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REVIEW

ADDICTION SSA

The efficacy and tolerability of pharmacologically active interventions for alcohol-induced hangover symptomatology: a systematic review of the evidence from randomised placebo-controlled trials

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Abstract

Aims: To compare quantitatively the efficacy and tolerability of pharmacologically active interventions in the treatment and prevention of alcohol-induced hangover.

Methods: Systematic review of placebo-controlled randomised trials in healthy adults that evaluated any pharmacologically active intervention in the treatment or prevention of hangover. We searched Medline, Embase, PsycINFO and CENTRAL from database inception until 1 August 2021. The primary efficacy outcome was any continuous measure of overall hangover symptoms and the primary tolerability outcome the number of people dropping out because of adverse events (AEs). Quality was assessed using the Grading of Recommendations Assessment Development and Evaluation (GRADE) framework.

Results: A total of 21 studies were included reporting on 386 participants. No two studies reported on the same intervention; as such, meta-analysis could not be undertaken. Methodological concerns and imprecision resulted in all studied efficacy outcomes being rated as very low quality. When compared with placebo, individual studies reported a statistically significant reduction in the mean percentage overall hangover symptom score for clove extract (42.5% vs 19.0%, $P < 0.001$), tolfenamic acid (84.0% vs 50.0%, $P < 0.001$), pyritinol (34.1% vs 16.2%, $P < 0.01$), *Hovenia dulcis* fruit extract ($P = 0.029$), L-cysteine ($P = 0.043$), red ginseng (21.1% vs 14.0%, $P < 0.05$) and Korean pear juice (41.5% vs 33.3%, $P < 0.05$). All studied tolerability outcomes were of low or very low quality with no studies reporting any drop-outs because of AEs.

Conclusions: Only very low quality evidence of efficacy is available to recommend any pharmacologically active intervention for the treatment or prevention of alcohol-induced hangover. Of the limited interventions studied, all had favourable tolerability profiles and very low quality evidence suggests clove extract, tolfenamic acid and pyritinol may most warrant further study.

KEYWORDS
alcohol, hangover, pharmacology, prevention, systematic review, treatment

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INTRODUCTION

Alcohol-induced hangover, or veisalgia, refers to the combination of negative mental and physical symptoms that can be experienced following a single episode of alcohol consumption starting when blood alcohol concentration (BAC) approaches zero [1, 2]. The physiological mechanisms underpinning hangover are complex and not fully understood [3]. Although alcohol and its metabolites are responsible for some symptoms, severity typically peaks when BAC has reduced to zero. Other factors including dehydration, immune dysregulation, hypoglycaemia, the presence of additional biologically active compounds in alcoholic drinks (i.e. congeners) and an individual's genetic factors are all thought to play a role in the manifestation of hangover symptomatology [3–6].

Hangover symptoms are distressing and can adversely affect an individual's activities of daily living alongside their employment and academic performance. Additionally, alcohol-related presenteeism and absenteeism has a large impact on population level economic productivity [7]. Recent estimates in the United States (US) suggest hangover symptoms may cost up to USD $2000 per employee per year [8]. An oft described remedy for relief of hangover symptoms is further consumption of alcohol or taking 'hair of the dog'. This practice can lead to repeated episodes of excessive alcohol use with potential for negative impact on an individual's mental and physical health leading to development of an alcohol use disorder [9]. As such, the existence of an effective and tolerable remedy for hangover not only has the potential to reduce distressing symptoms, but may also have use for some individuals as a means of harm reduction in preventing 'morning after' drinking.

Numerous remedies make claims to be effective against hangover symptoms with many marketed as hangover 'cures' [10], however up to date scientific examination of the literature is lacking. Although two previous systematic reviews have examined the evidence base for hangover treatment and prevention [11, 12], they have been narratively reported, make no attempt to quantitatively synthesise and compare data across interventions and are restricted to studies conducted over specific time periods. Numerous trials have also been conducted since publication of the most recent systematic review, therefore, the current available evidence syntheses do not consider the totality of the evidence base [13, 14], nor do they compare all studied interventions using quantitative techniques. When this is considered alongside the myriad anecdotal reports of efficacious therapies available in print and online media [15], a robust up to date synthesis of the literature is warranted to provide professionals and the public with accurate information as to what, if any, pharmacologically active interventions are evidence-based options.

To address this gap, we aimed to conduct a systematic review and meta-analysis to assess the efficacy and tolerability of pharmacologically active interventions in the treatment and prevention of alcohol-induced hangover. Additionally, we planned to use grading of recommendations assessment development and evaluation (GRADE) methodology to assess the quality of the evidence base and the strength of any resultant recommendations.

METHODS

This study is reported according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [16]. The study did not require ethical approval, there was no patient or public involvement, and the review protocol was pre-registered on PROSPERO (registration number: CRD42021272499).

Search strategy

We searched Medline, Embase, PsycINFO and CENTRAL from database inception until 1 August 2021 without language restriction. Studies were eligible for inclusion if they were conducted in healthy adults and reported placebo-controlled randomised controlled trials (RCTs) evaluating a pharmacologically active intervention in the treatment or prevention of alcohol-induced hangover. The full search terms were ([hangover* OR veisalgia] AND [random*] AND [placebo] AND [alcohol*]) and the complete study protocol can be found as Supporting information Table S1 in the online supplementary material.

Study selection

Two authors (E.R. and R.S.) initially assessed titles and abstracts and reviewed the full text of the remaining articles for inclusion. Any discrepancy was resolved by discussion and where agreement could not be reached a third author (C.D.) was consulted. All relevant references were checked for additional citations.

Data extraction

Two authors (E.R. and R.S.) independently extracted data from all eligible studies using a standardised data extraction spreadsheet that can be found as Supporting information Table S2 in the online supplementary material. In the case of incomplete reporting of data, we searched studies' online supplementary appendices, trial registries and contacted authors as necessary. Any discrepancies were resolved by discussion and where agreement could not be reached a third author (C.D.) was consulted.

The primary extracted efficacy outcome was any continuous measure of overall alcohol-induced hangover symptoms. A preferential hierarchy was developed a priori to extract the overall symptom score as (i) a reported single question score, (ii) a reported summation score of all collected alcohol-induced hangover symptoms or (iii) a reported mean score of all collected alcohol-induced hangover symptoms. Additional efficacy outcomes included any continuous measure of specific alcohol-induced hangover symptoms including headache, nausea, thirst, tiredness, dizziness, stomach ache and reduced concentration. These were chosen a priori based on previous research and represent the seven most commonly experienced symptoms of alcohol-induced hangover [17]. All symptom scores were extracted at

the reported time point closest to 12 hours following an alcohol challenge.

The primary tolerability outcome extracted was the number of people who dropped out because of adverse events (AEs). Additional tolerability outcomes included the number of reported AEs, and the number of severe, life-threatening adverse events (SAEs).

Quality assessment

The quality of each outcome estimate was assessed using the GRADE framework [18]. Each estimate is given a rating of high, moderate, low or very low quality based on scores in five domains: risk of bias, inconsistency, indirectness, imprecision and other considerations. Because of the randomised nature of the data the default quality score is high, which can be down-graded according to the quality of the evidence for each estimate. Two reviewers (E.R. and R.S.) independently scored the quality of each study, any discrepancy was resolved by discussion, and where agreement could not be reached a third author (C.D.) was consulted. Risk of bias was assessed using the Cochrane risk of bias assessment tool [19], (see Supporting information Figure S1 in the online supplementary material). Outcomes were downgraded by one increment if the weighted average number of methodological limitations across studies was one and downgraded by two increments if the weighted average number of methodological limitations across studies were two or more. Methodological limitations comprised one or more of the following: unclear randomisation sequence generation, unclear allocation concealment, a lack of blinding, inadequate allowance for drop-outs in the analysis, selective outcome reporting or unadjusted baseline inequality. Inconsistency refers to the level of heterogeneity between prevalence estimates and was assessed using the I^2 statistic. The overall quality rating was planned to be down-graded by one level if I^2 was ≥50% and <75%, and by two levels if I^2 was ≥75%. Indirectness refers to the extent to which the study population or outcomes differ from those specified in the inclusion criteria. Imprecision refers to the extent to which we are uncertain about the estimates and is based on examination of the CI. Outcomes were downgraded by one increment if the upper or lower 95% CI crossed the lower minimally important difference (MID) or the upper or lower 95% CI crossed the upper MID. Outcomes were downgraded by two increments if the upper CI simultaneously crossed the upper MID and the lower CI crossed the lower MID. Because no clinically validated MIDs have been previously developed in alcohol-induced hangover symptom scores, and as per standard GRADE methods, default MIDs were set at a relative risk (RR) of 0.75 and 1.25 for count outcomes and at 0.5 of the control group mean SD either side of the null line for continuous variables. GRADE also considers other potential sources of bias with publication bias assessed within this domain. Consistent with the Cochrane handbook [20], we planned to produce funnel plots only for outcomes where ≥10 studies would have been included in meta-analysis. A complete description of GRADE quality scoring for each outcome can be found in the GRADE Supporting information Tables S12–S19 in the online supplementary material.

Statistical analysis

Where they were reported by each included study, intervention and placebo measures of central tendency, measures of spread and *P* values were extracted and reported for each continuous efficacy outcome.

To aid comparability, and in preparation for planned combination in meta-analysis, all extracted measures of central tendency and spread were converted to means and SDs. For those studies reporting median scores these were converted, without any assumption as to the underlying distribution, using previously described standard methods [21]. To additionally aid comparability, means and SDs were converted to a percentage scale. If studies reported efficacy outcomes using Likert scales these were converted to percentage values based on the number of responses available in the Likert scale. If studies reported efficacy outcomes using visual analogue scales (VAS) these were converted to percentage values based on the millimetre distance of VAS used. Mean percentage difference point estimates were calculated for all efficacy outcomes using the difference in mean percentage between intervention and placebo. Where sufficient data was reported in the original article to enable reporting of the mean percentage difference 95% CI (i.e. individual raw data or CIs), these were also presented.

Tolerability outcomes were extracted as count variables and the measure of effect comparing intervention and placebo was planned to be examined via calculation of RR, 95% CI and associated *P* values.

Because high levels of heterogeneity were anticipated, we planned to combine studies using a random effects meta-analysis in Stata IC version 17, with the significance level set at 0.05.

RESULTS

The search generated 254 unique results and 15 additional references were identified from citation searching leading to a total of 269 records. We examined 46 full texts and included 21 studies. A total of 25 studies were excluded with common reasons for exclusion including reporting a non-protocol study design (n = 4), or lack of a placebo control (n = 10). Full reasons for each study's exclusion can be found as Supporting information Table S3 in the online supplementary material.

The 21 included studies analysed data from a total of 386 participants. The PRISMA diagram in Fig. 1 describes the study selection.

A description of all included study characteristics can be found in Table 1. Twenty-three interventions were studied, and no two included studies reported on the same intervention. As such, meta-analysis was not able to be undertaken. A third of all included studies were conducted in Japan or South Korea, eight were conducted exclusively with male participants and no studies were conducted, which included adults over age 65, the majority including only people below age 40. Extraction of all raw reported data, alongside transformation

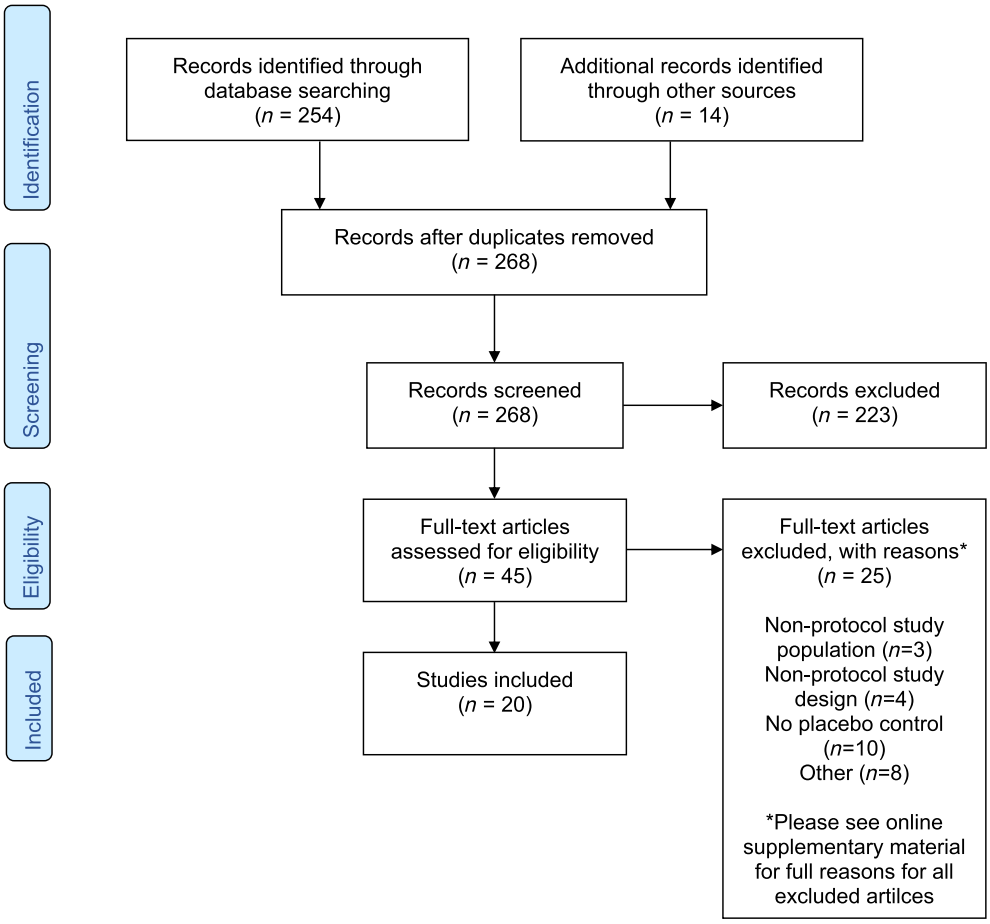


FIGURE 1 PRISMA flow diagram describing study selection

to percentage mean and SD scores for efficacy measurements, can be found in the online supplementary material as Supporting information Table S4.

Efficacy

The study reported intervention and placebo means, SDs and/or P values for overall hangover severity score can be found in Table 2. Similar measures for all other included individual hangover symptom score efficacy outcomes can found in the online supplementary material as Supporting information Tables S5–S11.

When compared to placebo, there was a statistically significant reduction in the mean percentage overall hangover symptom score for clove extract (42.5% vs 19.0%, −23.5% 95% CI = −29.6% to −17.4%, $P < 0.001$), tolfenamic acid (84.0% vs 50.0%, $P < 0.001$), pyritinol (34.1% vs 16.2%, −17.9% 95% CI = −30.5% to −5.4%, $P < 0.01$), *Hovenia dulcis* fruit extract ($P = 0.029$), L-cysteine ($P = 0.043$), red ginseng (21.1% vs 14.0%, $P < 0.05$) and Korean pear juice (41.5% vs 33.3%, $P < 0.05$).

In addition, there were statistically significant improvements across the majority of the specific individual alcohol-induced hangover symptoms studied for *Acanthopanax senticosus* extract and *Phyllanthus amarus* extract.

Because no two included studies reported data on the same intervention, no measurers of inconsistency or publication bias were able to be included in the GRADE quality score per outcome. Additionally, all included studies met the inclusion criteria therefore; none were downgraded because of indirectness. However, the majority of studies had significant methodological limitations alongside significant degrees of imprecision in outcome measures of treatment effect. This resulted in all studied efficacy outcomes, across all interventions, being rated as very low quality according to GRADE (please see the Cochrane risk of bias tool as Supporting information Figure S1 and individual GRADE Supporting information Tables S12–S19 in the online supplementary material for individual outcome quality assessments).

Tolerability

No studies reported any drop-outs because of AEs attributable to either intervention or placebo. Seven studies reported the number of AEs [22–28]; there were no statistically significant differences in the number of reported AEs attributed to intervention or placebo across all studies. Five studies reported the number of SAEs [14, 22, 23, 25, 27]; there were no reported SAEs in any included study. All results were of low or very low quality according to GRADE.

TABLE 1 Characteristics of included studies

Study ID	*Population description*	*Country*	*Alcohol challenge description*	*Intervention*	*F:M*	*Age, range (y)*
Shobha 2021 [13]	Healthy volunteers	India	NR	Curcumin: 45 mg curcumin oral anti-hangover film containing 'other ingredients' given before alcohol challenge	NR	>18
Jung 2021 [14]	Healthy volunteers	South Korea	Vodka (40% ABV) consumed with water at 1:1 ratio amounting to 0.8 g alcohol per kg body weight consumed within 30 min of a meal and with a small amount of snack	Duolac ProAP4: a double-coated capsule containing over 125 000 000 CFU/400 mg of probiotics, constituting (*Lactobacillus gasseri* CBT LGA1, *Lactobacillus casei* CBT LC5, *Bifidobacterium lactis* CBT BL3, and *Bifidobacterium breve* CBT BR3) four capsules per day for 15 days	0:40	19–65
Eriksson 2021 [35]	Healthy volunteers	Finland	Alcohol was consumed evenly in three doses in a period of 3 h. 1.5 g alcohol/kg bodyweight, served as 10% ABV (type not specified), mixed with lingonberry/ blackcurrant juice	L-cysteine: six tablets containing 200 mg L-cysteine, 50 mg thiamine, 1.4 mg riboflavin, 16 mg niacin, 1.4 mg pyridoxine, 50 μg biotin), 200 μg folic acid, 2.5 μg cobalamin and 80 mg ascorbic acid taken during alcohol challenge	0:19	21–60
Coppersmith 2021 [23]	Healthy volunteers	USA	12 oz. of 5.2% ABV Belgian-style wheat ale consumed one at a time until participants reached a BrAC of 0.1 g/210 L	NAC: 1–3 capsules of 600 mg NAC given following alcohol challenge dose based on the amount of alcohol consumed	18:31	>21
Scholey 2020 [22]	Healthy volunteers	Australia	Self-administered alcoholic beverages of participant choice to a maximum of 1.3 g alcohol/kg body weight following a meal	Rapid recovery: L-cysteine, thiamine,pyridoxine and ascorbic acid capsule given after immediately after alcohol challenge and again the following morning	13:7	25–43
Hara 2020 [24]	Healthy medical doctors	Japan	Self-reported hangover symptoms occurring during daily life	Loxoprofen: loxoprofen sodium 60 mg once orally taken when experiencing fatigue because of hangover	12:138	34 (30–39) MD (IQR)
Verster 2020 [36]	Healthy volunteers	NR	Self-administered alcohol including red/white wine, beer, champagne, and liquors available with light snacks (e.g. pretzels, potato chips, nuts)	SJP-001: (220 mg naproxen and 60 mg fexofenadine), 220 mg naproxen alone, or 60 mg fexofenadine alone taken before the start of alcohol consumption	2:3	35.2 (27–47)
George 2019 [25]	Healthy volunteers	USA	Several shots (1.5 fluid oz.) of alcohol (Jack Daniel's Whisky, TN, USA) to reach a BAL of 0.12%	Phyllpro: 10 days daily oral 750 mg/day of standardized ethanol extract of *Phyllanthus amarus* leaves taken before alcohol challenge	5:10	21–50
Mammen 2018 [26]	Healthy volunteers	India	240 mL of 42.8% alcohol (McDowell's V.S.O. P. Brandy) 1 g alcohol/kg body weight and a piece of cheese followed by a meal	Clovinol: 250 mg polyphenolic extract of clove buds taken before alcohol challenge	0:16	25–55
Kim 2017 [37]	Healthy volunteers	South Korea	360 mL of Korean Soju (50 g alcohol) 17.5% alcohol taken after a standard meal	HDE: 2520 mg HDE taken before alcohol challenge	0:26	20–40

TABLE 1 (Continued)

Study ID	*Population description*	*Country*	*Alcohol challenge description*	*Intervention*	*F:M*	*Age, range (y)*
Bang 2015 [38]	Healthy volunteers	South Korea	1.75 g alcohol/kg over 2 h; A prepared meal was given with alcohol	PEA: given 30 min before and soon after alcohol challenge	0:28	19–55
Lee 2014 [39]	Healthy volunteers	South Korea	100 mL of 40% ABV (Whiskey); One piece of cheese given with alcohol	Red Ginseng: 100 mL of red ginseng anti-hangover drink (RGD) given within 5 min of alcohol challenge	0:25	25–49
Lee 2013 [40]	Healthy volunteers	South Korea	540 mL of 20.1% ABV (Soju) following a low fat meal	Korean Pear Juice: 220 mL of Korean pear juice given 30 min before alcohol challenge	0:14	25.8 (0.86) Mean (SD)
Kokubo 2013 [41]	Healthy volunteers	Japan	0.4 g alcohol/kg body weight (5% ABV Beer) over 0.5 hours following a meal 2 h previously	L-ornithine: 500 mg L-ornithine monohydrochloride after alcohol challenge	1:10	35.5 (2.4) Mean (SD)
Wiese 2004 [42]	Healthy volunteers	USA	Up to 1.75 g alcohol/kg body weight (participant choice of alcohol) following a meal	Prickly Pear: 1600 IU *Opuntia ficus-indica* given before alcohol challenge	32:23	21–35
Pittler 2003 [27]	Healthy volunteers	UK	An average of 1.2 g alcohol/kg of body weight (participant choice of alcohol); A pasta meal was taken before alcohol challenge	Artichoke: 960 mg *Cynara scolymus* extract (LI120) from Cynara artichoke given before and after alcohol challenge	5:10	18–65
Laas 1999 [43]	Healthy volunteers	Estonia	100 g alcohol (Vodka 40% ABV). After alcohol challenge soft drinks, water, and a low-fat lunch were offered	'Morning-Fit': 250 mg dried yeast, 0.5 mg thiamine nitrate, 0.5 mg pyridoxine hydrochloride, and 0.5 mg riboflavin per tablet; 750 mg given after alcohol challenge	34:27	20–40
Bogin 1987 [44]	Healthy volunteers	USA	Estimated 0.1% BAC for each patient (participant choice of alcohol); No water was allowed after alcohol challenge	Propranolol: 160 mg long-acting propranolol given 2 h before alcohol challenge	4:6	21–25
Kaivola 1983 [28]	Healthy volunteers	Finland	Self-assessed alcohol challenge	Tolfenamic acid: 200 mg tolefenamic acid given before and after alcohol challenge	17:3	22–48
Myrsten 1980 [45]	Healthy firemen	Sweden	1.43 g alcohol/kg body weight (Swedish brannvin, beer and whiskey) consumed with food over 70 rain.	Chlormethiazole: 1 g at bedtime following alcohol challenge and 0.5 g early the following morning	0:12	24–46
Khan 1973 [46]	Healthy volunteers	Denmark	Non-restricted quantity of any desired beverage (whisky, cognac, gin, rum or aquavit) all 43% ABV at a party before a light meal	Pyritinol: 400 mg pyritinol three times throughout the evening at 3-hour intervals	6:11	21–40

Abbreviations: AHQ, Alcohol Hangover Questionnaire; AHS, Acute Hangover Scale; AHSS, Alcohol Hangover Severity Scale; BAL, blood alcohol level; BrAC, breath alcohol content; F, female; HDE, *Hovenia dulcis* Thunb. fruit extract; HSS, Hangover Symptom Scale; IQR, interquartile range; M, male; MD, median; mg, milligrams; NAC, N-Acetyl-L-Cysteine; NR, not reported; PEA, polysaccharide rich extract of *Acanthopanax Senticosus*; VAS, visual analogue scale.

TABLE 1 (Continued)

Study ID	*No. randomised*	*No. analysed*	*No. analysed in intervention arm*	*No. analysed in comparison arm*	*Name of scale used for hangover symptom assessment*	*Likert or VAS*	*Time of symptom measurement post alcohol challenge*
Shobha 2021 [13]	NR	NR	42	16	NR	4-point Likert	'the following day morning'
Jung 2021 [14]	54	40	40	40	AHQ	5-point Likert	8 h
Eriksson 2021 [35]	27	9 (nausea)/12 (headache and hangover)	9/12	9/12	NR	11-point Likert	10–12 h
Coppersmith 2021 [23]	62	49	45	46	HSS	5-point Likert	'in the morning'
Scholey 2020 [22]	23	20	20	20	Adapted from multiple hangover assessment scales	11-point Likert	'the following morning between 7:00 and 11:00'
Hara 2020 [24]	229	150	74	76	NR	100 mm VAS	'3 h after taking the medicine (for hangover symptoms)'
Verster 2020 [36]	13	5	5 SJP-001 5Fexofenadine 4 Naproxen	5	Alcohol Hangover Scale	8-point Likert	8 h
George 2019 [25]	16	15	15	15	Hangover Severity Score	7-point Likert	12 h
Mammen 2018 [26]	16	16	16	16	Adapted from AHSS	11-point Likert	11–12 h
Kim 2017 [37]	26	26	26	26	Korean validated versionof hangover questionnaire	5-point Likert	12 h
Bang 2015 [38]	28	28	28	28	AHS	8-point Likert	12 h
Lee 2014 [39]	25	25	25	25	Adapted from the HSS and the AHS	5-point Likert	24 h
Lee 2013 [40]	20	14	14	14	Adapted from the HSS	6-point Likert	15 h
Kokubo 2013 [41]	NR	11	11	11	NR	100 mm VAS	'the next morning after awakening'
Wiese 2004 [42]	64	55	55	55	Adapted from multiple hangover assessment tools	7-point Likert	'the following morning'
Pittler 2003 [27]	15	15	15	15	NR	10 cm VAS	10 h
Laas 1999 [43]	61	57	30	31	NR	5-point Likert	7–8 h
Bogin 1987 [44]	10	10	10	10	NR	5-point Likert	12 h
Kaivola 1983 [28]	30	30	30	30	Adapted from multiple sources	10 cm VAS overall score; 4-point Likert all other symptoms	8–12 h
Myrsten 1980 [45]	12	12	12	12	NR	4-point Likert	'the following morning'
Khan 1973 [46]	17	17	17	17	NR	20-point Likert	'the following morning'

Abbreviations: AHQ, Alcohol Hangover Questionnaire; AHS, Acute Hangover Scale; AHSS, Alcohol Hangover Severity Scale; BAL, blood alcohol level; BrAC, breath alcohol content; F, female; HDE, *Hovenia dulcis* Thunb. fruit extract; HSS, Hangover Symptom Scale; IQR, interquartile range; M, male; MD, median; mg, milligrams; NAC, N-Acetyl-L-Cysteine; NR, not reported; PEA, polysaccharide rich extract of *Acanthopanax Senticosus*; VAS, visual analogue scale.

TABLE 2 Difference in mean overall hangover score between all interventions and placebo

Study ID	*Intervention*	*Intervention: raw mean (SD)*	*Placebo: raw mean (SD)*	*P*[a]	*Intervention: mean % (SD)*	*Placebo: mean % (SD)*	*Mean difference (%), 95% CI*[b]
Mammen 2018 [26]	Clovinol	2.09 (0.74)	4.68 (1.08)	<0.001	19.0 (6.73)	42.5 (9.82)	−23.5 (−29.6 to −17.4)
Kaivola 1983 [28][cd]	Tolfenamic acid	5.0 (8.76)	8.4 (6.6)	<0.001	50.0 (87.64)	84.0 (65.73)	−34.0
Khan 1973 [46]	Pyritinol	3.24 (2.75)	6.82 (3.83)	<0.01	16.2 (13.75)	34.1 (19.15)	−17.9 (−30.5 to −5.4)
Kim 2017 [37]	HDE	NR	NR	0.029	NR	NR	NC
Eriksson 2021 [35]	L-cysteine/B and C vitamins	NR	NR	0.043	NC	NC	NC
Lee 2014 [39][d]	Red Ginseng	8.40 (6.35)	12.7 (8.2)	<0.05	14.0 (10.58)	21.1 (13.67)	−7.1
Lee 2013 [40]	Korean Pear Juice	23.31 (8.59)	29.08 (11.39)	<0.05	33.3 (12.27)	41.5 (16.27)	−8.2
Bang 2015 [38]	PEA	1.4 (0.1)	1.8 (0.2)	>0.05	17.5 (1.25)	22.5 (2.5)	−5.0
Wiese 2004 [42]	Prickly Pear	12.2 (6.6)	14.9 (8.4)	0.07	22.6 (12.22)	27.6 (15.55)	−5.0
Coppersmith 2021 [23][e]	NAC	7.25 (4.31)	7.75 (4.52)	0.86	29.0 (17.24)	31.0 (18.08)	−2.0
Scholey 2020 [22]	Rapid Recovery	3.22 (2.07)	3.18 (2.69)	0.962	29.3 (18.1)	28.9 (24.5)	0.6
Jung 2021 [14]	Duolac ProAP4	37.75 (10.82)	37.78 (10.26)	0.986	37.75 (10.82)	37.78 (10.26)	−0.03
George 2019 [25]	Phyllpro	1.47 (1.35)	1.67 (1.54)	>0.05	21.0 (19.29)	23.9 (22)	−2.9
Verster 2020 [36]	SJP-001	0.8 (0.8)	2.4 (1.3)	>0.05	10.0 (10.0)	30.0 (16.25)	−20.0
Verster 2020 [36]	Fexofenidine	1.6 (1.5)	2.4 (1.3)	>0.05	20.0 (18.75)	30.0 (16.25)	−10.0
Verster 2020 [36]	Naproxen	0.8 (0.5)	2.4 (1.3)	>0.05	10.0 (6.25)	30.0 (16.25)	−20.0
Bogin 1987 [44]	Propranolol	2.9 (1.1)	2.8 (0.9)	>0.05	58.0 (22)	56.0 (18)	+ 2.0
Pittler 2003 [27]	Artichoke	3.2 (2.6)	3.3 (2.4)	>0.05	32.0 (26)	33.0 (24)	−4.0 (−20.0–28.0)
Myrsten 1980 [45]	Chlormethiazole	NR	NR	>0.05	NC	NC	NC
Hara 2020 [24][e]	Loxoprofen	NR	NR	NR	–	–	–
Kokubo 2013 [41][d]	L-ornithine	NR	NR	NR	–	–	–
Laas 1999 [43]	Morning Fit	NR	NR	NR	–	–	–
Shobha 2021 [13]	Curcumin	NR	NR	NR	–	–	–

Note: Green results indicate a statistically significant ($P < 0.05$) result in favour of the intervention compared to placebo; Red results represent a result, in which data lack clear evidence for an effect of the intervention when compared to placebo ($P > 0.05$); Grey results show studies for which the outcome of overall hangover score is not reported.

Abbreviations: HDE, *Hovenia dulcis* Thunb. fruit extract; NAC, N-Acetyl-L-Cysteine; NR, not reported; PEA, polysaccharide rich extract of *Acanthopanax senticosus*; SJP-001220 mg Naproxen + 60 mg Fexofenadine.

[a]All *P* values are those reported in the original article;

[b]Mean difference % point estimates are calculated from the difference in mean % between intervention and placebo; Mean difference % 95% CIs are presented where sufficient data is reported in the original article to enable their calculation (i.e. CI's or raw data are reported in original article);

[c]Mean and SD calculated from graphical depiction in original article;

[d]Standard error of the mean (SEM) converted to SD;

[e]Mean (SD) converted from median and interquartile range (IQR).

DISCUSSION

Only very low quality evidence of efficacy is available for any studied pharmacologically active intervention for the treatment or prevention of alcohol-induced hangover symptoms. Of the limited interventions studied in placebo-controlled randomised trials no two studies reported on the same intervention. As such, meta-analysis was not possible and no results have been independently replicated. Although there was evidence of statistically significant improvements across a range of alcohol-induced hangover symptoms when comparing placebo to clove extract, tolfenamic acid, pyritinol, *H. dulcis* fruit extract, L-cysteine, red ginseng and Korean pear juice, all evidence was of very low quality. Although several studies report a lack of clear evidence for an effect of their studied intervention when compared to placebo, these estimates were also of very low quality. There did not appear to be any concerns regarding tolerability of any studied intervention, although only seven of the included trials (35%) reported the frequency of either AEs or SAEs.

The study has several strengths and limitations. We implemented robust methods to conduct the review, using a broad search strategy and a pre-defined protocol to capture evidence from RCTs. This is also the first systematic review in the treatment and prevention of alcohol-induced hangover to use GRADE methodology to assess the quality of the evidence base and the strength of resultant recommendations [18]. Although GRADE deemed all efficacy outcome estimates of very low quality this was despite two of GRADEs domains (inconsistency and publication bias) not being considered because of the literature representing only one trial per intervention. This serves to highlight that across almost all included studies significant methodological and reporting concerns were largely responsible for the downgrading of evidence quality. There was a general paucity of reported information on risk of bias issues including random sequence generation, allocation concealment and adequate blinding of outcome assessment. Few studies reported the overall number of randomised participants and did not report intention-to-treat analyses. Three quarters of all included studies (n = 16/21, 76%) reported data on sample sizes of fewer than 30 participants. Indeed, the evidence base for clove extract is based on data from only 16 participants. Of the ultimate 386 analysed participants, only 149 (38.6%) were female and eight included trials (38%) were conducted exclusively with male participants. There was also limited reporting regarding the nature, content and timing of alcohol challenges across studies including some considerable differences in the type of alcohol given and whether the challenge was given concomitantly with food, this likely leading to differential hangover severity and symptomatology across studies. A range of differing time points for measurement of hangover symptoms was also notable, these issues all serving to reduce comparability of outcome measures between trials. Reporting of measures of central tendency and measures of spread were also incomplete across studies, therefore, whereas some studies reported data on outcomes of interest, we are unable to report formal quantification of these estimates because of the study reporting either only P values, measures of central tendency without associated measures of spread or only narrative reporting of whether results met their threshold for demonstration of a statistically significant difference. Future studies should ensure methodological rigour, use validated scales to assess hangover symptomatology and adequately describe the nature of any alcohol challenge. There is also a clear need to improve the participation of women in hangover research. Given women's similar experience of hangover symptoms continued justification for trials recruiting only male participants going forward would seem discriminatory, and research teams should strive to ensure adequate representation.

Hangover symptoms can cause significant distress and have negative impacts on an individual's mental, physical and social well-being [17]. Although abstinence from alcohol or moderation of drinking habits is the only intervention able to definitively prevent development of hangover symptoms, alcohol consumption remains a legally sanctioned activity across the majority of the world with over 2.3 billion people estimated to have consumed alcohol regularly in 2016 [29]. Therefore, interventions aimed at reducing hangover symptoms are likely to have ongoing use in the alleviation of distressing symptoms and allowing more rapid return to activities of daily life. In considering a pharmacological option for the treatment or prevention of hangover symptoms, several of the studied interventions appear impractical. For example, those interventions examining agents requiring 14 or more days of use before the onset of hangover symptoms (e.g. Duolac ProAP4 [14]) may not appeal to individuals who are unable to accurately predict in advance when they are likely to consume excessive alcohol. Concerns are often raised that the pursuit of efficacious hangover remedies may lead people to be more likely to consume excessive amounts of alcohol [30, 31] and ultimately perpetuate development of alcohol-related harm. No conclusive evidence has validated this concern [8]. Indeed given the plethora of online and print media sources speculating as to which hangover remedies are efficacious, perhaps unsurprisingly given the prevalence of alcohol consumption and hangover, this suggests that remedies have proven efficacy is a question, in which there is considerable public interest. As such, this merits adequate scientific exploration in order that practitioners and the public be provided with accurate evidence-based information and do not rely on non-efficacious or potentially harmful interventions such as 'hair of the dog'. Interestingly, common analgesics such as paracetamol or aspirin have not been evaluated in RCTs in hangover.

The tolerability profile demonstrated by the studied interventions is reassuring in that there were no instances of SAEs and the few reported AEs appeared mild and occurred at rates similar to those experienced with placebo. Should individuals choose to take any of the trialled interventions, the majority of which are available without the need for prescription or input from a health professional, despite the very low quality nature of the evidence promoting their efficacy, they are unlikely to experience significant harm.

Although there is no evidence above a GRADE rating of very-low quality to recommend any studied pharmacologically active intervention for the treatment or prevention of alcohol-induced hangover symptoms favourable tolerability outcomes suggests there would be limited harm to individuals if they chose to use clove extract, tolfenamic acid, pyritinol, *H. dulcis* fruit extract, L-cysteine, red ginseng

or Korean pear juice and indeed these compounds appear to be the interventions with favourable efficacy profiles that most merit further study. Healthcare professional advice should remain that if individuals drink alcohol they should do so within safe drinking limits [32]. Professionals should also provide clinically appropriate screening for the diagnosis of alcohol use disorders [33, 34] and if asked should reiterate that the surest way of preventing hangover symptoms is to abstain from alcohol or drink in moderation.

DECLARATION OF INTERESTS

All authors have completed the ICJME Unified Competing Interest form (available on request from the corresponding author) and declare: None.

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AUTHOR CONTRIBUTIONS

Emmert Roberts: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; visualization. **Rachel Smith:** Data curation; investigation; validation. **Matthew Hotopf:** Conceptualization; methodology; resources; supervision; validation. **Colin Drummond:** Conceptualization; methodology; resources; supervision; validation.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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