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Phytochemistry, Ethnomedicine and Pharmacology of *Jatropha gossypiifolia* L: A Review

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Authors' contributions

This work was carried out in collaboration between all authors. Authors OTF and KBE designed the study, wrote the protocol and managed the first draft of the manuscript. Authors OL and SEO managed the literature searches and involved in the write up for the chemistry of the plant. Author OFK edited the final manuscript and supervised the review. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Jatropha gossypiifolia L. [*Euphorbiaceae*], widely known as "bellyache bush", is a medicinal plant native to Mexico, south America, India and commonly found in many west African countries such as Nigeria. Folkloric uses of the different parts of this plant in the tropics for the management of various diseases are enormous. Information was sourced from Hinari, JSTOR, PubMed, Medline, African Journals Online, Google Scholar, SCOPUS, and by reviewing the references of relevant literature. More recent studies showed the use of juice and extract of the plant in the management of sickle cell anaemia and the effect of its extracts on the reproductive system. Pharmacological studies have demonstrated significant action of different extracts and isolated compounds as haemostatic, anticholinesterase, antimicrobial, antiinflammatory, antidiarrheal, antihypertensive, and antiproliferative agents, among others, supporting some of its folkloric uses. The major secondary metabolites isolated from various extracts are terpenes-essential oils, alkaloids and coumarin - lignans. This review aims to provide an up to date overview of the phytochemistry,

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ethnomedicinal and pharmacological activities of *J. gossypiifolia* while providing an insight for future research towards both ethno pharmacological validation of its popular uses and its exploration as a new source of herbal medicinal products.

Keywords: Jatropha gossypiifolia; ethnomedicine; phytochemistry; secondary metabolites; ethnnopharmacology.

1. INTRODUCTION

The name "Jatropha" is derived from the Greek words "jatros," which means "doctor" and "trophe," meaning "food," which is associated with its medicinal uses [1]. The Jatropha genus is divided into two subgenera, Jatropha and curcas, from which the subgenus Jatropha has the widest distribution, with species found in Africa, India, South America, West Indies, Central America, and the Caribbean [2,3]. *Jatropha gossypiifolia* is widely used in folk medicine for the treatment of various diseases and its uses in traditional medicine are described for different parts [leaves, stems, roots, seeds, and latex] and preparations [fresh juice, infusion, decoction, and maceration, among others], by different routes [oral or topical]. Its use as an antihypertensive, anti-inflammatory, analgesic, haemostatic and anti-diabetic agent have been justified [1-3].

1.1 Botany

J. gossypiifolia is a small shrub with dark green or more frequently purplish-red dark leaves, with 16–19 cm of length per 10–12.9 cm of width; they are alternate, palmate, and pubescent, with an acuminate apex, chordate base, and serrated margin. The flowers are asexual, purple, and in cymose summits, with the calyx having five petals, which in male flowers may form a petiole tube. The fruit is capsular, with three furrows, containing a dark seed with black spots. Regarding the microscopic aspect of the plant leaves, some studies have shown key and important features for botanical identification of this species among other Jatropha species [3-9].

[A]. Whole plant of *J. gossypiifolia* L.

[B]. Leaves of *J. gossypiifolia* L.

[C]. Stem of *J. gossypiifolia* L.

[D] Leaf and flowers *Jatropha gossypiifolia* L.

Fig. 1. A-D, Pictures taken at Idu, Abuja Municipal Area Council, Nigeria by Omorogbe Liberty

1.2 Taxonomic Classification

Kingdom	Plantae
Unranked	Angiosperms
Unranked	Tracheophyta
Unranked	Magnoliopsida
Order	Malpighiales
Family	Euphorbiaceae
Subfamily	Crotonoideae
Tribe	Jatropheae
Genus	*Jatropha*
Species	*gossypiifolia*

Name *Jatropha gossypiifolia* Linn

Common/local names

bellyache-bush, wild cassava, pignut or fignut– English; botuje pupa [yoruba], ake mbogho [igbo] [source: 10;11] -Nigeria; erva-purgante, mamoninha ,peão-roxo, pião-roxo, pinhão-roxo, raiz-de-tiu [Source: pers. comm.] - Portuguese [Brazil]; piñón negro, Sibidigua, Tua Tua [Source: pers. comm.] – Spanish; lepro [Source: Bot H. P. Ahir] - Gujarati [India].

1.3 Ethnomedicinal Uses

Table 1. Ethnomedicinal uses of *Jatropha gossypiifolia* L.

Plant part	Popular use	Preparation/mode of use	Reference
Whole plant	Analgesic [headache]	Leaves heated and used as compress	[12]
	Analgesic [toothache]	Not specified	[1]
	Antimicrobial	Not specified	[1]
	Antipyretic	Decoction	[13]
	Dyscrasia	Not specified	[1]
	Dysphonia	Not specified	[1]
	Wound healing	Not specified	[14,15]
Aerial parts	Antianaemic [malaria treatment]	Decoction [oral route]	[16]
Leaves	Abscess	Bath	[17]
	Alopecia	Ash leaves	[18]
	Analgesic [eye pain]	Not specified	[19]
	Analgesic [headache]	Not specified	[19]
	Analgesic [headache and otitis]	Not specified	[20]
	Analgesic [general pain]	Decoction or infusion	[21]
	Analgesic [toothache]	Decoction or infusion	[21]
	Antianaemic	Decoction	[22]
		Decoction [oral route]	[23]
		Ash of leaves	[18]
	Anticonvulsant	Not specified	[1]
		Not specified	[22]
	Antidiabetic	Decoction	[24,25]
		Decoction [oral route]	[26]
	Antidiarrheal	Decoction [oral route]	[26]
		Not specified	[1]
	Antihemorrhagic	Decoction [oral route]	[26]
		Freshly crushed leaves used for cutaneous and nasal bleeding	[27]
	Anti- infective	Decoction [oral]	[26]
		Not specified	[28,29]
	Anti-inflammatory	Not specified	[19]
		Decoction	[22]
	Antipyretic	Infusion	[12]
		Not specified	[29]
Leaves		Not specified	[29]
	Antiseptic	Bath prepared from leaves	[12]
	Antithrombotic	Decoction or infusion	[21]
	Antiulcerogenic	Decoction [oral]	[26]
		Leaf juice	[30]
	Boils	pounded leaves applied locally	[31]
		Ash of leaves	[18]
	Burns	Combined with seeds of *Gossypium arboretum,* sugar, honey and fat of ram, prepared by grinding and applied topically	[32]
	Contraceptive and oxitotoxic	Not specified	[20]

Plant part	Popular use	Preparation/mode of use	Reference
	Depurative	juice is taken orally	[33]
	Detoxificant	Not specified	[34]
	Eczema	Ash of leaves	[18]
	Emetic	Squeezed, the juice obtained is drunk	[33]
	Gastrointestinal disorders	Not specified	[20]
	Gingivitis	Leaf juice	[30]
	Gonorrhoea	Ash of leaves	[18]
		Bath prepared from leaves	[12]
	Healing	Decoction	[26]
		Decoction or infusion	[21]
	Haemorrhoids	Used in combination with the leaves of *Nicotiana tobacum* and copper sulphate, boiled in water and steam is directed at the anal region.	[35]
	haemostatic	Decoction or infusion	[21]
	Hepatitis	Not specified	[36]
	Antipruritic	Application of the pounded leaves/decoction	[31,37]
	Leprosy	Leaf juice	[30]
		Decoction	[22]
		Decoction [oral route]	[23]
	Malaria	Used in association with leaves of *Azadirachta indica* and *combretum sp.,* boiled, for baths and taken orally	[38]
		Infusion prepared with leaves of *Azadirachta ghasalense and whole plant of ocimum canam* by oral route or body wash	[38]
leaves	Mastitis	Pounded leaves applied on swollen breasts	[31]
	Mycosis	Ash of leaves	[18]
	psychoactive	Not specified	[20]
	purgative	Not specified	[1,29]
	Rheumatism	Ash of leaves	[18]
	Scabies	Ash of leaves	[18]
	Skin diseases	Not specified	[1]
	stomachic	Decoction [oral route]	[26]
		Not specified	[29,34]
	Syphilis	Ash of leaves	[18]
	Thrush [oral candidiasis]	Ash of leaves	[18]
	Vaginal infection	Slightly boiled, used as douche	[33]
	Veneral diseases	Not specified	[34]
	Vermifuge	Ash of leaves	[18]
	Vertigo	Not specified	[1]
		Bath of leaves	[39]
	Wounds and rashes	Decoction [oral route]	[40]
		Decoction used as baths for cleaning wounds in dogs	[37]
	Wound disinfectant	Slightly boiled, used as wound wash.	40
Stem	Analgesic [toothache]	Not specified	[41]
	Antinaemic	Decoction [oral route]	[23]
	Anticancer	Decoction [oral] or topical route	[26]
	Emmenagogue	Decoction of barks	[42,34]
	Haemostasis	Application of sap	[40]
	Malaria	Decoction [oral route]	[23]
	Rheumatism	Not specified	[17]
	Antipruritic	stem sap is applied to the affected area	[40]
	Mouth cleanser	Young stem is chewed	[10]
Roots	Anticancer	Decoction [oral] or topical route	[43]
		Root bark used for cancer of the lungs	[44]
	Anticonvulsant	Not specified	[45]
	Antidiarrheal	Not specified	[30]

Plant part	Popular use	Preparation/mode of use	Reference
	Antimicrobial	Root bark used in bacterial infections	[44]
	Impotence	Decoction of *J. gossypifollia, Chiococca alba, Citrus aurantifolia, Desmodium canam, Roystonea regia, Senna occidentalis, Stachytarpheta jamaicensis,* and *Commelina erecta, Cyperus rotundus,* and sugar, by oral route	[32]
Roots	Leprosy	Not specified	[1,34]
	Snakebites	Not specified	[46,34]
	Urinary pain	Not specified	[34]
	Uterus diseases	Decoction [oral route]	[47,48]
Seeds	Analgesic [body pain]	Not specified	[40
	Analgesic [headache]	Not specified	[20]
	Antigripal	Used in strong colds	[12]
	Antihemorrhagic	Not specified	[49]
	Antiulcerogenic	Seed oil	[1]
	Antimicrobial	Not specified	[50]
	Contraceptive	Not specified	[20]
	Depurative	Not specified	[33]
	Emetic	Not specified	[42,33,48]
	Gastrointestinal disorders	Not specified	[20]
	Leprosy	Seed oil	[1]
	Mycosis	Seed oil	[1]
	Psychoactive	Not specified	[20]
	Purgative	Not specified	[1,47,40,51]
	Vaginal infection	Slightly boiled, used as douche	[33]
	Wound infection	Slightly boiled, used as douche	[33]
Fruits	Analgesic	Massaging pregnant women's bellies with Infusion	[17]
	Analgesic [headache]	Infusion or macerate in alcohol	[17]
	Analgesic [toothache]	Infusion or macerate in alcohol	[17]
	Laxative	Ingestion in natura of the powder fruit	[51]
	Numbness after bug stings	Infusion or macerate in alcohol	[17]
Latex	Alopecia	Not specified	[18
	Analgesic [eye pain]	Not specified	[19]
	Analgesic [general pain]	Drink or massage the affected area with latex	[21]
	Anticancer	Not specified	[18]
	Antihemorrhagic	Not specified	[47,39,27, 37]
	Antithrombotic	Oral route	[21
	Antiulcerogenic	Not specified	[13,30]
	Bite of venomous animals	fresh latex is applied to affected area	[12]
	Diuretic	A few drops of fresh latex in water	[52]
	Eczema	Not specified	[18]
Latex	Gingivitis	Not specified	[30]
	Gonorrhoea	Not specified	[18]
	Haemostatic	Not specified	[18,21]
	Infected wounds	fresh latex is applied on the affected area	[12,13]
	Leprosy	Not specified	[30]
	Mycosis	Not specified	[18]
	Purgative	A few drops of fresh latex in water	[52]
	Rheumatism	Not specified	[18]
	Scabies	Not specified	[18]
	Skin burns	fresh latex is applied to the affected area	[53]
	Stop itching of cuts and scratches	Not specified	[37]
	syphilis	Not specified	[18]
	Thrush [oral candidiasis]	Not specified	[18]
	Vermifuge	Not specified	[18]
		latex is applied to the affected area	[12]
	Wound healing	Drink or massage the affected area with	[21]

Plant part	Popular use	Preparation/mode of use	Reference
		latex	
	Toothache	Toothpowder	[54]
Oil	Wounds in lips and tongue	Applied topically	[54]
	Arthritis	Applied locally	[30]
	Purgative	Not specified	[30]
Not specified	Skin disease	Applied locally	[30]
	Alopecia	Infusion applied locally in dogs	[55]
	Analgesic	Not specified	[50]
	Anticancer	Poultices	[49]
	Anticancer	Not specified	[50,56]
	Antidiarrheal	Not specified	[57,58]
	Antihypertensive	Not specified	[58]
	Anti-inflammatory	Not specified	[50,57]
	Antipyretic	Not specified	[57]
	Antiseptic	Not specified	[58]
	Antiulcerogenic	Not specified	[57]
	Coughs and colds	Bark juice	[59]
	Detoxification	Not specified	[57]
	Diuretic	Not specified	[58]
	Eczema	Not specified	[57]
Not specified	Gum infection	Not specified	[57]
	Healing	Not specified	[58,60]
	Hydropsy	Not specified	[12]
	Leprosy	Not specified	[57]
	Purgative	Not specified	[12]
	Regulate menses	Not specified	[61]
	Rheumatism	Not specified	[12]
	Snake and scorpion bites	Not specified	[1,46]
	Stomach pain	Not specified	[57]
	Venereal diseases	Not specified	[57]
		Poultices	[37]
	Wounds	Used as bath	[57]

2. PHYTOCHEMISTRY

2.1 Phytochemical Screening of Various Extracts of *J. gossypiifolia*

The following constituents have been reported to be present in various extracts of *J. gossypiifolia* [10,62 and 50] [Table 2].

2.2 Chemical Constituents of Various Extracts of *J. gossypiifolia*

Various compounds have been isolated from different extracts/fractions obtained from parts of *J. gossypiifolia*. Some of the compounds have not been reported to be responsible for any particular pharmacological activity.

Table 2. Secondary metabolites present in *J. gossypiifolia*

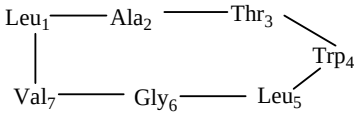
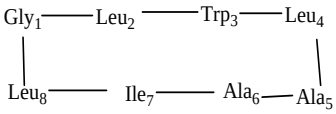
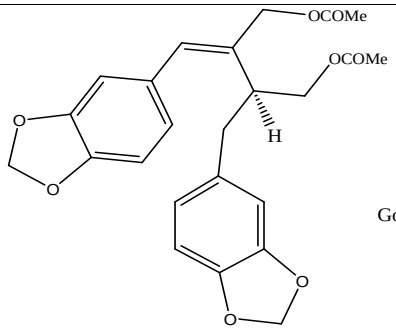
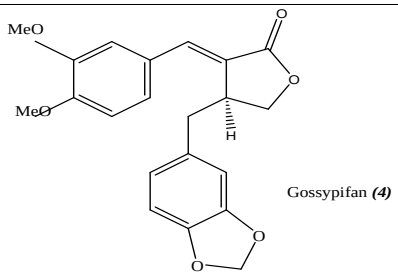
Secondary metabolites	Aqueous	Methanol	Acetone	Petroleum ether	Chloroform
Present	Phenols, starch, saponins	Carbohydrates, alkaloids, glycosides, phenols, starch and organic acids, steroids, phlobatannins	Alkaloids, phenols, flavonoids, organic acids, saponins, diterpenes	Carbohydrates, alkaloids, phenols, flavonoids, proteins, diterpenes	Phenols, proteins, diterpenes, flavonoids, phlobatannins
Absent	Carbohydrates, alkaloids, glycosides, flavonoids, proteins, amino acids, diterpenes, steroids and tannic acid	Flavonoids, proteins, amino acids, diterpenes, saponins, tannic acid, alkaloids	Carbohydrates glycosides, proteins, amino acids, starch, tannic acid	Glycosides, organic acids, amino acids, starch, saponins, tannic acid steroids	Carbohydrate, alkaloids, glycoside, organic acid, amino acid, starch, saponins, tannic acid and steroids, tannin

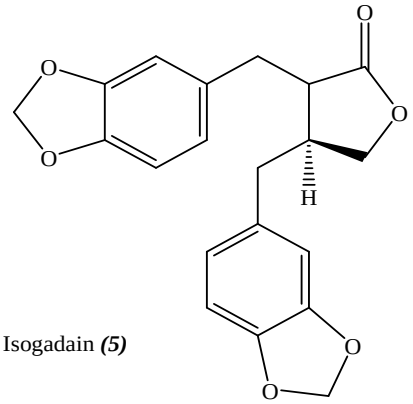
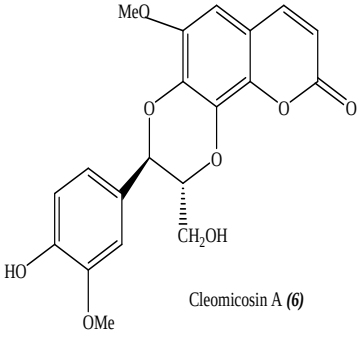
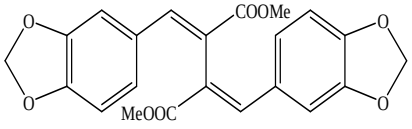
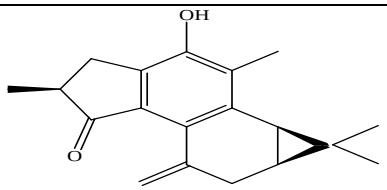
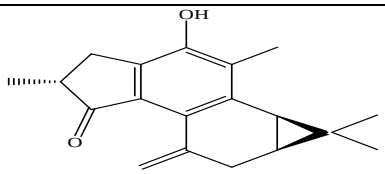
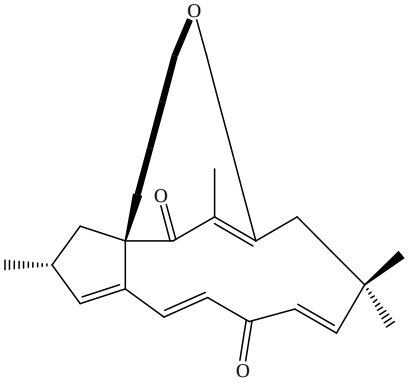
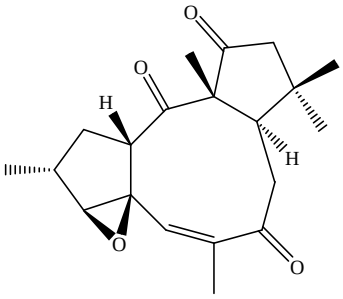
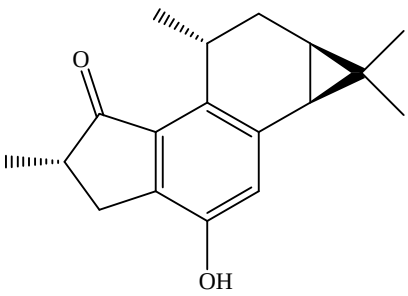
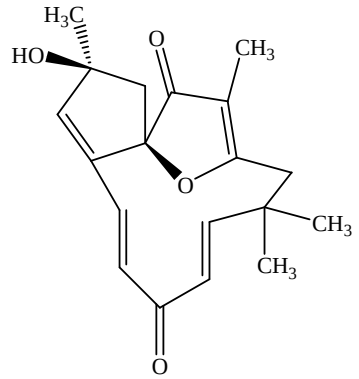
Table 3. Compounds isolated from *J. gossypiifolia L*. and their pharmacological uses

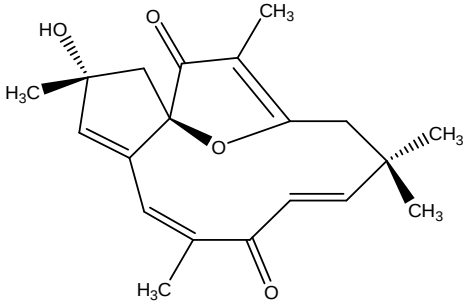
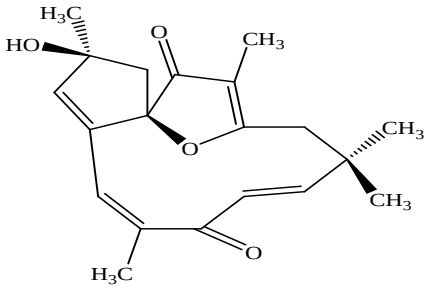
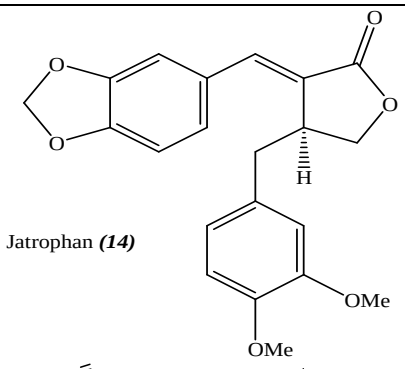
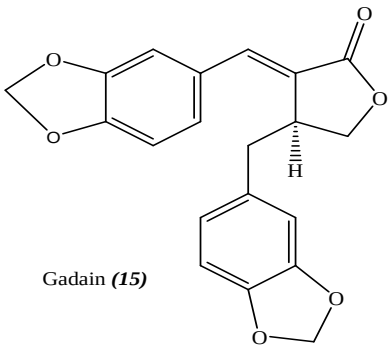
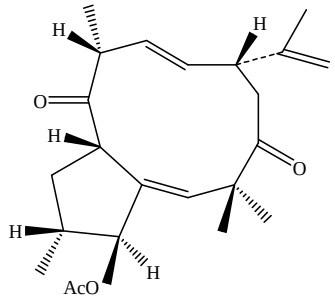
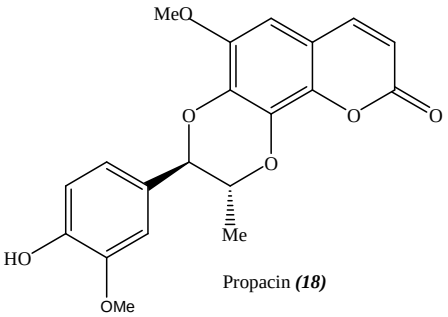
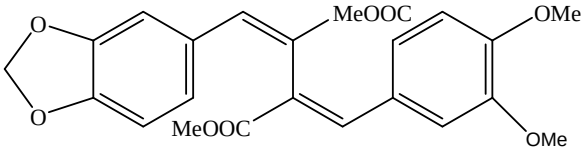
Compound	Pharmacologic uses	Part isolated from	Class	References
Cyclogossine A [1]	**	Latex	Protein	[63]
Cyclogossine B [2]	**			[64]
2,24,25-Trihydroxylanosta-1,7-dien-3-one [3]	**	Leaves	Triterpene	[65]
2,24,25-Trihydroxylanost-7-en-3-one [4]	**			
Ricinine [5]	**		Alkaloid	[66]
Gossypiline [6]	**	Aerial parts	Flavonoid	[67]
Gossypifan [7]	**			[68,69]
12-Deoxy-16-hydroxylphorbol [8]	**	Seed	Terpene-ester	[56]
Prasanthaline [9]	**	Stem	Coumarin-lignoid	[70]
Isogadain [10]	**			[71]
Cleomiscosin A [11]	**			[72,73]
Gossypidien [12]	**			
Jatrodien [13]	**			[74]
Jatropholone A [14]	**	Roots	Diterpene	[75]
Jatrophone B [15]	**			
Jatrophone [16]	Anticancer [*in vivo* and *in vitro*]			
Citlalitrione [17]	xx			[50]
Falodone [18]	Anticancer [*in vitro*]			
2β-hydroxy-5,6-isojatrophone [19]	Antileukemic [*in vivo* and *in vitro*]			[59]
2β-hydroxy-5,6-isojatrophone [20]				
Jatrophan [21]	**	Stem, root and seeds	Coumarin-lignoids,	[76]
Gadain [22]	**			[77]
Arylnapthalene [23]	**			[78]
Jatrophenone [24]	Antibacterial [*in vitro*]	Whole plant	Diterpenes	[79]
Propacin [25]	**			[80]
Piperidine [26]	**		Alkaloid	[81]
9-acetoxynerolidol	antifungal	seed		[50]

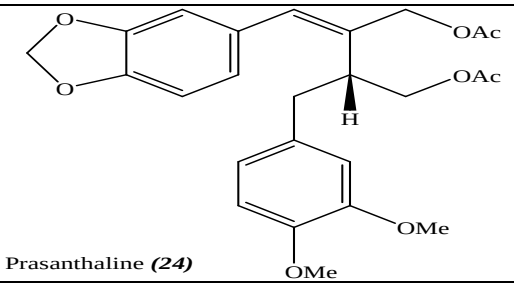
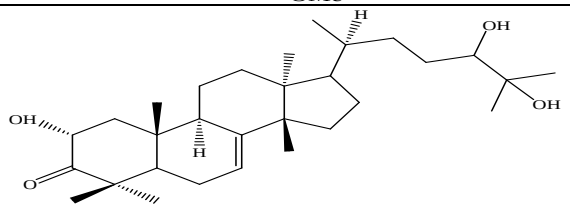
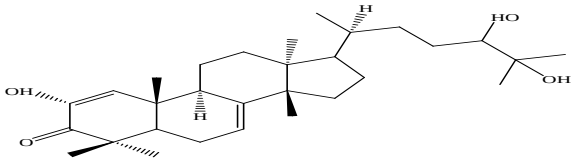
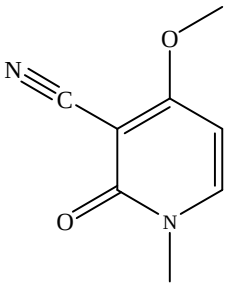
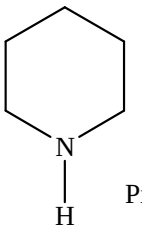
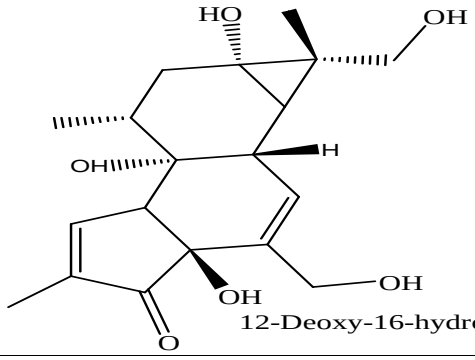
- *pharmacological activity not reported*

Table 4. Structures of chemical constituents of *J. gossypiifolia* [3]

Class	Structure
Protein	 Cyclogossine A ***(1)***  Cyclogossine B ***(2)***
Lignans	 Gossypiline ***(3)***  Gossypifan ***(4)***

Class	Structure
Coumarin lignoid	 Isogadain ***(5)***  Cleomicosin A ***(6)***  Gossypidien ***(7)***
Diterpene	 Jatropholone A ***(8)***  Jatropholone B ***(9)***
	 Jatrophone ***(10)***  Citlatrione ***(11)***
	 Falodone ***(12)***  2β - hydroxy-5,6-isojatrophone ***[13]***

Class	Structure
	 2α – hydroxyjatrophone
	 2β – hydroxyjatrophone ***[26]***
Coumarin-lignoids	 Jatrophan ***(14)***  Gadain ***(15)***  jatrophenone ***(17)***  Propacin ***(18)***  Jatrodien ***(25)***

Class	Structure
	 Prasanthaline ***(24)***
Triterpenes	 [13α,14β,20S]-2,24,25-trihydroxylanosta-1,7-dien – 3-one ***[19]***
	 [2α, 13α, 14β, 20S] -2,24,25- trihydroxylanost-7-en-3-one ***[20]***
Alkaloids	 Ricinine ***(21)***  Piperidine ***(27)***
Ester	 12-Deoxy-16-hydroxylphorbol ***(23)***

3. PHARMACOLOGICAL ACTIVITIES OF *Jatropha gossypiifolia L.*

Some folkloric uses of various plant parts of *J. gossypiifolia* have been scientifically justified and proven.

3.1 Analgesic and Anti-Inflammation

The methanolic extract of *J. gossypiifolia* leaves exhibited systemic acute and chronic anti-inflammatory activities. The extract, at 500 and 1000 mg/kg oral doses, inhibited the acute

carrageenan-induced paw oedema in rats and at 50 and 100 mg/kg oral doses, inhibited the chronic cotton pellet-induced granuloma formation in rats [57]. The leaf paste at 0.5 and 1 mg/ear showed significant reduction in TPA-induced local inflammatory changes in mouse ear oedema model [57]. At 100 and 200 mg/kg/day, for 7 days, by oral route, the methanol extract of *J. gossypiifolia* aerial and bark parts demonstrated significant analgesic activity in Eddy's hot plate and tail-flick models and anti-inflammatory activity in carrageenan-induced paw oedema in mice [34]. Nagaharika et al. [82] suggested that ethanol and water extracts from *J. gossypiifolia* leaves have anti-inflammatory activity, using the *in vitro* human red blood cell membrane stabilization method. The human red blood cell membranes are similar to the lysosomal membrane components, the prevention of hypotonicity-induced membrane lysis of these cells could be taken as a measure in estimating the anti-inflammatory property of compounds [34].

3.2 Anticholinesterase and Antibutrylcho-linesterase Inhibitory Potentials

The deficiency of Anticholinesterase and Butrylcholinesterase is one of characteristics of Alzheimer's disease and responsible for most of its symptoms, such as a decline in memory and cognition. Different extracts and fractions of roots, stem / bark and leaves of *J. gossypifolia* have been reported to exhibit acetylcholinesterase [ACh] and butylcholinesterase [BuCh] enzyme inhibitory activity. The methanolic extract from leaves showed an IC50 of 0.05 mg / mL. [83] while the lyophilized latex of the plant was able to inhibit time- and dose-dependently the acetylcholinesterase enzyme in nervous tissue of freshwater air breathing fish *Channa marulius.* [84,85]. Reports showed that ACh and BuCh enzyme inhibitory was maximal because most of the acetylcholinesterase inhibitors are known to contain nitrogen; the higher activity of *J. gossypiifolia* extracts is due to its rich alkaloid jatrophine content [86].

3.3 Anticancer Activity

Kupchan et al. [87] reported that the ethanolic extract from roots, and the compound jatrophone exhibited significant inhibitory activity *in vitro* against cells derived from human carcinoma of the nasopharynx and lymphocytic leukaemia and *in vivo* against four standard animal tumor systems, such as sarcoma, Lewis lung carcinoma, lymphocytic leukaemia, and intramuscular carcinosarcoma. Three derivatives of jatrophone were isolated from petroleum ether J. gossypiifolia root extracts viz 2β-hydroxyjatrophone and 2β-hydroxy-5, 6-isojatrophone exhibited profound antitumor activity. From the methanolic extract, diterpenes such as: Falodone and abiodone exhibited potent antineoplastic and proliferation inhibitory activity against A-549 human cancer cell lines [50]. Summarily, Alkaloids, lignoids and terpenoids of *J. gossypiifolia* have been reported to be responsible for its antineoplastic activity.

Table 5. Volatile oil constituents of *J. gossypiifolia* leaf (Abaoba et al. 2015)

Compounds	% Composition
β-Cycloctral	0.3
m-Cymene	0.4
Mthylcyclohexane	0.5
Ethylbenzene	0.5
Linalool	0.5
n-Nonanal	0.6
Toluene	0.7
Dimethylfulvene	0.7
α-Muurolene	0.9
α-Phellandrene	1.0
β-Caryophyllene	1.0
α-Cedrene	1.2
Acorenone	1.3
[Z]-9,17-Octadecadienal	1.8
[E]-β-Ionone	2.0
Globulol	2.0
m-Xylene	2.5
Cycloisosativene	2.8
Z,Z,Z-7,10,13-Hexadecatrienal	3.4
[E]- phytol	3.9
α -Cadinol	3.9
α-Copaene	4.1
epi-α-Cadinol	4.7
Cubenol	6.1
Tetradecanal	6.8
δ-Cadinene	7.7
Hexahydrofarnesylacetone	15.4
Germacrene D-4-ol	23.3
Total	**97.9**
Non-terpenes	0.6
Monoterpene hydrocarbons	1.4
Oxygenated monoterpenes	2.8
Diterpenes	3.9
Aromatic compounds	4.9
Fatty acids	10.0
Sesquiterpene hydrocarbons	17.7
Oxygenated sesquiterpenes	56.6

3.4 Antidiabetic Activity

Saleem et al. [86] demonstrated that the extracts from *J. gossypiifolia* plants showed significant α-glucosidase activity. α-glycosidase comprises a family of enzymes hydrolase, which is located in the brush-border surface membrane of small intestinal cells and it is the key enzyme by which the final step of digestion is catalyzed, so glycosidase inhibitors can stop the liberation of D-glucose from complex dietary carbohydrates and can delay glucose absorption which in turn reduce plasma glucose level and decrease hyperglycaemia [88,89,90].

3.5 Antihypertensive Activity

The vasorelaxant activities of *J. gossypiifolia* root and aerial plant part extracts have been reported. The aerial part extracts 125 and 250 mg/kg/day, over 4 weeks, by oral route in rats], in a dose dependent manner produced a reduction of systolic blood pressure in conscious normotensive animals. It also inhibited, in a concentration-dependent and non-competitive manner, the contractile response induced by norepinephrine or $CaCl_2$ [58].

3.6 Antimicrobial Activity

Dhale and Birari, [91] reported that the alcoholic leaf extracts exhibited significant antibacterial activity using the agar disc diffusion method. The macrocyclic diterpene jatrophenone, isolated from the whole plant was reported to exhibit significant *in vitro* antibacterial activity. Other extracts especially methanolic extracts of the leaf, seed and stem bark have been shown to have antibacterial, antifungal, antiviral and antiparasitic activities. Many organisms such as *E. coli*, S. *aureus*, *B. subtilis* have been reported to be sensitive the different extracts of the plant [92,10,2,79]. Some essential oils such as linalool, [E]-β-ionone, β-caryophyllene, hexahydrofarnesyl acetone and phytol have shown antimicrobial potentials [93].

3.7 Antipurgative Activity

Methanol extract of *J. gossypiifolia* leaves at 200 and 400 mg/kg oral doses in mice, exhibited highly significant antidiarrheal activity upon castor oil-induced diarrhoea, decreasing the mean number of stool and total weight of faecal output when compared to control group. The methanolic extract of the fruits also showed significant activity [94,95].

3.8 Antioxidant Activity

The ethyl acetate extract of the *J. gossypiifolia* whole plant exhibited profound DPPH scavenging, total antioxidant capacity, and lipid peroxidation activities due to its high phenolic content [94]. The methanol, ethyl acetate, and aqueous extracts of *J. gossypiifolia* leaf exhibited antioxidant activities in DPPH free radical, ferric thiocyanate, and nitric oxide scavenging *in vitro* models [94,96]. Jain et al. [48] reported that the ethanolic extract of *J. gossypiifolia* in the dose of 500 mg/kg, p.o., significantly increased glutathione, catalase, and peroxidase levels significantly *in vitro* and can be used in combating oxidative stress.

3.9 Antisickling Activity

The red blood cell membrane stabilization mechanism has also been implicated in the management of sickle cell anaemia [SCA] [97]. This might explain the folkloric use of *J. gossypiifolia* fresh juice in the management of SCA. The haemostatic action of the fresh juice might also explain its folkloric use in the management of SCA [40].

3.10 Haemostatic Activity

J. gossypiifolia latex and fresh juice, is widely used as a haemostatic agent for preventing bleeding disorders. The results of whole blood clotting time using Lee and White method and bleeding time using Ivy's method were significantly reduced when stem latex was introduced, signifying procoagulant activity. The mechanism of action is based on the precipitating action of the latex on bovine albumin, the latex has been reported to precipitate clotting factors thus bringing the coagulation factors into close contact, the activation of coagulation cascade leads to the generation of thrombin leading to the formation of a clot [40].

3.11 Hepatoprotective Activity

Regardless of some studies which showed the hepatotoxic potential of *J. gossypiifolia*, the hepatoprotective action of *J. gossypiifolia* aerial part extracts in carbon tetrachloride-induced liver damage in rats was demonstrated by Panda et al. [34]. The petroleum ether, methanol, and water extracts from the aerial parts of *J. gossypiifolia* significantly restored the serum

levels of serum glutamate oxaloacetate transaminase, serum glutamate pyruvate transaminase, serum alkaline phosphatase, total bilirubin, superoxide dismutase, and catalase [34].

3.12 Immunomodulatory Activity

Both synthetic and naturally occurring 1-phenylnaphthalene lignans and extracts from the whole plant of *J. gossypiifolia* modulated the immunity of the host by significantly increasing the proliferation of mouse spleen cell *in vitro.* [98].

3.13 Neuropharmacological Activity

Apu et al. [94] using the hole cross test model evaluated the neuropharmacological action of the methanol extract of *J. gossypiifolia* leaves and fruits at 200 and 400 mg/kg, by oral route. The extracts showed highly significant sedative and anxiolytic activity at a dose of 200 mg/kg, the results were replicated at 400 mg/kg dose when the elevated plus-maze test model was employed [50].

3.14 Tocolytic Activity

Based on the ethnopharmacological application of the plant as tocolytic remedy, the effects on calcium-evoked uterine smooth muscle contraction of the ethanolic extract and fractions were evaluated. The crude extract and, to a higher extent, the chloroform fraction reduced the calcium-evoked contractile response of the uterine smooth muscle, promoting a rightward displacement of calcium cumulative curves, as well as reducing the maximal contractions [99].

3.15 Effect on the Reproductive System

J. gossypiifolia leaf extract, by oral route, altered the major hormones involved in oestrous cycle regulation, demonstrating its antifertility effect in mice. The extract also exhibited oestrogenic and early abortifacient activities in female rats and spermatotoxic or antispermatogenic effect in male rats [100,101]. Thus the plant is said to have contraceptive effects. Oyedeji et al. [100] showed that the treatment of rats with *J. gossypiifolia* leaf extract, produced no significant changes in body weights of rats in the second, third and fourth weeks of treatment. This could be due to the absence of androgenic anorectic and lipolytic properties in the plant and androgens have been said to possess anabolic activities [102,103]. The ethanolic extract of *J. gossypiifolia* caused a significant decrease in testosterone levels and sperm motility thus suggesting that the extract inhibited the mechanism intervening in the process of hormone synthesis in the Leydig cells and was able to permeate the blood-testis barrier with a resultant alteration in the micro environment of the seminiferous tubules [100]. It has been reported that a decrease in sperm motility caused by chemical agents is due to their ability to permeate the blood-testis barrier [104]. Similarly there was an insignificant decrease in sperm viability as well as a significant increase in the percentage of morphologically abnormal sperm cells induced after treatment of rats with the leaf extract. This could be due to the ability of the extract to either interfere with the spermatogenic processes in the seminiferous tubules, epididymal functions or activities of testosterone on hypothalamic release factor and anterior pituitary secretion of gonadotropins which may result in alteration of spermatogenesis [105,106]. In another experiment by Oyedeji et al. [100], he showed that there was a decrease in sperm count caused by the extract in the treated rats. This might be as a result of decrease in plasma level of testosterone, because this hormone has been reported to be important in the initiation and maintenance of spermatogenesis [107]. A scanty germinal epithelia population was observed in the extract treated rats depicting suppressed sperm production. This scanty germinal epithelia population may be due to insufficient amount of testosterone, since it has been reported that spermatogenesis is activated by testosterone which is synthesized by Leydig cells and act on Sertoli cells and peritubular cells [108]. Oyedeji et al. [100] also revealed that the extract caused mild to severe interstitial edema. It has been reported that there were five pathophysiological causes of edema which can be due to [i] increased hydrostatic pressure [ii] reduced oncotic pressure [iii] lymphatic obstruction [iv] sodium retention or [v] inflammation [109]. Hence, the edema induced by this extract might be caused by any of the aforementioned causes. With these findings, though in animal models, it is advised that caution be exercised in the use of *J. gossypiifolia* especially for contraceptive purposes [101].

3.16 Wound Healing Activity

The juice from the leaves and sap from stem is used to stop bleeding, itching of cuts and skin. Servin et al. [110] showed that the administration of 1 mL/kg single dose of the hydro alcoholic extract from aerial parts of *J. gossypiifolia* had beneficial effects on the healing process of 1] colonic anastomosis in rats until the seventh day, when there was a decrease in the action of the extract; 2] sutures performed on the bladder of rats, 3] open skin lesions in rats; 4] suture healing of ventral abdominal wall of rats, through tensiometric measurement and macro- and microscopic aspect of postoperative period [110].

3.17 Other Activities

J. gossypiifolia is said to be a noxious weed and has been declared as a class 2 pest plant in some parts of Australia. Its emergence as a highly suitable feedstock plant for biodiesel production showing a promising economic exploitation of these raw materials as biodiesel in diesel engines and as a source of pesticide biomolecules e.g. ricinine from the ethyl acetate extract from senescent leaves. Some essential oils such as linalool, [E]-β-ionone, β-caryophyllene, hexahydrofarnesyl acetone and phytol have been reported to have larvicidal [111] and insecticidal activity [112]. Reports have shown that the diluted fresh latex *J. gossypiifolia* can be used as precipitating agent for biochemical determination of proteins in plasma, urine, and cerebrospinal fluid, with values comparable to those obtained from the conventional protein precipitants sodium tungstate and trichloroacetic acid and thus quite useful in biochemical analysis. However, caution must be taken to ensure that the extract is purified to remove interfering substances for it to be perfectly suitable for biochemical analysis. Leaf extract of *J. gossypiifolia* reduced the fecundity and egg viability against stored product insect pests *Tribolium castaneum*. The potential molluscicidal activity of *J. gossypiifolia* has also been evaluated as an alternative mode of prevention of schistosomiasis.

4. TOXICOLOGY

The toxic nature of *J. gossypiifolia* is mostly to its latex and seeds [113,114]. The latex is released from the aerial parts of the plant by mechanical injury and it causes irritation to the skin and mucous membranes. The seeds are rich in toxalbumins that are responsible for agglutination and haemolysis of erythrocytes as well as damage to other cell types and contain a lipoid resin complex that can cause dermatitis [1,49,113]. The adverse effects have been observed to be gastrointestinal disorders [abdominal pain, nausea, vomiting, and diarrhoea]. Other problems that could arise could be cardiovascular, neurological, and renal complications [114]. Cases of poisoning in humans usually occur by ingestion of the fruit and seeds because of its similarity to edible chestnuts [114]. Sukumaran et al. showed that the methanol and n-butanol extracts from unripened seeds of *J. gossypiifolia* was toxic against eggs and adults of two species of freshwater snails, *Lymnaea luteola* and *Indoplanorbis exustus*. The results indicated that n-butanol extract was the most effective and that the eggs were more susceptible than adults [113].

Some reports have demonstrated the toxic properties, while others show the absence of toxicity. However, it is important to observe the models used, doses administrated, and types of extract employed [solvent and plant part], among other aspects, to make the proper conclusions about the toxicity [113].

Awachie and Ugwu, [115] reported low toxicity of ethanol and methanol extracts in the *in vitro* cytotoxicity assay using brine shrimp larvae test. The irritant activity was visualized in mouse ear after 24 h of the application of the fractions and isolated compounds [56].

The crude ethanol extract from *J. gossypiifolia* leaves was reported to have relatively low oral acute toxicity in Wistar rats [116,117]. Rats treated with single doses of 1.2–5.0 g/kg by oral route were observed for 14 days, and the most important signs of toxicity were ptosis, reduction of body weight, and hind limb paralysis. Other significant alterations occurred only in males treated with 5.0 g/kg dose: Increase in creatinine, aspartate aminotransferase, sodium and potassium seric levels, reduction of urea and albumin, leucopenia and small alteration in color, and consistency of viscera. The median lethal dose [LD_{50}] was higher than 4.0 g/kg for males and higher than 5.0 g/kg for females [117]. In the histopathological evaluation some alteration was observed in liver and lung only at 5.0 g/kg, suggesting the relatively low toxicity of the extract [116]. However, in the chronic toxicological study [thirteen weeks of treatment],

this extract showed significant oral chronic toxicity in rats [118]. The most significant toxic signs indicated a reduction of the activity in the central nervous system and digestive disturbances. The histopathological analysis revealed hepatotoxicity and pulmonary damages. The lethality was 46.6% and 13.3% among males and females under the higher tested dose [405 mg/kg], respectively [118]. Based on this, Mariz et al. [119] discussed that the development of herbal medicine based on this species needs to prioritize the chemical refinement of the crude extracts to obtain less toxic fractions, which should be tested for their safety and therapeutic efficacy [119].

The toxicity of the stem latex of *J. gossypiifolia* was studied in Wistar rats by applying different doses of crude latex on incised skin daily for 18 days, based on the popular use of the latex as haemostatic agent in skin lesions [120]. It was observed that the application of the latex did not produce any significant difference in results of biochemical and haematological parameters obtained from the control and experimental animals, leading to the conclusion that the stem latex has no harmful effects [120].

5. CONCLUSION

Based on this review *J. gossypiifolia* presents an important potential for drug development based on popular uses and biological studies. However, further studies are necessary to verify important folkloric uses of the various parts of the plant. Further research into bioactivity guided fractionation of extracts and isolation of compounds responsible for various pharmacological activities such analgesic, anticholinesterase, antidiabetic, antihypertensive, antisickling and neuropharmacological activities. This is imperative for further formulation studies and drug development.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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