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Title:

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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Running Head:

PHARMACOLOGICAL INTERVENTIONS IN HANGOVER

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

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Abstract (Word Count: 274) (Max 300)

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 1st 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 due to adverse events (AEs). Quality was assessed using the Grading of Recommendations Assessment Development and Evaluation (GRADE) framework.

Results: 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 due to 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.

Introduction

Alcohol-induced hangover, or veisalgia, refers to the combination of negative mental and physical symptoms which 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) Whilst alcohol and its metabolites are responsible for some symptoms, severity typically peaks when blood alcohol concentration has reduced to zero. Other factors including dehydration, immune dysregulation, hypoglycemia, 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 USA suggest hangover symptoms may cost up to 2,000 dollars 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 utility 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. Whilst 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 thus 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 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

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We searched Medline, Embase, PsycINFO and CENTRAL from database inception until 1st August 2021 without language restriction. Studies were eligible for inclusion if they were conducted in healthy adults and reported placebo-controlled randomised controlled trials 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 table S1 in the online supplementary material.

**Study Selection**

Two authors (ER and RS) 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 (CD) was consulted. All relevant references were checked for additional citations.

**Data Extraction**

Two authors (ER and RS) independently extracted data from all eligible studies using a standardised data extraction spreadsheet which can be found as 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 (CD) 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 a) a reported single question score, b) a reported summation score of all collected alcohol-induced hangover symptoms or c) 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 due to 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 Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework. (18) Each estimate is given a rating of high, moderate, low or very low quality based upon scores in five domains: risk of bias, inconsistency, indirectness, imprecision and other considerations. Due to the randomised nature of the data the default quality score is high which can then be down-graded according to the quality of the evidence for each estimate. Two reviewers (ER and RS) independently scored the quality of each study, any discrepancy was resolved by discussion, and where agreement could not be reached a third author (CD) was consulted. Risk of bias was assessed using the Cochrane risk of bias assessment tool, (19) (see 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 downgraded by one level if $I^2$ was $\geq 50\%$ and $< 75\%$, and by two levels if $I^2$ was $\geq 75\%$. 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 confidence interval (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. As 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 standard deviation 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 $\geq 10$ studies would have been included in meta-analysis. A complete description of GRADE quality scoring for each outcome can be found in the GRADE 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.

In order 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 standard deviations. For those studies reporting median scores these were converted, without any assumption as to the underlying distribution, using previously described standard methods. (21) In order to additionally aid comparability, means and standard deviations 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% confidence interval (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.

As 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. 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 table S3 in the online supplementary material.

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

A description of all included study characteristics can be found in table one. 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, eighteen were conducted exclusively with male participants and no studies were conducted which included adults aged over 65, the majority including only people aged below 40. Extraction of all raw reported data, alongside transformation to percentage mean and standard deviation scores for efficacy measurements, can be found in the online supplementary material as table S4.

Efficacy:

The study reported intervention and placebo means, standard deviations and/or p values for overall hangover severity score can be found in table two. Similar measures for all other included individual hangover symptom score efficacy outcomes can found in the online supplementary material as 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.

As 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 thus non were downgraded due to 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 figure S1 and individual GRADE tables S12-S19 in the online supplementary material for individual outcome quality assessments).

Tolerability:

No studies reported any drop-outs due to adverse events 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 due 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.

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. Whilst there was evidence of statistically significant improvements across a range of alcohol-induced hangover symptoms when comparing placebo to clove extract, tolfenamic acid, pyritinol, Hovenia dulcis fruit extract, L-cysteine, red ginseng and Korean pear juice, all evidence was of very low quality. Whilst 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 randomised controlled trials. 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) Whilst GRADE deemed all efficacy outcome estimates of very low quality this was despite two of GRADEs domains (inconsistency and publication bias) not being considered due to 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 sixteen 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 was also incomplete across studies, thus whilst some studies reported data on outcomes of interest, we are unable to report formal quantification of these estimates due to 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 upon an individual’s mental, physical and social well-being. (17) Whilst 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) Thus interventions aimed at reducing hangover symptoms are likely to have ongoing utility 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 prior to 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 which 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 thus 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, Hovenia 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.

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References

10. Room RE, America GC, a Doctor A, Observance M, Center PT. True or False: You Can Cure a Hangover.
18. GRADE. http://www.gradeworkinggroup.org [ ]
Figure 1: PRISMA flow diagram describing study selection

Records identified through database searching (n = 254)
Records after duplicates removed (n = 268)
Records screened (n = 268)  
Records excluded (n = 223)
Full-text articles assessed for eligibility (n = 45)
Studies included (n = 20)
Full-text articles excluded, with reasons*
  (n = 25)
  Non-protocol study population (n=3)
  Non-protocol study design (n=4)
  No placebo control (n=10)
  Other (n=8)
*Please see online supplementary material for full reasons for all excluded articles

Additional records identified through other sources (n = 14)
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<th>Population description</th>
<th>Country</th>
<th>Alcohol challenge description</th>
<th>Intervention</th>
<th>F/M</th>
<th>Age (range)</th>
<th>Number randomised</th>
<th>Number analysed in intervention arm</th>
<th>Number analysed in comparison arm</th>
<th>Name of scale used for hangover symptom assessment</th>
<th>Likert or VAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy volunteers</td>
<td>India</td>
<td>NR</td>
<td>Curcumin: 45mg curcumin oral anti-hangover film containing other ingredients' given prior to alcohol challenge</td>
<td>NR</td>
<td>&gt; 18</td>
<td>NR</td>
<td>NR</td>
<td>42</td>
<td>16</td>
<td>NR</td>
</tr>
<tr>
<td>Healthy volunteers</td>
<td>South Korea</td>
<td>Vodka (40% ABV) consumed with water at 1:1 ratio amounting to 0.8g alcohol per kg body weight consumed within 90 min of a meal and with a small amount of snack</td>
<td>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</td>
<td>0:40</td>
<td>19 - 65</td>
<td>54</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>Alcohol hangover questionnaire (AHQ)</td>
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<td>Healthy volunteers</td>
<td>Finland</td>
<td>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</td>
<td>L-cysteine: Six tablets containing 200mg L-cysteine, 50mg thiamine, 1.4mg riboflavin, 16mg niacin, 1.4mg pyridoxine, 90mg biotin, 200 μg folinic acid, 2.5 μg cobalamin and 80mg ascorbic acid taken during alcohol challenge</td>
<td>0:19</td>
<td>21 - 60</td>
<td>27</td>
<td>9</td>
<td>9/12</td>
<td>9/12</td>
<td>NR</td>
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<td>Healthy volunteers</td>
<td>USA</td>
<td>12 oz of 82% ABV Belgian-style wheat ale consumed one at a time until participants reached a breath alcohol content (BrAC) of 0.07±0.01</td>
<td>NAC: 1 - 3 capsules of 600 mg N-Acetyl-L-Cysteine (NAC) given following alcohol challenge dose based on the amount of alcohol consumed</td>
<td>18:31</td>
<td>&gt; 21</td>
<td>62</td>
<td>49</td>
<td>45</td>
<td>46</td>
<td>Hangover Symptom Scale (HSS)</td>
</tr>
<tr>
<td>Healthy volunteers</td>
<td>Australia</td>
<td>Self-administered alcoholic beverages of participant choice to a maximum of 4 kg alcohol/kg body weight following a meal</td>
<td>Rapid Recovery: L-cysteine, thiamine, pyridoxine and ascorbic acid capsule given after immediately after alcohol challenge and again the following morning</td>
<td>13:7</td>
<td>25 - 43</td>
<td>23</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>Adapted from multiple hangover assessment scales</td>
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<tr>
<td>Healthy medical doctors</td>
<td>Japan</td>
<td>Self-reported hangover symptoms occurring during daily life</td>
<td>Loxoprofen: loxoprofen sodium 60 mg once orally taken when experiencing fatigue due to hangover</td>
<td>12:138</td>
<td>34 (30 - 39) MD (IQR)</td>
<td>229</td>
<td>150</td>
<td>74</td>
<td>76</td>
<td>NR</td>
</tr>
<tr>
<td>Healthy volunteers</td>
<td>NR</td>
<td>Self-administered alcohol including red/white wine, beer, champagne, and liquors available with light snacks (e.g., pretzels, potato chips, nuts)</td>
<td>SIP-001: (220mg naproxen and 60mg fexofenadine), 220mg naproxen alone, or 60mg fexofenadine alone taken before the start of alcohol consumption</td>
<td>2:3</td>
<td>35 2 (27 - 47)</td>
<td>13</td>
<td>5</td>
<td>5 SJP-001 5Fexofenadine 4 Naproxen</td>
<td>5</td>
<td>Alcohol Hangover Scale</td>
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<tr>
<td>Healthy volunteers</td>
<td>USA</td>
<td>Several shots (1.5 fluid oz or 3/4 alcohol of Jack Daniel’s Whisky, TN, USA) to reach a blood alcohol level (BALK) of 0.12%</td>
<td>Phyllpro: Ten days daily oral 750mg/day of standardized ethanol extract of Phyllanthus amarus leaves taken prior to alcohol challenge</td>
<td>5:10</td>
<td>21 - 50</td>
<td>16</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>Hangover Severity Score</td>
</tr>
<tr>
<td>Healthy volunteers</td>
<td>India</td>
<td>250ml of 42.8% alcohol (McDowell’s V.S.O.P. Brandy) 1g alcohol/kg body weight and a piece of cheese followed by a meal</td>
<td>Cluvinol: 250mg polyphenolic extract of clove buds taken prior to alcohol challenge</td>
<td>0:16</td>
<td>25 - 55</td>
<td>16</td>
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<td>16</td>
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<td>Adapted from Alcohol Hangover Severity Scale (AHSS)</td>
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<table>
<thead>
<tr>
<th>Healthy volunteers</th>
<th>Country</th>
<th>Interventions</th>
<th>Alcohol Challenge</th>
<th>BAC Challenge (g/kg)</th>
<th>BAC Challenge (Mean ± SD)</th>
<th>Scale</th>
<th>Likert</th>
</tr>
</thead>
<tbody>
<tr>
<td>South Korea</td>
<td>Volunteers</td>
<td>360 mL of Korean Soju (50 g alcohol)</td>
<td>17.5% alcohol taken after a standard meal</td>
<td>0.26</td>
<td>20 - 40</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>South Korea</td>
<td>Volunteers</td>
<td>1.75g alcohol/kg over 2 hours; A prepared meal was given with alcohol</td>
<td>PEA: Polysaccharide rich extract of Acanthopanax senticosus (PEA) given 30 minutes prior to and soon after alcohol challenge</td>
<td>0.28</td>
<td>19 - 55</td>
<td>28</td>
<td>28</td>
</tr>
<tr>
<td>South Korea</td>
<td>Volunteers</td>
<td>100 ml of 40% ABV (Whiskey); One piece of cheese given with alcohol</td>
<td>Red Ginseng: 100 ml of red ginseng anti-hangover drink (RGD) given within 5 minutes of alcohol challenge</td>
<td>0.25</td>
<td>25 - 49</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>South Korea</td>
<td>Volunteers</td>
<td>540mg of 20.1% ABV (Soju) following a low fat meal</td>
<td>Korean Pear Juice: 220 ml of Korean pear juice given 30 minutes prior to alcohol challenge</td>
<td>0.14</td>
<td>25 ± 8 (0.86)</td>
<td>Mean (SD)</td>
<td>20</td>
</tr>
<tr>
<td>Japan</td>
<td>Volunteers</td>
<td>0.4g alcohol/kg body weight (5% ABV Beer) over 0.5 hours following a meal two previously</td>
<td>L-ornithine: 500 mg L-ornithine monohydrochloride after alcohol challenge</td>
<td>1:10</td>
<td>35 ± 5 (2.4)</td>
<td>Mean (SD)</td>
<td>NR</td>
</tr>
<tr>
<td>USA</td>
<td>Volunteers</td>
<td>Up to 1.75g alcohol/kg body weight (participant choice of alcohol) following a meal</td>
<td>Prickly Pear: 1600 IU Opuntia ficus-indica given prior to alcohol challenge</td>
<td>3.23</td>
<td>21 - 35</td>
<td>64</td>
<td>55</td>
</tr>
<tr>
<td>UK</td>
<td>Volunteers</td>
<td>An average of 1.2g alcohol/kg body weight (participant choice of alcohol); A pasta meal was taken before alcohol challenge</td>
<td>Artichoke: 960mg Cynara scolymus extract (LI120) from Cynara Artichoke given prior to and after alcohol challenge</td>
<td>5:10</td>
<td>18 - 65</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Estonia</td>
<td>Volunteers</td>
<td>100% alcohol (Vodka 46% ABV). After alcohol challenge soft drinks, water, and a low-fat lunch were offered</td>
<td>Morning-Fit': 250 mg dried yeast, 0.5 mg d-hyamine nitrate, 0.5 mg pyridoxine hydrochloride, and 0.5 mg riboflavin per tablet; 750mg given after alcohol challenge</td>
<td>34:27</td>
<td>20-40</td>
<td>61</td>
<td>57</td>
</tr>
<tr>
<td>USA</td>
<td>Volunteers</td>
<td>Estimated 0.1% BAC for each patient (participant choice of alcohol); No water was allowed after alcohol challenge</td>
<td>Proneparanol: 160mg long-acting propranolol given 2 hours prior to alcohol challenge</td>
<td>4:6</td>
<td>21-25</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Finland</td>
<td>Volunteers</td>
<td>Self-assessed alcohol challenge</td>
<td>Tollifemacid: 200mg toleferamic acid given prior to and after alcohol challenge</td>
<td>17:3</td>
<td>22 - 48</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Sweden</td>
<td>Volunteers</td>
<td>1.43 g alcohol/kg body weight (Swedish brännvin, beer and whiskey) consumed with food over 24 rain</td>
<td>Chloromethiazole: 1g at bedtime following alcohol challenge and 0.5 g early the following morning</td>
<td>0:12</td>
<td>24 - 46</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Denmark</td>
<td>Volunteers</td>
<td>Non-restricted quantity of any desired beverage (whisky, beer, and whiskey) all 43% ABV at a party prior to a light meal</td>
<td>Pyritinol: 400mg pyritinol three times throughout the evening at 3-hour intervals</td>
<td>6:11</td>
<td>21 - 40</td>
<td>17</td>
<td>17</td>
</tr>
</tbody>
</table>

F: Female; M: Male; VAS Visual Analogue Scale; NR Not Reported; mg milligrams; MD median; IQR interquartile range; SD standard deviation
Table 2: Difference in mean overall hangover score between all interventions and placebo.

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Intervention</th>
<th>Intervention: Mean % (SD)</th>
<th>Placebo: Mean % (SD)</th>
<th>p*</th>
<th>Placebo: Mean % (SD)</th>
<th>Mean difference (%) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mammen 2018</td>
<td>Cleverol</td>
<td>2.89 (6.74)</td>
<td>4.68 (8.08)</td>
<td>&gt;0.05</td>
<td>19.0 (6.75)</td>
<td>42.5 (6.82)</td>
</tr>
<tr>
<td>Karvola 1985</td>
<td>Tolminamic acid</td>
<td>3.10 (6.76)</td>
<td>6.4 (6.6)</td>
<td>&gt;0.05</td>
<td>76.0 (87.44)</td>
<td>84.9 (60.73)</td>
</tr>
<tr>
<td>Khan 1973</td>
<td>Pynotil</td>
<td>5.24 (2.75)</td>
<td>6.82 (6.83)</td>
<td>&gt;0.01</td>
<td>16.2 (7.35)</td>
<td>34.1 (16.15)</td>
</tr>
<tr>
<td>Kim 2017</td>
<td>HDE</td>
<td>NR</td>
<td>NR</td>
<td>0.029</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Eriksson 2021</td>
<td>L-cysteine/B and C vitamins</td>
<td>NR</td>
<td>NR</td>
<td>0.043</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Lee 2004</td>
<td>Red Ginseng</td>
<td>6.40 (6.35)</td>
<td>12.7 (8.2)</td>
<td>&gt;0.05</td>
<td>14.0 (16.08)</td>
<td>23.0 (15.07)</td>
</tr>
<tr>
<td>Lee 2013</td>
<td>Korean Pear Juice</td>
<td>23.31 (8.39)</td>
<td>29.88 (11.39)</td>
<td>&gt;0.05</td>
<td>33.3 (12.27)</td>
<td>41.5 (16.27)</td>
</tr>
<tr>
<td>Bang 2016</td>
<td>PEA</td>
<td>1.6 (6.1)</td>
<td>1.8 (2.2)</td>
<td>&gt;0.05</td>
<td>17.5 (7.25)</td>
<td>22.5 (2.5)</td>
</tr>
<tr>
<td>Wiese 2004</td>
<td>Prickly Pear</td>
<td>12.2 (8.4)</td>
<td>14.9 (8.4)</td>
<td>0.87</td>
<td>21.6 (12.22)</td>
<td>27.6 (15.55)</td>
</tr>
<tr>
<td>Copperman 2021</td>
<td>NAC</td>
<td>7.25 (8.16)</td>
<td>7.75 (6.52)</td>
<td>0.86</td>
<td>29.0 (15.24)</td>
<td>31.8 (18.08)</td>
</tr>
<tr>
<td>Schonle 2020</td>
<td>Rapid Recovery</td>
<td>3.22 (2.07)</td>
<td>3.18 (2.09)</td>
<td>&lt;0.05</td>
<td>29.3 (18.1)</td>
<td>28.9 (24.3)</td>
</tr>
<tr>
<td>Hwang 2021</td>
<td>Duolac ProAP4</td>
<td>37.75 (10.82)</td>
<td>37.75 (10.26)</td>
<td>0.996</td>
<td>37.75 (10.62)</td>
<td>37.78 (10.26)</td>
</tr>
<tr>
<td>George 2019</td>
<td>PhySoo</td>
<td>1.47 (1.35)</td>
<td>1.47 (1.64)</td>
<td>&gt;0.05</td>
<td>21.0 (19.29)</td>
<td>23.4 (21.2)</td>
</tr>
<tr>
<td>Verster 2020</td>
<td>SJP-001</td>
<td>0.8 (0.8)</td>
<td>2.4 (1.3)</td>
<td>&gt;0.05</td>
<td>16.0 (16.0)</td>
<td>30.8 (16.25)</td>
</tr>
<tr>
<td>Verster 2020</td>
<td>Fexofenadine</td>
<td>1.6 (1.5)</td>
<td>2.4 (1.3)</td>
<td>&gt;0.05</td>
<td>26.0 (18.71)</td>
<td>34.9 (16.25)</td>
</tr>
<tr>
<td>Verster 2020</td>
<td>Naprofen</td>
<td>0.0 (0.5)</td>
<td>2.4 (1.3)</td>
<td>&gt;0.05</td>
<td>16.0 (6.25)</td>
<td>30.8 (16.25)</td>
</tr>
<tr>
<td>Bagin 1987</td>
<td>Propranolol</td>
<td>2.9 (3.1)</td>
<td>2.9 (2.9)</td>
<td>&gt;0.05</td>
<td>58.0 (22)</td>
<td>58.6 (22)</td>
</tr>
<tr>
<td>Pittler 2001</td>
<td>Artichoke</td>
<td>3.2 (2.6)</td>
<td>3.3 (2.4)</td>
<td>&gt;0.05</td>
<td>32.0 (26)</td>
<td>33.8 (26)</td>
</tr>
<tr>
<td>Meyers 1990</td>
<td>Chlorella</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Hara 2009</td>
<td>Loxoprofen</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Kekabe 2011</td>
<td>L-ornithine</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Laas 1999</td>
<td>Morning Fit</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Shobha 2021</td>
<td>Cicutum</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

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. CI: Confidence Interval; NR: Not Reported; SD: Standard Deviation; HDE: Hovenia dulcis Thunb. fruit extract; PEA: Pseudobasidio mycelium extract of A. aurantatum sensu stricto; NAC: N-Acetyl-L-Cysteine; SJP-001: 2,2' Dithipyridine + sifting Ficus elastica; 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% CI 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 standard deviation calculated from graphical depiction in original article; d Standard error of the mean, SD converted to SD, e Mean (SD) converted from median and interquartile range (IQR).