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INDUCED OSTEOARTHRITIC RAT MODELS

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25. **PRICE DYNAMICS AND SUPPLY DISRUPTIONS IN SYSTEMIC ANTIBIOTICS: A LONGITUDINAL ANALYSIS OF ATC J01 MEDICINES IN ROMANIA**

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https://doi.org/10.31925/farmacia.2026.2.1 **REVIEW**

ASSESSMENT OF THE IMPACT OF ALCOHOL-CONTAINING FOOD AND MEDICATION ON THE BLOOD-BRAIN BARRIER

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Abstract

Individuals are exposed to alcohol in their daily lives through beverages and unintentional intake while consuming alcohol-containing food and medication. Intentional alcohol ingestion is achieved through moderate, binge, and heavy alcohol drinking. In contrast, unintentional alcohol exposure can be a result of the consumption of alcohol-containing medication, food, and personal care. To date, studies reporting the blood alcohol concentration post-consumption of those products are very limited. On the other hand, alcohol exerts negative impacts on the central nervous system by affecting neurotransmission and changing the composition of the brain's biochemical moieties. Many studies have examined the effect of alcohol on the CNS. However, the research question of when alcohol starts showing a deleterious effect on the blood-brain barrier (BBB) has not been reviewed. This review aims to dissect how much and at what frequency alcohol consumption will induce BBB dysfunction. The food, medicine, and household products that contained alcohol were also summarized along with their potential blood alcohol concentration (BAC) of individuals post-product consumption. This review aims to contribute to greater awareness among researchers and authorities to improve consumers' safety.

Rezumat

Persoanele sunt expuse la alcool în viața de zi cu zi atât prin consumul de băuturi alcoolice, cât și prin ingestia neintenționată asociată consumului de alimente sau medicamente care conțin alcool. Ingestia intenționată de alcool poate avea loc sub diverse forme, precum consumul moderat, episoadele de consum excesiv (*binge drinking*) și consumul cronic intens. În schimb, expunerea neintenționată la alcool poate apărea ca urmare a utilizării unor medicamente, alimente sau produse de îngrijire personală care conțin alcool. Până în prezent, studiile care raportează concentrația de alcool în sânge după consumul acestor produse sunt limitate. Pe de altă parte, alcoolul exercită efecte negative asupra sistemului nervos central prin influențarea neurotransmisiei și prin modificarea compoziției biochimice a structurilor cerebrale. Numeroase studii au investigat efectele alcoolului asupra sistemului nervos central; cu toate acestea, problema momentului în care alcoolul începe să producă efecte toxice asupra barierei hematoencefalice (BBB) nu a fost analizată sistematic în literatura de specialitate. Acest studiu analizează cantitatea și frecvența consumului de alcool care pot determina disfuncția barierei hematoencefalice. De asemenea, sunt sintetizate principalele alimente, medicamente și produse de uz casnic care conțin alcool, împreună cu valorile potențiale ale concentrației alcoolului în sânge (BAC) care pot apărea după utilizarea sau consumul acestor produse. Prin această analiză se urmărește creșterea gradului de conștientizare în rândul cercetătorilor și al autorităților, în vederea îmbunătățirii siguranței consumatorilor.

Keywords: blood alcohol concentration, blood-brain barrier, dysfunction food, medication

Introduction

Alcohol is a small molecule produced by glucose fermentation. In pharmaceutical sciences, alcohol has been used in various processes to solubilize active pharmaceutical ingredients and extract active moieties from dried plants (1). Due to its small size and good partitioning between oil and water, alcohol easily crosses biological membranes, including the blood-brain barrier and the blood-placental barrier (2-5). Alcohol binds to several receptors and channels in the CNS, such as GABAA, NMDA receptors, and GIRK channels. It initiates $GABA_A$ receptor modulation, NMDA receptor inhibition, and GIRK channel activation in the brain, leading to the pharmacological effects of alcohol in the central nervous system (CNS) (6). The impacts of alcohol on the CNS are observed in both acute and chronic exposure. In the brain, alcohol acts as a stimulant, but at the same time, it also exerts a sedative effect (7).

In addition to the sedative and stimulant effects of alcohol, alcohol exposure in certain amounts is associated with brain oxidative stress and neuronal injury. Alcohol metabolism by CYP2E1 and alcohol dehydrogenase generates reactive oxygen (ROS) species, which further trigger lipid peroxidation. This process results in further accumulation of

ROS, a toxic moiety to neuronal cells. A considerable number of studies have reported the effect of alcohol on the brain and neurons (8-11). However, the review paper on the impact of alcohol on blood-brain barrier function is not available. This review aims to dissect the correlation between alcohol consumption patterns and blood-brain barrier dysfunction. A potential risk of medicine- and food-containing alcohol, personal care, and household products that contain alcohol has also been summarized. Finally, it discusses the correlation between blood alcohol concentration (BAC) and BBB function.

This review includes original and research articles published from 2000 to 2023 on the Scopus Database. The oldest original research articles were used when no scientific report was available regarding specific research findings. The literature search was performed from January to December 2023 using the keywords alcohol, blood-brain barrier, alcohol in food, alcohol in medicine, alcohol intake, and alcohol impact on the brain. The inclusion criteria include articles written in English and available in full text.

Pattern of Alcohol Consumption from Alcoholic Beverages

The primary sources of alcohol intake are beer (3 - 7% alcohol content), wine (9 - 15% alcohol content), and spirits (30 - 50% alcohol content). Spirit, which has the highest alcohol by volume, includes vodka, tequila, gin, whiskey, and grappa (12). Depending on drinking frequency, drinking patterns can be categorized as moderate, binge, or heavy drinking (13). Moderate drinking is defined by alcohol consumption of one drink *per* day for women, or two drinks *per* day for men. Typically, blood alcohol concentrations (BAC) in moderate drinkers are less than 50 mg/dL (Table II). The closest study on moderate drinking found that one drink in the Thai subpopulation produced a BAC of 20 mg/dL in males (200 lb) and 40 mg/dL in females (125 lb). With the Windmark equation to calculate BAC, one drink will produce a BAC of 0.02 mg/dL, and the addition of one or more drinks will double or triple the BAC proportionally using the Windmark Equation (14). Now several approaches are available to more accurately predict the BAC that also consider drinking history and the extreme conditions, such as individuals with obesity, pregnancy, or those with high muscular proportion, such as a bodybuilder. With this approach, the BAC can be calculated more accurately (15).

The second drinking pattern is binge alcohol drinking, which is also called “too much too fast”. In this case, an individual consumes more than 5 drinks for men and 4 for women within 2 hours (16, 17). This drinking pattern could produce a BAC above 80 mg/dL (17.4 mM), which is a legal limit for operating a motor vehicle in the USA and Canada (18). This limit is much lower: 50 mg/dL in other industrialized countries (19).

The third pattern of drinking is heavy drinking or “too much too often”. In this case, an individual consumes at least 15 drinks *per* week for men and 8 for women. This drinking pattern can produce a BAC above 150 mg/dL. Heavy drinking is also defined as when an individual has several episodes of binge drinking within a week (20).

Table I

Alcohol drinking pattern and the expected BAC

No.	Type of drinking	Drinking frequency		Expected BAC (mg/dL)	References
		Man	Women		
1	Moderate drinking	≤ 2 drinks/day	≤ 1 drink/day	< 50 mg/dL	(13)
2	Binge drinking	> 5 drinks within 2 hours	> 4 drinks within 2 hours	> 80 mg/dL	(16)
3	Heavy drinking	> 15 drinks/ week	> 8 drinks/week	> 150mg/dL	(20)

In identifying the drinking pattern, the number of drinks within a particular time frame is mentioned. Generally, one drink corresponds to 15 grams of alcohol (21). Those amounts of alcohol are approximately equal to 12 ounces of regular beer (usually containing 5% alcohol), 5 ounces of wine (usually containing 12% alcohol), or 1.5 ounces of distilled spirits (usually containing 40% alcohol. The BAC post-alcohol consumption can be predicted by the Winmark equation. However, in reality, the BAC is influenced by gender, total body water, the presence of food, the drinking history, and the type of alcoholic beverage consumed (14). Thus, it is very useful to record the BAC and drinking history of patients who came to the emergency unit due to alcohol consumption. These data will be valuable to increase understanding of drinking patterns and BAC.

Studies done in the region where alcohol drinking is common revealed that children experience their first alcohol ingestion and intoxication at an age below 13 years (22). Unfortunately, 90% of underage alcohol consumption occurs within the context of binge drinking (13). According to the 2016 National Survey on Drug Use and Health (NSDUH), 9% of adolescents (12 - 17 years) reported consuming alcohol in the past thirty days. Five percent of

them reported experiencing binge drinking in the past 30 days.

The BAC value that elicits toxicity varied between individuals. Alcohol intoxication in adolescents appears to present in BAC as low as 180 mg/dL, as compared to adults who experience alcohol intoxication typically at a BAC of 300 mg/dL (23, 24). Children experience alcohol intoxication at a lower BAC. Studies reported 11 kg toddlers who consume 6 mL of alcohol, 80%, resulting in a BAC of 50 mg/dL, experience CNS depression and hypoglycaemia. Higher BAC in toddlers, 100 mg/dL, was shown to elicit convulsions and potentially fatal hypoglycaemia (25). Together, these studies suggested that intentional alcohol consumption is common not only in adults but also in adolescents, and the alcohol toxic concentration in babies and children tends to be lower than that of adults.

Sources of Alcohol Exposure Beyond Alcoholic Beverages

Alcohol in medicinal and personal care products.

The non-intentional alcohol consumption potentially occurred *via* the consumption of alcohol-containing medicine, household products, and food. Alcohol is frequently used as a cosolvent to improve drug solubility in liquid dosage forms such as injectable drugs, syrup, and elixirs (26). Alcohol can also serve as a preservative and a flavour enhancer in oral liquid formulation. In herbal medicine, alcohol is commonly used as a solvent to extract active pharmaceutical moieties from a dried herb. Traces of alcohol in herbal medication were reported in several studies (27-29). Studies indicated the presence of alcohol in injectable drugs, including chemotherapy medication. Alcohol was added to the reconstitution of chemotherapeutics to increase its solubility. Studies showed that in one course of chemotherapy, the patient potentially can be administered intravenously 15.9 grams of ethanol (for gemcitabine) and 9.86 grams (for paclitaxel). Surprisingly, the amount of ethanol the patient received during one course of gemcitabine corresponds to one standard drink. This raised concern since an individual with different health statuses might have different alcohol metabolizing rates (30).

Not only in the chemotherapy drugs, but also in the injectable drugs for paediatrics, the presence of alcohol needs attention. Screening among herbal medicines indicated for children in Germany reported that among 18 medications that contain alcohol, children might receive 0.022 - 0.027 grams *per* single administration. In this report, the highest alcohol content in paediatric medication is 33.1% v/v (28). Alcohol is not only for prescribed medication, but also in over the counter (OTC) products for paediatrics, breastfeeding, and pregnant women (27, 31). Although data on exposure to alcohol-containing medication during early life is minimal, one study reported the presence of alcohol metabolites in a newborn baby. This funding suggested that young infants are indeed exposed to ethanol from medication (32).

In traditional medicine, alcohol is present as a solvent to extract active ingredients from dried herbs (33-35). A significant concentration of alcohol is present in homeopathic and herbal liquid formulations (27-29, 36). Studies on elixirs and homeopathic products suggest that several products contain ethanol exceeding 50% (37). Examination of fermented Ayurvedic medicine indicated that this medication contained alcohol up to 10.70%. Although alcohol is common in herbal medicine, some practices still fail to disclose its content on packaging and labelling. Studies in Malaysia revealed that, among five syrups that do not disclose ethanol as an excipient, ethanol was present in all products tested, with concentrations ranging from 0.1 - 2.0%. Estimation of the BAC after a single dose of these drugs suggests that the BAC value is very low and far from the limit set by EMA for the paediatric subpopulation, which is 12.5 mg/dL (27). These studies suggested that more studies are necessary to determine the predictive BAC in children post-administration of alcohol-containing herbal medication.

Another potential route of non-intentional alcohol exposure is from a personal product such as cosmetics, mouthwash, perfume, and hand sanitizer (38-42). During the COVID-19 pandemic (January - April 2022), the American Association of Poison Control Centers (AAPCC) National Poison Data Centre (NPDC) received significantly higher reports regarding unintentional exposure to alcohol from hand sanitizer (25, 43). In addition to hand sanitizer, mouthwash contains alcohol at 8 - 27%. The accidental consumption of alcohol from mouthwash and hand sanitizer remained high among children under six years old (44). Due to its high concentration of alcohol and easy accessibility, mouthwash has been illegally used as an alternative to commercial alcoholic beverages. Mouthwash has been reported to be used in suicide attempts and illegal alcohol consumption in the hospital for inpatients (45). These studies suggested that personal care products are a particular area in which regulation on labelling and closure design of personal care products requires more attention due to the risk of accidental alcohol ingestion.

Alcohol in food

In food, alcohol is present in some juices and bakery products. Studies have shown that apple, orange, and grape juices can contain 0.52 g/L of alcohol. Alcohol traces were also observed in fermented

dough during the preparation of bakery products. Although alcohol produced during dough fermentation is evaporated during baking, studies have shown that a trace of alcohol remains in the bread matrix (38, 46). Bakery products have very low alcohol content, ranging from 0.14 g/100 g to 0.29 g/100 g. However, some variants of bakery products, such as American-style burger rolls and French-style milk rolls, contain up to 1.28 g/100 g and 1.21 g/100 g of alcohol, respectively. Simulation on the consumption of these bakery products by children (20 kg) resulted in an alcohol intake higher than 6 mg/kg BW, a threshold set by the European Medicines Agency for alcohol-containing medication (38). Consistent with recent data, previous studies have also indicated that the alcohol trace in bakery products can reach up to 0.98 g/100 g. The bourbon cake's alcohol content is somewhat higher, reaching 1.66 g/100 g. Non-alcoholic soft drink in North America, indeed, has some alcohol traces even though in a very low concentration, *i.e.*, 0.000 - 0.084 g/100 mL (46).

Unintentional alcohol consumption potentially comes from our daily cooking. The use of alcoholic beverages, such as wine, in cooking is a common practice for preparing meaty dishes and sauces. In Chinese tradition, women consumed chicken wine soup every day for a month in the postpartum period to increase the mother's milk production. There is a case report that highlights that a newborn baby whose mother consumed Chinese wine chicken soup twice a day was reported experiencing intestinal distention (47). A separate study examined residual alcohol in Chinese chicken wine soup and found that the final dish contained 40 mg/mL, equivalent to 4 g/100 mL. With this ethanol content, consuming 400 ml of the soup is equivalent to one standard drink (15 grams of alcohol) (48). Alcohol pharmacokinetic studies on individuals post-consuming Chinese chicken wine soup (dose of 8 mL/kg BW) suggested that the maximum concentration of alcohol in the mother's blood was 30 mg/dL. In contrast, the alcohol concentration in the mother's milk was 23 mg/dL. In other words, every 100 mL of milk might contain 20 mg of alcohol. Both blood and milk reach maximum alcohol concentration at 20 minutes post-soup consumption. The studies revealed that alcohol disappeared from the blood circulation 2.5 hours post-consumption. (48). These studies suggest that unintentional alcohol intake by newborns whose mothers consume Chinese chicken wine soup needs to be examined further in terms of pharmacological impact on the newborn.

Another example of cuisine that uses alcohol as its ingredient, among other things, is braised bread, vinaigrette (sauce), steamed fish, spare ribs, and Rye bread porridge. The alcohol concentrations of these cuisines range from ND (not determined) to 2.62% v/v and 2.68% w/w. The studies also indicated that the longer the cooking time, the smaller the alcohol trace in the cuisine. For example, the initial alcohol concentration of the braised beef was around 5% v/v. With standard cooking time, braised beef contained 0.06-0.08% w/w. A longer cooking time, for example, three hours, could reduce the alcohol content to 0.02% w/w. Interestingly, the alcohol trace depends on the type of alcoholic beverage used. Beer-braised beef produced lower alcohol traces compared to wine-braised beef. Although there was a trace of alcohol in the dishes examined, the amount on the cooked dishes was considered low, below 2 grams *per* standard serving (49).

Unintentional ethanol consumption tends to produce low BAC, which is less likely to produce significant intoxication. However, the lethal dose for children is somewhat lower compared to adults. Litowits reported that a 3 g/kg dose of alcohol is lethal for children as compared to an adult lethal dose of 5 - 8 g/kg. (50). Many studies have examined BAC's correlation to brain toxicities. However, comprehensive studies evaluating the relationship between BAC and BBB function have not been conducted, especially in humans. The pharmacological consequences of alcohol on the brain and the BBB in children could be lower compared to adults (Table II).

Table II

Correlation between alcohol intake and blood alcohol concentration

No.	Population	Alcohol consumption	Blood Alcohol Concentration/BAC (mg/dL)	Comments	References
1	Thai men and women aged 22 - 38.	12 g	Below 30 mg/dL for females and below 35 mg/dL for males	Real measurement	(51)
2	Toddler 11 kg	6 mL of 80% alcohol	50 mg/dL	CNS depression and hypoglycaemia were observed	(25)
3	College students age 19 - 34	6 drinks *per* occasion	100 mg/dL	Real measurement	(16)
4	Pregnant women	Chinese chicken wine soup in a dose of 8 mL/kg	Mother's blood: 30 mg/dL Mother's milk: 23 mg/dL	Prediction	(48)

Blood-Brain Barrier Particularities

In addition to alterations in brain physiology in general, alcohol also potentially impairs BBB function. The BBB is a specialized cerebral microvasculature that separates the brain parenchyma from the blood circulation. It regulates the passage of substances into and out of the brain (52, 53). BBB is a neurovascular unit where brain endothelial cells (BEC) cooperate with other brain cells, such as pericytes, astrocytes, end processes, neuron endfeet, and basal lamina to produce a functional BBB. Although it is a multicellular structure, the endothelium is the first layer encountered by drugs, nutrients, and hormones as they enter the brain. The characteristic of the BEC is described below.

BBB is sealed with tight junction and adherence junction proteins

Unlike general capillaries, the gap between BECs is sealed by various tight junction (TJ) and adherens junction (AJ) proteins (4, 52). The intercellular space in TJ is occupied by several intercellular junction proteins, including occludin, claudins, ZO-1, and junctional adhesion molecules (JAMs). Below the TJ protein, there are VE-cadherin and nectin, which seal the AJ through a homotypic interaction (Figure 1). In terms of function, TJ and AJ proteins act as a physical barrier for small hydrophilic molecules to do passive diffusion through the paracellular space of brain micro-vessels.

In the BBB, tight junction proteins have been identified as a major physical barrier to paracellular transport. Occludin and claudins are the vital intercellular proteins in the TJ. The loss of occludin was associated with a compromised BBB and neuroinflammation (54-57). Among many claudin isoforms, claudin-5 is the main claudin isoform in the BBB (58, 59). Deletion of claudin-5 significantly impacts BBB integrity. This was demonstrated by the fact that *claudin-5*$^{-/-}$ knockout mice died within 10 hours after birth (60). The increased BBB permeability in the claudin-5 knockdown mouse was limited to molecules smaller than 800 Daltons, but not to macromolecules. These studies suggested that claudin-5 acts as a physical barrier to small molecules and other intercellular junction proteins, and that defence mechanisms contribute to the overall restrictiveness of the BBB (60).

The main constituent of the adherence junction is VE-cadherin. Similar to occludin and claudin, VE-cadherin forms homotypic interactions with the same molecule from adjacent BEC (61, 62). Nectin is an immunoglobulin-like adhesion molecule that binds in homotypic and heterotypic fashion with adjacent nectin molecules (63). Nectin plays an important role in determining cell polarity and the establishment of adherence junctions. Through a complex signalling process, the association of nectin with adjacent nectin molecules prevents the endocytosis of cadherin and leads to its distribution at the cell surface (64, 65). Thus, nectin interactions initiated cadherin-cadherin interactions and the formation of the AJ complex.

Although tight junction (TJ) and adherence junction (AJ) molecules exert different cellular distribution and functions, both are physically interconnected *via* ZO-1 and the cytoskeleton (66). Researchers have demonstrated the interdependence between the AJ and the TJ (67, 68). In this study, VE-cadherin indirectly regulated claudin-5 expression by removing the FoxO1 transcription factor, one repressor for claudin-5 expression (67). Such interactions between AJ and TJ proteins demonstrate the interrelatedness of the various proteins that form the complex junction between BEC (Figure 1).

Brain endothelial cells expressed no fenestrae

Unlike general capillaries, brain microvessels are characterized by continuous endothelial cells lacking fenestrae. Fenestrae are channels or pores with a 60 - 70 nm diameter that are usually present in peripheral capillaries. This pore allows molecules below 70 nm to diffuse freely into and out of peripheral capillaries (69). The fenestrae absent in the BEC coincide with low expression of plasmalemma vesicle-associated protein (PLVAP), a marker for brain endothelial impairment (70, 71). PLVAP forms a homodimer that organizes into a radial wheel-like structure and spans the fenestra opening surface of fenestrae and transendothelial channels (TEC) (72). This wheel-like structure seems to stabilize the opening of the fenestrae and TEC structure. Reduced PLVAP expression in BEC is associated with fewer fenestrae and TEC (69, 72). Furthermore, PLVAP upregulation in BEC is associated with BBB leakiness and was reported after cerebral ischemia and brain malignancies (72-74).

BBB exerts low vesicular transport activity.

Compared with non-CNS microvessels, BECs exhibit substantially less vesicular transport activity. This low vesicular transport activity appears to correlate with upregulation of Mfsd2a (a sodium-dependent lysophosphatidylcholine symporter-1) in BECs. Studies speculate that the Mfsd2a transporter is specific to BEC, as Mfsd2a is not found in non-CNS endothelial cells (75). In the BBB, Mfsd2a facilitates the entry of lysophosphatidylcholine (LPC)-esterified fatty acids, *i.e.*, lysophosphatidylcholine docosahexaenoic acid (LPC-DHA) (76, 77). Mfsd2a activity enables DHA enrichment in the lipid bilayer of brain endothelial cells. Further, the DHA creates a specific lipid environment in the endothelial BBB that inhibits caveolae-mediated transcytosis. (78). The importance of Mfsd2a for BBB function is demonstrated in the Mfsd2a$^{-/-}$ mouse. Mfsd2a-deficient mice exhibited normal CNS angiogenesis and tight junction formation.

However, they experienced a marked reduction in BBB integrity (79). The BBB alteration in Mfsd2a-deficient mice was not attributable to the loosening of tight junction molecules but rather to an increase in transcytosis activity (75, 78, 79).

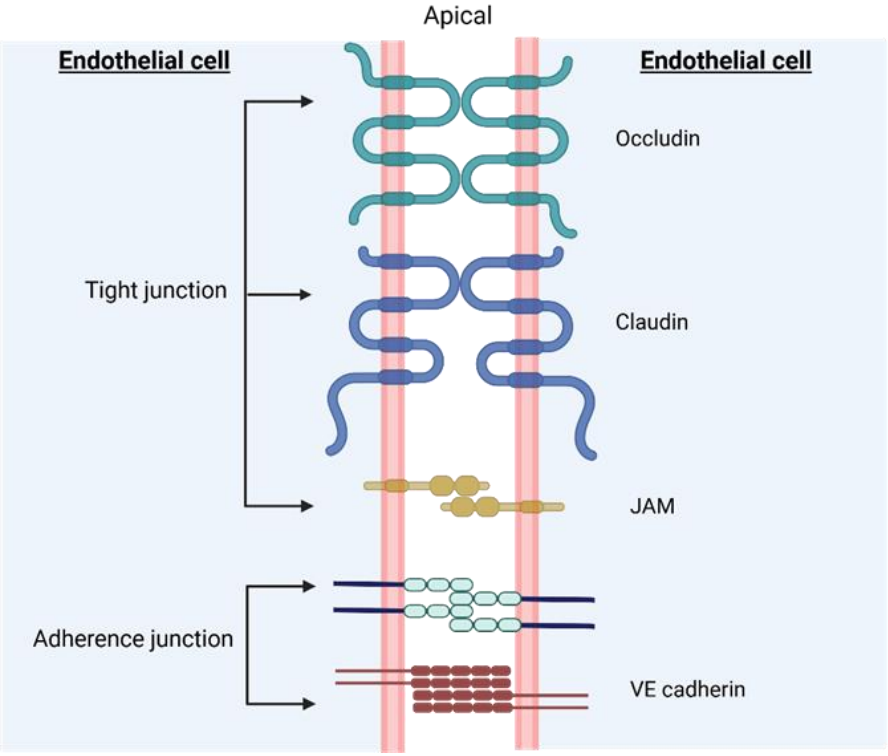

Figure 1.

The intercellular junction in the BEC is sealed by two classes of adhesion molecules: tight junction (TJ) and adherens junction (AJ). Tight junction proteins, including occludin, claudin, and junctional adhesion molecules (JAMs). Through their two extracellular loops, the four transmembrane domains of occludin and claudin form homotypic connections. JAMs are members of the immunoglobulin superfamily and facilitate the extravasation of leukocytes through endothelial cells. The adherens junction is composed of VE-cadherin and nectin and is located more abluminal than the TJ. VE-cadherin has five extracellular repeats that form both homo- and hetero-dimers in a calcium-dependent manner. Nectin is an immunoglobulin-like adhesion molecule comprised of three extracellular loops that bind in homotypic and heterotypic fashion with other nectin molecules.

Although vesicular transport is much lower in the BEC compared to the general micro-vessels, specific vesicular transport is necessary for the entry of peptides, proteins, and hormones into the brain. This vesicular transport includes adsorptive-mediated transport (AMT) and receptor-mediated transport (RMT). AMT is the non-specific type of vesicular transcytosis. It is initiated by the non-specific adsorption of a positive macromolecule to the negative charge of the lipid bilayers. The more specific entry of macromolecules such as insulin, glucagon, vasopressin, natriuretic peptide, transferrin, and the epidermal growth factor is facilitated by receptor-mediated transport (RMT) (2, 80, 81). This route requires specific ligand-receptor binding, which enables the entry of proteins/peptides into the brain. Some receptors that participate in the RMT of the BBB include the transferrin receptors (TfR), insulin receptors (IR), low-density lipoprotein receptors (LRP), and neonatal Fc receptors (FcRn) (53). Both AMT and RMT are saturable transport processes. Although RMT is more specific, its capacity is lower than that of AMT (82).

BBB transport is facilitated by uptake and efflux transporters

An additional feature of BEC is the expression of various influx and efflux transporters. Unlike RMT, which facilitates peptides and proteins, influx transporters primarily facilitate small hydrophilic molecules. Solute carriers (SLCs) facilitate the movement of select solutes into and out of the brain. This includes Glut-1 (SLC2A1), organic anion transporter (OAT), organic cation transporter (OCT), organic anion polypeptide transporter (OATP), creatine transporter (CRT), nucleotide transporter, monocarboxylate transporter (MCT), and large neutral amino acid transporter (LAT). The concentration of neurotransmitters, ions, nutrients, and other neuroactive agents within the brain parenchyma is regulated by these transporters.

In addition to the SLCs, BECs express ATP-binding cassette (ABC) transporters that facilitate the removal of waste products and xenobiotics (foreign substances) from the brain parenchyma into the lumen of brain microvessels. This includes P-glycoprotein (Pgp/ABCB1), breast cancer-related protein (BCRP/ABCG2), and multidrug resistance-associated protein-1, -3, -4, -5 and -6 (MRP) (83, 84). Interestingly, ABC transporters recognize a more diverse range of chemical structures than SLCs. Among many ABC transporters, Pgp and BCRP are the two main efflux transporters in the BBB (85, 86). The passage of many therapeutic agents into the brain is limited by two efflux transporters that recognize multiple molecular structures. (83, 87).

BBB has elevated mitochondrial activity.

CNS endothelial cells have a higher mitochondrial content compared to endothelial cells in the peripheral blood vessels. Brain endothelial mitochondria comprise 8 - 12% of cytoplasmic space. On the other hand, endothelial cells in non-CNS tissues have mitochondrial content of around 2 - 5% of the cytoplasmic volume (88). Higher mitochondrial activity in the BEC appears to provide the energy for their ATP-dependent transporters. Studies on the BBB in Alzheimer's patients showed that the BBB expresses much lower mitochondrial content, which reached 2.8% (89). Mitochondria are essential for maintaining BBB integrity. Exposure of endothelial cells to mitochondrial inhibitors, such as rotenone, FCCP, and oligomycin, increased BBB leakiness. Moreover, mitochondrial inhibition during stroke worsens BBB impairment (90). Together, these studies suggest that mitochondria play an important role in BBB integrity.

Effects of Chronic Alcohol Exposure on Blood-Brain Barrier Functions

Alcohol binge drinking is the most prevalent and most accessible misuse of substances in the community (91). Even if we are not aware, our bodies are exposed to alcohol substances. The difference lies in the frequency and level of alcohol exposure. Numerous studies have identified the impact of alcohol on the BBB. The discussion below will examine how far a particular blood alcohol concentration (BAC) level affects BBB integrity.

Studies on the effect of alcohol on the BBB were mostly done in mice (*in vitro* and *in vivo*). There is some available data on the human BBB, but most of it is from *in vitro* systems (Table III). A study examined the postmortem brain tissue of an alcoholic patient, which suggests that the alcoholic patient exhibited an impairment in BBB integrity *via* elevation of MMP-9 activity, reduction of Claudin-5, collagen type IV, and laminin enrichment in the CNS capillaries. Brain samples from alcoholic patients showed an elevation of leukocyte abundance in the brain, which suggests the impairment of BBB function (92). Unfortunately, the data did not include the drinking pattern and BAC records, which limits readers' assessment of the extent to which the drinking pattern triggers BBB breakdown.

In the human model, more comprehensive studies were conducted *in vitro*. The concentration range examined is quite wide, from 80 mg/dL to 460 mg/dL. Unfortunately, data on the impact of low concentrations of alcohol (far below 80 mg/dL) is currently not available for the human model of the BBB. Indeed, exposure of endothelial cells to high concentrations of alcohol (230 mg/dL and 460 mg/dL for 2 hours) is associated with increased myosin light chain kinase (MLCK) phosphorylation, redistribution of tight junction molecules from intercellular junctions, and cytoskeletal rearrangement (93). These events increased monocyte migration, suggesting that ethanol-induced brain breakdown is associated with increased MLCK phosphorylation. Separated studies in human *in vitro* models of the BBB examined the mechanism by which alcohol increases BBB porosity. A high alcohol concentration (230 mg/dL) also activated other pathways, elevating MMP-9 activity, followed by a reduction in tight junction immunoreactivity (94). The increase in catalase enzyme activity is also involved in the alcohol-induced blood-brain barrier permeability. Similar to MMP-9, the increase in catalase activities correlated with the reduction in tight junction immunoreactivity in the BEC (95). Together, this suggests that alcohol-induced increased permeability is mediated in part by the loosening of tight junctions and degradation of the basal membrane. Together, these studies imply that alcohol-induced BBB dysfunction occurs through several possible pathways, including MLCK phosphorylation, increased MMP-9 activity, and increased catalase activity. Unfortunately, the available report did not include an investigation into the impact of low BAC (well below 80 mg/dL) on BBB integrity. This data is very important to assess the impact of non-intentional alcohol exposure on BBB function.

In the mouse BBB model, the impact of ethanol exposure on the BBB has been more comprehensively reported, particularly in *in vivo* studies. Several *in vivo* data from mice suggested that BBB dysfunction was observed in alcohol exposure lower than 80 mg/dL. Studies on alcohol consumption, which correspond to 135 mg/dL (96), 45 - 135 mg/dL (97) and 144 - 199 mg/dL, were reported to induce impairment in BBB function. Consistent with the human *in vitro* model, *in vivo* mouse data indicated that alcohol-induced BBB dysfunction is

mediated by reduced immunoreactivity of tight junction molecules and the basement membrane.

Performing *in vivo* studies also allows the investigator to report the blood alcohol concentration (BAC) post-alcohol treatment. However, the BAC data can vary depending on the time frame of blood sampling after alcohol administration. Ideally, the BAC was measured within 1 - 2 hours post-alcohol exposure to capture the peak of alcohol plasma concentration (98). Thus, interpreting the published report required a close examination of the time of blood sampling before correlating the BAC value with the BBB function.

In vivo studies in mice allow investigators to create different drinking scenarios. Many studies examined the impact of binge alcohol drinking in adult mice on BBB function (96,99). Adolescent intermittent alcohol drinking is also an interesting topic to be examined in mice. Reported studies suggested that the BBB function in male mice is more affected by alcohol than in female mice during adolescence (100). Another scenario that can be modelled in mice is alcohol intake during the gestational period. Studies suggested that repeated alcohol exposure during pregnancy is associated with excessive angiogenesis in newborn mice, accompanied by a reduction in ZO-1 immunoreactivity (95). This finding supports the previous finding that tight junction molecules (ZO-1, Claudin-5, and occludin) are the major targets of alcohol-induced BBB dysfunction.

Another emerging finding regarding ethanol-induced BBB permeability is the alteration in vesicular transport across BECs. Recent studies suggested that long-term alcohol exposure in 4-month-old mice (10 g/kg) is associated with reduced expression of Major facilitator superfamily domain-containing protein 2 **(**MFSD2A) (101). This transporter plays a role in the transport of omega-3 fatty acids from the blood to the brain parenchyma and in their disposition within brain cells (75). Enrichment of omega-3 fatty acids in the membrane of BEC prevents the formation of caveolae, an initial step in vesicular transport across the BBB (78). In agreement with this study, the exposure of human BEC to alcohol 230 mg/dL for 4 days was associated with increased plasmalemma vesicle-associated protein/PLVAP (99). This protein is responsible for stabilizing endothelial fenestrae/pores (69). Together, studies to explore further the influence of alcohol exposure on the fenestration of the BBB and its vesicular transport are imperative.

In addition to "how much", "how long" is another issue that needs to be addressed regarding alcohol-induced BBB dysfunction. Studies from *in vitro* and *in vivo* studies on chronic alcohol intake suggest that repetitive exposure alters BBB function. However, the question of when the BBB begins to be altered is not addressed comprehensively. The *in vitro* studies suggest that BBB permeability is affected immediately after alcohol exposure. A model of acute alcohol exposure (230 mg/dL) in the human *in vitro* model of BBB suggested that two-hour ethanol exposure at a concentration corresponding to binge alcohol drinking can initiate tight junction and cytoskeleton re-arrangement (93, 102). However, BBB function, assessed using an impedance assay/TEER value, indicated increased BBB porosity as early as 30 minutes after initial alcohol exposure (230 mg/dL) (93,99). Additional supporting data to the TEER value and relocation of claudin-5 post-alcohol exposure were observed within 30 minutes of exposure. These studies suggested that not only chronic alcohol exposure, but also acute alcohol ingestion, potentially alters the physiology of the blood-brain barrier.

Another interesting finding in this field is that alcohol affects transporter activity and mitochondrial physiology (95, 103). Alcohol exposure (460 mg/dL) overnight to an *in vitro* model of human BBB is associated with reduced mitochondrial membrane potential, which leads to a release of ATP to the extracellular compartment. The mechanism by which alcohol alters mitochondria was preceded by increased expression of the purinergic receptor P2X7r, which led to increased expression of TRPV1 (a calcium ion channel). This event leads to an increase in intracellular calcium, which further triggers stress on the endoplasmic reticulum and the misfolding of proteins synthesized (103).

Based on Table III, impairment of the BBB in *in vivo* studies can be observed at a BAC as low as 41 mg/dL. In this study, the mice received 5% alcohol for 12 - 13 weeks. The experiment showed that chronic alcohol exposure, even at low concentrations (41 mg/dL), is associated with reduced expression of tight junction molecules, including claudin-5, occludin, and claudin (97). In agreement with the *in vivo* studies, the *in vitro* data on bovine brain microvessel endothelial cells (BBMEC) suggest that alcohol exposure at a concentration of 46 mg/dL for 48 hours increased MLCK activity, which further caused retraction of tight junction molecules from the intercellular junction and increased paracellular porosity (93). As the BAC of 40 mg/dL can be achieved after consuming two standard drinks, these studies suggest that researchers and legal authorities should evaluate this BAC in a more comprehensive BBB study to set a more rational BAC legal limit.

The concentration of 40 mg/dL is more likely to be achieved through alcohol drinking but less likely to be achieved through unintentional alcohol consumption. Studies showed that the consumption of one standard drink in the Thai population resulted in a BAC of 30 - 35 mg/dL (51). In other words, the

consumption of more than one standard drink may increase the possibility of changes in BBB phenotypes.

Alcohol consumption from food is less likely to cause BBB impairment, especially in those who have a bigger total body water, *i.e.*, adults. Exposure to a high concentration of alcohol might create a potential risk for children under 2 months. Mice pups being exposed to 3 g/kg alcohol daily during gestational days 14 - 19 experience sparse expression of the tight junction molecule, ZO-1 (5). For children, alcohol in a dose of 3 g/kg is considered lethal (50). This value is less likely to be present in the standard consumption of food-containing alcohol. However, this dose is possibly achieved when a baby or toddler accidentally ingests alcohol-containing medication and household products.

In summary, blood-brain barrier dysfunction is more likely to be present in voluntary alcohol consumption with more than one standard drink. The risk increases when alcohol is consumed chronically. The BAC resulting from non-intentional ethanol exposure through food and household items is predicted not to be sufficient to induce BBB impairment. The impact of alcohol on BBB integrity, especially the paracellular barrier, can be observed within 1 hour after exposure. This study required follow-up confirmation in the human *in vivo* model.

Table III

Attenuation of blood-brain barrier function following alcohol exposure in the *in vivo* and *in vitro* studies

Model	System	Cell line	Alcohol treatment	Blood Alcohol Concentration (BAC)	Effect to BBB	References
Human	*in vitro*	BMVEC	230 mg/dL, 2 hours, mimicking where BEC causes moderate to severe intoxication.	-	Phosphorylation of claudin-1, ZO-1, occludin, and MLCK, which trigger tight junction and cytoskeleton re-organization	(102)
		(hCMEC/D3)	80mg/dL, acute, and 4 days	-	No change in BBB permeability	(99)
		(hCMEC/D3)	230 mg/dL for 4 days	-	Increased PLVAP expression	(99)
		Human BMVEC	230 mg/dL, 48-hour		Increased expression and activity of MMP-1, -2 and -9. Increased degradation of the basement membrane, reduced TEER, increased 4kDa Dextran permeability and monocyte migration	(94)
		HBMVEC (D3 line)	100 mM for 1 hour (460 mg/dL)		Reduction of mitochondrial oxidative phosphorylation	(103)
		HBMEC	230 mg/dL and 350 mg/dL		Increased catalase enzyme expression by 45%, reduced expression of Claudin-5, ZO-1 and Glut-1	(95)
	ex vivo	Postmortem brain			Increased activity of MMP-9, reduction of claudin-5, laminin, and type IV collagen, increased leukocyte infiltration to the brain	(92)
Mice	*in vivo*	80-week-old mice	5% v/v for 11 - 12 weeks	9.1 - 28.8 mM (41 - 135 mg/dL)	Reduced occludin, ZO-1, and claudin-5 expression, reduced relocation of the waste to the perivascular space	(97)
		Adult mice	Binge drinking model Four cycles of the “drinking in the dark” protocol	135.2 ± 16 mg/dL	Reduced immunoreactivity of laminin and collagen type IV, increased IgG extravasation across the BBB.	(92)
		Mice	5% v/v for 8 - 9 weeks		Occludin is sparsely dis-	(104)

					tributed on the microvessel isolated from the alcohol-treated animal. aggregation of macrophages on the damaged site of the brain microvessels	
		mice	6.5 % v/v for 4 weeks	144 - 190 mg/dL	Reduced expression of claudin-5, occludin, and ZO-1, increased NF and EB extravasation	(105)
		Mice	Model of intermittent adolescent drinking 4 g/kg i.p. 12 times alcohol intubation	251 ± 37 mg/dL	The male, but not the female, group shows higher 20- and 70- kDa dextran permeability in several brain regions.	(100)
		Mice	Model of alcohol gestational exposure 3 g/kg daily from GD14-GD19		Sparse ZO-1 expression in the isolated microvessels from newborn mice. Increase vascular angiogenesis in newborn mice.	(95)
		Mice	Model of binge alcohol drinking, 2 g/kg i.p 7 days	230 mg/dL	Reduction of claudin-5 RNA expression	(99)
		Mice (4 months)	Model for long-term alcohol exposure, 10 mL/kg for 60 days,	N/A	Reduced expression of ZO-1, occludin, and VE-Cadherin, reduced expression of Mfsd2a and RAGE, and increased BBB permeability were examined using Evans blue injection.	(101)
	in vitro	MBEC (Primary)	230 mg/dL and 460 mg/dL		Increased catalase enzyme expressio by 45%, reduced expression of Claudin-5, ZO-1 and Glut-1	(95)
		Bend3	115 mg/dL and 460 mg/dL		Both concentrations reduced cell viability by 26.5 - 33.7% at 24 h, reduced TEER by 20% at 24 h, and reduced claudin-5 expression at alcohol 460 mg/dL	(106)
Bovine	*in vitro*	Bovine BMEC	46 mg/dL, 2 hour minutes		Increased MLCK activity to phosphorylate the tight junction protein, reduced TEER value by 10%, and increased monocyte migration	(93)
		Bovine BMEC	230 mg/dL, 2 hours		Increased MLCK activity to phosphorylate the tight junction protein, reduced TEER value by 10%, and increased monocyte migration	(93)

Conclusions

Alcohol is present in our everyday lives in alcoholic drinks, medicinal, household, and personal care products. Among organs, the BBB is part of the organ that is sensitive to alcohol in the bloodstream. Data from animal models suggest that a BAC of 40 mg/dL is sufficient to impair BBB function. More comprehensive studies, especially clinical studies,

are necessary to investigate the effect of a 40 mg/dL BAC on the BBB. Patient recruitment can be performed by offering the alcohol-intoxicated patient who has been admitted to the emergency for further examination using Magnetic Resonance Imaging to evaluate the BBB functions. Different contrast agents can be used to assess BBB leakiness at different BACs in patients. Studies can also differentiate the impact of age on the BBB leakiness upon different BACs. The fact that BBB impairment tends to be present in higher BAC suggests that intentional alcohol drinking and accidental alcohol consumption from medicine and household products potentially damage the BBB. Regarding this, food and drug authorities need to consider the potential harm of alcohol when babies and toddlers accidentally consume medicine and household products. In the context of medicinal products, more translational research is necessary to reduce the use of ethanol in paediatric medications. In addition, when the use of ethanol is unavoidable, the development and enforcement of childproof packaging are imperative. Learning from Chinese chicken wine soup studies, the potential risk of other alcohol-containing foods is an interesting topic to be investigated when it comes to consumption by pregnant women, babies, or toddlers. A well-designed animal model that investigates the lowest concentration BAC that creates BBB impairment in the foetus, newborn, baby, and toddler is necessary to provide safety data for the drug authority.

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Conflict of interest

The authors declare no conflict of interest.

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