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BOTANICALLY DERIVED FRIEDELANE TYPE ISOPRENOIDS: A MINI-REVIEW ON THEIR PESTICIDAL POTENTIALS.

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ABSTRACT

Friedelane-type isoprenoids are naturally occurring pentacyclic triterpenes that includes friedelin and its derivatives. Several reports on their numerous biological activities in both *in vivo* and *in vitro* experimental models have been reported. This report is a review on the pesticidal friedelane-type isoprenoids of botanic origin, their mechanisms of action and salient structure activity relationship. Generally, the type and stereochemistry of the substituent at position C-3 of the friedelane 1 triterpene skeleton greatly affects biological activity of these phyto-constituents.

KEYWORDS: Friedelin derivatives, botanical sources, pesticides, structure activity relationship.

Abbreviations

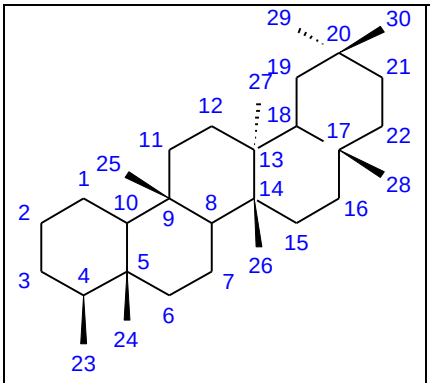
- GI_{50} Half maximal inhibition of cell proliferation concentration.
- IC_{50} Half maximal inhibitory concentration Ppm Parts per million.
- *Sf9Spodoptera frugiperda* pupal ovarian cell.

INTRODUCTION

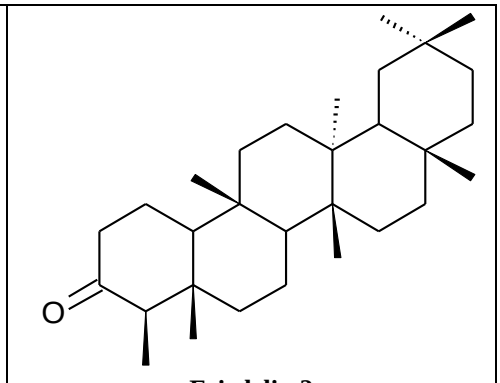
The biological effects of natural resources from plants have been used for thousands of years in combating human ailments, as pesticides, as insect repellents and even as chemical weapons. Natural products have a diversity of structures which play a lead role in the discovery and development of new compounds for new drugs,[1] cosmetics and agrochemicals. There are many classes of these natural resources which include, alkaloids, terpenoids (or isoprenoids), glycosides, flavonoids, coumarins and tannins among others. Pesticides are substances (chemical or biological) used in the control of pests and includes; insecticides, herbicides, rodenticides, larvicides, fungicides, and nematicides. Synthetic pesticides have been found to have deleterious effects on the ecosystem as compared to the use of botanicals and other natural means of pest control. Thus, increased focus on the use of biological and other nature derived agents which are eco-friendly in the control of pests is now of interest. Plants secondary metabolites are known to play ecological role being secreted as a defense response to attack by diseases and predators.[2] The terpenoids are sometimes referred to as the isoprenoids and are a class of secondary metabolites whose chemical structures are made up of one or more isoprene units. Depending on the number of isoprene units, they could be sub-classified into: hemiterpenoids (one isoprene unit), monoterpenoids (two isoprene units), sesquiterpenoids (three isoprene units), diterpenoids (four isoprene units), sesterterpenoids (five isoprene units), triterpenoids (six isoprene units) and tetraterpenoids (eight isoprene units). Isopentenylpyrophosphate and dimethylallyl pyrophosphate are the biological isoprenes from which their biosynthetic ancestry is derived by way of the mevalonate pathway.[3] Triterpenoids are a sub-class of isoprenoids made of six isoprene unit and include the true triterpenoids and related steroids and their glycosides like saponins, and cardiac glycosides of botanical origin. Some have been investigated for their possible application as pesticides.[4] They are highly ubiquitous in plants of which friedelin 2, a saturated pentacyclic triterpene ketone is a classic example. Other synonyms of Friedelin 2 are Friedelan-3-one; 3-friedelanone; and D:A-Friedooleanan-3-one. Friedelin and all its structurally related analogues are referred to as the friedelane-type triterpenoids or friedelane-type isoprenoids. This report is a review on the pesticidal friedelane-type isoprenoids of botanic origin reported in literature, their mechanisms of action and salient structure activity relationship.

METHODOLOGY

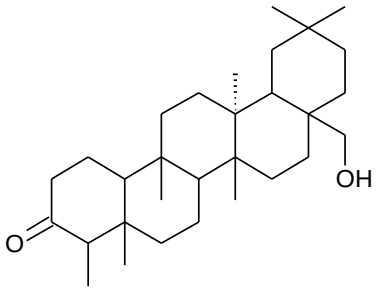
This mini-review was done based on a search of relevant literature on plant-derived triterpenoid friedelin 2 and five of its common naturally occurring derivativesL canopyllol 3, epifriedelinol 4, epifriedelinol acetate 5, friedelinol 6, friedelinol acetate 7 and all related synonyms of the parent triterpenoid friedelin 2 such as : Friedelan-3-one; 3-friedelanone; and D:A-Friedooleanan-3-one as confirmed from databases like: Pubmed, Google Scholar, Scopus, SciFinder, PubChem, ChemSpider, and ScienceDirect. Relevant data on pesticidal activities of these phyto-constituents within the period 1990-2019 were used for this mini-review.



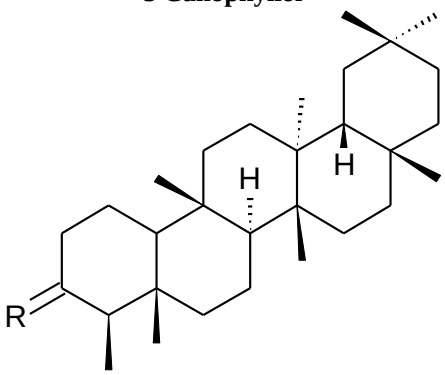
Friedelane triterpene skeleton 1



Friedelin 2



3 Canophyllol



Epifriedelinol **4**: R= β – OH, H
Epifriedelinol acetate **5**: R= β-OAc, H
Friedelinol **6**: R= α-OH, H
Friedelinol acetate **7**: R= α-OAc, H
Friedelin **2**: R= O

Physical Properties of Friedelin

Friedelin **2** (molecular formula $C_{30}H_{50}O$) has a molecular weight of 426.7174 g/mol. At room temperature, it is a white solid. It is soluble in alcohol and chloroform with a solubility of 1:250 and 1:8 respectively, but not soluble in water.[5] This forms the basis for the use of chloroform and alcohol in its extraction from plants. It has a boiling point at about 477.2 ^{o}C at 760 mmHg,[5] and a melting point of 262-265 ^{o}C [5]. Friedelin **2** has a density of about 1.0 g/cm^3,[5] a refractive index of 1.50,[5] and an optical activity of - 12 ^{o}±3 ^{o} in chloroform.[5]

Diagnostic Spectra Characteristics

Except for the normethyl or demethyl derivatives, the nuclear magnetic resonance (^{1}H and ^{13}C NMR) spectra of all friedelane-type isoprenoids are evident for eight angular methyl groups one of which has its protons as a diagnostic doublet at position 23 (i.e. the H-23, 3Hd) resonating in the region around δ_H 1.0 ppm. The other seven has their protons resonating as singlets all of which

upfield in the region δ_H: 0.75-1.2 ppm in their ^{1}H NMR spectra. All the angular methyl moieties have their corresponding carbon signals being upfield in the region δ_C: 6.8-35 ppm.[6-8] They like every other triterpenoid give a characteristic chromogenic (violet to purple coloration) reaction with the Liebermann-Buchard reagents. The mass spectrum of friedelin, the parent analogue shows diagnostic fragmentation ions peaks at m/z : 426 [M+], and 411 [M-CH_3], and the base peak at m/z 125 due to ring B cleavage with subsequent loss of a methyl group to produce fragmentation ion peak at m/z 109.[8]

Botanical Sources

Friedelin 2 has been found to be one of the most ubiquitous triterpenes in nature. It has been isolated as a bio-active principle of certain plant parts e.g. from the n-hexane extract of *Azima tetracantha* Lam leaves, the leaves of *Combretum duarteanum* Cambess[9] the leaves of M*aytenus ilicifolia*.[10,11] and the leaves of *Maytenus imbricate*.[12] the chloroform fraction of the ethyl acetate extract of the stem bark of *Prosopis africana* (Guill. & Perr.) Taub.,[13] chloroform fraction of the stem of *Caesalpinia minax* Hance,[14] the leaves of *Alchornea latifolia* Sw,[15] the dichloromethane fraction of the ethanol extract of the dried stems of *Celastrus vulcanicola*,[16] methanol extracts of: the stem of *Alchornea cordifolia*,[17] *Maytenus robusta*,[18] and the stem bark of *Mallotus philippensis*,[14] the dichloromethane extract of the leaves of *Marila pluricostata*[19] and the petroleum ether extract of the root bark of *Terminalia avicennioides* Guill & Perr,[20] It has also been isolated from the stem bark of *Syzygium guineense* Wild. DC (Myrtaceae).[8]

Friedelane-Type Triterpenoids With Herbicidal Activity

Canophyllol 3 and epifriedelinol 4 from the ethanol dried stem extract of *Celastrus vulcanicol,* at 100µm showed herbicidal potential. Canophyllol 3 had an I_{50} of 124 µM and epifriedelinol 4 had an I_{50} of 82 µM[16] . Whereas 3 acted as interferes with photosynthesis by inhibiting Hill's reaction, 4 does same through energy transfer inhibition interacting and enhancing the light-activated Mg^{2+}-ATPase.[23] Epifriedelinol 4, epifriedelinol acetate 5, friedelinol 6, friedelinol acetate 7, and Friedelin 2 had a phototoxic effect on *Lactuca sativa.* They inhibited root enlongation to 44%, 68%, 36%, 50% and 38% when they were introduced to the plant respectively.[24] These friedelane-type triterpenoids had a non-specific phytotoxic effect implying their interference with plant membranes as opposed to working as chemical signals.[19] Previous studies have shown that Friedelin 2 inhibited radicle growth of *Echinochloa crusgalli*[24] while the root inhibition of *L. sativa* by friedelinol 6 and Friedelin 2 has also been demonstrated.[25]

Structure Activity Relationship

From the study of Moiteiro *et al*,[25] one can see that the group on position C-3 plays a huge role as a 3β-hydroxyl on epifriedelinol 4 led to decreased phytotoxic effect than an α-hydroxy group as seen on friedelinol 6.

Insecticidal Activity

In a study by Gonzalez-coloma *et al.,*[24] It was observed that epifriedelinol 4 and Friedelin 2 had an anti-feedant effect with an ED_{50} value of 8.65 µg/cm^2 and 14.41 5 µg/cm^2 respectively on *Leptinotarsa decemlineata* in choice tests. Anti-feedant activity on *Myzus persicae* was moderately perpetrated by epifriedelinol 4 (65%, 35%), friedelin 2 (15%, 42%) and friedelinol 6 (66%, 34%) when introduced to the aphids on the control disk and treated disk respectively. It was suspected that these anti-feedant activities might be neuro-receptor facilitated including GABA and different receptors. Gonzalez-coloma *et al.,*[24] observed that a dosage of 40 µg/ larvae, friedalane triterpenes generally were very toxic to *Spodoptera littoralis.* Epifriedelinol 4 (67%,52%), friedelinol 6 (59%, 32%), friedelinol acetate 7 (73%, 56%) and Friedelin 2 (79%, 77) drastically reduced *S. littoralis* food consumption and biomass gain respectively. Their activities indicate intense post-ingestive anti-feedant as well as insect growth regulator (IGR) without further harmful impact. Friedelinol 6 and friedelinol acetate 7 (which were non-cytotoxic) behaved as digestive toxins while the cytotoxic Friedelin 2 and epifriedelin may have acted unspecifically on cell membranes in addition to acting as digestive toxin. This indicates that IGR has multiple biological mechanisms.[24] On the pupal ovarian tissue of the insect *Spodoptera frugiperda*, epifriedelinol 4 (ED_{50}= 16.21 µg/ml), Friedelin 2 (ED_{50} = 16.52 µg/ml) and epifriedelinol acetate 5 (ED_{50} = 79.52 µg/ml) were toxic with epifriedelinol 4 exhibiting selective toxicity.[24]

Structure Activity Relationship

Epifriedelinol 4 was more active than Friedelin 2 against *L. decemlineata* because it had a β-hydroxyl group at position C-3 while Friedelin 2 had an oxo group at that position.[23] Substitution of the friedelin ketone at C-3 by an α- or β -hydroxy group as in friedelinol 6 and epifriedelinol 4, or an α-acetoxy group as in friedelinol acetate 7, led to increased larval post - ingestive activity on *S. littoralis*.[24] Presence of a β-hydroxy group at C-3 of epifriedelinol 4 caused a selective cytotoxicity on Sf9 which disappeared on the presence of α-hydroxyl group at C-3 of friedelinol 6. Presence of an oxo group on C-3of Friedelin 2 resulted in an unspecific cytotoxicity. The very intense *L. sativa* root elongation inhibition was due to the presence of the 3-oxo or 3β-hydroxy group as seen on Friedelin 2 and epifriedelinol 5 respectively. The substituent and arrangement on C-3 is very crucial as a 3β- hydroxyl on epifriedelinol 5 led to an increased insecticidal action than an α-hydroxy group as seen on friedelinol 6.[25]

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