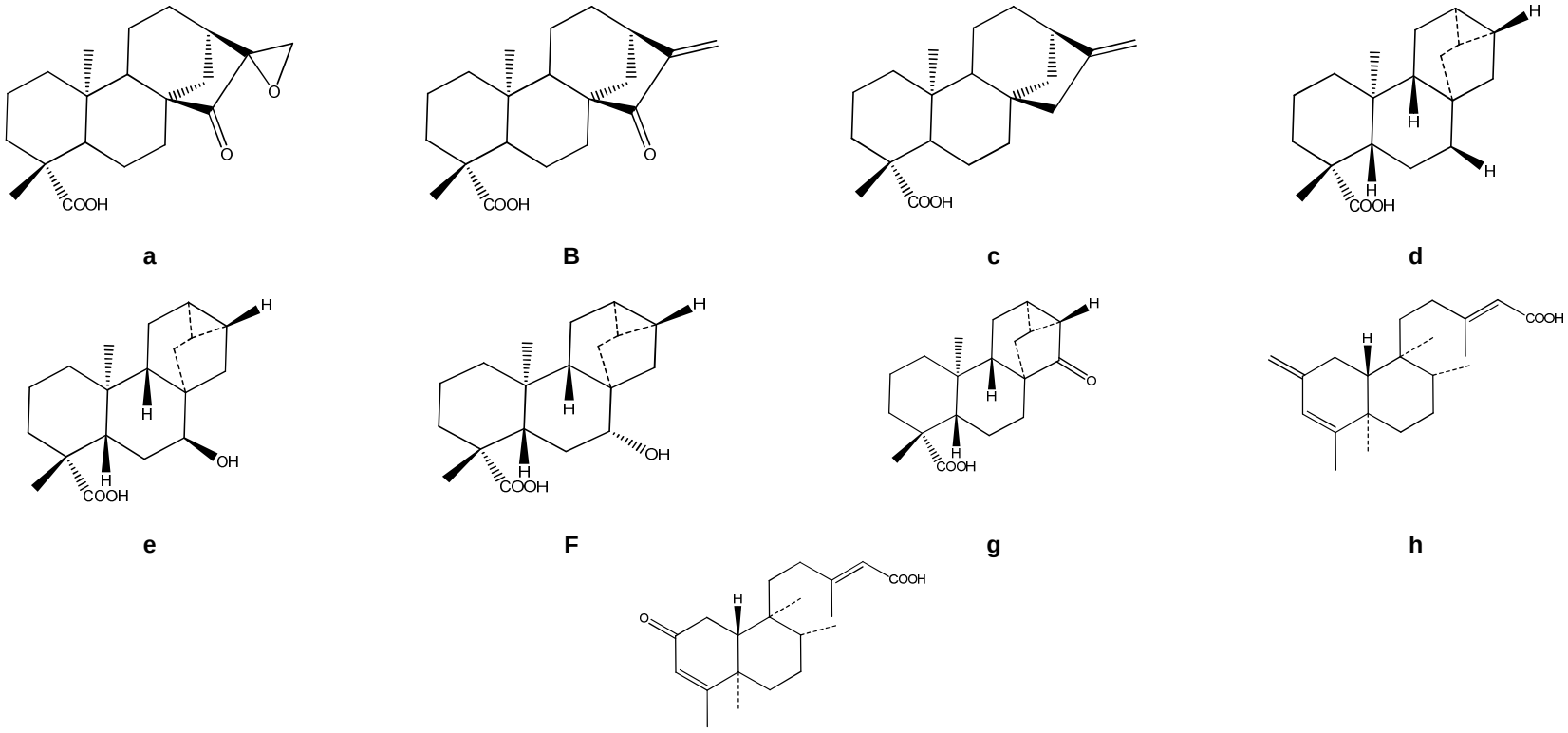


**Fig. 4. Chemical structures of (a) xylopioxyde (16, 17-epoxy-15-oxo-*ent*-kauran-19-oic acid), (b) 15-oxo-ent-kaur-16-en-19-oic acid, (c) *ent*-kaur-16-en-19-oic acid, (d) Trachyloban-19-oic acid, (e) 7β-hydroxytrachyloban-19-oic acid, (f) 7α-hydroxytrachyloban-19-oic acid, (g) 15-oxo-(-)-trachyloban-19-oic acid, (h) kolavenic acid and (i) 2-oxo-kolavenic acid**

### 3.3 Essential Oils

Among the commonest groups of chemical compounds conspicuously present in the various parts of *Xylopia aethiopica* are the essential oils. Different studies conducted on these essential oils have shown the presence of a wide diversity of chemical compounds. In one of the early studies conducted, Ogan [49] identified for the first time, an aromatic aldehyde specifically, cuminal (*p*-isopropyl-benzaldehyde) as a component of the essential oils obtained from the fruits of *Xylopia aethiopica*. After almost a decade later, Karawya et al. [50] also analysed the essential oil from the dried fruits of *Xylopia aethiopica* and the only aldehyde identified was cuminic aldehyde at a concentration of 6.5%, corroborating Ogan's work. Other compounds were also identified; namely β-pinene a monoterpene hydrocarbon, bisabolene a sesquiterpene hydrocarbon, terpinene-4-ol which is an alcohol and the oxide 1, 8-cineole among others.

Ogunwande et al. [51] also reported for the first time, the presence of Zerumbone, a known sesquiterpene ketone as a constituent of *Xylopia aethiopica*. Elsewhere, Ayedoun et al [11] identified about 60 components in the essential oil obtained from the fruits and leaves of *Xylopia aethiopica* sourced from Benin of which about 45 have previously been identified. The components that occurred in relatively high quantities are α-pinene (4-16%), sabinene (3-35%), β-pinene (12-42%), 1,8-cineole (trace-15%) and (Z)-β-ocimene (trace-18%). The leaf oil additionally contained 14.9% of elemol. In another research to investigate the composition of the essential oil of *Xylopia aethiopica* dried fruits from Benin, Poitou et al. [52] identified and characterized forty-one compounds representing 82.3% of the oil. Two major fractions were identified, namely oxygenated (28.8%) fraction and the hydrocarbon fraction which comprised mainly of monoterpenes (>50% of the whole oil), with sabinene (36.0%) as the main component. 1, 8-cineole (12.8%), linalool (3.9%) and terpinen-4-ol (7.0%) were the major oxygenated monoterpene constituents identified. The major sesquiterpenoid components identified were β-elemene (0.81%) and β-eudesmol (1.9%). These results are in agreement with the findings of Ayedoun et al. [11] except that α-pinene, β-pinene and a few other compounds occur in much lower quantities in the samples analyzed by Poitou et al. [52]. Again, Tomi et al. [53] identified the component of essential oil obtained from the seeds of *Xylopia aethiopica* sourced from Guinea. It was observed that monoterpenes were the most predominant (81.4-84.1%); prominent among them were hydrocarbons; namely β-pinene (37.0-40.5%) and α-pinene (13.6-18.4%) which are the major constituents, sabinene (7.1-7.6%) and 1, 8-cineole (6.5-8.4%). Also present in some of the analysed plant samples were α-phellandrene (7.9%) and germacrene D (6.5%), which are sesquiterpenes. Yapi et al. [21] analysed the chemical composition of 48 essential oil samples isolated from the leaves of *Xylopia aethiopica* harvested in six Ivoirian forests. The analysis was carried out using GC-FID and $^{13}$C-NMR. The findings were not so different from what has been reported in previous research; about 23 components were identified accounting for 82.5–96.1% of the oil composition. Here again, the monoterpene hydrocarbons β-pinene (up to 61.1%) and α-pinene (up to 18.6%) were the most dominant together with the sesquiterpene hydrocarbon germacrene D (up to 28.7%). The essential oil of *Xylopia aethiopica* dried fruits from Mali have been analysed using combined GC and GC/MS. The principal constituents identified were β-pinene, γ-terpinene, trans-pinocarveol, *p*-cymene, α-cadinol, α-pinene and 1,8-cineole. Among these, β-pinene was the most prominent [54]. Lamaty et al. [10] analysed the essential oil of *Xylopia aethiopica* fruits from Cameroon by GLC and GC-MS. It was reported that monoterpene hydrocarbons (66.6%) were the most conspicuous among which sabinene is the most abundant (23.9%), oxygenated compounds particularly terpinen-4-ol and α-terpineol made up 25.1% of the oil and 8.3% of the oil was sesquiterpenene hydrocarbons with α-muurolene making up 4.3% of the latter.

Juliani et al. [7] evaluated the composition of essential oil of *Xylopia aethiopica* sourced from Ghana and like the previous works done; it was observed that the essential oil was characterized by high levels of monoterpenes. The main constituents identified were β - pinene, 1,8 cineole, α-pinene and myrtenol. Also (E)-sabinol, terpin-4-ol and α-terpineol were detected but in lower levels. However, unlike other studies carried out, sabinene was also present in relatively lower levels. Considering an earlier research conducted by Karioti et al. [55], essential oil of the leaf, fruit, root and stem bark of *Xylopia aethiopica* from Ghana was shown to contain monoterpenes hydrocarbons (particularly α and β-pinene) as major constituent. This is consistent with the findings reported by Juliani et

al. [7] and other similar studies conducted elsewhere. The main constituent of both root and stem bark essential oils is *trans-m-mentha-1, 8-diene* (30.4 and 30.7%, respectively). The study, however, reported an unusually high level of germacrene D (24.5, 19.4, and 25.1% for leaf, fresh and dried fruit essential oils respectively), which is mostly reported to either be absent or exist in trace amounts in various *Xylopia aethiopica* essential oil samples investigated. Additionally, Karioti et al. [55] showed that these essential oils significantly scavenge superoxide anion radicals suggesting the potential antioxidant activity of these essential oils. Yet again, Koba et al. [56] evaluated essential oil extracted from air-dried fruits of *Xylopia aethiopica* harvested in Togo and the chemical composition examined by GC and GC/MS. Thirty-five compounds were identified and these represented 89.9% of total oil. The major constituents identified were ß-pinene (23.6%), α-pinene (11%), sabinene (9.8%), germacrene D (8.3%) and 1, 8 cineole (8.2%). The general trend of results obtained in all these studies, particularly the various compounds identified in the essential oil of *Xylopia aethiopica* is illustrative of the fact that similar species of plants will usually have identical chemical composition. On the contrary, the variations observed in composition and/or concentration of some components, especially those sourced from different countries could possibly be a reflection of the influence of the geographical origin on the chemical composition of plants belonging to the same species.

In a study to characterize the key aroma compounds in dried fruits of *Xylopia aethiopica* using aroma extract dilution analysis, Tairu et al. [3] observed that β-pinene, myrtenol, and β-phellandrene were important contributors to the overall odour of the *Xylopia aethiopica* fruit. It was also revealed that linalol, α-farnesene, (E)-β-ocimene, and α-pinene are responsible for the flowery and terpeny odour notes detected in the corresponding odour-active regions. Most of these chemical constituents discussed potentially possess one biological activity or the other and thus it is imperative that researchers critically investigate these compounds for any relevant pharmacological activity.

Furthermore, it is observed from this study that, there are many more compounds present in various parts of *Xylopia aethiopica* that are yet to be isolated and characterized. Therefore further research should be carried out in this regard to identify more compounds and also investigated their biological activity. In cases where some biological activity is observed, the possibility of chemically modifying the lead molecule to obtain a more active compound should also be considered.

## 4. PHARMACOLOGICAL PROPERTIES

### 4.1 Analgesic, Anti-inflammatory, Anti-Allergic and CNS Effects

An ethanolic extract of the fruits of *Xylopia aethiopica* showed significant analgesic activity against acetic acid-induced visceral nociception, formalin-induced paw pain (both neurogenic and inflammatory), thermal pain as well as carrageenan-induced mechanical and thermal hyperalgesia in rats and mice when the extract was administered orally. Xylopic acid isolated from the dried fruits of *Xylopia aethiopica* also showed comparable results [57]. The aqueous ethanolic fruit extract of *Xylopia aethiopica* at concentrations of 100, 300 and 600 mg/kg all exhibited good anti-arthritic effect when Adjuvant arthritis was induced in Sprague-Dawley rats by intraplantar injection of Complete Freund's Adjuvant into their right hind paw. The anti-arthritic effect was achieved as a result of the suppression of both inflammation and the destruction of the joint in adjuvant arthritic rats [58]. The anti-anaphylactic and anti-inflammatory effects of the aqueous ethanolic fruit extract of *Xylopia aethiopica* have been investigated by Obiri and Osafo [59]. In this study, it was reported that the aqueous ethanolic fruit extract when administered orally at doses of 30–1000 mg/kg 1 hour before administering compound 48/80 (an anaphylactic reaction inducer), there was significant anti-anaphylactic effects. This anti-anaphylactic effect was dose-dependent, in that increasing the dose of the extract led to a resultant increase in the median survival of the mice used for the study. Similar results were observed when the extract was investigated for its effect on Lipopolysaccharide (LPS)-induced allergy, pinnal inflammation (passive cutaneous anaphylaxis, PCA), clonidine-induced catalepsy and carrageenan-induced paw oedema. Ameyaw and others also showed that an ethanolic extract and xylopic acid from the dried fruits of *Xylopia aethiopica* was able to improve vincristine-induced tactile and cold allodynia, as well as mechanical hyperalgesia. This suggests that the ethanolic fruit extract of *Xylopia aethiopica* and its major kuarane diterpene

xylopic acid have anti-allodynic and anti-hyperalgesic properties in vincristine-induced neuropathic pain [60].

In an investigation of the neuropharmacological effects of an ethanolic fruit extract of *Xylopia aethiopica* and xylopic acid, *in vivo* experiments involving mice were conducted. From the results of this study, ethanolic fruit extract of *Xylopia aethiopica* and xylopic acid both showed significant central nervous system depressant effects in pentobarbitone-induced hypnosis and spontaneous activity test. Xylopic acid significantly decreased spontaneous locomotion at 30-1000 mg/kg doses ($F_{7, 48}$=6.320 p<0.0001) while the ethanolic extract of *Xylopia aethiopica* caused a significant reduction in activity ($F_{6, 42}$=6,078 p<0.0001) at doses of 300 and 1000 mg/kg. Xylopic acid showed a significant and dose dependent reduction of the onset of sleep from doses of 100-1000 mg/kg and also sleep duration was prolonged significantly, only at 300 and 1000 mg/kg. Again, it was reported that the ethanolic extract (which was obtained by extracting the plant material with ethanol and subsequent evaporation of the latter to obtain a dry mass) did not have a significant effect on the onset of sleep. However, it significantly ($F_{6, 42}$=133.0 p<0.0001) prolonged sleep duration in a dose-dependent manner. Xylopic acid and the ethanolic fruit extract of *Xylopia aethiopica* both showed neuromuscular coordination impairment potential at doses above 300 mg/kg. The ethanolic fruit extract of *Xylopia aethiopica* significantly increased seizure threshold at all doses while xylopic acid had no effect on PTZ (Pentylenetetrazole)-induced convulsion. The ethanolic fruit extract of *Xylopia aethiopica* exhibited an induction of hepatic enzymes at lower doses whereas xylopic acid showed a bidirectional effect by inhibiting hepatic enzymes at lower doses and inducing these enzymes at higher doses. It was also suggested that, both the ethanolic fruit extract of *Xylopia aethiopica* and xylopic acid may be metabolized by hepatic enzymes [61].

## 4.2 Cytotoxic Effects

Elsewhere, the anticancer activity of *Xylopia aethiopica* methanolic fruit extract was studied using human cancer cell lines C-33A (cervical), KB (oral), MCF-7 (breast), A549 (lung) and mouse embryo fibroblast (NIH3T3). In order to investigate the antitumor activity of the extract, the antiproliferative activity of the extract against the various cell lines was first studied. It was noticed that the C-33A cell was the most sensitive to the extract-induced growth inhibition. In addition, the extract showed an inhibition of the proliferation of C-33A cancer cells *via* cell cycle arrest at sub-G0/G1 and G2/M phases. This was corroborated by an increased level of p21 and p53 gene transcripts in extract treated cells [62]. The methanolic seed extract of *Xylopia aethiopica* has been shown to inhibit by more than 50%, the proliferation of three tested cancer cells namely MiaPaCa-2 (prostate cancer cells), CEM/ADR5000 and CCRF-CEM (both of which are leukemia cells) at a concentration of 20µg/mL, the $IC_{50}$ values were 6.86, 3.91 and 7.4µg/mL respectively. The degree of resistance was also determined as 1.9 [63]. Six compounds were isolated from *Xylopia aethiopica* namely lupeol(**1**), 16α-hydroxy-ent-kauran-19-oic acid(**2**), 3,4´,5-trihydroxy-6´´,6´´-dimethylpyrano[2,3-g]flavone(**3**), 3-O-β-sitosterol β-D-glucopyranoside(**4**), isotetrandrine(**5**) and trans-tiliroside(**6**). Fractions from the methanol extract of *Xylopia aethiopica* as well as compounds **2, 3, 5** and **6** were investigated on drug-sensitive and multi-drug ressistant cancer cell lines for cytotoxicity (the cytotoxicity of compounds **1** and **4** isolated from *Uapaca togoensis* has been previously reported and so was not tested in this study). The results of a resazurin assay showed that compounds **3** and **5** displayed cytotoxicity on all tested cancer cell lines with $IC_{50}$ values ranging from 2.61 µM (against leukaemia CCRF-CEM cells) to18.60 µM (against gliobastoma U87MG.ΔEGFR cells) and from 1.45 µM (against Hep G2 cells) to 7.28 µM (against MDA-MB-231-pc DNA cells), respectively. It is also worth noting that compounds 3 and 5 exhibited less toxicity towards normal AML12 hepatocytes than against hepatocarcinoma HepG2 cells suggesting their selectivity and as such makes them good candidate anti-neoplastic agents [64]. In an earlier study by Kuete et al. the crude methanolic extract of *Xylopia aethiopica* seeds were tested for their cytotoxicity against a panel of human cancer cell lines including sensitive and multi-drug resistant phenotypes. Cytotoxicity was determined by the resazurin assay and compared with doxorubicin as a positive control drug. The extract showed minimum and maximum $IC_{50}$ values of 4.11 µg/mL (against CCRF-CEM cells) and 30.60 µg/mL (against HL60AR cells) against the cell lines tested making the former a good candidate for further anticancer research involving sensitive and drug-resistant cancer cell lines as the American National Cancer Institute recommends 30 µg/mL

as the upper $IC_{50}$ limit considered promising for purification of a crude extract [65,66]. Choumessi et al. [9] reported that a 70% ethanolic extract of *Xylopia aethiopica* exhibited antiproliferative activity against a panel of cancer cell lines with estimated $IC_{50}$ values of 12 µg/mL against HCT116 colon cancer cells, 7.5 µg/mL and >25 µg/mL against U937 and KG1a leukemia cells, respectively. Fractionation of the extract by HPLC led to the isolation of the active fraction which induced DNA damage, cell cycle arrest in G1 phase and apoptotic cell death. The structure of the active compound in this HPLC fraction was determined to be ent-15-oxokaur-16-en-19-oic acid by spectroscopy. Adaramoye et al. [67] studied the effect of methanolic extract of *Xylopia aethiopica* dried fruits and vitamin C against γ-radiation-induced liver and kidney damage in male Wistar rats. *Xylopia aethiopica* (XA) and vitamin C (VC) were given orally at a dose of 250 mg/kg body weight, orally for 6 weeks prior to and 8 weeks after irradiation (5 Gy). The extract was reported to protect the hepatic and renal tissues of the rats from adverse effects of whole body gamma radiation by reducing radiation-induced increase in serum, kidneys and liver lipid peroxidation even after 8 weeks of exposure. Lipid peroxidation is most often than not, an indication of an overabundance of reactive oxygen species (ROS) and if not controlled may result in various pathological conditions such as atherogenesis and cancer. According to this study, the extract suppressed the detrimental effects of reactive oxygen species generated by the ionizing radiation through its ability to boost the levels of antioxidant enzymes like catalase and superoxide dismutase, induce phase II drug metabolizing enzyme (glutathione–*S*-transferase,) and, overall, enhance the recovery process. At the end of the study, all the animals in the un-irradiated group survived (100%), while 83.3% and 66.7% survived in XA-treated and VC-treated, groups respectively. In a similar study to evaluate the protective effect of methanolic extract of *Xylopia aethiopica* (XA) on γ-radiation-induced testicular damage in rats, it was observed that pre-treatment with XA and VC significantly ($p < 0.05$) increased sperm motility by 122% and 95%, respectively, compared with the untreated group. Again, XA and VC increased live/dead ratio of spermatozoa by 59% and 37%, respectively, relative to the untreated rats [68]. The findings of the current study suggest that *Xylopia aethiopica* has a protective effect by inhibiting oxidative damage in testes of irradiated rats. It however contradicts results of research conducted by Woode et al. [14] and Nwangwa [20] which both suggest that extracts of *Xylopia aethiopica* exhibit a dose dependent reduction in both sperm count and motility, as will be discussed later. As such, further research is required to either corroborated or annul these findings.

## 4.3 Antioxidant Effect

The free radical scavenging effects, the antioxidant and ion toxicity preventive effect of ethanolic extracts of *Xylopia aethiopica* stem bark was investigated by Moukette et al. [69] From the results of this research, it was observed that vitamin C used as standard had a significantly ($p < 0.05$) lower value of $IC_{50}$ on nitric oxide (NO), hydroxyl (OH), 2,2-diphenyl-1-picrylhydrazyl (DPPH) and 2,2′-azinobis(3-ethylbenzthiazoline)-6-sulfonic acid (ABTS) radicals as compared to the extracts. The extracts also showed a protective effect against lipid peroxidation. It may therefore be inferred from this study that *Xylopia aethiopica* has a good antioxidant and protective potential against ion-mediated oxidative damage and may be considered as a potential drug against metal mediated toxicity. Phenol-rich fruit extracts of *Xylopia aethiopica* exhibited very good free radical scavenging ability in a concentration dependent fashion (0.08-0.53 mg/mL). Again in assessing the ferric reducing antioxidant property of the extract, the study showed that the extract possesses good reducing potentials [70].

## 4.4 Hypoglycemic, Cardiovascular and Other Pharmacological Effects

Furthermore, the anti-diabetic effect of *Xylopia aethiopica* has also been studied. A chloroformic extract of the dried fruits of *Xylopia aethiopica* administered orally at a dose of 250 mg/kg showed an 82% reduction in the blood glucose concentration of alloxan monohydrate induced diabetic Wistar albino rats while diabetic non treated rats and glibenclamide treated rats showed a 6.9% and 74% reduction respectively. It was however reported that, a lower reduction of 23% was observed when the *Xylopia aethiopica* extract was administered at a dose of 100mg/kg. This suggests that the hypoglycemic effect of *Xylopia aethiopica* fruit extract is dose dependent [71]. In another study, an aqueous extract obtained from the dried fruits of *Xylopia aethiopica* administered at a concentration of 0.26% $^{w}/_{v}$ exhibited some influence on the

biochemical profile in Wistar Albino rats. For instance, it was revealed that the extract caused a marked reduction in the plasma cholesterol, triglyceride and sodium levels in the treated rats. These findings pre-suggest that the extract has some beneficial effects of reducing cardiovascular risk factors that are not genetic. Also, the extract was shown to induce hypokalemia [37]. Nwozo and others [72] conducted a study on Wistar rats to determine the effect of a methanolic extract *Xylopia aethiopica* at a dose of 250 mg/kg on serum and post mitochondrial fractions of visceral organs in experimental hypercholesterolemia. It was observed that when the extract was administered simultaneously with a cholesterol feed, there was a 33.75% reduction in serum cholesterol levels while simultaneous administration of a cholesterol feed with Questran® (cholestyramine) showed a 23.94% reduction in serum cholesterol levels of hypercholesterolemic rats. Also, the low density lipoprotein cholesterol level was reduced by 49.09% and 78.92% in serum and 64.97% and 37.29% in the liver when the cholesterol feed was combined with the plant extract and Questran, respectively, compared with untreated hypercholesterolemic rats. It was also reported that the extract inhibited decreases in enzymatic antioxidants, especially in glutathione, which showed greater than a 300% increase as compared to untreated hypercholesterolemic animals.

A study to investigate the ocular dynamics following a systemic administration of aqueous seed extracts of *Xylopia aethiopica* revealed that the extract, when administered orally at a dose of 300mg in visually active volunteers, caused a 17.48% reduction in intraocular pressure, suggesting that it could be used as an adjuvant in the management of glaucoma. In addition, a 31.1% reduction in the near point of convergence and an 8.98% increase in the amplitude of accommodation were also observed. However, the extract had no effect on the pupil size, visual acuity both at far and near and the volunteers remained orthophoric in the vertical direction before and after the administration of the extract [17]. These findings were a somewhat corroboration of an earlier study conducted by Uzodike and Onuoha [73]. Here, oral administration of 20mL of a 58.33 mg/mL aqueous fruit extract of *Xylopia aethiopica* showed an initial 1.26% increase in intra ocular pressure within 30 minutes of ingestion by the volunteers. However, a reduction in intra ocular pressure was observed thereafter, with a 0.09% and 2.60% reduction observed after 60 and 90 minutes respectively. These findings therefore call for the conduct of further research to isolate the possible bioactive compounds responsible for this activity and a study of their mechanism of action if possible.

As mentioned earlier, an ethanolic extract of the dried fruits of *Xylopia aethiopica* was shown to cause a significant ($P<0.05$) dose related reduction in sperm count and motility in male albino rats, but does not affect the morphology significantly. The testicular histology also showed a disorientation of the basal layer and histoarchitecture of the seminiferous tubules. The rats that received higher doses were affected much more than those with lesser doses, suggesting the dose dependency of this effect [20]. The effect of xylopic acid on sex hormones and spermatogenesis in male rats has been investigated as well. Here, xylopic acid isolated from the dried fruits of *Xylopia aethiopica* was administered orally to male Sprague-Dawley rats at doses of 10, 30 and 100 mg/kg for 28 days. It was observed that oral administration of xylopic acid showed no significant change in the body weight of the rats when compared with the control. However, there was a dose dependent reduction in the weight of the testis and epididymis of treated animals ($p <0.001$) compared with the control group. Examination of the seminiferous tubules also showed a significant ($P <0.001$) reduction in diameter for all treated rats compared to control. There was also a significant reduction ($p<0.05$) in serum prolactin concentration after 7 and 28 days of treatment. Treatment for 7 days showed no significant change in the serum follicle stimulating hormone (FSH) levels compared with the control group but FSH levels increased significantly when treatment was continued for 28 days ($P<0.05$). Luteinizing hormone levels increased significantly in a dose dependent faction after 7 as well as 28 days of treatment. Serum testosterone levels increased significantly ($p <0.05$) in rats treated with xylopic acid at doses of 10 and 30 $mgkg^{-1}$ for 7 days. However, continuous treatment for 28 days significantly ($p = 0.05$) decreased serum testosterone levels at all dose levels. Xylopic acid significantly decreased epididymal sperm count ($F_{3,\ 16} = 69.16$, $p < 0.001$) in a dose dependent manner in treated rats compared with control group. There was also a significant decrease in sperm motility ($F_{3,\ 16} = 43.95$, $p < 0.001$) and sperm viability ($F_{3,16} = 15.68$, $p < 0.001$) compared with the control group. It is however worth noting that

after two weeks of recovery, seminiferous tubular cytoarchitecture was restored to normal [14]. These findings, although not conclusive, point out the fact that traditional medicines having extracts of *Xylopia aethiopica* as an active ingredient can potentially cause male infertility which is a major problem in the world today.

Yet still, the cardiovascular and diuretic activities of kaurene derivatives of *Xylopia aethiopica* in Wistar rats was investigated by Somova et al. [74]. It was observed that Xylopic acid, a major compound in the dried fruits of *Xylopia aethiopica*, produced more pronounced and significant hypotensive effect on both systolic blood pressure (SBP) and diastolic blood pressure (DBP) at 20, 30 and 60 mins after an intraperitoneal administration of the former at a dose of 20 mg/kg body weight, with a significant gradual decrease in heart rate (HR) by 14, 15 and 20%, respectively. In a 5 day follow-up monitoring of blood pressure and heart rate, xylopic acid (20 mg/kg) showed significant decrease of SBP on the 1st and 4th day (7 and 8%, respectively) with a 14% decrease in heart rate. Again, it was observed that a 10 mg/kg dose each of *ent*-kaur-16-en-19-oic acid and *ent*-kaur-16-en-15-one-19-oic acid both of which are also kaurene derivatives of *Xylopia aethiopica* showed rapid decrease in SBP (by 17 and 18%, respectively) with no corresponding change in DBP and a significant decrease in HR by 20 and 55%, respectively. It was reported that, no alpha or beta receptor blocking activity with the adrenaline and isoprenaline tests was observed. Another kaurenoid, 15α-Hydroxy-ent-kaur-16-en-19-oic acid derived from the alkaline hydrolysis of xylopic acid also exhibited calcium antagonist effect on isolated rat aorta. The diuretic activity of xylopic acid, ent-kaur-16-en-19-oic acid and ent-kaur-16-en-15-one-19-oic acid was very high, comparable to that of hydrochlorothiazide (half of its Lipshitz value at comparable doses) after 5 and 24 hours. At comparable doses, 5 and 24 hours after oral administration, these compounds exhibited a half of the saluretic activity and comparable natriuretic activity to that of hydrochlorothiazide. No carbonic anhydrase inhibition was detected.

Finally, Diderot N. T and others studied the inhibitory effect of some diterpenes isolated from the bark of *Xylopia aethiopica* against the enzymes prolyl endopeptidase (PEP) and α-thrombin. Here, it was reported that 2-oxo-kolavenic acid, ent-kaur-16-en-19-oic acid and trachyloban-19-oic acid all exhibited a dose-dependent inhibitory activity against prolyl endopeptidase enzyme in an *In vitro* enzyme assay. Kolavenic acid also significantly inhibited both PEP and α-thrombin when compared to the positive controls, bacitracin and leupeptin respectively. Methyl trachyloban-19-oate and benzyl trachyloban-19-oate are methyl and benzyl ester derivatives of and trachyloban-19-oic acid respectively and both showed significant inhibitory activity against α-thrombin when compared with positive control leupeptin [45]. These findings could potentially serve as a gateway to discovering new anti-thrombotics and for that matter agents for the management of conditions like myocardial infarction which is a disease of major concern in recent times.

Most of these investigations discussed have more or less served as a confirmation of the enormous medicinal uses of the various parts of *Xylopia aethiopica* in traditional medicine. Also, some of the studies have invariably revealed potential therapeutic indications of the plant that have not been fully exploited as yet. Generally, it could be observed that most of the studies carried out on *Xylopia aethiopica* are either *in vitro* or animal studies; this review therefore seeks to arouse the interest of researchers into carrying out clinical investigations on the isolates and extracts of the plant with promising pharmacological activities.

## 5. ANTIMICROBIAL ACTIVITY

### 5.1 Antibacterial and Antifungal Activities

*Xylopia aethiopica* has gained wide application in traditional medicine partly because of its usefulness as an effective antimicrobial agent. Extracts and isolates from various parts of the plant through *in vitro* studies have confirmed its anti-microbial activity. For instance, Konning et al. [24], reported that a 3%($^{w}/_{v}$) methanol extract of *Xylopia aethiopica* (dried fruits) showed some antimicrobial activity against gram negative (*Escherichia coli* and *Pseudomonas aeruginosa*) and gram positive (*Staphylococcus aureus* and *Bacillis subtilis*) bacteria. It also exhibited good antifungal activity against *Candida albicans* and *Aspergillus niger*. The ethanol extract of the dried fruits of *Xylopia aethiopica* was also investigated for antimicrobial activity. In this study, the agar diffusion method was used to determine both the zones of inhibition and the minimum inhibitory concentration (MIC). The extract exhibited activity against *E. coli, S. typhi, Candida albicans, B. aurium* with 15mg/mL MIC. The extract however, did not show any activity against *S. aureus* and *B. subtilis*. This study has

therefore shown to some extent that *Xylopia aethiopica* ethanol extract contain compounds that could be further investigated as potential source of broad spectrum antibacterial agents [12]. Hot water extracts of *Xylopia aethiopica* dried fruits in a research conducted by Awuah [75] exhibited anti-fungal activity with *Rhizopus sp*. and *Ustilago maydis* being the most susceptible microorganisms while *Ustilaginoidea virens* was the least susceptible among the organisms tested. The essential oil of *Xylopia aethiopica* has been shown to possess antibacterial as well as antifungal activity. In a study, the disk diffusion method was employed for antimicrobial assay with the minimum and maximum zones of growth inhibition as 18mm (against *Bacillus subtilis*) and 32 mm (against E. *coli*) respectively [76]. In another study, essential oil from various parts of *Xylopia aethiopica* showed varying degrees of activity against gram positive and gram negative bacteria and the fungi used in the study. Interestingly, none of the tested essential oils showed activity against *Escherichia coli* [77]. Again, the essential oils obtained from the dried seeds of *Xylopia aethiopica* by hydrodistillation, showed varying degrees of both antifungal and antibacterial activities against the microorganisms tested. *Salmonella Typhi* was the most susceptible among the tested microorganisms with zones of growth inhibition of 17.0, 13.0 and 10.0 mm at concentrations of 5.00, 3.75 and 2.50 mg/mL respectively using the paper disc method. *E. coli* was surprisingly susceptible with zones of inhibition of 9.0, 11.0 and 14.0 mm at the concentrations of 2.50, 3.75 and 5.00mg/mL respectively [78]. Once more, Asekun and Adeniyi [79] also showed that the essential oil of *Xylopia aethiopica* fruits possess good antifungal activity but showed no activity against *Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* at a concentration of 5 mg/mL. These findings are mostly in agreement with the results reported by Fleischer et al. [77] except that the latter reported that *Staphylococcus aureus* was most sensitive among the microorganisms tested. Again, the findings somewhat contradict the results of the study conducted by Tatsadjieu et al. [76] and David et al. [78] as the results of the study conducted by these two groups of researchers showed that *Escherichia coli* was susceptible to the essential oil from *Xylopia aethiopica*. In any case, all these findings point out one thing, that there may be specific compounds in these extracts and essential oils giving rise to the said antimicrobial activities and that the composition of the essential oil varies based on the geographical location of the plant. It is therefore necessary that further research be conducted to identify specific compounds in these extracts that are responsible for the various anti-microbial activities. The identified compound could further be modified chemically for a possible optimization of the activity it possesses.

The use of essential oil from *Xylopia aethiopica* in the inactivation of bacteria has been investigated. In this study, the survival of *Salmonella enteritidis,* a food spoiling bacteria exposed to essential oil from *Xylopia aethiopica* at various temperatures (55° and 60℃) was assessed. The experiment revealed that, in the presence of the essential oil and increased temperature, using the Weibull model, the treatment time needed to inactivate 7 log cfu/mL of S. *enteritidis* was shorter as compared to the case where heat treatment alone was employed. For instance, using the thermal treatment at 55℃, in the absence of the essential oils, the time required to reach such cell reduction was 190 minutes. However, the time was reduced to 9.31 minutes upon the addition of 50 mg/mL of essential oil from *Xylopia aethiopica* [80]. In a similar study, it was shown that the essential oil of *Xylopia aethiopica* dried fruits containing myrtenol, a monoterpenoid in highest concentration (12%), showed moderate antibacterial activity against some gram positive and gram negative food spoiling bacteria investigated in this research [81]. These results show much promise for developing stabilization/preservation procedures especially in the food industry that will as well safeguard food quality i.e. reduce the damage due to heat treatments.

## 5.2 Anti-protozoan Effects

Aside the anti-bacterial and anti-fungal activities exhibited by *Xylopia aethiopica,* it has also been shown to possess anti-protozoan activity. In developing regions of Africa like the Ghana where neglected tropical diseases, especially those caused by protozoa still prevail, this may lead to a great breakthrough because *Xylopia aethiopica* is readily available in these regions and can potentially be a cheap source of medicine to eradicate such diseases. Malaria is a protozoan infection that is also prevalent in the tropics, in recent times; the causative organisms (plasmodium parasites) have shown alarming degrees of resistance to the artemisinins which are currently the most effective medicines for

malaria treatment. It is therefore worth the while to investigate the activity of various compounds obtained from *Xylopia aethiopica* against malaria parasites and other relevant protozoa. It is important to state that some research has been conducted in this direction and there has so far been promising out comes. For example, Boampong *et al* showed that xylopic acid, a pure compound isolated from the dried fruits of *Xylopia aethiopica* possess prophylactic antimalarial activities comparable to that of Sulphadoxine/pyrimethamine and a curative antimalarial activity similar to Artemether/lumefantrine. In this study, each male ICR mice (25–30 g) was infected with $1X10^6$ *Plasmodium berghei* (NK65) and after three days the animals were treated once daily with three doses of xylopic acid (10, 30, and 100 mg/kg p.o.) (Groups 1–3), 4 mg/kg p.o. of artemether/lumefantrine (A/L) (standard drug: group 4), and 10 mL/kg p.o. normal saline (group 5) for 5 days. On the fourth and fifth days of treatment, it was observed that mice in group 3 (100 mg/kg of xylopic acid) and group 4 (4 mg/kg A/L) showed percentage reduction in parasitaemia of 92.8% and 99.6%, and 91.7% and 99.6% respectively. Although the percentage reduction in parasitaemia of the mice in groups 1 and 2 were much less, there was however, no significant difference in percentage chemosuppression caused by 4 mg/kg of A/L as compared to the percentage chemosuppression produced by the various doses of xylopic acid on these days. Xylopic acid again exhibited significant ($P$ <0.05) prophylactic activity against *Plasmodium berghei In vivo* at all of the three doses tested, seen as reduction in parasite count compared to the vehicle-treated group. In the same study, xylopic acid (30 and 100 mg/kg) exhibited a significant reduction ($P$ < 0.05) in lipopolysaccharide-induced fever in rats. Prednisolone, used as positive control also significantly reduced ($P$ < 0.05) lipopolysaccharide-induced fever in the rats [82]. Essential oil from *Xylopia aethiopica* stem bark have also shown to possess antimalarial properties. In a study conducted by Boyom et al. [83], when tested against the W2 strain of *Plasmodium falciparum,* the essential oil demonstrated anti-plasmodial activity with an $IC_{50}$ (concentration that killed 50% of parasites relative to negative control) of 17.8 µg/mL [83]. In spite of these ground breaking findings, further studies like forming and testing semi-synthetic derivatives of xylopic acid and other bioactive compounds from *Xylopia aethiopica* on the malaria parasites should be considered as this may reveal further findings.

Still on the investigation of the anti-protozoan activity of *Xylopia aethiopica*, Soh et al. [13] showed that two epoxide derivatives obtained by oxidation of xylopic acid, 15α-acetoxy-16,17α-ent-epoxy-kauran-19-oic and 15α-acetoxy-16,17β-epoxy-ent-kauran-19-oic acid possess good trypanocidal activity against *Trypanosoma brucei* ($ED_{50}$ 52 and 127 µM, respectively) with no detected cytotoxicity on MRC-5 fibroblast. However, ent-kaur-16-en-19-oic acid and 15-oxo-ent-kaur-16-en-19-oic acid displayed cytotoxic effects on MRC-5 fibroblast and this calls for further studies into their potential to be used as an anti-cancer agent. In another research, kaurenoic acid and its derivatives have been investigated for activity against trypomastigote forms of *Trypanosoma cruzi*, the causative agent of Chagas'disease. In this *in vitro* assay, kaurenoic acid, kaurenol, acutifloric acid and stemodin (with $ED_{100}$ 1.363, 1.386, 1.599 and 1.390µg/mL respectively) all showed a complete elimination of parasites from the blood of previously inoculated male Swiss albino mice (18-20 g) [84].

## 6. TOXICOLOGY

Generally, herbal medicines are perceived to be a safer source of medicine, this perception emanates from the idea of ‘‘green is safe’’. As such, not much research and clinical studies are conducted to assess the safety or toxicity of most herbal preparations in use as is done in the case of orthodox medicines. The story is no different in the case of *Xylopia aethiopica*. Despite its extensive use in traditional medicine and although a remarkable number of *In vitro* and animal studies have been conducted to confirm its therapeutic uses, not much has been done in assessing the safety or toxicity of most of its bioactive constituents. Conversely, it is worthy of note that some research has been conducted in this regard. In a test for acute toxicity using the brine shrimp (*Artemia salina*) bioassay, it was observed that the hexane extract of *Xylopia aethiopica* dried fruits had low toxicity with $LC_{50}$ of 0.30 ng/mL whilst xylopic acid and its derivative, deacetyl xylopic acid both showed an $LC_{50}$ of 0.50 ng/mL. Again, in qualitative/semi quantitative test for toxicity, the Hippocratic test on rats was used in a 5 day follow-up period after a single intraperitoneal (i.p.) injection. Here, the hexane extract, xylopic acid and deacetyl xylopic

acid all showed no toxicity at a dose of 20 mg/kg body weight [74]. In another research, the essential oil from the fruits of *Xylopia aethiopica* was showed to be toxic to *Artemia salina* at concentrations ranging from 10 to 1000 µg/mL [79]. Koba et al. [56] investigated the *In vitro* cytotoxicity of essential oil from *Xylopia aethiopica* fruits. The cytotoxicity was evaluated using the human epidermal cell line HaCaT. Here, it was observed that at concentrations in the range of 50-1500 µg/mL, the tested essential oil did not show any cytotoxicity but rather induced a significant increase in cell viability (up to 130%), suggesting their potential as cytoprotectors or antioxidants. At higher concentrations ranging from 1600 to 3000 µg/mL, a similar toxicity profile was recorded.

Xylopic acid isolated from the dried fruits of *Xylopia aethiopica*, in a study conducted by Woode et al. [14], when administered at doses of 10, 30 and 100 mg/kg to male albino rats, caused visible cytotoxic activity by clearing all matured spermatozoa, germ cells and other cell in the seminiferous tubules when compared with the control group. These effects were however reversed when the treated rats were allowed a two-week treatment free period of recovery. These findings therefore suggest that xylopic acid possesses reversible spermatotoxic and antifertility effects at the doses tested.

An ethanolic extract of a combination of equal quantities of *Alstonia congensis* bark and *Xylopia aethiopica* fruits have been investigated for acute and sub-acute toxicity. In the acute toxicity study, there were no observable changes in the behaviour and sensory nervous system responses. Also no adverse gastrointestinal effects were observed in male and female mice used in the experiment. At a 20.0 g/kg dose, all the mice that received the extract survived beyond the 24 hours of observation. It was therefore inferred that the median acute toxicity value ($LD_{50}$) of the extract must be above 20.0 g/kg body weight. Although not entirely representative, these findings to some extent show that ethanolic extract of *Xylopia aethiopica* fruits is relatively safe [85]. However, it is necessary that further research be conducted to determine what doses are safe and effective when administered to humans.

## 7. CONCLUSION

Although *Xylopia aethiopica* has shown to be of potential pharmacological benefits, research and published data on pre-clinical and clinical studies conducted on its bioactive constituents are largely lacking. There is therefore the need for further research to be conducted on various extracts and isolates of *Xylopia aethiopica* that showed promise during *in vitro* and animal studies, to ascertain its potency, safety and efficacy in humans. Also chemical modification of isolated compounds with confirmed biological activity should be considered as this may lead to obtaining highly optimized and more effective semi-synthetic derivatives.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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