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PHYTOCHEMICAL, THERAPEUTIC AND PHARMACOLOGICAL SIGNIFICANCE OF *JATROPHA MULTIFIDA*: A REVIEW.

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ABSTRACT
Jatropha multifida is an endogenous plant to Tropical Americas. A wide range of health benefits have been attributed to its various parts in African folklore as in the treatment of infection, pain, fever, inflammation, tumor, injury. Various components as alkaloids, flavonoids, phenolic acids, tannins, glycosides etc. are present in this plant which codes for numerous biological actions. The present article includes the detailed exploration of the various pharmacological properties reported so far.

KEYWORDS: *Jatropha multifida*, Pharmacology, Plant.

1. INTRODUCTION

Generally, *Jatropha* species are considered as multifaceted, deficiency tolerant, perpetual plant of Euphorbiaceae family comprises of near 170 species. The genus emblematize of this plant "*Jatropha* is a Greek word *(jatros*=doctor) and *(trophy*=nutrition) which means medicinal use". Their large scale production is done for procuring quality biodiesel and has multiple industrial applications. Researcher's curiosity has been piqued by biologically active compounds secluded from several Jatropha species against diseases and disease-causing micro-organisms. *Jatropha multifida* Linn. often designated as "coral bush" is a rapidly rising shrub, bush or tiny shrub/tree up to height of 1.30 m. It is an endogenous plant to Tropical Americas but now extensively grown for its attractive plants and flora (flower) in Tropical to sub-tropical areas throughout the world. It is easily disseminated by seeds or cuttings. It is often called "Penicillin, Iodine and Betadin plant". In vitro study by Woo et al, proved that the stem of *J. multifida* can be employed in cosmetic industries as it possesses skin whitening properties [**Woo et al., 2019**]. Wound dressings have been prepared from the plant secreted fluid of *J.multifida* by modification in the polyethylene oxide polyethylene glycol dimethacrylate hydrogel (PEO-PEGDMA). Different concentrations of *J. multifida* plant fluid (0%-15%) were prepared, increase in tensile strength and the % of elongation of hydro-gel film was reported [**Haryanto et al., 2018**].

1.1 Vernacular Names (Synonyms)

Common Names: Adenoropium multifidum (L) Pohl, Jatropha janipha, Manihot multifida English Name: Coral plant, Coral bush, Physic Nut.
Sanskrit Name: Bhadradanti, Brihadanti, Jyotishka, Virechani, Vishabhadra, Dugdhagarbha.

1.2 Morphology of the plant

Roots : Tuberous
Latex : white
Seed : sweet; oleaginous
Leaves are long petioled, 7.5-12.5 centimeter in diameter, dark green and whitish underneath, palmately cut into narrow caudate segments. Parts of *Jatropha multifida* are represented in Fig. 1.

Fig. 1 Flowers and leaves of *Jatropha multifida.*

The leaves of *Jatropha multifida* are distinguished by amphibrach paracytic and tetracytic stomata **[Thomas, 2016]**.

Flowers on terminal cymes are vivid coral red with little scarlet centers and small yellow petals. The pungent yellowish fruits are usually three angled capsules with three seeds apiece. The latex from the trunk represses a yellow- green volatile oil with an onion-like odor. Morphological examination done on the genus Jatropha in which *J.multifida* has the highest stomatal length of ~27.50 µm amidst highest number of stomata with ~17.5µm, stomata type: paracytic [**Soyewo et al., 2015**]. Decoctions of the roots are a cure for indigestion. The entire plant parts are utilized as a fish poison in the region of Philippines. Fruit of the plant is utilitarian in piles, wounds, pains, skin diseases and enlarged spleen. Seed is favorable as emetic, purgative, aphrodisiac, fattening, tonic grounds for "kapha", "vata", "pitta", and burning commotion. The oil possesses the property of disintegrating lepromae. The seed or the seed oil should not be used as cathartic, because they enclose toxic diterpenes, with irritant & co-carcinogenic properties [**Plant resources of South East Asia, 1999**].

The phytochemical investigation of the plant has revealed about numerous metabolites as, anthraquinone, saponins, cardiac glycoside, terpenoids, and cyanogenic glycosides[**Mina, 2013**] & phenolic acids [**Naz, 2019**], phloroglucinols and cyanoglucosides, glycoflavones, proanthocyanidins [**Thomas, 2016**]. Phytochemical study of the sap reveals the occurance of leucoanthocyanes, mucilage, reducing compounds. In another study phytochemicals screening manifested the existence of alkaloid, flavonoids, tannin and polyphenol [**Budi et al., 2020**].

Several compounds isolated from *Jatropha multifida* are mentioned in Table 1.

S. No.	Name (structure)	References
1.	Multifolone	**Das et al., 2008**
2.	Coumarino-lignan	
3.	15-epi-4*(E)*-Jatrogrossidentadione	
4.	Pictolinarigenin, Cleomiscosin	
5.	Jatrophone, Multifidone 15-*epi*-4*(E)*-Jatrogrossidentadione acetate 15-O-AcetylJapodragrone	**Das et al., 2009**
6.	Citlaitrione, Jatropholone B, Multidione*	
7.	8,11,13-triene	
8.	4*(E)*-Jatrogrossidentadione, 15-*epi*-4*(E)*-Jatrogrossidentadione	**Chokchaisiri et al., 2019**
9.	Tetradecyl-(*E*)-ferulate	**Kanth et al., 2011** **Alekhya,2013** **Syam et al., 2017**
10.	Multifidanol, Multidenol, Jatrophenone, Jatrophone, Japodagrone, Jatrothrin	
11.	Fraxidine(8-hidroxy-6,7-dimethoxy coumarin)	
12.	p-butyl-2chloro-5-formyl 1H-imidazole, Fraxetin	
13.	4-ethoxy-6-((hydroxymethoxy)methyl)-2H-chromen-2-one,	**Hamid et al., 2013**
14.	Jatrogrossidentadione,	**Falodun et al., 2014**
15.	Vitexin, Isovitexin	**Hirota et al., 2012**
16.	Jatrmulone A, jatrointolone A, Jatrophodione A	**Zhu et al., 2008**
17.	Multifidol (2-methylbutyryl)phloroglucinol	**Kosai et al., 1989**
18.	Multifidol glucosides	
19.	Labaditin	
20.	Jatrophenols I, Jatrophenols II, Jatrophenols III	**Marzouk et al., 2012**
21.	Ferulic acid, Quercetrin, Vicinin-II, Isoorientin,	
22.	15-epi-4*(Z)*-Jatrogrossidentadione, 4*(Z)*-Jatrogrossidentadione, Jatrogrossidione	**Chokchaisiri et al., 2019**
23.	Vanillic acid, Syringic acid	**Thomas et al., 2016**
24.	4'-OMe apigenin, Acacetin, Luteolin	
25.	3α-acetoxy-7,24-dienetirucallicc acid	**Li et al., 2021**
26.	Jatroidaine A	
27.	Scoparone, Scopoletin, Glaberide, Pinoresinol, Mediresinol	**Woo et al., 2019**
28.	Globeride, Pinoresil, Matairesinol	
29.	Scoparone and Scopoletin	
30.	Fraxidine	**Syam et al., 2017**
31.	2-Carene, 1,3,8-p-Menthatriene, L-Pinocarveol,	
32.	4-Isopropenylcyclohexanone, 2-Ethyl furan, D-Carvone	

33.	Eicosane, Di-n-decylsulfone, Tetracosane, Glubulol, β-Eudesmol, Isopropyl myristate	**Wintola et al., 2019**
33.	Multifidin	**Berg et al., 1995**
34.	Multifidinn	

The cytotoxic efficacy of compounds "Mulfifidanol and Mulfidenol" against malignant cell lines has shown acclamatory results. Compounds Jatromulone A, Jatrolintolone A, Jatrophodione A were tested for their Inhibitory action against Thioredoxinn reductase were examined. (TrxR), which has redox balancing and antioxidant properties, can be used as a target for cancer chemotherapy. Compounds Mulfifidol and mulfifidol are 2 naturally materializing and immunologically active acylphlorogllucinols which have been secluded from the *J. multifida* latex. Compounds Jatrophenols I, Jatrophenols II, Jatrophenols III are the 3 new biapigenin di-C glucosides while some other compounds Jatromulone A, Jatrophenols I, Jatrophenols II, Jatrophenols III are polyphenolic metabolites derived from 80% aqueous methanolic extract of *J. multifida* Linn. leaves, have analgesic, anti-inflammatory and anti-hypertensive activity. Compounds 14β & 15β- deoxy Jatrogrossidentadione are microcyclic lathyrane diterpenoids extracted from the methanol of the stem of *Jatropha multifida*. They had shown antileishmanial, antimalarial and antimicrobial activities [**Falodun et al., 2014**]. Compound Jatroidaine A is an advance triterpene (tetranortirucallane), and it analogues were obtained from the branches and leaves. Compounds Scoparone and Scopoletin are coumarins while other compounds (Globeride, pinoresil, matairesinol) are lignoids [**Woo et al., 2019**]. Compound Fraxidine has been isolated from ethyl acetate fraction with LC50 value 3.69 µg/mL [**Syam et al., 2017**]. Bioactive essential oils, compounds were obtained from *J. multifida* leaf through solvent free microwavee extraction and hydrodistilation extraction, scrutinized by gas chromatography-mass spectrometry [**Wintola et al., 2019**]. *J. multifida'*s toxicity is ascribed to its seeds. The seeds are well known to contain two main toxins which could bring about clinical symptoms after ingestion. The first type includes a conglomeration of diterpenoid esters, including the tigliane type, such as citlalitrione, riolozatrion and curcusones [**Shukla et al., 2015**] causing cardiac and respiratory depression. Toxalbumins, which are protein synthesis inhibitors, are the second type. Phorbol esters, the most toxic molecules, are found in Jatropha species which are acknowledged to contain Piscicidal, molluscicidal, rodenticidal, antimicrobial, insecticidal and cytotoxic properties [**Chioma et al., 2021**]. Because poisoning symptoms are generic, primarily gastrointestinal in nature and emulates fungal/bacterial infections and most scarce occurrences go unrecorded, they are often overlooked. Different cases of *Jatropha multifida* poisoning after intake of its parts have been promulgated as below.

According to a case report Koltin et al. four siblings (ages three, four, five and seven years) were admitted to an emergency department roughly 3 hours after consuming the fruit of *J. multifida* with symptoms of watery diarrhea, vomiting and constricted and reactive pupils. Symptoms were similar to organophosphte poisoning but plasma acetylcholinesterse activity levels differentiated between the two. [**Koltin et al., 2006**] A report by Panicker et al., where 19 school children consumed seeds that caused nausea, vomiting, diarrhea followed by abdominal pain. Presence of poisonous ingredients in the plant (phorbol ester) causes dehydration, hemolysis of blood & other side effects. The aqueous pull out of *J.multifida* leaves at a dose of ~600 mg/kg give rise to lower body weight in the mice in a Subacute toxicity study [**Agban et al., 2020**]. This demonstrates that the plant's aqueous extract would be toxic. In the discipline of toxicology, study has to be done in order to expound their response. A skin toxicity investigation on rats using the sap of *J.multifida* had shown no irritant effect which proves that its sap can be applied on skin in treatment of wounds [**Victorien et al., 2012**].

1.3 Biological Activities

1.3.1 Antibacterial Activity/ Antimicrobial Activity

Several other Jatropha species as *Jatropha curcas* possess good anti-microbial activity **[Mohite et al.,2018, Jaiganesh et al.,2013].** Ethyl acetate, $ChCl_3$, hexane, methanolic extract of *Jatropha multifida* inhibited the *B. subtilis* growth & *S.aureus* growth at a concentration of 200µg/disk. Only extracts from the rootwood had shown activity in against to *E.coli* [**Aiyelaagbe, 2000].** Prastiyanto et al conducted study on three Jatropha species named *J.multifida, J.curcas and J.gossypifolia* to assess the antibacterial activity of the latex of these plants to compute MIC and MBC using Blood agar plate and Mueller-Hinton agar diffusion method. Results showed that due to the presence of flavonoids compounds, these species have antibacterial properties [**Prastiyano et al.,2020**]. In vitro antibacterial activity against the morbific bacteria *S.aureus* was reported by the methanolic extract at various concentrations using the Kirby bauer diffusion method. Several concentrations of *J.multifida* sap (100%, 50%, 25%, 12.5%, 6.25%) were tested against *MRSA* and *S.aureus.* The average diameter of the sap induced inhibitory zone had a range of 11.29-16.00 mm (*S.aureus*), while 12.15-17.61mm for MRSA, which was found more effective than *S.aureus* [**Putri et al., 2021**].

1.3.2 Antifungal Activity

The suitability of *J.multifida* as an antifungal along with 3 other plant species was demonstrated. Anti-fungal sensitivity was inspected by Kirby-bauerr disc diffusion method, MBC and MIC was analyzed by broth tube dilution method. Results proved that *J.multifida*

(200mg/ml) was less active against *F. solani* and had MIC and MFC >200mg/ml [**Chioma et al., 2021**]. Anti-fungal screening of the compound, Lupenone isolated from the leaves of this plant, against the yeast *C.tropicalis* was reported [**Oliveira et al., 2019**]. Latex of *J.multifida* was screened against two strains of fungi yielding a MIC value of 0.5ml and a Maximum Inhibitory Concentration of 0.2 ml [**Olagunju et al., 2016**].

1.3.3 Anti-hepatitis Activity

Jatropha multifida with 4 other plants were examined for in vitro anti-hepatitis C activity against HCV RNA virus. According to the findings, extracts of *A. muricata* and *P. americana* roots possess inhibitory activity against HCV and more research is needed before they can be used as an antiviral source against Hepatitis C virus [**Falodun et al., 2013**].

1.3.4 Antioxidant Activity

Oxidative stress caused by free radicals impacts the phenomenon of numerous degenerative diseases in particular coronary heart disease, premature aging and cancer. Presence of phenols and flavonoids was regarded in the leaves and latex extract amenable for in vitro antibacterial activity against the morbific bacteria *S.aureus* was reported by the methanolic extract of *J.multifida* at various concentrations [**Carvalho, 2018**]. The studies of Hirota et al. showed that several extracts of *Jatropha multifida* bark and leaves give antioxidant activity by making use of Phosphomolybdenum and DPPH assay. The antioxidant activity of the bark extract was higher than that of leaf extract [**Hirota et al., 2012**].

1.3.5 Anti-cancer Activity

Chloroform fraction of *Jatropha multifida* elicited cell cycle arrest at G1 checkpoint bringing about apoptosis in MCF-7 cells may be correlated to its capability to change the metabolic activities. Slight changes in cell morphology and β1 integrinn localization within MCF7 after treatment were observed. These results divulged the probable implementation of JMR-ch in cancer treatment [**Erhauruyi, 2014**]. In another study, three separate extracts of *J.multifida* (n-hexane, ethanol and ethyl acetate) were tested against MCF-7 cells using the M.T.T. method. IC50 values of different extracts were as; Ethanolic extract: 418.51µg/ml, Ethyl acetate extract: 258.38µg/ml, n-hexane extract: 312.21µg/ml. Ethyl acetate [E.A.] extract showed the highest cytotoxicity [**Werdyani et al., 2019**].

1.3.6 Anti-inflammatory Activity/ Analgesic Activity

Anti-inflammatory activity has been reported in *Jatropha gossypifolia* **[Kakade et al., 2011].** In vivo study of the methanolic root bark extract at different doses was subjected to evaluation of anti-inflammatory and analgesic properties[**Falodun et al., 2013**].In another study, this activity was performed in wistar rats by administration with crude leaf extracts [**Anani et al., 2016]**.

1.3.7 Antihypertensive Activity

For the evaluation of hypotensive activity, Marzouk et al. conducted a study in which rat received a suspension of deoxycorticosterone acetate for 6 weeks. Aqueous methanolic extract of the leaves was administered orally for two weeks and estimation of systolic blood pressure produced decisive results **[Marzouk et al., 2012].**

1.3.8 Anti-herpes simplex type-1 Activity

Different extracts of root of *J. multifida* were tested for anti-HSV1. It was found that n-hexane extract showed appreciable anti-HSV1 property **[Chokchaisiri et al., 2019**].

1.3.9 Hemostatic Activity

In African folkfore, *Jatropha multifida*, is used as a hemostatic, generally to medicate wounds. So, scientific study has been done on applying *J.multifida's* sap on wounds. Blood coagulation time, Quick time, test of milk precipitation, activated cephalin time, total protein of blood samples were estimated to assess it's hemostatic properties in vitro and in vivo skin toxicity studies were conducted on rats [**Victorien et al., 2012**].

1.3.10 Anti-tubercular Screening

The different extracts of *J.multifida* leaves were demonstrated against *M. tuberculosis* H37Rv using the Micro-plate Alamar Blue Assay at different concentrations. The inhibition activity was displayed much at concentration of 128µg/ml [**Mina et al., 2013**].

1.3.11 Antimalarial Activity

Sundaryono et al. demonstrated the ethanolic extract of stem were tested for anti-malarial activity on rats by counting number of erythrocytes using hemocytometer, infected using *P. berghei*. After 24 hours, an augment in the number of uninfected erythrocytes in comparison to other groups proved that the antimalarial activity of *J. multifida* may be due to the presence of flavonol glycoside in *J. multifida* stem [**Sundaryono et al., 2015**]. Another Study was executed to determine the effect of administration time (morning and evening) of the hydroalcoholic extract of the plant on the liver and kidney of male swiss albino mice in the treatment of malaria which causes an increase in liver weight of the mice [**Franck et al., 2020**].

1.3.12 Antileishmanial Activity

Three known metabolites, microcyclic lathyrane diterpenoids, have been isolated from the methanolic extract of the stem. All the compounds were active against *Leishmania donovani*. IC50 values of compound 1: 11.90 µg/ml, compound 2: 4.69µg/ml, compound 3: 4.56µg/ml while Amphotericin B was as control with IC50 value: 0.28µg/ml [**Falodun et al., 2014**].

1.3.13 Anthelmintic Activity

16 poisonous plants including *J.multifida* were reported for in vitro antihelmintic activity. *J.multifida* was effectual against nematodes at a concentration of 1

mg/ml with no cytotoxicity activity which was performed using brine shrimp lethality assay [**McGaw et al., 2005**].

1.3.13 Anti-complement Activity

Inhibitory property of latex from *J.multifida* on complement pathway activity in the human serum was reported. Crucial anti-complement constituents was a non-dialysable procyanidin type compounds with catechin as building unit which has the ability to deplete CA^{2+} from the incubated medium due to which this polymer inhibits CP activation of the complement cascade, Mg^{2+} was not bound by non-dialyzable proanthocyanidin so inhibition of AP complement activity was unexposed [**Kosai et al., 1989**].

1.3.14 Wound Healing

Other species of Jatropha are known to possess wound healing properties **[Sharma et al., 2012].** Anti-wound Iodine ointment of ethanolic extract of leaves of iodine plant (*Jatropha multifida*) with concentration of 75% was made by Budi et al which satisfy the demands of ointment quality starting from organoleptic test, homogeneity test and ph tests. **[Budi et al., 2020].** In *silico* analysis of the healing activity of hexane leaf extract of *J.multifida* by increase in proliferation of cell lineage were reported due to triterpenes, flavonoids and arylpropanoids **[Lemos et al., 2021].** Thomas et al. demonstrated the wound healing potential of iota carrageenaan polyvinyl alcohol hydrogel film as a JTS carrier in vivo wound healing studies with 98% wound closure by 10 days compared to non-treated group **[Thomas et al., 2020].**

1.3.15 Anti-melanin Activity

The chloroform, methanolic, hexane, and water extracts of the stem were trialed against the (α-MSH), 3-isobutyl-1-methylxanthin induced mouse melanin cell lines (B16F10) for anti-melanin deposition activity. Consequences show that the chloroform extracts have skin whitening properties by inhibiting TYR activity [**Woo et al., 2019**].

1.3.16 Vegetable Fungicidal Activity

According to the report by Suwastini et al. the red chilies, which was affected with anthracnose disease caused by fungus *Colletotrichum capsici* and *C. Gloeosporioides*, treated with the extract of *J.multifida* begotten prominent results [**Suwastini et al., 2020**].

1.3.17 Treatment of Dengue Hemorrhagic Fever

Ethyl acetate and crude extracts from *Jatropha multifida* stem bark can enhance the platelet counts of *M. musculus* enduring from thrombocytopenia [**Sundaryono et al., 2019**].

DISCUSSION

There are diverse bioactive metabolites present in this plant which are yet to be fully discovered and explored for their numerous biological actions. Various flavonoids such as flavones, flavanones, anthocyanins etc. present exert pharmacological effects as anti-inflammatory, antithrombogenic, antiviral, antiatherosclerotic, antibacterial, antiosteoporotic effects which is yet needed to be thoroughly inquired [**Agrawal, 2011**]. Tannins which are biologically active constituents of this plant possess various biological activities including antimicrobial, antioxidant, cardioprotective and anticancer [**Smeriglio et al., 2017**]. Saponins exhibit antitumour, antimutagenic, anticancer, immunomodulatory, anti-inflammatory, anti-allergic, antihepatotoxic, antiviral, antiphlogistic activities [**Lacaille et al., 1996**]. Thus, these properties possessed by these components have to be more traversed. part from this, there have been various phytochemical, pharmacognostical studies and quantitative estimation of other *Jatropha* species **[Viswanathan et al., 2018, Dubey et al., 2020, Jain et al., 2020, Sridevi et al., 2012, Saini et al., 2018]** which needs to be done in case of *Jatropha multifida*. Furthermore, formulation of plant mediated synthesis of silver nanoparticles seems to be very popular, non-toxic and eco-friendly. Due to their higher absorbance and biocompatibility, these are formulated in order to produce better anti-oxidant, anti-cancer, anti-inflammatory **[Siddiq Hussein, 2014]** and anti-bacterial activities. *Jatropha multifida* Linn. is still not explored for the synthesis of nanoparticles and its applications in pharmaceutical and agricultural industries. Although traditionally, *J.multifida* has been considered non-toxic and is the most often used as a mouthwash, still the eventuality of *J.multifida* toxicity has not been acknowledged by the general public and professional groups of folkloric medicine. Pharmaceutical preparations of the various extracts of this plant in different dosage forms such as pastes, creams and gels formulation can be an engrossing area of research.

CONCLUSION

This review paper discusses numerous studies conducted on the different parts of *Jatropha multifida*. However, more focus should be made on additional in vivo studies of various bioactive substances isolated from this plant. Apart from this, further toxicity studies and estimation of the lethal dose of the plant extract should be done in future. A detailed and systematic study of in vivo antibacterial activity, anti-candidal, ant malarial activities of the sap is required for further exploration in near future.

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