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Dairy Product as a Preventative and Therapeutic Method in Alcohol Liver Disease

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Abstract. Alcohol is one of the most prevalent global causes of chronic liver damage. Alcohol-related liver disease (ALD) is a prominent cause of liver disease related mortality, yet few treatments are now available. Important variables in the development of ALD or alcoholic liver cirrhosis include inflammation, oxidative stress, innate immunity, angiogenesis, and fibrosis. Due to biological constituents of diary product, including as lactoferrin, bioactive peptide, immunoglobulins, lactose, and vitamins, it has become a popular candidate for the treatment of ALD, since it has a number of immune-enhancing properties. This paper summarized the attributing factor, parthenogenesis, and current preventative and treatment methods for ALD to provide a comprehensive understanding of the disease. The preventive and therapeutic effects of milk, fermented milk, whey, and camel milk against ALD were then analyzed. These methods are anticipated to add the protective and therapeutic choices for alcohol-related liver damage in clinical use, either alone or in combination with other medications.

Keywords: alcohol, alcohol-induced liver disease, milk, dairy product

1. Introduction

There are over 2 billion alcoholics worldwide, over seventy-five million have been identified as having an alcohol disorder and being at risk for liver disease [1]. Alcohol-related liver disease (ALD) as a prominent cause of liver disease related mortality, accounting for 47.9% of deaths from liver cirrhosis and 0.9% of all fatalities worldwide [2]. The most dangerous type of the disease, severe alcoholic hepatitis, typically manifests as acute hepatitis sickness, profound jaundice, and underlying cirrhosis. Its 30-day fatality rate ranges from 20 to 50% [3]. The only available treatment remained is corticosteroids, which have a 60% short-term response rate but no longer outperform placebo in terms of long-term survival [3]. Patients' only curative option is liver transplantation [4]. Therefore, it is crucial to create new treatments for people who have severe alcoholic hepatitis.

There are not many treatments available at this time, and the most prevalent type of steroid medication, corticosteroids, are not effective enough [5]. In addition to this, administering cytokine treatment can be a laborious and pricey process [6]. Therefore, it is an urgent demand for the development of fresh medications which are both safe and effective. Many earlier experiments that used natural products as hepatotoxic agent protectors showed meaningful result [7, 8]. Due to biological constituents of diary product, such as lactoferrin, bioactive peptide, immunoglobulins,

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lactose, and vitamins, it has become a popular candidate to treat ALD, since it contains a number of features that boost immunity.

2. Alcohol liver disease

2.1. Attributing factor of ALD

One of the most strongly related factors to ALD is cumulative alcohol usage. A meta-analysis of several research revealed that drinking moderate amounts of alcohol (25 g per day) considerably raised the likelihood. In addition, the relative risk increased by increasing does, doubling at 50 g/d and about tripling at 100 g/d [9]. Regardless of the absolute levels of alcohol use, drinking habits and the kind of beverage affect the likelihood for ALD. For instance, red wine consumers may have a lower incidence of ALD than the individuals who consume other alcoholic beverages [10]. Additionally, it indicates that drinking alcohol outside of mealtimes, consuming multiple types of alcoholic beverages as opposed to just one, and drinking during the week as opposed to only on the weekends all raise the risk of disease [11].

Other environmental factors, such as co-existing viral infection, also have a negative impact on the outcome of ALD [12]. ALD development is also influenced by female gender, ethnicity [13] and the difference between monozygotic and dizygotic [14].

2.2. Pathogenesis of alcohol induced liver

Liver is an important metabolism organ, which metabolize 90% ingested alcohol in human. Alcohol ingestion cause liver injury mainly by inflammation, oxidative stress, innate immunity, angiogenesis, and fibrosis [15].

Alcohol is known to have a direct hepatotoxic effect. Additionally, to the development of an immune response, this damage might manifest as a variety of functional abnormalities [16]. Alcohol is processed in the liver through the oxidative and non-oxidative pathways, respectively (FIGURE 1, FIGURE 2) [5]. Alcohol dehydrogenase (ADH) converts alcohol to acetaldehyde throughout the oxidative pathway, acetaldehyde will cause DNA and cellular damage, inflammation and fibrogenesis in liver. Then acetaldehyde is further catalyzed by acetaldehyde dehydrogenase (ALDH) to acetate, which also damage the liver by increasing the synthesis of Acetyl-CoA, which is important in enhancing histone acetylation). When the level of acetyl co-A is too high, it will cause acetylate the histone and remove the positive charge of it, which lead to the less interaction of histone with negative charge DNA, and loose the gene contain region, finally increase the level of gene transcription. It is harmful especially when histone acetylation occurs at specific gene promotor such as, IL-6 and TNF-α, which play important role in liver damage as inflammation cytokines. Alcohol can also be converted to acetaldehyde via MEOS, CYP2E1, which is another oxidative pathway [15]. Like the ADH pathway, it will generate high level of oxidative stress by produce ROS. The intense oxidative stress will activate some transcription factor, such as NF-κB, and lead to inflammation. In non-oxidative metabolism pathway, catalase catalyze the ethanol into acetate, to damage the mitochondrial and lead to alcoholic steatosis [17].

Apart from that, alcohol can cause liver injury by changing the activity of human microbiota activity. It can cause intestinal bacteria overgrowth in inner mucus layer, which should be devoid of bacteria in healthy individual, and change the gut microbial composition. The alcohol ingestion will also cause the damage to tight junction protein, which is used to tightly bound intestinal epithelial cell. This will lead to the opening of the intercellular distance of gut cell, and allow bacteria component or product, such as endotoxin get in the human body and induce inflammation [18].

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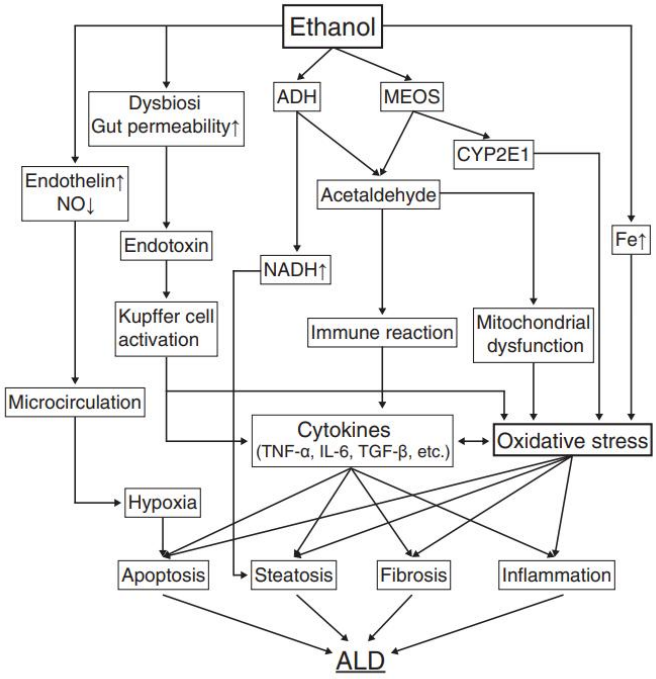


Figure 1. Summary of the mechanisms of alcoholic live disease (ALD) development [15].

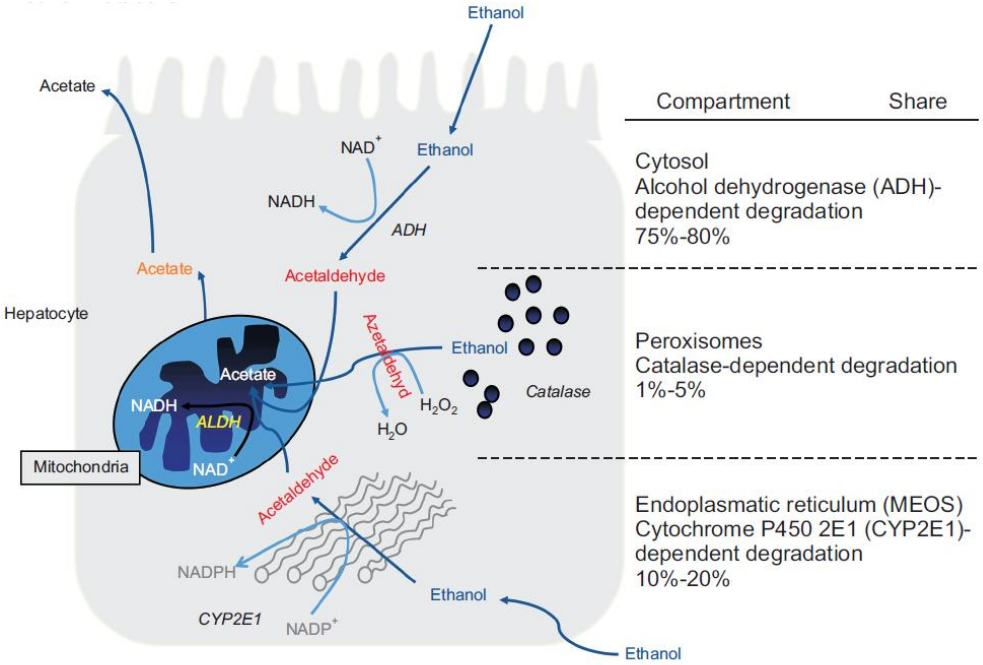


Figure 2. Alcohol metabolism by enzyme ADH, CYP2E1 and catalase. ADH and CYP2E1 participated in oxidative alcohol metabolism pathways, catalase participates in non-oxidative alcohol metabolism pathway. However, both 3 of the enzyme damaged liver cell by generating acetaldehyde and finally synthesis acetate in mitochondria [5].

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2.3. Current preventative and therapeutic method

Presently, there are no effective medications or therapies that can change the progression of ALD in people [3]; therefore, ALD can be treated most effectively and without harm by simply not drinking [19]. Although liver cirrhosis is reversible in rare instances, the majority of cases are incurable, in that case, only liver transplantation remains a final treatment [4]. Fortunately, as research progresses, nutritional techniques treating ALD, including immune-regulating foods, are becoming increasingly appealing as promising therapies with fewer adverse effects than synthetic medications [16].

3. Dairy product as a preventative and therapeutic method in alcohol liver disease

3.1. Milk

Milk is a common but important diary product; it contains many nutrient and essential protein [20]. Milk immunity comes from immune factors and immune-modulating parts in milk. It has antibodies that strengthen the immune system and lower the risk of many diseases [20]. Milk contains a lot of functional components, like lactoferrin and bioactive peptide, which make it possible to as a candidate to treat ALD injury.

Lactoferrin (Lf) is a natural sources protein discovered in milk. It has many biological actions, some of which may be helpful in the treatment of ALD. In D. M. Li et. al. study, they investigated the roles of Lf in alcohol-induced damage in rat model. Furthermore, the possible mechanisms were investigated from the perspectives of hepatic metabolism and gut microflora [21]. The results of their study showed Lf was able to reduce chronic ALD injury in mice, and this alleviation was connected with rebalance of redox and modulation of lipid synthesis [21].

In the human daily diet, there are various unknown bioactive peptides, which researchers have isolated from food and demonstrated to be helpful to people [22]. Bioactive peptides have been found to exhibit a variety of biological activity and are advantageous to human health, including antidiabetic, antihypertension, antioxidation, and immune modulation, and regulating immune responses [23]. In Qia Xu et. al. study, they use mouse model to research the function of the PGPIPN (Pro-Gly-Pro-Ile-Pro-Asn), which was a kind of milk-derived hexapeptide, used as a drug in previous study [24, 25], in preventing and reducing ALD injury [22]. According to the findings of this study, PGPIPN could be employed as a viable treatment for ALD injury.

3.2. Fermented milk

Fermented milk or yogurt is a popular diary product. Because yoghurt is a prebiotic and may contain microorganism, it is frequently associated with probiotics, suggested to be advantageous for metabolic, cardiovascular, and immune health [26, 27]. Regular yoghurt consumption has been shown to be negatively proportional to the incidence of newly diagnosed nonalcoholic fatty liver [28]. It was discovered that daily yoghurt consumption reduces hepatic steatosis in those with nonalcoholic fatty liver [29]. Therefore, it may play a role in liver protection. Additionally, yoghurt is a suitable food matrix for the administration of probiotic microorganisms.

In the study of He Qiuwen et al., they investigated whether probiotic yoghurt can also assist with ALD. The strain they used is *Bifidobacterium animalis* spp. *lactis* Probio-M8 (Probio-M8), which have showed properties of gut flora modification, anti-inflammation and antioxidant in previous study [30, 31]. The results showed rats fed Probio-M8-fermented milk preserved the integrity of their gut microbiota, reduced oxidative stress and hepatic inflammation, and alleviated liver damage. In addition, the fermented milk corrected ALD by restoring the variety, richness of the gut microbiota composition. After the intervention, the fecal metabolites that may assist regulate liver metabolism and relieve ALD-related symptoms is increased. They suggested that drinking probiotic-fermented milk could mitigate the ALD injury. But the relationship between probiotic milk consumption, gut microbiota changes, and disease relief still need to be validated in the further experiment [32].

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3.3. Whey

Whey is the remaining transparent liquid component of milk after cheese production [33]. It is rich in amino acid, protein, lactose, minerals and vitamin [33]. Additionally, whey demonstrates a vast array of biological activity, including immune-promoting, lipide regulation, oxidative stress release, antitumor, antihypertensive, antibacterial and antiviral properties [34, 35]. These characteristics indicate that whey performs a variety of physiological roles, and can be used to treat ALD and alleviate ALD injury.

In a 2014 study, Zhao et al used fermented whey liquid (WFL), which inoculate with *Lactobacillus caseu*, on alcohol induced mice, then investigate whether WFL demonstrate hepatic protective and therapeutic effect. The result showed WFL can reduce CYP2E1 (an indicator of level of free radicals, the higher the CYP2E1 expression, the higher the number of free radicals) expression in mice fed alcohol. It also decreased ALT, AST, MDA, and TG levels and boosted SOD, GPx, and GSH activity, consequently lowering liver damage. WFL can thereby stop alcohol-related liver damage [33].

In Radic et al study, they investigated the protective and therapeutic effect of orally intake whey on pathohistological malformation in mouse model liver. In addition, they investigate the effects of whey on the activation of AOE, as also p53, a proapoptotic protein, and NF-κB, which is an oxidative sensitive transcription factor. They results showed whey supplements partially counteract degenerative processes and mitigate liver damage, which means parallel use of whey and ethanol can demonstrate protective effect [36].

3.4. Camel milk

Camel Milk (CM) is distinct from milk from other ruminants. CM is high in minerals, vitamin, polyunsaturated fatty acid and linoleic acids and has no allergic properties such as lactose-intolerant [37]. Is believed to offer, anti-diabetic, hepatoprotective, and TB, asthmatic, edema preventing properties [38, 39]. Several studies have found that camel milk can help prevent and treat a variety of diseases, including ALD [16, 38, 39].

The first pilot study with hepatoprotective effect of CM was conducted in 1982 by Sharmanov et al. in patient with chronic active hepatitis. Sharmanov reported improvements in the clinical and analytical results of patients who drank camel milk in their research [40].

Darwish H. A. et al. subsequently carried out research in 2012 to investigate the preventive impact of CM to ALD. In their study, mice were separated into four groups, the experimental groups consumed 56% ethanol each day. The treatment groups received CM prophylactically and therapeutically, respectively. The serum concentrations of liver-related enzymes and compounds were measured. Malondialdehyde, total antioxidant capacity, TNF-alpha, and caspase-3 activity were evaluated. In addition, a histological study of liver tissue was performed. Following intake of CM, all evaluated parameters demonstrated improvement. These findings also demonstrated that Camel milk is useful for reducing ALD-related tissue damage[38].

In a 2020 study conducted by L. Ming, X. Qiao, L. Yi, et al., it also researched the protective effect of camel milk on ethanol intake, but more focus on gut microbiota and transcriptome level. Analysis of serum biochemical indices and histopathology demonstrated that the CM intake group had decreased hepatic inflammation. Camel milk altered the microbial diversity, with an increased percentage of Lactobacillus, and a decreased amount of Bacteroides, Alistipes, and the RC9 gut group according to 16S rRNA sequencing. The study shows that camel milk controls hepatic inflammation and ameliorates the gut flora imbalance caused by acute alcohol injury, suggesting that camel milk may be effective in protecting ALD injury [39].

In 2021, L. Ming, X. Qiao, L. Yi, et al. conduct more comprehensive research. In addition to preventing alcohol-induced disorder and lipid accumulation, camel milk reduces the production of inflammatory factor and oxidative stress to protect mice from ALD, as shown by analysis of blood and liver biochemical markers of rat models. The gut microbial community of the camel milk treated group resembled the untreated group more than the model group, which means that pre- and post-alcohol gavage administration of camel milk prevents and ameliorates the gut flora imbalance. In

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addition, the liver tissue transcriptome and proteome analysis demonstrated that CM could treat ALD injury in rat by modulating inflammatory markers and immune abnormalities [16].

4. Conclusion

One of the most frequent and widespread factors of chronic liver disorders worldwide is alcohol. Important variables in the development of ALD or alcoholic liver cirrhosis include inflammation, oxidative stress, innate immunity, angiogenesis, and fibrosis. In this paper, the protective and therapeutic effect of diary product, including milk, fermented milk, whey, and camel milk, was reviewed. And we have been gaining some insight into the potential mechanism of diary product, but a comprehensive understanding of the molecular and cellular interaction during ALD is lacking, which need further research to investigate. And the lack of animal models that can replicate the full range of ALD in humans is a serious barrier to ALD research. There are considerable differences between rodent and human alcohol metabolism. We propose that further research using a primate or human model is necessary to reach more solid conclusions.

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