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REVIEW

Friedelin and 3β-Friedelinol: Pharmacological Activities

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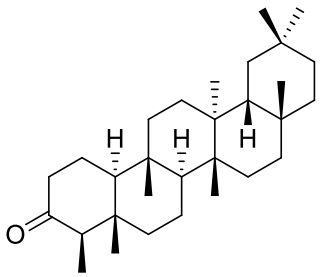
Abstract

The interest in herbal medicine as a source of drug leads is being reinforced, especially for tackling challenging therapeutic areas such as antimicrobial resistance, cardiovascular diseases, cancer, and multiple sclerosis. Friedelin and 3β-friedelinol are pentacyclic triterpenoids commonly distributed in plants and are found in edible fruits and vegetables. More than 400 naturally occurring friedelane triterpenoids have been identified. Friedelin and its derivative 3β-friedelinol are reported to have significant pharmacological potential, including antibacterial, anti-viral, and cytotoxic properties. Friedelane triterpenoids could be considered as promising candidates in drug development against human coronaviruses, including SARS-CoV-2. The natural sources of friedelane triterpenoids have been examined, which include the families Celastraceae, Hippocrateaceae, Euphorbiaceae, Flacourtiaceae, and Guttiferae. The purpose of this review is to summarize the structural elucidation, physicochemical properties, spectroscopic data, natural origin, biosynthesis, quantification techniques, and the reported pharmacological activities of friedelin and its derivative 3β-friedelinol. The review explores the potential beneficial effects of these bioactive triterpenes and discusses ways to enhance their pharmacological significance.

Keywords Nutraceuticals · Terpenes · Antibacterial · Anti-inflammatory · Cytotoxic · Antiviral

Introduction

The drug discovery process faces both benefits and obstacles when dealing with natural compounds as they possess unique features in contrast to traditional synthetic molecules. Friedelin (**1**) is one of the major pentacyclic terpenes present in the cork of different plants (Pires et al. 2011; Duarte and Bordado 2015). Friedelin is one of the primary fundamental chemicals of the friedelane-type triterpenoid. To date, more than 400 naturally occurring friedelane triterpenoid have been identified, which have a diverse range of bioactivities (Pires et al. 2011). The friedelane triterpenoids have a diverse range of bioactivities, including friedelin (Das et al. 2018). Friedelin showed diverse biological activities such as anti-inflammatory, antibacterial, and antiviral agents that represent these compounds as promising candidates for drug development. Friedelin and its reduced derivative 3β-friedelinol (**2**) are abundantly available in nature and frequently coexist with each other. These two triterpenoids have been found in lower plants such as lichens, some oceanic green algae (Basuki et al. 2013; Emsen et al. 2018), certain forms of peat, and brown coal (Basuki et al. 2013). Friedelin has also been reported in certain species of fungus, including *Ganoderma applanatum* (Richter et al. 2015) and *Armillaria mellea* (Juan Guo and Guo 2011). These two compounds also widely co-occur in families of higher plants such as Euphorbiaceae, Fagaceae, Celastraceae, and Asteraceae (Caneschi et al. 2014; Yoon et al. 2017; Alves et al. 2018; Herrera et al. 2018).



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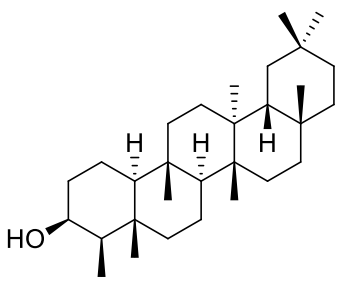

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Search Strategy

Data from various databases such as the Egyptian Knowledge Bank, Scopus, Web of Science, PubMed, Google Scholar, Elsevier databases, and Dr. Duke's Phytochemical and Ethnobotanical Databases were gathered until July 2022. All possible keywords pertaining to friedelin, 3β-friedelinol or its epimer (3α-isomer), natural origins, isolation, structure, solubility, synthesis, bioavailability, applications, biological effectiveness, mechanism, harmful effects, pharmacokinetics, and clinical studies were utilized in the search.

Discussion

Natural Sources

Triterpenes are present in a wide range of organisms including plants, fungi, and occasionally animals. Among these, friedelin and its derivatives are naturally occurring triterpenes that have been extracted from both higher plant families and lower organisms such as lichens and fungi. These triterpenes have been mainly isolated from *Jatropha* and *Euphorbia* species of the Euphorbiaceae family and other families, such as Asteraceae (Fig. S1). Friedelin (**1**) and 3β-friedelinol (**2**) have been isolated from various plant families, which are listed in Table S1.

Chemical Structure

Triterpenes are a group of natural compounds consisting of 30 carbon atoms, polymerized to form six isoprene units with the molecular formula $C_{30}H_{48}$. Most triterpene skeletons are tetracyclic and pentacyclic; however, acyclic types have also been identified from natural sources. There is a wide range of triterpenes with almost 200 distinct skeletons identified, with the pentacyclic structure being the most prevalent. The most common pentacyclic triterpenes belong to lupine, oleanane, taraxerane, multiflorane, glutinane, bauerane, pachysanane, ursane, and friedelane types (Fig. S2) (Rascon-Valenzuela et al. 2017). The pentacyclic triterpenoids are plant-specialized metabolites with diverse biological interests, such as hepatoprotective, anti-inflammatory, cytotoxic, antiulcerogenic, and anti-hypertensive.

Friedelin (**1**) was the first naturally occurring normal friedelane isolated; it has the molecular formula $C_{30}H_{50}O$, and its molecular weight equals 426.7. It is a pentacyclic triterpenoid substituted by an oxo group at C-3; therefore, it is a cyclic terpene ketone or the 3-keto-derivative of the hydrocarbon friedelane (Hastings et al. 2016). The structure of friedelin was elucidated through the formation of its enol esters, carbonyl derivatives, and to the saturated parent hydrocarbon friedelane. In addition, the structure of friedelin was formerly established through preparation of dehydrogenation studies and the isomerization of friedel-3-ene to olean-13(18)-ene (Pires et al. 2011; Lu et al. 2021). Chromic acid oxidation of friedelin affords a keto acid, friedelonic acid, and $C_{30}H_{52}O_2$, without the loss of carbon, together with the preceding data, limited the oxo function to two positions C-1 or C-3. Proof of the location of the oxygen at C_3 which seemed most reasonable for biosynthetic reasons was obtained in several ways discussed in the literature. Using single-crystal X-ray diffraction, the preferred configuration of friedelin was identified. Additionally, the structure of an epifriedelinol (**2**) derivative produced via chemical synthesis was confirmed by a single-crystal X-ray study (Wanxing et al. 2004; Oliveira et al. 2012; Shan et al. 2013; Aswathy et al. 2022).

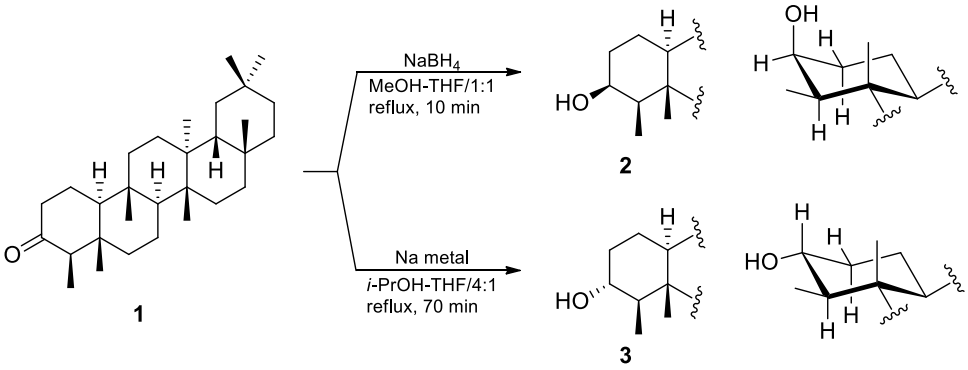
Reduction of Friedelin

Upon reduction of friedelin (friedelan-3-one) with sodium metal, friedelinol (**3**, friedelan-3α-ol) is produced as the major product, while *epi*-fridelinol (**2**, friedelan-3β-ol) is produced with lithium aluminum hydride or sodium borohydride with a high degree of stereospecificity (Xu et al. 2004; Kuiate et al. 2007). LeFevre et al. (2001) reduced friedelin by using $NaBH_4$ or Na metal, independently. There were different stereochemical results in the friedelinol products: $NaBH_4$ reduction of the keto group at C-3 of friedelin, by an alpha attack of the hydride, primarily yields the axial 3β-alcohol *epi*-fridelinol (**2**, friedelan-3β-ol), as a consequence of the hindering effect of the axial methyl group at C-5 of the friedelane core; this result is in contrast with the unhindered cyclohexanone $NaBH_4$ reductions which result in the more stable equatorial alcohol by the axial attack of the hydride. The reduction of friedelin with Na metal produces the more stable equatorial alcohol (**3**, friedelan-3α-ol) as its primary product (Scheme 1).

Friedelin Physicochemical Properties

Friedelin (CAS Number: 559–74-0; friedooleanan-3-one and friedelan-3-one) was isolated as white needle crystals with a melting point of 262–263 °C (266–269 °C) (Salama 1986) with a positive specific optical rotation $[\alpha]^{25}{}_{D} + 2.0°$ (*c*.1.0, MeOH). It is freely soluble in chloroform, sparingly soluble in ethanol, and insoluble in water, and this triterpene is an extremely weak basic compound (based on its pKa –7.4) (Mann et al. 2011; Ambarwati et al. 2019).

The mass spectrum by electron impact ionization for friedelin exhibited a fragmentation pattern with cations at *m/z* 426 $[M]^+$, 411, 341, 273, 245, 231, 215, and 189. The



Scheme 1 Reduction of friedelin (**1**) by NaBH4 and Na metal produces mainly the axial alcohol *epi*-friedelinol (**2**, friedelan-3β-ol) and the equatorial alcohol friedelino (**3**, friedelan-3α-ol), respectively. Adapted from Lefevre et al. (2001)

HPLC-ESI-MS showed the following ions: in the positive mode, a protonated molecule at *m/z* 427.39344 $[M+H]^+$, and a cationic molecule at *m/z* 449.37538 $[M+Na]^+$; in the negative mode, a deprotonated molecule at *m/z* 425.37889 $[M-H]^-$, which confirmed the molecular mass of 426.38562 Da for friedelin (Rhourri-Frih et al. 2009; Huang et al. 2021). IR (nujol) of friedelin showed absorption bands at 2927 (CH stretching), 1707 (C = O stretching), and 1380 (gem-dimethyl group) cm^{-1} (Ambarwati et al. 2019).

Friedelinol Physicochemical Properties

3β-Friedelinol or *epi*-friedelinol was obtained as colorless crystals, with a melting point range to be 280–282 °C. The IR spectrum showed the presence of OH functionality in the molecule (ν_{max} 3500 cm^{-1}). The mass spectrum gave a molecular ion peak at *m/z* 428. It is soluble in chloroform, sparingly soluble in ethanol, and insoluble in water. The ^{13}C NMR spectrum reveals the presence of 30 signals: eight methyl, eleven methylene, five methine, and six quaternary carbons. The β orientation of the hydroxyl group at C-3 was confirmed by the coupling constant value at 3.0 Hz, coupling between H-3 and H-4, and H-2 (Manoharan et al. 2005). Table S2 summarizes the NMR data for friedelin as well as the two epimers of friedelinol.

Biosynthesis

Friedelin is a friedelane-type triterpene that is synthesized via the mevalonate pathway; the most important step is the complicated cyclization of the C-30 linear precursor 2,3-oxidosqualene by the catalyzation of oxidosqualene cyclase (Zhou et al. 2019; Gao et al. 2022) through protonation, cyclization, several rearrangements, and, finally, deprotonation to the friedelin (Han et al. 2019). Friedelin is the most highly isolated pentacyclic triterpene in plants. Friedelin and its derivatives offer prospective sources for creating novel pharmaceuticals or dietary supplements (Gao et al. 2022). To supply the crucial precursor 2,3-oxidosqualene, which is cyclized into a variety of triterpene skeletons by OSCs, some researchers have used microbes like *Saccharomyces cerevisiae*. To produce these valuable products, molecular biology approaches have been applied to manipulate microorganisms instead of resorting to chemical methods that involve hazardous chemicals and have a negative impact on the environment (Thimmappa et al. 2014).

Quantification and Quality Control

Several analytical methods have been used for the quantification and identification of friedelin and its derivative friedelinol such as HPLC-DAD, HPLC-UV, and GC-MS. Friedelin and friedelinol were quantized by HPLC with evaporative light scattering detection (ELSD) together with shionone, the chemical marker from the roots (*Radix asteris*) of the Chinese traditional medicinal plant *Aster tataricus* L.f.. Asteraceae. Tian et al. (2009) used the C_{18} column with gradient elution with acetonitrile and 0.05% acetic acid. They validated the method for linearity, sensitivity, precision, repeatability, stability, and accuracy. All calibration curves displayed strong linear regression ($R^2 > 0.9991$), with overall intra-day and inter-day variations of 1.61–2.97 and 1.74–2.42%, respectively. The established method showed good precision and accuracy, with overall recoveries of 97.35–101.13% for the three triterpenoids since their quantification is important for the quality control of *Radix asteris* (Wang et al. 2009). Pires et al. (2011) analyzed friedelin isolated from a black condensate of cork sample, the wastes of the insulation corkboard industry, using HPLC coupled to a UV detector (202 nm). Also, a friedelin-rich fraction was separated from an EtOH-soluble extract of *Cissus quadrangularis* L., Vitaceae, using HPLC with a C-18 column at a wavelength of 205 nm (Aswar et al. 2010). LC–MS was also used to purify friedelin from the citrus-derived tetracyclic triterpenoids nomilin and limonin from both the rind and pulp of limon fruits (Jose et al. 2014). In another study, Abhimanyu et al. (2017) developed an HPTLC technique for the assessment of friedelin in the leaf and bark of *Putranjiva roxburghii* Wall., Putranjivaceae. In addition, two ayurvedic polyherbal formulations containing extracts of *P. roxburghii* (Femiforte: 40 mg/tablet; Femiplex

tablets: 13.05 mg/tablet) were also analyzed. On a TLC aluminum precoated plate (60 F_{254}), materials were analyzed using a mobile phase of toluene:chloroform (9:1, *v/v*). The plate was scanned at 580 nm after derivatization with vanillin/sulfuric acid. With this approach, a compact spot for friedelin was exhibited at R_f value of 0.43 ± 0.01. The International Council for Harmonization's (ICH) criteria for linearity, precision, accuracy, and robustness were used to validate this method. The established method for the quantification of FRN was shown to be straightforward, specific, accurate, and robust with a good linearity relationship (100–500 ng/spot) and a correlation coefficient (r^2) value of 0.9892 for friedelin. The limit of detection and limit of quantitation were found to be 32.15 and 97.44 ng/band, respectively.

GC-MS analysis was used to quantify friedelin in leaves extracts of *Azima tetracantha* Lam., Salvadoraceae (Jose and Panneerselvam 2019). Vistuba et al. (2013) (Fig. S3) conducted a noteworthy study that aimed to quantify friedelin and 3β-friedelinol using gas chromatography with flame ionization detection (GC-FID) through multiple injections in a single experimental run (MISER). This technique was applied to the two compounds that were isolated from *Maytenus ilicifolia* Mart. ex Reissek, Cekastraceae, leaf extract. ZB-50 (30 m × 0.25 mm × 0.15 µm) column with a stationary phase composition of 50% phenyl-50% dimethylpolysiloxane was used. The injector temperature was set to 280 °C, and the FID detector temperature was set to 320 °C for the split mode injection of the samples (1 µl). The column's temperature was set to 300 °C in isothermal mode. Helium was employed as the carrier gas, at a constant flow rate of 1.5 ml/min. The MISER technique allowed for the execution of three injections in a single run. When numerous injections were used instead of a single injection, an increase in the instrumental throughput was seen by a factor of about 2.6. This technique demonstrated good linearity for both analytes with $R^2 > 0.99$. Additionally, the results for the limits of quantification for friedelin and 3β-friedelinol were 0.79 mg/l and 1.16 mg/l, respectively. Also, the triterpenes in a triterpenoid-rich extract prepared from bamboo shavings of *Phyllostachys nigra* (Lodd. ex Lindl.) Munro, Poaceae, were identified by GC–MS and their contents determined as friedelin (24.9%), friedelan-3-β-ol (22.3%), lupenone (6.1%), lupeol (5.0%), α-amyrin (7.1%), and oleanan-3-one (8.2%) (Zhang et al. 2004).

Pharmacological Activities

Antiviral Activity

Secondary metabolites from nine medicinal plants, including friedelin, have been studied to identify possible therapeutic compounds that could be used to alter the network of genes responsible for SARS-CoV-2 disease in humans and to better comprehend the dynamics of essential proteins engaged in interactions between viruses and their hosts (Fatoki et al. 2021). Friedelin was selected as a potential compound that has binding affinity greater than −9.0 kcal/mol against target $3CL^{pro}$ of coronaviruses, which has a potential role in the virus replication using lopinavir and ritonavir as 3CLpro-referenced inhibitors for comparison (Gyebi et al. 2021; Mosquera-Yuqui et al. 2022). Friedelin was also found to inhibit SARS-CoV-2 main protease; enzyme (Mpro) (PDB: 6LU7) with binding energy equal of −7.9 ± 0.02 kcal/mol and RNA-dependent RNA polymerase (RdRp) of SARS-CoV-2 with binding energy equal of −7.1 ± 0.01 kcal/mol (Jamiu et al. 2021; Kar et al. 2021).

Fatoki et al. (2021) used five SARS-CoV proteins and 2 other human proteins in which friedelin showed high binding energy against papain-like protease (PLpro), RNA-dependent RNA polymerase (nsp12), helicase (nsp13), 3-chymotrypsin-like protease (3CLpro), 2'-*O*-ribose methyltransferase (nsp16) of SARS-CoV-2, DNA-PK with CK2 alpha in human. Friedelin also was found to have a promising inhibitory effect against the human IL-6 and IFN-γ with a binding energy score of −10.4 ± 0.02 kcal/mol and −10.1 ± 0.01 kcal/mol respectively (Kar et al. 2022). Friedelin and friedelinol were investigated together with another 19 triterpenoids and one flavonoid glycoside, that were isolated from *Euphorbia neriifolia* L., Euphorbiaceae. Analyzing the anti-human coronavirus (HCoV) activity of the isolated triterpenoids revealed the structure-activity relationship (SAR) of these isolates. The fact that friedelinol showed stronger anti-viral activity than the positive control, actinomycin D, suggests the significance of the friedelane skeleton as a potential scaffold for developing new anti-HCoV-229E medicines (Chang et al. 2012). It was suggested that exposure to friedelin and 3-β-friedelinol enhanced cell viability, causing a greater number of cells to multiply and survive with the inhibited virus; thus, anti-human coronavirus (HCoV-229E) activity of these compounds was compared to actinomycin D at 0.02 g/ml and percentage of cell survival at 5 mg/ml was compared with a non-treated control: friedelin 109%, 3-β-friedelinol 132%, and actinomycin D 69.5% (Chang et al. 2012). Any significant anti-HIV activity, such as inhibition of reverse transcriptase (Huerta-Reyes et al. 2004; Jaipetch et al. 2019) or protease (Magadula 2010), has been described for friedelin and related triterpenes.

Anti-inflammatory, Analgesic, and Antipyretic

The effects of friedelin as an anti-inflammatory, analgesic, and antipyretic have been investigated using a variety of animal models, including those produced by carrageenan, croton oil, acetic acid, cotton pellets, and arthritis (Antonisamy et al. 2011). The analgesic efficacy of friedelin was

assessed using the acetic acid-induced abdominal constriction reaction, the formalin-induced paw-licking response, and the hot-plate test. The antipyretic activity was tested in rats using the yeast-induced hyperthermia test. Antonisamy et al. (2011) found that in carrageenan-induced paw oedema and croton oil-induced ear oedema, friedelin (40 mg/kg) showed maximum inhibition of 52.5 and 68.7% ($p < 0.05$), respectively, in the acute phase of inflammation. Friedelin (40 mg/kg) reduced the development of granuloma tissue triggered by cotton pellets by 36.3% ($p < 0.05$) and by 54.5% of paw thickness in the adjuvant-induced arthritis test. In mice, this triterpene decreased acetic acid-induced vascular permeability. In addition, friedelin demonstrated significant ($p < 0.05$) analgesic efficacy in both the acetic acid-induced abdominal constriction response and the formalin-induced paw-licking reaction. In rats, FRN treatment resulted in a significant dose-dependent improvement in pyrexia.

In a recent study, Ferrini et al. (2022) examined the biological effects of the ethanol extract produced from aeroponically grown roots of *Cannabis sativa* L., Cannabaceae. The anti-inflammatory (LPS-stimulated alterations in the expression of markers in U937 cells as interleukins, and TNF-α) and antioxidant (in either acellular or cellular conditions) effects of the ethanolic extract of the aeroponic roots were investigated together with its isolated compounds (β-sitosterol, friedelin, and friedelinol). The plant extract showed significant activity in both the DPPH free-radical scavenging effect and the Fe^{+2}-chelating capacity at concentrations (10 to 1000 µg/ml). It showed antioxidant activity with EC_{50} 420.1 ± 2.1 and 385.5 ± 3.0 µg/ml for DPPH scavenging activity and chelating activity, respectively. The three tested compounds also revealed dose-related scavenging and chelating actions, yet to a minor extent than the entire extract. Friedelin has DPPH scavenging activity equals to EC_{50} 832.4 ± 1.7 µg/ml and friedelinol equals to 875.1 ± 1.7 µg/ml. Friedelin and friedelinol exhibited chelating activity with EC_{50} values of 883.5 ± 7.2 µg/ml and 547.6 ± 6.3 µg/ml, respectively (Ferrini et al. 2022). The anti-inflammatory was investigated by several markers such as IL-6, IL-8, TNF-α, IkB-α, iNOS, IRAK-1, and miR-146a. Importantly, the pretreatment with aeroponic roots of *C. sativa* ethanolic extract and 3 isolated compounds significantly prevented LPS-induced overexpression of all the selected genes.

Jiang et al. (2022) aimed to investigate the mechanism behind friedelin alleviating tendinopathy. The authors discovered that friedelin enhanced the mechanical strength of the Achilles tendon, decreased inflammatory cell infiltration, restored the orderly arrangement of collagen fibers, and promoted tenogenesis, all of which slowed the progression of tendinopathy. By improving the interaction between p62 and p65 and successfully inhibiting the activation of the NF-κB pathway, friedelin increased the autophagic degradation of p65 and reduced tenocytes inflammatory response. These findings thus reveal a novel pharmacological mechanism behind the anti-inflammatory properties of friedelin and introduce a new possibility for the treatment of tendinopathy. Sarfare et al. (2022) studied the phytochemical characterization of corn silk and among the isolated compounds is friedelin. It was found that in LPS-induced macrophages, friedelin inhibited iNOS activity and decreased nitrite levels by 88.5 ± 0.5 at 50 µM. Friedelin also showed inhibition of NF-κB (51 ± 1.5%). Dutta et al. (2021) studied the *in vitro* anti-inflammatory activity of friedelin and isolated compounds from *Cynanchum acidum* (Roxb.) Oken, Apocynaceae, using protein denaturation/egg albumin test. The percentages of protein denaturation by friedelin at concentrations 100, 200, 300, 400, and 500 µg were 15.6, 27.36, 38.42, 59.64, and 78.94%, respectively. The standard used was diclofenac at 100 µg (90.52%). *Garcinia humilis* (Vahl) C.D.Adams, Clusiaceae, is a plant widely known for its traditional use as an anti-inflammatory medicinal plant. Nunes et al. (2021) studied *G. humilis* methanol extract and some of its isolated compounds on the inflammatory cells in *in vitro* models using LPS-induced RAW 264.7; one of the isolated compounds is friedelin together with canophyllol, amentoflavone, and 3-desmethyl-2-geranyl-4-prenylbellidypholine xanthone (10 µM). The compounds were tested using macrophage nitric oxide (NO) and TNF release. The isolated substances were tested for their ability to generate NO. Following 24-h incubation with LPS, macrophages exhibited increased release of nitrite compared to their baseline levels. The release of NO and TNF was reduced by RAW264.7 by the substances friedelin, amentoflavone, and 3-demethyl-2-geranyl-4-prenylbellidypholine xanthone. At 10 µg/ml and 10 µM, *G. humilis* and all compounds did not produce cell cytotoxicity.

Tian et al. (2021) investigated how friedelin affected LPS-induced pneumonia and how nuclear factor kappa B (NF-κB) contributed. In addition, utilizing human pulmonary alveolar epithelial cells as a model, they examined the effect of LPS on cell apoptosis and its protection by friedelin. The findings demonstrated that friedelin inhibited NF-κB signaling, which in turn reduced LPS-induced acute pneumonia in neonatal rats and resulted in cellular apoptosis. In conclusion, this research demonstrated that friedelin has a significant protective impact on lung tissues that have been exposed to LPS.

Interesting research used pharmacology bioinformatics, molecular docking, and experimental validation using ulcerative colitis (UC) model mice, which aims to elucidate the therapeutic effect of the bioactive chemical friedelin against UC. Through target searching, PPI network building, and enrichment analysis, friedelin's targets and possible mechanisms on UC were hypothesized. Shi et al. (2021) examined the effects of friedelin on dextran sulfate sodium

(DSS)-induced colitis. Body weight, disease activity index (DAI), and colon length were used to determine the severity of UC. By measuring both proinflammatory and anti-inflammatory cytokines, it was possible to assess the degree of inflammation. Autophagy inhibition was used to count the number of autophagosomes around epithelial cells using a transmission electron microscope. By using immunofluorescence staining, the expressions of the AMPK-mTOR signaling pathway and the ATG5 protein, which is associated with autophagy, were identified. In this research, 1111 UC-related targets and 17 putative friedelin targets were found. From overlapping targets for UC and friedelin, 10 therapeutic targets for friedelin against UC were discovered. Fourteen essential targets were removed from the PPI network during creation using target amplification and confidence-boosting. The outcomes of molecular docking demonstrated that the top 5 active targets had docking scores that exceeded threshold values. Friedelin reduces UC through anti-inflammatory pathways and the molecular function of autophagy, according to gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis. Following that, animal studies demonstrated that intraperitoneal injection of friedelin alleviated DSS-induced body weight loss, DAI reduction, colon length shortening, and colonic pathological damage with reduced myeloperoxidase and proinflammatory cytokines (IL-1β and IL-6) and increased IL-10 levels, as well as more autophagosomes in transmission electron microscopy data. According to the KEGG pathway results and experiment verification, the AMPK-mTOR signaling pathway was found crucial to the action of friedelin on autophagy. Additionally, the 3 mechanisms of action confirmed the function of autophagy as an enhancement of the pharmacologic action of friedelin in UC model mice. In summary, friedelin was found to reduce the severity of DSS-induced colitis in mice via controlling autophagy and suppressing inflammation.

As Toukam and co-authors (Toukam et al. 2018) investigated the stem bark of *Pterocarpus erinaceus* Poir, Fabaceae, they isolated friedelin with other novel and known compounds. The anti-inflammatory and free radical scavenging activities of the compounds were assessed. The anti-denaturation of serum bovine albumin was used to measure the *in vitro* anti-inflammatory potential. Friedelin was the most active against the denaturation of the protein (IC_{50} 14.87 ± 1.51 µg/ml). Sodium diclofenac was used as reference drug (IC_{50} 7.20 ± 0.97 µg/ml).

Kleinia odora DC., Asteraceae, is a wild plant found in Saudi Arabia that is ingested by both animals and humans. The plant contains triterpenes, which have anti-inflammatory properties. In their study of the plant, Shehata et al. (2018) isolated friedelin together with lupeol acetate, lupenone, lupeol, epilupeol, and oleanolic acid. They investigated their anti-inflammatory activity as a free radical scavenger using DPPH assay. Friedelin gave the result of DPPH SCA % equals to 31.01 ± 0.24, 36.01 ± 0.98, and 54.51 ± 0.29 at concentrations 1, 10, and 100 µM respectively. Although friedelin had a moderate level of activity, lupeol acetate and lupenone showed the highest activity. Triterpene treatment of cells (human PBMCs) caused considerable reductions in NF-κB p65 nuclear levels in a concentration-dependent manner, with lupeol acetate and lupenone compounds resolving the highest activity. According to the measured concentration, levels of TNF-α, IL-1β, and IL-6 were also noticeably higher in supernatants. Likewise, the most active compounds were lupeol acetate and lupenone (Shehata et al. 2018).

Ouédraogo et al. (2017) investigated the isolated compounds and extracts of *Pterocarpus erinaceus*, which is known in Burkina Faso's folk medicine as an anti-inflammatory medicine, for their anti-inflammatory and antioxidant activities. Friedelin, 3α-hydroxyfriedelan-2-one, α-sophoradiol, and stigmasterol were isolated from dichloromethane extract and maltol-6-*O*-apiofuranoside-glucopyranoside isolated from methanol. Croton oil-induced edema of mouse ear protocol is used to investigate the local anti-inflammatory properties of samples. Dichloromethane extract, friedelin, 3α-hydroxyfriedelan-2-one, and α-sophoradiol had a substantial anti-inflammatory impact on ear edema. However, the effect of 3-hydroxyfriedelan-2-one was greater than that of the other substances.

The anti-neuroinflammatory of phytoconstituents from leaves of *Hydrangea viburnoides* (Hook.f. & Thomson) Y.De Smet & C.Granados, Hydrangeaceae (friedelin, 3β-friedelinol, and 4-epifriedelin) was evaluated using LPS-stimulated BV2 microglias. Among tested compounds, friedelin and 3β-friedelinol showed that the production of NO was downregulated moderately when the concentration was 80 µM with inhibition 46.6 and 45.4%, respectively, although there was significant effect on cell viability (Li et al. 2016). Cyclooxgenase (COX-1) inhibitory activities of friedelin and 3β-friedelinol were studied by Kim et al. (2012) while investigating the plant *Portulaca oleracea* L., Portulacaceae, and its isolated compounds. COX-1 inhibition (%) at the concentration of 250 µg/ml of 3β-friedelinol was 43.1% while friedelin had no inhibition against COX-1.

The stem bark of *P. erinaceus* friedelin and other isolated constituents were examined for anti-inflammatory activities by using carrageenan-induced edema of mouse paw and croton oil-induced edema of mouse ear. Mast cell activation and the release of chemicals in response to carrageenan injection and croton oil treatment were inhibited by the MeOH and DCM extracts, friedelin, lupeol, and epicatechin (Noufou et al. 2012).

In a study examining *Commiphora berryi* Engl., Burseraceae, stem bark extract, and its isolated substances, Kumari et al. (2011) used *in vitro* evaluation of soybean lipoxygenase (SBL) inhibitory activity of the compounds and extracts to test their anti-inflammatory potential. Friedelin

demonstrated a promising SBL enzyme inhibition with an IC_{50} of 35.8 µM even though friedelin was previously found to be ineffective against 5-LOX dependent LTC4 production in bone marrow-derived mast cells (Zhang et al. 2010). The fact that pentacyclic triterpenes with a keto group were essential for their inhibition of 5-LOX provided Chaudhary et al. (2011) support for their finding. Relating to friedelin, the strong SBL inhibitory activity of this compound according to Chaudhary et al. (2011) can be attributed to its pentacyclic triterpene ring structure, which is helped by specified functional groups, such as the 3-keto at ring A, which facilitates better binding to the SBL effector site.

Friedelin isolated from *Acer mandshuricum* Maxim., Sapindaceae, showed anti-inflammatory effects when tested on TNF-α release in the LPS-stimulated murine RAW264.7 macrophage cell line. Friedelin has inhibition to 23.5% at concentrations of 100 µM (Ding et al. 2010).

Human leukocyte elastase (HLE) inhibitory activity of friedelin and two hydroxylated derivatives of friedelin (canophyllol and 29-hydroxy-friedelan-3-one) were investigated to assess their anti-inflammatory activity and whether it is related to their elastase inhibitory activity. HLE activity (% control) is 68, 3, and 37% for friedelin, canophyllol, and 29-hydroxy-friedelan-3-one, respectively (Mitaine-Offer et al. 2002 a).

Vasodilator Activity

Friedelin, the major compound present in bark of bamboo *Bambusa tuldoides* Munro, Poaceae, showed a potential vasodilation response on the phenylephrine-induced vasoconstriction on rats' thoracic aortas in a dose-dependent manner. The thoracic aortas of rats were removed from their thoraxes 6 h after friedelin injection, and the vascular responses to phenylephrine were studied to assess vascular responsiveness ex vivo. In the three test groups, the vasodilation rates were roughly 6, 16, and 36%, respectively. Friedelin, at doses of 10, 30, and 100 µmol/l, displayed significant vasodilator effects on phenylephrine-induced vasoconstriction in the rat thoracic aortas ($p < 0.05$, $p < 0.01$). The maximum vasoconstrictor force to phenylephrine (1 µM) in SD rats was observed with the higher dose of friedelin (100 µmol/l) and was 0.66 ± 0.28 mN/mg wet tissue, which was significantly lower than 1.02 ± 0.23 mN/mg wet tissue in the control group ($p < 0$) (Jiao et al. 2007).

Hypolipidemic Activity

The assessment of hypolipidemic effect of friedelin from *A. tetracantha* was reported by Duraipandiyan et al. (2016) in two models. In the first one, hyperlipidemia in rats was included using Triton WR-1339 and the second model was achieved by feeding the rats a high-fat diet. Friedelin at 50 and 70 mg/kg had a substantial lipid-lowering effect ($p < 0.01$) demonstrated by reversal of plasma levels of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triacylglycerides (TG). After 15 days, the rats on a high-fat diet showed a significant increase ($p < 0.01$) in liver TC and TG levels. The friedelin-treated groups revealed a baseline level of the liver's TC and TG levels. In all models, the hypolipidemic activity of friedelin was compared to that of the lipid-lowering medication fenofibrate.

Hepatoprotective and Antioxidant Activities

Sunil et al. (2013) evaluated the potentiality of friedelin for its *in vitro* free radical scavenging effect using DPPH, hydroxyl, nitric oxide (NO), and superoxide radical assays. Friedelin had an excellent scavenging action with IC_{50} of 21.1 mM (DPPH), 19.8 mM (hydroxyl), 22.1 mM (NO), and 21.9 mM (superoxide). Furthermore, lipid peroxidation was strongly suppressed by friedelin. In an *in vivo* antioxidant study, CCl_4-induced oxidative stress in rats resulted in a significant increase in the levels of the enzymes glutamate oxaloacetate transaminase (SGOT), glutamate pyruvate transaminase (SGPT), and lactate dehydrogenase (LDH), as well as a decrease in the levels of the liver enzymes superoxide dismutase (SOD). Friedelin pre-treatment of rats at 40 mg/kg for 7 days returned these levels to normal and demonstrated liver protection comparable to silymarin (25 mg/kg) as standard. These findings conclusively proved that friedelin had notable antioxidant and liver-protective properties.

A recent study by Sanduh et al. (2022) tested friedelin as a candidate for inhibition of the activated JNK/NF-κB (c-Jun *N*-terminal kinase) signaling pathway in scopolamine (SPN)-induced mouse model of neurodegeneration or oxidative stress. Behavioral tests, such as the Morris water maze (MWM) and the Y-maze, were performed on the treated animals to determine whether they had memory problems. Using a lipid profile, antioxidant enzyme, and western blotting investigations, the underlying mechanism was discovered. To forecast how friedelin will attach to the p-JNK protein's binding pocket, molecular docking studies were conducted. According to the results, scopolamine increased levels of thiobarbituric acid reactive substances (TBARS) in mouse brain, inhibited catalase (CAT), peroxidase (POD), superoxide dismutase (SOD), and reduced glutathione (GSH), and affected the neuronal synapse (both pre- and post-synapse), resulting in associated memory dysfunction. Contrarily, the administration of friedelin prevented oxidative stress, glial cell activation, and neuro-inflammation caused by scopolamine while also inhibiting p-JNK, NF-β, and their downstream signaling components. Additionally, the administration of friedelin enhanced neuronal synapses

and restored scopolamine-induced memory impairment along with the suppression of β-secretase enzyme (BACE-1) to stop amyloidogenic pathways of amyloid production. Overall, the findings demonstrate that friedelin is considered an effective natural neuro-therapeutic drug that can reverse SPN-induced neuropathology, a hallmark of Alzheimer's disease. On the other hand, Toukam et al. (2018) tested friedelin with the other isolated compounds from the stem bark of *P. erinaceus* for their antioxidant activity using the DPPH scavenging test using L-ascorbic acid as a reference. After 30 min of storage in the dark and vigorous shaking, the reaction was carried out in duplicate, and a UV-vis spectrophotometer was used to quantify the decrease in absorbance at 517 nm. Friedelin was found to be inactive.

Ouédraogo et al. (2017) investigated the phytochemical characteristics of *P. erinaceus*. Friedelin, 3α-hydroxyfriedelan-2-one, α-sophoradiol, and stigmasterol were isolated from DCM extract and maltol-6-*O*-apiofuranoside-glucopyranoside isolated from MeOH were examined for their antioxidant activities by lipoxygenase (LOX) inhibition assay and lipid peroxidation (LPO) inhibition assay. Friedelin, α-sophoradiol, and maltol-6-*O*-apiofuranoside-glucopyranoside inhibited LOX substantially, but their inhibitory effects were weaker than zileuton, the positive control.

Antihyperglycemic Activity

The traditional use of *A. tetracantha* as an antihyperglycemic inspired Sunil et al. (2021) to investigate the major compound friedelin as an antihyperglycemic agent. STZ (streptozotocin)-treated rats (induced diabetes) had changes in bodyweight, blood glucose, insulin, SGOT, SGPT, SALP, liver glycogen, and total protein levels. The rats were treated for 28 days with friedelin, at dosages of 20 and 40 mg/kg which dramatically restored later abnormal markers to near-normal values. In the skeletal muscles and liver of diabetic rats, friedelin improved the translocation as well as activation of GLUT2 and GLUT4 through PI3K/p-Akt signaling cascade. This result demonstrated the antihyperglycemic effects of friedelin via an insulin-dependent signaling cascade mechanism, which may pave the way for the development of a drug to treat type 2 diabetes mellitus (Sunil et al. 2021). In a study, the pharmacokinetics and toxicity profile of *Myrianthus libericus*'s bioactive metabolite, friedelin was investigated as well as the plant's potential mechanisms of hypoglycemic activity. The extract and friedelin were tested for *in vitro* hypoglycemic effects using glucose uptake assays in C_2C1_2 myotubes. The compound's pharmacokinetic and toxicological features were also examined *in silico*. The extract significantly reduced the activity of α-amylase and encouraged glucose absorption in C_2C1_2 cells when combined with friedelin. While friedelan-3-one only upregulated PI3K and GLUT-4 transcripts to support glucose transport, the extract dramatically ($p < 0.001$) upregulated PI3K and PPARγ transcripts with a matching increase in GLUT-4 transcripts within the muscle cells. Friedelin has been proven to be non-carcinogenic and non-hepatotoxic, and with good oral bioavailability and potential as a therapeutic candidate (Harley et al. 2021).

In another research, α-glucosidase inhibitory activity for all the fractions of *Antidesma bunius* (L.) Spreng., Phyllanthaceae, was performed; in a bioguided isolation approach, the ethylacetate (EtOAc) fraction was the most active with IC_{50} of 19.33 µg/ml, while acarbose and miglitol as standards have IC_{50} values of 5.75 and 59.76 µg/ml, respectively. Mauldina et al. (2017) isolated 3 triterpenes from the active fractions: friedelin, β-sitosterol, and betulinic acid. They investigated α-glucosidase inhibition of the isolated compounds as compared to reference drugs. The results showed that the IC_{50} values of friedelin, β-sitosterol, and betulinic acid were 19.51, 49.85, and 18.49 µg/ml, respectively. An interesting docking study on the phytochemical constituents of *Syzygium cumini* (L.) Skeels, Myrtaceae, which is used in folklore Indian medicine to treat diabetic patients, was carried out. This study has a computational approach to investigate molecular targets of 22 compounds isolated from the plant including friedelin and 3β-friedelinol to the enzyme *α*-amylase using Lamarckian genetic algorithm methodology and Autodock software. The results show that analysis of binding energy of ligands with target receptors was remarkably lower, especially for friedelin (− 9.54 kcal/mol) and 3β-friedelinol (− 8.98 kcal/mol). This indicates that they can suppress the action of the α-amylase enzyme more potently than the synthetic medication acarbose (Smruthi et al. 2016). In another docking study, friedelin and 3β-friedelinol together with other 13 compounds were investigated as protein tyrosine phosphatase 1B (PTP1B) inhibitors from *Anoectochilus brevilabris* Lindl., Orchidaceae, aimed to treat diabetes. The compounds were initially investigated *in vitro* for their inhibitory efficacy against PTP1B, followed by molecular docking simulation in PTP1B inhibition using Autodock VINA. Friedelin had IC_{50} (µM) of 6.21 ± 0.02 and a binding energy of –8.1 kcal/mol. While 3β-friedelinol showed IC_{50} of 3.75 ± 0.14 µM and binding energy of –8.3 kcal/mol (Cai et al. 2015). Sharma et al. (2015) isolated friedelin with other compounds and examined them for their insulin secretory activity on isolated mouse islets and MIN-6 pancreatic β-cell line. At 200 µM, friedelin showed moderate activity in comparison to coixol which was more potent than the control drug tolbutamide.

Gastroprotective Activity

Antonisamy et al. (2015) investigated the gastroprotective activity of friedelin isolated from the hexane extract of leaves of *A. tetracantha* in an ethanol-induced gastric model.

Apoptosis level, pro- and anti-inflammatory cytokines, lipid peroxidation, nitric oxide, stomach vascular permeability, and antioxidant enzymes have all been studied. The stomach damage generated by ethanol was prevented by pretreatment with friedelin. Prostaglandin E2, constitutive nitric oxide synthase (cNOS), anti-inflammatory cytokines, antioxidant enzyme activity, and mucus weight have all been dramatically enhanced. However, following the consumption of friedelin, there has been a considerable reduction in vascular permeability, pro-inflammatory cytokines, inducible nitric oxide synthase (iNOS), caspase 3, and apoptosis levels. The results of this investigation strongly supported the potentiality of friedelin to be an antiulcer drug after further studies (Antonisamy et al. 2015). On the other hand, a related study carried out by Navarrete et al. investigated the gastroprotective activity of root bark of *Semialarium mexicanum* (Miers) Mennega, Celastraceae, aqueous, ethanolic extracts, and isolated constituents including friedelin. The gastroprotective assay was carried out *in vivo* by absolute ethanol-induced gastritis to rats and acidified acetylsalicylic acid-induced ulcers, using bismuth subsalicylate as a positive control. In this study, friedelin isolated from the active fraction showed weak gastroprotective activity with 21.9 ± 12% protection (dose: 100 mg/kg) compared with 46.2 ± 5.6% protection of the positive control (100 mg/kg) (Navarrete et al. 2002).

Antibacterial Activity

In a recent study, Kamdem et al. (2022) investigated friedelin as one of the eight isolated compounds of DCM:MeOH (1:1) stem-bark extract of *Cola lateritia* K.Schum., Malvaceae. The isolated compounds were investigated for *in vitro* antibacterial activity against 12 species of Gram-positive and Gram-negative bacteria. The standard control drugs are ampicillin, streptomycin, and nalidixic acid. All tested substances displayed a wide range of antibacterial activity, and their efficacy varied depending on concentration. Friedelin was the least active of all the identified compounds, with MIC values ranging from 18.5 to 588 µg/ml for the various bacterial strains when compared to the other compounds and standard antibiotics. Given that friedelin is the least polar of all the isolated compounds, its poor activity can be explained by its structure and polarity. The polarity of the molecules is a crucial element that regulates how the cell membrane interacts with various molecules. Polar substituents or polar compounds have higher activity than nonpolar substituents or compounds, according to the structure-activity relationship (SAR) (Kamdem et al. 2022). However, Kuete et al. (2007) had different results when investigating friedelin and eight compounds isolated from *Psorospermum laurentii* (De Wild.) Byng & Christenh., Hypericaceae, leaves, twigs, and roots, for their antimicrobial activity. Using disc diffusion and well micro-dilution techniques, Gram-positive bacteria (six species), Gram-negative bacteria (12 species), and two *Candida* species were selected to carry out the screening. The test organisms' degree of sensitivity to isolated chemicals ranged from 25 to 90%. Friedelin was discovered to be the most active compound with MIC values ranging from 2.44 to 78.12 µg/ml (Kuete et al. 2007; Salih et al. 2018). In their study on *Atalantia retusa* Merr., Rutaceae, Ragasa et al. (2012) tested friedelin among other isolated compounds for their antimicrobial activities against seven microorganisms (*Pseudomonas aeruginos*a, *Staphylococcus aureus*, *Escherichia coli*, *Bacillus subtilis*, *Candida albicans*, *Trichophyton mentagrophytes*, and *Aspergillus niger*); friedelin gave clearing zone in (mm) and Activity Index (AI) equals to (16 mm, AI = 0.6), (15 mm, AI = 0.5), (11 mm, AI = 0.1), (AI > 55 mm, AI > 4.5), (13 mm, AI = 0.3), (15 mm, AI = 0.5), and (no inhibition growth in a test organism, AI = 0), respectively. Friedelin exhibited the highest activity against *B. subtilis*, even surpassing the activity of the standard antibiotic chloramphenicol (Ragasa et al. 2012). Based on another study, friedelin had a mild antifungal effect on *T. mentagro phytes*, *Scopulariopsis* sp., *T. rubrum* 57/01, and *C. albicans* with a MIC value of > 250 µg/ml, and *T. sinii*, *E. floccosum*, *A. niger,* and *Magnethophora* sp. with a MIC value of 125 µg/ml, and good activity with a MIC value of 62.5 µg/ml against *T. rubrum* 296 and *C. lunata* (Duraipandiyan et al. 2010). On the other hand, in another research with a MIC value of > 1000 µg/ml; friedelin had no activity on Gram-negative bacteria: *E. cloacae*, *E. coli*, *P. aeruginosa*, *S. mirabilis*; Gram-positive bacteria: *B. cereus*, *S. aureus*, *S. saprophytes*, *S. agalactinae*, and *S. typhimurium* as well as the yeasts *C. albicans* and *C. tropicalis* (Pretto et al. 2004). According to a previous study, friedelin was effective against the following bacteria, with zones of inhibition shown in parentheses: *S. aureus* (15.50 mm), *S. typhi* (13.00 mm), and *P. aeruginosa* (15.00 mm) (Ogunnusi et al. 2010).

Anti-mycobacterium

Salih et al. (2018) tested the anti-mycobacterium activity of *Terminalia laxiflora* Engl. and *T. brownii* Fresen., Combretaceae, based on their use in traditional medicine to alleviate TB symptoms and infectious diseases. Fractions and nine isolated compounds were examined using the agar diffusion and microplate dilution procedures against *Mycobacterium smegmatis* ATCC 14468. The inhibition zones and MIC values were determined and compared to those of rifampicin. In this screening, friedelin showed poor inhibition of the growth of *M. smegmatis* with a MIC of 250 µg/ml (Salih et al. 2018). However, in another study, friedelin isolated from *T. avicennioides* Guiil. & Perr. root bark showed MIC of 4.9 µg/ml against the attenuated *Mycobacterium bovis* used in the Bacillus Calmette-Guerin tuberculosis vaccine

(Mann et al. 2008, 2011; Salih et al. 2018). Another study has reported that friedelin exhibited a minimum inhibitory concentration of 128 µg/ml against mycobacterium TB (Higuchi et al. 2011; Salih et al. 2018).

Antimalarial Activity

Azebaze et al. (2007) screened the antimalarial and vasorelaxant activities of friedelin isolated from the leaves of *Allanblackia gabonensis* (Pellegr.) Bamps, Clusiaceae, using a radioactive micro-method. The extract and the isolated compounds were tested against two strains of *Plasmodium falciparum* (CQ-sensitive F32 and CQ-resistant FcM29). The IC_{50} (µM) values for friedelin against the two species of *P. falciparum* FcM29 were > 200 and 145.8 after 24 and 72 h, respectively. While its activity against *P. falciparum* F32 was > 200 after both 24 and 72 h, respectively. In addition, the authors determined cytotoxicity using human melanoma cells of the A375 line, which were cultured under the same conditions as *P. falciparum*. IC_{50} (µM) value of friedelin was > 200 after 24 h; it had high cytotoxicity, giving cytotoxicity/antimalarial IC_{50} ratios of < 1, unlike other tested compounds. In addition, the authors determined the cytotoxicity using human melanoma cells of the A375 line, which were cultured under the same conditions as the *P. falciparum*. Friedelin IC_{50} (µM) value was > 200 after 24 h. It had high cytotoxicity, giving cytotoxicity/antimalarial IC_{50} ratios of < 1, unlike the other tested compounds (Azebaze et al. 2007). All results were compared to chloroquine with IC_{50} 0.036, 0.036, 0.57, and 0.57 against F32/24 h, F32/72 h, FcM29/24 h, and FcM29/72 h, respectively.

Anti-osteoclastogenic Activity

The MeOH extract of the aerial portions of *Dendropanax trifidus* (Thunb.) Makino ex Hara, Araliaceae caused a significant dose-dependent inhibition of receptor activator of NF-$_K$B ligand (RANKL)-induced differentiation of bone marrow-derived macrophages to osteoclasts. In a bioguided manner, Kim et al. (2018) isolated friedelin and tested it for anti-osteoclastogenic activities among other compounds from the active fraction. The effects of all isolated components on the RANKL-induced production of $TRAP^+$–MNCs were assessed at 30 µM compared to vitamin D3 and ibandronate sodium. Friedelin significantly inhibited TRAP activity at 30 µM.

Eastern Nigeria mistletoe and *Loranthus micranthus* Hook.f., Loranthaceae extracts with isolated compounds including friedelin were investigated for their osteogenic activities. ALP assay, mineralization assay, and expression of the osteogenic genes bone morphogenetic protein-2 (BMP2) and osteoblast transcription factor (RUNX2) in primary calvarial cells taken from newborn rats were used to investigate the osteogenic potentiality. Friedelin showed significant loss of osteoblast viability; and therefore, it was not considered further (Omeje et al. 2014).

Diuretic Activity

In an early study, while investigating *Antidesma montanum* var. *wallichii* (Tul.) Petra Hoffm., Phyllanthaceae, friedelin was isolated among other triterpenoids. *In vivo* assay on rats was used to assess the diuretic efficacy, and only friedelin, at 64 mg/kg (*p.o.*), showed 99% activity when compared to chlorothiazide (125 mg/kg) (Rizvi et al. 1980).

Cholinesterase Inhibitory Activity

Friedelin and other compounds isolated from *Garcinia celebica* L., Clusiaceae were investigated for their cholinesterase enzyme inhibitory activities by an *in vitro* experiment. Acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) enzymes were used to assess the cholinesterase inhibitory activities. The % inhibition at 50 µg/ml for friedelin is 34.3 and 55.9 for AChE and BChE, respectively. AChE inhibition IC_{50} was not determined for friedelin and the BChE inhibition IC_{50} was 66.2 µg/ml compared to galanthamine with IC_{50} of 0.6 µg/ml (2.09 mM) against AChE and 5.55 µg/ml (19.3 mM) against BChE. Friedelin is considered inactive as it showed inhibition of less than 50% (Jamila et al. 2015).

Cytotoxic Activity

Friedelin and 3β-friedelinol were screened together with other isolated compounds from *Irvingia malayana* Oliv. ex A.W.Benn., Irvingiaceae, in cytotoxicity and the syncytium forming microassay by Jaipetch et al. (2019). In 96-well microtiter plates, *in vitro* sulforhodamine B assay was used to determine the cytotoxic activity of the isolated compounds. Ellipticine was employed as a positive control with (ED_{50}, µM) 1.90, 2.15, 2.36, 2.15, 1.91, 2.07, and 1.99 against P-388, KB, HT-29, MCF-7, A-549, ASK, and CL, respectively. Seven cell lines were used: human oral nasopharyngeal carcinoma; HT-29, P-388, murine lymphocytic leukemia; KB, human breast carcinoma; A-549, human lung carcinoma; ASK, human colorectal adenocarcinoma; MCF-7, rat glioma cell, and CL; Chang liver normal cell. The cytotoxic activity potency was represented as 50% effective dose (ED_{50}). ED_{50} values of friedelin and 3β-friedelinol were 50 µM, and therefore inactive (Jaipetch et al. 2019). The $^{\Delta Tat/Rev}$MC99 virus and 1A2 cell line system were utilized in the syncytium assay, a cell-based assay. Starting with the compound's final concentration of 3.9 to 125 µg/ml, azidothymidine was used as positive control ($IC_{50} > 10^{-2}$ µM). The outcome was given as 50% effective concentration (EC_{50}).

In addition, a colorimetric cytotoxicity experiment utilizing phenazine methosulfate and XTT tetrazolium salt was prepared and was carried out concurrently. The process was the same as the syncytium assay, but the medium was used in place of the virus, and it was examined twice. The optical density at A450 was measured with a reference at A650 after the soluble formazan had developed. It was calculated as a 50% inhibitory concentration (IC_{50}). The IC_{50} and EC_{50} of friedelin and 3β-friedelinol were more than 250 µM and their selectivity index: IC_{50}/EC_{50} is less than 1, and therefore identified as inactive compounds (Jaipetch et al. 2019).

In another study, four terpenes were isolated namely friedelin, arborinol, isoarborinol, and spathulenol, as well as the glycoside vitexin, from *Glycosmis parviflora* (Sims) Little, Rutaceae, to study their cytotoxic activity *in vitro*. Using the sulforhodamine B assay, the cytotoxicity of each isolated compound was assessed against several cell lines. Friedelin had no cytotoxic effects on any of the cell lines tested ($IC_{50} > 100$ µg/ml) (Nguyen et al. 2020). Also, while investigating the plant *Luehea ochrophylla* Mart., Malvaceae, extract, fractions, and chemical constituents including friedelin were assessed for their cytotoxic activity against the MDA-MB-231, MCF-7, HCT-116, and Vero cells by 3-(dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) colorimetric method. Friedelin was discovered to be inactive, with only lupeol and β-sitosterol-3-*O*-D-glucopyranoside inhibiting more than 50% of the cancer cell lines tested (Araújo et al. 2019). A rare endemic plant from the Philippines known as *Atalantia retusa* Merr., Rutaceae, has been found to possess strong antinociceptive and anti-inflammatory properties. Ragasa et al. (2012) tested the isolated compounds including friedelin for their cytotoxic activities and antimicrobial activities. Cytotoxicity assay carried out was against the human cancer lung adenocarcinoma A549, colon carcinoma HCT116, and the non-cancer Chinese hamster ovary AA8 using the MTT assay. Friedelin and two other compounds (retusenol and dischidiol) with HCT 116 and A548 had no linear interpolation, making it impossible to calculate the IC_{50} value. This suggested that these substances had no cytotoxic effect on these cell lines (Ragasa et al. 2012). Friedelin and the isolated compounds from *A. mandshuricum* were examined for their cytotoxic activities using MTT assay; they were assessed against human acute promyeloid leukaemia (HL-60), human ovarian cancer (SK-OV-3), human lung adenocarcinoma epithelial (A549), and human colon cancer (HT-29) cell lines. Gi_{50} (µM) values of friedelin were 12.2 ± 1.1, 12.7 ± 1.0, 11.1 ± 0.9, and 13.5 ± 1.1 for HL-60 (leukemia), SK-OV-3 (ovary), A549 (lung), and HT-29 (colon), respectively (Ding et al. 2010). Mitoxantrone was used as positive control with Gi_{50} (µM) of 7.8 ± 0.8, 11.0 ± 1.0, 8.3 ± 0.8, and 8.9 ± 0.8 against HL-60, SK-OV-3, A549, and HT-29 cell lines. In an early study, the authors carried out a cytotoxicity assay using human melanoma cells of the A375 line; 96-well plates were filled with a suspension of melanoma cells in culture media that contained 2×10^5 cells/ml, and 100 ml of pure culture medium (as a control), and 3*H*-hypoxanthine incorporation was used to determine cell growth and the IC_{50} values. It was found that friedelin had IC_{50} (µM) value > 200 after 24 h (Azebaze et al. 2007).

Three triterpenoids were isolated with friedelin skeletons from *Polygonum pubescens* Blume, Polygonaceae: 19α-hydroxyfriedelin, 16α-hydroxyfriedelin, and 3β-friedelinol. The crude methanolic extract and its major secondary metabolites were assessed for their cytotoxic activity on the Vero cell line. 3β-Friedelinol IC_{50} value was discovered to be less than the recommended value (4 µg/ml), indicating that it is a potentially potent cytotoxic agent in compared to vincristine sulfate/positive standard with an IC_{50} of 7.64 µM/ml (Dash et al. 2021).

Perspective on Future Directions

The use of friedelin (**1**) and 3β-friedelinol (**2**) as nutraceutical and cosmeceutical agents as well as the industrial applications became a new trend. Since they have broad biological activities, for example, their potential cytotoxic activity indicates they have a promising future in the control and treatment of cancer disease. Their promising activity against COVID-19 must be considered in future research. The increasing prevalence of severe bacterial and viral infections, coupled with their ability to develop resistance towards existing treatment methods, highlights the urgent necessity to discover and create novel compounds to fight against them. Friedelin must be one of them due to its low toxicity and promising activity. Additionally, friedelane triterpenes should be incorporated into future therapies due to their hepatoprotective and gastroprotective potential. Upcoming research needs to be concentrated on improving the efficiency of terpenes, while maintaining their bioactivity and bioavailability besides stability through storage, preparation, and consummation. It is important to explore new drug delivery methods utilizing nanoformulations or encapsulation to enhance both the stability and biological effectiveness.

Conclusions

Friedelin and its derivative 3β-friedelinol are regarded as intriguing molecules due to their natural origin and promising therapeutic potential, as demonstrated by various studies conducted *in silico*, *in vitro*, and *in vivo*. Drug discovery through natural sources is a laborious and challenging process. However, it is regarded as one of the most fruitful

approaches by leveraging ethnopharmacological knowledge of plants through evidence-based research and analysis. Researchers can attribute the pharmacological use of the plants to active fractions or active compounds. Therefore, the abundance of friedelin in plants allowed it to be considered in a lot of research papers. Friedelin had significant *in vivo* anti-inflammatory, analgesic, antipyretic, antimicrobial, antiviral, hypolipidemic, gastroprotective, antioxidant, and antihyperglycemic activities. The diverse activities of friedelin make it one of the compounds that requires further research for promising drug development. Most of the findings regarding the cytotoxicity of friedelin indicate its inactivity. This underscores the importance of establishing a structure-activity relationship (SAR) to comprehend the effective interaction of the molecule with certain targets and its inability to interact with others.

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Declarations

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