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IVY LEAF (*HEDERA HELIX*): PHYTOCONSTITUENTS, THERAPEUTIC POTENTIAL & PHARMACOLOGICAL ACTIVITIES – AN INTEGRATIVE REVIEW

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ABSTRACT: *Hedera helix* L. (commonly known as ivy leaf), belonging to the Araliaceae family, is a widely acknowledged medicinal plant that has been traditionally utilized for treating respiratory conditions, especially productive cough, bronchitis, and inflammatory airway issues. The therapeutic benefits of ivy leaf are primarily due to its abundant phytochemical constituents, which include triterpene saponins (such as α -hederin, hederacoside C, and hederasaponins), flavonoids (including rutin, quercetin, and kaempferol), phenolic acids (like chlorogenic acid and caffeic acid), coumarins, sterols, volatile oils, and various other antioxidant components. These bioactive substances are responsible for a range of pharmacological effects, including bronchodilation, mucolytic action, expectorant properties, anti-inflammatory effects, antimicrobial activity, antitussive effects, and antioxidant capabilities. From a mechanistic perspective, α -hederin improves the responsiveness of β_2 -adrenergic receptors by preventing their internalization, which results in elevated levels of intracellular cyclic AMP, relaxation of airway smooth muscles, and enhanced mucus clearance. Standardized extracts of ivy leaf, particularly dry hydroethanolic formulations like EA 575®, have shown clinical effectiveness in managing both acute and chronic bronchitis, upper respiratory tract infections, and cough-related disorders in individuals of all ages. A variety of dosage forms, including syrups, drops, tablets, effervescent tablets, and combined herbal preparations, are available on the market. Techniques for extraction and standardization, such as hydroalcoholic extraction and HPLC analysis, are crucial for maintaining consistent quality, safety, and phytochemical content. Toxicological assessments reveal a favorable safety profile when used at recommended dosages, with mild gastrointestinal disturbances and infrequent allergic reactions being the most commonly noted adverse effects. The overall review demonstrates that *Hedera helix* possesses a broad spectrum of bioactive phytoconstituents responsible for multiple pharmacological activities, including respiratory, anti-inflammatory, antimicrobial, antioxidant, anticancer, and immunomodulatory effects. Advances in extraction, standardization, formulation, and safety evaluation further support its therapeutic potential and justify continued research into its clinical applications.

INTRODUCTION: Leaves of *Hedera helix* (ivy) have long been used to treat productive cough and chronic inflammatory bronchitis.

Its therapeutic effects are believed to come from a variety of active compounds that may work together in additive or even synergistic ways.

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This comparative study aimed to analyze the composition of key bioactive components such as flavonoids, phenolic acids, triterpene saponins, amino acids, and fast-acting antioxidants¹. The therapeutic effects of ivy leaves are mainly attributed to a rich variety of bioactive compounds. These include triterpene saponins such as α -

hederin, hederasaponin C, hederacoside E, and hederacoside F. Pharmacological studies have shown that ivy leaf extracts possess multiple beneficial actions, including mucolytic (mucus-thinning), antispasmodic, bronchodilator, and antibacterial effects. Because of these properties, they are commonly used in the treatment of productive cough, upper respiratory tract infections, and chronic inflammatory bronchial conditions². The bronchodilatory (bronchospasm-relieving) and mucus-clearing (secretolytic) effects of dry extracts from ivy leaves can be explained by their ability to enhance the responsiveness of β_2 -adrenergic receptors in the airways. Recent studies have shown that α -hederin helps prevent the internalization of β_2 -adrenergic receptors (β_2 AR) when they are stimulated. As a result, more receptors remain active on the cell surface. In experiments, cells pre-treated with α -hederin such as alveolar type II cells and human airway smooth muscle cells showed increased binding of β_2 AR and a higher level of intracellular cyclic AMP (cAMP), which is a key messenger involved in relaxing airway muscles and improving mucus clearance³.

Taxonomical Classification⁴:

Kingdom: Plantae

Division: Magnoliophyta (Angiosperms)

Class: Magnoliopsida (Dicotyledons)

Order: Apiales

Family: Araliaceae

Genus: Hedera

Species: *Hedera helix*

Plant Description: *Hedera helix* L. (ivy leaf) is a perennial, evergreen woody climber belonging to the family Araliaceae. *Hedera helix* L., sometimes known as common ivy (CI), is an evergreen vine that clings to walls, fences, tree trunks, and other vertical surfaces. Because CI reduces the effects of urban heat islands and enhances urban air quality, governments in Europe have advised planting it in urban areas. These vertical greenery systems would need to be regularly trimmed in order to produce a potentially intriguing new biomass resource for

urban biorefinery concepts. Additionally, CI extracts include pharmaceutically active substances including α -hederin and hederacoside C, which are the active ingredients of cough syrups that are sold commercially⁵.

Hedera L. taxa's trichomes have long been a crucial feature in species delineation. *Hedera* has two different types of trichomes: stellate and scale-like.

Using scanning electron microscopy, this study investigated the trichome variation in sixteen currently identified *Hedera* taxa. Trichome morphology measurements were made, and differences between taxa were analysed. *H. maderensis* Rutherford subsp. *maderensis* has the longest rays, the biggest fusion of rays, and the longest overall length among the taxa having scale-like trichomes.

In addition to having the longest and widest rays among the species with stellate trichomes, *H. helix* has the largest overall⁶.



FIG. 1:

Botanical Assessment: *Hedera helix* L. is a climbing species that belongs to the Araliaceae family. It is a perennial plant that reaches heights of 20 to 30 meters. The development can occur at ground level as ground cover, or upward if there is an appropriate support (vertical surfaces like trees, walls, or rocks) to which it attaches itself using aerial roots. Ivy thrives in soils with varying pH levels but favors a neutral condition (optimal pH = 6.5).

It favors damp, shaded areas and cannot withstand harsh, direct sunlight; variations in climate affect the growth of ivy in wooded regions.

The leaves are arranged alternately, measuring between 5 –10 cm in length, and consist of two varieties: juvenile leaves (palmate, with five lobes, found on creeping and climbing stems) and adult leaves (cordate, unlobed, present on fertile flowering stems).

The flowers have an umbel shape with a diameter of 3 –5 cm, and the fruits are purple-black, measuring 6 –8 mm in diameter ⁷.

Ayurvedic Significance: Traditional families in the Himalayan foothills used hemp-like braided ivy vines as temporary splints for broken limbs, according to post-independence research in India. This practice was based more on practical immobilization than chemical action, though some Ayurvedic elders claimed that topical application of a hot ivy leaf pastes simultaneously reduced swelling more quickly than standard bandaging alone.

The fact that these tales persisted in oral traditions and were occasionally documented in local gazettes serves as a reminder of how dynamic and regionally specific the story of *Hedera helix* truly is ⁸. In the Ayurvedic medicinal system, ivy leaf has the following characteristics:

Guna (Quality): Laghu, Ruksha, Tikshna

Rasa (Taste): Tikta

Vipaka (post-digestive effect): Katu

Virya (Potency): Ushna

Prabhav (Specific action): Hridya

Phytoconstituents of *Hedera helix*: The preliminary phytochemical analysis of *Hedera helix* indicated that the plant comprises unsaturated sterols, tannins, phenolic compounds, terpenoids, glycosides, alkaloids, flavonoids, carbohydrates, reducing sugars, and saponins ^{9, 10, 11}. The chemicals included triterpene saponins such as helixoside A, helixoside B, 3-O- β -glucosyl hederagenin, 3-O- β -glucosyl-(9 $\rightarrow$ 10)- β -glucosyl oleanolic acid, and 3-O- β -glucosyl-(9 $\rightarrow$ 10)- β -glucosyl hederagenin staunoside A (3-O- β -glucosyl-28-O- β -glucosyl-(9 $\rightarrow$ 14)- β -glucosyl hederagenin); polyacetylenes like falcarinon, falcarinol, and panaxidol ((Z)-9, 10-epoxy-1-heptadecene-4,6-diyn-3-one); fatty acids including petroselinic, oleic, cis-vaccenic, and palmitoleic; as well as β -lectins ^{12, 13}.

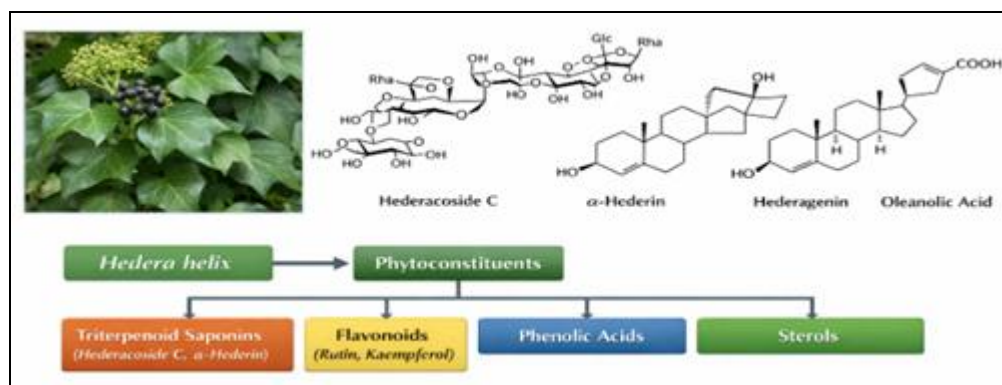


FIG. 2: PHYTOCONSTITUENTS OF *HEDERA HELIX*

In contrast, the chemical groups derived from the plant are triterpene saponin derivatives such as hederagenin, oleanolic acid, bayogenin (2 β -OH-hederagenin), hederasaponin C (=hederacoside C), and hederasaponins B, D, E, F, G, H, and I, along with hederasaponin A, 3-sulfates of oleanolic acid ^{14, 16, 17} and echinocystic acid, and 3-sulfate of 28-O- β -gentiobiosyloleanate = helicoside L-8a; monodesmosides like α -hederin and hederagenin 3-O- β -glucoside; volatile oils such as germacrene B,

β -elemene, γ -elemene (elixin), methylethyl ketone, methylisobutyl ketone, trans-2-hexanal, trans-2-hexanol, germacrene D, β -caryophyllene, sabinene, α -, β -pinene, limonene, and furfural; ^{14, 15, 20} phenolic acids including caffeic, chlorogenic (5-O-caffeoylquinic), neochlorogenic (3-O-caffeoylquinic), 3,5-O-dicaffeoyl-quinic, 4,5-O-dicaffeoyl-quinic, and rosmarinic [(R)-(+)-enantiomer]; dihydroxybenzoic, protocatechuic, and p-coumaric acids; ^{14, 15, 17} flavonoids such as

quercetin, kaempferol, rutin (quercetin 3-O-rutinoside), isoquercitrin (quercetin 3-O-glucoside), astragalin (kaempferol 3-O-glucoside), and kaempferol 3-O-rutinoside;¹⁸ coumarins like scopolin (scopoletin 7-O-glycoside);¹⁵

polyacetylenes including faltarion, faltarinol, and 11,12-dehydrofaltarinol;^{14, 15, 19} anthocyanin: cyanidin 3-monoside;¹⁴ and sterols such as cholesterol, campesterol, stigmasterol, sitosterol, and α -spinasterol;^{14, 15} 5 α -stigma-7-en-3 β -ol; A.

TABLE 1:

Part	Class of Compounds	Compounds
Leaves	Triterpene saponins	Hederasaponin C (hederacoside C), Hederasaponins B, D, E, F, G, H, I; Hederasaponin A; α -hederin; Hederagenin 3-O- β -glucoside; Derivatives of hederagenin, oleanolic acid, bayogenin
	Flavonoids	Quercetin, Kaempferol; Rutin, Isoquercitrin, Astragalin, Kaempferol 3-O-rutinoside
	Coumarins	Scopolin (Scopoletin 7-O-glycoside)
	Polyacetylenes	Faltarion, Faltarinol, 11,12-dehydrofaltarinol
	Phenolic acids	Caffeic, Chlorogenic, Neochlorogenic, Dicafeoyl-quinic acids, Rosmarinic acid, Protocatechuic, p-coumaric
	Anthocyanins	Cyanidin 3-monoside
	Sterols	Cholesterol, Campesterol, Stigmasterol, Sitosterol, α -spinasterol
Stems	Volatile oil	Germacrene B, β -elemene, γ -elemene, Methyl ethyl ketone, Methylisobutyl ketone, trans-2-hexanal, Germacrene D, β -caryophyllene, Sabinene, α -pinene, β -pinene, Limonene, Furfural
	Saponins	α -Hederin, Hederacoside C (Hederasaponin C), Hederagenin, Hederasaponins B-I
	Sterols	β -Sitosterol, Stigmasterol, Campesterol
Fruit	Phenolic compounds	Chlorogenic acid, Caffeic acid, Neochlorogenic acid
	Triterpene saponins	helicoside A (3-O- β -glucosyl-(1 $\rightarrow$ 2)- β -glucosyl-28-O- β -glucosyl -(1 $\rightarrow$ 6)- β -glucosyl hederagenin), helicoside B (oleanolic acid 3-O- β -glucosyl-(1 $\rightarrow$ 2)- β -glucosyl 28- O- β -glucosyl-(1 $\rightarrow$ 6)- β -glucosyl, 3-O- β -glucosyl hederagenin, 3-O- β -glucosyl-(1 $\rightarrow$ 2)- β -glucosyl oleanolic acid, 3-O- β -glucosyl-(1 $\rightarrow$ 2)- β -glucosyl hederagenin, stenoside A (3-O- β -glucosyl- 28-O- β -glucosyl-(1 $\rightarrow$ 6)- β -glucosyl hederagenin)
	Fatty acids polyacetylenes	petroselinic, oleic, cis- vaccenic, palmitoleic faltarion, faltarinol, panaxidol ((Z)-9,10-epoxy-1-heptadecene-4,6-diyn-3-one)

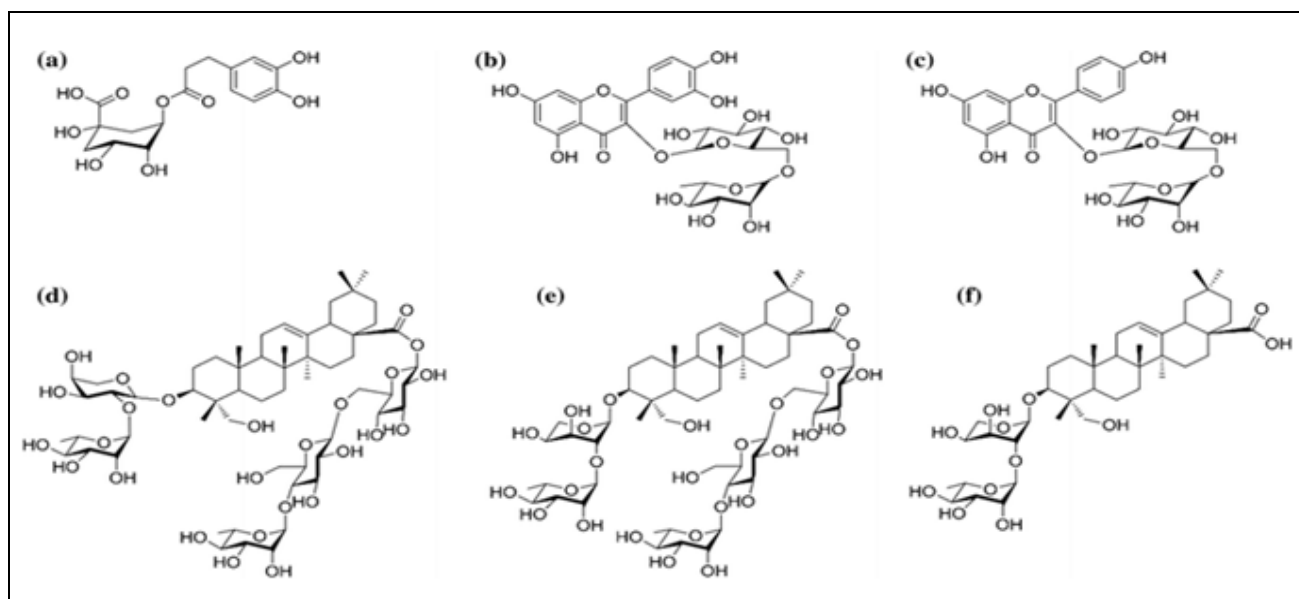


FIG. 3: STRUCTURES OF SIX COMPOUNDS: A CHLOROGENIC ACID, B RUTIN, C NICOTIFLORIN, D HEDERACOSIDE C, E HEDERASAPONIN B, AND FA-HEDERIN FROM LEAVES OF *HEDERA HELIX* L.

Therapeutic Potential and Pharmacological Activities:

Respiratory Activity: The respiratory benefits of *Hedera helix* are mainly linked to its active

saponin, α -hederin, which shows strong bronchodilatory activity. Experimental studies suggest that α -hederin enhances airway relaxation indirectly by improving the responsiveness of β 2-

adrenergic receptors. It appears to prevent receptor internalization and desensitization, especially under conditions of high muscarinic stimulation, thereby maintaining receptor availability and increasing intracellular cyclic AMP levels. This ultimately supports smooth muscle relaxation in the airways^{21, 22, 23}.

Animal studies further support these findings, showing that ivy leaf extracts can reduce bronchoconstriction triggered by allergens such as ovalbumin and inflammatory mediators. In addition, α -hederin has demonstrated anti-inflammatory effects by lowering cytokines like IL-17 and regulating gene expression involved in airway remodeling. Histological observations in asthma models revealed reduced mucus-secreting goblet cells and decreased thickening of airway structures following treatment^{24, 25, 26}.

Clinical evidence aligns with these experimental results. Trials in patients, particularly children with asthma or bronchitis, have reported improvements in lung function parameters such as expiratory flow rates and vital capacity. Large observational studies also indicate that ivy leaf preparations help reduce cough severity, mucus production, and airway resistance, with good safety and tolerability. Combinations with other herbal agents, such as thyme, have shown enhanced effectiveness in reducing symptoms of bronchitis and improving overall respiratory health^{27, 28, 29}.

Anti-Inflammatory and Analgesic Activity: *Hedera helix* also demonstrates notable anti-inflammatory activity. Experimental studies show that its extracts can significantly reduce inflammation, with effects comparable to standard anti-inflammatory drugs such as Diclofenac in certain models³⁰. Both crude and purified saponin extracts have been effective in reducing acute and chronic inflammation, suggesting that different constituents may contribute to different stages of the inflammatory response³¹. Studies using animal pain models indicate that various solvent fractions, particularly chloroform and aqueous extracts, can reduce pain responses effectively. These effects are likely due to the combined action of saponins and phenolic compounds, which may interfere with inflammatory mediators and pain signaling pathways³².

Anti-Cancer Activity: Research into the anticancer potential of *Hedera helix* has shown promising results, particularly in laboratory-based studies. Extracts of the plant have demonstrated cytotoxic effects in screening assays and have been shown to inhibit the growth and proliferation of cancer cells^{33, 34}. Compounds such as α -hederin, hederagenin, and β -amyrin appear to play important roles in these effects.

These compounds can induce programmed cell death (apoptosis) through mechanisms involving oxidative stress and regulation of key apoptotic proteins^{35, 36}. (Additionally, α -hederin has been reported to enhance the effectiveness of certain chemotherapy drugs, including 5-Fluorouracil, suggesting a possible role as an adjunct in cancer treatment. However, these findings are largely preclinical and require further validation in human studies^{37, 38}.

Antimicrobial and Antiviral Activity: *Hedera helix* possesses a broad range of antimicrobial properties. They have been shown to act against both Gram-positive and Gram-negative bacteria, as well as fungal organisms³⁹. The antibacterial effects are particularly evident in methanolic and ethyl acetate extracts, while α -hederin exhibits strong antifungal activity, especially against *Candida* species^{40, 41}. In terms of antiviral activity, ivy extracts have demonstrated the ability to enhance the effectiveness of antiviral drugs such as Oseltamivir in influenza models^{42, 43}. This combination has been associated with reduced viral replication and inflammation. Certain compounds, such as hederasaponin B, also show direct antiviral effects by interfering with viral protein synthesis, indicating multiple mechanisms of action^{44, 45}.

Anti-Parasitic Activity: The antiparasitic activity of *Hedera helix* is mainly attributed to its saponin content. Studies have shown that these compounds are effective against protozoan parasites such as *Leishmania* species^{46, 47}. Additionally, the plant exhibits anthelmintic activity against parasitic worms such as *Haemonchus contortus*. Experimental studies indicate reductions in egg counts and parasite load following treatment, although results may vary depending on dosage and experimental conditions^{48, 49}.

Anti-oxidant Activity: *Hedera helix* shows significant antioxidant potential, primarily due to its phenolic compounds and saponins. Various extracts have demonstrated strong free radical scavenging activity in laboratory assays, particularly those obtained using methanol and ethyl acetate^{50, 51}.

Furthermore, certain saponins, including α -hederin, have been shown to inhibit lipid peroxidation, which is an important mechanism in preventing cellular damage caused by oxidative stress. These properties highlight the potential of *Hedera helix* in managing oxidative stress-related conditions⁵².

Effects on the Digestive System: The plant also exerts notable effects on the gastrointestinal system. Studies have shown that aqueous extracts of *Hedera helix* can protect against gastric ulcers, significantly reducing ulcer formation in experimental models. This suggests a possible cytoprotective effect on the gastric mucosa^{53, 54}. In addition, α -hederin influences gastrointestinal motility by promoting smooth muscle contraction through calcium influx mechanisms. Interestingly, the plant also exhibits antispasmodic activity in certain models, indicating that its effects on gut

motility may vary depending on concentration and context. These dual actions are likely due to the presence of both saponins and phenolic compounds^{55, 56}.

Antimutagenic and Immunomodulatory Activity: α -Hederin has shown the ability to counteract mutagenic effects caused by certain chemical agents, including Doxorubicin. This protective effect may be related to the activation of detoxifying enzymes that reduce DNA damage^{57, 58}.

In addition, ivy leaf extracts exhibit immunomodulatory properties. Studies have shown that they can reduce the production of pro-inflammatory cytokines such as IL-6 in immune cells, suggesting potential benefits in inflammatory and immune-related conditions, particularly those affecting the respiratory system^{59, 60}.

Anti Thrombin Activity: Some fractions of *Hedera helix* have demonstrated moderate antithrombin activity in laboratory studies. Compounds such as β -amyrin, stigmasterol, and hexadecanoic acid appear to contribute to this effect⁶¹.

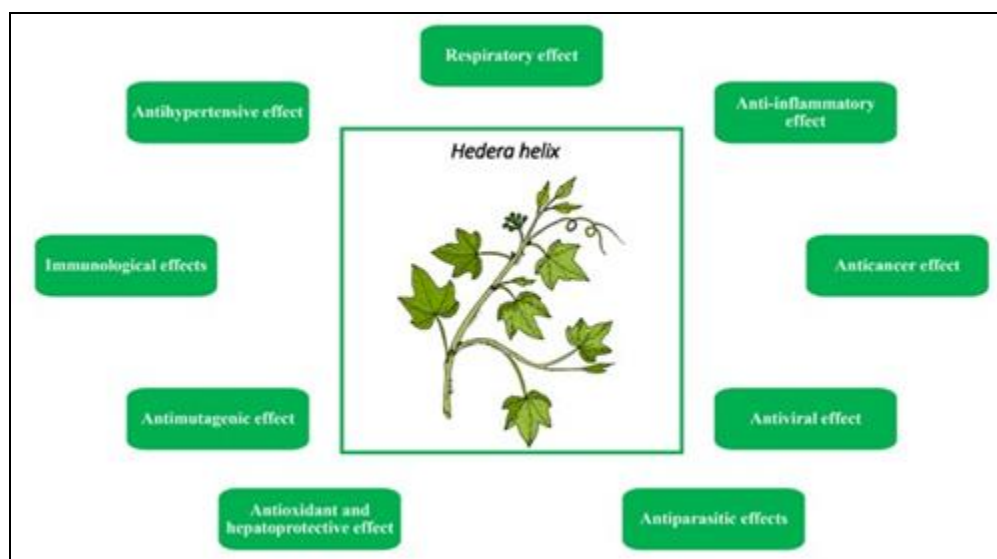


FIG. 4: THERAPEUTIC APPLICATIONS OF HEDERA HELIX (IVY LEAF) EXTRACTS

Toxicity and Side Effects: Common ivy (*Hedera helix* subsp. *helix*) is a widely recognized native and decorative plant found in Europe. Since 1899, there have been consistent reports of contact dermatitis associated with ivy. Recently, it has been proposed that allergic contact dermatitis resulting from this plant may be frequently misdiagnosed, in

part due to the unavailability of commercial patch test allergens⁶². The oral LD50 of ivy leaf extracts in mice was greater than 3 g/kg body weight. The oral LD50 of saponin mixtures derived from ivy leaves, which contained 60% and 90% of hederacoside C, as well as hederasaponin C and α -hederin, was greater than 4 g/kg body weight.

The intraperitoneal LD50 of α -hederin was recorded at 1.8 g/kg body weight, while the saponin mixture containing 60% hederacoside C had an LD50 of 2.3 g/kg body weight. The dry leaf extract induced diarrhea in rats, but no fatalities were observed within 72 hours when administered orally at doses up to 4.1 g/kg body weight^{63, 66, 67}. A daily oral administration of the dry leaf extract at a dose of 1.5 g/kg body weight for 100 days in rats did not result in any hematological, biochemical, or histological alterations. However, hemolytic effects were noted following the oral administration of a hydroethanolic dry extract of the leaves at a dosage of 4 g/kg body weight over a period of 90 days⁶³.

In a study involving 361 patients, treatment with a fixed fluid extract combination of thyme and ivy leaves (5.4 ml three times daily for 11 days) was well tolerated, showing no significant difference in the frequency or severity of adverse events when compared to the placebo group. No severe or serious adverse events were reported⁶⁵. Adverse events were noted in 1.2% of 5181 children treated with Prospan cough syrup. Forty-six patients (0.5%) discontinued treatment due to adverse events, primarily gastrointestinal issues. The predominant adverse events included gastrointestinal disorders at a rate of 1.5% (diarrhea 0.8%, abdominal and epigastric pain 0.4%, nausea and vomiting 0.3%) and skin allergies at 0.1%. Other adverse events occurring at a frequency of less than 0.1% included dry mouth and thirst, anorexia, eructation, stomatitis, anxiety, headache, and drowsiness⁶⁴. However, fresh leaves and leaf juice were associated with allergic contact dermatitis. Exposure to common ivy may result in sensitization, leading to a delayed hypersensitivity reaction. The underlying mechanism was identified as a type IV reaction following initial sensitization. Consequently, individuals with frequent exposure to common ivy, and thus at a heightened risk of sensitization, should don suitable protective clothing^{68, 69}.

CONCLUSION: *Hedera helix* (ivy leaf) is a scientifically validated medicinal plant with significant therapeutic value, particularly in the management of respiratory disorders. Its pharmacological efficacy is primarily attributed to a diverse range of bioactive phytoconstituents, including triterpene saponins (especially α -hederin

and hederacoside C), flavonoids, phenolic acids, coumarins, sterols, volatile oils, and polyacetylenes. These constituents collectively contribute to its bronchodilatory, expectorant, mucolytic, anti-inflammatory, antimicrobial, antioxidant, immunomodulatory, and other pharmacological activities. Clinical and experimental evidence supports the use of standardized ivy leaf extracts in the treatment of productive cough, acute and chronic bronchitis, and other respiratory tract disorders, with favorable efficacy and safety profiles when administered at recommended doses.

Advances in extraction techniques, phytochemical characterization, and analytical standardization have further improved the quality, consistency, and therapeutic reliability of ivy leaf preparations. Although emerging studies also suggest promising anticancer, antiviral, antiparasitic, gastroprotective, and antithrombotic properties, most of these findings are based on preclinical investigations and require further validation through well-designed clinical trials. Overall, *Hedera helix* represents an important medicinal plant with broad pharmacological potential and substantial clinical relevance. Future research should focus on elucidating its molecular mechanisms, establishing long-term safety, optimizing dosage formulations, and conducting large-scale randomized clinical studies to expand its evidence-based therapeutic applications and facilitate its integration into modern phytopharmaceutical practice.

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CONFLICT OF INTEREST: Nil

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