



## Short Communication

## Unknown safety and efficacy of alcohol hangover treatments puts consumers at risk

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## ABSTRACT

It is important that hangover products are both safe and effective. The aims of the current study were to evaluate (a) the ingredients of currently marketed hangover treatments, (b) whether companies make disease modification claims for these products, and (c) the extent and quality of any independent scientific evidence on their efficacy and safety. Of eighty-two hangover products identified, the most common ingredients were vitamin B, vitamin C, milk thistle extract (silymarin), dihydromyricetin (DHM), and N-acetyl L-cysteine (NAC), often in combination. Fifty-one products (62.2% of the 82 evaluated products) contained one or more vitamins of which the dose exceeded the corresponding daily recommended intake level. For 9 (28.1%) of 32 products that reported the dose of Vitamin B3 and 2 (8.0%) of 25 products that reported the dose of Vitamin B9 the corresponding tolerable upper intake level was exceeded. Further, in many other cases the dose of other ingredients was not reported (e.g., dosages of DHM and NAC were not reported by 59% and 73% of the products containing these ingredients), and corresponding tolerable upper limits are unknown. A review of scientific literature revealed no peer-reviewed human data demonstrating either safety or efficacy of any of the 82 evaluated hangover products. Further, the product name and/or package/insert included explicit disease modification claims in 64.6% of the products. Finally, 45.1% of the products contain NAC as an ingredient. As NAC is registered as a drug by the US Food and Drug Administration (FDA), it is prohibited as an ingredient in dietary supplements or foods. We conclude that, in the interest of consumers, independent research supporting the safety and efficacy of hangover treatments should be a minimum requirement for hangover treatment claims irrespective whether the products are registered as medicinal drugs or dietary supplements.

## 1. Introduction

The alcohol hangover is defined as the combination of negative mental and physical symptoms, which may be experienced the day after a single episode of alcohol consumption, starting when blood alcohol concentration (BAC) approaches zero (Verster, Scholey, van de Loo, Benson, & Stock, 2020). Alcohol hangover negatively impacts a number of aspects of health, resulting in impaired cognitive performance (Gunn, Mackus, Griffin, Munafo, & Adams, 2018), negative mood (Van Schroyen Lantman, Mackus, van de Loo, & Verster, 2017), and functional impairment of daily activities such as driving a car (Verster et al., 2014; Alford et al., 2020). A 2015 report estimated the annual cost to the US economy from hangover-related absenteeism and presenteeism at \$173

billion (Sacks, Gonzales, Bouchery, Tomedi & Brewer, 2015). Despite a market need (Mackus, van Schroyen Lantman, van de Loo, Nutt & Verster, 2017), no evidence-based hangover treatments are currently marketed (Pittler, Verster & Ernst, 2005; Verster & Penning, 2010; Jayawardena, Thejani, Ranasinghe, Fernando & Verster, 2017).

Despite the absence of any evidence base, several products registered as dietary supplements are marketed on the internet as reducing the severity of hangover symptoms. From a consumer perspective, it is important that such products are both safe and effective, irrespective whether they are registered as drugs or dietary supplements (Mackus et al., 2017). The aims of the current study were therefore to evaluate (a) the ingredients of currently marketed hangover treatments, (b) whether disease claims are made for these products, and (c) if there is

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independent scientific evidence on their efficacy and/or safety.

## 2. Methods

To address the first aim of the study, a search on US Amazon (www.amazon.com, NY 10,001 area) for ‘hangover treatment’ was conducted on December 14, 2019. The search returned 378 hits. Products were regarded as irrelevant and removed from further analysis if they met any of the following criteria: (1) their primary use was not hangover-related (e.g., face masks), (2) they were marketed for general (daily) use without any reference to alcohol or hangover (e.g. vitamins and herbs), (3) they were products solely for rehydration purposes, unrelated to alcohol consumption (e.g., sports), (4) they were ‘sports drinks’ or other soft drinks. Duplicates were also removed.

Ingredients of the hangover products were gathered from the package, insert, or product websites. Daily recommended intake (DRI), i.e. the amount of a nutrient recommended per day for Americans 4 years of age or older, was taken from US Food and Drug Administration (FDA, 2016). The Tolerable Upper Intake Level (UL), i.e. the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects to almost all individuals in the general population 19 years of age and older, was taken from the Food and Nutrition Board (2019). Unless otherwise specified, the UL represents total intake from food, water, and supplements.

To address the second aim of the study, the product name and/or package and insert were evaluated for any disease claim. Specifically, any term such as “cure”, “treat”, “correct”, “prevent”, or similar was regarded as a disease-related claim. Also, inclusion of the word ‘hangover’ in the product name met the criterion for a claim.

To address the third aim of the study, a literature search was conducted to identify peer-reviewed, published scientific studies that investigated the efficacy and safety of the marketed products. To this end, a PubMed search was conducted, including cross references. We also searched the websites of the companies marketing the corresponding hangover products.

## 3. Results

The search revealed  $N = 82$  hangover products. Where possible, the nutrition information of the 82 products was retrieved. Except for vitamins (requiring mandatory reporting), doses of other ingredients were often not reported or named only as constituents of the ‘proprietary blend’. The products came in various delivery forms including capsules ( $N = 46$ ), tablets (10), powders (10), drinks and other liquids (9), transdermal patches (5), gummies (1), or an aromatic scent (1). Two hundred and fifteen different vitamins, minerals, ‘natural’ ingredients (e.g., plant extracts), and synthetic organic chemicals were included in these products, of which the 50 most frequently used ingredients are listed in Table 1. The most common ingredients were vitamin B, vitamin C, milk thistle extract (silymarin), dihydromyricetin (DHM), and N-acetyl L-cysteine (NAC), often in combination. The number of ingredients and their doses varied greatly across products. Tolerable upper intake levels and daily recommended intake levels are established for vitamins and several minerals, and in several products these were exceeded. For example, 51 products (62.2% of the total number of evaluated products) contained one or more vitamins of which the dose exceeded the corresponding daily recommended intake level. For 9 (28.1%) of 32 products that reported the dose of Vitamin B3 and 2 (8.0%) of 25 products that reported the dose of Vitamin B9 the corresponding tolerable upper intake level was exceeded. Further, in many other cases the dose of other ingredients was not reported (e.g., dosages of DHM and NAC were not reported by 59% and 73% of the products containing these ingredients), and corresponding tolerable upper limits are unknown. It therefore remains to be determined whether the included dosages are either safe or effective.

Analysis revealed that 53 products (64.6%) made explicit disease

claims via the product name and/or package/insert. In addition, 37 of the 82 products (45.1%) listed N-acetyl L-cysteine (NAC) as an ingredient. NAC is registered by FDA as a drug and thus prohibited from use in dietary supplements. The literature search revealed no peer-reviewed, scientific evidence supporting either efficacy or safety for any of the 82 products.

## 4. Discussion

Eighty-two hangover products were identified, of which the most commonly used ingredients were vitamin B, vitamin C, milk thistle extract (silymarin), dihydromyricetin (DHM), and N-acetyl L-cysteine (NAC), often in combination. While the majority (64.6%) of the products made explicit disease claims, a review of scientific literature revealed no peer-reviewed human data on the safety or efficacy of any product.

An important source for a classification of diseases and health conditions is the International Classification of Diseases 11th Revision (ICD-11). Unfortunately, the ICD-11 is unclear with regard to the alcohol hangover, which has no separate classification. Instead ICD 11 uses ‘alcohol hangover’ and ‘hangover from alcohol’ as matching terms for ‘alcohol intoxication’ (ICD-11, 2021). This is factually incorrect as, by definition, hangover symptoms occur *after* the intoxication phase (Verster, Scholey, van de Loo, Benson, & Stock, 2020). This confusion illustrates the imperative for further hangover research and its dissemination, and may contribute to disagreement among international agencies as to whether hangover constitutes a disease. It is worth noting that the US FDA defines disease as ‘damage to an organ, part, structure, or system of the body such that it does not function properly (e.g., cardiovascular disease), or a state of health leading to such dysfunctioning (e.g., hypertension)’, only diseases resulting from essential nutrient deficiencies being excluded from this definition (Food and Drug Administration, 1998).

Products that are intended to treat or prevent a disease meet the US FDA classification for drugs (Federal Food, Drug, and Cosmetic Act, 2021). In the context of hangover, this is explicitly confirmed in recent warning letters from the FDA (e.g., FDA, 2020). In these letters FDA states that “A hangover is a sign or symptom of alcohol intoxication, a disease. Like all poisonings, alcohol intoxication causes dose-related dysfunctioning and damage, ranging from mild impairments to death. Alcohol intoxication causes temporary damage to brain function, causing impairments of judgment, attention, reflexes, and coordination. Therefore, according to FDA, “alcohol intoxication meets the definition of disease” (FDA, 2000). As such, in the US companies should follow the common procedures required for drug registration, including conducting studies assessing the efficacy and safety of their product.

Paradoxically, in the US (and elsewhere) most hangover treatments are registered as dietary supplements. With some exceptions, disease modification claims are not permitted for dietary supplements. According to FDA guidelines, except for analgesic-antacid combinations, which are allowed to make claims regarding the treatment or prevention of hangover, no disease modification claims regarding hangover can be made for dietary supplements (Food and Drug Administration, 2000, Food and Drug Administration, 2002). Specifically, the FDA mandates that the product name, package, and website do not refer to a disease or include terms such as “cure”, “treat”, “correct”, “prevent” or similar terms that suggest treatment or prevention of a disease (i.e. in this case hangover) (Food and Drug Administration, 2000, Food and Drug Administration, 2002). In fact, reference to scientific literature demonstrating the efficacy of a dietary supplement are, in most cases, also considered a disease claim (Food and Drug Administration, 2002). In July 2020, FDA issued warning letters to seven companies marketing so-called hangover treatments for violation of these guidelines (Voelker, 2020).

There are certain critical considerations when designing an efficacy study. Firstly, there can be considerable inter-individual differences influencing conditions such as hangover development and severity.

Table 1

Top 50 most reported ingredients of 82 hangover treatments sold on US Amazon per December 14, 2019.

	Ingredient	Number of products	Dose not specified	Reported dose range	Daily recommended intake (DRI)	Products exceeding DRI <sup>5</sup>	Tolerable upper intake level (UL)	Products exceeding UL <sup>6</sup>
1	Vitamine B1 (thiamine)	48 (58.5%)	3 (6.3%)	0.4–200 mg	1.2 mg	42 (93.3%)	ND	ND
2	Vitamin B6/(pyridoxine HCL)	45 (54.9%)	2 (4.4%)	0.6–100 mg	1.7 mg	41 (95.3%)	100 mg	0 (0%)
3	Milk thistle extract (Silymarin)	40 (48.8%)	27 (60.0%)	2.975–500 mg	ND	ND	ND	ND
4	DHM (dihydropyricetin), hovenia dulcis <sup>1</sup>	39 (47.6%)	23 (59.0%)	200–1200 mg	ND	ND	ND	ND
5	N-acetyl L-cysteine (NAC)	37 (45.1%)	27 (73.0%)	50–1200 mg	ND	ND	ND	ND
6	Vitamin B12 (cynocobalamin)	37 (45.1%)	1 (2.7%)	1–1000 µg	2.4 µg	33 (91.7%)	ND	ND
7	Vitamin C (ascorbic acid)	36 (43.9%)	1 (2.8%)	11.25–1100 mg	90 mg	27 (77.1%)	2000 mg	0 (0%)
8	Vitamin B3 (niacin, nicotinic acid)	33 (40.2%)	1 (3.0%)	6–110 mg	16 mg	23 (71.9%)	35 mg	9 (28.1%)
9	Vitamin B5 (pantothenic acid)	33 (40.2%)	1 (3.0%)	1.375–110 mg	5 mg	23 (71.9%)	ND	ND
10	Vitamin B2 (riboflavin)	32 (39.0%)	1 (3.1%)	0.325–85 mg	1.3 mg	27 (87.1%)	ND	ND
11	Magnesium, magnesium citrate	31 (37.8%)	1 (3.2%)	3–225 mg	420 mg	0 (0%)	350 mg	0 (0%)
12	Vitamin B9 (folate)	26 (31.7%)	1 (3.8%)	120–250,000 µg	400 µg	12 (48.0%)	1000 µg	2 (8.0%)
13	Potassium, potassium citrate	23 (28.0%)	1 (4.3%)	10–430 mg	4700 mg	0 (0%)	ND	ND
14	(R-) Alpha lipoic acid	22 (26.8%)	16 (76.2%)	20–150 mg	ND	ND	ND	ND
15	Prickly pear (opuntia ficus indica)	21 (25.6%)	17 (81.0%)	40–150 mg	ND	ND	ND	ND
16	Sodium	21 (25.6%)	1 (4.8%)	5–406 mg	2300 mg	0 (0%)	ND	ND
17	Taurine	20 (24.4%)	16 (80%)	10–200 mg	ND	ND	ND	ND
18	Vitamin E (d-alpha tocopherol)	19 (23.2%)	1 (5.3%)	1.31–90 mg	15 mg	8 (44.4%)	1000 mg	0 (0%)
19	Zinc	19 (23.2%)	2 (10.5%)	0.48–30 mg	11 mg	2 (11.8%)	40 mg	0 (0%)
20	Calcium / calcium carbonate/ calcium disodium	18 (22.0%)	4 (22.2%)	5–150 mg	1300 mg	0 (0%)	2500 mg <sup>2</sup>	0 (0%)
21	Ginger root (zingiber officinale)	15 (18.3%)	9 (60.0%)	40–750 mg	ND	ND	ND	ND
22	Vitamin B7 (biotin)	13 (15.9%)	0 (0.0%)	5–900 µg	30 µg	11 (84.6%)	ND	ND
23	grape seed extract (vitis vinifera)	12 (14.6%)	8 (66.7%)	8–100 mg	ND	ND	ND	ND
24	Curcumin (tumeric root extract)	11 (13.4%)	9 (81.8%)	50–60 mg	ND	ND	ND	ND
25	Glutamine <sup>3</sup>	11 (13.4%)	7 (63.6%)	10–900 mg	ND	ND	ND	ND
26	L-theanine	11 (13.4%)	9 (81.8%)	20–174 mg	ND	ND	ND	ND
27	Selenium	11 (13.4%)	0 (0.0%)	25 – 400 µg	55 µg	3 (27.3%)	400 µg	0 (0%)
28	Total carbohydrates	11 (13.4%)	0 (0.0%)	3–14 g	275 g	0 (0%)	ND	ND
29	Manganese	10 (12.2%)	0 (0.0%)	1.56–4 mg	2.3 mg	1 (10.0%)	11 mg	0 (0%)
30	L-Cysteine	9 (11.0%)	4 (44.4%)	0.150–400 mg	ND	ND	ND	ND
31	Asian/Korean ginseng (panax ginseng)	8 (9.8%)	6 (75.0%)	10–174 mg	ND	ND	ND	ND
32	Artichoke leaf	8 (9.8%)	5 (62.5%)	15–125 mg	ND	ND	ND	ND
33	Choline	8 (9.8%)	3 (37.5)	20–825 mg	550 mg	1 (20.0%)	3500 mg	0 (0%)
34	Chromium	8 (9.8%)	0 (0.0%)	10–200 µg	35 µg	6 (75.0%)	ND	ND
35	green tea extract	8 (9.8%)	7 (87.5%)	10 mg	ND	ND	ND	ND
36	Chicory root (cichorium intybus)	7 (8.5%)	5 (71.4%)	50–100 mg	ND	ND	ND	ND
37	(L-)glutathione	7 (6.1%)	6 (85.7%)	50 mg	ND	ND	ND	ND
38	schisandra berry extract	7 (8.5%)	4 (57.1%)	50–600 mg	ND	ND	ND	ND
39	White willow bark (salicin)	7 (8.5%)	4 (57.1%)	4–120 mg	ND	ND	ND	ND
40	Added sugars	7 (8.5%)	1 (14.3%)	1–12 g	50 g	0 (0%)	ND	ND
41	(Acetyl) L-carnitine	6 (7.3%)	6 (100%)	–	ND	ND	ND	ND
42	Co-enzym Q10 (ubiquinone 10)	6 (7.3%)	5 (83.3%)	15 mg	ND	ND	ND	ND
43	Dandelion root (taraxacum officinalis)	6 (7.3%)	3 (50.0%)	15–100 mg	ND	ND	ND	ND
44	Kudzu flower (pueraria lobata)	6 (7.3%)	4 (66.7%)	90–375 mg	ND	ND	ND	ND
45	Acai berry	5 (6.1%)	4 (80.0%)	20 mg	ND	ND	ND	ND
46	Copper	5 (6.1%)	0 (0.0%)	0.5–500 µg	0.9 mg	0 (0%)	10 mg	0 (0%)
47	Vitamin A (retinol)	5 (6.1%)	1 (20.0%)	600–3000 µg	900 µg	2 (50%)	3000 µg	0 (0%)
48	Vitamin B6 (pyrodoxal 5-phosphate)	4 (4.8%)	1 (25.0%)	0.5–20 mg	ND	ND	ND	ND
49	Bupleurum root (bupleurum chinense)	4 (4.8%)	3 (75.0%)	100 mg	ND	ND	ND	ND
50	Caffeine	4 (4.8%)	0 (0.0%)	45–150 mg	ND	ND	ND <sup>4</sup>	ND

Abbreviation: ND = not determined.

Notes:

Note: The various 'natural ingredients' (e.g., fruit and herb extracts) also contribute to intake levels of vitamins and minerals/elements. These are not included in the ingredient count in this Table.

<sup>1</sup> Also includes DHM from Japanese raisin tree, vine leaf tea extract, ampelopsis grossedentata leaf.<sup>2</sup> The UL for females 51 years and older is 2000 mg.<sup>3</sup> Also includes L-glutamine, L-analyt L-glutamine, and glutaminergic acid.<sup>4</sup> The European Food Safety Authority (EFSA) concluded that the general population of healthy adults is not at risk for potential adverse effects from caffeine at daily consumption levels up to 400 mg caffeine. EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies). (2015). Scientific Opinion on the safety of caffeine. EFSA J. 13:4102, doi: <https://doi.org/10.2903/j.efsa.2015.4102>.

<sup>5</sup> The percentage of the number of products with a dose above the DRI of the total number of products that reported a dose for the ingredient.

<sup>6</sup> The percentage of the number of products with a dose above the UL of the total number of products that reported a dose for the ingredient.

These include factors beyond the amount of alcohol consumed (Verster, Kruisselbrink, Slot, et al., 2020), such as age (Verster, Severeijns et al., 2021) and reverse tolerance (Verster et al., 2019). These potentially confounding influences can be minimized by comparing the effects of the product with a placebo in the same subjects (i.e., a crossover, within-subject design). Second, the observation that a product reduces some hangover-related symptoms (but not others) is not sufficient to demonstrate efficacy. The primary endpoint for efficacy studies should be overall hangover severity, preferably assessed with a 1-item hangover severity scale score (Verster, van de Loo, Benson, Scholey, & Stock, 2020). Third, statistical tests directly comparing overall hangover severity scores of the product and placebo should be two-tailed. One-tailed analyses, with *a priori* assumptions regarding efficacy are rarely warranted. Put simply, in theory a given product could also worsen the hangover state (Benson, Scholey, & Verster, 2021).

In addition to the need for evidence-based support of efficacy, consumers further state that proven safety is an important condition for buying a hangover product (Mackus et al., 2017). While there is scientific evidence that some of the ingredients and dosages listed in Table 1 can be considered safe when administered individually, their pharmacokinetic and pharmacodynamic properties when administered in combination are often unknown. Their combined use may result in unwanted interactions, including with over-the-counter or prescription medicines. For example, an *in vitro* study found that dihydromyricetin has the potential to cause pharmacokinetic drug interactions with other co-administered drugs metabolized by CYP3A4, CYP2E1 and CYP2D6 enzymes (Liu, Sun, Rui, & Li, 2017). Also, the rationale for choosing specific dosages of ingredients is rarely reported. This lack of investigating effective and safe dosages is worrisome and may result in either too low (ineffective) dosages, or dosages that are too high in terms of safety. It is important to note that over 75% of all reported adverse drug effects are dose-related (Lazarou, Pomeranz, & Corey, 1998). One could thus argue that FDA should more closely regulate the industry and require empirical evidence prior to approving release of a new product into the public domain.

In this context, self-regulation by industry seems ineffective. From the current analysis it appeared that almost two-third of companies (64.6%) violate current legislations by making explicit disease claims for their dietary supplement via the product name and/or package/insert. In other cases companies provided vague descriptions referring to the alleged effects of their product (e.g., “to help you bounce back after drinking” or “wake up clear after drinking”), possibly to circumvent legislation. However, none of the companies provided any independent, peer-reviewed, published, scientific evidence for their claims. Further, nearly half of the products (45.1%) contain N-acetyl L-cysteine (NAC) as ingredient. NAC was approved as mucolytic drug for the treatment of chronic respiratory disease by FDA on September 14, 1963. Unless NAC was marketed as a dietary supplement or as a food before this date, its inclusion as an ingredient in dietary supplements or foods is prohibited. This is not the case for NAC, so its inclusion as ingredient does not meet the criteria as defined under section 201(ff)(3)(B)(i) of the *Federal Food, Drug, and Cosmetic Act* (2021). In other words, it is not allowed to include NAC as ingredient in dietary supplements. From a consumer perspective, more important than its regulatory status is the question as to what extent there is evidence whether NAC is actually effective in the treatment of hangover. Despite the popularity of NAC as an ingredient of hangover products, there is no peer-reviewed published data on its efficacy in the treatment of hangover. Instead, results from a listed study (clinicaltrials.gov identifier NCT02541422) indicated that NAC had no significant effects on reducing hangover severity. Moreover, its use was associated with an increased number of adverse effects compared to placebo. A second study (clinicaltrials.gov identifier NCT03104959) examining NAC for the treatment of hangover was terminated before

completion, and no findings were reported.

Unfortunately the lack of research is somewhat typical for this product category. For example, similar to NAC, there is also a lack of evidence for the efficacy of DHM (dihydromyricetin) from *Hovenia dulcis*. A literature search revealed only one study which originally reported some positive effects of *Hovenia dulcis* extract in reducing hangover symptoms (Kim et al., 2017). However, when the authors reanalyzed the data and directly compared *Hovenia dulcis* with placebo no significant differences were found (Verster, van Rossum, Lim, Kwon, & Scholey, 2021). While NAC and DHM are both heavily promoted as being effective and have been marketed for considerable time, no further efforts have been taken by industry to adequately demonstrate their safety and efficacy in the treatment of hangover. Finally, also for the most common ingredients of hangover products, vitamins and minerals, research demonstrating their efficacy in reducing or preventing hangovers is lacking. Taken together, these findings challenge the effectiveness of self-regulation by industry.

Paradoxically, at present companies are not required to take responsibility for the efficacy and safety of their products, nor do they register them as drugs. The current legislation for dietary supplements disincentivizes companies to conduct well-powered, independent efficacy trials as these may attract FDA scrutiny of the investigational product as an unapproved new drug to address hangover. We therefore propose that current regulations for hangover products should be reconsidered. In the interest of consumers independent, high-quality research is needed to demonstrate the safety and efficacy of hangover treatments, irrespective whether they are registered as medicinal drugs or dietary supplements.

## 5. Role of funding sources

None.

## 6. Contributors

Literature and data search: JV and CVR, data analysis: JV and CVR, data interpretation: JV, CVR, AS, writing draft correspondence: JV and AS, approval of final version: JV, CVR, AS.

## Declaration of Competing Interest

Dr. Scholey reports personal fees from Sen-Jam Pharmaceutical, grants from BioRevive, outside the submitted work; and in the past 36 months Scholey has held research grants from Abbott Nutrition, Arla Foods, Bayer, BioRevive, DuPont, Kemin Foods, Nestlé, Nutricia-Danone, Verdure Sciences. He has acted as a consultant/expert advisor to Bayer, Danone, Naturex, Nestlé, Pfizer, Sanofi and has received travel/hospitality/speaker fees from Bayer, Sanofi and Verdure Sciences. Dr. Verster reports personal fees from ZBiotics, personal fees from Sen-Jam Pharmaceutical, personal fees from More Labs, personal fees from Toast!, personal fees from Tomo, outside the submitted work; and in the past 36 months Verster has held grants from Janssen and Sequential Medicine, and acted as a consultant/expert advisor to Red Bull. MSc van Rossum has nothing to disclose.

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