Effect of Opuntia ficus indica on Symptoms of the Alcohol Hangover

Jeff Wiese, MD; Steve McPherson, MD; Michelle C. Odden, BS; Michael G. Shlipak, MD, MPH

Background: The severity of the alcohol hangover may be related to inflammation induced by impurities in the alcohol beverage and byproducts of alcohol metabolism. An extract of the Opuntia ficus indica (OFI) plant diminishes the inflammatory response to stressful stimuli.

Methods: In this double-blind, placebo-controlled, crossover trial, 64 healthy, young adult volunteers were randomly assigned to receive OFI (1600 IU) and identical placebo, given 5 hours before alcohol consumption. During 4 hours, subjects consumed up to 1.75 g of alcohol per kilogram of body weight. Hangover severity (9 symptoms) and overall well-being were assessed on a scale (0-6), and blood and urine samples were obtained the following morning. Two weeks later, the study protocol was repeated with OFI and placebo reversed.

Results: Fifty-five subjects completed both the OFI and placebo arms of the study. Three of the 9 symptoms—nausea, dry mouth, and anorexia—were significantly reduced by OFI (all \( P < .05 \)). Overall, the symptom index was reduced by 2.7 points on average (95% confidence interval, -0.2 to 5.5; \( P = .07 \)), and the risk of a severe hangover (\( \geq 18 \) points) was reduced by half (odds ratio, 0.38; 95% confidence interval, 0.16-0.88; \( P = .02 \)). C-reactive protein levels were strongly associated with hangover severity; the mean symptom index was 4.1 (95% confidence interval, 1.2-7.1; \( P = .007 \)) higher in subjects with morning C-reactive protein levels greater than 1.0 mg/L. In addition, C-reactive protein levels were 40% higher after subjects consumed placebo compared with OFI.

Conclusions: The symptoms of the alcohol hangover are largely due to the activation of inflammation. An extract of the OFI plant has a moderate effect on reducing hangover symptoms, apparently by inhibiting the production of inflammatory mediators.

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Proteins protect the integrity of the cellular nucleus and matrix materials, repair altered proteins, and eliminate damaged proteins. An early peak of heat shock proteins has been shown to reduce the vascular damage and morbidity in mice exposed to extreme stress. In one study of subjects exposed to high-altitude conditions, those with the highest early peak of heat shock proteins had the lowest severity and incidence of headache, nausea, and weakness. Of note, this symptom complex is similar to that of the alcohol hangover.

An extract from the skin of the prickly pear fruit, *Opuntia ficus indica* (OFI), has been shown to accelerate the synthesis of heat shock proteins and to decrease oxidative injury. We hypothesized that OFI might decrease the symptoms of the alcohol hangover by dampening the inflammatory response to hangover.

### METHODS

#### SUBJECTS

Eligible participants were healthy, nonsmoking men and women, aged 21 to 35 years, with a history of having experienced at least one alcohol-related hangover. Subjects were recruited from the Tulane Medical School and the Tulane School of Public Health, New Orleans, La. Exclusion criteria included a history of hypertension, renal dysfunction, gastrointestinal tract bleeding, peptic ulcer disease, liver disease, cardiac disease, lung disease, active tuberculosis, diabetes, alcohol hypersensitivity, alcoholism, and an allergic reaction to either alcohol or the prickly pear fruit. Subjects taking medications prohibiting alcohol consumption were also excluded. Subjects were instructed not to consume analgesic medications during the 24 hours before the study. The study was approved by the institutional review boards at Tulane University and University of California, San Francisco, and each subject provided informed consent. All subjects who applied for participation met inclusion and exclusion criteria.

#### INTERVENTION

*Opuntia ficus indica* (Tex-OE; Extracts Plus Inc, San Diego, Calif) is a dietary supplement formulated in a gelatin capsule of 800 IU per capsule. The extract is produced by drying the cactus fruit and using a standard solvent extraction procedure. Two capsules of the placebo material and 2 OFI capsules in identical gelatin capsules were prepared by the quality control department of the manufacturer.

#### STUDY DESIGN

The timeline of the study is demonstrated in Figure 1. The study began with baseline measurements of vital signs and collection of blood and urine specimens. Subjects were then assigned by means of sealed opaque envelopes to begin the study protocol with either OFI or placebo. All investigators and subjects were blinded to treatment assignment.

Subjects were escorted to a supervised environment where each consumed a standard meal (cheeseburger, fries, and a soda). During 4 hours, subjects consumed up to 1.75 g of alcohol per kilogram of body weight, a quantity demonstrated to safely produce hangover in previous trials. Subjects selected one liquor type to be consumed during both phases of the study. The choices included liquors with low (vodka, gin, rum) and high (bourbon, scotch, tequila) congeners. Subjects were permitted to drink nonalcoholic beverages freely during the study. After alcohol consumption ceased, subjects were observed for 1 hour, and then a final blood alcohol concentration (BAC) was obtained by breath testing (Alcosensor IV; Intoximeters, St Louis, Mo). Subjects were then returned to their homes by limousine service. Subjects returned to the study facility the following morning, at which time blood and urine samples were obtained, hangover symptoms were assessed, and BAC was again measured.

The protocol was repeated after a 2-week washout period. Subjects consumed the same type of alcohol as during the first session, but intervention and placebo were reversed. At the second session, subjects were not permitted to consume a quantity of alcohol greater than the amount they consumed at the first session, but they could consume less. Study subjects were requested not to smoke tobacco or to use nonsteroidal medications, pain-relieving medications, or aspirin during the study period.

We determined the sample size for this study on the basis of a 25% difference in the symptom index after OFI and placebo. With a 2-tailed α of .05, 30 subjects were required to achieve a statistical power of 80%.

#### ALCOHOL INGESTED

Subjects ingested commercially available alcohol in 1 of 6 categories: vodka, gin, rum, bourbon, scotch, or tequila. Low-congener alcohols (vodka, 3 g/100 L; gin, 4 g/100 L; rum, 60 g/100 L) were defined as those with less than 1 g/L of the 7 most common congeners: acetaldehyde, ethyl formate, ethyl acetate, methanol, n-propanol, i-butanol, and i-amyl alcohol. High-congener alcohols (bourbon, 285 g/100 L; scotch, 252 g/100 L; tequila, 130 g/100 L) contained 1 g/L or greater of the same congeners.

#### OUTCOME MEASURES

Hangover Symptoms

The primary end point was the mean hangover symptom index, determined by a survey that we adapted from previous hangover assessment tools. Subjects used a 7-point scale (0, no symptoms; 6, worst possible symptoms) to assess the 9 symptoms most frequently experienced during the alcohol hangover (nausea, headache, anorexia, dry mouth, soreness, weakness, tremulousness, diarrhea, and dizziness). Also on a 7-point scale, subjects assessed their overall well-being (0, high well-being; 6, poor well-being). Surveys were completed at baseline and during each hangover period.

The secondary end point was the incidence of a severe hangover, operationally defined as one that would prevent the sub-
Therefore, we present a randomized comparison of the symptom index as the outcome, and then adjusted for CRP and cortisol levels. We used multivariate linear regression models with treatment assignment as the predictor and hangover symptom index. We began our analyses by evaluating whether the symptom index scores approximated a normal distribution. We used the skewness and kurtosis test and found no evidence to reject the presence of a normal distribution (P = .17 for placebo, P = .50 for OFI). Therefore, we present a randomized comparison of the symptom index using a paired t test. Physiological measures were compared from baseline to hangover in the placebo group, and between placebo and OFI, by means of the paired t test. Subgroup analyses with both the symptom index and physiological outcomes were conducted by stratification, and a test for interaction was used to determine the presence of effect modification. To determine the effect of OFI on the occurrence of severe hangovers, we determined the odds ratio and 95% confidence intervals (CIs), overall and within subgroups.

We next determined the association of CRP and cortisol levels with hangover severity. Because CRP levels had a rightward skew, we dichotomized CRP levels as being undetectable (<1.0 mg/L) or detectable. The mean symptom index was then compared between the 2 groups, overall and after stratification by treatment. The mean symptom index was also compared among participants with cortisol levels above and below the median value.

Finally, we evaluated whether CRP and cortisol levels appeared to mediate the observed effect of OFI on the hangover symptom index. We used multivariate linear regression models with treatment assignment as the predictor and hangover symptom index as the outcome, and then adjusted for CRP and cortisol levels.

All analyses were conducted using STATA 7.0 software (STATA Corp, College Station, Tex). Values of 2-sided P ≤ .05 were considered statistically significant. Data are presented as mean ± SD unless otherwise indicated.

### RESULTS

Among the 64 subjects recruited to enter the trial, 55 completed both the placebo and OFI arms of the study. Of the 9 participants who completed only 1 arm of the study, 4 were assigned to receive placebo and 5 to receive OFI. The mean BAC and symptom index of the 9 subjects lost to follow-up were not significantly different from those of subjects who completed the protocol. Characteristics of the 55 subjects completing the study are summarized in Table 1. The BAC was less than 1 mg/dL (0.217 mmol/L) for all participants during hangover measurements.

Among the 9 symptoms evaluated in the hangover symptom index, nausea, anorexia, and dry mouth were significantly improved with OFI compared with placebo (Table 2). The other 6 symptoms were not significantly affected by OFI, but none was worse with OFI than placebo. Mean symptom index did not differ in men and women (13.1 ± 7.8 vs 13.8 ± 7.6, P = .62). The mean score for overall well-being was 2.75 ± 0.99 with OFI and 3.10 ± 1.16 with placebo (P = .04), indicating that subjects taking OFI had higher well-being. Overall, the mean symptom index was reduced 18% with OFI (−2.7 points; P = .07) compared with placebo (−3.10 ± 1.16 with OFI vs −2.30 ± 1.22 with placebo; P = .21).

The reduction of symptoms with OFI compared with placebo was greater in persons reaching a higher BAC (≥125 mg/dL [27.1 mmol/L]) (16.0 ± 9.1 vs 12.2 ± 5.7; P = .08) than in persons with lower BAC (<125 mg/dL) (13.6 ± 7.6 vs 12.2 ± 7.5; P = .47); and in persons consuming high-congener alcohols (16.3 ± 7.5 vs 12.4 ± 7.5; P = .05) compared with low-congener alcohols (13.2 ± 7.5 vs 11.9 ± 7.5; P = .58). However, neither of these possible interactions was statistically significant (P = .43 and P = .38, respectively).

The distribution of the overall hangover symptom indexes did appear to differ when persons were assigned to OFI or placebo (Figure 2). The risk of a severe hangover (symptom index ≥ 18) was halved with OFI compared with placebo (Table 3). This effect was similar in persons consuming high- and low-congener alcohols, but was modestly stronger in persons reaching higher BACs. Of note, among the 10 worst hangovers experienced in this trial (symptom index ≥ 25), 9 were in subjects who consumed placebo (Figure 2).

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**Table 1. Characteristics of the 55 Participants Who Completed the Study Protocol**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, No. (%) female</td>
<td>32 (58)</td>
</tr>
<tr>
<td>Age, y</td>
<td>27 ± 13</td>
</tr>
<tr>
<td>Height, cm</td>
<td>172 ± 74</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>72 ± 100</td>
</tr>
<tr>
<td>Hangovers per month, No.</td>
<td>1.7 ± 1.5</td>
</tr>
<tr>
<td>Drinks per week, No.</td>
<td>17 ± 22</td>
</tr>
<tr>
<td>Blood alcohol concentration (placebo) at 1 AM, mg/dL</td>
<td>131 ± 44</td>
</tr>
<tr>
<td>Blood alcohol concentration (drug) at 1 AM, mg/dL</td>
<td>124 ± 48</td>
</tr>
</tbody>
</table>

**Table 2. Comparison of Symptom Severity Scores With Placebo and Opuntia ficus indica (OFI) in 55 Subjects**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Placebo</th>
<th>OFI</th>
<th>Paired t Test, P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>1.8 ± 1.6</td>
<td>1.0 ± 1.2</td>
<td>.004</td>
</tr>
<tr>
<td>Headache</td>
<td>1.8 ± 1.5</td>
<td>1.5 ± 1.4</td>
<td>.34</td>
</tr>
<tr>
<td>Anorexia</td>
<td>1.6 ± 1.6</td>
<td>1.1 ± 1.2</td>
<td>.03</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>3.2 ± 1.7</td>
<td>2.5 ± 1.4</td>
<td>.04</td>
</tr>
<tr>
<td>Soreness</td>
<td>1.4 ± 1.4</td>
<td>1.2 ± 1.4</td>
<td>.46</td>
</tr>
<tr>
<td>Weakness</td>
<td>1.9 ± 1.2</td>
<td>1.7 ± 1.3</td>
<td>.38</td>
</tr>
<tr>
<td>Tremulousness</td>
<td>1.3 ± 1.3</td>
<td>1.2 ± 1.2</td>
<td>.55</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0.4 ± 0.9</td>
<td>0.4 ± 1.0</td>
<td>.78</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1.8 ± 1.7</td>
<td>1.6 ± 1.3</td>
<td>.67</td>
</tr>
<tr>
<td>Symptom index</td>
<td>14.9 ± 8.4</td>
<td>12.2 ± 6.6</td>
<td>.07</td>
</tr>
</tbody>
</table>

SI conversion factor: To convert blood alcohol concentration to millimoles per liter, multiply by 0.217.

Values are mean ± SD unless otherwise specified.
Several physiological measures were compared at baseline and during hangover after consumption of OFI and placebo (Table 4). The CRP levels increased by 50% with hangover in participants who received placebo (P<.001), but this effect was not seen in those who received OFI (P=.47). There was a 2-fold increase in cortisol levels with hangover in subjects who received placebo and an even higher effect in the OFI group. The hangover was not associated with changes in bicarbonate, glucose, aspartate aminotransferase, or alanine aminotransferase levels. Urine specific gravity was increased similarly in subjects treated with OFI and placebo.

The association of CRP and cortisol levels with hangover symptoms was further explored. The proportion of subjects with undetectable CRP levels (≤1.0 mg/L) was 24% with placebo but 49% with OFI (P=.005). The CRP levels appeared to be strongly associated with hangover severity, as the mean symptom index was about 40% higher in subjects with detectable CRP levels (4.1 points; 95% CI, 1.2–7.1; P = .007) (Figure 2). This effect was similar when subjects consumed OFI or placebo, but the incidence of CRP elevations was lower with OFI. Higher cortisol levels were modestly associated with lower symptom scores. The mean symptom index was 14.6±7.6 in persons with cortisol levels at or below the median (17 µg/dL) compared with 13.2±7.8 in persons with cortisol levels above the median (P=.36).

We evaluated whether the effect of OFI on CRP and cortisol levels mediated its apparent effect on the hangover symptom index. In the 50 participants with complete CRP and cortisol measures, the unadjusted reduction in symptom score with OFI compared with placebo was 2.7 points (95% CI, −0.2 to 5.5). After adjustment for CRP levels, the effect of OFI use on the symptom index was reduced to 1.9 (95% CI, −1.1 to 4.8). Additional adjustment for cortisol levels further decreased the association of OFI with the symptom index to 1.2 (95% CI, −1.9 to 4.2), suggesting that more than half of the effect of OFI was due to modulation of the inflammatory response. We also evaluated the effect of congener content on the hangover symptom index. Persons consuming high-congener alcohols had a more severe hangover (symptom index 1.8 points higher [95% CI, −1.1 to 4.7]); adjusting for differences in the level of CRP among these participants reduced the association of high congener content to a 0.9-point-higher symptom index (95% CI, −2.0 to 3.9). This suggests that the congener content may contribute to the inflammatory response induced by alcohol use.

**COMMENT**

In this randomized, placebo-controlled, crossover trial, we found hangover symptom severity to be moderately reduced by an extract of the prickly pear plant, Opuntia ficus indica. This effect was observed chiefly through the reduction in the symptoms of nausea, dry mouth, and anorexia. Adjustment for CRP and cortisol levels appeared to explain most of the observed difference in symptom severity between OFI and placebo. Overall, the risk of a severe hangover was reduced by half with OFI.

This study is the first, to our knowledge, to demonstrate that CRP levels are elevated during the alcohol hangover and strongly associated with hangover severity. This supports previous work suggesting that inflammation may play a role in the pathogenesis of the alcohol hangover, and it indicates that interrupting this inflammatory response could mitigate the symptoms of the alcohol hangover.1,29,30 This observation could also explain the increased cardiovascular mortality observed in persons with frequent hangovers.13

Levels of intracellular heat shock proteins are known to rise during physiological stress when the body is responding to cellular damage. The OFI extract has been shown to accelerate the production of heat shock proteins (especially heat shock proteins 27, 68, and 72) during stress.39,40,46 In patients who have undergone the stress of deep-sea diving or high-altitude climbing, the accelerated heat shock protein response correlates with a reduction in symptoms.40 This study suggests that augmented heat shock protein production may similarly reduce the cellular damage or inflammation associated with the alcohol hangover, which we believe to be a period of physiological stress.

The inflammatory hypothesis is further supported by the observation that the most severe hangovers were observed in those consuming alcohols with high congener contents, and OFI was somewhat more effective in this subgroup. Congeners are impurities that are the by-product of the alcohol distillation process and have been implicated in eliciting an inflammatory response that may contribute to the symptoms of the alcohol hangover.16-21 We hypothesize that the augmented reduction in hangover symptoms in this subgroup is due to the accelerated production of heat shock proteins by OFI.

This study was designed to assess the effect of OFI on reducing symptoms of the alcohol hangover experienced by the average alcohol consumer. The study protocol simulated conditions experienced by recreational alcohol consumption, including dancing and socialization. Previous research suggests that a portion of the alcohol hangover symptoms may be due to physical activity unrecognized during alcohol consumption (ie, vigorous dancing).1 This design is an important component of the study’s validity, and it improves its generalizability to the average alcohol consumer.

The crossover design allowed us to isolate the effect of the intervention, as each subject served as his or her own control.
own control. The type and amount of alcohol consumed were the same for each individual, and the rate of consumption, which was regulated by the investigators, was the same on both occasions. The amount of physical activity exerted during the study sessions was not measured directly, but appeared grossly to be the same during the 2 sessions.

One limitation of this study’s design is that it did not allow for measurement of serial heat shock proteins during the consumption of alcohol. Although OFI’s mechanism of accelerating heat shock proteins has been well described, it is possible that a mechanism other than acceleration of heat shock protein production was responsible for the reduction of hangover symptoms and the prevention of CRP elevation. It is unlikely that the improvement in symptoms was due to a stimulant within the OFI formulation; OFI or placebo was taken before consumption of alcohol and 20 hours before the assessment of the hangover. Subsequent studies in an inpatient research center permitting serial blood sampling would better elucidate the physiological characteristics of OFI or future anti-inflammatory products in reducing hangover symptoms.

In addition, our protocol specified that OFI be consumed on an empty stomach to maximize its absorption. Future research would be needed to determine whether the intervention has the same effect when taken after alcohol consumption.

Our study protocol allowed participants to consume a dose of alcohol consistent with what an average drinker might consume on a heavy night of drinking (5–10 drinks). The protocol simulated a normal party and allowed subjects to return to their homes to sleep in their own beds. For safety considerations, the protocol precluded administration of alcohol doses in excess of 1.75 g/kg. This limit of the quantity of alcohol consumed by subjects may have dampened the observed effect of OFI, as it appeared most effective in subjects with a BAC greater than or equal to 125 mg/dL. The effect of OFI may be greater in persons consuming larger quantities of alcohol. The alcohol hangover is more severe in older adults, whereas the subjects in this study were young adults aged 21 to 35 years.10 It is possible that the effect of OFI would be different in older persons, who might have a greater severity of hangover for a given amount of alcohol consumed.

We did not regulate consumption of nonalcoholic beverages. Previous studies have suggested that alcohol intoxication may blunt the subject’s recognition of dehydration.23-25 Requiring a fixed amount of nonalcoholic beverages may improve the accuracy of hydration measurements.

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holic beverages may have mitigated this effect and artificially reduced the severity of the alcohol hangover, thereby reducing the study’s generalizability. Conversely, we did not limit consumption of nonalcoholic beverages because we believed it to be unsafe for study participants. Instead, the protocol sought to simulate wild-type alcohol consumption and allow study subjects to choose the amount of nonalcoholic beverages consumed. Measures of dehydralion such as the bicarbonate level and urine specific gravity were not different when subjects consumed OFI or placebo.

Finally, we anticipate the concern that decreasing hangover symptoms may indirectly foster increased use and abuse of alcohol. Hangover has never been shown to effectively deter alcohol consumption, however, and no evidence indicates that alleviation of hangover symptoms would result in further consumption. Excessive alcohol consumption and the resulting hangover are pervasive problems and we believe that reducing the harm induced by the hangover would be worthwhile. Whereas the best prevention for the hangover would obviously be abstinence from alcohol, the impairment associated with the alcohol hangover is well documented and a reasonable goal would be to attenuate the effects of a hangover. Whether these harmful effects of the hangover on public safety can be prevented in parallel to the associated symptoms remains to be tested in future studies.

In summary, the alcohol hangover is a common condition that causes substantial impairment to affected individuals and considerable economic costs to society. This study suggests that the symptoms of the alcohol hangover are in part mediated through an inflammatory reaction, demonstrated by elevated CRP levels. An extract of the Opuntia ficus indica plant appeared to reduce the severity of the alcohol hangover by inhibiting this inflammatory response.

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The design and study protocol were entirely written by the study investigators. All clinical data were collected, all analyses were conducted, and the manuscript was written solely by the investigators.

Corresponding author: Jeff Wiese, MD, General Internal Medicine Section SL-12, Tulane University Health Sciences Center, 1430 Tulane Ave, New Orleans, LA 70112 (e-mail: jwiese@tulane.edu).

**Figure 3.** Comparison of symptom indexes in persons with undetectable ($\leq 1.0 \text{ mg/L}$) vs detectable ($>1.0 \text{ mg/L}$) C-reactive protein (CRP) levels (n = 54) (error bars represent SEM). OFI indicates Opuntia ficus indica.


