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A REVIEW OF THE ANTIINFLAMMATORY AND ANALGESIC CONSTITUENTS OF THE FAMILY ANNONACEAE

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ABSTRACT

Inflammatory and pain-related disorders constitute a significant global health burden, often treated with synthetic drugs that can elicit adverse side effects. The Annonaceae family, a botanical group traditionally employed in various cultures for its therapeutic properties, has shown potential as a source of natural anti-inflammatory and analgesic agents. This review paper aims to critically evaluate the scientific literature on the anti-inflammatory and analgesic properties of the Annonaceae family to consolidate current knowledge, highlight research gaps, and suggest directions for future research. The methodology of this review involved a systematic search of databases for studies on Annonaceae species, focusing on their reported uses in traditional medicine and the scientific validation of these uses. Studies were included if they provided data on the phytochemical content, pharmacological activities, and mechanisms of action related to anti-inflammatory and analgesic effects. The results indicate that several species within the Annonaceae family contain bioactive compounds, such as acetogenins, alkaloids, and essential oils, which exhibit significant anti-inflammatory and analgesic activities. Some notable examples include Annona muricata, Annona senegalensis, and Annona squamosa, which have been documented for their potential in treating a variety of inflammatory and painful conditions. Pharmacological screenings have provided evidence supporting the traditional uses of these plants, demonstrating their effectiveness in reducing inflammation and pain in both in vivo and in vitro studies. The Annonaceae family shows great promise as a natural source of anti-inflammatory and analgesic compounds. However, more rigorous scientific studies, including clinical trials, are essential to fully understand the therapeutic potential and safety profile of these plant species. This review underscores the need for further exploration of Annonaceae species, to develop safer, natural alternatives to synthetic drugs for the management of pain and inflammation.

KEYWORDS: Annonaceae, anti-inflammatory, chemical constituents, pharmacological activities.

INTRODUCTION

Inflammation is the body's innate response to harmful stimuli, such as pathogens, damaged cells, or irritants. While it is a protective mechanism aimed at eliminating the initial cause of cell injury, clearing out necrotic cells and tissues, and initiating tissue repair, chronic inflammation can lead to various diseases, including arthritis, diabetes, and cancer. Pain, a complex experience associated with tissue damage, often accompanies inflammation. Managing inflammation and pain is, therefore, crucial for improving quality of life and treating various health conditions.[1]

The exploration of medicinal plants for therapeutic purposes has been a cornerstone of pharmaceutical discovery, offering promising avenues for novel anti-inflammatory and analgesic treatments. Among these, the Annonaceae family, a diverse group of species widely distributed across tropical and subtropical regions, has garnered scientific interest for its significant ethnopharmacological applications. Traditionally, various cultures have harnessed the therapeutic potentials of Annonaceae species, utilizing them in folk medicine to alleviate pain and inflammatory conditions. This historical use underscores the importance of investigating the family's bioactive compounds for modern therapeutic applications.[2],[3]

The Annonaceae family, which has over 2,000 species, including the well-known genera *Annona*, and *Xylopia*, has been used in traditional medicine across different cultures to treat a myriad of health issues. Many species within this family have been reported to possess anti-inflammatory and analgesic properties, drawing the attention of researchers aiming to validate and understand the traditional uses of these plants.[4]

The search for natural anti-inflammatory and analgesic agents is propelled by the ongoing need to address side effects associated with synthetic drugs and the global burden of inflammatory and pain-related disorders. The identification of plant-derived compounds with these properties offers a sustainable and potentially less adverse alternative to conventional treatments. In this context, the Annonaceae family presents a rich repository of chemical entities, with several species having been documented for their anti-inflammatory and analgesic effects through preliminary pharmacological screenings,[5],[6]

Millions of people worldwide deal with chronic pain and inflammation daily, conditions that significantly reduce the quality of life and increase healthcare costs. While modern medicine offers various treatments, including synthetic drugs, for these ailments, these solutions often come with undesirable side effects such as dependency and long-term health risks. This dilemma underscores the urgent need for alternative treatments that are both effective and carry fewer side effects. The Annonaceae family, with its historical use in traditional medicine across various cultures for treating inflammation and pain, presents a promising avenue for research. Yet, the potential of these plants to offer safer, natural alternatives has not been fully explored or understood within the scientific community.[7]

Therefore, the research was to conduct a thorough review and analysis of the available scientific literature on the Annonaceae family's anti-inflammatory and analgesic constituents. This review aims to consolidate current knowledge, identify research gaps, and suggest future directions for exploring the Annonaceae family as a source of new and safer anti-inflammatory and analgesic drugs. Addressing this problem, the research seeks to contribute to the fields of ethnopharmacology and drug discovery, potentially being useful as a lead to the development of novel treatments for patients suffering from inflammation and pain.[8]

The exploration of Annonaceae species for their medicinal properties is fragmented, with research scattered across different species, regions, and methodologies. This lack of consolidated knowledge hampers the ability of researchers and healthcare professionals to fully understand and leverage the anti-inflammatory and analgesic moieties of this plant family. Preliminary studies suggest significant benefits, yet the specific compounds responsible for these effects, their mechanisms of action, and optimal dosages remain poorly defined. Without a comprehensive review and analysis of existing research, the development of Annonaceae-based treatments remains a problem, leaving a gap in the development of bioactive agents against chronic pain and inflammation[9], hence the need for this review to present at a glance, the established antiinflammatory and analgesic constituents of the Annonaceae family. This study aims to systematically gather and evaluate the existing literature on the anti-inflammatory and analgesic constituents of Annonaceae species.

METHODOLOGY

The information presented in this review was gathered through comprehensive search of academic research databases, peer-reviewed journals, and search engines. Searches of the Cochrane Library, Academia, PubMed, ResearchGate, and Google Scholar databases were performed using the keywords: Annonaceae, inflammation, pain management, chronic pain, analgesia, chemistry of Annonaceae family, antiinflammatory properties of Annonaceae, analgesic properties of Annonaceae, mechanism of action, and phytochemical constituents of Annonaceae.

Pharmacological activities and bioactive constituents of the Annonaceae family

1. *Annona muricata* Linn.

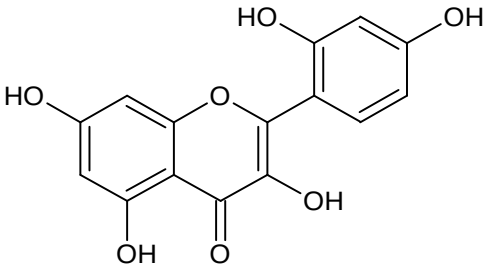
The Fruits of *A. muricata* are used to prepare syrups, canches, ice-creams and various beverages and have traditional uses to treat cancer, bacterial and parasitic infections and hypertension. Fruit is eaten as a natural medicine for pain related diseases as arthritic pain, arthritis and rheumatism. Leaves administered as a decoction and drunk are used to treat headaches and when applied topically, are used to treat abscesses and rheumatism. Leaf-infusion has been used to treat hypertension, heat and palpitation of the heart. Crushed seeds have shown anthelmintic properties. Plant has also been used to treat respiratory problems- bronchitis and cough, pain and inflammation. Crushed leaves or decoction may be taken orally to treat cancer and mouth-wound infections.[10]

GC-MS analysis of *A. muricata* fruits revealed the presence of alkaloids- annonaine, nornuciferine, asimilobine; annonaceous acetogenins- epomusenin A & B, epomurinin A & B, cis-annoreticuin, muricin J, K and L; and phenolics-5-caffeoylquinic acid, p-coumaric acid and its methyl ester, dicaffeoylquinic acid, feruloylglycoside, 4-feruloyl-5-caffeoylquinic acid. Essential oil compounds of the *A. muricata* fresh fruit pulp contained methyl 2-hexenoate, ethyl 2-hexenoate, methyl 2-octenoate and methyl 2-butenoate as main compounds. Additionally, α-caryophyllene, 1,8-cineole, linalool, (*R*)-terpineol, linalyl propionate and calarene were found in high concentrations.[11]

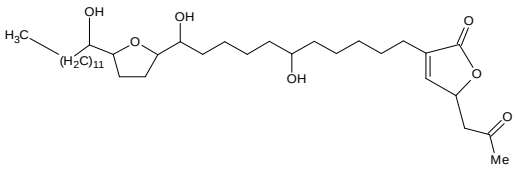
GC and GC-MS analysis of the leaf revealed acetogenins annomuricin A, B, C and E, annomutacin, annohexocin, muricapentocin, muricatocin A, B and C, gigantetronenin, annonacin A, annopentocin A, B and C, murihexocins A, B and C, annocatacin B, annocatalin, muricoreacin; the alkaloids – annonaine, isolaureline, xylopine, annonamine, (S)-norcorydine, (R)-4-*O*-methylcoclaurine, (R)*O*, *O*- dimethylcoclaurine; the flavonoids/phenols- Quercetin 3-*O*-α-rhamnosyl-(1→6)-β-D- sophoroside, daidzein, argentinine, fisetin,

genistein, morin, myricetin, robinetin, vitexin, gallic acid, epicatechin, quercetin 3-*O*-rutinoside, quercetin 3-*O*-neohispredoside, quercetin 3-*O*-robinoside, catechin, chlorogenic acid, kaempferol 3-*O*-rutinoside, quercetin 3- O-glucoside, quercetin, kaempferol; and the megastigmanes- annoionol A, B & C; annoionoisides, vomifoliol, roseoside, citroside A, blumenol C, loliolide, (Z)-3-hexenyl β-D-glucopyranoside, anthraquinones, vitamins, essential oil and carotenes. The essential oil constituents were α-pinene, β-pinene, ρ-mentha-2,4(8)-diene, β-elemene and germacrene D. The leaf essential oil constituents were β-caryophyllene, δ-cadinene, epi-α-cadinol and α-cadinol. Composition of essential oils was noted by different researchers from different locations. Roots contain acetogenins- montecristin, cohibin A & B, cis solanin, cis-panatellin, cis-uvariamicin I & IV, cis-reticulatacin, chatenaytrienin 1-3, muridienin 3 & 4, coronin, sabadelin, muricadienin while the seeds contain murisolin, muricatacin, corossolone, annonacin, corrossolin, solamin, isoannonacin, gigantetrocin B, muricatetrocin A & B, annocatacin A, arianacin, javoricin, cis-annonacin-10-one, longifolicin, muricin A-I, and the alkaloids reticuline, coclaurine, coreximine, atherospermine, stepharine, anomurine and anomuricine.[12]

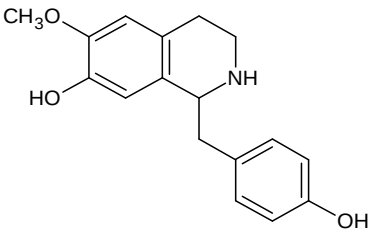
The fruit pulp was reported to contain the alkaloids reticuline, N-Methylcoclaurine; the acetogenins montecristin, epomurinins A & B, sabadelin, annonacin, corrossoline and muricenin; flavonoids and phenolic acids- dicaffeoylquinic acid, coumaric acid, kaempferol, luteolin and glycosides, morin, myricetin; vitamins and carotenoids- α and β carotenes, vitamin C, lutein, lycopene, cryptoxanthin β, α and γ- tocopherols. Over 120 acetogenins were reported to occur as part of the 212 compounds reported in *A. muricata* using GC-MS studies.[13]



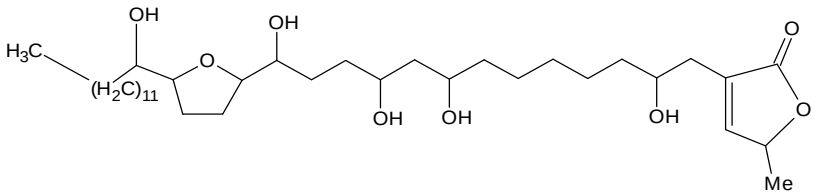
Annohexocin



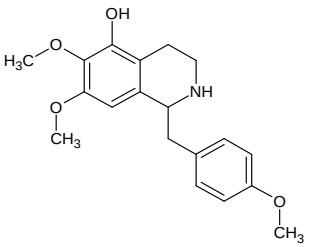
Isoannonacin



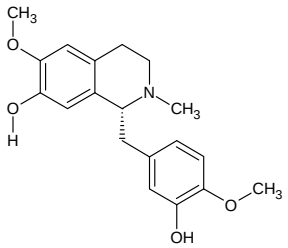
Coclaurine



Muricatocin A



Anomuricine (6,7-Dimethoxy-1{4,methoxy phenyl}



Reticuline methyl-1,2,3,4-tetrahydroisoquinolin-5-ol

Figure 1: Chemical structures of compounds from *A. muricata.*

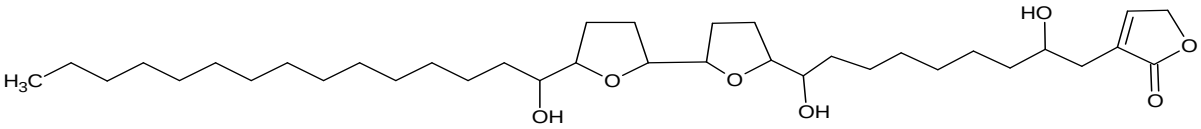
The plant *A. muricata* has demonstrated anticancer, antimicrobial, anti-ulceric, wound-healing, antioxidant, antiprotozoan, insecticidal, larvicidal, cytotoxic, anti-arthritic, anti-parasitic, anticonvulsant, antimalarial, antidiabetic and hepato-protective activities. In addition, plant has shown anti- inflammatory, sedative, smooth muscle relaxant, hypotensive, analgesic and antispasmodic effects. Seed acetogenin constituents-Muricin A-I were reported to show toxicity against human hepatoma cells and toxicity against lung, breast and colon cancer cells. The leaf acetogenins also showed toxicity against human hepatoma cells as well as lung, colon, pancreatic cancer cells. The fruit acetogenins, muricin J, K and L showed toxicity against prostate PC-3 cancer cells. Leaf extract was found toxic against chloroquine sensitive and resistant strains of *P. falciparum* thus confirming anti-plasmodial activity.[14]

2. *Annona reticulata* Linn

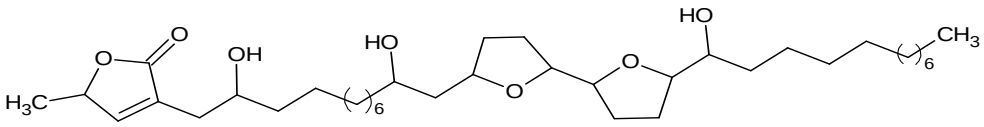
The stem bark of *A. reticulata* is astringent and its extract is taken as tonic. Decoction of stem bark or dried or pulverized unripe fruit is administered in dysentery and diarrhea. Leaves administered as tea drink or decoction relieves colic, malaria symptoms, syphilis while crushed leaves or paste are used topically as poultice for abscesses and ulcers. Root decoction is taken for fever and epilepsy while root bark extract is used against toothache.[15]

Chromatographic techniques on *A. reticulata* seeds resulted in discovering a new gamma-lactone acetogenin, named cis-/trans-isomurisolenin, and the identification of six other known cytotoxic acetogenins: annoreticuin, annoreticuin-9-one, bullatacin, squamocin, cis-/trans-bullatacinone, and cis-/trans-murisolinone. The structural identification of these substances was achieved through mass spectrometry and other spectral analysis techniques. Among these compounds, several exhibited significant cytotoxic effects on four types of cancer cell lines: Hep 2,2,15, Hep G2, KB, and CCM2.[16]

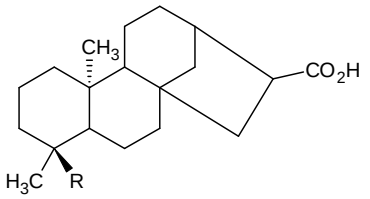
The leaf essential oil of *A. reticulata* contains sesquiterpenes and aromatic esters containing (E, E)-farnesyl acetates, ar-turmerone, benzyl benzoate and γ-terpinene as major constituents. Leaf exracts gave annonaretin A, kaurenoic acid, taraxerol, β-sitosterol, 16α-hydro-19-al-ent-kauran-17-oic acid, 6β-hydroxystigmast-4-en-3-one, 17-acetoxy-16β-ent-19-oic acid, 16α-hydro-ent-kauran-17, 19-dioic acid and (2S)-di-*O*-methylquiritigenin. Significant variations were observed in the compositions of essential oils from the fruits and leaves of all Annona species studied, but α-pinene, camphene, β-myrcene, α-copaene, β-elemene, β-caryophyllene, germacrene D, δ-cadinene, spathulenol and caryophyllene oxide seem to be common to all species. The root oil was found to be rich in spathulenol, δ-cadinene, α-muurolene, β-bisabolene and α-bergamotene.[17]



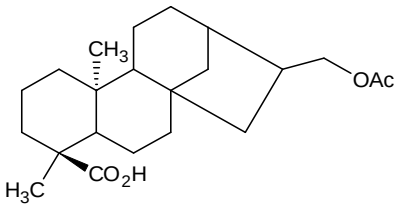
Rolliniastatin-2



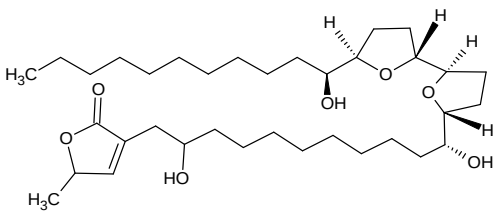
Bullatacin



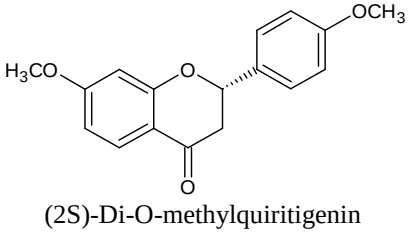
R=CHO, 16α-hydro-19-al-ent-kauran-17-oic acid
R=CO_2H, 16α-hydro-ent-kauran-17, 19-dioc acid



17-acetoxy-16β-ent-kauran-19-oic acid



Molvizarin



(2S)-Di-O-methylquiritigenin

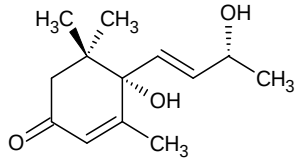
Figure 2: Chemical structures of compounds from *Annona reticulata* Linn.

The plant has shown anti-inflammatory, anti-malarial and analgesic activities. Annonaceous acetogenins are well known for their anti-inflammatory activities and solamin, annoreticulin-9-one, annomonicin, squamone and rolliniastatin have shown this activity.[18]

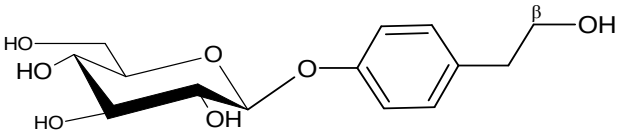
3. *Annona glabra* Linn.

A. glabra is used in traditional medicine as an anti-inflammatory and anticancer drug. Leaves and leafy shoots are used in the preparation of cough mixture. The fruit has an edible yellow pulp. The plant contains an essential oil with several biological activities such as analgesic and anti-inflammatory activities. Terpenes present in the fruit can be used in cosmetics and pharmaceuticals for the production of useful products.[19][20]

GC-MS study of *A. glabra* gave acetogenins, *ent*-kaurenes, peptides and alkaloids. Fresh fruits and stem gave annoglabasin G (16α-hydro- 19-acetoxy-*ent*-kauren-17-al), Plant gave 18 kaurene diterpenoids-including 16β-hydro-*ent*-kauren-17-oic acid, 16α-hydro-ent-kauren-17-oic acid, 19-nor-ent-kauren-4α-ol-17-oic acid, 16α-hydro 19-ol-ent-kauren-17-oic acid *ent*-kaur-16-en-19-oic acid, 16α-hydroxy-*ent*-kauran-190oic acid, 16α, 17-dihydro-*ent*-kauran-19-oic acid, 16β, 17-dihydro-*ent*-kauran-19-oic acid, 16α-hydro-*ent*-kauran-17, 19-dioic acid, 16β-hydroxy-17-acetoxy-*ent*-kauran-19-oic acid; four acetogenins- annomontacin, annonacin, isoannonacinine and squamocin; 5 steroids including β-sitosterol, stigmasterol, β-sitosteryl-D-glucoside, stigmasteryl-D-glucoside, 6-*O*-palmitoyl-β-sitosteryl -D-glucoside; 2 oxoaporphines- liriodenine and lysicamine; 1 dioxoaporphine- annobraine (lettowianthine); 5 aporphines- (-)-nor nuciferine, (-)- annonaine, (-)-N-formylanonaine, (-)-asimilobine and (+)- nordomesticine; 1 proaporphine identified as (+)-stepharine; 2 protoberberines- (-)-kikemanine, dehydrocorydalmine; 1 azaanthraquinone- 1-aza-4-methyl-2-oxo-1, 2- dihydro-9, 10-anthracenedione and 2 amides- N-*trans*-feruloyltyramine and N-p-coumaroyltyramine. Other compounds are dihydrophaseic acid 1, 3'-di-*O*-β-D-glucopyranoside, icariside D_2, icariside D_2 6'-*O*-β-D-xylopyranoside, 3, 4-dimethoxyphenyl -*O*- β-D-glucopyranoside, 3, 4- dihydroxybenzoic acid, blumenol A, cucumegastigmane 1 and icariside B_1. The main compounds of *Annona glabra* were β-caryophyllene, germacrene D, α-cadinol and β-elemene. In another study, the most abundant compounds were terpenoids, principally α-pinene, limonene, α-phellandrene and (*E*)-β-ocimene. The concentrations and compounds found sometimes vary according to many factors-season, location, stage of maturity of leaves or fruits etc.[21]

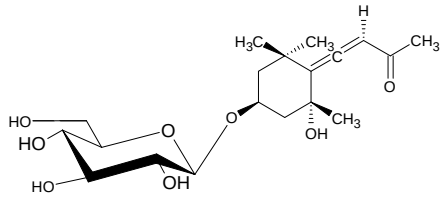


Blumenol A

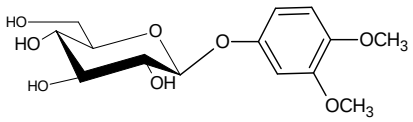


R=H, Icariside D_2

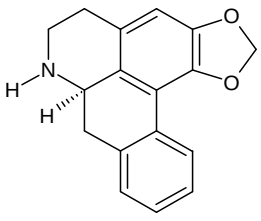
R=Xylopyranosyl, Icariside D_2-6-O-β-D-xylopyranoside



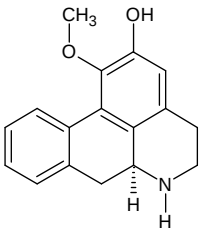
Icariside B_1



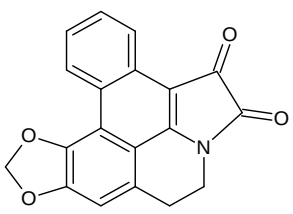
3,4-DimethoxyphenylO-β-D-glucopyranoside



Asimilobine



Annonaine

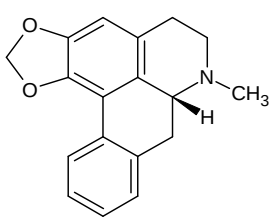


Annobraine (Lettowianthine)

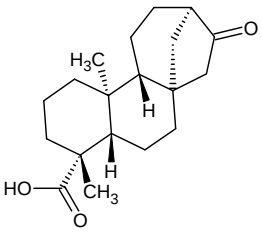
Figure 3: Isolated compounds from *Annona glabra* Linn.

4. *Annona senegalensis* Persoon

Traditionally, *A. senegalensis* is used as a stimulant and pain reliever. Extracts of the plant are used to treat swelling around the eyes, aches and pains- toothache, headache, malaria and mouth infection. All parts of *A. senegalensis* contain varying amounts of essential oils. GC-MS analysis of the volatile components of fruit or leaf oil include car-3-ene, linalool, citronellal, thymol, citronellol, geranial, 1,2-benzene diol, butylated hydroxytoluene and derivatives, fatty acids-hexadecanoate, oleic acid, 13-octadecadien-1-ol, octadecanoic acid, 9,17-octadecadienal; alkanes-hexadecane, tetracosane, heneicosane, pentadecane, tetratriacontane and squalene. The essential oil of air-dried leaves contained germacrene D, β-caryophyllene, γ-cadinene and α-humulene. Other isolates include the diterpenoids- kaur-16-en-19-oic, kaurenoic acid, cavacrol, 1-dodecanol, kaur-160en-18-oic acid and β-caryophyllene. Cyclopeptides isolated from the seeds were cyclosenegalen A & B and glabrin A which are also constituents of other *Annona* species. Annogalene, annosenegalin, acetogenins, kaurenoic acid and derivatives and the alkaloid (-)-roemerine are the major bioactive constituents of *A. senegalensis*. *Annona senegalensis* demonstrated antimalarial, analgesic, anti-inflammatory for the root extract while leaf extracts showed strong anti-inflammatory and trypanocidal properties.[18]



(-)-Roemerine



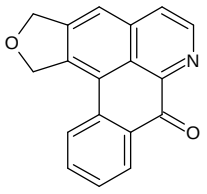
Kaurenoic acid

Figure 4: Chemical structures of compounds from *Annona senegalensis* Persoon.

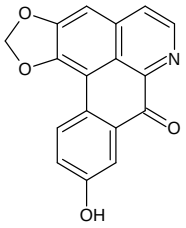
5. *Annona squamosa* Linn.

The leaves of *A. squamosa* are used as a vermifuge and for treating cancerous tumours in traditional medicine. It is also applied as a paste or lotion to abscesses, insect bites and other skin problems. The leaves have also been used as insecticide, anthelmintic and styptic. Stem bark is used as a powerful astringent, anti-dysenteric and vermifuge. Root- bark scrapings or decoction are used for toothache and whole root is purgative. Powdered seed is used to kill fleas and headlice and is believed to have antifertility/abortifacient activity.[22]

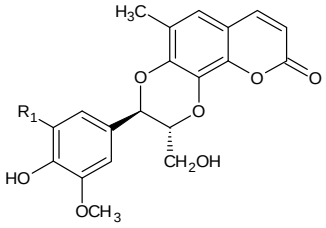
Isolation and characterization of the seeds of *A. squamosa* yielded amino-acids, mono and sesquiterpenes, kaurenes, acetogenins and alkaloids including annonaine. Seeds furnished acetogenins-squamostanal A, squamosin- O_1 *and* O_2, squamosatin-A, squamocins B to N and three lignans consisting of coumarin moiety- cleomiscosin A, B and C. Other isolated compounds were liriodenine, oxoanalobine, duguevalline, roemeolidine and N, Nitrosoxylopine. Leaf oil components were β-cedrene, β-caryophyllene, germancrene D, β-elemene and β-pinene.[12]



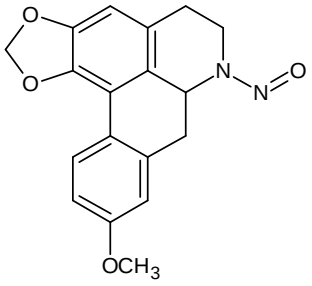
Liriodenine



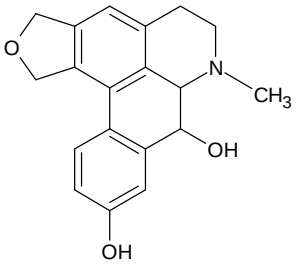
Oxoanalobine



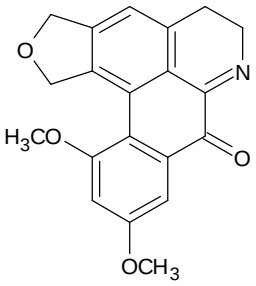
R=H, Cleomiscosin A
R=CH_3, Cleomiscosin C



N-Nitrosoxylopine



Roemerolidine



Diguevalline

Figure 5. Chemical structures of compounds from *Annona squamosa* Linn.

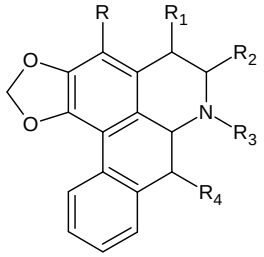
The isolated aporphine alkaloids-N-Nitrosoxylopine, roemerolidine and duguevalline demonstrated *in vitro* anti-inflammatory activity. *A. squamosa* extracts displayed anti-inflammatory and analgesic activities. *Annona* essential oils possess several biological activities

such as anticancer, analgesic and anti-inflammatory properties.

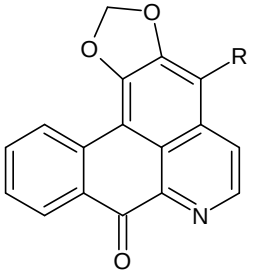
6. Artabotrys

Plants of the Artabotrys genus have been used over the years traditionally for the treatment of malaria, diarrhea, backache, and inflammations.[23] Genus *Artabotrys* belongs to the custard apple family Annonaceae (the subfamily Annonoideae, the tribe Unoneae), including over one hundred species of small shrubs and woody climbers.[24] The plants of this genus are native to tropical and subtropical areas, especially highly concentrated in Africa and Eastern Asia. Traditional uses of *Artabotrys* species included treating a variety of illnesses, such as cholera, scrofula, and malaria.[25]

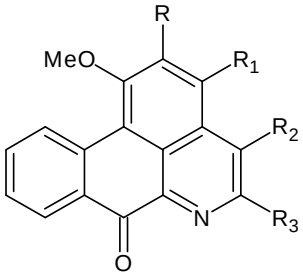
Compounds such as Anonaine, isolated from *A. odoratissimus* and *A. aurantiacus*, exhibit anti-inflammatory and anti-malarial properties while others, like Artabonatine F from *A. uncinatus* roots, showed analgesic activity. Atherospermidine, found in several Artabotrys species, also shows anti-inflammatory and anti-malarial effects. Compounds like Aurantiacine A and (+)-Flavinantine from A. aurantiacus liana are noted for their antiplasmodial properties. Additionally, compounds such as Artaboterpenoid A from *A. hexapetalus* stem and Artabotryol A from *A. odoratissimus* seeds are highlighted for their anti-inflammatory and anti-malarial activities.[26]



R=R_1=R_2=R_3=R_4=H: Anonaine
R=OMe, R_1=R_2=R_3=R_4=H: (-)-norstephalagine



R=OMe: Atherospermidine
R=H: Artabonatine A

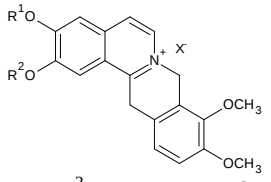


R=R_1= H, R_2=R_3= OMe: Artabonatine C
R=R_1= H, R_2= OMe, R_3= OH: Artabonatine D

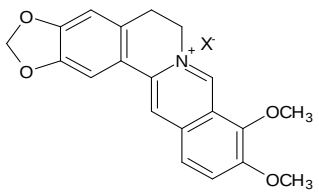
Figure 6: Chemical structures of compounds from Artabotrys.

7. *Enantia chlorantha* Oliv.

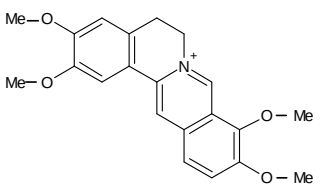
E. chlorantha is a multipurpose medicinal plant and used traditionally for the treatment of pains, malaria as well as inflammations. The stem bark is furnished with Osupupine, an isoquinoline alkaloid identified as 1-(3',4'-dimethoxy-2'-hydroxybenzylidene)-1,2,3,4-tetrahydro-6,7-dimethoxy-*n*-formylisoquinoline. The stem bark also furnished protoberberine alkaloids, berberine, palmatine (berbericinine), columbamine and jatrorrhizine. 7,8-Dihydro-8-hydroxy palmatine and palmatine were reported from an extract of the stem bark that was found to have anti-HIV activity. The root bark, in addition, gave 2 oxyaporphines-O-methyl moschatoline and lysicamine. The leaf gave flavonic heterosides, phenanthrine alkaloids and the alkaloids atherospermine and argentinine.[27]



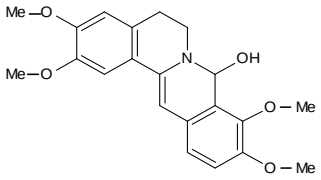
R^1 = H ; R^2 = CH_3, Jatrorrhizine
R^1 = CH_3 ; R^2 = H, Columbamine



Berberine



Palmatine



7,8-Dihydro-8-hydroxy palmatine

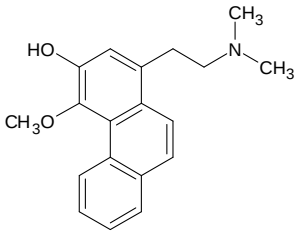
Figure 7: Chemical structures of compounds from *Enantia chlorantha* Oliv.

Stem bark extract showed anti-inflammatory properties. It was shown that an aqueous extract of the plant was able to repair or reverse the liver damage produced in experimental rabbits. Protoberberines isolated from stem bark synergistically had preventive and curative effects on artificially-provoked liver injury. Berberine demonstrated anti-inflammatory and anti-malarial properties. It was confirmed that aqueous extract of plant possess potent anti-malarial activities comparable to that of chloroquine and may be ascribed to the significant presence of alkaloids and phenolics. Osupupine was highly active against chloroquine-resistant *Plasmodium falciparum.*[28]

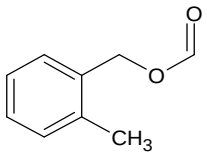
8. *Dennettia tripetala* Barker F.

D. tripetala fruit has a peppery spicy taste and is used traditionally as a remedy for fevers, cough, toothache, nausea etc. and the fruits are commonly eaten as spice or stimulant. Young leaves and fruits have a distinctive spicy taste and have been chewed or eaten as appetite stimulant and for the relief of cough. The various parts, in combination with other plant parts are used to treat infantile convulsions, typhoid, worm infestation and vomiting.[29]

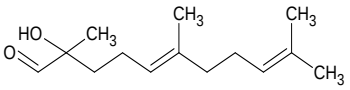
Chemical compounds such as dennetine (2, 6-dimethoxychromone), 3-phenanthrene alkaloids-uvariopsine, stephenanthrine, argentinine and vanillin have been isolated from the roots; GC-MS analysis of the fruit essential oil gave 2-phenylnitroethane (72.41%), linalool (18.0%) and (6E) – nerolidod (4.51%), o-cymene, β-ocimene, copaene, ∝-farnescene, caryophyllene and its oxide, eudesmol. *D. tripetala* fruit essential oils contain 1-nitro-pentane, α- and β-cinene, camphene, β-myrcene, α-phellandrene, p-cymene, (+)-4-carene, β-ocimene, linalool, α-terpinene, phenylethyl-alcohol, borneol, terpin-4-ol, α-terpineol, safrole, 2-methylphenyl formate, elemene, caryophyllene, humulene, α-farnescene, caryophyllene oxide, copaene, 4-epi-cubenol, guaiol, α-eudesmol, trans-cadinol, azulen-5-ol, ascorbic acid 2,6-dihexadecanoate and 9-octadecenoic acid. Leaf fatty acid composition, caprylic, capric, lauric, myristic (tetradecanoic), myristoleic (Tetradec-9-enoic), palmitic, palmitoleic (hexadec-9-enoic), stearic, oleic (cis-9-Octadecenoic), linoleic (Cis, cis-9, 12-octadecadienoic), linolenic (cis, cis-9,12,15-octadecatrienoic) acid.[30]

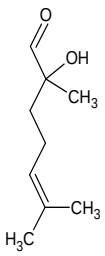


Argentinine

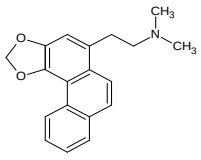


2-methylphenyl) methyl Formic acid ester

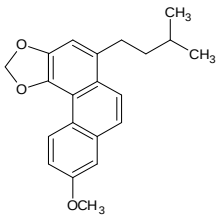




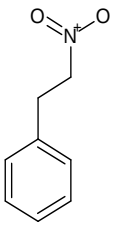
Linalool



Stephenathrine



Uvariopsine



2- Phenyl nitroethane

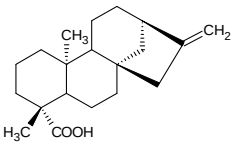
Figure 8: Chemical structures of compounds from *Dennetia tripetala* Barker F.

9. *Xylopia aethiopica* (Dunal) A.Rich.

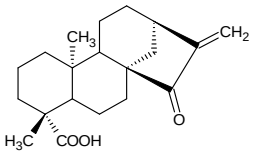
X. aethiopica (Dunal) A.Rich. (Annonaceae). The plant is commonly known as "spice tree," "Africa pepper," "Ethiopian pepper," or "Guinea pepper." The fruits are reported to have high nutritive and medicinal values including being used for the treatment of pain. Several scientific studies have confirmed the traditional use of *X. aethiopica* against pain and inflammation.[31] found that the antiinflammatory actions of the ethanolic extract of the 70% aqueous ethanol extract of the fruits of *X.*

aethiopica are exerted through the inhibition of histamine release from mast cells. The extract (30–300 mg/kg) was inhibited by 23–62% mouse pinnal inflammation. The analgesic and anti-inflammatory properties of the methanol extract of *X. aethiopica* have been investigated by the acetic acid–induced pain (writhing) model in mice and carrageenan-induced inflammation in rats as a model of acute inflammation.[32] Also, the ethanol extract of *X. aethiopica* and its major diterpene, xylopic acid, inhibited acetic acid–induced visceral nociception, formalin-induced paw pain (both neurogenic and inflammatory), and thermal pain as well as carrageenan-induced mechanical and thermal hyperalgesia in murine models.[33]

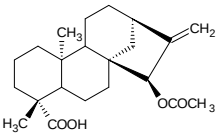
GC-MS analysis of the Fruit revealed kaurene diterpenes-xylopic acid, xylopioxyde, kaur-15-ene, 13-epimanoyloxide, ent-kaur -16- en-19-oic acid and 15-oxo-ent-kaur-16-en-19-oic acid; terpenes and derivatives- ∝ and β-pinene, 1,8-cineole, o-cymene, pinocarveol, α-terpineol, myrtenol, cumic alcohol, elemol, (+)-spathulenol, cis-∝-copaene-8-ol, and fatty acid-hexadecanoic acid methylester.[34] Trunk bark constituents were also analyzed along with root bark and fresh and dried fruits. The major constituents were monoterpene hydrocarbons with β-pinene as major component; trans-m-mentha-(7), 8-diene was the main compound in the essential oils of the leaves and the barks of roots and stems.[35]



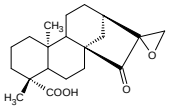
ent-kaur-16-en-19-oic acid



15-oxo-ent-kaur-16-en-19-oic



Xylopic acid,
15α-acetoxy-ent-kaur-16-en-19-oic acid



Xylopioxyde

Figure 9: Chemical structures of compounds from *Xylopia aethiopica* (Dunal) A.Rich.

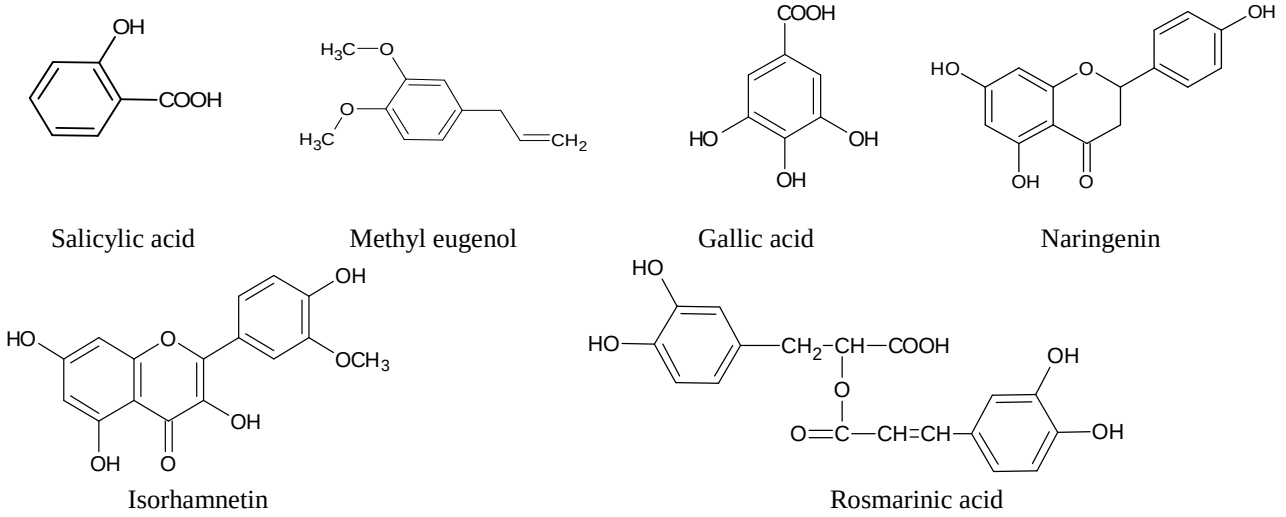
The essential oil showed strong antibacterial, antioxidant and antifungal effects making the fruit useful in the treatment of diseases caused by microbes and fungi. *X. aethiopica* extracts showed anti-anaphylactic, analgesic and anti-inflammatory actions in mice, while the seeds have shown carminative, analgesic and restorative properties.

10. *Monodora myristica* (Gaertn.) Dunal

The seeds of *M. myristica* are useful as a seasoning because of its aromatic flavor; the kernel is a well-known condiment used as a spice in both African and Continental dishes. The ground seed, prepared as a soup is a stimulant to relieve constipation; it has shown diuretic properties, it is antiseptic and is valuable in treating mild fever. Various communities have used the seeds and its essential oil constituents in the treatment of headache and hypertension. Stem bark extract is used to treat stomachache, haemorrhoids, rheumatism and febrile pains. The seeds are aromatic and are traded for their economic values in use as condiment. The powdered seeds extracts have been used, taken internally to treat stomach complaints and relieve constipation and sprinkled on sores for healing. The oil in various parts have proven beneficial.[36]

Seeds, the most useful part of the plant contain 5-9% of essential oil and about 35-36% of a red-brown fixed oil containing linoleic acid (46.9%) and oleic acid (35%) as major constituents. Flavonoid compounds found in the seed are-catechin, daidzein, genistein, apigenin, naringenin and its chalcone derivative, kaempferol, luteolin, epicatechin, myricetin, isorhamnetin, quercetin, rutin, 4-O-methyl epicatechin and epigallocatechin-3-O-gallate; phenol and its derivatives are phenylacetic acid, salicylic acid, cinnamic acid, protocatechuic acid, gentisic acid, p-coumaric acid, vanillic acid, safrole, eugenol and its isomer and its methyl derivatives-methyl eugenol and methyl isoeugenol, gallic acid, caffeic acid, ferulic acid, syringic acid, piperic acid, sinapic acid, shogaol, 3-O-caffeoyquinic acid, chlorogenic acid, rosmarinic acid and Phenyl-6-O-malonyl-β-D-glucoside. Terpene derivatives include myrcene, carvacrol, elemicin, myristicin and other constituents- gingerol, coumestrol, glycitein, capsaicin, curcumin, miquelianin, eriocitrin, gallocatechin derivatives, papain and lupeol. Seed essential oil constituents were linalool (15.10%), δ-cadinene (11.09%), germacrene-D-4-ol (25.48%) and traces of γ-terpinene, trans-p-menth-2-en-1-ol, α-terpineol, p-thymol, caryophyllene, γ-muurolene, β-patchoulene and α-cadinol. The plant growing in Cameroon contains seeds with α-phellandrene, α-pinene, myrcene, limonene and pinene. The stem bark oil constituents were α-cubebene, caryophyllene, α-farnescene, γ-muurolene, α-elemene (17.98%), γ-cadinene (31.31%), acoradiene, cis-nerolidol (7.62%) and traces of guaiol, cadinadiene, copaene and α-bisabolol. Leaf essential oil contains β-caryophyllene, α-

humulene and α-pinene. These compounds were identified through GC-MS analysis.[36]



Salicylic acid | Methyl eugenol | Gallic acid | Naringenin

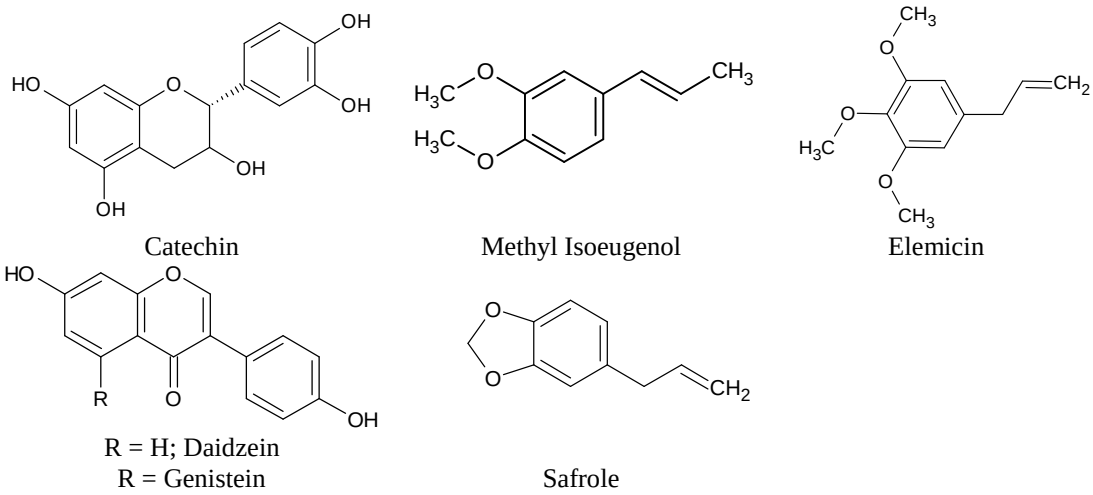
Isorhamnetin | Rosmarinic acid

Figure 10: Chemical structures of compounds from *Monodora myristica* (Gaertn.) Dunal.

The Plant is antiseptic, anti-inflammatory, anti-oxidant, hypotensive and antisickling and was found to lower cholesterol and modulate lipid peroxidation in laboratory animals. *Monodora myristica* was found to ameliorate antioxidant levels as well as serum AST and ALT activities, just as the seed flavonoid-rich fraction ameliorated carbon tetrachloride-induced hepatotoxicity and oxidative stress in rats, and the root bark extract ameliorated acute and chronic inflammation. Aqueous extracts could reverse liver toxicity induced by high cholesterol diets and exert hypocholesterolemic effect.[37]

11. *Monodora tenuifolia* Benth

The stem bark and root extracts are used to treat toothache (use as chew stick). The edible fruits provide an aromatic seed which are traded and used as condiment. The powdered seeds are used in various forms for treating malaria. Chemical compounds identified from *M. tenuifolia seeds* include the flavonoids-catechin, daidzein, genistein, apigenin, naringenin and its chalcone derivative, kaempferol, luteolin, epicatechin, myricetin, isorhamnetin, quercetin, rutin, 4-O-methyl epecatechin and epigallocatechin-3-O-gallate; phenol and derivatives-phenol, phenylacetic acid, salicylic acid, cinnamic acid, protocatechuic acid, gentisic acid, p-coumaric acid, vanillic acid, safrole, eugenol and its isomer and methyl derivatives-methyl eugenol and methyl isoeugenol, gallic acid, caffeic acid, ferulic acid, syringic acid, piperic acid, sinapic acid, shogaol, 3-O-caffeoyquinic acid, chlorogenic acid, rosmarinic acid and Phenyl-6-O-malonyl-β-D-glucoside. Terpene derivatives include myrcene, carvacrol, elemicin, myristicin and other constituents- gingerol, coumestrol, glycitein, capsaicin, curcumin, miquelianin, eriocitrin, papain, lupeol, dimethylallylindole and 6-(3-Methylbuta-1,3-dienyl) indole. These were identified using GC-MS analysis.[38]



Catechin | Methyl Isoeugenol | Elemicin

R = H; Daidzein
R = Genistein

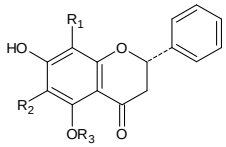
Safrole

Figure 11: Chemical structures of compounds from *Monodora tenuifolia* Benth.

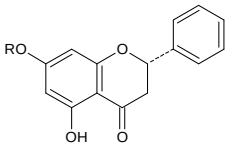
12. *Uvaria chamae* P. Beauv.

The plant *U. chamae* is used traditionally in the treatment of fevers. Whole fruit macerate is taken orally for malaria.[39]

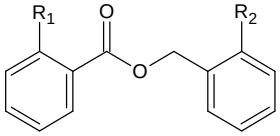
In a typical herbal formula, the roots of *U. chamae* and *Hippocratea pallens* Planch (Celastraceae) are chopped and boiled in water. The extract is allowed to cool. This is strained and drunk in regular doses as appropriate to manage urinary problems, particularly urine retention. This medication is indicated also for nose bleeding, epilepsy, typhoid & yellow fever, jaundice and pile. In the same way a decoction of *U. chamae* root, *Entandrophragma utile* (Cedar) stem bark and *Cyperus esculentus* root and seed may be taken at regulated doses to treat infertility and impotence and associated health problems. The flavonoids in *U. chamae* are pinocembrin, pinostrobin, chamanetin 5-methylether, isochamanetin, dichamanetin-5-methyether, diuvaretin, chamuvaritin, uvarinol, chamanetin, isouvaretin, uvaretin, dichamanetin, chamuvarinin. GC-MS analysis of the essential oil revealed C-benzylated monoterpene chamanen, benzyl benzoates and thymoquinoldimethylether. A sample of *U. chamae* growing in Badagry, Nigeria afforded an essential oil with I-Nitro-2-phenylethane (63.2%), linalool (9.9%) and germancrene D (6.6%) as major constituents.[40]



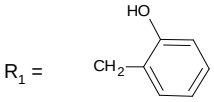
benzoate



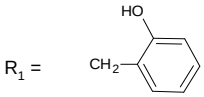
R=H, Pinocembrin;
R=CH3 =pinostrobin
R1=H,R2=OCH3,Omethoxybenzybenzoate



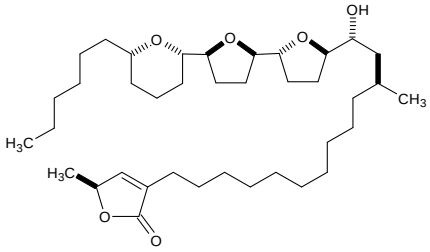
R1 = R2 = H, Benzyl



R2 =R3=H, Chamanetin



R2= H, R3=CH3, Chamanetin 5-methyl ether



(+)- chamuvarinin

Figure 12: Chemical structures of compounds from *Uvaria chamae* P. Beauv.

13. *Duguetia lanceolata* A.St.-Hil.

Many species of Annonaceae have been used to treat inflammatory diseases in folk medicine. Pharmacological studies have shown that some terpenoids and essential oils from this family have significant anti-inflammatory effects, such as caryophyllene oxide and the essential oil of *D. lanceolata*. The essential oil from the branches of *D. lanceolata*, which is rich in β-elemene (8.3%), β-caryophyllene (6.2%), caryophyllene oxide (7.7%), β-eudesmol (7.2%), β-selinene (7.1%), and δ-cadinene (5.5%), played a crucial role as a protective factor against carrageenan-induced acute inflammation.[41]

GC-MS analysis of essential oil from the bark of the underground stem of *Duguetia furfuracea*, revealed (*E*)-asarone (21.9%), bicyclogermacrene (16.7%), 2,4,5-trimethoxystyrene (16.1%), α-gurjunene (15.0%), and cyperene (7.8%), was shown to have anti-inflammatory effects.[42]

14. *Saccopetalum tomentosum* (Roxb.) Hook.f. & Thomson

The leaf extract of S. tomentosum showed anti-inflammatory activities and sub-acute toxicity of hydro-ethanolic. Results of anti-inflammatory has shown that the tested extract 200mg/kg was found more active with the inhibition percent of oedema by the tested extracts at 2 dose level 100mg/kg and 200mg/kg using the formalin-induced rat paw oedema model using diclofenac sodium as the reference drug.[43]

Antiinflammatory Constituents of the Annonaceae Family

The family Annonaceae, known for its diverse genera and species, has been extensively studied for its rich content of bioactive compounds with anti-inflammatory and analgesic properties. *Annona glabra* stands out with its notable anti-inflammatory compounds such as annonaceous acetogenins, annomontacin, annonacin, isoannonacinine, squamocin, and annoreticulin-9-one. Its analgesic properties are also attributed to essential oils containing terpenes, β-caryophyllene, germacrene D, α-

cadinol, and β-elemene. These compounds have been isolated and their efficacy documented in various pharmacological studies, emphasizing their potential in managing inflammatory and pain-related conditions.[44]

Another species, *Annona reticulata*, has been reported to contain anti-inflammatory compounds such as annoreticuin, annoreticuin-9-one, bullatacin, squamocin, cis-/trans-bullatacinone, and cis-/trans-murisolinone. Its analgesic properties are linked to sesquiterpenes and aromatic esters, including (E E)-farnesyl acetates, ar-turmerone, benzyl benzoate, and γ-terpinene. Studies on these compounds have highlighted their ability to inhibit key inflammatory pathways and provide relief from pain, supporting their traditional use in folk medicine.

Annona senegalensis also contributes significantly to the Annonaceae family's medicinal profile. It contains anti-inflammatory compounds such as germacrene D, β-caryophyllene, γ-cadinene, α-humulene, kaur-16-en-19-oic acid, kaurenoic acid, annogalene, annosenegalin, and acetogenins. Essential oils derived from its leaves and fruit further support the analgesic potential. Research has demonstrated that these compounds exhibit strong anti-inflammatory and analgesic effects, making them valuable candidates for further drug development and therapeutic applications.[45][46]

Annona squamosa has been identified to contain anti-inflammatory compounds like squamostanal A, squamosin-O1 and O2, squamosatin-A, squamocins B to N, cleomiscosin A, B, and C, liriodenine, oxoanalobine, duguevalline, and roemeolidine. Its analgesic properties are attributed to β-caryophyllene, germacrene D, β-elemene, and β-pinene. These compounds have effectively reduced inflammation and alleviate pain in various experimental models.[47] The studies and references on these bioactive compounds underline their significance and validate the traditional medicinal uses of these species within the Annonaceae family.

CONCLUSION

Alkaloids such as annonaine, reticuline, and atherospermidine have been identified across various species, demonstrating significant bioactivities, including anti-inflammatory and analgesic effects. Annonaceous acetogenins, a unique class of compounds to the Annonaceae family, have shown potent cytotoxic activities against various cancer cell lines and also exhibit anti-inflammatory properties. Terpenes and essential oils containing compounds like β-caryophyllene and germacrene D were prevalent across the species studied, contributing to the anti-inflammatory and analgesic activities. Flavonoids and phenolic acids, known for their antioxidant properties, further support the anti-inflammatory potential of Annonaceae species.

These findings highlight the potential for the development of novel anti-inflammatory and analgesic agents derived from natural products. The diversity of chemical compounds identified suggests multiple mechanisms of action could be exploited in the development of new therapeutic agents. The evident biological activities of these compounds, particularly the anti-inflammatory and analgesic effects, underscore the importance of further pharmacological studies to fully understand their potential in drug development. Moreover, the adverse effects associated with conventional anti-inflammatory drugs, such as NSAIDs and corticosteroids, necessitate the search for alternative therapies with fewer side effects. The Annonaceae family, with its diverse pharmacological properties, offers a promising reservoir of compounds for developing safer and more effective therapeutic agents.

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