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**Review Article**

# CHEMISTRY AND BIOLOGICAL ACTIVITY OF SOME ALANTOLOIDS FROM INULA SPECIES - A REVIEW

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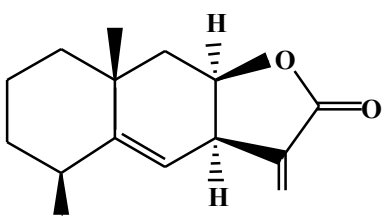
## ABSTRACT

The compounds present in plants of genus *Inula* exhibit wide spectrum of biological and medicinal activities. These plants are rich source of wide variety of bioactive secondary metabolites such as tannins, terpenoids, alkaloids, and flavonoids. Alantolactone and Isoalantolactone are the major compounds present in *Inula* plants. The selection of the plants in the present study is primarily based on their chemistry, biological and medicinal properties reported. This review attempts to summarize the current status of reported various activities of *Inula* species. Some very interesting findings have been observed and thus recorded and reported in this review.

**Keywords:** *Inula*, Sesquiterpenoids, Secondary metabolites, Alantolactone, Isoalantolactone.

## INTRODUCTION

Natural product chemistry has always been one of the most aspiring fields of chemistry. Among the natural products, sesquiterpene lactones having α-methylene-γ-lactone moiety are studied the most for their chemistry, mechanistic pathway, their chemical transformations and synthesis because of their bioactive nature. Sesquiterpenoids, marvellously varied group of compounds have challenged the intelligence and technical skill of chemists and biochemists interested in structure, chemistry, synthesis and biological origin. The genus *Inula*, belongs to family Asteraceae.[1] A plant has its origin in Temperate and Alpine Western Himalayas and is now critically endangered Himalayan herb.[2] There are about 100 species of the genus Inula widely found in Europe, Asia, and Africa, mostly in the Mediterranean, with more than 20 species being distributed in China.[3] The plant contains eudesmanolide group of sesquiterpene lactones. Roots of these plants are rich source of essential oil. These molecules may be used directly or considered as a model for developing better molecules. The isomeric lactones, alantolactone (1), isoalantolactone (2) and inunal (3), major compounds present in the roots of genus *Inula* are known to exhibit wide variety of biological activities viz. antispasmodic[4], antifungal[5] and antimalarial[6] , antibacterial[7] and plant growth regulatory activity.[8-9]

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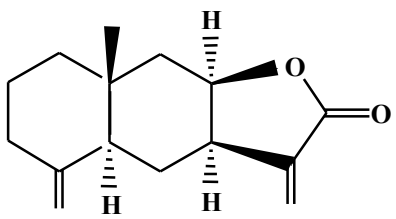


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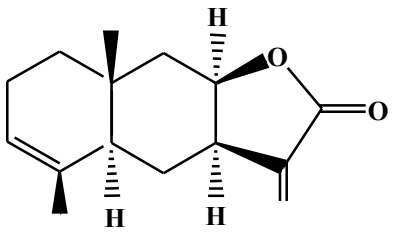


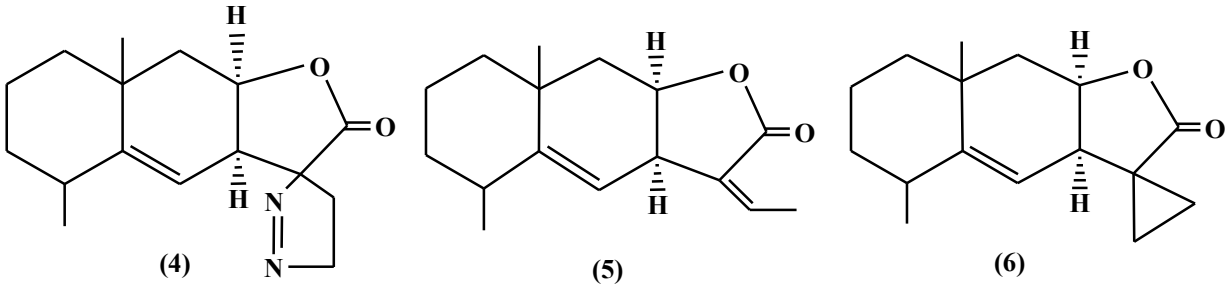

(3)

Due to its various medicinal properties, it is being over exploited from the wild habitat. Many of them have long been used as Chinese folk medicine, and most frequently employed for their peptic, relieving phlegm,

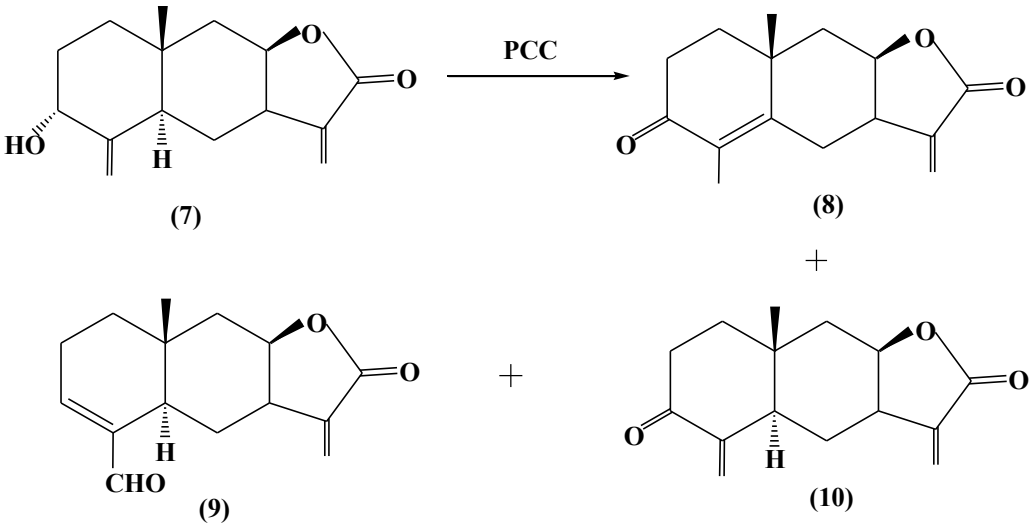
detumescence and anti-inflammatory properties. Alantolides play an important role in the molecular modifications of several eudesmane sesquiterpenes.[10] Two major alantoloids namely alantolactone and isoalantolactone have been extensively studied by many groups of scientists for their medicinal and biological activity. [11-12] The various compounds present in Inula species and their transformation reactions have been discussed in the present review. Further pharmacological significance and biological activity of the various compounds present in genus inula have been discussed in detail.

## Chemical Reactions

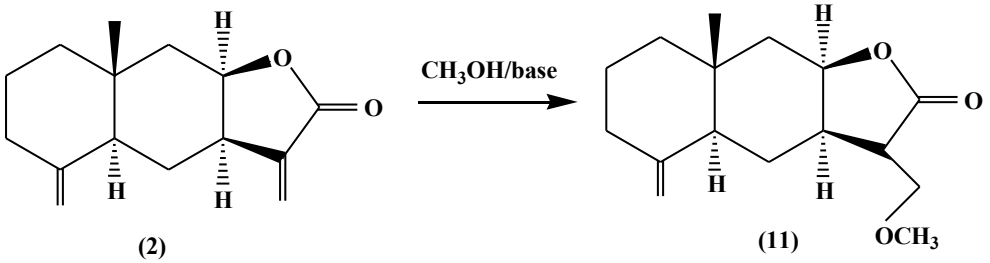
The biogenesis of eudesmanolides to eremorphilanolides involves a biogenetic type transformations 1,2 shift of the angular methyl group at C-10 and such methyl migration has been considered to occur during the biogenesis of various types of terpenoids and steroids.[13] Alantolactone on reaction with diazomethane afforded major crystalline pyrazoline derivative (4) besides other minor products (5-6).[14]




Oxidation of isotelkin (7), a sec-allylic alcohol with pyridinium chlorochromate (PCC) yielded compound (8), inunal (9) and oxiisoalantolactone (10). [15]

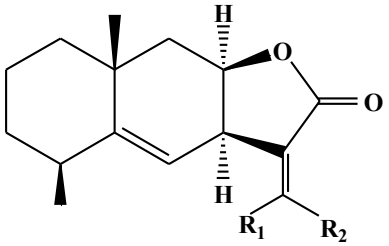


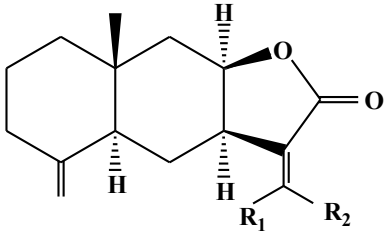

Isoalantolactone (2) afforded a crystalline 13-methoxy dihydroisoalantolactone derivative (11) on dissolving in the methanol in the presence of little base.[16]




Incorporation of trisubstituted double bond (12) or a cyclopropane ring (14) in position of the conjugation of the γ-lactone carbonyl bring about enhancement of their biological activity over the parent compounds in case of (16) and (17). An E and Z- isomerism brings about a distinct change in the biological activity of terpenoid lactone. Thus the activity of 13-methyl alantolactone, Z-isomer (12) is reduced to almost one half

at 15 g/L on its isomerisation to E-isomer (13) , whereas this situation is reserved in the case of 13-methyl isoalantolactone, Z-isomer (14) and its E-isomer (15).[17]



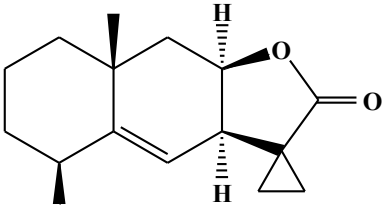


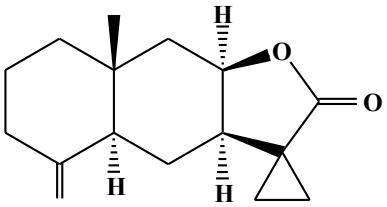
**(12)** $R_1 = H, R_2 = CH_3$

**(13)** $R_1 = CH_3, R_2 = H$

**(15)** $R_1 = H, R_2 = CH_3$

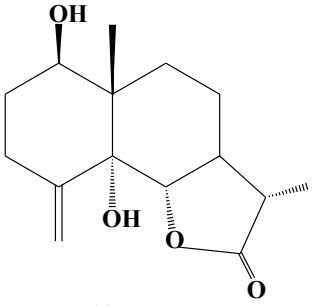
**(16)** $R_1 = CH_3, R_2 = H$

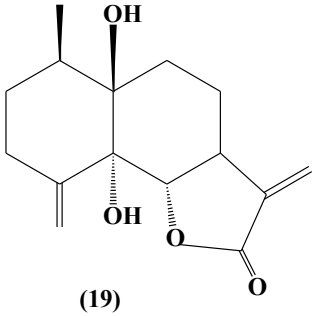




**(14)** **(17)**

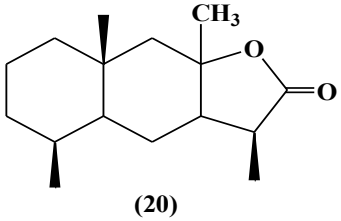
During the dehydrogenation process conversion of (α-methyl-γ-lactones) artemin (18) to tenactin (19) has been reported. Its structure and stereochemistry were determined on the basis of chemical transformations and spectral evidence.[18]

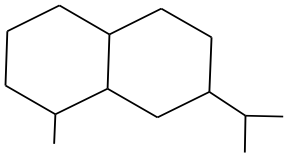


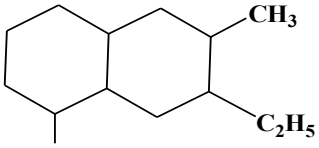


**(18)** **(19)**

The dehydrogenation of isoalantolactone (2) and 7-methyl-tetrahydroalantolactone (20) by pyrolysis in the presence of Se or Pd-C at temperature around 350ºC to yield the alkylated naphthalene eudalene (21) and 2,5-dimethyl-3-ethyl naphthalene (22) has been reported.[19]

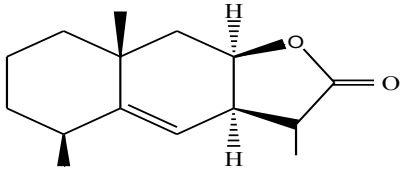


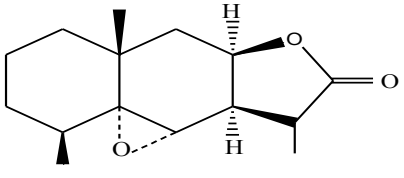




**(20)** **(21)** **(22)**

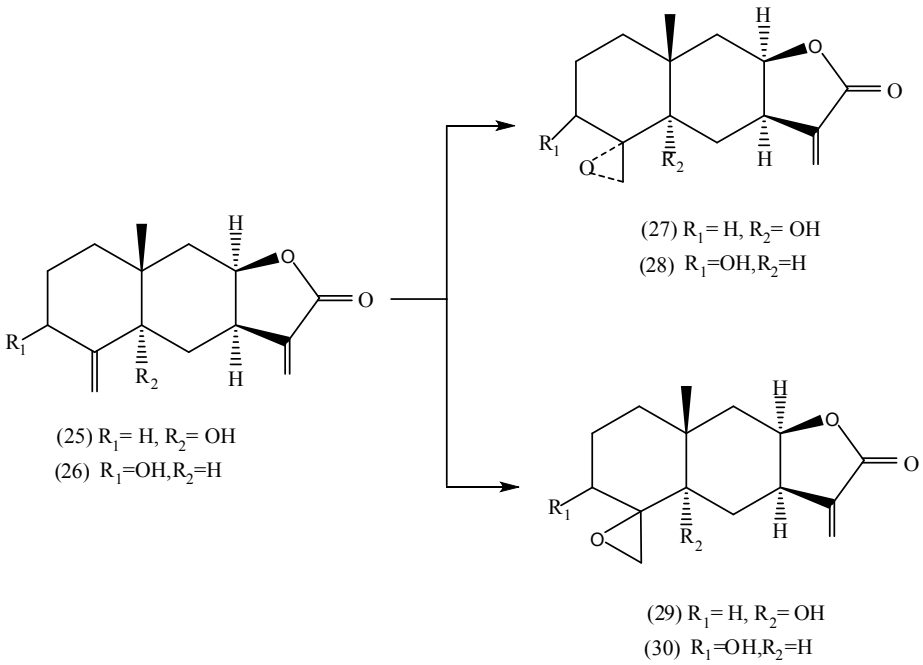
Dihydroalantolactone (23) on treatment with perbenzoic acid afforded 5,6-epoxy dihydroalantolactone (24).[20]



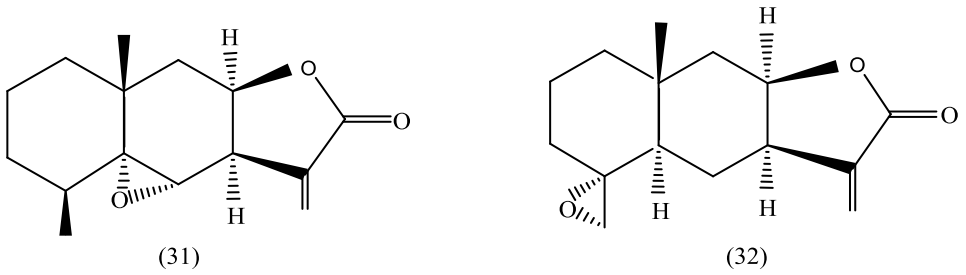


(23) (24)

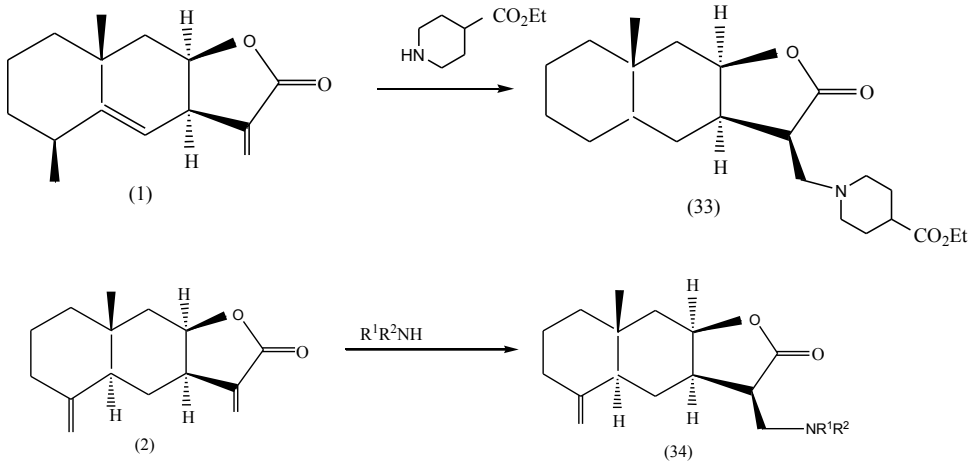
Epoxidation of telkin (25) and (26) with perbenzoic acid afforded corresponding α and β epoxy derivatives (27-30) respectively. [21]



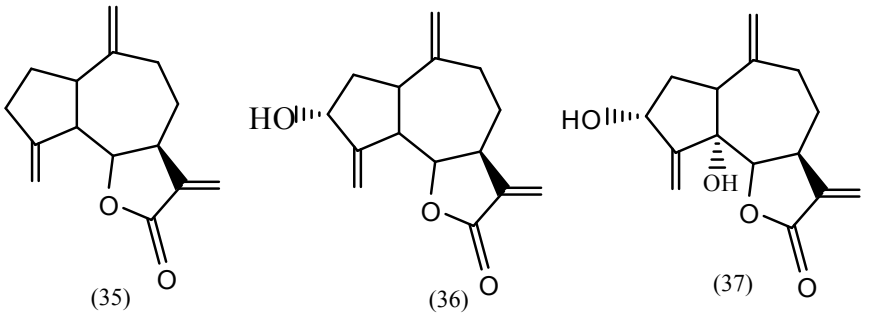

The epoxidation reactions of alantolactone (1) and isoalantolactone (2) with trifluoroacetic acid ($CF_3CO_3H$) and sodium carboante ($Na_2CO_3$) in the dichloromethane as the solvent at 0 $^0$C gives the compounds (31-32).[22]



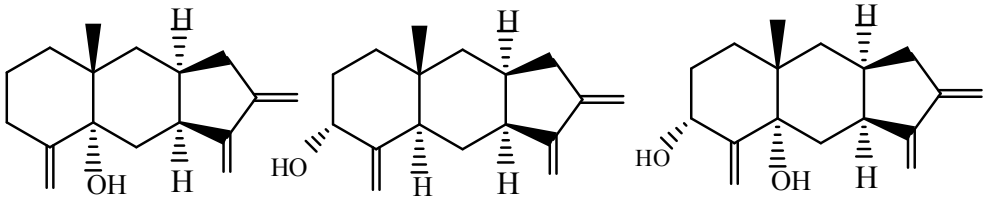

Hydrogenated 3-aminomethylnapthofuran-2-ones (33-34) were synthesized by the reaction of natural alantolactones with pharmocophoric amines.[23]




Sesquiterpene lactones having α-methylene-γ-lactone moiety like dehydrocostus lactone (35) and isoalantolactone (2) on treatment with $SeO_2$/TBHP/$CH_2Cl_2$ resulted into formation of allylic oxidation products (36, 37 & 38, 39, 40).[24]

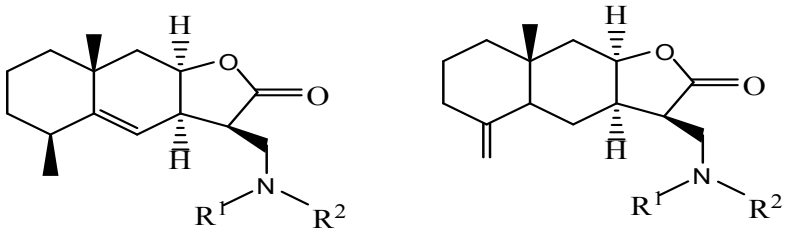


(35) (36) (37)



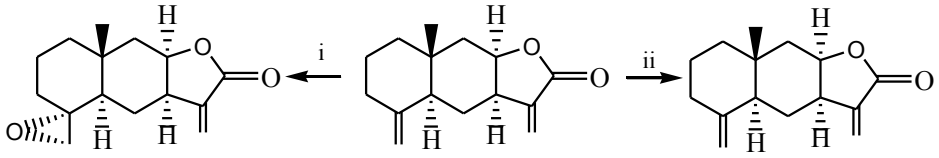
(38) (39) (40)

Stereoselective Michael-type addition of amines to alantolactone (1) and isoalantolactone (2) gives a two series of cytotoxic α-aminomethyl substituted lactones (41 and 42). The lactones 1 and 2 and their amine adducts induce apoptosis and act as alkylating agents.[25]



(41) (42)

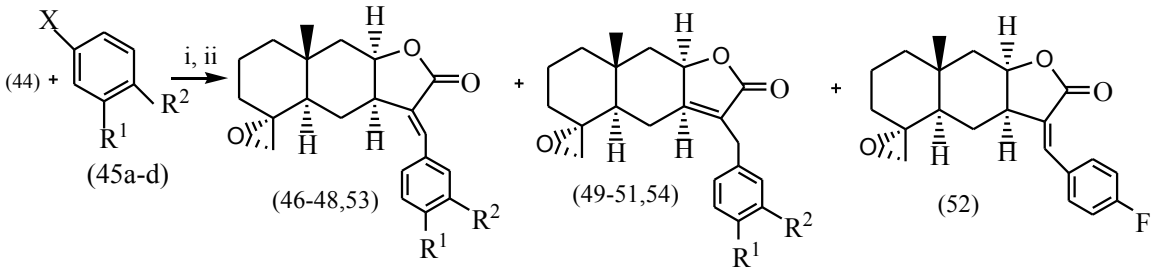
The Heck reaction of the eudesmane-type methyledene lactone, alantolactone (1), aloalantolactone (43) and 4,15-epoxyisoalantolactone (44) with haloarenes afforded nine products (46-54). The yield and the ratio of the arylation products depend on the reaction conditions and structures of lactones.[26]



(44) (1) (43)

i = mCPBA, $CH_2$, $20^0$C

ii= $CF_3$, COOH, $20^0$C



(45a-d) (46-48,53) (49-51,54) (52)

i = $Pd(OAc)_2$ , $(2\text{-}MeC_6H_4)_3P$, DMF, $Et_3N$

ii = $Pd(OAc)_2$ , MeCN, DMF, $Et_3N$

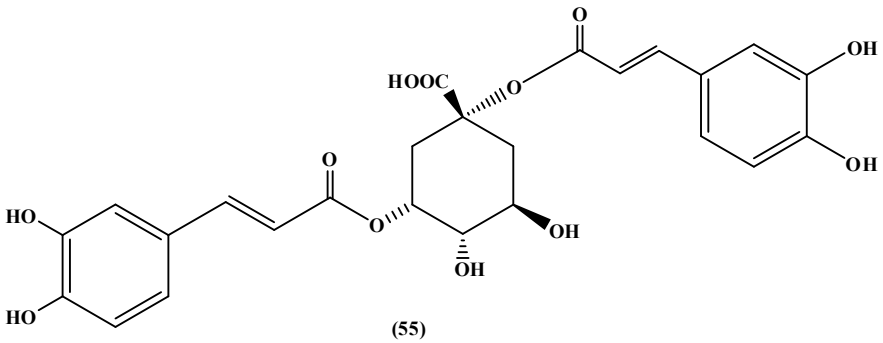
$R^1$= F, $R^2$ = H ( 45a,46,49,52) $R^1$=$R^2$ = OMe (45b,47,50)

$R^1$=$R^2$=OH (45c,48,51) , $R^1$= Br, $R^2$ = H ( 45d,53,54)

## Pharmacological Significance

### *Antioxidant Activity*

Antioxidants are very useful in improving the quality of life by preventing or postponing the onset of degenerative diseases. They act as scavengers of free radicals which are responsible for causing a large number of diseases including cancer, cardiovascular disease, neural disorders, Alzheimer's disease, mild cognitive impairment, Parkinson's disease, alcohol induced liver disease and ageing etc. The antioxidant activity of alantolactone (1) and isoalantolactone (2) isolated from *Inula helinium* was reported.[27] Antioxidant activity of 1,3-dicaffeoylquinic acid (1,3-diCQA) (55) was measured using 2,2'-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) and 1,1-diphenyl-2-picrylhydrazyl (DPPH) assays. The results demonstrated the antioxidant capacities and free-radical scavenging activities of 1,3-diCQA. The antioxidant activity of 1,3-diCQA and its ability to scavenge reactive oxygen species (ROS) indicated the potential use of this compound to treat disorders involving ROS and oxidative damage, such as age-related and certain degenerative diseases.[28]

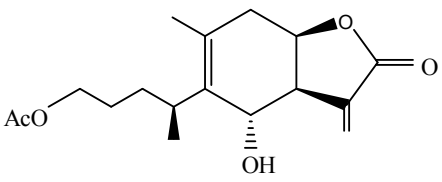



(55)

The isolates of *Inula graveolens* were evaluated for its antioxidative properties. Its methanolic extract showed strong antioxidant activity (64.28%) as well as strong reducing power (increased as the extract concentration increased) and ferrous ion chelating (96%) abilities. Moreover, the methanolic extract showed the highest free radical scavenging activities for superoxide anion and hydroxyl radical, reaching 93.43 and 91.38%, respectively. This study suggested that the methanolic extract of *Inula graveolens* L. possessed antioxidant activity that might be helpful in preventing or slowing the progress of various oxidative stress related diseases.[29] The further work reported that with increase in concentration there is increase in antioxidant properties of various extracts isolated from the *I. helenium*.[30] Looking from the earlier findings, much of the work has not been done so far related to the antioxidant properties of genus Inula.

### *Antiproliferative Activity*

Treatment of cancer and microbial infections have drawn the attention and interest of researchers due to their great impact on the population's health. During the last 20 years, apoptosis (programmed cell death) has been extensively studied as an ideal method to kill cancer cells and chemical agents that induce apoptosis. Three sesquiterpene lactones 1-O-acetylbritannilactone (56) isoalantolactone (2) and britannilactone (57), isolated from the roots of *Inula helenium* and the flowers of *Inula japonica* were studied for their antitumor activities in the cell lines of HeLa, HEC-1, SHIN3, HOC-21 and HAC-2, and their structure activity relationship and the possible mechanism was explored.[31]

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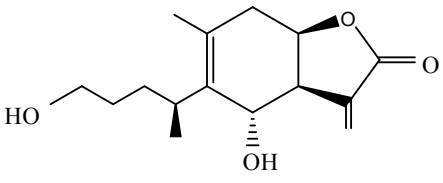
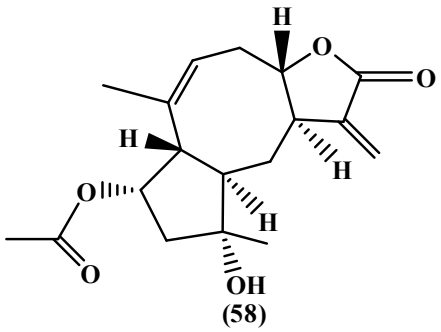



(57)

The antiproliferative activity of gaillardin, sesquiterpene lactone isolated from *Inula oculus* on MCF7 (human breast adenocarcinoma), WEHI164 (mouse fibrosarcoma) HepG2 (hepatocellular carcinoma), MDBK (bovine kidney cells) HT29 (human colon adenocarcinoma) and A549 (non-small cell line carcinoma) cells was evaluated through MTT assay. $IC_{50}$ values of gaillardin on the above mentioned cell lines were 8, 15.28, 6.2,11, 1.81 and 4.76 µg/ml respectively. According to the results of MTT (Microculture tetrazolium) assay, the antiproliferative activity of the *Inula oculus* extract could be partly related to the presence of gaillardin (58) in the chloroform soluble fraction of the plant.[32]




**(58)**

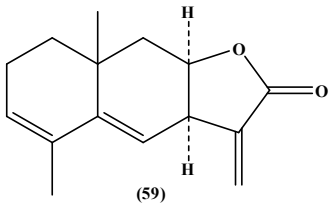
The methanolic extract of the roots of *Inula helenium* showed a high inhibitory activity for cell growth against MK-1, HeLa and B16F10 cell lines. Significant activity was found in the hexane-soluble fraction from which seven sesquiterpenes, namely, germacrane (4α,5β-epoxy-1(10),11(13)-germacradiene- 8,12-olide), elemane (igalane), and five eudesmanes (alantolactone, isoalantolactone, 11a,13-dihydroalantolactone, 11α,13-dihydro-isoalantolactone, 5-epoxyalantolactone) were isolated. *In vitro* antiproliferative activities of the isolates against MK-1, HeLa and B16F10 cells were reported. The *n*-hexane fraction showed strong antiproliferative activity against MK-1, HeLa and B16F10 cells followed by chloroform reaction, while the ethyl acetate and *n*-butanol fractions had a very low activity. The water fraction showed no antiproliferative activity for any cell lines, suggesting that the aliphatic compounds exhibited the antiproliferative activity.[33] The cytotoxic activity of hexane and dichloromethane fractions of *I. viscosa* were evaluated against cervical cancer cell lines through the inhibition of proliferation and induction of apoptosis caspase-dependent and involving a mitochondria-mediated signaling pathway.[34] Out of thirteen compounds isolated from *Inula viscosa* antiproliferative activity was observed in four flavonoids (nepetin, 3,3′-di-O-methylquercetin, hispidulin, and 3-O-methylquercetin). 3,3′-di-O-methylquercetin and 3-O-methylquercetin showed selective antiproliferative activity against MCF-7 cells, with $IC_{50}$ values of 10.11 and 11.23 µg $mL^{-1}$, respectively. Both compounds exert their antiproliferative effect by inducing apoptosis as indicted by the presence of DNA fragmentation, nuclear condensation, and formation of apoptotic bodies in treated cancer cells. Methylated quercetins isolated from *Inula viscosa* had improved anticancer as compared to flavonoids and were found to be anticancer agents.[35]

### *Cardioprotective Activity*

Cardiovascular disease includes a large range of diseases that affect the heart or blood vessels which is a major cause of death in advanced countries. The plant derivatives remain the basis for a major proportion of commercial medication used today for the treatment of heart disease, high blood pressure, pain, asthma and other diseases. The cardioprotective potential of *Inula racemosa* in myocardial ischemic-reperfusion injury in wistar male albino rats was tested. The study demonstrated that the cardioprotective effect of *I. racemosa* resulted to improved antioxidant status, haemodynamic and left ventricular contractile function subsequent to suppression of oxidative stress.[36-37] The ethanolic extract of *Inula racemosa* roots and its fractions (n-hexane, chloroform, n-butanol and aqueous) were tested for *in vitro* cytotoxicity against cancer cell lines in colon, ovary, prostrate, lung, CNS and leukaemia. The bioactive constituents from *I. racemosa* could be used as a potential anticancer agent with possible therapeutic implications.[38] A combination of *Commiphora mukul* and *Inula racemosa* (1:1 ratio) was studied in 200 patients with ischemic heart disease.

The major symptoms included chest pain, with ST-segment and T-wave changes on electrocardiogram (ECG), suggested myocardial ischemia in about 80 per cent of the patients. The subjective levels of chest pain and dyspnoea also improved after treatment.[39]

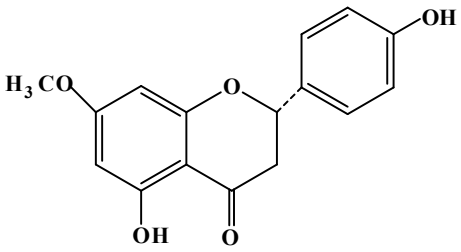
Cardiac activity of isolated constituents of *Inula racemosa* on isolated frog heart showed that compound (59) decreased heart rate and force of contraction at 40 mcg/ml. Actions of Adrenaline were blocked by this compound which acts as an agonist for Propranolol. The studies indicated that the compound (59) produces a negative ionotropic and negative chronotropic effect on frog's heart. These studied can be utilized as a cardiac marker for exploring the cardiac activity of the plant *Inula racemosa*.[40]




(59)

*Antiinflammatory Activity*

Inflammation is a disorder involving localized increase in the number of leukocytes and a variety of complex mediator molecules. Synthetic molecules like no-inflamatory drugs and selective Cox-2 inhibitors increase the incidence of adverse cardiovascular thrombotic effects. The anti-inflammatory activity of methanolic extract of *Inula graveolens* L. was investigated. The effect of the extract was studied on formalin induced paw edema (chronic inflammation). The extract showed significant antiinflammatory activity at the dose of 400mg/kg on the first day ($P < 0.05$), and the hind paw edema of rat disappeared after 6 days ($P < 0.01$) as compared to standard drug Diclofenac sodium (50mg/kg).[41] The anti-inflammatory properties of three flavanones isolated from *Inula viscosa*, sakuranetin (60), 7-O-methylaromadendrin (61), and 3-acetyl-7-O-methylaromadendrin (62), were tested both *in vitro* and *in vivo*. Acute inflammation *in vivo* was induced by means of topical application of 12-O-tetradecanoylphorbol 13-acetate (TPA) (47) to mouse ears or by subcutaneous injection of phospholipase A into mouse paws.[42]

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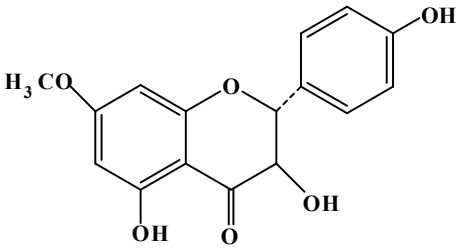


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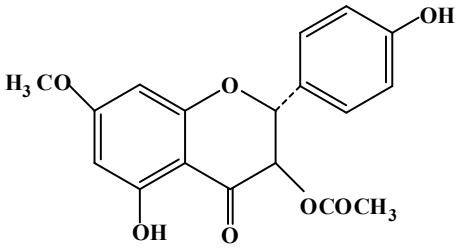



(62)

The ethanolic extract of *Inula racemosa* is found to be active in the Type-I allergic conditions because of their ability to inhibit the release of mediators from mast cells and thus influence the course of the disease by preventing the harmful effects of the released mediators. Based on this study, it could be suggested that *Inula racemosa* stabilizes mast cells in the rat.[43]

***Anticancer Activity***

Two new eudesmane-type sesquiterpene lactones were isolated from the roots of *Inula racemosa* and their structures were elucidated as 3β-hydroxy-11α, 13-dihydroalantolactone and 11α-hydroxy-eudesm-5-en-8β,12-olide. Their cytotoxic activities against five human cancer cell lines tested revealed that isoalantolactone (2) exhibited weak cytotoxic activity against BEL-7402 and HCT-8 cell lines. The anti-inflammatory activities were also tested, but none of them was found to be passive.[44] Petroleum ether, ethanol (95%) and water extracts of air dried roots of *Inula racemosa* were obtained by successive extractions. Petroleum ether extract at a dose of 4 mg/ml (55.41±3.04) and 10 mg/ml (48.87±1.36) exerted significant antagonistic effect ($p<0.05$) on histamine induced (1.6µg/ml) contraction as compared to its ethanol and water extract. A dose dependent contraction was observed in goat tracheal chain preparation. Significant control of milk-induced eosinophilia in mice was found at a dose of 50 and 100mg/kg i.p. by petroleum ether extract (44.77 and 54.36 % respectively) as compared control group (43.1±2.41). Same dose dependent inhibition of milk induced leukocytosis 59.53 and 77.47% by petroleum ether extract supported the adaptogenic potential of drug. Challenge with clonidine induced mast cell degranulation in mice was inhibited by standard mast cell stabilizer disodium cromoglycate (DSCG 200µg/kg, i.p.) as 14±1.22 (83.57%) when compared with control group.[45]

The Ergolide isolated from the flower of *Inula helianthus* was found to be extremely cytotoxic against cultured cancer cell.[46]

### *Antipyretic, Antiphlogistic and Antiseptic Activity*

*Inula viscosa* showed balsamic, antipyretic, antiphlogistic and antiseptic properties. Pharmacological test on rabbits, made hyperpyretic in laboratory, gave satisfactory antipyretic results. Gas chromatographic separation from a high-boiling fraction of seven azulenes, two of them identified as 1,4-dimethyl-azulene (about 50%) and chamazulene (32%), confirmed the antiphlogistic action ascribed to the plant. Advanced instrumentation research revealed eucalyptol fraction of essential oil obtained from fresh leaves of *Inula viscosa*. This data supports the balsamic, antipyretic, antiphlogistic and antiseptic properties of *Inula viscose*.[47]

## Biological Activity

### *Antifungal Activity*

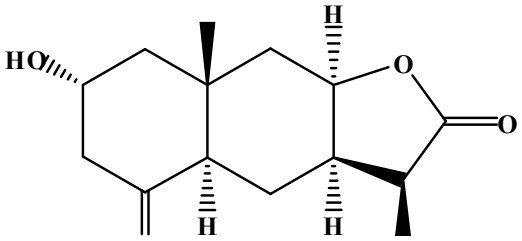
Isoalantolactone exhibited strong activities against phytopathogenic fungi *Gaeumannomyces graminis*, *Rhizoctonia cerealis* and *Phytophthora capsici*, whose infections were the causes of severe crop diseases.[48]

Pyrazolines of alantolactone and isoalantolactone isolated from roots of *Inula racemosa* exhibits antifungal potential against *Alternaria brassicae* and *Penicillium italicum* and *Rhizoctonia solani*. All the compounds exhibited fairly good fungitoxicity against the test fungi with $ED_{50}$ values of less than 500 µg $mL^{-1}$.[49]

Alantolactone (1), isoalantolactone (2) and inunal (3), showed in vitro antifungal activity against *T. mentagrophytes* and *Microsporum canis*.[50] Leaves of *Inula viscosa* were dried and extracted with a mixture of acetone and n-hexane. The oily, water-insoluble pastes obtained after evaporation of the solvents were used for the control of foliar diseases in growth chambers. The results showed that *I. viscosa* may be used as an herbal source for fungicidal preparations against foliar diseases caused by pathogens belonging to the families Oomycetes, Ascomycetes, and Basidiomycetes.[51] The crude extract from *I. japonica* flowers was extracted with chlororform and compound 1-O-acetylbritannilactone (ABL) was obtained. The inhibitory effects of compound ABL against *Sphaerotheca fuliginea*, *Pseudoperonospora cubensis*, *Botrytis cinerea*, *Alternaria solani* and *Phytophthora infestans* was tested.[52] The behaviour of *Inula falconeri* extract against plant pathogens, hexane fraction (concentration gradients of 1.25, 2.5, and 5 mg/disc) was demonstrated, significant zones of inhibition against *Alternaria alternata* and *Rhizoctonia solani* were observed whereas only an insignificant effect against *Fusarium oxysporum* was observed.[53]

### *Antibacterial Activity*

*Inula helenium* proved to be completly effective against the 200 tested staphylococci, with 93% of isolates falling within the ++ and +++ groups. The minimum bactericidal concentration of *I. helenium* was examined on a subset of isolates and values ranged from 0.9 to 9.0 mg $mL^{-1}$.[54] The hydrodistilled essential oil of fresh aerial parts of *Inula viscosa* (L.) was found to contain nerolidol (25.3%), isocostic acid (10.1%), costic acid (8.0%), neo-intermedeol (6.4%) and caryophyllene oxide (5.5%), as major components as characterized by various techniques. The plant exhibited a good antibacterial activity against *P. aeruginosa* ATCC (21mm), *P. aeruginosa* HS (21mm) and *Klebsiella pneumoniae* (20mm).[55] The aerial parts of *Inula graveolens* afforded a new eudesmanolide, 11,13-dihydroivalin (63) and four known sesquiterpene lactones, ivalin (64), inuviscolide (65) and 8-epi-xanthatin-1β,5β-epoxide (66). The structures were established by spectral methods and the compounds were evaluated for their cytotoxic and antibacterial activity.[56]

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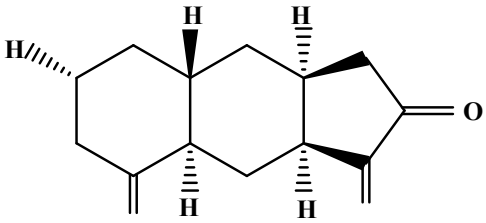


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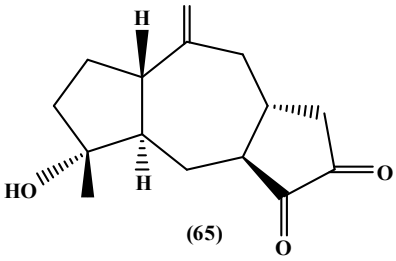


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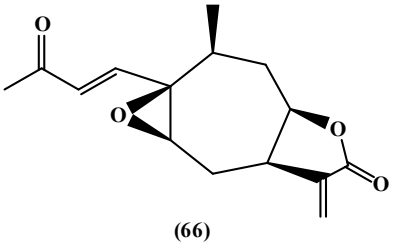
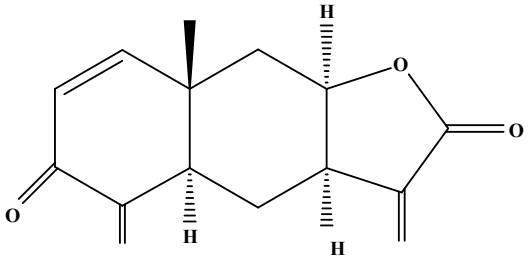



(66)

## *Insecticidal and Antifeedant Activity*

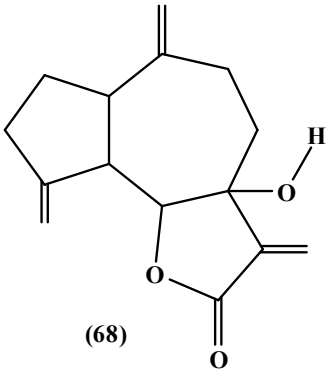
The insecticidal activity of isoalantolactone (2) against *Sitophillus oryzae* was studied using poisoned food technique. The same method and positive and negative controls mentioned in the repellency test were adopted in grain treatments.[57] The root extract of inula had antifeedant activity against mammals and insects, and was found to be a potent inhibitor of plant seed germination and seedling growth. Encelin (67) showed antifeedant activity.[58]




(67)

## *Nematicidal Activity*

*Inula viscosa* extracts were tested for their effectiveness in control of *Meloidogyne javanica* in laboratory. In a field experiment, a reduction of 40% in root galling index by one of two formulations was observed on lettuce plants.[59] Alantolactone (1) showed nematicidal activity against root knot nematode whereas 7α-hydroxy-3-desoxyzaluzanin (68) exhibited molluscicidal activity.[60]

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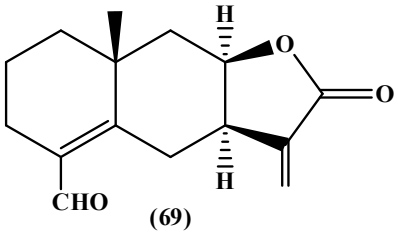


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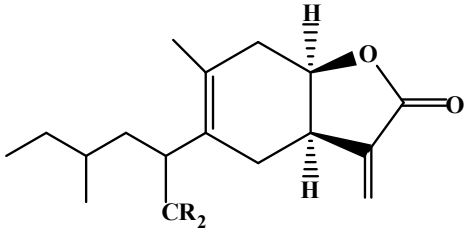


(70)

### *Plant Growth Regulator Activity*

Presence of an α-methylene group in conjugation with the lactone carbonyl is essential for the plant growth regulator activity of the terpenoid lactones.[6] The isolation of a new plant growth regulator, epoxy alantolide, isoinunal (69) from *Inula racemosa* and phytotoxicity of isoalantolactone (2) with respect to seed germination and seedling growth of wheat was assayed. Introduction of hydroxyl group does not affect the root initiation activity whereas ether bridge between $C_4$ and $C_{10}$ increased the root formation manifold in case of dehydrocostus lactone. Stereochemistry was reported to be very specific factor contributing towards biological activity.[62-63]

### *Cytotoxic Activity*

Onion bulbs were exposed to of the *Inula viscosa* extract for macroscopic and microscopic analysis. All the tested extracts have been observed to have cytotoxic effects on cell division in *Allium cepa.*[64] Sesquiterpene lactone (70) isolated from *Inula britannica* displayed cytotoxic activity.[65]

### Perspective

Studies of isolation, reactions, biological and medicinal activities indicated that it will be impossible to find perfect compounds without any side effects in on biological and medicinal activity long time. Therefore, we believe that development of existing compounds in Inula plants could be the best way to discover new biological and medicinal compounds. There are mainly three compounds present in genus Inula plants i.e. alantolactone, isoalantolactone and inunal but the other compounds which are present in lesser quantity may also possess biological and medicinal activity. The transformed compounds may exhibit significant biological activity. As the plant exhibits broad spectrum and significant bioactivities, the compounds could pave a way for commercialization for treatment or control of various diseases.

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