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Chemical constituents and biological applications of *Lippia nodiflora*

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Abstract

Lippia nodiflora has been reviewed for its biological activities and phytochemical constituents. The plant is found to predominantly contain triterpenoids, flavonoids and steroids amongst others and is found to possess analgesic, anti-inflammatory, antioxidant, antinociceptive, antimicrobial, antipyretic, antitumor, lipid peroxide scavenging and free radical scavenging activities. For future studies it would be valuable to investigate the biologically active constituents responsible for the various activities of the plant demonstrated in the traditional system of medicine.

Key words:

Antitumor; anti-inflammatory; triterpenoids; flavonoids; steroids.

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L*ippia nodiflora* (*Phyla nodiflora*) is a small perenial herb belonging to the family verbenaceae. Its branched stems bear numerous leaves and it bears small pink or white flowers. The plant is distributed all over the world particularly in Africa, sub-continent and most of the tropical and subtropical regions, particularly in maritime areas close to rivers [1-5]. Traditional medicine reports various biological activities for *L. nodiflora*, therefore, the aim of this paper is to review the current advances in the isolation of the various chemical constituents and pharmacology of the plant. This database may provide the guidance for researchers for further investigations in the field.

Traditional medicine reports that a poultice comprising of the fresh plant is a cure for cervical glands. Leaves and fruit are eaten for the treatment of irritation of the internal piles, and for joint and knee pain. A mixture of *L. noiflora* and the seeds of *Cuminum cyminum* is utilized as a cure for gonorrhea. A decoction of the plant with *Leucas aspera* and the roots of *Ocimum gratissimam* is know to possess anti-malarial properties. A mixture of the extracts of the leaves of *L. noiflora* leaves, onion and ginger oil is used to treat Alopecia [1, 5-7].

L. nodiflora is reported to possess acrid, cooling, aphrodisiac, astringent, anthelmintic, alexiteric, emmenagogue, bactericide, diuretic, antiseptic, antitussive, antipyretic and anti-inflammatory properties and is effective against bronchitis, respiratory diseases, arthritis, fever, dyspepsia, hookworm, gonorrhea, ulcers, stomachic, wounds, burning sensation, asthma, thirst, loss of consciousness, diaper rash, erysipelas, neuralgia, sores, spasms and vertigo [7-14].

Biological activities

Antioxidant, antimicrobial, antitumor, free radical scavenging and lipid peroxide scavenging activities, total phenolic content, and hepatoprotective effects

Durairaj *et al*. examined the methanol extract of *L. nodiflora* for *in vitro* antimicrobial and lipid peroxide scavenging activities. The antimicrobial activity of the extract was examined using the disc diffusion method. The Lipid peroxide scavenging activity was assessed by measuring the change in optical density of the prepared concentrations (20-320 µg/ml). The activity was compared with the standard antioxidants such as BHA, BHT. The IC_{50} values for lipid peroxide scavenging were: MELN (226.52 µg/mL), BHA (25.62 µg/mL), and BH (17.13 µg/mL), the activity of the extract found to increase in a concentration dependent manner. The plant showed appreciable antimicrobial lipid peroxide scavenging activities [15].

The methanolic extract of the plant was assessed for antioxidant activity and hepatoprotective effects in paracetamol induced liver injury (750 mg/kg,). The extract was administrated orally for seven days at doses of 200 and 400 mg/kg and the parameters such as serum glutamate oxaloacetate transaminase (SGOT), glutamate pyruvate transaminase (SGPT), alk. phosphatase (ALP), bilirubin and total proteins with enzymic and non-enzymic antioxidant level were measured. The inhibition of the increase in liver weight was found to be more

effective in the higher dose (400 mg/kg) as compared to the lower dose (200 mg/kg). The levels of SGOT, SGPT, ALP, bilirubin and lipid peroxidn were reduced significantly ($p < 0.001$), while the levels of total proteins, glutathione (GSH), catalase (CAT) and superoxide dismutase (SOD) increased significantly ($p < 0.001$) in a dose dependent manner. The activity of the extract was found to be equivalent to that of the standard (silymarin, 25 mg/kg), thus the plant was found to exhibit hepatoprotective effects probably due to the antioxidative potential on hepatocytes [16].

The methanolic extract of *L. nodiflora* was examined for *in vitro* antioxidant potential, the extract was found to exhibit effective reducing power, free radical scavenging, superoxide anion radical scavenging, hydroxyl radical scavenging, hydrogen peroxide radical scavenging, and nitric oxide scavenging activity, while the total phenolic content was found to be increasing with increasing concentration [17].

The plant was assessed for antitumor activity using ehrlich's ascites carcinoma (EAC) bearing swiss albino mice. The mice were administrated with the methanol extract at 200 and 400 mg/kg of body weight daily for nine days after 24 hours of tumour inoculation. The methanolic extract indicated significant ($p < 0.001$) decrease in tumour volume, viable cell count and packed cell volume, the life span of the mice was also found to be increased. For the mice treated with the methanol extract the hematological profiles reverted to more/less normal levels, while the serum enzymes, total proteins and bilirubin were altered narrowly. The methanol extract increased the levels of reduced glutathione (GSH), catalase (CAT) and superoxide dismutase (SOD) and reduced the levels of lipid peroxidation. The plant was found to bear good antitumor activity, which was supposed to be due to the increased of antioxidant activity [18].

Shukla *et al*. assessed the methanol extract of *L. nodiflora* for total phenolic content, antioxidant and free radical scavenging activity using 1, 1-diphenyl, 2-picryl hydrazine (DPPH) radical scavenging assay, H_2O_2 scavenging assay, nitric oxide (NO) radical scavenging assay, nitro blue tetrazolium (NBT) reduction test, β-carotenelineolate bleaching assay and total reduction ability by Fe^{3+}-Fe^{2+} transformation. For DPPH radical scavenging activity, H_2O_2 scavenging activity, NO scavenging activity and reduction test the IC_{50} values of the extract were found to be 799.7 µg/mL, 53.1 µg/mL, 61.5 µg/mL and 45.6 µg/mL, respectively. The IC_{50} values for ascorbic acid (standard) were found to be 511.3 µg/mL, 33.0 µg/mL, 42.4 µg/mL and 94.8 µg/mL, respectively. The total phenolic content indicated by the folin-ciocalteu phenol reagent was found to be 114.8 µg/mL total phenolics for 1 mg of the extract. The study related the antioxidant activity of the extract to the presence of flavonoids [9].

Anti-inflammatory, analgesic, antinociceptive, and antipyretic activities

Forestieri *et al*. examined the decoctions, petroleum ether, ethanol, and aqueous extracts of the leaves of *Afrormosia laxiflora*, *Ficus glomerata*, *Lantana camara*, *Lippia geminate*, *L. nodiflora*, and the whole plants of *Cyathula prostrate*, *Synedrella nodiflora* in rats and mice, the examination showed appreciable analgesic, anti-inflammatory, and antipyretic activities for almost all the extracts [8].

Ahmed *et al*. examined the methanolic extract of the leaves of *L. nodiflora* for antinociceptive activity in carrageenin-induced paw edema in rats and anti-inflammatory activity against acetic acid induced writhing in white albino mice. Significant ($P < 0.001$) anti-inflammatory and antinociceptive activities comparable to phenylbutazone and diclofenac sodium, respectively, were observed [19].

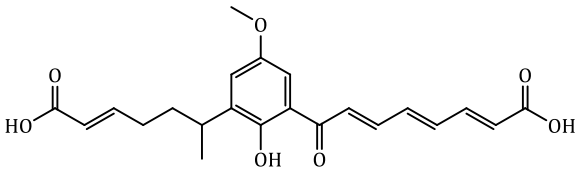
Balakrishnan *et al*. isolated cyclo-pentano phenanthrenol from *L. nodiflora*; the crude methanol extract and the isolated compound were assessed for anti-inflammatory activity. Human peripheral blood mononuclear cells were used as models to examine intracellular protein levels of pro-inflammatory mediators (MAPK and NF-$_K$B) and the mitogen induced lymphocyte proliferation, cytokine mRNA expression (TNF-α, IL-1β and IL-6). The NO release levels, on treatment with the extract and the isolated compound were correlated with the underlying iNOS mRNA expression in the murine macrophage cell line RAW 264.7. In the cell line RT-PCR for COX-2, MMP2 and MMP9 were also conducted. As an *in vitro* model for the rat basophilic leukemia cell line RBL-2H3 was employed for PLA2 activity. The crude extract (20 µg/mL) and the isolated compound (10 µg/mL) were used to assess the activity. Cyclo-pentano phenanthrenol was found to inhibit TNF-α, IL-1β and IL-6 expression, prostaglandin biosynthesis via PLA2, NO release via iNOS suppression and COX-2 inhibition and the activation of intracellular targets, MAPK and NF-$_K$B. Thus the compound was concluded to exhibit anti-inflammatory activity [20].

The essential oils of the leaves of *Lippia* alba, *Lippia* aff. gracilis, *Lippia* gracilis, *Lippia* microphylla and *L. nodiflora* were tested for larvicidal activity against the instar larvae of Aedes aegypti. The higher larvicidal activity (LC_{50} = 26.3 µg/mL) was observed for the oil of *L. gracilis*, while appreciable activity was observed for the oil of *L. nodiflora* [21]. Zheng suggested that since *L. nodiflora* contains nodifloretin, β-sitosterol glucoside, stigmasterol glucoside, nodifloridin A, and nodifloridin B, it could be used in proper doses for the treatment of hepatitis [22]. Narayanan *et al*. suggested that the plant extracts of any of the two plants, *Datura metel*, *Murraya koenigii*, *L. nodiflora*, and *Wrightia tinctoria* possess antidandruff application [23].

Chemical constituents

The plant contains a variety of constituents such as: triterpenoids, flavonoids, phenols, steroids, and many others, among these flavonoids were the most commonly found. Joshi isolated noifloridin A (1) and nodifloridin B (2) along with lactose, maltose, glucose, fructose, and xylose from the plant [24-25]. Barua *et al*. isolated nodifloretin (3) β-sitosterol glycoside and stigmasterol glycoside from the leaves of *L. nodiflora* [26-27]. Barnabas and Nagarajan reported from the flowers of *L. nodiflora*, two flavone glycosides, 6-hydroxyluteolin-7-O-apioside and luteolin-7-O-glucoside, and three flavones 6-hydroxyluteolin, nepetin, and batatifolin [28]. Tomás-Barberán *et al*. Isolated from *L. nodiflora*, twelve flavone

sulfates Hispidulin 7-sulfate (4), Hispidulin 7,4'-disulfate (5), Jaceosidin 7,4'-disulfate (6), Nepetin 3',4'-disulfate (7), Nodifloretin 6,7-disulfate (8), 6-Hydroxyluteolin 6,7-disulfate (9), Nodifloretin 7-sulfate (10), 6-Hydroxyluteolin 6-sulfate (11), 6-Hydroxyluteolin 7-sulfate (12), Jaceosidin 7-sulfate (13), Nepetin 7-sulfate (14), and Hispidulin 4'-sulfate (15), along with the known compounds Nepetin, Hispidulin, and Jaceosidin [29]. Nair *et al*. isolated two new flavone glycosides lippiflorin A (16) and lippiflorin B (17), along with the known compound nepetin and batalilfolin from the ethanol extract of *L. nodiflora* [30]. Khalil *et al*. isolated from the alcoholic extracts of *L. nodiflora*, two phenylpropanoid compounds, acteoside (18) and 2'-O-acetylechinacoside (19), and a flavone demethoxycentaureidin [31]. Ravikanth *et al.* isolated halleridone and hallerone as their acetyl derivatives from the leaves of *L. nodiflora* [32]. Siddiqui *et al*. isolated from the methanolic extract of the aerial parts of *L. nodiflora* a new triterpenoid lippiacin (20) a new steroid 4', 5'-dimethoxybenzoloxystigmasterol (21), along with the known stigmasterol and *β*-sitosterol [1, 6].



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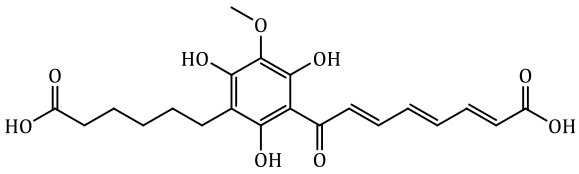

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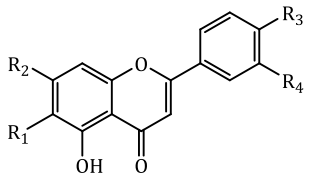
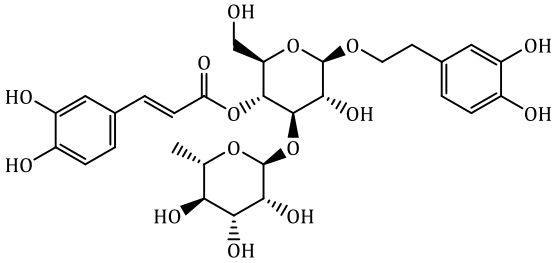


(3) R_1 = OH, R_2 = OH, R_3 = OH, R_4 = OCH_3
(4) R_1 = OCH_3, R_2 = OSO_3H, R_3 = OH, R_4 = H
(5) R_1 = OCH_3, R_2 = OSO_3H, R_3 = OSO_3H, R_4 = H
(6) R_1 = OCH_3, R_2 = OSO_3H, R_3 = OSO_3H, R_4 = OCH_3
(6) R_1 = OCH_3, R_2 = OH, R_3 = OSO_3H, R_4 = OSO_3H
(7) R_1 = OSO_3H, R_2 = OSO_3H, R_3 = OH, R_4 = OCH_3
(8) R_1 = OSO_3H, R_2 = OSO_3H, R_3 = OH, R_4 = OH
(9) R_1 = OH, R_2 = OSO_3H, R_3 = OH, R_4 = OCH_3
(10) R_1 = OSO_3H, R_2 = OH, R_3 = OH, R_4 = OH
(11) R_1 = OH, R_2 = OSO_3H, R_3 = OH, R_4 = OH
(12) R_1 = OCH_3, R_2 = OSO_3H, R_3 = OH, R_4 = OCH_3
(13) R_1 = OCH_3, R_2 = OSO_3H, R_3 = OH, R_4 = OH
(14) R_1 = OCH_3, R_2 = OH, R_3 = OSO_3H, R_4 = H
(15) R_1 = OH, R_2 = O-L-arabinosyl, R_3 = OH, R_4 = OH
(17) R_1 = OH, R_2 = O-L-arabinosyl, R_3 = OH, R_4 = O-L-rhamnoside



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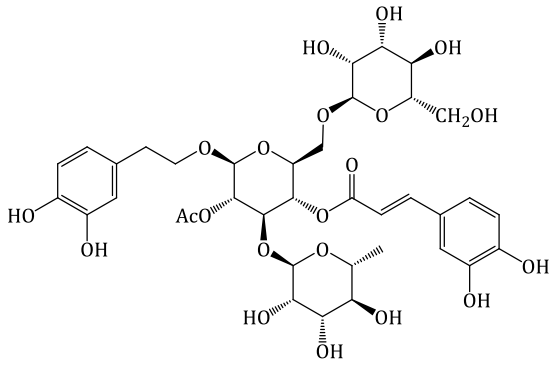

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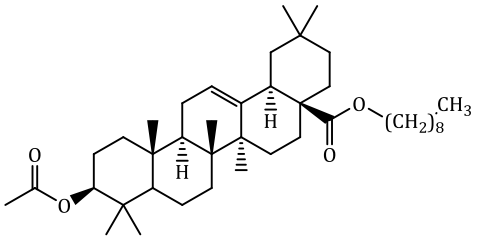

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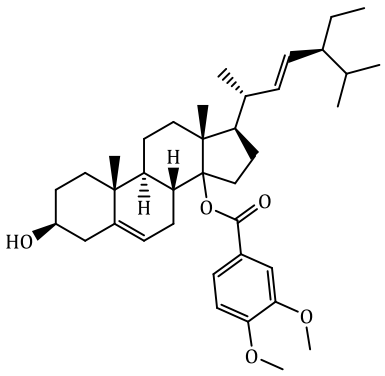

(21)

Kaur and Shukla, fractionated several constituents from the *Phyla nodiflora* using multi component solvent systems; Hexane:Toluene:Ethyl acetate (2:1.5:0.5) for methanol extract and Hexane:Ethyl acetate (3:1) for chlorofrom and petroleum ether extract. Five different phenolic components were isolated and were compared using a HPTLC, among these extracts, the highest number of constituents were isolated from the butanol extract [33].

Volatile constituents

The extracts of *L. nodiflora* were steam-distilled to

afforded a mixture hydrocarbons and a mixture of oxygenates. In the hydrocarbon fraction, among the 14 constituents the major constituent was *β*-caryophyllene (20%). Among the oxygenated fraction 18 components were found to have concentrations greater than 0.5%, while 12 constituents were found to be in amounts less than 7%, while five components (1-octen-3-ol, phenethyl alcohol. linalool, p-cymen-8-ol, and methylsalicylate) were found to be in amounts between 10 to 20% of the total [34].

Future prospects and conclusion

The plant *L. nodiflora* is widespread all over the world, and has been extensively used in traditional medicine for various ailments. Most of the studies, focused on the screening for preliminary *in vitro* activities on the extracts of the plant, and certain compounds have been isolated. However, very little work has been done on the biological activity and medicinal applications of the isolated compounds and hence extensive investigations are required to isolate biologically active compounds to combat diseases.

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