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REVIEW

Jatropha Diterpenes: a Review

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Abstract Terpenes are the largest group of phytochemicals that exhibit diverse functions in mediating antagonistic and beneficial interactions in, and among, organisms. For many years the abundance and distribution of terpenoid compounds in plants have benefitted both nature and human civilization. *Jatropha* species, belonging to the family Euphorbiaceae, are a rich source of terpenoid compounds. Among the terpenes, diterpenoid compounds have dominated the research area in *Jatropha* species with respect to their novel chemical structures and medicinal values. The present review describes the chemistry and biological activities of an array of *Jatropha* diterpenes. The diterpenes isolated from *Jatropha* species belongs to rhamnofolane, daphnane, lathyrane, tigliane, dinorditerpene, deoxy preussomerin and pimarane skeletal structures. Among the 68 diterpenes collated in this review, the biological activity of compounds varied distinctly—the majority of the diterpenes exhibited cytotoxic, antitumor and antimicrobial activities in vitro. To name a few, jatrophone, spruceanol and jatrophatrione exhibited antitumor properties against P338 lymphocytic leukemia and japodagrol against KB carcinoma cells. Whereas, curcusone B exhibited anti-invasive effects against cholangiocarcinoma cells. The phorbol esters (*Jatropha* factor **C1**–**C6**) and Jatropherol exhibited insect deterrent/cytotoxic properties. Many diterpenes (jatrophalactam, faveline derivatives, multifolone, curcusone, jatrophone derivatives etc.) showed in-vitro cytotoxic activity, while japodagrin, jatrogrossidione derivatives and jatropholone derivatives exhibited antimicrobial activities. *Jatropha* diterpenoids having a wide spectrum of bioactivity could form lead compounds or could be used as templates for the synthesis of new compounds with better biological activity for utilization in the pharmaceutical industries.

Keywords *Jatropha* · Diterpenes · Anticancer · Cytotoxic · Antibacterial

Introduction

Plants produce numerous low and high molecular weight compounds generally classified as primary and secondary metabolites or natural products [1]. The significance of plant secondary metabolites in medicine, agriculture and industries has attracted numerous scientists to venture into their chemical synthesis, biosynthesis and biological activities. Despite this, comparatively little is known about their actual role in nature [2]. Plant secondary metabolites can be divided into 3 broad categories, (a) terpenes or terpenoids, (b) alkaloids and (c) phenolic compounds. The compounds classified as terpenes contribute arguably the largest and most diverse class of natural products [1].

Among the many terpene structures (~25,000) reported, very few have been investigated from a functional perspective. Terpenes are vital for life in most organisms exerting metabolic control and mediating inter and intra species interactions, for example, pollination and defense in plants. Aside from the facts that plants manufacture these compounds in response to herbivory or stress factors, it has also been shown that flowers can emit terpenoids to attract pollinating insects and even attract beneficial mites, which feed on herbivorous insects [3, 4]. Kessler and Baldwin [5] have reported that herbivorous insects can

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cause the release of terpenes from plants and also induce the release of signals that attract predatory species. Cheng et al. [6] have reported that terpenes may act as chemical messengers influencing the expression of genes involved in plant defensive functions or influence gene expression of neighboring plants. Many terpenes are reported to act as toxins, growth inhibitors or deterrents to microorganisms and animals [1].

Terpenes are classified based on the number and structural organization of carbons formed by the linear arrangement of isoprene units followed by cyclization and rearrangements of the carbon skeleton with an empirical feature known as the isoprene rule. The term terpene refers to a hydrocarbon molecule, while terpenoid refers to a terpene that has been modified, for example by the addition of oxygen [3]. In plants, terpenoid biosynthesis occurs by two different pathways to synthesize the main building block IPP (Inositol pyrophosphate), (a) the Mevalonic acid pathway or HMG-CoA reductase pathway that occurs in cytosol and produces IPP for sesquiterpenoids, (b) MEP/DOX (methylerythritol phosphate/1-deoxy-D-xylulose) pathway forms IPP in the chloroplast for mono and diterpenoids. The diterpene compounds are derived from geranyl geranyl pyrophosphate (GGPP) and are further classified according to their biogenetic origin as acyclic (phytanes), bicyclic (labdanes, halimane, clerodanes), tricyclic (pimaranes, abietanes, cassanes, rosanes, vouacapanes, podocarpanes), tetracyclic (trachlobanes, kauranes, aphidicolanes, stemodanes, stemaranes, bayeranes, atisanes, gibberellanes), macrocyclic diterpenes (taxanes, cembranes, daphnanes, tiglianes, ingenanes) and mixed compounds, in accordance with the number and the cyclization patterns displayed by their skeletal structure [7–11]. The detailed information about the biogenetic origin and classification of terpenes are not dealt within this review and can be found elsewhere.

Increased resistance in many pathogens towards currently used medicines has rooted interest in the identification of novel anti-infective compounds. The Euphorbiaceae is a family with 300 genera and around 7,500 species that contain numerous diterpenoids and triterpenoids having various biological activities (example: cytotoxic, anti-proliferative and wound healing), as well as controverting biological activities such as tumor promoting and antitumor activity [12]. Despite the reports that many species of Euphorbiaceae are toxic, many species have found commercial importance (example: *Hevea* for rubber, *Ricinus* for castor oil and *Manihot* for cassava) and as ornamental plants. Some species of genus *Euphorbia* and certain other genera of the subfamily Euphorbioideae, the resins are reported to be toxic and potentially carcinogenic due to the high concentration of diterpenes (Source: http://tinyurl.com/yhrvcjz). The seeds of *Croton*, *Euphorbia*, *Jatropha* and *Ricinus* (castor-oil plant) are known to produce purgatives; and even poisoning of humans and livestock. Diterpenes such as phorbol esters from *Croton* species have been used in many tumor initiation studies and at low concentrations these compounds are also being explored for antitumor properties [13–16]. Based on in-vitro studies, many diterpene compounds of plant origin seem to have potential pharmaceutical applications exhibiting antihypertensive, anticancer, antiretroviral, anti-inflammatory, analgesic and antibacterial activities. In addition, they may function as antioxidants, hallucinogens and sweeteners; and stimulate contraction of the uterus [17–25]. The majority of diterpenes of Euphorbiaceae origin are from casbane, labdane or clerodane skeletons. Some diterpene esters (tigliane, daphnane and ingenane) have proven to be limited to Crotonideae and Euphorbioideae subfamilies. Ingestion of these diterpenes esters are toxic to livestock and humans [26]. All of the tumor promoting and skin irritant diterpene esters found to date are based on tigliane, daphnane and ingenane skeletons and all have been isolated from Euphorbiaceae species. The diterpenoids of lathyrane and casbane skeleton obtained from other species of Euphorbiaceae have been found to exhibit anti-leukemic, cytotoxic, antitumor activities.

The diterpenoid constituents in Euphorbiaceae species illustrate a complex skeletal structure. Diterpene series of tigliane are found to be a mixture of closely related compounds. There are a total of 25 esters of tigliane diterpene alcohols phorbol and 4-deoxy-4 alpha-phorbol, which have been isolated from croton oil. Most abundant and potent biologically active compound is TPA (12-*O*-tetradecanoylphorbol-13-acetate) present in croton oil [27], shown to be a tumor promoter. The compounds in daphnane ester series also occur in complex mixtures. The most compounds in this class are intra molecular 9,13,14-*ortho*-(2-hexadecanoic acid) esters. Diterpene irritants belonging to ingenane series are structurally related. For example, diterpene with basic parent terpene alcohols such as 17-hydroxyingenol, ingenol and 20-deoxy-17-hydroxyingenol has been isolated from the latex of *Euphorbia hermentiana* [28]. Clerodane diterpenes have shown to act as vasorelaxants [29].

In addition, this section of the article makes no attempt to review literature exhaustively. The readers should consult the references cited for more detailed information.

Jatropha

Jatropha (Euphorbiaceae) is a genus of approximately 175 succulent plants, shrubs and trees (some are deciduous, like *Jatropha curcas* L.). Irrespective of the species, extracts from different parts such as leaf, stem, bark and roots of the *Jatropha* plant have been used in ethno-medicines for a

Table 1 Diterpene constituents of *Jatropha* species

Sl. No.	Diterpenes	*Jatropha* species	Biological activities	References[a]
1	Jatrophone	*J. gossypifolia* *J. elliptica*	Antitumor Cytotoxic Molluscicidal Leishmanicidal Gastroprotective	32, 33, 36, 43
2	2α-OH Jatrophone	*J. gossypifolia*	Cytotoxic	36
3	2β-OH Jatrophone	*J. gossypfolia*	Cytotoxic	36
4	2β-OH-5,6-isoJatrophone	*J. gossypifolia*	Cytotoxic	36
5	9β, 13α-dihydroxyisabellione	*J. isabelli*	Cytotoxic	33
6	Japodagrin	*J. podagrica*	Antibacterial	45
7	Japodagrone	*J. podagrica*	Antibacterial	45
8	15-*O*-acetyl japodagrone	*J. multifida*	NA	46
9	Jatrophatrione	*J. microrhiza*	Antitumor	47
10	Jatrophenone	*J. gossypifolia*	Antibacterial	48
11	Riolozatrione	*J. dioica*	Antibacterial	49
12	Jatrowedione	*J. wedelliana*	NA	50
13	Integerrimene	*J. integerrima*	NA	51
14	Citlalitrione	*J. dioica,* *J. integerrima and* *J. gossypifolia*	NA	52–54
15	Caniojane	*J. grossidentata,* *J. integerrima and* *J. curcas*	Antiplasmodial Cytotoxic	51, 55
16	1, 11 bisepicaniojane	*J. integerrima*	Antiplasmodial	51, 55

long time [30]. In the past two decades, studies on the utilization of *Jatropha* oil (non edible) as a feedstock for biofuel has gained momentum, resulting in industrial scale cultivation. Apart from the seed oil (30–35%), *Jatropha* is also a rich source of phytochemicals that can be utilized in nutritional, agricultural and pharmaceutical industries [31]. Commercially, aqueous/alcoholic extracts from stem/bark of *Jatropha macarantha* are being sold as raw drugs which are used as a male sexual stimulant (http://www.rain-tree.com/huanarpo-macho-extract.htm).

Jatropha is one of the richest sources of phytochemicals such as alkaloids, lignans, cyclic peptides and terpenes having a broad range of biological activities [32]. Among the terpenes, diterpenes characterized from different species of *Jatropha* have a range of biological activities like antitumor, cytotoxic, anti-inflammatory,

Table 1 continued

Sl. No.	Diterpenes	*Jatropha* species	Biological activities	References[a]
17	2-epicaniojane	*J. integerrima*	NA	51, 55
18	Spruceanol	*J. divaricata*	Cytotoxic Antitumor	56–59
19	Cleistanthol	*J. divaricata*	Antitumor	56, 58, 59
20	*ent*-3β,14α-hydroxypimara-7,9(11),15-triene-12-one	*J. divaricata*	NA	56
21	*ent*-15(13→8)abeo-8β(ethyl)pimarane	*J. divaricata*	NA	56
22	Jatrogrossidione	*J. grossidentata*	Leishmanicidal Trypanocidal	44, 60
23	Isojatrogrossidion	*J. grossidentata*	NA	53, 60
24	2-epi-isojatrogrossidion	*J. grossidentata*	NA	60
25	2-epi-Jatrogrossidione	*J. gaumeri*	Antimicrobial	61
26	2-Hydroxyisojatrogrossidion	*J. grossidentata, J. wedelliana and J. podagrica*	Antibacterial Antifungal	60
27	2-epihydroxyisojatrogrossidion	*J. grossidentata, J. wedelliana and J. podagrica*	Antibacterial Antifungal	60
28	(4E)-jatrogrosidentadione acetate	*J. multifida*	NA	53, 60
29	(4E)-jatrogrossidentadione	*J. multifida*	NA	53
30	15-epi-4E-jatrogrossidentadione	*J. grossidentata and J. gaumeri*	NA	60, 61
31	15-O-acetyl-15-epi-(4E)-jatrogrossidentadion	*J. curcas*	NA	62

molluscicidal, insecticidal and fungicidal properties (Table 1). The basic skeletal structures and chemical structures of diterpenes are illustrated in Figs. 1 and 2. Since this review addresses only diterpenoids from *Jatropha*, it should be realized that the plant is also able to synthesize other classes of terpenes and other

Table 1 continued

Sl. No.	Diterpenes	*Jatropha* species	Biological activities	References[a]
32	(14E)-14-O-acetyl-5,6-epoxyjatrogrossidentadion	*J. curcas*	NA	62
33	3β-acetoxy-12-methoxy-13-methyl-podocarpa- 8,11,13-trien-7-one	*J. curcas*	NA	62
34	3β,12-dihydroxy-13-methylpodocarpane-8,10,13-triene	*J. curcas*	NA	62
35	Jatropholone A	*J. isabelli*	Gastroprotection Cytotoxic Molluscicidal Antiplasmodial	33, 44, 55
36	Jatropholone B	*J. isabelli*	Gastroprotective effect molluscicidal	37
37	2α-Hydroxyjatropholone	*J. integerrima*	Antibacterial Antiplasmodial	55
38	2β-hydroxyjatropholone	*J. integerrima*	Antibacterial Cytotoxic	55
39	Curcasone A	*J. curcas*	Antiinvasive effects in tumor cells	63, 64
40	Curcasone B	*J. curcas*	Antiinvasive effects in tumor cells	63, 64
41	Curcasone C	*J. curcas*	Cytotoxic	63, 64
42	Curcasone D	*J. curcas*	Cytotoxic	63, 64
43	Jatropherol	*J. curcas*	Insecticidal Rodenticidal	67, 68
44	Japodagrol	*J. podagrica*	Antitumor	69

secondary metabolites. In the present review state-of-the-art information on the known diterpenes in *Jatropha* species is collated and discussed. In addition, an attempt has been made to highlight their important chemical and biological features with respect to agricultural and pharmaceutical applications.

Table 1 continued

Sl. No.	Diterpenes	*Jatropha* species	Biological activities	References[a]
45	Curculathyrane A	*J. curcas*	NA	70
46	Curculathyrane B	*J. curcas*	NA	70
47	(+) Jatrophol	*J. curcas*	NA	71
48	Multifolone	*J. multifida*	NA	53
49	Multifidone	*J. multifida*	Cytotoxic	72
50	Multidione	*J. multifida*	NA	73
51	*Jatropha* factor C1	*J. curcas*	Cytotoxic	13, 31, 32, 74, 81
52	*Jatropha* factor C2	*J. curcas*	Molluscicidal,	
53	*Jatropha* factor C3	*J. curcas*	Rodenticidal	
54	*Jatropha* factor C4	*J. curcas*		
55	*Jatropha* factor C5	*J. curcas*		
56	*Jatropha* factor C6	*J. curcas*		
57	Heudolotinone	*J. curcas*	NA	95, 96
58	Jatrophalactam	*J. curcas*	Cytotoxic	97
59	Faveline,	*J. phyllacantha*	Cytotoxic	98
60	Deoxofaveline	*J. phyllacantha*	Cytotoxic	98
61	Faveline methyl ether	*J. phyllacantha*	Cytotoxic	98
62	Phyllacanthone	*J. phyllacantha*	NA	99
63	Palmarumycin CP1	*J. curcas*	Antibacterial	100
64	Palmarumycin JC1	*J. curcas*	Antibacterial	100
65	Palmarumycin JC2	*J. curcas*	Antibacterial	100
66	(4Z)-Jatrogrossidentadion,	*J. grossidentata, J.wedelliana and J. podagrica*	Antibacterial Antifungal	45, 60
67	(4Z)- 15-Epijatrogrossidentadion,	*J. grossidentata, J.wedelliana and J. podagrica*	Antibacterial Antifungal	45, 60
68	Jaherin	*J. Zeyheri*	Antibacterial	101

NA not applicable

[a] Most relevant references listed. For comprehensive set of references, see relevant section

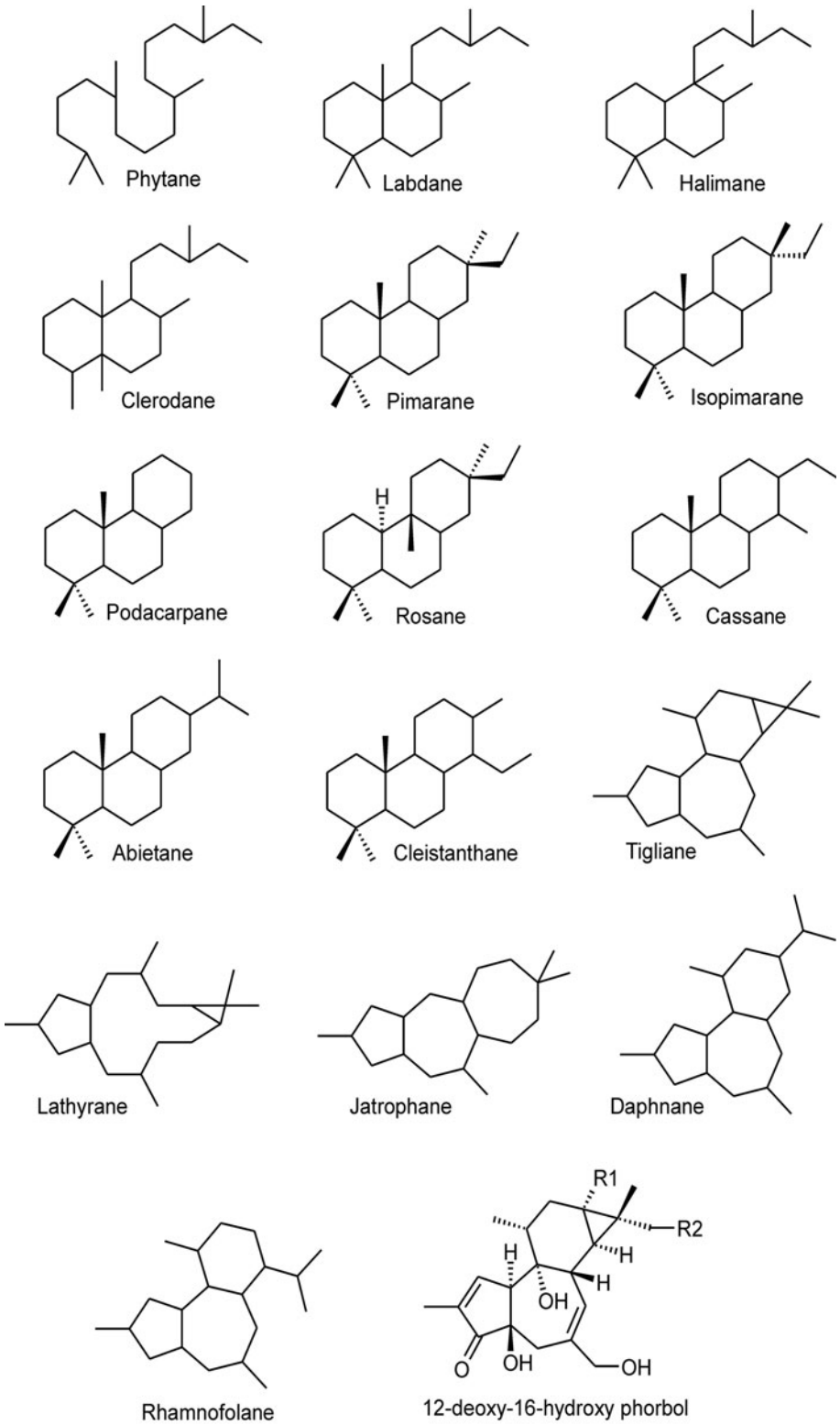


Fig. 1 Major basic skeletons of *Jatropha* diterpenes

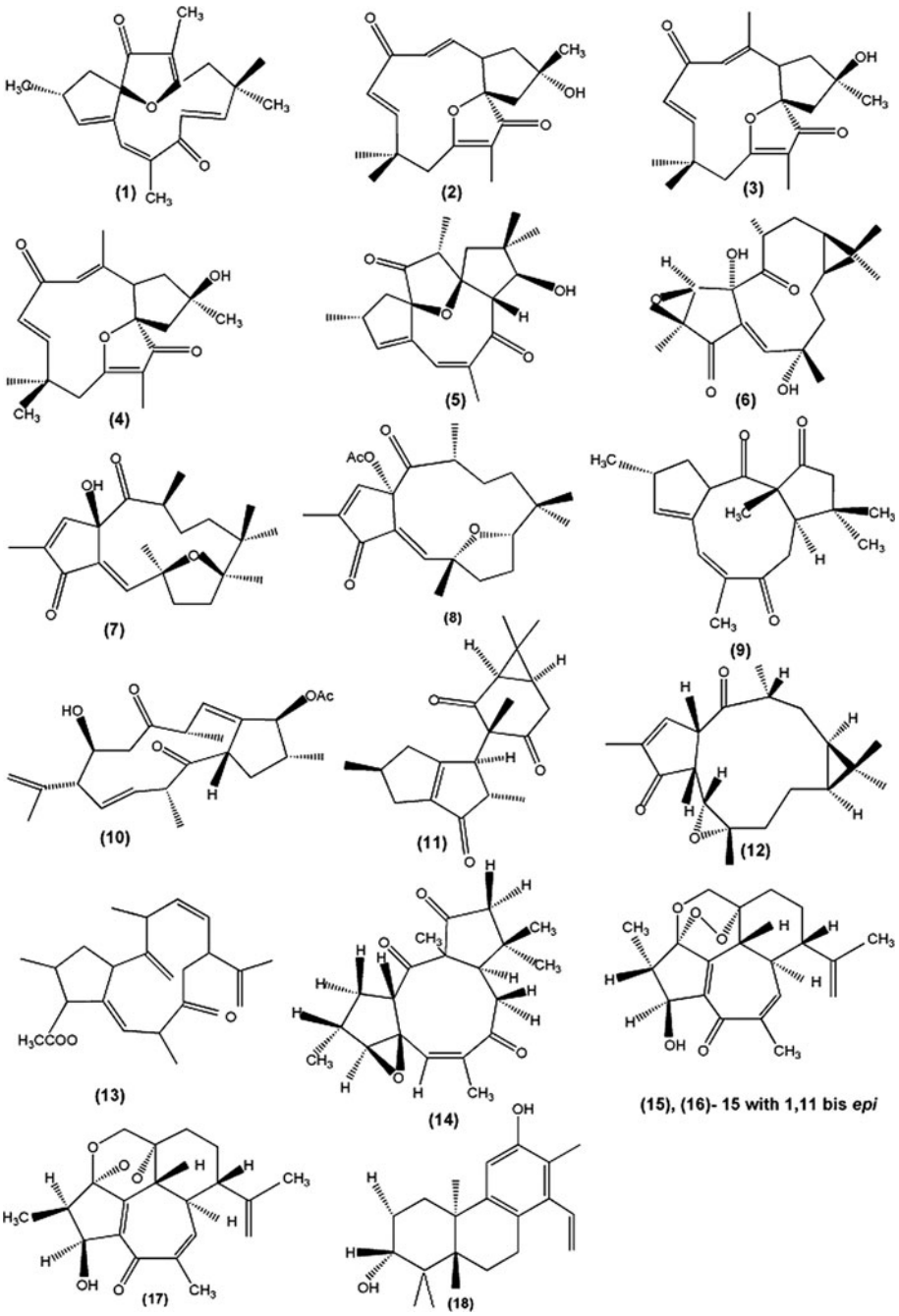


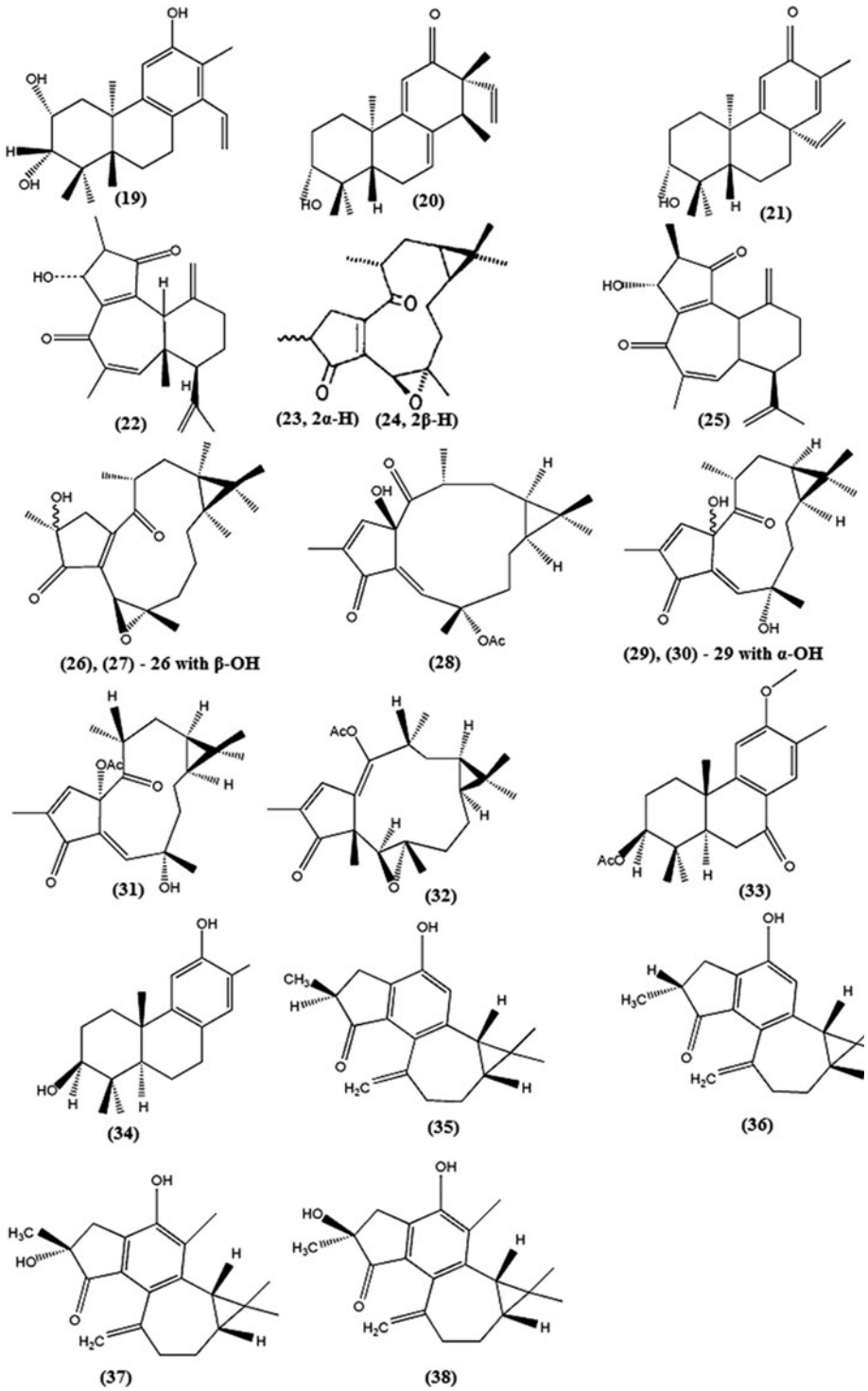
Fig. 2 Chemical structures of *Jatropha* diterpenes

Diterpenes from *Jatropha*

Jatrophone

Jatrophone (**1**, $C_{20}H_{24}O_4$, *M*r. 328.40) is a macrocyclic diterpene isolated from *J. gossypifolia* and *J. elliptica*. The natural derivatives of jatrophones, termed as hydroxyl jatrophones (2α-OH jatrophone (**2**), 2β-OH jatrophone (**3**, $C_{20}H_{24}O_4$, *M*r. 328.16) and 2β-OH-5, 6-isojatrophone (**4**, $C_{20}H_{24}O_4$, 328.16) were isolated from the roots of *J. gossypifolia*. Jatrophone and another diterpene, jatrophatrione were postulated as being derived from GGPP via oxidation of casbene. Jatrophone possesses multiple biological activities such as cytotoxicity, inhibition of insulin release, relaxation effect of induced muscle contraction, relaxant action in rat portal vein, inhibition of lymphocytes activation, anti-protozoal activity, inhibition of tumor cells, molluscicidal activity and gastroprotective effects [32–38]. Under basic conditions, upon treatment with small molecular weight thiols (*n*-propylthiol, mercaptoethanol and dithiothreitol) jatrophone undergoes a Michael addition reaction to the C8–C9 enone double bond

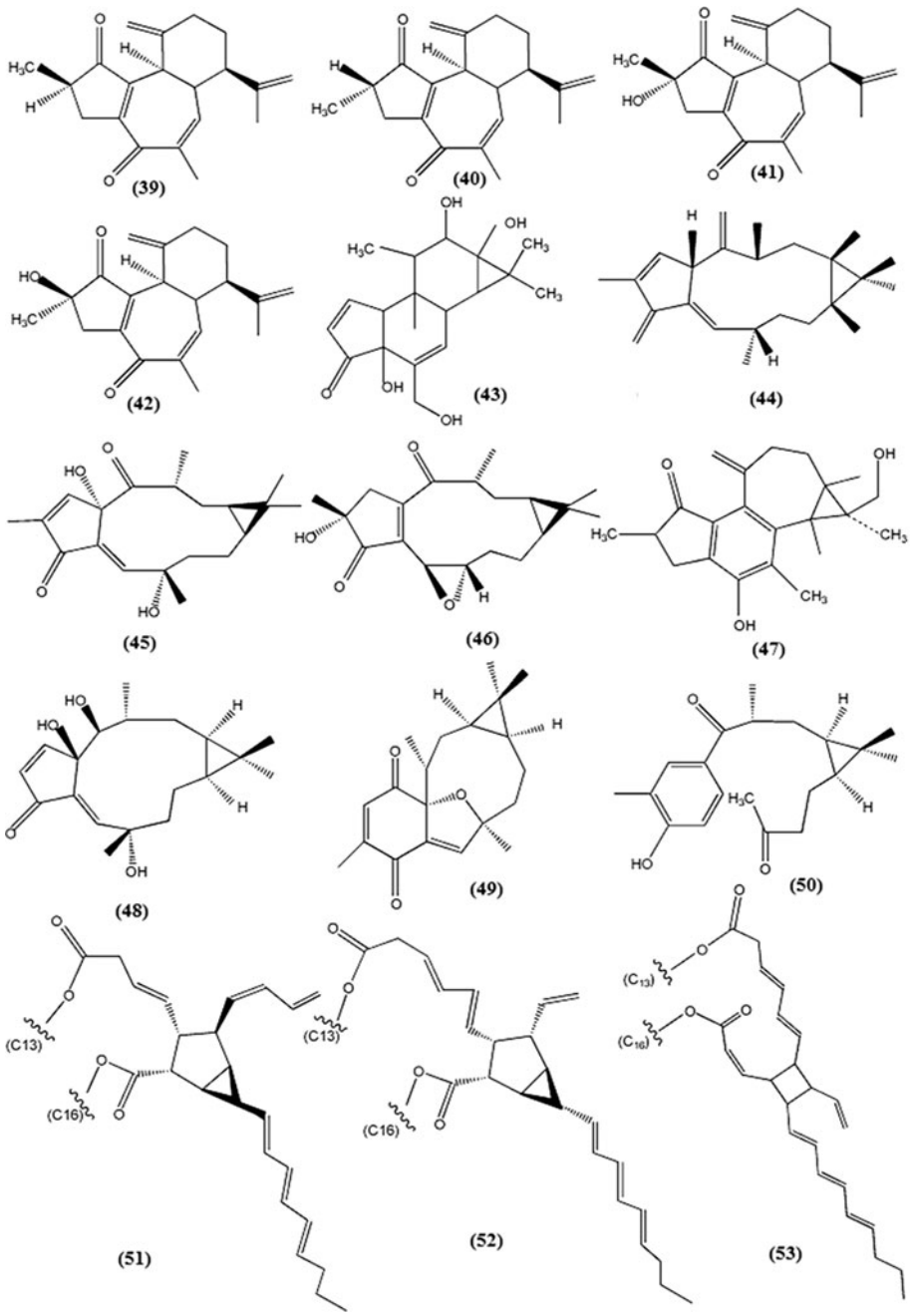
Fig. 2 continued



with concomitant transannular ring closure. In a similar way, it also reacts with thiol groups in proteins, such as bovine serum albumin and DNA dependent RNA polymerase from *Escherichia coli*. This susceptibility to nucleophilic conjugate addition was suggested to be responsible for the antitumor activity of jatrophone in vitro [35].

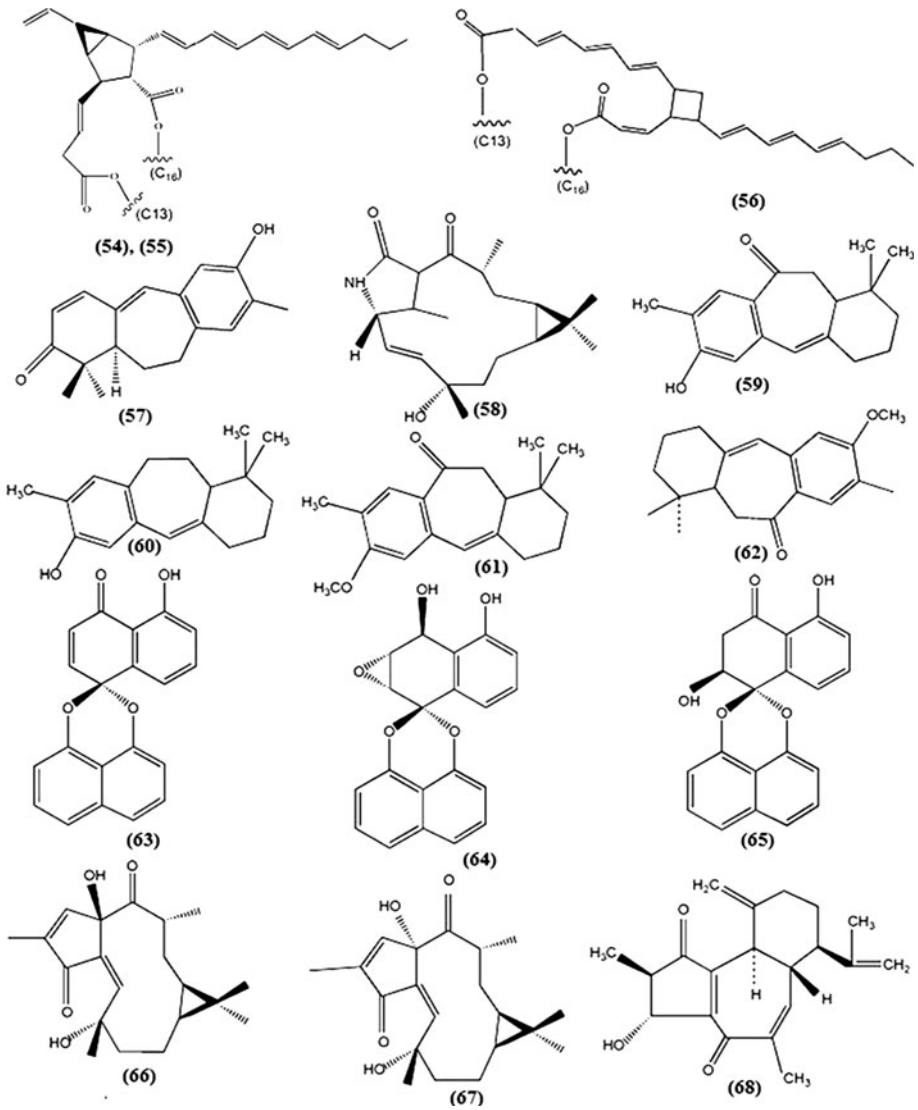
Jatrophone was also found to be cytotoxic (ED_{50} (Effective Dose), 0.01 μg/ml) in vitro against the P-388 lymphocytic leukemia test system and the activity was higher when compared to its hydroxyl derivatives, 2α-OH jatrophone (ED_{50}, 0.03 μg/ml), 2β-OH jatrophone (ED_{50}, 0.06 μg/ml), 2β-OH-5, 6-isojatrophone (ED_{50}, 2.2 μg/ml). Similar cytotoxic results of jatrophone was observed when

Fig. 2 continued



tested in Eagle's carcinoma of the nasopharynx test system in vitro (KB; ED_{50}, 87 pg/ml) when compared to 2α-OH jatrophone (ED_{50}, 0.16 μg/ml), 2β-OH jatrophone (ED_{50}, 0.07 μg/ml), 2β-OH-5, 6-isojatrophone (ED_{50}, 0.03 μg/ml). However, the information about the test reference compounds has not been reported [36]. A new jatrophone derivative 9β, 13α-dihydroxyisabellione (**5**) and jatrophone were isolated from the rhizomes of *J. isabelli* and evaluated for gastroprotective effects in mice. In brief, test samples were orally administered to mice prior to inducing a lesion by a solution mixture containing 0.3 M HCl/60% EtOH and the percentage of the reduction of the lesion was calculated by comparing with a control (12% Tween 80, vehicle). The anti-secretory drug, lansoprazole (20 mg/kg) was used as reference compound which exhibited a gastroprotective effect of 73%. Whereas, jatrophone elicited a strong gastroprotective effect (88%) at a dose of 25 mg/kg body weight, while 9β,13α-dihydroxyisabellione exhibited only 35% gastroprotection at a dosage of 25 mg/kg body weight in mice. However, jatrophone should be tested at <25 mg/kg body weight to ascertain effective gastroprotective dosage. Similarly, jatrophone also exhibited strong cytotoxicity towards fibroblasts and AGS cells with an IC_{50} (Inhibitory concentration) of 2.8 and 2.5 μM respectively, when

Fig. 2 continued



compared to 9β,13α-dihydroxyisabellione (IC_{50}, 87.5 and 200 μM respectively). The test reference compound lansoprazole exhibited cytotoxicity with an IC_{50} of 306 and 162 μM respectively against fibroblasts and AGS cells [37].

Against fibroblasts CCL-171, AGS CRL-1739, lung HTB-58, bladder HTB-1, leukemia CCL-240 jatrophone exhibited anti-proliferative effects (IC_{50} in μM): 0.29, 0.51, 1.8, 1.7 and 5.1 respectively. Whereas, for 9β, 13α-dihydroxyisabellione (IC_{50} in μM) was 35.9, 13.7, 33.3, 20.1, >100 (μM) respectively. The reference compound etoposide exhibited activity (IC_{50} in μM) at 3.9, 0.36, 2.5, 2.8 and 0.80 μM respectively [38]. Jatrophone (1–300 μM) caused a concentration-dependent relaxant effect on sustained contraction in rat uterine muscle induced by spasmogenic compounds (acetylcholine (Ach, 100 μM), oxytocin (Ot, 30 mlU/ml) and KCI (80 mM)). Jatrophone exhibited a relaxant effect with an IC_{50} (μM) in the order of potency, Ach (14.2) > Ot (19.0) > KCI (48.3). The relaxant effect of jatrophone was not modified by phorbol myristate acetate (10 nM, an activator of protein kinase C), forskolin (10 nM, an activator of adenilcyclase), 3-isobutyl-1-methylxanthine (10 μM, an inhibitor of phosphodiesterase), TMB-8 (10 μM, an inhibitor of intracellular calcium) and W-7 (10 μM, an inhibitor of calmodulin). The increased concentration of calcium (0.2–2 mM) in the medium also did not reverse the relaxation effect caused by jatrophone [39]. Menezes et al. [40] have reported the effect of jatrophone on insulin secretion. The insulin secretion measured in collagenase-isolated rat islets (in the absence of glucose) had 122 microU/islet per 90 min and in the presence of glucose (16.7 mM), 445 microU/islet per 90 min. In the presence of jatrophone, glucose-induced insulin release was inhibited with an ID_{50} close to 8 μM/l and complete inhibition was observed at 100 μM/l. At higher concentrations (100 μM/l) jatrophone also caused a reduction in glucose metabolism by the islets. The authors suggested that lower concentrations

(10 μM/l) of jatrophone could be used to study the mechanism of glucose or other secretagogues induced insulin release [40]. Silva et al. [41] reported that jatrophone, exhibited a vasorelaxant effect in rat portal vein contractions induced by phorbol 12-myristate 13-acetate (PMA, 0.1–3 μM)), noradrenaline (NA, 0.01–100 μM), endothelin-1 (ET, 0.01 −10 nM) or KCI (4–128 mM) with IC_{50} of 86 nM, 13, 11 and 9 μM respectively. Whereas, reference compounds staurosporine and H-7 (PKC inhibitors) also exhibited a relaxant effect (IC_{50}) induced by PMA (0.75 nM, H-7 was not tested), NA (25.23 nM, 7.6 μM) ET (35.31 nM, no effect) and KCl (28.45 nM, 0.92 μM) respectively; indicating that jatrophone was less potent than staurosporine and almost equipotent to H-7. Jatrophone (0.02–0.32 μM) exhibited an inhibition of human lymphocyte proliferation induced by phytohemagglutinin (5 μg/ml) or by 12-*O*-tetradecanoyl phorbol-13-acetate (TPA, 100 ng/ml) plus ionomycin (0.15 μM), with IC_{50} values of 53.4 nM and 48.4 nM respectively. It also inhibited murine lymphocyte proliferation stimulated by concanavalin A (5 μg/ml), with an IC_{50} value of 63.5 nM. In addition, jatrophone inhibited both spontaneous and TPA-stimulated natural killer activity and the expression of CD69, suggesting that the inhibition was not due to toxicity [42].

Jatrophone extracted from the rhizome of *J. elliptica* (Pohl.) was molluscicidal against the snail *Biomphalaria glabrata* with a (24 h) LC_{50} of 1.16 ppm, while the test reference compound (cupric carbonate) was effective at 50 ppm causing 100% mortality. It also inhibited (LC_{90}) egg mass production at 2.06 ppm, but the test reference compound was not reported [43]. In another study, after 24 h of infection with *L. amazonensis* (strain PH8), BALB/c mice were subcutaneously treated with jatrophone (25 mg/kg/day) for 13 consecutive days. At this concentration, jatrophone was highly active against the virulent strain when compared to the reference compound (*N*-methylglucamine antimoniate, 112 mg Sb^v per kg/day). However, jatrophone was too toxic in vivo at a dose of 25 mg/kg/day, rendering its use in chemotherapy of leishmaniasis. It also exhibited strong in-vitro antiprotozoal activity (IC_{100}, 5 μg/ml) against *L. brasiliensis*, *L. amazonensis* and *L. chagasi*; when compared to the IC_{100} of reference compounds glucantime (>100 μg/ml), ketoconazole (50 μg/ml) and pentamidine (1 μg/ml) [44].

The above in-vitro studies suggest that jatrophone could be targeted as a potential therapeutic agent as well as a bio control agent against schistosomiasis vector snails. However, systematic in vivo studies are needed.

Japodagrin and Japodagrone

Japodagrin (**6**, $C_{20}H_{28}O_5$, *M*r. 371.18) is a macrocyclic diterpenoid isolated from the root extracts of *J. podagrica*. It is also called 1, 2, epoxy-15-epi-4*E*-jatrogrossidentadion. Although the structure represents a lathyrane ring system, the compound has tri-substituted epoxide on C-1 and C-2. It exhibited antibacterial activity against *Bacillus subtilis* (ATCC 6051) and *Staphylococcus aureus* (ATCC25923) with an inhibitory zone of 16 and 12 mm at 20 μg/disk. The reference compounds, streptomycin and gentamycin (20 μg/disk) exhibited zones of inhibition with a diameter of 35 and 26 mm; and 34 and 28 mm respectively against *B. subtilis* and *S. aureus*. Another diterpene, japodagrone (**7**, $C_{20}H_{28}O_4$; *M*r. 332.19) isolated from the root extracts of *J. podagrica* also inhibited *B. subtilis* (ATCC 6051) with an inhibitory zone of 12 mm with a 20 μg/disk. The structure of japodagrone represents a jatrophane skeleton [45]. Similarly, Das et al. [46] have reported the presence of an acetyl derivative of japodagrone, 15-*O*-acetyl japodagrone in *J. multifida* (**8**, $C_{22}H_{30}O_5$, *M*r. 397.19).

Jatrophatrione

Jatrophatrione is a tricyclic diterpene (**9**, $C_{20}H_{26}O_3$, *M*r. 314.42) isolated from chloroform extracts of *J. macrorhiza* roots [47]. It has tumor inhibitory effect (0.5 mg/kg) and is particularly active against the in-vitro P338 (3PS) lymphocytic leukemia test system. Activity in the 3PS is defined as an increase in the survival of treated animals (T) over that of controls (C) resulting in a T/C >125%; Jatrophatrione 130% and 141% at 1 and 0.5 mg/kg, respectively. The test reference compound used in the experiment is not reported [47]. The mechanism of the action responsible for bioactivity is assumed to be similar to that of jatrophone, which is based on the similarity of spectral data between them. However, jatrophatrione lacks the enone double bond at C-8 and C-9 which covalently captures thiol groups in proteins [35, 47].

Jatrophenone and Riolozatrione

Jatrophenone is a macrocyclic diterpene (**10**, $C_{22}H_{30}O_4$) isolated from the dichloromethane:methanol extract of the whole plant (*J. gossypifolia*). The authors reported the presence of antibacterial activity against *S. aureus* comparable to the test reference compound penicillin G; but data has not been published. Another diterpene, riolozatrione (**11**, $C_{20}H_{26}O_3$, *M*r. 314.42) was extracted from the roots of *J. dioica*. Root extracts containing riolozatrione exhibited antibiotic activity against *S. aureus*. Riolozatrione may possibly arise from the rearrangement of lathyrol derivative or a macro cyclic precursor. It is based on the riolozane skeleton consisting of two five-membered rings sharing a common double bond. One five-member ring exhibits a flattened envelope conformation, while the other

containing an α,β-unsaturated ketone moiety is more planar. The double bond deviates from planarity by 6.5°. A cyclohexanedione moiety containing a fused cyclopropane ring is attached to the five-membered ring containing the keto function. The six-member ring exhibits a 1,2-diplanar conformation. The biological activity of purified riolazatrione has not been reported [48, 49].

Jatrowedione

Jatrowedione (**12**, $C_{20}H_{28}O_3$, *M*r. 317) is a lathyrane diterpene isolated from the stem extracts of *J. wedelliana*. The compound contains a tri-substituted double bond, two carbonyls, a tri-substituted epoxide, five methyls, three methylenes, five methines and a quaternary carbon. The structure of jatrowedione is similar to jatrogrossidione. However, the main structural difference is that jatrowedione lacks a hydroxyl group at C-15 when compared to jatrogrossidione. The biological activity has not been reported [50].

Integerrimene

Integerrimene is a macrocyclic diterpene (**13**, $C_{22}H_{30}O_4$, *M*r. 358.21) with a novel 8,9-*seco*-rhamnofolane skeleton isolated from the roots of *J. integerrima*. This class of diterpenes possibly arises biogenetically either from lathyrane type diterpenes by ring opening of the cyclopentane ring or from cembrane diterpenes via cyclization. Integerrimene is also a possible precursor of rhamnofolane by further condensation. The biological activity has not been reported [51].

Citlalitrione

Citlalitrione is epoxytrione diterpene (**14**, $C_{20}H_{26}O_4$, *M*r. 330.40) isolated from root and stem extracts of *J. dioica* and *J. integerrima*; and also from the dried whole plant material of *J. gossypifolia*. The structure is closely related to jatrophatrione/jatrophone, which include an unprecedented (5.9.5) tricyclic core. On the basis of close relationship to jatrophone which exhibits in-vitro antitumor effects, citlalitrione has received attention for the de novo construction of anticancer agents [52–54].

Caniojane derivatives

Caniojane (**15**, $C_{20}H_{24}O_5$, *M*r. 344.16), a diterpenoid containing a peroxide bridge, was isolated from *J. grossidentata*, *J. integerrima* and *J. curcas* roots. Whereas, 1,11-bisepicaniojane (**16**) and 2-epicaniojane (**17**, $C_{20}H_{24}O_5$, *M*r. 344.16) was isolated from a hexane extract of *J. integerrima* roots. All these are rhamnofolane diterpenoids. The caniojane and 1,11-bisepicaniojane are presumably formed by cyclo-addition of oxygen to 2-epi-jatrogrossidione from α and β side. Both caniojane and 1,11-biscaniojane comprise anti plasmodial activity against *Plasmodium falciparum* with an IC_{50} of 3.3 and 7.9 μg/ml respectively, whereas the test reference compound dihydroartemisinine was active at 4 nM (IC_{50}). In addition, caniojane was also cytotoxic against African green monkey kidney fibroblasts at 12.9 μg/ml (IC_{50}) and exhibited antituberculosis effect against *Mycobacterium tuberculosis* H37Ra with a minimum inhibitory concentration of 25 μg/ml. The test reference compound ellipticine and kanamycin was active at an IC_{50} (μg/ml) of 0.7 and 2.5 respectively for African green monkey kidney fibroblasts and *M. tuberculosis* [55].

Spruceanol and Cleistanthol

The spruceanol (**18**, $C_{20}H_{28}O_2$, *M*r. 300.2) and cleistanthol (**19**, $C_{20}H_{28}O_3$, *M*r. 316.44) belonging to cleistanthane series of diterpenes were isolated from acetone extracts of *J. divaricata* (aerial parts (stem/bark)) [56]. Spruceanol was reported to be responsible for cytotoxic and antitumor activity. However, the information on biological activity of these compounds isolated from *Jatropha* species is scarce compared to other Euphorbia plants. For example, spruceanol (SSC-312885) isolated from *Cunuria spruceana* displayed in-vitro anti leukemic activity (ED_{50}, 3.2 μg/ml) against the P-388 test system. The test reference compound has not been reported [57]. Similarly, both spruceanol and cleistanthol isolated from *Givotia madagascariensis* and *Phyllanthus* species displayed antitumor activity against HM02, Hep G2, MCF7 cells and also exhibited significant antioxidant properties with an IC_{50} of 0.29 and 0.12 mM, respectively [58, 59].

Pimarane diterpenes

The pimarane diterpenes, ent-3β, 14α-hydroxypimara-7,9(11),15-triene-12-one (**20**, $C_{20}H_{28}O_3$) and ent-15 (13 → 8) abeo-8β (ethyl) pimarane (**21**, $C_{20}H_{28}O_3$) were isolated from the aerial parts of *J. divaricata* [56]. No information is available on their biological activity.

Jatrogrossidione and Jatrogrossidentadione derivatives

Jatrogrossidione (**22**, $C_{20}H_{26}O_3$, *M*r. 314.189), was isolated from the roots of *J. grossidentata* [60]. Jatrogrossidione has a strong in-vitro leishmanicidal activity with an IC_{100}, of 0.75 μg/ml against all Leishmania strains (*L. amazonensis* strain (MHOM/GF/84/CAY H- 142), *L. brasiliensis* strain (MHOM/BR/75/M2903) and *L. chagasi* strain (MHOM/BR/74/PP75)) when compared to reference compounds glucantime, ketoconazole and pentamidine (>100, 50 and

1 μg/ml respectively). In in vivo, *L. amazonensis* (strain PH8) infected (24 h) BALB/c mice were subcutaneously treated with jatrogrossidione (25 mg/kg/day) for 13 consecutive days showed a reduction in the infection up to 1–5 weeks and was less effective from 5–8 weeks. However, at this concentration, jatrogrossidione was less effective and slightly toxic to the test animals when compared to the nontoxic reference compound (*N*-methylglucamine antimoniate, 112 mg Sb^v per kg/day). Jatrogrossidione also exhibited strong in-vitro trypanocidal activity against *T. cruzi* strains (IC_{100} of 1.5 μg/ml against Tulahuen strain and IC_{100} of <5 μg/ml against C8CL1, 1979CL1 and YC12 strains) when compared to reference compounds (≥25 μg/ml for both Nifurtimox and Benznidazole). It was also found to be toxic (in vitro) against amastigote forms of Leishmania infecting macrophages at <0.25 μg/ml (IC_{50}) [44]. In addition, Isojatrogrossidion and 2-epi-isojatrogrossidion ($C_{20}H_{28}O_3$, *M*r. 316.20) has been reported from the root extracts of *J. grossidentata*. However, no biological activity has been reported.

The rhamnofolane diterpene, 2-epi-Jatrogrossidione (**25**), isolated from roots of *J. gaumeri*, also exhibited antimicrobial activity (25 μg) against *B. subtilis* [61]. In addition, (4*Z*)-jatrogrossidentadion (**66**), (4*Z*)-15-epi-jatrogrossidentadion (**67**), 2-hydroxyisojatrogrossidion (**26**) and 2-epi-hydroxyisojatrogrossidion (**27**, $C_{20}H_{28}O_4$, *M*r. 332.199) were isolated from *J. grossidentata*, *J. wedelliana* and *J. podagrica*, respectively [60]. With 20 μg/disk, these compounds exhibited antibacterial activity against *B. subtilis* with a inhibition zone of 20, 17, 31 and 35 mm respectively, and against *S. aureus* with a inhibition zone of 10, 9, 21 and 26 mm, respectively.

The lathyrane diterpene, 4*E*-jatrogrossidentadione acetate (**28**, $C_{22}H_{30}O_5$) extracted from shade dried plant material of *J. multifida* has a close structural relationship with (4*E*)-Jatrogrossidentadione (**29**). The former is a monoacetyl derivative of the latter with two hydroxyl groups at C-6 and C-15 [53]. Another lathyrane diterpene 15-epi-4*E*-jatrogrossidentadione (**30**) was isolated from *J. grossidentata* and *J. gaumeri* [60, 61]. Likewise, four different diterpenes were isolated from the dried plant of *J. curcas.* The first diterpene is designated as 15-*O*-acetyl-15-epi-(4*E*)-jatrogrossidentadione (**31**, $C_{22}H_{30}O_5$) is a monoacetyl derivative of 15-epi-4*E*-jatrogrossidentadione and the second diterpene is designated as 14*E*-14-*O*-Acetyl-5,6-epoxyjatrogrossidentadione (**32**, $C_{22}H_{30}O_4$) was found to be structurally similar to **31** containing cyclopentenone and cyclopropane moieties. The main difference between **31** and **32** is that compound **32** contains an epoxide ring at C-5, C-6 (instead of a double bond at C-4, C-5) and contains tetrasubstituted double bond at C-14, C-15 with an acetoxy group at C-14 instead of a carbonyl group at C-14 in **31**. The other two diterpenes are 3β-acetoxy-12-methoxy-13-methyl-podocarpa-8,11,13-trien-7-one (**33**; $C_{21}H_{28}O_4$) and 3β,12-dihydroxy-13-methylpodocarpane-8,10,13-triene (**34**; $C_{18}H_{26}O_2$). The compound **33** has a dehydropodocarpane skeleton containing four methyl groups, acetoxy group at C-3β; and the acetoxy, the methyl, and methoxy groups were placed at C-12 and C-13 respectively in the ring C and a carbonyl group at C-7 respectively [62]. The compound **34** is a podocarpane diterpenoid similar to **33**, except that it had no acetoxy or methoxy group or any carbonyl group. It contains 2 hydroxyl groups (one at C-3 (β configuration) and the other at C-12) and the aromatic methyl group at C-13 [62]. The biological activity has not been reported.

Jatropholone

Jatropholones (**A** and **B**) which are the β and α C-16 isomers were isolated from *J. elliptica*, *J. grossidentata*, and *J. curcas*. Both jatropholone **A** (**35**) and **B** (**36**) differ remarkably in the gastro-protective activity in the HCl/EtOH-induced gastric lesions model in mice. Jatropholone **A** presented a dose-related response, with the maximum effect (54% lesion reduction) at the highest dose (100 mg/kg); whereas, jatropholone **B** showed a strong action at all the doses, reducing lesions by 83–91%. Further, the cytotoxicity of jatropholones was assessed towards fibroblasts and AGS cells. Jatropholone **B** was non-cytotoxic to both AGS cells and fibroblasts (>1,000 μM), while jatropholone **A** displayed a selective effect against AGS cells (IC_{50}, 49 μM) and nontoxic to fibroblasts (>1,000 μM). The test reference compound, lansoprazole exhibited a gastro-protective effect of 73% at 9.4 mg/kg, cytotoxic to AGS cells and fibroblasts at 162 and 306 (IC_{50}, μM). The biological effects of jatropholones **A** and **B** against AGS cells and gastro-protection were dependent on stereochemical characteristics, the presence of C-16 methyl group at the C-2 position [33]. In another study, Theoduloz et al. [38] reported that the jatropholones show anti-proliferative activity against fibroblasts CCL-171, AGS CRL-1739, lung HTB-58, bladder HTB-1, leukemia CCL-240. Jatropholone B exhibited anti-proliferative activity (IC_{50} in μM) at 0.29, 0.51, 1.8, 1.7 and 5.1 respectively. The reference compound etoposide exhibited (IC_{50} in μM) activity at 3.9, 0.36, 2.5, 2.8 and 0.80 respectively. Whereas, jatropholone A exhibited anti-proliferative effects (IC_{50} in μM) at a concentration of >100 (μM) against the above cell lines. In addition to the presence of C2 methyl group, free hydroxyl group at C14 found influencing the anti-proliferative effect [38]. A mixture of Jatropholone **A** and **B** extracted from the rhizome of *J. elliptica* was molluscicidal against the snail *B. glabrata* with an LC_{50} of 58.04 ppm [44]. Similarly, two other diterpenes (α-hydroxyjatropholone (**37**) and

2β-hydroxyjatropholone (**38**)) were isolated from the roots of *J. integerrima*. Both compounds were inactive against *M. tuberculosis* H37Ra. Jatropholone A, jatropholone B and α-hydroxyjatropholone were noncytotoxic; and 2β-hydroxyjatropholone was cytotoxic against African green monkey kidney fibroblasts (IC_{50}, 49.4 μg/ml). The test reference compound ellipticine was cytotoxic at 0.7 μg/ml [55]. Furthermore, jatropholone A and α-hydroxyjatropholone exhibited antiplasmodial activity against *P. falciparum* with an IC_{50} of 5.4 and 4.1 μg/ml respectively, when compared to the test reference compound dihydroartemisinine (IC_{50}, 4 nM). Whereas, both 2β-hydroxyjatropholone and jatropholone B were inactive against *P. falciparum* [55].

Curcusone

Curcusones are rhamnofolane diterpenoids ($C_{20}H_{24}O_2$, *M*r. 296.40) isolated from the roots of *J. curcas*. There are four types of curcusones (Curcusone **A** (**39**); Curcusone **B** (**40**): $C_{20}H_{24}O_2$, 296.408; Curcusone **C** (**41**): $C_{20}H_{24}O_3$, 312.40; Curcusone D (**42**)) belonging to the class of crotophorbolanes. They are structurally related; curcusones A and B, and curcusones C and D are epimeric pairs [63]. Curcusone B exhibited an anti-metastatic effect at nontoxic doses (10 μM) to KKU-100 cells (cholangiocarcinoma cell line). At this concentration, in-vitro invasion of KKU-100 cells was suppressed by 90%, mainly by suppressing cell motility and matrix metalloproteinase-2 (MMP-2) activities in the medium. Consequently, disruption of the actin cytoskeleton, reduction in myosin regulatory light chain phosphorylation and activation of PI3 kinase/Akt signalling was observed. The IC_{50} values (μM) for the curcusone B treated on KKU 100 cells survival, adhesion, invasion, motility and MMP-2 secretion were 25.1, 31.7, 5.7, 7.9 and 4.7 respectively. However, further studies are needed to elucidate the functional mechanism of Curcusone B as a anti-metastatic agent. Whereas, curcusone **C** and **D** were reported to have antifungal/antibacterial activity (*Botrytis cinerea*, *Rhizoctonia solani* and *B. subtilis*) even at low doses (50 μg) [64, 65]. Curcusone **A** and **C** are reported to enhance hyperthermic (V-79 cells) oncotherapeutics in Chinese hamster, suggesting anticancer activity [66].

Jatropherol

The ethanol extract from *J. curcas* seeds exhibited insecticidal activity. Further purification of this extract showed two diterpenes, **Ja2** and **Ja3** with extraction rates of 0.033% and 0.019% of the *J. curcas* seed weight. Both **Ja2** and **Ja3** caused high mortality in 3rd instar larvae of silkworms when exposed in food. Wherein, **Ja3** exhibited stronger toxicity than **Ja2** with an LC_{50} of 0.37 mg/ml [67, 68].

Jatropherol-I (**43**), a phorbol-type diterpene was extracted by ultrasonic extraction of the seeds and is present at a concentration of 0.039% seed weight. Jatropherol-I exhibited insecticidal activity against *Bombyx mori* L., *Lipaphis erysimi* and *Pieris rapae*. Bioactivity of Jatropherol I was higher against *B. mori* than *P. rapae*. After exposure to jatropherol-I for 72 h, LC_{50} in *B. mori* and *P. rapae* was 0.22 and 0.83 mg/ml, respectively; while AFC_{50} was 0.14 and 0.57 mg/ml, respectively. Jatropherol-I also exhibited contact toxicity against aphids with an LC_{50} of 0.11 μg/insect and 0.062 mg/ml, respectively. The antifeedant activity (AFC_{50}) to *L. erysimi* was 18 μg/ml. The oral toxicity of jatropherol-I to mice was 82.2 mg/kg body weight. The mechanism of action of jatropherol was suggested as being a result of activating protein kinase C (PKC). It was also found that PKC could be activated by jatropherol-I not only in vitro but also in vivo. In in vitro, Jatropherol-I increased the PKC activity of silkworm midgut cells (4.99-fold higher than that of the control at 100 μg/ml), and in vivo the PKC activity and the phosphorylation were enhanced with increasing dosages and time [67, 68].

Jatropherol-I isolated from *J. curcas* oil and seed kernel was also found highly toxic to third instar silkworm larvae after ingestion with LC_{50} values of 0.58, 0.22 and 0.16 mg/ml at 48, 72 and 120 h respectively. The acute toxicity was associated with changes in the activities of several midgut enzymes and pathological changes in midgut epithelial cells [67, 68].

Japodagrol

A new cytotoxic macrocyclic diterpenoid named Japodagrol (**44**, $C_{20}H_{28}0_4$, *M*r. 332.43), was isolated from *J. podagrica*. The compound contains inter- and intramolecular hydrogen bonds. The 5-membered ring is closed to a half-chair (pseudo-C2) form. It showed significant inhibitory activity in vitro against P-388 lymphocytic leukemia and KB carcinoma cell cultures (ED_{50}, 2.5 and 5.6 μg/ml respectively). The information on the test reference compound has not been reported [69].

Curculathyranes

These are lathyrane diterpenoids ($C_{20}H_{28}O_4$) isolated from *J. curcas*. Two types of curculathyranes have been reported (**A** and **B**) having the same general structure; the difference was the opening of the epoxide ring in curculathyrane **B** to give a second carbon–carbon double bond and a second alcohol moiety. The substitution patterns of curculathyrane **A** (**45**) and **B** (**46**), are supposed to be the biosynthetic precursors of the curcusones [70]. To the best of our

knowledge, information on the biological activity is not available.

Jatrophol

Jatrophol (**47**, $C_{20}H_{24}O_3$) was isolated from methylene chloride-hexane root extracts of *J. curcas* (4.8 mg% yield from dried roots). Although the structure is similar to jatropholone B, it differs by an additional hydroxy group at C-18 [71]. The biological activity has not been reported.

Multifolone

Multifolone is a lathyrane diterpene (**48**, $C_{20}H_{30}O_4$) extracted from the shade-dried plant material of *J. multifida*. The structure is closely related to 4*E*-jatrogrossidentadione but contains only one carbonyl at C-3 and 3 hydroxyl groups at C-6, C-14, C-15 [53]. Information on its biological activity is not available.

Multifidone

Multifidone is a lathyrane diterpene (**49**, $C_{20}H_{26}O_3$, *M*r. 337.17) isolated from the stems of *J. multifida.* It contains a characteristic six-membered **A** ring in contrast to a cyclopentane ring found in other lathyrane diterpenes of *Jatropha* species. Multifidone exhibited cytotoxic activity against four different cancerous cell lines; THP-1 (human acute monocytic leukemia), HL-60 (human promyelocytic leukemia), A-549 (human lung carcinoma) and A-375 (human malignant melanoma), with the potency, from higher to lower, in the order mentioned had an IC_{50} (μM) of 45.6, 120.7, 127.12 and159.05, respectively. The positive control (Etoposide) exhibited cytotoxicity (IC_{50}, μM) at 2.16, 1.83, 9.51 and 3.92 respectively [72].

Multidione

Multidione is a lathyrane diterpene (**50**, $C_{20}H_{28}O_3$, *M*r. 317.21) isolated from the stems of *J. multifida.* The compound has a phenolic moiety and a long side chain at C-4, structurally similar to the B ring of other lathyrane-diterpenoids such as (4*E*)-jatrogrossidentadione in *seco*-form. The side chain has four methyl groups, two carbonyl groups and a cyclopropane ring. The compound was suggested to be derived biogenetically from a related lathyrane diterpenoid [73]. The biological activity has not been reported.

Phorbol esters

Phorbol esters are diterpenes having a tigliane skeletal structure. Six phorbol esters (*Jatropha* factors **C1**–**C6**) have been characterized from *J. curcas* seed oil [74] and designated as **C1** (**51**), **C2** (**52**), **C3** (**53**), epimers **C4** (**54**) **and C5** (**55**) and **C6** (**56**), with the molecular formula $C_{44}H_{54}O_8Na$ (*M*r. 733.37). All isolated substances are intra-molecular diesters of the same diterpene, 12-deoxy-16-hydroxyphorbol (Fig. 1). *Jatropha* factor **C1** contains a bicyclohexane unit, a vinyl group, a nonatrienyl residue, and a single carbonyl ester chain at C-12. The factor **C2** differed from factor **C1** in the length of the carbon chain (C-6 in factor **C1** and C-8 in factor **C2**), the length of the ester chain connecting the bicyclohexane unit with C-13 (C-5 in factor **C1** and C-7 in factor **C2**), and the configuration at C-6 and C-8 in factors **C1** and **C2**, respectively. The epimers **C3** and **C4** share the same diterpene moiety as *Jatropha* factors **C1** and **C2**. *Jatropha* factors **C6** and **C3** contain a cyclobutane ring. The *Jatropha* factor **C6** differed from **C3** in having a trisubstituted cyclobutane unit rather than a tetrasubstituted unit in the latter and in the length of the ester chain at C-13 of the phorbol unit. *Jatropha* factors **C4** and **C5** were isolated as epimers. These two units differed from factor **C1** in length and the position of the carbon chains and the orientation of the bicyclohexane unit relative to the phorbol. The intra molecular diesters (**C1–C6**) were reported to be built from two separated monoester groups and the two dicarboxylic groups bound to the OH-13 and OH-16 of the phorbol moiety [13, 74].

Phorbol esters are amphiphylic molecules and have a tendency to bind phospholipid membrane receptors. During the normal signal transduction process, DAG (diacyl glycerol) activates PKC, which is involved in various other signal transduction pathways. The phorbol esters act as an analogue for DAG and are strong PKC activators. These phorbol esters hyperactivate PKC triggering cell proliferation, thus amplifying the efficacy of carcinogens. Phorbol esters are co-carcinogens which themselves do not induce tumors but promote tumor growth following exposure to a subcarcinogenic dose of carcinogen [13]. Apart from the co-carcinogenic activity, many phorbol esters (reported from other plant source) also exert beneficial biological effects without tumor promotion, such as prostratin [75]. Some naturally occurring phorbol esters are reported to be tumor inhibitors [76] and Phorbol 12-tigliate 13-decanoate has been shown to be active against the P 388 lymphocytic leukemia in mice [77, 78].

The concentration of phorbol esters in *J. curcas* varies with different genotypes ranging from 2 to 3 mg g^{-1} kernel and 2 to 4 mg g^{-1} oil from *J. curcas* [79]. In recent studies at our laboratory, a phorbol ester concentration in *J. curcas* oil as high as 8 mg g^{-1} has been observed (our unpublished data). Although phorbol esters are lipophilic, they get strongly bound to the matrix of kernel meal [80]. Studies in the last decade have shown that *J. curcas*

exhibits toxicity in a broad range of species, from microorganisms to higher animals [32]. The toxic effects studied in higher animals are mainly by force-feeding raw or defatted seed meals, leaves or their various organic solvent/aqueous extracts, since the animals do not consume them voluntarily. Li et al. [81] have reported that phorbol esters isolated from *Jatropha* had an LD_{50} of 28 mg/kg body weight in mice and the major target organs for the toxicity were liver, kidney, intestine and heart. Oral administration of oil had an LD_{50} of 6 ml/kg body mass in rats [82]. The rats exhibited diarrhoea, hemorrhagic eyes; and an autopsy showed inflammation of the gastro-intestinal tract [82]. *Jatropha curcas* oil at a dose of 2 g/kg body mass caused significant acute toxicity by inhibiting the birth of pups in rats [83]. The methanol:water (9:1) extracts of *J. curcas* oil exhibited skin toxicity towards rabbit (100 µl), mice and rats (50 µl). The common symptoms of topical application were erythema, edema, necrosis, scaling and thickening of the skins [82]. Feeding of *J. curcas* seeds, fruits or leaves caused toxicity depending on the dose and the animal species tested. Raw or defatted seeds when force-fed to fish, chicks, pigs, goat, mice and rats caused severe toxicity symptoms before death [84–88]. Various organic and aqueous extract also exhibited different toxic symptoms depending on dose, mode of administration and sensitivity of the animals being tested [89–91]. For example, acetonitrile extract of *J. curcas* (seed or oil) when given to Albino rats at an oral dose of 50 mg/kg body mass (single dose) produced mild toxicological, biochemical and histopathological changes [90–92]. The methanol, petroleum ether and dichloromethane extracts of *J. curcas* fruit caused fetal resorption, indicating pregnancy terminating effect in rats [93]. The irritant methanol fraction from *J. curcas* oil induced tumor promotion upon topical initiation by 7,12-dimethylbenz(*a*)anthracene (DMBA) in mice, with 36% of the animals having skin tumors in 30 weeks [94]. The detailed information about phorbol esters structure-bioactivity relationship is covered elsewhere [13].

Heudolotinone

It is a dinorditerpene (**57**, $C_{18}H_{20}O_2$) isolated from air-dried aerial parts of *J. curcas* and is supposed to be derived from an abietane skeleton [95, 96]. The biological activity has not been reported.

Jatrophalactam

Jatrophalactam is a lactam diterpenoid (**58**, $C_{20}H_{29}NO_3$, *M*r. 331.21) containing a unprecedented 5/13/3 tricyclic skeleton and is isolated from the roots of *J. curcas.* It is suggested to be biosynthesized from the diterpenoid, casbene. Jatrophalactam exhibited no significant inhibitory activity in vitro against human cancer cell lines A549 (human lung cancer), HT-29 (human colon cancer), and A431 (human epidermal squamous cell carcinoma) [97].

Faveline, Deoxofaveline and Faveline Methyl Ether

These are tricyclic benzocycloheptene derivatives isolated from the bark of *J. phyllacantha* (synonym: *Cnidoscolus phyllacanthus*). The deoxofaveline (**59**, $C_{18}H_{24}O$, *M*r. 256.18), faveline (**60**, $C_{18}H_{22}O_2$, *M*r. 270.16) and faveline methyl ether (**61**, $C_{19}H_{24}O_2$, *M*r. 284.17) exhibited cytotoxic activity against P-388 murine leukemia cells with an IC_{50} of 1.8, 18.6, and 1.0 µg/ml, respectively. The information about the test reference compound has not been reported [98].

Phyllacanthone

Phyllacanthone is isolated from a hexane extract of the trunk bark of *J. phyllacantha* (synonym: *C. phyllacanthus*). It is a bis-*nor* diterpene (**62**, $C_{19}H_{24}O_2$, *M*r. 284.19) having an isopisiferin type skeleton 2′3. The information about the test reference compound has not been reported [99].

Palmarumycins

Three Palmarumycins have been isolated from the stems of *J. curcas*. These are generally fungal metabolites. Palmarumycin **CP1** (**63**, $C_{20}H_{12}O_4$) is a spiroketal naphthoquinone. Palmarumycin **JC1** (**64**, $C_{20}H_{14}O_5$) is a closely related to palmarumycin **CP1**. The three aromatic rings in both the molecules were similar but the substitution pattern in the non-aromatic ring was different. They differed by the presence of a hydroxyl group and an epoxide linkage at C-1 and C-2, C-3 respectively. Palmarumycin **JC2** is a keto-hydroxy deoxypreussomerin (**65**, $C_{20}H_{14}O_5$). The structure is similar to **JC1** except hydroxyl group at C-1 in **JC1** has been oxidized to a keto group in **JC2**; and the presence of a hydroxyl group at C-3 instead of an epoxide linkage like in JC2. All these compounds (**CP1**, **JC1** and **JC2**) exhibited antibacterial activity at 30 µg/ml against *S. aureus* with an inhibition zone of 11, 10, 10 and 13 (diameter in mm) respectively [100].

Jaherin

Jaherin is a daphnane diterpene (**68**, $C_{20}H_{24}O_3$) isolated from *J. zeyheri*. It is a tricyclic dione alcohol having antimicrobial and antifungal properties. It is active against *S. pyogenes*, *Microsporum canis*, *Absidia corymbifera* and

Trichophyton rubrum. Information about the test reference compound has not been reported [101].

Constraints

Phytomedicines containing plant derived compounds have become (directly or indirectly) an important source for the discovery of many drugs. Despite the great diversity of compounds synthesized by plants, substantial qualitative and quantitative variations in the content of bioactive natural products were considered to be a disadvantage rather than an advantage in phytochemical drug discovery and therefore never fully exploited in pharmaceutical bio prospecting [102]. It is known that under stress conditions, varied geo-climatic conditions, microenvironments, harvest time and physical/chemical stimuli or elicitors could alter the content of bioactive secondary metabolites and impede isolation/characterization of interesting compounds [102, 103]. For example, some of the phytochemicals which are synthesized by enzymatic pathways are highly inducible, such as alkaloids, phenylpropanoids, and terpenoids [102]. However, considering the above factors, *Jatropha* phytochemicals appear to be poorly characterized and checked randomly for bioactivity, for example antitumor and antibacterial activities; and for the latter, less sensitive and non-specific assays or broad spectrum assays have been used. Also, the reported studies do not clearly mention important variables for the tested *Jatropha* samples such as location and their characteristic with respect to soil, temperature, precipitation, harvesting time, healthy or diseased state, among others, challenging the reproducibility of biological activities in relevance to the practical significance. The majority of the reported *Jatropha* diterpene bioactivity studies are targeted towards microbial susceptibility or cell viability when cell lines are used.

In addition, the validation and significance of the test methods used in the studies are questionable. The rapid screening of natural product mixtures requires the availability of a reference library of natural compounds and simple methods for the identification of putative lead compounds avoiding the potential for false-positive results. For example, microbial susceptibility assays, it is argued to have varied standards across many countries. There are reports discussing the disadvantages of disk diffusion method over the dilution method. However, the disk diffusion methods are justifiable only when followed using regulatory standards [104–107]. In many of the studies reporting on *Jatropha* diterpenes, the information about the regulatory standards, reference compounds and selection criteria of microbes used in the experiments are not mentioned. Thus, the antimicrobial activities reported for *Jatropha* diterpenes are questionable in the context of reproducibility. In the majority of the cases, the *Jatropha* diterpenes are primarily evaluated to ascertain their bioactivity, at a dose which is beyond practical applicability or lacks comparison with the standard active compounds.

Similarly, cell-based assays are usually chosen for drug discovery. These assays measure the growth inhibition effect of the test compound on a particular cell line. The preliminary information on compound cellular penetration and toxicity can be obtained using cell-based assays [108]. Baker et al. [108] have also reported that the cell-based activities are less sensitive, more variable, resource intensive with respect to time and even cytotoxic effects of interested compounds may mask a more specific activity indicating the disadvantage of cell-based assay methods. Many of the *Jatropha* diterpenes studied for cytotoxicity and antitumor properties using cell lines lack the proper reference compounds. The reference compounds hold particular importance in expressing effective nature as well as practical applicability of the compounds.

Although, the bioactivities from plant extracts (such as seed, roots and leaf extracts) have not been discussed in this review, their use (either in a formulation or alone) could be advantageous and cost effective in agriculture in tackling pests and insects [32, 109–113]. The requirement of considerable resources during isolation and purification hinders the use of purified plant compounds in pesticides/insecticides over synthetic compounds or plant extracts.

The discovery of any drug (of natural or synthetic origin) is not an easy task. Generally, subsequent to isolation and purification, the compounds or a mixture are primarily screened for potential bioactivity, either through an arbitrary cut-off, or by comparing them with known biological marker compounds. The novel active components (extracts or compounds) are referred to as "hits". The potential "hit" compounds are further subjected to chemical and biological evaluation to obtain the compounds of higher priority termed as a "lead" compound. A "lead" compound is a compound which has well-defined purity, possesses genuine structure–activity relationships for the target assay(s), has a well-defined minimum structure for activity, has a selective activity among many other factors. The promising lead compounds are further evaluated in humans categorized as Phase I, Phase II and Phase III clinical studies (usually taking 4–7 years). After meeting the standard regulations (e.g. FDA), the effective compound (alone or in combination with other compounds or as a formulation) is marketed and observed for efficacy and long-term side effects (Phase IV) [114, 115]. Considering the above requirements, the *Jatropha* diterpenes reported can be regarded as "hits" and point out the need for more specific standard target assays to elucidate potential lead compounds. Despite the problems, extensive studies on

Jatropha diterpenes are needed to fully exploit the pharmaceutical and agricultural possibilities.

Conclusions

The use of *Jatropha* species in ethno medicines has led to the search for new bioactive molecules of pharmaceutical or agricultural importance. Of the many *Jatropha* species, only a few have been extensively researched for bioactive compounds such as diterpenes. Most of the diterpenes isolated were obtained in the search for new bio-control agents and their definite natural roles in plants remain to be discovered. The isolated diterpenoids exhibit diverse biological activities in vitro. Jatrophone, jatrophatrione, spruceanol, cleistanthol, curcusones (A and B) and japodagrol posses in-vitro antitumor activities. The hydroxy derivatives of jatrophones, jatropholones, curcusones, multifidone, jatrophalactam and faveline are cytotoxic. The caniojane derivatives, jatrogrossidione, hydroxy jatropholones, palmarumycin, jaherin and jatrogrossidentadion exhibit antimicrobial activities. Recent advances in analytical chemistry have also led to the identification and comparison of the novel chemical structures of these diterpenes, which could also be used as a template for the synthesis of new diterpene derivatives with modified functional and physical properties. In addition, phorbol type diterpenes (*Jatropha* factor C1-C6 and jatropherol) isolated from *Jatropha* species have rodenticidal, piscicidal, molluscicidal and insecticidal activities, indicating their potential as bio-control agents. However, more specific target-based studies are required to exploit the potential of *Jatropha* diterpenes in agro/pharmaceutical applications.

The abundance and novelty of diterpenes present in the *Jatropha* species could form a new 'feedstock' for the pharmaceutical industries. The maximum utilization of these bio molecules could only be possible if the pharmaceutical industry gets continuous feedstock supplies in the future. In recent years, increased interest in the utilization of non-edible *Jatropha* seed oil as a feedstock for biodiesel production has encouraged many developing countries to cultivate *Jatropha* on an industrial scale. By 2015, approximately 12.8 million hectares of land is projected to be under *Jatropha* cultivation [116]. This would generate a huge amount of raw materials for both biodiesel and the pharmaceutical industries. The symbiotic existence among agro-pharmaceutical-biofuel industries could open new avenues for the sustainable eco-friendly development.

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