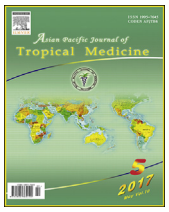
HOSTED BY
ELSEVIER

Contents lists available at ScienceDirect

Asian Pacific Journal of Tropical Medicine

journal homepage: http://ees.elsevier.com/apjtm



Review http://dx.doi.org/10.1016/j.apjtm.2017.05.003

# *Euphorbia neriifolia* L.: Review on botany, ethnomedicinal uses, phytochemistry and biological activities

Prashant Y. Mali, Shital S. Panchal✉

*Department of Pharmacology, Institute of Pharmacy, Nirma University, Ahmedabad, Gujarat, India*

ARTICLE INFO

*Article history:*
Received 23 Feb 2017
Received in revised form 23 Mar 2017
Accepted 17 Apr 2017
Available online 18 May 2017

*Keywords:*
*Euphorbia neriifolia*
Botany
Ethnomedicinal uses
Phytochemistry
Anti-cancer

ABSTRACT

The present review is intended to provide information on botany, ethnomedicinal uses, phytochemistry and biological activities of various parts of *Euphorbia neriifolia* (*E. neriifolia*). *E. neriifolia* has several ethnomedicinal uses. The latex of *E. neriifolia* is used as laxative, purgative, rubefacient, carminative and expectorant as well as in treatment of whooping cough, gonorrhoea, leprosy, asthma, dyspepsia, jaundice, enlargement of the spleen, tumours, stone in the bladder, abdominal troubles and leucoderma. Leaves are brittle, heating, carminative, and good for improving the appetite and treatment of tumours, pains, inflammations, abdominal swellings and bronchial infections. Roots are used as symptomatic treatment of snake bite, scorpion sting and antispasmodic. Various plant parts or whole *E. neriifolia* extract and its isolates have been reported scientifically using various *in-vivo* and *in-vitro* experimental methods for anaesthetic, analgesic, anti-anxiety, anti-convulsant, anti-psychotic, anti-arthritis, anti-carcinogenic, antidiabetic, anti-diarrhoeal, anti-inflammatory, anti-thrombotic, antimicrobial, antioxidant, antiulcer, cytotoxic, death-receptor expression enhancing, dermal irritation, diuretic, haemolytic, immunomodulatory, radioprotective, scorpion venom and wound healing properties. It is reported to have chemical constituents like, neriifolin-S, neriifolin, neriifoliene, euphol, neriifolione, cycloartenol, nerifoliol, lectin, euphonerins A–G, 3-O-acetyl-8-O-tigloylingol, taraxerol, antiquorin, *etc*. Identified chemical constituents are still required to be explored for their advanced isolation techniques and biological activities.

## 1. Introduction

*Euphorbia neriifolia* (*E. neriifolia*) Linn. sp. Pl. (451.1753) belonging to the family Euphorbiaceae. It consist of 5 subfamilies, 49 tribes, 317 genera and 800 species [1,2]. There are about half dozen species of *Euphorbia* genus are under the name of snuk and it synonyms. The latex of *E. neriifolia* is an active ingredient of many Ayurvedic formulations like Abhaya lavana, Avittoladi bhasma, Citrakadi taila, Jatyadi varti, Snuhidugdhadi varti, Snuhi ghrta and Jalodarari ras. *E. neriifolia* has been traditionally indicated in Vatavyadhi, Gulma, Udara, Sula, Sotha, Arsas, Kusta and Medoroga [3,4]. *E. neriifolia* is worldwide scattered in Baluchistan, Burma, India and Malaysian Islands. Inside India, it is frequent in rocky ground throughout Deccan Peninsula and Orissa. It is habitually cultivated for hedges in villages all over India [5,6]. The taxonomy of plant consist of domain: Eukaryota, kingdom: Plantae, sub-kingdom: Tracheobionta, division: Magnoliophyta, super-division: Spermatophyte, class: Magnoliopsida, sub-class: Rosidae, order: Euphorbiales, genus: *Euphorbia*, family: Euphorbiaceae and species: *neriifolia* Linn. [7,8]. The methodology was used for data collection of this review by searching the keywords '*E. neriifolia*', 'Thuar', 'Indian spurge tree', 'Snuhi', 'Common milk hedge' including traditional Ayurvedic and Indian classical books, pharmacopoeias, journals by on-line and offline databases with no specific timeline. The collected information on plant has been set manually since 1963–2016 and was prearranged chronologically. The present review provides the summary of up-to-date information on botany, ethnomedicinal uses, phytochemistry and biological activities.

First author: Prashant Y. Mali, Department of Pharmacology, Institute of Pharmacy, Nirma University, Ahmedabad, Gujarat, India.
Tel: +91 9822284089
E-mail: pymali2008@rediffmail.com
✉Corresponding author: Shital S. Panchal, Ph.D, Department of Pharmacology, Institute of Pharmacy, Nirma University, Ahmedabad 382481, Gujarat, India.
Tel: +91 07552896237, +91 9687626589
Fax: +91 0755 2896660
E-mail: shital.panchal@nirmauni.ac.in
Peer review under responsibility of Hainan Medical University.

## 2. Botany

### 2.1. Whole plant

*E. neriifolia* is glabrous erect branched succulent, xerophytic tree or shrub up to 20 ft or 1.8–4.5 m high with jointed cylindrical or obscurely 5-angled branches [1,4].

### 2.2. Fruits and flowers

Fruits are looking like capsule. Style 3-fid, stigmas slightly dilated and minutely toothed. The flowers are yellowish green in colour. Flowers and fruits occur during December to May months [1,9].

### 2.3. Leaves

The fresh young leaves are simple, dark green in colour having leathery texture. The surface is glabrous with reticulate venation. The average leaf size is (8–14 ± 2) cm (length) and (4–8 ± 2) cm (breadth) and (1.3 ± 0.2) mm (thickness) with pointed and acute tip [10]. Peri-clinical divisions in the third and fourth layers of peripheral meristem initiate the leaf [11].

### 2.4. Branches

The saccular branches have a pair of strong stipular spines on tubercles of the branchlet which is confluent in 5 vertical spinal lines or ribs. Branches are more and less obtusely 5-gonous in segment. Bunches of succulent thick leaves occur on the branchlets [1,9]. Central meristem is prominent throughout plasto-chronic phases. There is close histogenic relationship between central and peripheral meristem [11].

### 2.5. Bark and stem

#### 2.5.1. Macroscopy

The trunk is covered with reticulate bark. Stem is cylindrical, succulent, glabrous, internodes are 4–10 cm in length and 2–6 cm in diameter. Nodes are constricted 1–4 cm in diameter which show spirally running rows of tubercles inserted on flat and creamish white corky bases. A small circular gland is being located at the base of the tubercle. The nodal region shows shorter spines having 1–5 mm length and a bud adjacent to it. Taste is acrid or astringent. Dried stems are tough, shrivelled, longitudinally ridged, furrowed and wrinkled. It is easily breakable at the node which exposing hollow pith attached with white parenchymatous papery scales [5,12].

#### 2.5.2. Microscopy

Transverse section of stem showed a layer of epidermis embedded with stomata and shielded externally with a well developed striated cuticle. The hypodermis is a wide zone consisting of vertically placed and radially elongated narrow cellular bands of chlorenchyma alternating with parenchymatous bands. The hypodermis is embedded with plenty of small sized oil globules and latex tubes. The cortex is wide and centrally located parenchymatous pith encircled by continuous ring of pentagonal stellar region. The innermost cells have cortical zones and are embedded with plenty of starch grains. The pith is very wide composed of very big sized thin walled parenchymatous cells. The stellar region is a narrow ring of angular xylem consisting of isolated or grouped radially arranged 2–3 vessels, thin walled fibres, parenchyma and medullary rays in continuation with phloem. The pericycle is distinct, parenchymatous and embedded with isolated spherical thick walled non-lignified fibres. Laticiferous vessels are embedded with grandular latex [12].

### 2.6. Seed

Seeds are flat containing soft hairs [9].

### 2.7. Powder

Powder is cream yellow in colour. It has fragments of straight walled cells of epidermis embedded with plenty of actinocytic and few paracytic stomata. Striated cuticle cells are simple with branched laticiferous vessels and dumb-bell shaped starch grains. Plenty of stone cells were observed in powder. They have thick and thin walled fibres and sclereids from the spine [4,13]. The fine powder was mounted in glycerin and stained with iodine, phloroglucinol, conc. HCl and Sudan III. Observed features revealed that the leaf powder contains numerous idioblastic, rosette, square, prismatic and acicular shaped calcium oxalate crystals and starch grains. The powder also showed the presence of well arranged annular vessels, anomocytic stomata, unicerrate multicellular trichome with blunt tip. The epidermal cells, spongy parenchyma, xylem parenchyma, vittae-volatile contain schizogonous cells, polyhedral or sharp angled starch grains and lignified xylem fibres were present. After treatment with HCl, the calcium oxalate crystals are changed into needle shaped crystals from the acicular shape [10].

### 2.8. Latex

Latex is a milky-sap-like fluid found in cells or vessels and usually executed after tissue injuries that make up the laticiferous system [14].

## 3. Ethnomedicinal uses

### 3.1. Latex

Latex is acrid, laxative, pungent and good for tumours, abdominal troubles and leucoderma. It is also used as a purgative, rubefacient, carminative, expectorant, whooping cough, gonorrhoea, dropsy, leprosy, asthma, dyspepsia, jaundice, enlargement of the spleen, colic and stone in the bladder. It is use to remove cutaneous eruptions and warts. It is liable to cause dermatitis [1,5]. Milk-juice executed from injured fleshy cylindrical stems is used by Vaidyas in medicine as drastic cathartic and to relieve earache. Clove, long-peppers, chebulic myrobalans and trivrit root *etc*., are used to soak in this juice for some months and then dried. It is used as a drastic purgative in the enlargement of liver and spleen, syphilis, dropsy, general anasarca, leprosy, *etc*. For instance, when we take cloves four ounce, soak them into one seer of the milk for 40–50 d and then triturate into mortar, it will produce highly perfumed twelve ounce mass. This perfumed mass well is mixed with 360 grains

of Rasakarpur called 'Corrosive sublimate' in to prepare 180 pills. Two of such pills can be administered to a patient at bed time, coated with little fresh cream, so that the pills can be swallowed carefully without touching teeth. It may produce cathartic action from the early morning till 10 a.m. with watery stools. The patient should be given luke-warm aqua-ani seed two to three ounce after every motion and bread with butter as a diet. In 20–40 d a patient suffering with any of above diseases is cured. As expectorant, especially in asthma, it is given in doses of 5 drops of latex after mixing it with a little honey or syrup. For asthma, madar flowers, agaba root and gokaran root are steeped in the juice, powdered and given with honey and chebulic myrobalans, dose is 4 grains. After heating with salt, it is given in whooping cough, dropsy, leprosy, enlarged liver and spleen, dyspepsia, jaundice, colic, *etc*. Juice mixed with ghee is given in syphilis, in visceral obstructions and in spleen and liver enlargement due to long continued intermittent fevers. Externally juice is applied to remove warts. It is used to drop into ear to get relief in earache. Juice mixed with soot (of ghee-lamp) was used as anjan in ophthalmia. Juice is used in treatment of unhealthy ulcers and scabies. Application of juice to glandular swellings can prevent suppuration. It is mixed with margosa oil for topical application to rheumatic limbs. Turmeric powder mixed with juice of *E. neriifolia* is useful in treatment of piles. Thread steeped in the above mentioned mixture is used in ligaturing external haemorrhoids [15].

### 3.2. Leaves

Leaves are brittle, heating, carminative, improve the appetite, good for treatment of tumours, pains, inflammations, abdominal swellings and bronchial infections [1]. Wounds are cured by applying the steamed leaves of snuhi for 5–6 d [3]. Juice of the leaves is accepted as a cure for earache in the Philippine Islands. Administration of a succus consisting of equal parts of juice and simple syrup in doses of 10–20 mL minimum three times a day in asthma was found to give relief to the fits [1,5].

### 3.3. Stems

The stem, which is roasted in ashes and expressed juice mixed with honey and borax is given in small doses to promote expectoration of phlegm. Pulp of the stem mixed with fresh ginger is used to prevent hydrophobia [15].

### 3.4. Roots

Root is used as symptomatic treatment of snake bite, scorpion sting and as a antispasmodic [1,3]. Crushed root mixed with black-pepper is employed in treatment of scorpion-stings and snakebites both internally and externally. Root-bark boiled in rice-water and arrack is useful for treatment of dropsy [15].

### 3.5. Whole plant

*E. neriifolia* is used as laxative, carminative and alexipharmic. It is also useful in treatment of tumours, bronchitis, delirium, piles, loss of consciousness, enlargement of the spleen, inflammations, ulcers, fevers and anaemia [1]. The *E. neriifolia* classically consists of caraka, susruta and vagbhata categorization. Caraka has rasa properties with katu and tikta actions. Susruta has virya properties with usna action and vagbhata has guna, vipaka and karma properties. Guna has laghu, tiksna and snigdha actions. Vipaka has katu action and karma has kapha-vatahara, dipana, recana actions. The caraka has vatavyadhi, gulma, udara, sula, sotha, arsas, kusta, medoroga indications [3,4].

## 4. Phytochemistry

The fluorescence analysis of leaves of *E. neriifolia* was performed. It showed the visibility of varying colours that represents the presence of active phytoconstituents in the leaves. The results of phytochemical screenings of hydro-ethanolic, petroleum ether, benzene, chloroform, ethyl acetate, ethanol and aqueous extracts of leaves mainly revealed the presence of proteins, glycosides, alkaloids, phenolics, flavonoids, saponins and terpenoids in appreciable, moderate and trace amount. The proteins and amino acids were possessed in negligible amount [10]. The ethanolic extract of leaves showed presence of tannins, reducing sugar, triterpenoidal saponin, flavonoids, alkaloids and there is absence of fixed oils and glycosides. The leaf extracts such as chloroform, ethanol, ethyl acetate, butanol and aqueous of *E. neriifolia* were found phlobotannins, flavonoids, saponins, tannins, terpenoids, phenols and cardenoloids. Conversely, all these extracts were tested and showed the absence of sterols, anthraquinones and cardiac glycosides [16,17]. Hydro-alcoholic extract of leaves shows presence of flavonoids, sugar, tannins, triterpenoidal saponin, alkaloids and cardiac glycosoids [18,19]. Latex contains water, water solubles (69.4–93.3) and caoutchouc (0.2–2.6%) [5]. Gum resin is the active principle, wax, traces of alkaloid, caoutchouc, chlorophyll, sugar, mucilage, tannin, carbohydrates, calcium oxalate, quercetin, gallic acid and traces of essential oil [15]. Dried and fresh latex showed the presence of steroids and triterpenoids. Total diterpene and triterpene content was found to be 24.50% and 16.23% respectively in the fresh latex of *E. neriifolia* [20]. *E. neriifolia* has been reported to have physical and chemical constituents in different parts as shown in Tables 1 and 2 respectively.

**Table 1**
Physical constituents present in *E. neriifolia*.

| Parameters | Values (%) | Ref |
|---|---|---|
| Leaves | | [10] |
| Foreign organic matter | 0.87 ± 0.03 | |
| Alcohol soluble extractives | 14.32 ± 0.04 | |
| Water soluble extractives | 26.31 ± 0.12 | |
| Loss on drying or moisture content | 3.45 ± 0.09 at 105 °C | |
| pH | 6.40 ± 0.20 (1%) & 5.80 ± 0.04 (10%) aqueous solution | |
| Total ash | 7.36 ± 0.07 | |
| Acid insoluble ash | 0.82 ± 0.04 | |
| Water soluble ash | 4.54 ± 0.11 | |
| Latex | | [20] |
| Refractive index | 1.41 ± 0.12 | |
| Weight per mL | 1.14 ± 0.08 gm | |
| Percent solid content | 10.95% | |
| pH | 5.20 ± 0.17 | |
| Resinous matter | 18.32% | |

**Table 2**
Chemical constituents present in different parts of *E. neriifolia*.

| Plant part | Phytoconstituents | Extractive solvents | Ref |
|---|---|---|---|
| Latex (fresh latex from stem) | Neriifolin-S and neriifolin | 20 mM tris buffer at pH-8, 10 mM sodium acetate buffer at pH 4.5 | [21,22] |
| Latex (fresh) | 9,19-cyclolanost-22 (22′),24-diene-3β-ol (Neriifoliene), 5α-eupha-8,24-diaene-3β-ol (Euphol) | Cold n-hexane, ethyl acetate, methanol | [23] |
| Latex (fresh) | Neriifoliene and euphol | n-hexane | [24] |
| Latex (dried) | 9,19-cyclolanost-20 (21)-en-24-ol-3-one (Neriifolione), cycloartenol | Successively with petrol, benzene, acetone | [25] |
| Latex | Neriifoliol | Alcohol | [26] |
| Latex | Lectin | – | [27] |
| Leaves | Euphonerins A–G | Methanol | [28] |
| Leaves | 3-O-acetyl-8-O-tigloylingol | Methanol | [28] |
| Leaves | 3,12-di-O-acetyl-8-O-tigloylingol, (24R)-cycloartane-3β,24,25-triol, 5,4′-dihydroxy-3,7,3′,5′-tetramethoxyflavone, pachypodol (5,4′-dihydroxy-3,7,3′-trimethoxyflavone), combretol (5-hydroxy-3,7,3′,4′,5′-pentamethoxyflavone) (Flavonols) | Methanol | [28] |
| Leaves | Friedelan 3α- & 3β-ols, taraxerol | Petroleum ether (40–60°) | [29] |
| Leaves | Glut-5 (10)-en-1-one | Petroleum ether (40–60°) | [30] |
| Leaves | Euphol (8,24-Euphadien-3 beta-ol) | Cold methanol (70%) | [31] |
| Leaves | 2-(3,4-dihydroxy-5-methoxy-phenyl)-3 and 5-dihydroxy-6,7-dimethoxychromen-4-one | Ethanol | [32,33] |
| Leaves | Quercetin | Benzene, chloroform, ethyl acetate and hydro-ethanolic | [34] |
| Leaves | Rutin | Chloroform, ethyl acetate, ethanol and hydro-ethanolic | [34] |
| Bark | 12-Deoxy-4 beta -hydroxyphorbol-13-dodecanoate-20-acetate, euphol, euphorbol hexacozonate, n-hexacosanol and 24-methylene cycloartenol | – | [35] |
| Stems | Friedelan 3γ-ol, waxes, taraxerol | Petroleum ether (40–60°) | [29] |
| Stems | Glut-5 (10)-en-1-one | Petroleum ether (40–60°) | [30] |
| Stems | ent-3,4-seco-4.16b,17-trihydroxykauran-3-oic acid, ent-16b-hydroxykauran-3,4-lactone, 13b,19-dihydroxy-3,15-dioxoatis-16-ene, 13b-hydroxy-3,15-dioxoatis-16-ene, 16b,17,19-trihydroxy-3-oxo-atisane, 4,13b-dihydroxy-14-oxo-3,4-secoatis-16-en-3-oic acid, 4,13b-dihydroxy-14-oxo-3,4-secoatis-16-en-3-oic acid methyl ester, 1a,3a-dihydroxyent-abieta-8(14),13(15)-dien-16,12-olide | Ethanol-water (3 × 5 L, 9:1, v/v) | [31] |
| Root (chopped fresh roots) | Antiquorin and ent-3fl, 13-dihydroxyatis- 16-en-14-one (Neriifolene) | Ethanol (95%) | [36,37] |

## 5. Biological activities

### 5.1. Anaesthetic

Evaluation of anaesthetic activity of alcoholic and aqueous extract of fresh stem of *E. neriifolia* was carried out by using foot-withdrawal reflex method in frog and intradermal wheal method in guinea pig. Alcoholic extract of stem of *E. neriifolia* possesses good anaesthetic action. However, aqueous extract does not reflect such action [38].

### 5.2. Analgesic

Analgesic activity of hydro-alcoholic extract of leaves of *E. neriifolia* has been evaluated using Eddy's hot plate and tail-flick method. Results revealed that the extract shows marked analgesic activity which is comparable to diclofenac sodium [39]. Analgesic activity of hydro-alcoholic extract of leaves (400 mg/kg) using thermal, mechanical and chemical stimulus reveals that the extract significantly inhibits pain (432.22%) threshold after 60 min. Treatment with hydro-alcoholic extract increases tail flick and tail clip at 45 min. The acetic acid induced writhing episode protection is 53.83% at the above dose [40].

### 5.3. Anti-anxiety, anti-convulsant, anti-psychotic

Anti-anxiety, anti-convulsant and anti-psychotic effects of hydro-alcoholic extract of leaves of *E. neriifolia* have been reported by Bigoniya and Rana, 2005. The extract remarkably reduces apomorphine-induced stereotypy or devoid of catalepsic effect which is signifying the specific dopaminergic receptor modulating action. Extract has also shown the protective effect against maximal electro-shock-induced convulsion and anxiolytic action in elevated plus-maze. However, it does not produce anti-psychotic effect against scopolamine-induced amnesia [41].

### 5.4. Anti-arthritis

Anti-arthritis activity was studied using neriifolione isolated from the latex of *E. neriifolia* using Fruend's adjuvant arthritis

model in rats. The oral administration of neriifolione (0.2 mg/100 gm) showed 51% inhibition of rat paw volume. However, it was found to be more toxic. Therefore, it appears to be less promising clinically [42].

### 5.5. Anti-carcinogenic/renal carcinogenesis/hepatocarcinogenesis

Saponin fraction of leaf of *E. neriifolia* was studied against $CCl_4$-induced hepatotoxicity. The treatment increases serum glutamic-oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT) and alkaline phosphatase (ALP) levels and notably improves histopathological alterations. Saponin fraction decreases the sleeping time induced by thiopentone which indicated the protective effect on metabolizing enzymes of liver. Saponin restores the depleted hepatic superoxide dismutase (SOD) and reduced glutathione (GSH) levels by enhancing the antioxidant status of liver [16]. Protective effect of hydro-ethanolic extract of *E. neriifolia* on diethyl nitrosamine (DENA) induced abnormalities in metabolic enzymatic, non-enzymatic and biochemical parameters has been reported by Sharma *et al.*, 2011. DENA treatment significantly decreased ($P < 0.001$) the glutathione-S-Transferase (GST) and GSH content as well as increased SGOT, SGPT and ALP level. Hydro-ethanolic extract shows its chemo-preventive property by improving the levels of antioxidant and alleviating raised biochemical parameters in DENA induced carcinogenesis by reducing the formation of free radicals. The anti-carcinogenic effect of extract of leaves of *E. neriifolia* and isolated flavonoid was also investigated against DENA induce renal carcinogenesis. The renal marker like serum urea and creatinine, xenobiotic markers like Cyt P450 and Cyt b5, lipid peroxidation (LPO), catalase (CAT), SOD, GSH and GST along with levels of SGOT, SGPT, ALP, total protein (TP) and total cholesterol (TC) were considered to find out progression of the renal carcinogenesis. DENA treatment have ($P < 0.001$) enhanced the Cyt P450, Cyt b5 and LPO levels and decreased SOD, GST, CAT and GSH levels. Treatment with *E. neriifolia* (EN) and isolated flavonoid fraction of *E. neriifolia* (ENF) neutralized the oxidative stress induced by DENA and exert its defencive property by regaining the normal levels of SOD, GST, CAT, GSH, SGOT, SGPT, ALP, TC, TP, creatinine, urea, Cyt P450 and Cyt b5. DENA treated group of animals showed the alterations in normal renal histo-architecture with characteristic inflammation and necrosis [43–45]. Impact of DENA on liver also studied and it was found that hydro-ethanolic extract and isolated flavonoid fraction was showed protecting hepatic effect [46,47].

### 5.6. Antidiabetic

Effect of ethanolic extract of *E. neriifolia* leaves against alloxan induced diabetic model in rat is reported by Mushir and Patel, 2012 [48]. Parameters such as oral glucose tolerance test, fasting blood glucose level and serum lipid levels were assessed. Oral glucose tolerance test showed decrease in fasting blood glucose levels after 60 min of extract administration. After 15 d, the extract treated animals showed maximum reduction of fasting blood glucose levels at the dose 400 mg/kg. The serum lipid levels were reduced which was comparable to the normal group rats.

### 5.7. Anti-diarrhoeal

Anti-diarrhoeal activity of hydro-alcoholic extract of leaf of *E. neriifolia* is reported by Bigoniya and Rana, 2010, in rats using castor oil-induced diarrhoea model. The extract shows laxative effect by increase in soaked defecation along with castor oil [40].

### 5.8. Anti-inflammatory/anti-thrombotic

The petroleum ether fraction of latex was tested for anti-inflammatory effect by Bigoniya *et al.*, 2010 [40], in carrageenan induced rat paw oedema. The fraction of latex inhibits 42.40 and 35.25% oedema at the dose levels of 750 and 500 mg/mL which may be due to the presence of triterpenes like, euphol, cycloartenol and nerifoliol [20]. Hydro-alcoholic extract of *E. neriifolia* leaves reduces mean paw volume in carrageenan treated rats and in cotton pellet induced granuloma extract showed considerable anti-inflammatory property [39,40]. Anti-inflammatory activity of dried latex, petrol-benzene and acetone extracts from dried latex and isolated neriifolione and cycloartenol from the latex of *E. neriifolia* were evaluated [42]. Anti-thrombotic activity of petroleum ether and ethanol extract of roots and leaves of *E. neriifolia* has been reported by Hasan *et al.*, 2010 [49].

### 5.9. Antimicrobial

Antimicrobial activity of crude saponin of *E. neriifolia* against bacteria like *Escherichia coli* (*E. coli*) (ATCC 25922), *Pseudomonas aeurginosa* (ATCC 10145), *Staphylococcus aerugenosa* (ATCC 25923) and *Candida albicans* (MTCC 227) was performed using agar well diffusion technique. *E. neriifolia* did not show antibacterial activity up to 10 mg/mL concentration [17]. Anti-microbial effect of various extracts viz. chloroform, ethanol, ethyl acetate, butanol and aqueous of leaves of *E. neriifolia* was studied using *Staphylococcus aureus*, *Klebsiella pneumonia*, *E. coli*, *Pseudomonas vulgarius* (*P. vulgarius*), *Pseudomonas fluroscens*. The highest effect was seen in chloroform extract against *P. vulgarius* with the zone of inhibition of 8 mm followed by ethanol extract against *Klebsiella pneumonia* with the zone of inhibition of 5 mm. The water and ethyl acetate extract exhibit very less effect [18]. Antimicrobial efficacy of methanol extract of stem of *E. neriifolia* was assessed against *Staphylococcus aureus* (ATC-2245), *Staphylococcus aerugenosa* (U59), *E. coli* (K-88), *Pseudomonas aeurginosa*, *Salmonella typhi* (12), *P. vulgarius* (CC-52), *Aspergillus niger* (36) and *Candida albicans* using disc diffusion and micro dilution assays. Streptomycin and ampicillin were used as standard antibacterial drugs and amphotericin-B was used as reference antifungal drug. The results of these assays have ensured that the stem of *E. neriifolia* possesses significant antimicrobial activity which was comparable to that of standard drugs [50].

### 5.10. Antioxidant

Antioxidant effect of saponins isolated from the leaves of *E. neriifolia* was evaluated using various assays like, hydrogen donating ability, reducing power, anti-lipid peroxidation and scavenging activity by superoxide and hydroxyl radicals. Saponins showed potent antioxidant activity for all five assays

except scavenging activity by hydroxyl radicals [17]. Antioxidant property of crude hydro-alcoholic extract of *E. neriifolia* using inhibition of DPPH, $H_2O_2$, superoxide anions, reducing power, FRAP and metal chelating activities was evaluated by Kumara *et al.*, 2011 [18]. % inhibition of lipid peroxidation showed antioxidant activity of 76.15% compared to that of ascorbic acid (75.6%), butylated hydroxyanisole (BHA) (60.8%) and butylated hydroxytoluene (BHT) (75.6%). % inhibition of metal chelating capacity of extract was found to be 73.24%. Antioxidant activity of euphol isolated from leaves of *E. neriifolia* was carried out using DPPH, hydroxyl radical, reducing power and superoxide radical scavenging assays. Euphol exerts free radical scavenging activity and hydrogen donating capacity which is comparable to α-tocopherol [31]. Antioxidant activity of *E. neriifolia* leaf extract was also evaluated by TAC, FRAP, TBA, FTC and non-specific activity assays. The extract has possessed antioxidant properties [51]. Effects of leaf extract of *E. neriifolia* on rat liver and kidneys was evaluated using various haematological, biochemical, histological and antioxidant enzyme parameters for the period of 21 and 45 d. The extract showed considerably ($P < 0.001$) increase in liver and kidney SOD and CAT with decrease in LPO [52].

### 5.11. Antiulcer

Antiulcer potential of hydro-alcoholic extract of leaves of *E. neriifolia* (400 mg/kg) was reported against pyloric ligation and ethanol induced gastric ulceration models. The extract showed increased levels of total hexoses, hexosamine, sialic acid and total carbohydrate content with decreasing levels of total protein content of gastric juice. Treatment with extract reduced ulcer index [40].

### 5.12. Cytotoxicity

*In-vitro* cytotoxicity assay of euphol isolated from triterpenoidal sapogenin fraction of *E. neriifolia* leaf was assessed using murine F1B16 melanoma cell line. Results of assay revealed that 50% inhibition concentration was 173.78 μg/mL [31]. Anticancer activity of methanolic extracts of *Euphorbia hirta* (*E. hirta*), *Euphorbia tirucalli* and *E. neriifolia* against B16F10 melanoma cancer cell line was performed. All plants showed significant cytotoxicity on B16F10 melanoma cell line in concentration range 10–1 000 μL using SRB and MTT assay. Fifty percent inhibition concentration of methanolic extract of *E. neriifolia*, *E. hirta* and *Euphorbia tirucalli* was 198.26, 185.41 and 20.10 by SRB assay and 212.78, 240.98 and 237.07 by MTT assay. Methanolic extract of all these three plants showed significant activity against B16F10 melanoma cells [53]. $LC_{50}$ rate of methanol, ethyl acetate and acetone extracts of *E. hirta* and *E. neriifolia* was also determined by using brine shrimp lethality assay. $LC_{50}$ value of ethyl acetate and acetone extract of *E. hirta* and methanolic extract of *E. neriifolia* was found 71.15, 92.15 and 49.55 μg/mL respectively [54].

### 5.13. Death-receptor expression enhancing activity

The increasing death-receptor 5 expression property of 07 cycloartane triterpenes, euphonerins A–G (1–7), 3-O-acetyl-8-O-tigloylingol (8) and ingol diterpenes isolated from the methanol extract of leaves of *E. neriifolia* along with 3,12-di-O-acetyl-8-O-tigloylingol (9), (24R)-cycloartane-3β,24,25-triol (10) and 03 known flavonols (11–13) was studied. Among these compounds, 1–11 showed death-receptor 5 expression enhancing property [28].

### 5.14. Dermal irritation and sensitization

Dermal irritation test was performed in rabbits. The petroleum ether, acetone, chloroform and water fractions of dried latex of *E. neriifolia* were prepared. Petroleum ether fraction was found be non-irritating with primary irritation index (PII) score of 0.43/0.11 for erythema. Acetone, chloroform, and water fractions cause skin irritation because of occurrence of high diterpene content [20].

### 5.15. Diuretic

Hydro-alcoholic extract of *E. neriifolia* leaf is reported for increase in urine volume by enhancing hypernatraemic and hyperchloraemic diuretic activity in rats [40].

### 5.16. Haemolytic

Haemolytic activity of saponins isolated from *E. neriifolia* leaf was carried out using haemolytic index assay. The 300 μg/mL concentration of *E. neriifolia* crude saponins was showed lytic effect against erythrocytes. Moreover, 100 μg/mL concentration of silymarin was showed 97.05% haemolysis as well as 100 g/mL concentration of triton showed 100% haemolysis [17].

### 5.17. Immunomodulatory

Immunomodulatory potential of alcoholic extract of leaves of *E. neriifolia* by non-specific and specific immune response assays was assessed [55]. Extract increased lymphocyte count and showed good phagocytic potential ($P < 0.001$). Extract significantly ($P < 0.05$) potentiated delayed type hypersensitivity reaction in rats against sheep red blood cells (SRBC) at 24 h (20.63%) and 48 h (12.24%) after treatment. *E. neriifolia* (400 mg/kg) has stimulated the humoural immune response that exhibiting 270.88% increment in antibody titre after 21 d treatment. *E. neriifolia* is a potent immunostimulant which stimulates phagocytosis as well as cell mediated immunity. Extract showed significantly increased haemopoietic activity and increased survival rate of rats. Immunomodulatory activity of hydro-alcoholic extract of dried leaves of *E. neriifolia* was assessed using survival rate, carbon clearance, haemagglutination antibody titre and footpad swelling assays [56].

### 5.18. Pesticidal effect

Pesticidal activity of latex of *E. neriifolia* against agricultural larvae, *Mythimna seperata*, *Helicoverpa armigera* and *Raphidopalpa forcicollis* was studied [57]. The 0%, 25%, 50%, 75% and 100% diluted concentrations of latex of plants were spread over pest larvae for 12 h, 24 h and 48 h. Mortality rates of all three larvae against different plant latex were recorded. Mortality rate of selected extract of *E. neriifolia* was found to be 32.99%.

### 5.19. Radioprotective

Radioprotective property of euphol isolated from the leaves of *E. neriifolia* was assessed against radiation induced chromosomal aberrations [31]. Pre-treatment with 75 μg/mL of euphol reduced 33.5% of total chromosomal aberrations as compared to 71.5% of total chromosomal aberrations after radiation treatment alone at 4 Gy.

### 5.20. Scorpion venom activity

Sixty-four plant species have been tested against fibroblast cell lysis after *Heterometrus laoticus* scorpion venom treatment. More than 40% effectiveness was observed against cells treated with venom pre-incubated with the extract of *E. neriifolia* [58].

### 5.21. Wound healing property

Wound healing property of aqueous extract of latex of *E. neriifolia* was evaluated using guinea pigs [59]. The extract facilitates the healing process by increasing the tensile strength, DNA content, epithelization and angiogenesis. Wound healing effect was also evaluated by excision wound and dead space wound methods [60]. The extract showed considerably improved hydroxyproline content, protein content and CAT level and decreases in SOD level in granulation tissue.

## 6. Toxicology

### 6.1. Pre-clinical studies

Toxicity study of *E. neriifolia* saponin fraction was performed as per OECD guideline No. 420 and 425. A dosage series at 50, 100 and 150 mg/kg was chosen [16]. Acute toxicity study of ethanolic extract of *E. neriifolia* was performed. After time-line of 24 h, 72 h and 14 d animals were observed for any lethality and death [48]. $LD_{50}$ of alcoholic extract of *E. neriifolia* leaves was determined according to the OECD guideline No. 420 and 425 at doses 100, 200 and 400 mg/kg [55]. Toxicological studies indicated various pathological changes in the liver, heart and kidney [61].

### 6.2. Clinical studies

*E. neriifolia* is the ingredient of 'Kshaarasootra' used in Indian medicine for curing anal-fistula. 'Kshaarasootra' is formulated by smearing a surgical linen thread with fresh latex of *E. neriifolia* and alkaline powder of *Achyranthes aspera* and turmeric powder from dried rhizomes of *Curcuma longa*. 'Kshaarasootra' is quiet effective in treating various fistulous tracks. Indian Council of Medical Research completed a multicentric randomized clinical trial to assess efficiency of "Kshaarasootra" in the management of fistula-in-ano in 265 patients. Results of trial discovered that the long term outcome with 'Kshaarasootra' (recurrence in 04 patients) treatment is better than that with surgery (recurrence in 11 patients) although the initial healing time was longer (8 week without and 4 week with surgery). 'Kshaarasootra' have offered an efficient, ambulatory and safe treatment for patients with fistula-in-ano [62]. Common milk hedge (*E. neriifolia*) is grown as a hedge plant in various parts of India. The latex of this plant is in the form of a white milky juice and has corrosive effect on contact with skin and mucous membrane. Cases of deliberate ingestion of this juice have rarely been reported in literature. One such rare case of ingestion of the latex with attendant of Alva's Health Centre, Moodabidri-574227, Dakshina Kannada, Karnataka, India clinical manifestations has been performed here. In a case, 20 year old girl was bring to the emergency space with a history of deliberate ingestion of the milky juice of the common milk hedge. She had prepared about 100 mL of milky juice of the plant mixed with water and drank it following a quarrel with her mother. On admission, she has complained of burning epigastric pain and vomited twice. There was no history of diarrhoea. On examination, her general physical condition was essentially normal, except for mild epigastric tenderness and her vital parameters were also normal. Routine laboratory investigations have revealed that, Hb 13 g%, total leucocyte count 8 700/cu mm, differential count – N65, L30, E5, RBS 123 mg% and blood urea 34 mg%. Serum electrolytes, renal parameters and liver function tests were normal. Urine examination did not disclose abnormal findings while stool examination was negative for occult blood. The patient was managed with I.V. fluids, parenteral ranitidine, antacids and parenteral ondansetron for 24 h. She was discharged after two days and was lost to follow up. The patient in this case has consumed a fairly large amount of milky juice but did not develop any corrosive effect except for mild gastric irritation. No systemic features of toxicity were observed. The relatively mild manifestations were probably due to dilution of the latex with water [63].

## 7. Conclusion

According to the literature, most of the pharmacological activities of *E. neriifolia* are investigated on leaf extracts or fraction of extracts by using ethanol as an extractive solvent. Ethanol extracts generally contain reducing sugar, flavonoids, tannins, alkaloids and triterpenoidal saponins. Method for isolation of triterpenoidal saponins from the latex of *E. neriifolia* has been established. Similarly for other chemical constituent's isolation technique are required to be developed. Based on reported biological activities *E. neriifolia* extracts and isolates can be explored for their therapeutic potential by use of modern assay methods. Molecular mechanisms should be established for therapeutic applications. However, reports indicated pathological changes in various organs, hence it should be considered for further plants.

## Conflict of interest statement

We declare that we have no conflict of interest.

## Acknowledgement

Authors are thankful to Director, Institute of Pharmacy, Nirma University, Ahmadabad, Gujarat, India for encouragement and availing of the internet and library facilities for the literature search of this review.

## References

[1] Kirtikar KR, Basu BD. *Indian medicinal plants*. 2nd ed., vol. III. Allahabad: Lalit Mohan Basu; 2006, p. 2201-2204.

[2] Webster GL. Classification of the Euphorbiaceae. *Ann Mo Bot Gard* 1994; **81**: 03-32.
[3] Chunekar KC. *Illustrated Dravyaguna Vijnana*. 2nd ed., vol. II. Varanasi: Chaukhambha Orientalia; 2005, p. 924-925.
[4] Controller of Publications, Ministry of Health and Family Welfare, Department of Indian Systems of Medicine and Homoeopathy, Government of India. *The ayurvedic pharmacopoeia of India. Part-I*. 1st ed., vol. I. New Delhi: National Institute of Science Communication (CSIR); 2001, p. 100.
[5] Anonymous. *The wealth of India, a dictionary of Indian raw materials and industrial products (Raw materials)*, Vol. III (D–E). New Delhi: Central Institute of Medicinal and Aromatic Plants; 2003, p. 226-228.
[6] Ved DK, Sureshchandra ST, Barve V, Srinivas V, Sangeetha S, Ravikumar K, et al. *Plant details*. Bengaluru: FRLHT's ENVIS Centre on Medicinal Plants; 2016. [Online]. Available from: http://envis.frlht.org/plant_details.php?disp_id=936&parname=0 [Accessed on 11th April 2017]
[7] Anonymous. *Global information hub on integrated medicine (Globinmed)*. [Online]. Kaula-Lampur: Herbal Medicine Research Centre, Institute of Medical Research. Available from: http://www.globinmed.com/index.php. [Accessed on 21st April 2017].
[8] Anonymous. *The plant list, version 1.1*. 2013 [Online]. Available from: http://www.theplantlist.org/tpl1.1/record/kew81079 [Accessed on 21st April 2017]
[9] Oommachan M. *The flora of Bhopal (Angiosperm)*. Bhopal: J.K Brothers; 1976.
[10] Sharma V, Pracheta J. Microscopic studies and preliminary pharmacognostical evaluation of *Euphorbia neriifolia* L. leaves. *Indian J Nat Prod Res* 2013; **4**(4): 348-357.
[11] Shah JJ, Jani PM. *Shoot apex of Euphorbia neriifolia L.*. **30B(2)**. Proceeding Nation Instit Sci India; 1963, p. 80-91.
[12] Tandon N, Sharma P. *Quality standards of Indian medicinal plants*, Vol. XI. New Delhi: Indian Council of Medical Research; 2013.
[13] Bigoniya P, Rana AC. A comprehensive phyto-pharmacological review of *Euphorbia neriifolia* Linn. *Pharmacog Rev* 2008; **2**(4): 57-66.
[14] Bigoniya P. Euphorbia latex: a magic potion or poison. In: Gupta VK, editor. *Traditional and folk herbal medicine: recent researches*, Vol I. New Delhi: Daya Publishing House; 2012.
[15] Nadkarni's KM, Nadkarni AK. *Indian materia medica*. . 3rd ed.Vol. I. Bombay: Popular Prakashan; 2007.
[16] Bigoniya P, Rana AC. Protective effect of *Euphorbia neriifolia* saponin fraction on $CCl_4$-induced acute hepatotoxicity. *Afr J Biotech* 2010; **9**(42): 7148-7156.
[17] Bigoniya P, Rana AC. Hemolytic and *In-vitro* antioxidant activity of saponin isolated from *Euphorbia neriifolia* leaf. In: Govil JN, Singh VK, Siddiqui NT, editors. *Recent progress in medicinal plants, natural products-II*, Vol. 18. Texas: Studium Press; 2017.
[18] Kumara SM, Pokharen N, Dahal S, Anuradha M. Phytochemical and antimicrobial studies of leaf extract of *Euphorbia neriifolia*. *J Med Plant Res* 2011; **5**(24): 5785-5788.
[19] Pracheta J, Sharma V, Paliwal R, Sharma S. Preliminary phytochemical screening and *in-vitro* antioxidant potential of hydro-ethanolic extract of *Euphorbia neriifolia* L. *Int J Pharm Tech Res* 2011; **3**(1): 124-132.
[20] Bigoniya P, Shukla A, Singh CS. Dermal irritation and sensitization study of *Euphorbia neriifolia* latex and its anti-inflammatory efficacy. *Int J Phytomed* 2010; **2**(3): 240-254.
[21] Yadav RP, Patel AK, Jagannadham MV, Neriifolin S. A dimeric serine protease from *Euphorbia neriifolia* Linn.: purification and biochemical characterization. *Food Chem* 2012; **132**(3): 1296-1304.
[22] Yadav RP, Patel AK, Jagannadham MV. Purification and biochemical characterization of a chymotrypsin-like serine protease from *Euphorbia neriifolia* Linn. *Process Chem* 2011; **46**(8): 1654-1662.
[23] Mallavadhani UV, Satyanarayana KVS, Mahapatra A, Sudhakar AVS. A new tetracyclic triterpene from the latex of *Euphorbia neriifolia*. *Nat Prod Res* 2004; **18**(1): 33-37.
[24] Mallavadhani UV, Satyanarayana KVS, Mahapatra A, Sudhakar AVS, Narasimhan K, Pandey DK, et al. Development of diagnostic microscopic and chemical markers of some *Euphorbia* latexes. *J Integr Plant Biol* 2006; **48**(9): 1115-1121.
[25] Ilyas M, Parveen M, Kunwar Mohammad YA. Neriifolione, a triterpene from *Euphorbia neriifolia*. *Phytochem* 1998; **48**(3): 561-563.
[26] Roa DN, Row LR. The crystalline principles of Euphorbiaceae. Part III. *Curr Sci* 1965; **14**: 432.
[27] Seshagirirao K, Prasad MN. Purification and partial characterization of a lectin from *Euphorbia neriifolia*. *Biochem Mol Biol Int* 1995; **35**(6): 1199-1204.
[28] Toume K, Takafumi N, Tahmina H, Takashi O, Midori AA, Takashi K, et al. Cycloartane triterpenes and ingol diterpenes isolated from *Euphorbia neriifolia* in a screening program for death-receptor expression-enhancing activity. *Planta Med* 2012; **78**(12): 1370-1377.
[29] Anjaneyulu V, Row LR. The crystalline principles of Euphorbiaceae. Part IV. *Curr Sci* 1965; **21**: 608-609.
[30] Anjeneyulu ASR, Row LR, Subrahmanyam, Murty KS. Crystalline constituents from Euphorbiaceae—XIII: the structure of a new triterpene from *Euphorbia neriifolia* L. *Tetrahedron* 1973; **29**(23): 3909-3914.
[31] Bigoniya P, Rana AC. Radioprotective and *in-vitro* cytotoxic sapogenin from *Euphorbia neriifolia* (Euphorbiaceae) leaf. *Trop J Pharm Res* 2009; **8**(6): 521-530.
[32] Jun-Hua L, Abdul L, Mumtaz A, Gui-Ping Z, Wen-Juan X, Lei M, et al. Diterpenoids from *Euphorbia neriifolia*. *Phytochem* 2012; **75**: 153-158.
[33] Sharma V, Janmeda P. Extraction, isolation and identification of flavonoid from *Euphorbia neriifolia* leaves. *Arab J Chem* 2014; http://dx.doi.org/10.1016/j.arabjc.2014.08.019.
[34] Sharma V, Janmeda P. Chromatography fingerprinting profile studies on the flavonoids of *Euphorbia neriifolia* (Linn.) leaves. *Int J Drug Dev Res* 2013; **5**(1): 286-296.
[35] Baslas RK, Agrawal R. Chemical examination of the bark of *Euphorbia neriifolia* Linn. *Indian J Pharm Sci* 1980; **42**(2): 66-67.
[36] Ng AS. Diterpenes from *Euphorbia neriifolia*. *Phytochem* 1990; **29**(2): 662-664.
[37] Koh LL, Ng AS, Tan GK. Structure of a diterpene from Euphorbia neriifolia. *Acta Cryst* 1992; **C48**: 753-754.
[38] Lahon LC, Khanikor HN, Ahmed N. Preliminary study of local anaesthetic activity of *Euphorbia neriifolia* Linn. *Indian J Pharmacol* 1979; **11**(3): 239-240.
[39] Gaur K, Rana AC, Nema RK, Kori ML, Sharma CS. Anti-inflammatory and analgesic activity of hydro-alcoholic leaves extract of *Euphorbia neriifolia* Linn. *Asian J Pharm Clin Res* 2009; **2**(1): 26-29.
[40] Bigoniya P, Rana AC. Pharmacological screening of *Euphorbia neriifolia* leaf hydro-alcoholic extract. *J Appl Pharm* 2010; **1**(2): 1-17.
[41] Bigoniya P, Rana AC. Psychopharmacological profile of hydro-alcoholic extract of *Euphorbia neriifolia* leaves in mice and rats. *Indian J Exp Biol* 2005; **43**(10): 859-862.
[42] Ilyas M, Parveen M, Hasan MHM, Omer AB. A novel triterpene (Neriifolione): a potent anti-inflammatory and antiarthritic agent from *Euphorbia neriifolia*. *Hamdard Med* 2003; **XLVI**(2): 97-102.
[43] Sharma V, Janmeda P, Paliwal R, Singh L, Sharma V, Sharma S. Anticarcinogenic potential of *E. neriifolia* leaves against n-nitrosodiethylamine-induced nephrotoxicity in mice. *Biochem Cell Arch* 2011; **11**(2): 393-398.
[44] Sharma V, Janmeda P. Chemopreventive role of *Euphorbia neriifolia* (Linn) and its isolated flavonoid against n-nitrosodiethylamine-induced renal histopathological damage in male mice. *Toxicol Int* 2013; **20**(1): 101-107.
[45] Pracheta J, Sharma V, Singh L, Paliwal R, Sharma S, Yadav S, et al. Chemopreventive effect of hydroethanolic extract of *Euphorbia neriifolia* leaves against DENA-induced renal carcinogenesis in mice. *Asian Pac J Cancer Prev* 2011; **12**(3): 677-683.
[46] Sharma V, Janmeda P. Protective assessment of *Euphorbia neriifolia* and its isolated flavonoid against N-nitrosodiethylamine-induced hepatic carcinogenesis in male mice: a histopathological analysis. *Toxicol Int* 2014; **21**(1): 37-43.
[47] Pracheta J, Sharma V, Paliwal R, Sharma S, Singh L, Janmeda BS, et al. Chemoprotective activity of hydro-ethanolic extract of

*Euphorbia neriifolia* Linn. leaves against DENA-induced liver carcinogenesis in mice. *Biol Med* 2011; **3**(2): 33-44.

[48] Mushir IM, Patel VM. Anti diabetic potential of *Euphorbia neriifolia* Linn. in alloxan induced diabetic rats. *J Pharm Res* 2012; **5**(5): 2571-2573.

[49] Hasan M, Ganeshpurkar A, Bansal D, Dubey N. Protective effect of *Euphorbia neriifolia* extract on experimentally induced thrombosis in murine model. *Niger J Exp Clin Biosci* 2014; **2**: 86-89.

[50] Datta S, Nayak SS, Dinda SC. Exploration of antimicrobial potential of methanol extract of stems of *Euphorbia neriifolia*. *Int Res J Pharm* 2013; **4**(1): 271-273.

[51] Pracheta J, Sharma V, Paliwal R, Sharma SP. *In-vitro* free radical scavenging and antioxidant potential of ethanolic extract of *Euphorbia neriifolia* Linn. *Int J Pharm Pharmacet Sci* 2011; **3**(1): 238-242.

[52] Bigoniya P, Rana AC. Subacute effect of *Euphorbia neriifolia* Linn. on hematological, biochemical and antioxidant enzyme parameters of rat. *Acad J Plant Sci* 2009; **2**(4): 252-259.

[53] Babar RS, Kataware UP, Mali NN, Patil SB, Naikwade NS. *In-vitro* cytotoxicity activity of *Euphorbia hirta, Euphorbia tirucalli* and *Euphorbia neriifolia* extract against B16F10 melanoma cell line. *Inven Impact Ethnopharmacol* 2012; **3**(3). Available from: http://inventi.in/journal/article/impact/3/3174/ethnopharmacology/pi [Accessed on 21st April 2017]

[54] Patil SB, Magdum CS. Determination of $LC_{50}$ values of extracts of *Euphorbia hirta* Linn and *Euphorbia neriifolia* Linn. using brine shrimp lethality assay. *Asian J Res Pharm Sci* 2011; **1**(2): 42-43.

[55] Bigoniya P, Rana AC. Immunomodulatory activity of *Euphorbia neriifolia* leaf hydro-alcoholic extract in rats. *Indian Drugs* 2008; **45**(2): 90-97.

[56] Gaur K, Rana AC, Chauhan LS, Sharma CS, Nema RK, Kori ML, et al. Investigation of immunomodulatory potential of *Euphorbia neriifolia* Linn. against betamethasone induced immunosuppression. *Int J Pharmacog Phytochem Res* 2009; **1**(1): 8-11.

[57] Singh C, Pandey DN, Shukla S. Pesticidal effect of *Euphorbia, Nerium* and *Calotropis* latex on some larvae of crop damagining pests. *Int J Pharm Pharm Sci* 2012; **4**(Suppl 4): 256-260.

[58] Nunthawun U, Arunrat C, Sompong T, Tarinee A, Chattong C, Sakda D. Screening of plants acting against *Heterometrus laoticus* scorpion venom activity on fibroblast cell lysis. *J Ethnopharmacol* 2006; **103**(2): 201-207.

[59] Rasik AM, Shukla A, Patnaik GK, Dhawan BN, Kulshrestha DK. Wound healing activity of latex of *Euphorbia neriifolia* Linn. *Indian J Pharmacol* 1996; **28**(2): 107-109.

[60] Bigoniya P, Rana AC. Wound healing activity of *E. neriifolia* leaf extract. *J Nat Remed* 2007; **7**(2): 94-101.

[61] Rizvi SSA. Toxicological and insecticidal activity of latex of *Euphorbia neriifolia* Linn. *Indian J Pharmacol* 1969; **1**: 9.

[62] Shukla N. Multicentric randomized controlled clinical trial of Kshaarasootra (Ayurvedic medicated thread) in the management of fistula-in-ano. Indian Council of Medical Research. *Indian J Med Res* 1991; **94**: 177-185.

[63] Naik SB. Common milk hedge (*Euphorbia neriifolia*) juice ingestion: a clinical case report. *J Indian Soc Toxicol* 2009; **5**(2): 30-31.