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PHYTOCHEMICAL AND PHARMACOLOGICAL PROFILE OF IXORA: A REVIEW

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ABSTRACT: Medicinal herbs used in modern medicine are occupying a very significant place as raw materials for important drugs. India officially recognizes over 3000 plants for their medicinal value. It is generally estimated that over 6000 plants in India are used in traditional, folk and herbal medicine. Traditionally *Ixora* is found to be useful for many ailments like hepatic disorder, cancer, microbial infection, antioxidant, pain, inflammation, etc. and has been documented for various medicinal properties. The genus Ixora has been reported to possess different classes of compounds mainly triterpenoids (lupeol, urosilic acid, oleanolic acid betunolic acid, amyrins, etc.), aromatic acrid oils, tannins, saponins, carbohydrate, fatty acids, flavanoids (rutin, formononetin, β-sitosterol, quercetin and kaempferol) and sterols. Out of many species of Ixora much research was done on *I. coccinea* and some part of the work on *I. chinensis*, I. javanica, I. finlaysoniana, I. parviflora and I. macrothyrsa. The main aim is to provide a comprehensive review on the phytochemical and pharmacological aspects of various species of Ixora. In the present review, efforts are made in addressing its ethnomedicinal uses, chemical constituents and reported pharmacological activities.

INTRODUCTION: Herbal medicine is fast emerging treatment as an alternative to available synthetic drugs for treatment of various diseases, possibly due to lower costs and reduced side effects. Various chemical compounds have been isolated from medicinal plants. More than 70% of the developing world's population now depends on the traditional medicinal system, otherwise known as complementary or alternative systems of medicine¹.

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Ixora is a genus of flowering plants in the Rubiaceae family. It consists of tropical evergreen trees and shrubs and holds around 500 species with its centre of diversity in Tropical Asia. *Ixora* also grows commonly in subtropical climates in the United States, such as Florida.

The common names are West Indian Jasmine, Rangan, Kheme, Ponna, Chann tanea, Techi, Pan, Santan, Jarum-jarum, Jungle flame, Jungle geranium and many more. They are mostly shrubs and small trees that are part of the under storey plant community in the tropical forest, but some species can become very tall. People of the region have been using *Ixora's* for generations, not only for ornamental purposes but more importantly because of their medicinal values. *Ixora* is a popular flowering plant in gardens. Red *Ixora* flowers are commonly used in Hindu worship, as well as in Indian folk medicine.

Distribution:

Ixora is said to be native to Asia and whose name derives from an Indian deity. There are about 400 species spread from Africa to India to Southern Asia. Members of *Ixora* prefer acidic soil, and are suitable choices for bonsai. It is also a popular choice for hedges in parts of South East Asia, like in Thailand. In tropical climates they flower year round. This plant which blooms throughout the year is easy to grow.

Several popular cultivars are dwarfs, usually staying under 3 ft (1 m) in height. Leaves are coriaceous, from 2 cm to 6 inches in length, sessile or sub-sessile, oblong and obtuse 2 . They differ in leaf size, plant height, flower size and color. The

Taxonomic Hierarchy:

flower appears in clusters, which are produced at the end of branches. Each cluster may contain up to 60 individual flowers. The flower is very small and tubular, with four petals. It comes in a variety of brilliant colors like red, orange, yellow, white and pink. The style is forked at the tip, and it protruded slightly out of the corolla tube.

The fruit is a berry containing 1-2 seeds. Miniature ones have small leaves and are bushy. Ixora flowers last well when picked and put into a vase making attractive with water, an home arrangement. Ixora flower has traditionally been associated with enhanced sexuality and the rekindling of passion. Phytochemical studies indicate that the plant contains important phytochemicals such as lupeol, ursolic acid, oleanolic acid, lecocyanadin, sitosterol, rutin, anthocyanins, proanthocyanidins, glycosides of kaempferol and quercetin.

Kingdom	Plantae – plantes, Planta, Vegetal, plants
Subkingdom	Viridaeplantae – green plants
Infra kingdom	Streptophyta – land plants
Division	Tracheophyta – vascular plants, tracheophytes
Subdivision	Spermatophytina – spermatophytes, seed plants, phanerogames
Infradivision	Angiospermae – flowering plants, angiosperms
Class	Magnoliopsida
Superorder	Asteranae
Order	Gentianales
Family	Rubiaceae – madders, rubiacees
Genus	Ixora
	Direct Children:
Species	Ixora acuminata Roxb. – bola de nieve
Species	Ixora casei Hance
Species	Ixora coccinea L. – scarlet jungle flame
Species	Ixora ferrea (Jacq.) Benth. – palo de hierro
Species	Ixora finlaysoniana Wall. ex G. Don
Species	Ixora grandiflora Zoll. & Moritzi – large flower jungle flame
Species	Ixora macrothyrsa (Teijsm. & Binn.) T. Moore
Species	Ixora pavetta Andrews – torch tree
Species	Ixora thwaitesii Hook. f. – white jungle flame
Species	Ixora triantha Volkens
Species	Ixora arborea (I. parviflora)
Species	Ixora duffi
Species	Ixora javanica (I. singaphorensis)
Species	Ixora alba
Species	Ixora albersii
Species	Ixora chinensis

Ixora coccinea, I. chinensis (Chinese Ixora), *I. singaporensis* (*I. javanica*) and *I. parviflora* (*I. arborea*) are the most common species offered in nurseries. Another species is *I. finlaysoniana* which originated from India to Indo-china and this shrub

produces fragrant white flowers. As a result of hybridization and natural crossing many varieties have developed which are of horticultural importance. The species and varieties have been arranged according to the color and flower. Out of so many species of *Ixora*, the most commonly available species with work done on it are only 4-5 species. Much of the work has happened on *I. coccinea*.

Ixora coccinea Linn.³

Synonyms: *Ixora grandiflora* Bot. and *Ixora bandhuca* Roxbg.

Common Names: Jungle of geranium or Flame of woods or Red Ixora.

It is an evergreen shrub found throughout India. Depending on the medical condition, the flowers, leaves, roots, and the stem are used to treat various ailments in the Indian traditional system of medicine, the Ayurveda, and also in various folk medicines.

The word "*Ixora*" is a Portuguese version of Iswari, name of Goddess Parvati to which the flowers of *I. coccinea* are offered, while the word "coccinea" is a Latin word meaning Scarlet coloured ⁴. It bears flowers which are numerous having bright scarlet colour in dense, senssile corymbiform cymes. The plant *I. coccinea* is native to India and is found mostly in Konkan region. It is cultivated throughout India as an ornamental plant ⁵.

The fruits, when fully ripe, are used as a dietary source. *I. coccinea* is a dense, multi-branched evergreen shrub, commonly 4–6 ft (1.2–2 m) in height, but capable of reaching up to 12 ft (3.6 m) high. It has a rounded form, with a spread that may exceed its height. The glossy, leathery, oblong leaves are about 4 in (10 cm) long, with entire margins, and are carried in opposite pairs or whorled on the stems. Small tubular, scarlet flowers in dense rounded clusters 2-5 in (5–13 cm) across are produced almost all year long ⁶.

There are numerous named cultivars differing in flower colour (yellow, pink, orange) and plant size. Several popular cultivars are dwarfs, usually staying under 3 ft (1 m) in height. *Ixora* 'Nora Grant' is a popular dwarf and 'Super King' is a popular hybrid with much larger flower clusters than the species. Many new cultivars and hybrids of *I. coccinea* have come to market in the last couple of decades, leading to resurgence in popularity for the beautiful flame-of-the-woods. It is traditionally used as hepatoprotective, chemoprotective, antimicrobial, anti-oxidant, antinociceptive, anti-mitotic and anti-inflammatory activities. Decoction of roots was used for nausea, hiccups and anorexia. Powered roots are used for sores and chronic ulcers in Indo-China, root decoction is used to clarify the urine, poultice fresh leaves and stems for sprains, eczema, boils and contusions⁷.



RED IXORA

YELLOW FLOWERS

FIG.2a FIG.2b 8, 9: Preliminary phytochemical screening 8, 9: Presence of major phytoconstituents such as alkaloids, glycoside, flavonoids, steroids, triterpenoids, tannins, saponins, resins etc.

Chemical constituents:

Fifty-four components have been identified in the essential oil of I. coccinea flower, representing 99.97% of the total components detected. The oil is composed mainly of triterpenes 62.60%, monoterpenes 31.73%, sesquiterpenes 3.35% and an ester 2.29%. The major constituents of triterpenes were ursolic acid (27.34%), oleanolic (20.16%) and lupeol (15.10%). Ixora coccinea flower is of ursolic acid chemotype. Geranyl Acetate (8.74%) is the major monoterpenes, followed by Linalyl acetate (6.79%), Nervl acetate (6.49%), Terpineol acetate (4.91%), and Borneol acetate (4.77%); Ethyl cinnamate (2.29%) an ester while the sesquiterpenes are Cyperene (2.72%) and α -Copaene (0.63%)¹⁰.

A new triterpene, ixorene with dammarane skeleton was isolated from the leaves of *I. coccinea*, along with the three known constituents β -sitosterol, lupeol and D-mannitol. The structure was elucidated on the basis of extensive 1D and 2D-NMR studies and mass spectrometry as 17 β dammara-12, 20-diene-3 β -ol¹¹. The air-dried flowers of *I. coccinea* afforded two new cycloartenol esters, lupeol fatty ester, lupeol, ursolic acid, oleanolic acid and sitosterol. The structures were elucidated by extensive 1D and 2D NMR spectroscopy and MS¹².

Two novel derivatized peptides, designated as ixorapeptide I and ixorapeptide II, in addition to 28 other known compounds, were isolated from the methanolic extract of I. coccinea using bioassayguided fractionation. The structures of metabolites 1 and 2 were determined by interpretation of the spectroscopic data and Marfey's method. Compound 1 exhibited selective potency against Hep3 β liver cancer cell line with an IC₅₀ value of $3.36 \,\mu\text{g/mL}$, and compound 2 did not show notable cytotoxicity toward cancer cell lines but could inhibit superoxide anion generation and elastase release with IC_{50} values of 0.21 and 0.27µg/mL

respectively. Moreover, kaempferol and luteolin from this plant showed inhibition with IC_{50} values of 3.55 and 2.56µg/mL, respectively on platelet aggregation induced by collagen ¹³.

The anticancer activity of the leaves of *I. coccinea* (Rubiaceae) was found to be due principally to the known alkaloid, camptothecin. The presence of camptothecin was confirmed by RP-HPLC analysis. The average content of camptothecin both in mature and young leaves was 2.8% and it paves way for new findings ¹⁴.

Chemical investigation of the roots led to the isolation of six phytoconstituents namely: 9, 12octadecadienoic acid, di-n-octyl phthalate, β amyrin, kaempferol-7-oglucoside, kaempferitrin and quercitrin¹⁵.



FIG. 1a Chemical constituents structures in I.coccinea



FIG. 1b Chemical constituents structures in I.coccinea

Macroscopy:

The plant is a dense, multi – branched evergreen shrub, commonly 4-6 ft (1-2-2m) in height, but capable of reaching up to 12 ft (3.6 m). Leaves are oblong are about 10cm long, with entire margins and are carried in opposite pairs or whorled on the stem. They are sessile to short – petiolate, blades elliptic, oblong or obovate, usually leathery, base cordate to rounded, apex rounded, mueronate or shortly tapering; stipules basally sheathing, lobes Triangular, Flowers sessile; calyx lobes short, triangular, persistent, corolla tube usually 1-1.5 inches long, lobes lanceolate to ovate, less than 0.25 inches long, acute or sometimes obtuse fruit thinly fleshy and reddish black.

Microscopy:

The leaf is dorsiventral, hypostomatic and mesomorphic. It has thick midrib projecting both adaxially and abaxially. The midrib has adaxial broadly conical hump and wide semicircular abaxial past. The midrib is 1.1 mm thick. The adaxial past is 400 µm wide.

The abaxial part is 900 μ m thick. The epidermal layer of thin midrib consists of small, squarish, thick walled cells with prominent cuticle, the cells are with prominent cuticle and the cells are 22 μ m thick. The lower semicircular midrib has parenchymatous ground tissue. The cells are wide thin walled, angular and compact. Calcium oxalate crystals are occasionally seen in some of the

parenchyma cells. The vascular system of the midrib consists of an adaxially flattened closed cylinder of xylem and phloem; within the cylinder are two small rectangular segments of vascular bundles. The outer cylinder has a thin layer of xylem fibers and short radial files of narrow, thick walled angular xylem elements.

The abaxial epidermis has comparatively small cells which are square in shape, the cuticle is thicker; stomata are present on the lower epidermis. These are two layers of palisade cells along the upper part. The cells are wide, cylindrical and the palisade zone in 60 μ m in height. The spongy parenchyma cells are in 4 (or) 5 rows. They are large thin travelled, spherical lobed and form wide air – chambers. The vascular strands of the lateral veins are circular with thick cylinder of fibers and small central case of xylem and phloem ¹⁶.

Pharmacological actions: Pharmacological studies suggest that the plant possesses antioxidative, antibacterial, gastroprotective, hepatoprotective, antidiarrhoeal, antinociceptive, antimutagenic, antineoplastic and chemopreventive effects, thus lending scientific support to the plant's ethnomedicinal uses.

Anti-oxidant activity:

The anti-oxidant activity of the methanol extract of Ixora coccinea Linn. was reported by DPPH free radical scavenging assay, reducing power and total antioxidant capacity using phosphor molybdenum method. The methanolic extract showed significant activities in all antioxidant assays compared to the standard antioxidant in a dose dependent manner and remarkable activities to scavenge reactive oxygen species (ROS) may be attributed to the high amount of hydrophilic phenolics. In DPPH radical scavenging assay the IC_{50} value of the extract was found to be 100.53 µg/mL while ascorbic acid had the IC₅₀ value 58.92 μ g/mL. Thus *Ixora coccinea* extract showed strong reducing power and total antioxidant capacity ¹⁷. One method has been developed to isolate quercitrin from Ixora coccinea leaves, which depends on fractionation of defatted hydro-alcoholic extract by different polarity solvents followed by purification through column chromatography. Isolated quercitrin has been characterized by using UV, IR, Mass spectral data, NMR data and also confirmed by using HPTLC

and elemental analysis. The isolated quercitrin was shown a challenging potency to scavenge DPPH free radicals and also nitric oxide free radicals with very low IC_{50} value ¹⁸. A comparative study of *in vitro* and *in vivo* antioxidant property of different *Ixora* species was also reported ¹⁹.

Anti-inflammatory activity:

The anti-inflammatory potential of an aqueous leaf extract (ALE) of Ixora coccinea (Rubiaceae) in rats by carrageenan-induced paw edema (acute inflammatory model) and cotton pellet granuloma tests (chronic inflammatory model) at oral (500, 1000 and 1500 mg/kg) was reported. In the former test, ALE significantly impaired both early and late phases of the inflammatory response and also the edema maintained between the two phases. In the latter test, it significantly suppressed granuloma formation (only highest dose tested). Collectively, these data showed promising anti-inflammatory activity against and both acute chronic inflammation²⁰.

The anti-inflammatory activity of methanolic leaf extract (MLE) of I. coccinea Linn. showed dosedependent activity in carrageenan-induced rat paw edema model (r = 0.7; P<0.01). MLE at a dose of 500, 1000, and 1500 mg/kg showed maximum inhibition of edema 36.7, 46.5, and 64.5% respectively (P<0.01). Oral administration of MLE of rats at a dose of 1500 mg/kg significantly inhibited peritoneal phagocytic cell infiltration (45.9%; P<0.05), impaired nitric oxide (NO) production in peritoneal cells (40.8%; P<0.01) and showed antihistamine activity (54.9%; P<0.01). In vitro treatment of rat peritoneal cells with MLE inhibited NO production dose-dependently (82.2% at 400 μ g/ml, r = 0.99; P<0.05). MLE also possessed significant, dose-dependent in vitro antioxidant activity (r = 0.88; P<0.01; IC₅₀ value = 8.0 μ g/ml), membrane stabilizing activity (r = 0.81; P < 0.01; IC_{50} value = 6.4 ng/ml) and lipid peroxidation activity (36.7% at 250 μ g/ml; P<0.01)

Anthelmintic activity:

The anthelmintic activity of *I. coccinea* roots in different extracts against Indian earthworm, *Pherituma posthuma* was reported ²². Chloroform soluble fraction showed good anthelmintic activity

than ethyl acetate soluble, methanolic and petroleum ether extract.

Antileishmanial activity:

The in vitro antileishmanial activity of ethyl acetate and methanol extracts from I. coccinea leaf was evaluated against Leishmania donovani (strain AG 83) promastigotes by in vitro promastigote cell toxicity assay by using MTT [3-(4,5dimethylthiazol-2-yl)-2,5 dipheny ltetrazolium bromide] was reported and both the extracts showed markedly inhibited growth ²³.

Anti-asthmatic activity:

The anti-asthmatic activity of hydroalcoholic extract of *Ixora coccinea in* an ovalbumin induced asthmatic rat model was reported ²⁴. The extracts at a dose of 1000 and 1500 mg kg⁻¹ supressed eosinophilia and significantly inhibited AHR in rat. Histopathological studies using hematoxylin and eosin showed the reduced inflammatory cell infiltration and repaired the damaged epithelial cells, which proves the anti-asthmatic properties of *I. coccinea.*

Anti-diarrhoeal Activity:

The anti-diarrhoeal activity of aqueous extract of the leaves 25 and flowers 26 of *I. coccinea* against a castor oil induced diarrhoea model in rats was reported. The weight and the volume of the intestinal content induced by castor oil were studied by the enteropooling method. Loperamide was used as a positive control. The plant-extract showed significant (P<0.001) inhibitor activity against castor oil induced diarrhoea and castor oil induced enteropooling in rats at the dose of 400 mg/kg. There was significant reduction in gastrointestinal motility by the charcoal meal test in rats.

Antimicrobial activity:

The antimicrobial activities of leaf extracts of *Ixora* coccinea Linn. and Commelina benghalensis L. was studied by using various organisms by means of agar diffusion method. Susceptibility of some Gram-negative organisms (Escherichia coli, Pseudomonas aeruginosa, Salmonella typhi) and Gram-positive organisms (Staphylococcus aureus) were tested. Antibacterial activity was determined by measuring the diameter of zones of inhibition (mm) produced after incubation. The organisms

were more sensitive to the hexane, chloroform extract of the leaves, whereas extracts from other solvents like chloroform and hexane showed moderate to weak activity, respectively ²⁷.

Hypoglycaemic and Hypolipidaemic activity:

There is a report on the hypoglycaemic and the hypolipidaemic activity of the aqueous extract of the leaves of *Ixora coccinea* Linn in alloxan induced diabetic albino rats. The aqueous extract of leaves of showed significant reduction (p<0.01) in the blood glucose levels and the serum lipid profile levels, with 400 mg/kg of body weight in the alloxan induced diabetic rats as compared to the controls ²⁸.

Hepatoprotective activity:

The hepatoprotective activity in ethanolic extracts of three different plants I. coccinea, Rhinacanthus nasuta, Spilanthes ciliata was reported on the aflatoxin B1 (AFB1) -intoxicated livers of albino Wistar rats. Biochemical parameters, male including serum hepatic enzymes (glutamate oxaloacetate transaminase, glutamate pyruvate transaminase and alkaline phosphatase), were studied. Pathological examination of the liver tissues supported the biochemical findings. The three plant extracts, IC, RN and SC, showed significant anti-lipid peroxidant effects in vitro²⁹.

Wound healing activity:

The wound healing activity of alcoholic extract of the flowers of *I. coccinea* was reported by using a dead space wound model in rats. Significant increases in granuloma tissue weight, tensile strength, hydroxyl proline and glycosaminoglycan content were observed in extract treated rats. The drug induced a hypertropic effect on the thymus gland but had no effect on the adrenals 30 . The wound healing efficacy of root extract of I. *coccinea* Linn. was also reported taking five groups of animals and dividing each containing six animals. Two wound models including incision and excision wound models were used in this study. The parameters studied were tensile strength on incision wound model and in terms of wound contraction for excision wound model were compared with standard Nitrofurazone (NFZ) ointment (0.2% w/w). Six extracts (ethanol, aqueous, petroleum ether, benzene, chloroform and ethyl acetate) of I. coccinea were screened for in

vitro growth inhibiting activity against different bacterial strains viz, Staphylococcus aureus, **Bacillus** pumilius, **Enterococcus** faecalis. typhi Escherichia coli. Salmonella and Pseudomonas aeruginosa and fungi Candida albicans and Aspergillus niger were compared with drugs ciprofloxacin the standard and chloramphenicol for antibacterial and griseofulvin for antifungal screening. The serial dilution and cup (or) well plate methods were used for the antimicrobial study and MIC was determined.

The ethanolic extract showed significant (P<0.001) wound healing activity when compared to standard drug NFZ with respect to normal control group. Amongst all, ethanolic extract showed highly significant antibacterial activity against all bacterial strains used in this study when compared to standard. The aqueous extract showed moderate significant inhibition against all bacterial strains when compared to standard. All the extracts were shown negligible activity against the fungal strains used in this study ³¹.

I. coccinea enhances cutaneous wound healing by upregulating the expression of collagen and basic fibroblast growth factor 32 .

Antinociceptive activity:

The antinociceptive potential of leaves of Ixora coccinea was reported by three models of nociception (tail flick, hot plate and formalin tests). One of four doses (500, 750, 1000 or 1500 mg/kg, n=8/dose) of aqueous leaf extract (ALE) or 1 ml of distilled water was orally administered to male rats. The results showed that ALE possesses antinociceptive activity, considerable when evaluated in hot plate and formalin test but not in tail flick test ³³.

Analgesic and Anti-inflammatory activities:

There was a report on the Analgesic and Antiinflammatory activities of methanolic extract of *I. coccinea* flowers ³⁴ *In vivo* anti-inflammatory activity was evaluated in rats by using carageenaninduced paw edema, as an acute anti-inflammatory model. Quantitative estimation of total polyphenolic content of *I. coccinea* flowers was estimated after oral administration of extract 100 mg/kg in carrageenan injection, which showed significantly decreased paw volume. Methanolic extract of flowers also exhibited significant analgesic activity. The response of licking or jumping latency was recorded in seconds by using hot plate method. Presence of phytochemical like flavonoids, glycosides, and tannins in the extract might contributed to the observed analgesic and anti-inflammatory activities.

Analgesic, Anti-inflammatory and Anti-pyretic activities:

The ethanolic extract of *I. coccinea* leaves explored analgesic, anti-inflammatory and antipyretic agents using the hot-plate, acetic acid-induced writhing, carrageenan-induced paw edema and brewer's yeast-induced pyrexia tests in rodents ³⁵. The extract was prepared by soaking the dried powdered leaves in ethanol for 2 days. The filtrate thus obtained by filtration and evaporation was considered as a stock solution and was used in all experimental models.

Oral administration of extract (250 and 500 mg/kg) significantly (p<0.05) increased the reaction time in the hot-plate test. I coccinea (250 and 500 mg/kg) produced 56.14% and 63.16% inhibition (p<0.05) in acetic acid-induced writhing. It also (250 and mg/kg) produced significant 500 (p < 0.05)inhibition of paw edema pronounced at 6 h after carrageenan injection. Intraperitoneal administration of IC (250 and 500 mg/kg) lowered the body temperature in brewer's yeast-induced hyperthermia.

Cytotoxic and Antitumour activity:

The antitumour activity of *I. coccinea* L. flowers studied in comparison to intraperitoneally transplanted Dalton's lymphoma (ascitic and solid tumours) and Ehrlich Ascites Carcinoma (EAC) tumours in mice. Intraperitoneal administration of 200 mg/kg of the active fraction (AF) of the *I. coccinea* flower increased the life-span of DLA and EAC ascitic tumour-bearing mice by 113 and 68%, respectively. The AF inhibited tritiated thymidine incorporation in cellular DNA which proves the anti-tumor activity of *I. coccinea* plant³⁶.

Chemoprotective activity:

The chemoprotective effect of flowers on cisplatin induced toxicity in mice was also reported ³⁷. The active fraction from *I. coccinea* flowers prevented a decrease in body weight, haemoglobin levels and

leucocyte counts of mice treated with cisplatin. It also significantly prolonged the life span of cisplatin treated mice and maintained their blood urea nitrogen levels in the near normal range, indicating its chemoprotective effects.

Cardioprotective activity:

The effect of methanolic extract of *I. coccinea* Linn. leaves against doxorubicin-induced cardiac toxicity in rats was reported by pretreating with the methanolic extract of leaves (200 and 400 mg/kg, orally) for 1 week followed with the simultaneous treatment with doxorubicin (cumulative dose of 15 mg/kg in six divided doses for 2 weeks) along with the extracts for the next 14 days. On the 22nd day hemodynamic parameters such as blood pressure and ECG were recorded.

Biochemical study including biomarkers like creatine kinase- MB (CK - MB), lactate dehydrogenase (LDH), SGOT and SGPT, tissue antioxidant markers viz. catalase (CAT), superoxide dismutase (SOD) and extent of lipid peroxidation viz. malondialdehyde (MDA) was estimated. Histopathology of heart was also done to assess the cardioprotective effect, which confirmed the cardioprotection provided by the methanolic extract due to its antioxidant properties ³⁸.

Anti-ulcer activity:

Fresh leaf extract of *Ixora coccinea* Linn. was reported for its anti-ulcer activity in pyloric ligation (PL) and hypothermic-restraint stress (HRS) induced gastric ulcer models in Albino rats. At doses of 100 and 200 mg/kg were found to be protective effect in PL (45.86 and 75.02%) induced ulcer models and significantly reduced free and total acidity by P < 0.01 and P < 0.001 respectively. Conclusively, MEIC was found to possess potent anti ulcerogenic property and could act as a potent therapeutic agent against ulcer disease ³⁹.

The antiulcer and *in-vitro* antioxidant activities of Methanolic flower extract of *I. coccinea* (MEIC) and Methanolic Polyherbal Extract (MPE) of *I. coccinea* flowers, *Psidium guajava* roots, *Neolamarckia cadamba* leaves was investigated by inducing ulcers by pyloric ligation and aspirin. The animals were treated with Omeprazole 20 mg/kg, MEIC 200 mg/kgbwt and 400mg/kgbwt, MPE 200 mg/kgbwt and 400 mg/kgbwt. Gastric volume, pH, free acidity, total acidity, mean ulcer index and percentage of ulcer inhibition was calculated in both models. In *in-vitro* antioxidant, Nitric oxide scavenging activity and lipid peroxidation content were estimated. All the extracts of MEIC and MPE, dose dependently reduced the volume of acid secretion, free acidity, and total acidity in both ulcer models. But a slight difference in pH was observed in aspirin induced ulcer model. MPE has shown (79%) a highly significant ulcer curative potential and decreased ulcer formation in both ulcer models.

A preliminary phytochemical analysis revealed the presence of different phytochemical constituents such as glycosides, flavonoids, terpenoids, tannins, saponins. It also produced significant reduction in Free radical scavenging and Lipid peroxidation content. Synergistic effect was produced by using MPE and it has shown highly significant ulcer curative potential ⁴⁰.

Nano particle biosynthesis:

The synthesis of gold nanoparticles in aqueous medium using flower extracts of *Ixora coccinea* as reducing and stabilizing agent. On treating chloroauric acid solution with extract, rapid reduction of chloroaurate ions is observed leading to the formation of the highly stable gold nanoparticles in solution. The study also showed that gold nanoparticles with antibiotic show more inhibitory zones than compared to the standard antibiotics ⁴¹.

Neuroprotective activity:

The neuroprotective activity of *Ixora coccinea* leaves extract was determined experimentally by inducing neurotoxicity i.e., AlCl₃ and 3-nitroproponic acid induced neurotoxicity in experimental models in albino rats ⁴².

Chromatographic Fingerprint Analysis:

The chemical composition of *Ixora coccinea* methanolic flower extract was carried out using HPLC, HPTLC and Gas Chromatography–Mass Spectrometry technique. HPLC analysis of *I. cocccinea* methanolic flower extract revealed the: presence of Biochin A, Myricetin, Quercetin, Rutin, Diadzein and formononetin, HPTLC fingerprint revealed the presence of ursolic acid

and GC-MS with 24 phytochemicals among which some are of biological importance. The result of this study offers a platform for using *I. coccinea* pharmacologically ⁴³.

Anxiolytic activity:

Anxiolytic activity of *I. coccinea* ethanolic extract was evaluated in Swiss Albino mice by elevating plus maze paradigm test and Hole board test, which showed a significant (P<0.01) effect in a dose dependent manner when compared with the standard dose of diazepam⁴⁴.

Antityrosinase and Antioxidant activities:

The different parts of *I. coccinea*, in various solvents were examined for antityrosinase and antioxidant activities. The methods for screening are based on tyrosinase inhibitior potency using mushroom tyrosinase and antioxidant activity using 2, 2-diphenyl picryl hydrazyl (DPPH) radical scavenging, inhibition of lipid peroxidation, ferric reducing power and phenol estimation. Among the parts investigated for skin whitening activity, the flowers were found to possess the superior activity.

The methanolic extract of bark had the highest inhibition of DPPH when compared to flowers and leaves. However, the antioxidant potential of leaves and flowers were also comparable with bark. The inhibition of lipid peroxidation & the phenolic content was maximum in the leaves when compared to bark and flowers. Bark exhibited the best ferric reducing power when compared to other parts. Thus, *I. coccinea* serves as a potential source of ingredient for formulating the cosmetic products ⁴⁵.

Ixora chinensis ⁴⁶:

Synonyms: *Ixora stricta* Roxb. Common names: Cambodia: Kamrontea Filipino: Chinese Ixora ⁴⁷, santan-pula Indonesian: Siantan Malay: Pechah priok Vietnamese: B[ooj]ng trang d[or]

In southern China, one of the most common native species is *Ixora chinensis* identified by its almost stalkless leaves and red flowers. It is widespread in Southeast Asian gardens and use to treat various ailments like rheumatism and wounds.

Botanic description

It is a shrub with many stems, upto 2 m tall. Leaves obovate-oblong, 6-10 cm x 2.5-5 cm, coriaceous, base rounded, cordate or sometimes obtuse, apex obtuse, petiole short, stipules longawned. "Branchlets of inflorescence opposite, red; flowers with corolla tube 3-3.5 cm long, lobes circular-obovate, broadly rounded at apex, 6 mm x 6 mm, orange-red or white (cultivated plants only), not fragrant." Fruit is globose and black. The differences between the widely cultivated *I. chinensis* and *I. coccinea* are sometimes obscure as a result of selection for rare or extreme forms.



FIG: 3a I. chinensis (white)



FIG: 3b I. chinensis (Orange)



FIG: 3c I. chinensis (Red)

I. CHINENSIS IS WIDELY CULTIVATED AS AN ORNAMENTAL PLANT

Note: *Ixora chinensis* and *I. coccinea* are often confused even by nurseries and both have mainly red to yellow flowers, with tubes never longer than 5 cm and very small sepals.

-I. chinensis: cuneated leaf base, round petals.

-I. coccinea: heart shaped leaf base, pointy petals.

There are so many varieties that it's hard to distinguish both species by the petals shape, and even to differ them from other species by the flower color. But the shape of the base of the leaf is constant, and can be safely used to distinguish *I. chinensis* from *I. coccinea*.

Plant description:

It is a shrub, 1 m tall. Leaves are subsessile, 6-10 x 3-6 cm, oblong, elliptic, elliptic-obovate, entire and glabrous. Stipules are broad, triangular, awned and glabrous. Inflorescence is trichotomously branched with dense corymbs; bracts small and subulate. Flowers are pink, scarlet or orange, central flowers sessile and two side flowers pedicellate, pedicel 2.5 mm long, each with a pair of small bracteoles. Calyx-tube 1.5 mm long, pubescent; lobes are 0.5 mm long, tinted red. Corolla-tube is 1.5-2 cm long, minutely hairy; lobes elliptic, acute 5-6 mm long. Staminal filaments very short; anthers 3 mm long, reflexed. Style exserted and stigma is 2-lobed.

Distribution:

Indigenous to Malaya, Java and China; cultivated in India, Pakistan and other tropical countries.

Chemical constituents:

Seven compounds were isolated from petroleum ether and ethanol fractions of *I. chinensis*, and were identified as D-mannitol, stearic acid, 1, 5cyclooctadiene, β -sitosterol, (10E)-9-oxo-octadec-10-en-12-ynoic acid, azelaic acid and dihydro masticadienolic acid. Ixora liphatic acid, is new and the other compounds are firstly isolated from this plant. A C₁₈ conjugated tetraenoic acid was isolated from *I. chinensis* seed oil. The roots of *I. chinensis* also contain an iridoid derivative called ixoside (1, 8-dehydroxyforsythide). Chinese *Ixora* flowers mainly consist of flavonoids and anthocyanins⁴⁸.

As flavonoids, anthocyanins are present in flowers of *Ixora chinensis* and are pH sensitive ⁴⁹. It has been hypothesized that the flower extract could be utilized as an indicator for different types of acid base titrations ⁵⁰.



FIG. 2 Chemical constituents of Ixora chinensis

Pharmacological actions:

The roots are used in Asian medicine to relieve stomach problems. In Malaysia a decoction of the root is used after childbirth. In the Philippines an infusion of the fresh flowers is said to be a remedy against incipient tuberculosis and haemorrhage. An infusion of leaves or flowers is used against headache. In Indonesia, a decoction of the roots is used against bronchial disorders; a decoction of the flowers is prescribed in amenorrhoea and hypertension. It is also used to treat headache and stomachache and as a remedy for incipient tuberculosis. In a modified tumour promotion test, complete inhibition of all kinds of tumours was exhibited by decoctions of flowers of *I. coccinea* and *I. chinensis*.

Ixora parviflora

Ixora parviflora Vahl is an ornamental shrub cultivated in gardens for white cluster of flowers and evergreen foliage. It is found throughout the greater part of India, from the gangetic plain eastwards to Assam and southwards to Kerala and in Nicobar Islands.



FIG: 4 Ixora parviflora

Synonym(s): *Ixora arboreoa* Roxb.

Common names:

Bengali/Vernacular Name: Shet Rangan, Gandhal Rangan

English Name: Torch Tree, Torch-wood Ixora Ayurvedic Name: Nevaari, Nevaali, Ishara, Rangan Siddha/Tamil Name: Shulundu-kora, Korivi

Botanical description

It is a small much branched evergreen tree or shrub. Leaves are opposite, subsessile, 7-15 cm long, coriaceous, elliptic or oblong, obtuse or shortly acuminate. Flowers are white, small very numerous, in clusters, in sessile cymes, brachiate with 3-5 pairs of short branches.

Chemical constituents:

A new flavone glycoside isolated from the stem of *I. arborea* has been characterized as chrysin 5-O- β -D-xylopyranoside on the basis of spectral data, colour reactions and degradation studies ⁵¹. Leaves contains ixoral and β -sitosterol ⁵². Bark contains fatty matter, tannin and red colouring matter. Seeds yield an oil, which contains linoleic, oleic, stearic and palmitic acids as major components and myristic, lauric, capric and behenic acids as minor ones. 6, 7-dimethyl hydroxy coumarin has been isolated from the aerial parts.

A total of four compounds namely betulin, erythrodiol, lupeol, and stigmasterol were isolated from the leaf extract of *I. arborea* for the first time 53 .

Five compounds viz: chlorogenic acid, apigenin, quercetin, apigenin-7-O-fi-D-gluco pyranoside and quercetin-3-O-fi-D-galactopyranoside were isolated for the first time from the alcoholic extract of the flowers of *Ixora parviflora* Vahl.



FIG. 3b Chemical compounds in Ixora parviflora

Decoction of the bark is used for anaemia and general debility. Flowers are used in whooping cough. Fruits and roots are given to females when the urine is high coloured. Ethanol (50%) extract of aerial parts is antiviral, hypotensive and spasmolytic. The roots paste with groundnut oil is applied for scabis.

Pharmacological actions: Antioxidant activity ⁵⁴:

The antioxidant (free radical scavenging) activity of the *I. arborea* extracts was investigated on the stable radical 1, 1-diphenyl-2-picrylhydrazyl (DPPH) by the method developed by Brand-Williams etc.

Antimicrobial activity:

The disc diffusion method was used to test antimicrobial activity of the *I. arborea* extractives

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bacteria (Bacillus against 13 cereus. В. megaterium, B. subtilis, Staphylococcus aureus, Sarcina lutea, Escherichia coli, Pseudomonas Salmonella paratyphi, S. aeruginosa, typhi, Shigella boydii, S. dysenteriae, Vibrio mimicus & V. parahemolyticus) and 3 fungi (Candida albicans, Aspergillus niger & Sacharomyces cerevisiae).

Antimicrobial activity was carried out using disc diffusion assay against fungi, gram-positive and gram-negative bacteria. All methanolic extracts of different parts of Ixora species showed a broad-spectrum of antibacterial and anti yeast activities, which inhibited the growth of at least one bacterium or yeast ⁵⁵.

Cytotoxic activities:

Brine shrimp lethality bioassay technique was applied for determination of general toxic property of the plant extractives.

Ixora finlaysoniana:

Ixora finlaysoniana Wall.ex.G.Don. is a handsome woody shrub with showy flowers in clusters and evergreen foliage 56,57 . *Ixora* wood is febrifuge and the root is aperient, diuretic and deobstruent 58 . The dried entire plant of *I. finlaysoniana* is used in Thailand as a strength medicine 59 , while the ethanolic extract of the plant was proved to have estrogenic, abortifacient and anti-implantation effects 60 .

Chemical constituents:

A hydrocarbon alcohol, nonacosanol, α -amyrin and β -sitosterol were isolated from the n-hexane fraction of the methanolic extract of the plant. From the chloroform fraction, four compounds were isolated; 3-hydroxyhexan-5-olide, protocatechuic acid, gallic acid and β -sitostreol glucoside.

In addition to three compounds were isolated from the ethyl acetate fraction; arasorboside, D-1-Omethyl-myo-inostiol and galactitol ⁶¹ and the isolation of apigenin-4-O- \Box -D-glucopyranoside and 11-hydroxy-dodec-5-en-2-one ⁶². The botanical study of the stem and leaf of *Ixora finlaysoniana* cultivated in Egypt was previously carried out ⁶³.



FIG. 4 Chemical compounds in Ixora finlaysoniana

Both *I. coccinea* and *I. parviflora* showed a promising result in *in-vitro* and *in-vivo* antioxidant activity ⁶⁴.

Ixora javanica:



FIG: 5a Ixora finlaysoniana



FIG: 5b Ixora javanica (Red)

This species is also seen frequently in nurseries.

Synonyms: Ixora singaphorensis

Common names: Ponna, kheme, chann tanea, pan, todong periuk, pechah periuk, jarum-jarum, ki soka, areng-arengan, Te prey, Jungle flame, and Jungle Geranium.

Ixora javanica (Common red ixora) is a broad bushy shrub, with lance-shaped medium green

leaves. The flowers are single red to pink and bloom in late summer.

The antitumour agent from *Ixora javanica* flowers shows broad activity against transplantable solid tumours (DLA) in mice by inhibiting the growth of tumour and arresting the growth of already formed tumours; with lesser activity against Ascites tumours. In vitro cytotoxic studies showed 50% cytotoxicity to Dalton's lymphoma (DLA) and Ehrlich Ascites tumour cells at a concentration of 12 micrograms and 65 micrograms, respectively, with no activity against normal lymphocytes but preferential activity for lymphocytes derived from leukemia patients (ALL) (CML), and K 562 suspension cell culture. Tritiated thymidine incorporation studies indicated the mechanism of action of the agent at the site of DNA synthesis. The purified fractions contained Ferulic acid, Pyrocatacheuic acid and caffeic acid ⁶⁵.



FIG. 5 Chemical compounds in Ixora javanica

It was reported that the topical application of 100 mg/kg body weight of I. javanica flower extract inhibited the growth and delayed the onset of papilloma formation in mice initiated with 7, 12dimethylbenz [a] anthracene (DMBA) and promoted using croton oil. The extract at the same dose, when administered orally inhibited the growth of subcutaneously injected 20 methylcholanthrene (MCA)-induced soft tissue fibrosarcomas significantly. Oral administration of 200 mg/kg of the extract inhibited the growth of intraperitoneally transplanted sarcoma-180 and Ehrlich ascites carcinoma tumours besides showing an increase in the life span of the treated mice. Toxicity studies showed that the blood urea nitrogen levels were elevated post treatment. The active compounds responsible for the above inhibitory effects on tumour growth were identified as ferulic acid (4-hydroxy-3-methoxy cinnamic acid) and its regionmer 3-hydroxy-4-methoxy cinnamic acid ⁶⁶.

Hepatoptotective activity of *I. javanica* D.C. flowers was reported against CCl₄ induced Liver Damage in Rats. Ethyl acetate and ethanolic extracts at a dose of 200 and 400 mg/Kg body weight, p. o. offered significant (P<0.001) hepatoptrotective action by reducing the serum marker enzymes like SGPT, SGOT, ALP, biliribin and cholesterol in test doses which was comparable with that of the standard silymarin. The ethyl acetate and ethanolic extract was able to restore the biochemical levels to normal which were altered due to CCl₄ intoxication in freshly isolated rat hepatocytes and also in animals ⁶⁷.

Ixora macrothyrsa:

The potent drug principles of *Ixora macrothyrsa* flower was identified against Methicillin resistant *Staphylococcus aureus* and *Acinetobacter baumannii*. Hot extraction soxhlet method was performed for the extraction of *Ixora macrothyrsa* flowers. The study revealed that ethanolic extracts of the flowers are rich source of phytochemicals compare to acetone and methanol extracts ⁶⁸. The phenol estimation was performed for ethanol extract using the standard protocol ⁶⁹. Ascorbic acid was used as standard.

Ixora longifolia J.E. Smith: ⁷⁰ Synonyms:

Ixora amboinica (Blume) DC. *Ixora fulgens* auct. non Roxb.

Vernacular names: Indonesia: jarong-jarong (Moluccas).

Distribution: The Moluccas.

Uses: The roots have been reported long ago to be used against pain in the side in the Moluccas, both internally and externally; chewing the roots has been reported to ease toothache.

Observations: A shrub 1.5-3 m tall; leaves lanceolate or oblong-lanceolate, 15-30 cm x 9-11 cm, herbaceous or subcoriaceous, base rounded or subacute, apex acuminate, with about 13 secondary veins, petiole 1-1.5 cm long, stipules broadly triangular, shortly awned; inflorescence loose, shortly pubescent, peduncle 3 mm long, with up to 100 flowers; flowers with calyx tube 0.5 mm long, lobes broadly ovate and 0.5 mm long, corolla tube 4 cm long, lobes about 1 cm long, acute, red; fruit

red turning black at maturity. *I. longifolia* is found in abandoned fields and dense scrub up to the beach, but it is less common at higher elevations ⁷¹.

	CHEMICAL	CONSTITUENTS	OF VARIOUS SPECIES:
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S.No.	Species	Main constituents	References
1.	Ixora coccinea Linn.	Leaves:	
		• Triterpenoid: lupeol,	10
		• Ixorene (a new Dammarene triterpene)	11
		 Proanthocyanidins: ixora tannin A-2 (a trimeric A-type 	
		proanthocyanidin), procyanidin A2, cinnamtannin B-1	
		 Flavonoids: epicatechin, kaempferol- quercetin-rhamnosides and 	1.5
		quercitrin.	15
		Alkaloid: camptothecin	14
		Flowers:	14
		 Triterpenoids: ursolic acid, cycloartenol esters, lupeol esters, lupeol, 	
		oleanolic acid	12
		• Sterol: sitosterol	12
		• Flavonoids: biochanin A, myricetin, quercetin, rutin, daidzein	
		formononetin, monoglycosides of cyanidin and delphinidin, rutin,	
		kaempferol-3-rutinoside, traces of leucocyanidin glycoside	
		Above-ground parts:	
		 Triterpenoids: lupeol, 3-acetylbetulic acid, betunolic acid, α-amyrin, β- 	
		amyrin, ursolic acid, 3-acetylursolic acid, oleanonic acid	
		• Sterols: 6β-hydroxystigmast-4-en-3-one, sitosteryl-3- <i>O</i> -β-d-glucoside,	
		β-sitosterol, stigmasterol	
		• Flavonoids: kaempferol, kaempferol-7- <i>O</i> -α-rhamnoside, kaempferitrin,	
		luteolin, (-)-epicatechin, (+)-catechin	
		 Proanthocyanidin: epicatechin-4β-8, 2β-O-7-ent-epicatechin 	
		• Coumarins: scopoletin, coumarin, <i>erythro</i> -1',2'-albiflorin	
		• Diterpenoids: 16α-hydro-19-acetoxy-(-) kauran-17-oic acid, 16α -	
		hydro-19-ol-(–)-kauran-17-oic acid	
		• Quinones: 1,4-dihydroxy-3-methyl anthraquinone, tocopheryl quinone	
		• Peptides: Ixora peptides I and II	
		Roots:	
		• Fatty acids: palmitic, stearic, oleic and linoleic acid	
	 Essential oil: β-sesqui phellandrene (main constituent) 		
	 9, 12-Octadecadienoic acid, Di-n-octyl phthalate, β-Amyrin, 		
		Kaempferol-7-oglucoside, Kaempferitrin and Quercitrin	
		Kaempieroi-7-ogiucoside, Kaempieritini and Quercitini	13
			15
2.	Ixora chinensis	D-mannitol, stearic acid, 1, 5-cyclo octadiene, β-sitosterol, (10E)-9-oxo-octadec-	48
		10-en-12-ynoic acid, azelaic acid and dihydro masticadienolic acid.	10
		 Fatty acids: palmatic acid, oleic acid, stearic acid, linolic acid.' 	
		• <i>Flowers:</i> Flavonoids, anthocyanins	49
3.	Ixora parviflora Vahl	Stem:	
		 Flavone glycoside : chrysin 5-O-β-D-xylopyranoside 	51
		Leaves:	
		 Ixoral and β-sitosterol. Betulin, erythrodiol, lupeol & stigmasterol. 	52
		Bark:	53
		• Fatty matter, tannin and red colouring matter.	
		- I any matter, tanini and red colouring matter.	
		Seeds (oil):	
		 Linoleic, oleic, stearic and palmitic acids as major components and 	
		• Enforce, order, stearce and paintic acids as major components and myristic, lauric, capric and behenic acids as minor ones.	
		Aerial parts:	
		1	
		• 6,7-dimethylhydroxy coumarin	
		Flowers:	
		• chlorogenic acid, apigenin, quercetin, apigenin-7-O-fi-D-	
		glucopyranoside & quercetin-3-O-fi-D- galactopyranoside.	

4.	Ixora finlaysoniana	Stem:	62
		• Apigenin-4'-O-D-glucopyranoside Leaf: 11-hydroxy-dodec-5-en-2-	
		one.	
		Fatty acids:	
		 palmatic acid, oleic acid, stearic acid, linolic acid. 	
		Phenolic acids:	61
		 protocatechuic acid, ferulic acid, gallic acid. 	
		Triterpenes:	
		 β-sitosterol, sitosterol-3-O-β-D-glycoside. 	
		Other constituents:	
		 nonacosanol, α-amyrin, β-sitosterol 3-hydroxyhexan-5-olide, protocatechuic acid, gallic acid, β-sitostreol glucoside, parasorboside, 	
		D-1-O-methyl-myo-inostiol and galactitol.	
5.	Ixora javanica	Phenolic acids:	65
		 ferulic acid, pyrocatacheuic acid and caffeic acid. 	
		Ferulic acid (4-hydroxy-3-methoxy cinnamic acid) and its regionmer 3-	66
		hydroxy-4-methoxy cinnamic acid.	
6.	Ixora undulate	Phenolic acids and flavonoidal glycosides.	
7.	Ixora macrothyrsa	Flowers: Rich source of phytochemicals.	68
8.	Ixora longifolia	Leaves, roots, flowers: Rich source of phytochemicals.	71

CONCLUSION: The extensive literature survey revealed that Ixora species have different important medicinal properties with diverse pharmacological spectrum. This article briefly reviews the phytochemical, pharmacological, therapeutic applications and traditional knowledge of the genera Ixora. The different species had been extensively used traditionally but various pharmacological activities have not been tested. Further evaluation needs to be carried out on Ixora species in order to use in formulations for their practical clinical applications, which can be used for the welfare of the mankind. This is an attempt to compile and document the information on different aspects of *Ixora* species and highlight the needs for research and development in future.

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