Declinol, a Complex Containing Kudzu, Bitter Herbs (Gentian, Tangerine Peel) and Bupleurum, Significantly Reduced Alcohol Use Disorders Identification Test (AUDIT) Scores in Moderate to Heavy Drinkers: A Pilot Study

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Abstract

It is well established that inherited human aldehyde dehydrogenase 2 (ALDH-2) deficiency reduces the risk for alcoholism. Kudzu plants and extracts have been used for 1,000 years in traditional Chinese medicine to treat alcoholism. Kudzu contains daidzin, which inhibits ALDH-2 and suppresses heavy drinking in rodents. Decreased drinking due to ALDH-2 inhibition is attributed to aversive properties of acetaldehyde accumulated during alcohol consumption. However not all of the anti-alcohol properties of daidzin are due to inhibition of ALDH-2. This is in agreement with our earlier work showing significant interaction effects of both pyroazole (ALDH-2 inhibitor) and methyl-pyroazole (non-inhibitor) and ethanol’s depressant effects. Moreover, it has been suggested that selective ALDH 2 inhibitors reduce craving for alcohol by increasing dopamine in the nucleus accumbens (NAc). In addition there is significant evidence related to the role of the genetics of bitter receptors (TAS2R) and its stimulation as an aversive mechanism against alcohol intake. The inclusion of bitters such as Gentian & Tangerine Peel in Declinol provides stimulation of gut TAS2R receptors which is potentially synergistic with the effects of Kudzu. Finally the addition of Radix Bupleuri in the Declinol formula may have some protective benefits not only in terms of ethanol induced liver toxicity but neurochemical actions involving endorphins, dopamine and epinephrine. With this information as a rationale, we report herein that this combination significantly reduced Alcohol Use Disorders Identification Test (AUDIT) scores administered to ten heavy drinkers (M=8, F=2; 43.2 ± 14.6 years) attending a recovery program. Specifically, from the pre-post comparison of the AUD scores, it was found that the score of every participant decreased after the intervention which ranged from 1 to 31. The decrease in the scores was found to be statistically significant with the p-value of 0.00298 (two-sided paired test; p-value = 0.00149 for one-sided test). Albeit this being a small pilot, we are encouraged about these significant results, and caution any interpretation until larger controlled studies are executed.

Keywords: Declinol; Kudzu; Daidzin; ALDH 2 inhibitors; Dopamine; Gentian and tangerine peel; Radix burpleuri; Alcoholism and reward deficiency

Introduction

Declinol is blended formula developed by one of us (SK) consisting of a number of key ingredients such as Kudzu, Bitter Herbs (Gentian, Tangerine Peel) and Bupleurum and other herbs (Table 1). The primary indication of this complex and the pilot study described in this article involve Declinol’s effect in alcoholism. Because this the first report on Declinol, we are compelled to briefly review these three important ingredients role in alcoholism including both central and peripheral actions.

Kudzu

The herb called kudzu is a high climbing, coarse textured twining and trailing type of perennial vine found in parts of Asia and naturalized elsewhere [1]. Chinese traditional medicine makes use of the buge root that grows to the size of an adult human body - kudzu called gèn in China, is a major source for many modern herbal products as well as traditional Chinese medications. In China, the kudzu or gèn is found growing in shaded areas along mountains, in the fields and along roadsides, in thickets and thin forests all over the country.

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as 5-hydroxyindole-3-acetaldehyde (5-HIAL) and/or DOPAL derived correlation studies using structural analogs of daidzin led to the metabolism. Keung [6] following experimentation suggested that suppress ethanol intake of this species without blocking acetaldehyde this effect by daidzin is not like a classical ALDH-2 inhibitor because ethanol intake of golden hamsters by inhibiting ALDH-2. However, suppression and raise the possibility that daidzin may in fact suppress due to CNS mechanisms. In fact Keung et al. [5] demonstrated a second is daidzin, followed by daidzein.

Keung et al. [2] reported that Daidzin is a potent, selective, and reversible inhibitor of human mitochondrial aldehyde dehydrogenase (ALDH) and this natural compound suppresses free-choice ethanol intake by Syrian golden hamsters. Other ALDH inhibitors, such as disulfiram (Antabuse) and calcium citrate carbimide (Temposil), have also been shown to suppress ethanol intake of laboratory animals and are thought to act by inhibiting the metabolism of acetaldehyde produced from ingested ethanol. The anti-craving effect of disulfiram may also be due to inhibition of dopamine beta hydroxylase thereby increasing neuronal dopamine [3].

Moreover, in vitro, daidzin potently suppresses hamster liver mitochondria-catalyzed acetaldehyde oxidation. Accordingly, the authors suggest that their results indicate that (i) the action of daidzin differs from that proposed for the classic, broad-acting ALDH inhibitors (e.g., disulfiram), and (ii) the daidzin-sensitive mitochondrial ALDH is not the one and only enzyme that is essential for acetaldehyde metabolism in golden hamsters. Additionally, Lin et al. [4] also showed that daidzin, are efficacious in lowering blood alcohol levels and shorten sleep time induced by alcohol ingestion in rat models of alcoholism. Furthermore, other isoflavonoids found in Kudzu were also evaluated by Lin et al. [4]. When given orally to P rats at a dose of 100 mg/kg/day, daidzin, daidzein, and puerarin decreased ethanol intake by 75%, 50%, and 40%, respectively without negative effects on overall water consumption. In fact Lin et al. [4] suggested the anti-craving effects of these compounds may be due to CNS mechanisms. In fact Keung et al. [5] demonstrated a direct correlation between ALDH-2 inhibition and ethanol intake suppression and raise the possibility that daidzin may in fact suppress ethanol intake of golden hamsters by inhibiting ALDH-2. However, this effect by daidzin is not like a classical ALDH-2 inhibitor because it does not also inhibit the cytosolic form, of liver ALDH-1, which is a very efficient catalyst of acetaldehyde oxidation. Thus daidzin can suppress ethanol intake of this species without blocking acetaldehyde metabolism. Keung [6] following experimentation suggested that correlation studies using structural analogs of daidzin led to the hypothesis that the mitochondrial MAO/ALDH-2 pathway may be the site of action of daidzin and that one or more biogenic aldehydes such as 5-hydroxyindole-3-acetaldehyde (5-HIAL) and/or DOPAL derived from the action of monoamine oxidase (MAO) may be mediators of its antidipsotropic action.

Another area of investigation into the antidipsotropic effects of Kudzu and associated ingredients relate to potential anti-anxiety activity an important element in relapse and drug seeking [7]. Interestingly, extracts of kudzu have been used as a hangover remedy in China for many centuries, and therefore Overstreet et al. [8] tested the ability of NPI-031G (puerarin), an isoavoline isolated from kudzu, to counteract anxiogenic effects associated with withdrawal from chronic alcohol exposure. These studies [8] showed NPI-031G (50 and 150 mg/kg ip) significantly increased the social interaction and locomotor activity reduced by withdrawal from 17 days of alcohol (%5) diet. The effects of NPI-031G resembled those of the benzodiazepine antagonist, flumazenil (5 mg/kg), and the 5-HT (2C) antagonist, SB 242084 (1 mg/kg). Importantly, these findings are consistent with NPI-031G being a weak benzodiazepine site antagonist. Based on intensive investigations [8] and suggestions that long-term GABA agonists such as rimonabant, a cannabinoid CB1 receptor inhibitor, induce unwanted mood changes (i.e. suicidal ideation) we are proposing that GABA antagonistic properties may indeed be quite beneficial especially in long-term therapy.

Purified puerarin another ingredient in Kudzu root was also shown to suppress alcohol intake in the short term as well reducing withdrawal reactions in high ethanol preferring rats. However this effect does not seem to be due a central brain mechanism [9].

While the literature seems to support an effect of Kudzu and especially isoavonoid constituents to suppress ethanol intake in animal models, in contrast, Shebek and Rindone [9,10] were unable to reproduce this effect in humans. Specifically, in a prospective, randomized, double-blind controlled clinical trial they found no difference between Kudzu and placebo after a one month treatment period in either reducing alcohol craving and or promoting sobriety.

However, Lukas et al. [10] from McLean Hospital designed a study to test the efficacy of a kudzu extract in a clinical population. Specifically, male and female “heavy” alcohol drinkers were treated with either placebo or a kudzu extract for 7 days and then given an opportunity to drink their preferred brand of beer while in a naturalistic environment. They found that Kudzu treatment resulted in significant reduction in the number of beers consumed.

The current evidence favors the safety of Kudzu root although some have questioned the potential build-up of acetaldehyde following its administration to humans [11,12]. On the other side of the safety issue, Singh et al. [12] evaluated the protective effects of puerarin from kudzu root against alcohol-induced toxicities. Alcohol withdrawal after 70 days of drinking generated severe withdrawal symptoms including seizure-type EEG activity. Puerarin suppressed the addiction-mediated abnormalities but did not affect the inflammation-related abnormalities.

Research to date supports the role of certain known ingredients in Kudzu root like the natural product 7-O-glucosyl-4'-hydroxyisoflavone (daidzin), isolated from the kudzu vine (Pueraria lobata), a known specific inhibitor of ALDH2 that suppresses ethanol consumption. This compound has provided a strategic model to develop other selective ALDH-2 such as CVT-10216 showing anti-relapse properties [13,14]. All of this extensive work led to the question as to how does for example, 7-O-glucosyl-4'-hydroxyisoflavone inhibit ALDH2. It is well known that the ALDH2*2 gene encoding the inactive variant form of mitochondrial aldehyde dehydrogenase (ALDH2) protects nearly all

<table>
<thead>
<tr>
<th>English Name</th>
<th>Latin Name</th>
</tr>
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<tbody>
<tr>
<td>Kudzu Root</td>
<td>Puerariae Radix</td>
</tr>
<tr>
<td>Gentian Root</td>
<td>Gentianae Radix</td>
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<tr>
<td>Bupleurum Root</td>
<td>Bupleuri Radix</td>
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<tr>
<td>Plantago Seed</td>
<td>Plantaginis Semen</td>
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<tr>
<td>Water Plantain</td>
<td>Alismatis Rhizoma</td>
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<tr>
<td>Chocolate Vine</td>
<td>Akebiae trifoliate Caulis</td>
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<tr>
<td>Dried Rehmannia Root</td>
<td>Rehmannia Radix Exsiccata seu Recens</td>
</tr>
<tr>
<td>Chinese Angelica Root</td>
<td>Angelicae sinesis Radix</td>
</tr>
<tr>
<td>Licorice Root</td>
<td>Glycyrrhizae Radix</td>
</tr>
<tr>
<td>Tangerine Peel</td>
<td>Citri Reticulatae Perciparium Virde</td>
</tr>
</tbody>
</table>

Table 1: List of ingredients in decimal compound.
carriers of this gene from alcoholism. Inhibition of ALDH2 has hence become a possible strategy to treat alcoholism [15]. Accordingly, Lowe et al. [14] found that the structure of daidzin/ALDH2 in complex at a 2.4 resolution shows the isoflavone moiety of daidzin binding close to the aldehyde substrate-binding site in a hydrophobic cleft. Moreover, it also includes glucosyl function binding to a hydrophobic patch immediately outside the isoflavone-binding pocket. These observations provide an explanation for both the specificity and affinity of daidzin (IC50 = 80 nM) and the affinity of analogues with different substituents at the glucosyl position.

**Bitter herbs (Gentian, tangerine peel)**

Bitter herbs have a long and successful tradition of use for a number of health purposes [16]. Bitters have been used for centuries to improve digestion, and are still commonly used in many cuisines to be taken before meals to stimulate digestive powers. It used to be assumed that bitters only stimulated receptors in the mouth, and then somewhat in the digestive tract. It has been demonstrated however, that bitter receptors exist throughout the entire gastro-intestinal tract [17,18]. When triggered by bitter compounds, these receptors then stimulate a myriad of bodily functions [19-21]. In addition to digestion, these receptors promote absorption of nutrients, blood sugar homeostasis, and can even help with weight control. Moreover, specific bitter receptors seem to promote the elimination of absorbed toxins from the gut [22-24].

One of the herbs in Declincol, Gentian, is considered the king of the bitter herbs. In tests, it was found that the bitter taste from Gentian can still be perceived even when diluted down to 1 part in 12,000 [25]. Tangerine Peel has some bitter qualities as well, and is an excellent complement to the actions of Gentian. Tangerine Peel delivers several novel flavonoids that all offer numerous health advantages including enhancing metabolism, promoting detoxification, and protecting cells from free radical damage. Most importantly extracts of Tangerine Peel have been shown to enhance learning and memory. Kawahata et al. [25] recently reported on the enhancement properties of Tangerine Peel extracts to facilitate potently-mediated transcription linked to the upstream cAMP/PKA/ERK/CREB pathway in hippocampal neurons.

A final point about bitters and alcohol intake: It has been demonstrated in fact, that people who have a genetic variation that decreases their sensitivity to bitter taste compounds are at a higher risk for alcohol dependence [32]. They found that a single nucleotide polymorphism (SNP) located within the TAS2R13 gene (rs1015443 [C1040T, Ser259Asn]) showed a significant association with measures of alcohol consumption accessed via the Alcohol Use Disorders Identification Test (AUDIT). Analyses with other SNPs in close proximity to rs1015443 suggest that this locus is principally responsible for the association. This study is in agreement with earlier studies by Hinrichs et al. [32] that showed a coding single-nucleotide polymorphism (cSNP), K172N, in hTAS2R16, a gene encoding a taste receptor for bitter beta-glucopyranosides, associated with alcohol dependence (p = 0.00018). This gene is located on chromosome 7q in a region reported elsewhere to exhibit linkage with alcohol dependence. This association is most important in African Americans who carry this allele at a frequency of 26% compared to only 0.6% in whites. In addition others [33,34] have reported on an association between a TAS2R16 SNP and alcohol intake, and the putative TAS2R38–alcohol relationship was confirmed, although these polymorphisms did not explain sensory or hedonic responses to sampled Scotch whisky.

Furthermore, Duffy et al. [34] reported using multiple regression analyses, greater bitterness from 3.2 mMPROP was a significant predictor of greater ethanol intensity and less alcohol intake. Interestingly, genotype was a significant predictor of alcohol intake, but not ethanol intensity. A final point about bitters and alcohol intake: It has been scientifically shown that bitter compounds can positively affect glucose balance, and therefore promote healthy glucose metabolism [35,36]. Specifically, Dotson et al. [35] observed that a TAS2R haplotype is associated with altered glucose and insulin homeostasis. They also found that one SNP within this haplotype disrupts normal responses of a single receptor, TAS2R9, to its cognate ligands ofloxacin, procainamide and pirenzepine. Together, these findings suggest that a functionally compromised TAS2R receptor negatively impacts glucose homeostasis, providing an important link between alimentary chemosensation and metabolic disease. This finding coupled with the understanding of the role of insulin on dopaminergic neurons; provide impetus to utilize bitter agonists such as Gentian and Tangerine Peel to potentially obviate compromised TAS2R9 polymorphisms [37].

**Radix bupleuri and bupleurans**

Bupleurans, a major constituent of Bupleuri radix (Chai hu) contains triterpene saponins including saikosaponins A, B1–4, D, E, F and H and related compounds including saikogenins A–G. Two biologically active polysaccharides, bupleurans 2IIb and 2IIc, have also been isolated from the roots of *B. falcatum* [38].
Chai hu (Bupleuri radix), one of the most frequently used herbs in Chinese herbal medicine, has positive benefits in cases of liver toxicity especially due to alcoholism [39], analgesic properties [40] as well as sedative activity [41].

Most interestingly, in vivo studies have confirmed the sedative effects of Radix Bupleuri. Both the crude saikosaponin fraction and saikogenin A are reported to have significant sedative effects [41]. In vivo studies, using the rod climbing test, demonstrated that the sedative effect of the saikosaponins (200–800 mg/kg) in mice was similar to that of meperbamate (100 mg). Oral administration of saikosides extracted from B. chinense (B. fukatum) or saikosaponin A has also been reported to prolong cyclobarbital sodium-induced sleep. Furthermore, intraperitoneal injection of saikogenin A inhibited rod climbing in mice and antagonized the stimulant effects of methamphetamine and caffeine [42]. In terms of anti-alcohol effects by enhancing neurotransmitter levels such as serotonin the synergism may result in reduction of ethanol induced behavioral depression (mood) [43,44]. Moreover, Chen et al. [44] found that chai hu (radix bupleuri) in liver stagnation and spleen deficiency syndrome patients compared to baseline levels, plasma beta-EP was significantly increased (p < 0.01), while E and DA were markedly decreased (p < 0.01) after the administration of herbals containing radix bupleuri in the experimental group. While this effect may not have a direct relationship to the neural mechanism purported for ethanol per se [45,46] it does show important effects on neurotransmitter levels.

Finally, crude saponins of B. fukatum, administered orally to rats at a daily dose of 500 mg/kg for 3 days, normalized liver functions as determined by serum alkaline phosphatase levels in rats treated with carbon tetrachloride [47,48]. Treatment of rats with saikosaponins 2 hours before treatment with D-galactosamine inhibited the increase in serum aspartate aminotransferase and alanine aminotransferase levels produced by damage of liver tissues [47,49]. Conversely, saikosaponins did not affect an increase in serum alanine aminotransferase and experimental cirrhosis in rats caused by carbon tetrachloride intoxication [49].

Hepatitis C is a major public health problem internationally. Many patients cannot benefit from the current treatment regimen (interferon/ribavirin combinations) due to its side effects or ineffectiveness. Unfortunately according to World Health Organization (WHO) approximately 300 million people worldwide are infected with Hepatitis C virus (HCV). In the Western Hemisphere 0.5-1% of the population is infected with HCV. Moreover, 70-80% of people infected with HCV become chronic carriers of the disease. The world health community is seriously challenged because each year, about 2 million people die from the chronic effects, especially cirrhosis of the liver and hepatocellular carcinoma. The primary mechanism in the course and outcome of HCV-infection is T-cell mediated immune response. In essence, a lack of appropriate immune response leads to chronic attack that induces prolonged cell lysis, especially in live cells (hepatocytes). Radix Bupleuri found in Xiao-Chai-Hu-Tang or Sho-sai-ko-to (SST), a compound of seven botanical extracts used for liver diseases traditionally in East Asia, was shown to reduce transaminases and the incidence of hepatocellular carcinoma in hepatitis B patients [51]. In a recent trial using SST Deng et al. [51] showed improvement of aspartate aminotransferase; alanine aminotransferase and reduced viral load of HCV-infection which met the pre-defined criteria for clinical “response.”

Based on this detailed historical literature we decided to combine Kudzu, bitter herbs (Gentian and Tangerine Peel) and Bupleurum in a complex with other herbs and evaluate their putative benefits in terms of attenuation of Alcohol Use Disorders Identification Test (AUDIT) scores in moderate to heavy drinkers. To our knowledge the present pilot is the first such study in the world that has systematically evaluated this novel complex in humans.

Methods and Materials

Ten patients were enrolled in a 60 day study to determine the effectiveness of a natural compound Declinol (Table 1) to curb cravings for alcohol. Most of the subjects came from church programs for alcohol dependence and were recruited via general assembly announcement and written flyer. Nine of the ten participants had previously tried other programs to eliminate alcohol cravings and intake with little or no success. The study was done in an at-home basis to allow for better compliance and prove if this program could be successful without daily intervention in a natural setting [11]. Each subject had full time access to the study coordinator and had weekly contact with the coordinator during the full 8 week term. Subjects were all Caucasian, lower to middle income, residing in a small Midwestern town. Each subject was interviewed in person and determined to be actively drinking on a regular basis, all exceeding what would be considered normal consumption ranging from 1-2 times per week to drinking on a daily basis. Several of the subjects had been drinking for many years and often drank to or past the point of inebriation. Final inclusion of subjects was based on completing the AUDIT questionnaire that demonstrated either hazardous levels of drinking or alcohol dependence. All subjects reviewed a full protocol of the study and signed informed consent forms prior to beginning. Subjects were given an 8 week supply of the compound with instructions and dosing logs. They were asked to follow all instructions noting changes on a bi-weekly basis. After completion of the program each subject re-took the AUD questionnaire and also filled out an exit interview. The Declinol Compound for the study was manufactured according to cGMP guidelines and was processed at an FDA registered, OTC, Rx facility.

Physical characteristics of Declinol

Declinol utilizes a proprietary and patent-pending encapsulation technology that enhances the absorption and bio-availability of its herbal compounds. The active ingredients are all encapsulated, or enveloped, using specific processing techniques, within phosphatidyl choline based spheres that act as transport vehicles. The process mimics natural actions that take place within the gut to enable proper absorption of nutrients, especially phyto-nutrients and fat soluble vitamins. The body’s own process in this regard creates micelles, single layer or uni-lamellar spheres in the size range of approximately 100 nanometers that typically can transport single nutrients. However due to dietary and physiological inefficiency, this process can often be hampered. The technology utilized with Declinol creates multi-layer or multi-lamellar spheres that are readily available and can transport multiple nutrients simultaneously. The nature of these spheres, possessing several layers, also allows both fat and water soluble nutrients to be combined in the same sphere.

This technology affords several advantages. The multi-lamellar spheres range in size from 200-500 nanometers. At this size, absorption is improved as the combination of nutrients reaching the small intestine can spread out over a larger surface area thereby allowing more area for absorption to occur. In addition, the natural tendency of the spheres is to adhere to the walls of the small intestine for an extended period of time. This also permits diffusion of nutrients to be more thorough. As the mixture of varying nutrients are arranged into a more uniform...
particle size within the transport sphere, there is a stronger tendency for these nutrients to move across the walls of the small intestine together. This phenomenon therefore can create a strong synergy of action as complementary nutrients are made available in a timely fashion for ongoing bodily processes. Even the make-up of the actual transport spheres offers advantages. Comprised of 100% food grade material, these spheres, upon releasing their payload of nutrients, are broken down and utilized by the system to improve overall well-being. Studies using both animal and human models have demonstrated that this type of technology can increase nutrient absorption from 50-400% [52-54].

Demographics of subjects

From this pilot study with the sample size n=10, the gender distribution is eight males and two females, with the age distribution of 43.2 ± 14.6 years (Table 2). All the statistical analysis was performed using the Cran-R.

Results

From the pre-post comparison of the AUDIT scores, it was found that the score of every participant decreased after the intervention which ranged from 1 to 31. The decrease in the scores was found to be statistically significant with the p-value of 0.00298 (two-sided paired test; p-value = 0.00149 for one-sided test) (Figure 1). The pre AUDIT score was 16.0 ± 9.48 whereby the post AUDIT score 8 weeks later following Declinol administration was 3.5 ± 4.03. The summary of the responses after the intervention is as follows after omitting the missing values (Table 2). Table 2 shows the proportions of the responses of each item. The resultant responses ranged from 50-100%. The two lowest values (Table 2). Table 2 shows the proportions of the responses of each item.

Due to the lack of data on the pre-intervention, it cannot be said statistically whether the results were affected by the intervention. A further clinical study with a larger sample size is required to confirm the results.

Discussion

This is the first ever pilot results showing that the complex Declinol, significantly reduced Alcohol Use Disorders Identification Test (AUDIT) scores in moderate to heavy drinkers in a naturalistic setting (Figure 1 and 2; Table 3). While this is a small pilot study requiring additional large scale controlled studies, we are encouraged.

The role of Kudzu is not surprising especially in light of the important role aldehyde plays in ethanol intoxication and the genetics of human mitochondrial aldehyde dehydrogenase (ALDH) both sites of action observed for Kudzu. Since in part, the effect of this herbal is similar to a disulfiram effect to inhibit the enzyme Dopamine beta –hydroxylase (DBH) whereby neuronal dopamine increases may have profound mechanistic meaning for drug seeking behavior [55]. There are two

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facets that are important in preventive tactics related to alcoholism. It is well established that polymorphisms in alcohol dehydrogenase (ADH) family constitutes one of the key sets of enzymes responsible for the oxidation of alcohol. The ADH4 gene, an important member of this family, is a functional and positional candidate for alcohol dependence. Also polymorphisms of the Dopamine D2 receptor gene (ANKK1 loci) have been associated with severe alcoholism [56]. In one study comparison between the patients with alcohol dependence and syndrome (ADS) and the patients from the control group demonstrated statistically significant association of ADH4 (rs180075) with the alcohol dependence syndrome. The A/A genotype and the A allele were more common in patients with ADS. Also, analysis of the association of the ANKK1 gene revealed statistically significant differences (p = 0.004) between the ADS group and the control group [57]. We are proposing that possibly the anti-alcohol effects may be due to an effect on ADS as well impacting gene expression (mRNA) to augment the neuronal synthesis of dopamine via inhibition of DBH.

The typical modern diet is lacking in bitter taste profiles. This lack of bitter flavor ingestion compromises not only overall health, but may allow for a greater risk of alcohol intake. The bitter compounds contained in Declinol can promote better health overall, while also helping to better ensure that the T2R2 receptors in the human gut are stimulated adequately.

One of the ancillary factors in alcohol dependence is blood sugar imbalances. In fact our laboratory hypothesized [58] that one such genetic factor that influences behavior including drug and food seeking is a predisposition to glucose craving and the overall effect of dopaminergic activity in the reward center of the brain. This defect drives individuals to engage in activities of behavioral excess, which will increase brain dopamine function, for which we created the term Reward Deficiency Syndrome (RDS) [59] to categorize such biological influences on behavior. Consuming large quantities of alcohol or carbohydrates (carbohydrate bingeing) stimulates the brain’s production and utilization of dopamine. So too does the intake of crack/cocaine and the abuse of nicotine. We are proposing that a novel approach to nutritional supplementation may be required to target the RDS role in alcoholism and glucose homeostasis [60]. Alcohol quickly effects blood sugar, especially in the brain [61]. Certainly an added stress of attempting to eliminate alcohol usage is the drastic swings in blood sugar, which when occurring may stimulate a stronger desire to drink [62]. Any natural means to balance blood sugar can therefore be of great cessation benefit to alcohol programs.

While we only selected a small number of patients (Table 2) to study in this pilot because we wanted to capture a positive effect prior to a much larger study being planned in the future, we are encouraged with these preliminary results. Importantly, 40% of these patients relapsed more than five times indicating serious problems with alcohol abuse/dependence. Certainly we caution any real interpretation which must await further study.

Finally, the role of Disulfram because of its inhibition of Dopamine – Beta –Hydroxylase thereby increasing brain dopamine has been also proposed for cocaine abuse or possibly other RS behaviors [63]. Currently we do not have a reasonable explanation as to why the subjects on Declinol did not have benefits related to both their inability to handle set- backs and or sleep (Table 3 and Figure 2). We are cognizant that alcohol abuse induces severe effects on brain reward circuitry affecting stress/anxiety as well as reticular formation (sleep region) in the brain. These problems may have to be addressed in future studies and may require additional therapies and neurochemical epigenetic modifications.

Conclusions
A major limitation to this pilot is the small number of subjects evaluated and as such we caution any definitive interpretation of these interesting results. However, this pilot serves as the basis to further these studies and confirmation in a much larger cohort may have important treatment ramifications for not only alcoholism but possibly RDS behaviors as well.

Consent
Written informed consent was obtained from the patients for the publication of this pilot study and the accompanying data. A copy of the written consent is available for review by the Editor- in-Chief of this journal.

Conflict of Interest
Steve Kushner has a minority interest in Declinol, LLC.

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