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Ginseng integrative supplementation for seasonal acute upper respiratory infections: A systematic review and meta-analysis

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ABSTRACT

Background: The aim of the review was to assess whether ginseng can be a useful supplementation for seasonal acute upper respiratory infections (SAURIs).
Methods: All clinical studies investigating ginseng efficacy for the treatment or prevention of SAURIs were included in the review. Medline, EMBASE, Web of Science, Scopus, Cochrane Library, Google Scholar were systematically screened for relevant articles up to May 26th, 2020. The risk of bias was assessed with the Cochrane tool (RoB 2).
Results: Nine articles (describing ten trials about *P. ginseng* or *P. quinquefolius*) were included in the review. Evidence globally indicated some useful activity of intervention when administered in adjunct to influenza vaccination. The results of our quantitative synthesis suggested a significant effect on SAURIs incidence (RR = 0.69 [95 % C.I. 0.52 to 0.90], $p < 0.05$), as well as a significant reduction of their duration if only studies with healthy individuals were included in the analysis (MD = -3.11 [95 % C.I. −5.81 to -0.40], $p < 0.05$). However, the risk of bias was high-to-unclear for most included trials, and publication bias couldn't be excluded.
Discussion: Limitations of existing evidence don't allow to draw conclusions on the topic. Nevertheless, it is not excluded that ginseng supplementation in adjunct to influenza vaccination and standard care might be useful for SAURIs prevention and management in healthy adult subjects, but further high-quality trials are needed to support this hypothesis.
Other: This research was not funded. The protocol was registered in PROSPERO under the following code: CRD42020156235.

1. Introduction

1.1. Rationale

Seasonal acute upper respiratory infections (SAURIs) refer to infectious conditions involving the upper respiratory tract which mostly occur during cold months of the year, especially in winter.[1,2] Common symptoms of SAURIs often include cough, sore throat, runny nose, nasal congestion, sneezing, headache, fever, malaise, and myalgias.[2] The etiology of SAURIs is mostly viral, with bacteria approximately accounting for only 15 % of all cases.[1,2] In particular, over 200 different viruses can cause acute upper respiratory infections, and such viruses generally belong to one of the following six microbial families: orthomyxoviruses (influenza), paramyxoviruses (respiratory syncytial virus), parainfluenza viruses, coronaviruses, picornaviruses (common cold), herpes viruses, and adenoviruses.[1] From an epidemiological point of view, the most relevant ones are picornaviruses like rhinoviruses, often responsible for the common cold, and flu viruses, which can cause influenza.[2] Despite several similarities, these two diseases show slightly different epidemic trends: influenza exhibits the typical seasonal incidence during wintertime, whereas the common cold can potentially occur all the year long but its incidence only peaks in cold months of the year.[3] Although usually self-limiting, SAURIs can be sometimes followed by severe respiratory, cardiovascular or general complications with poor clinical outcomes especially in elderly subjects, fragile individuals or patients with important comorbidities.[4] According to the Centers for Disease Control and Prevention (CDC), over the last influenza season in the United States (2018-2019), it was estimated that flu-related hospitalizations were around 810.000, with 61.000 flu-associated deaths.[5] From a socio-economic perspective, the average annual

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total economic burden of influenza to the US healthcare system and society was calculated to be around $11.2 billion,[6] and the total impact of non-influenza-related viral respiratory tract infections was estimated to be approximately $40 billion annually,[7] with the common cold being responsible for 40 % of all time lost from working activities.[3] Therefore, taken together, all these data highlight that SAURIs have a relevant impact not only on individual wellbeing and quality of life, but also on public health, community resources and productivity.

To date, the common treatment of SAURIs is mostly symptomatic (with a limited array of antiviral medications to be used in selected conditions) and, beyond basic hygienic rules employed for the prevention of airborne infections, prophylactic strategies involving a specific vaccination are only available for a few microorganisms like influenza viruses.[8,9] Among all medicinal herbs, ginseng is a complementary herbal remedy with a long-standing tradition, especially in some Asian and American countries, where it is still used for the treatment and prevention of various diseases, including SAURIs.[10–13] Surveys have also shown that physicians, pharmacists, and patients have a favorable general attitude towards the integrative clinical use of medicinal plants, but a lack of knowledge regarding actual properties and limits of such interventions has been reported even among health professionals, thus underscoring the necessity to study the topic in depth and to better disseminate relevant information for the promotion of evidence-based practices.[14–16]

The main ginseng species used in clinical practice are Korean ginseng (*Panax ginseng*), American ginseng (*Panax quinquefolius*), and Chinese ginseng (*Panax notoginseng*).[17,18] Some of the main constituents of these three ginseng species are polysaccharides and saponins like dammarane ginsenosides, which are transformed by the drug preparation procedure (steaming and heating) into ginsenosides Rg3, Rg5, Rk1, later converted by the intestinal microflora into bioactive substances such as compound K, ginsenoside Rh1, and protopanaxatriol (PPT).[18,19] Although similar, the chemical composition of *P. ginseng*, *P. notoginseng*, and *P. quinquefolius* shows some differences with regard to the type and quantity of specific ginsenosides.[18] In particular, the ratio between ginsenosides Rg1/Rb1 varies among the three species, and the majority of ginsenosides found in Korean ginseng are Rb1, Rg1, Rb2, whereas in American ginseng they are Rb1, Re, Rd, and in Chinese ginseng they are Rb1, Rg1, Ra3, and R1.[18] Differences have been also observed in the volatile composition of the three species, mainly characterized by the presence of various sesquiterpenes.[20] Additionally, regardless of biochemical differences due to specific botanical origins, both the preparation method [21] and the individual characteristics of enteric microflora [18] can influence the type and quantity of bioactive compounds that are absorbed through the intestine. In order to minimize such variability, controlled preparation methods have been developed, including fermentation with enzymes or microorganisms for the reduction of the impact of metabolization by the intestinal microflora,[18] and standardized extracts with a minimum amount of ginsenosides have been proposed for clinical uses.[17]

1.2. Objectives

The aim of the review was to assess whether ginseng can be a useful integrative supplementation for the prevention and/or treatment of seasonal acute upper respiratory infections (SAURIs).

2. Materials and methods

2.1. Protocol and registration

This review was conducted in accordance with the PRISMA guidelines.[22] The protocol was registered both in Open Science Framework (link: https://osf.io/rw369, DOI: 10.17605/OSF.IO/RW369), and in PROSPERO (code: CRD42020156235). A copy of the review protocol can be also found in the Appendix 1 of this article for a rapid consultation. The Appendix 2 contains the 27-item PRISMA checklist.

2.2. Eligibility criteria

All articles describing the efficacy of ginseng for the treatment or prevention of seasonal acute upper respiratory infections (SAURIs) were included in the review.

The following PICOS criteria for inclusion and exclusion of studies in the systematic review were applied:

2.2.1. Population

Inclusion: patients (any age) with SAURIs (e.g.: influenza or common cold), reporting at least a respiratory symptom like runny nose, sneezing, cough, sore throat, nasal or sinus congestion, in combination with at least a systemic symptom like fever, chills, myalgia, fatigue, headache. All relevant studies were included regardless of their participants' comorbidities.

Exclusion: patients affected by non-respiratory or chronic infections.

2.2.2. Intervention

Inclusion: the oral administration of any extract obtained from ginseng (*Panax ginseng*, *Panax notoginseng*, or *Panax quinquefolius*) at any dosage over a well defined period (regardless of its duration).

Exclusion: the administration of a multicomponent remedy including ginseng, unless ginseng is the main component of the formulation accounting for the majority ($>$ 90 %) of its composition.

2.2.3. Control

Inclusion: any type of control (placebo, no treatment) or comparison (treatment-as-usual, other therapies), including no comparison.

Exclusion: none.

2.2.4. Outcomes

Inclusion: primary therapeutic outcome (efficacy): duration, severity, and type of symptoms; primary preventive outcome (efficacy): incidence of SAURIs during the study period; secondary outcome (safety): adverse events reported in each included study.

Exclusion: other outcomes only.

2.2.5. Study design

Inclusion: any study involving humans, both clinical trials and observational studies.

Exclusion: preclinical studies with laboratory animals or cellular models.

All studies written in English, French, Spanish, Italian, or Portuguese were included regardless of their date of publication. Only studies described in articles already published in a scientific journal by the date of search were included in this work.

2.3. Information sources

The main information sources were Medline (accessed via PubMed), EMBASE, Web of Science, Scopus, and Cochrane Library. Additional sources were the Clinical Trials Register of the U.S. National Library of Medicine (ClinicalTrials.gov), the European Union Clinical Trials Register, the Chinese Clinical Trial Registry, and Google Scholar.

All sources were first screened up to November 1 st, 2019. Then, the original search has been conducted again and updated on May 26th, 2020.

2.4. Search

The search strategy for Medline, searched through PubMed, was the following one:

(ginseng[Title/Abstract] OR panax[Title/Abstract] OR notoginseng [Title/Abstract] OR quinquefolius[Title/Abstract] OR ginsenoside

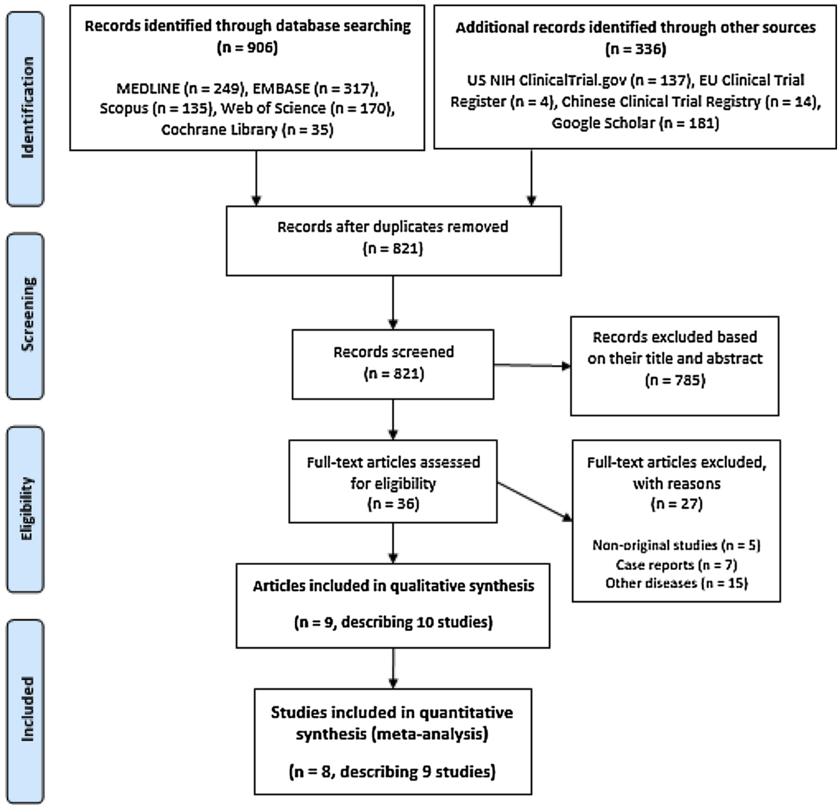

Fig. 1. PRISMA flow diagram describing the process of article screening and selection.
Caption: The structure of the flowchart was adapted from Moher et al., 2009. doi:10.1371/journal.pmed1000097

[Title/Abstract] OR gintonin[Title/Abstract]) AND (influenza[Title/Abstract] OR "influenza-like"[Title/Abstract] OR flu[Title/Abstract] OR "flu-like"[Title/Abstract] OR rhinitis[Title/Abstract] OR cold[Title/Abstract] OR respiratory[Title/Abstract])

Specific search strategies used for each source were summarized in a table, along with the number of retrieved results (Supplementary Material A).

2.5. *Study selection*

Details about article screening and study selection process were reported in a flowchart (Fig. 1).

Two reviewers (M.A.; D.D.) independently screened and selected studies for inclusion in the systematic review. Disagreements between individual judgements were resolved with the discussion of each decision with the third author (F.F.) until consensus was reached. The entire procedure was performed with the help of a dedicated software (EndNote Program, version X4).

The following PICOS criteria for inclusion and exclusion of studies in the meta-analysis were applied:

2.5.1. *Population*

Adult subjects with SAURIs (e.g.: influenza or common cold) and no relevant comorbidities. In order to maximize retrievable evidence on the topic and to reduce the risk of publication bias, data from studies involving sub-healthy participants were also included. Sub-healthy subjects were defined as individuals affected by a stable and mild or early-stage chronic condition, taking no drugs and not affected by any other relevant disease. Additional analyses were performed to evaluate the impact of studies not involving healthy subjects on the overall result of our quantitative synthesis.

2.5.2. *Intervention*

The oral administration of any extract obtained from ginseng (*Panax ginseng*, *Panax notoginseng*, or *Panax quinquefolius*) at any dosage over a well defined period (minimum: 8 weeks).

2.5.3. *Control*

The oral administration of placebo pills.

2.5.4. *Outcomes*

Outcome 1: the risk ratio for being infected throughout the study period.

Outcome 2: the duration of disease symptoms (measured in days) after being infected.

2.5.5. *Study design*

Randomized Controlled Trials (RCTs).

2.6. *Data collection process*

One reviewer (M.A.) manually extracted data from included studies using an a priori designed Excel form, while another one (D.D.) performed an additional check to ensure the correctness of extracted data by the first reviewer. Disagreements were resolved with the third author (F.F.) until consensus was reached. When article full-texts or essential details of included studies were missing, authors were contacted both by email and through ResearchGate®. However, no additional useful information was collected in this way, and for one study it was only possible to retrieve the article abstract.[23] Despite this, considering that the study summary provided sufficient information to meet the PICOS criteria, it was decided to include the trial all the same in order to maximise retrievable evidence on the topic.

2.7. Data items

The following data were extracted: participants' demographics and baseline characteristics (including their influenza vaccination status), details regarding intervention (e.g.: ginseng type, dose, duration of administration) and comparison type, outcome measures (duration, severity, and symptoms of SAURIs; incidence of SAURIs during the study period; microbial etiology of respiratory infections; reported adverse events), information about study design, funding sources and country where the trial was performed. End-of-study significant differences between groups in any efficacy or safety outcome were also reported.

The most relevant data were summarized in a table (Table 1), an extended version of which was reported in the supplementary materials of the present work (Supplementary Material B).

2.8. Risk of bias in individual studies

Version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2) was used for the quality assessment of included RCTs.[24] Analyzed domains were the following ones: risk of bias arising from the randomization process, risk of bias due to deviations from the intended interventions, missing outcome data, risk of bias in measurement of the outcome, risk of bias in the selection of the reported result, and the overall risk of bias.

Results of the assessment was adequately considered to inform the qualitative data synthesis in the discussion section of the review. Two reviewers were involved in the quality assessment of included studies (M.A.; D.D.). Disagreements between reviewers' judgements were resolved by discussing any relevant issue with a third reviewer (F.F.).

All details regarding the risk of bias final assessment were displayed in Fig. 2.

2.9. Summary measures

In the first meta-analysis, the chosen measure of effect size was the relative risk (RR) for being infected throughout the study period. The Mantel-Haenszel method was used to weight each trial and, when necessary, the treatment arm continuity correction (TACC) was applied.[25] Results of this meta-analysis were graphically displayed with a L'Abbé plot, a dedicated scatter plot for binary data (Fig. 3).

In the second meta-analysis, the chosen measure of effect size was the duration of disease symptoms (measured in days) after being infected. The mean difference (MD) was adopted to combine data of all includible studies and the inverse variance method was used to weight each included trial. Results of this meta-analysis were graphically displayed with a forest plot (Fig. 4).

2.10. Synthesis of results

Data synthesis was conducted per trial arm, thus using aggregated data rather than individual participant data. Trials with three arms (two interventional/ginseng-based and one control/placebo arm) were considered as if they were two different studies: the first one comparing one intervention with control, while the second one comparing the other intervention with control. A random-effects model was adopted for both meta-analyses. The Hartung-Knapp-Sidik-Jonkman adjustment for random-effects models was applied, since it is demonstrated that it outperforms the standard DerSimonian-Laird method.[26]

The threshold for significance of the overall effect size was set at $p < 0.05$.

I^2 was used as a measure of consistency, and I^2 values of 25 %, 50 %, and 75 % were interpreted as representing small, moderate and high levels of heterogeneity, respectively.[27]

Statistical analysis was performed with "R-Studio" software by two authors (D.D.; M.A.), and, in cases of disagreement, a third author (F.F.) was consulted to reach consensus.

2.11. Risk of bias across studies

Following the Cochrane recommendations, publication bias was assessed with a dedicated funnel plot, the Egger's test and the trim-and-fill method in the first meta-analysis (where the number of trials was close to 10), but this approach was not feasible in the second meta-analysis, due to the limited number of included studies.[28] In particular, first of all, the funnel plot was visually assessed, and asymmetry as well as an irregular arrangement of points (representing included studies) were considered suggestive for publication bias.[29] Then, the Egger's test was performed and, as recommended by its authors, a statistically significant result was interpreted as an indication of publication bias.[30] Afterwards, if previous tests were positive, the trim-and-fill method was applied as a sensitivity analysis in order to provide an estimated effect of intervention after adjusting it for the publication bias.[28,31,32]

The p-curve method was adopted for both meta-analyses to further assess the risk of bias across studies and to detect any potential "p-hacking".[33,34] The p-curve method was used to test if the sets of included studies were, on average, powered enough to detect a true effect of studied intervention, and to correct for the potentially inflated estimates that arise from the publication of results intentionally modified to be significant ("p-hacking").[33,34]

All these analyses, aimed at assessing the potential risk of bias across studies, were performed with "R" software.

2.12. Additional analyses

A qualitative subgroup analysis was performed with regard to the patient's specific etiology of reported acute upper respiratory infection (influenza viruses or other microorganisms), ginseng subspecies (*Panax ginseng*, *Panax notoginseng*, or *Panax quinquefolius*), outcome of interest (therapeutic efficacy or prevention), and study design.

A quantitative sub-group analysis was performed by separating studies in which different ginseng subspecies were administered to patients.

Another sub-group analysis was performed by separating studies characterized by high versus non-high overall risk of bias (rated in accordance with the above mentioned Cochrane tool), in order to analyze to what extent the result was influenced by the inclusion of potentially flawed trials.

Finally, given that in one included trial sub-healthy individuals with early-stage chronic leukemia were recruited,[35] a leave-one-out analysis was performed to estimate the effect size of intervention exclusively based on data of studies with healthy subjects.

It was not possible to perform any meta-regression to find explanations for heterogeneity, due to the limited number of included studies.

3. Results

3.1. Study selection

The search of electronic databases and trial registries globally yielded 1242 results, and 821 articles remained when duplicates were removed. After the screening and selection process, nine articles describing ten studies were included in the review.[23,35–42] In one article, two trials were reported, labeled as "Trail A: CVT-E002 9907" and "Trail B: CVT-E002 2000 − 1" respectively.[36] Details about the article screening and selection process were reported in a dedicated flow diagram (Fig. 1).

Table 1
Main characteristics of included studies.

Reference	POPULATION				INTERVENTION	CONTROL	OUTCOMES				STUDY
First author, date	N	Age	Health	Flu vaccine	Type (n, PP)	Type (n, PP)	Outcome measure	Preventive efficacy (infected patients: %)	Therapeutic efficacy (duration of disease: days)	Therapeutic efficacy (symptoms severity)	Design
High et al., 2012 [35]	293	Adults, Elderly	CLL	Some	P. quinquefolius (137)	Placebo (143)	Symptomatic + Jackson Cold Scale	51 % vs 56 % (ns)	8.5 ± 17.2 vs 6.8 ± 13.3 (ns)	Yes	RCT
Hwang et al. 2019 [42]	45	Adults	None	None	P. ginseng GS-3K8 (14) (a) and GINST (15) (b)	Placebo (15)	Symptomatic	64.3 % (a) vs 80.0 % (ns) 26.7 % (b) vs 80.0 % (*)	3.89 ± 4.65 (a) vs 12.25 ± 12.69 (ns) 9.25 ± 1.22 (b) vs 12.25 ± 12.69 (ns)	–	RCT (pilot)
Lee et al., 2012 [41]	100	Adults	None	None	P. ginseng (49)	Placebo (49)	Symptomatic	24.5 % vs 44.9 % (*)	5.2 ± 2.3 vs 6.3 ± 5.0 (ns)	No	RCT
McElhaney et al., 2004 (Trial A: CVT-E002 9907) [36]	89	Elderly	None	Some	P. quinquefolius (35)	Placebo (43)	Symptomatic + laboratory confirmation of influenza or RSV infection	Symptoms-confirmed infections: 34 % vs 36 % (ns). Lab-confirmed flu: 1% vs 7% (*). Lab-confirmed flu or RSV infections: 1% vs 9% (*)	No significant difference between groups.	No	RCT
McElhaney et al., 2004 (Trial B: CVT-E002 2000−1) [36]	109	Elderly	None	Some	P. quinquefolius (48)	Placebo (45)				No	RCT
McElhaney et al., 2006 [37]	43	Elderly	None	All	P. quinquefolius (22)	Placebo (21)	Symptomatic	31.8 % vs 61.9 % (*)	5.6 ± 2.9 vs 12.6 ± 7.6 (*)	–	RCT
McElhaney et al., 2011 [38]	783	Elderly	None	All	P. quinquefolius Full-dose (196) (a) and half-dose (210) (b)	Placebo (197)	Symptomatic + Jackson Cold Score + laboratory confirmation of influenza or RSV infection	Symptoms-confirmed infections: 19.4 % (a); 20.0 % (b) vs 28.9 % (*). Lab-confirmed: 4.6% (a); 4.3% (b) vs 6.1% (ns)	2.93 ± 7.2 (a); 3.13 ± 7.9 (b) vs 4.87 ± 11.2 (ns; p = 0.05)	No (p = 0.05)	RCT
Predy et al., 2005 [39]	323	Adults	None	None	P. quinquefolius (130)	Placebo (149)	Symptomatic + Jackson Cold Scale	54.6 % vs 63.8 % (ns)	8.7 ± 7.2 vs 11.1 ± 8.1 (*)	Yes	RCT
Scaglione et al., 1996 [23]	227	?	?	All	P. ginseng (114)	Placebo (113)	Symptomatic	13.2 % vs 37.2 % (*)	?	?	RCT

(*continued on next page*)

Table 1 (*continued*)

Reference	POPULATION				INTERVENTION	CONTROL	OUTCOMES				STUDY
First author, date	N	Age	Health	Flu vaccine	Type (n, PP)	Type (n, PP)	Outcome measure	Preventive efficacy (infected patients: %)	Therapeutic efficacy (duration of disease: days)	Therapeutic efficacy (symptoms severity)	Design
Vohra et al., 2008 [40]	46	Children	None	None	P. quinquefolius Full-dose (13) (a) and low-dose (14) (b)	Placebo (15)	Symptomatic (ICHPPC) + CARIFS score	–	1.5 ± 1.6 vs 1.9 ± 2.2 (a) (ns) 1.9 ± 1.5 vs 1.9 ± 2.2 (b) (ns)	–	RCT (pilot)

Legends:
POPULATION.
N patients = number of patients randomized in each included trial.
Age = elderly if age > 65 years old, adults if age range is 18–65, adolescents if age range is 12–18, children if age < 12 years old.
Health = health comorbidities (CLL: Chronic Lymphocytic Leukemia; none: healthy participants with no relevant comorbidities).
Flu vaccine = flu vaccination status (all: all patients vaccinated; some: some patients vaccinated; none: no patients vaccinated).
INTERVENTION.
Type (n, PP) = type of intervention and number of patients assigned to the intervention group who completed the study (per-protocol).
CONTROL.
Type (n, PP) = type of control and number of patients assigned to the control group who completed the study (per-protocol).
OUTCOMES.
CARIFS = Canadian Acute Respiratory Illness and Flu Scale.
ICHPPC = International Classification of Health Problems in Primary Care.
RSV = Respiratory Syncytial Virus.
Preventive efficacy (infected patients: %) = percentage of patients who developed a seasonal acute respiratory infection at least once during the study period (significant - $p < 0.05$ - difference between groups).
Therapeutic efficacy (duration of disease: days) = duration of disease in days (see Supplementary Table A.3 for further details) (significant - $p < 0.05$ - difference between groups).
Therapeutic efficacy (symptoms severity) = report of any significant ($p < 0.05$) difference in disease symptoms severity favoring ginseng intervention groups (yes/no/not reported) (significant - $p < 0.05$ - difference between groups).
(*) = statistically significant ($p < 0.05$).
(ns) = non-statistically significant ($p \geq 0.05$); when p = 0.05, it was explicitly indicated in the table.
- = not investigated.
? = irretrievable data.

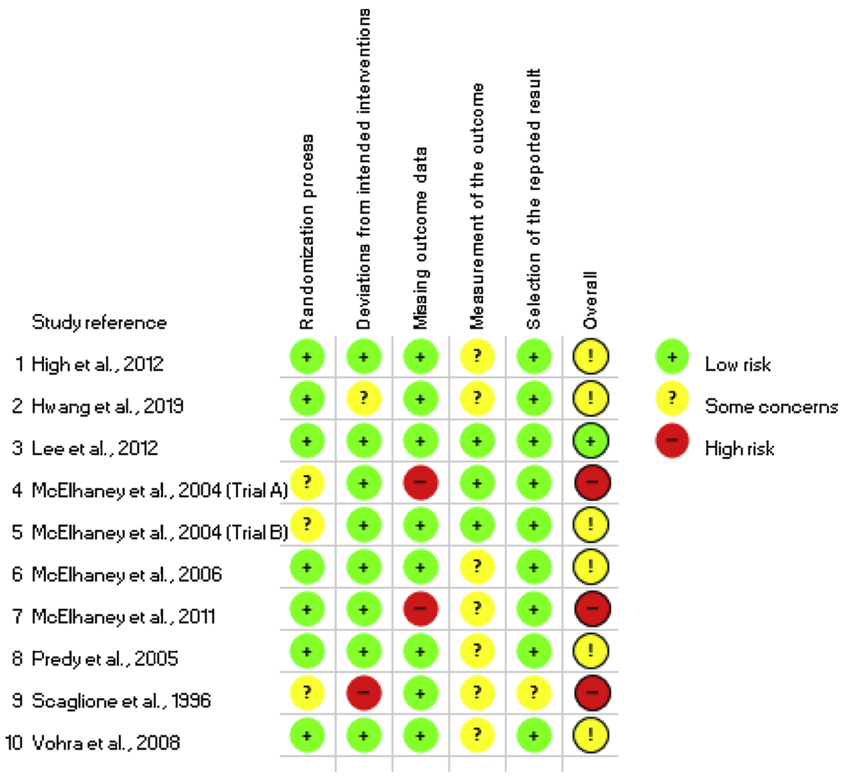

Fig. 2. Risk-of-bias assessment of included trials.
Caption: The risk of bias of included studies was assessed with the Cochrane's tool (RoB 2). Analyzed domains were the randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome, selection of the reported result, and the overall risk of bias. Standard conventional symbols were used to indicate low, unclear or high risk of bias, as described in the figure.

3.2. Study characteristics and results (PICOS)

3.2.1. Population

Overall, 2058 patients were recruited in included studies, and the number of subjects ranged from a minimum of 43 to a maximum of 783 (median: 1045) across trials comprised in the systematic review. Females were more represented than males, accounting, on average, for around 57 % of study populations. In one study, participants were children with a mean age of 5 years old,[40] whereas in four trials (described in three articles) only elderly subjects, aged 65 and above, were

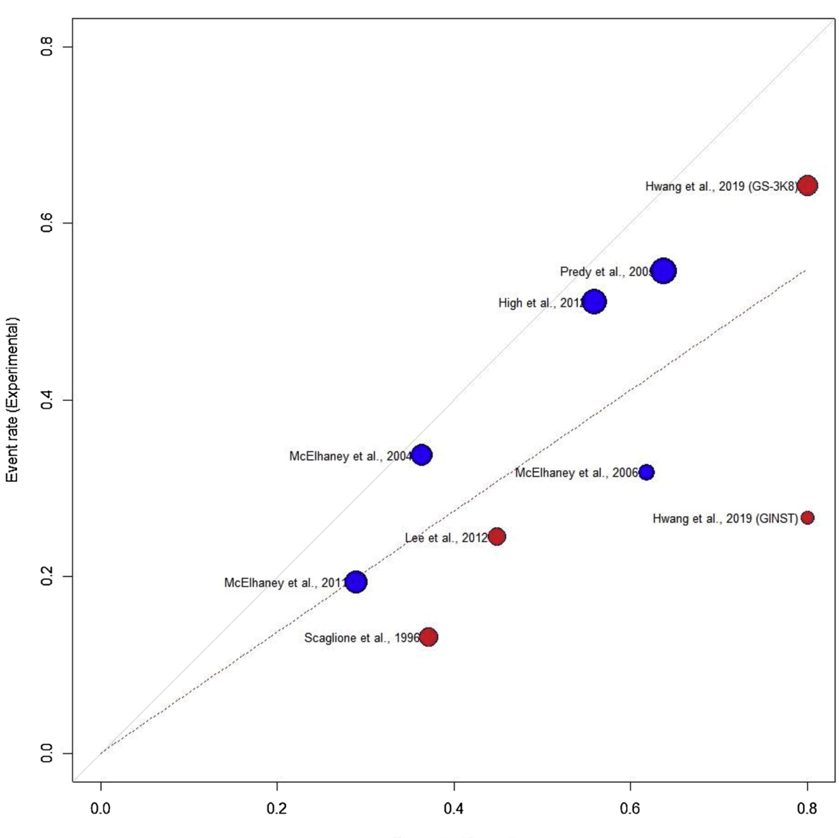

Fig. 3. L'Abbé plot referred to the first meta-analysis: risk for developing a respiratory infection.
Caption: The first meta-analysis aimed to assess the relative risk for developing a seasonal acute upper respiratory infection at least once during the study period (winter seasons). Intervention was defined as taking ginseng and all trials were placebo-controlled. Each point represented a study included in the quantitative synthesis (red: *P. ginseng*; blue: *P. quinquefolius*). The X axis indicated the event rate in the control group, whereas the Y axis displayed the event rate in the experimental intervention group.

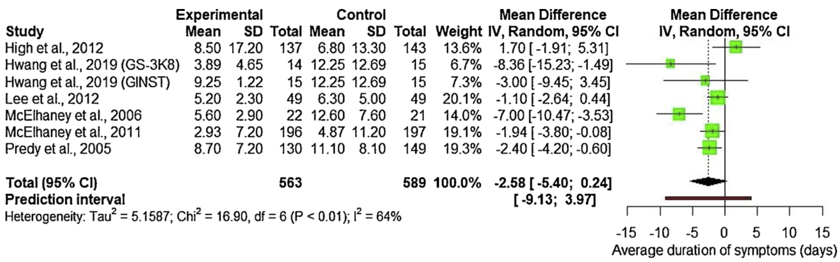

Fig. 4. Forest plot representing the second meta-analysis: duration of symptoms.
Caption: Forest plot referred to the meta-analysis about the duration of symptoms (measured in days) of seasonal acute upper respiratory infections. Means and standard deviations were reported in columns and a random-effect model was adopted to better estimate overall size effects. Experimental intervention was represented by taking ginseng extracts, and control by taking placebo pills.

recruited.[36–38] In one trial, study population was composed of patients with Chronic Lymphocytic Leukemia (CLL) [35]; in all the other included RCTs, participants were healthy subjects with no relevant comorbidities. Influenza vaccination status of participants varied across included studies: in four trials, subjects were recruited only if not vaccinated against the flu in the past 3 [40] or 6 months [39,41,42]; in three studies, patients were all vaccinated [23,37,38]; in the remaining included RCTs, flu vaccination status was heterogeneous with only some participants being vaccinated, but no significant differences between groups were detected.[35,36] Lifestyle habits (tobacco smoking or alcohol drinking) of study subjects, when reported, were described in the Supplementary Material B.

3.2.2. Intervention

In seven studies *P. quinquefolius* was administered to participants,[35–40] whereas in three trials *P. ginseng* was given to patients.[23,41,42] No included study investigated the effects of *P. notoginseng* on SAURIs.

In two studies, one group of participants was administered the ginseng extract given to the main intervention group but at a low-dose regimen. [38,40] In one trial, intervention groups were given two different types of ginseng extracts named "GS-3K8" and "GINST" respectively. [42] In all but one RCTs, intervention was administered daily for 8–16 weeks, whereas in the trial conducted by Vohra and colleagues, ginseng was only given to patients at the onset of respiratory symptoms for a few days, thus only testing its therapeutic but not its preventive efficacy.[40]

As reported in the Supplementary Material B, the most commonly chosen dosage of *P. quinquefolius* extract for adults was 200 mg twice a day; the daily dose was adjusted in children depending on their weight, never exceeding the upper threshold of 26 mg/kg.[40] For *P. ginseng* extracts, the recommended dose was 3 g a day in two studies,[41,42] while no information about this detail was retrievable for the other included trial.[23]

3.2.3. Control

All included trials were placebo-controlled and, as described by study authors, participants randomly assigned to control groups were given placebo pills seemingly indistinguishable from ginseng capsules. In three included studies, it was explicitly reported that placebo composition was formulated in such a way as to taste of ginseng when ingested in order to further conceal its inert composition. [40–42]

3.2.4. Outcomes

The main health condition of interest, namely the occurrence, length and severity of SAURIs, was defined according to symptomatic criteria in all included studies, as shown in Table 1 and in the Supplementary Material B. Additionally, in order to ameliorate the outcome assessment, authors of three trials [35,38,39] resorted to the Jackson Cold Score, a long-established questionnaire aimed at evaluating the symptoms severity of respiratory diseases of viral origin.[43] In one study involving pediatric patients,[40] investigators used the Canadian Acute Respiratory Illness Flu Scale (CARIFS), a measure for assessing the severity of childhood respiratory infections.[44] In three trials, when a clinical diagnosis of acute infection was made by study investigators, patients were tested in order to find a laboratory confirmation of the specific microbial etiology of disease.[36,38]

With regard to the preventive efficacy of ginseng administration (percentage of patients who developed a SAURI at least once during the study period), in seven trials a significant result in favor of intervention was found, [23,36–38,41,42] in one trial this outcome was not reported,[40] and in two trials the difference between groups was not significant. [35,39] In the two trials in which the preventive efficacy of ginseng administration and the microbial etiology of SAURIs were analyzed together, pooled results showed a significant result in favor of intervention for a reduced incidence of laboratory-confirmed influenza illness.[36]

When considering the therapeutic efficacy of ginseng administration (days of sickness), in two trials intervention was significantly associated with a decrease in the duration of disease,[37,39] data regarding this outcome were not retrievable in one trial,[23] while in the other included studies the difference between groups was not significant, as reported in Table 1. If the efficacy of ginseng administration in reducing the severity of symptoms was taken into account, in two trials a significant effect associated with intervention was found,[35,39] in four trials this outcome was not assessed,[23,37,40,42] while in the remaining included studies no significant difference between groups was detected, as displayed in Table 1.

In general, ginseng administration appeared safe and well tolerated by patients involved in included studies, with no significant differences between intervention and placebo groups in terms of analyzed safety outcomes, such as the frequency, severity or type of adverse effects (Supplementary Material B). In four trials, no differences in main hematological parameters, including blood markers of liver and kidney function, were detected.[23,41,42,45] Laboratory safety data of one trial [39] were retrieved from another article [45] in which, in a subgroup of 42 study subjects whose blood was analyzed, intervention was associated with a significant increased proportion of CD4 and NK cells.

3.2.5. Study design

All studies included in the review were randomized double-blind placebo-controlled trials. Two RCTs were pilot studies principally aimed at assessing intervention safety and the feasibility of larger trials on the topic.[40,42] Follow-up duration ranged from 8 weeks to 6 months across included studies, as reported in the Supplementary Material B.

3.2.6. Risk of bias within studies

The overall risk of bias of individual studies was rated as low for one trial,[41] high for three studies,[23,36,38] and some concerns were raised for the remaining RCTs. The most relevant concerns regarded the patients' self-reporting modality of SAURIs-related symptoms and the participants' dropout rates. All details of the risk of bias assessment were reported in Fig. 2.

3.3. Quantitative synthesis

3.3.1. Meta-analysis 1: risk for developing an infection throughout the study period

The overall result of the first meta-analysis, which included 9 trials involving 1550 participants, significantly favored ginseng-based interventions in terms of relative risk for developing an infection throughout the study period (RR = 0.69 [95 % C.I. 0.52 to 0.90], $p < 0.05$, $I^2 = 58.4$ %) (Fig. 3 and Supplementary Material C).

With regard to the ginseng type, the subgroup analysis revealed that there was a significant difference between groups ($p < 0.05$). When pooling only data from the four studies investigating the efficacy of *P. ginseng*, the result was RR = 0.50 [95 % C.I. 0.26 to 0.98], $I^2 = 53.1$ %; while the relative risk calculated on the basis of the five studies with *P. quinquefolius* was RR = 0.84 [95 % C.I. 0.70–1.01], $I^2 = 5.8$ % (Supplementary Material C).

No significant difference was found between groups when comparing studies characterized by a high risk of bias with studies judged to be at non-high risk of bias (p = 0.49) (Supplementary Material C).

After the leave-one-out analysis with the exclusion of the only trial not involving healthy subjects,[35] the overall result in favor of intervention of the first meta-analysis remained significant (RR = 0.65 [95 % C.I. 0.48 to 0.88], $p < 0.05$, $I^2 = 57.3$ %), as well as the difference between the two groups of studies investigating *P. ginseng* or *P. quinquefolius*, respectively ($p < 0.05$) (Supplementary Material C).

3.3.2. Meta-analysis 2: duration of disease symptoms

The overall result of the second meta-analysis, which included 7 trials involving 1152 participants, favored ginseng-based interventions, although not significantly, in terms of duration of disease symptoms measured in days (MD = -2.58 [95 % C.I. −5.40 to 0.24], p = ns, $I^2 = 64.0$ %) (Fig. 4).

After excluding from the analysis the trial with a high risk of bias,[38] the result didn't change substantially and remained non-significant (MD = -2.85 [95 % C.I. −6.54 to 0.84], p = ns, $I^2 = 70.0$ %) (Supplementary Material C).

When performing a leave-one-out analysis and excluding the only trial not involving healthy subjects,[35] the overall result in favor of intervention of the first meta-analysis became significant (MD = -3.11 [95 % C.I. −5.81 to -0.40], $p < 0.05$, $I^2 = 60.2$ %) (Supplementary Material C).

If both trials were excluded,[35,38] the overall result became MD = -3.66 [95 % C.I. −7.34 to 0.02], p = 0.05, $I^2 = 67.8$ % (Supplementary Material C).

3.3.3. Risk of bias across studies

With regard to the first meta-analysis, the funnel plot visually showed some degree of asymmetry with an over-representation of small studies yielding positive results in favor of intervention (Supplementary Material C). The Egger's test confirmed this asymmetry with statistical significance (intercept: -2.58 [95 % C.I. −4.15 to -1.01], $p < 0.05$) (Supplementary Material C). When applying the trim-and-fill method, the adjusted overall result of the first meta-analysis still favored intervention, but not significantly (RR = 0.81 [95 % C.I. 0.57–1.14], p = 0.19, $I^2 = 57.3$ %) (Supplementary Material C). Further analyses failed to detect a significantly right skewed p-curve (p = 0.13), with a power estimate of 28 % (C.I.: 5%–81%), but the test for flatness was not significant (p = 0.44).

With regard to the second meta-analysis, the p-curve referred to the C.8 sub-analysis including only studies with healthy subjects was significantly right skewed ($p < 0.05$), the test for flatness was not significant (p = 0.63), and the power estimate was 45 % (C.I. 5%–88%) (Supplementary Material C). The p-curve referred to the C.9 sub-analysis including only studies at non-high risk of bias with healthy subjects was significantly right skewed ($p < 0.05$), the test for flatness was not significant (p = 0.88), and the power estimate was 73 % (C.I. 17%–97%) (Supplementary Material C).

4. Discussion

4.1. Mechanisms of action

Pre-clinical laboratory studies underscore that ginseng extracts have antimicrobial properties against viruses usually involved in SAURIs such as rhinoviruses, influenza viruses, and respiratory syncytial virus.[46–48] Based on available data, it has been hypothesized that ginseng extracts can synergically exert their antimicrobial effects through different mechanisms of action, including a direct antiviral activity (inhibition of virus penetration and replication) and the enhancement of host immunity, to which the majority of ginseng effects are attributed.[46,47,49] Furthermore, laboratory studies have shown that the antiviral activity of ginseng against a broad range of influenza viruses appears dose-dependent,[47] and that the administration of ginseng extracts to mice can boost the immune response to influenza vaccination, thus acting as a vaccine adjuvant.[46] In fact, an action on cellular (macrophages, B cells, and T cells) and humoral components of the immune system have been suggested both for *P. ginseng*[50] and for *P. quinquefolius*.[51] Overall, the mechanisms of action of all ginseng species have been mostly studied on the basis of pre-clinical studies and, for infectious diseases, are hypothesized to be a general boost of the immune system, including an adjuvation of influenza vaccination.

4.2. Efficacy

In a previous systematic review of clinical studies published up to December 2007, it was concluded that *P. quinquefolius* seemed effective in shortening the duration of acute respiratory infections in healthy adults, although it was unclear whether it could reduce the incidence or severity of common colds.[52] The findings of our qualitative synthesis suggested that, with regard to the overall preventive or therapeutic efficacy of each ginseng subspecies, the most relevant supporting evidence was about *P. ginseng* and *P. quinquefolius*. The included trial characterized by the highest methodological quality, thus being the only one with a low risk of bias, indicated that ginseng may be useful to reduce the incidence of acute respiratory infections, although no significant difference compared to placebo was found with regard to a potential reduction of disease duration and severity.[41] Among RCTs which remained after the exclusion of pilot studies and trials characterized by a high risk of bias, the use of ginseng was demonstrated to have a significant action even on the reduction of SAURIs severity and duration.[35,37,39] However, some concerns were raised about their methodological quality. Overall, in the majority of included RCTs analyzing the preventive efficacy of ginseng, a significant result in favor of intervention was found,[23,36–38,41,42] whereas in two trials the difference between groups was not significant.[35,39] In one of these two studies, patients with chronic leukemia were recruited, and their haematological health condition might have weakened the immune boosting effect of ginseng, possibly due to an insufficient drug dose or to the impairment of toll-like receptor pathways in such patients.[35] In the other trial, although no difference between intervention and control groups was observed in the number of subjects who had at least one cold during the study period, a significant difference between groups was reported when analyzing the proportion of participants who experienced two or more colds, as well as the severity of symptoms.[39] Here, the exclusion of many potentially eligible subjects from the study before randomization due to missing information, along with a consistent drop-out rate during the trial period (exceeding 20 %), might have influenced the results. Nevertheless, it is interesting to notice that in both trials, study subjects were not vaccinated against influenza.[35,39] Furthermore, in those RCTs in which the preventive efficacy of ginseng and the microbial etiology of SAURIs were analyzed together, pooled results showed a significant result in favor of intervention for a reduced incidence of laboratory-confirmed influenza illness, with a study population almost entirely vaccinated against the flu.[36] Globally, these results indicate that ginseng supplementation can be an option only in adjunct to vaccination, and not as an alternative to it.

Among others, factors which might have influenced study results beyond the potential pharmacological action of ginseng include the involvement of subjects with heterogeneous characteristics, the self-reporting modality of clinical outcomes, limited information about the microbial etiology of SAURIs, and the use of various ginseng extracts with a different biochemical composition of active substances. Thus, it is important not only to plan future studies with a more homogenous design, but also to test different ginseng extracts and to properly characterize the etiology of SAURIs in order to better describe the clinical action of different ginseng-derived compounds on each infectious microorganism.

The overall result of the first meta-analysis indicated that ginseng supplementation can significantly diminish the risk of developing SAURIs on average by 31 % (RR = 0.69) if compared with placebo (Fig. 3). The average reduced risk remained significant and was 35 % (RR = 0.65) when only studies with healthy participants were included in the analysis (Supplementary Material C). With regard to the ginseng type, the subgroup analysis suggested that the efficacy of *P. ginseng* may be different from (and possibly superior to) *P. quinquefolius* in preventing the onset of SAURIs, and further investigations are advised to study this aspect more in depth (Supplementary Material C). However, if studies at high risk of bias were excluded from the first meta-analysis, the overall result changed to RR = 0.76 [95 % C.I. 0.56–1.04] (Supplementary Material C). Additionally, the funnel plot and the Egger's test indicated a potential risk of publication bias, and, when adjusting the first meta-analysis for this bias, the result, although still favoring intervention, was not statistically significant (RR = 0.81 [95 % C.I. 0.57–1.14]) (Supplementary Material C). The p-curve analysis provided a borderline result, failing to demonstrate both the presence and the absence of an evidential value (Supplementary Material C). Therefore, on the basis of available evidence included in our quantitative synthesis and on their risk-of-bias assessment, it is not possible to affirm that ginseng supplementation can significantly reduce the incidence of SAURIs because the true effect might be different from the estimated effect. Nevertheless, considering both the overall result of the first meta-analysis and the above mentioned pre-clinical findings, existing data don't exclude that ginseng supplementation in adjunct to vaccination might have some preventive effects on SAURIs, and more high-quality RCTs are advocated to better study this potential activity.

The overall result of the second meta-analysis indicated that ginseng supplementation cannot significantly reduce the duration of SAURIs symptoms if compared with placebo (Fig. 4). However, when the study with sub-healthy individuals was removed from the analysis,[35] the result favoring intervention became significant, thus suggesting a potential effect of ginseng supplementation to reduce the duration of SAURIs by around 3 days on average (Supplementary Material C). In this meta-analysis, it was not possible to quantitatively assess the risk of publication bias with a funnel plot plot and the Egger's test, due to the limited number of included studies. The p-curve method didn't demonstrate a potential risk of "p-hacking" (Supplementary Material C). If the study at high risk of bias was excluded,[38] the p-curve shape further ameliorated, thus suggesting a higher average power estimate of the set of included studies. It is possible that, by conducting more high-quality trials on the topic with healthy subjects, the result in favor of intervention may be confirmed.

4.3. Safety and tolerability

Globally, data from included trials suggested that studied ginseng extracts were relatively safe and well-tolerated by recruited subjects. In two systematic reviews investigating the safety of *P. ginseng*, it was concluded that this ginseng type shows a safe profile in the limited number of available RCTs on the topic, involving both healthy subjects and patients with various clinical conditions, and its use is generally associated with a low incidence of adverse effects.[53,54] Based on available data, the safety profile of *P. quinquefolius* appears equally good, even on a relatively long-term (up to 12 weeks).[55,56] The oral consumption of all ginseng species has been reported to be sometimes responsible for adverse effects like hypertension, tachycardia, dry mouth, gastrointestinal disturbances, insomnia, and nervousness.[56,57] Three cases of manic psychosis associated with ginseng consumption have been reported in predisposed individuals.[58,59] A possible, although controversial, estrogenic effect has been also described,[56,60,61] as well as a potential increased risk of operatory bleeding following its high-dose oral intake.[62] Therefore, ginseng administration is contraindicated in patients who are expected to undergo surgery, or affected by psychotic disorders, mania, estrogen-dependent diseases, hormonal dysfunctions, hypertension, or hyperthyroidism.[63] Additionally, possible interactions with several medicinal drugs have been described, including anticoagulants, monoamine oxidase inhibitors, anti-diabetic agents, antiretroviral compounds, diuretics, and cytochrome P450 − 3A4 substrates, as well as caffeine-based and other stimulating substances.[56,61,63,64] However, the ginseng-drugs interaction profile is not still fully clear to date, and, for example, with regard to warfarin, some authors suggest a potential inhibition of its anticoagulant effect,[65,66] whereas others underscore no significant interaction in experimental settings.[67,68] Based on results of vitro studies,[61] ginseng administration is to be avoided in pregnant women, especially during the first trimester, due to potential risks to the fetus.[63] Although ginseng has been reported to be well tolerated if administered to children at a proper dose and for a short time period,[40,69] data are still very limited in this specific category of patients: therefore, extreme caution is required in the pediatric population. Furthermore, it has to be reported that some adverse effects wrongly attributed to ginseng, like androgenization, have been eventually discovered to be caused by adulterants,[61] thus urging the need for stricter controls by health authorities over ginseng production and marketing. Overall, provided that clinical safety data of ginseng consumption are scant, further studies are advised and medical supervision is required for its safe and proper use. Nevertheless, as shown by the results of included trials, its short-term administration can be considered quite safe in healthy adults taking no drugs.

4.4. Limitations

Evidence base on the topic is limited. Among included RCTs, two studies were pilot trials involving a small number of participants,[40,42] and it was not possible to retrieve the full-text version of a relevant article.[23] For most included RCTs some concerns were raised with regard to their overall risk of bias, especially when considering missing information, drop-out rates, and the symptoms self-reporting modality. Our analysis also individuated a potential risk of publication bias, thus indicating a possible over-representation in the scientific literature of under-powered small trials yielding positive results. Finally, "p-hacking" couldn't be totally excluded.

5. Conclusions

Limitations of existing evidence don't allow to draw conclusions on the topic. Nevertheless, it is not excluded that ginseng supplementation in adjunct to influenza vaccination and standard care might be useful for SAURIs prevention and management in healthy adult subjects, but further high-quality trials are needed to support this hypothesis.

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Declaration of Competing Interest

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Appendix A. Supplementary data

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