

SECONDARY METABOLITE COMPOUNDS FROM JATROPHA SPECIES

A Review by Carla W. Sabandar

Several secondary metabolite compounds from some *Jatropha* species were successfully isolated and identified. Biological activities of some compounds were examined and validated that made *Jatropha* species become interest for researchers and society, recently.

***Jatropha curcas* Linn.**

J. curcas Linn. is a small tree or large shrub, which can reach a height of three to five meters, but under favorable conditions it can attain a height of 8 or 10m. The plant shows articulated growth, with morphological discontinuity at each increment. The branches contain latex. Normally, five roots are formed from seedlings, one central and four peripheral. A tap root is not usually formed by vegetatively propagated plants. Leaves five to seven lobed, hypostomic and stomata are of paracytic (Rubiaceous) type [1]. The trees are deciduous, shedding the leaves in dry season. Flowering occurs during the wet season and two flowering peaks are often seen, i.e. during summer and autumn. In permanently humid regions, flowering occurs throughout the year. The inflorescence is axillary panicle polychasial cymes. The plant is monoecious and flowers are unisexual; occasionally hermaphrodite flowers occur [2]. A flower is formed terminally, individually, with female flowers (tricarpellary, syncarpous with trilobular ovary) usually slightly larger and occurs in the hot seasons. In conditions where continuous growth occurs, an unbalance of pistillate or staminate flower production results in a higher number of female flowers. Ten stamens are arranged in two distinct whorls of five each in a single column in the androecium, and in close proximity to each other. In the gynoecium, the three slender styles are connate to about two-thirds of their length, dilating to massive bifurcate stigma [2]. The rare hermaphrodite flowers can be selfpollinating. The flowers are pollinated by insects especially honey bees. Each inflorescence yields a bunch of approximately 10 or more ovoid fruits. With good rainfall conditions nursery plants may bear fruits after the first rainy season, and directly sown plants after the second rainy season. Three, bivalve cocci is formed after the seeds mature and fleshy exocarps dry. The seeds mature about 3-4 months after flowering. The seeds are black and the seed weight per 1000 is about 727g, there are 1375 seeds/kg/in the average [1]. *J. curcas* Linn. is cultivated as a medicinal plant in many tropical and subtropical countries. It is suitable for preventing soil erosion and shifting of sand dunes. Various parts of the plant hold potential for use as a source of oil, animal feed or medicinal preparations. Recently, their seeds were investigated mainly as a potential source of oil that was recognized as an adequate substitute motor fuel [3].

Ethyl acetate extracts of leaves of *J. curcas* Linn. contain a complex of 5-hydroxypyrrolidin-2-one and pyrimidine-2,4-dione (uracil) [4]. The seed kernels of *J. curcas* Linn. were rich in crude protein, CP (31-34.5%) and lipid (55-58%). The major fatty acids found in the oil were oleic (41.5-48.8%), linoleic (34.6-44.4%), palmitic (10.5-13.0%), stearic (2.3-2.8%), *cis*-11-eicosenoic and *cis*-11,14-eicosadienoic acids [5]. Seed oil contains 12-deoxy-16-hydroxyphorbol (**1**) belonging to phorbol ester which has tumor-promoting activity [6]. The common diterpene 12-deoxy-16-hydroxyphorbol in six different diterpene esters from the *J. curcas* Linn. oil have been determined using HPLC methods which were named as *Jatropha factors* C1 to C6 (**2-7**) [7]. From the latex of *J. curcas* Linn., a novel cyclic octapeptide was

isolated and named curcacycline A (**8**) which displays a moderate inhibition of classical pathway activity of human complement and proliferation of human T-cells [8], curcacycline B (**9**) [9], jatrophidin I (**10**) [10] has antifungal activity, and pohlianin A (**78**) [11] has antifungal and antimalarial activity [10]. Diterpene compounds such as tigliane (**11**), jatrophone (**12**) and dinorditerpene (**13**), 3-*O*-acetylaeuritolate acid (**14**), a triterpenoid have been identified from this plant [12]. The roots of *J. curcas* Linn. is a rich source of diterpenes of the daphnane and lathyrane skeletons [13]. From hexane extract of this plant well known jatropholones A (**15**), B (**16**) [14], curculathyrane A (**17**) and B (**18**), and curcusone A-D (**19-22**) [13]. Polar fraction of crude extract of the roots of *J. curcas* Linn. contains propacin (**23**), (+)-jatrophol (**24**), (+)-marmesin (**25**) and jatrophine (**26**) [13]. Two type of lathyrane, 15-*O*-asetil-15-*epi*-(4*E*)-jatrogrossidentadione (**27**) and isojatrogrossidentadione (**28**) and two podocarpanes, 3 β -acetoxy-12-methoxy-13-methyl-podocarpa-8,11,13-triene-7-one (**20**) and 3 β ,12-hydroxy-13-methyl-podocarpa-8,10,13-triene (**30**) have been isolated and identified from aerial part of *J. curcas* Linn. [15]. Compound 5 α -stigmastane-3,6-dione (**31**), β -sitosterol (**32**), stigmasterol (**33**), taraxasterol (**34**), daucasterol (**35**), nobiletin (**36**), 5-hydroxy-6,7-dimethoxycoumarin (**37**), 6-methoxy-7-hydroxycoumarin (**38**), 3-hydroxy-4-methoxybenzaldehyde (**39**), 3-methoxy-4-hydroxybenzoate acid (**40**), glyceride-1, 2*S*-tetracosanoate acid (**41**) and caniojane (**42**) have been isolated from the roots of *J. curcas* Linn. [14].

Aqueous extracts of leaves of *J. curcas* Linn. were evaluated for antihelmintic activity on adult Indian earthworms *Pheretima poshtuma* that indicated significant activity [16]. Methanolic extract of this plant has shown antiulcer activity on aspirin-induced gastric lesions in Wistar rats [17]. The *in vitro* antimicrobial activity of crude ethanolic, methanolic and water extracts of the stem bark of *J. curcas* Linn. against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Streptococcus faecalis*, *Staphylococcus epidermidis*, *Shigella dysenteriae*, *Micrococcus kristinae*, *Klebsiella pneumonia*, *Bacillus cereus*, *Bacillus subtilis*, *Proteus vulgaris* dan *Serratia marcescens* were investigated [18]. Toxicity of seed oil of *J. curcas* Linn. was evaluated against *Callosobruchus maculatus* insects dan its parasite, *Dinarmus basalis* [19]. The research of nickel toxicity induced in *J. curcas* Linn. has shown a correlation between responses of antioxidant enzymes as well as PAL activities and nickel concentrations in *J. curcas* Linn. cotyledons. The lower nickel concentrations and higher *superoxide dismutase* (SOD), *peroxidase* (POD), *catalase* (CAT) dan *phenylalanine ammonia lyase* (PAL) activities suggest the tolerance capacity to protect the plant from oxidative damage [20].

***Jatropha chevalieri* Beille.**

Isolation compound of latex of *J. chevalieri* has resulted cyclic peptide, chevalierin A (**43**), B (**44**) and C (**45**). Compound **43** was evaluated that has antimalarial activity with IC₅₀ 8.9 μ M [21].

***Jatropha elliptica* (Pohl) Müll. Arg.**

J. elliptica (Pohl) Müll. Arg., a shrub annual herb distributed throughout the North and the West of Brazil and has been reported to possess several medicinal properties [22,23,24]. *J. elliptica* is used in the folk medicine for treatment of neoplasia, inflammation, ulcers and diuretic diseases among others [24]. The ethanolic extract of root has shown molluscicidal activity [12].

A penta-substituted pyridine namely diethyl 4-phenyl-2,6-dimethyl-3,5-pyridinecarboxylate (**46**) was assayed for *in vitro* antibacterial and resistance-modifying activity against strains of *S. aureus* possessing the MsrA and NorA resistance efflux mechanisms. Antibiotic efflux studies indicated that the title compound acts as an inhibitor of the NorA efflux pump and restores the level of intracellular drug concentration [12]. This compound was isolated from rhizomes of *J. elliptica* which has crystal structure was monoclinic ($P12_1/n1$ (no.14), $a = 11.204 (5) \text{ \AA}$, $b = 8.368 (5) \text{ \AA}$, $c = 18.817 (5) \text{ \AA}$, $\beta = 99.366 (5)^\circ$, $V = 1740.7 \text{ \AA}^3$, $Z = 4$, $R_{gt}(F) = 0.054$, $wR_{ref}(F^2) = 0.154$, $T = 293 \text{ K}$) [25]. Isolation compound of the roots of *J. elliptica* has resulted diterpenoid compound **12**, **14**, **15**, **16**, **23**, pentatriacontanyl ferulate (**47**), fraxetin (**48**) and mixtures of compound **32** and **33** [26]. Compound **12**, extracted from *J. elliptica* inhibited [^3H]glutamate binding. These results may indicate a neurochemical parameter possibly related to the antinoceptive activity of these natural compounds [27]. Several biological activities have been reported for **12**, including the molluscicidal effect [24], reaction of biological thiols (inhibition tumor activity) [28], interaction with sRNA from Escherichia coli [29], inhibition of insulin release [30], relaxation effect of induced uterine contraction [31], relaxant action in rat portal vein [32], inhibition of lymphocytes activation, probably through inhibition of the protein kinase C pathway [33], antiprotozoal activity [34], antileishmanial activity [35], antileukemic activity against P-388 lymphocytic leukemia at 27 and 12 mg/kg cytotoxicity (ED_{50}) against KB cell culture at $0.17 \mu\text{g/ml}$ [36].

***Jatropha gaumeri* Greenm.**

Isolation of secondary metabolite compound from roots extract of *J. gaumeri* was obtained as 2-*epi*-jatrogrossidione (**49**), a rhamnofolane diterpene and 15-*epi*-4*E*-jatrogrossidentadione (**50**), a lathyrane diterpene. Compound **49** has antimicrobial activity and **50** without biological activity. Crude leaf extract of *J. gaumeri* contains compound **32**, **34**, triterpenes α -amyrin (**51**) and β -amyrin (**52**), which responsible for the antioxidant activity.

***Jatropha gossypifolia* Linn.**

J. gossypifolia (synonym: *Adenoropium gossypifolia* Pohl, *J. elegans*) belonging to the family Euphorbiaceae [38] is a shrub herb, height 1.8 meter, gregarious with palmately 3-5 lobed leaves and dark red, crimson or purplish flowers. Leaf margins, petioles and stipules are covered with glandular hairs [39]. *J. gossypifolia* is grows naturally almost entire tropical area in the world [40]. This plant is a native of Brazil, naturalized in many parts of India. It grows on nearly all type of soils within its range. It is common in waste lands, roadsides, poorly tended agricultural fields and river overflow area [41]. Another opinion said that *J. gossypifolia* is native to the Carribbean and tropical America but is now widespread throughout the tropical world. It has been listed as a weed in India, Brazil, Jamaica and Trinidad [42]. Flowering in India occurs from February through July. Sometimes both flowers and fruits will be present at the same time on plant. Upon drying, the capsule valves spring open propelling the seeds a few centimeters [41].

J. gossypifolia is reported to be beneficial to dyscrasia, anemia, vertigo and dysphonia [38]. It is an antibiotic, insecticidal and used in toothache and act as blood purifier [43]. The leaves are employed to carbuncles, eczema and itches, act as purgative and swollen. A decoction of the leaves is useful for stomachache, venereal disease and as blood purifier [44]. The leaves, either in decoction or boiled like

spinach, as a purgative remedy for 'dry belly-ache'. It is used to prepare tea for constipation, the part used not being specified but it is probably the leaves [45]. Extracts of the plant are used as a purgative and emetic, and to treat headache, diarrhea, venereal disease, skin sores, mouth sores and cancer [40]. The seed are used to purgative, its oil similar to Castrol oil (*Jatropha*) [45]. The use of the seeds in herbal medicine is advised against because of their high toxicity [46]. The seed oil is used as an emetic, purgative and stimulant. It is also applied for ulcers and leprosy and is beneficial in adenites and worm infestation [44]. The roots are recommended for leprosy and as an antidote for snake bite [38]. *J. gossypifolia* in many country is used as medicinal plant, variously. In India, it is used to treat diarrhea [47] and the roots are employed to dysentery [48]. Decoction of *J. gossypifolia* in Trinidad are beneficial to treat wound and reduce pain. This beneficial similar to etnoveterinary remedies by certain hunter to treat snakebites, scorpion stings, for injuries and mange of their dogs [49]. Ethnomedicine use in Tobago and Trinidad are to treat snatch wound, sores and swollen [50]. In Ghana, decoction of leaves of *J. gossypifolia*, *Combretum ghaselensis* and the whole part of *Ocimum canum* are used to malarial [51]. In Ekiti, Nigeria, *J. gossypifolia* were cultivated to serve as boundary plants, erosion control and healing of mouth cancer [52]. In Southern Nigeria, the extract from fresh leaf applied with crushed leaf is routinely used by herbalists and local people to stop bleeding from the skin and nose [53,54] and in Suriname, the fruits are used as a purgative [55].

Ogundare *et al.* [39] has been reported the antimicrobial activity of leaves extracts of *J. gossypifolia* against 10 microorganisms (*E. coli*, *B. subtilis*, *Salmonella typhi*, *S. aureus*, *Proteus mirabilis*, *Carynebacterium diptheriae*, *P. aeruginosa*, *S. dysentriae*, *S. pneumonia*, *Candida albicans*), which shown inhibition against *S. typhi*, *S. aureus*, *P. aeruginosa* and *C. albicans*.

Compounds belonging to diterpenoid have been isolated from the whole plant were citlalitrione (**53**) [56] and jatrophenone (**54**) [57]. Compound **54** was found to posses antibacterial activity against *Staphylococcus aureus*. Its activity was comparable to that of the standard compound, penicillin G [57]. A coumarino-lignoid, propacin (**23**) also was obtained [58]. The seed oil of *J. gossypifolia* contains a phorbol ester, **1** was found to posses activity as a tumor-promoter [6]. Two lignans have been isolated from *J. gossypifolia* was gossypidien (**55**) [60] that isolated from its stems and gossypifan (**56**) [61] that isolated from aerial parts of this plant. A coumarino-lignoid, cleomiscosin (**57**) was obtained by soxhletation with hexane and ethyl acetate [62]. Furthermore, two lignins namely isogadain [(+)-savinin or hibalactone] (**58**) [63] and diester jatrodien (**59**) [64]. Catechin [**60**] also isolated from its stems bark. The latex contains cyclogossine B (**61**) [65], a cyclic octapeptide. Cyclogossine A and B was possessed to antimalarial activity [50]. Chemicals composition of lipid extracts of leaves of *J. gossypifolia* (Table 2) have been identified by GC-MS [59]. The roots of *J. gossypifolia* contains **12** [66], **15** and **16** [26]. Biotransformation of **12** by *Aspergillus niger* ATCC (American Type Culture Collection) 16404 afforded the new diterpene 9 β -hydroxyisabellione (**62**) [67]. The cytotoxicity of the compounds as IC₅₀ values on AGS and lung fibroblasts was 2.4 and 2.8 μ M for **12** and 53.1 and 260 μ M for **62**, respectively [62]. Chemicals composition of lipid extracts of leaves of *J. gossipifolia* are propanoid acid, glycerol, 2-pentenoic acid, arabitol, 3,7,11,15-tetramethyl-2-hexadecene-1-ol, D-xylofuranose, D-mannitol, hecadedcanoid acid, inositol, oleic acid, octadecenoic acid, octacosan, octacosanol, stigmasterol, α -Sitosterol, α -Amyrin, Lup-20(29)-en-3-on and betulin [59].

***Jatropha grossidentata* Pax et Hoffm.**

J. grossidentata Pax et Hoffm. is a shrub known as 'Caniroja' by the Ayoreo Indians living in the central-northern part of the Paraguayan Chaco. The powdered roots are smoked in shamanic practices [68]. The petroleum ether and ethyl acetate extract of *J. grossidentata* roots showed *in vitro* activity against *Trypanosoma cruzi* and *Leishmania* strains at 10 µg/mL. Several diterpenes have been isolated from the roots, the main compound being the rhamnofolane jatrogrossidione (**49**) [69,70]. Compound **49** showed a strong *in vitro* leishmanicidal and trypanocidal activity with IC₁₀₀ of 0.75 and 1.5-5.0 µg/mL, respectively.

***Jatropha integerrima* Jacq.**

J. integerrima Jacq. (syn. *J. pandurifolia* Andr.) is a shrubby tree of which the medicinal properties have not been reported. Its latex is however known to be toxic. The leaves, if accidentally chewed can cause squeamish, stomachalgia and can be very purgative [71]. CH₂Cl₂ extracts of latex of *J. integerrima* contains two new cyclic heptapeptides, integerrimides A (**63**) and B (**64**). Both peptides **63** and **64** at 50 µM inhibited to a certain degree cell proliferation of human ICP-298 melanoma cells, as well as cell migration of human Capan II pancreatic carcinoma cells, both both compounds were inactive in HSV-1, antifungal and antimalarial assays [71]. The roots of *J. integerrima* contains rhamnofolane endoperoxide 2-epicaniojane together with caniojane and 1,11-bisepicaniojane (**65**) and integerrimene (**66**), a 8,9-seco-rhamnofolane skeletons and a possible biogenetic precursor [72].

***Jatropha multifida* Linn.**

Latex of *J. multifida* contain a novel non-cyanogenic cyanoglucoside, 1-cyano-3-β-D-glucocyranosyloxy-(Z)-1-methyl-1-propene was named multifidin A (**67**) [73]. Previously, isolation of multifidol (**68**) and its glucoside (**69**) [74], two cyclic peptides, labaditin (**70**) [75], a cyclic decapeptide and biobollein (**71**) [76], a cyclic nonapeptide have been reported.

***Jatropha podagrica* Hook.**

Tetramethylpirazine (TMPZ) [77] is an alkaloid found in *J. podagrica* that causes vasodilation [78] and reduces thrombosis [79]. The roots of *J. podagrica* contains a new aliphatic acid named japodic acid (**72**) with a gem-dimethyl cyclopropane ring [80]. Compound **72** showed mild insect growth inhibition activity against *Helicoverpa zea* and were inactive in the antibacterial assays. Methanolic and chloroform extract of the roots of *J. podagrica* contains fraxidin (**73**) and erythrasinate (**74**). Both compounds exhibited antibacterial activity against *Bacillus subtilis* [80]. Two peptides, podacycline A (**75**), a cyclic nonapeptide and podacycline B (**76**), a cyclic heptapeptide were isolated from the latex of *J. podagrica* [81]. Podacycline B was found to possess high cytotoxicity against Dalton's lymphoma ascites (DLA) and Ehrlich's ascites carcinoma (EAC) cell lines with IC₅₀ values of 13.2 and 15.5 µM, in addition to moderate anthelmintic activity against earthworms *Megascolex konkanensis*, *Pontoscotex corethruses* and *Eudrilus* sp. at a dose of 2 mg/mL [82].

***Jatropha pohliana* Müll. Arg**

J. pohliana Müll. Arg. (Syn: *Adenophorum molissimum* Pohl, *Adenophorum luxurians* Pohl, *Jatropha molissimma* (Pohl) Baill., *Jatropha pohliana* var. *mollissima* (Pohl) Müll. Arg., *Jatropha luxurians* (Pohl) Baill.) known as *Pinhão-bravo* and *pinhão-de-purga* [83].

Three cyclic peptides, pohlianin A (**77**), B (**78**) and C (**79**) was isolated from the latex of *J. pohliana*, which found to possess antimalarial activity with IC₅₀ values of 57 µM, 25 µM and 16 µM, respectively. Compound **9** being the more potent [11].

***Jatropha tanjorensis* J.L. Ellis & Soroja**

J. tanjorensis has medium thick stout stem with sparse branching, sparse pigmentation. Leaves alternate, palmately five lobed, light green to dark green with no pigmentation except on very young leaves, margins distantly serrate, long petiole with dense pigmentation. Cymose inflorescence with coinflorescence, monoecious unisexual and bisexual, medium sized green with pale pink tinged flowers, 8 yellow stamens arranged in a single layer, highly sterile pollen. Fruit not seen [84]. *J. tanjorensis* is popular as a natural remedy against malaria infection and hypertension in some parts of Nigeria, however there is dearth in scientific validation of these claims [85]. Edo people in Nigeria consumed the leaves as a vegetable and known as *catholic vegetable* [86]. Phytochemical screening of *J. tanjorensis* leaf revealed that it contains bioactive principles such as alkaloids, flavonoids, tannins, cardiac glycosides, anthraquinones and saponins [87].

***Jatropha unicostata* Balf.**

Relative composition of the leaves of *J. unicostata* were unidentified sterol (0.9%), campesterol (4.9%), stigmasterol (36.5%), sitosterol (56.4%), stigmastanol (1.3%); 76 mg 3-oxo-steroids: campest-4-en-3-one (6.6%), stigmast-4,22-diene-3-one (19.8%), stigmast-4-en-3-one (78.3%); 26 mg dioxosteroids: campest-4-en-3,6-dione (5.6%), stigmast-4,22-diene-3,6-dione (42.2%), stigmast-4-en-3,6-dione (52.2%). The observed ketosteroids might be constituents of the latex from *J. unicostata*. Fraxetin (7,8-dihydroxy-6-methoxy-coumarin) and luteolin (3',4', 5,7-tetrahydroxyflavone) were isolated as main constituents from the ethyl acetate fraction [88].

Jatropha weddelliana

J. weddelliana is a shrub found in calcimorphic and dry soils of the highlands bearing the 'pantanal' of Mato Grosso do Sul, Brazil [89]. Hexane extracts of the roots of *J. weddelliana* contains 14 and 32. A diterpene with type of lathyrane skeletons named jatrowedione (**80**) was isolated from the stems extracts of this plant [90].

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Notification: Structures described separately and downloadable in The Structures of Secondary Metabolites of *Jatropha* Species.