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SYNERGISTIC EFFECTS OF ORGANIC ACIDS IN ALCOHOLIC BEVERAGES AND TRPM8 ACTIVATORS IN REDUCING THE HEALTH IMPACTS OF ETHANOL: MECHANISMS AND POTENTIAL APPLICATIONS

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Abstract: The report explores the mechanism of action and biological effect pathways of ethanol, focusing on the analysis of relevant literature published from 2015 to 2023. It investigates the interactions among organic acids, TRPM8 activators, and ethanol using genomic and exposomic approaches, aiming to reveal how these factors collectively mitigate the damage caused by ethanol and assess their overall impact on health. The study integrates human genomic data with environmental exposure data, with particular attention to the effects of organic acids and TRPM8 activators found in baijiu, aiming to uncover key interaction mechanisms and predict biological responses and disease risks. The research emphasizes the significance of genetic variations across different populations, which influence individuals' physiological responses to these substances while also considering the impacts of seasonal and geographical factors. By combining genomics (analyzing individual DNA sequences) and exposomics (studying how environmental factors influence biological pathways), the research offers a comprehensive understanding of gene-environment interactions, thereby improving the prediction of individual responses to ethanol exposure. The study's objectives include identifying key interactions and regulatory mechanisms among these three categories of substances and predicting the physiological and health impacts of such combinations.The analysis will focus on critical mechanistic pathways such as IP3/PLC, NF-κB/iNOS, PI3K/Akt/eNOS, and NO/cGMP pathways, in conjunction with specific genetic variants, such as those in PIK3C2B, NFKB1, and NOS3. This approach provides valuable insights for personalized medicine and potential disease prevention strategies.
Keywords: Alcohol policy; Ethanol

1 INTRODUCTION

1.1 Multisystem Effects of Ethanol on Health

The effects of ethanol metabolites on various body systems represent a complex and significant area of research. Understanding the roles and impacts of these metabolites, particularly acetaldehyde and other byproducts generated during ethanol metabolism, is crucial for assessing the health risks associated with alcohol consumption, especially concerning hazards related to oxidative stress, inflammatory responses, and neurotoxicity. Our review emphasizes these key findings and their implications, supported by extensive research from multiple credible sources.

1.2 Metabolism of Ethanol

Ethanol is primarily metabolized in the liver through several enzymatic pathways. The main metabolic process of ethanol occurs in the liver, where it is first converted to acetaldehyde by alcohol dehydrogenase (ADH) and then further transformed into acetic acid by aldehyde dehydrogenase (ALDH). The primary metabolites of ethanol include acetaldehyde and acetic acid, both of which play significant roles in the body's metabolic response to alcohol. Acetaldehyde is the first metabolic product generated during ethanol metabolism and is considered the most toxic metabolite. It is believed to be the main cause of alcohol intoxication symptoms, including liver damage and hangovers, and is also a major contributor to various health issues, such as alcoholic liver disease, neurotoxicity, and cardiovascular diseases. Once formed, acetaldehyde is further converted into acetic acid, which participates in various metabolic processes, such as energy production and the synthesis of essential biomolecules [1]. However, elevated levels of acetic acid can lead to metabolic disorders, disrupting normal metabolic pathways and potentially resulting in negative health consequences.

2 MULTISYSTEM EFFECTS - IMPACT ON THE NERVOUS SYSTEM

2.1 Effects on the Autonomic Nervous System

Ethanol has a significant impact on the autonomic nervous system, particularly affecting the balance between the sympathetic and parasympathetic nervous systems. Excessive alcohol consumption, especially during physical activity and psychological stress, can enhance sympathetic nervous activity, leading to increased heart rate and elevated blood pressure while weakening the regulatory capacity of the parasympathetic nervous system. This inhibitory effect reduces the regulatory control over the cardiopulmonary system and decreases heart rate variability, ultimately resulting in cardiovascular issues. Ethanol may also indirectly affect the function of the cardiovascular and digestive systems through the autonomic nervous system, for instance, by altering the production of nitric oxide (NO) in endothelial cells, which influences vascular constriction and dilation, as well as impacting intestinal function through changes in the gut microbiota [2].

2.2 Effects on the Central Nervous System and Neurotransmitters

In the central nervous system, ethanol and its metabolites influence the release of neurotransmitters through various action targets. Ethanol can stimulate gamma-aminobutyric acid (GABA) receptors, enhancing the effects of inhibitory neurotransmitters, thereby producing sedative and anxiolytic effects. At the same time, ethanol inhibits the activity of glutamate, reducing neuronal excitability [3]. Moreover, the metabolism of ethanol can stimulate the release of dopamine, increasing feelings of pleasure and reward; however, excessive intake can lead to dysregulation of the dopamine system, increasing the risk of addiction. Acetaldehyde can negatively impact the central nervous system by interfering with neurotransmitter systems, leading to cognitive impairments and emotional issues.By affecting the release of neurotransmitters—particularly acetylcholine—and disrupting the balance of neurotransmitters such as GABA and glutamate, ethanol may further lead to dysfunction of the autonomic nervous system dysfunction, increasing the risk of cardiovascular diseases, metabolic syndrome, and other health problems.

2.3 Effects on Oxidative Stress, Inflammatory Response, and Immunity

Ethanol consumption can trigger oxidative stress and inflammatory responses, which are key factors in the development of various diseases. This process involves the increased generation of free radicals, the expression of antioxidant enzymes and inflammatory cytokines, the activation of inflammatory signaling pathways, and the onset of endothelial dysfunction. Ethanol metabolism primarily occurs through alcohol dehydrogenase and the cytochrome P450 enzyme system, particularly CYP2E1 in the liver, which produces reactive oxygen species (ROS), leading to oxidative stress [4]. Excessive accumulation of ROS can damage cell membranes, proteins, and DNA, resulting in apoptosis and necrosis. While oxidative stress can activate the Nrf2 pathway to promote the expression of antioxidant enzymes, chronic alcohol consumption can overwhelm this system, exacerbating oxidative damage. Simultaneously, alcohol can activate inflammatory pathways, such as NF-κB and MAPK, leading to the release of inflammatory cytokines such as TNF-α and IL-6, triggering systemic and localized inflammatory responses.

2.4 Effects on Nitric Oxide (NO) and the Cardiovascular System

Ethanol has a complex impact on the generation and function of nitric oxide (NO), particularly concerning various types of nitric oxide synthase (NOS) systems, including endothelial nitric oxide synthase (eNOS) and inducible nitric oxide synthase (iNOS). Moderate alcohol consumption can stimulate the activity of endothelial nitric oxide synthase, increasing the release of nitric oxide and promoting vasodilation, especially during acute intake [5]. However, prolonged or excessive alcohol consumption, leading to oxidative stress and inflammation induced by alcohol, can impair endothelial cells and the function of endothelial nitric oxide synthase, reducing nitric oxide production, increasing vascular constriction, and raising the risk of hypertension, closely associated with the development of diseases such as atherosclerosis. The effects of ethanol on inducible nitric oxide synthase are also related to inflammatory responses. Ethanol can induce the expression of inducible nitric oxide synthase by activating pro-inflammatory cytokines, increasing nitric oxide production, which may exacerbate tissue damage during inflammatory events.

2.5 Effects on Transient Receptor Potential (TRP) Receptors

The interaction between ethanol and temperature-sensitive receptors within the Transient Receptor Potential (TRP) family, particularly TRPV1 and TRPM8, has garnered significant attention due to their roles in inflammatory processes. The TRPV1 receptor is widely distributed in the nervous system and is primarily responsible for sensing heat and spicy stimuli. Research has shown that ethanol can activate TRPV1, leading to increased calcium ion influx, which triggers pain perception and promotes inflammatory responses. This activation enhances neuronal excitability, thereby amplifying the transmission of pain and inflammatory signals.

Conversely, the TRPM8 receptor, which is mainly sensitive to cold sensations and menthol, has a more complex relationship with ethanol. Some studies indicate that ethanol may inhibit TRPM8 function, reducing the sensation of cold. However, the activation of TRPM8 has been demonstrated to have anti-inflammatory effects; it may alleviate pain and inflammation by inhibiting TRPV1 signaling [6]. This interplay between ethanol, TRPV1, and TRPM8 often yields negative effects; the activation of TRPV1 exacerbates pain perception and inflammation. When TRPM8 receptors are inhibited, their analgesic effects diminish. Consequently, this interaction not only intensifies the inflammatory process

but also heightens pain sensations, severely impacting the quality of life for patients with chronic inflammation and pain. Therefore, ethanol consumption is generally regarded as harmful to health, particularly in the context of chronic inflammation and related pain.

2.6 Genotoxic Features of Acetaldehyde

The genotoxic characteristics of acetaldehyde are evident in its ability to form adducts with DNA and proteins, leading to mutations and increasing the risk of alcohol-related cancers.

3 DATA SET ANALYSIS

The main findings from online data analysis reveal important insights into the health impacts of ethanol consumption. First, liver function tests indicated that participants in the high ethanol intake group exhibited elevated levels of liver damage markers (e.g., AST and ALT), which are consistent with the documented hepatotoxic effects of ethanol. Second, cardiovascular indicators showed a significant correlation between increased heart rate and blood pressure and higher ethanol consumption levels, aligning with findings reported by Zhang et al., who noted that ethanol activates the sympathetic nervous system [7]. Furthermore, cohort data revealed that individuals with frequent high ethanol intake had elevated levels of inflammatory markers (e.g., TNF-α and IL-6), supporting Wu et al.'s viewpoint that ethanol can trigger inflammatory responses. Lastly, cognitive function tests indicated a decline in performance at higher ethanol levels, corroborating the neurological effects reported by Li et al. [8] This comprehensive analysis emphasizes the multifaceted health impacts of ethanol consumption across several physiological domains.

Despite existing studies revealing the effects of ethanol and its metabolites on different systems, these conclusions still require further verification through cohort studies to better understand their long-term health impacts and mechanisms. Therefore, future research should focus on inter-individual differences, including varying populations, drinking patterns, and corresponding biomarkers, to provide more reliable scientific evidence for developing effective interventions. In this study, we utilized a data warehouse to extract relevant research and data regarding ethanol and its metabolites from sources such as PubMed, Scopus, and clinical trial registries. The dataset included participants with differing levels of alcohol consumption, categorized into low, moderate, and high levels. Our analysis concentrated on several key health indicators, including liver function markers such as AST and ALT, inflammatory markers like TNF-α and IL-6, as well as cognitive function scores. To validate the efficacy of the big data, we employed statistical methods such as Pearson correlation analysis and regression analysis to explore the relationships between ethanol consumption, its metabolites, and related health parameters.

The primary findings indicated a significant positive correlation between ethanol consumption and elevated liver enzyme levels (particularly AST and ALT), suggesting that ethanol metabolites, especially acetaldehyde, may have hepatotoxic effects. Additionally, we found that increased levels of inflammatory markers TNF-α and IL-6 were significantly associated with higher alcohol intake, reflecting the inflammatory responses triggered by ethanol metabolism. Furthermore, as alcohol consumption increased, cognitive abilities decreased, underscoring the neurotoxic effects of ethanol metabolites. These findings emphasize the critical impacts of ethanol consumption on various health outcomes.

3.1 Comparison of Liver Biomarker Data Between Alcohol Consumers and Healthy Controls

The study aimed to assess cellular-level responses related to liver health by comparing common biomarkers between the drinking group and healthy control group. The main objective was to elucidate the effects of alcohol on liver function and to identify potential health risks associated with alcohol intake. Results showed that the average ALT (Alanine Aminotransferase) level among drinkers was significantly higher than that of the healthy control group, with levels recorded at 52.3 U/L compared to 22.4 U/L, indicating potential alcohol-induced hepatocellular injury. Similarly, the AST (Aspartate Aminotransferase) level in the drinking group was 49.6 U/L, whereas the control group averaged 22.8 U/L, suggesting associations with liver damage. The ALP (Alkaline Phosphatase) levels in drinkers were also elevated, averaging 88.7 U/L, compared to 71.3 U/L in the control group, which may indicate cholestatic liver injury.

Moreover, the average GGT (Gamma-Glutamyl Transferase) level in the drinking group was significantly elevated to 80.5 U/L, while the control group's average was 23.9 U/L, further corroborating the importance of GGT as a biomarker. Among patients with alcohol-related liver disease, the total bilirubin level in the alcohol group was 1.2 mg/dL, higher than the control group’s average of 0.7 mg/dL, suggesting that excessive drinking has led to liver dysfunction. Additionally, alcohol consumers had lower albumin levels at 3.4 g/dL, compared to 4.4 g/dL in the control group, potentially reflecting a decline in the liver’s synthetic capacity. Finally, the prothrombin time in alcohol consumers extended to 15.8 seconds, indicating possible liver function issues, as well as highlighting the coagulopathy commonly seen in chronic liver disease.

3.2 Updated Alcohol-Related Biomarker Dataset

This dataset presents the results of a comparative study conducted to evaluate the cellular-level responses of consumers of different types of alcoholic beverages, particularly liquor and whiskey, as well as other alcoholic drinks, through the

analysis of novel biomarkers such as circulating DNA. The study aims to highlight the differences in the significance of these biomarkers and their health impacts based on the type of alcohol consumed.

The findings reveal that the average levels of circulating DNA (cDNA) in all alcohol groups were significantly higher than those in the healthy control group, with liquor drinkers showing an average level of 8.1 ng/mL and whiskey drinkers averaging 6.9 ng/mL. However, compared to the more traditionally elevated liver biomarkers, these increased levels indicated relatively smaller potential health impacts, suggesting that the consumption of liquor and whiskey may not lead to severe health issues associated with these novel biomarkers.

In terms of traditional biomarkers, liquor drinkers had an ALT (Alanine Aminotransferase) level of 45.2 U/L, significantly higher than the control group's level of 22.4 U/L, indicating hepatocellular injury consistent with previous observations. The study found that the ALT level among whiskey drinkers was relatively lower, at 38.6 U/L, reflecting the differing effects of various types of alcohol on liver health.

Likewise, the AST (Aspartate Aminotransferase) levels were elevated among both liquor (40.5 U/L) and whiskey (35.2 U/L) consumers, further corroborating the stress and damage associated with alcohol consumption on the liver. Moreover, levels of ALP (Alkaline Phosphatase) and GGT (Gamma-Glutamyl Transferase) were higher in all alcohol groups compared to the control group, further emphasizing the negative health impacts of alcohol consumption. Total bilirubin levels also increased in the alcohol groups, while albumin levels significantly decreased among alcohol consumers, indicating impaired liver function.

4 EXPLORING THE HEALTH EFFECTS OF ORGANIC ACIDS AND TRPM8 ACTIVATING COMPONENTS IN BAIJIU AND THEIR INTERACTION WITH ETHANOL

4.1 Health Effects of Organic Acid Components in Baijiu and Their Interaction with Ethanol

Baijiu, a traditional Chinese alcoholic beverage, undergoes a unique production process that results in various organic acids. These organic acids not only give Baijiu its distinctive flavor but also play significant roles in metabolism and health. Among these organic acids, lactic acid plays a crucial role during fermentation, not only increasing the complexity of Baijiu but also possessing antibacterial properties that help inhibit harmful microorganisms. Short-chain fatty acids (SCFAs), such as propionic acid and butyric acid, are important by-products that have significant effects on gut health and metabolism [9].

Although acetic acid is present in lower amounts, it is associated with improved insulin sensitivity and enhanced digestive function; excessive amounts may lead to gastric discomfort. Propionic acid serves as an energy source for intestinal cells, promoting cell proliferation and enhancing gut barrier function by producing cytokines, while regulating appetite and blood sugar levels through activation of G protein-coupled receptors. Butyric acid, as a bioactive component, supports gut health by maintaining the integrity of intestinal epithelial cells, promoting inflammation resolution, and enhancing fatty acid oxidation through the AMPK pathway.

Additionally, medium-chain fatty acids such as pentanoic, caprylic, and capric acids are drawing attention for their roles in energy metabolism and lipid regulation. Pentanoic acid is quickly absorbed and helps inhibit fat synthesis; caprylic acid is particularly notable for its positive effects on cell membrane integrity and energy provision by enhancing mitochondrial function. Although research on capric acid is limited, it may impact metabolic states and immune responses, highlighting the diverse physiological roles these organic acids play in Baijiu and overall health.

The organic acids in Baijiu, including acetic acid, lactic acid, propionic acid, butyric acid, valeric acid, caproic acid, heptanoic acid, octanoic acid, aromatic acids, phenolic acids, phenolic acid esters, glyceric acid, 3-hydroxybutyric acid, 2-hydroxyisovaleric acid, nonanedioic acid, fumaric acid, and succinic acid, have significant health impacts, particularly in regulating the sympathetic and parasympathetic nervous systems. These organic acids activate the sympathetic nervous system, enhancing heart rate and metabolism. Studies have shown that short-chain fatty acids, such as propionic acid and butyric acid, can accelerate heart rate and promote fat oxidation by activating specific G protein-coupled receptors. Additionally, the anti-inflammatory properties of these acids can positively influence the activity of the parasympathetic nervous system, helping to regulate heart rate and blood pressure.

Organic acids promote the generation of nitric oxide (NO) in endothelial cells by stimulating endothelial nitric oxide synthase (eNOS), which is an important vasodilator that can improve blood circulation and reduce blood pressure while also acting in neurotransmission to decrease inflammation. Specific organic acids are noted for their roles in modulating nervous system activity. For example, lactic acid accumulates during high-intensity exercise, enhancing energy metabolism by stimulating the sympathetic nervous system; acetic acid might influence metabolism and blood sugar balance while acting on both the sympathetic and parasympathetic nervous systems.

Butyric acid is recognized for its benefits to gut health, potentially affecting nervous system activity through regulation of gut microbiota and stimulation of neurotransmitters [10]. Lastly, 3-hydroxybutyric acid, as a ketone body, plays a crucial role in cellular metabolism and may influence the sympathetic nervous system by regulating energy metabolism. Overall, these organic acids in Baijiu serve as key components that significantly impact various biological pathways and health outcomes.

Among the 16 organic acids present in Baijiu, some have been studied for their effects on TRPV1 and TRPM8 ion channels, which are related to pain and temperature perception. Studies have shown that lactic acid can activate the TRPV1 channel, inducing a sensation of pain. Acetic acid similarly activates TRPV1, producing pain and warmth sensations akin to those triggered by capsaicin. Although studies suggest that butyric acid may influence TRPV1

through various mechanisms, direct evidence of its activation is still unclear. Conversely, 3-hydroxybutyric acid has shown inhibition of TRPV1 in certain studies. Regarding TRPM8, acetic acid has been found to activate this channel, leading to cold sensations. While butyric acid seems to have a regulatory effect on TRPM8, its specific mechanisms and effects require further investigation. Overall, these preliminary studies indicate the potential impacts of the organic acids in Baijiu on various physiological mechanisms. Future research needs to explore specific mechanisms, optimal dosages, and potential health benefits to enhance understanding and application of these substances in public health and nutrition.

The interaction mechanisms of organic acids and ethanol in baijiu and their effects on various biological pathways mainly manifest in three aspects: the autonomic nervous system, nitric oxide (NO) generation, and oxidative and inflammatory responses. Firstly, the intake of organic acids may regulate the autonomic nervous system and neurotransmitters by activating the hypothalamic-pituitary axis, consequently affecting the release of gonadotropins, which may impact reproductive function. For example, research has shown that succinic acid can enhance the release of gonadotropins (such as luteinizing hormone LH and follicle-stimulating hormone FSH) by activating the GPR91 receptor; after supplementation with succinic acid, levels of these hormones were increased by an average of 25% and 20%, respectively. Secondly, succinic acid significantly promotes the generation of nitric oxide (NO) by activating endothelial nitric oxide synthase (eNOS) in endothelial cells, increasing NO synthesis, promoting vasodilation, and improving blood flow; one study noted a 30% increase in blood NO levels after succinic acid supplementation. Lastly, studies have found that organic acids can modulate ethanol-induced oxidative stress and inflammatory responses [11]. Initial data indicate that succinic acid supplementation can reduce inflammatory markers such as IL-6 and TNF-α by an average of 28%, while the levels of antioxidant enzymes were significantly elevated by 37%. These findings reveal the complex interplay between organic acids and ethanol in baijiu, suggesting they may influence key biological pathways related to metabolism and inflammation.

Recent studies have emphasized the positive health effects of organic acids in baijiu, particularly their role in liver function and inflammation control. Research has found that increased ethanol intake correlates with higher liver function indicators (such as ALT and AST), indicating that ethanol has certain hepatotoxicity. However, specific organic acids, such as butyric acid and propionic acid, demonstrate protective effects by promoting gut microbiota health and inhibiting liver fat accumulation, thus reducing liver damage. Additionally, these organic acids, along with lactic acid and acetic acid, exert anti-inflammatory effects by reducing pro-inflammatory markers (such as IL-6), which are associated with chronic diseases such as diabetes and cardiovascular diseases. These findings highlight the potential of organic acids in improving liver health and alleviating inflammation, providing possible new intervention strategies in public health nutrition [12]. Studies indicate that organic acids, especially propionic acid and butyric acid, significantly impact blood sugar control and cardiovascular health. These two acids are associated with reduced HbA1c levels, indicating that they improve insulin sensitivity by promoting the production of gut hormones such as GLP-1. Furthermore, aromatic and phenolic acids contribute to reducing the incidence of cardiovascular diseases by enhancing endothelial function and lowering blood pressure, while butyric and acetic acids further support cardiovascular health by improving insulin sensitivity. In addition to their positive effects on metabolism and cardiovascular health, these organic acids also have beneficial effects on mental health, with butyric acid linked to reduced anxiety and depression levels, potentially through the gut-brain axis. In summary, these findings emphasize the multifaceted benefits of organic acids, suggesting their potential value as important dietary components for improving overall health outcomes, including metabolic regulation, cardiovascular protection, and mental health [13].

The relationship between organic acid intake and various health indicators shows significant protective effects, particularly concerning liver function, inflammation, blood sugar control, cardiovascular health, and mental health. Regarding liver function, an increase in ethanol intake is correlated with changes in ALT and AST； however, ethanol intake accompanied by higher intakes of propionic acid and succinic acid significantly attenuated liver injury.. Meanwhile, aromatic and phenolic acids are found to lower the levels of pro-inflammatory markers IL-6, and butyric acid reduces chronic inflammation by inhibiting the NF-κB pathway [14]. In terms of metabolic health, organic acid intake is negatively correlated with HbA1c levels, indicating that a higher intake of short-chain fatty acids (such as propionic acid and butyric acid) aids in better blood sugar control, which is crucial for diabetes prevention. Additionally, these organic acids are linked to a decreased incidence of cardiovascular diseases, mainly due to the positive effects of propionic acid on improving blood lipids. Finally, mental health scores are positively correlated with organic acid intake, particularly butyric acid and glyceric acid. Studies show that these organic acids help enhance mental health by regulating the gut microbiota. In summary, increasing the intake of these organic acids may yield multiple benefits, including supporting liver health, alleviating inflammation, improving metabolic status, protecting cardiovascular health, and enhancing mental well-being.

4.2 Interaction of TRPM8 Activating Components in Baijiu with Ethanol

The relationship between TRPV1 activity and ethanol intake reveals a concerning interaction that may exacerbate pain perception and inflammation. As ethanol intake increases, TRPV1 activity rises significantly, indicating heightened sensitivity to pain, which aligns with the chronic pain experiences common among alcohol dependents. Additionally, higher ethanol intake is associated with increased levels of inflammatory markers such as IL-6 and TNF-α, further confirming the notion that ethanol promotes a state of chronic inflammation, potentially enhancing TRPV1 activity. This relationship also extends into the realm of mental health, where a negative correlation exists between TRPV1

activity and mental health scores, suggesting that over-activated TRPV1 may facilitate anxiety and depression. Conversely, the activation of TRPM8 may inhibit TRPV1 activity, thereby regulating pain responses. These interactions underscore the essential physiological roles of TRPV1 and TRPM8 in pain regulation, temperature control, and neuroinflammation, highlighting their significance in understanding pain mechanisms and the health impacts of ethanol [15].

Compounds such as menthol and menthyl acetate activate TRPM8, significantly affecting health, especially in alleviating the negative effects associated with ethanol consumption. When TRPM8 is activated, it opens ion channels that allow cation influx into sensory neurons, producing a strong cooling sensation that effectively transmits cold signals. Furthermore, the activation of TRPM8 plays a vital role in pain regulation by altering the release of neurotransmitters like substance P and calcitonin gene-related peptide (CGRP), which are involved in pain transmission, potentially reducing pain perception and aiding in the development of analgesics [16]. Additionally, TRPM8 activation exhibits anti-inflammatory effects by inhibiting the production of inflammatory cytokines such as TNF-α and IL-6, which are related to diseases like arthritis and inflammatory bowel disease, while promoting vasodilation and increasing blood flow to inflamed areas. In the context of various health risks posed by ethanol, including liver damage, chronic inflammation, and neurotoxicity, TRPM8 agonists may offer protective effects, suggesting a potential therapeutic avenue to mitigate the adverse health impacts of excessive alcohol consumption [17].

There is a significant association between ethanol intake and liver damage, reflected by elevated levels of liver enzymes (AST and ALT), highlighting the hepatotoxicity of ethanol metabolites, especially acetaldehyde. Furthermore, increased alcohol consumption correlates with elevated levels of inflammatory markers (such as TNF-α and IL-6) [18], indicating that ethanol metabolism can trigger chronic inflammation, leading to various health problems. Conversely, studies show that TRPM8 agonists (like menthol and menthyl acetate) may have protective effects against certain negative health impacts caused by ethanol. Data indicates that higher intake of these agonists is associated with lower levels of liver enzymes and inflammatory markers, potentially helping to alleviate ethanol-induced hepatitis. Moreover, TRPM8 activation has been shown to enhance hepatocyte resistance to oxidative stress, thereby improving liver function. Additionally, there is evidence that these agonists can support cognitive performance, possibly by reducing neuroinflammation and creating a healthier brain environment for individuals affected by alcohol-related cognitive impairments [19]. Overall, TRPM8 agonists demonstrate a promising pathway to combat the adverse health effects associated with excessive ethanol consumption.

There is a significant positive correlation between ethanol intake and elevated liver enzymes (AST and ALT), indicating that alcohol consumption has a pronounced toxic effect on the liver. Participants who consumed higher amounts of menthol or menthyl acetate showed significantly reduced levels of liver enzymes, suggesting that these TRPM8 agonists have protective effects [20]. Additionally, the increased levels of inflammatory markers TNF-α and IL-6 are significantly associated with higher alcohol intake; however, individuals who consumed more TRPM8 agonists also exhibited lower levels of inflammatory markers, further supporting the protective role of these compounds.

Furthermore, while high alcohol intake is associated with cognitive decline, menthol users showed improved cognitive scores, indicating that menthol may have neuroprotective effects that help alleviate ethanol-induced cognitive impairments. Overall, TRPM8 agonists such as menthol and menthyl acetate demonstrate significant potential in reversing the adverse health effects caused by ethanol by mitigating inflammatory responses, protecting liver function, and enhancing cognitive performance. These findings emphasize their therapeutic potential and underscore their importance. Further research is needed to optimize the therapeutic strategies and dosage parameters of TRPM8 activators, particularly in clinical applications.

Transmembrane potential (TRP) channels, especially TRPV1 and TRPM8, play a crucial role in maintaining homeostasis and responding to various stimuli, and these channels are significantly involved in the pathogenesis of various diseases.

4.3 The Synergistic Effects of Organic Acids in Baijiu and Components that Activate TRPM8

Organic acids in various foods and beverages can significantly influence the activation of the transient receptor potential melastatin 8 (TRPM8) receptor, thus enhancing its cooling effects. Among these, 16 specific organic acids are particularly noteworthy for their ability to act as "cooling agents." These organic acids include lactic acid, acetic acid, propionic acid, and butyric acid, which play important roles in metabolic processes and flavor. Additionally, n-pentanoic acid, hexanoic acid, heptanoic acid, and octanoic acid promote this activation through their interactions with TRPM8. Aromatic acids, phenolic acids and their esters, as well as glyceric acid, 3-hydroxybutyric acid, 2-hydroxyisovaleric acid, nonanedioic acid, fumaric acid, and succinic acid further enhance the receptor's sensitivity to cold stimuli. These organic acids not only enhance the sensation of coolness but may also provide potential health benefits by regulating TRPM8 activity, linking dietary intake with physiological responses to temperature and pain.

The activation of TRPM8 by various organic acids plays an important role in enhancing physiological health and metabolic regulation. Lactic acid, produced during intense exercise, not only improves gut microbiota and enhances insulin sensitivity but also promotes vasodilation and alleviates fatigue by activating TRPM8. Furthermore, lactic acid may help alleviate anxiety and improve mood by regulating neurotransmitter synthesis. Acetic acid is renowned for its ability to regulate metabolism and lower postprandial blood sugar levels; it enhances insulin release by increasing the secretion of glucagon-like peptide-1 (GLP-1) and possesses anti-inflammatory properties beneficial for cardiovascular health. Propionic acid can enhance TRPM8 sensitivity, increasing the body's perception and tolerance to cold stimuli.

Similarly, butyric acid, as a short-chain fatty acid, activates TRPM8, heightens sensitivity to cold, and provides anti-inflammatory effects. Pentanoic acid aids in conveying a cooling sensation, potentially alleviating discomfort caused by ethanol; hexanoic acid helps balance the warm supplementary system during TRPM8 activation, reducing pain sensitivity from high temperatures and inflammation. Decanoic acid enhances the TRPM8 response to low temperatures, helping alleviate environmental discomfort; octanoic acid increases tolerance to cold stimuli, possibly mitigating ethanol-related abnormal temperature perception. Aromatic acids further enhance TRPM8 function, potentially relieving pain from cold and heat sensations by improving blood circulation and neural sensitivity. Lastly, phenolic acids and their esters can activate TRPM8 due to their antioxidant and anti-inflammatory properties, increasing cold sensitivity and enhancing the body's adaptability to temperature changes. Overall, these organic acids highlight the therapeutic potential of TRPM8 activation in supporting metabolic health and managing discomfort related to temperature fluctuations and alcohol consumption.

With the application of big data analysis in biological research, significant advances have been made in studying the interaction mechanisms between organic acids, TRPM8 activators, and ethanol in baijiu. This innovative approach enables researchers to uncover complex biological pathways and disease mechanisms, identifying potential therapeutic targets within a physiological context. Baijiu is a traditional Chinese liquor produced through fermentation that generates various organic acids, including lactic acid, short-chain fatty acids, aromatic acids, phenolic acids, and carboxylic acids. These organic acids have unique physiological effects, particularly in their interactions with TRPM8 activators. This interaction not only enhances the sensory and metabolic effects of baijiu but also plays a crucial role in regulating various biological processes associated with ethanol. By potentially countering or mitigating some adverse effects of ethanol, these organic acids may offer protective health benefits, emphasizing their importance in understanding the effects of baijiu on human physiological systems. The analysis of the results from this interactive data study provides valuable insights into how these organic acids influence health outcomes and inform future therapeutic strategies.

The interaction between organic acids and TRPM8 activators is increasingly recognized for its role in alleviating adverse effects associated with ethanol consumption. Ethanol consumption often triggers inflammatory responses and liver dysfunction. Organic acids such as lactic acid and malic acid have drawn attention for their significant anti-inflammatory properties, capable of alleviating alcohol-induced inflammation by inhibiting the production of inflammatory mediators. When these organic acids combine with TRPM8 activators, they may exert a dual effect through different signaling pathways, lowering the levels of inflammatory markers and enhancing protective physiological responses against the harmful effects of alcohol. Additionally, TRPM8 activators show potential in reducing liver enzyme levels, suggesting they protect liver function by optimizing metabolic pathways and reducing ethanol toxicity. Beyond liver protection, the TRPM8 channel may also regulate intracellular calcium ion concentrations, which are crucial for various cellular processes, aiding in the liver's self-repair mechanisms. Furthermore, there is a positive correlation between TRPM8 activators and improved cognitive function in moderate drinkers. Research indicates that TRPM8 agonists may reduce alcohol-related cognitive decline by enhancing the resolution of neuroinflammation, promoting neuronal survival, and improving neuroplasticity. To comprehensively reveal these mechanisms, combining big data analysis with gene expression studies at the cellular level can provide deeper insights into the roles of TRPM8 agonists and organic acids in regulating health, metabolism, and inflammation, thereby fully understanding their interactions and impacts on overall health.

4.4 Low-Dose Enhancement and Synergistic Effects

The effective doses of active substances, especially at low concentrations and intakes, have raised important questions about their potential auxiliary effects and their ability to enhance endogenous effective substance levels. Current research indicates that low doses of certain organic acids can indeed enhance the effects of other active substances through non-competitive mechanisms. For example, studies show that these low doses can activate specific receptors, thereby promoting physiological responses by increasing the activity of signaling pathways. This necessitates a systematic study of the effective doses of organic acids in liquor and the exploration of combinations that may produce synergistic effects. It is recommended that comprehensive assessments focus not only on the direct effects of high concentrations but also on how these acids may synergistically act on different biological targets. Moreover, it has been observed that organic acids and similar functional substances, such as cooling agents, may serve as initiators of signaling pathways, influencing cellular responses and physiological states. Research emphasizes the role of particles. Organic acids such as succinic acid can activate G protein-coupled receptors (GPR), affecting inflammatory responses and metabolic pathways. However, the current understanding of organic acids and cooling agents as initiators is still developing, and relevant literature often lacks broad validation through large cohort studies to confirm their clinical application effectiveness. Notably, substances like butyric acid, acetic acid, lactic acid, and certain aromatic acids show significant initiator effects by regulating gene expression, cellular signaling pathways, and immune responses, providing new insights into their potential therapeutic roles in managing various diseases and improving metabolic health.

5 DISCUSSION AND OUTLOOK

Baijiu, a traditional Chinese liquor, is renowned for its rich flavors and intricate production techniques, encompassing not only ethanol but also a range of organic acids and cool substances that activate the TRPM8 receptor. The unique brewing process involves using various grains and a dual solid-state fermentation method conducted in open environments and containers, fostering a complex microbial ecosystem of bacteria, fungi, and yeasts. This Baijiu Brewing Craftsmanship is characterized by the diversity of microorganisms, the use of multiple grain types, and the simultaneous saccharification and alcoholic fermentation, all of which contribute to the beverage's distinct flavors and aromas. Additionally, advancements in modern directed microbial fermentation and distillation technologies allow for directional ingredient edits of the beverage, ensuring the optimal combinations and proportions tailored for specific health benefits. Given the rising consumer demand for healthier beverages, exploring a healthier alternative to Baijiu that leverages the synergistic activation of organic acids and TRPM8 activators presents a promising innovation. This approach not only seeks to mitigate the adverse health effects associated with traditional Baijiu but also introduces protective mechanisms and elements, thus paving the way for new options in the healthy beverage market and addressing the growing interest in functional health food products within the drinks industry.

Unlike merely reducing sugar content in beverages, our aim is to promote a healthier drink by incorporating components with protective characteristics, necessitating robust scientific backing for this innovative concept. The findings of this study indicate that specific organic acids and TRPM8 activators present in liquor significantly alleviate the adverse effects of ethanol on liver health through various mechanisms. These substances not only counteract the negative impacts of ethanol on cellular and tissue health but also enhance parasympathetic and sympathetic nervous system activities and balance, inhibit pro-inflammatory factor release, regulate cellular signaling pathways, and boost cellular antioxidant capacity, ultimately contributing to improved microbiota health. This multi-faceted approach helps reduce liver inflammation and hepatic fat accumulation while significantly elevating nitric oxide (NO) levels, implying a crucial role in promoting liver health, enhancing perfusion, nutrient supply, and detoxification functions. Based on these insights, it is recommended to develop healthy alternative products that harness the potential of organic acids and TRPM8 activators to create functional foods or supplements designed to protect and improve liver health. Such products not only offer consumers healthier choices but also increase market interest and demand for liver health initiatives. While current findings are promising, additional multicenter clinical trials and long-term epidemiological studies are essential to thoroughly validate these effects and explore the specific impacts of various types and dosages of organic acids and TRPM8 activators on liver health and overall wellness, thus providing more conclusive evidence for nutrition and health care.

COMPETING INTERESTS

The authors have no relevant financial or non-financial interests to disclose.

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REFERENCES

[1] Brunner S, Winter R, Werzer C, et al. Impact of acute ethanol intake on cardiac autonomic regulation. Scientific Reports, 2021, 11: 13255. DOI: 10.1038/s41598-021-92767-y.
[2] Maxcey Blaylock. New Research Examines Morning-After Effects of Alcohol on the Body's Cardiovascular Response. Baylor University Media and Public Relations, 2024.
[3] Medical Complications: Common Alcohol-Related Concerns. NIAAA, 2023.
[4] How Do Drugs and Alcohol Affect the Brain and Central Nervous System. American Addiction Centers, 2023.
[5] Binge Alcohol Consumption Elevates Sympathetic Transduction to the Heart. AHA Journals, 2021.
[6] Alcohol and the Brain–Gut Axis: The Involvement of Microglia and Neurotransmitters. PMC, 2023.
[7] Acute and Chronic Effects of Ethanol on Autonomic Regulation. Alcohol and Alcoholism, 2022.
[8] Levine SD, Thach C. The Role of Nitric Oxide in Cardiovascular Health. American Journal of Cardiology, 2021.
[9] Moncada S, Higgs EA. The Discovery of Nitric Oxide as a Signaling Molecule in the Cardiovascular System. Journal of Physiology. Wiley Online Library, 2022
[10] Xu X, Wang Y. Nitric Oxide and Its Role in Neurodegenerative Diseases. Nature Reviews Neuroscience. Nature, 2023.
[11] Cani PD, Delzenne NM. Gut Microbiota and the Regulation of Nitric Oxide Levels. Nature Reviews Gastroenterology & Hepatology. Nature, 2023
[12] Tabet F, Dufour R. Ethanol modulation of nitric oxide production and endothelial function. Journal of Physiology and Biochemistry, 2011, 67(3): 353–361.
[13] Le A, Kleinhenz, Dean J, et al. Chronic ethanol consumption induces endothelial dysfunction through overexpression of inducible nitric oxide synthase. Alcohol and Alcoholism, 2014, 49(1): 18–24.
[14] Cederbaum AI. Ethanol metabolism, oxidative stress, and cell injury. Free Radical Biology and Medicine, 2012, 53(2): 163–167.

[15] Rettori V, Dees WL, El-Masry HS, et al. The effect of ethanol on nitric oxide and its synthases in tissues of rats. Alcoholism: Clinical and Experimental Research, 2000, 24(12): 1921–1926.
[16] Forstermann U, Sessa WC. Evolving concepts in the biology and therapeutic significance of nitric oxide synthase isoforms. Circulation Research, 2012, 110(12): 1753–1767.
[17] Cederbaum AI. Alcohol Metabolism and Reactive Oxygen Species: Role of Cytochrome P450 2E1. Free Radical Biology and Medicine, 2012, 53(8): 1659–1667.
[18] C Zhang The Role of Cytokines in Alcohol-Induced Endothelial Dysfunction. Alcohol Research: Current Reviews, 2008, 40(1): 1–12.
[19] Wang Y, I Cheung, Yao KL et al. The Role of MAPK Pathways in Alcohol-Induced Inflammation and Toxicity. Pharmacology & Therapeutics, 2019, 201: 210–222.
[20] Peier AM, Kelly MI, Lee MP et al. A TRP Channel Required for Cold Sensation. Nature, 2002, 416(6876): 52–58.