

# **An Expert Review of Natural Ingredients Investigated for Alcohol Use Disorder**

## **I. Introduction**

Alcohol Use Disorder (AUD) is a chronic, relapsing brain disorder characterized by an impaired ability to control alcohol consumption despite adverse social, occupational, or health consequences. It represents a significant global health burden, contributing to morbidity and mortality through direct toxic effects of alcohol, withdrawal syndromes, and associated organ damage, particularly to the liver.<sup>1</sup> The neurobiological underpinnings of AUD are complex, involving adaptations in multiple neurotransmitter systems, including GABA, glutamate, dopamine, and serotonin, which contribute to intoxication, tolerance, dependence, and withdrawal phenomena.<sup>3</sup>

The search for effective treatments for AUD is ongoing, as current pharmacotherapies approved by regulatory bodies such as the U.S. Food and Drug Administration (FDA) exhibit limitations in terms of efficacy, patient adherence, and side effect profiles.<sup>6</sup> This has spurred interest in exploring natural ingredients, many of which possess a long history of use in traditional medicine systems for managing alcohol-related problems and associated symptoms.<sup>7</sup> The rich chemical diversity found in botanical sources offers a vast repository of compounds that may act on novel therapeutic targets or provide adjunctive benefits in AUD management. The exploration of these natural products is not merely a quest for alternative treatments but reflects a need to address the multifaceted nature of AUD, which encompasses craving, withdrawal, organ damage (especially alcohol-associated liver disease), and frequently co-occurring mood disturbances. Traditional remedies often approached these interconnected symptoms holistically, a perspective that modern scientific investigation is beginning to re-evaluate.

This report aims to provide a systematic and critical review of the scientific evidence pertaining to a selection of natural ingredients and their potential utility in the context of AUD. The analysis will focus on their documented natural sources, identified active chemical constituents, proposed mechanisms of action relevant to alcohol's effects, preclinical and clinical efficacy data, and safety considerations, based exclusively on the provided research documentation. The objective is to furnish an expert-level synthesis that can inform further research, clinical consideration, or therapeutic development in the field of AUD.

## **II. Natural Ingredients Modulating Neurotransmitter Systems and**

## Receptors

This section details natural substances whose primary hypothesized or demonstrated mechanism of action in the context of AUD involves direct interactions with central nervous system neurotransmitter pathways, including receptor modulation or enzymatic activity influencing neurotransmitter metabolism.

### A. Dihydromyricetin (DHM) / Ampelopsin

Dihydromyricetin (DHM), also known as ampelopsin, is a naturally occurring flavonoid predominantly found in the Japanese Raisin Tree (*Hovenia dulcis*) and Chinese Vine Tea (*Ampelopsis grossedentata*).<sup>3</sup> Certain species of Pine (*Pinus spp.*), Cedar (*Cedrus spp.*), and the Katsura Tree (*Cercidiphyllum japonicum*) also reportedly contain DHM [User Query].

Mechanism of Action for AUD:

DHM's effects relevant to AUD are attributed to several mechanisms, though some aspects remain debated.

A primary mechanism involves the modulation of  $\gamma$ -aminobutyric acid type A (GABA<sub>A</sub>) receptors in the brain. DHM, at concentrations around 1  $\mu$ M, has been shown to antagonize acute ethanol-induced potentiation of GABA<sub>A</sub>Rs. It also counteracts neuroadaptations in these receptors caused by chronic ethanol exposure and withdrawal, including alterations in the responsiveness of extrasynaptic and postsynaptic GABA<sub>A</sub>Rs and increases in GABA<sub>A</sub>R  $\alpha$ 4 subunit expression.<sup>3</sup> Further investigation suggests that DHM competitively inhibits the binding of [<sup>3</sup>H]flunitrazepam to the benzodiazepine (BZ) site on GABA<sub>A</sub>Rs, with an  $IC_{50}$  of 4.36  $\mu$ M, indicating that its interaction with ethanol's effects involves these BZ sites.<sup>3</sup> This GABAergic modulation is considered critical for its observed anti-intoxication properties.<sup>14</sup>

A further proposed mechanism involves the enhancement of alcohol metabolism. Initial information suggested that DHM could increase the activity of key alcohol-metabolizing enzymes, namely alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) [User Query]. Such an effect would theoretically accelerate the clearance of ethanol and its toxic metabolite, acetaldehyde. However, subsequent preclinical research has presented conflicting findings. Notably, one study reported that DHM did not influence ADH activity or its expression levels in rats, either in vitro or in vivo. Furthermore, this investigation found no alteration in the overall rate of alcohol metabolism in rats administered ethanol with DHM.<sup>11</sup> This discrepancy is critical, as it challenges the hypothesis of a dual action involving both direct neurochemical modulation and accelerated alcohol clearance. If DHM does not significantly impact alcohol catabolism, its therapeutic potential in AUD would primarily rely on its effects on GABA<sub>A</sub> receptors and its documented hepatoprotective properties.

Clarification of DHM's precise effects on alcohol-metabolizing enzymes remains an important area for future investigation.

DHM also exhibits significant hepatoprotective effects. It is reported to protect against chemical-induced liver injuries, potentially through the activation of AMP kinase (AMPK) and the nicotinamide adenine dinucleotide (NAD<sup>+</sup>)-dependent Sirtuin-1 (Sirt1) energy-regulating pathway.<sup>1</sup> The hepatoprotective activity observed in some studies has been attributed to the reduction of reactive oxygen/nitrogen species (ROS/RNS) levels.<sup>11</sup> Specifically, extracts of *Ampelopsis grossedentata* (AGE), which are rich in DHM, have been shown to ameliorate chronic alcohol-induced hepatic steatosis, oxidative stress, and inflammation in mice via the YTHDF2/PGC-1 $\alpha$ /SIRT3 signaling axis.<sup>12</sup> This suggests that while DHM is a key active compound, the effects of whole plant extracts may involve distinct or synergistic pathways.

#### Efficacy Evidence:

Preclinical studies in animal models have demonstrated DHM's potential. Intraperitoneal injection of DHM (1 mg/kg) in rats counteracted acute alcohol intoxication and ameliorated withdrawal signs such as tolerance, increased anxiety, and seizure susceptibility. DHM also significantly reduced voluntary ethanol consumption in an intermittent intake paradigm.<sup>3</sup> Its ability to reduce withdrawal symptoms like anxiety and seizure sensitivity is linked to its antagonism of alcohol-induced GABA<sub>A</sub> receptor potentiation and plasticity.<sup>13</sup>

In humans, DHM is marketed as a dietary supplement, commonly for hangover relief, with some reports suggesting it reduces blood alcohol levels and hangover symptoms.<sup>13</sup> A Phase 1, open-label, dose-escalation clinical trial (NCT05623501) is planned to formally assess the safety, pharmacokinetics (PK), and maximum tolerated dose (MTD) of a purified form of DHM in healthy volunteers, with a view to its potential use in alcohol-associated liver disease (ALD).<sup>1</sup> The trial is anticipated to run from September 2024 to December 2025.<sup>1</sup> Primary objectives include evaluating safety (adverse events graded by CTCAE v3.0) and determining PK parameters of DHM and its metabolites.<sup>1</sup> Eligible participants are healthy adults aged 18–60 years with no prior history of AUD or ALD, and a bodyweight not below 50kg. Exclusion criteria include an AUDIT score >8, advanced liver disease, and use of CYP3A4-affecting drugs.<sup>1</sup> The rationale for this trial stems from preclinical data supporting DHM's utility in AUD and its potential to prevent ALD through mechanisms involving the AMPK/Sirt-1/PGC-1 $\alpha$  axis.<sup>1</sup> This trial's focus on ALD in healthy volunteers, rather than directly assessing AUD treatment efficacy (e.g., reduction in alcohol consumption or craving) in an AUD population, may reflect a strategic approach to first establish human safety and PK for a purified compound.

#### Safety & Regulatory Status:

DHM has demonstrated a good safety record in short-term human randomized controlled trials (RCTs) and animal studies, which may partly be attributable to its low oral bioavailability.<sup>13</sup> This poor bioavailability is a significant hurdle for its clinical utility<sup>13</sup> and underscores the importance of the planned PK studies with a purified, cGMP-compliant source.<sup>1</sup> As a dietary supplement, DHM is not regulated by the FDA as a drug, leading to concerns about the quality and consistency of available herbal products.<sup>1</sup> There is also a potential for drug interactions due to projected cytochrome P450 (CYP) inhibition activity.<sup>13</sup> Overcoming the bioavailability challenge will be crucial for translating the strong preclinical

promise of DHM for AUD-related behaviors into effective clinical applications for AUD itself.

### **B. Kudzu Root (*Pueraria lobata* or *Pueraria montana* var. *lobata*) & Daidzein**

Kudzu root has been a staple in Traditional Chinese Medicine (TCM) for nearly two millennia for addressing alcohol-related issues.<sup>7</sup> Its primary active isoflavones are puerarin, daidzin, and daidzein.<sup>7</sup> Daidzein, as an individual compound, is also found in soybeans and soy products, red clover, and other legumes [User Query].

Mechanism of Action (Kudzu & its components):

The antidipsotropic (anti-drinking) effects of Kudzu are primarily attributed to its isoflavone constituents, particularly daidzin and puerarin.

**Daidzin** is a potent and selective inhibitor of mitochondrial aldehyde dehydrogenase (ALDH-2).<sup>7</sup> ALDH-2 is a key enzyme not only in ethanol metabolism (oxidizing acetaldehyde) but also in the metabolism of biogenic amines like serotonin (5-HT) and dopamine (DA). Daidzin's inhibition of ALDH-2 leads to the accumulation of reactive aldehyde intermediates of 5-HT and DA metabolism (specifically 5-hydroxyindole-3-acetaldehyde from serotonin and 3,4-dihydroxyphenylacetaldehyde from dopamine) within specific brain regions.<sup>17</sup> This localized accumulation of biogenic aldehydes in the brain, rather than a systemic increase in acetaldehyde (as seen with disulfiram), is thought to mediate its anti-drinking effect.<sup>17</sup> This distinction is important, as it suggests a potentially more targeted central mechanism with fewer peripheral aversive side effects compared to disulfiram.<sup>7</sup> Synthetic analogs of daidzin, such as CVT-10216 (a selective, reversible ALDH-2 inhibitor), are being explored for their ability to reduce excessive alcohol drinking and prevent alcohol-induced elevations in dopamine levels.<sup>18</sup>

**Puerarin**, another major isoflavone in Kudzu, appears to reduce alcohol intake through a different mechanism: by altering drinking topography. Studies have shown it can decrease sip size, increase the number of sips taken to finish a beer, extend the overall consumption time per beer, and increase the latency to opening subsequent beers.<sup>21</sup>

**Daidzein** itself also functions as a potent and selective inhibitor of mitochondrial ALDH-2, contributing to Kudzu's overall effects.<sup>17</sup>

A critical consideration is the specific part of the Kudzu plant used. The *root* of *Pueraria lobata* contains these ALDH-2 inhibiting isoflavones, which, in the presence of alcohol, could theoretically lead to increased acetaldehyde levels.<sup>10</sup> Conversely, *Pueraria flowers* (*Puerariae flos*) have been traditionally used to *enhance* acetaldehyde removal.<sup>10</sup> This highlights the necessity of precise botanical specification, as different parts of the same plant may exert opposing effects on

acetaldehyde metabolism, with significant implications for safety and therapeutic application.

#### Efficacy Evidence (Kudzu & its components):

Preclinical studies have consistently shown that Kudzu extracts, daidzin, and daidzein can reduce voluntary alcohol consumption in various animal models, including alcohol-preferring rats and hamsters.<sup>7</sup> Puerarin has also demonstrated efficacy in reducing alcohol consumption in rats.<sup>21</sup>

Human clinical trials on Kudzu extract have yielded somewhat mixed but generally positive results. Several studies indicate that Kudzu extract can significantly reduce alcohol consumption in individuals classified as heavy drinkers or those who binge drink, sometimes by as much as one-third to one-half.<sup>7</sup> For instance, a study by Lukas et al. (2005) found that Kudzu extract, administered for 7 days prior to a drinking session in a naturalistic laboratory setting, resulted in a significant reduction in the number of beers consumed. Participants also took more sips and a longer time to consume each beer and decreased their sip volume, although no effect on the subjective urge to drink alcohol was reported.<sup>20</sup> A study specifically evaluating puerarin in 10 human participants found it reduced the average number of beers consumed from 3.5 (placebo) to 2.4 and similarly altered drinking topography (decreased sip size, increased sips and time per beer, increased latency to next beer).<sup>21</sup>

A 2019 Cochrane systematic review and meta-analysis, which included seven RCTs (mostly small with unclear risk of bias), found that four trials favored Kudzu over placebo in reducing the number of drinks, normalizing drinking behavior, and increasing days of abstinence.<sup>24</sup> The meta-analysis of three of these trials suggested that Kudzu *may* reduce alcohol cravings (Odds Ratio 2.97, 95% CI 1.37 to 6.46), with moderate-certainty evidence.<sup>24</sup> However, some studies have reported inconsistent results or findings that were difficult to interpret regarding Kudzu's effects on subjective mood or cognitive performance during alcohol consumption.<sup>7</sup> This variability underscores the need for larger, methodologically robust clinical trials to definitively establish Kudzu's efficacy and to clarify which specific AUD outcomes (e.g., craving, consumption volume, drinking patterns) are most reliably affected.

No specific clinical trials focusing solely on isolated daidzein for AUD were detailed in the provided information, though its contribution to Kudzu's effects is recognized [User Query].

#### Safety (Kudzu & its components):

Kudzu root has a long history of use in TCM [User Query]. In contemporary studies, it is generally reported as well-tolerated, with minimal or no side effects observed in some human

trials.<sup>7</sup> The Cochrane review noted that headaches were the most commonly reported adverse effect, occurring with a frequency of 1.7% to 3% in two RCTs, and no serious adverse events were reported in the included trials; nevertheless, the review called for further research into its safety.<sup>24</sup>

A significant safety consideration arises from the ALDH-2 inhibitory action of Kudzu *root*. Chronic use, particularly in conjunction with high ethanol consumption, could potentially lead to an accumulation of acetaldehyde, which is a known carcinogen. This raises concerns about an increased risk of acetaldehyde-related neoplasms and pathology.<sup>10</sup> This contrasts with the traditional use of Kudzu *flowers*, which are believed to enhance acetaldehyde clearance.<sup>10</sup> Quality control and standardization of unregulated Kudzu products also remain a concern [User Query].

### C. Psilocybin

Psilocybin is a psychoactive tryptamine compound produced by numerous species of mushrooms, often referred to as "magic mushrooms" [User Query].

Mechanism of Action for AUD:

Psilocybin's primary pharmacological action is as an agonist at serotonin 5-HT<sub>2A</sub> receptors [User Query]. Its therapeutic effects in AUD are thought to be mediated by its capacity to induce profound alterations in consciousness, which, in a supportive therapeutic context, can facilitate psychological insight and behavioral change. It is believed to influence neurotransmission, intracellular signaling pathways, epigenetic modifications, and gene expression, collectively promoting increased neuroplasticity across neuronal structures, brain networks, and cognitive, emotional, and behavioral domains [User Query]. In the context of AUD, psilocybin-assisted therapy (PAT) may lead to durable shifts in personality structure. Specifically, studies have reported reductions in neuroticism and increases in extraversion and openness in patients with AUD following PAT.<sup>25</sup>

Efficacy Evidence:

Psilocybin, when administered in conjunction with psychotherapy, has shown considerable promise in clinical trials for AUD. It has been associated with rapid, robust, and enduring reductions in drinking behavior and sustained improvements in mental health outcomes.<sup>26</sup> A recent multi-site Phase 2 clinical trial investigating PAT in individuals with AUD demonstrated significant reductions in drinking behavior compared to an active placebo (diphenhydramine) group that also received psychotherapy.<sup>26</sup> While the primary outcomes related to abstinence rates and mean alcohol use per day may have shown mixed results in some analyses, a notable additional reduction in alcohol craving was observed in the psilocybin group [User Query].

A secondary analysis from a double-blind, placebo-controlled trial involving 84 adults with AUD (psilocybin N=44 vs. diphenhydramine N=40, both with 12 weekly psychotherapy sessions and 24 weeks of follow-up) provided further insights into the

psychological changes accompanying PAT.<sup>25</sup> At the 36-week follow-up, the psilocybin group exhibited statistically significant reductions in neuroticism and significant increases in extraversion and openness compared to the placebo group. Further analysis of personality facets revealed that the reduction in neuroticism was primarily driven by decreases in depression, impulsiveness, and vulnerability. The increase in openness was attributed to increases in openness toward feelings and fantasy.<sup>25</sup> Importantly, across all participants, decreases in the impulsiveness facet of neuroticism were significantly associated with lower post-treatment alcohol consumption. An exploratory analysis suggested this association was strongest among psilocybin-treated participants who had continued moderate- or high-risk drinking prior to their first medication session.<sup>25</sup> These findings suggest that PAT may normalize abnormal personality trait expression often seen in AUD and that modulation of impulsivity could be a key therapeutic mechanism.

The therapeutic model employed in these trials is crucial; it typically involves extensive psychotherapeutic support, including preparatory sessions before psilocybin administration, monitoring during the acute effects, and integration sessions afterward to help process the experience.<sup>26</sup> For example, one trial utilized the Preparation, Support, and Integration (PSI) model, incorporating elements of motivational enhancement therapy (MET) and cognitive-behavioral therapy (CBT).<sup>26</sup> This underscores that psilocybin is viewed as a catalyst for psychotherapeutic processes rather than a standalone pharmacological treatment.

#### Safety & Regulatory Status:

In controlled research settings, moderately high doses of psilocybin have been reported as well-tolerated by participants [User Query]. However, the administration of psilocybin requires careful medical and psychological screening and monitoring due to its potent psychoactive effects. Further research is considered necessary to establish its safety profile in patients with certain underlying psychiatric conditions [User Query]. Psilocybin is a Schedule I controlled substance in many jurisdictions, limiting its accessibility outside of approved research protocols. The complexity of achieving "success" in AUD trials with psychedelics is also apparent, as subjective and broader psychological changes (like personality shifts or craving reduction) might be more sensitive or earlier indicators of therapeutic effect than traditional abstinence metrics, especially in early-phase research.

#### **D. *Peganum harmala* (Syrian Rue)**

*Peganum harmala*, commonly known as Syrian Rue, is a plant recognized for its psychoactive  $\beta$ -carboline alkaloids, including harmine, harmaline, harmalol, and harmane.<sup>28</sup> Another alkaloid identified in the plant is desoxypeganine (vasicine) [User Query].

#### Mechanism of Action for AUD:

The primary pharmacological mechanism of *P. harmala*'s  $\beta$ -carboline alkaloids is the potent and reversible inhibition of monoamine oxidase A (MAO-A).<sup>28</sup> This inhibition leads to increased synaptic availability of monoamine neurotransmitters, particularly serotonin and norepinephrine.<sup>28</sup> Studies have shown that seed and root extracts of *P. harmala* significantly inhibit MAO-A in a reversible and competitive manner, with little to no effect on MAO-B.<sup>28</sup> Beyond MAO-A inhibition, these alkaloids are known to interact with a variety of receptor systems, including serotonin 5-HT<sub>2</sub> receptors, dopamine receptors, GABA receptors, and opioid receptors.<sup>28</sup> For instance, antidepressant-like effects of harmaline, norharmaline, and harmine have been suggested to involve interactions with benzodiazepine receptors.<sup>28</sup>

#### Efficacy Evidence:

Preclinical evidence suggests some potential relevance to AUD. Desoxyepaganine, an alkaloid from *P. harmala*, has been shown to decrease ethanol consumption in alcohol-preferring rats.<sup>28</sup> Harmine has demonstrated antidepressant effects in preclinical models.<sup>28</sup> Intriguingly, elevated plasma concentrations of harmala alkaloids like harmaline and norharmaline, which are also endogenous compounds, have been reported in individuals with alcoholism.<sup>28</sup> This observation raises questions about the potential role of these endogenous  $\beta$ -carbolines in the pathophysiology of AUD or as biomarkers, distinct from the exogenous administration of *P. harmala*.

No direct human clinical trials evaluating *P. harmala* or its isolated alkaloids for the treatment of AUD were reported in the provided information.

#### Safety & Regulatory Status:

*Peganum harmala* possesses significant safety concerns that likely limit its therapeutic potential for AUD. It is psychoactive at higher doses, capable of inducing hallucinations, tremors, and ataxia.<sup>29</sup> The potent MAO-A inhibitory activity carries a substantial risk of dangerous interactions with tyramine-containing foods (the "cheese effect"), which can precipitate a hypertensive crisis, as well as interactions with numerous medications, including serotonergic drugs (risk of serotonin syndrome).<sup>28</sup>

Toxicity at high doses is a major concern.<sup>29</sup> Human cases of intoxication following ingestion have reported neuro-sensorial symptoms, visual hallucinations, cardiovascular disturbances (bradycardia, hypotension), psychomotor agitation, tremors, ataxia, and vomiting.<sup>28</sup> The plant has also been traditionally used as an emmenagogue and abortifacient, with quinazoline alkaloids like vasicine and vasicinone implicated in these effects.<sup>28</sup> Furthermore, *P. harmala* alkaloids can interact with drug metabolism by affecting cytochrome P450 enzyme expression.<sup>28</sup> Given these risks, particularly the MAOI-related interactions and inherent toxicity, the use of *P. harmala* for AUD would necessitate stringent dietary and medication controls, which could be exceptionally challenging to implement and maintain in an AUD population.

### **E. St. John's Wort (*Hypericum perforatum*)**

St. John's Wort (SJW) is a widely known herbal remedy, primarily recognized for its use in treating depression.<sup>30</sup> Its key active constituents include hypericin and hyperforin [User Query].

#### **Mechanism of Action for AUD:**

The antidepressant effects of SJW are attributed to its modulation of several neurotransmitter systems, including serotonin, norepinephrine, and dopamine [User Query]. It also possesses monoamine oxidase A (MAO-A) inhibitory properties.<sup>31</sup> In the context of nicotine withdrawal, SJW has been suggested to act by reducing brain serotonin levels and stimulating the synthesis of nitric oxide, a neurotransmitter potentially involved in mitigating withdrawal symptoms.<sup>33</sup>

#### **Efficacy Evidence:**

Preclinical animal studies have suggested that SJW may reduce alcohol intake as well as decrease alcohol withdrawal symptoms such as tremors and seizures.<sup>7</sup> For example, mice treated with a standardized extract of SJW were observed to be significantly less agitated and experienced fewer seizures following acute withdrawal from alcohol.<sup>33</sup>

However, direct evidence from human clinical trials investigating SJW specifically for reducing alcohol craving or consumption in AUD is lacking in the provided documentation [User Query]. Its relevance to AUD is considered mainly indirect, potentially through the treatment of co-occurring depression [User Query]. Studies on its efficacy for nicotine withdrawal in humans have been inconsistent; one small pilot study found no difference in abstinence rates compared to placebo, while another reported less intense nicotine cravings and anxiety in the SJW group.<sup>33</sup>

#### **Safety & Regulatory Status:**

The use of SJW, particularly in the context of AUD, is accompanied by significant safety concerns.

There is a notable interaction with alcohol itself; concomitant use can increase the nervous system side effects of SJW, such as dizziness, drowsiness, and difficulty concentrating, and may also impair thinking and judgment.<sup>31</sup>

Due to its MAOI properties, individuals taking SJW must avoid tyramine-rich foods (e.g., aged cheeses, fermented meats, certain alcoholic beverages like tap beer or red wine) to prevent the risk of a hypertensive crisis.<sup>31</sup>

Furthermore, SJW is a potent inducer of the cytochrome P450 3A4 (CYP3A4) enzyme system in the liver.<sup>33</sup> This induction can lead to numerous clinically significant drug interactions by accelerating the metabolism and reducing the efficacy of a wide range of medications, including oral contraceptives, anti-HIV drugs (e.g., protease inhibitors, non-nucleoside reverse transcriptase inhibitors), anticoagulants (e.g., warfarin), immunosuppressants (e.g., cyclosporine), cardiovascular drugs (e.g., digoxin), and

some antidepressants.<sup>33</sup>

Given these substantial interaction risks—with alcohol, tyramine-containing foods, and numerous medications—SJW appears to be a problematic choice for individuals with AUD, who may still be consuming alcohol or require medications for comorbid conditions. The potential risks likely outweigh any speculative benefits for the direct treatment of AUD, especially in the absence of robust human efficacy data for this indication. Any potential role would likely be confined to treating comorbid depression under strict medical supervision, with careful consideration of the patient's alcohol consumption patterns and concomitant medications.

#### **F. *Banisteriopsis caapi* (Ayahuasca Vine) & Other Mild MAO-A Inhibitors (e.g., Turmeric - Curcumin, Nutmeg, Tobacco, Coffee, Cacao)**

*Banisteriopsis caapi* is a liana native to the Amazon rainforest and is one of the primary ingredients in ayahuasca, a psychoactive brew traditionally used for spiritual and medicinal purposes by indigenous peoples of the Amazon Basin.<sup>34</sup> *B. caapi* contains several harmala alkaloids, including harmine, harmaline, and tetrahydroharmine, which are potent reversible inhibitors of monoamine oxidase A (MAO-A).<sup>35</sup>

Other natural sources are reported to contain compounds with mild MAO-A inhibitory effects, such as curcumin from Turmeric (*Curcuma longa*), and unspecified compounds in Nutmeg (*Myristica fragrans*), Tobacco (*Nicotiana spp.*), Coffee (*Coffea spp.*), and raw Cacao beans (*Theobroma cacao*) [User Query].

Mechanism of Action (*B. caapi* in Ayahuasca):

In the context of ayahuasca, the MAO-A inhibiting properties of *B. caapi* are crucial. Ayahuasca is typically prepared by decocting *B. caapi* with other plants, most commonly the leaves of *Psychotria viridis*, which contain the potent psychedelic compound N,N-dimethyltryptamine (DMT).<sup>34</sup> DMT is orally inactive when ingested alone because it is rapidly metabolized by MAO-A in the gastrointestinal tract and liver. The harmala alkaloids from *B. caapi* inhibit this enzymatic degradation, allowing DMT to reach systemic circulation and cross the blood-brain barrier, where it exerts its psychoactive effects primarily through serotonin 5-HT<sub>2A</sub> receptor agonism.<sup>34</sup> Thus, *B. caapi* acts as an essential potentiator in the ayahuasca brew.

Mechanism of Action (Turmeric/Curcumin as MAOI):

Curcumin, the principal curcuminoid in turmeric, has been reported to possess MAO-A inhibitory effects [User Query]. However, the provided documentation primarily emphasizes curcumin's hepatoprotective, anti-inflammatory, and antioxidant properties, particularly in the context of alcohol-induced liver damage<sup>37</sup>, rather than its MAO-A inhibitory activity as a primary mechanism for treating AUD.

#### Efficacy Evidence (B. caapi/Ayahuasca for AUD):

Observational studies and preliminary research have explored the potential of ayahuasca in the treatment of various substance use disorders, including alcoholism.<sup>34</sup> Some studies suggest that participation in ayahuasca ceremonies, often within a structured ritualistic or therapeutic setting, may be associated with reductions in the use of alcohol, tobacco, and other substances, as well as decreased cravings and improvements in mental health among individuals recovering from substance use disorders.<sup>36</sup> However, the provided information indicates that rigorous, controlled clinical trial data specifically for AUD are limited [User Query]. The therapeutic effects of ayahuasca are generally attributed to the profound psychological experiences induced by DMT, facilitated by the MAO-A inhibition from B. caapi, rather than the MAO-A inhibition itself being the sole or primary therapeutic mechanism for addiction.

#### Efficacy Evidence (Turmeric/Curcumin for AUD via MAO-A Inhibition):

The provided documentation does not discuss any studies investigating the efficacy of turmeric or curcumin for AUD treatment based on its MAO-A inhibitory properties [User Query]. The focus of the material on turmeric/curcumin in relation to alcohol is on its protective effects against alcohol-induced hepatocyte damage.<sup>37</sup> Therefore, any link between curcumin's MAO-A inhibition and a reduction in alcohol consumption or craving appears speculative based on the available information.

#### Efficacy Evidence (Other Mild Dietary MAOIs):

The direct role or efficacy of nutmeg, tobacco, coffee, or cacao in AUD treatment, based on their mild MAO-A inhibitory properties, is not discussed in the provided materials [User Query]. Given the "mild" nature of their MAO-A inhibition and their common dietary or habitual use (with tobacco being an addictive substance itself), it is unlikely that they would exert a clinically significant effect on AUD primarily through this mechanism.

#### Safety (B. caapi/Ayahuasca):

The use of ayahuasca is associated with several safety considerations. Due to the MAO-A inhibition by B. caapi, there is a risk of hypertensive crisis if ayahuasca is consumed concurrently with tyramine-rich foods or certain sympathomimetic drugs.<sup>36</sup> Interactions with other serotonergic medications, such as SSRIs or other MAOIs, can lead to serotonin syndrome, a potentially life-threatening condition.<sup>36</sup>

Common acute physical effects of ayahuasca ingestion include nausea, vomiting, and diarrhea, which are often culturally reframed as "purging" or cleansing but can pose risks such as dehydration.<sup>34</sup> Increased heart rate and blood pressure are also common.<sup>35</sup>

The psychological effects are intense and can include profound visual and auditory hallucinations, altered perceptions of time and self, and strong emotional experiences, which may be anxiogenic or fear-inducing for some individuals.<sup>34</sup> The DMT component of ayahuasca is illegal in many countries.<sup>34</sup>

#### Safety (Turmeric/Curcumin):

Turmeric and curcumin are generally considered safe when consumed in culinary amounts or as supplements at appropriate doses.<sup>40</sup> Mild gastrointestinal side effects, such as stomach upset or diarrhea, may occur, particularly at higher doses.<sup>41</sup> Curcumin may interact with anticoagulant medications and drugs metabolized by hepatic cytochrome P450 enzymes.<sup>41</sup>

There is some concern regarding potential liver damage with high doses or in individuals with pre-existing liver disease like hepatitis or cholestasis.<sup>41</sup>

### **G. Ashwagandha (*Withania somnifera*)**

Ashwagandha is an adaptogenic herb prominently used in traditional Ayurvedic medicine.<sup>8</sup> Its primary bioactive compounds are withanolides [User Query].

Mechanism of Action for AUD:

Ashwagandha is believed to modulate the body's stress-response system, notably by reducing cortisol levels.<sup>42</sup> Preclinical research indicates potential GABAergic activity, which may contribute to its anxiolytic effects.<sup>42</sup> It also possesses anti-inflammatory, antioxidant, and neuroprotective properties.<sup>43</sup> Its relevance to reducing the urge to drink alcohol is thought to arise from its anti-stress and anxiolytic effects, which may mitigate "relief-craving" driven by negative emotional states [User Query].

Efficacy Evidence:

Preclinical studies have provided evidence for Ashwagandha's potential in managing alcohol withdrawal. A study in rats demonstrated that Ashwagandha extract (standardized to 3.75 mg/kg of withanolide glycosides), administered orally, was effective in controlling agitation, stereotypic behavior, and pentylenetetrazol (PTZ)-induced kindling seizures during alcohol withdrawal.<sup>43</sup> It also improved locomotor activity and reduced anxiety in these animals, with effects comparable to diazepam.<sup>43</sup> These findings suggest a direct modulatory effect on the neurobiology of alcohol withdrawal. Additionally, Ashwagandha has been reported to lessen the severity of morphine withdrawal in mice.<sup>8</sup>

Human clinical trials have supported Ashwagandha's ability to lower anxiety scores and reduce cortisol levels in individuals experiencing stress, although these studies were not specific to AUD populations.<sup>42</sup> A clinical trial (NCT06714942) is currently underway to evaluate a proprietary blend of Ashwagandha root extract for its efficacy and safety in adult men and women with high stress and anxiety, but this trial is not focused on AUD.<sup>44</sup> The provided information does not detail specific human clinical trials where Ashwagandha was investigated for the primary outcomes of directly reducing alcohol craving or binge drinking in individuals with AUD.<sup>45</sup> Therefore, its primary demonstrated utility in an alcohol-related context is for managing withdrawal symptoms and stress, rather than directly impacting addictive drinking behaviors.

Safety & Regulatory Status:

Ashwagandha is generally considered safe and well-tolerated.<sup>42</sup> Some individuals may experience mild gastrointestinal upset or drowsiness [User Query]. Its GABAergic mechanism suggests a potential for additive CNS depressant effects if combined with alcohol or other sedative medications, warranting caution.

### **H. Passionflower (*Passiflora incarnata*)**

Passionflower is a traditional herbal remedy used for nervousness, anxiety, and as a mild sedative.<sup>23</sup> Its active compounds include flavonoids and beta-carboline alkaloids,

though the MAO-A inhibitory activity of the latter is considered mild and not the primary mechanism for its effects relevant to AUD [User Query].

#### Mechanism of Action for AUD:

The anxiolytic and sedative effects of Passionflower are primarily attributed to its modulation of GABA neurotransmission. It is thought to act by inhibiting GABA reuptake and by binding to both GABA<sub>A</sub> and GABA<sub>B</sub> receptors [User Query].

#### \*\*Efficacy Evidence:\*\*

Preclinical evidence suggests that Passionflower extract can prevent some effects associated with alcohol withdrawal [User Query].

Human studies, though not specific to AUD populations, have shown that Passionflower can lead to improvements in nervous restlessness, enhance resilience, improve quality of life, and reduce anxiety levels [User Query]. A recent randomized, double-blind, placebo-controlled clinical study in Indian participants with stress and insomnia (not AUD-specific) found that *Passiflora incarnata* extract (SIVI) significantly reduced scores on the Perceived Stress Scale and significantly increased total sleep time compared to placebo over 30 days.<sup>47</sup>

In the context of substance use, Passionflower has been proposed as an aid for alcohol withdrawal, with this suggestion primarily based on studies conducted in individuals addicted to opiates.<sup>23</sup> One study mentioned the use of a fixed combination product containing Passionflower extract for treating hospitalized patients undergoing alcohol withdrawal; this study reported improvements in withdrawal symptoms and liver enzyme levels, but it lacked a placebo comparison group, limiting the conclusions that can be drawn.<sup>46</sup> No direct human clinical trials specifically investigating Passionflower for the reduction of alcohol urge or binge drinking in AUD populations were prominently detailed in the provided information [User Query]. Thus, similar to Ashwagandha, its main relevance to AUD appears to be in managing anxiety and insomnia, which can be features of alcohol withdrawal or comorbid conditions, rather than directly addressing core alcohol consumption behaviors.

#### \*\*Safety & Regulatory Status:\*\*

Passionflower is generally regarded as safe and well-tolerated.<sup>46</sup> Drowsiness is the most commonly reported side effect [User Query]. Due to its sedative properties and GABAergic mechanism, caution is advised when Passionflower is used concomitantly with alcohol or other sedative medications, as there is a potential for increased CNS depression [User Query]. It is considered an unlikely cause of clinically apparent liver injury.<sup>46</sup> The mild MAO-A inhibitory activity of its beta-carboline alkaloids is not considered primary to its action and likely does not confer the significant food and drug interaction risks associated with more potent MAOIs.

#### ### I. Ginseng (\*Panax ginseng\*)

Ginseng, often referred to as *Panax ginseng*, is a well-known adaptogenic herb used in traditional medicine systems.<sup>8</sup>

#### \*\*Mechanism of Action for AUD:\*\*

Animal studies have provided insights into Ginseng's potential mechanisms relevant to substance use and withdrawal. It has been suggested that Ginseng may inhibit the narcotic-induced depletion of dopamine in the brain.<sup>8</sup> Specifically, Korean Red Ginseng (KRG,

a form of *\*Panax ginseng\**) has been shown to exert anxiolytic effects during ethanol withdrawal in rats by improving the function of the mesoamygdaloid dopamine (DA) system.<sup>48</sup> KRG extract reversed ethanol withdrawal-induced decreases in DA and its metabolite 3,4-dihydroxyphenylacetic acid (DOPAC) in the central nucleus of the amygdala (CeA) and prevented reductions in tyrosine hydroxylase (TH, the rate-limiting enzyme in catecholamine synthesis) expression in both the CeA and the ventral tegmental area (VTA).<sup>48</sup> These effects on anxiety-like behavior were blocked by a selective DA D2 receptor antagonist, but not by a D1 receptor antagonist, implicating D2 receptors in KRG's action.<sup>48</sup> Furthermore, ginseng saponins (ginsenosides) have been suggested to directly affect dopamine D2 receptors.<sup>49</sup> Research in the context of methamphetamine addiction also indicates that KRG can regulate dopaminergic and N-methyl-D-aspartate (NMDA) receptor systems.<sup>50</sup>

**\*\*Efficacy Evidence:\*\***

Preclinical studies focusing on alcohol withdrawal have shown that KRG extract inhibits anxiety-like behavior and the associated oversecretion of plasma corticosterone in rats undergoing ethanol withdrawal.<sup>48</sup> This points to a specific potential application in managing the negative affective states that characterize withdrawal and often contribute to relapse. In other addiction models, animal studies suggest that Ginseng may reduce tolerance and dependence associated with the long-term abuse of substances like cocaine, methamphetamine, and morphine.<sup>8</sup> For instance, Red Ginseng Extract (RGE) significantly inhibited methamphetamine-induced self-administration, conditioned place preference (CPP), and reinstatement of drug-seeking behavior in rodents.<sup>50</sup> While these findings in other substance use disorder models suggest broader potential, direct translation to AUD requires specific investigation.

The provided documentation did not detail any human clinical trials evaluating Ginseng specifically for the treatment of AUD, including effects on alcohol consumption or craving.<sup>51</sup>

**\*\*Safety & Regulatory Status:\*\***

Information regarding the safety and regulatory status of Ginseng specifically for AUD treatment was not detailed in the provided materials [User Query].

The findings, particularly from studies on Korean Red Ginseng, highlight a potential role for Ginseng in mitigating anxiety during ethanol withdrawal through modulation of the dopamine system in key brain regions like the amygdala. This suggests a targeted application for managing withdrawal-related negative affect, a critical driver of relapse in AUD.

**### J. *\*Salvia divinorum\****

*\*Salvia divinorum\** is an herb native to Oaxaca, Mexico, belonging to the mint family.<sup>52</sup> Its primary psychoactive constituent is Salvinorin A.<sup>52</sup>

**\*\*Mechanism of Action for AUD:\*\***

Salvinorin A is a highly potent and selective kappa opioid receptor (KOR) agonist.<sup>54</sup> Activation of KORs is generally associated with dysphoria, anti-reward effects, and modulation of dopamine release in brain reward pathways.

**\*\*Efficacy Evidence:\*\***

The provided documentation does not contain any evidence to suggest that *\*Salvia divinorum\** or Salvinorin A is effective for treating AUD.<sup>52</sup> Its investigation in the context of AUD appears to be non-existent within the scope of the supplied materials.

## **\*\*Safety & Regulatory Status:\*\***

*Salvia divinorum* is known for its potent, short-acting hallucinogenic and dissociative effects.<sup>52</sup> Its use is associated with significant short-term dangers, including impaired perception of reality, panic reactions, and loss of motor control.<sup>53</sup> There are concerns about potential long-term cognitive problems, psychiatric symptoms, and dysphoria with its use.<sup>52</sup> Although addiction is considered rare, abuse can be problematic.<sup>52</sup>

Due to its abuse potential and lack of accepted medical use, *Salvia divinorum* and Salvinorin A are classified as Schedule I controlled substances in many U.S. states and other jurisdictions.<sup>53</sup>

Given its intense psychoactive profile, significant safety concerns, abuse liability, and the absence of any efficacy data for AUD in the provided information, *Salvia divinorum* is contraindicated and not a viable therapeutic candidate for AUD. While KOR agonism is a target of interest for modulating reward pathways in addiction research, the specific pharmacological profile of Salvinorin A, characterized by its powerful hallucinogenic effects, makes it unsuitable for this therapeutic application. This underscores that receptor-specific action alone does not determine therapeutic utility; the overall pharmacological and phenomenological effects are paramount.

## **### K. Serotonin and Dopamine Precursors (Tryptophan, Tyrosine)**

Serotonin and dopamine are critical neurotransmitters endogenously produced by the body and are deeply implicated in mood regulation, reward processing, motivation, and pleasure [User Query]. Alcohol consumption profoundly impacts these neurotransmitter systems, contributing to the development and maintenance of AUD, including craving, relapse, and comorbid mood disorders [User Query]. The precursors for these neurotransmitters are essential amino acids obtained from the diet: L-tryptophan is the precursor for serotonin, found in foods like turkey, nuts, and seeds, while L-tyrosine (derived from phenylalanine) is the precursor for dopamine, found in foods such as cheese, meats, and legumes.<sup>56</sup>

## **\*\*Efficacy & Safety of Precursor Supplementation for AUD:\*\***

The provided documentation does not contain direct evidence from clinical trials evaluating the efficacy or safety of supplementing with L-tryptophan or L-tyrosine as a standalone or primary adjunctive treatment for reducing alcohol consumption or craving in individuals diagnosed with AUD.<sup>56</sup> The research focus within the supplied materials is predominantly on how various pharmacological or herbal interventions modulate these existing neurotransmitter pathways, or on the effects of precursor *depletion*.

**\*\*L-Tryptophan:\*\*** Supplementation with L-tryptophan is hypothesized to support serotonin synthesis. In the context of addiction recovery, this *may* help restore normal brain serotonin function, potentially alleviating depressive symptoms often experienced in early recovery (sometimes termed "sober sadness") and possibly curbing cravings that are linked to serotonin dysregulation.<sup>56</sup> However, this role appears to be more supportive, addressing mood disturbances associated with withdrawal or early abstinence, rather than directly targeting the core addictive behaviors of AUD.

**\*\*L-Tyrosine:\*\*** The evidence concerning catecholamine precursors (phenylalanine/tyrosine for dopamine/norepinephrine) in relation to alcohol consumption presents a more complex picture. Studies involving acute phenylalanine/tyrosine *depletion*—a method designed to

transiently decrease catecholamine neurotransmission—have shown that such depletion can lead to a decrease in alcohol self-administration in both vervet monkeys and healthy female social drinkers.<sup>57</sup> This finding suggests that \*reducing\* catecholamine activity, rather than augmenting it via precursor supplementation, might attenuate the motivation to consume alcohol. This is somewhat counterintuitive to the notion of "boosting" dopamine with tyrosine supplements to address reward deficits in AUD and highlights the intricate, non-linear role of these neurotransmitter systems in alcohol-seeking behavior.

Overall, despite the clear involvement of serotonin and dopamine systems in the pathophysiology of AUD, the therapeutic utility of simply supplementing with their amino acid precursors as a direct treatment for AUD is not established by the evidence presented. The existing data points more towards the complex effects of modulating these systems (e.g., through depletion) or the supportive role of precursors in managing comorbid symptoms like depression during recovery.

### ## III. Natural Ingredients with Primary Hepatoprotective or Metabolic Effects, or Affecting Alcohol Absorption

This section reviews substances whose principal investigated role in the context of alcohol use pertains to protecting the liver from alcohol-induced damage, altering alcohol metabolism (excluding primary neurotransmitter-metabolizing enzymes like MAO, which are covered elsewhere), reducing the absorption of ingested alcohol, or managing associated gastrointestinal complications. Some of these agents may also possess secondary CNS effects.

#### ### A. \*Salvia miltiorrhiza\* (Danshen)

\*Salvia miltiorrhiza\*, also known as Danshen, is an herb widely utilized in Traditional Chinese Medicine (TCM).<sup>8</sup> One of its key active compounds identified in relation to alcohol effects is miltirone, a type of tanshinone.<sup>61</sup>

#### \*\*Mechanism of Action for AUD:\*\*

The primary mechanism by which \*Salvia miltiorrhiza\* and its constituents are proposed to affect alcohol consumption is by reducing the absorption of alcohol from the gastrointestinal (GI) tract.<sup>8</sup> Specifically, miltirone has been shown to hamper alcohol absorption from the gut. Preclinical studies in rats demonstrated that miltirone markedly reduced blood alcohol levels when alcohol was administered intragastrically (i.g.), but not when administered intraperitoneally (i.p.), supporting a GI-localised effect.<sup>62</sup>

In addition to this peripheral action, \*Salvia miltiorrhiza\* extracts have been reported to reduce alcohol-seeking behavior in alcohol-preferring rats, an effect potentially mediated via central neurotransmitter systems, including dopaminergic, serotonergic, and adrenergic pathways.<sup>8</sup> Further complexity is added by findings that miltirone itself has been characterized as a low-affinity ligand for central benzodiazepine receptors. It has been shown to inhibit the ability of diazepam to potentiate GABA-induced chloride currents and may ameliorate symptoms associated with ethanol withdrawal by inhibiting the upregulation of GABA<sub>A</sub> receptor  $\alpha 4$  subunit mRNA in cultured hippocampal neurons.<sup>61</sup> This suggests a potential, albeit less emphasized, central nervous system component to its actions that could contribute to its effects on alcohol-related behaviors, extending beyond simple absorption blockade.

#### Efficacy Evidence:

Preclinical studies have shown that standardized extracts of *Salvia miltiorrhiza*, as well as purified miltirone, can reduce excessive alcohol drinking and relapse-like behaviors in selectively bred Sardinian alcohol-preferring (sP) rats.<sup>61</sup> Treatment with *Salvia miltiorrhiza* extract (at doses of 50, 100, and 200 mg/kg, i.g.) markedly reduced lever responding for alcohol, the amount of self-administered alcohol, and the breakpoint for alcohol in an operant self-administration paradigm in sP rats.<sup>63</sup>

Despite these promising preclinical findings, no human clinical trials evaluating *Salvia miltiorrhiza* or miltirone for the treatment of AUD were detailed in the provided information.<sup>60</sup>

#### Safety & Regulatory Status:

Danshen has a long history of use in TCM [User Query]. In preclinical studies, miltirone was found not to affect the severity of alcohol withdrawal syndrome in alcohol-dependent rats, suggesting its utility may be more for reducing consumption than for managing withdrawal.<sup>62</sup> It is advised that *Salvia miltiorrhiza* should not be used concomitantly with anticoagulant medications such as warfarin unless under the direction of a qualified healthcare practitioner, due to potential interactions affecting blood clotting.<sup>60</sup> The preclinical data strongly supports its potential in reducing alcohol intake and relapse, positioning Danshen as a candidate for limiting consumption rather than managing established dependence and withdrawal.

#### **B. *Thymus vulgaris* (Thyme)**

*Thymus vulgaris*, commonly known as thyme, is a familiar culinary herb that also has a history of use in traditional medicine for various ailments, including hangover symptoms.<sup>9</sup> Its chemical constituents include terpenoids, saponins, phenols, and cardiac glycosides [User Query].

#### Mechanism of Action for AUD:

The primary mechanism by which thyme extract has shown potential relevance to alcohol-related conditions, specifically alcohol withdrawal, is through its significant antioxidant effects. In animal models of alcohol withdrawal, thyme extract has been demonstrated to decrease markers of lipid peroxidation (such as malondialdehyde, MDA) and nitric oxide (NO) levels, while concurrently increasing the levels of reduced glutathione (GSH) and the activity of the antioxidant enzyme catalase (CAT) in both brain and liver tissues.<sup>9</sup> These antioxidant actions are believed to contribute to its neuroprotective and hepatoprotective properties during the oxidative stress associated with alcohol withdrawal. The anxiolytic and memory-enhancing effects observed during withdrawal are linked to its capacity to mitigate neurotoxicity and oxidative stress, which are often exacerbated by GABA/glutamate imbalances during this period.<sup>64</sup>

#### Efficacy Evidence:

Preclinical studies in mice have investigated the effects of an aqueous extract of *T. vulgaris* on alcohol withdrawal syndrome. In these studies, thyme extract, particularly at doses of 100 mg/kg and 200 mg/kg, exhibited anxiolytic properties, as evidenced by increased entries into

and time spent in the open arms of the elevated plus-maze.<sup>64</sup> The extract (at 200 mg/kg) also improved spatial short-term memory, indicated by an increased percentage of spontaneous alternation in the Y-maze test.<sup>64</sup> Furthermore, the administration of thyme extract was found to reduce neuronal degeneration in the brain and hepatocyte damage in the liver induced by chronic alcohol administration and subsequent withdrawal.<sup>64</sup> No human clinical trials specifically evaluating thyme for the treatment of AUD or alcohol withdrawal were detailed in the provided information. Its traditional use for hangovers<sup>9</sup> may be related to its antioxidant and hepatoprotective effects, as hangover states are partly mediated by oxidative stress and the toxic effects of alcohol metabolites like acetaldehyde. This suggests a broader potential for mitigating acute alcohol-induced damage.

#### Safety & Regulatory Status:

Thyme is widely used as a culinary herb and in traditional medicine, suggesting a general level of safety for consumption in typical amounts [User Query]. However, specific human safety data pertaining to its use at therapeutic doses for AUD treatment or alcohol withdrawal management are not detailed in the provided materials [User Query].

The current evidence positions thyme primarily as a potential agent for alleviating some symptoms of alcohol withdrawal, such as anxiety and memory impairment, largely through its robust antioxidant and neuroprotective actions.

### **C. *Gynostemma pentaphyllum* (Jiaogulan)**

*Gynostemma pentaphyllum*, often referred to as "Southern Ginseng" or Jiaogulan, is an herb used in traditional medicine, particularly in certain regions of China.<sup>65</sup> It contains a group of saponins known as gypenosides, some of which are structurally similar or identical to the ginsenosides found in *Panax ginseng*.<sup>65</sup>

#### Mechanism of Action for AUD:

*Gynostemma pentaphyllum* is recognized for its antioxidant and anti-inflammatory properties.<sup>65</sup> An ethanol extract of the plant has been noted to have potential anxiolytic effects, suggesting a role in stress reduction [User Query]. In animal models of nonalcoholic fatty liver disease (NAFLD), *G. pentaphyllum* extract has been shown to attenuate disease progression, potentially by upregulating peroxisome proliferator-activated receptor alpha (PPAR $\alpha$ ) and its downstream target genes involved in lipid metabolism, such as acyl-CoA oxidase (ACO) and carnitine palmitoyltransferase-1 (CPT-1).<sup>66</sup>

#### Efficacy Evidence:

Preclinical research has demonstrated that *G. pentaphyllum* extract can alleviate fatty degeneration and hepatic fibrosis in mouse models of NAFLD.<sup>66</sup>

Clinical studies specifically investigating *G. pentaphyllum* for AUD are reported to be limited.<sup>67</sup> One clinical trial focusing on hair health in 100 adults, where participants consumed 340 mL/day of a *G. pentaphyllum* extract for 24 weeks, incidentally found no significant differences in alcohol intake between the treatment and placebo groups.<sup>68</sup> Other limited

clinical studies have explored its potential in managing conditions such as type 2 diabetes, obesity, and NAFLD.<sup>65</sup>

The available evidence from the provided documentation does not directly support the use of *G. pentaphyllum* for reducing alcohol consumption, craving, or managing withdrawal symptoms in AUD. Its relevance appears more speculative, possibly as an adjunctive therapy for general liver health if comorbid with conditions like NAFLD, or due to its general antioxidant and anti-inflammatory effects. The presence of gypenosides similar to ginseng saponins might imply shared adaptogenic or neuroprotective properties, but this requires direct investigation in an AUD context.

#### Safety & Regulatory Status:

*Gynostemma pentaphyllum* is generally considered well-tolerated [User Query]. Potential adverse reactions that have been reported include severe nausea and an increase in bowel movements.<sup>67</sup> One source indicated that human toxicity data were not available.<sup>65</sup>

#### **D. *Monolluma quadrangula* (formerly *Caralluma quadrangula*)**

*Monolluma quadrangula* is a succulent plant that has seen traditional use for conditions such as diabetes and peptic ulcers.<sup>69</sup> Its phytochemical constituents include pregnane glycosides.<sup>71</sup>

#### Mechanism of Action for AUD/GI Protection:

A hydroalcoholic extract of *Monolluma quadrangula* demonstrated gastroprotective effects against ethanol-induced gastric mucosal injuries in rats. These protective effects were mediated by an increase in gastric pH, enhanced mucus production, increased activity of antioxidant enzymes (such as superoxide dismutase and catalase), and modulation of heat shock protein 70 (Hsp70) and Bax protein expression [User Query]. Ethanol extracts of the plant have also shown antidiabetic effects.<sup>69</sup>

#### Efficacy Evidence:

Preclinical studies have confirmed the gastroprotective activity of *M. quadrangula* extract against ethanol-induced gastric injury in rats [User Query]. Antidiabetic effects have also been observed in rat models.<sup>69</sup>

However, there are no direct studies reported in the provided materials that investigate the efficacy of *Monolluma quadrangula* in reducing alcohol consumption, cravings, or managing withdrawal symptoms associated with AUD.<sup>2</sup> The documented protective effects against ethanol-induced gastric injury could offer an indirect benefit for individuals with AUD who suffer from gastrointestinal complications such as alcohol-related gastritis or ulcers, but this does not constitute a treatment for AUD itself. The current research focus highlighted in the snippets appears to be more on its traditional uses for diabetes and related metabolic conditions (e.g., hyperuricemia, xanthine oxidase inhibition) or the cytotoxic properties of its pregnane glycosides, rather than on AUD.<sup>69</sup>

#### Safety & Regulatory Status:

*Monolluma quadrangula* is used in folk medicine.<sup>69</sup> A specific safety profile for its use in AUD treatment has not been established based on the provided information [User Query].

### **E. *Geranium schiedeanum***

*Geranium schiedeanum* is a plant species whose extracts have been investigated for their hepatoprotective properties, particularly against ethanol-induced toxicity.<sup>74</sup> The plant contains polyphenolic compounds, with tannins being notably implicated in its protective effects.<sup>74</sup> An active fraction of the extract has been found to contain ellagic acid, gallic acid, and 3-O- $\alpha$ -L arabinofuranoside-7-O- $\alpha$ -L-rhamnopyranoside of Kaempferol as majority components.<sup>77</sup>

Mechanism of Action for AUD/Hepatoprotection:

The hepatoprotective effects of *Geranium schiedeanum* against ethanol-induced liver toxicity are thought to be related to its ability to modulate oxido-reduction processes and attenuate lipid peroxidation.<sup>76</sup>

Efficacy Evidence:

Preclinical studies in rats have demonstrated significant hepatoprotective effects of *G. schiedeanum* extract in a challenging model of ethanol-induced liver toxicity combined with partial hepatectomy (PH), which impairs the liver's regenerative capacity.<sup>77</sup> In rats subjected to PH and ethanol administration (PH-EtOH group), treatment with *G. schiedeanum* extract (PH-Gs-EtOH group) resulted in:

- A marked reduction in mortality (0% in PH-Gs-EtOH vs. 33% in PH-EtOH group).<sup>77</sup>
- Improved restitution of liver mass (69.22% in PH-Gs-EtOH vs. 60.68% in PH-EtOH) and significantly higher hepatic DNA concentration (9.10 mgDNA/g liver in PH-Gs-EtOH vs. 4.80 mgDNA/g liver in PH-EtOH), indicating enhanced liver regeneration.<sup>77</sup>
- Normalization of serum liver enzymes, aspartate aminotransferase (AST) and alanine aminotransferase (ALT), which were elevated by ethanol toxicity.<sup>77</sup>
- Significant reduction in oxidative stress markers, specifically thiobarbituric acid reactive substances (TBARS), in both serum and liver tissue.<sup>77</sup>
- Amelioration of histological damage in the liver, with diminished fatty change (steatosis) and inflammation compared to the ethanol-only group.<sup>77</sup>
- Normalization of serum biochemical parameters, including glucose, cholesterol, and albumin, and a reduction in elevated bilirubin levels.<sup>77</sup>

These findings suggest a robust protective and regeneration-supportive activity against severe alcohol-induced liver stress. However, no direct studies investigating the effect of *Geranium schiedeanum* on reducing alcohol consumption or craving in the context of AUD were found in the provided materials [User Query]. Its benefits are clearly in the realm of managing alcohol-associated liver disease (ALD), a common and serious complication of AUD, rather than treating the core behavioral aspects of

the disorder itself.

#### Safety & Regulatory Status:

*Geranium schiedeanum* has traditional uses as an antiseptic and antipyretic [User Query]. An acetone-water extract of the plant was found to be non-toxic in acute oral toxicity studies in rats, with an LD<sub>50</sub> value greater than 5000 mg/kg.<sup>75</sup> Specific safety data for its use in AUD treatment were not detailed [User Query].

#### **F. *Aegle marmelos* (Bael)**

*Aegle marmelos*, commonly known as Bael, is a fruit-bearing tree with extensive traditional use in Indian systems of medicine, such as Ayurveda.<sup>81</sup> The plant is rich in a variety of bioactive compounds, including alkaloids (such as aegeline, marmesin, skimmianine), tannins, coumarins, and terpenoids, distributed across its fruit, leaves, bark, and roots.<sup>81</sup>

#### Mechanism of Action for AUD/Related Effects:

*Aegle marmelos* exhibits a range of pharmacological properties, including antioxidant, anti-inflammatory, hepatoprotective, and antidiabetic activities.<sup>81</sup> Relevant to potential AUD applications, an ethanolic leaf extract of *A. marmelos* has shown antidepressant-like activity in mice, with a suggested involvement of the GABAergic system [User Query]. Its hepatoprotective actions are attributed to its antioxidant compounds, which can neutralize free radicals and protect the liver from oxidative stress, and its anti-inflammatory compounds (alkaloids, coumarins) that modulate inflammatory responses.<sup>81</sup>

#### Efficacy Evidence:

Preclinical studies have provided some evidence for its protective effects in alcohol-related damage. The leaves of the Bael tree have been shown to exert liver-protecting effects in rat models of alcohol-induced liver damage.<sup>81</sup> As mentioned, its ethanolic leaf extract demonstrated antidepressant-like activity in mice [User Query].

Despite these potentially relevant preclinical findings (hepatoprotection and CNS effects), the provided materials did not contain direct studies investigating the efficacy of *Aegle marmelos* in reducing alcohol consumption or cravings in the context of AUD.<sup>83</sup> The combination of liver protection and potential CNS modulatory effects (anxiolytic/antidepressant via GABA) could theoretically be beneficial for individuals with AUD, who often suffer from both liver complications and mood disturbances. However, this specific dual potential does not appear to have been directly investigated for core AUD symptoms based on the available information.

#### Safety & Regulatory Status:

*Aegle marmelos* is widely used in traditional Indian medicine, suggesting a long history of human exposure.<sup>81</sup> However, potential adverse effects and interactions should be considered. These may include allergic reactions, gastrointestinal upset (bloating, gas, constipation), effects on blood sugar control (relevant for diabetics), and interactions with medications for

blood pressure and blood clotting.<sup>81</sup> Specific safety considerations for its use in AUD treatment were not detailed [User Query].

### **G. *Aralia elata***

*Aralia elata*, also known as Japanese Angelica Tree, is an herb with traditional applications related to alcohol intoxication, often as a component of Chinese herbal formulas designed to prevent or mitigate such effects.<sup>8</sup> Bioactive compounds include triterpenoid saponins, notably elatosides A and B, which have been identified as potent inhibitors of ethanol absorption.<sup>88</sup> An ethyl acetate fraction (AEEF) of *A. elata* has also been studied for its neuroprotective effects and contains a variety of compounds.<sup>89</sup>

Mechanism of Action for AUD:

*Aralia elata* appears to exert effects relevant to alcohol use through at least two distinct mechanisms:

1. **Inhibition of Alcohol Absorption:** Extracts of *A. elata*, and specifically its saponins elatosides A and B, are potent inhibitors of alcohol absorption from the gastrointestinal tract.<sup>8</sup> This action would reduce peak blood alcohol concentrations and overall systemic exposure to ingested alcohol. Sesquiterpenes with an  $\alpha$ -methylene- $\gamma$ -butyrolactone moiety, also found in related species or potentially in *Aralia*, have similarly been shown to selectively inhibit ethanol absorption.<sup>88</sup>
2. **Neuroprotection against Chronic Alcohol Exposure:** An ethyl acetate fraction from *Aralia elata* (AEEF) has demonstrated neuroprotective effects against ethanol-induced neurodegeneration in preclinical models. AEEF reduced ethanol-induced cytotoxicity and oxidative stress in neuronal cell cultures (MC-IXC cells). In mice chronically exposed to alcohol, AEEF treatment improved learning, memory ability, and spatial cognition; ameliorated oxidative stress biomarkers in brain tissue (SOD, MDA); increased acetylcholine (ACh) levels and decreased acetylcholinesterase (AChE) activity (indicative of improved cholinergic function); and prevented alcohol-induced neuronal apoptosis by improving mitochondrial activity and modulating apoptotic signaling pathways (including p-JNK, p-Akt, BAX, and p-Tau).<sup>89</sup>

Efficacy Evidence:

The evidence for *Aralia elata*'s effects in the context of alcohol is primarily from preclinical animal studies. Its traditional use as a component of herbal formulas to prevent or mitigate alcohol intoxication aligns with the findings on absorption inhibition.<sup>8</sup> The neuroprotective effects against chronic alcohol exposure have been demonstrated in cell culture and mouse models.<sup>89</sup>

No human clinical trials specifically evaluating *Aralia elata* for AUD treatment (i.e., reducing

consumption, craving, or managing withdrawal) were detailed in the provided materials.<sup>8</sup> The dual potential of *Aralia elata*—reducing acute alcohol absorption and offering neuroprotection against chronic alcohol-induced damage—makes it an interesting candidate. These distinct effects appear to be mediated by different components or fractions of the plant (elatosides for absorption inhibition, AEEF for neuroprotection), underscoring the importance of phytochemical characterization for targeted therapeutic development.

#### Safety & Regulatory Status:

The safety of *Aralia elata* is largely inferred from its traditional use [User Query]. Specific safety data pertaining to its use in AUD treatment were not provided in the available documentation [User Query].

### **H. *Acanthopanax sessiliflorus* (syn. *Eleutherococcus sessiliflorus*)**

*Acanthopanax sessiliflorus* (also known as *Eleutherococcus sessiliflorus*) is a medicinal plant utilized in traditional practices, particularly in East Asia.<sup>92</sup> Its bioactive constituents include triterpenoids, phenylpropanoids, flavonoids (such as rutin and kaempferol glycosides), and lignans like scoparone [User Query]. Eleutherosides, particularly eleutheroside B (syringin) and eleutheroside E (acanthoside D), are considered key functional substances.<sup>94</sup>

#### Mechanism of Action for AUD/Related Effects:

*Acanthopanax sessiliflorus* is reported to possess a range of potential biological activities, including antioxidant, anti-aging, antiplatelet aggregation, and antitumor properties [User Query]. It may also improve glucose metabolism and exert beneficial effects on the cardiovascular and immune systems [User Query]. An ethanolic extract of *A. sessiliflorus* fruits (ASE) has demonstrated prebiotic potential by promoting the growth of probiotic strains, and its fermented byproduct (ASE-LHF, fermented with *L. helveticus*) exhibited immune enhancement activity in macrophage and microglial cell lines, mediated by the activation of NF- $\kappa$ B and ERK MAPK signaling pathways.<sup>92</sup>

Of particular relevance to addictive disorders, a 70% ethanol extract of *Acanthopanax koreanum* (AK extract, a related species often discussed alongside *A. sessiliflorus* or used interchangeably in some contexts, though species specificity is important) and its components, including eleutheroside B (EB) and chlorogenic acid (CGA), were found to ameliorate nicotine dependence and withdrawal symptoms in mice.<sup>95</sup> This effect was associated with the normalization of dopamine concentrations and the expression levels of nicotine acetylcholine receptor  $\alpha 7$ , as well as DRD1 (dopamine receptor D1), ERK, and CREB in the brain.<sup>95</sup>

#### Efficacy Evidence:

The most directly relevant efficacy data from the provided snippets pertains to nicotine dependence, not alcohol use disorder. The study on AK extract showed that it and its components effectively mitigated nicotine-induced conditioned place preference and withdrawal symptoms in mice, suggesting a modulatory effect on dopaminergic reward

pathways.<sup>95</sup>

No direct studies on the efficacy of *Acanthopanax sessiliflorus* in reducing alcohol consumption, craving, or managing alcohol withdrawal symptoms in either preclinical alcohol models or human clinical trials for AUD were found in the provided materials.<sup>92</sup>

While the findings in nicotine dependence models are intriguing due to shared neurobiological substrates with alcohol addiction (e.g., dopamine system involvement), these results cannot be directly extrapolated to AUD without specific investigation. The traditional uses and general health benefits (antioxidant, immune-modulating) are noted, but their specific application to AUD is not established by this evidence.

#### Safety & Regulatory Status:

The safety of *Acanthopanax sessiliflorus* is primarily inferred from its traditional use [User Query]. Specific safety data for its application in AUD treatment were not detailed in the provided documentation [User Query].

### **I. *Sorghum bicolor* (Sorghum)**

*Sorghum bicolor* is a globally significant cereal crop, valued for its grain, which is used for human food, animal feed, and ethanol production.<sup>97</sup> It is also used in the brewing of traditional alcoholic beverages and the production of syrup.<sup>98</sup>

#### Natural Sources & Key Active Compounds:

Sorghum grains are rich in phenolic compounds, including phenolic acids (e.g., ferulic acid, p-coumaric acid), flavonoids (e.g., flavones, flavanones, 3-deoxyanthocyanidins like luteolinidin and apigeninidin, which are unique to sorghum), and condensed tannins (proanthocyanidins, particularly in pigmented varieties).<sup>99</sup> Some of these phytochemicals, such as ferulic acid and p-coumaric acid, are predicted to be capable of permeating the blood-brain barrier [User Query]. Red sorghum varieties generally contain significantly greater amounts of these secondary metabolites compared to white varieties.<sup>100</sup>

#### Mechanism of Action Related to Alcohol:

*Sorghum bicolor* possesses antioxidant and anti-inflammatory properties, largely attributed to its rich phenolic content.<sup>99</sup> Extracts from sorghum have been shown to offer protective effects against alcohol-induced hepatocyte damage in vitro [User Query]. The condensed tannins, in particular, are potent antioxidants due to their electron-donating properties and ability to chelate metal ions and proteins, which can also influence enzyme activities and nutrient absorption.<sup>100</sup>

#### Efficacy Evidence:

The primary context in which *Sorghum bicolor* and alcohol are discussed in the provided materials is its use as a raw material for producing alcoholic beverages (e.g., Chinese liquor like Moutai, Wuliangye).<sup>97</sup> Studies have investigated how different sorghum varieties and their physicochemical properties (e.g., waxy vs. non-waxy, starch content) and associated microbial diversity during fermentation influence the flavor profile and quality of the resulting

liquor.<sup>97</sup>

However, there are no direct studies presented in the provided documentation that assess the efficacy of *Sorghum bicolor* or its extracts in reducing voluntary alcohol consumption, craving, or withdrawal symptoms as a treatment for AUD.<sup>99</sup> Its relevance in the context of AUD from a therapeutic perspective (rather than as a substrate for alcohol production) would likely stem from its antioxidant and hepatoprotective phytochemicals, which could theoretically mitigate some of the alcohol-induced oxidative stress and liver damage. However, this is speculative and not supported by direct intervention studies for AUD in the materials.

#### Safety & Regulatory Status:

As a major food crop, *Sorghum bicolor* is generally considered safe for consumption [User Query].

#### **J. Milk Thistle (*Silybum marianum*)**

Milk thistle is an herbal remedy widely recognized for its purported hepatoprotective (liver-protective) properties.<sup>6</sup> Its primary active constituent is silymarin, which is a complex of flavonolignans, with silybin (or silibinin) being the most biologically active component.<sup>6</sup>

#### Mechanism of Action for AUD/Liver Protection:

Silymarin, and specifically silybin, is believed to exert its hepatoprotective effects through several mechanisms. It promotes liver cell repair and regeneration, protects liver cells from damage caused by toxins (including those derived from alcohol metabolism), and possesses antioxidant and anti-inflammatory properties.<sup>6</sup> It may stabilize hepatocyte membranes, act as a free radical scavenger, and exhibit antifibrotic activity.<sup>6</sup> These actions are thought to help counteract the pathological processes involved in alcoholic liver disease (ALD). However, silymarin has poor water solubility and bioavailability, which can limit its clinical efficacy.<sup>6</sup>

#### Efficacy Evidence:

Despite its widespread use and plausible mechanisms, the clinical evidence for milk thistle's effectiveness, even specifically for liver protection in the context of alcohol abuse, remains inconclusive and somewhat controversial.

Numerous clinical trials have investigated milk thistle for alcoholic liver disease and viral hepatitis, but systematic reviews have often yielded mixed results. A 2007 Cochrane systematic review of 13 RCTs (915 patients) assessing milk thistle for alcoholic and/or hepatitis B or C virus liver diseases concluded that it could not demonstrate significant effects of milk thistle on overall mortality or complications of liver diseases when combining all trials or focusing on high-quality trials.<sup>103</sup> While some low-quality trials suggested beneficial effects, particularly on liver-related mortality, these were not confirmed in higher-quality studies.<sup>103</sup> The authors of this Cochrane review questioned the beneficial effects and highlighted the lack of

high-quality evidence, calling for more adequately conducted and reported RCTs.<sup>103</sup>

A more recent 2022 systematic review (referenced in the User Query but not provided as a snippet) focused on liver outcomes and mortality in ALD and reportedly found no significant effects. Another meta-analysis, focusing on silibinin capsules for ALD (PROSPERO CRD42024509676, including RCTs up to December 2023), concluded that silibinin capsules showed clinical efficacy and safety as an adjuvant therapy to alleviate ALD, though the underlying mechanisms were still considered unclear.<sup>6</sup> This suggests ongoing research and potentially differing conclusions based on the specific preparations (e.g., silibinin vs. whole silymarin) and patient populations studied.

Importantly, there is no strong indication from the provided materials that milk thistle directly modulates brain neurochemistry in a way that would reduce alcohol craving or consumption signals related to AUD itself [User Query]. Its role is primarily investigated for liver health.

#### Safety & Regulatory Status:

Milk thistle is generally considered safe for most people, with few reported side effects.<sup>102</sup> Mild gastrointestinal disturbances, such as laxative effects or upset stomach, may occur [User Query]. It can potentially interact with medications that are metabolized by the liver, and caution is advised [User Query]. Given the severity of liver disease, its use should be under medical supervision.<sup>102</sup>

#### **K. Prickly Pear Cactus (*Opuntia ficus indica*)**

Prickly Pear Cactus, scientifically known as *Opuntia ficus indica* (also referred to as nopal), has been investigated for its potential to alleviate symptoms of alcohol hangover.<sup>104</sup>

#### Mechanism of Action for Hangover/Inflammation:

The proposed mechanism for its effects on alcohol hangover involves the reduction of the inflammatory response to alcohol consumption [User Query]. Alcohol intake can induce an inflammatory cascade, and an extract of the *Opuntia ficus indica* (OFI) plant is thought to diminish this inflammatory response. This was evidenced in one study by significantly lower levels of C-reactive protein (CRP), a marker of inflammation, in participants who took OFI extract before alcohol consumption compared to placebo.<sup>104</sup>

#### Efficacy Evidence:

An older double-blind, placebo-controlled, crossover trial published in 2004 (Wiese et al.) investigated the effect of an OFI extract (1600 IU, Tex-OE™) given 5 hours before alcohol consumption (up to 1.75 g/kg) on hangover symptoms in 64 healthy young adults (55 completed both arms).<sup>104</sup>

The study found that the OFI extract did not significantly reduce the overall hangover symptom index score ( $P=.07$ ) compared to placebo. However, it did significantly reduce the

risk of experiencing a severe hangover (defined as a total symptom score  $\geq 18$  points) by approximately half (Odds Ratio 0.38).<sup>104</sup> Three specific hangover symptoms—nausea, dry mouth, and anorexia (loss of appetite)—were significantly reduced by the OFI extract.<sup>104</sup> Symptoms like headache, soreness, weakness, shakiness, diarrhea, and dizziness were not significantly different from placebo.<sup>105</sup>

The study also found that C-reactive protein levels were strongly associated with hangover severity, and CRP levels were 40% higher the morning after alcohol consumption when subjects had taken placebo compared to when they had taken the OFI extract.<sup>104</sup> This supports the hypothesis that inflammation plays a significant role in alcohol hangover symptoms.

The provided documentation from the 2014-2025 period does not suggest any direct evidence or studies indicating that Prickly Pear Cactus reduces alcohol urge, craving, or binge drinking behavior associated with AUD, beyond its potential effects on hangover symptoms.<sup>104</sup> Its application appears limited to mitigating some aspects of the post-intoxication state. No further research corroborating the initial 2004 study's findings on hangover was noted in one review.<sup>105</sup>

#### Safety & Regulatory Status:

Specific safety details for Prickly Pear Cactus extract in the context of AUD or hangover treatment were not extensively detailed in the User Query. However, it was noted that prickly pear cactus may lower blood glucose and should be used with caution in patients with diabetes.<sup>105</sup> Hangover products containing prickly pear extract recommend dosing before alcohol consumption.<sup>105</sup>

## **IV. Natural Ingredients with Limited or No Direct Evidence for AUD from Provided Material**

This section briefly addresses ingredients listed in the initial query for which the provided documentation offered minimal or no direct evidence pertaining to efficacy in core AUD symptoms such as reducing alcohol consumption, craving, or managing withdrawal, even if mentioned for other related conditions.

### **A. *Cannabis indica***

*Cannabis indica* was mentioned in the provided information as a potentially promising natural product for delirium tremens (DTs), a severe and potentially life-threatening form of alcohol withdrawal.<sup>8</sup> One source cited case reports from the mid-19th century suggesting that *Cannabis indica*, when administered orally in sequential doses, provided rapid relief from symptoms of DTs.<sup>8</sup> Another source, describing homeopathic uses, lists *Cannabis indica* for conditions including delirium tremens, among others like delusions and convulsions, attributing to it a "great soothing influence in many nervous disorders".<sup>107</sup>

However, the provided snippets did not detail modern scientific evidence, clinical research, specific mechanisms of action for this indication, or contemporary safety concerns related to the use of *Cannabis indica* for treating DTs or other severe alcohol withdrawal symptoms.<sup>8</sup> Standard medical management for DTs typically involves benzodiazepines and supportive care in a hospital setting to manage agitation, prevent seizures, and address physiological instability.<sup>109</sup> The psychoactive nature of cannabis and the variability in its constituents would present significant challenges for its use in such a critical condition without rigorous study.

## V. Synthesis and Concluding Remarks

This review has synthesized information from provided documentation on a range of natural ingredients investigated for their potential effects on Alcohol Use Disorder (AUD) or related conditions such as alcohol withdrawal and alcohol-associated liver disease. The evidence base is highly heterogeneous, spanning traditional uses, preclinical animal and in vitro studies, and a limited number of human clinical trials.

Several ingredients demonstrate promise through specific mechanisms and preliminary efficacy data:

- **Dihydromyricetin (DHM)** shows consistent preclinical efficacy in reducing alcohol consumption, intoxication, and withdrawal symptoms, primarily via GABA<sub>A</sub> receptor modulation. *A planned Phase 1 clinical trial for alcohol-associated liver disease will provide crucial human safety and pharmacokinetic data, though its poor bioavailability remains a hurdle. The contradictory evidence regarding its impact on alcohol metabolism warrants further clarification.* \* **Kudzu Root** and its isoflavones (daidzin, puerarin) have a long history of traditional use and a body of preclinical and clinical evidence suggesting they can reduce alcohol consumption and, according to a Cochrane review, potentially alcohol cravings. The mechanism involving central ALDH-2 inhibition by daidzin (affecting biogenic amine metabolism rather than systemic acetaldehyde) and puerarin's alteration of drinking topography are notable. However, inconsistent results in human studies and concerns about standardization and potential acetaldehyde accumulation with Kudzu root (versus flower) highlight the need for more rigorous, well-characterized research. \* **Psilocybin**, in conjunction with psychotherapy (PAT), has emerged as a promising intervention, with Phase 2 clinical trial data indicating rapid and enduring reductions in drinking behavior and craving. Its mechanism likely involves serotonin 5-HT<sub>2A</sub> receptor agonism, enhanced neuroplasticity, and significant modulation of personality traits (e.g., reduced neuroticism and

impulsiveness, increased openness), which correlate with improved drinking outcomes. The necessity of integrated psychotherapeutic support is a key feature of this treatment modality.

- **Ashwagandha** and **Passionflower** show potential primarily for managing anxiety and stress, which can be components of alcohol withdrawal or comorbid conditions contributing to relapse. Ashwagandha has preclinical support for alleviating multiple alcohol withdrawal symptoms via GABAergic and stress-modulating actions. Passionflower, also acting on GABA systems, has human data supporting its anxiolytic and sedative effects. For both, direct evidence for reducing core alcohol consumption or craving in AUD patients is limited.
- **Ginseng** (*Panax ginseng*), particularly Korean Red Ginseng, demonstrates preclinical efficacy in attenuating anxiety-like behavior during ethanol withdrawal by modulating the mesoamygdaloid dopamine system. This points to a specific application in managing withdrawal-related negative affect.

Several other substances show primary relevance to mitigating alcohol-induced organ damage or affecting alcohol absorption, rather than directly treating core AUD neurobiology:

- *Salvia miltiorrhiza* (**Danshen**) reduces alcohol absorption from the GI tract and shows preclinical efficacy in reducing alcohol intake, with miltirone also exhibiting some central GABAergic activity.
- **Aralia elata** presents a dual benefit in preclinical models: inhibition of alcohol absorption and neuroprotection against chronic alcohol-induced damage.
- **Geranium schiedeanum** exhibits potent hepatoprotective effects against severe ethanol toxicity in animal models of liver regeneration.
- **Milk Thistle** (*Silybum marianum*) is widely used for liver health, but systematic reviews on its efficacy for alcoholic liver disease have yielded inconclusive results, with a need for higher-quality trials.
- **Thyme** (*Thymus vulgaris*), **Gynostemma pentaphyllum**, **Monolluma quadrangula**, and **Aegle marmelos** show antioxidant, anti-inflammatory, or gastroprotective/hepatoprotective effects in preclinical or limited clinical settings, suggesting adjunctive roles in managing alcohol-related physical complications.

Conversely, some substances carry significant safety concerns that likely outweigh their potential benefits for AUD:

- *Peganum harmala* (**Syrian Rue**), a potent MAO-A inhibitor, has substantial risks of food and drug interactions and inherent toxicity.
- **St. John's Wort** (*Hypericum perforatum*), also an MAOI and a potent CYP3A4

inducer, has significant interaction risks with alcohol and numerous medications.

- ***Salvia divinorum***, a potent KOR agonist with strong hallucinogenic effects, lacks efficacy evidence for AUD and has abuse potential.

The investigation of **serotonin and dopamine precursors** (tryptophan, tyrosine) for AUD is complex; acute tyrosine *depletion* has paradoxically been shown to reduce alcohol intake in some studies, while tryptophan supplementation may play a supportive role in mood during recovery. Direct clinical trial evidence for precursor *supplementation* as an AUD treatment is lacking in the provided materials.

Overarching Challenges and Future Directions:

The exploration of natural ingredients for AUD faces several common challenges:

1. **Methodological Rigor:** Many studies, particularly older human trials, are small, lack adequate controls, or have unclear methodology. Larger, well-designed, placebo-controlled RCTs are essential.
2. **Standardization and Bioavailability:** Herbal products suffer from variability in active compound concentrations. Standardization of extracts and addressing issues of poor bioavailability (as seen with DHM and curcumin) are critical for consistent and effective therapeutic development.
3. **Mechanism of Action:** While many substances have multiple proposed mechanisms, pinpointing the primary drivers of therapeutic effects in AUD is often complex and requires further elucidation. Understanding whether effects are central, peripheral, or both is key.
4. **Safety and Interactions:** Thorough safety evaluation, including long-term use and potential interactions with alcohol and commonly prescribed medications, is paramount, especially for substances with MAOI properties or those affecting CYP enzymes.
5. **Translational Gap:** Promising preclinical findings often do not translate directly to human efficacy. Bridging this gap requires careful dose selection, appropriate patient populations, and relevant outcome measures in clinical trials.

Future research should focus on the most promising candidates, employing rigorous clinical trial methodologies. Investigating combinations of natural products or their use as adjuncts to existing AUD treatments may also yield valuable outcomes. A deeper understanding of the specific phytochemicals responsible for observed effects and their precise molecular targets will facilitate the development of more targeted and effective natural product-based therapies for Alcohol Use Disorder. The traditional knowledge that often guides the initial selection of these substances should be integrated with modern scientific validation to unlock their full therapeutic

potential in a safe and evidence-based manner.

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