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Review

Alcohol-Induced Headache with Neuroinflammation: Recent Progress

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Abstract: Ethanol and other congeners in alcoholic beverages and foods are known triggers of alcohol-induced headaches (AIHs). Recent studies implicate AIHs as an important underlying factor for neuroinflammation. Studies show the relationship between alcoholic beverages, AIH agents, neuroinflammation, and the pathway they elicit. However, studies elucidating specific AIH agents' pathways are scarce. Works reviewing their pathways can give invaluable insights into specific substances' patterns and how they can be controlled. Hence, we reviewed the current understanding of how AIH agents in alcoholic beverages affect neuroinflammation and their specific roles. Ethanol upregulates transient receptor potential cation channel subfamily V member 1 (TRPV1) and Toll-like receptor 4 (TLR4) expression levels; both receptors trigger a neuroinflammation response that promotes AIH manifestation—the most common cause of AIHs. Other congeners such as histamine, 5-HT, and condensed tannins also upregulate TRPV1 and TLR4, neuroinflammatory conditions, and AIHs. Data elucidating AIH agents, associating pathways, and fermentation parameters can help reduce or eliminate AIH inducers and create healthier beverages.

Keywords: alcoholic beverage; alcohol-induced headache; ethanol; congeners; neuroinflammation

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1. Introduction

Alcoholic beverages and other alcohol containing foods trigger headaches [1]. Consumers complain about headaches after consuming certain amounts of alcohol—especially red wines and inferior alcoholic beverages [2]. The International Headache Society (IHS) issued an ICHD III report in 2013 [3], the third edition of the International Headache Classification, which defines alcohol-induced headaches (AIHs) as headaches that occur immediately after or a while longer after ingesting alcoholic beverages. The ICHD report classifies AIHs into two categories. The classification parameter is the time lapse between consumption and headache manifestation: (1) AIH manifestation within 3 h after alcohol consumption is termed immediate alcohol-induced headache, and (2) manifestations after 5–12 h are termed delayed alcohol-induced headache. Whether an AIH effect manifests immediately or is delayed depends on groups, regions, and the specific alcoholic beverages consumed. Different alcoholic beverage types are the prominent AIH factor documented in several pieces of literature [1,4–6].

Alcoholic beverage intake causes AIHs, a health risk to consumers, which could mean sales and developmental limitations for beverage companies. Therefore, elucidating specific components of alcoholic beverages that could trigger AIHs and the pathway they elicit would be of paramount research interest. Although data from studies are controversial, congeners—a by-product of fermentation other than ethanol—also trigger AIHs. A study reported that congener-induced AIHs differ significantly amongst beverage types: bourbon,

whiskey, and vodka [7]. Furthermore, high amounts of congeners such as flavonoids and biogenic amine in red wine trigger migraines [5]. Alcoholic beverages with high congener contents, such as bourbon, have been reported to elicit more severe AIH conditions than beverages with lower congener content [8,9].

However, Chabriat and colleagues [10] argued that white wine—with lower congener content—has greater AIH manifestation than red wine. Although some studies suggest that congener content does not correlate with AIH manifestation, other studies link specific categories of congeners to AIH manifestations [11,12]. However, due to the scarcity of relevant experiments, the effects of different congener categories on AIH manifestation have rarely been verified, and most experiments have only focused on the molecular level.

Conclusively, the effects of congener substances will only be settled through further experimentations. Nonetheless, reviewing related studies is a worthwhile guide to elucidating the cause and effect of substances associated with AIH manifestations. Other studies would also showcase controllable parameters that could lower or limit the production of harmful by-products. Such information will enhance the production of high-quality, healthier alcoholic beverages with little or no AIH effects.

2. Hypotheses on the Causes of AIHs

It is hard to differentiate AIHs from other primary headaches (e.g., migraines and cluster headaches). They possess similar symptoms and share common pathological mechanisms. Due to these, some AIH hypotheses have been propounded.

2.1. Direct Inflammation in the Trigeminal System

Sensory neuropeptides induce meningeal vessel vasodilation in the trigeminal neurons. Neuropeptide release is an underlying mechanism for migraines [13]. Nicoletti et al. [9] also suggested that ethanol directly induces meningeal nociceptor stimulation, elicits inflammation in the trigeminovascular system, and accompanies meningeal vessels' vasodilation (see Figure 1). The same inflammation factors were transferred into the trigeminal system during an ethanol-induced migraine. The factors were then conveyed to the somatosensory cortex to elicit AIHs.

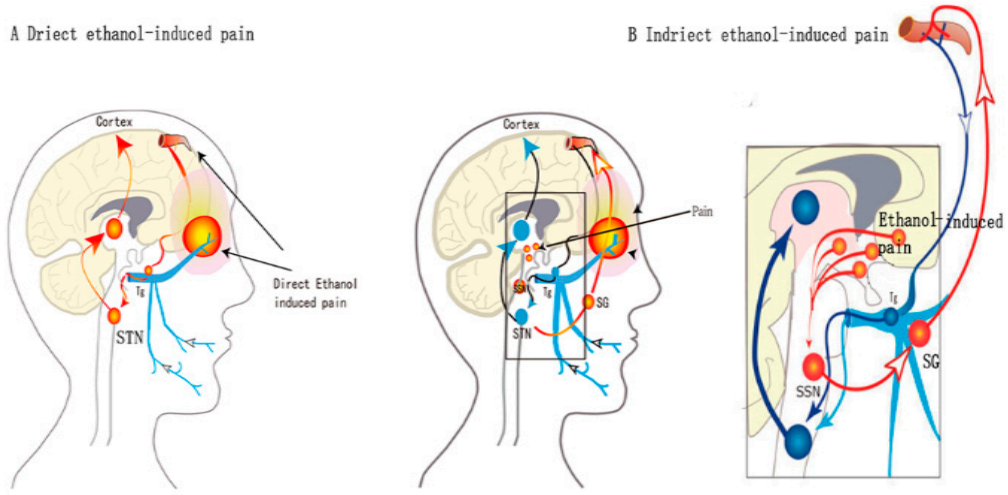

Figure 1. Ethanol-induced pain transmission in the trigeminovascular system. (**A**) Direct ethanol-induced pain: ethanol stimulates meningeal nociceptors in the Tg (trigeminal ganglion), eliciting pain signals, which are then transmitted in the spinal trigeminal nucleus (STN) to the thalamic nuclei (Th), and ultimately to the somatosensory cortex. (**B**) Indirect ethanol-induced pain: the SNN (superior salivatory nucleus) accepts ethanol-induced pain signals from different limbic and hypothalamic brain parts. The SNN transmits the pain signals to the sphenopalatine ganglion (SG); activation of the SG elicits vasodilation and the release of inflammatory factors by meningeal nociceptors, and the pain signal is then expressed through the direct pathway described above.

2.2. Indirect Inflammation in the Trigeminal System

Another AIH hypothesis suggests that alcoholic beverages stimulate headaches. The first step is through different neuronal pathways in the superior salivatory nucleus (SSN) [14,15]. Alcoholic beverages also stimulate headaches through the activation of meningeal nociceptors (vasodilation of meningeal vessels), which releases inflammatory factors into the trigeminal system and, ultimately, the somatosensory cortex, thus inducing the manifestation of headache [16]. Alternatively, alcoholic beverages activate SNN and later sensitize meningeal nociceptors and the trigeminal system, thus eliciting AIHs.

2.3. Induction of CSD

Cortical spreading depolarization (CSD) is a phenomenon that describes changes in ion homeostasis, increases in mitochondrial activity, energy demand, and cerebral blood flow [17,18]. Studies have suggested that CSD may be an important underlying mechanism of migraines [19]. Vasodilation and inflammation were also observed during CSD treatment [20]. Changes in neurovascular tissues are coupled with inflammatory factor release in the trigeminal system. These factors later culminate in the somatosensory cortex, which links CSD with migraines.

However, it has been suggested that CSD is associated primarily with chronic alcohol intake, and related articles [21,22] did not find headache symptoms in acute alcohol intake experiments. Interestingly, acute amounts of alcohol were used to attenuate the speed of CSD propagation in these studies.

2.4. Induction of Vascular Changes

Moderate alcohol intake has long been considered to protect against coronary artery disease through its vasodilatory effects [23]. Results from several studies [24,25] have also demonstrated the vasodilatory role of alcoholic beverages in brain tissues following acute alcoholic beverage consumption. However, contrasting evidence suggests that acute alcohol consumption may also induce vasoconstriction [26]. In addition, these vascular changes were always observed with inflammation in the trigeminal system.

A previous study suggested that AIHs are mainly induced by neuroinflammation [27] and that CSD or changes in blood vessels are mere concomitant phenomena. Another study that supports this notion used an anti-inflammatory drug (ketorolac-toradol) to reverse AIHs [28]. Therefore, the preceding section of this review will outlay the relationship between alcoholic substances, AIHs, and neuroinflammation.

3. Ethanol, AIH, and Neuroinflammation

3.1. Ethanol and Its Metabolism In Vivo

3.1.1. TRPV1

Transient receptor potential cation channel, subfamily V, member 1 (TRPV1), also known as the capsaicin/heat receptor and the vanilloid receptor, is a confirmed pain trigger mentioned in numerous studies. Several inflammatory studies have shown that the expression of TRPV1 is upregulated in AIH animal models [29,30]. Meanwhile, several studies have reported phenomena such as greater alcohol consumption and weaker withdrawal severity in TRPV1$^{-/-}$ mutant mice [31–35]. These experiments implicate TRPV1 for the alcoholic beverages' consumption hangover symptoms and AIH effects.

Nicoletti et al. [9] demonstrated that ethanol-induced neurogenic inflammation in the trigeminal system and meningeal vessels vasodilation are caused by the activation of TRPV1 and the release of calcitonin gene-related peptide (CGRP) [36] and substance P (SP) [37]. They measured CGRP and SP in a group treated with a TRPV1 antagonist and found that CGRP and SP were decreased by 70% compared with the control group under the same ethanol treatment.

CGRP has been acknowledged [38] as a trigger for vasodilation through mitogen-activated protein kinase (MAPK) activation, as well as an inflammatory mediator for cytokines (i.e., TNF-α [39]). An in vivo study indicates that CGRP triggers vasodilation in

porcine coronary arteries [37]. Blocking TRPV1 with an antagonist—capsazepine—resulted in lower CGRP expression and decreased arterial dilatation. It could be explained that TRPV1 sensitization first elicits a Ca^{2+} influx, and Ca^{2+} then triggers a rapid downstream signaling pathway resulting in the release of inflammatory mediators such as CGRP and SP (see Figure 1). The release of these neuropeptides can be suppressed if Ca^{2+} is removed [9], supporting the notion that ethanol promotes Ca^{2+} inflow. Inflammatory mediators, such as CGRP and SP, promote the downstream cascade of neuroinflammation factors and cytokines, which culminate in neuroinflammation.

SP can also sensitize TRPV1, which is associated with phosphatidylinositol-4,5-bisphosphate (PIP2) cleavage, diacylglycerol (DAG) production, and the activation of protein kinase C (PKC). According to some studies [40,41], PKC can activate TRPV1 at its C terminus. Ethanol treatment upregulated PKCε expression in Western blotting and plasma membrane tests. These results reveal that PKC is an important TRPV1 sensitization ligand [42].

Peralta et al. found that TRPV1 mRNA was upregulated in alcohol-treated 5-month-old wild-type mice relative to untreated mice, suggesting that ethanol was significantly associated with TRPV1 expression. The same study showed that the activation of TRPV1 was markedly associated with c-Jun N-terminal kinase (JNK) and p38 MAPK (modulated by miR-183c and miR-200s) [43]. Sakakibara and colleagues compared oral epithelial cells from patients with different levels of alcohol consumption. Patients with a history of lengthier alcohol consumption had significantly higher TRPV1 mRNA expression levels in their epithelial cells than patients without this history [44].

However, changes in TRPV1 protein levels have not been observed in response to ethanol treatment. Ethanol treatment (0.3% concentration) did not affect TRPV1 protein levels in either the plasma membrane or the total cell proteins of HEK293 cells [45]. Additionally, acetate may also cause AIHs through the release of adenosine. However, this effect can be blocked by the anti-inflammatory drug ketorolac [46]. Additional evidence suggests that adenosine induces hyperalgesia through TRPV1 phosphorylation. This result implies that acetate may also affect AIHs through TRPV1 [47,48]. Thus, ethanol and acetate may affect AIHs by activating TRPV1. Additionally, ethanol may affect TRPV1 activity through its sensitization rather than upregulation.

3.1.2. TLR4

Toll-like receptor 4 (TLR4) expression is also associated with AIHs, and its effects are ascribed to neuroinflammation [49]. Evidence suggests that ethanol can affect TLR4-induced neuroinflammation, which then elicits AIHs. A study showed that TLR4 knockout mice exhibited less ethanol-induced inflammatory damage [50]. The result supports the motion that TLR4 has AIH effects.

Unlike TRPV1, TLR4 affects changes in gene expression, protein abundance [51,52], and activation [53,54] in response to ethanol and its metabolites. These results are confirmed in many studies. It was confirmed that miR-125b (the upstream miRNA for TLR4) was upregulated in alcohol-treated wild-type mice compared with untreated mice. Ethanol elicited upregulation of TLR4 mRNA [43]. A study found that ethanol upregulated TLR4 mRNA and protein expression levels in the microglial cell membrane and total cell protein. Maximal TLR4 mRNA levels were observed after 30 min of ethanol treatment [51].

Ethanol treatment elicits high levels of TNF-α and IL-1β after 7–24 h. High levels of inductive nitric oxide synthase (iNOS) and cyclo-oxygenase (COX-2) are observed 3–7 h after ethanol treatment, accompanied by the upregulation of TLR4 [55]. A team observed that treating mice with 6 g/kg ethanol increased mRNA levels of chemokines, such as CCL2, MCP-1, and IL-6 [56]. Another study found that interleukin (IL) 6, IL-10, and IL-12 were upregulated via TLR4 after mice models were treated with 6 g/kg ethanol [57].

A study showed that the TRL4 inflammation downstream factors, such as TNF-α and IL-1β, were reduced following ethanol exposure in the $TLR4^{-/-}$ mutant relative to the wild type. Another research demonstrated that ethanol did not affect TNF-α, IL-1β,

COX-2, and iNOS in the cerebral cortex of the TLR4$^{-/-}$ mutant [58]. Additionally, the levels of NF-κB, COX-2, MyD88, CD40, and TRIF were suppressed, and neuropathic pain was attenuated in animal models when TLR4 was blocked by butylated hydroxytoluene (BHT) and *Rhodobacter sphaeroides'* lipopolysaccharide (LPS-RS) [44,59].

Many studies confirm that the upregulation of TLR4 delays AIH manifestation. The release of inflammation factors, e.g., TNF-α, IL-1β, COX-2, and iNOS, were significantly affected by ethanol treatment and TLR4 overexpression. In contrast, the release time of these substances was closely associated with AIHs, with a 5–12 h delay [60].

Activated TLR4 co-localizes with adaptor proteins (i.e., CD14 and MD2, see Figure 2) in lipid rafts [52]. TLR4 transmits signals to adaptor protein molecules such as TIR-domain-containing adaptor-inducing IFNβ (TRIF) and myeloid differentiation primary response gene88 (MyD88). Both of these adaptor proteins induce the activation of transcription nuclear factors (TnFs) such as NF-κB, activator protein 1 (AP-1), and interferon regulatory factor 3 (IRF3). Eventually, TnFs promote the release of cytokines such as IL-1β [61,62], TNF-α [63], MCP-1, and inflammatory mediators such as COX-2 and iNOS [55]. The expression of the aforementioned induces inflammation (Table 1).

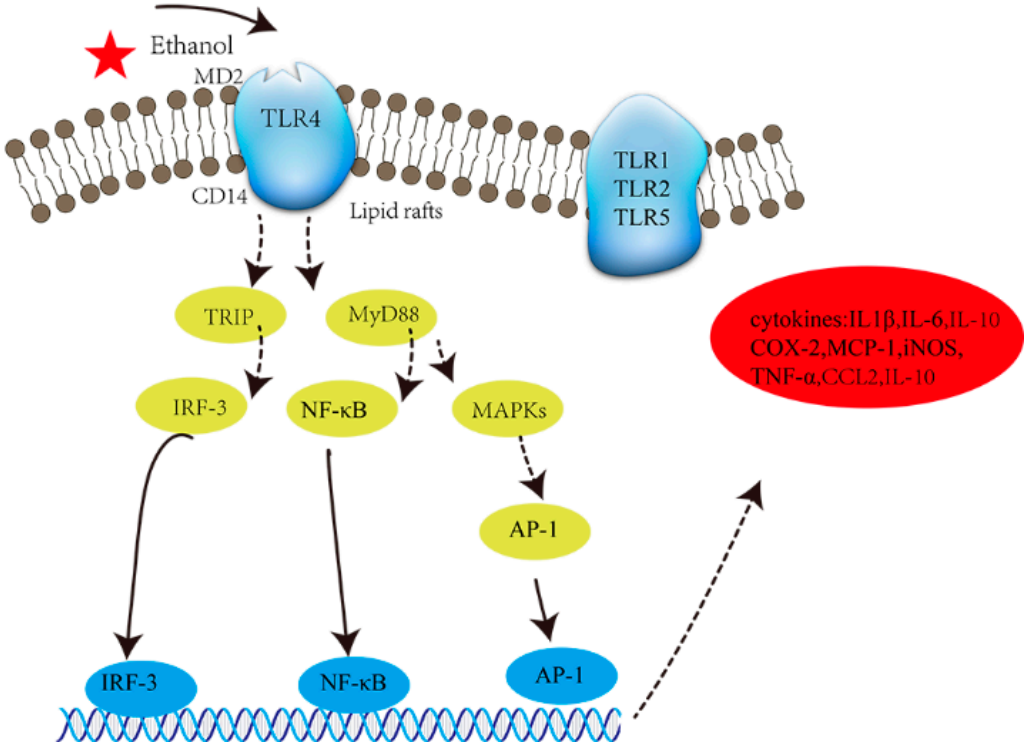

Figure 2. The activation of TLR4. Key: MD2: myeloid differential protein 2; CD14: membrane CD14; MAPK: mitogen-activated protein kinase; MCP-1: monocyte chemoattractant protein-1; IL-6: interleukin-6; TNF-α: tumor necrosis factor-α; IL1β: interleukin-1β; CCL2: chemokine ligand 2.

Ethyl-b-D-glucuronide (EtG) is a minor metabolite of ethanol. EtG makes up 0.04% of ethanol derivatives [64] and has a similar structure to glucuronic acid (GA) [65]. It elicits pain through TLR4 sensitization. Lewis et al. [66] studied the effects of ethanol and EtG on TLR4. These compounds sensitize TLR4 and elicit allodynia (a rat model of AIHs) when administered by intrathecal injection. They also induce the overexpression of secreted alkaline phosphatase (SEAP) in Sprague Dawley rats. TLR4 antagonists reduced this allodynia and SEAP secretion by blocking TLR4.

Table 1. Research on the effects of ethanol and its derivatives on AIHs and neuroinflammation in vivo.

Compound	Animal Model	Animal Type	Triggering Site	Molecules Involved	References
Ethanol	Wild	Rat, tissues	Lowers TRPV1 thermal threshold	Ca^{2+}↑ CGRP↑ SP↑	[67]
Ethanol	Wild	Guinea pig, Dunkin Hartley	Lowers TRPV1 thermal threshold	Ca^{2+}↑ CGRP↑ SP↑	[67]
Ethanol	Wild	White rabbit, New Zealand	Lowers TRPV1 thermal threshold	ND	[36]
Ethanol	Wild	Guinea pig, Dunkin Hartley	Lowers TRPV1 thermal threshold	Ca^{2+}↑ CGRP↑ SP↑	[37]
Ethanol	Wild	Guinea pig, Dunkin Hartley	Lowers TRPV1 thermal threshold; vasodilation of meningeal vessels; enhancement of blood flow	CGRP↑ SP↑	[9]
Ethanol	Wild	Rat, Sprague Dawley	Enhances cell apoptosis	CGRP↑ TNF-α↑	[68]
Ethanol	Wild, $TRPV1^{-/-}$	Mouse, C57BL/6	More ethanol consumption; weaker withdrawal severity	$TRPV1^{-/-}$	[32]
Ethanol	Human	Oral epithelial cells	TRPV1↑	mRNA↑	[44]
Acetate	Wild	Rat, Sprague Dawley	Enhances AIH severity	Adenosine↑	[46]
Ethanol	$TLR4^{-/-}$	Rat, Wistar	Activates TLR4	COX-2↓ iNOS↓	[58]
Ethanol	Wild, $TLR4^{-/-}$	Mouse, C57BL/6	Upregulates cytokine	TLR4↑ IL-1β↑	[63]
Ethanol	Wild	Rat, Wistar	Activates TLR4	TLR4↑ iNOS↑ COX-2↑ IL-1β↑	[53]
Ethanol	Wild	Brain tissue, Mouse, C57BL/6	Activates TLR4	TNF-α↑ MCP-1↑	[54]
Ethanol	Wild	Mouse, C57BL/6	Activates TLR4	CCL2↑ MCP-1↑ IL-6↑	[56]
Ethanol	Wild	Mouse, B6C3F1	Activates TLR4	IL-6↑ IL-10↑ IL-12↑	[57]
Ethanol	Wild	Rat, Wistar	Activates TLR4 in lipid raft	TLR4↑ TRIF↑ IRF3↑	[52]
Ethanol	Wild, $TLR4^{-/-}$	Mouse, C57BL/6	Upregulates TLR4 and TRPV1	miR-125b↑ miR-200s↑ miR-183↑ mRNA↑	[43]
Ethanol	Wild, $TLR4^{-/-}$	Rat, Wistar, Mouse, C57BL/6	Upregulated TLR4 and cytokine	TLR4↑ iNOS↑	[51]
Ethanol	Wild, $TLR4^{-/-}$	Rat, Wistar, Mouse, C57BL/6	Upregulation of cytokine	iNOS↑ COX-2↑ TNF-α↑ IL-1β↑	[55]

Table 1. *Cont.*

Compound	Animal Model	Animal Type	Triggering Site	Molecules Involved	References
Ethanol	Wild	Rat, Wistar	Blocks TLR4	TLR4↓ MyD88↓ CD40↓ TRIF↓	[59]
Ethanol and EtG	Wild	Rat, Sprague Dawley	Enhanced AIH	TLR4↑ SEAP↑	[66]
Ethanol	Wild	Rat, Sprague Dawley	Blocks NF-κB; attenuates AIH	NF-κB↓ COX-2↓	[44]
Ethanol	Wild, $TRPV1^{-/-}$	Mouse, C57BL/6	Reduces sensation	$TRPV1^{-/-}$	[31]
Ethanol	Wild, $TRPV^{-/-}$	Mouse, C57BL/6	Reduces inflammation	$TRPV1^{-/-}$ and Ca^{2+} removal	[69]
Ethanol	Wild, $TLR4^{-/-}$	Mouse, C57BL/6	Reduces ethanol-induced neuroinflammatory damage	$TRPV1^{-/-}$	[50]

ND: not determined; EtG: ethyl-b-D-glucuronide; GA: glucuronic acid; CBF: cortical blood flow; Cpla2: cytosolic phospholipase A2; PARP: poly ADP-ribose polymerase; IL-1RI: interleukin-1 receptor I.

3.2. Effects of Ethanol and Its Metabolites In Vitro

3.2.1. TRPV1

A previous study suggested that ethanol could increase capsaicin sensitivity by decreasing the thermal threshold of the TRPV1 channel in human embryonic kidney 293 (HEK 293) cells from −42 to −34 °C. Advances in the research field have allowed the ethanol effect to be studied on the expression of certain proteins. A study elucidated the effects of ethanol on the expression of the transient receptor potential (TRP) channel in brain microvascular endothelial cells (BMVECs). Although they did not find expression of TPRV1 in BMVECs, ethanol upregulated TRPV2 and TRPV4 mRNA and protein levels [70], which increased 2 h after treatment with 17.4 mm ethanol. A related work demonstrated that TRPV1 mRNA was upregulated by ethanol treatment [43,44]. However, no significant changes in TRPV1 protein levels were observed between control and ethanol-treated cells [45] (Table 2).

TRPV1 can be potentiated by several triggers, including protein kinase A (PKA) [71] and PKC [72]. Most in vivo studies indicate that ethanol directly activates TRPV1 via PKC [37,73]. However, TRPV1 was activated through PIP2 versus PKC in HEK293 cells [45], and the same study showed that depletion of PIP2 limited TRPV1 sensitization by ethanol. Although no unified theory has emerged to describe the relationship between TRPV1 sensitization and the ethanol-inducible pathway, in vitro and in vivo experiments mentioned above suggest that ethanol may activate TRPV1 through the Ca^{2+}-SP/PIP2/PKC pathway (Figure 3).

Table 2. Research on the effects of ethanol and its derivatives in vitro.

Compound	Origin	Cells Tested	Triggering Site	Molecules Involved	References
Ethanol	Rat	HEK293 DRG TGN	Lowers TRPV1 thermal threshold	Ca^{2+}↑ CGRP↑ SP↑	[67]
Ethanol	Human	BMVEC	Upregulates TRPV2	mRNA↑	[70]
Ethanol	Human, rat	HEK293	Upregulates TRPV1	PIP2↑	[45]
Ethanol	Rat	HEK293F	Lowers TRPV1 thermal threshold	Ca^{2+}↑	[74]
Acetaldehyde	Human, rat	HEK293	Lowers TRPV1 thermal threshold	PKA↑ PKC↑	[75]

Table 2. *Cont.*

Compound	Origin	Cells Tested	Triggering Site	Molecules Involved	References
Ethanol	Rat	Brain slice	Upregulates PC	HMGB1↑ TLR2↑ TLR3↑ TLR4↑	[76]
Ethanol	Rat, mouse	Microglial cells	Upregulates cytokine	TLR4↑ NF-κB↑ MAPK↑ IRF3↑ TNF-α↑ IL-1β↑	[55]
Ethanol	Human	Peripheral blood monocyte	Upregulates PC	TLR4↑ LPS↑ IkBα↑ NIK↑ MCP-1↑ TNF-α↑	[77]
Ethanol	Rat	Primary cultures of rat cortical astrocytes	Upregulates cytokine	NF-κB↑ TLR4↑ IL-1RI↑ IL-1β↑	[61]
Ethanol	Rat	Primary cultures of rat cortical astrocytes	Upregulates PC and cytokine	TLR4↑ MAPK↑ NF-κB↑ AP-1↑ IRAK↑ COX2↑ iNOS↑ IL-1RI↑ IL-1β↑	[62]
Ethanol and EtG	Human	HEK293	Induces tactile allodynia	TRL4↑ SEAP↑ NF-κB↑	[66]

DRG: dorsal root ganglion; TGN: trigeminal root ganglion; NIK: NF-κB inducing kinase; SEAP: secreted alkaline phosphatase; PIP2: phosphatidylinositol (4,5) bisphosphate; PKA: protein kinase A; PKC: protein kinase C; PC: proinflammatory cytokine; HMGB1: high mobility group box 1; IRAK: interleukin-1 receptor-associated kinase.

3.2.2. TLR4

Several studies report ethanol-induced responses through the TLR4 receptor, an in vitro neuroinflammatory trigger [66,75]. Another study found that after 30 min of ethanol treatment, NF-κB and AP-1 were upregulated in cultured rat cortical astrocytes. There was also the upregulation of iNOS and COX-2, culminating in the production of IL-1RI and IL-1β [62] (see Table 2). In subsequent research, it was confirmed that lipid rafts were vital to the recruitment of IL-1R1 and TLR4 receptors and triggered their endocytosis by cavesomes [61]. This stimulated their downstream signaling and ultimately induced the upregulation of IL-1β. The other related inflammation factors in the TLR4 receptor signal transduction pathway, such as TNF-α, MCP-1, and NF-κB, were also upregulated in a series of cell tests [55,76,77].

In addition to ethanol, EtG and acetaldehyde have also been suggested to elicit AIHs via TRPV1 or TLR4 [66,75]. A study observed that TRPV1 and TLR4 mRNA levels were upregulated by ethanol in wild-type mice [43]. $TLR4^{-/-}$ mutant mice showed higher TRPV1 mRNA expression relative to the control group in response to ethanol treatment. Thus, multiple lines of evidence imply that TRPV1 and TLR4 promote AIHs through neuroinflammation.

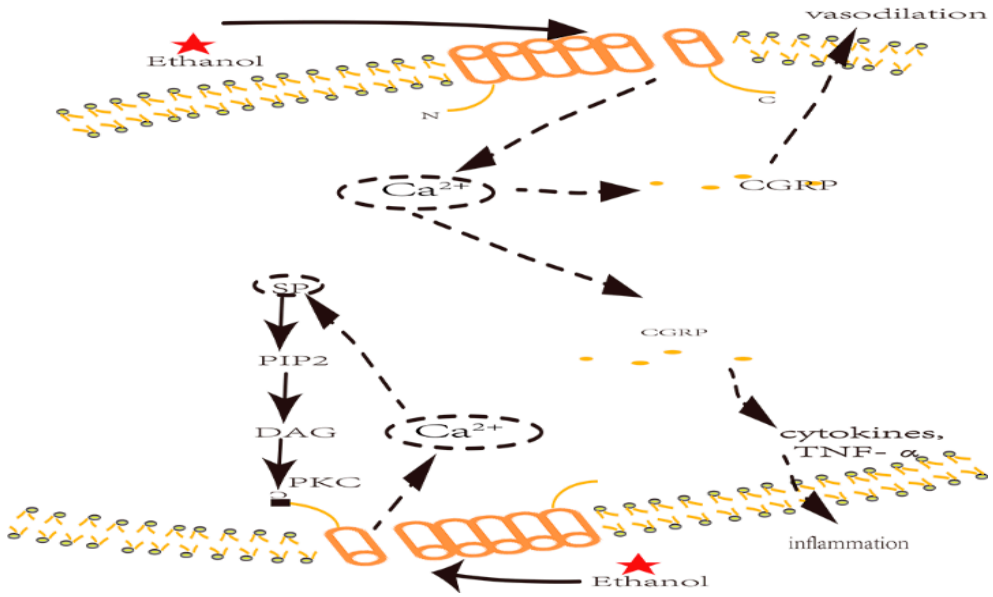

Figure 3. TRPV1 inflammation nociceptor activation and ethanol-induced neuroinflammation. Key: CGRP: calcitonin gene-related peptide; PKC: protein kinase C; NGF: nerve growth factor; LDCV: large dense-core vesicle; SP: substance P; PIP2: phosphatidylinositol biphosphate; DAG: diacylglycerol.

A study proposed that lipopolysaccharide (LPS) affects neuroinflammation via TRPV1 and TLR4. The upregulation of TLR4 activates TRPV1 via PKCξ [78]. Other studies that investigated this hypothesis reported that LPS [79], histamine [80], and other substances [81] could sensitize TRPV1 through the upregulation of TLR4. Additionally, the AP-1 transcription factor was activated in a TRPV1-independent and -dependent manner with Ca^{2+} inflow observed, linking both TRPV1 and TLR4 stimulation through AP-1 [82]. These results show a consistent relationship among ethanol, TRPV1, TLR4, and AIHs: ethanol first promotes TLR4, which induces the sensitization of TRPV1. Together they promote downstream inflammation factors (e.g., CGRP, SP, TNF-α, IL-1β, and PKC) that elicit AIHs with neuroinflammation.

4. Effects of Congeners and Their Metabolites on AIHs and Neuroinflammation

4.1. Phenol

4.1.1. Stimulation of 5-HT

Experts believe that the presence of certain congeners triggers and exacerbates AIH manifestation through the release of 5-hydroxytryptamine (5-HT) from platelets [4]. This notion is supported by a previous clinical study that showed a decreased prevalence of headaches when a 5-HT antagonist was used [83].

Research suggests that ethanol promotes the release of 5-HT, stimulates platelets' reabsorption of 5-HT, and induces anesthesia [84]. Most articles have reported a reduction in the viscosity of the platelet membrane after red wine consumption; however, this effect has not been observed for other alcoholic beverages [85,86]. The work of Littlewood and Jarman (1985) suggests that inhibition of phenol sulphotransferase induces the release of 5-HT from pre-loaded platelets after red wine consumption. It has been suggested that red wine stimulates the profuse release of 5-HT compared with other alcoholic beverages; therefore, neither beer nor white wine affects 5-HT [4]. These results suggest that congeners in red wine influence AIHs by promoting the release of 5-HT [6,87]. Another study consolidated the notion that the release of 5-HT by congener substances triggers AIH manifestations [88].

A study attributed this phenomenon to the different flavonoid contents in red wines [89], suggesting that increased release of 5-HT is triggered by flavonoids of 500 Da molecular weight or greater. Interestingly, 5-HT inhibitors are present in certain wines, and resveratrol is the most prominent among the phenols inhibitors associated with 5-HT [90]. Congener

phenols may include substances with both positive and negative effects on the release of 5-HT, thereby increasing the complexity of AIH manifestations. Therefore, it can be said that the severity of AIH manifestation would depend on the concentrations and influence of these substances—a plausible theory and curious issue around wine-induced headaches [1,2].

4.1.2. Stimulation of Primary Enzymes

Effects on MAO

Previous studies show that monoamine oxidase (MAO) can metabolize ethanol extract of *Barringtonia acutangula* (EBA) into 5-HT. However, phenols, such as resveratrol, are confirmed MAO inhibitors [90]. Quercetin (3,3,4′,5,7-pentahydroxyflavone) has also shown the ability to inhibit MAO [91] and could therefore reduce the amount of 5-HT in alcoholic beverages. Several studies reveal that these phenols could potentially alleviate AIH manifestations [92,93]. *Hovenia dulcis*, an oriental raisin tree, was shown to significantly reduce AIHs by suppressing inflammatory responses. This function was shown to be due to its kaempferol and quercetin components [94] (see Table 3).

Effects on Metabolic Enzymes

A study comparing different kinds of whiskey aged between 5 and 20 years found that older whiskies had 7.4 times more congener contents than younger whiskies. However, older whiskies produced low concentrations of acetaldehyde and acetate in rat blood [95]. This study implied that nonvolatile congeners could lower AIH manifestation by inhibiting alcohol dehydrogenase (ADH) activity. ADH activity is induced by low concentrations of acetaldehyde and acetate contents. The same research group analyzed the components of older whiskies' congeners and found that their chief constituent was condensed tannins (proanthocyanidins) in another related study [96].

4.1.3. Stimulation of TRPV1 and TLR4

5-HT (i.e., serotonin secreted from platelets) functions as an endogenous mediator and trigger for headache and activates 5-HT receptors in the sensory fiber terminals [97]. Therefore, 5-HT plays a pivotal role in AIH manifestation. However, there is no evidence to confirm that 5-HT release in neurons can elicit headaches after alcoholic beverage consumption.

Research has significantly shown that 5-HT can amplify TLR4, IL-8, IL-1β, and TNF-α via NADPH oxidase 2 (NOX2), suggesting that activation of TLR4 may be influenced by 5-HT in vessels [98]. Additionally, 5-HT activates TRPV1 by inducing Ca^{2+} influx and promoting CGRP, suggesting a possible pathway connecting 5-HT and AIH manifestation [99]. Sumatriptan (a 5-HT_{1B} agonist), ketanserin (a 5-HT_{2A} antagonist), and granisetron (a 5-HT_3 antagonist) reduce CGRP and Ca^{2+} releases by blocking TPRV1 in trigeminal neurons. In contrast, the 5-HT_1 receptor agonist reduced inflammatory nociceptive stimulation versus the 5-HT_2 and 5-HT_3 agonists.

Also, eriodictyol, just like some phenols, influences 5-HT as described above [100]. Eridictyol is one of the few condensed tannins in red wine and whiskey. It antagonizes TRPV1 by reducing Ca^{2+} influx and attenuates allodynia produced by treatment with several chemical agonists. In addition, eugenol, a common phenol in red wine and other alcoholic beverages (e.g., beer, whiskey), was also shown to inhibit TRPV1 by reducing Ca^{2+} influx [101].

Table 3. Research on the effects of phenols in congeners.

Compound	Origin and Materials	Triggering Site	Molecules Involved	References
Flavonoids	Human, PRP	Upregulates 5-HT	Flavonoids↑	[4]
Ketanse and pizotifen	Human, patients with headaches	Blocks headache with 5-HT antagonists	5-HT↓	[102]

Table 3. *Cont.*

Compound	Origin and Materials	Triggering Site	Molecules Involved	References
Red wines	Human, patients with headaches	Upregulates 5-HT	ND	[6]
Resveratrol	Rats, Sprague Dawley and brain tissue	Lowers 5-HT expression	Enzyme activity of MAO↓	[90]
Flavonoids	Human, PRP	Upregulates 5-HT	Flavonoids (greater than 500 Da)↑	[89]
Quercetin	Mouse	Lowers 5-HT expression	Enzyme activity of MAO↓	[93]
Quercetin	Human	Lowers 5-HT expression	Enzyme activity of MAO↓	[92]
Nonvolatile fractions (caffeic acid, vanillin, syringaldehyde, Ellagic acid)	Mouse	Lowers blood acetaldehyde level and depresses ethanol metabolism	ADH↓	[95]
Nonvolatile fraction	Mouse	Lowers blood acetaldehyde and acetate levels; depresses ethanol metabolism; prolongs drunkenness	ADH↓ LORR↑	[96]
GFM and linoleic acid	Mouse, BALA/c; HepG2 cells	Promotes ethanol metabolism	ADH↑ ALDH↑ CYP2E1↑ Catalase↑	[103]
Flavonoids and 5-HT	Mouse, C57BL/6 HT-29, cells	Neuron Inflammation	TLR4↑ IL-8↑ IL-1β↑ TNF-α↑	[98]
Flavonoids and 5-HT	Rat, Sprague Dawley TG cells	Neuron Inflammation	Ca^{2+}↑ CGRP↑	[99]
Eriodictyol	Mouse, Swiss Rat, Wistar	Attenuates allodynia	Ca^{2+}↓	[100]
Eugenol	C2D7 cells TG/DRG neurons	Attenuates pain	Ca^{2+}↓	[101]

PRP: platelet-rich plasma; GFM: ginsenoside-free molecules; LORR: loss of righting reflex.

4.2. Histamine

A study earlier reported that histamine, the most potent biogenic amine, elicits a headache sensation [104]. Diamine oxidase (DAO) (Table 4) can attenuate headaches by reducing serum histamine levels [105,106]. Wantke et al. suggested that histamine, a common biogenic amine in red wine, plays a vital role in AIH inducement. The study reported that histamine-rich wines increased AIHs significantly more than histamine-poor wines [107]. In contrast, another study reported no correlation between the histamine content of wine and AIH manifestation. Also, plasma histamine significantly increased after consuming histamine-poor wine [108]. Furthermore, no significant change was observed in methylhistamine and methylimidazole acetic acid levels—following the consumption of low-histamine or high-histamine wines. Results from this study implied that histamine did not affect AIH manifestation directly or through its metabolites. Peatfield and colleagues reported no significant difference in headache responses to Chianti (higher histamine content) *versus* Valpolicella (higher histamine content). They found that headaches were not blocked by antagonist enzyme treatments for histamine H1 and H2 (metabolism enzymes for histamine) [102]. Although wines with high histamine content may not increase AIH manifestation, blood histamine content significantly increased after consuming high-histamine alcoholic beverages [109]. Therefore, the current model suggests that red wines can increase blood histamine content to a greater extent than other alcoholic beverages [110–112].

It was reported that histamine could activate TRPV1 and induce headaches [113]. They found that histamine-sensitized TRPV1 elicits pain through the PKC pathway in a mouse

model. Histamine also promoted TLR4 expression in human gingival fibroblasts [114] and endothelial cells [115]. According to Min and colleagues, histamine-induced reduced intracellular Ca^{2+} inward currents in TLR4-deficient sensory neurons [80]. Reducing histamine sensitivity in TLR4 deficient neurons was also accompanied by a decrease in TRPV1 activity. These suggest that histamine activates TRPV1 via Ca^{2+} inflow and upregulates TLR4 via the sensitization of TRPV1 and Ca^{2+} inflow.

Table 4. Research on the effects of histamine and methanol.

Compound	Origin and Materials	Triggering Site	Molecules Involved	References
		Histamine		
High-histamine wines	Human	Increased AIH	ND	[107]
Histamine	Mouse, inflammation model	Sensitized TRPV1 and increased pain	Ca^{2+}↑ PKC↑	[113]
Histamine	Human, patients	Reduced headache	Increased DAO; unchanged histamine values	[106]
Histamine	Human, patients	Reduced headache	Increased DAO; unchanged histamine values	[105]
Histamine	Human, endothelial cells	Enhanced sensitivity	TLR4↑	[115]
Histamine	Human, gingival fibroblasts cells	Enhanced sensitivity	TLR4↑	[114]
Histamine	Mouse, Wild, KO-TLR4 DRG neurons HEK293	TLR4 expression Promoted histamine-mediated sensitivity by increasing the TRPV1 channel	TLR4↓ Ca^{2+}↓	[80]
		Methanol		
Methanol	Human	Increased headache	ND	[116]
Methanol	Human	Increased hangover	Slower metabolism of methanol	[117]
Methanol	Human	Increased MCS	ND	[118]

DAO: diamine oxidase; MCS: methanol content in serum.

4.3. Methanol

Methanol has been considered a pivotal substance in AIH manifestation [118]. A significant difference in methanol concentrations amongst different experimental groups was observed after 13 h. Results suggested a significant correlation between methanol and AIH manifestation [116]. ADH metabolizes methanol more slowly than ethanol which may be the reason for the more severe effect of methanol on AIHs [117]. Fruit brandy, with a 10- to 30-fold methanol concentration than red wine or other spirits, produced 30 times the serum methanol content 1–1.5 h after beverage intake [118]. However, results suggest that the amount of methanol in the blood correlates with the amount consumed from alcoholic beverages. Therefore, the methanolic content in a beverage is an important causal factor for AIHs (see Table 4). However, no mechanistic information is available linking methanol and AIH manifestation.

4.4. Fusel Oil

Fusel oil consists mainly of higher alcohols (e.g., propyl alcohol, isoamyl alcohol, and phenyl ethanol), which are also regarded as AIH triggers. Alcoholic beverages such as whiskey, brandy, red wine, and vodka contain very high contents of fusel oil [119]. However, a study observed that fusel oil had no marked effect on ethanol-induced emetic responses. It was, however, suggested that fusel oil might alleviate hangover symptoms [120]. They found significant differences in taste-aversive behavior toward whiskey, sake, wine, and beer. Whiskey or other alcoholic beverages with high fusel oil content suppressed this behavior significantly. Although several studies have considered the potential role of fusel

oil in AIH manifestation, no research has confirmed if fusel oil in alcoholic beverages consistently causes AIHs.

4.5. Linoleic Acid

The presence of congeners affects the metabolism of ethanol by stimulating primary enzymes such as alcohol dehydrogenase (ADH), aldehyde dehydrogenase (ALDH), cytochrome P450 proteins (CYP2E1), and catalase (CAT) [92,94] (see Figure 4). Do and colleagues confirmed that linoleic acid in ginsenoside eliminated ROS and activated primary enzymes in mice and cellular models, attenuating AIH manifestation [103]. Linoleic acid from ginsenoside is not an original material produced through the fermentation process; therefore, it is not a typical congener. Nonetheless, its effects suggest a research direction for investigating volatile materials in alcoholic beverages [121]—such as ethyl acetate and ethyl lactate in whiskey, brandy, and rum—for their ability to stimulate primary metabolic enzymes.

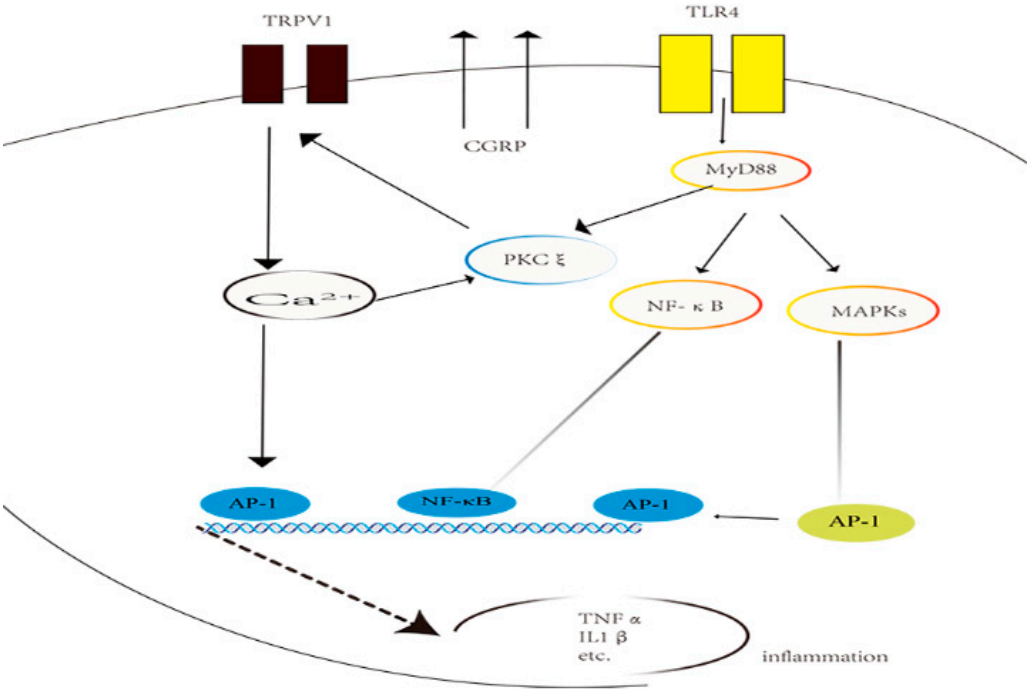

Figure 4. Activation of TLR4 and TRPV1. Key: TRPV1: transient receptor potential cation channel subfamily V member 1; TLR4: Toll-like receptor 4; CGRP: calcitonin gene-related peptide; MyD88: myeloid differentiation primary response 88; MAPKs: mitogen-activated protein kinase; NF-κB: nuclear factor-κB; IL1β: interleukin-1β; TNF-α: tumor necrosis factor alpha; PKC-ξ: protein kinase C ξ; AP-1: activator protein 1.

5. Conclusions and Perspective

The consumption of fermented food and beverage products could be pleasant [122,123]; however, the increasing health concerns around AIHs prompt in-depth mitigative research activities. Ethanol has always been considered the main factor in AIH manifestation. Also, many experiments implicate ethanol in AIH manifestation and neuroinflammation through its molecular effects on TLR4 and TRPV1. Although, further experiments confirming these routes are still needed, especially the pathway between TLR4 and TRPV1.

The mechanisms by which flavonoids affect AIHs are still unclear. Adopting appropriate experiments to verify relevant pathways in animal and cell models should be promoted. Specifically, information is lacking on condensed phenols (e.g., quercetin, eugenol, and eriodictyol) that may be able to attenuate the influence of ethanol on neuroinflammation. The molecular mechanisms that underline these effects should be studied in animal models or preclinical studies.

Histamine is an important congener component of alcoholic beverages. Although many small-scale clinical experiments have tested its effects on AIHs [124–126], AIH responses have not been consistent [5,95]. Evidence suggests that histamine may influence AIHs through a significant relationship with TRPV1 and TLR4, and this is a promising direction for future research.

Other congeners (e.g., methanol, fusel oil, and volatile fatty acids) are either AIH triggers or inhibitors. However, evidence linking them to AIH-related neuroinflammation pathways is still fragmented, and more clinical experimentations are needed to augment existing knowledge. Appropriate experiments would elucidate the functions of congeners and the pathways they elicit for their AIH effects.

The theory of AIH induction through neuroinflammation has more significant support than other theories involving vascular changes and CSD. Inflammatory factors are transmitted in the trigeminal nerves after TRPV1 is activated and TLR4 is upregulated and activated. This might also be the main mechanism triggered by ethanol in its AIH effect. Additionally, acetate [46], acetaldehyde [75], and EtG [66] have also been implicated in AIH manifestation. They probably also induce AIH effects through the activation of TRPV1 and TLR4. Besides ethanol and its metabolites, TRPV1 and TLR4 are also affected by treatment with histamine, 5-HT (via flavonoid metabolites), and condensed phenols (e.g., quercetin, eugenol, and eriodictyol). Methanol, fusel oil, and fatty acids have been identified as triggers or inhibitors of AIHs. Although clear evidence for their effects is scarce, their possible harmful or beneficial traits still need further studies and verifications. The continued development of these lines of research will provide greater insight into the molecular mechanisms of AIHs. It will provide a basis for manipulating ethanolic and congener contents in alcoholic beverages for healthier options.

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Abbreviations

ADH—alcohol dehydrogenase; AIH—alcohol-induced headaches; ALDH—aldehyde dehydrogenase; BMVECs—brain microvascular endothelial cells; CAT—catalase; CBF—cortical blood flow; CCL2—C-C motif chemokine ligand; CGRP—calcitonin gene-related peptide; COX-2—cyclooxygenase-2; Cpla2—cytosolic phospholipase A2; CSD—cortical spreading depolarization; CYP2E1—cytochrome P450 proteins; DAG—diacylglycerol; DAO—diamine oxidase; DRG—dorsal root ganglion; EtG—ethyl-b-D-glucuronide; GA—glucuronic acid; HEK293—human embryonic kidney 293; HIS—International Headache Society; HMGB1—high mobility group box 1; ICHD—International Headache Classification; IL—interleukin; IL-1RI, interleukin-1 receptor I; iNOS—inductive nitric oxide synthase; IRAK—interleukin-1 receptor-associated kinase; JNK—c-Jun N-terminal kinase; LDCV—large dense core vesicle; LPS—lipopolysaccharide; MAO—monoamine oxidase; MAPK—mitogen-activated protein kinase; MCP-1—monocyte chemoattractant protein-1;

MCS—methanol content in serum; mRNA—messenger ribonucleic acid; MyD88—myeloid differentiation primary response gene88; ND—not determined; NF-κB—nuclear factor-κB; NGF—nerve growth factor; NIK—NF-κB inducing kinase; NOX2—NADPH oxidase 2; PARP—poly ADP-ribose polymerase; PC—proinflammatory cytokine; PIP2—phosphatidylinositol (4,5) bisphosphate; PKA—protein kinase A; PKC—protein kinase C; ROS—reactive oxygen species; SEAP—secreted alkaline phosphatase; SG—sphenopalatine ganglion; STN—spinal trigeminal nucleus; SP—substance P; SSN—superior salivatory nucleus; Tg—trigeminal ganglion; TGN—trigeminal root ganglion; Th-thalamic nuclei; TLR4—toll-like receptor 4; TnFs—transcription nuclear factors; TNF-α—tumor necrosis factor alpha; TRIF—TIR-domain-containing adaptor-inducing IFNB; TRP—transient receptor potential; TRPV1—transient receptor potential cation channel subfamily V member 1; 5-HT—5-hydroxytryptamine.

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