IOSR Journal Of Pharmacy www.iosrphr.org
(e)-ISSN: 2250-3013, (p)-ISSN: 2319-4219
Volume 8, Issue 5 Version. I (May 2018), PP. 41-53

Pharmacological and therapeutic activities of *Hedera helix*- A review

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Abstract: The phytochemical analysis of *Hedera helix* revealed that the plant contained unsaturated sterols, oils, tannins, phenolic compounds, terpenoids, glycosides, alkaloids, flavonoids, carbohydrates, reducing sugars, saponins, vitamins and minerals. The pharmacological studies showed that *Hedera helix* possessed respiratory, anti-inflammatory, analgesic, immunological, anticancer, antimutagenic, antimicrobial, anti-parasitic, gastrointestinal, and antithrombin activity. The current review discussed the chemical constituents, pharmacological and therapeutic importance of *Hedera helix.*

Keywords: *Hedera helix*, therapeutic, chemical constituents, pharmacology

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Date of Submission: 28-05-2018
Date of acceptance: 11-06-2018

I. INTRODUCTION:

In the last few decades there has been an exponential growth in the field of herbal medicine. It is getting popularized in developing and developed countries owing to its natural origin and lesser side effects. Plants generally produce many metabolites which are used as pharmaceuticals, agrochemicals, flavours, fragrances, colours, biopesticides and food additives[1-35]. *Hedera helix* contained wide range of metabolites and produced wide range of pharmacological effects. The current review will discussed the chemical constituents, pharmacological and therapeutic importance of *Hedera helix.*

Plant profile:

Synonyms:

Hedera arborea Garsault, *Hedera arborea* Carrière, *Hedera arborea* var. variegata Hibberd, *Hedera* aurantiaca (Hibberd) Carrière, *Hedera baccifera* G. Nicholson, *Hedera chrysophylla* (Hibberd) Carrière, *Hedera combwoodiana* Carrière, *Hedera communis* Gray, *Hedera communis* var. sterilis Gray, *Hedera conglomerata* (G. Nicholson) Carrière, *Hedera cordata* Carrière, *Hedera cordifolia* G. Nicholson, *Hedera digitata* G.Nicholson, *Hedera*

diversifolia Stokes, *Hedera donerailensis* K. Koch, *Hedera elegantissima* G.Nicholson, *Hedera floribunda* Sennen, *Hedera glimii* G. Nicholson, *Hedera gracilis* (Hibberd) Carrière, *Hedera grandifolia* G. Nicholson, *Hedera helix* f. arborea (Garsault) Schelle, *Hedera helix* var. arborescens Lodd. ex Loudon, *Hedera helix* var. aurantiaca Hibberd, *Hedera helix* var. aurea Hibberd, *Hedera helix* f. aureovariegata (Weston) P. D. Sell, *Hedera helix* var. aureovariegata Weston, *Hedera helix* f. baltica (Rehder) Rehder, *Hedera helix* var. baltica Rehder, *Hedera helix* f. cavendishii (Paul) Tobler, *Hedera helix* var. cavendishii Paul, *Hedera helix* var. chrysophylla Hibberd, *Hedera helix* var. conglomerata G. Nicholson, *Hedera helix* f. conglomerata (G. Nicholson) Tobler, *Hedera helix* var. corrugata Hibberd, *Hedera helix* var. crenata Hibberd, *Hedera helix* f. cullisii Tobler, *Hedera helix* var. dealbata Hibberd, *Hedera helix* var. deltoidea Hibberd, *Hedera helix* var. digitata Bosse, *Hedera helix* f. discolor (Hibberd) Tobler, *Hedera helix* var. discolor Hibberd, *Hedera helix* var. erecta A. E. Schulze, *Hedera helix* var. europaea Voss, *Hedera helix* var. glymii Paul, *Hedera helix* f. glymii (Paul) Tobler, *Hedera helix* var. gracilis Hibberd, *Hedera helix* f. helix, *Hedera helix* var. helvetica Lawr, *Hedera helix* var. hodgensii Moore & More, *Hedera helix* f. irica P. D. Sell, *Hedera helix* var. leucocarpa Seem, *Hedera helix* var. lobatomajor G. H. M. Lawr, *Hedera helix* f. lobatomajor (G.H.M.Lawr.) P. D. Sell, *Hedera helix* var. lucida Hibberd, *Hedera helix* var. luteola Hibberd, *Hedera helix* var. marmorata G. Nicholson, *Hedera helix* f. marmorata (G.Nicholson) Tobler, *Hedera helix* var. meagheri A. E. Schulze, *Hedera helix* var. melanocarpa Seem., *Hedera helix* var. minima Hibberd, *Hedera helix* f. minima (Hibberd) Tobler, *Hedera helix* var. palmata Paul, *Hedera helix* var. palmatoaurea Hibberd, *Hedera helix* var. pedata Hibberd, *Hedera helix* var. pennsylvanica Hibberd, *Hedera helix* var. scutifolia Hibberd, *Hedera helix* var. sublutea Hibberd, *Hedera helix* var. succinata Hibberd, *Hedera helix* var. sulphurea Hibberd, *Hedera helix* var. tortuosa Hibberd, *Hedera helix* var. tricolor Rehder, *Hedera helix* var. triloba Hibberd, *Hedera helix* var. variegata (Hibberd) G. Nicholson, *Hedera helix* var. walthamensis Paul, *Hedera humirepens* Röhl, *Hedera marginata* G.Nicholson, *Hedera minor* G. Nicholson, *Hedera palmata* (Paul) Carrière, *Hedera pennsylvanica* G.Nicholson, *Hedera poetica* Salisb, *Hedera purpurea* Carrière and *Hedera willsiana* G. Nicholson[36].

Taxonomic classification:

Kingdom: Plantae, **Phylum**: Spermatophyta, **Subphylum**: Angiospermae, **Class**: Dicotyledonae, **Order**: Araliales, **Family**: Araliaceae, **Genus**: *Hedera*, **Species**: *Hedera helix*[37]

Common names:

Arabic: Habl Almasakeen, Habl Almasajeen, Leblab Kabeer; **English:** Ivy, Atlantic ivy; Common ivy; English ivy; **Finland:** Köynneliäs muratti; **French:** Bourreau des arbres; Herbe de St Jean; lierre; Lierre commun; **Germany:** Efeu; Gemeiner Efeu; **Italy:** Edera;

Netherlands: Klimop; **Portuguese**: Hera; **Spanish**: Hiedra; Yedra comun; **Sweden:** Murgroena; Murgröna[38-39].

Distribution:

It was distributed in **Africa** (Algeria, Libya, Morocco, Tunisia); **Asia** (Armenia, Georgia, Russian Federation, Iran, Iraq, Palestine, Lebanon, Syria, Turkey); **Europe** (Belarus, Latvia, Lithuania, Moldova, Ukraine, Austria, Belgium, Germany, Hungary, Czechoslovakia, Netherlands, Poland, Switzerland, Denmark, Ireland, Norway, Sweden, United Kingdom, Albania, Bulgaria, Former Yugoslavia, Italy, Romania, France, Portugal, Spain); **Australasia** (Australia, New Zealand); **Northern America** (Canada, United States) and it was cultivated widely[39].

Description:

It is evergreen woody perennial plant. The stem is long, either creeping or climbing and may attain a length of up to 30 m. When old, stems may reach a diameter of over 10 cm and even produce a short trunk. The stem is attached to the substrate by numerous small roots produced at each leaf node, which bear vascular-arbuscular mycorrhiza. The deep green, glossy, leathery leaves are evergreen, heterophyllous, and mostly palmately lobed on sterile stems whereas those on flowering stems are ovate and larger. Leaves of the plant are usually less than 8 cm across, they are long-lived and have a strong smell when crushed. The perfect, sometimes protandrous, yellow-green flowers, 5-7 mm across, are clustered on terminal inflorescences born on stems climbing to canopy height. The fruit, a drupe 6-9 mm in diameter, is green turning dark purplish/black when mature and contains 2-5 seeds[38. 40-42].

Traditional uses:

It was used in common cold associated with cough and for the symptomatic treatment of acute and chronic inflammatory bronchial disorders[43]. The leaves were used as analgesic and anti-inflammatory, the leaves and berries were taken orally as an expectorant for the treatment of cough and bronchitis[44]. The boiled leaves of *Hedera helix* was applied to the part of the body afflicted, fight ringworm, scabies and worm[45].

It was used to treat depression, as stimulant, narcotic and hallucinogenic depending on the amount that was drunk[46]. A decoction of the leaves of *Hedera*. was used in diabetes in Turkey[47]. Topically, it was used as a soothing and antipruriginous, as a protective treatment for cracks, grazes, chapped skin and insect bites[48]

Part used medicinally:

The medicinal parts were the leaves and berries[49].

Chemical constituents:

The preliminary phytochemical analysis of *Hedera helix* revealed that the plant contained unsaturated sterols, tannins, phenolic compounds, terpenoids, glycosides, alkaloids, flavonoids, carbohydrates, reducing sugars and saponins[44, 50-53].

The chemical groups isolated from the plant fruits were included **triterpene saponins**: helixoside A, helixoside B, 3-O- β-glucosyl hederagenin, 3-O- β-glucosyl-(1→2)- β-glucosyl oleanolic acid 3-O- β-glucosyl-(1→2)- β-glucosyl hederagenin staunoside A (3-O- β-glucosyl-28-O-β-glucosyl-(1→6)- β-glucosyl hederagenin); **polyacetylenes:** falcarinon, falcarinol, panaxidol ((*Z*)-9,10-epoxy-1-heptadecene-4,6-diyn-3-one); **fatty acids:** petroselinic,oleic, *cis*-vaccenic, palmitoleic; and **β-lectins**[54-57]. While, the chemical groups isolated from the plant leaves included **triterpene saponins derivatives**: hederagenin, oleanolic acid, bayogenin (2β-OH-hederagenin), hederasaponin C (=hederacoside C) and hederasaponins B, D, E, F, G, H and I, hederasaponin A, 3-sulfates of oleanolic acid and echinocystic acid, 3-sulfate of 28-O-β-gentiobiosyloleanate = helicoside L-8a; **monodesmosides**: α-hederin, hederagenin 3-O-β-glucoside; **volatile oil**: germacrene B, β-elemene , γ-elemene (elixen), methylethyl ketone, methylisobutyl ketone, *trans*-2-hexanal, *trans*-2-hexanol, germacrene D, β-caryophyllene, sabinene, α-, β-pinene, limonene, furfurol; **phenolic acids**: caffeic, chlorogenic (5-O-caffeoylquinic), neochlorogenic (3-O-caffeoylquinic), 3,5-O-dicaffeoyl-quinic; 4,5-O-dicaffeoyl-quinic, rosmarinic [(R)-(+) enantiomer]; dihydroxybenzoic protocatechuic, *p*-coumaric; **flavonoids**: quercetin, kaempferol, rutin (quercetin 3-O-rutinoside), isoquercitrin (quercetin 3-O-glucoside), astragalin (kaempferol 3-O-glucoside), kaempferol 3-O-rutinoside; **coumarins:** scopolin (scopoletin 7-O-glycoside); **polyacetylenes**: falcarinon, falcarinol**,** 11,12-dehydrofalcarinol; **anthocyanin:** - cyanidin 3-monoside ; **sterols:** cholesterol, campesterol, stigmasterol, sitosterol, α-spinasterol; 5α-stigma-7-en-3β-ol; **Alkaloid**: emetin; **aminoacids; Vitamins:** E, C, pro-vitamin A and **carbohydrates**[39, 58-65].

Powdered dried leaves of *Hedera helix* contained 21.83mg/g of hederacoside C, 0.41mg/g alpha-hederin, and 0.02mg/g hederagenin[66-69].

The air-dried *Hedera helix* extract contained hydrocarbons pentacosane, heptacosane and hentriacontane. It was rich in methyl esters of several carboxylic acids, stigmasterol and α– and β–amyrin[70].

The total phenolic and total flavonoid contents in the leaves extract of *Hedera helix* were: 131.25±1.54 mg gallic acid equivalents/g extract, and 18.61±0.37 mg quercetin equivalents/g extract respectively[50].

Phenolic constituents isolated from commercial dry extract of *Hedera helix* were included rutin, kaempferol 3-O-rutinoside, quercetin 3-O-glucoside, kaempferol 3-O-glucoside, quercetin, kaempferol, chlorogenic acid, neochlorogenic acid, 4,5-O-dicaffeoyl-quinic acid, 3,5-O-dicaffeoyl-quinic acid as well as rosmarinic, caffeic, and protocatechuic acids[58, 71].

Abscisic acid was identified in the acid fraction of extracts from leaves of juvenile and adult *Hedera helix* [72].

Pharmacological effects:

Respiratory effects:

The bronchiolytic effect of α-hederin was demonstrated by isometric tension measurements using bovine tracheal smooth muscle strips. α-Hederin increased isoprenaline-induced relaxation indirectly, probably by inhibiting heterologous desensitization induced by high concentrations of muscarinic ligands like methacholine[73].

Alpha-hederin (1 µM) inhibited internalization of β2-adrenergic receptor-GFP fusion proteins, whereas neither hederacoside C nor hederagenin (1 µM each) influenced the receptor regulation[74].

Alpha -hederin inhibited the internalization of β2-adrenergic receptors (ß2AR) under stimulating conditions. α-Hederin pretreated alveolar type II cells and human airway smooth muscle cells revealed an increased ß2AR binding and an elevated intracellular cAMP level[75].

The ethanolic leaves extract (50 mg/kg of body weight) administered orally in the compressed air model in guinea pigs inhibited dose-dependently the broncho-constriction induced by the inhalation of ovalbumin (57% inhibition) and platelet activating factor (43% inhibition)[76].

The effect of α-hederin (0.02 mg/kg) on lung tissue pathology and the levels of the inflammatory mediators; IL-2 mRNA, IL-17 mRNA, and MicroRNAs (miRNA)-133a was evaluated in a rat ovalbumin (OVA)-sensitized model of asthma. Levels of IL-2 and IL-17 mRNA were higher in the OVA-sensitized group than controls, while the level of miRNA-133a gene expression was lower. Pretreatment with α-hederin decreased IL-17 mRNA levels and increased miRNA-133a gene expression compared with OVA-sensitized animals. All pathological changes in pretreated groups were lower than the OVA-sensitized group. The results showed a beneficial effect of α-hederin in OVA-sensitized rats, suggesting that α-hederin affected the IL-2 and IL-17 secretion pathways and altering miRNA-133a expression[77].

The effect of oral administration of *Hedera helix* (100 mg/kg, once daily for one week) on lung histopathology was evaluated in a murine model of chronic asthma in mice sensitized with ovalbumin. Airway histopathology was evaluated by using light and electron microscopy. *Hedera helix* administration reduced goblet cell counts and the thicknesses of basement membrane in the asthmatic airways[78].

A double blind, placebo-controlled, randomized cross-over study was carried out on 30 children suffering from partial or uncontrolled mild persistent allergic asthma. Patients either received ivy leaves dry extract for four weeks in addition to their inhaled corticosteroid therapy or placebo, followed by a wash-out phase before switching to the other treatment. There was a significant improvement of MEF(75-25), MEF25 and VC after treatment with ivy leaves dry extract (MEF(75-25) change in the mean 0.115 l/s, p=0.044; MEF25 change in the mean 0.086 l/s, p=0.041; VC change in the mean 0.052 l, p=0.044), but not after treatment with placebo. For the primary outcome parameters (relative change

of FEV1 and MEF(75-25) before bronchodilation) no effect was detected in the cross-over analysis (FEV1 p=0.6763 and MEF(75-25) p=0.6953)[79].

The efficacy of the extracts from dried ivy leaves (*Hedera helix*) in treatment of chronic airway obstruction was studied in children suffering from bronchial asthma. Drops containing ivy leaf extract were significantly superior to placebo in reducing airway resistance (P=0.04). Syrup and suppositories showed non-inferiority in comparison with drops. The trials indicated that ivy leaf extract preparations improved the respiratory functions of children with chronic bronchial asthma[80].

9657 patients (5181 children) with bronchitis (acute or chronic bronchial inflammatory disease) were treated with a syrup containing dried ivy leaf extract. After 7 days of therapy, 95% of the patients showed improvement or healing of their symptoms. The safety of the therapy was very good with an overall incidence of adverse events of 2.1% (mainly gastrointestinal disorders 1.5%). The additional application of antibiotics had no benefit respective to efficacy of syrup of dried ivy leaf extract alone, and increased the relative risk for the occurrence of side effects by 26%[81].

Two 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 0-12 yr 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 respectively. 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[82].

The changes in the symptoms of cough after treatment with a combined herbal preparation containing dry ivy leaf extract as main active ingredient, decoction of thyme and aniseed, and mucilage of marshmallow root and its tolerability were investigated in an open clinical trial. The study was carried out on 62 patients. The results showed that at the final visit, all symptom scores showed an improvement as compared to baseline. Doctors and patients assessed efficacy as good or very good in 86% and 90% of the cases, respectively. Tolerability was assessed as good or very good by 97% of the doctors and patients[83].

A double-blind, randomized study was conducted to assess the efficacy and tolerability of ivy leaves soft extract with another ivy leaves extract. The study was carried out on 590 patients with acute bronchitis. They were treated for 7 days (±1). The Bronchitis Severity Score (BSS) decreased gradually and to a similar extent from day 1 to day 7 in both treatment groups. Starting from values of 6.2-6.3±1.2, the BSS decreased by approximately 4.7-4.9 points until day 7, so that patients left the study with a mean BSS of

1.4-1.6. The BSS subscales cough, sputum, rhales/rhonchi, chest pain during coughing, and dyspnoea improved to a similar extent in both treatment groups. Overall, 2.7% of patients (per group and overall) experienced an adverse event, all of which were non-serious. Fewer patients younger than ten years had adverse events than would have been expected from their share of the study population[84].

The efficacy and tolerability of a fixed fluid extract combination of thyme and ivy leaves (5.4 ml three times daily, 11-day treatment) were evaluated by double-blind, placebo controlled, multicentre study, performed on 361 outpatients suffering from acute bronchitis with productive cough. The efficacy of the treatment was evaluated by the patient's daily counting of coughing fits during the daytime (manual counter), assessment of acute bronchitis related symptoms and by the investigator's assessment of the most important symptoms of acute bronchitis using the Bronchitis Severity Score (BSS). The mean reduction in coughing fits on days 7 to 9 relative to baseline was 68.7 % under thyme-ivy combination compared to 47.6 % under placebo ($p < 0.0001$). In the thyme-ivy combination group, a 50 % reduction in coughing fits from baseline was reached 2 days earlier compared to the placebo group. Treatment was well tolerated with no difference in the frequency or severity of adverse events between thyme-ivy combination and placebo groups. Severe or serious adverse events were not reported. Accordingly, the authors concluded that the oral treatment of acute bronchitis with thyme-ivy combination for about 11 days was superior to placebo in terms of efficacy. The treatment was safe and well tolerated[85].

The additive effect of the *Hedera helix* (HH) and *Rhizoma coptidis* (RC) extracts mixture was studied for antitussive and expectorant activities in animals. The extracts of HH and RC significantly increased tracheal secretion and inhibited cough. The mixture of HH and RC extracts in a 1:1 concentration at a dose of 200 mg/kg showed a more potent effect on phenol red secretion (25.25±3.14) and cough inhibition (61.25±5.36) than the individual use of each extracts [phenol red secretion: HH 13.39±4.22 ($p=0.000$), RC 20.78±2.50 ($p=0.010$); cough inhibition: HH 9.89±4.14 ($p=0.010$), RC 30.25±7.69 ($p=0.000$)]. A 3:1 ratio mixture of HH to RC demonstrated an optimal expectorant effect ($P<0.001$), it showed expectorant and antitussive effects in a dose-dependent manner[86].

Anti-inflammatory and analgesic effects:

The ethanolic extract of *Hedera helix* was tested for antiinflammatory properties. Intraperitoneal injections of 7.5 ml/kg bw ethanol extract showed antiinflammatory activity (88.89% inhibition) in formalin-induced paw oedema, as compared to diclofenac which showed 94.44%. The effect of ethanol extract of *Hedera helix* was also investigated in arthritis. It possessed significant antiinflammatort effect manifested by visible reduction in arthritic symptoms[87].

The possible antiinflammatory effects of a crude saponin extract (CSE) and a saponin's purified extracts (SPE) of *Hedera helix* were studied in carrageenan- and cotton pellet induced acute and chronic inflammation models in rats. Both the CSE and SPE of

Hedera helix possessed antiinflammatory effects. The most potent extract was the CSE of *Hedera helix* at 100 and 200 mg/kg bw doses with 77% acute anti-inflammatory effects. The SPE of *Hedera helix* was more potent than the CSE in chronic antiinflammatory effect (60% and 49%, respectively)[88].

The methanolic extract of the whole plant was partitioned with hexane, chloroform and ethyl acetate. The analgesic activity of the crude extract and subsequent solvent fractions of *Hedera helix* was carried in NMRI mice. In acetic acid induced writhing test, the crude extract provoked 33.33 and 55.90% pain reduction at 50 and 100 mg/kg ip respectively. When fractionated, the hexane fraction of the plant did not produce significant reversal of induced pain. The chloroform fraction of the plant exhibited prominent pain inhibition (48.71 and 65.70% at 50 and 100 mg/kg ip respectively). For ethyl acetate fraction, significant activity was observed (40.76 and 59.76%) at 50 and 100 mg/kg ip respectively, while, aqueous fraction elicited most profound effect (50.77 and 70.71%) blockade of noxious stimulation at 50 and 100 mg/kg ip respectively[89].

Anticancer effects:

The results of cytotoxicity demonstrate that eight fractions of air-dried *Hedera helix* extract possessed cytotoxic activity when tested on the brine shrimp bioassay and β-amyrin was the compound which responsible for this activity[70].

Brine shrimp bioassay of *Hedra helix* showed that the methanolic extract of the leaves possessed cytotoxic activity (LC_{50}: 802.73 µg) . Further investigation showed that the active compound was phenolic compound with LC_{50}: 161.84 µg[90].

The anti proliferative effect of the extracts of leaves and unripened fruits of *Hedera helix* was investigated in rat prostate cancer cell lines with different metastatic potentials: Mat-LyLu cells (strongly metastatic) and AT-2 cells (weakly metastatic). Cell kinetics (proliferation and mitotic activity) and motility were inhibited by ethanolic leaf extract of *Hedera helix*. The ethanolic extract of *Hedera helix* fruit suppressed Mat-LyLu cell migration, with no effect on proliferation. The opposite effects were observed in AT-2 cells; migration was not affected but proliferation was inhibited[91].

The cytotoxic effects of monodesmosidic triterpenoid saponin were investigated on cultured mouse B16 melanoma cells and noncancer mouse 3T3 fibroblasts. α-Hederin inhibited the proliferation of both cell types. The compound also induced vacuolisation of the cytoplasm and membrane alterations resulting in cell death[92].

The ability of alpha-hederin to improve the efficacy of 5-fluorouracil (5-FU) was evaluated. A combinations of alpha-hederin and 5-FU using at fixed-concentration and combination were performed *in vitro* on HT-29 cells. The results showed that alpha-hederin at sub-IC_{50} cytotoxic concentrations enhanced 5-FU cytotoxicity about 3.3-fold ($P<0.001$). Simultaneous combination of alpha-hederin and 5-FU at their IC_{50} ratio showed either a synergistic effect at a moderate cytotoxic range (25% of cell growth inhibition) or an

antagonistic effect at a high level of growth inhibition. The data indicated that it was possible to optimize colorectal cancer cell sensitivity to 5-FU with alpha-hederin[93].

The apoptosis inducing effect of hederagenin in human colon cancer LoVo cells and its possible mechanism were investigated. MTT assay showed that hederagenin significantly inhibited the viability of LoVo cells in a concentration-dependent and time-dependent manner by IC_{50} of 1.39 μM at 24 h and 1.17 μM at 48 h. The apoptosis ratio was significantly increased to 32.46% and 81.78% by the induction of hederagenin (1 and 2 μM) in Annexin V-FITC/PI assay. Hederagenin also induced the nuclear changes characteristic of apoptosis. Hederagenin increased significantly ROS generation in LoVo cells. Real-time PCR showed that hederagenin induced the up-regulation of Bax and down-regulation of Bcl-2, Bcl-xL and Survivin. Western blotting analysis showed that hederagenin decreased the expressions of apoptosis-associated proteins Bcl-2, procaspase-9, procaspase-3, and polyADP- ribosepolymerase (PARP), while the expressions of Bax, caspase-3, caspase-9 were increased [94].

Antimicrobial effect:

The mixture of saponins of the leaves of *Hedera helix,* with a large amount of hederacoside C, possessed significant antibacterial activity against Gram-positive bacteria (*Bacillus* spp, *Staphylococcus* spp, *Enterococcus* spp and *Streptococcus* spp) with MIC values of 0.3-1.25 mg/ml, and against Gram-negative bacteria (*Salmonella* spp, *Shigella* spp, *Pseudomonas* spp, *Escherichia coli* and *Proteus vulgaris*) with MIC values of 1.25-5 mg/ml, and against *Candida albicans* with MIC value of 2.5 mg/ml[95].

The antimicrobial activity of different extracts of *Hedera helix* (whole plant) was investigated against three strains of Gram-positive bacteria (*Staphylococcus aureus*, *Staphylococcus epidermidis* and *Bacillus subtilis*) and two Gram-negative bacteria (*Escherichia coli* and *Klebsiella pneumonia*). The ethyl acetate and methanol extracts of *Hedera helix* were the most active, they showed activity against three selected Gram positive and two Gram negative bacterial stains and displayed highest inhibitory zone at the tested concentration (22 mg/ml)[51] .

Antibacterial activity of the leaves extracts was investigated by using disc diffusion assay. The diameters of growth inhibition were 9.3, 7.3 and 12.6mm against *S. aureus*, *P. aeruginosa* and *E coli* respectively[50].

The antifungal activity of triterpenoid saponins was investigated *in vitro* by the agar dilution method. Monodesmosidic hederagenin derivatives exhibited a broad spectrum activity against yeast as well as dermatophyte species. α-Hederin was the most active compound, and *Candida glabrata* was the most susceptible strain[96].

The mode of anti-candidal action of α-hederin, was investigated by a haploinsufficiency screen. Saponin cytotoxicity was attributed to membrane damage. However, α-hederin did not induce hypersensitivity with an aminophospholipid translocase deletion strain that was frequently hypersensitive to membrane damaging agents. The

haploinsufficiency profile of α-hederin was most similar to that reported for drugs such as caspofungin that inhibited the synthesis of the fungal cell wall[97].

The potential antiviral properties was evaluated against influenza A/PR/8 (PR8) virus in a mouse model with suboptimal oseltamivir that mimics a poor clinical response to antiviral drug treatment. Suboptimal oseltamivir resulted in insufficient protection against PR8 infection. Oral administration of ivy extract with suboptimal oseltamivir increased the antiviral activity of oseltamivir. Ivy extract and its compounds, particularly hedrasaponin F, significantly reduced the cytopathic effect in PR8-infected A549 cells in the presence of oseltamivir. Compared with oseltamivir treatment alone, coadministration of the fraction of ivy extract that contained the highest proportion of hedrasaponin F with oseltamivir decreased pulmonary inflammation in PR8-infected mice. Inflammatory cytokines and chemokines, including tumor necrosis factor-alpha and chemokine (C-C motif) ligand 2, were reduced by treatment with oseltamivir and the fraction of ivy extract. Analysis of inflammatory cell infiltration in the bronchial alveolar of PR8-infected mice revealed that CD11b+Ly6G+ and CD11b+Ly6Cint cells were recruited after virus infection, and the coadministration of the ivy extract fraction with oseltamivir reduced infiltration of these inflammatory cells[98].

The antiviral activity of hederasaponin B from *Hedera helix* against EV71 subgenotypes C3 and C4a was evaluated in vero cells. The results demonstrated that hederasaponin B and 30% ethanol extract of *Hedera helix* 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 inhibition of viral capsid protein synthesis[99].

Anti-parasitic effects:

Saponins of *Hedera helix* possessed antileishmanial activity *in vitro* on promastigote and amastigote forms of *Leishmania infantum* and *Leishmania tropica*. Monodesmosides were found to be as effective on promastigote forms as the reference compound (pentamidine). Against amastigote forms only hederagenin exhibited a significant activity which was equivalent to that of the reference compound, (N-methylglucamine antimonate)[100].

In vitro anthelmintic activity of crude extracts of the ripe fruits of *Hedera helix* was investigated on eggs and adult nematode parasites, *Haemonchus contortus*. Aqueous extract of *Hedera helix* was also evaluated for *in vivo* anthelmintic activity at dose of 1.13 and 2.25 g/kg in sheep artificially infected with *Haemonchus contortus*. ED_{50} for egg hatch inhibition was 0.12 and 0.17 mg/ml for aqueous and hydro-alcoholic extracts, respectively. There was no statistically significant difference in the activity of the two extract types ($P>0.05$). Hydro-alcoholic extract showed better *in vitro* activity against adult parasites compared to the aqueous extract. Significant faecal egg count reduction (FECR) was detected in groups treated with both doses of *Hedera helix* ($P<0.05$) on day 2

post-treatment. On day 7 post-treatment significant reduction was detected only for higher dose of *Hedera helix* (P<0.05) while on day 14 post-treatment there was no significant FECR in both groups treated with *Hedera helix*. The percentage of larvae recovered from culturing faeces obtained from groups of sheep treated with lower and higher doses of *Hedera helix* was 47.52% and 36.07%, respectively, which was significantly lower than (P<0.05) that recovered from the control group (60%). Significant (P<0.05), dose dependent total worm count reduction (WCR) was observed for groups of sheep treated with *Hedera helix*. Increasing the dose of *Hedera helix* improved the efficacy against the male than the female parasites[101].

The *in vivo* activity of an alcoholic extract of *Hedera helix* (20 and 70% alcoholic extract) was studied in experimental ulcer of zoonotic cutaneous leishmaniasis (CL) in Balb/c mice. The results revealed that the main lesion size did not decrease significantly, and the small lesions did not completely disappear after treatment by *Hedera helix* alcoholic extract. Amastigotes counts (mean ± SD) of the skin lesions decreased in placebo control and 20% concentration groups, but in negative control and 70% concentration groups the number of parasites did not reduce[102].

Three extracts prepared from *Hedera helix* were tested for both *in vitro* and *in vivo* anthelminthic activity. Saponic complex 60% (CS 60), purified saponic complex 90% (CSP 90) and alpha hederin were evaluated *in vitro* using *Fasciola hepatica* and *Dicrocoelium* spp. The same extracts were assayed for their effects on *Dicrocoelium* in naturally infected sheep. After an exposure of 24 hours *in vitro*, both *Fasciola hepatica* and *Dicrocoelium* spp were killed by alpha-hederin at concentrations of 0.005 and 0.001 mg/ml respectively. When sheep naturally infected with *Dicrocoelium*, were treated po, with CS 60 and CSP 90, the worms were eliminated after three doses, one of 500 and two of 800 mg/kg[103].

Antioxidant effect:

The DPPH radical scavenging activity of *Hedera helix* ethyl acetate stem extracts was 84.95%, methanol stem extracts 68.24%, dichloromethane stem extracts 52.35% and n- hexane stem extracts 44.75%[44].

Scavenging effects of different concentrations of the methanol extract of *Hedera helix* leaves on DPPH-free radical (%) were: 25.95±1.02 , 32.68±1.26 , 43.58±1.89, 66.23±2.02, 86.78±2.58 , 86.80±2.48 , 94.47±3.85, 95.28±3.49 and 95.95±2.58 % for the concentration of 50, 100, 200, 400 ,500, 1000, 2000, 3000 and 4000 µg/ml respectively. The antioxidant activity of the leaves extracts assessed with β-carotene bleaching method (%) were 16.70±2.59, 42.13±3.69, 50.45±3.59, 58.08±3.48, 60.36±4.29, 61.03±5.96, 62.50±3.59, 63.61±2.24 and 75.85±2.59 for the concentrations of 50, 100, 200, 400, 500, 1000, 2000, 3000 and 4000 µg/ml respectively[50].

The methanolic extract of the whole plant was partitioned with hexane, chloroform and ethyl acetate. The antioxidant activity of the crude extract and subsequent solvent

fractions of *Hedera helix* was studied by DPPH radical scavenging assay. The results of scavenging effect of extract/ fractions of *Hedera helix* against DPPH free radical at various concentrations revealed that the crude extract possessed concentration dependent quenching effect against DPPH with maximum effect of 84.88% at 100 µg/ml. Upon fractionation, hexane did not produce any effect. The chloroform fraction exerted marked scavenging effect in concentrations dependant manner with maximum effect (80.55%) at 100 µg/ml. The ethyl acetate and aqueous fraction also possessed significant effect in a concentrations dependent manner with maximum scavenging effect of 55.10% and 55.74% at 100 µg/ ml, respectively[89].

The antioxidant activities of α-hederin, hederasaponin-C, and hederacolchisides-E and F were investigated using different antioxidant tests. α-hederin, hederasaponin-C, as well as hederacolchisides-E and F exhibited a strong total antioxidant activity. At the concentration of 75 pg/ml, these saponins showed 94, 86, 88 and 75% inhibition on lipid peroxidation of linoleic acid emulsion, respectively[67].

Effect on digestive system:

The ulcer preventive efficacy of water extracts of *Hedera helix* was investigated in ethanol-induced ulcer model in rats. Water extracts of *Hedera helix* (300 mg/kg, ip) significantly ($P<0.01$) decrease the ulcer index (1.38 vs 3.17 in control) and rise macroscopic curative ratio (56.6%)[104].

The effect of two main active substances extracted from the plant (α-hederin and hederacoside C) and the whole dry extract of *Hedera helix* on gut motility was evaluated on isolated rat stomach corpus and fundus strips. Results revealed that α-hederin in the concentration ranged from 25 to 320µM significantly changed the spontaneous motoric activity of rat stomach smooth muscle. The observed reaction (the contraction, and its force) was concentration dependent. Hederacoside C, did not alter the motility of rat isolated stomach corpus and fundus strips when administered in the concentration up to 100 µM, however, if applied in the concentration of 350 µM it induced a remarkable contraction of smooth muscle. Eventually, the whole extract of *Hedera helix* in a dose containing 60 µM of hederacoside C produced a strong contraction which strength was comparable with the reaction induced by acetylcholine[105].

The effect of α-hederin on smooth muscle was studied on rat isolated stomach corpus and fundus strips, under isotonic conditions. The results revealed that the application of verapamil significantly inhibited the contraction evoked by α-hederin. The incubation of stomach strips in calcium-free modified Krebs-Henseleit solution did not change the force of the observed contraction in comparison to the reaction of the preparations incubated in regular incubation solution (M K-HS). The replacement of M K-HS by calcium-free chelator-containing solution inhibited totally the reaction to α-hederin. Accordingly, it appeared that α-hederin-induced contraction resulted from the influx of calcium which was located in

intercellular spaces or bound to the outside of the cell membrane. The Ca^{2+} influx occurs predominantly through voltage-dependent calcium channels of L-type[106].

in vitro antispasmodic activity on isolated guinea-pig ileum with acetylcholine as spasmogen was carried out to determine the antispasmodic activity of *Hedera helix*. In order to determine the phytochemical basis for the antispasmodic activity, bioassay guided fractionation and subsequent isolation of phenolic compounds (flavonols, caffeoylquinic acids) and saponins (hederacoside C, alpha-hederin, hederagenin) was also carried out. Significant activity was found for both saponins and phenolic compounds, the PE values being approx. 55 and 49 for alpha-hederin and hederagenin, 54 and 143 for quercetin and kaempferol, and 22 for 3,5-dicaffeoylquinic acid, respectively. In view of their relative high concentration in the plant, the saponins contribute most to the anti-spasmodic activity, followed by dicaffeoylquinic acids and the flavonol derivatives[107].

Antimutagenic effect:

α-Hederin exerted an antimutagenic effect against the clastogenicity of doxorubicin. The possible antimutagenic mechanisms of this compound included induction of metabolic enzymes which inactivated doxorubicin[66, 108]. α-, β-, and δ-Hederin from *Hedera helix* were found non-mutagenic, it even showed antimutagenic activity in a dose dependent manner against known promutagens: benzo[α]pyrene (1 µg) and mutagenic urine concentrate from a smoker (5 µl) using a modified liquid incubation technique of the *Salmonellal* microsomal assay[109].

Immunological effect:

The influence of the ivy leaves dry extract EA 575® was evaluated in the LPS-induced release of IL-6 from murine macrophages (J774.2). EA 575® was tested in concentrations between 40 and 400 µg/ml. EA 575® decreased the LPS-induced IL-6 release in a dose-dependent manner and statistically significant (25 ± 4%, 32 ± 4%, and 40 ± 7%) at concentrations of 80, 160, and 400 µg/ml, respectively. Patients with inflammatory airway diseases therefore may benefit from therapies targeting the IL-6 pathway[110].

Anti-thrombin effect:

All the fractions obtained from *Hedera helix* were tested for *in vitro* antithrombin activity. The results demonstrate that fractions 310-317 of air-dried *Hedera helix* extract possessed antithrombin activity (73%) from which the two amyrins were identified. The antithrombin activity of authentic samples of α-amyrin and β-amyrin was also tested under identical conditions. The results suggest that the activity of the fractions 310-317 was attributed to the existence of β-amyrin which appear to possess similar activity. Fractions 303-308 also exhibited antithrombin activity (56%) from which stigmasterol was isolated. The antithrombin activity exhibited by an authentic sample of stigmasterol tested under identical

conditions appeared to be similar. Fractions 521-540 also presented some antithrombin activity (51%). Hexadecanoic acid, isolated from this fraction showed similar activity when tested under identical conditions[70].

Toxicity and side effects:

Oral LD_{50} of ivy leaf extracts in mice was >3 g/kg bw, Oral LD_{50} of saponin mixtures from ivy leaf containing 60% and 90% of hederacoside C, and of hederasaponin C and α - hederin was >4 g/kg bw. Intraperitoneal LD_{50} of α-hederin was1.8 g/kg bw and saponin mixture containing 60% of hederacoside C was 2.3 g/kg bw. Dry leaves extract caused diarrhea, but no death in rats within 72h, when used up to 4.1 g/kg bw in rats orally[76, 111-112].

Daily oral administration of leaves dry extract 1.5 g/kg bw for 100 days in rats caused no haematological, biochemical and histological effects. However, haemolytic effects were recorded after oral administration of a hydroethanolic dry extract of the leaves at a dose of 4 g/kg bw for 90 days[76].

Treatment with a fixed fluid extract combination of thyme and ivy leaves (5.4 ml three times daily for 11day) in 361 patients, was well tolerated with no difference in the frequency or severity of adverse events between thyme-ivy combination and placebo groups. Severe or serious adverse events were not reported[85].

Adverse events were reported in 1.2% of 5181 children treated with Prospan cough juice. Forty six (0.5%) patients discontinued therapy due to adverse events, mainly gastrointestinal disorders. The main adverse events were: gastrointestinal disorders 1.5% (diarrhoea 0.8%, abdominal and epigastric pain 0.4%, nausea and vomiting 0.3%), skin allergy 0.1%. Other adverse events occurring with a frequency of less than 0.1% were: dry mouth and thirst, anorexia, eructation, stomatitis, anxiety, headache and drowsiness[81].

However, fresh leaves and the leaf juice caused allergic contact dermatitis. Contact with common ivy may lead to sensitization and then a delayed hypersensitivity reaction. The pathogenic mechanism was a type IV reaction following a sensitization exposure. Therefore, those with frequent exposure to common ivy and thus a high risk of sensitization should wear appropriate protective clothing[113-114].

The prevalence of sensitization to *Hedera helix* pollen was studied by skin prick test (SPT) on allergic subjects. Eleven out of 62(17.7%) patients had a positive SPT with common ivy pollen extract. The main differences found were the number of pollen species to which patients were allergic. Patients with atopic dermatitis had a nine-fold higher frequency of positive skin tests with *Hedera* extracts, than subjects with other allergic diseases[115].

Dose:

External uses: Suppositories: children 4-10 years: 960 mg per day. A poultice can be prepared by mixing (1:3) fresh *Hedera helix* leaves with linseed meal. Enternal uses:

Ethanol-containing preparations (in daily doses): 250-420 mg for adult, 150-210 mg for children 4-12 years, 50-150 mg for children 1-4 years, 20-50 mg for children 0-1 year. Ethanol-free preparations: 300-945 mg for adults; 200-630 mg for children 4-12 years; 150-300 mg for children 1-4 years; 50-200 mg for children 0-1 years. The tea was prepared by adding 1 heaped teaspoonful (0.3-0.8 g) of dried leaves to 250 ml of boiling water and steeping for 10 minutes and taken 1-3 times daily, sweetened if desired[49, 76, 116].

II. CONCLUSION:

The current review discussed the chemical constituents, pharmacological effects and therapeutic importance of *Hedera helix* as a promising medicinal plant with wide range of pharmacological activities which could be utilized in several medical applications because of its effectiveness and safety.

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Prof Dr Ali Esmail Al-Snafi "Pharmacological and therapeutic activities of Hedera helix- A review." IOSR Journal of Pharmacy (IOSRPHR), vol. 8, no. 05, 2018, pp. 41-53