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Pharmacological and therapeutic effects of *Lippia nodiflora* (*Phyla nodiflora*)

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ABSTRACT: The phytochemical analysis of *Lippia nodiflora* showed that the plant contained flavonoids, steroids, glycosides, alkaloids, terpenoids, quinols, quinol glucosides, steroids, phenylpropanoids, resin, volatiles, tannins and phenolics. Lippia nodiflora possessed diuretic, antihyperuricemic, antiurolithiatic, hepatoprotective, antimicrobial, antihyperlipidemic, hypotensive, antioxidant, antidiabetic, anti-diarrhoeal, anticancer, sedative, anticonvulsant, anxiolytic, antimelanogenic, hair growth enhancement and antidandruff effects. This review discussed the chemical constituents, pharmacological and therapeutic effects of Lippia nodiflora.

Keywords: Lippia nodiflora**,** constituents, pharmacology, therapeutic

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I. INTRODUCTION

Recent reviews revealed that the medicinal plants possessed central nervous[1-2], cardiovascular[3-4], antioxidant[5-6], reproductive[7-10], gastro-intestinal[11-14], respiratory[15-16], antidiabetic[17-19], antimicrobial[20-21], antiparasitic[22-23], dermatological[24], anticancer[25-26], anti-inflammatory, antipyretic and analgesic[27-29], immunological[30], and many other pharmacological effects. The phytochemical analysis of *Lippia nodiflora* showed that the plant contained flavonoids, steroids, glycosides, alkaloids, terpenoids, quinols, quinol glucosides, steroids, phenylpropanoids, resin, volatiles, tannins and phenolics. *Lippia nodiflora* possessed diuretic, antihyperuricemic, antiurolithiatic, hepatoprotective, antimicrobial, antihyperlipidemic, hypotensive, antioxidant, antidiabetic, anti-diarrhoeal, anticancer, sedative, anticonvulsant, anxiolytic, antimelanogenic, hair growth enhancement and antidandruff effects. This review will designed to highlight the chemical constituents and pharmacological effects of Lippia nodiflora.

Plant profile:
Synonyms:

Blairia nodiflora, Diototheca repens, Lantana larranagae, Lantana repen, Lippia aegyptiaca, Lippia fruticosa, Lippia incisa, Lippia incisa, Lippia litoralis, Lippia nodiflora var. minor, Lippia nodiflora var. repens, Lippia nodiflora var. rosea, Lippia nodiflora var. sarmentosa, Lippia repens, Lippia sarmentosa, Phyla chinensis, Phyla fruticosa, Phyla incise, Phyla nodiflora var. antillana, Phyla nodiflora f. copiapina, Phyla nodiflora var. incisa, Phyla nodiflora var. longifolia, Phyla nodiflora var. Sericea, Phyla nodiflora var. texensis, Phyla yucatana var. parviflora, Piarimula chinensis, Platonia nodiflora, Verbena capitata, Verbena cuneata, Verbena elliptica, Verbena fruticosa, Verbena globiflora, Verbena lanata, Verbena nodiflora, Verbena repens, Verbena sarmentosa, Zapania nodiflora, Zappania nodiflora, Zappania repens and Zappania suberosa[31].

Taxonomic classification:
Kingdom: Plantae, **Subkingdom**:Viridiplantae, **Infrakingdom**: Streptophyta, **Superdivision**: Embryophyta **Division**: Magnoliophyta, **Subdivision**: Spermatophytina, **Class**: Magnoliopsida, **Superorder** :Asteranae, **Order**: Lamialas, **Family**: Verbenaceae, **Genus**: Phyla, **Species**: *Phyla nodiflora* (*Lippia nodiflora*)[32].

C**onnon names:**
Arabic: Blaiha, Lippia, Barbeen Jedawi; **Bengali:** Bhui okar, Karghas, Bakkan; **Chinese**: guo jiang teng; **English**: Lippia, Capeweed, carpetweed, fogfruit, matgrass, turkey-tangle, turkey-tangle frogfruit; **Hindi**: Bukkan, Jalpapli; **Marathi**: Ratolia Vakkan; **Pakistan**: Bukan; **Sanskrit** : Vasir Vasuka; **Swedish**: grodverbena; **Tamil**: Poduthalai**; Thailand**: Yaa Riet Pla[33-35].

Distribution:

It was distributed in **Africa**: (Algeria, Egypt, Morocco, Tunisia, Chad, Eritrea, Ethiopia, Somalia, Sudan, Kenya, Tanzania, Uganda, Burundi, Central African Republic, Zaire, Ghana, Guinea-Bissau, Mali, Mauritania, Nigeria, Senegal, Angola, Malawi, Mozambique, Zambia, Zimbabwe, Botswana, Namibia and South Africa); **Asia**: (Afghanistan, Cyprus, Iran, Iraq, Palestine, Jordan, Lebanon, Syria, Turkey, China, Japan, Taiwan, : India, Nepal, Pakistan, Sri Lanka, Myanmar, Thailand, Vietnam, East Timor, Indonesia, Malaysia, Singapore and Philippines); **Europe**: (Switzerland, Albania, Greece, Italy, France and Spain); **Australasia (**Australia); **Southern America**: (Bahamas, Bermuda, Cayman Islands, Cuba, Dominican Republic, Guadeloupe, Haiti, Jamaica, Martinique, Trinidad and Tobago, Turks and Caicos Islands, Belize, Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, Panama, Venezuela, Brazil, Argentina, Chile and Uruguay) and it was widely naturalized in tropical and subtropical areas all over the word[33].

Description:

It is perennial, prostrate herb with somewhat woody rootstock, rooting at nodes, appressedly pubescent to glabrescent. Leaves oblanceolate, obovate to spathulate, somewhat fleshy, 5-40 mm long, 4-20 mm broad, serrate above, entire below, glabrous to appressedly pubescent, subsessile to sessile, obtuse, rarely subacute. Spikes 1-4.5 cm long, 6-8 mm broad, solitary, axillary, peduncled, appressedly pubescent to glabrous. Flowers very small, white, rarely pinkish, c. 3 mm long; bracts c . 2 mm long, mucronate or acuminate, imbricate. Calyx flattened, shorter than bracts, hyaline-membranous, deeply dissected with lanceolate lobes, pubescent. Corolla slightly exceeding the bracts, unequally 4-lobed with spreading lobes. Fruit ovate, c. 1.6 mm long, subcompressed, enclosed by the persistent calyx, separating at maturity into two, 1-seeded pyrenes[36-37].

Traditional uses:

The aerial parts were used as anodyne, antibacterial, emmenogogue, parasiticide, refrigerant, febrifuge, cooling, in treatment of wounds, asthma, thirst and loss of consciousness[38-39]. The plant made into a poultice to be used as maturant for boils. The infusion of leaves and tender stalks was used in children for indigestion and to women after delivery. Chutney made from the plant leaves and fruits were eaten to relive the irritation of internal piles[40]. In Ayurveda and Unani system of medicine, the plant was used as aphrodisiac, diuretic, and for the treatment of heart diseases, ulcers, bronchitis, fevers, cold, knee joint pain and in lithiasis[41].

Parts used

Leaves, roots, whole plant[35].

Physicochemical characteristics:

Physicochemical properties of *Phyla nodiflora* were: water soluble extractive value (21.44±0.009% w/w), alcohol soluble extractive (13.39±0.03% w/w), total ash (20.85±0.09% w/w) and loss on drying (15.68±0.05% w/w)[42].

Chemical constituents:

The preliminary phytochemical screening showed that the aerial parts of Lippia nodiflora contained flavonoids, steroids, glycosides, alkaloids, terpenoids, quinols, quinol glucosides, steroids, phenylpropanoids, resin, volatiles, tannins and phenolics [43]. Many compounds were isolated from different parts of *Lippia nodiflora* included: flavonoids [nodifloretin (or 6-hydroxy-3'- methoxyluteolin or batatifolin), 6-hydroxyluteolin-7-O-apioside, luteolin-7-O-glucoside, eupafolin, hispidulin-7-sulfate, hispidulin-7,4'-disulfate, jaceosidin-7,4'-disulfate, nepetin-3',4'-disulfate, nodifloretin-6,7-disulfate, 6-hydroxyluteolin-6,7-disulfate, nodifloretin-7-sulfate, 6-hydroxy-luteolin-6-sulfate, 6-hydroxyluteolin-7-sulfate, jaceosidin-7-sulfate, nepetin-7-sulfate, hispidulin-4'-sulfate, hispidulin, jaceosidin, lippiacian, demethoxycentaureidin (or 5,7,3'-trihydroxy-6,4'-dimethoxy flavone), ganzalitosin I (or 5-hydroxy- 3',4',7-trimethoxy flavones), 3,7,4',5'-tetrahydroxy-3'-methoxyflavone, 4'-hydroxywogonin, onopordin, cirsiliol, larycitrin and 5,7,8,4'-tetrahydroxy-3'-methoxyflavone][44-53]; phytosterol (β-sitosterol glucoside, stigmasterol glucoside, β-sitosterol, 4', 5'-dimethoxybenzoloxystigmasterol and stigmasterol)[52-54]; triterpene (3β-19α-dihydroxy-urs-1,20-(30)- diene, ursolic acid, pomolic acid and Lippiacin)[54-55]; quinol [halleridone (or benzofuranone renglyolone) and hallerone][46, 55]; iridoid (loganin and catalpol)[24]; steroids [4', 5'-dimethoxybenzoloxystigmasterol and beta-sitosterol][48, 55]; phenylethanoid glycosides [arenarioside, acteoside, verbascoside and 2'-O-acetylechinacoside][50, 56-57]; resin (α-copaene, β-bisabolene)[58]; other compounds such as nodifloridin A, nodifloridin B, nodiflorin A, nodiflorin B, cornoside, α-ethyl-galactose, 7-arabinose and 4'-rhamnoside were also isolated from the plant[45, 54, 59].

Quantitative analysis showed that the methanolic extract of the aerial parts of *Lippia nodiflora* contained phenolic compounds (98.31 ± 0.004 mg GAE/g), total flavonoids (60.88 ±0.001 mg QE/g), flavonols

(27.46 ± 0.002 mg QE/g), total tannin 5.97 ± 0.021 mg TAE/g and saponin 3.52 ± 0.017 mg DE/g. 2,7-dioxatricyclo [4.3.1.0 (3, 8)] decan-4-one (35.75%), stigmasterol (16.86%), benzoic acid, 4-etoxy-, ethyl ester (13.73%), azacyclotridecan-2-one (11.86%) and n-hexadecanoic acid (10.12%) were isolated from the aerial parts of Lippia nodiflora[60]. However, Priya and Ravindhran found that the aerial parts of *Phyla nodiflora* contained alkaloids: 0.589, phenolics: 0.411, carbohydrates: 1.421, flavonoids: 0.312, amino acids: 2.214, proteins: 1.356, chlorophyll a: 10.975, chlorophyll b: 1.835, total chlorophyll: 12.810, carotenoids: 2.079 and anthocyanins: 0.183 mg/g[61].

The essential oil components which were identified in the *Lippia nodiflora* were: 1 -mettryl-4isopropylcyclohexane: 7.8%, 1-octen-3-ol: 15.29%, 1-octen-3-o ne: < 1.0 %, 2-phenethyl alcohol: 16.40%, 2, 6-dimethyloctane: 12.3%, 3-octanol: 3.95%, 6-methyt-3,5-heptadien-2-one 1.65%, α-terpineol: 4.86%, β-pinene: 8.1%, ϒ-terpinene: 6.3%, p-cymen-B-ol: 10.61%, benzaldehyde 6.80%, benzyl alcohol 2.59%, carvacrol: 3.22 %, carvone: <1.0%, dihydrobenzofuran: <1.0%, eugenol: <1.0%, linalool 13.79%, methyl salicylate: 10.63%, phenylacetaldehyde: 2.68%, terpinolene: 1.5%, thymol: 2.74%,α-copaene: 8.4%, 4,10-dimethyl-7- isopropyl-bicyclo-[4.4.0] l.4 decadiene: 4.8%, α-bergamotene: 4.2%, β-bisabolene: 3.6%, β-caryophyllene: 18.7%, δ-cadinene 4.2% and calamenene 19.9%][47].

Lippia nodiflora contained many elements: aluminum: 3.88-4.39, calcium 32455.49-33939.17, copper 18.59-19.66, iron 91.61-122.67, magnesium 18429.39-18644.43, manganese 21.57-22.40, phosphorus 2834.09-2913.53, sulphur 807.67-830.73 and zinc 52.81-57.79 mg/kg[62].

Pharmacological effects:

Diuretic, antihyperuricemic and antiurolithiatic effects:

Two phenylethanoid glycosides, arenarioside and verbascoside, and three flavonoids, 6-hydroxyluteolin, 6-hydroxyluteolin-7-O-glycoside and nodifloretin were isolated from *Lippia nodiflora* methanolic extract. The isolated compounds inhibited xanthine oxidase activity, with IC_{50} values between 7.52 ± 0.01 and 130.00 ± 2.25 μM [56-57]. The antihyperuricemic effects of the *Lippia nodiflora* methanol extract, fractions, and chemical constituents and their mechanism of action were investigated in potassium oxonate- and hypoxanthine-induced hyperuricemic rats. Oral administration of methanol extract showed a dose-dependent reduction of the serum uric acid level of hyperuricemic rats. Bioactivity-guided purification of the most antihyperuricemic fraction led to isolation of two phenylethanoid glycosides, arenarioside and verbascoside and three flavonoids, 6-hydroxyluteolin, 6-hydroxyluteolin-7-O-glycoside, and nodifloretin. The serum uric acid reduction effect of the isolated compounds ranged from 22.08% to 66.94%. Flavonoids mainly accountable for the uric acid lowering effect of *Lippia nodiflora* through the inhibition of XOD/XDH activities and partially by uricosuric effect[63].

Lippia nodiflora ethanol extract exhibited antiurolithiatic effect. The extract significantly prevented the formation of the calcium oxonate stone, dissolved the pre-formed calcium oxolate stone in the kidney of rats induced by gentamycin and calculi producing diet due to its ability to increase the urinary pH and excretion of the calcium and oxolate, and also to reduce the urine super-saturation with the calculogenic ions[38].

The diuretic activity of petroleum ether, chloroform, methanol and aqueous extract of the dried aerial parts of *Phyla nodiflora* (250 and 500 mg/ kg ip), was studied in rats. The volumes of urine, urinary concentration of sodium and potassium ions were estimated. The results showed that methanol and aqueous extract at 500 mg/kg possessed significant ($p<0.05$) increase in the urine volume and electrolyte excretion ($p<0.001$) when compared to control[64].

The diuretic potential of methanol extract of *Lippia nodiflora* (200 and 400 mg/kg bw, ip) was studied in hydrated rats and their urine output was monitored over a period of 5 and 24 h after drug administration. The extract at doses of 200 and 400 mg/kg caused significant increase in volume of urine with increase in Na^+, Ca^{2+} and Cl^- excretion accompanied by the excretion of K^+ in dose dependent manner[65].

Hepatoprotective effects:

The hepatoprotective activity of ethanolic leaf extract of *Lippia nodiflora* (100 and 200 mg/kg bw/ day, orally, for 15 days) was evaluated against CCl_4- induced hepatic damage in rats. Both doses restored the elevated levels of total bilirubin, aspartate transaminase, alanine transaminase and alkaline phosphatase in CCl_4 intoxicated rats to normal levels. The hepatoprotective activity was dose dependent[66].

The hepatoprotective and antioxidant activity of methanol extract of Lippia nodiflora (200 and 400mg/kg, orally, for 7) was evaluated in acute experimental liver injury induced by paracetamol. The methanol extract possessed significant ($p<0.001$) hepatoprotective effect, it decreased the activity of SGOT, SGPT, ALP, decreased bilirubin and lipid peroxidation, while it significantly ($p<0.001$) increased the levels of total proteins, glutathione, catalase and superoxide dismutase in a dose dependent manner[67].

The hepatoprotective effect of crude flavonoid fraction (25, 50 mg/kg for 21 days) of aerial parts of *Lippia nodiflora* was evaluated in ethanol induced oxidative stress in liver in rats. The crude flavonoid fraction

showed significant ($p<0.05$) protective effect by decreasing the elevated liver marker enzymes, total bilirubin, lipid peroxidation marker and ameliorated the diminished serum total protein as well as antioxidant levels in a dose dependent manner[68].

The hepatoprotective effect of methanolic extracts of *Lippia nodiflora* was studied in HepG2 cells. The extract reduced reactive oxygen species production against LPS induced toxicity on HepG2 cells, and decreased the apoptotic gene expression and protect the liver cells against toxicity[69].

Antimicrobial activity:

The antibacterial activity of the stems and leaves extracts of *Phyla nodiflora* was studied against Staphylococcus aureus, Micrococcus luteus, Proteus micrococcus luteus and Shigella boydii. The antifungal activity of the extracts was studies against Aspergillus niger and Candida albicans. The ethanol extracts showed significant antibacterial and antifungal activity, they showed zone of inhibition of 3 to 12 mm. The zone of inhibition produced by petroleum ether fraction was 6 to 10 mm against all tested organisms. The zone of inhibition produced by aqueous fraction was 10 to 12 mm against all tested organisms except, Staphylococcus aureus and Micrococcus luteus[70].

The antimicrobial activity of hexane, chloroform, ethyl acetate and methanol extracts of aerial parts of *Phyla nodiflora* was evaluated against human pathogenic bacteria [Staphylococcus aureus (+ MTCC 96), Staphylococcus epidermidis (+ MTCC2639), Klebsiella pneumoniae (- MTCC432), Enterococcus faecalis (+ MTCC 126), Shigella flexneri (- MTCC 1457), Methicillin resistant Staphylococcus aureus (+) clinical isolate, Micrococcus luteus (+MTCC 106), Salmonella paratyphi B (-) clinical isolate, Salmonella typhi (- MTCC733), Pseudomonas aeruginosa (- MTCC 424), Escherichia coli (- MTCC 2939), Vibrio cholerae (- MTCC 3906)], and fungi [Candida albicans, Candida krussie, Candida tropicalis, Trichophyton mentagrophytes, Microsporum gypseum and Malassezia pachydermatis]. All the extracts possessed inhibitory effects on both bacteria and fungi. Ethyl acetate extract showed the most potent antibacterial and antifungal activity. The MIC of the ethyl acetate extract of the aerial parts ranged between 0.078 and 0.312mg/ml. Similarly for methanol extract of the roots, the MIC ranged between 0.625 and 2.5 mg/ml. The ethyl acetate extract inhibited growth of Staphylococcus aureus, Salmonella typhi and Malassezia pachydermatis at 0.312 mg/ml and Klebsiella pneumoniae at 0.078 mg/ml. Methanol extract of the roots inhibited the growth of Staphylococcus aureus at 0.625 mg/ml and the growth of K. pneumoniae, Salmonella typhi and M. pachydermatis at 2.5 mg/ml. The minimum bactericidal concentration **(**MBC) of ethyl acetate extract of the aerial parts against Staphylococcus aureus, Salmonella typhi and Malassezia pachydermatis was at 0.625 mg/ml and Klebsiella pneumoniae was at 0.156 mg/ml. The MBC value of methanol extract of the roots ranged between 1.25 mg/ml to 5 mg/ml[71].

The methanolic extract from the leaves and flowers of *Lippia nodiflora* showed concentrations – dependent antimicrobial activity against Bacillus subtilis, Bacillus cereus, Micrococcus luteus, Staphylococcus aureus, Pseudomonas aeruginosa, Klebsiella pneumonia, Klebsiella oxytoca and Esherichia coli. They also possessed antifungal activity against Aspergillus niger and Candida albicans. Bacteria were more sensitive than fungi, and Gram positive bacteria were more sensitive than Gram negative ones[72].

Aqueous extract of *Lippia nodiflora* exerted a concentration – dependent antibacterial activity against Esherichia coli but showed no activity e against Staphylococcus aureus and Pseudomonas aeruginosa. Ethanolic extract possessed antibacterial activity against Gram positive (Staphylococcus aureus) and Gram negative (Esherichia coli) but not effective against Pseudomonas aeruginosa[73].

The methanolic extract of the whole *Lippia nodiflora* showed antibacterial activity against Pseudomonas aueroginosa, Escherichia coli and Staphylococcus aureus with inhibition zone of 15, 8 and 7 mm, respectively[74].

The antimicrobial activity of the extracts of *Lippia nodiflora* was tested against E. coli, Salmonella typhi, P. alcaligens, Proteus mirabilis and E. aerogenes. All extracts showed concentration dependent antimicrobial activity against all the tested bacteria. MICs of acetone extract were 13, 14, 11, 10 and 16 mm; chloroform extract were 16, 10, 8, 13 and 15 mm; ethanol extract were 17, 19, 14, 16 and 12 mm; and methanol extract were 15,18, 14, 11 and 12 mm at 200µl concentration respectively[75].

The antibacterial activity of *Phyla nodiflora* crude extract and sub fractions (n-hexane, chloroform, ethyl acetate, n-butanol and aqueous) was studied against Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae, Salmonella typhi, Staphylococcus epidermidis, Staphylococcus aureus (MRSA) and Bacillus subtillus. Ethyl acetate and chloroform fractions showed excellent activity against Bacillus subtilis, Staphylococcus epidermidis and Staphylococcus aureus, The n-hexane and n-butanol fractions of plant were active against Escherichia coli and Pseudomonas aeruginosa, ethyl acetate, chloroform, n-butanol and n-hexane fractions showed promising activity against Salmonella and Staphylococcus aureus (MRSA), almost all fractions active against Staphylococcus aureus[76].

The methanolic extract from *Lippia nodiflora* showed antimicrobial activities against Escherichia coli, Proteus vulgaris, Klebsiella pneumonia, Bacillus cereus, Bacillus subtilis, Staphylococcus aureus, Pseudomonas

aeruginosa and B. clausii as well as Aspergillus niger and Candida albicans. Increasing concentrations of extracts increased the antimicrobial activities against all the tessted microorganisms. Bacteria were more sensitive than fungi. In both Gram negative and Gram positive bacteria tested, Klebsiella pneumonia, Pseudomonas aueroginosa and Bacillus subtilis showed more sensitivity than the other tested species. Thirteen mm zone of inhibition observed against Klebsiella pneumonia, Bacillus cereus and Bacillus subtilis, 12 mm against Escherichia coli and Proteus vulgaris and 11 and 10 mm against Pseudomonas aueroginosa and Staphylococcus aureus respectively in 250 µg/disc methanolic extract of Lippia nodiflora. Methanolic extract of *Lippia nodiflora* in 500 µg/disc showed the highest inhibition zone against P. vulgaris, K. pneumonia, B. cereus and B. subtilis and lowest inhibition zone against B. clausii. Fungi exhibited the same zone of inhibition (11 at 250 µg per disc) for both Aspergillus niger and Candida albicans. At 500 µg per disc, highest zone of inhibition (14 mm) occurred against A. niger and lowest zone of inhibition (11 mm) occurred against C. albicans[77].

The antimicrobial activity of the methanol extract of whole *Lippia nodiflora* was studied against Staphylococcus aureus (MTCC 96), Staphylococcus epidermidis (MTCC 435), Proteus vulgaris (MTCC 1429), Escherichia coli (MTCC 433), Salmonella paratyphi A (MTCC735), Salmonella paratyphi B (clinical isolate), Klebsiella pneumonia (MTCC 432), Salmonella typhimurium (MTCC 98), Candida albicans (MTCC 183) and Cryptococcus neoformans (Clinical isolate). The methanol extract of *Lippia nodiflora* possessed antimicrobial activity against Staphylococcus epidermidis, Staphylococcus aureus, Proteus vulgaris, Salmonella paratyphi A, Escherichia coli and Salmonella paratyphi B, at concentrations below 500 µg/ml. Klebsiella pneumonia and Salmonella typhimurium did not show response, while, the extract exerted antifungal activity against Candida albicans and Cryptococcus neoformans at 400 and 500µg/ml[78].

Five medicinal plants (*Phyla nodiflora*, *Lawsonia inermis*, *Cassia fistula*, *Vernonia cinerea* and *Aristolochia bracteolate*) were tested as antifungal therapy against fungal pathogen isolated from infected nail (Candida sp.). Ethanol extracts of *Phyla nodiflora* leaves exhibited complete inhibitory effect against the tested nail fungus, while, aqueous extract showed 75% inhibition after 48 hrs[79].

The crude extracts of *Lippia nodiflora* were tested for antifungal effects against Aspergillus niger, A. flavus, Paecilomyces varioti, Microsporum gypseum and Trichophyton rubrum. All crude extracts including ethanol, methanol, ethyl acetate, chloroform and aqueous extracts showed high activity against the tested microorganisms. Ethanol and aqueous extracts appeared to be the most effective antifungal agents compared to methanol, chloroform and ethyl acetate[62].

Anti-inflammatory activity:

The anti-inflammatory activity of the methanolic extract of *Lippia nodiflora* was studied using carrageenin-induced edema model in the rat hind paw, while the antinociceptive activity was tested in the acetic acid-induced writhing model in mice. The extract showed a significant ($p < 0.001$) anti-inflammatory activity comparable to phenylbutazone and a significant ($p < 0.001$) antinociceptive activity comparable to diclofenac sodium[80].

Aqueous extract of *Lippia nodiflora* possessed anti-inflammatory activity in carrageenan induced mice paw edema at 100 and 200 mg /kg bw ($p < 0.01$). However, the ethanolic extracts didn't induced anti-inflammatory effects in both doses[73].

The anti-inflammatory potential of cyclo-pentano phenanthrenol isolated from *Lippia nodiflora* was studied using in vitro inflammation models with studying of its mechanism of action. The results demonstrate that cyclo-pentano phenanthrenol inhibited TNF-α, IL-1β and IL-6 expression, NO release via iNOS suppression, prostaglandin biosynthesis via PLA2 and COX-2 inhibition and the activation of intracellular targets, MAPK and NF-κB. The anti-inflammatory potential of cyclo-pentano phenanthrenol could be attributed to the inhibition of MAPK phosphorylation and NF-κB translocation[81].

The mode of anti-inflammatory effect of the methanol extract of *Lippia nodiflora* and compound, 5-hydroxy-3',4',7-trimethoxyflavone (HTMF) isolated from Lippia nodiflora was studied in vitro. The data obtained from the spectroscopic method revealed that the quenching of intrinsic fluorescence of LOX was produced as a result of the complex formation of LOX-HTMF. The binding mode analysis of HTMF within the LOX enzyme suggested that hydrogen bond formation, hydrophobic interaction and π-π stacking could account for the binding of HTMF. Molecular dynamics results indicated the interaction of HTMF with LOX and the stability of ligand-enzyme complex was maintained throughout the simulation[82].

Hypotensive effect:

The methanolic extract (500 mg/kg bw/ day for 14 days) of *Lippia nodiflora* caused significant decrease in the systolic pressure in DOCA-Salt hypertensive wister rats[83]. The efficacy of chloroform, ethyl acetate, methanol and water extracts (500 mg/kg, orally) of whole plant *Lippia nodiflora* was studied in uninephrectomized DOCA-salt hypertensive rats. Among all these extracts, methanolic extract reduced the systolic blood pressure significantly[84].

Antioxidant effect:

The antioxidant and free radical scavenging activity of defatted methanolic extract of aerial parts of *Lippia nodiflora* was evaluated using in vitro methods. In DPPH radical scavenging activity, H_2O_2 scavenging activity, NO scavenging activity and NBT reduction assay, the IC_{50} values were 799.74 µg/ml, 53.15 µg /ml, 61.51 µg/ml and 45.60 µg/ml respectively. In the reduction power assay increase in absorbance was observed in a dose dependant manner. Total phenolic content of the extract was114.89 µg/ml total phenolics equivalent to gallic acid/1 mg[85].

The antioxidant potential of methanol extract of Lippia nodiflora was evaluated in vitro using total antioxidant activity, reducing power, free radical, superoxide anion radical, hydroxyl radical, hydrogen peroxide, nitric oxide scavenging, and total phenolic content. The methanol extract exhibited concentration dependent (50, 100, 200, and 400 µg/ml) potent total antioxidant activity (58.96%, 63.07%, 68.29%, and 74.59%, respectively), which were comparable to the standard drug α -tocopherol (400 µg/ml). The methanol extract also exhibited an effective reducing power, free radical scavenging, superoxide anion radical scavenging, hydroxyl radical scavenging, hydrogen peroxide radical scavenging, and nitric oxide scavenging activity[86].

The antioxidant constituent in the methanol extract of *Lippia nodiflora* was studied with the using of bioassay-guided fractionation. The ethyl acetate fraction revealed a strong antioxidant activity, through in vitro DPPH radical-scavenging assay. The bioactive compound was determined as 2-(3, 4-dimethoxyphenyl)-5-hydroxy-7-methoxy-4H-chromen-4-one (5-hydroxy-3', 4', 7-trimethoxyflavone). The isolated compound demonstrated an excellent antioxidant activity through all antioxidant assays and also significantly inhibited lipid peroxidation at a concentration of 50 µg/ml[87].

The free radical scavenging activity of the methanol and ethyl acetate extract of leaf and stem of *Phyla nodiflora* was determined using 2,2- diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging assay. Both leaf extracts exhibited lower EC_{50} values (0.4271 mg/ml and 0.6177 mg/ml for ethyl acetate and methanol respectively) which indicated high antioxidant activity[88].

The lipid peroxide scavenging activity of the methanol extract of whole *Lippia nodiflora* was studied in vitro. The results showed that the percentage inhibition of the methanol extract increased in concentration dependent manner. The IC_{50} values of the MELN, BHA and BHT for lipid peroxide scavenging were 226.52 µg/ml, 25.62 µg/ml and 17.13 µg/ml respectively[78].

Antidiabetic effect:

The antidiabetic property of *Lippia nodiflora* methanol extract was studied in streptozotocin induced diabetic rats for 15 days. The extract at three dose levels caused significant increase in the liver, muscle glycogen and serum insulin level and a significant decrease in fasting blood glucose, glycosylated hemoglobin levels and serum marker enzymes. The total cholesterol and serum triglycerides levels were also significantly reduced and the HDL cholesterol levels was significantly increased. Histochemical study of pancreas was further confirmed the beneficial biochemical findings[89].

The antidiabetic property of γ-sitosterol isolated from *Lippia nodiflora* (20 mg/kg bw, orally once daily for 21 days) was screened in streptozotocin (STZ) induced diabetic rats. Insulin secretion in response to glucose was evaluated in isolated rat islets. γ-sitosterol significantly decreased blood glucose and glycosylated hemoglobin with a significant increase in plasma insulin level, body weight and food intake. γ-Sitosterol increased insulin secretion in response to glucose. Immunohistochemical study of pancreas also confirmed the biochemical findings[90].

Anti-diarrhoeal activity:

The anti-diarrhoeal activity of *Lippia nodiflora* leaves aqueous extract was studied in rats using castor oil-induced diarrhoea model. The extract (100 mg/kg) significantly ($p < 0.001$) protected against castor oil-induced diarrhoea and castor oil induced enteropooling[91].

Anticancer effect:

The anticancer effect of the methanol and ethyl acetate extract of leaf and stem of *Phyla nodiflora* was studied in MCF7 cells. The proliferation assay was performed using 3-(4,5- dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) method. DNA fragmentation caused by apoptosis event was evaluated through DNA extraction. MCF7 cells were inhibited by all the extracts with IC_{50} ranging from 90-120 µg/ml. DNA extracted from treated cells showed the formation of DNA laddering. The results showed that *Phyla nodiflora* inhibited the growth of breast cancer cells through apoptosis induction[88].

The in vitro anticancer effect of *Lippia nodiflora* leaf extract was studied against human lung cancer cell line (NCI-H460). The leaf extracts possessed high antiproliferative activity against the tested cell line, as

determined with MTT assay. The IC_{50} value was 10 µg/ml. The extract treated groups exhibited high DCF fluorescence (enhanced ROS levels), significant increase in mitochondrial depolarization compared to control groups. Nuclear morphology showed induced apoptosis in cells treated with leaf extract was also observed by microscopic examination using dual staining method of acridine orange-ethidium bromide[92].

The antitumor activity of the methanolic extract (200 and 400 mg/kg bw daily for 9 days after 24 h of tumor inoculation) was studied against Ehrlich's ascites carcinoma on Swiss albino mice. The results showed that the methanolic extract possessed antitumor activity with significant decrease in tumor volume and increase in life span of tumor bearing mice. The methanolic extract was also significantly ($p < 0.001$) decreased the levels of lipid peroxidation and increased the levels of GSH, CAT and SOD, the antitumor activity could be attributed to the increase of antioxidant activity in EAC bearing mice[93].

Antihyperlipidemic effect:

γ-sitosterol showed antihyperlipidemic activity as evidenced by significant decrease in serum total cholesterol, triglycerides and very low density lipoprotein-cholesterol levels coupled with elevation of high density lipoprotein-cholesterol levels in streptozotocin (STZ) induced diabetic rats. A significant decrease in the activities of alanine aminotransaminase, aspartate aminotransaminase, alkaline phosphatase and acid phosphatase in γ-sitosterol treated rats were recorded compared to diabetic control rats which indicated its protective role against liver damage[90].

Neuropharmacological effect:

The neuropharmacological profile of petroleum, chloroform and ethanolic extracts of aerial part of *Lippia nodiflora* was evaluated in experimental models using potentiation of diazepam-induced sleeping time, locomotor activity, motor coordination, exploratory behavior pattern, elevated plus maze and maximal electroshock convulsions. Diazepam at doses of 5, 4, and 1 mg/kg was used as standard. The results showed that the ethanolic extract of *Lippia nodiflora* at both doses (250 and 500 mg/kg oraally) and its chloroform extract at a higher dose of 500 mg/kg produced significant central inhibitory (sedative), anticonvulsant and anxiolytic effects in mice. The petroleum ether extract of the plant at both dose levels (250 and 500 mg/kg orally) did not produce any central effects[94].

Antimelanogenic effect:

The methanolic extract of the aerial part of *Phyla nodiflora* was studied for anti-melanogenesis. The results showed that the extract was not cytotoxic and significantly reduced the cellular melanin content and tyrosinase activity in a dose-dependent manner ($p < 0.05$). It also exhibited a significant antimelanogenesis effect ($p < 0.05$) by reducing the levels of phospho-cAMP response element-binding protein and microphthalmia-associated transcription factor, inhibiting the synthesis of tyrosinase, tyrosinase-related proteins (TRP-1 and TRP-2), decreasing the cellular melanin content, and significantly activated the phosphorylation of mitogen-activated protein kinases, including phospho-extracellular signal-regulated kinase, c-Jun N-terminal kinase, and phospho-p38, and inhibited the synthesis of microphthalmia-associated transcription factor, thus decreasing melanogenesis[43].

Effect on hair growth:

The ethyl acetate soluble fraction of ethanolic extract of Eclipta alba and *Lippia nodiflora* was tested for their effects on hair growth. 5 % and 10 % extract of E. alba and *Lippia nodiflora* alone and incombination of 5 % of E. alba and 5 % of *Lippia nodiflora* in gel formulation was applied topically over the shaved skin of black mice and assessed for 30 days. The topical use of gel containing extracts of E. alba and L. nodiflora alone and incombination significantly increased the rate of hair growth compared with negative control[95].

Antidandruff activity:

The antidandruff activity of ethanolic extract and isolated compound of Eclipta alba and *Lippia nodiflora* was studied using the disc diffusion assay. Suspension containing 5×10^6 CFU/ml of dandruff causing organism (Malassezia furfur) was swabbed on the surface of the sterile SDA plates using a sterile cotton swab. Sterile filter paper discs impregnated with the isolated compound doses (25 µg/ml and 50 µg/ml) and ethanolic extract (250 µg/ml and 500 µg/ml) per disc was aseptically placed over the seeded SDA plates. The results showed that the Malassezia furfur was sensitive to all the concentrations of ethanolic extract and isolated compound of *Lippia nodiflora* [96].

Effect on blood clotting:

Ethanolic extract of *Lippia nodiflora* significantly hasten blood clotting when used in a dose of 100 mg/kg ($p< 0.05$) and 200 mg /kg ($p< 0.01$). The effect of the ethanolic extract appeared dose dependent. However, aqueous extract didn't exerted significant effects on blood clotting time in both doses[73].

II. Conclusion

The current review discussed the chemical constituents, pharmacological and therapeutic characteristics of *Lippia nodiflora* as a promising medicinal plant with wide range of pharmacological activities which could be utilized in several medical applications because of its effectiveness and safety.

References

[1]. Al-Snafi AE. Medicinal plants with central nervous effects (part 2): plant based review. IOSR Journal of Pharmacy 2016; 6(8): 52-75.
[2]. Al-Snafi AE, Talab TA and Majid WJ. Medicinal plants with central nervous activity - An overview (Part 1). IOSR Journal of pharmacy 2019, 9(3): 52-102.
[3]. Al-Snafi AE. Medicinal plants with cardiovascular effects (part 2): plant based review. IOSR Journal of Pharmacy 2016; 6(7): 43-62.
[4]. Al-Snafi AE. Medicinal plants for prevention and treatment of cardiovascular diseases - A review. IOSR Journal of Pharmacy 2017; 7(4): 103-163.
[5]. Al-Snafi AE. Medicinal plants with antioxidant and free radical scavenging effects (part 2): plant based review. IOSR Journal of Pharmacy 2016; 6(7): 62-82.
[6]. Al-Snafi AE. Medicinal plants possessed antioxidant and free radical scavenging effects (part 3)- A review. IOSR Journal of Pharmacy 2017; 7(4): 48-62.
[7]. Al-Snafi AE. Medicinal plants affected reproductive systems (part 2) - plant based review. Sch Acad J Pharm 2016; 5(5): 159-174.
[8]. Al-Snafi AE. Medicinal plants affected male and female fertility (part 1)- A review. IOSR Journal of Pharmacy 2016; 6(10): 11-26.
[9]. Al-Snafi AE. Arabian medicinal plants affected female fertility- plant based review (part 1). IOSR Journal of Pharmacy 2018; 8(7): 46-62.
[10]. Al-Snafi AE. Arabian medicinal plants affected male fertility- plant based review (part 1). IOSR Journal of Pharmacy 2018; 8(7): 63-76.
[11]. Al-Snafi AE. Medicinal plants affected contractility of smooth muscles- A review. IOSR Journal of Pharmacy 2018; 8(11): 22-35.
[12]. Al-Snafi AE. Beneficial medicinal plants in digestive system disorders (part 2): plant based review. IOSR Journal of Pharmacy 2016; 6(7): 85-92.
[13]. Al-Snafi AE. Arabian medicinal plants possessed gastroprotective effects- plant based review (part 1). IOSR Journal of Pharmacy 2018; 8(7): 77-95.
[14]. Al-Snafi AE. Arabian medicinal plants for the treatment of intestinal disorders- plant based review (part 1). IOSR Journal of Pharmacy 2018; 8(6): 53-66.
[15]. Al-Snafi AE. A review of medicinal plants with broncho-dilatory effect- part 1. Scholars Academic Journal of Pharmacy, 2015; 5(7): 297-304.
[16]. Al-Snafi AE. Therapeutic properties of medicinal plants: a review of their respiratory effects (part 1). International Journal of Pharmacological Screening Methods 2015; 5(2):64-71.
[17]. Al-Snafi AE. Medicinal plants with antidiabetic effects (part 2): plant based review. IOSR Journal of Pharmacy 2016; 6(7): 49-61.
[18]. Al-Snafi AE, Majid WJ and Talab TA. Medicinal plants with antidiabetic effects - An overview (part 1). IOSR Journal of pharmacy 2019, 9(3): 9-46.
[19]. Al-Snafi AE. Traditional uses of Iraqi medicinal plants. IOSR Journal of Pharmacy 2018; 8 (8): 32-96.
[20]. Al-Snafi AE. Medicinal plants with antimicrobial activities (part 2): Plant based review. Sch Acad J Pharm 2016; 5(6): 208-239.
[21]. Al-Snafi AE. Antimicrobial effects of medicinal plants (part 3): plant based review. IOSR Journal of Pharmacy 2016; 6(10): 67-92.
[22]. Al-Snafi AE. Antiparasitic effects of medicinal plants (part 1)- A review. IOSR Journal of Pharmacy 2016; 6(10): 51-66.
[23]. Al-Snafi AE. Antiparasitic, antiprotozoal, molluscicidal and insecticidal activity of medicinal plants (part 2) – plant based review. Sch Acad J Pharm 2016; 5(6): 194-207.
[24]. Al-Snafi AE. Clinically tested medicinal plant: A review (Part 1). SMU Medical Journal 2016; 3(1): 99-128.
[25]. Al-Snafi AE. Medicinal plants with anticancer effects (part 2)- plant based review. Sch Acad J Pharm 2016; 5(5): 175-193.

[26]. Al-Snafi AE. Anticancer effects of Arabian medicinal plants (part 1) - A review. IOSR Journal of Pharmacy 2017; 7(4): 63-102.
[27]. Al-Snafi AE. Medicinal plants possessed anti-inflammatory antipyretic and analgesic activities (part 2)-plant based review. Sch Acad J Pharm 2016; 5(5): 142-158.
[28]. Al-Snafi AE. Arabian medicinal plants with antiinflammatory effects- plant based review (part 1). Journal of Pharmacy 2018; 8 (7): 55-100.
[29]. Al-Snafi AE. Arabian medicinal plants with analgesic and antipyretic effects- plant based review (Part 1). IOSR Journal of Pharmacy 2018; 8(6): 81-102.
[30]. Al-Snafi AE. Immunological effects of medicinal plants: A review (part 2). Immun Endoc & Metab Agents in Med Chem 2016; 16(2): 100-121.
[31]. The plant list, Phyla nodiflora, http://www.theplantlist.org/tpl/record/kew-153218
[32]. ITIS, Phyla nodiflora, https://www.itis.gov/servlet/SingleRpt/SingleRpt? search_ topic =TSN&search_value=32197#null
[33]. U.S. National Plant Germplasm System, Phyla nodiflora, https://npgsweb.ars-grin.gov/ gringlobal/ taxonomydetail.aspx?101146
[34]. Sharma RA and Singh R. A review on *Phyla nodiflora* Linn.: A wild wetland medicinal herb. Int J Pharm Sci Rev Res 2013; 20(1): 57-63.
[35]. Philippine Medicinal Plants, Phyla nodiflora, http://www.stuartxchange.org/ Busbusi.html
[36]. Flora of Pakistan, Phyla nodiflora, http://www.efloras.org/florataxon.aspx? flora _id =5& taxon_id=200019371
[37]. Flora of Zimbabwe, Phyla nodiflora, https://www.zimbabweflora.co.zw/ species data/ species. php?species_id=148750
[38]. Dodoala R, Divit B, Koganti K and Prasad VSRG. Effect of ethanolic extract of *Phyla nodiflora* (Linn) Greene against calculi producing diet induced urolithiasis. Indian Journal of natural products and resources 2010; 1: 314-321.
[39]. The Useful Plants of India, Third Edition, New Delhi, Publication and Information Directorate, Council of Scientific and Industrial Research, 1986: 450.
[40]. Nadkarni KM. Indian Materia Medica, Vol 1, Bombay, India, Popular Prakashan, 1954: 746.
[41]. Anonymous. Medicinal plants of India. Indian Council of Medical Research, Vol II, 1987.
[42]. Priya SE and Ramalingam R. Pharmacognostical characterization of *Phyla nodiflora* l. (Verbenaceae): A valuable medicinal plant. Asian Journal of Pharmaceutical and Clinical Research 2015; 8(3): 256-261.
[43]. Yen FL, Wang MC, Liang CJ, Ko HH and Lee CW. Melanogenesis inhibitor(s) from *Phyla nodiflora* extract. Evidence-Based Complementary and Alternative Medicine 2012, http://dx.doi.org/10.1155/2012/867494
[44]. Lin FJ, Yen FL, Chen PC, Wang MC, Lin CN, Lee CW and Ko HH. HPLC-fingerprints and antioxidant constituents of Phyla nodiflora. Hindawi Publishing Corporation, The Scientific World Journal 2014, http://dx.doi.org/10.1155/2014/ 528653
[45]. Nair AGR, Ramesh P, Nagarajan S and Subramanian S. New flavone glycosides from Lippia nodiflora. Ind J Chem 1973; 2:1316-1317.
[46]. Ravikanth V, Ramesh P, Diwan PV and Venkateswarlu Y. Hallerone and halleridone from *Phyla nodiflora* (L.) Greene. Biochemical Systematics and Ecology 2000; 28: 905-906.
[47]. Terblanche FC and Kornelius G. Essential oil constituents of the genus Lippia (Verbenaceae)- A literature review. Journal of Essential Oil Research 1996; 8:471-485.
[48]. Siddiqui BS, Ahmad F, Sattar F and Begum S. Chemical constituents from the aerial parts of *Lippia nodiflora* Linn. Arch Pharmacology Research 2007; 30(12): 1507-1510.
[49]. Tomás-Barberán FA, Harborne JB and Self R. Twelve 6-oxygenated flavone sulphates from *Lippia nodiflora* and Lippia canescens. Phytochemistry 1987;26: 2281–2284.
[50]. Khalil AT, Lahloub MF and Salama OM. Phenolic compounds from Lippia nodiflora. Journal of Pharmaceutical Sciences 1995; 11(2): 256-265.
[51]. Barua AK, Chakrabarti P and Sanyal PK . Structure of nodifloretin, new flavone from Lippia nodiflora. Transactions of the Bose Research Institute 1971; 33-34(3): 5-8.
[52]. Barua AK, Chakrabarti P and Sanyal PK . Nodifloretin, a new flavone from Lippia nodiflora. Journal of the Indian Chemical Society 1969; 46(3): 271-272.
[53]. Barnabas C, Gunasingh G and Nagarajan S. Flavonoids from the flowers of *Phyla nodiflora* Linn. Indian Journal of Chemistry, Section B 1980; 19B(9): 822.
[54]. Akhtar M F Chemical and biological investigations of medicinal herbs Phyla nodiflora, Ruellia patula and Ruella brittoniana. Ph.D. Thesis. University of Karachi, Pakistan, 1993.
[55]. Siddiqui BS, Ahmed F, Ali SK, Perwaiz S and Begum S. Steroidal constituents from the aerial parts of *Lippia nodiflora* Linn. Nat Prod Res 2009; 23(5):436-441.

[56]. Cheng LC. Phytochemical studies of Lippia nodiflora L Michx and its anti-hyperuricemic activity. PhD thesis, University of Science, Malaysia 2016.
[57]. Cheng LC, Murugaiyah V and Chan KL. In vitro xanthine oxidase Inhibitory studies of *Lippia nodiflora* and isolated flavonoids and phenylethanoid glycosides as potential uric acid-lowering agents. Nat Prod Commun 2015; 10(6):945-948.
[58]. Elakovich SD and Stevens KL.Volatile constituents of Lippia nodiflora. Journal of Natural Products 1985; 48(3):504–506.
[59]. Joshi BC. Chemical examination of Lippia nodiflora. Vijnana Parishad Anusandhan Patrika 1970; 11(4): 219-214.
[60]. Sudha A and Srinivasan P. Physicochemcial and phytochemical profile of aerial parts of *Lippia nodiflora* L. IJPSR 2013; 4(11): 4263-4271.
[61]. Priya SE and Ravindhran R. Phytochemical analysis and antimicrobial properties of extracts from aerial parts of *Phyla nodiflora* (L) Greene. Int J Curr Microbiol App Sci 2015; 4(2): 347-358.
[62]. Pirzada AJ, Iqbal P, Shaikh W, Kazi TG and Ghani KU. Studies on the elemental composition and anti fungal activity of medicinal plant *Lippia nodiflora* L against skin fungi. Journal of Pakistan Association of Dermatologists 2005; 15: 113-118.
[63]. Cheng LC, Murugaiyah V and Chan KL. Flavonoids and phenylethanoid glycosides from *Lippia nodiflora* as promising antihyperuricemic agents and elucidation of their mechanism of action. J Ethnopharmacol 2015;176:485-493.
[64]. Shukla S, Patel R and Kukkar R. Study of phytochemical and diuretic potential of methanol and aqueous extracts of aerial parts of *Phyla nodiflora* linn. Int J Pharm Pharm Sci 2009; 1:85-91.
[65]. Senthilkumar GP, Mazumder UK and Ray SK. Study on diuretic activity and electrolytes excretion of methanol extract of *Lippia nodiflora* (Verbenaceae) in rats. Oriental Pharmacy and Experimental Medicine 2008; 8(1):39-46.
[66]. Palanisamy S, Dheeba B, Ravichandran V, Veena V, Balakumar S and Shanmugasundaram A. Evaluation of hepatoprotective efficacy of *Lippia nodiflora* L against carbon tetrachloride induced hepatic damage in rats. Journal of Cell and Tissue Research 2008; 8(3): 1595-1598.
[67]. Durairaj AK, Vaiyapuri TS, Kanti MUK and Malaya G. Protective activity and antioxidant potential of *Lippia nodiflora* extract in paracetamol induced hepatotoxicity in rats. Iran J Pharmcol Ther 2008; 7: 83-89.
[68]. Sudha A, Sumathi K, Manikandaselvi S, Prabhu NM and Srinivasan P. Anti-hepatotoxic activity of crude flavonoid fraction of *Lippia nodiflora* L on ethanol induced liver injury in rats. Asian Journal of Animal Sciences 2013; 7: 1-13.
[69]. Arumanayagam S and Arunmani M. Hepatoprotective and antibacterial activity of *Lippia nodiflora* Linn. against lipopolysaccharides on HepG2 cells. Pharmacogn Mag 2015;11(41):24-31.
[70]. Ravikumar VR and Sudha T. Phytochemical and microbiological observations on Phyla nodiflora. IJRPC 2011; 1(2): 117-120.
[71]. Priya SE and Ravindhran R. Phytochemical analysis and antimicrobial properties of extracts from aerial parts of *Phyla nodiflora* (L) Greene. Int J Curr Microbiol App Sci 2015; 4(2): 347-358.
[72]. Zare Z, Ahmed M, Sattari TN, Iranbakhsh A and Mehrabian S. Antimicrobial activity of leaf and flower extracts of Lippia nodiflora L. (Verbenacea). Journal of Plant Protection Research 2012; 52(4): 401-403.
[73]. Al-Snafi AE and Faris AN. Anti-inflammatory and antibacterial activities of *Lippia nodiflora* and its effect on blood clotting time. J Thi Qar Sci 2013;4(1):25-30.
[74]. Salve S D and Bhuktar A S. Pharmacognostic study of *Phyla nodiflora* linn. Int J Pharmacy 2012;3(3): 255-260.
[75]. Pagu MV,Elavarasan P and Jeya KR. In vitro antimicrobial activity of *Lippia nodiflora* crude extract against selected microorganisms. BTAIJ 2011; 5(2):93-95.
[76]. Zakir Ullah, Rehman A, Najeeb Ullah, Khan SA, Ullah Khan S and Ahmad I. Antibacterial study of *Phyla nodiflora* Linn. Journal of Chemical and Pharmaceutical Research 2013; 5(3):86-90.
[77]. Regupathi T, Chitra K, Ruckmani K, Nagarajan S and Lalitha KG. Antimicrobial potential of *Lippia nodiflora* Linn. Int J Pharm Phytopharmacol Res 2014; 4 (3): 145-149.
[78]. Durairaj AK, Vaiyapuri TS, Mazumder UK and Gupta M. Antimicrobial and lipid peroxide scavenging activity of *Lippia nodiflora* (Verbenaceae). Pharmacologyonline 2007;3: 177-189.
[79]. Niranjan K. In vitro screening of herbal plant extracts on human nail fungus. Vingnanam Journal of Science 2016; 13(1-2):73-77.
[80]. Ahmed F, Selim MST, Das AK and Choudhuri MSK. Anti-inflammatory and antinociceptive activities of *Lippia nodiflora* Linn. Pharmazie 2004;59(4): 329-330.

[81]. Balakrishnan G, Janakarajan L, Balakrishnan A and Lakshmi BS. Molecular basis of the anti-inflammatory property exhibited by cyclopentano phenanthrenol isolated from Lippia nodiflora. Immunol Invest 2010;39(7):713-739.
[82]. Sudha A and Srinivasan P. In vitro, fluorescence-quenching and computational studies on the interaction between lipoxygenase and 5-hydroxy-3',4',7-trimethoxy flavone from *Lippia nodiflora* L. J Recept Signal Transduct Res 2015;35(6):569-577.
[83]. Gadhvi R, Mishra G, Nagendra Reddy M and Nivserkar M. Antihypertensive efficacy of Lippia nodiflora – whole plant on uninephrectomized doca – salt hypertensive rats. IOSR Journal of Pharmacy 2012; 2(6): 24-28.
[84]. Gadhvi R, Reddy MN and Joshi S. Antihypertensive and renoprotective effect of different fractions of whole plant *Lippia nodiflora* Linn. on uninephroctimized DOCA-salt hypertensive rats. International Journal of Pharma and Bio Sciences 2015; 6(3): 392-399.
[85]. Shukla S, Saluja AK and Pandya SS. In-vitro antioxidant activity of aerial parts of *Lippia nodiflora* Rich. Pharmacologyonline 2009; 2: 450-459.
[86]. Durairaj A, Thamilselvan V, Senthilkumar GP, Mazumder UK and Gupta M. Antioxidant and free radical scavenging effects of Lippia nodiflora. Journal Pharmaceutical Biology 2008; 46(10-11):762-771.
[87]. Sudha A and Srinivasan P. Bioassay-guided isolation and antioxidant evaluation of flavonoid compound from aerial parts of *Lippia nodiflora* L. Biomed Res Int 2014; doi: 10.1155/2014/549836.
[88]. Teoh PL, Mohd Ali R and Cheong BE. Potential anticancer effect of *Phyla nodiflora* extracts in breast cancer cell line, MCF7. World Journal of Pharmacy and Pharmaceutical Sciences 2013; 2(6): 6053-6061.
[89]. Balamurugan R and Ignacimuthu S. Antidiabetic and hypolipidemic effect of methanol extract of *Lippia nodiflora* L. in streptozotocin induced diabetic rats. Asian Pac J Trop Biomed 2011; S30-S36.
[90]. Balamurugan R, Duraipandiyan V and Ignacimuthu S. Antidiabetic activity of γ-sitosterol isolated from *Lippia nodiflora* L in streptozotocin induced diabetic rats. Eur J Pharmacol 2011;667(1-3):410-418.
[91]. Begum VH, Muthukumaran P and Suganthi K. Evaluation of anti-diarrhoeal activity of *Lippia nodiflora* leaves extracts in experimental rats. IJPPR Human 2016; 6 (1): 140-149.
[92]. Vanajothi R, Sudha A, Manikandan R, Rameshthangam P and Srinivasan P. Luffa acutangula and *Lippia nodiflora* leaf extract induces growth inhibitory effect through induction of apoptosis on human lung cancer cell line. Biomedicine and Preventive Nutrition 2012; 2(4): 287-293.
[93]. Durairaj A, Mazumder UK, Gupta M and Selvan VT. Effect on inhibition of proliferation and antioxidant enzyme level of *Lippia nodiflora* in EAC cell line treated mice. Journal of Complementary and Integrative Medicine 2009; 6(1), doi: 10.2202/1553-3840.1233
[94]. Thirupathy KP, Tulshkar A and Vijaya C. Neuropharmacological activity of *Lippia nodiflora* Linn. Pharmacognosy Research 2011; 3(3):194-200.
[95]. Regupathi T, Chitra K, Ruckmani K, Lalitha KG and Kumar M. Formulation and evaluation of herbal hair gel for hair growth potential**.** Journal of Pharmacology & Clinical Research 2016; 2(2), doi: 10.19080/JPCR.2017.02.555581
[96]. Regupathi T and Chitra K Antidandruff activity of Eclipta alba (l.) Hassk and *Lippia nodiflora* Linn. International Journal of Research in Pharmaceutical Sciences 2015;6(2):185-188.

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