The effects of *Hedera helix* on viral respiratory infections in humans: A rapid review

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A R T I C L E I N F O

A B S T R A C T

Brief overview: Based on the evidence identified in this rapid review, *Hedera helix* preparations and herbal complex preparations including *H. helix* may be a therapeutic option for treating early symptoms of respiratory tract infections. The best effectiveness for *H. helix* preparations has been proven for coughing, as an expectorant and to reduce the frequency and intensity of cough. Only weak evidence was found for all other researched symptoms. Both adults and children tolerate *H. helix* well. Currently, there is insufficient evidence to recommend the use of this supplement in the treatment or prevention of COVID-19. However, the current evidence justifies further research to better understand its applicability in coronavirus infections.

Verdic: tCurrent evidence suggests *H. helix* may improve the frequency and intensity of cough associated with viral respiratory infection. The overall applicability of additional findings is limited by the poorly defined outcome measures employed. However, studies focused explicitly on expectoration did report an increased conversion from dry to productive cough, and an improvement in expectoration amount, consistency and colour. These effects may be explained by a related finding of reduced oropharyngeal congestion and improved inflammatory markers (erythrocyte sedimentation rate and c-reactive protein). A decrease in frequency of night cough and respiratory pain was also reported, as was improved sleep quality and reduced cough-related sleep disturbance.

Some studies also measured general respiratory tract infection symptoms and identified clinical improvement or resolution of fever, fatigue, sore throat, sneezing, wheezing, nasal congestion, post-nasal drip and body-ache. A reduced need for antibiotic prescriptions was also identified. While not consistently reported, the majority of studies also found *H. helix* reduced the overall severity of viral bronchitis and related conditions. Tolerability was rated as between 'good' and 'high'. Adverse events were rare or non-existent in almost all studies, and those that were reported were defined as non-serious and not drug-related.

1. Background

Hedera helix (Common Ivy, English Ivy, Gum Ivy, Hederae Helicis Folium, Herbes à Cors, Hiedra Común, Ivy, Lierre, Lierre Commun, Lierre Grimpant, True Ivy, Woodbind) [1] leaf preparations are commonly used in the treatment of acute inflammatory respiratory conditions [2] including acute bronchitis of viral origin [3,4], and some chronic respiratory conditions including bronchial asthma [5] and chronic inflammatory recidivating bronchitis [6]. A 2011 systematic review investigating the use of *H. helix* in acute upper respiratory tract infections (URTIs) noted that *H. helix* preparations were generally very well tolerated and safe [2]. All the included trials endorsed *H. helix*'s effectiveness in treating URTIs, including

symptoms of cough, expectoration, dyspnoea and shortness of breath [2]. However, the authors also stated the need for further randomised controlled trials to confirm *H. helix's* effectiveness against placebo, and other pharmaceutical and herbal medicines for the treatment of acute URTIs [2]. Clinical trials have established the safety and efficacy profile of *H. helix* preparations in paediatric [2,3,6–8] and adult populations [2,4,8]. Active constituents of *H. helix* include hederasaponin-C, hederacoside C, hederagenin and alpha-hederin [1,9,10].

Herbal medicine is a core component of naturopathic practice worldwide [11]. Preparations made from *H. helix* are widely available in Australia, Europe, the Eastern Mediterranean region, and North, Central and South America [2,8,12,13]. The broncholytic and secretolytic effects of *H. helix* preparations cause an expansion of the bronchial tubes and increase the production of surfactant in the lungs, thus helping maintain alveolar function, while also breaking up bronchial secretions for ease of expectoration [8–10]. Cough is one of the most common early symptoms of COVID-19 infection (along with fever and fatigue) [14–16] with dyspnoea and increased sputum production also commonly present [15]. Onset of pulmonary oedema and pneumonia may also occur as the illness progresses, potentially resulting in further exacerbation of dyspnoea [15,17]. For these reasons, *Hedera helix* was chosen as a naturopathic therapy for the current rapid review, to investigate whether evidence could be found for its potential use in acute viral infections like COVID-19.

2. Search strategy

2.1. Research question

Does *Hedera helix* improve outcomes in humans with acute respiratory viral infections or chronic respiratory disease resulting from acute viral respiratory infections?

2.2. Inclusion/exclusion criteria

2.2.1. Inclusion criteria
Human clinical trials of paediatric and/or adult populations that investigated the use of *Hedera helix* in acute viral respiratory tract infections, or chronic respiratory disease resulting from acute viral respiratory infections, were included. Studies that focused on monotherapy using *H. helix* products, as well as studies where *H. helix* was used in conjunction with other herbal or pharmaceutical medications were included. Populations with chronic respiratory conditions were included where their condition explicitly started as an acute viral respiratory infection. There were no language exclusions.

The searches were date limited after scoping searches on systematic reviews investigating the role of *H. helix* in the treatment of respiratory viral infections was performed. A systematic review of clinical trials investigating *H. helix* in acute upper respiratory tract infections was published in 2011 [2]. Therefore, studies investigating the use of *H. helix* in acute respiratory viral infections were limited to trials from 2010−2020. A systematic review investigating the use of *H. helix* in chronic bronchial asthma was published in 2003 [5]. Therefore, studies looking at the use of *H. helix* in chronic respiratory conditions were limited to trials from 2002−2020.

2.2.2. Exclusion criteria
In vitro trials, in vivo animal studies, and studies that investigated bacterial or fungal based respiratory diseases were excluded. Studies were also excluded where the population presented with a chronic respiratory condition that was not explicitly described as originating from an acute respiratory infection (e.g. chronic asthma, COPD [Chronic Obstructive Pulmonary Disease]).

3. Databases

Medline (Ovid); EMBASE (Ovid); AMED (Ovid); CINAHL (EBSCO); Web of Science; Scopus

4. Search terms (example)

4.1. Medline (Ovid)

4.1.1. Search strategy for papers investigating *Hedera helix* and acute viral respiratory disease
Influenza, Human/ OR Influenza A Virus, H1N1 Subtype/OR Influenza A virus/OR Influenza A Virus, H3N2 Subtype/OR Middle East Respiratory Syndrome Coronavirus/OR respiratory tract infections/OR bronchitis/OR common cold/OR exp sinusitis/OR Influenza.mp OR H1N1.mpOR MERS−COV.mp OR Flu.mp OR Bronchit*.mp OR sinusit*.mp OR rhinosinusit*.mp OR common cold.mp OR rhinit*.mp OR Dyspn?ea.mp OR Sputum.mp OR Cough.mp OR Severe Acute Respiratory Syndrome.mp OR Pneumonia, viral.mp OR (breathing or lung or pulmonary or respir*).mp OR Respiratory Function Tests.mp OR (respiratory adj2 (infect* or illness or symptom* or acute or virus*)).mp AND [exp Hedera/ or Hedera.mp OR Ivy.mp OR Prospan.mp OR Panoto-S.mp OR (EA 575.mp) OR (Ivy leaves.mp) OR (Ivy leaves extract.mp)]

4.1.2. Search strategy for papers investigating *Hedera helix* and chronic viral respiratory disease
Influenza, Human/ OR Influenza A Virus, H1N1 Subtype/OR Influenza A virus/OR Influenza A Virus, H3N2 Subtype/OR Middle East Respiratory Syndrome Coronavirus/OR respiratory tract infections/OR bronchitis/OR common cold/OR exp sinusitis/OR Influenza.mp OR H1N1.mpOR MERS−COV.mp OR Flu.mp OR Bronchit*.mp OR sinusit*.mp OR rhinosinusit*.mp OR common cold.mp OR rhinit*.mp OR Dyspn?ea.mp OR Sputum.mp OR Cough.mp OR Severe Acute Respiratory Syndrome.mpOR Pneumonia, viral.mpOR (breathing or lung or pulmonary or respir*).mp OR Respiratory Function Tests.mp AND Chronic disease.mp AND [exp Hedera/ or Hedera.mp OR Ivy.mp OR Prospan.mp OR Panoto-S.mp OR (EA 575.mp) OR (Ivy leaves.mp) OR (Ivy leaves extract.mp)]

4.2. Screening and data extraction

Two authors (LB and DM) screened English language citations by title and abstract, and one author screened the German language citations by title and abstract (RL). Discrepancies were discussed to confirm papers to be included in the full text screening. Similarly, two authors screened citations by full text (DA and LB), and any discrepancies were resolved on discussion. Two authors extracted data from the included papers (DB and LB), and AS verified the accuracy of data extraction and reporting.

4.3. Critical appraisal

The revised Cochrane Risk of Bias tool for randomised trials (RoB2) [18] was used to assess the study findings of the prospective intervention studies. Retrospective and cross-sectional observation studies were assessed using a tool developed by Hoy et al. [19] for assessing risk of bias in prevalence studies. Three authors assessed the Risk of Bias in included papers (JC, DB and T-AP)

5. Rapid review results

Searches of the six databases identified 486 results, including 344 duplicates leaving 142 citations to be screened. After screening by title and abstract, 76 papers were excluded. The full text of the remaining 66 papers were screened, and a further 53 were

excluded as they did not meet the inclusion criteria. (Wrong study design = 31, wrong indication = 2, unable to obtain full text = 7, systematic review or meta-analysis = 12, summary of another research paper = 1.) The remaining 13 articles were included in this rapid review.

The thirteen included studies consisted of five observational studies [3,4,6,7,20], four randomised controlled trials [9,13,21,22], two open-label trials [23,24], one controlled clinical trial [25] and one retrospective analysis of case notes [26]. Two studies were reported as double-blind [9,22], two as single-blind [13,21], and two as open-label [23,24].

Studies were conducted across two World Health Organisation (WHO) regions [27]. The three trials conducted in the Eastern Mediterranean Region were all conducted in Pakistan [13,21,25]; the remaining ten trials were conducted in the European region, specifically in Germany [3,6,9,22,26], Slovenia [7], Switzerland [4,23], and Russia [20,24].

The thirteen included studies comprised a total pool of 210,481 participants, with sample sizes ranging between 36 and 173,226. Five studies recruited children only (with ages ranging between one month and 18 years [3,6,7,20,24], three studies recruited adults only (aged ≥18 years) [22,23,26], and four studies recruited both adults and children (aged ≥2 years) [4,9,13,21]; one study [25] did not describe the sample. Conditions under investigation varied from bronchitis (n = 3) [3,4,9], to non-specific respiratory tract infection symptoms (i.e. cough n = 2) [21,22], respiratory tract infection (n = 4) [7,13,24,26], non-specific inflammatory airway disease (n = 2) [6,23] and bronchial obstruction-syndrome (n = 1) [20]; one study [25] did not describe the presenting condition. One study included both acute bronchitis and chronic bronchitis, as well as other chronic respiratory diseases with intense formation of viscous mucous [23].

Hedera helix was administered in oral form in all thirteen studies, with seven studies [3,4,6,7,9,20,22] using a single-herbal formulation and six studies [13,21,23–26] using a multi-herbal formulation. The intervention was administered most frequently in syrup form (n = 4) [4,7,21,24], followed by tablet (n = 1) [25], ethanolic extract (n = 1) [22], drop [9] and granulated [13] forms. Four studies [3,6,20,26] used multiple forms of administration (i.e. syrup, drops, liquid, effervescent tablet, lozenges, powder, inhalant), and one study [23] did not describe the product form. Treatment duration ranged from 7 days to 20 days, with a median duration of 8.5 days. Dosage of *H. helix* was difficult to quantify in most studies due to inadequate or incomplete reporting of product composition. Of the eight studies reporting a control/comparator, three used a placebo control [13,21,22], two used an active control [4,9], one used standard treatment [24], and one used case controls [26]; in one study [25], the type of control/comparator was not described.

5.1. Critical appraisal

5.1.1. Prospective intervention studies (n = 7)

For Domain 1 (randomisation process), two studies were rated as having a high risk of bias [24,25], one was rated as having some concerns [23] and the remaining four studies were rated as low [9,13,21,22]. For Domain 2 (treatment assignment), one trial was identified as high risk of bias [24], two trials were rated as having some concerns [23,25], and four trials rated as low risk of bias [9,13,21,22]. Under Domain 3 (missing outcome data), one trial was considered to have high risk of bias [24], with six trials rated as low [9,13,21–2325]. For Domain 4 (measure of outcomes), one study was rated as high risk [25], one was rated as having some concerns [24], and five were rated as low risk of bias [9,13,21–23]. In Domain 5 (selective reporting), three trials were rated as having some concerns [13,21,25], with the remaining four trials rated as having

low risk of bias [9,22–24]. Overall, two studies were judged as having high risk of bias [24,25], three were rated as having some concerns [13,21,23] and two were judged as low risk of bias [9,22].

5.1.2. Retrospective and cross-sectional observation studies (n = 6)

For Domain 1 (representative target population), one study was identified as high risk of bias [3], the remainder were rated as low risk of bias [4,6,7,20,26]. For Domain 2 (representative sampling frame) one study was identified as high risk of bias [3], five studies were rated as low bias [4,6,7,20,26]. Under Domain 3 (random selection/census taken), four trials were rated as high risk of bias [3,7,20,26], one was rated as having some concerns [6] and one was rated as low [4]. For domain 4 (non-response bias), one trial was identified as high risk of bias [20], five trials were rated as low risk of bias [3,4,6,7,26]. Under Domain 5 (direct data collection), one trial was considered to have high risk of bias [26], with five trials rated as low [3,4,6,7,20]. For Domain 6 (acceptable case definition), all studies were judged to be low risk of bias [3,4,6,7,20,26]. Under Domain 7 (instrument reliability/validity), one trial was identified as high risk of bias [6], one was rated as having some concerns [20], the remaining four trials were rated as having low risk of bias [3,4,7,26]. In Domain 8 (data collection) and Domain 9 (prevalence period) all trials were judged to be at low risk of bias [3,4,6,7,20,26]. For Domain 10 (appropriate numerators/denominators) one trial was considered to have high risk of bias [3], one was identified as moderate risk of bias [20] and four were found to be at low risk of bias [4,6,7,26]. Overall, one study was identified as high risk of bias [3], two were rated as having some concerns [6,20] and three were judged to have a low risk of bias [4,7,26].

These judgements should be taken into consideration when interpreting the findings of this review (See Additional File 1 Risk of Bias Summary Tables).

5.2. Summary of findings

The thirteen included studies reported on twelve distinct outcomes, including frequency/intensity of cough, characteristics of expectoration, severity/resolution of respiratory tract infection (RTI) symptoms, mucosal congestion, inflammatory biomarker activity, need for antibiotic therapy, global severity of disease, duration of sick leave, wellbeing, sleep quality, tolerability of intervention, and adverse events.

Cough frequency/intensity was assessed in six studies using an undefined cough questionnaire [21,23], undefined measure of cough frequency/intensity [20,24], visual analogue scale [22], or Verbal Category Descriptive Score (VCDS) [22]. All six studies reported an improvement in cough frequency and/or intensity in the intervention group, with three studies demonstrating improvements relative to placebo [21,22] or standard treatment [24].

Global severity of disease was assessed in five studies, using either the Bronchitis Severity Score (BSS) [3,4,9,22] or the Clinical Global Impression (CGI) scale [3]. Two studies [3,22] reported improvements in BSS and/or CGI among participants receiving *H. helix* preparations, with one study [22] demonstrating comparative improvement against placebo. Cwientzek et al. [9] found the intervention to be noninferior to active control (i.e. another *H. helix* preparation). Outcome data could not be extracted from one study [4].

Four studies assessed changes in the characteristics of expectoration using either a four-point scale [6,23] or an undefined measure [7,24]. Two studies reported an improvement in expectoration in the intervention group, including expectoration amount [6,23], consistency, ease and colour [23]. One study found a higher rate of conversion from dry cough to productive cough in the intervention group relative to standard treatment [24]. The

fourth study [7] also reported an improvement in expectoration, decrease in night cough frequency and decrease in respiratory pain in children aged 2–14 years with acute respiratory infection, but did not articulate how this outcome was measured.

Changes in general RTI symptoms were measured in two studies, using either an undefined questionnaire [21], or a four-point clinical improvement scale [13]. For both studies, a greater proportion of participants in the intervention group (i.e. multi-herbal formulations containing *H. helix*) reported clinical improvement or resolution of fever, fatigue, sore throat, sneezing, wheezing, nasal congestion, post-nasal drip and/or body ache relative to participants receiving placebo. Differences between groups were found to be statistically significant for all symptoms in Khan et al.'s 2018 study [13]. The treatment group in Ali et al.'s 2017 study [21] showed statistically significant levels of improvement in cough, fever, sore throat, wheezing, postnasal drip and body ache after treatment with the *H. helix* formulation compared with the placebo group.

Mucosal congestion and inflammatory biomarker activity (i.e. erythrocyte sedimentation rate [ESR] and serum C-reactive protein [CRP]) were assessed in one study [24]. When compared with standard treatment, administration of a multi-herbal formulation containing *H. helix* for 7–17 days was associated with a statistically significant improvement in oropharyngeal mucosal congestion, ESR and CRP concentration in children with acute viral RTI.

Two studies assessed need for antibiotic therapy [24,26]. Both studies reported fewer antibiotic prescriptions among participants receiving *H. helix* preparations versus participants receiving standard therapy [24] or case controls [26].

Duration of sick leave was measured in one study [26]. Sick leave duration was shown to be significantly shorter among participants receiving *H. helix* preparations versus case controls.

Change in wellbeing was assessed in one study using a five-point rating scale [6]. This study reported an improvement in wellbeing in participants receiving *H. helix* syrup/cough drops.

Changes in sleep quality were evaluated in two studies, using either an undefined measure [3], or a five-point rating scale [6]. The studies reported an improvement in sleep quality [6] or cough-related sleep disorder/disturbance [3] over an average period of 7–11 days among participants receiving *H. helix* preparations.

Five studies examined the tolerability of the intervention using either an undefined method [20,22,24] or a five-point scale [6,9]. Tolerability/compliance was rated as either good [9,22,24], good to very good [6], or high [20].

Adverse events were specifically assessed in twelve studies [3,4,6,7,9,13,20–25]; only one study did not explicitly report on adverse events [26]. Four papers reported that no cases of adverse events occurred among participants receiving *H. helix* preparations [13,20,21,24]. Only one adverse event, a case of diarrhoea, was reported in Kruttschnitt et al.'s study [4]; data on this participant were not included in the final study sample as authors were not able to obtain complete data from this subject [4]. One four year old boy developed a skin rash after being administered *H. helix* in Beden et al.'s paediatric study [7]. Schaefer et al. reported fewer cases of adverse events in the *H. helix* group versus control group (i.e. 9 vs. 12 cases), with all events stated to be "non-serious, of mild or moderate severity and not drug-related" [22, p507]. Cwientzek et al. [9] reported an adverse event rate of 2.7 % in each group (n = 7 in the treatment group; n = 7 in the control group), of which all events were non-serious and primarily gastrointestinal in nature. Schmidt et al. [6] reported five cases of non-serious adverse effects among participants receiving *H. helix* preparations, including four gastrointestinal complaints (diarrhoea, nausea or vomiting), and one dermatitis event.

6. Clinical significance

Based on the evidence identified in this rapid review, *Hedera helix* preparations and herbal complex preparations including *Hedera helix* may be a therapeutic option for treating early symptoms of respiratory tract infections in adults and children. The best effectiveness for *H. helix* preparations has been proven for coughing. There is limited evidence suggesting *H. helix's* possible value in night coughing and cough-related sleep disturbance. Weak evidence also suggests *H. helix* may improve cough expectoration and other global virus-related symptoms (e.g. fever, fatigue, sore throat, body-ache, etc.). Currently, there is insufficient evidence to recommend the use of this supplement in the treatment or prevention of COVID-19. However, the current evidence justifies further research to better understand its applicability in coronavirus infection.

Disclaimer

This article should not replace individual clinical judgement. The views expressed in this rapid review are the views of the authors and not necessarily from the host institutions. The views are not a substitute for professional medical advice.

Authors' contributions

LB and RL refined the research question and developed the search strategies. LB undertook the searches. DM and LB screened the English-language citations by abstract and title. RL screened the German-language citations by abstract and title. DA and LB screened the full text articles. DB, LB and AB extracted data from the included papers. JC, DB and T-AP performed the Risk of Bias assessments and JC drafted the Risk of Bias summary. ML drafted the results. DA drafted the clinical summary. LB drafted the background, search strategy and methods sections of the manuscript. AS drafted the overview and verdict sections. LB, ML, and AS critically revised the Rapid Review.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.aimed.2020.07.012.

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