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Ketone bodies and inflammation modulation: A mini-review on ketogenic diet's potential mechanisms in mood disorders

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Abstract: Mental disorders such as depression and anxiety inflict significant burdens on individuals and society. Commonly prescribed treatments often involve cognitive therapy and medications. However, for patients resistant to these conventional methods, alternative therapies like the Ketogenic Diet (KD) offer a promising avenue. KD and its key metabolite, β-hydroxybutyrate (BHB), have been hypothesized to alleviate mental disorders through anti-inflammatory actions, a crucial pathway in the pathophysiology of depression. This mini-review examines 15 clinical trials exploring the influence of KD and BHB on inflammation and their potential roles in managing mental disorders. Both human and animal studies were scrutinized to elucidate possible cellular and molecular mechanisms. Out of the 15 trials, 10 reported reduced levels of at least one inflammatory mediator or mRNA post KD or BHB treatment, while two observed an elevation in anti-inflammatory agents. These findings suggest that KD and BHB could modulate cellular inflammatory pathways, highlighting their potential for therapeutic application in mental disorders.

List of Abbreviations

5-HT	Serotonin
ALOX	Arachidonate 5-Lipoxygenase
BHB	β-hydroxybutyrate
bw	Body weight
CMD	Common mental disorders
COX	Cyclooxygenase
CRP	C-reactive protein
ELISA	Enzyme-linked immunosorbent assay
FoxO1	Forkhead O1
GAD	Generalized anxiety disorder
HDAC	Histone deacetylase
IDO	Indoleamine 2,3 dioxygenase
IFN-γ	Interferon-gamma
IL	Interleukin
KD	Ketogenic diet
LPS	Lipopolysaccharide
MAOA	Type A monoamine oxidase
MCP	Monocyte chemotactic protein
MnSOD	Manganese Superoxide Dismutase
NF-κB	Nuclear factor-kappa B
NLRP	NLR family pyrin domain containing
PI3K	Phosphoinositide 3-kinases
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
SCOT	Succinyl-CoA:3-ketoacid-CoA transferase
TNF	Tumor necrosis factor
TRP	Tryptophan

Introduction

Common mental disorders (CMD) refer to two main diagnostic categories: depressive and anxiety disorders. According to the World Health Organization, in 2015, the proportion of the global population with depression was estimated to be 4.4%. The prevalence was more common among females (5.1%) than males (3.6%) (World Health Organization, 2017). The proportion of anxiety disorders was estimated to be 3.6%, which also appears to be more common among females (4.6%) than males (2.6%) (World

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Health Organization, 2017). Both these mental disorders are a leading cause of disability, imposing a substantial burden on individuals and society (Friedrich, 2017; Stein and Craske, 2017).

While cognitive therapy and medications are the first-line treatment for CMD, 10%–30% of the patients do not respond to antidepressant medicines. Additionally, they exhibit symptoms such as declined physical health and social/occupational function, or even suicidal intentions (Pilkington, 2018). Therefore, alternative and complementary therapies for the prevention and treatment of CMD are urgently needed.

Though the pathology of CMD is not fully understood, the mutual and functional role of the immune system in the development of CMD symptomology has been highlighted by recent findings. Inflammation, mainly mediated by cytokines and chemokines that are secreted by immune cells, is generally considered a defense mechanism upon infection. However, chronic and excessive inflammation may interfere with synaptic remodeling, transcription, and epigenetics. It may also harm the integrity of neuronal function, influence neurocircuitry and/or neurotransmitter systems, and produce behavioral alternations (van Velzen *et al.*, 2017). Mounting evidence indicates that inflammatory cytokines are responsible for the development of CMD. For instance, epidemiological studies using data collected from 147,478 individuals from the UK Biobank and 2,905 from the Netherlands Study of Depression and Anxiety indicate that the inflammation level was associated with core depressive and anxiety symptoms of low mood, anhedonia, and other symptoms (van Eeden, 2022; Milaneschi *et al.*, 2021). In animal model studies, evidence shows that activated immune responses are observed in many CMD animal models, and treatment with several kinds of cytokines could produce depressive and anxiety-like behaviors (Camara *et al.*, 2013; Murray *et al.*, 2013). Furthermore, CMD occurs more frequently in those who already have medical disorders associated with immune dysfunction (Gałecki and Talarowska, 2018). Therefore, anti-inflammatory agents and treatments are considered effective ways to fight CMD.

The ketogenic diet (KD) is a dietary regimen that contains high fat and low carbohydrate content. It is an established treatment for refractory epilepsy, including some inflammation-induced epileptic encephalopathies (Ma and Suzuki, 2019).

Nowadays, ketone supplementations are available for use, and people can use the supplementations to achieve nutritional ketosis easily (Kovács *et al.*, 2019). There are two primary forms of ketone supplements, ketone salts, and ketone esters. Both will be metabolized to β-hydroxybutyrate (BHB) after absorption (O'Malley *et al.*, 2017; Hashim and VanItallie, 2014). The anti-inflammatory properties of BHB are attracting increasing attention. However, the efficacy and underlying mechanisms of KD and BHB are not fully understood. Therefore, this review aims to discuss the therapeutic utility of KD and ketone supplementations, as substitutions for KD, in CMD treatment, focusing on their anti-inflammatory properties.

Materials and Methods

Literature search strategy

Abstracts of publications identified in PubMed (http://www.ncbi.nlm.nih.gov/pubmed) and Ovid (including Medline, PsychINFO, NURSING, and EMBASE), Scopus, and EBSCO (including CINAHL) were searched and reviewed for relevant papers. The search took place on 22 August 2022 and was not restricted by publication date. Two searches included (1) evaluations on the status of inflammation in mood disorders using animal models, and (2) the anti-inflammation properties of KD or BHB in patients. The exact search terms were depression (Title/Abstract) OR depressive symptom (Title/Abstract) OR anxiety (Title/Abstract) OR anxiety symptom (Title/Abstract) AND (ketogenic diet (Title/Abstract) OR ketone body (Title/Abstract) OR ketone ester (Title/Abstract) OR ketone diester (Title/Abstract) OR ketone salt (Title/Abstract) OR ketone supplements (Title/Abstract) OR ketosis (Title/Abstract) for (1), and, inflammation (Title/Abstract) OR inflammatory (Title/Abstract) OR cytokine (Title/Abstract) OR anti-inflammation (Title/Abstract)) AND (ketogenic diet (Title/Abstract) OR ketone body (Title/Abstract) OR ketone ester (Title/Abstract) OR ketone diester (Title/Abstract) OR ketone salt (Title/Abstract) OR ketone supplements (Title/Abstract) OR ketosis (Title/Abstract)) for (2) and each part was carried out in a single search. Due to limited evidence, the first search was concluded using narrative descriptions. The second search was carried out based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) search strategy (Page *et al.*, 2021), and subsequent reference narrowing is described in Fig. 1. The Prism checklist can be found as Suppl. Table S1 in the supplementary file. Two authors carried out the search and screen separately using the Covidence system (https://www.covidence.org/). The flow chart of the selection of studies is shown in Fig. 1.

Inclusion and exclusion criteria

For search (2), randomized crossover or parallel controlled trials assessing the impact of KD or BHB on human inflammation status measures were included in the current analysis. There were no exclusion criteria for study duration, diet, ketone supplement type or dose, or participants' sex and age, sample size, or health status. Studies assessing the impact in animal models were separated from human trials and analyzed separately. Studies of case reports were excluded.

Data extraction

Data were extracted from 15 studies that were selected to meet the inclusion and exclusion criteria. Intervention type and duration, sample characterization, subject status, study

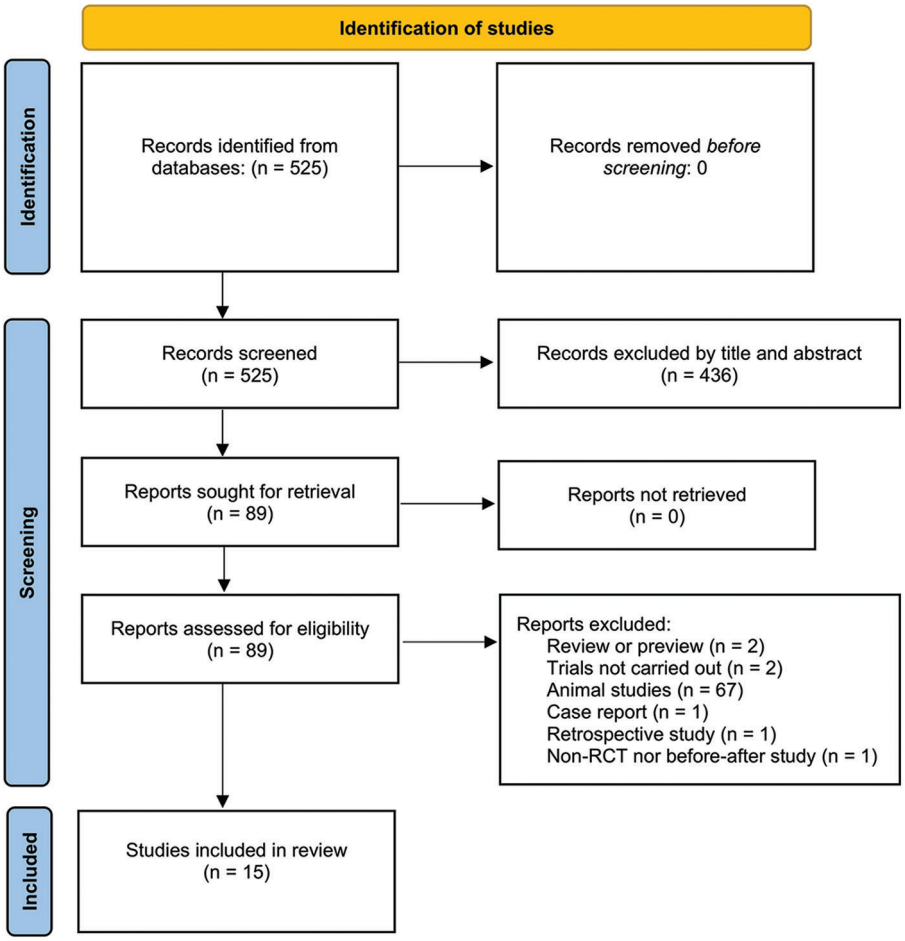

FIGURE 1. PRISMA flow chart of the study.

design, assay, and inflammatory mediators were extracted from each study to provide descriptive characteristics of participants. For animal studies, the findings have been discussed in a non-systematic way as an elaboration on the proposed mechanisms.

Results

For the results of search (2), based on the PRISMA principles shown in Fig. 1, we retrieved 15 articles that have been summarized in Table 1.

Among the studies, 13 studies included KD as an intervention (Bock *et al.*, 2018; Bosco *et al.*, 2018; Castaldo *et al.*, 2021; Rhyu and Cho, 2014; Cipryan *et al.*, 2020a, 2020b; Paoli *et al.*, 2021; Bertoli *et al.*, 2015; Kong *et al.*, 2020; Khodabakhshi *et al.*, 2021; Rosenbaum *et al.*, 2019; Monda *et al.*, 2020; Shaw *et al.*, 2020), while only 2 studies employed ketone body administration as an intervention (Shaw *et al.*, 2020; Martin-Arrowsmith *et al.*, 2020). Alteration of multiple cytokines or other inflammatory mediators such as adiponectin, resistin, etc., were reported.

Among the studies, 10 of 15 (66.7%), reported at least one inflammatory mediator (C-reactive protein (CRP), leptin, interleukin (IL)-1β, IL-2, IL-6, IL-12p40, interferon (IFN)-γ and/or tumor necrosis factor (TNF)-α) (Bosco *et al.*, 2018; Castaldo *et al.*, 2021; Cipryan *et al.*, 2020b, 2020a; Kong *et al.*, 2020; Shaw *et al.*, 2020; Khodabakhshi *et al.*, 2021, Monda *et al.*, 2020) or the mRNA of the indicated inflammatory mediators (IFN-γ mRNA, Shaw *et al.*, 2020) was decreased by KD or BHB intervention. However, 3 studies reported that no changes were observed (Bock *et al.*, 2018; Rhyu and Cho, 2014;). Further, 2 reported that an anti-inflammation mediator (adiponectin and/or IL-10) was increased (Rosenbaum *et al.*, 2019; Monda *et al.*, 2020; Bertoli *et al.*, 2015). The selected studies conducted on humans showed that KD has great potential in treating inflammatory diseases, showing the potential to be utilized as a treatment for CMD based on the inflammation hypothesis of the pathology of CMD. However, the evidence of BHB is far from convincing, and further studies are warranted. The details of the above studies are listed as Table 1.

Discussion

Inflammation is our body's defense system protecting us against infection, cellular damage, and other harmful agents, both exogenously and endogenously (Suzuki, 2018a; Suzuki *et al.*, 2020). During inflammation, cytokines play a significant role in mediating cellular signaling and immunological responses. Cytokines are a category of small proteins (5~20 kDa) secreted by a broad range of cells, including immune cells such as macrophages, lymphocytes, mast cells, endothelial cells, fibroblasts, myocytes, adipocytes, and other kinds of cells (Ma *et al.*, 2020; Suzuki, 2018b). The subcategories of cytokines include chemokines,

TABLE 1

Summary of studies included in the systematic mini-review analysis

Study	Intervention type and duration	Subjects	Subject status	Design and comparison	Assays and sample species	Mediators of inflammation
Bock *et al.* (2018)	Ketogenic diet 6 months	KD, n = 16 non-KD, n = 8 Adults	Multiple sclerosis patients	RCT KD *vs.* non-KD	Real-time PCR, blood cells	ALOX mRNA, COX2 mRNA and ALOX15 mRNA→
Bosco *et al.* (2018)	Ketogenic diet 6 months	KD, n = 6 Adults	Overweight divers	Before-after study Post *vs.* Pre*	ELISA, blood samples	IL-1β, IL-6 and TNF-α↓
Castaldo *et al.* (2021)	Ketogenic diet 4 weeks	KD, n = 30 Adults	Psoriasis patients	Before-after study Post *vs.* Pre	ELISA, blood samples	IL-1β, IL-2↓ IL-4, TNF-α and IFN-γ→
Rhyu and Cho (2014)	Ketogenic diet 3 weeks	KD, n = 10, non-KD, n = 8 Adults	Taekwondo athletes	RCT KD *vs.* non-KD	ELISA, blood samples	IL-6, TNF-α and IFN-γ→
Cipryan *et al.* (2020b)	Ketogenic diet 4 weeks	KD, n = 9, non-KD, n = 9 Adults	Moderately trained subjects**	RCT KD *vs.* non-KD	ELISA, blood samples	Leptin↓, pre- and post-KD intervention, KD group Adiponectin, Resistin, IL-6→
Cipryan *et al.* (2020a)	Ketogenic diet 12 weeks	KD, n = 12, non-KD, n = 12 Adults	Healthy subjects	RCT KD *vs.* non-KD	ELISA, blood samples	Adiponectin↑ Leptin↓
Paoli *et al.* (2021)	Ketogenic diet 2 months	KD, n = 9 non-KD, n = 10 Adults	Healthy bodybuilders	RCT KD *vs.* non-KD	Methods not recorded, blood samples	IL-6, TNF-α↓, between groups post KD intervention IL-1, →
Bertoli *et al.* (2015)	Ketogenic diet 12 weeks	KD, n = 10 Children	Glut1 deficiency syndrome patients	Before-after study Post *vs.* Pre	Methods not recorded, blood samples	CRP, IL-6, TNF-α→
Kong *et al.* (2020)	Ketogenic diet 4 weeks	KD, n = 20 Adults	Overweight/ obese patients	Before-after study Post *vs.* Pre	Immunoassay, blood samples	Leptin↓ TNF-α, MCP-1→
Shaw *et al.* (2020)	Ketone body R, S-1,3-butanediol, one-time administration, 0.35 g/kg bw, Exercise involved, only pre-exercise results were pooled	KB, n = 9 Adults	Trained cyclists	Crossover RCT with repeated measures, Post *vs.* Pre	Real-time PCR, blood cells	IFN-γ mRNA↓ IL-4 mRNA, IL-10 mRNA→
Khodabakhshi *et al.* (2021)	Ketogenic diet 12 weeks	KD, n = 30 non-KD, n = 30 Adults	Patients undergoing chemotherapy	RCT KD *vs.* non-KD	ELISA and Photometry method blood samples	TNF-α, IL-10↓, between groups CRP→
Rosenbaum *et al.* (2019)	Ketogenic diet 4 weeks	KD, n = 17 Adults	Overweight/ obese patients	Before-after study Post *vs.* Pre	Methods not recorded, blood samples	Adiponectin, CRP↑, pre- and post-intervention IL-6→
Martin-Arrowsmith *et al.* (2020)	Ketone body ketone monoester, twice-time a day administration 360 mg/kg bw Exercise involved, only pre-exercise results are pooled	KD, n = 10 non-KD, n = 10 Adults	Healthy subjects	RCT KB *vs.* Placebo	ELISA, blood samples	MCP-1↑ between groups IL-1β, IL-6, IL-8, IL-10, IL-12p40, TNF-α→

Table 1 (continued)

Study	Intervention type and duration	Subjects	Subject status	Design and comparison	Assays and sample species	Mediators of inflammation
Monda *et al.* (2020)	Ketogenic diet 8 weeks	KD, n = 20 Adults	Obese patients	Before-after study Post *vs.* Pre	ELISA, blood samples	Adiponectin, IL10↑, pre- and post-KD intervention TNF-α, CRP↓, pre- and post-KD intervention IL-6→
Shaw *et al.* (2020)	Ketogenic diet 31 days Exercise involved, only pre-exercise results were pooled	n = 8 Adults	Trained endurance athletes	Crossover RCT Post *vs.* Pre	ELISA, blood samples	IL-10↓, pre- and post-KD intervention IL-1β, IL-2, IL-4, IL-6, IL-8, IL-12p40, IFN-γ and TNF-α→

Notes: KD, ketogenic diet; KB, ketone bodies. RCT; randomized, controlled trial; ALOX, arachidonate 5-Lipoxygenase; COX, cyclooxygenase; ELISA, enzyme-linked immunosorbent assay; IL, interleukin; PCR: polymerase chain reaction; TNF, tumor necrosis factor; IFN, interferon; CRP, C-reactive protein; MCP, monocyte chemotactic protein; and bw, body weight. * Pre means the time point immediately before a KD or BHB intervention, while Post means the time point immediately after a KD or BHB intervention. **Moderately trained indicates at least three exercise sessions/week.

interferons, interleukins, lymphokines, and tumor necrosis factors, all involved in fighting off infections and other immune responses (Aw *et al.*, 2018). However, inflammation that acts against wrong stimuli may induce unwanted cytokine production, thus bringing undesired consequences. A large body of studies has reported that pro-inflammatory or inflammatory cytokines increase in CMD patients (Hou *et al.*, 2017; Gelman, 2019; Zou *et al.*, 2018; Martinez *et al.*, 2018; Jia *et al.*, 2019; Petralia *et al.*, 2019). The evidence on the cytokine secretion profile collected from papers published in the recent five years is depicted in Fig. 2.

According to a case-controlled study conducted in generalized anxiety disorder (GAD) patients, significantly higher ratios of TNF-α/IL-10, TNF-α/IL-4, IFN-γ/IL-10, and IFN-γ/IL-4 were found in the GAD group compared to the control group (patient group: n = 54; control group: n = 64) (Hou *et al.*, 2017). In pregnant women with severe anxiety and depression, the levels of Th1-(IL-6, TNF-α, IL-2, IFN-γ), Th17-(IL-17A), and Th2-(IL-9, IL-10, and IL-13) were higher than those in the control group (n = 139, patient group; n = 40, control group) (Gelman, 2019). In one report, patients with major depressive disorders had significantly higher levels of IL-1β, IL-10, and TNF-α but significantly lower levels of IL-8 (n = 117, patient group; n = 102, control group) (Zou *et al.*, 2018). In another report, IL-1, IL-6, TNF-α, IFN-γ, and IL-10 were found to be associated with depression scores in people with alcohol and drug use disorder (n = 80, patient) (Martinez *et al.*, 2018). Further, a significantly positive correlation between serum cortisol levels and Hamilton Depression Rating Scale scores was observed in 89 male depression patients (Jia *et al.*, 2019). In women with postpartum depression, significant fluctuation of TNF-α and IL-18 were found (Petralia *et al.*, 2019). Therefore, targeting pro-inflammatory and inflammatory cytokines and their signaling pathways might be novel strategies to treat CMD.

Although the mechanism of inflammation in CMD has not been fully explained, the loss of regulation of inflammatory agents and neurotransmitters seems to be the key. The imbalance of neurotransmitters, including serotonin (5-HT), norepinephrine, and dopamine has been reported and treated to be the reason for CMD (Yan, 2018; Naoi *et al.*, 2018). Meanwhile, inflammatory cytokines trigger neuroinflammation, microglial activation, and disturbance of neurotransmitters, resulting in CMD pathophysiological process (Morris *et al.*, 2016). Let us consider the loss of the regulation process of 5-HT as an example. According to the cytokine theory, the initiation of stress increases the production of cytokines, including TNFs, and ILs. IFNs may contribute to the pathophysiological process of CMD. Increased levels of the abovementioned inflammatory cytokines may activate the production of the indoleamine 2,3 dioxygenase (IDO), with subsequent production of tryptophan (TRP) catabolites along the IDO pathway, decreasing the availability of TRP and serotonin and contributing to the progress of CMD (Morris *et al.*, 2016). Conversely, phytochemical supplementation that suppresses pro-inflammatory cytokines, thus inhibiting type A monoamine oxidase (MAOA), has been reported to be efficient in relieving depression (Yan, 2018). Therefore, the use of anti-inflammatory compounds and diets that exhibit anti-inflammatory properties may be a strategy for CMD treatment.

Introduced as a treatment for refractory epilepsy in the first place, the KD has been reported for its anti-inflammatory properties in recent years. This provides a potential contributing role in treating CMDs, based on the inflammation hypothesis of the pathology of CMD. For example, in a lipopolysaccharide (LPS)-induced inflammation model in rats, a 2-week administration of KD attenuated LPS-induced fever, and reduced blood and hippocampal IL-1β concentration to alleviate inflammation (Barua *et al.*, 2018). In another rodent inflammation model built by inducing a hind paw inflammation, a KD significantly reduced decreased paw swelling, plasma extravasation, and the peripheral inflammatory response (Ruskin *et al.*, 2021). In a paper published in 2016, after a one-month feeding period of KD mice then received LPS by intraperitoneal injection it was reported that KD mice had significantly low expression of nuclear factor-kappa B (NF-κB), IL-6, and TNF-α (Nandivada *et al.*, 2016). These

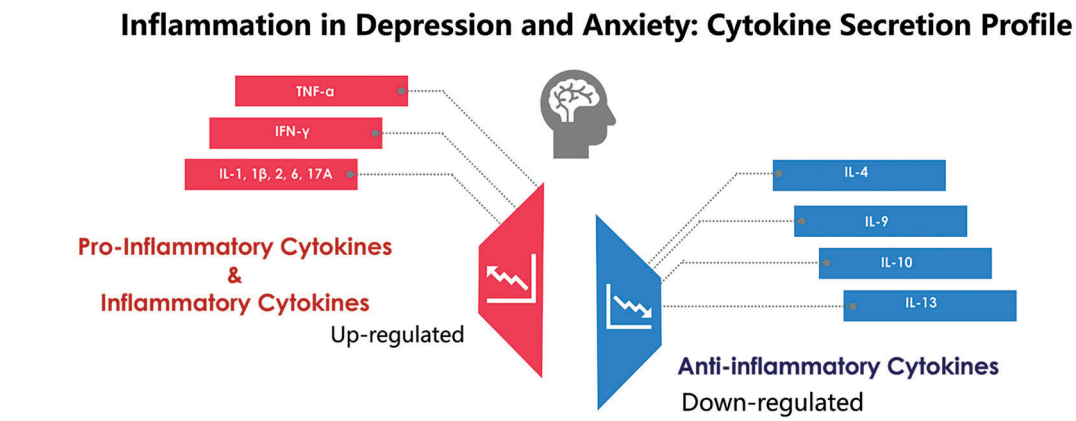

FIGURE 2. Inflammation in depression and anxiety: the cytokine secretion profile reported in the recent five years.

studies showed that a KD has excellent potential in serving as an anti-inflammation therapy for inflammation. In the neuroscience field, KD also attracts great attention. In a memory impairment and central nervous system-inflammation murine model, pre-feeding of a one-week KD (12.2 g polyunsaturated fatty acids in 100 g per KD) decreased circulating inflammatory cytokines including IL-1β, IL-6, TNF-α, IL-12, IL-17A, IFN-γ, MCP-1, MIP-1α and MIP-1β (Kim *et al.*, 2012). In a spinal cord injury rat model, KD suppressed the NF-κB pathway and the expression of TNF-α, IL-1β, and IFN-γ (Lu *et al.*, 2018). In another mouse model, motor dysfunction was induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine treatment, and pre-treatment of KD decreased IL-1β, IL-6, TNF-α (Yang and Cheng, 2010).

The anti-inflammatory properties of a KD may be attributed to the ability to activate peroxisome proliferator-activated receptor-gamma (Jeong *et al.*, 2011; Zhang *et al.*, 2018), subsequently decreasing systematic inflammation (Zhang *et al.*, 2018). Furthermore, increasing evidence shows that the enhanced levels of BHB, the metabolite of fatty acids during a KD, may contribute to playing an anti-inflammatory role (Prattichizzo *et al.*, 2018; Zitvogel *et al.*, 2017).

Although clinical trials on patients with common mental disorders aiming to elicit the anti-inflammatory properties of BHB have not yet been carried out, animal studies have provided some clues. For example, exogenous ketone body administration has been shown to decrease anxiety-related behaviors evaluated by an open-arm system in rodents (83-days sub-chronic beta-hydroxybutyrate-mineral salt supplementation) (Kovács et al., 2018), possibly by interacting with the Adenosine A1 receptor (Kovács et al., 2018). In another study, BHB administration has also been shown to reduce depressive-like behaviors in rodents as evaluated by chronic unpredictable stress and sucrose preference experimental methods (Kovács et al., 2018). *In situ* BHB administration has been reported to suppress macrophage/microglia activation (Huang *et al.*, 2018). Although the underlying mechanisms have not been elucidated yet, one of the possible mechanisms to ameliorate depressive and anxiety symptoms is by suppressing inflammation (Kong *et al.*, 2017).

The anti-inflammatory properties of BHB have been reported extensively. A study conducted in a rodent model revealed the protective effect of BHB on neuroinflammation. In this study, repeated BHB administration reduced depressive and anxiety behaviors in animals undergoing chronic unpredictable stress (Kong *et al.*, 2017). Additionally, pre-treatment of BHB reduced hippocampal IL-1β and TNF-α (Yamanashi *et al.*, 2017). BHB could alleviate inflammation by attenuating NLR family pyrin domain containing (NLRP)-3 inflammasome formation in IL-1β/IL-18 over-expression mice (Yamanashi *et al.*, 2017). Suppression of the activation of the NLRP3 inflammasome by preventing K+ efflux and reducing apoptosis-associated speck-like protein with a caspase-recruitment domain (ASC) oligomerization and speck formation in human monocytes has also been documented (Kajitani *et al.*, 2020). In BV2 cells, BHB supplementation inhibited LPS-induced inflammatory responses and NLRP3 inflammasome protein level, shifting the activation of macrophages/microglia from the proinflammatory M1 to the anti-inflammatory M2a type (Deng *et al.*, 2021). In both mice and human neutrophils separated from the blood, BHB suppressed IL-1β production by inhibiting both priming and assembling procedures in the activation of the NLRP3 inflammasome (Youm *et al.*, 2015). On the other hand, when the ketolytic, rate-limiting enzyme SCOT (succinyl-CoA:3-ketoacid-CoA transferase 1; encoded by Oxct1) was deleted, markers of sterile inflammation and macrophage infiltration were shown to be attenuated in mice that underwent transverse aortic constriction surgery. Further, the NLRP3 expression was

also reduced, indicating that elevated circulating BHB might be linked to reduced inflammation through an NLRP3-mediating manner (Goldberg *et al*., 2017).

Calorie restriction is well known for its anti-inflammation activities (Ottaviano and Zaman, 2023). Other studies also reported that BHB might exert its anti-inflammatory effects as a calorie restriction mimic (Kim *et al*., 2019). In one report, BHB administration upregulated Forkhead Box1 (FoxO1) and its target genes catalase/manganese superoxide dismutase (MnSOD). Both play critical roles in quenching inflammation-induced reactive oxygen species, thus ameliorating renal inflammation in aging rats (Kim *et al*., 2019) by down-regulating TNFSF6, TNF-α, PI3K, NF-κB and toll-like receptor 1 on LPS-stimulated macrophages (Qiao *et al*., 2020). Another role of BHB during anti-inflammation might be as the inhibitor of histone deacetylase (HDAC), as HDAC inhibition is well-known to have anti-inflammatory effects. For example, in HEK293 cells, HDAC activity decreased with the elevation of BHB concentration, indicating that BHB function as an HDAC inhibitor is dose-dependent (Shimazu *et al*., 2013). In the same study, it was also shown that dietary BHB exhibited protective effects on cells against oxidative stress via up-regulation of FoxO3a, which shares a similar function as FoxO1, and its target gene, catalase and mitochondrial MnSOD2 (Shimazu *et al*., 2013). To summarize, numerous studies also show the potential role of BHB in the treatment of CMD. However, since most of the studies are conducted in animals, and the mechanisms are speculative, further studies are urgently encouraged to validate the safety, effectiveness, and mechanisms of BHB application for human CMD treatment.

Conclusions

The anti-inflammatory properties of KD or BHB, the biomarker metabolite during KD administration, are attracting the attention of researchers. In this review, we summarized 15 clinical trials that employed KD or BHB to study their effects on the prevention and treatment of inflammation. Most of them documented favorable results. A KD or BHB-based therapy may thus contribute to relieving neuroinflammation and depressive and anxiety behaviors and have the potential to become a part of the CMD-treatment strategy.

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Ethics Approval: Not applicable.

Conflicts of Interest: The authors declare that they have no conflicts of interest to report regarding the present study.

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Supplementary Materials

TABLE S1. Prisma checklist