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Review Article

A review of pharmacological effects of xylopic acid

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ABSTRACT

Xylopic acid (15 β -acetyloxy-kaur-16-en-19-oic acid) is a kaurene diterpene that can be obtained from various *Xylopicia* spp. Xylopic acid has demonstrated several pharmacological activities in vitro and in vivo. The compound has shown promising effect as a potent analgesic, anti-inflammatory and anti-allergic agent. Xylopic acid is a CNS depressant and was able to ameliorate anxiety-like symptoms in mice in addition to its neuroprotective effects. Deleterious effects of xylopic acid on the reproductive system of mice have been well documented but extensive toxicity study detailing effect of the acid upon chronic exposure needs to be determined. Due to the heavy consumption of *X. aethiopicia* fruits, it is recommended that the pharmacokinetics of xylopic acid be determined to ascertain the possible food-drug interaction that may occur when conventional drugs are taken together with foods containing xylopic acid.

Keywords: Xylopic acid, Pain, Inflammation, CNS disorders, Infections, *Xylopicia aethiopicia*

INTRODUCTION

Xylopic acid (15 β -acetyloxy-kaur-16-en-19-oic acid) is a kaurene diterpene usually obtained from the dried unripe fruit of *Xylopicia aethiopicia* (Dunal) A. Rich (Annonaceae) and other *Xylopicia* spp. Scientific reports on its isolation and characterization dates as far back as 1968.¹ Xylopic acid has been reported to possess several pharmacological activities but has not yet received much attention in order to move to the next level of drug development. Again, some important scientific data such as its pharmacokinetic profile are clearly missing from

literature. This review seeks to highlight the beneficial and safety profile of xylopic acid and identify the relevant research gaps for further research geared towards the full drug development of this small molecule.

SOURCES OF XYLOPIC ACID

Xylopic acid has been identified and isolated from fruits of *Xylopicia aethiopicia*, (Annonaceae), aerial parts of *Wedelia paludosa* D.C. (Asteraceae), fruit of *Xylopicia frutescens* Aubl. (Annonaceae) and, *Xylopicia sericeae* A. St. - Hil. (Annonaceae).²⁻⁴ *Xylopicia aethiopicia* can be

found in Ghana, Nigeria, Benin, Brazil, Cameroon Ethiopia etc. and the content of xylopic acid in the fruit of *X. aethiopica* has been found to vary in the fruit of the plants in these countries. This implies geographic location and environmental factors affect xylopic acid content in the fruit of *X. aethiopica*. Example, fruit samples from Cameroon were found to have the highest average content (0.7983 mg/g) followed by Ghana (0.5969 mg/g), Nigeria (0.5469 mg/g) and Benin (0.5302 mg/g).⁵ Quantification of the content of xylopic acid in the other plant sources has not yet been reported.

CHEMISTRY OF XYLOPIC ACID

Physicochemical properties

Xylopic acid is a whitish powder or crystal when isolated. It has other chemical names such as 15 β -acetyloxy-kaur-16-en-19-oic acid. The IUPAC name is 15-acetyloxy-5,9-dimethyl-14-methylidene-tetracyclohexadecane-5-carboxylic acid.^{1,10,4,9} The acid has a molecular formula of C₂₂H₃₂O₄ and a molecular weight of 360.494 g/mol.⁶ The melting point of xylopic acid has been determined to be 260-261°C. The acid is sparingly soluble in petroleum ether, DMSO, ethanol, methanol, ethyl acetate and soluble in chloroform.⁷ Other natural compounds closely related to xylopic acid are; kaurenoic acid, steviol, grandifloric acid, an epimer of xylopic acid, 15-oxo-ent-kaur-16-en-19-oic acid, xylopioxyde (16,17-epoxy-15-oxo-ent-kauran-19-oic acid).^{1,2,8,9}

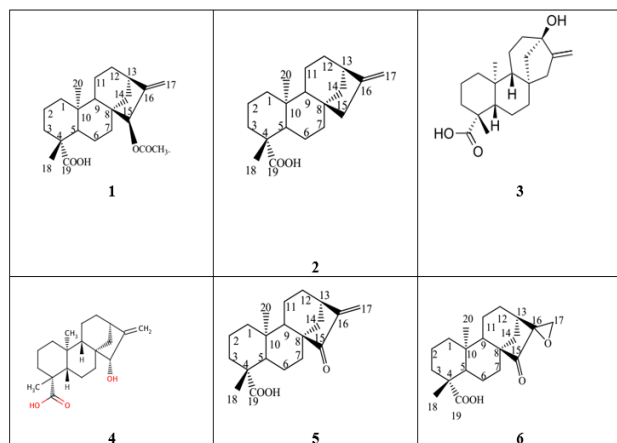


Figure 1: Natural compounds closely related to (1) xylopic acid, (2) kaurenoic acid, (3) steviol, (4) grandifloric acid, (5) 15-oxo-ent-kaur-16-en-19-oic acid and (6) xylopioxyde.^{1,2,8,9}

Derivatives of xylopic acid

Novel derivatives of xylopic acid have been synthesized and characterized.⁸ The various derivatives, namely esters, amide and deacetylated analogues were synthesized in moderate to high yields (47.11-93.52%) and characterized. The ester derivatives were: an ethyl ester of xylopic acid produced by acid catalysis, which

appeared to be more polar than the xylopic acid starting material, a butyl ester; and a relatively low yield of benzyl ester.^{9,10} It was reported that deacetylation of xylopic acid initially produced the β -OH epimer, which upon prolonged heating slowly converts to the α -OH epimer.

Santos and colleagues also synthesized and characterized a number of active anti-malarial derivatives by the reaction of xylopic acid with various compounds.² Hydrolysis of the ester moiety of xylopic acid with potassium hydroxide, in methanol, under reflux, yielded a hydroxyl acid derivative. Esterification of the hydroxyl acid with methyl iodide yielded methyl ent-15 α -hydroxy-kaur-16-en-19-oate. Sodium hydride and propargyl bromide reaction with the hydroxyl group of methyl ent-15 α -hydroxy-kaur-16-en-19-oate yielded propargyl ether.

Soh and colleagues first isolated xylopioxyde from the fruit *Xylopic aethiopica*.⁹ They successfully converted xylopic acid to 15-hydroxy-ent-kaur-16-en-19-oic acid, 15-oxo-ent-kaur-16-en-19-oic acid and two epimers of 15-acetoxy-16,17-ent-epoxy-kauran-19-oic acid through the oxidation of xylopic acid. The α and β epimers demonstrated significant trypanocidal activity against *T. brucei* (ED₅₀ 127 and 52 μ M, respectively) with no detected cytotoxicity on mammalian cells (MRC-5 fibroblast).

THERAPEUTICALLY BENEFICIAL AND OTHER ACTIVITIES OF XYLOPIC ACID

Xylopic acid has been recognized to display diverse pharmacological properties with potential therapeutic benefits. It has been shown to possess anti-inflammatory, analgesic, anti-pyretic, anti-microbial, cytotoxic, anti-allergic, neuroprotective, anti-malarial, anti-androgenic and spermatotoxic properties.

Anti-inflammatory and anti-oxidant activities of xylopic acid

Xylopic acid demonstrated in vitro anti-inflammatory effect in a preliminary anti-inflammatory study using the protein denaturation model, and in vivo anti-inflammatory assay. In addition, xylopic acid showed anti-arthritis property in the adjuvant-induced arthritis model in rats. The anti-inflammatory activity of xylopic acid was attributed to the modulation of pro-inflammatory markers namely histamine, serotonin, bradykinin and phospholipid/arachidonate pathways of inflammation. The compound also exerted an inhibitory effect on the expression of intercellular adhesion molecule-1 (ICAM-1) and cellular component recruitment in inflammatory processes present in acute inflammatory models. Other mechanisms reported to be involved in the anti-inflammatory effect of xylopic acid were inhibition of the serum expression of pro-

inflammatory cytokines, IL-6 and TNF- α , in chronic inflammation.^{11,12}

Ekuadzi and colleagues also reported the anti-inflammatory effect of xylopic acid in an in vivo assay using the carrageenan-induced pleural inflammation model in mice.¹³ In the same study, they reported the ability of xylopic acid to increase catalase, superoxide dismutase, and glutathione levels and decrease lipid peroxidation level in reactive oxidative assays signifying the antioxidant activity of xylopic acid. This was corroborated with their findings that xylopic acid was able to prevent potential lung tissue damage by reducing significantly the signs of inflammation; neutrophil infiltration, oedema, and alveoli septal thickening in carrageenan-treated lung tissues.

Similarly, xylopic acid has been established to possess anti-colitic activity through the inhibition of reactive oxygen species. It decreased gross mucosal injury caused by acetic acid and decreased colonic epithelial expression of argyrophilic nucleolar organization regions. Xylopic acid in that study increased the activity of superoxide dismutase and catalase while decreasing the activity of myeloperoxidase and the expression of malonaldehyde confirming previous reports from other works.^{12,13}

The anti-uveitogenic effect of xylopic acid has also been reported.¹⁴ Prophylactic administration of xylopic acid caused a significant reduction in vasodilatation of iris vessels, exudation, polymorphonuclear neutrophils in the aqueous humour of uveitic rats indicating its ocular anti-inflammatory effects.

The anti-inflammatory activity of xylopic acid appear therefore to be mediated systemically and may signify the pharmacokinetic distribution of xylopic acid and/or its active metabolites into the various body compartments or body fluids.

Analgesic activity of xylopic acid

Xylopic acid demonstrated significant analgesic effect in various in vivo pain models including musculoskeletal pain, colic pain, neuropathic pain, neurogenic pain, thermal hyperalgesia, cold allodynia and inflammatory pain. Xylopic acid's antinociceptive effect was reported to be mediated through the opioidergic, adenosinergic, muscarinic cholinergic, NO/cGMP, serotonergic and α_2 -adrenergic systems.¹⁵⁻¹⁷

In an attempt to identify alternate therapies for chemotherapy-induced neuropathy, xylopic acid was studied by researchers and was found to produce an effective therapeutic potential against paclitaxel-induced neuropathic pain, a type of pain difficult to treat clinically.¹⁷ The group also reported that xylopic acid possessed anti-allodynic and anti-hyperalgesic effects in vincristine-induced neuropathy. In addition, oral combinatory therapy of xylopic acid with pregabalin

produced synergistic analgesic properties devoid of any significant toxic effects in a rat model of paclitaxel-induced neuropathic pain.¹⁷ A similar isobolographic study employing lower doses of xylopic acid and morphine or diclofenac combinations showed that xylopic acid demonstrates synergistic analgesic effects when co-administered with morphine and diclofenac.¹⁸

Anti-pyretic activity of xylopic acid

The ability of xylopic acid to reduce pyrexia has also been demonstrated by Boamong and colleagues. Xylopic acid demonstrated anti-pyretic effect on lipopolysaccharide-induced pyrexia in a murine model of pyrexia. The antipyretic property of xylopic acid was attributed to its ability to inhibit the production and/action of IL-2 and PG E2.¹⁹

Antimicrobial activity of xylopic acid

Numerous studies have shown the antibacterial and antifungal potential of xylopic acid and its synthesized derivatives. For instance, xylopic acid and its novel ester, amide and de-acetyl derivatives showed antimicrobial activity against *Staphylococcus aureus*, *Staphylococcus pyrogenes*, *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Candida albicans*.^{20,21} Although xylopic acid has been reported to be active against *C. parapsilosis*, it was not active against fluconazole-resistant strains of *C. parapsilosis*. Xylopic acid in combination with kaurenoic acid however produced synergistic antifungal effect against fluconazole-resistant strains of *C. parapsilosis*.²²

Anti-allergic

Xylopic acid has been shown to act as an anti-allergic agent.²³ The compound provided anti-allergic effect in the passive cutaneous anaphylactic, systemic anaphylactic studies, pinnal inflammation reaction, LPS-induced septic shock, compound 48/80 - induced passive cutaneous anaphylaxis and clonidine - induced catalepsy models. The mechanism of action of xylopic acid in these allergic models was attributed to its ability to modulate the release of histamine and possible competitive H₁ receptor blockade which would otherwise result in immediate hypersensitivity.

Neuroprotective

Excess reactive oxygen species (ROS) production due to the oxidation of dopamine can result in neurodegenerative diseases such as Parkinson's and Alzheimer's disease. Xylopic acid attenuated LPS-induced depressive-like symptoms by reducing immobility, increasing sucrose preference and enhancing social interaction.²⁴ This activity is reported to be due to the significant reduction of oxidizing enzyme myeloperoxidase and reduced lipid peroxidation by xylopic acid whiles increasing the activity of superoxide

dismutase, catalase and glutathione.^{12,13,24} From the above mechanisms, it was stated that xylopic acid potently increases brain derived neurotrophic factor (BDNF) as well as reduced neurodegeneration indicating its neuroprotective property and further contribute to its myriad beneficial CNS effects.

Antimalarial

Xylopic acid possesses prophylactic and curative antimalarial properties in rodents which makes it an ideal antimalarial agent. It is reported to significantly reduce the effect of *Plasmodium berghei* infection similar to artemether/lumefantrine, the standard drug.¹⁹ The beneficial effect of co-administration of cryptolepine, a plant-derived alkaloid, and xylopic acid using *P. berghei* has been demonstrated.²⁵ An observed synergistic anti-plasmodial effect which did not have any significant deleterious effect on the kidney, liver and spleen was reported although high doses of the combinatory therapy showed significant effect on the testis. This effect on the testis could be accounted for by the reported spermatotoxic effect of xylopic acid on the weight of the male reproductive organs, serum testosterone, testicular glycogen, cholesterol, protein and malondialdehyde.²⁶⁻²⁸ Again, cryptolepine has been demonstrated to be a potent cytotoxic and this could partly explain the observed deleterious effect of the combination therapy.²⁹

Santos and colleagues however reported a low in vitro antimalarial activity for xylopic. In that report, the in vitro antimalarial activity of xylopic acid against *P. falciparum* W2 strain that is chloroquine-resistant and mefloquine-sensitive was determined using the parasite lactate dehydrogenase assay (pLDH) assay.² The IC₅₀ of xylopic acid was determined to be >138.7 M indicating its low potential of being developed as an antimalarial agent. Preliminary study employing chloroquine resistant Dd2 strain also showed that the compound was not active against this strain of *P. falciparum*. The difference in the in vitro and in vivo activity could be due to possible biotransformation of xylopic acid in vivo to produce active metabolites by human CYP450s. Xylopic acid has been postulated to be a substrate of liver metabolizing enzymes. It exhibits a biphasic effect by being an inhibitor of the enzymes at low doses and inducer at high doses.³⁰ Thus, in the absence of liver metabolism in the in vitro assay xylopic acid may not be transformed into the active metabolite explaining the lack of activity.³¹

Anti-androgenic and spermatotoxic

Xylopic acid has been shown to decrease testicular and epididymal weight; and serum testosterone levels.^{27,28} This indicates that xylopic acid possesses anti-androgenic and spermatotoxic property. The mechanism of action is proposed to involve direct effect of xylopic acid on germ cells and other cells of the testis.²⁹ Confirmatory research showed that the fruit extract of *Xylopic aethiopia* (which contains xylopic acid as its major secondary metabolite)

reduced the weight of reproductive organs, serum testosterone; testicular glycogen, cholesterol, protein and malondialdehyde; while testicular superoxide dismutase increased. This may explain the mechanism behind xylopic acid-induced male infertility observed in rodents.²⁶

CNS effect of xylopic acid

Xylopic acid has shown CNS depressant activity in vivo at lower doses. Higher doses above 300 mg/kg caused neuromuscular impairment and sedation.³⁰ Research into epilepsy and anxiety using xylopic acid has seen some success. Xylopic acid has shown some evidence to be active in the management of convulsion by delaying the onset of pentylenetetrazole-induced seizures but neither reduced the frequency nor duration of seizures induced with PTZ.³⁰ Xylopic acid may have some anticonvulsant effect depending on the pathophysiology of the convulsion. Further work is needed to confirm the possible anticonvulsant effect of xylopic acid by employing agents that induce convulsions via different mechanisms. Using mice and zebrafish models of anxiety disorders xylopic acid produced anxiolytic-like effect in the open field and elevated plus maze tests in mice and the novel tank test in zebrafish.³² Other CNS disorders such as a possible nootropic (memory, reactivity, motivation and learning) effect of xylopic acid have just recently been shown.³³ Further research in this area may reveal additional benefits of xylopic acid as a drug for CNS disorders.

SAFETY PROFILE OF XYLOPIC ACID

Cytotoxicity, genotoxicity and mutagenicity

Although some terpenoids have been found to be genotoxic, cytotoxic and mutagenic, report on xylopic acid indicated that it devoid of genotoxic, cytotoxic and mutagenic activities.³⁴ The LD₅₀ of xylopic acid has been suggested to be above 1000 mg/kg in the Irwins test. This suggests xylopic acid does not cause observable physical toxicity and death when administered acutely. On the contrary, preliminary data from our laboratory indicates that xylopic acid destroys spermatozoa by decreasing sperm motility, sperm count and induces sperm death at 100 mg/kg in rats. Paradoxically, the same dose increases the sperm count. This points to the possible toxic effect of xylopic acid on the reproductive system in men. Acute, sub-acute and chronic toxicity studies on xylopic acid have not been done despite the extensive pharmacological works done on the acid. Lack of adequate toxicity data makes research on this compound far from complete and further works in this area is highly recommended. It is worth noting that xylopic acid is the most predominant active principle in the fruit of *X. aethiopia*. *X. aethiopia* is a spice globally used to prepare variety of cuisine.⁵ This implies all categories of people including pregnant women and children are exposed to both the beneficial and potential harmful

effect of xylopic acid. It is important to caution men of child bearing age to avoid or reduce the consumption of the fruit of *X. aethiopica* due to the potential harmful effect on reproduction.

CONCLUSION

Traditional knowledge about *X. aethiopica* laid the foundation for exploring the pharmacological benefits of xylopic acid. To this end, xylopic acid has not been used clinically for diseases but has experimentally shown possibility to be used as an agent for inflammation, pain, allergies, CNS disorders, malarial and neuroprotection. Due to the heavy consumption of *X. aethiopica* (indirectly xylopic acid), the possibility of food-drug interaction should be investigated due to the possibility of xylopic acid inhibiting or inducing cytochrome P450s liver enzymes responsible for the metabolism of several drugs and xenobiotics. Drugs that induce or inhibit these enzymes present with important drug-drug interaction by decreasing the efficacy of the drugs or increasing the toxicity of the drug.

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