REVIEW

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Chemical constituents and pharmacological properties of Radix Inulae

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Radix Inulae is used as a gastric and antibacterial agent in traditional Chinese and Tibetan medicines. Most of its chemical constituents have been identified and include a series of sesquiterpenes with various carbon skeletons such as: eudesmanolide, elemanolide, germacranolide, sesquicaranolide, guaianolide and humulane. Certain organic solvent fractions and sesquiterpenes from Radix Inulae have been found to significantly inhibit the growth of tumor cell strains *in vitro*. They also show antibacterial, cardiovascular and hypoglycaemic as well as insulin-sensitization activities. The present review summarizes research on the chemistry and biological activity of Radix Inulae.

1. Introduction

Radix Inulae, a commonly used folk medicine called Tu-Mu-Xiang or Zang-Mu-Xiang in Chinese, is the roots of *Inula helenium* L. or *I. racemosa* Hook. f., and belongs to the Asteracea family. According to Traditional Chinese Medicine (TCM) theory, Radix Inulae is pungent and bitter in flavor, warm in nature and attributive to the spleen, stomach and kidney meridians in channel entry; it can strengthen the spleen and stomach, promote circulation of Qi and alleviate pain. Radix Inulae is used to treat upper body pain, emesis and diarrhoea, and to kill parasites in TCM therapy (Jiangsu New Medical College 1985). Meanwhile, Radix Inulae is sweet, bitter and pungent in flavor, and sour and sweet in postdigestive taste according to Traditional Tibetan medicine (TTM); it can cure blood disorders and phlegm fever (Pasang 1999), and is used in the treatment of digestive and cardiovascular system illnesses. Moreover, in some European pharmacopoeias, Radix Inulae is officially listed as a diuretic, diaphoretic, expectorant and anthelmintic remedy (Stojakowska et al. 2005). Furthermore, in combination with other herbal medicines, Radix Inulae can be used clinically to cure diseases of the digestive system, such as chronic constipation, diabetic gastroparesis, gastroesophageal reflux disease, functional dyspepsia *etc.* (Wang 2001).

Extensive chemical research on Radix Inulae began in the 1960's, and many novel compounds were isolated and found to have various biological activities. Recently, more attention has been paid to Radix Inulae because of its diverse chemical constituents and related bioactivities, particularly cytotoxic, antibacterial and cardiovascular activities. However, the chemical constituents and pharmacological activities of Radix Inulae have not yet been compiled. In this paper, all the compounds isolated from Radix Inulae from the 1970's to the present are tabulated and cataloged, and pharmacological and clinical research on the extracts and compounds isolated is also reviewed.

2. Chemical research

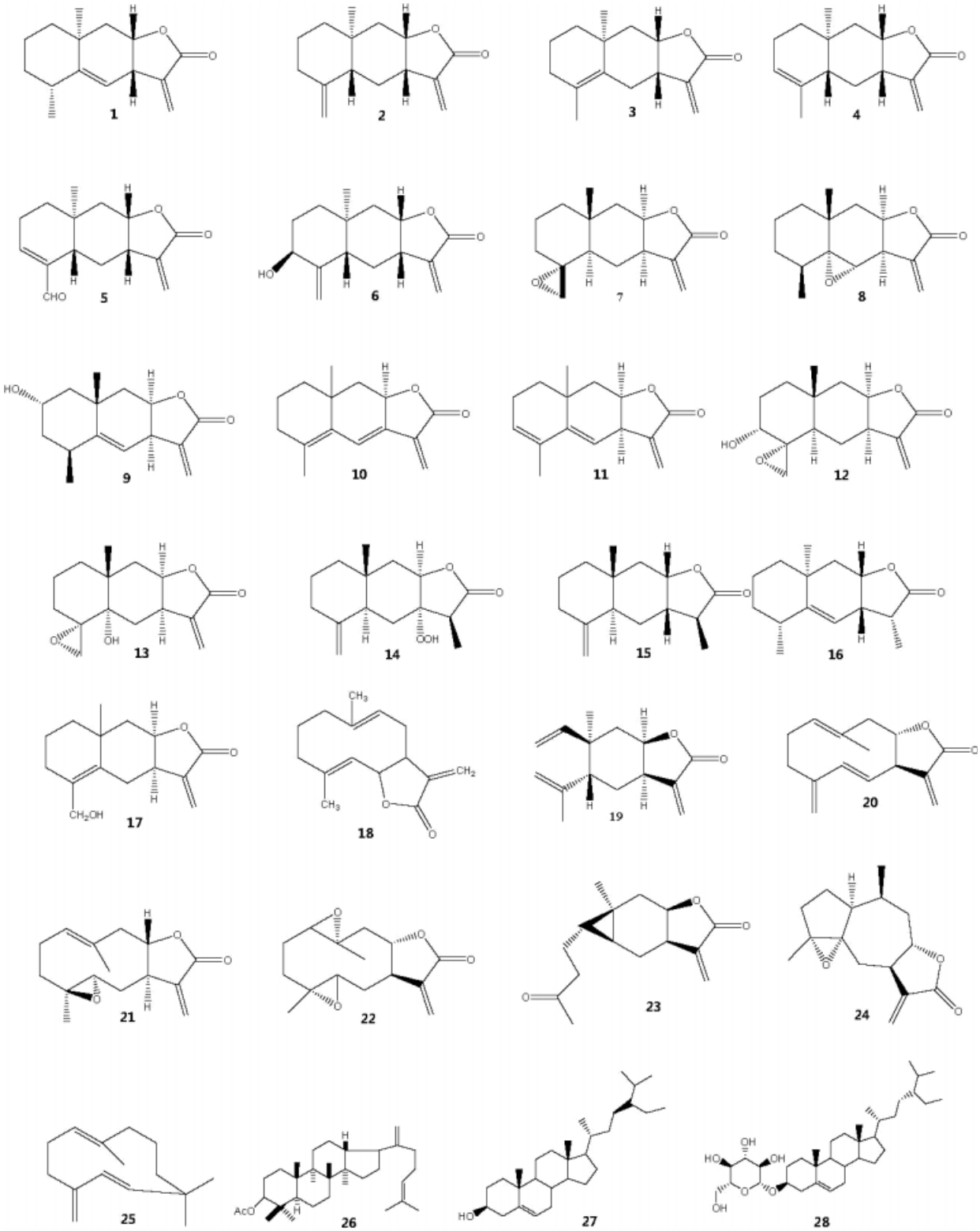
According to the literature, 28 compounds have been isolated from Radix Inulae. Most of them have been confirmed to be sesquiterpenes. Their chemical structures are shown in the scheme below and their names, class and corresponding plant sources are listed in Table 1. These compounds include eudesmanolide (**1–18**), elemanolide (**19**), germacranolide (**20–22**), sesquicaranolide (**23**), guainolide (**24**) and humulane (**25**) sesquiterpenes and several others (**26–28**).

The essential oil from the roots of *I. racemosa* has been investigated and 16 compounds have been identified (Bokadia et al. 1986). The major chemical constituents of the oil were sesquiterpenes (*ca* 60%), of which heptadeca-1,8,11,14-tetraene was the most abundant constituent (*ca* 22%). Table 2 summarizes their names and the relative abundance of the constituents identified from the essential oil. Our comprehensive literature search indicates that no research on the essential oil of *I. helenium* has been reported.

3. Pharmacological and clinical research

Traditionally, *Inula helenium* is used to cure digestive system diseases in China and some European countries. *Inula racemosa* can treat cardiovascular system and digestive system illnesses in traditional Tibetan medicine theory. Both *Inula helenium* and *Inula racemosa* can be utilized as antibacterial and anti-inflammatory agents. Recent work has ascertained their antibacterial activity. Both *I. helenium* and *I. racemosa* have attracted more scientific attention because of their sesquiterpene constituents, which

Scheme Structures of compounds from Radix Inulae



show a broad spectrum of biological activities as discussed below.

3.1. Antibacterial activities

In the 1960's, Olechnowicz et al. first reported the antibiotic activity of *I. helenium* (Olechnowicz et al. 1960). Several years later, they demonstrated that alantolactone isolated from *I. racemosa* showed significant antifungal activity *in vitro*. Wahab et al. selected a strain of *Fusarium solani* (Mart.) Sacc., isolated from a patient with mycotic keratitis, produced experimental keratomycosis in albino rabbit cornea, and observed the survival of internal tissues of albino mice for various time period. They discovered that alantolac-

Table 1: Chemical constituents isolated from Radix Inulae

No.	Compound Class and Name	Source	Ref.
	Eudesmanolides (Sesquiterpenes)		
1	Alantolactone	*I. helenium* *I. racemosa*	Ferdinand et al. 1978; Cantrell et al. 1999
2	Isoalantolactone	*I. helenium* *I. racemosa*	Ferdinand et al. 1978; Cantrell et al. 1999; Tan et al. 1998
3	Alloantolactone	*I. helenium*	Ferdinand et al. 1978
4	Isoalloantolactone	*I. racemosa*	Baljit et al. 1985
5	Inunal	*I. racemosa*	Baljit et al. 1985
6	Isotelekin	*I. racemosa*	Baljit et al. 1985
7	4(15)-Epoxy isoalantolactone	*I. racemosa*	Kalsi et al. 1988
8	5α,6α-Epoxyalantolactone	*I. racemosa*	Kalsi et al. 1988
9	2α-Hydroxy alantolactone	*I. helenium*	Vajs et al. 1989
10	Alantodiene	*I. racemosa*	Kalsi et al. 1989
11	Isoalantodiene	*I. racemosa*	Kalsi et al. 1989
12	4,(15)-α-Epoxyisotelekin	*I. racemosa*	Rita et al. 1990
13	4,(15)-α-Epoxytelekin	*I. racemosa*	Rita et al. 1990
14	7-Hydroperoxy-11αH, 13-dihydro isoalantolactone	*I. racemosa*	Rita et al. 1990
15	11αH,13-Dihydroisoalantolactone	*I. helenium*	Cantrell et al. 1999
16	11αH,13-Dihydroalantolactone	*I. helenium*	Konishi et al. 2002
17	Isoinunal II	*I. racemosa*	Kalsi et al. 1988
18	Isocostunolide	*I. helenium*	Chen et al. 2007
	Elemanolides (Sesquiterpenes)		
19	1,3,11(13)-Elematrien-8β,12-olide	*I. helenium*	Konishi et al. 2002
	Germacranolides (Sesquiterpenes)		
20	1(10),4(15),5(6),11(13)-Germacratetraene-8, 12-olide	*I. helenium*	Ferdinand et al. 1978
21	4β, 5-epoxy-1(10),11(13)-Germacradiene-8, 12-olide	*I. helenium*	Konishi et al. 2002
22	11(13)-Dehydroeriolin	*I. helenium*	Ferdinand et al. 1978
	Sesquicaranolides (Sesquiterpenes)		
23	Carabrone	*I. helenium*	Vajs et al. 1989
	Guaianolides (Sesquiterpenes)		
24	4α,5α-Epoxy-10α-14H-inuviscolide	*I. helenium*	Vajs et al. 1989
	Humulane (Sesquiterpenes)		
25	Isohumulene	*I. helenium*	Ferdinand et al. 1978
	Other compounds		
26	Dammadienol acetate	*I. helenium*	Ferdinand et al. 1978
27	β-Sitosterol	*I. racemosa*	Tan et al. 1998
28	Daucosterol	*I. racemosa*	Tan et al. 1998

tone strongly inhibited the growth of *F. solani* at 100–200 mg/ml (Wahab et al. 1979). Meanwhile, the antibiotic activities of isoalantolactone, another main constituent of Radix Inulae have also been reported. Three compounds from the roots of *I. racemosa*, β-sitosterol, daucosterol and isoalantolactone have been tested for antifungal activity. Isoalantolactone exhibited significant activity against five strains of human pathogenic fungi at different concentrations (Tan et al. 1998). In addition, its antimicrobial activities against five bacteria, six human and six plant pathogenic fungi were reported in 2001. Liu et al. found that isoalantolactone showed very strong toxicities at 500 mg/mL against 3 soil borne phytopathogenic fungi and weaker antibacterial activities against five bacteria. They suggested the lactone could be considered as a lead compound for a project aiming to develop new fungicide(s) (Liu et al. 2001).

Table 2: Constituents of essential oil from the roots of *I. racemosa* (Bokadia et al. 1986)

No.	Components	Relative Abundance (%)
1	p-Cromene	0.4
2	2-Furfural	0.3
3	Norbornyl acetate	0.1
4	Benzaldehyde	0.1
5	Sesquiterpene hydrocarbone	0.3
6	β-Elemene	4.1
7	α-Pinene oxide	0.3
8	α-Humulene	1.0
9	α-Farnesene	0.2
10	ar-Curcumene	1.6
11	Heptadeca-1,8,11-triene	3.1
12	α-Ionone	6.6
13	Heptadeca-1,8,11,14-tetraene	22.0
14	2-Phenylethanol	2.9
15	Phenylacetonitrile	2.1
16	β-Ionone	2.2

Other lactones, such as certain fractions of *I. helenium* root extracts, were also found to have antibiotic activities against *Mycobacterium tuberculosis*. For example, researchers tested the activity of the isolated compounds against *M. tuberculosis* using a radiorespirometric bioassay and found that alantolactone, isoalantolactone and 11αH,13-dihydroisoalantolactone gave MICs of 32, 32, 128 mg/ml, respectively (Cantrell et al. 1999).

Not only compounds from natural plants but also compounds from tissue cultures exhibit antibiotic activities. It was found that 10-isobutyryloxy-8, 9-epoxythymol isobutyrate, a major constituent of *I. helenium* and *I. royleana* root cultures, showed moderate antimicrobial activity against five bacteria strains (Stojakowska et al. 2005). Researchers also observed that some extracts of Radix Inulae displayed strong anti-microorganism activity (Seo et al. 2002; Tosun et al. 2005).

3.2. Cardiovascular activity

Certain extracts or fractions of Radix Inulae have shown cardiovascular activity even though it is still unknown which compounds in the extracts play a key role in this important biological activity. Patel et al. reported that rats given extracts of *I. racemosa* roots had smaller increases in the levels of SGOT, LDH, CPK, cAMP, cortisol, pyruvate, lactate, and glucose than those in an untreated control group. Their results suggested Radix Inulae might have a cardioprotective effect (Patel et al. 1982).

In 2006, four major chemical fractions, A, B, C and D, were collected from *I. racemosa*. The fraction D was shown to decrease heart rate and force of contraction at 40 mg/ml; the action of adrenaline can be blocked by fraction D which also acts as an agonist for propranolol. These studies indicated that fraction D can produce negative ionotropic and chronotropic effects on frog heart (Lokhande et al. 2006).

The cardiovascular activity of Radix Inulae has also been utilized clinically as a remedy in some countries. *I. racemosa* has been used alone or with other medicinal plants clinically for ischemic heart disease. It can improve patients with ST-segment depression on ECG. When combined with *Commiphora mukul*, 26% of the subjects had a complete restoration of normal ECG, while another 59% showed improvement in the ECG at the end of the six-month study period (Singh et al. 1993; Tripathi et al. 1984).

3.3. Cytotoxicity

Konishi et al. observed MeOH extracts and the hexane-soluble fraction of *I. helenium* showed high cell growth inhibitory activities against MK-1, HeLa and B16F10 cell lines. They also determined the antiproliferative activities of seven compounds from the hexane fraction and concluded that the 11, 13-dehydro lactone fraction among these isolated sesquiterpenes contributed to the antiproliferative activity (Konishi et al. 2002). Sixty-one Russian medicinal plants for alleviating symptoms of diseases in cancer patients were investigated (Spiridonov et al. 2005). Researchers found that extracts of *I. helenium* roots possessed marked cytotoxicity at a concentration of 10 mg/mL. The cytotoxicity of helenin (40% alantolactone and 60% isoalantolactone) isolated from *I. helenium* was evaluated along with four pharmaceutical antineoplastic drugs. It was found that helenin suppressed cell growth at concentrations of 1–2 mg/mL, which exceeds the cytotoxicities of cyclophosphamide and fluorouracil.

It is also worth mentioning that extracts of *I. helenium* roots displayed highly selective toxicity toward four different tumor cell lines, but a much lower toxicity against healthy human peripheral blood lymphocytes. They performed extensive studies on the cytotoxicity of the extract by electron microscopy and observed that the morphology of cellular breakdown resembled necrotic rather than apoptotic cell death (Dorn et al. 2006).

Isocostunolide, an interesting compound isolated from the fractions of *I. helenium* roots, could effectively induce apoptosis in three cancer cell lines with an IC_{50} of 3.2, 5.0, and 2.0 μg/mL, respectively. The researchers found the levels of pro-caspase-8, Bid, pro-caspase-3, and poly (ADP-ribose) polymerase (PARP) decreased, but the level of Fas was increased markedly in a dose-dependent manner. They believe this compound induces apoptosis through a mitochondria-dependent pathway in A2058 cells (Chen et al. 2007). We suggest that isocostumolide has great potential to be a lead candidate as an antitumor drug.

3.4. Hypoglycaemic and insulin-sensitization effects

Tripathi et al. observed that the roots of *I. racemosa* can improve glucose metabolism in experimental animals. They suggested that this activity was probably secondary to the potentiation of insulin sensitivity in peripheral tissues (Tripathi et al. 1995). Gholap et al reported that the roots of *I. racemosa* can decrease serum concentrations of the thyroid hormones thyroxine (T4) and triiodothyronine (T3) in corticosteroid-induced hyperglycaemic mice; but no marked changes were observed in thyroid hormone concentrations compared with a standard corticosteroid-inhibiting drug. In their follow-up studies, they found that extracts of *I. racemosa* can decrease the serum concentration of both cortisol and glucose; it is thought that the hypoglycaemic effects of the extracts were mediated through its cortisol inhibiting potency. In their studies, *I. racemosa* was also found to exhibit antiperoxidative, hypoglycaemic and cortisol lowering activities, which suggested that this plant extract may potentially regulate corticosteroid-induced diabetes mellitus (Gholap et al. 2003, 2004).

3.5. Other activities

Additionally, Radix Inulae displays some interesting pharmacological activities such as killing parasites, allergy and so forth in the lab oratory or clinic.

Boiled-water extracts of *I. helenium* showed strong suppressive effects on the egg-laying capacity of *Clonorchis sinensis in vivo*. This extract can also induce morphological changes in the worms (Rhee et al. 1985a; 1985b). Aqueous extracts of *I. helenium* roots orally were able to kill the larvae and eggs of *Ascaris lumbricoides* in less than 40 and 20 days, respectively (El Garhy et al. 2002).

The sensitizing capacity of alantolactone and isoalantolactone have been studied *in vitro* and *in vivo*. It was found that alantolactone was a better sensitizer than isoalantolactone (Stampe et al. 1982; Alonso et al. 1992). There are some other case and epidemiological reports about the allergic effects of extracts of *I. helenium* or herbal-remedies containing *I. helenium* (Pazzaglia et al. 1995; Paulsen et al. 2001, 2002; Aalto-Korte et al. 2007). It is very interesting that alcoholic extracts of *I. racemosa* roots showed an antiallergic effect in experimental models of type I hypersensitivity, viz. egg albumin induced passive cutaneous anaphylaxis (PCA) and mast cell degranulation in albino rats (Srivastava et al. 1999).

4. Summary

Radix Inulae is a traditional herbal medicine widely used in Asia and Europe. Its extracts and isolated compounds have been determined to have very interesting biological activities, suggesting that Radix Inulae could be a lead compound to develop further potential drugs. Even though much of the chemical research on Radix Inulae has focused on its less polar constituents, we believe it is necessary to evaluate all of its chemical constituents systematically as a whole for biological activity. Regrettably, we have not yet found any pharmacological reports about traditional uses of Radix Inulae for the treatment of digestive system diseases.

In China, *I. helenium* and *I. racemosa* roots have been used clinically for a long time; however, the chemical and pharmacological evidence to support its medical applications remains adequate.

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