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Impact of drinking alcohol on gut microbiota: recent perspectives on ethanol and alcoholic beverage

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Excessive alcohol intake is a leading cause of morbidity and mortality worldwide. Perspective of alcohol-associated disease development is shifting, from the traditional aspect of direct tissue damage by alcohol and its metabolites, to gut microbe involvement. It has been shown that alcohol not only changes the gut environment, but also modulates the composition of gut microbiota and is associated in the development of alcohol-associated diseases. Alcohol is consumed in the form of ethanol in alcoholic beverages. However, literature is limited on the effects of alcoholic beverages on gut microbiota and alcohol-induced injury. In this review, we aim to clarify the influence of gut microbiota and their relationship with alcoholic beverages in addition to direct damage from ethanol.

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Introduction

Alcohol abuse is an important risk factor for many health and social problems and a leading cause of global disease. Alcohol is absorbed in the gastrointestinal tract (GIT), transferred to the liver and lungs where it is metabolized. In this process, ethanol and its metabolites cause health complications including direct toxicity, oxidative stress, and accumulation of fatty acid ethyl esters [1]. Acetaldehyde is a toxic substance, and it was considered a major onset factor of diseases induced by alcohol intake [2]. Recently, another possibility has been raised that gut microbiota altered by alcohol intake is involved in developing alcohol-associated diseases, and that these diseases can be alleviated through recovery of changes in the composition of gut microbes caused by alcohol.

It was known that microbes living in the gut were associated with the risk of intestinal diseases such as inflammatory bowel disease, irritable bowel syndrome, and colorectal cancer [3]. Since the first commercialization of the next-generation sequencing (NGS) assay in 2004 [4], research on the gut microbes have been actively conducted regarding all the microorganisms in an environment, that is, microbiota, and microbiome which designate the collection of their genomes [5]. The analysis gut microbiota had led to new findings that it is also linked to obesity, cardiovascular diseases, nonalcoholic fatty liver, and neuro-psychiatric diseases, which emphasize its importance in human health [3]. In addition, it is possible to identify the changes in the composition of the gut microbiota affected by alcohol at the level of genes and species through the analysis of gut microbiome. Recently, studies have been supported to conduct researches on the effects of alcohol on gut microbiota and the underlying mechanisms of alcohol-related diseases mediated in the gut microbiota.

Alcoholic beverage is a general term for beverages containing alcohol and mainly includes fermented liquors such as beer and wine, and spirits distilled from them. Although alcohol is consumed only as liquors in humans, most previous studies have focused on the effects on gut microbiota caused by the intake of pure ethanol. This implies the understanding of alcoholic beverages association with gut microbiota and alcohol-induced damage is limited. Therefore, this review aims to summarize the changes and development of disease caused by alcohol, focusing on gut microbes, and discusses the experimental results on the relationship between intake of alcoholic beverages, gut microbes, and their physiological function.

Alcohol metabolism and the impact on the gut microbiota

After minimal absorption of alcohol occurs in the mouth and esophagus, ~20% of alcohol consumed is gradually absorbed in the stomach, followed by ~70% of alcohol absorbed from the small intestine [6]. Alcohol is mainly metabolized in the liver by alcohol dehydrogenase (ADH), which transforms alcohol into acetaldehyde and causes serious toxic damage to tissues and gut microbes. Alcohol has been reported to cause dysbiosis in the GIT that increase gram-negative bacteria [7,8], decrease short-chain fatty acid (SCFA)-producing bacteria [9], disrupting intestinal barrier integrity caused by endotoxin produced by gram-negative bacteria [10], and increased permeability of the intestinal mucosa [11].

Using various models, some have suggested that alcohol consumption can directly alter the composition of the gut microbiota. Rats who voluntarily consumed 20% ethanol on alternate days for 13 weeks showed decreased α-diversity and β-diversity, decreased abundance of *Lactobacilli*, and increased *Bacteroidetes* compared to the non-exposed control group [12••]. In our previous study, with a lower concentration (0.8 g/kg/day) and short-term ethanol administration for 7 days in mice, α-diversity of fecal microbiota was decreased, and the abundance of phylum *Bacteroidetes* were decreased compared to the control group [13••]. Barr *et al.* [14] reported that in rhesus macaques, who consumed 4% ethanol as drinking water, increased *Bacteroidetes* and decreased *Proteobacteria* were observed in the colon [14]. Another primate study showed that spontaneous alcohol intake of 4% ethanol solution decreased α-diversity and increased abundance of *Firmicutes* in the fecal microbiome of rhesus macaques [15]. In humans, the fecal microbiota of over consumers, consuming 118.9 g/day of alcohol for >10 years showed higher abundance of phylum *Proteobacteria* and lower abundance of *Faecalibacterium* than the control group who consumed an average of 2.5 g/day [9]. To date, most studies have reported that alcohol consumption directly affects the composition of gut microbes, causing dysbiosis and inflammation in the gut. In contrast, in the human fecal microbiota analysis conducted by Kosnicki *et al.* [12••], biodiversity was increased in human drinkers compared to the control group [12••]. When analyzing the changes in the gut microbiota, a rough trend (changes in the abundance of *Proteobacteria*, *Bacteroides*, *Firmicutes*, and *Faecalibacterium*) at the phylum level was seen, but the results of previous studies were not consistent depending on the alcohol concentration, model systems, and organs [9,12••,13••,14,15]. According to the study by Fan *et al.* [16], abundance of class *Bacilli* in phylum *Firmicutes* were decreased, further genera *Streptococcus* and *Lachnoanaerobaculum* in phylum *Firmicutes* were increased in the heavy drinker group [16]. This strongly suggested that the analysis of taxonomic rank below genus levels is necessary than at phylum level.

Gut-liver axis: alcohol-induced liver damage and gut microbiota

The intestinal hyperpermeability due to alcohol intake makes it easier for bacterial cells and their metabolites to enter the portal and the systemic circulation system, thus changes in gut microbiota, due to alcohol, can affect the GIT and other organs in the body [17]. The liver is especially damaged by alcohol, causing injuries including hepatic steatosis, hepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma. In mice treated with alcohol for 3 weeks, liver injury and lipid accumulation were seen along with intestinal bacterial overgrowth. In addition, compositional changes in the gut microbiota such as reduced abundance of phylum *Firmicutes* and enhanced abundance of *Bacterioidetes* and *Verrucomicrobia* were observed [18]. Canesso *et al.* [19] revealed that germ-free mice treated with ethanol (10% v/v) for 7 days at a 5 mg/kg binge were protected from liver injury compared to the conventional mice receiving equal amounts of ethanol [19]. This is contrary to the results of significant liver injury and inflammation in germ-free mice reported by Chen *et al.* [20] when compared to conventional mice through ethanol binge drinking [20]. In a recent study, hepatic steatosis and changes in abundance of genera *Ruminococcus*, *Coprococcus*, and *Streptococcus* were observed in the rats administered with 10% v/v ethanol solution for 12 months [21]. Fecal microbiota transplantation (FMT) of alcohol-resistant donor mice in alcohol fed mice prevented liver steatosis and inflammation, and recovered gut homeostasis, whereas humanized germ-free mice using FMT from alcoholic hepatitis patients showed severe liver inflammation and necrosis by alcohol intake [22,23]. In a non-human primate model, distinct liver steatosis was induced along with the increased abundance of *Firmicutes* and *Proteobacteria* and decreased abundance of *Bacteroidetes* in fecal samples from rhesus macaque through voluntary ethanol supplementation for 3 years [24]. In addition, patients with alcohol-associated liver disease showed a decrease in α-diversity and a specific gut microbiota signature (reduction of *Akkermansia*, increase in *Bacteroides*) [25–27,28••]. Interestingly, the auto-brewery syndrome (ABS), in which gut fermentation results in high blood ethanol without alcohol intake, directly shows the risk of alcohol-induced liver injury. Yaun *et al.* [29••] recently revealed the strains of *Klebsiella pneumonia* capable of producing high alcohol concentrations in individuals with ABS. Furthermore, feeding this strain into mice caused hepatic steatosis similar to that of mice fed ethanol, without ethanol administration [29••]. Another study described by Duan *et al.* [30••] showed that the proportion of *Enterococcus* spp. were significantly increased in patients with alcoholic hepatitis compared with controls, and cytolysin secreted by *Enterococcus faecalis* was associated with the liver injury, severe clinical outcomes, and increased mortality in patients with alcoholic hepatitis [30••]. Targeting cytolysin-positive *E. faecalis* by bacteriophages abolished alcohol-induced liver injury and steatosis in a humanized mouse model. These results support that gut the microbiota is strongly associated with alcohol-induced liver injury, and that the gut microbiota is promising for treating alcohol-related liver diseases.

Alcohol and gut-brain interaction

The latest studies on alcohol and gut microbiota are expanding their impact on brain associated disorders beyond the liver diseases [31,32]. The existing perception of the harmful effect of alcohol has focused on the direct alteration of neurotransmitters and their receptors by alcohol and its metabolites (typically acetaldehyde). However, recent experimental evidence has emphasized that gut microbiota influences brain function, causing alcohol-related psychiatric behavior change [33].

Peterson *et al*. reported that the vapor route of ethanol administration increases *Alistipes* and decreases *Clostridium* IV and XIVb compared with control mice [34]. In a meta-analysis of alcohol-induced gut microbiota and behavioral changes, alcohol alters neurotransmitters such as γ-aminobutyric acid (GABA), serotonin, and dopamine produced by gut microbes, and causes behavioral changes including emotional behavior, memory, sleep, and depression disorders in mammalian models [35]. Mice applied with FMT from patients with alcoholism, induced spontaneous alcohol preference, anxiety-like and depression-like behavior, and changes in brain-derived neurotransmitters [36]. These studies suggest that gut microbiota is an important mediator of neuropsychiatric behavior through gut-brain axis interaction, which supports a potential of gut microbiota as a new therapeutic target for treating alcohol-related brain damage. However, access to the role of gut microbiota on alcohol-induced physiological mechanisms in humans remains limited. The results of experimental animal models including rodents and non-human primates may differ from those of humans [12••]. In addition, the gut microbiota in humans easily changes due to environmental factors such as diet, smoking, drinking pattern, use of antibiotics, and fasting, which makes it difficult to clearly distinguish whether the changes in gut microbiota are caused by alcohol intake.

Alcoholic beverages and gut microbiota: can poison be a medicine?

Alcohol containing ethanol and its metabolite, acetaldehyde, has been designated a World Health Organization (WHO) group 1 human carcinogen and undoubtedly acts as a poison to human health [37]. Interestingly, Shimizu *et al*. reported that moderate/lifelong (1% in drinking water) alcohol consumption increased the lifespan by 4 weeks in the senescence-accelerated mouse prone 8 (SAMP8) model compared to the water consuming group [38]. Recognition impairment, spinal curvature, and skin conditions were also observed slower in SAMP8 mice receiving the alcohol solution, leading to positive effects on health, such as delayed aging and extended lifespan. Gut microbiota also showed a tendency of higher *Lactobacillales* order and lower *Clostridium* cluster XI than in mice receiving only water, which suggests that changes in gut microbiota caused by moderate alcohol intake have a beneficial effect for preventing aging. These results differ from those mentioned above, which led to dysbiosis and biodiversity reduction, liver injury, and damages in brain and behavioral function by alcohol consumption, mediated by gut microbes. Ethanol administration through a Lieber-DeCarli liquid diet, drinking water, and binge, which have been widely used in animal experiments, do not reflect the actual impact because there are differences in the amount of ethanol intake, drinking method, and chemical composition in alcoholic beverages. Considering the WHO's designation of a heavy drinker, when ingested 0.67–1 g/kg/day (40–60 g/day based on 60-kg adult), binge drinking at a high concentration (3–8 g/kg/day) is unlikely to happen clinically [39], even when the basal metabolic rate in rodents is seven times higher than humans [40]. To date, few studies have only observed the changes in gut microbiota caused by direct consumption of alcoholic beverages at physiological consumable concentration.

Alcoholic beverages are made from raw materials grains, fruits, and other sources of monosaccharides and polysaccharides through fermentation (brewing) and post-fermentation processes (filtration, distillation, mixing, and sterilization, among others.). Through these processes, various microorganisms and their metabolites are included in alcoholic beverages. Studies have shown consumption of alcoholic beverages may affect gut microbiota depending on the alcoholic beverages [13••,41,42]. Red wine, which has been most frequently studied for its beneficial effects on health, showed increased abundance of *Prevotella*, *Bifidobacterium*, *Bacteroides uniformis*, and *Enterococcus* during chronic consumption [41]. Besides, its consumption was positively associated with an increase in α-diversity of gut microbiota [43••]. The intake of Chinese baijiu, a distilled liquor from fermented grains, at a concentration of ~2.7 g/kg/day for 15 days alleviated ethanol-induced liver injury, reduction of *Akkermansia* abundance, and increases the relative abundance of *Prevotella* compared to pure ethanol intake [42]. Our recent study revealed that α-diversity of fecal microbiota was increased in mice who consumed Makgeolli, an alcoholic beverage fermented with rice, at a concentration of 0.8 g/kg/day for 7 days compared to the mice receiving equal amount of pure ethanol [13••]. In addition, these mice administered Makgeolli showed the increased abundance of the phylum *Bacteroidetes*, reduction of *Firmicutes*, elevated production of short-chain fatty acids such as butyric acid and propionic acid, and protection against ethanol-induced colonic inflammation. Studies have suggested the potential protective effect against dysbiosis of gut microbiota by the abundant polyphenols in beer, despite the lack of direct experimental evidences [44–46]. From these results, it can be presumed that most of the useful effects of alcoholic beverages are due to microorganisms and raw materials contained in, or metabolites derived from them. Most of fermented liquor contains several health beneficial components such as polyphenols, amino acids, vitamins, other functional ingredients, and microbes that can be potential probiotics, but they are rare in distilled liquors such as Vodka, Gin, and Soju. In addition, recent studies have reported the evidence of interactions between the gut microbiota and trace elements including iron, copper, magnesium, and calcium, and the effect of this interaction on the health of the host [47]. Here, we summarized beneficial components and microbes in representative alcoholic beverages and their mineral composition which could affect health benefits

Table 1

The health beneficial composition of representative alcoholic beverages and their effect on gut microbiota

Class	Liquor	Source	Alcohol (%)	Representative beneficial compounds	Minerals	Fermentative microbes	Changes in gut microbiota	References
Wine								
	Red wine	Red grapes Oak	11–14	Catechin Epigallocatechin Gallic acid Malvidin-3-glucoside Rutine Quercetin Myricetin Caffeic acid Resveratrol	Calcium Chloride Copper Iron	*Saccharomyces* spp. *Lactobacillus* spp. *Leuconostoc* spp.	Increased phyla *Proteobacteria, Fusobacteria, Firmicutes, Bacteroidetes* (compared with individuals received Gin), Increased *Barnesiella,* Increased α-diversity Decreased *Bifidobacterium*, *B. coccoides*, *C. leptum*, and *Lactobacillus*	[41,43••,51,52]
	White wine	White grapes	11–13	Catechin Epigallocatechin Gallic acid Caffeic acid	Calcium Chloride Copper Iron	*Saccharomyces* spp.	Increased α-diversity	[43••,53]
Beer								
	Larger Pale Pilsner	Barley Malt Hop	4.2–5.0	Hydroxybenzoic acid derivatives Hydrocinnamic acid derivatives ρ-Coumaric acid Caffeic acid Sinapic acid Ferulic acid Catechin	Magnesium Potassium Calcium Phosphorus	*Saccharomyces* spp. *Brettanomyces* spp.	Increased α-diversity and β-diversity by non-alcoholic beer (not in alcoholic beer)	[44,54]
Rice wine								
	Makgeolli	Rice Nuruk	5–6	Oligosaccharides Dietary fiber β-glucan Niacin Thiamin Yeast Lactic acid bacteria	Calcium Phosphorus Potassium Sodium	*Aspergillus* spp. *S. cerevisiae* *L. plantarum* *Pediococcus* spp.	Increased α-diversity and phylum *Bacteroidetes* and *Muribaculum intestinale* sp., Decreased phylum *Firmicutes* (compared with mice administered pure ethanol)	[13••,55]
	Sake	Rice Koji	12–18	Dietary fiber Oligosaccharides Peptides		*Aspergillus* spp. *S. cerevisiae* *Lactobacillus* spp. *Pseudomonas* spp.	Increased *Lactobacillaceae* by intake of sake cake and rice malt (w/o ethanol)	[56,57]
Spirits								
	Whiskey	Barley Wheat Oak	40–46	Gallic acid Ellagic acid Vanillic acid Vanillin Syringic acid ρ-Coumaric acid	–	–	–	[58]

Table 1 (*Continued*)

Class	Liquor	Source	Alcohol (%)	Representative beneficial compounds	Minerals	Fermentative microbes	Changes in gut microbiota	References
	Brandy	Grapes Oak	35–60	Gallic acid Ellagic acid Syringic acid Vanilic acid Vanillin ρ-Hydroxybenzoic acid	–	–	–	[59]
	Rum	Sugarcane Oak	35–50	Gallic acid Ellagic acid Syringic acid Benzoic acid Protocatechuic acid ρ-Hydroxybenzoic acid	–	–	–	[60]
	Chinese Baijiu	Sorghum Rice Daqu/xiaoqu	28–65	Tetramethyl pyrazine	–	*P. pentosaceus*, *L. plantarum*, *S. cerevisiae*, *P. kudriavzevii*, *W. anomalus*	Increased *Akkermansia* compared with ethanol group	[42,61]

and changes in composition of gut microbiota by the chronic consumption (Table 1). Through the several studies showing beneficial effects of low or moderate consumption of alcoholic beverages compared to the non-ethanol group on gut health [13••,38], perhaps consumption of alcoholic beverages may partially have health beneficial effects. However, most studies only suggest the beneficial effects mitigating disruption induced by pure ethanol at the same concentration. Careful interpretation and discussion, along with sufficient data collection is need, to determine whether consumption of alcoholic beverages is beneficial for gut microbiota and health.

Prospects of gut microbiota and alcoholic beverages

In terms of the relationship between gut microbiota and alcohol, there is no doubt that an integrated study is needed, to observe the changes in gut microbiota and disease development. To date, our knowledge of the underlying reason for morbidities is limited, as studies have relied almost exclusively on long-term heavy/binge drinking experimental animal models, using pure ethanol and colon biopsies/fecal samples from patients with alcohol-associated diseases. Clinical studies using alcoholic beverages have also been investigated based on the epidemiological results that analyze the correlation between wine intake and alcohol-related diseases, thus there is a limit to investigating a clear causal relationship and mechanism between them. Therefore, the dose-dependent, site-dependent, and type-dependent impact of chronic alcoholic beverage consumption in the absence of obvious alcohol-related disorders needs to be further studied.

As mentioned in this review, although gut microbiota is known to be involved in the pathogenesis of alcohol-associated diseases, the understanding of the role of the fungal microbiome (mycobiome) in developing alcohol-induced physiological changes is still insufficient. It is possible the changes in mycobiota in the GIT are caused by intake of *S. cerevisiae*, and fungi contained in fermented liquor would also play an important role in developing these diseases [48]. Moreover, ABS showing endogenous ethanol production in the GIT by fungi such as *S. cerevisiae*, *S. boulardii*, and *Candida spp.* spontaneously induces the development of non-alcoholic fatty liver disease (NAFLD) [29••,49], which suggests that gut mycobiota also plays a pivotal role in developing alcohol-induced diseases.

Conclusion

It has continuously been proved that alcohol-associated diseases can be controlled by gut microbiota, and it can be considered a 'hidden organ' with essential functions in host homeostasis [50]. To use gut microbiota beneficially for human health mediated by alcohol, our understanding should be increased by conducting further integrated

studies. Still, it is plausible that gut microbiota will be a treatment and preventive agent used for alcoholic diseases.

Conflict of interest statement

Nothing declared.

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References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- •• of outstanding interest

1. Guo R, Ren J: **Alcohol and acetaldehyde in public health: from marvel to menace**. *Int J Environ Res Public Health* 2010, **7**:1285-1301.
2. Salaspuro M: **Key role of local acetaldehyde in upper GI tract carcinogenesis**. *Best Pract Res Clin Gastroenterol* 2017, **31**:491-499.
3. Chang CS, Kao CY: **Current understanding of the gut microbiota shaping mechanisms**. *J Biomed Sci* 2019, **26**:59.
4. Alekseyev YO, Fazeli R, Yang S, Basran R, Maher T, Miller NS, Remick D: **A next-generation sequencing primer-how does it work and what can it do?** *Acad Pathol* 2018, **5**:2374289518766521.
5. Malla MA, Dubey A, Kumar A, Yadav S, Hashem A, Abd Allah EF: **Exploring the human microbiome: the potential future role of next-generation sequencing in disease diagnosis and treatment**. *Front Immunol* 2018, **9**:2868.
6. Levitt MD, Li R, Demaster EG, Elson M, Furne J, Levitt DG: **Use of measurements of ethanol absorption from stomach and intestine to assess human ethanol metabolism**. *Am J Physiol Gastrointest Liver Physiol* 1997, **273**:G951-G957.
7. Meroni M, Longo M, Dongiovanni P: **Alcohol or gut microbiota: who is the guilty?** *Int J Mol Sci* 2019, **20**.
8. Malaguarnera G, Giordano M, Nunnari G, Bertino G, Malaguarnera M: **Gut microbiota in alcoholic liver disease: pathogenetic role and therapeutic perspectives**. *World J Gastroenterol* 2014, **20**:16639-16648.
9. Bjorkhaug ST, Aanes H, Neupane SP, Bramness JG, Malvik S, Henriksen C, Skar V, Medhus AW, Valeur J: **Characterization of gut microbiota composition and functions in patients with chronic alcohol overconsumption**. *Gut Microbes* 2019, **10**:663-675.
10. Patel S, Behara R, Swanson GR, Forsyth CB, Voigt RM, Keshavarzian A: **Alcohol and the intestine**. *Biomolecules* 2015, **5**:2573-2588.
11. Tang YM, Zhang LJ, Forsyth CB, Shaikh M, Song SW, Keshavarzian A: **The role of miR-212 and iNOS in alcohol-induced intestinal barrier dysfunction and steatohepatitis**. *Alcohol Clin Exp Res* 2015, **39**:1632-1641.
12. •• Kosnicki KL, Penprase JC, Cintora P, Torres PJ, Harris GL, Brasser SM, Kelley ST: **Effects of moderate, voluntary ethanol consumption on the rat and human gut microbiome**. *Addict Biol* 2019, **24**:617-630.
13. •• Lee JE, Ha JS, Park HY, Lee E: **Alteration of gut microbiota composition by short-term low-dose alcohol intake is restored by fermented rice liquor in mice**. *Food Res Int* 2020, **128**:108800.
14. Barr T, Sureshchandra S, Ruegger P, Zhang J, Ma W, Borneman J, Grant K, Messaoudi I: **Concurrent gut transcriptome and microbiota profiling following chronic ethanol consumption in nonhuman primates**. *Gut Microbes* 2018, **9**:338-356.
15. Zhang X, Yasuda K, Gilmore RA, Westmoreland SV, Platt DM, Miller GM, Vallender EJ: **Alcohol-induced changes in the gut microbiome and metabolome of rhesus macaques**. *Psychopharmacology (Berl)* 2019, **236**:1531-1544.
16. Fan X, Peters BA, Jacobs EJ, Gapstur SM, Purdue MP, Freedman ND, Alekseyenko AV, Wu J, Yang L, Pei Z: **Drinking alcohol is associated with variation in the human oral microbiome in a large study of American adults**. *Microbiome* 2018, **6**:59.
17. Starkel P, Leclercq S, de Timary P, Schnabl B: **Intestinal dysbiosis and permeability: the yin and yang in alcohol dependence and alcoholic liver disease**. *Clin Sci (Lond)* 2018, **132**:199-212.
18. Yan AW, Fouts DE, Brandl J, Stärkel P, Torralba M, Schott E, Tsukamoto H, Nelson KE, Brenner DA, Schnabl B: **Enteric dysbiosis associated with a mouse model of alcoholic liver disease**. *Hepatology* 2011, **53**:96-105.
19. Canesso MCC, Lacerda NL, Ferreira CM, Gonçalves JL, Almeida D, Gamba C, Cassali G, Pedroso SH, Moreira C, Martins FS *et al.*: **Comparing the effects of acute alcohol consumption in germ-free and conventional mice: the role of the gut microbiota**. *BMC Microbiol* 2014, **14**:240.
20. Chen P, Miyamoto Y, Mazagova M, Lee KC, Eckmann L, Schnabl B: **Microbiota protects mice against acute alcohol-induced liver injury**. *Alcohol Clin Exp Res* 2015, **39**:2313-2323.
21. Posteraro B, Paroni Sterbini F, Petito V, Rocca S, Cubeddu T, Graziani C, Arena V, Vassallo GA, Mosoni C, Lopetuso L: **Liver injury, endotoxemia, and their relationship to intestinal microbiota composition in alcohol-preferring rats**. *Alcohol Clin Exp Res* 2018, **42**:2313-2325.
22. Ferrere G, Wrzosek L, Cailleux F, Turpin W, Puchois V, Spatz M, Ciocan D, Rainteau D, Humbert L, Hugot C *et al.*: **Fecal microbiota manipulation prevents dysbiosis and alcohol-induced liver injury in mice**. *J Hepatol* 2017, **66**:806-815.
23. Llopis M, Cassard AM, Wrzosek L, Boschat L, Bruneau A, Ferrere G, Puchois V, Martin JC, Lepage P, Le Roy T *et al.*: **Intestinal microbiota contributes to individual susceptibility to alcoholic liver disease**. *Gut* 2016, **65**:830-839.
24. Wang H, Yan Y, Yi X, Duan Y, Wang J, Li S, Luo L, Huang T, Inglis B, Li X *et al.*: **Histopathological features and composition of gut microbiota in rhesus monkey of alcoholic liver disease**. *Front Microbiol* 2019, **10**:165.
25. Addolorato G, Ponziani FR, Dionisi T, Mosoni C, Vassallo GA, Sestito L, Petito V, Picca A, Marzetti E, Tarli C: **Gut microbiota compositional and functional fingerprint in patients with alcohol use disorder and alcohol-associated liver disease**. *Liver Int* 2020, **40**:878-888.
26. Ciocan D, Rebours V, Voican CS, Wrzosek L, Puchois V, Cassard A-M, Perlemuter G: **Characterization of intestinal microbiota in alcoholic patients with and without alcoholic hepatitis or chronic alcoholic pancreatitis**. *Sci Rep* 2018, **8**:1-12.
27. Seo B, Jeon K, Moon S, Lee K, Kim WK, Jeong H, Cha KH, Lim MY, Kang W, Kweon MN *et al.*: ***Roseburia* spp. abundance associates with alcohol consumption in humans and its administration ameliorates alcoholic fatty liver in mice**. *Cell Host Microbe* 2020, **27**:25-40 e26.
28. •• Grander C, Adolph TE, Wieser V, Lowe P, Wrzosek L, Gyongyosi B, Ward DV, Grabherr F, Gerner RR, Pfister A *et al.*: **Recovery of ethanol-induced *Akkermansia muciniphila* depletion ameliorates alcoholic liver disease**. *Gut* 2018, **67**:891-901.
29. •• Yuan J, Chen C, Cui J, Lu J, Yan C, Wei X, Zhao X, Li N, Li S, Xue G *et al.*: **Fatty liver disease caused by high-alcohol-producing *Klebsiella pneumoniae***. *Cell Metab* 2019, **30**:1172.
30. •• Duan Y, Llorente C, Lang S, Brandl K, Chu H, Jiang L, White RC, Clarke TH, Nguyen K, Torralba M *et al.*: **Bacteriophage targeting of gut bacterium attenuates alcoholic liver disease**. *Nature* 2019, **575**:505-511.

31. Sherwin E, Dinan TG, Cryan JF: **Recent developments in understanding the role of the gut microbiota in brain health and disease**. *Ann N Y Acad Sci* 2018, **1420**:5-25.

32. Leclercq S, Starkel P, Delzenne NM, de Timary P: **The gut microbiota: a new target in the management of alcohol dependence?** *Alcohol* 2019, **74**:105-111.

33. Leclercq S, de Timary P, Delzenne NM, Stärkel P: **The link between inflammation, bugs, the intestine and the brain in alcohol dependence**. *Transl Psychiatry* 2017, **7**:e1048.

34. Peterson VL, Jury NJ, Cabrera-Rubio R, Draper LA, Crispie F, Cotter PD, Dinan TG, Holmes A, Cryan JF: **Drunk bugs: chronic vapour alcohol exposure induces marked changes in the gut microbiome in mice**. *Behav Brain Res* 2017, **323**:172-176.

35. Qamar N, Castano D, Patt C, Chu T, Cottrell J, Chang SL: **Meta-analysis of alcohol induced gut dysbiosis and the resulting behavioral impact**. *Behav Brain Res* 2019, **376**:112196.

36. Zhao W, Hu Y, Li C, Li N, Zhu S, Tan X, Li M, Zhang Y, Xu Z, Ding Z *et al.*: **Transplantation of fecal microbiota from patients with alcoholism induces anxiety/depression behaviors and decreases brain mGluR1/PKC epsilon levels in mouse**. *Biofactors* 2020, **46**:38-54.

37. Humans IWGotEoCRt: **IARC monographs on the evaluation of carcinogenic risks to humans. Ingested nitrate and nitrite, and cyanobacterial peptide toxins**. *IARC Monogr Eval Carcinog Risks Hum* 2010, **94** v-vii, 1-412.

38. Shimizu C, Oki Y, Mitani Y, Tsuchiya Y, Nabeshima T: **Moderate-dose regular lifelong alcohol intake changes the intestinal flora, protects against aging, and keeps spatial memory in the senescence-accelerated mouse prone 8 (SAMP8) model**. *J Pharm Pharm Sci* 2016, **19**:430-447.

39. Ghosh Dastidar S, Warner JB, Warner DR, McClain CJ, Kirpich IA: **Rodent models of alcoholic liver disease: role of binge ethanol administration**. *Biomolecules* 2018, **8**.

40. Terpstra A: **Differences between humans and mice in efficacy of the body fat lowering effect of conjugated linoleic acid: role of metabolic rate**. *J Nutr* 2001, **131**:2067-2068.

41. Queipo-Ortuno MI, Boto-Ordonez M, Murri M, Gomez-Zumaquero JM, Clemente-Postigo M, Estruch R, Cardona Diaz F, Andres-Lacueva C, Tinahones FJ: **Influence of red wine polyphenols and ethanol on the gut microbiota ecology and biochemical biomarkers**. *Am J Clin Nutr* 2012, **95**:1323-1334.

42. Fang C, Du H, Zheng X, Zhao A, Jia W, Xu Y: **Solid-state fermented Chinese alcoholic beverage (baijiu) and ethanol resulted in distinct metabolic and microbiome responses**. *FASEB J* 2019, **33**:7274-7288.

43. •• Le Roy CI, Wells PM, Si J, Raes J, Bell JT, Spector TD: **Red wine consumption associated with increased gut microbiota alpha-diversity in 3 independent cohorts**. *Gastroenterology* 2020, **158**:270-272 e272.

44. Hernández-Quiroz F, Nirmalkar K, Villalobos-Flores LE, Murugesan S, Cruz-Narváez Y, Rico-Arzate E, Hoyo-Vadillo C, Chavez-Carbajal A, Pizano-Zárate ML, García-Mena J: **Influence of moderate beer consumption on human gut microbiota and its impact on fasting glucose and β-cell function**. *Alcohol* 2020, **85**:77-94.

45. Quesada-Molina M, Muñoz-Garach A, Tinahones FJ, Moreno-Indias I: **A new perspective on the health benefits of moderate beer consumption: Involvement of the gut microbiota**. *Metabolites* 2019, **9**:272.

46. Moreno-Indias I: **Benefits of the beer polyphenols on the gut microbiota**. *Nutr Hosp* 2017, **34**:41-44.

47. Skrypnik K, Suliburska J: **Association between the gut microbiota and mineral metabolism**. *J Sci Food Agric* 2018, **98**:2449-2460.

48. Szabo G: *Gut-liver Axis Beyond the Microbiome: How the Fungal Mycobiome Contributes to Alcoholic Liver Disease*. 2018.

49. Malik F, Wickremesinghe P, Saverimuttu J: **Case report and literature review of auto-brewery syndrome: probably an underdiagnosed medical condition**. *BMJ Open Gastroenterol* 2019, **6**.

50. Liu S: **The development of our organ of other kinds—the gut microbiota**. *Front Microbiol* 2016, **7**:2107.

51. Lingua MS, Fabani MP, Wunderlin DA, Baroni MV: **From grape to wine: changes in phenolic composition and its influence on antioxidant activity**. *Food Chem* 2016, **208**:228-238.

52. Cuervo A, Reyes-Gavilán CGdl, Ruas-Madiedo P, Lopez P, Suarez A, Gueimonde M, González S: **Red wine consumption is associated with fecal microbiota and malondialdehyde in a human population**. *J Am Coll Nutr* 2015, **34**:135-141.

53. Markoski MM, Garavaglia J, Oliveira A, Olivaes J, Marcadenti A: **Molecular properties of red wine compounds and cardiometabolic benefits**. *Nutr Metab Insights* 2016, **9**:51-57.

54. Wannenmacher J, Gastl M, Becker T: **Phenolic substances in beer: structural diversity, reactive potential and relevance for brewing process and beer quality**. *Compr Rev Food Sci Food Saf* 2018, **17**:953-988.

55. Mi-Kyeong K, Sung-Soo P: **Research trends on quality characteristics and physiological functions of Korean traditional Makgeolli (Korean rice wine): a literature review**. *J Korean Soc Food Sci Nutr* 2019, **48**:149-160.

56. Akaike M, Miyagawa H, Kimura Y, Terasaki M, Kusaba Y, Kitagaki H, Nishida H: **Chemical and bacterial components in sake and sake production process**. *Curr Microbiol* 2020, **77**:632-637.

57. Kawakami S, Ito R, Maruki-Uchida H, Kamei A, Yasuoka A, Toyoda T, Ishijima T, Nishimura E, Morita M, Sai M *et al.*: **Intake of a mixture of sake cake and rice malt increases mucin levels and changes in intestinal microbiota in mice**. *Nutrients* 2020, **12**.

58. White B, Smyth MR, Lunte CE: **Determination of phenolic acids in a range of Irish whiskies, including single pot stills and aged single malts, using capillary electrophoresis with field amplified sample stacking**. *Anal Methods* 2017, **9**:1248-1252.

59. Garcia-Moreno MV, Sanchez-Guillen MM, de Mier MR, Delgado-Gonzalez MJ, Rodriguez-Dodero MC, Garcia-Barroso C, Guillen-Sanchez DA: **Use of alternative wood for the ageing of brandy de Jerez**. *Foods* 2020, **9**.

60. Regalado EL, Tolle S, Pino JA, Winterhalter P, Menendez R, Morales AR, Rodriguez JL: **Isolation and identification of phenolic compounds from rum aged in oak barrels by high-speed countercurrent chromatography/high-performance liquid chromatography-diode array detection-electrospray ionization mass spectrometry and screening for antioxidant activity**. *J Chromatogr A* 2011, **1218**:7358-7364.

61. Zheng X-W, Han B-Z: **Baijiu (白酒)**, Chinese liquor: history, classification and manufacture. *J Ethnic Foods* 2016, **3**:19-25.