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Ethnopharmacology, Phytochemistry and Pharmacology of *Inula racemosa* Hook. F.

V. Sharma[1], K. Hem[1], D. Sharma[2], V. Pratap Singh[2], N. Kumar Singh[1,*]

[1]*Ayurvedic Pharmacy Research Laboratory, Rajiv Gandhi South Campus, Banaras Hindu University, Mirzapur – 231 001, UP, India.*
[2]*Department of Medicinal Chemistry, Faculty of Ayurveda, Institute of Medical Sciences, Banaras Hindu University, Varanasi – 221 005, UP, India.*

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ABSTRACT

The plant *Inula racemosa* Hook. F. (Asteraceae), usually known as Pushkarmula, found almost in all parts of the India ascending to an altitude of 4,200 m from the sea level. *I. racemosa* is an important medicinal plant in Indian system of medicine (Ayurveda) and Traditional Chinese Medicine (TCM). This plant is used by ethnic groups for the treatment asthma, chronic bronchitis, pulmonary disorders, tuberculosis, skin diseases, cardiac disorders, obesity, diabetes, lung cancer etc. Major phytochemical compounds reported from the roots of *I. racemosa* belong to sesquiterpene lactones, which have a wide range of biological activities. Pharmacological activities reported for the plant *I. racemosa* are anti-inflammatory, analgesic, antifungal, antibacterial, hepatoprotective, anti-allergic, antioxidant, anti-asthmatic, adaptogenic, adrenal beta blocking, hypoglycemic and cardioprotective activity.

1. Introduction

Inula racemosa Hook. F. (Asteraceae), usually known as Pushkarmula, found almost in all parts of the India ascending to an altitude of 4,200 m from the sea level. The plant *I. racemosa* distributed from temperate to sub-alpine belts. *I. racemosa* is an important traditional drug in Indian system of medicine (Ayurveda), Chinies Traditional Medicine (TMC) and Europe [1]. *I. racemosa* is a tall stout shrub up to 15 m, bearing large leathery leaves, rough above, densely hairy beneath, toothed and arranged in a racemose manner. Lower leaves are narrowed to a winged leaf stack. Upper leaves are lanceolate and stem clasping. The flower heads are many, 3.5 - 5.0 cm in diameter, yellow in color and arising in terminal racemes, large, shady yellow daisies produced in mid to late summer. Fruits are slender achenes, 0.4 cm long, and beard with 0.75 cm long reddish pappus hairs. Roots are about 15 cm long and 0.5 to 2.0 cm in diameter, cylindrical, straight or somewhat curved. Surface of the root is rough due to longitudinal striations and cracks, scars of lateral rootlets and rhytidoma present. Fractures of the root are short and smooth [2, 3].

2. Ethnopharmacology

Root of *I. racemosa* is used in Kashmir as adulterant of *Sassurea costus* [4-6] and *Saussurea lappa* for the treatment of asthma, chronic bronchitis and pulmonary disorders [7]. The root powder of *I. racemosa* is used in the treatment of asthma [8], tuberculosis, skin diseases [9] cardiac disorders, obesity [10-14], diabetes [15,16], as an antiseptic, aphrodisiac [17], to boost the appetite [18] in India. Roots of this plant have been used in Europe and Asian countries as folk medicine for the cure of cardiac disorders [1]. The roots of *I. racemosa* along with leaf of *Ocimum sanctum*, *Terminallia bellirica* and *Piper longum* are processed together and given twice daily along with meals for symptomatic relief of lung cancer [19]. Roots Powder of *I. racemosa* along with *Commiphora mukul* is also employed for curing myocardial ischemia [20]. Externally, the root paste is applied in the dressing of wounds [21]. Roots of the plant are used as antiseptic, anti-helmintic, diuretic, expectorant, hypotensive and stimulant to the peristaltic movements by the tribal's of Ladakh [22]. In Traditional Chinese medicine, *I. racemosa* has been used for the treatment of abdominal swelling and pain, acute enteritis, bacillary dysentery, stimulating the spleen, alleviating the pain especially between the neck and the shoulders, relieving the depression of the liver, and to prevent abortion [23-25]. Local American people used this plant for the treatment of tuberculosis [26]. Root powder of *I. racemosa* is used as a tooth powder for various diseases of teeth, for the treatment of liver diseases, abscess and boils. Root powder of *I. racemosa* is given with honey for the treatment of heart diseases. The root of *I. racemosa* is an essential ingredient of a number of polyherbal formulations used for the treatment of cardiac diseases and inflammatory conditions of the spleen and liver. Root powder of *I. racemosa* act as diuretic, rejuvenating and anti-ageing agent when taken with luke warm water [27, 28]. In Ayurvedic classical texts like Charaka Samhita, Bhavprakasha Nighantu, Dhanvantri Nighantu and Raj Nighantu, root of *I. racemosa* described as Shvasahara and Hikkanigrahana dravya (agent used for the treatment of inflammation, anorexia, cough, cardiac diseases, bronchial asthma, bronchitis, anemia and general debility) [27,29].

3. Phytochemistry

Phytochemical compounds isolated from the roots of *I. racemosa* are racemosalactones A–E (**1-5**) [30], alloalantolactone (**6**), isoalloalantolactone (**7**), inunal (**8**), isotelekin (**9**) [31], 5-*α*-epoxyyalantolactone (**10**), 4(15)-*α*-epoxyisoalantolactone (**11**), isoinunal (**12**), telekin (**13**), 5-*α*,6-*α*-epoxyalantolactone (**14**) [32], trinorsesquiterpenoids (4R,5S,10S)-5-hydroxy-11,12,13-trinoreudesm-6-en-8-one (**15**), (4R,5R,10S)-5-hydroxy-11,12,13-trinoreudesm-6-en-8-one (**16**), (4R,5R,10R)-4,15-epoxy-11,12,13-trinoreudesm-8-one (**17**) [33], 11,12,13-trinoreudesm-5-en-7-*β*,8-*α*-diol (**18**) [33,24] alantolactone (**19**), isoalantolactone (**20**), dihydroisoalantolactone (**21**) [34], dihydroepoxyalantolactone (**22**), alantodiene, (**23**), isoalantodiene (**24**) [35], 3-oxoalloalantolactone (**25**), dihydro-4(15)-*α*-epoxyisoalantolactone (**26**) [32,36], 3-*β*-hydroxy-11-*α*,13-dihydroalantolactone (**27**), 11-*α*-hydroxyeudesm-5-en-8-*β*,12-olide (**28**) [37], 11,13-dihydroalantolactone (**29**), 11,13-dihydroisoalantolactone (**30**) [32,38], macrophyllilactone E (**31**) [32,39], 11,13-dihydro-2-*α*-hydroxyalantolactone (**32**) [32,40], 11,13-dihydroivalin (**33**) [32,41], 11-*β*-H-2-*α*-hydroxyeudesman-4(15)-en-12,8-*β*-olide (**34**) [32,42], 11,12,13-trinoreudesm-5-ene-7-*β*,8-*α*-diol (**35**) [32,43], racemosin A (**36**), (7R,8R,10R)-8-hydroxyeudesma-4(5),11(13)-dien-12-oic acid (**37**), (4S,8R,10R)-13-dimethoxyeudesma-5(6),7(11)-dien-12,8-olide (**38**), (4S,8S,10R)-12-hydroxyeudesma-5(6),7(11)-dien-12,8-olide (**39**) [44],

*Corresponding Author
Email Address: narendra_pharma1982@rediffmail.com (Narendra Kumar Singh)

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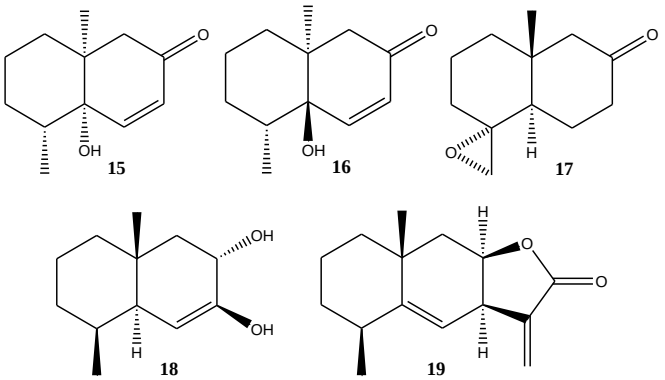
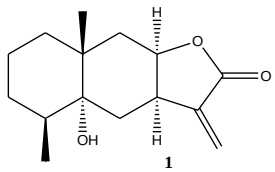
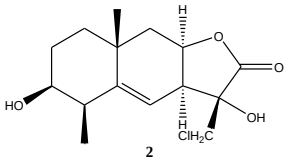
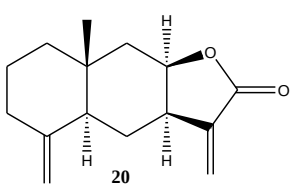
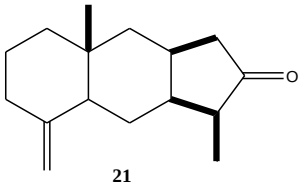
13-hydroxy-5,7(11)-eudesmadien-8,12-olide (**40**) [44,45], 4-*α*-H-eudesma-11(13)-en-4,12-diol (**41**) [44,46], 3-oxo-eudesma-4,11-dien-12,8-*β*-olide (**42**) [44,47], 11-*α*,13-dihydroalantolactone (**43**) [44,48], [1(10)E]-5-*β*-hydroxygermacra-1(10),4(15),11-trien-8,12-olide (**44**) [44,49], 2-*α*-hydroxyeudesma-4,11(13)-dien-12,8-*β*-olide (**45**) [44,50], dehydroivangustin (**46**) [44,51], 1-one-4-epi-alantolactone (**47**), 4-*α*,13-dihydroxy-5,7(11)-eudesmadien-12,8-olide (**48**) [52], septuplinolide (**49**) [52,53], 13-acetyloxy-5,7(11)-eudesmadien-12,8-olide (**50**) [52,54], *n*-decanyl docosdienoate (**51**) *n*-hexadecanyl behenate (**52**), eudesmanolide ester, 15-tricosterienyl eudesmolide (**53**), 15-nonadecenyl eudesmalolide (**54**), 15-tetracosdienyl eudesmalolide (**55**), 15-tetracosenyl eudesmalolide (**56**) [55] 4,(15)-*α*-epoxyisotelekin (**57**), 4,(15)-*α*-Epoxytelekin (**58**), 7-hydroperoxy-11-*α*-H,13-dihydroisoalantolactone (**59**) [56] *β*-sitosterol (**60**), daucosterol (**61**) [57], aplotaxene (**62**), phenylacetonitrile (**63**) [58], epoxyalantolactone (**64**) [59], 8-oxo-tri-nor-eudesm-6-en-5-*α*-ol and trinoreudesm-5-en-7-*β*-8-*β*-diol [60].

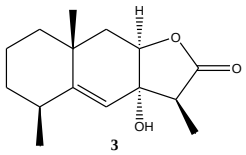


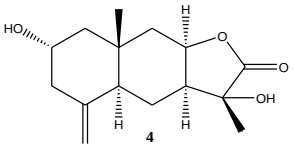


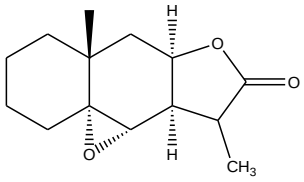


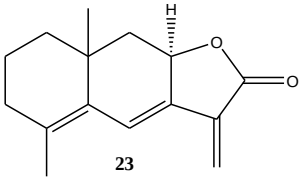


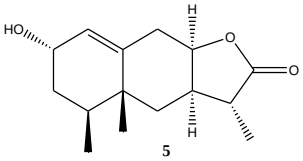


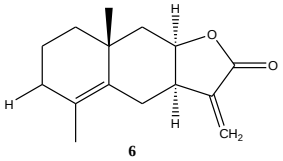


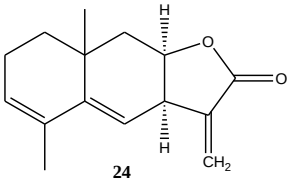


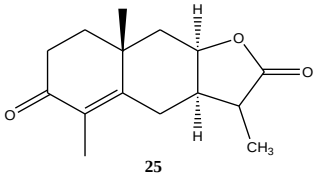


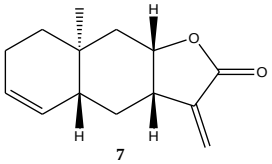


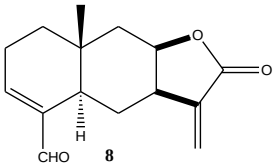


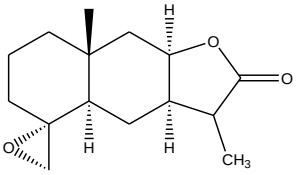


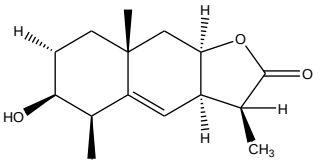


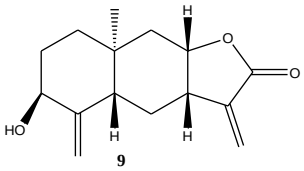


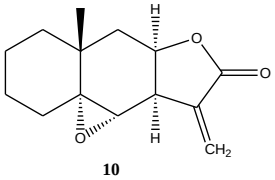


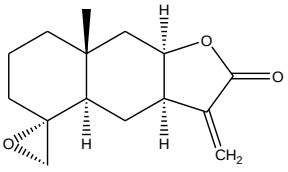


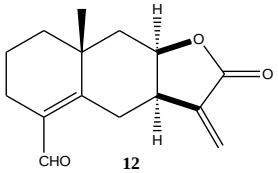


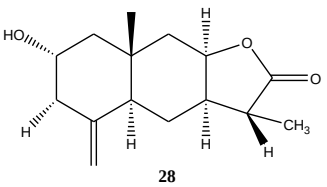


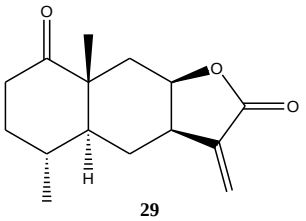


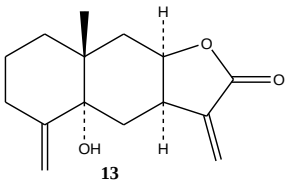


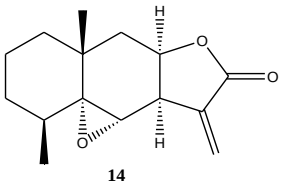


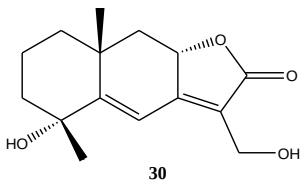


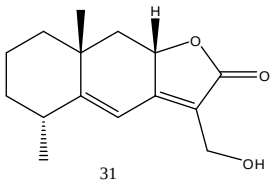


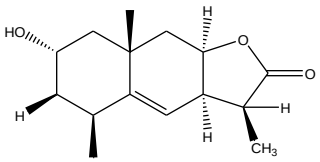












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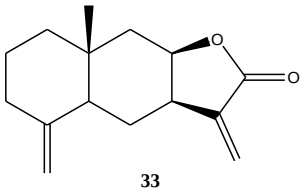

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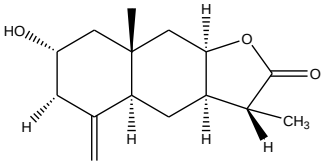

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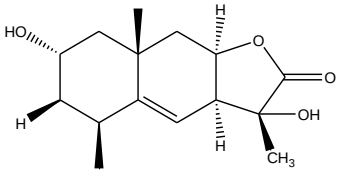

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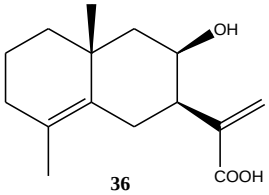

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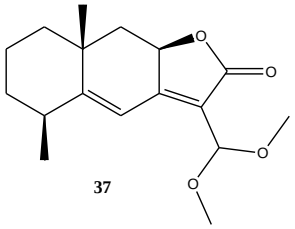

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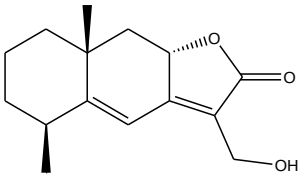

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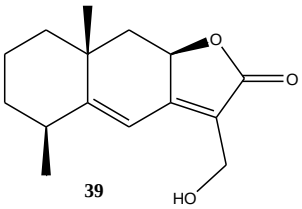

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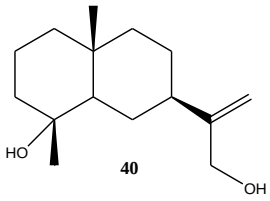

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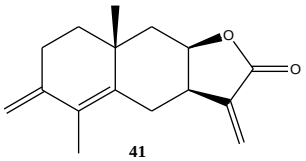

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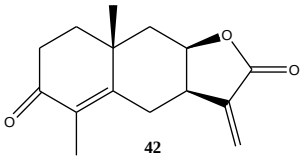

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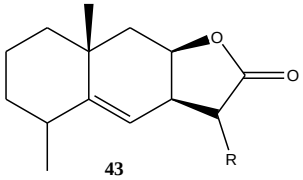

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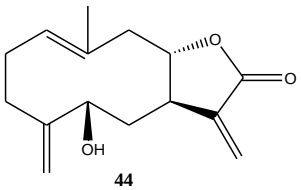

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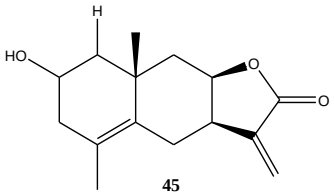

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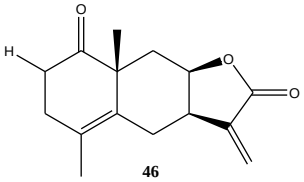

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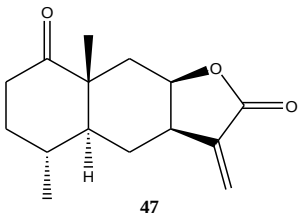

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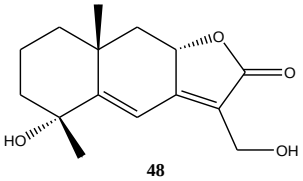

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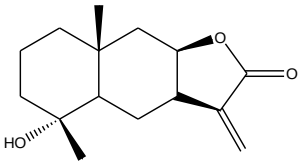

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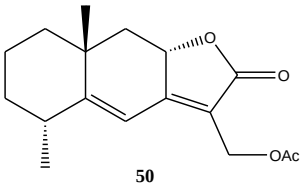

50

CH_3-$(CH_2)_7$-CH=CH-$(CH_2)_6$-CH=CH-$(CH_2)_3$-COO-CH_2-$(CH_2)_8$-CH_3

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CH_3-$(CH_2)_{20}$-COO-$(CH_2)_{15}$-CH_3

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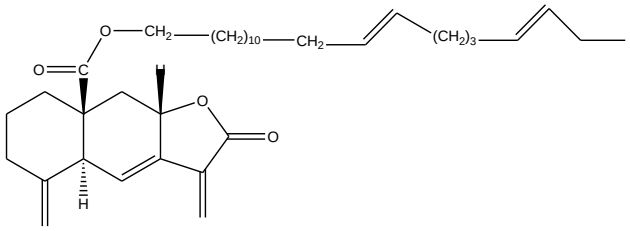

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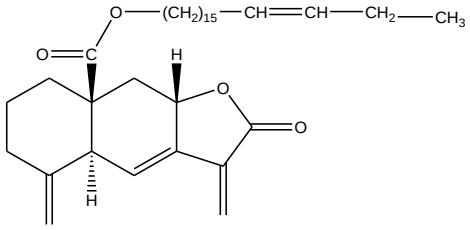

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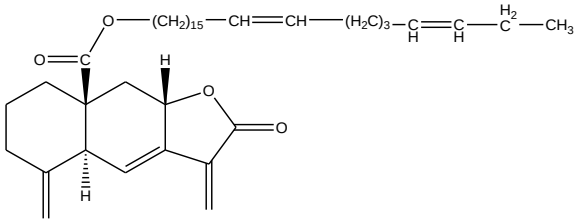

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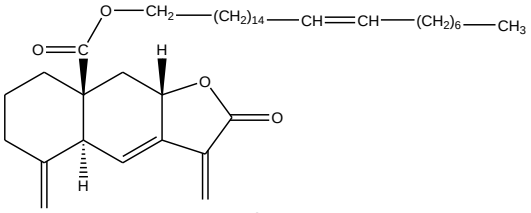

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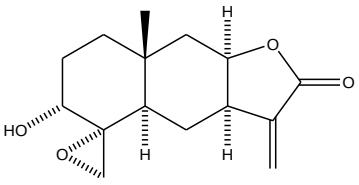

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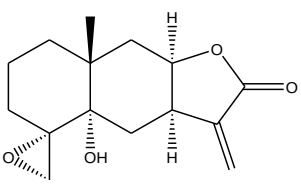

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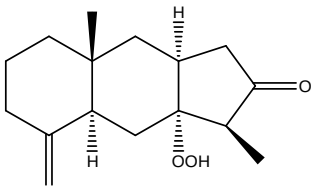

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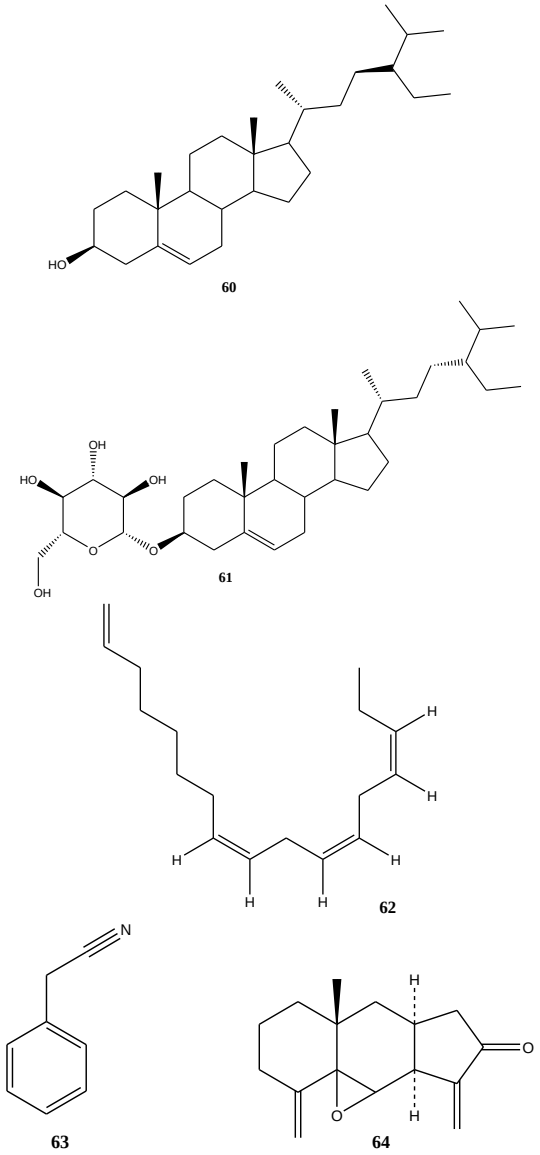

Fig. 1 Structures of **61 - 64**

4. Pharmacology

4.1 Acute Toxicity Study

Acute toxicity studies of hydro-alcoholic extract of the roots of *I. racemosa* was performed in wister rats. LD_{50} value of hydro-alcoholic was found to be 2100 $mgkg^{-1}$ [61].

4.2 Anti-Inflammatory Activity

The anti-inflammatory activity of the ethanol extract of the roots of *I. racemosa* was evaluated by carageenan-induced paw edema in rats. Ethanol extract showed maximum inhibition (34.17%) at a dose of 200 $mgkg^{-1}$, body weight (b.w.) after 2 h of drug administration in carageenan-induced paw edema. Aspirin (100 $mgkg^{-1}$) was used as standard drug produced 17.50% of inhibition in paw edema [62]. In another study, aqueous extract of the roots of *I. racemosa* showed maximum inhibition (60%) at a dose of 400 $mgkg^{-1}$, b.w. after 8 h of drug administration in carageenan-induced paw edema in rats, whereas standard drug indomethacin (20 $mgkg^{-1}$) produced 69% of inhibition [25].

4.3 Analgesic Activity

Analgesic effect of ethanol extract of the roots of *I. racemosa* was performed in albino rats of either sex by using hot plate. Ethanol extract of the plant showed latency in percentage protection (42.99%) at a dose of 200 $mgkg^{-1}$, b.w. after 2 h of drug administration. Standard drug aspirin (100 $mgkg^{-1}$) produced 65.47% latency of percentage protection [62].

Analgesic effect of aqueous extract of the roots of *I. racemosa* was performed in albino mice of either sex by acetic acid-induced writhing and tail immersion methods. Aqueous extract of plant at a dose of 400 $mgkg^{-1}$ showed higher latency of percentage protection in acetic acid-induced writhing model (63%), whereas in tail immersion model the highest enhanced reaction time was observed at 400 $mgkg^{-1}$ (8.65 ± 1.63 at 3 h) [25].

4.4 Cytotoxic Activity

In-vitro cytotoxic activity of 95% ethanol extract of *I. racemosa* roots and its different fractions (n-hexane, chloroform, n-butanol and aqueous) was evaluated on colon, ovary, prostate, lung, CNS and leukemia cancer cell lines using sulphorhodamine-B dye and MTT assay for HL-60 cell line. The major constituents of hexane fraction i.e. alantolactone and isoalantolactone was studied for its mode of action in HL-60 cells. The lowest IC_{50} value (10.25 μgmL^{-1}) was found for n-hexane fraction for Colo-205, a colon cancer cell line, whereas 17.86 $\mu g{\cdot}mL^{-1}$ was the highest IC_{50} value found for CNS cancer cell line (SF-295) [63].

Ma et al isolated racemosalactones A, alantolactone, isoalantolactone, alloalantolactone, 5-α-epoxyalantolactone, α-epoxyisoalantolactone and isotelekin from the methanol roots extract of *I. racemosa*. All the isolated compounds were evaluated for their antiproliferative activities using human non-small-cell lung cancer (A-549), hepatocellular carcinoma (HepG-2) and human fibrosarcoma (HT-1080) cells using CCK-8 dye. All the tested compounds exhibited antiproliferative activities with IC50 values ranging from 0.38 to 4.19 μgmL^{-1} against human non-small-cell lung cancer A-549, hepatocellular carcinoma HepG-2, and human fibrosarcoma HT-1080 cells. Isolated compounds alantolactone and isoalantolactone were evaluated for antiproliferative activity against human umbilical vein endothelial cells (HUVECs). IC_{50} values for these two compounds were found to be 2.4 and 2.5 μgmL^{-1}, respectively [30].

Zhang et al isolated septuplinolide, 11-*α*-13-dihydro-2-*α*-hydroxy-alantolactone, 11,13-dihydroivalin and isoalantolactone from the ethanol roots extract of *I. racemosa*. All the isolated compounds were evaluated for their cytotoxic activities using human lung cancer (A-549), human liver cancer (BEL-7402), human stomach cancer (BGC-823), human colon cancer (HCT-8) and human ovarian cancer (A-2780) cell lines using MTT assays. All the tested compounds exhibited moderate anticancer activities [37].

Macrophyllilactone E, isoalantolactone isolated from *I. racemosa* was evaluated for their anti-platelet activating factor against the release of *β*-glucuronidase in rat's polymorphonuclear leukocytes, whereas ginkgolide used as a positive control. For these two compounds, inhibition ratio was found to be 65.4% and 80.5% respectively at a concentration of 10 μM whereas ginkgolide produce 68.3% inhibition [37].

Ma et al isolated (4R, 5R, 10S)-5-hydroxy-11, 12, 13- trinoreudesm-6-en-8-one isolated from the methanol roots extract of *I. racemosa*. Isolated compound was evaluated for antiproliferative activity using human lung cancer (A-549), hepatocellular carcinoma (HepG-2) and human fibrosarcoma (HT-1080) cells lines using CCK-8 viability assay. The tested compound exhibited antiproliferative activities with IC_{50} values 3.71, 5.94 and 3.95 μgmL^{-1} respectively against human non-small-cell lung cancer (A-549), hepatocellular carcinoma (HepG-2), and human fibrosarcoma (HT-1080) cell lines respectively [33].

Zhang et al isolated alantolactone, [1(10)E]-5-*β*-hydroxygermacra-1(10),4(15),11-trien-8,12-olide, 2-α-hydroxyeudesma-4,11(13)-dien-12,8-β-olide from the 95% ethanol roots extract of *I. racemosa* using MTT assay. Both isolated compounds evaluated for their inhibition of LPS-induced nitric oxide production in RAW264.7 macrophages.). IC_{50} values for all compounds were found to be 7.39 ± 0.36, 6.35 ± 0.26 and 5.39 ± 0.18 μM, respectively [44].

The cytotoxicity of ethanol roots extract of *I. racemosa* was evaluated using the SRB (Sulphorhodamine-B) and MTT assay on normal human liver cell. CTC_{50} value was found to be 666.14 ± 22.44, 690.14 ± 6.74 $\mu g{\cdot}mL^{-1}$ by using MTT and SRB assay respectively in Chang liver cells (normal human liver cell) [21].

4.5 Antifungal Activity

Isoalantolactone isolated from the methanol roots extract of *I. racemosa* was evaluated for antifungal activity against the human pathogenic fungi *Aspergillus flavus, Aspergillus niger, Geotrichum candidum, Candida tropicalis* and *Candida albicans*. The tested compound inhibited the growth of *A. niger, A. flavus, G. candidum, C. albicans* and *C. tropicalis* with MICs values 50, 50, 25, 25 and 25 μgmL^{-1} respectively [57].

4.6 Antibacterial Activity

Antibacterial activity of the ethanol and aqueous roots extract of *I. racemosa* was evaluated by disc diffusion method against *E. coli* and *S. aureus*. The aqueous extract of the plant exhibited significant antimicrobial activity for these two microorganisms tested, with MIC values of 6.25 $mgmL^{-1}$ and 12.5 $mgmL^{-1}$ respectively, whereas ethanol extract also had potent activity against microorganisms, with MIC of 15.625 $mgmL^{-1}$ [64].

4.7 Hepatoprotective Activity

Hepatoprotective and curative effect of hydroalcoholic extract of the roots of *I. racemosa* against hepatic ischemic/reperfusion injury in rats was examined. The plant extract at the dose of 200 and 400 $mgkg^{-1}$ produced significant hepatoprotection by decreasing the elevated levels of aspartate transaminase, alanine transaminase, alkaline phosphatase and lactate dehydrogenase. It had been also seen that *I. racemosa* increased the free radicals scavenging activity in the early period of hepatic ischemia/reperfusion injury in rats [65].

In-vitro hepatoprotective activity of ethanol roots extract of *I. racemosa* was evaluated for its effect on the Chang cell line (normal human liver cells) against carbon tetrachloride induced hepatotoxicity. The cells which are exposed only with toxicant CCl_4 showed 42% viability while the cells which were pretreated with extract at concentration of 600 μgmL^{-1} and 300 μgmL^{-1} showed an increase in percentage viability (78%) and the results were highly significant when compared to CCl_4 intoxicated cells [21].

Hepatoprotective activity isolated compound isoalantolactone was evaluated against CCl_4 (2.0 $mLkg^{-1}$ b.w.) induced liver injury in male wistar rats, at a dose of 100 $mgkg^{-1}$ b.w. Silymarin (10 $mgkg^{-1}$) was used as a standard drug. The degree of protection was measured using biochemical parameters such as serum glutamate oxaloacetate transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), alkaline phosphatase (ALP) and bilirubin. The tested compound decreased the levels of these enzymes in a significant manner, similar to silymarin treated animal group when compared with CCl_4 treated group [66].

4.9 Anti-Allergic Activity

Mast cell stabilizing activity of 90% ethanol roots extract of *I. racemosa* was evaluated on degranulation of rat peritoneal mast cell induced by compound 48/80 and egg albumin. Effect of plant extract on egg albumin induced mast cell degranulation in rats at concentration of 5, 10, 20 and 40 μgmL^{-1} produced dose related inhibition of 18.85, 39.96, 58.97 and 71.65% respectively. Whereas, kitotifen (standard drug, 10 μgmL^{-1}) was found to inhibit degranulation to an extent of 78.22%. Effect of *I. racemosa* extract on compound 48/80 induced mast cell degranulation in rats at same concentration showed reduction in degranulation to 20.36, 37.08, 59.52 and 41.28% respectively while standard drug kitotifen was found to inhibit degranulation to an extent of 77.52% [15].

In another experiment, anti-allergic activity of alcohol extract of roots of *I. racemosa*, was studied in experimental models of type-I hypersensitivity, *viz*. egg albumin induced passive cutaneous anaphylaxis (PCA) and mast cell degranulation in albino rats. The plant extract showed significant protection against egg albumin induced passive cutaneous anaphylaxis, both in case of single dose administration as well as with administration of extract for seven consecutive days. Alcohol extract of roots of *I. racemosa* also showed significant protection of mast cell degranulation induced by compound 48/80, indicating a possible stablizing effect on the biomembrane of mast cells [61].

The hydroalcoholic extract of the roots of *I. racemosa* was found to have potent antihistamine activities as revealed by blockade of histamine-induced contractions of isolated tracheal chain of guinea pig. The drug also offered marked protection against bronchospasm induced by histamine, pollens of *Zea maize*, *Holoptelia* sp., and *Acacia arabica* in guinea pigs. The beneficial effects of *I. racemosa* in bronchial asthma appear to be due to its antihistaminic, anti-5-HT and antiallergic properties [67].

4.10 Mosquito Larvicidal Activity

Quin et al isolated 11,13-dihydroisoalantolactone, macrophyllilactone E, 5-*α*-epoxyalantolactone and epoxyisoalantolactone from the ethanol roots extract of *I. racemosa*. Mosquito larvicidal activity of all these isolated compounds was evaluated against the larvae of *Aedes albopictus and Asian tiger* mosquitoes. The tested compound 11,13-dihydroisoalantolactone and macrophyllilactone E exhibited strong larvicidal activity against the early fourth-instar larvae of *A. albopictus* with LC_{50} values of 21.86 μgmL^{-1} and 18.65 μgmL^{-1} respectively, whereas 5-α-epoxyalantolactone and epoxyisoalantolactone also possessed larvicidal activity against the Asian tiger mosquitoes with LC_{50} values of 29.37 μgmL^{-1} and 35.13 μgmL^{-1} respectively [68].

4.11 Antioxidant Activity

Antioxidant activity of 70% ethanol extract of the roots of *I. racemosa* was performed in Albino rats. The effect of daily oral administration of alcoholic extract (suspended in 1% gum acacia) of the roots of *I. racemosa* to rats for 21 days was investigated for lipid peroxide formation and reduced glutathione (GSH) content. The level of GSH in blood and liver was found significantly higher in treated animals as compared to control (1% gum acacia). Result showed that *I. racemosa* has antioxidant properties because greater availability of GSH to the cell would lead to higher rate of destruction of deleterious hydrogen peroxide and lipid peroxides by glutathione peroxidase [69].

4.12 Antiasthmatic Activity

The anti-asthmatic activity of the roots extracts of *I. racemosa* was evaluated by measuring the antagonistic effect on histamine induced contraction, milk induced eosinophilia, leukocytosis and protection against mast cell degranulation in wistar rats. Petroleum ether extract the plant at a dose of 4 $mgmL^{-1}$ (55.41 ± 3.04) and 10 $mgmL^{-1}$ (48.87 ± 1.36) exert significant antagonistic effect on histamine induced (1.6 μgmL^{-1}) contraction as compared to its ethanol and aqueous extract. Milk-induced eosinophilia in mice of petroleum ether extract at a dose of 50 & 100 $mgkg^{-1}$. Intraperitoneal (i.p.) was found to be 44.77% and 54.36% respectively as compared control group (43.1 ± 2.41). Similarily, dose dependent inhibition of petroleum ether extract at a dose of 50 and 100 $mgkg^{-1}$, i.p. on milk induced leukocytosis (59.53% and 77.47%) supports the adaptogenic potential of the drug. Pretreatment with petroleum ether extract at a dose of 100 $mgkg^{-1}$, i.p. significantly offered protection (74.68%) against mast cell degranulation when compared with control group [8].

4.13 Antimutagenic and Antiapoptotic Effects

Protective effect of aqueous root extract of *I. racemosa* was evaluated on 4-nitroquinoline-1-oxide -induced DNA damage and apoptosis in mice bone marrow cells. Aqueous root extract of *I. racemosa* (100, 200 and 400 $mgkg^{-1}$, b.w.) with or without treatment with 4-nitroquinoline-1-oxide (4-NQO) were administered orally for five consecutive days. Antiapoptotic effect of aqueous root extract of *I. racemosa* (400 $mgkg^{-1}$, b.w.) was measured by the use of Annexin V-FITC assay kit. 4-NQO-induced genetic damage in mice was modulated by aqueous root extract of *I. racemosa via* effective restoration of micronuclei and apoptotic cells formations. The potential protective effects might be due to the synergistic effects of secondary metabolites present in aqueous root extract of *I. racemosa* [70].

4.14 Adaptogenic Activity

Adaptogenicity potential of 90% ethanol roots extract of *I. racemosa* was investigated in the forced swim test model in albino mice. The animals treated with 100 $mgkg^{-1}$ and 200 $mgkg^{-1}$ of ethanol root extract of *I. racemosa* showed a significant decrease in the immobility period with simultaneous increase in antioxidant markers, adrenaline and serotonin levels [18].

4.15 Adrenergic β-Receptor Blocking Activity

The adrenergic *β*-receptor blocking activity of the petroleum ether extract of the roots of *I. racemosa* was evaluated in rats. The plant extract showed lowered plasma insulin and glucose levels within 75 min of oral administration and it significantly neutralize adrenaline induced hyperglycaemia. Furthermore, the extract showed negative inotropic and negative chronotropic effects on frog heart. These findings suggest that *I. racemosa* exhibited *β*-receptor blocking activity [71].

4.16 Hypoglycemic Activity

Endocrine response of ethanol roots extract of *I. racemosa* was evaluated in relation to glucose homeostasis in rats. It was found that alcoholic extract of the roots of *I. racemosa* lowers blood glucose level and enhances liver glycogen without increasing plasma insulin level in rats [72].

Antidiabetic effect of *I. racemosa* roots powder was performed in 15 patients of age above 35 years suffered from the complications of diabetes mellitus like polyurea, polydypsia and polyphagia etc. have been selected for clinical study. All the patients were treated with 1 table spoonful of *I. racemosa* roots powder three times in a day for three months duration. The response was estimated on the parameter of Joslin's Clinica. After the treatment blood glucose level of all patients was found to be normal [73].

Roots of *I. racemosa* was evaluated for the amelioration of corticosteroid (dexamethasone) induced hyperglycaemia in mice. Corticosteroid administration in the animals increased the serum glucose level. Roots of *I. racemosa* decreased the serum concentrations of the thyroid hormones tetraiodothyronine (T4) and triiodothyronine (T3) in corticosteroid-induced hyperglycaemic mice which was found comparable with standard drug ketoconazole. Findings of the results suggest that hypoglycemic effect of the extract was mediated through its cortisol inhibiting potency [74, 75].

Ethanol extract of the roots of *I. racemosa* was evaluated for the effect on glucose metabolism in albino rats. Blood glucose, plasma insulin and liver glycogen levels were measured after 2, 4, 8, 16 and 24 hours of drug administration. At a dose of 400 $mgkg^{-1}$, b.w. plasma glucose level decreased after 4 hours of drug administration and returned to normal at 16 hours. Liver glycogen level was increased significantly as compared to control group at 4 hours after drug administration. A significant reduction in plasma insulin level was observed 4 hours after drug administration, and returned to normal at 8 hour, and remained low upto 16 hours [76].

Water decoction of the root of *I. racemosa* has been reported not only to lower the fasting blood glucose in normal rabbits, but also to protect the rabbit against glucose included hyperglycemia [77].

Chronic treatment with methanol root extract of *I. racemosa* produced significant reduction in blood sugar level in alloxan-induced hyperglycemia model as compared to alloxan treated animals. The body weight, food intake, water intake and urine output were significantly reversed to normal by methanol extract of *I. racemosa* treatment [78].

4.17 Cardioprotective Activity

The cardioprotective potential of hydroalcohol extract of roots of *I. racemosa* was evaluated against isoproterenol-induced myocardial infarction in rats. The rats were treated with isoproterenol (85 $mgkg^{-1}$, subcutaneous) exhibited myocardial infarction, like decrease in arterial pressure, heart rate, contractility, relaxation along with increased left ventricular end diastolic pressure, as well as decreased endogenous myocardial enzymatic and non-enzymatic antioxidants. Isoproterenol also significantly induced lipid peroxidation and increased leakage of myocyte injury marker enzymes. Pretreatment with *I. racemosa* extract (100 and 200 $mgkg^{-1}$ per day, per oral) for 21 consecutive days, significantly restored the reduced form of glutathione and endogenous antioxidant enzymes superoxide dismutase, catalase, glutathione peroxidase from the heart, which were depleted after isoproterenol administration [79].

In another experiment it has been found that ethanol roots extract of *I. racemosa* possess cardioprotective activity against isoproterenol induced myocardial infarction treated wistar rats by restoring electrocardiographic, histopathological and biochemical changes. Myocardial infarction was induced in the wistar rats by isoproterenol administration (200 $mgkg^{-1}$ subcutaneously twice at an interval of 24 h). Ethanol roots extract of *I. racemosa* markedly restrained isoproterenol-induced electrocardiographic changes indicative of its cell membrane protecting effects. At a dose of 400, 600 and 800 $mgkg^{-1}$ daily for a period of 10 days, it improved cardiac function, decreased oxidative stress, cardiac injury, maintained cell membrane integrity and lipid peroxidation process in a dose dependent manner. In addition, it has normalized histopathological changes caused by isoproterenol administration [80].

In another experiment myocardial ischemia was induced in rats by isoproterenol administration (20 mg / 100 g subcutaneously twice at an interval of 24 h). The petroleum ether extract of roots of the plant *I. racemosa* and alantolactone, which have been isolated from the roots of the plant were subjected for evaluation of their cardioprotective activity in myocardial ischemia. Lipid peroxides and glutathione contents were anticipated. It has been found that the alantolactone as well as petroleum ether extract effectively reduces the lipid peroxide levels in the ischemic rats and brings the glutathione content to near normal level [81].

A combination of the plant *C. mukul* and *I. racemosa* in 1:1 ratio was studied in 200 patients suffered with ischemic heart disease. The major symptoms included chest pain, with ST-segment and T-wave changes on the electrocardiogram (ECG), suggested myocardial ischemia in about 80 percent of the patients. Pretreatment with combination of the plant *C. mukul* and *I. racemosa* in 1:1 ratio to the patients caused improvement in precordial pain and dyspnea, restoration of normal ECG patterns, and significant reductions in cholesterol, triglycerides and total lipid levels [82].

The isolated compound from *I. racemosa* was evaluated for the cardioprotective activity on isolated frog heart at a dose 40 μgmL^{-1} showed that alantolactone decreased heart rate and force of contraction. The study indicated that the alantolactone produces a negative ionotropic and negative chronotropic effect on frog's heart [83].

Cardioprotective activity of ethanol root extract of *I. racemosa* was evaluated in wistar male albino rats having myocardial ischemic reperfusion injury. The extract at a dose of 100 $mgkg^{-1}$ for 30 days appreciably restored the myocardial antioxidant status evidence by increased superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), reduced glutathione (GSH) and prevented leakage of cardiomyocytes specific enzymes, creatine phosphokinase isoenzyme and lactate dehydrogenase (LDH). The result suggested cardioprotective effect of *I. racemosa* likely resulted to improve antioxidant status, haemodynamic and left ventricular contractile function subsequent to suppression of oxidative stress [84].

5. Conclusion

In the present study data surmised on ethnopharmacology, phytochemistry and pharmacology of the roots of *I. racemosa* up to December, 2015. Literature survey revealed that more than 64 compounds isolated from the roots of *I. racemosa*. Most of the compounds isolated from the roots of *I. racemosa* belong to sesquiterpene lactone category which have a wide range of biological activities. Racemosalactones A, alantolactone, isoalantolactone, alloalantolactone, 5α-epoxyalantolactone, α-epoxyisoalantolactone, (4R, 5R, 10S)-5-hydroxy-11, 12, 13- trinoreudesm-6-en-8-one and isotelekin isolated from the methanol roots extract of *I. racemosa* showed antiproliferetive activity. Septuplinolide, 11-*α*-13-dihydro-2-*α*-hydroxy-alantolactone, 11,13-dihydroivalin, [1(10)E]-5-*β*-hydroxygermacra-1(10),4(15),11-trien-8,12-olide, 2-α-hydroxyeudesma-4,11(13)-dien-12,8-β-olide and isoalantolactone isolated from the ethanol roots extract of *I. racemosa* showed moderate anticancer activity. Macrophyllilactone E and isoalantolactone showed anti-platelet activating activity. Isoalantolactone showed hapatoprotective activity and antifungal activity against the human pathogenic fungi *Aspergillus flavus, Aspergillus niger, Geotrichum candidum, Candida tropicalis* and *Candida albicans*. 11,13-Dihydroisoalantolactone, macrophyllilactone E, 5-*α*-epoxyalantolactone and epoxyisoalantolactone showed mosquito larvicidal activity.

Literature survey revealed that *I. racemosa* is an important medicinal plant. Further clinical study of isolated compounds may be conducted to get potential candidates for the treatment of cancer, malaria, cardiovascular diseases and liver disorders.

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