Navigating the Therapeutic Landscape of Alcohol Use Disorder: From Traditional Botanicals to Novel Biochemical Targets

1. Introduction: The Quest for Effective Interventions in Alcohol Use Disorder (AUD)

Alcohol Use Disorder (AUD) is a chronic relapsing brain disorder characterized by an impaired ability to stop or control alcohol use despite adverse social, occupational, or health consequences.[1] This condition imposes a significant public health burden and substantial socioeconomic costs globally. In the United States alone, AUD affects millions of individuals, with estimates around 28.3 million people.[2] The complexity of AUD, stemming from a multifactorial pathophysiology involving genetic predispositions, neurobiological adaptations, psychological factors, and socio-environmental influences, presents considerable challenges for effective treatment.[3]

Current FDA-approved pharmacotherapies for AUD, namely naltrexone, acamprosate, and disulfiram, form the cornerstone of medical management.[1] While these medications offer benefits, their efficacy can be modest for certain individuals, and issues related to side effects and patient adherence can limit their overall impact.[3] This underscores an ongoing and urgent need for a broader array of therapeutic options that can cater to the diverse presentations and underlying mechanisms of AUD.

This report aims to provide a comprehensive exploration of established, lesser-known (particularly herbal), and novel interventions designed to reduce alcohol consumption, alleviate cravings, and manage withdrawal symptoms. A central focus will be on delineating the mechanisms of action, evaluating the efficacy based on available scientific evidence, and assessing the safety profiles of these interventions. There is a burgeoning interest in natural products and traditional systems of medicine, such as Traditional Chinese Medicine (TCM) and Ayurveda, as potential sources for novel therapeutic agents for AUD.[6] The multifactorial nature of AUD, characterized by complex dysregulation across multiple neurotransmitter systems including GABA, glutamate, dopamine, serotonin, opioids, and the endocannabinoid system [3], suggests that a multifaceted therapeutic approach is likely to be more effective than any single intervention. Consequently, the exploration of diverse therapeutic modalities, including those derived from traditional knowledge and those targeting novel biochemical pathways, holds significant promise for advancing the treatment of AUD.

This investigation also acknowledges a notable translational gap: while many herbal remedies and novel compounds show promise in preclinical studies, robust human clinical trial evidence is often lacking, a critical consideration in evaluating their true therapeutic potential.[8]

2. Herbal Interventions for Reducing Alcohol Consumption and Cravings: A Focus on Lesser-Known Botanicals

The search for effective AUD treatments has increasingly turned towards traditional herbal medicines, many of which have a long history of use for alcohol-related problems. This section focuses on several botanicals, prioritizing lesser-known herbs where scientific investigation, even if limited to single studies, suggests potential utility.

2.1. *Hovenia dulcis* (Japanese Raisin Tree) and *Ampelopsis grossedentata* (Vine Tea) - Dihydromyricetin (DHM)

Hovenia dulcis and *Ampelopsis grossedentata* are two botanicals that have garnered attention for their active compound, dihydromyricetin (DHM), and its effects on alcohol metabolism and intoxication.

Mechanism of Action:
Hovenia dulcis is primarily recognized for its hepatoprotective effects against alcoholic liver injury.5 Its extracts contain various bioactive compounds, including DHM, quercetin, and beta-sitosterol, which contribute to these effects via multiple pathways. These pathways encompass the enhancement of ethanol metabolism, modulation of the immune response, anti-oxidative stress mechanisms, and regulation of autophagy.5 A key action of DHM is the enhancement of alcohol metabolism by increasing the activity of alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) enzymes. This leads to a more rapid conversion of ethanol to acetaldehyde and subsequently to acetate, thereby reducing the accumulation of toxic acetaldehyde.5 Naringenin, another constituent found in Hovenia dulcis, aids in re-establishing the NADH/NAD ratio, which is often disrupted by ethanol metabolism.5
Beyond its metabolic effects, DHM has been shown to directly counteract acute alcohol intoxication and withdrawal signs, such as tolerance, increased anxiety, and seizure susceptibility. This is achieved through its modulation of GABAA receptors (GABAARs). DHM antagonizes ethanol-induced potentiation of GABAARs and reverses the neuroadaptations in these receptors caused by chronic ethanol exposure and withdrawal, including the upregulation of the GABAARα4 subunit. Evidence suggests that this interaction involves the benzodiazepine (BZ) binding sites on GABAARs.[10]
Ampelopsis grossedentata, also rich in DHM, has been shown to ameliorate chronic alcohol-induced hepatic steatosis, oxidative stress, and inflammation, potentially

through the YTHDF2/PGC-1α/SIRT3 signaling axis.[11]

Efficacy:
Preclinical studies have demonstrated that DHM reduces alcohol consumption in animal models.10 Furthermore, it has shown efficacy in mitigating alcohol-associated liver damage. Extracts of vine tea (Ampelopsis grossedentata) alleviate hepatic lipid accumulation, oxidative stress, and inflammation induced by chronic ethanol exposure.11 DHM itself has been found to reduce ethanol-induced liver steatosis and triglyceride accumulation and improve mitochondrial health in animal models.12
Safety:
Both Hovenia dulcis and Ampelopsis grossedentata have a history of use in traditional Chinese medicine and are consumed as herbal teas, suggesting a degree of safety.11 A Phase 1 clinical trial is planned to formally assess the safety, pharmacokinetics, and maximum tolerated dose of a purified form of DHM in healthy volunteers, with a view to its potential use in alcohol-associated liver disease.14 While DHM is available as a dietary supplement in the United States, the lack of FDA regulation over such products raises concerns about quality control and standardization.14

2.2. *Pueraria lobata* (Kudzu) - Puerarin, Daidzin

Kudzu root (*Radix puerariae*) has been a staple in Chinese medicine for nearly two millennia for addressing alcohol-related issues.[6] Its primary active isoflavones, puerarin and daidzin, are subjects of modern research.

Mechanism of Action:
Puerarin, an isoflavone from Kudzu, has been shown in human studies to reduce alcohol intake by altering drinking topography. Individuals treated with puerarin tended to decrease their sip size, take more sips to finish a beer, and take longer to consume each beer. Additionally, the latency to opening the next beer was increased.15 The precise central mechanism for these behavioral modifications is not fully elucidated but likely involves modulation of alcohol's reward or satiety signals.
Daidzin, another key isoflavone, selectively suppresses ethanol intake in various rodent models.[17] Its principal mechanism of action is the potent and selective inhibition of mitochondrial aldehyde dehydrogenase (ALDH-2).[17] This inhibition is distinct from the action of disulfiram; instead of causing a systemic buildup of acetaldehyde, daidzin's ALDH-2 inhibition leads to the accumulation of biogenic aldehydes derived from serotonin (5-hydroxyindole-3-acetaldehyde, 5-HIAL) and dopamine (3,4-dihydroxyphenylacetaldehyde, DOPAL) metabolism within specific brain regions. These accumulated biogenic aldehydes are thought to mediate the antidipsotropic (anti-drinking) effect.[17] Importantly, daidzin does not appear to function as a general ethanol-sensitizing agent by causing widespread acetaldehyde toxicity.[17]

Efficacy:
Animal studies suggest that Kudzu extract significantly reduces alcohol craving.6 A placebo-controlled human study found that individuals who had an opportunity to binge drink significantly reduced their alcohol consumption after taking 2 grams of a standardized Kudzu extract approximately 2.5 hours before drinking.6 In a pilot study involving heavy drinkers, puerarin administered at 1200 mg daily for one week led to a reduction in average beer consumption from 3.5 to 2.4 beers per 1.5-hour session.15 Other research indicates that Kudzu extract can reduce the number of drinks consumed per week by a third to a half in heavy drinkers not undergoing formal treatment, decrease the number of heavy drinking days, and increase the number of abstinent days.19 Synthetic versions of daidzin are also being explored, with the hypothesis that they reduce alcohol cravings by preventing alcohol from elevating dopamine levels in the brain.20
Safety:
Kudzu has a long history of use in TCM.6 One human study reported no side effects from Kudzu extract.20 However, general side effects sometimes associated with Kudzu supplementation include upset stomach, dry mouth, and dizziness.21 As with many herbal supplements, the quality and standardization of unregulated Kudzu products can be a concern.22

2.3. *Salvia miltiorrhiza* (Danshen)

Salvia miltiorrhiza, also known as Danshen, is a widely utilized herb in Chinese medicine with emerging evidence for its effects on alcohol consumption.

Mechanism of Action:
One proposed mechanism is the reduction of alcohol absorption from the gastrointestinal tract.6 The active compound miltirone, a tanshinone found in Salvia miltiorrhiza, has been demonstrated in animal studies to hamper alcohol absorption from the gut when alcohol is administered intragastrically, but not when given intraperitoneally. This suggests a peripheral effect on absorption rather than systemic metabolic alteration.8 Additionally, Salvia miltiorrhiza extracts have been shown to reduce alcohol-seeking behavior in rats, potentially through actions on central neurotransmitter systems, including dopaminergic, serotonergic, and adrenergic pathways.6
Efficacy:
Standardized extracts of Salvia miltiorrhiza have been shown to selectively reduce excessive alcohol drinking and relapse-like drinking behaviors in Sardinian alcohol-preferring (sP) rats, a well-established animal model of genetic predisposition to high alcohol consumption.8 In operant self-administration paradigms, treatment with Salvia miltiorrhiza extract (at doses of 50, 100, and 200 mg/kg, administered intragastrically) markedly decreased lever responding for alcohol, the total amount of alcohol self-administered, and the breakpoint for alcohol (a measure of motivation) in sP rats. These effects were selective for alcohol, as the extract did not alter sucrose self-administration.8 Further studies have indicated that the miltirone content within Salvia miltiorrhiza extracts positively correlates with their efficacy in reducing alcohol intake. Pure miltirone itself (at 2.5-10 mg/kg, i.g.) reduced alcohol intake in

alcohol-experienced rats and delayed the acquisition of alcohol drinking behavior in alcohol-naive rats.23

Safety:

Salvia miltiorrhiza has a long history of use in Chinese medicine.6 Preclinical studies suggest a degree of selectivity in its anti-alcohol effects. However, comprehensive human safety data specifically for AUD treatment are not detailed in the available information. It is noteworthy that miltirone did not affect the severity of alcohol withdrawal syndrome in alcohol-dependent rats, suggesting it may not be useful for managing withdrawal but could be targeted more at reducing consumption.23

2.4. *Thymus vulgaris* (Thyme)

Thymus vulgaris, commonly known as Thyme, is traditionally used for various ailments and has recently been investigated for its potential benefits in the context of alcohol withdrawal.

Mechanism of Action:

Thymus vulgaris extract has demonstrated significant antioxidant effects in animal models of alcohol withdrawal. It has been shown to decrease levels of malondialdehyde (MDA), a marker of lipid peroxidation, and nitric oxide (NO), while increasing levels of reduced glutathione (GSH) and catalase (CAT) activity in both the brain and liver of mice undergoing alcohol withdrawal.24 These antioxidant actions contribute to its neuroprotective and hepatoprotective properties. Histopathological studies have shown that thyme extract reduces neuronal degeneration in the hippocampus (specifically in the CA1, CA2, CA3, and dentate gyrus regions) and mitigates hepatocyte damage induced by chronic alcohol administration in mice.24 The anxiolytic and memory-enhancing effects observed during alcohol withdrawal are likely linked to the mitigation of neurotoxicity and oxidative stress, which are exacerbated by the GABA/glutamate imbalance characteristic of withdrawal states.24

Efficacy (in mice during alcohol withdrawal):

In preclinical studies, Thymus vulgaris extract exhibited anxiolytic properties. At doses of 100 and 200 mg/kg, it significantly increased the number of entries and the time spent in the open arms of the Elevated Plus Maze (EPM), a standard test for anxiety-like behavior in rodents.24 In the Open Field Test, the extract reduced rearing behavior and increased crossings, further supporting an anxiolytic effect.24 For memory enhancement, the extract (at 200 mg/kg) significantly increased the percentage of spontaneous alternation in the Y-maze, indicating improved spatial short-term memory in mice during alcohol withdrawal.24

Safety:

Thyme is widely used as a culinary herb and in traditional medicine, including for relieving hangover symptoms.24 The preclinical study in mice indicates protective effects during alcohol withdrawal. However, human safety data pertaining to its use for AUD treatment or alcohol withdrawal management are not available in the provided documents. Phytochemical screening of Thymus vulgaris has identified various secondary metabolites, including terpenoids, saponins, phenols, and cardiac glycosides, which may contribute to its

pharmacological activities.26

2.5. *Peganum harmala* (Syrian Rue)

Peganum harmala, or Syrian Rue, is a plant known for its psychoactive β-carboline alkaloids, including harmine, harmaline, harmalol, and harmane.

Mechanism of Action:
The primary mechanism of action of these β-carboline alkaloids is the potent and reversible inhibition of monoamine oxidase A (MAO-A).27 MAO-A is a key enzyme in the metabolism of monoamine neurotransmitters such as serotonin and norepinephrine; its inhibition leads to increased synaptic availability of these neurotransmitters. Beyond MAO-A inhibition, harmala alkaloids interact with multiple neurotransmitter systems, including serotonin 5-HT2 receptors, dopamine receptors, GABA receptors, and opioid receptors.27 One specific alkaloid, desoxypeganine (also known as vasicine), found in P. harmala, was reported in an older study to dose-dependently decrease ethanol consumption in female Alko (alcohol-preferring) rats, without affecting food and fluid intake.27
Efficacy:
An ethanolic extract of Peganum harmala seeds (PHE), at doses of 1.25, 2.5, and 5 mg/kg orally, demonstrated nootropic (cognitive-enhancing) effects and improved memory in mice, along with a reduction in brain MAO-A activity.29 Harmine, a principal alkaloid, has shown antidepressant effects in preclinical models and is considered to have potential for treating mood disorders 27, which are often comorbid with AUD. Interestingly, ethanol (10%) has been shown to suppress harmaline-induced tremors in mice, an effect relevant to essential tremor models where harmaline is used to induce tremor.31 This indicates an interaction between ethanol and harmala alkaloids, though the direct implication for reducing alcohol consumption is complex.
Safety:
Peganum harmala is psychoactive, particularly at higher doses, and can induce effects such as hallucinations, tremors, and ataxia.27 The MAO-A inhibitory activity carries a significant risk of interactions with tyramine-containing foods (e.g., aged cheeses, cured meats, certain alcoholic beverages), which can lead to a hypertensive crisis (the "cheese effect").28 It can also interact with various medications. While used in traditional medicine for conditions like nervous system disorders, the potential for toxicity at high doses and drug/food interactions are major safety concerns.27 Pharmaceutical-grade harmine hydrochloride has been found to be well-tolerated at oral doses below 2.7 mg/kg in healthy adults, with higher doses causing mild to moderate gastrointestinal and neurological side effects.32

2.6. *Gynostemma pentaphyllum* (Jiaogulan)

Gynostemma pentaphyllum, often called Jiaogulan or "Southern Ginseng," is used in traditional medicine, particularly in parts of China.

Mechanism of Action:
The plant contains a variety of saponins known as gypenosides, some of which are structurally identical to the ginsenosides found in Panax ginseng.33 It is recognized for its antioxidant and

anti-inflammatory properties.34 An ethanol extract of Gynostemma pentaphyllum has been studied for its potential anxiolytic effects in a normal human population, suggesting a possible role in stress reduction.36

Efficacy:

Clinical studies evaluating Gynostemma pentaphyllum for specific therapeutic applications in AUD are limited. Its traditional uses are broad, and modern research has suggested potential roles in managing conditions like type 2 diabetes, obesity, fatty liver disease, and modulating immune responses.33 One clinical trial focused on hair health, which included an assessment of alcohol consumption as a lifestyle factor, found no significant differences in alcohol intake after 24 weeks of supplementation with Gynostemma pentaphyllum.34 Another study investigating an extract (ActivAMP®) in overweight individuals reported reductions in body weight and fat mass, but alcohol consumption was not a primary outcome measure.37 It is traditionally consumed as an herbal tea and has a history of folk use, particularly in the Guizhou province of China.33

Safety:

Gynostemma pentaphyllum is generally considered well-tolerated. Potential adverse reactions, though not common, may include severe nausea and an increase in bowel movements.33 Information regarding its safety during pregnancy and lactation is lacking.33

2.7. *Monolluma quadrangula* (formerly *Caralluma quadrangula*)

Monolluma quadrangula is a succulent plant with a history of use in traditional medicine for conditions such as diabetes and peptic ulcers.[40]

Mechanism of Action:

A hydroalcoholic extract of Monolluma quadrangula has demonstrated gastroprotective effects against ethanol-induced gastric mucosal injuries in rats. This protection appears to be mediated by an increase in gastric pH, enhanced gastric wall mucus production, increased activity of endogenous antioxidant enzymes like catalase and superoxide dismutase (SOD), a decrease in malondialdehyde (MDA) levels, upregulation of the heat shock protein Hsp70, and downregulation of the pro-apoptotic protein Bax.42 Ethanolic extracts have also shown antidiabetic effects in animal models, potentially by mechanisms such as increasing glucose removal from the blood, decreasing glucagon release, increasing insulin secretion, directly stimulating glycolysis in peripheral tissues, or reducing glucose absorption from the gastrointestinal tract.40 While general reviews discuss alcohol's impact on neurotransmitter systems like GABA, glutamate, serotonin, and dopamine 43, there is no direct information in the provided sources linking Monolluma quadrangula to the modulation of these systems in the context of AUD.

Efficacy:

The plant is traditionally used for diabetes and peptic ulcers.40 No direct studies investigating its efficacy in reducing alcohol consumption or cravings were found in the provided materials. Its documented protective effects against ethanol-induced gastric injury 42 and its general antioxidant properties 40 could offer indirect benefits for individuals with AUD who experience gastrointestinal complications, but this does not equate to a direct anti-addiction

effect.
Safety:
Monolluma quadrangula is used in folk medicine.40 However, its safety profile concerning specific AUD treatment has not been established from the available information.

2.8. *Geranium schiedeanum*

Geranium schiedeanum is a plant species whose extracts have been investigated for hepatoprotective properties.

Mechanism of Action:
Extracts of Geranium schiedeanum contain polyphenolic compounds, notably tannins, which are known for their antioxidant activities.47 Its hepatoprotective effects against ethanol-induced toxicity are thought to be related to the modulation of oxido-reduction processes and the attenuation of lipid peroxidation.47
Efficacy:
In a study involving rats with ethanol-induced liver toxicity during liver regeneration (post-partial hepatectomy), an extract of Geranium schiedeanum (300 mg/kg) demonstrated significant hepatoprotective effects. These included reduced mortality, improved restitution of liver mass, normalization of liver enzyme levels (alanine aminotransferase, aspartate aminotransferase), sustained or increased albumin levels, decreased bilirubin, and a reduction in oxidative stress markers such as thiobarbituric acid-reactive substances (TBARS).49 The extract also appeared to modify metabolic processes related to glucose and lipid levels.49 However, no direct studies on its ability to reduce alcohol consumption or craving were found in the provided sources; the focus is primarily on its liver-protective capabilities.
Safety:
Geranium schiedeanum has traditional uses, for example, as an antiseptic and antipyretic.48 Specific safety data regarding its use in the context of AUD treatment are not detailed.

2.9. *Aegle marmelos* (Bael)

Aegle marmelos, commonly known as Bael, is a fruit-bearing tree with extensive traditional use in Indian systems of medicine.

Mechanism of Action:
Bael is rich in a variety of phytochemicals, including alkaloids (such as aegeline and marmesin), tannins, coumarins, and terpenoids.51 These compounds contribute to its diverse pharmacological activities, which include antioxidant, anti-inflammatory, hepatoprotective, and antidiabetic properties.51 An ethanolic leaf extract of Aegle marmelos has shown antidepressant-like activity in mice, with a suggested mechanism involving the facilitatory action of its phytoconstituents (e.g., flavonoids, tannic acid, marmesinin) on the GABAergic system.55 While the GABA system is crucial in AUD, a direct link between Aegle marmelos and GABAergic modulation for alcohol effects is not explicitly made in the snippets.
Efficacy:
Aegle marmelos is traditionally used for a wide array of conditions, including digestive ailments, fever, and more.51 A fermented beverage combining bael and Indian gooseberry has

been noted for its high antioxidant content.56 However, there are no direct studies in the provided materials that investigate the efficacy of Aegle marmelos in reducing alcohol consumption or cravings. Its traditional applications and some of its neuropharmacological effects, such as potential GABAergic modulation leading to antidepressant effects 55, might hold relevance for AUD, but this remains speculative based on current information. General discussions on GABA_A receptors and alcohol 57 provide context but are not specific to this herb.

Safety:

The plant is widely used and valued in traditional Indian medicine.51 However, specific safety considerations for its use as an AUD treatment are not detailed in the provided information.

2.10. *Aralia elata*

Aralia elata is another herb with traditional applications related to alcohol intoxication.

Mechanism of Action:

Animal studies suggest that Aralia elata is a potent inhibitor of alcohol absorption from the gastrointestinal tract.6

Efficacy:

It is a component of a compound Chinese herbal formula traditionally employed to prevent or mitigate alcohol intoxication.6 Evidence for its efficacy is primarily from animal studies focusing on reducing absorption.

Safety:

Its safety is inferred from its traditional use context. Specific safety data for AUD treatment are not provided.

2.11. *St. John's Wort* (*Hypericum perforatum*)

St. John's Wort is a well-known herbal remedy, primarily for depression.

Mechanism of Action:

Its antidepressant effects are thought to involve the modulation of serotonin, norepinephrine, and dopamine neurotransmission.

Efficacy:

The provided snippets do not contain studies directly investigating St. John's Wort for reducing alcohol craving or consumption.

Safety:

Crucially, St. John's Wort presents significant safety concerns when considered in the context of alcohol use. It can interact with alcohol, increasing nervous system side effects such as dizziness, drowsiness, and difficulty concentrating.59 Furthermore, it necessitates the avoidance of tyramine-rich foods (e.g., aged meats and cheeses, red wine, tap beer) due to the risk of a hypertensive crisis, as some compounds in St. John's Wort may inhibit MAO.59 It is also a potent inducer of cytochrome P450 3A4 (CYP3A4), leading to numerous potential drug interactions.61 These interactions make its use problematic for individuals who may be consuming alcohol or taking other medications.

2.12. *Acanthopanax sessiliflorus* (Eleutherococcus sessiliflorus)

Acanthopanax sessiliflorus is a medicinal plant used in traditional practices.

Mechanism of Action:
The plant contains a diverse array of phytochemicals, including triterpenoids, phenylpropanoids, and flavonoids. One identified compound, scoparone (a lignan), possesses anti-inflammatory and analgesic effects.62 Extracts have demonstrated potential for antioxidant activity, anti-aging effects, antiplatelet aggregation, and antitumor properties. There are also suggestions it may improve glucose metabolism and benefit cardiovascular and immune systems.62
Efficacy:
The fruits of Acanthopanax sessiliflorus are traditionally used as an analgesic, tonic, antidiabetic, antihypertensive, anti-inflammatory, antitumor, and immune-stimulating agent.62 The root barks are used for strengthening tendons and bones and promoting blood circulation.62 However, the provided snippets do not contain direct studies on its efficacy in reducing alcohol consumption, craving, or managing alcohol withdrawal. General information on alcohol withdrawal syndrome 63 or meta-analyses of other AUD medications 65 are not specific to this herb.
Safety:
Safety is inferred from its traditional use. Specific safety data for AUD treatment are not detailed.

2.13. *Sorghum bicolor* (Sorghum)

Sorghum bicolor is a globally important cereal crop, with some varieties and extracts showing potential health benefits.

Mechanism of Action:
Sorghum is rich in phenolic compounds, including phenolic acids, flavonoids, and condensed tannins, which possess antioxidant and anti-inflammatory properties.66 Some of its phytochemicals, such as ferulic acid and p-coumaric acid, have been predicted to be blood-brain barrier permeant, suggesting potential for central nervous system effects.68
Efficacy:
Alcoholic extracts of certain sorghum varieties have demonstrated cytotoxicity against ovarian cancer cells and the ability to chemosensitize these cells to paclitaxel in vitro.66 In the context of brewing, the use of sorghum malt can influence the final alcohol content of beer, with increased proportions of sorghum malt sometimes leading to decreased alcohol content.67 In vitro studies using HepG2 cells (a human liver cell line) have shown that sorghum extracts can offer protective effects against alcohol-induced hepatocyte damage by reducing reactive oxygen species (ROS) and malondialdehyde (MDA) production.70 However, there are no direct studies in the provided materials that assess the efficacy of Sorghum bicolor extracts in reducing voluntary alcohol consumption, craving, or withdrawal symptoms as a treatment for AUD. Information on cinnamyl alcohol dehydrogenase genes in sorghum 71 pertains to lignin biosynthesis and is not directly relevant to AUD treatment. Similarly, discussions on alcohol

withdrawal generally 72 or ethanol production from sorghum 73 do not address its therapeutic use for AUD.
Safety:
As a widely consumed food crop, sorghum is generally considered safe. The safety of specific extracts for AUD treatment applications has not been detailed.
The exploration of these botanicals reveals that several traditionally used herbs possess plausible mechanisms of action relevant to AUD, such as enhancing alcohol metabolism (DHM), modulating GABAergic systems (DHM, potentially components of Kudzu or *Aegle marmelos*), or providing antioxidant and hepatoprotective benefits (*Hovenia*, *Thymus*, *Geranium*, *Sorghum*, *Aegle*). This convergence suggests that traditional medicine systems may have empirically identified plants that address key neurobiological disruptions in AUD. However, many herbal extracts are complex mixtures, potentially acting via multiple pathways (e.g., *Hovenia dulcis*, *Salvia miltiorrhiza*). This multi-target characteristic could be advantageous for a complex disorder like AUD but complicates the precise delineation of mechanisms and ensures consistent effects without rigorous standardization. The variability in phytochemical content [33] and lack of standardization for many supplements [22] are significant hurdles for research and clinical application. Furthermore, while prioritization of lesser-known herbs based on preclinical data is a valid discovery strategy, the general lack of human clinical trials for many (e.g., *Aralia elata*, *Monolluma quadrangula*, *Geranium schiedeanum* for direct AUD outcomes) highlights a critical research gap. Safety is also a paramount concern, particularly for herbs with MAOI activity like *Peganum harmala* [27] and St. John's Wort (due to tyramine interactions) [59], which can pose serious risks if not managed appropriately.

3. Neurobiological Targets and Categorization of Interventions

Understanding the primary neurobiological targets of various interventions is crucial for developing a rational basis for AUD treatment and for identifying novel therapeutic avenues. Alcohol profoundly impacts multiple neurotransmitter systems and physiological processes.

3.1. GABAergic System Modulators

The γ-aminobutyric acid (GABA) system is the primary inhibitory neurotransmitter system in the brain. Alcohol's acute effects include the potentiation of GABAergic transmission, particularly at GABAA receptors, contributing to its sedative, anxiolytic, and intoxicating effects. However, chronic alcohol exposure leads to significant neuroadaptations, including reduced GABAA receptor function and alterations in receptor subunit composition (e.g., upregulation of α4-containing GABAARs). These changes contribute to tolerance development and the hyperexcitability observed

during alcohol withdrawal, which can manifest as anxiety, tremors, and seizures.[10] Consequently, restoring balance to the GABAergic system is a key therapeutic strategy in AUD.

Several substances act on the GABA system:

- **Dihydromyricetin (DHM):** As discussed, DHM directly antagonizes ethanol's potentiation of GABAARs, reverses ethanol-induced receptor plasticity (including α4 subunit expression changes), and appears to interact with benzodiazepine binding sites on GABAARs.[10]
- **Baclofen:** A GABA-B receptor agonist, baclofen is used off-label for AUD and has been shown to be safe in patients with cirrhosis.[1] It may reduce anxiety and craving.[74] High-dose baclofen has been reported in case studies to effectively suppress alcohol craving and withdrawal symptoms.[74] Its mechanism likely involves alleviating withdrawal-related hyperexcitability and anxiety.[74]
- **Puerarin/Daidzin (from Kudzu):** While daidzin's primary described mechanism is ALDH-2 inhibition, the resulting accumulation of biogenic aldehydes like 5-HIAL and DOPAL could indirectly influence GABAergic pathways involved in reward and craving. The ethanolic leaf extract of *Aegle marmelos* has been suggested to possess GABA facilitatory action contributing to its antidepressant effects in mice [55], though its direct relevance to AUD via GABA modulation is speculative.
- *Thymus vulgaris***:** Its protective effects during alcohol withdrawal may partly stem from counteracting the neurotoxicity associated with GABA/glutamate imbalance.[24]
- **Gabapentin:** A calcium channel modulator that also affects GABAergic transmission. It is used to alleviate alcohol withdrawal symptoms.[76] Studies suggest its efficacy in AUD treatment is more pronounced in individuals experiencing significant withdrawal symptoms.[76] It has been shown to normalize GABAergic transmission in the central amygdala of alcohol-dependent animals.[10]
- **Acamprosate:** This FDA-approved medication is thought to modulate N-methyl-D-aspartate (NMDA) glutamate receptors and may also interact with GABAA receptors, helping to restore the balance between excitatory and inhibitory neurotransmission disrupted by chronic alcohol use. It is primarily used to prevent relapse and reduce craving in abstinent individuals.[1] It is generally more effective when initiated after the patient has achieved abstinence.[79]
- **Topiramate:** An anticonvulsant with multiple mechanisms of action, including enhancement of GABAA receptor function and antagonism of AMPA/kainate glutamate receptors.[81] It has demonstrated efficacy in reducing heavy drinking, promoting abstinence, and decreasing alcohol craving.[81]
- **Phosphodiesterase-4 (PDE4) Inhibitors (e.g., Apremilast):** These agents can

modulate GABAergic transmission in the central nucleus of the amygdala (CeA), a key brain region in AUD.[83]

- **Investigational: TMEM132B:** This transmembrane protein acts as a GABAAR auxiliary subunit, promoting the receptor's cell surface expression and enhancing alcohol's allosteric effects. Knockout or specific knockin mice disrupting TMEM132B-GABAAR interaction exhibit decreased GABAergic transmission, diminished potentiation of GABAAR currents by alcohol, reduced anxiolytic and sedative/hypnotic effects of alcohol, and significantly increased compulsive, binge-like alcohol consumption.[57] This highlights TMEM132B as a novel target for modulating GABAergic responses to alcohol.

3.2. Opioid System Modulators

The endogenous opioid system plays a critical role in mediating the rewarding and reinforcing effects of alcohol. Alcohol consumption can trigger the release of endogenous opioids (e.g., endorphins, enkephalins), which then act on opioid receptors (mu, delta, kappa) in brain reward pathways. Blocking these receptors can attenuate the pleasurable effects of alcohol and reduce craving.[3]

Substances targeting the opioid system include:

- **Naltrexone:** An opioid receptor antagonist, naltrexone is FDA-approved for AUD. It reduces relapse rates, return to heavy drinking, and the number of drinking days.[2] It works by blocking opioid receptors, thereby diminishing the reinforcing (pleasurable) effects of alcohol. It is available in both oral (typically 50 mg/day) and long-acting injectable formulations.[2] Studies suggest naltrexone may enhance some of the sedative effects of alcohol while reducing its positive reinforcing effects.[85]
- **Nalmefene:** Another opioid antagonist, nalmefene primarily targets mu and delta opioid receptors, while also acting as a partial agonist at kappa-opioid receptors. It is used to reduce alcohol cravings and overall consumption, particularly in individuals aiming for harm reduction (i.e., reduced drinking rather than complete abstinence). It is typically taken on an as-needed basis, 1-2 hours before an anticipated drinking occasion.[78]
- **Ibogaine:** This psychoactive alkaloid, derived from *Tabernanthe iboga*, has a complex pharmacology that includes interactions with opioid receptors. Animal studies suggest it can reduce alcohol consumption.[6] However, ibogaine is associated with significant safety concerns, including cardiac arrhythmias, neurotoxicity, and fatalities, particularly if administered without proper medical screening and supervision during withdrawal from other substances.[86]
- *Peganum harmala* **alkaloids:** As mentioned, β-carbolines like harmaline from

Syrian Rue have been shown to interact with opioid receptors. The analgesic effects of *P. harmala* extracts in animal models can be prevented by naloxone, an opioid antagonist, indicating an opioid-modulated mechanism.[27]

3.3. Serotonergic System Modulators

The serotonin (5-hydroxytryptamine, 5-HT) system is extensively involved in regulating mood, sleep, appetite, impulsivity, and cognitive function, all of which can be disrupted in AUD. Alcohol's effects on the serotonin system are complex and can vary depending on acute versus chronic exposure and the specific brain region and receptor subtype involved. Dysregulation of serotonergic pathways is frequently implicated in the development and maintenance of AUD, including craving and relapse.

Interventions modulating the serotonin system include:

- **Daidzin (from Kudzu):** As previously detailed, daidzin's inhibition of ALDH-2 leads to an accumulation of 5-hydroxyindole-3-acetaldehyde (5-HIAL), the aldehyde metabolite of serotonin. This accumulation, rather than direct receptor interaction, is thought to mediate daidzin's antidipsotropic effects.[17]
- *Salvia miltiorrhiza***:** Extracts from this herb are suggested to reduce alcohol-seeking behavior in rats by acting on brain centers that involve serotonergic transmission, among other systems.[8]
- *Peganum harmala* **alkaloids (Harmine, Harmaline):** The MAO-A inhibitory properties of these β-carbolines lead to increased synaptic concentrations of serotonin. Additionally, these alkaloids have been reported to interact directly with 5-HT2 receptors.[27]
- **Sertraline:** A selective serotonin reuptake inhibitor (SSRI) commonly used as an antidepressant. A meta-analysis indicated that sertraline, either alone or in combination with other medications like naltrexone and acamprosate, is associated with improved treatment success in AUD.[3] This suggests that addressing comorbid depressive symptoms or underlying serotonergic dysregulation can be beneficial.
- **Meta-Chlorophenylpiperazine (mCPP):** This compound is a non-selective serotonin receptor agonist. In research settings, mCPP challenge has been shown to induce alcohol craving in individuals with alcoholism, further highlighting the involvement of the serotonergic system in craving.[88]

3.4. Dopaminergic System Modulators

The mesolimbic dopamine pathway, originating in the ventral tegmental area (VTA) and projecting to the nucleus accumbens (NAc) and other forebrain regions, is central

to the brain's reward system. Alcohol, like many drugs of abuse, increases dopamine release in the NAc, which is believed to mediate its rewarding and reinforcing properties, thus promoting continued consumption.[46] Chronic alcohol use leads to neuroadaptations in the dopamine system, contributing to anhedonia during withdrawal and persistent craving.

Substances that may modulate the dopaminergic system in the context of AUD include:

- **Daidzin (from Kudzu):** Similar to its effect on serotonin metabolism, daidzin's inhibition of ALDH-2 results in the accumulation of 3,4-dihydroxyphenylacetaldehyde (DOPAL), the aldehyde metabolite of dopamine.[17] There is also a suggestion that synthetic daidzin analogs might reduce alcohol cravings by preventing alcohol-induced increases in dopamine levels.[20]
- **Ginseng (*Panax ginseng*):** Animal studies indicate that ginseng may reduce tolerance and dependence associated with long-term abuse of stimulants like cocaine and methamphetamine. This effect is hypothesized to involve the inhibition of narcotic-induced depletion of dopamine in the brain.[6] Its relevance to alcohol-induced dopamine dysregulation is plausible but less directly studied in the provided snippets.
- *Salvia miltiorrhiza*: As with serotonin, extracts are suggested to act on brain centers involving dopaminergic transmission to reduce alcohol-seeking behavior.[8]
- *Peganum harmala* **alkaloids:** These β-carbolines interact with dopamine D1 and D2 receptors, and their MAO-A inhibitory action also affects dopamine metabolism by slowing its degradation.[27]
- **Nociceptin/Orphanin FQ (N/OFQ):** This neuropeptide, acting via the NOP receptor, has been found to inhibit dopamine production related to the reward process. Activation of NOP receptors can eliminate conditioned place preference for alcohol in animal models, suggesting an interference with alcohol's rewarding effects mediated by dopamine.[90]

3.5. Alcohol Metabolizing Enzyme Modulators (ADH, ALDH)

The primary enzymes responsible for alcohol metabolism are alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH). ADH converts ethanol to acetaldehyde, a highly toxic compound. ALDH, particularly the mitochondrial form ALDH-2, then converts acetaldehyde to acetate, which is less harmful. Genetic variations in these enzymes, especially ALDH-2, significantly influence alcohol metabolism, acetaldehyde accumulation (leading to the "flushing response" common in some Asian populations), and consequently, the risk of developing AUD. Interventions can either enhance these

enzymes to speed up alcohol clearance or inhibit them (like disulfiram) to create an aversive reaction to alcohol.

Substances that modulate ADH and/or ALDH activity include:

- **Dihydromyricetin (DHM) (from *Hovenia dulcis*, *Ampelopsis grossedentata*):** DHM has been shown to increase the activity of both ADH and ALDH. This dual enhancement accelerates the overall metabolism of alcohol, leading to a faster clearance of ethanol and a reduction in the accumulation of toxic acetaldehyde.[5]
- **Daidzin (from *Pueraria lobata* / Kudzu):** Daidzin is a potent and selective inhibitor of mitochondrial ALDH-2.[17] This is a distinct mechanism from the broad ALDH inhibition caused by disulfiram. As discussed, this specific ALDH-2 inhibition by daidzin leads to the accumulation of biogenic aldehydes from neurotransmitter metabolism rather than systemic acetaldehyde accumulation. One snippet also suggests that Kudzu flower extract might increase blood alcohol levels more rapidly [19], which could imply an effect on absorption or initial metabolism, although this needs careful reconciliation with daidzin's known ALDH-2 inhibitory action.

3.6. HPA Axis Modulators (Hypothalamic-Pituitary-Adrenal Axis)

The HPA axis is the body's primary stress response system. Stress and HPA axis dysregulation are critically implicated in all stages of AUD, from initiation and escalation of drinking to withdrawal and relapse. Alcohol acutely stimulates the HPA axis (leading to cortisol release), and chronic alcohol use can lead to profound HPA axis dysregulation, contributing to negative affective states during withdrawal and heightened stress reactivity, which can trigger craving and relapse.

While less explicitly detailed for specific mechanisms in the provided snippets, some substances may exert their effects, at least in part, by modulating the HPA axis:

- **Ashwagandha (*Withania somnifera*):** This herb is a well-known adaptogen, traditionally used to help the body cope with stress. Adaptogens are thought to modulate the HPA axis and normalize stress responses. The provided information mentions that Ashwagandha lessens the severity of morphine withdrawal in animals [6], and its potential role in mitigating alcohol-related HPA axis dysregulation and stress-induced relapse is plausible, though not directly confirmed in the snippets for alcohol.
- **Baclofen:** The anxiolytic effects of baclofen [74] could be partly mediated by dampening HPA axis hyperactivity, as anxiety and stress are key drivers and outputs of HPA axis activation.
- **Gabapentin:** Its efficacy in alleviating alcohol withdrawal symptoms [76], which

often include HPA axis hyperactivity and associated anxiety, suggests a potential indirect modulatory effect on this system.

The following table summarizes key interventions discussed, categorized by their primary proposed neurobiological target(s) relevant to AUD:

Table 1: Summary of Investigated Substances by Primary Neurobiological Target(s) for AUD

Substance Name	Primary Neurobiological Target(s)	Key Active Compound(s) (if applicable)	Primary Effect on Alcohol Use	Key Source(s)
Dihydromyricetin (DHM)	GABA_A Receptors, ADH/ALDH Enzymes	Dihydromyricetin	$\downarrow$Intoxication, $\downarrow$Withdrawal, $\downarrow$Consumption, Hepatoprotection	5
Kudzu (*Pueraria lobata*)	ALDH-2 Inhibition (Daidzin), Drinking Topography (Puerarin)	Daidzin, Puerarin	$\downarrow$Consumption, $\downarrow$Binge Drinking	16
Salvia miltiorrhiza	$\downarrow$Alcohol Absorption, Dopaminergic/Serotonergic/Adrenergic Systems	Miltirone, Tanshinones	$\downarrow$Alcohol Seeking, $\downarrow$Consumption (animals)	8
Thymus vulgaris	Antioxidant, Neuroprotection during Withdrawal (GABA/Glutamate related)	Thymol, Carvacrol, etc.	$\downarrow$AWS Symptoms (anxiety, memory loss in mice)	24

Peganum harmala	MAO-A Inhibition, Serotonin/Dopamine/Opioid/GABA Receptors	Harmine, Harmaline	$\downarrow$Consumption (desoxypeganine in rats), Antidepressant	27
Naltrexone	Opioid Receptors (Antagonist)	Naltrexone	$\downarrow$Relapse, $\downarrow$Heavy Drinking, $\downarrow$Craving	2
Acamprosate	NMDA (Glutamate) Receptors, GABA_A Receptors	Acamprosate	$\downarrow$Relapse, $\downarrow$Craving	2
Baclofen	GABA_B Receptors (Agonist)	Baclofen	$\downarrow$Craving, $\downarrow$AWS Symptoms (some evidence)	1
Topiramate	GABA_A Enhancement, Glutamate Antagonism	Topiramate	$\downarrow$Heavy Drinking, $\uparrow$Abstinence, $\downarrow$Craving	81
Gabapentin	Calcium Channels, GABA Modulation	Gabapentin	$\downarrow$AWS Symptoms, $\downarrow$Consumption (esp. with high withdrawal)	76
Apremilast (PDE4 Inhibitor)	PDE4 Enzyme, GABA Transmission (CeA)	Apremilast	$\downarrow$Binge Drinking, $\downarrow$Consumption	83

Nalmefene	Opioid Receptors (Antagonist/Partial Agonist)	Nalmefene	$\downarrow$Consumption, Harm Reduction	[78]

The categorization of these substances reveals that many interventions, particularly herbal ones like *Peganum harmala*, may exert their effects by influencing multiple neurotransmitter systems simultaneously.[27] This contrasts with the more targeted approach of many modern pharmaceuticals. Such multi-system effects could be advantageous in treating a complex disorder like AUD, where dysregulation occurs across numerous interconnected neural pathways. Alcohol itself has widespread effects [45], and thus, interventions that can modulate several of these systems might offer a more holistic therapeutic benefit. This complexity is inherent in traditional herbal remedies which often contain a multitude of active compounds.

Furthermore, a distinction can be observed between substances primarily targeting withdrawal mechanisms versus those aimed at craving and relapse. For instance, gabapentin and baclofen are often highlighted for their utility in managing withdrawal symptoms, which are heavily influenced by GABA/glutamate dysregulation and HPA axis hyperactivity.[75] In contrast, naltrexone and acamprosate are mainstays for relapse prevention, targeting reward pathways (opioid system) and neurochemical imbalances (GABA/glutamate) that drive craving.[78] Some agents, like DHM, show promise in addressing both acute intoxication/withdrawal and ongoing consumption.[10]

It is also apparent that interventions can operate through peripheral mechanisms, central neurobiological actions, or both. For example, herbs like *Salvia miltiorrhiza* (via miltirone) and *Aralia elata* are proposed to reduce alcohol's impact by limiting its absorption from the gastrointestinal tract.[6] This approach differs fundamentally from agents that target neurotransmitter receptors within the brain, such as DHM's action on GABAARs.[10] Peripherally acting agents might offer the advantage of fewer central nervous system side effects but may not address the underlying neuroadaptations and cravings that sustain AUD. Conversely, centrally acting agents target the core neurobiology of addiction but carry a higher potential for CNS-related side effects. Some compounds, like DHM, appear to bridge this divide, exhibiting both hepatoprotective/metabolic effects (peripheral/systemic) [5] and direct central GABAergic actions.[10] This diverse array of targets and mechanisms underscores the potential for developing a more nuanced and personalized pharmacopeia for AUD.

4. Novel and Emerging Biochemical Targets for Alcohol Use

Disorder

Beyond the classical neurotransmitter systems, research is actively exploring novel biochemical targets that play a role in the pathophysiology of AUD. These emerging areas offer new hope for developing innovative treatments.

4.1. The Endocannabinoid System (ECS)

The endocannabinoid system (ECS), comprising endocannabinoid ligands (e.g., anandamide [AEA], 2-arachidonoylglycerol [2-AG]), their receptors (primarily cannabinoid receptor type 1 and type 2), and metabolic enzymes (e.g., fatty acid amide hydrolase [FAAH] for AEA degradation, monoacylglycerol lipase [MAGL] for 2-AG degradation), is deeply implicated in regulating reward, stress responses, sleep, mood, and appetite – all of which are highly relevant to AUD.[93]

Alcohol consumption significantly interacts with and alters ECS signaling. Acute alcohol administration can increase endocannabinoid levels in key brain regions like the nucleus accumbens.[93] Conversely, chronic alcohol exposure can lead to detrimental neuroadaptations, such as decreased CB1R expression and reduced G-protein coupling efficiency, compromising overall endocannabinoid signaling.[93] Genetic variations within ECS components also contribute to individual differences in alcohol responses and AUD vulnerability. For instance, a common single nucleotide polymorphism (SNP) in the FAAH gene (rs324420, c.385C>A, Pro129Thr), which results in a less stable FAAH protein and consequently higher AEA levels, has been associated with increased alcohol consumption and risk of AUD in some human populations.[93] Similarly, variations in the CNR1 gene, which encodes the CB1R, are linked to alcohol-related phenotypes.

The therapeutic potential of targeting the ECS for AUD is an area of active investigation, though it presents complexities.

- **FAAH Inhibition:** While inhibiting FAAH would increase anandamide levels, which might be expected to have beneficial anxiolytic or mood-elevating effects, preclinical studies have paradoxically shown that FAAH knockout or pharmacological inhibition can lead to increased preference for alcohol and higher alcohol consumption in rodents.[93] This suggests that simply "boosting" anandamide signaling globally might not be a straightforward therapeutic strategy for reducing alcohol intake and could even be counterproductive. However, the broader concept of bolstering endocannabinoid tone is still being explored for its therapeutic relevance at different stages of AUD.[94]
- **CB1R Modulation:** Given that CB1Rs mediate many of alcohol's effects on the

ECS and reward pathways, they are a logical target. Animal models with CB1R knockout exhibit reduced voluntary alcohol consumption and self-administration.[93] Historically, CB1R antagonists/inverse agonists (e.g., rimonabant) were developed for obesity and showed promise for addiction; however, their development was halted due to significant psychiatric side effects, such as depression and anxiety. This highlights the challenge of therapeutically targeting CB1Rs without inducing adverse mood changes.

- **Palmitoylethanolamide (PEA):** While not extensively detailed for alcohol in the provided snippets, PEA is an endocannabinoid-like lipid mediator. It is an N-acylethanolamine, like anandamide, and is known to exert anti-inflammatory, analgesic, and neuroprotective effects. PEA primarily acts by activating peroxisome proliferator-activated receptor alpha (PPAR-α). It can also indirectly modulate the ECS by inhibiting FAAH activity (the "entourage effect"), thereby increasing anandamide levels. Given its established roles in mitigating neuroinflammation and pain, PEA is a plausible candidate for addressing AUD-related neuroinflammation, withdrawal symptoms, or negative affective states, though direct evidence for reducing alcohol consumption is needed.

The complexity of the ECS's role – where both increases and decreases in signaling components can be linked to problematic alcohol use depending on the specific element, context, and chronicity – underscores the need for more nuanced therapeutic approaches rather than broad agonism or antagonism.

4.2. Neuroinflammatory Pathways

A significant body of evidence now implicates neuroinflammatory processes as pivotal players in the development and progression of AUD.[95] Alcohol itself acts as a trigger for innate immune signaling within the brain. This neuroinflammation involves the activation of glial cells, primarily microglia and astrocytes, which then release a cascade of pro-inflammatory mediators, including cytokines (e.g., tumor necrosis factor-alpha, interleukin-1beta [IL-1β], interleukin-6 [IL-6]) and chemokines.[95]

This neuroinflammatory response is not merely a consequence of alcohol-induced damage but actively contributes to the behavioral and neurobiological hallmarks of AUD. It has been linked to an escalation of alcohol consumption, increased craving, the development of tolerance, the severity of withdrawal symptoms, and alcohol-related neurodegeneration.[95] A critical aspect of this relationship is its bidirectional nature: alcohol consumption triggers neuroinflammation, and the resulting neuroinflammatory state can, in turn, drive further alcohol consumption, creating a pernicious feed-forward cycle that perpetuates the disorder.[95] Toll-Like

Receptors (TLRs), particularly TLR4 which recognizes pathogen-associated molecular patterns and damage-associated molecular patterns (including those generated by alcohol-induced cellular stress), are key upstream mediators in alcohol-induced neuroinflammation.[96]

Targeting these neuroinflammatory pathways offers a novel therapeutic strategy for AUD.

- **Phosphodiesterase-4 (PDE4) Inhibitors:** PDE4 is an enzyme that specifically degrades cyclic adenosine monophosphate (cAMP), a crucial intracellular second messenger. By inhibiting PDE4, these drugs increase intracellular cAMP levels, which can lead to broad anti-inflammatory effects and modulate neuronal function. Several PDE4 inhibitors have shown promise:
    - **Apremilast:** An FDA-approved drug for psoriasis and psoriatic arthritis, apremilast has demonstrated efficacy in reducing binge-like alcohol intake in various preclinical animal models and has also reduced excessive alcohol drinking in a human laboratory study.[83] Its mechanism appears to involve the regulation of GABAergic transmission within the central nucleus of the amygdala (CeA).[83] Chronic alcohol exposure has been shown to increase the transcript levels of *Pde4a* and *Pde4b* subtypes in the CeA.[83]
    - **Rolipram:** A non-selective PDE4 inhibitor, rolipram has been shown in animal studies to reduce alcohol consumption and preference.[97] It also ameliorates cognitive deficits in animal models of alcoholic dementia, an effect linked to the PDE4B/cAMP/PKA signaling pathway.[98] However, its clinical utility has been hampered by side effects, notably emesis (nausea and vomiting).[97]
    - **A33:** A more selective PDE4B inhibitor, A33 has been reported to reduce alcohol consumption in mice without inducing the emetic side effects associated with less selective PDE4 inhibitors like rolipram.[98]
    - **Ibudilast:** A non-selective phosphodiesterase inhibitor with anti-inflammatory properties (including PDE4 inhibition), ibudilast has been found to decrease alcohol relapse behavior in both rodents and human patients.[83]
- **Other Anti-inflammatory Approaches:**
    - **Minocycline:** A tetracycline antibiotic with known anti-inflammatory properties, primarily through the inhibition of microglial activation, has shown potential in preclinical models.[96]
    - **PPARγ agonists (e.g., pioglitazone):** These drugs can counter inflammation by interfering with the Nf-κB pathway and reducing pro-inflammatory cytokine release. Pioglitazone has been shown to curb drinking behavior in animal models.[96]
    - **Gut-Brain Axis Modulators:** Recognizing that systemic inflammation and gut

dysbiosis can contribute to neuroinflammation, interventions targeting the gut-brain axis are being explored. These include probiotics, antioxidants like N-acetylcysteine, and conventional anti-inflammatory drugs such as aspirin.[96]

The investigation of apremilast exemplifies a promising strategy of repurposing existing FDA-approved drugs with known anti-inflammatory mechanisms for AUD treatment.[92] This approach can expedite the drug development process by leveraging established safety and pharmacokinetic profiles.

4.3. Neuropeptide Systems (e.g., Nociceptin/Orphanin FQ (N/OFQ) - NOP Receptor System)

Neuropeptide systems are increasingly recognized for their modulatory roles in stress, reward, mood, and pain – processes intricately linked to AUD. The Nociceptin/Orphanin FQ (N/OFQ) system and its cognate receptor, the NOP receptor (also known as ORL-1 or kappa-type 3 opioid receptor), represent one such emerging target.[90]

N/OFQ is a 17-amino acid neuropeptide that is the endogenous ligand for the NOP receptor, a G protein-coupled receptor. The N/OFQ-NOP system is widely distributed in the brain, including in areas critical for reward processing (e.g., hypothalamus, amygdala), stress responses, and emotional regulation.[90] Unlike classical opioid peptides that primarily produce analgesia, N/OFQ can have complex, sometimes opposing, effects on pain perception depending on the site of action (e.g., hyperalgesia when administered in the brain, analgesia spinally).[90]

In the context of AUD and other substance use disorders:

- Nociceptin has been found to inhibit dopamine production related to the reward process.[90]
- Activation of NOP receptors in animal models has been shown to eliminate conditioned place preference induced by various drugs of abuse, including alcohol, morphine, cocaine, and methamphetamine.[90] This suggests that N/OFQ signaling can counteract the rewarding effects of these substances.
- The NOP receptor is considered a potential target for medications aimed at alleviating substance abuse disorders.[90]

The therapeutic potential of modulating the N/OFQ-NOP system is being explored through both agonists and antagonists:

- **NOP Agonists:** Have shown potential as powerful, non-addictive analgesics in non-human primates.[91] Their role in AUD is nuanced; while NOP activation can

reduce drug reward, chronic administration of NOP agonists has been reported to attenuate the analgesic effects of opiates, which could complicate their use.[91]

- **NOP Antagonists:** Several selective NOP receptor antagonists have been developed (e.g., SB-612,111, J-113,397, LY-2940094).[91] These are under investigation for conditions like depression and Parkinson's disease.[91] In the context of pain, blocking NOP receptors can lead to an increased pain threshold and decreased tolerance development to analgesic opioids.[90] Their direct utility in reducing alcohol consumption or alleviating withdrawal-induced negative affect is an area for further research, but the system's involvement in reward and stress pathways makes NOP antagonists plausible candidates.

The development of selective ligands for the NOP receptor allows for more precise investigation of its roles in AUD and other neuropsychiatric conditions.[91]

These novel targets – the ECS, neuroinflammatory pathways, and neuropeptide systems like N/OFQ-NOP – are not isolated entities. They often interact with classical neurotransmitter systems. For instance, NOP receptor activation can influence dopamine levels [90], and PDE4 inhibitors can modulate GABAergic transmission in the CeA.[83] This interconnectedness reinforces the view of AUD as a systems-level brain disorder, suggesting that the most effective future therapies may involve interventions that can modulate multiple interacting pathways or target key regulatory nodes within these complex networks.

5. Synthesizing Evidence: Comparative Effectiveness from Meta-Analyses and Systematic Reviews

To gain a clearer perspective on the relative utility of various interventions for AUD, it is essential to examine evidence from meta-analyses and systematic reviews. These types of studies synthesize data from multiple primary investigations, providing more robust estimates of treatment effects and safety.

5.1. Pharmacological Interventions for AUD

Several medications have received regulatory approval for AUD, and their efficacy has been evaluated extensively.

- **Key FDA-Approved Medications:**
  - **Naltrexone and Acamprosate:** Multiple meta-analyses confirm that naltrexone and acamprosate are effective first-line pharmacotherapies for AUD when used in conjunction with psychosocial interventions.[2] For oral naltrexone (typically 50 mg/day), the number needed to treat (NNT) to

prevent one person from returning to any drinking was 18, and for preventing a return to heavy drinking, the NNT was 11.[2] For acamprosate, the NNT to prevent one person from returning to any drinking was 11.[2] These medications target different aspects of AUD: naltrexone, an opioid antagonist, reduces the rewarding effects of alcohol, while acamprosate is thought to restore balance to GABA and glutamate systems disrupted by chronic drinking, thereby reducing craving and withdrawal-related distress.[3]
    - **Combination Pharmacotherapy:** A recent meta-analysis and meta-regression study found that combination therapies involving naltrexone, acamprosate, and the SSRI antidepressant sertraline led to an average 4.045% increase in abstinence rates compared to monotherapies, with an NNT of 25.[3] This suggests that targeting multiple neurobiological pathways simultaneously may offer incremental benefits.
- **Off-Label Medications:**
    - **Baclofen:** A GABA-B agonist, baclofen can be used off-label for AUD and has been noted as safe and effective in patients with cirrhosis.[1] However, a review concerning its use for Alcohol Withdrawal Syndrome (AWS) concluded that there is currently insufficient evidence to support its use as a first-line treatment for AWS, indicating a need for more research.[75]
    - **Topiramate:** An anticonvulsant with multiple mechanisms of action, topiramate has demonstrated efficacy in reducing problematic alcohol use, increasing the proportion of days abstinent, and reducing the number of heavy drinking days and drinks per drinking day.[81]
    - **Gabapentin:** This anticonvulsant, which modulates calcium channels and GABAergic transmission, has shown efficacy for treating alcohol withdrawal symptoms.[76] Its benefit for AUD treatment appears more pronounced in individuals with a history of significant withdrawal.[76] A large multisite trial of gabapentin enacarbil extended-release (GE-XR) did not meet its primary outcome for AUD, but subsequent machine learning analyses identified potential responder subgroups (e.g., those with more baseline heavy drinking days, lower anxiety/depression).[76]
- **Side Effect Profiles and Safety:** Common side effects for approved medications include diarrhea with acamprosate and nausea with naltrexone.[2] Other agents carry more significant risks: St. John's Wort has numerous drug interactions and tyramine restrictions [59]; ibogaine is associated with severe cardiac and neurotoxic risks [86]; and some PDE4 inhibitors like rolipram have dose-limiting side effects such as emesis.[97]
- **Influence of Patient Variables:** The effectiveness of combination pharmacotherapies can be influenced by patient characteristics such as gender,

age, country of study, and the presence of psychiatric comorbidities.[3] For example, combined therapy appeared more effective in populations with a lower proportion of males, and older individuals tended to show better outcomes.[3]

5.2. Supplemental and Herbal Interventions

The evidence base for supplemental and herbal interventions is generally less extensive than for FDA-approved pharmaceuticals.

- **Systematic Reviews on Herbal Remedies:**
  - A concise review of herbal and natural products identified Kudzu (*Pueraria lobata*), *Salvia miltiorrhiza*, *Aralia elata*, Ibogaine, *Cannabis indica* (for delirium tremens), and the Ayurvedic formula Mentat™ as promising, based largely on traditional use, animal studies, and some preliminary human trials.[6] However, this review critically noted that most studies on these interventions were small, conducted many years ago, and often lack replication through large, well-controlled placebo-controlled trials.[6]
  - Despite these limitations, there is expressed interest among individuals with hazardous drinking patterns in using herbal supplements to reduce alcohol consumption, particularly if they are also interested in conventional pharmacotherapy.[7] Kudzu remains an area of ongoing research interest for reducing alcohol consumption.[7]
- **Specific Supplements with Notable Evidence:**
  - **Dihydromyricetin (DHM):** Preclinical evidence for DHM's efficacy in hepatoprotection and reducing alcohol intoxication and withdrawal symptoms is substantial.[10] Human clinical trials are beginning to emerge, which will be crucial for validating these preclinical findings.[14]
  - **Kudzu (*Pueraria lobata* - Puerarin, Daidzin):** Human pilot studies have demonstrated that Kudzu extracts or its constituent puerarin can reduce alcohol consumption in heavy drinkers and individuals prone to binge drinking.[16] Daidzin's well-defined mechanism of ALDH-2 inhibition provides a strong rationale for its effects.[17]

5.3. Comparative Insights

Comparing pharmacological and supplemental interventions reveals important distinctions in their evidence base and regulatory status.

- Pharmacological agents approved for AUD typically have a more extensive body of evidence from rigorous, multi-phase randomized controlled trials (RCTs), which are then synthesized in meta-analyses.[2] This forms the basis for their regulatory approval and clinical guidelines.

- Herbal and supplemental interventions often have a strong foundation in traditional use and may possess promising preclinical (animal model) data. However, the quantity and quality of human clinical trial evidence are frequently limited, with fewer large-scale, placebo-controlled studies.[6] This difference reflects an "evidence hierarchy" discrepancy, where the level of scientific scrutiny and validation often differs significantly.
- The safety profiles for approved medications are generally well-characterized through clinical development programs and post-marketing surveillance. For many dietary supplements, especially those that are unregulated, concerns about quality control, standardization of active ingredients, and comprehensive long-term safety data can be significant.[22]

The growing trend towards combination therapy in pharmacological treatments for AUD [3], aiming to target multiple neurobiological mechanisms, resonates with the inherently multi-component nature of many traditional herbal remedies. If the active constituents and mechanisms of these herbal products can be clearly defined and standardized, they might offer an inherent "combination" effect. Furthermore, the findings from studies like the gabapentin GE-XR trial, where machine learning identified potential responder profiles despite overall null results [76], and the observed influence of patient variables on combination therapy outcomes [3], collectively point towards an increasing emphasis on personalized medicine in AUD. This suggests a shift from seeking a universal "cure" to identifying which interventions are most effective for specific individuals based on their unique biological and clinical characteristics. For many promising supplements, the lack of high-quality primary human studies remains a significant barrier to drawing firm conclusions from systematic reviews and integrating them confidently into evidence-based practice.

6. Application of Interventions Across the Spectrum of Alcohol Misuse

The diverse nature of alcohol misuse, ranging from at-risk binge drinking to established, severe AUD with physical dependence, necessitates a nuanced approach to intervention. Different strategies and substances may be appropriate depending on the severity of the problem, treatment goals, and individual patient characteristics.

6.1. Prevention of Binge Drinking in At-Risk Individuals

Binge drinking, typically defined as consuming four or more drinks for women and five or more drinks for men in about two hours [19], is a common pattern of excessive alcohol use, particularly among younger adults, that carries significant health and safety risks.

Interventions for this group often focus on harm reduction, aiming to reduce the frequency or intensity of drinking episodes rather than mandating immediate and total abstinence.

- **Kudzu Extract (*Pueraria lobata*):** Several studies suggest Kudzu's potential in this domain. A human study found that individuals who took Kudzu extract 2.5 hours prior to a binge drinking opportunity consumed significantly less alcohol.[6] It has also been reported to help heavy drinkers reduce their overall alcohol consumption even when they are not in formal treatment programs.[19] The mechanism may involve altering drinking topography, leading to slower consumption and reduced overall intake per session.[16]
- **Nalmefene:** This opioid antagonist is particularly suited for individuals who wish to reduce their alcohol consumption rather than achieve complete abstinence. It is taken on an as-needed basis before anticipated drinking occasions and has been shown to reduce the number of heavy drinking days and overall alcohol intake.[78]
- **Phosphodiesterase-4 (PDE4) Inhibitors (e.g., Apremilast):** Preclinical data indicate that apremilast can reduce binge-like alcohol intake in animal models.[83] A human laboratory study also showed that apremilast reduced the number of drinks consumed per day.[92] These findings suggest a potential role for PDE4 inhibitors in mitigating heavy drinking episodes.
- **Dihydromyricetin (DHM):** DHM's ability to counteract acute alcohol intoxication and reduce voluntary alcohol consumption in animal models is well-documented.[10] By potentially making individuals feel the effects of alcohol sooner or altering its rewarding properties, DHM might indirectly help reduce the total amount consumed during a binge episode.

6.2. Treatment of Established, Severe Alcohol Use Disorder

Severe AUD is characterized by high levels of alcohol consumption, significant physical dependence, the emergence of withdrawal symptoms upon cessation or reduction of intake, and substantial negative impacts on health, social functioning, and occupational performance.[1] Treatment for severe AUD is often multifaceted, requiring medically supervised detoxification followed by long-term relapse prevention strategies.

- **FDA-Approved Medications:** Naltrexone, acamprosate, and disulfiram are the primary pharmacological treatments for moderate to severe AUD.[1] Combination therapies using these agents, sometimes with adjunctive medications like sertraline, are increasingly considered to enhance efficacy.[3]
- **Topiramate:** This anticonvulsant has demonstrated efficacy in reducing

problematic alcohol use, increasing days of abstinence, and decreasing the number of heavy drinking days in individuals with AUD, many of whom likely fall into the moderate to severe category.[81]

- **Dihydromyricetin (DHM):** Strong preclinical evidence suggests that DHM can reduce alcohol dependence and alleviate withdrawal symptoms.[10] The ongoing Phase 1 clinical trial investigating DHM for alcohol-associated liver disease (ALD) [14] is particularly relevant, as ALD is a common and serious complication of severe, chronic AUD.
- **Baclofen:** High-dose baclofen has been anecdotally reported and described in case studies to effectively suppress cravings and other symptoms of alcohol dependence, particularly in individuals with severe, treatment-refractory AUD.[74] Its safety profile in patients with liver disease is an added advantage.[1]
- **Gabapentin:** May be particularly beneficial for individuals with severe AUD who have a history of significant withdrawal symptoms, as it can help manage these and potentially reduce drinking.[76]
- **Herbal Interventions:** While many traditional herbs like Kudzu, *Salvia miltiorrhiza*, and components of *Peganum harmala* show promise in reducing alcohol intake in animal models of preference or dependence [8], robust human clinical trial data for their use in severe AUD are often lacking. If proven effective and safe through rigorous trials, their role would likely be as adjunctive treatments or for managing specific symptom clusters.

6.3. Management of Alcohol Withdrawal Syndrome (AWS)

AWS occurs when an individual with physical dependence on alcohol abruptly stops or significantly reduces their intake. Symptoms can range from mild (e.g., anxiety, tremors, insomnia) to severe and life-threatening (e.g., seizures, delirium tremens).[63] AWS is primarily driven by an imbalance between inhibitory (GABA) and excitatory (glutamate) neurotransmission, leading to central nervous system hyperexcitability and autonomic hyperactivity.[24]

- **Benzodiazepines:** These are the first-line pharmacological treatment for AWS, effectively reducing symptoms and preventing progression to more severe complications like seizures and DTs.[75]
- **Gabapentin:** Has demonstrated efficacy in treating various symptoms of AWS, including anxiety, agitation, and sleep disturbances, and may reduce the need for benzodiazepines in some cases.[76]
- **Baclofen:** There is some evidence, including case reports and smaller trials, suggesting that baclofen can suppress AWS symptoms. However, current evidence is insufficient to recommend it as a first-line treatment for AWS.[75]

- *Thymus vulgaris* **(Thyme):** Preclinical research in mice indicates that thyme extract possesses anxiolytic, memory-enhancing, hepatoprotective, and antioxidant effects during alcohol withdrawal, suggesting a potential ameliorative role.[24] Human data are lacking.
- **Dihydromyricetin (DHM):** Animal studies have shown that DHM can reduce signs of alcohol withdrawal, including tolerance development, anxiety-like behaviors, and susceptibility to seizures.[10]
- **Ibogaine:** While there is some historical and anecdotal mention of ibogaine for withdrawal, its use in this context is highly dangerous and contraindicated without prior, medically supervised detoxification from alcohol. Alcohol withdrawal itself can be life-threatening, and administering ibogaine during acute withdrawal can exacerbate risks of cardiac arrhythmias, seizures, and even fatalities.[6] It is critical that individuals are fully detoxified from alcohol under medical care *before* any consideration of ibogaine treatment.[86]
- *Salvia miltiorrhiza* **(Miltirone):** In contrast to some other agents, miltirone, an active compound in *Salvia miltiorrhiza*, was found to *not* affect the severity of AWS in alcohol-dependent rats [23], suggesting its utility may be limited to reducing intake rather than managing withdrawal.

The choice of intervention must be carefully tailored to the specific stage and severity of alcohol misuse and the individual's treatment goals. For instance, preventing a binge in an at-risk individual might involve as-needed medications like nalmefene or potentially Kudzu taken prophylactically before a drinking event. In contrast, managing severe AUD with a high risk of withdrawal necessitates inpatient medical detoxification, often with benzodiazepines, followed by long-term relapse prevention medications such as naltrexone or acamprosate. Some agents, like DHM, exhibit a desirable versatility by showing potential across multiple stages – from counteracting acute intoxication and reducing withdrawal severity to potentially decreasing ongoing consumption and mitigating alcohol-related liver damage.[10] This multi-pronged action makes such compounds particularly noteworthy. However, safety remains paramount, especially during the vulnerable period of alcohol withdrawal. The significant risks associated with using substances like ibogaine during acute AWS without prior medical stabilization highlight that "natural" does not inherently mean "safe," particularly in severe AUD.[86] This underscores the critical need for medical supervision and careful, evidence-based selection of interventions. A significant opportunity lies in developing and validating interventions specifically for early-stage problematic drinking and binge drinking prevention, an area historically less addressed by traditional AUD pharmacotherapies which have often focused on more severe

dependence.

7. Spotlight on Promising Interventions: Documenting Significant Positive Outcomes ("Illustrious Recovery")

The term "illustrious recovery" can be interpreted in various ways within the context of AUD treatment research. It can refer to statistically robust efficacy demonstrated in large clinical trials, dramatic improvements in individuals with severe, treatment-resistant AUD, or groundbreaking preclinical findings that pave the way for entirely new therapeutic classes with novel mechanisms. This section highlights interventions that have shown particularly significant positive outcomes, reflecting this spectrum.

7.1. Dihydromyricetin (DHM) (from *Hovenia dulcis / Ampelopsis grossedentata*)

DHM stands out due to its multifaceted actions against alcohol's effects.

- **Significant Positive Outcomes:**
  - **Preclinical Efficacy:** In animal models, DHM has consistently demonstrated an ability to counteract acute alcohol intoxication, reduce voluntary alcohol consumption, and alleviate a range of alcohol withdrawal symptoms, including tolerance, anxiety, and seizure susceptibility.[10] The underlying mechanism involving direct modulation of GABAA receptors is relatively well-elucidated.[10]
  - **Robust Hepatoprotection:** DHM shows significant protective effects against ethanol-induced liver damage. Studies in mice have reported amelioration of hepatic steatosis, reduction in triglyceride accumulation in both liver and serum, and improvements in mitochondrial health.[5] It has also been observed to reduce alcohol-induced histopathological changes in the liver.[12]
  - **Dual Metabolic and Central Mechanisms:** The liver-protective effects are linked to DHM's ability to activate alcohol-metabolizing enzymes (ADH and ALDH) [5], alongside its antioxidant and anti-inflammatory properties, and modulation of signaling pathways like the YTHDF2/PGC-1α/SIRT3 axis.[11] This is complemented by its direct actions on brain GABAA receptors.
- **Illustrative Evidence:** The convergence of strong preclinical data supporting both direct anti-alcohol effects (on intoxication, withdrawal, and consumption) and significant hepatoprotective actions, backed by well-defined central and metabolic mechanisms, positions DHM as a highly promising therapeutic candidate. The initiation of a Phase 1 human clinical trial to assess DHM for alcohol-associated liver disease [14] represents a critical step towards translating these preclinical successes into clinical application. This progression from traditional use and animal studies to formal human trials is a hallmark of a

promising intervention.

7.2. Kudzu (*Pueraria lobata* - Puerarin and Daidzin)

Kudzu and its active isoflavones have a long history in traditional medicine and have yielded encouraging results in human studies.

- **Significant Positive Outcomes:**
  - **Reduced Alcohol Consumption in Humans:** Several human studies, though relatively small, have reported reductions in alcohol consumption with Kudzu-derived interventions.
    - A standardized Kudzu root extract (2 grams), when taken 2.5 hours before a drinking session, significantly reduced beer consumption in a placebo-controlled study involving individuals who engage in binge drinking.[6]
    - Purified puerarin (1200 mg/day for one week) led to an approximate 30% reduction in average beer consumption (from 3.5 to 2.4 beers) during a 1.5-hour laboratory drinking session in heavy drinkers. This was accompanied by notable changes in drinking topography, such as slower drinking rates and smaller sip volumes.[15]
    - In non-treatment-seeking heavy drinkers, Kudzu extract reportedly reduced the number of drinks consumed per week by 34-57%, decreased the frequency of heavy drinking days, and increased the number of days of complete abstinence from alcohol.[19]
  - **Unique Mechanistic Insight (Daidzin):** The discovery that daidzin selectively inhibits mitochondrial ALDH-2, leading to the accumulation of biogenic aldehydes from neurotransmitter metabolism rather than a systemic acetaldehyde buildup, provides a distinct and compelling mechanistic rationale for its effects on alcohol intake.[17] This differentiates it from aversive therapies like disulfiram.
- **Illustrative Evidence:** The human clinical data demonstrating a tangible reduction in alcohol consumption in naturalistic or semi-naturalistic settings is a significant positive outcome, particularly for a botanical intervention. The consistent effect on reducing the *quantity* of alcohol consumed per episode, even if subjective craving is not always diminished [19], represents a valuable harm reduction achievement. The well-defined biochemical action of daidzin adds scientific credibility.

7.3. PDE4 Inhibitors (especially Apremilast)

The targeting of neuroinflammatory pathways via PDE4 inhibition is a novel and

promising approach for AUD.

- **Significant Positive Outcomes:**
  - **Broad Preclinical Efficacy (Apremilast):** Apremilast has demonstrated the ability to reduce binge-like alcohol intake, decrease motivation for alcohol self-administration, and reduce drinking even in the face of negative consequences in a variety of preclinical animal models. This includes efficacy in genetically selected mouse and rat lines that exhibit high alcohol drinking behaviors.[83]
  - **Successful Human Clinical Translation (Apremilast):** A double-blind, placebo-controlled human laboratory study involving non-treatment-seeking individuals with AUD found that apremilast (90 mg daily) significantly reduced the number of drinks consumed per day and the proportion of heavy drinking days when compared to placebo. The drug was also reported to be well-tolerated.[83]
  - **Novel Mechanism of Action:** Apremilast's efficacy is linked to its ability to reduce alcohol drinking and co-occurring mechanical allodynia (a pain-related symptom), and its modulation of GABAergic transmission within the central nucleus of the amygdala (CeA) provides a strong neurobiological underpinning.[83] This targets the neuroinflammatory component of AUD.
- **Illustrative Evidence:** The successful translation of robust preclinical findings across multiple relevant AUD animal models to positive human clinical data with apremilast—a drug already FDA-approved for other inflammatory conditions—is a particularly noteworthy achievement. This "drug repurposing" strategy offers a potentially faster route to new AUD treatments. Targeting neuroinflammation represents a paradigm shift from traditional neurotransmitter-focused therapies.

7.4. Naltrexone and Acamprosate (Established Pharmacotherapies)

These medications are the most well-established pharmacological interventions for AUD, with a wealth of supporting evidence.

- **Significant Positive Outcomes:**
  - **Meta-analytic Support:** Numerous systematic reviews and meta-analyses consistently demonstrate the efficacy of naltrexone and acamprosate in AUD treatment. Naltrexone is effective in reducing relapse to any drinking and, particularly, heavy drinking. Acamprosate is effective in preventing a return to any drinking and supporting abstinence.[2]
  - **Clinical Guideline Recommendation:** Both naltrexone and acamprosate are considered first-line pharmacotherapies for AUD when used as part of a comprehensive treatment plan that includes psychosocial interventions.[2]

- **Illustrative Evidence:** The sheer volume of research, encompassing a large number of clinical trials and tens of thousands of participants (e.g., one meta-analysis included 118 trials with 20,976 participants [2]), and the consistent findings across these high-level evidence syntheses make naltrexone and acamprosate the most well-documented "success stories" in terms of established efficacy in broad AUD populations. Their Numbers Needed to Treat (NNTs) are within ranges considered acceptable and clinically meaningful for chronic medical conditions.

7.5. Baclofen (Especially High-Dose for Severe AUD)

While its broader efficacy across the AUD spectrum is still debated, baclofen has garnered attention for its effects in some individuals, particularly those with severe and refractory AUD.

- **Significant Positive Outcomes (Case Reports/Small Studies):**
  - There are compelling case reports, such as the one by Bucknam [74], describing patients with long histories of severe, treatment-resistant alcohol dependence who experienced a complete and prolonged suppression of alcohol craving and consumption following treatment with high-dose baclofen (e.g., up to 140 mg/day, with one patient initially self-prescribing up to 270 mg/day). In such cases, patients have described the drug as a "miracle drug".[74] These reports often highlight a dramatic turnaround in individuals for whom other treatments had failed.
  - Baclofen is also noted for its potential utility in patients with AUD who have co-occurring liver disease, as it is not primarily metabolized by the liver.[1]
- **Illustrative Evidence:** Although larger randomized controlled trials (RCTs) on baclofen have yielded mixed results or have focused on specific subpopulations, the profound positive responses observed in some individuals with severe, difficult-to-treat AUD when using high doses (as famously reported by Dr. Ameisen in his self-case report, and echoed in reports like Bucknam's [74]) represent "illustrious recoveries" for those particular patients. These accounts have fueled ongoing research and clinical interest in high-dose baclofen, despite the need for more definitive large-scale evidence.

The concept of an "illustrious recovery" is indeed context-dependent. It can range from the statistically significant, population-level benefits seen with established drugs like naltrexone and acamprosate in large clinical trials, to the life-altering turnarounds observed in individual cases of severe, treatment-resistant AUD with agents like high-dose baclofen. For researchers, a novel compound like DHM or a repurposed drug like apremilast showing strong preclinical efficacy coupled with a clear,

druggable mechanism and successful early human translation also represents an illustrious path forward. Interventions with well-understood mechanisms, such as DHM's dual action on GABAA receptors and alcohol metabolizing enzymes, daidzin's specific ALDH-2 inhibition, or apremilast's PDE4 inhibition leading to CeA GABA modulation, often inspire greater confidence. Such mechanistic clarity facilitates rational drug development, the identification of biomarkers, and the potential tailoring of treatments to patient subgroups most likely to benefit. Highlighting these varied "success stories" provides both hope and tangible directions for future research and the evolution of AUD treatment.

8. Conclusion: Navigating the Landscape of AUD Interventions and Future Horizons

The exploration of interventions for Alcohol Use Disorder reveals a diverse and evolving landscape, stretching from ancient traditional herbal remedies to modern pharmacotherapies and cutting-edge research into novel biochemical targets. This report has systematically examined a range of substances, including lesser-known botanicals like *Hovenia dulcis* (DHM), *Pueraria lobata* (Kudzu), *Salvia miltiorrhiza*, and *Thymus vulgaris*, alongside established medications such as naltrexone and acamprosate, and emerging therapeutic strategies targeting neuroinflammatory pathways (e.g., PDE4 inhibitors like apremilast), the endocannabinoid system, and neuropeptide systems like the NOP receptor.

The most promising interventions often exhibit a combination of plausible mechanisms of action, supportive efficacy data (ranging from preclinical to human clinical trials), and acceptable safety profiles. Dihydromyricetin (DHM) stands out for its dual action in enhancing alcohol metabolism, providing hepatoprotection, and directly counteracting alcohol's effects on brain GABA systems. Kudzu, through its active compounds puerarin and daidzin, has demonstrated an ability to reduce alcohol consumption in human studies, with daidzin possessing a unique mechanism involving ALDH-2 inhibition. PDE4 inhibitors, particularly apremilast, represent a significant advancement by targeting neuroinflammatory processes, with apremilast showing positive results in both preclinical models and human clinical studies for reducing alcohol intake. Established pharmacotherapies like naltrexone and acamprosate continue to be vital tools, supported by extensive meta-analytic evidence for their efficacy in relapse prevention.

Categorizing these interventions by their primary neurobiological targets—GABAergic, opioid, serotonergic, dopaminergic systems, alcohol metabolizing enzymes, and HPA axis modulation—provides a framework for understanding the multifaceted nature of

AUD and for identifying potential synergies or gaps in current therapeutic approaches. It is evident that many substances, especially herbal ones, may exert their effects through multiple pathways, which could be advantageous for a complex disorder like AUD but also necessitates careful research to delineate specific contributions and ensure consistency.

Despite the progress, critical research gaps remain. There is a pressing need for rigorous, large-scale human clinical trials for many herbal interventions that show promise in preclinical studies or have a strong tradition of use. This includes further investigation into *Salvia miltiorrhiza*, the application of *Thymus vulgaris* for AWS in humans, and the careful evaluation of components from plants like *Peganum harmala*, considering its MAOI properties. Elucidation of the precise active compounds in herbal preparations and the development of standardized extracts are crucial for ensuring consistent efficacy and safety. Long-term safety and efficacy studies are also required for newer agents and novel applications of existing drugs. A significant frontier is the development of biomarkers and the use of genetic information and clinical profiles to predict treatment response, paving the way for more personalized medicine in AUD. The observation that patient variables such as gender, age, and psychiatric comorbidities significantly influence outcomes with combination therapies underscores this need.

Future investigations should continue to explore the therapeutic potential of targeting neuroinflammatory pathways beyond PDE4 inhibition, further unraveling the complexities of the endocannabinoid system's role in AUD, and developing modulators for neuropeptide systems like the NOP receptor. Combination therapies, potentially integrating promising and well-validated supplemental interventions with existing pharmacotherapies, warrant further study. Moreover, research focusing on interventions tailored to specific AUD subtypes or endophenotypes—such as individuals with high craving, severe withdrawal profiles, or prominent comorbid anxiety or depression—could yield more effective and targeted treatments.

Ultimately, the most effective approach to managing AUD is likely to be holistic and integrative, combining evidence-based pharmacological and supplemental interventions with robust psychosocial support, including counseling and mutual-help groups.[4] The journey is shifting from the pursuit of a single "magic bullet" to the development of a sophisticated and targeted toolkit of interventions capable of addressing the diverse manifestations and underlying mechanisms of this heterogeneous disorder. Continued interdisciplinary research, bridging ethnopharmacology, neuroscience, clinical pharmacology, and data science, is paramount to unlocking the full potential of these varied therapeutic avenues and

improving long-term outcomes for the millions affected by Alcohol Use Disorder. The evolving understanding of AUD's neurobiology, coupled with the innovative exploration of both traditional wisdom and modern scientific discovery, offers an optimistic outlook for the future of its treatment.

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