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Review Article

Sources, Structure, Synthesis and Biological Activities of Jatrophone: A Macrocyclic Diterpene

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ABSTRACT

Jatrophone (JAT) is a macrocyclic diterpene isolated from several *Jatropha* and *Euphorbia* species. Jatrophone and jatrophane derivatives are of wide interest because of their diverse biological and pharmacological activities. The goal of this article is to summarize the natural sources, synthesis, and biological activities of JAT. This review was performed through a systematic search in electronic databases, for example, Egyptian Knowledge Bank databases (Web of Science, Scopus, and PubMed), and Google Scholar, covering the period from 1970 to February 2022. A total of 788 articles were identified through Google Scholar, 92 in Scopus and 75 in Web of Science, and 32 in PubMed databases and after subsequent removal of duplication and irrelevant articles, resulted in 60 articles. The results revealed diverse biological activities for jatrophone such as inhibitory effects on insulin release, lymphocyte activation, and tumour cell proliferation. In addition, it showed relaxation of muscle contraction and rat portal vein, also, anti-protozoal, molluscicidal activities and gastroprotective effects. In conclusion, this review reported natural sources of JAT and explicated its wide biological activities thus suggesting that JAT is a potentially promising pharmacological candidate. However, more detailed safety and pharmacokinetic investigations are required.

***Keywords*:** Euphorbiaceae, Jatrophone, Jatrophane Diterepene, Macrocyclic Diterpene, Biological Activities.

Introduction

For the past 60 years, naturally produced compounds were discovered to be a direct source of medicinal ingredients and the origins of pharmaceutical development.[1] Plants produce compounds with low and high molecular weights, which are categorized as natural compounds or primary and secondary metabolites. Secondary metabolites in plants are classified into three types: 1- terpenes or terpenoids, 2- phenolic compounds, and 3- alkaloids. Terpenes are the natural compounds that make up questionably the most diverse and large numbered group of natural products.[2] Only a few of the 25,000 terpene structures described were studied from a practical standpoint. They are essential for the survival of extreme species, as they regulate metabolism and mediate interactions between and within species, such as defence and pollination in plants. Apart from the fact that plants produce terpene compounds in reaction to herbivory or stress, flowers have been proven to produce terpenoids to attract pollinators and even helpful mites that eat herbivorous insects. [3, 4] Diterpene compounds comprise a large class of natural compounds isolated from the family Euphorbiaceae and many other families. Macrocyclic diterpenes of jatrophane, lathyrane, terracinolide, ingenane, pepluane, paraliane, and segetane skeletons are the major ones of considerable biological potential. They have a diverse set of biological and therapeutical characteristics, such as anti-inflammatory, anti-viral, anti-cancer, and multidrug resistance-reversing effects. [5] Among macrocyclic diterpenes, JAT and JAT derivatives showed great interest from several authors and were subjected to huge numbers of investigations.

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This review summarizes the most recent research on JAT (**1**), a major macrocyclic diterpene isolated from several *Jatropha* and *Euphorbia* species with emphasis on the natural source, isolation methods, biological and pharmacological activities, and structure-activity relationship.

Methods

Search Strategy

A systematic search in the literature was performed from online databases including the Egyptian Knowledge Bank database, Google Scholar, Scopus, PubMed, Web of Science, and Elsevier databases, up to February 2022. The search was performed using all available terms for jatrophone, isolation, structure, solubility, synthesis, bioavailability, uses, biological activity, mechanism, toxicity, pharmacokinetics, and clinical investigations.

Results and Discussion

Chemical classes of diterpenes

Diterpenes are organic compounds that are made up of two isoprene units. Animals, plants, fungi, algae, coral, and other organisms contain these compounds. Daphnane, kaurene, tiglilane, abietane, dolabellane, pimarane, dolastane, labdane, jatrophane, prenylated guaiane diterpene, tonantzitlolone, casbane, and miscellaneous are the different types of diterpene compounds (Figure 1).

Daphnane diterpene is a type of diterpene that has a 5/7/6-tricyclic ring attached to it, and a polyhydroxy group at positions C-3, C-4, C-5, C-9, C-13, C-14, or C-20. In addition, several daphnane-type diterpenes have ortho ester groups that bind to C-9, C-13, and C-14.[6]

Tiglilane is a macrocyclic diterpene with a fundamental structure that resembles that of the daphnane type. Also, tiglilane diterpenes include a tetracyclic ring structure with 5/7/6/3 rings.

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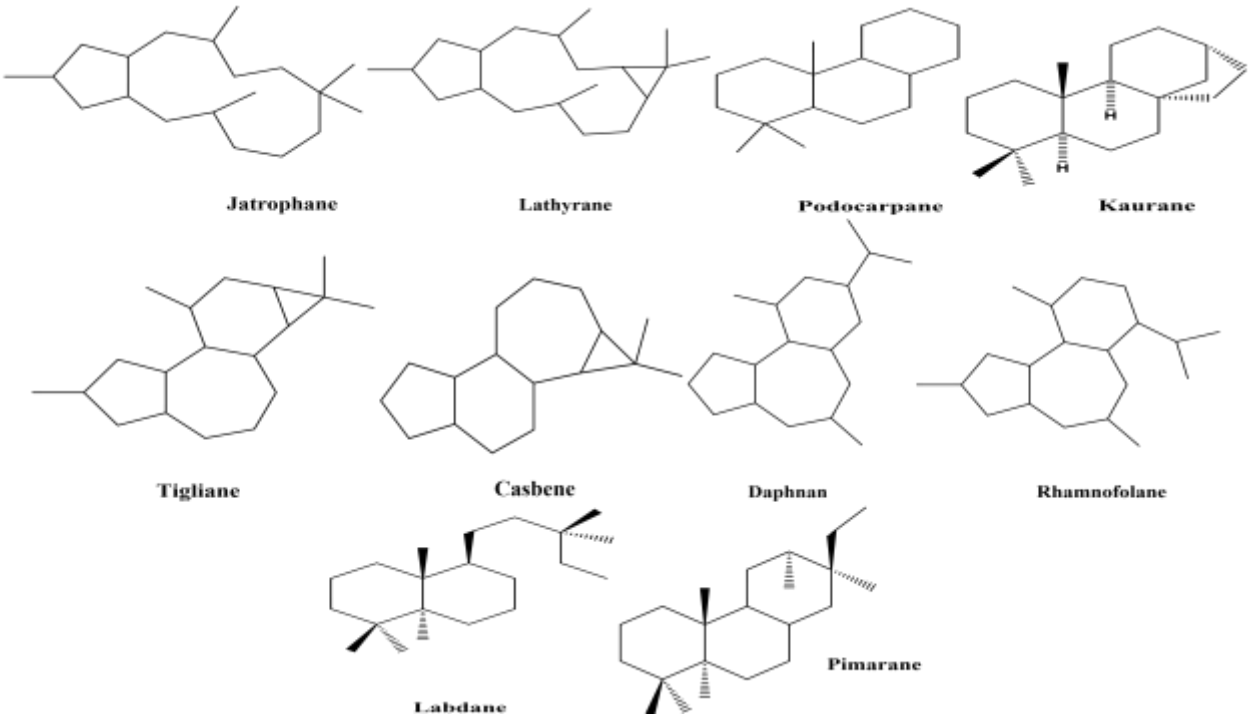

Figure 1: Basic skeletons of some classes of diterpenes.

Hydroxy groups can be found in the C-4, C-9, C-13, and C-20 positions in many tigliane diterpenoids. Carbonyl groups can be formed in C-3, and between C-1 and C-2, as well as C-6 and C-7, and olefin bonds can be detected.[7]

Kaurane diterpene belongs to the tetracyclic class of diterpenes. The kaurene structure is formed of four rings containing three cyclohexane rings that combine to form a perhydrofenanthrenic structure and one cyclopentane ring created by a two-carbon bridge connecting C-8 and C-13.[8]

Abietane diterpene is a 20-carbon tricyclic diterpene. Rosmanol, jiadifenoic acid C, sugiol, and other compounds fall within this category. [9]

Pimarane diterpene is a type of tricyclic diterpene, which differs in the configuration of the methyl group at C-17. Jiadifenoic acids L, 4-epi-isopiric acid, forskolin, and others are among them.[10]

Labdane is a bicyclic diterpene, its fundamental structure is made up of two cyclohexene rings (C-1 to C-10) linked to form a decalin system and five-carbon chains (C-11 to C-16) bonded to C-9. Five methyl branches are attached at C-4 (for C-18 and C-19), C-8 (for C-17), C-10 (for C-20), and C-13 (for C-16).[11]

Casbane is macrocyclic diterpene comprising fourteen membered as well as a cyclopropane ring. This type is considered to be a precursor to a series of macrocyclic diterpenes. These types include jatropholon A, jatropholon B, 2-*α*-hydroxyjatropholon and 2-*β*-hydroxyjatropholon.[12]

Lathyrane diterpene is one of the most diverse classes of tricyclic diterpenes. That is made up of a ring system with 5/11/3 members. The biogenetic progenitor of these diterpenes is the hydrocarbon nucleus of casbene and its saturated counterpart. Between C4 and C15 or C5 and C6, they can have an epoxy function, as well as double bonds between C5 and C6. Lathyrane diterpene types include curculathyranes, multifolone, multidione and lathyranlacton, lathyranes diterpene, and others.[13, 14]

Jatrophane diterpene is a bicyclic pentadecane diterpene. The diterpene jatrophane has a 5/12 bicyclic system and is made up of four isoprene units, namely acyl groups, acetyl, butanoyl, isobutyryl, benzoyl, and other substituents are commonly found in the structure.[15] The subclasses of jatrophane diterpenes include jatrophone, japodagron, citlatrione, and jatrophenone. [16] Jatrophanes and their derivatives exhibit a wide range of biological activities, including inhibition of the CaCdr1p and/or CaMdr1p efflux pumps in *Candida albicans*,[17] P-glycoprotein modulators with reverse multidrug resistance,[18,19] paclitaxel-like microtubule interaction, [20] mild cytotoxic agents against a wide range of tumour cells. [21, 22] JAT exhibits anti-inflammatory properties as well,[23, 24] and antiviral activity against HBV.[25]

Chemical structure of jatrophone

Jatrophone ($C_{20}H_{24}O_3$) is a bicyclic and macrocyclic pentadecane diterpene. First, it was isolated and described as the antileukemic constituent of *J. gossypiifolia* (Euphorbiaceae) and has received considerable attention. Natural jatrophone derivatives, known as hydroxyl jatrophones 2*α*-OH jatrophone, 2*β*-OH jatrophone, ($C_{20}H_{24}O_4$) and 2*β*-OH-5, 6-isojatrophone ($C_{20}H_{24}O_4$), were isolated from *J. gossypifolia* roots,[26, 27] The chemical structure of jatrophone is shown in Figure 2. JAT was isolated as colorless crystals, with the chemical formula of $C_{20}H_{24}O_3$ as determined using HRMS [ESI]: *m/z* 313.1797 [calcd. 313.1804 for $C_{20}H_{24}O_3H^+$, $[M+H]^+$]. It has specific rotation: $[\alpha]^{20}{}_D$=+295 (c=1.5,$CHCl_3$) and its infrared spectrum showed bands at υ: 2960, 1693, 1660, 1612, 1402 cm^{-1} (KBr).[28] The ultraviolet spectrum exhibited absorption at λ_{max} 285 nm and a melting point of 142-144^{0}C,[29] and 154-155^{o}C.[28] The structure elucidation of jatrophone was primarily based on spectroscopic analysis of ^{1}H and ^{13}C NMR reports containing 2DNMR experimental (HMBC, NOESY and COSY) and X-ray study. [28, 29] It is remarkable to know that the main structure of the molecule of JAT, is the 3(2H)-furanone ring (the macrocyclic ring), which is found in an increasing number of anticancer agents. [30]

NMR data for JAT in [CDCl3] (100 MHz for ^{1}H-NMR and 400 MHz for ^{13}C-NMR).

^{1}H-NMR: δ_H: 2.17 (dd, 13.7, 5.9, H-1a), 1.88 (dd, 13.7, 7.8, H-1b), 3.00 (ddq, 7.8, 7.0, 5.9, H-2), 5. 83 (br s, H-3), 5.84 (br s, H-5), 6.02 (d, 16.4, H-8), 6.47 (d, 16.4. H-9), 2.89 (d, 14.7, H-11a), 2.43 (d, 14.7,

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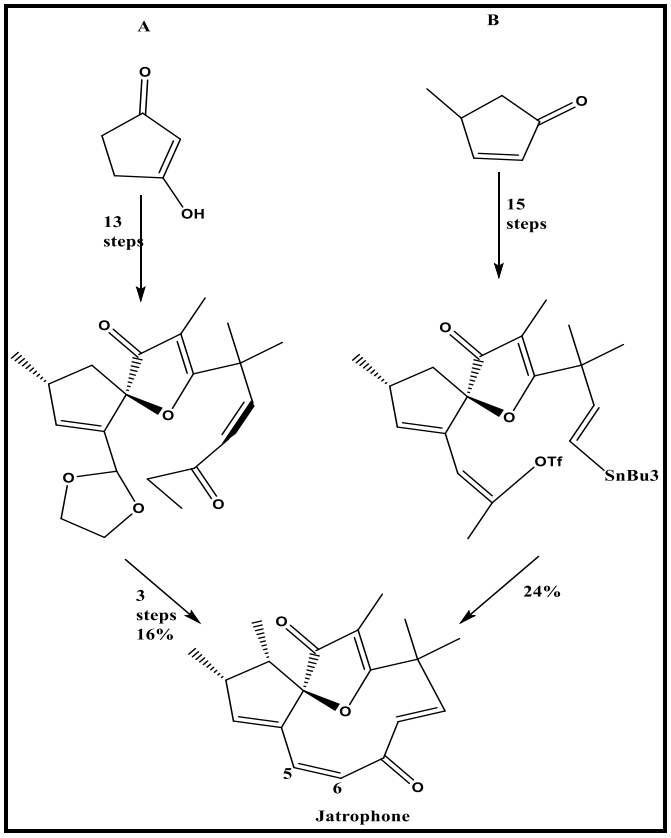
H11b), 1.01 (d, 7, H-16), 1.90 (s, H-17), 1.27 (s, H-18), 1.39 (s, H-19), 1.77 (s, H-20).
^{13}C-NMR: δ_C: 42.42 (C-1), 38.28 (C-2), 123.68 (C-3), 137.05 (C-4), 147.05 (C-5), 141.72 (C-6), 201.94 (C-7), 128.66 (C-8), 159.00 (C-9), 36.59 (C-10), 41.17 (C-11), (C-),183.21 (C-12), 112.36 (C-13), 203.85 (C-14), 99.71 (C-15), 18.93 (C-16), 20.69 (C-17), 30.35 (C-18), 26.86 (C-19), 6.00 (C-20).

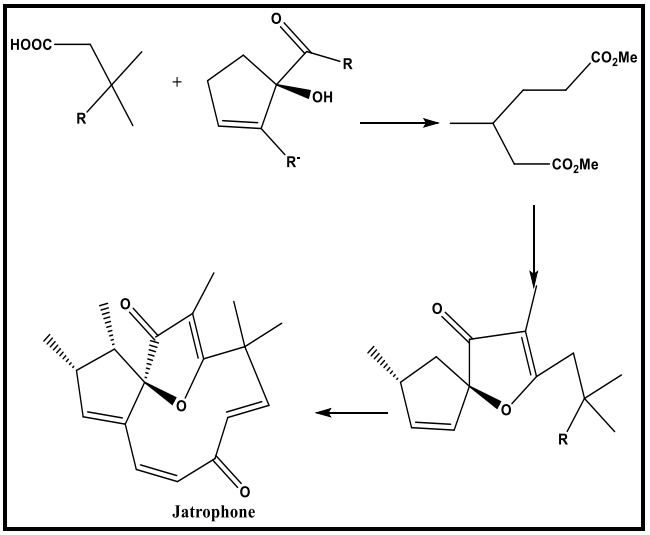
Isolation and quantification of jatrophone
In most of the published research papers on the isolation of jatrophone, it was reported that the first step was the extraction with alcohol such as ethanol followed by fractionation of the crude extract with dichloromethane or partitioning of the alcohol extract utilizing a (9:1) ratio of n-hexane and methanol/water. Dichloromethane or n-hexane fraction had been purified further on a silica gel column chromatography with *n*-hexane/ ethyl acetate and ethyl acetate.
Due to the wide biological spectrum of jatrophone, Fröhlich *et al*. [25]reported an analytical method to quantify the diterpene jatrophone in the fraction of dichloromethane from *J. isabellei* underground parts to evaluate its anti-inflammatory and antinociceptive activities.[31] An ultra-fast liquid chromatography-diode array detector (UFLC-DAD) method was created and tested. The identification and separation of jatrophone were carried out by MS ~~mass~~ analysis using a mass spectrophotometer of Bruker micro TOF-QII, source type APPI, in positive mode and coupled to the liquid chromatographic system. Several chromatographic conditions were tried to obtain a better resolution and separation of the jatrophone. Elution in a gradient, the mobile phase flow rate was 1.0 ml/min analysis beginning with 47:53 H_2O-MeCN, up to 65% MeCN over 12 min and then to 75% MeCN more than 15 minutes with the total running time of 23 minutes and jatrophone eluted at R_t 7.8 minutes. The technique used to quantify jatrophone was validated following the ICH and the ANVISA guidelines,[31] and it was observed that the method was linear, specific, precise, and accurate.

Synthesis of jatrophone
Jatrophone was first synthesized in 1981 by Smith *et al*. (Scheme 1 A) starting with 4-methyl-2-cyclopenten-1-one, the synthesis needed 16 stages. The key step in the synthesis was to generate the macrocycle, which yield 23% with an aldol-type reaction to create the C5-6 double bond.[32] Another study regarding the synthesis of jatrophone and its epimer (Scheme 1 B), in which the key step involved the palladium-catalyzed carbonylative coupling of a vinyl triflate with an organostannane to afford the macrocycle used to create C6-7 and C7-8 bonds with 24% yield. Starting with 4-methyl-2-cyclopenten-1-one, the complete synthesis sequence needed 16 stages.[33] Han, Wiemer [34] described optically active (±)-jatrophone synthesis (Scheme 2). From (R)-(+)-3-methyladipic acid, a convergent sequence yields the natural enantiomer in 12 steps and an overall yield of over 15%. Important steps contain the production of the jatrophone C-ring via a Wadsworth-Homer-Emmons variant, a Pd-catalyzed cross-coupling that incorporates the CSX6 double bond with the requisite 2-stereochemistry, and the macrocycle is produced by condensation of an acetylenic aldehyde.[34]

Natural sources
Jatrophone is a diterpene of natural origin isolated from various sources, most notably plant roots. Considerable amounts of this diterpene were isolated from *Jatropha* and *Euphorbia* species of the Euphorbiaceae family (Figure 3). Jatrophone (Figure 2) and jatrophone derivatives (Figure 4) have been isolated from various plants and materials are listed in table 1. The first isolation of JAT from hexane fraction of the ethanol extract of roots of *J. gossypiifolia* was conducted.[26,27] Jatrophone and 2β-hydroxyjatrophone have been isolated from the *n*-hexane fraction of *J. elliptica* roots.[35] In addition, JAT has been isolated also from the ethanol extract of roots and stems of *J. gossypiifolia*,[36] dichloromethane fraction of the ethanolic extract of underground parts of *J. isabellei*,[31] petroleum ether-ethyl acetate fraction of the methanol extract of roots of *J. gossypiifolia*,[37] *n*-hexane fraction of the methanol extract of roots of *J. ribifolia*,[38] and also has been isolated by modified extraction method from rhizomes of *J. isabellei*.[39] Sahidin, Ginting, Manggau,[40] isolated JAT from *J. gossypiifolia*.



Scheme 1



Scheme 2

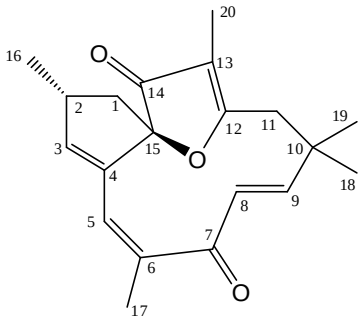


Figure 2: Structure of jatrophone (1)

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from methanol extract, Pertino, Schmeda-Hirschmann, Rodríguez, Theoduloz [12] isolated jatrophone and 9*β*, 13*α*-dihydroxyisabellione from petroleum ether and ethyl acetate fractions of rhizomes of *J. isabelli*.[12] In another study, three diterpene jatrophone types (Euphoheliosnoid A-C) were isolated from ethyl acetate extract of the whole plant of *Euphorbia helioscopia*.[41] Also, JAT was isolated from the ethanol extract of the rhizomes of *J. elliptica*,[42] petroleum ether and ethyl acetate extracts of *J. isabellii*.[43] JAT was isolated from *J. elliptica* tubers extracted with ethanol[44] and ethanol fraction of tubercule of *J. elliptica*.[45] JAT, 2*α*-hydroxyjatrophone, 2*β* –hydroxyjatrophone, and 2*β*-hydroxy-5, 6-isojatrophone were isolated from petroleum ether extract of roots of *J.gossypiifolia*.[46] Euphornin (a polyacylated diterpene of jatrophone types) was isolated from chloroform extract of the plant *E. maddeni*.[47]

Structure-activity relationship of jatrophone

D'Alagni, De Petris, Marini-Bettolo, Temussi,[48] reported that Jatrophone interacted with proteins and nucleic acids. The carbonyl groups (C7, C14) of JAT reacted with the RNA phosphate groups via hydrogen bonding in the interaction with *Escherichia coli* sRNA. As determined by its melting temperature, jatrophone promoted the stability of sRNA. Jatrophone biotransformation by *Aspergillus niger* gave further information on jatrophone's general reactivity, The new compound 9*β*-hydroxyisabellione was produced by the *Aspergillus niger* culture. (Figure 5), a Michael addition reaction product, which shows a single diastereoisomer, owing to the face's advantageous access to the C8–C9 double bond. Because of the proximity, C12 forms a new bond., resulting in the formation of a new ring (Figure 5), JAT and 9β-hydroxyisabellione showed favorable effects against two cancer cell models, human AGS (gastric epithelial) and MRC-5 (lung fibroblast) Pertino, Schmeda-Hirschmann, Santos, Rodriguez, Theoduloz [28] Jatrophone has been identified as a promising and potent lead compound, which has a core structure distinct from previous agents. To examine structure-activity relationship of JAT, a focused chemical library based on it was synthesized (Figure 6). The reaction scheme contains 1, 4-Michael addition reactions in conjugated systems of C7–C9 or C14-C12.The carbonyl groups were also evaluated using Grignard reagents (at C7 and C14). To assess the overall electronic impact of heteroatoms in the activity of JAT, a variety of electrophilic addition processes were employed. Compounds **26**, **27**, and **29** resulted from Heck-mediated cross-coupling reactions of jatrophone. Compounds **30**, **31**, and **36** were obtained by adding soft noncarbon nucleophiles (H_2O, MeOH, iPrOH) to the C9 of JAT. The compound library was evaluated for cytotoxicity against *P. falciparum* strains 3D7 and K1 as well as a collection of mammalian cell lines, including HepG2 (human liver carcinoma), BJ (human foreskin fibroblast), Raji (Burkitt lymphoma), and EK293 (transformed human embryonic kidney) lines of cells. Antimalarial action was found in many jatrophone derivatives against the 3D7 and K1 strains, however, only a few compounds were comparable to jatrophone. Electron-rich aromatic group at C9 (compounds **26 and 27**) had limited antimalarial activity, whereas compounds **20 and 29** were the most active.[39]

Biological activity

Cytotoxic activity

Jatrophone isolated from *J. gossypifolia* roots at 27 and 12 mg/kg, demonstrated potent antileukemic activity against P-388 lymphocytic leukemia as well as cytotoxicity (ED_{50}) (0.17 *μ*g/ml) against KB human carcinoma of the nasopharynx cell culture.[26]

In another study, JAT showed a good cytotoxic effect against hepatocellular cancer cell line HepG2 (IC_{50} 3.2 *μ*g/ml), cell line for colon cancer WiDr (IC_{50} 8.97 *μ*g/ml) and cell line for cervical cancer HeLa (IC_{50} 5.13 *μ*g/ml), the potential anticancer activity was evaluated using MTT assays.[49] In addition, from petrol ether extract of *J. gossypiifolia* roots, three anticancer derivatives of jatrophone were isolated: 2- hydroxyjatrophone, 2-hydroxy-5, 6-isojatrophone, and 2-hydroxyjatrophone (Figure 4). *In vitro*, JAT was discovered to be more cytotoxic (ED_{50} 0.01 *μ*g /ml) than its hydroxy derivatives, 2*α*-OH jatrophone (ED_{50}, 0.03 *μ*g /ml), 2*β*-OH jatrophone (ED_{50},0.06 *μ*g /ml), 2*β*-OH-5, 6-isojatrophone (ED_{50}, 2.2 μg /ml) against the P-388 lymphocytic leukemia cell line.

Jatropha isabellii

Jatropha gossypiifoliae

Jatropha elliptica

Euphorbia helioscopia

Euphorbia maddeni

Figure 3: Examples of some plants bearing jatrophone

when examined *in vitro* in Eagle's carcinoma of the nasopharynx (ED_{50}, 87 *μ*g/ml), similar cytotoxic results were shown in comparison to 2*α*-OH jatrophone (ED_{50}, 0.16 *μ*g /ml), 2*β*-OH jatrophone (ED_{50},0.07 *μ*g /ml), and 2*β*-OH-5, 6-isojatrophone (ED_{50}, 0.03 *μ*g /ml) (46). Moreover, jatrophone and its derivatives 9*β*,13*α*-dihydroxyisabellione and 13*α*-hydroxy-9*β*-acetoxyisabellione (Figure 4) demonstrated a potent antitumour activity, they had a lower level of activity against fibroblasts CCL-171, AGS CRL-1739, lung HTB-58, bladder HTB-1, leukemia CCL-240, JAT had anti-proliferative activity (IC_{50} in *μ*M): 0.29, 0.51, 1.8, 1.7 and 5.1, respectively. While 9β -13*α* dihydroxyisabellione (IC_{50} in *μ*M) was 35.9, 13.7, 33.3, 20.1, 100 (*μ*M), respectively. The IC_{50} for the value reference compound etoposide were 3.9, 0.36, 2.5, 2.8 and 0.80 *μ*M of the previous cell lines, respectively.[50] Mechanistically, JAT (0.02-0.32 *μ*M) inhibited human lymphocyte proliferation in a concentration-dependent and equipotent manner when tested with 5 μg/ml of phytohemagglutinin or a mixture of 100 *μ*g/ml of 12-O-tetradecanoyl phorbol-13-acetate and 0.15 *μ*M ionomicyn, with IC_{50} values of 53.4 nM and 48.4 *n*M, respectively. Jatrophone also inhibited the proliferation of murine lymphocytes activated by 5 *μ*g/ml of concanavalin A, in a concentration-dependent manner, with IC_{50} value of 63.5 nM. These findings that jatrophone is a strong inhibitor of lymphocyte activation, most likely by inhibiting the protein kinase C pathway.[51] In another work, JAT was extremely cytotoxic to the VERO cell line for IC_{50} of 0.43 *μ*g/ml,[37] and against murine P-388 leukemia cells with IC_{50} > 100 *μ*g/ml,[52] also toward Hela cell line and WiDr cell lines with IC_{50} 5.13 and 8.97 *μ*g/ml, respectively.[40]

JAT isolated from the *J. isabelli*, has been tested on TNBC cells (Triple-negative breast cancers); at the level between receptor complex and the activation of *β*-catenin, it interfered with the WNT TOPFLASH reporter.

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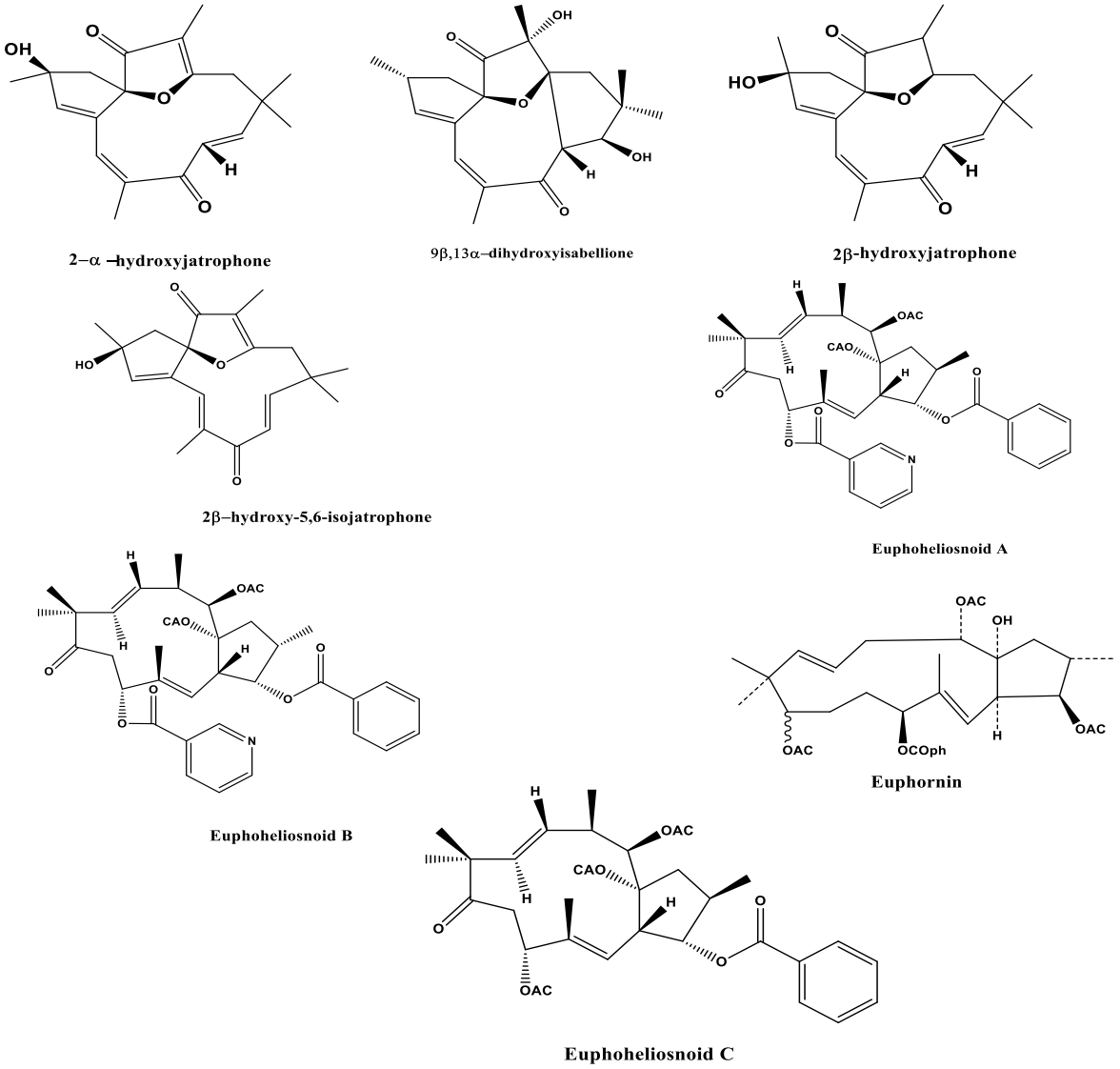

Figure 4: Chemical structures of some jatrophone derivatives

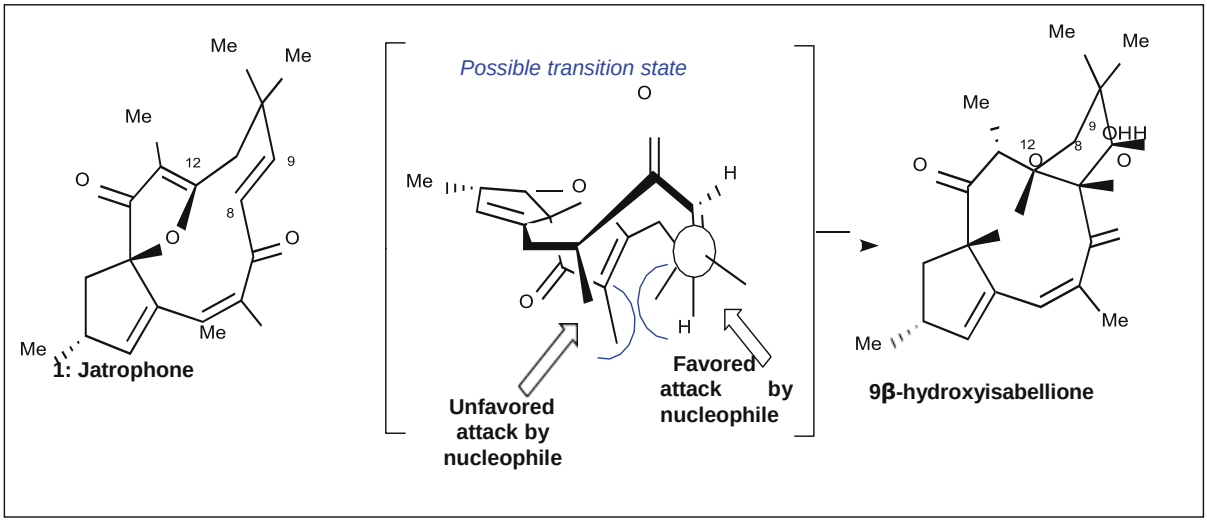

Figure 5: Incubation of jatrophone with *Aspergillus niger* produces 9*β*-hydroxyisabellione

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Table 1: Natural sources of jatrophone and jatrophone derivatives

Botanical name	Plant part	Extract/Fraction	Compounds	Geographical distribution	Ref.
J. gossypiifolia	Roots	*n*-Hexane fraction /ethanol extract	Jatrophone	Costa Rica	[26, 27]
J. gossypiifolia	Roots	Petroleum ether (60-80) extract	2*α*-hydroxyjatrophone, 2*β*-hydroxyjatrophone, and 2*β*-hydroxy-5,6-iso jatrophone	Los Santos, Panama	[46]
J. isabelli	Rhizomes	Methanol extract	Jatrophone	Paraguay	[39]
J. gossypiifolia	Stem barks	Methanol extract	Jatrophone	Pusat koleksi dan pengembangan Tanaman Obat TradisionalMasyarakat Sulawesi Tenggara, Indonesia	[40]
J. isabelli	Rhizomes	Petroleum ether (60-80) and ethyl acetate fractions	Jatrophone and 9*α*, 13*β*-dihydroxyisabellione	Paraguay	[12]
J. gossypiifolia	Roots and stems	Ethanol extract	Jatrophone	Florida, USA	[36]
J. elliptica	Tubers	Ethanol extract	Jatrophone	AL, Brazil	[44]
J. ribifolia	Roots	*n*-Hexane fraction/methanol extract	Jatrophone	Naviraí, Mato Grosso do Sul, Brazil.	[38]
J. elliptica	Roots	*n* Hexane fraction	Jatrophone and 2*β*-hydroxyjatrophone	Campo Grande, Brazil.	[35]
J. elliptica	Tubercules	Ethanol fraction	Jatrophone	Mato Grosso, Brazil.	[45]
J. gossypiifolia	Roots	Petroleum ether (60-80)-ethyl acetate fraction /methanol extract	Jatrophone	Iguosa estate, Benin City, Nigeria	[37]
E. helioscopia	Whole plant	Ethyl acetate extract	Euphoheliosnoid (A-C)	Shujiao, Zhejiang Province, China	[41]
J. isabellei	Underground parts	Dichloromethane fraction / ethanol extract	Jatrophone	(State of Rio Grande do Sul, Brazil	[31]
J. elliptica	Rhizomes	Ethanol extract	Jatrophone	Goias, Brazil.	[42]
J. isabellii	Rhizomes	Petroleum ether (60-80) and ethyl acetate extracts	Jatrophone	Cordillera, Paraguay	[43]
E. maddeni	Whole plant	Chloroform extract	Euphornin	Kullu, Himachal Pradesh, India	[47]

In many metastatic cell lines, higher WNT10B expression was also associated with enhanced resistance to JAT exposure. JAT interrupted cell cycle progression and caused the canonical Wnt-direct targets genes AXIN2, HMGA2, MYC, PCNA, and CCND1 to lose expression. JAT decreased steady-state levels of non-phosphorylated (activated)-catenin protein but not total-catenin levels. It also reduced the expression of key EMT markers and greatly hampered scratch wound healing experiments, implying that jatrophone has a direct role in preventing TNBC cells from migrating.[36]

In vitro, the anti-proliferative activity of JAT demonstrated concentration-dependent selectivity with complete suppression development of glioma(U251), breast cancer(MCF-7), Adriamycin resistant ovarian cancer(NCI-ADR/RES), kidney(786-0), prostate cancer1 (PC-3), colon cancer (HT29) and leukemia (K-562) with IC_{50} values respectively , 0.57 μg ml-1, 9.2 μg ml-1, 0.96 μg ml-1, 4.2 μg ml-1, 8.4 μg ml-,, 16.1 μg ml-1 and 0.21 µg ml-1.[38]

The neutral red absorption method was used to test the cytotoxicity of the new JAT derivative and its acetate against fibroblasts and AGS cells, which had a high activity with IC_{50} values (2.8 and 2.5µM), respectively.[12] Nakazibwe [53] evaluated the antiproliferative and apoptotic characteristics extracted from the stem bark of *J. gossipyfolia* on human cancer cells. It was tested on oral (HSC3), lung (H1299) and leukaemia (K562) cell lines. The rate of antiproliferation was measured using the MTT test for monolayer cells and the Trypan Blue Exclusion assay for suspension cells in the presence of JAT at varying doses. Despite a considerable drop in percentage cell viability, JAT did not significantly restrict the growth of K562, H1299, and HSC3 cells, according to the findings.

Antiviral activity

Li, Xu, Yue[54] reported that, in pulmonary epithelial cells, JAT suppressed viral proliferation and oxidative damage caused by RSV (Respiratory syncytial virus); JAT is a potential antiviral agent that could be produced to treat respiratory tract infections.

Relaxant effect

Jatrophone (1–300 µM) had a concentration-dependent relaxant action on spasmogenic drugs (Acetylcholine (100 µM), Oxytocin (30 mlU/ml) and KCI (80 mM)) induced persistent contractions in rat uterine muscle. The relative potency order was: acetylcholine greater than oxytocin greater than KCl. Jatrophone's relaxant effect unchanged by phorbol myristate acetate (10 *n*M,), forskolin (10 *n*M,), 3-isobutyl-1-methylxanthine (10 μM) TMB-8 (10 μM,) and W-7 (10 μM,).The relaxing effect generated by JAT was not reversed by increasing the calcium concentration in the media (0.2–2 mM).[55]

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Table 2: Biological activities of jatrophone and jatrophone derivatives

Biological Activity	Botanical Name	Compounds	Ref.
Analgesic activity	*Jatropha.gossypifolia*	Jatrophone	37
	Jatropha elliptica	Jatrophone	56
Antiprotozoal activity	*Jatropha gossypifolia*	Jatrophone	37
	Jatropha.isabelli	Jatrophone	39
	Jatropha gossypifolia	Jatrophone	52
		Jatrophone	48
Antiviral activity	*Jatropha.*gossypiifolia	Jatrophone	54
Cytotoxic activity	*Jatropha.*gossypiifolia	Jatrophone	36
	Jatropha.gossypiifolia	Jatrophone	49
	Jatropha.gossypiifolia	Jatrophone	37
	Jatropha.ribifoli	Jatrophone	38
	Jatropha.gossypifolia	Jatrophone	40, 52
	Jatropha.gossypiifolia	Jatrophone	53
	Jatropha.isabelli	Jatrophone , 9*β*,13*α*-dihydroxyisabellione and 13*α*-hydroxy-9*β*-acetoxyisabellione	50
	Jatropha.isabelli	Jatrophone and 9*α*, 13*β*-dihydroxyisabellione	12
	Jatropha elliptica	Jatrophone,	51
	Jatropha.gossypiifolia	Jatrophone , 2*α*-hydroxyjatrophone, 2*β*-hydroxyjatrophone, and 2*β*-hydroxy-5,6-isojatrophone	46
	Jatropha.gossypiifolia	Jatrophone	26
Effect on Platelet Aggregation	*Jatropha.*elliptica	Jatrophone	44
Gastroprotective effect	*Jatropha* isabelli	Jatrophone and 9*α*, 13*β*-dihydroxyisabellione	12
Insulin release inhibition	*Jatropha* elliptica	Jatrophone	57
Molluscicidal Activity	*Jatropha* elliptica	Jatrophone	42
Neuroprotective Effects	*Jatropha isabelli*	Jatrophone	58
Relaxant effect	*Jatropha elliptica*	Jatrophone	42
	Jatropha .elliptica	Jatrophone	59
	Jatropha .elliptica	Jatrophone	60
	Jatropha elliptica	Jatrophone	45

Furthermore, **Silva, Brum, Calixto**[59] evaluated the vasorelaxant effect of JAT, with IC_{50} of 86 *n*M, 13, 11 and 9 μM on portal vein contractions in rats generated by phorbol 12-myristate 13-acetate (0.1–3 μM), noradrenaline (0.01–100 μM), endothelin-1 (0.01 -10 nM) or KCI (4–128 μM). While staurosporine and H-7(reference compounds) as well as had a relaxing effect (IC_{50}) showed that phorbol 12-myristate 13-acetate (0.75 *n*M), H-7 was not tested, noradrenaline (25.23 *n*M, 7.6 μM), endothelin-1 β5.31 *n*M, no effect) and KCl (28.45 μM, 0.92 μM) respectively; suggesting when JAT had a lower potency than staurosporine and nearly as potent as H-7.[59] Analyzing the vasorelaxant effect of JAT in the isolated rat aorta, it was stated that JAT (1 to 300 μM) relaxed the precontraction of the rat aortic rings in a concentration-dependent manner of norepinephrine (1 μM) and KCl (80μM), with EC_{50} of 11 and 24 μM.[60] JAT (1.6-12.8 μM) inhibited histamine-induced contractions, bradykinin and acetylcholine in the guinea-pig ileum longitudinal muscle in a concentration-dependent manner. In the mentioned tissue, it inhibited acetylcholine and bradykinin about 5 to 8-fold more potently than uterine muscle. In addition, JAT inhibited guinea-pig ileum, guinea-pig urinary bladder, electrically stimulated rat left atrium, and dog ureter contractions in a concentration-dependent manner /ml), 2*β*-OH jatrophone (ED_{50},0.07 μg /ml), 2*β*-OH-5, 6-isojatrophone (ED_{50}, 0.03 μg /ml).[45]

Antibacterial and antiprotozoal activity

Sahidin, Ardiansyah, Muhammad, Marianti[52] showed that JAT was effective against 4 bacterial strains (*Acetobacter sp., Escherichia coli, Staphylococcus aureus and Streptococcus sp.),* 4 fungal strains (*Aspergillus niger, Penicillium sp. (grey), Penicillium sp. (white)* and *Rhizopus sp.*). JAT has a growth inhibition zone of 36 mm against *S. aureus* (bacteria) and 44 mm against *A. niger* (fungi). In another study, BALB/c mice that reacted with JAT (25 mg/kg/day) for thirteen sequential days after a 24-hour infection with *Leishmania amazonensis* (strain PH8), in comparison to the reference substance (N-methylglucamine antimoniate, 112 mg Sb^v per kg/day), jatrophone was significantly potent against the virulent strain at a dose of 25 mg/kg/day.

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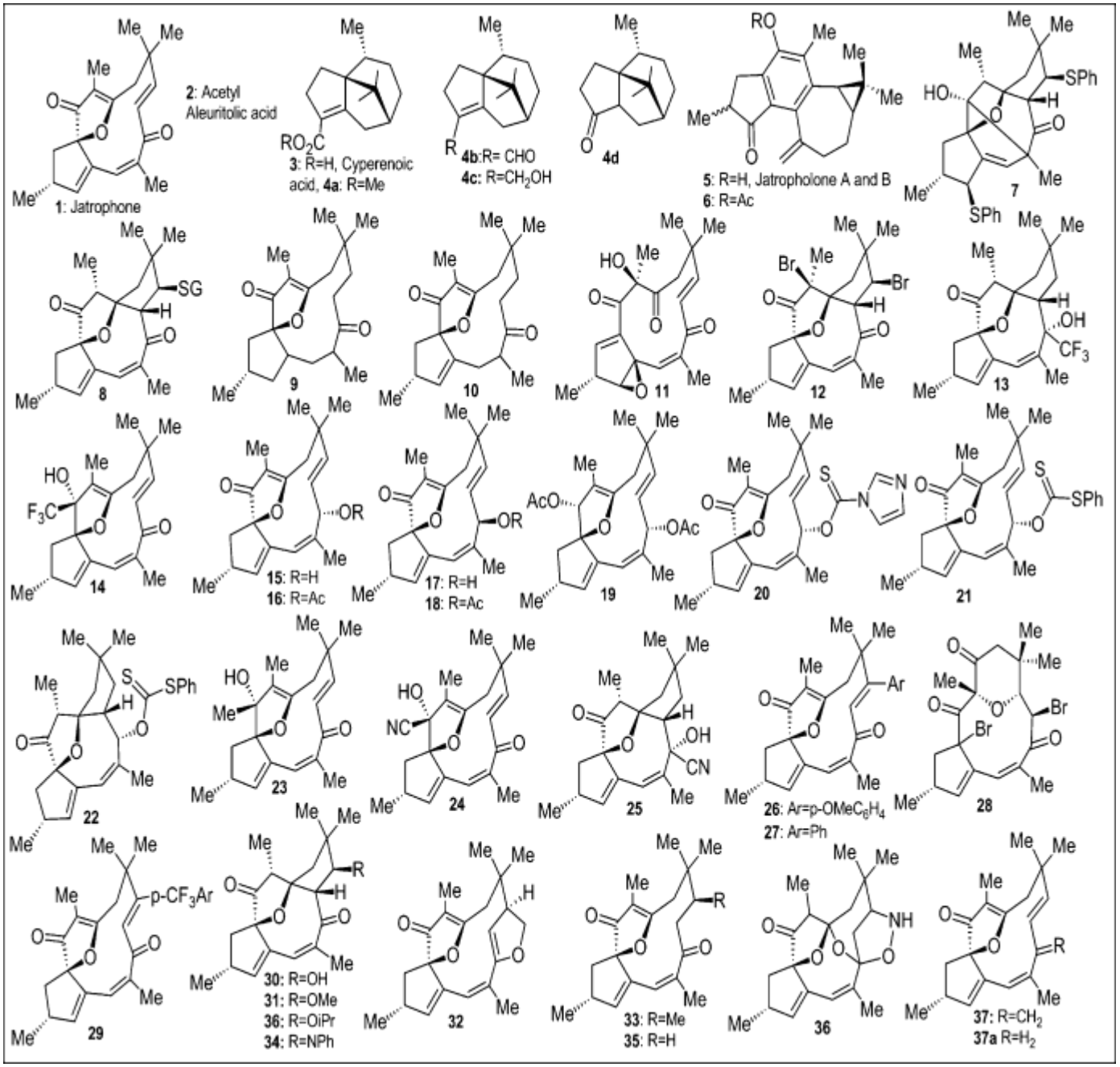

Figure 6: Jatrophone focused compound library synthesized to in order to investigate the structure-activity relationship of jatrophone against the malaria strains 3D7 and K1.[39]

But jatrophone was toxic *in vivo* at this dose. In comparison to the IC_{100} of reference substances glucantime (100 μg/ml), ketoconazole (50 μg/ml) and pentamidine (1 μg/ml). It also demonstrated potent antiprotozoal activity *in vitro* with IC_{100} 5 μg/ml against *L. brasiliensis*, *L. amazonensis* and *L. chagasi*.[43] Jatrophone also demonstrated significant antiplasmodial and antileishmanial activity against *P. falciparum* (D6 strain), *P. falciparum* (W2 strain) and *L. donovani* with IC_{50} of 0.55, 0.52 and < 0.4 μg/ml, respectively, and no significant antimicrobial activity was observed against the tested organisms.[37]

In the study of new antimalarial compounds, JAT has been identified as an effective antimalarial agent with IC_{50} values of 5.7/5.9 and 6.1/5.9μM against two malaria strains, 3D7 (chloroquine-sensitive *P. falciparum*) and K1 (chloroquine- and pyrimethamine-resistant *P. falciparum* expressing the chloroquine efflux transporter and upregulating MDR efflux pump expression).[39] The interaction of JAT with sRNA from *Escherichia coli* improved the polynucleotide's stability. The optical characteristics of JAT appear to be dependent on the jatrophone/nucleotide ratio. The observed behavior can be explained by the existence of several forms of JAT and sRNA interactions. The ^{1}HNMR spectra indicate a multiplicity of resonances even for a jatrophone/nucleotide ratio as low as 0.17, which can be explained by the occurrence of two separated binding modes incorporating the JAT molecule.[48]

Effect on platelet aggregation

Jatrophone (2.5-100 μM) isolated from *J. elliptica*, markedly inhibited platelet aggregation, induced by several agents in different animal species. For up to 30 minutes, the effect was dose-dependent and reversible. This nonspecific effect could be due to jatrophone's effect of an intracellular phase in the signal transduction pathway that is shared

by all agonists, or at the extracellular and/or intracellular Ca2' mobilization levels.[44]

Gastroprotective activity

Jatrophone and a new JAT derivative 9*β,* 13*α*-dihydroxyisabellion, were extracted from *J. isabelli* rhizomes and examined for gastroprotective properties in mice. Mice were given the test samples orally, before the lesion was induced by a mixture of the solution including 0.3 M HCl/60% EtOH, and the ratio of lesion decrease was determined by comparison with a control (12% Tween-80, vehicle). The antisecretory drug lansoprazole (20 mg/kg) was employed as a standard compound, which showed a gastroprotective action of (73%), while at a dose of 25 mg/kg body weight JAT elicited a strong (88%) gastric protective effect, and 9*β*, 13*α*-dihydroxyisabellion showed with a (35%) gastric protective effect in mice at a dose of 25 mg/kg body weight.[12]

Inhibition of insulin release

In collagenase-isolated rat islets, insulin secretion was assessed (in the absence of glucose), and was found to be 122 micro/islet per 90 minutes, when glucose is present (16.7 mM) was found to be 445 microU/islet per 90 minutes. Insulin release induced by glucose was suppressed with an ID_{50} close to 8μM/L in the presence of JAT, and total inhibition was found at 100 μM/L. JAT also produced a decrease in glucose metabolism by the islets at higher concentrations (100μM/L). Lower concentrations of JAT (10μ M/L) could be utilized to investigate the glucose-dependent mechanism or other secretagogue-induced insulin release, according to the authors. [57]

Molluscicidal activity

Jatrophone and a combination of jatropholones A and B extracted from the rhizome of *J. elliptica*, were examined against the snail *Biomphalaria glabrata*. JAT possessed LC_{50} of 1.16 ppm as a molluscicide and LC_{50} of 1.14 ppm for egg mass assay, while the mixture of jatropholone A and B showed LC_{50} of 58.04 ppm as a molluscicide and wasn't active versus the second assay at a concentration up to 100 ppm.[42]

Neuroprotective activity

Zolezzi, Lindsay, Serrano, Ureta, Theoduloz, Schmeda-Hirschmann, Inestrosa[58] evaluated the neuroprotective effect of JAT, which induced calcium levels to rise and promoted neuroprotection against apoptosis, synaptic protein loss, and LTP (hippocampal long-term potentiation) inhibition triggered by oligomers.[58]

Analgesic activity

Analgesic activity was studied for JAT isolated from *J. gossypifolia* roots utilizing the acetic acid-induced writhing and hot plate model in mice, showing that JAT had a potent analgesic activity in the acetic acid-induced writhing test and also in the hot plate test showed reductions of (54.03%) and (66.35%) at 5 and 10 mg/kg, respectively.[37] In another study, the inhibitory effect of rutin (160µ M), geraniin (200µ M) and quercetin (500 µM) extracted from *Phyllantus* and JAT (650µ M) isolated from *J. elliptica* on the binding of [3H] Glutamate and [3H] GMP-PNP in membrane preparations obtained from rat cerebral cortex. The authors showed that quercetin or JAT inhibited the binding of [3H] glutamate and that geraniin or quercetin inhibited the binding of [3H] GMP-PNP, a GTP analogue. These results might justify the antinociceptive activity of these natural compounds. [56]

Perspectives and future directions

Jatrophone (**1**) is an excellent lead compound for the development of a new phytotherpeutic agent to treat various diseases. Reviewing the literature revealed a lack of a simple method for isolating JAT that produces a greater yield in less time and at a lower cost than solvent-solvent extraction. Furthermore, jatrophone had been established only by one method using UFLC-DAD for its quantification. Analytically, a simple method is required for JAT and its bioactive derivatives, particularly in biological fluids. Jatrophone showed broad biological activities, such as anticancer, anti-protozoal, and molluscicidal activities and its effects on insulin release, lymphocyte activation and tumour cell proliferation. However, more detailed safety and pharmacokinetic investigations are required. There are currently no trials for the production of JAT through tissue culture or biotransformation of related diterpenes. Furthermore, more derivatives must be prepared to investigate their activity, construct structure-activity relationships, and comprehend their mechanisms of action.

Conclusion

This article provides an updated report on JAT (**1**), a significant diterpene isolated from several species of *Jatropha* and *Euphorbia* with promising pharmacological potential. JAT possesses anticancer, anti-protozoal, and molluscicidal activities and it showed inhibitory effects on insulin release, lymphocyte activation and tumour cell proliferation. In addition, it showed relaxation of muscle contraction and on rat portal vein, and gastroprotective effects. Soon, more in-depth mechanistic research underpinning these beneficial qualities will be needed to clarify the interaction between jatrophone and receptor sites. According to this review, JAT could be used as a direct medicinal agent or as a chemical template for the design, synthesis, and semi-synthesis of new drugs to treat a variety of human diseases.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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