IVY LEAF

Hedera helix L.

Family

Araliaceae.

Parts Used

Leaf.

Description

Ivy leaf is a popular evergreen climbing plant native to Europe. It is well known as an ornamental and vigorous climber, growing to 20 to 30 metres high where any suitable surfaces (trees, cliffs, walls) are available. However it will also grow as a ground cover where there are no vertical surfaces available. Ivy climbs by means of aerial rootlets which cling to the surface and allow it to spread easily. The leaves are alternate, 50 to 100mm long and occur as either palmately five-lobed juvenile leaves on creeping and climbing stems or unlobed cordate adult leaves on flowering stems exposed to full sun. The greenish-yellow flowers are rich in nectar and found from late summer until late autumn in 3 to 5cm umbels. After flowering a purple-black to orange-yellow berry appears, ripening in late winter. While the berries are an important source of food for many birds they are poisonous to humans.[1]

Traditional Use

Ivy leaf was held in high esteem among the ancients. Its leaves were used to form wreathes, including the wreath of Bacchus (or Dionysus), the Roman God of wine. Ivy leaves were bruised and gently boiled in wine and drunk to reduce the effects of intoxication. 17th Century herbalist

Nicholas Culpeper says "There seems to be a very great antipathy between wine and ivy; for if one hath got a surfeit by drinking wine, his speediest cure is to drink a draught of the same wine wherein a handful of ivy leaves, being first bruised, have been boiled".[2]

Greek priests gave wreathes of ivy to newly-married persons and the ivy has throughout the ages been regarded as the emblem of fidelity. The custom of decorating houses and churches with ivy at Christmas was forbidden by one of the early Councils of the Church, on account of its pagan associations, but the custom still remains. The traditional European indications for ivy leaf were primarily for the respiratory tract. Extracts have been used as antispasmodics and as topical treatments for dermal infections and itching, as well as for weight loss. Ivy leaf also has been traditionally used for arthritis, scrofula, fevers, skin parasites, burns and infections.[3]

Constituents

Saponins: 3 to 4% content including hederasaponin C (hederacoside C), hederaginins and oleanolic acid; flavonoids and phenolics including rutin, quercetin and kaempferol, caffeic acid and dihydroxy-benzoic acid; sterols including stigmasterol, sitosterol cholesterol, campesterol and α-spinasterol; coumarin glycoside scopoline and the polyacetylenes falcarinol and falcarinone; volatile oil including germacrene D, ß-caryphyllene, sabinene and α- and ß-pinene; hamamiletol.[4,5,6]

Actions

Expectorant, antispasmodic, secretolytic, anti-inflammatory and analgesic.

Pharmacological Activity

Respiratory Activity

The results of a 2017 nonrandomised, noninterventional, multicentre, open label, post authorisation effectiveness study (PAES) supports the efficacy of a medicine containing dry ivy leaf extract prescribed for the treatment of productive cough in the course of respiratory tract infections. The study group consisted of 464 patients aged two to 12 years with a productive cough. Improvement in cough was reported in 93.3% of children, improvement in chest pain on coughing was reported in 84.7%, in wheezing in 90%, in difficult breathing in 88.7% and decline or normalisation of body temperature was found in 96%.[7]

A 2016 clinical trial proved consistent superiority of an ivy leaf cough liquid treatment versus placebo and confirmed it to be a safe and efficacious option for the treatment of acute cough. In this randomised, placebo controlled, double blind trial 181 adult patients with acute cough were treated with either ivy leaves cough liquid, or with placebo, three times a day for one week. The study revealed that subjects treated with ivy leaf showed statistically significant and clinically relevant reductions in cough severity and severity of symptoms associated with cough and bronchitis compared to the placebo group. A remarkable early onset of efficacy was observed as significant reductions of cough severity were detected within 48 hours after the first intake of ivy leaf. At all following visits and even seven days after the end of treatment this significant treatment advantage was detected in comparison to placebo.[8]

The mechanism of the expectorant and secretolytic activity (increasing the production of serous mucus in the respiratory tract and making the phlegm thinner and less viscous) of ivy observed in clinical practice has not been established experimentally yet. It is hypothesised that it is probably sub-emetic doses of saponins that activate a gastro-pulmonary mucokinetic (clearing mucous) vagal reflex, which stimulates the bronchial glands to secrete a watery fluid.[9]

Ivy leaf extract in the form of syrup, and of cough drops, was confirmed as an effective and safe treatment of cough in children in a 2012 study. Two galenical formulations of an ivy herbal extract, syrup and cough drops were tested for their efficacy and safety in the paediatric treatment of cough and bronchitis in two independent open, non-interventional studies with identical design. Two-hundred and sixty-eight children aged 0 to 12 years were treated with one of the two preparations for up to 14 days. The effects on cough-related symptoms were addressed on a verbal rating scale. At the end of the study the

major symptoms rhinitis, cough and viscous mucus, were found to be only mildly expressed or absent in 93, 94.2 and 97.7% of cases. The global effect was rated as 'good' or 'very good' in 96.5% of cases. Tolerability and compliance were found 'good' to 'very good' in 99% (syrup) and 100% (drops) of patients on completion of the study. A subgroup analysis according to four different age and dosing groups did not reveal differences in treatment response. Safety was confirmed and corresponded to literature findings. Five adverse events classified as mild and non-serious were reported (1.9%).[10]

Ivy is mostly used for the treatment of bronchial inflammatory diseases as well as asthma, particularly in European countries, although the drug's efficacy has not been documented with placebo controlled clinical and experimental studies that have appropriate methodology. Ivy has been widely used to treat bronchial asthma for many years and preclinical studies show that ivy leaf extracts have spasmolytic, bronchodilating and antibacterial effect which is mainly attributable to the triterpene saponins contained in them. However effects of this herb on lung histopathology are still far from clear. A 2012 study aimed to determine the effect of oral administration of ivy on lung histopathology in a rodent model of chronic asthma. Analysis of the lungs showed that goblet cell hyperplasia markedly decreased in ivy–treated mice. As goblet cell hyperplasia and associated mucous hypersecretion is a pathophysiological feature of asthma, treatment with compounds that alter mucus and decrease goblet cells like ivy could serve as therapeutic options for this disease. Mice were divided into four groups; I (Placebo), II (ivy), III (Dexamethasone) and IV (Control). All mice except controls were sensitised and challenged with ovalbumin (egg white protein). Then mice in group I received saline, group II 100 mg/kg ivy and group III 1 mg/kg dexamethasone, once daily for one week. Goblet cell numbers and thicknesses of basement membrane were found significantly lower in group II, but there was no statistically significant difference in terms of number of mast cells, thicknesses of epithelium and subepithelial smooth muscle layers between group I and II. When ivy and dexamethasone groups were compared with each other, thickness of epithelium, subepithelial muscle layers, number of mast cells and goblet cells of group III were significantly ameliorated when compared with the group II. Although ivy administration reduced only goblet cell counts and the thicknesses of basement membrane in the asthmatic airways, dexamethasone ameliorated all histopathologic parameters except thickness of basement membrane better than ivy. The study had some important limitations. First of all, the level of cytokines which has an important role in asthma pathogenesis could not be evaluated. Small numbers of animals were used for this project and finally, the results found may not translate to positive findings in human clinical trials.[11]

Ivy leaves extracts are authorised in medicinal products for the treatment of acute bronchitis. Different studies and the long experience on the market show safety and efficacy of this drug. A double-blind, randomised study was conducted to assess the efficacy and tolerability of ivy leaves soft extract with another ivy leaf extract. 590 patients with acute bronchitis participated in this study. They were treated with test or comparator for seven days. The Bronchitis Severity Score (BSS) decreased gradually and to a similar extent from day one to day seven in both treatment groups. The BSS subscales cough, sputum, rales/rhonchi, chest pain during coughing and dyspnoea improved to a similar extent in both treatment groups.[12]

Recently it was reported that 9657 patients (5181 children) with bronchitis (acute or chronic bronchial inflammatory disease) were treated with a syrup containing dried ivy leaf extract in a postmarketing study and after seven days of therapy, 95% of the patients showed improvement of their symptoms.[13]

An earlier study evaluated the results of three studies that investigated effects of extracts from dried ivy leaves in the treatment of chronic airway obstruction in children suffering from bronchial asthma. They reported that ivy leaf extract preparations improve lung function in children with bronchial asthma.[14]

A systematic review was conducted to assess the effectiveness and tolerability of ivy for acute upper respiratory tract infections (URTIs). All studies reported that ivy extracts were effective to reduce symptoms of URTI, however the evidence was marred by serious methodological flaws and lack of placebo controls. It has to be taken into account that other popular cough medications, for example,

acetylcysteine and other OTC antitussives and decongestants, also lack a sound evidence base.[15]

It was recently claimed that the secretolytic and bronchodilating properties found in ivy are due to its saponins, particularly alpha-hederin as an inhibitor of the B2 receptors endocytosis, establishing an indirect B2 sympathomimetic action.[16]

A trial looked at the changes in the symptoms of cough after treatment with a combined herbal preparation containing dry ivy leaf extract as the main active ingredient, decoction of thyme and aniseed, and mucilage of marshmallow root. The 62 patients in the study had either irritating cough as a consequence of common cold, bronchitis or respiratory tract diseases with formation of viscous mucus. The mean daily intake was 10mL and duration of treatment averaged 12 days. Treatment results were assessed on the basis of changes in the symptom scores for cough and expectoration and safety, efficacy and tolerability were also analysed from the judgments of the doctors and patients. There was an improvement in symptom scores with 86 to 90% of patients claiming good or very good results while tolerability was good or very good in 97% of patients.[17]

Commercial dry extract of ivy used for the treatment of disorders of the respiratory tract is often standardised towards papaverine, which was shown to be an antispasmodic constituent in the gastrointestinal tract. However, researchers investigated other fractions and isolates for antispasmodic activity and their contribution to the activity of the extract was calculated. Significant antispasmodic activity was found *in vitro* for both saponins and phenolic compounds in ivy though, in view of their relative high concentration, the saponins contribute most to the anti-spasmodic activity followed by dicaffeoylquinic acids and the flavonol derivatives.[18]

Anti-inflammatory Activity

In 2013 an ethanolic ivy extract was tested for its anti-inflammatory properties. The visible reduction in arthritic symptoms due to ivy suggests the potential of the plant extract against inflammation and arthritis. Intraperitoneal injections of 7.5ml/kg weight ethanol extract showed anti-inflammatory activity with 88.89% inhibition as compared to the reference drug diclofenac, which showed 94.44% inhibition in formalin-induced paw oedema. As formalin-induced paw oedema closely resembles human arthritis, the anti-arthritic property of ethanol extract of ivy was also investigated.[19]

The anti-inflammatory potential of constituents from ivy was investigated and compared to the drug indomethacin in induced acute paw oedema in rats. In the first phase of inflammation the ivy constituents were ineffective, unlike indomethacin, however in the second phase of inflammation the ivy isolate hederasaponin-C was shown to be an effective anti-inflammatory, possibly by blocking bradykinin or prostaglandin pathways.[20]

The methanolic extract of ivy leaves showed significant analgesic and anti-inflammatory activities that were comparable to the test drugs (morphine 20mg/kg and indomethacin 50mg/kg respectively). The findings suggest that the methanolic leaf extract of ivy possesses analgesic (which may be peripherally mediated) and anti-inflammatory activities possibly through an antihistamine action. Based on the results of the study the authors concluded that the methanolic extracts of ivy leaf have potential dose-dependent analgesic and anti-inflammatory activities. Hence this study has confirmed the use of the plant in traditional medicine as a pain reliever in the treatment of headache, backache, as an aid in child birth and in the treatment of inflammatory diseases such as haemorrhoids, rheumatism and chronic gout.[21]

Triterpene and steroid saponins, and sapogenins, of medicinal plants ivy, horse chestnut (*Aesculus hippocastanum* L.), and butcher's broom (*Ruscus aculeatus* L.) are claimed to be effective for the treatment/prevention of venous insufficiency. Researchers evaluated the inhibitory effects of these plant constituents on the activity of elastase and hyaluronidase. The sapogenins of ivy were found to non-competitively inhibit hyaluronidase activity in a dose dependent fashion, while both the saponins hederacoside C and alpha-hederin were very weak inhibitors.[22]

The possible anti-inflammatory effects of a crude saponin extract (CSE) and saponin purified extracts (SPE) of ivy leaf were assessed in acute and chronic inflammation models in rats. Both the CSE and SPE of ivy were found to have anti-inflammatory

effects. The herb was found to exert 77% acute anti-inflammatory effects compared with the anti-inflammatory drug indomethacin which yielded an 89.2% acute anti-inflammatory effect.[23]

Saponins isolated from ivy have also been shown to possess antioxidant activities.[24]

Antiviral, Antiparasitic and Antifungal Activity

A 2014 study has discovered that hederasaponin B and ivy containing hederasaponin B could be novel drug candidates with broad-spectrum antiviral activity against various subgenotypes of enterovirus 71 (EV71), the predominant cause of hand, foot and mouth disease (HFMD). The antiviral activity of hederasaponin B from ivy against EV71 subgenotypes C3 and C4a was evaluated. The results demonstrated that hederasaponin B and 30% ethanol extract of ivy containing hederasaponin B showed significant antiviral activity against EV71 subgenotypes C3 and C4a by reducing the formation of a visible CPE. Hederasaponin B also inhibited the viral VP2 protein expression, suggesting the inhibition of viral capsid protein synthesis.[25]

Cutaneous leishmaniasis (CL) is common and endemic in many areas of Iran caused by a species of a protozoan parasite belonging to the genus Leishmania. There is not any effective vaccine against leishmaniasis so therapy is important for prevention and separation of disease. Herbal extracts for treatment of CL is cost-effective, applicable topically to lesions and can avoid the development of drug resistance. The aim of a 2014 study was to evaluate the *in vivo* activity of an alcoholic extract of ivy on the experimental ulcer of CL in mice. This study showed that the main lesion size did not decrease significantly, or the small lesions did not completely disappear after treatment by ivy. The study did not support the *in vivo* antileishmanial effect of ivy. The authors recommended further studies using major components of ivy, especially hederasaponin (saponin K10), to investigate the antileishmanial effect of this plant on Leishmania.[26]

An earlier study investigated the *in vitro* antileishmanial activity of three saponins isolated from ivy, alpha-hederin, beta-hederin and hederacolchiside A1. Results observed in Leishmania showed that the saponins exhibited a strong antiproliferative activity on all stages of development of the parasite by altering membrane integrity and potential: hederacolchiside A1 appeared to be the most active compound against both promastigotes and amastigotes. Results observed in human monocyte cells demonstrated that the saponins exerted also a potent antiproliferative activity against human monocytes by producing a significant DNA synthesis inhibition. The ratio between antileishmanial activity on amastigotes and toxicity to human cells suggested that the saponins could be considered as possible antileishmanial drugs.[27]

Ivy has been studied for antifungal activity and anthelmintic activity on liver flukes.[28,29]

Anticancer and Hepatoprotective Activity

The findings of a 2014 study suggest that hederagenin, a derivative of oleanolic acid isolated from the leaves of ivy, might be a promising therapeutic candidate for human colon cancer. Colorectal cancer has become one of the leading causes of cancer morbidity and mortality throughout the world. Hederagenin has been shown to have potential anti-tumour activity. The study was conducted to evaluate whether hederagenin could induce apoptosis of human colon cancer LoVo cells and explore the possible mechanism. The results indicated that the disruption of mitochondrial membrane potential might contribute to the apoptosis of hederagenin in LoVo cells.[30]

Researchers analysed the effects of the saponin, alpha-hederin, from ivy leaf, on mouse B16 melanoma cells and non-cancer mouse fibroblasts *in vitro*. They found that alpha-hederin is cytotoxic and inhibits proliferation in both cell lines at rather low concentrations (< 5 micrograms/mL) after only eight hours of treatment. The cytotoxicity decreased in the presence of serum due to binding of the saponin. Alpha-Hederin also induces vacuolisation of the cytoplasm and membrane alterations leading to cell death.[31]

The saponin alpha-hederin from ivy leaf was also examined in liver cancer cells and could suppress gene expression in cancer cells or antagonise the DNA binding potential of a nuclear Ah receptor.[32]

Ivy leaf may also help support liver health through protecting liver cells from damage. Components of ivy leaf, sapindoside and fulvotomentoside alpha-

hederin, prevented liver damage from paracetamol via decreased depletion of glutathione dependent enzymes and increased clearance of the drug in the urine.[33] Another study found the treatment of mice with alpha-hederin decreases the levels and activities of several P450 enzymes. The suppression of P450 appears to be one of mechanisms by which alpha-hederin protects mice from the hepatotoxicity of some chemicals.[34]

Antiulcer Activity

A comparative 2013 phytochemical study of the biologically active water extracts of ivy and *H. colchica*, and evaluation of their ulcer preventive efficacy in ethanol-induced ulcer model in rats was carried out. Water extracts of *H. colchica* and ivy (300mg/kg, i.p.) significantly ($p < .01$) decrease the ulcer index (0.50 and 1.38 vs 3.17 in control) and rise macroscopic curative ratio (84.2% and 56.6%, respectively).[35]

Indications

- Respiratory disorders including:
  - cough associated with the common cold
  - asthma
  - acute and chronic bronchitis
- Inflammation and pain disorders such as:
  - arthritis
  - gout
  - headache

Energetics

Drying.

Use in Pregnancy

Not recommended.

Contraindications

No serious adverse events with a therapeutic dose of the herbal preparations are reported in literature, or reference sources, with a well-documented history.

Drug Interactions

None known.

Administration and Dosage

Liquid Extract:	1:2
Alcohol:	30%
Weekly Dosage:[36]	5 to 10mL

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