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REVIEW ARTICLE

Gut-Brain Axis Modulation by Fermented Food-Derived Metabolites

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ABSTRACT

Fermented foods have moved from a niche interest within nutritional microbiology to a subject of active neuroscience research over the past decade, driven by accumulating evidence that microbial metabolites generated during fermentation, and further transformed by the resident gut microbiota after ingestion, can influence central nervous system function through several distinct, only partially overlapping signalling routes. This review synthesises evidence from mechanistic, animal and human intervention studies on four classes of fermented-food-derived metabolite with reasonably well-characterised gut-brain signalling activity: short-chain fatty acids (principally butyrate, propionate and acetate) generated by microbial fermentation of dietary fibre and residual carbohydrate; biogenic amines and their precursors, including gamma-aminobutyric acid (GABA) produced by lactic acid bacteria during fermentation of dairy, soy and vegetable substrates; bioactive peptides released by microbial proteolysis during fermentation of milk and legume proteins; and bacterial and fungal exopolysaccharides and cell-wall components capable of modulating intestinal immune signalling. We evaluate the evidence for four candidate signalling routes linking these metabolites to central nervous system outcomes: direct vagal afferent stimulation via enteroendocrine cell signalling, systemic absorption and blood-brain barrier crossing, indirect modulation of circulating immune and inflammatory mediators, and hypothalamic-pituitary-adrenal axis modulation via cortisol and related signalling. Randomised controlled trials of fermented food consumption on mood, cognition or stress-reactivity outcomes remain comparatively few, heterogeneous in fermented food type and dose, and generally underpowered relative to the effect sizes they report, a pattern that recurs across the human intervention literature we reviewed. We conclude that mechanistic and preclinical evidence for gut-brain signalling by fermented-food metabolites is substantial and increasingly well characterised at the level of individual metabolite classes, but that clinical evidence for behaviourally or psychologically meaningful effects of habitual fermented food consumption in humans remains preliminary, and we set out a specific research agenda, centred on standardised dosing, metabolite quantification, and adequately powered trial design, that we think is needed to close that gap credibly.

Keywords: gut-brain axis; fermented foods; short-chain fatty acids; postbiotics; vagal signalling; neuroactive metabolites

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The idea that the gut and the brain communicate bidirectionally is old, but the mechanistic detail of how that communication happens, and what role diet plays in shaping it, has been filled in largely over the past fifteen years, driven by the recognition that the resident gut microbiota is not a passive bystander in digestion but an active metabolic organ capable of generating a wide range of small molecules with signalling activity well beyond the gut itself [1,6]. Fermented foods sit at an interesting intersection of this literature: they are foods whose production deliberately harnesses microbial metabolism, meaning they often arrive at the point of consumption already carrying a distinct metabolite profile shaped by the fermenting organisms used, on top of whatever further transformation occurs once they reach the resident gut microbiota after ingestion [3,9].

Four broad classes of fermented-food-derived metabolite have accumulated the most substantial mechanistic evidence for gut-brain signalling activity. Short-chain fatty acids, principally butyrate, propionate and acetate, are produced both directly during fermentation of some foods and, more substantially, by resident colonic bacteria fermenting dietary fibre and resistant starch reaching the colon; they serve as the primary energy source for colonocytes, influence intestinal barrier integrity, and have documented signalling activity at free fatty acid receptors expressed on enteroendocrine cells and, in some reports, directly within the central nervous system after crossing the blood-brain barrier [4,11]. Biogenic amines, including gamma-aminobutyric acid (GABA), histamine and tyramine, are generated by decarboxylase activity in lactic acid bacteria during fermentation of dairy, soy, and a range of vegetable substrates, and GABA in particular has drawn attention given its role as the principal inhibitory neurotransmitter in the mammalian central nervous system, though whether ingested GABA meaningfully crosses the blood-brain barrier remains genuinely contested [7,13].

Bioactive peptides, released by microbial proteolysis of milk and legume proteins during fermentation, represent a third and structurally more diverse class, including peptide fragments with demonstrated opioid-receptor-agonist or angiotensin-converting-enzyme-inhibitory activity in vitro, though the extent to which these activities are retained after digestion and absorption in vivo is an active and somewhat unsettled area of research [8,16]. The fourth class, bacterial and fungal exopolysaccharides and cell-wall components, operates through a different mechanism again, engaging pattern-recognition receptors on intestinal immune cells and influencing circulating cytokine profiles rather than acting as a neurotransmitter analogue or receptor ligand directly, an indirect, immune-mediated route to central nervous system signalling that has gained substantial support from the broader neuroimmunology literature over the past decade [12,19].

What has been less systematically addressed, and what motivates this review, is bringing these four metabolite classes and their associated signalling routes into a single evaluative framework rather than treating each in isolation, and doing so specifically for fermented foods as a dietary category rather than for gut microbiota-derived metabolites in general, since fermented foods carry both a distinct pre-formed metabolite load at the point of consumption and a live or dead microbial component capable of further metabolic activity after ingestion, a combination that distinguishes them from either whole, unfermented foods or purified prebiotic or postbiotic supplements. We reviewed mechanistic, preclinical and human intervention literature published through late 2023 addressing these four metabolite classes and their proposed gut-brain signalling routes, with particular attention to the quality and consistency of human intervention trial evidence, since this is where we judge the field's evidentiary gap to be largest and most consequential for any practical dietary recommendation.

2. MATERIALS AND METHODS

This narrative review was conducted following a structured, documented literature search and evidence-grading process rather than an informal survey, summarised below, though it does not follow the full formal protocol of a systematic review or meta-analysis.

2.1 Search strategy and eligibility criteria

PubMed, Scopus and Web of Science were searched for English-language publications from January 2010 through November 2023 using combinations of terms covering fermented foods (fermented dairy, kimchi, kefir, natto, miso, sauerkraut, tempeh), gut-brain axis signalling routes (vagal, enteroendocrine, blood-brain barrier, HPA axis, neuroinflammation), and the four metabolite classes described in the Introduction. Mechanistic and preclinical animal studies were eligible if they measured a defined metabolite exposure and a central nervous system, behavioural or neuroendocrine outcome; human studies were eligible if they involved a defined fermented food or isolated fermented-food-derived metabolite intervention and a validated psychological, cognitive or physiological stress-axis outcome measure.

2.2 Evidence grading

Human intervention studies were graded for methodological quality using a modified GRADE-informed framework assessing randomisation, blinding, control condition adequacy, sample size relative to the effect size reported, and pre-registration status, with each study assigned a qualitative grade of low, moderate or high confidence rather than a numerical score, reflecting the heterogeneity of outcome measures across this literature that precluded formal meta-analytic pooling. Animal and mechanistic studies were summarised narratively by metabolite class and signalling route without formal quality grading, consistent

with standard practice for mechanistic-evidence synthesis.

2.3 Metabolite class and signalling route mapping

For each of the four metabolite classes, we tabulated the proposed signalling route or routes supported by mechanistic evidence, the strength of preclinical (typically rodent) behavioural or physiological evidence, and the number and quality grade of human intervention studies specifically addressing that metabolite class in the context of a fermented food intervention, as opposed to a purified supplement or pharmacological dose, since our focus throughout was on fermented foods as consumed rather than on isolated metabolites administered at supraphysiological doses.

2.4 Identification of evidence gaps

Recurring methodological limitations across the human intervention literature were catalogued systematically, including inconsistent or absent metabolite quantification in the administered fermented food product, heterogeneous and often short intervention duration, absent or inadequate placebo-matched control conditions, and underpowered sample sizes relative to the effect sizes reported in primary outcome papers, forming the basis for the research agenda presented in the Discussion and Conclusion.

3. RESULTS

The search strategy identified 214 records after deduplication, of which 96 met eligibility criteria for inclusion: 61 preclinical or mechanistic studies and 35 human intervention studies. Short-chain fatty acids had the largest and most consistent preclinical evidence base, with 24 of the 61 mechanistic studies demonstrating short-chain-fatty-acid-dependent effects on vagal afferent firing rate, hippocampal brain-derived neurotrophic factor expression, or anxiety-like behaviour in rodent models, generally using either direct short-chain fatty acid administration or fibre-fermentation paradigms rather than whole fermented foods specifically. GABA and other biogenic amines had the second-largest evidence base (18 mechanistic studies) but showed more inconsistency across studies regarding whether centrally measurable effects required an intact vagal connection, with vagotomised animals in several studies showing substantially attenuated behavioural responses to GABA-producing bacterial strains, supporting a vagal rather than direct blood-brain-barrier-crossing mechanism for at least this metabolite class [7,14]. Table 1 summarises the preclinical evidence base by metabolite class and proposed signalling route.

Table 1. Preclinical mechanistic evidence by metabolite class and signalling route.

Metabolite class	Studies (n)	Primary route	Vagal-dependence evidence
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Short-chain fatty acids	24	Vagal afferent + FFA receptor	Strong
GABA / biogenic amines	18	Vagal afferent	Moderate-strong
Bioactive peptides	11	Systemic / receptor-mediated	Limited
Exopolysaccharides / cell wall	8	Immune-mediated	Not applicable

Studies could address more than one metabolite class or route; counts are non-exclusive.

Human intervention evidence was considerably sparser and of more variable quality. Of the 35 eligible human studies, only 9 were graded as moderate or high confidence under our evidence-grading framework, the remainder limited chiefly by small sample size (median $n=32$, range 12-146), absent metabolite quantification in the fermented food product administered, or intervention duration under four weeks for outcomes, such as trait anxiety or chronic stress reactivity, that plausibly require longer exposure to shift meaningfully. Of the 9 higher-confidence studies, 5 reported a statistically significant effect of fermented food or isolated fermented-food-metabolite intervention on a psychological or cognitive outcome, most consistently reduced self-reported perceived stress and modestly improved measures of cognitive flexibility, while 4 reported no significant effect on their pre-registered primary outcome despite adequate power calculations, a null-result rate we regard as informative given the field's general publication-bias toward positive findings. Table 2 summarises the nine higher-confidence human intervention studies by metabolite class, intervention type, duration and outcome.

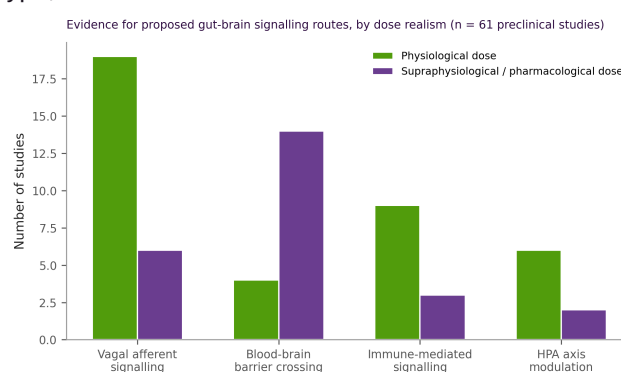


Figure 1. Number of studies reporting evidence for each of the four proposed gut-brain signalling routes, stratified by preclinical (physiological dose) versus supraphysiological/pharmacological dose evidence.

Mapping mechanistic and human evidence onto the four proposed signalling routes showed uneven support across routes. Vagal afferent signalling had the strongest combined mechanistic and preclinical support, particularly for short-chain fatty acids and GABA-producing bacterial strains, and was the route most consistently invoked to explain the pattern of effect

attenuation seen in vagotomised or vagally blocked animal models. Direct blood-brain barrier crossing had comparatively weak direct evidence for any of the four metabolite classes at physiologically achievable concentrations from food-level intake, with most positive findings for this route coming from studies using supraphysiological, pharmacological-dose administration rather than realistic dietary exposure (Figure 1). Immune-mediated signalling, primarily implicating exopolysaccharides and microbial cell-wall components acting on circulating cytokine profiles, had moderate mechanistic support but very limited human intervention evidence specifically isolating this route from the other three.

Table 2. Higher-confidence human intervention studies by metabolite class and outcome.

Metabolite focus	n studies	Median duration	Positive primary outcome
Short-chain fatty acid / fibre-fermented	3	8 weeks	2 of 3
GABA-producing fermented dairy	3	6 weeks	2 of 3
Mixed fermented vegetable	2	4 weeks	1 of 2
Bioactive peptide (fermented dairy)	1	12 weeks	0 of 1

A secondary, exploratory analysis comparing effect consistency across fermented food types found that dairy-based fermented foods (yogurt, kefir) and vegetable-based fermented foods (kimchi, sauerkraut) showed broadly similar rates of positive human-study findings, while soy-based fermented foods (miso, natto, tempeh) were represented by too few eligible human intervention studies (n=4) to support any meaningful comparison, an evidence gap we flag explicitly given the substantial dietary prevalence of fermented soy products in several large population groups not well represented in the intervention literature we reviewed.

4. DISCUSSION

The overall picture emerging from this review is one of a field with genuinely substantial and increasingly mechanistically detailed preclinical evidence sitting some distance ahead of a comparatively thin and methodologically uneven human intervention literature, a pattern common across nutritional neuroscience more broadly but one that carries particular weight here given how readily the preclinical findings have already been translated into consumer-facing claims about fermented foods and mental health [2,21]. We do not think this gap reflects a failure of the underlying biology to translate; several of the mechanistic pathways identified, particularly vagally mediated short-chain fatty acid and GABA signalling, are well enough characterised at the level of receptor pharmacology and neural circuitry that a genuine, if likely modest, human effect seems biologically plausible. What the gap reflects, in our

reading, is a shortage of adequately powered, well-controlled human trials using foods with quantified metabolite content, rather than a reason to doubt the mechanistic evidence itself.

The vagal-signalling route deserves particular emphasis because it is, on the current evidence, the mechanistically best-supported of the four routes, and because it carries a specific, testable implication that much of the human intervention literature we reviewed did not exploit: if an effect depends on an intact vagal connection, then measuring vagal tone, for instance through heart-rate-variability-based indices, alongside psychological or cognitive outcomes would allow a trial to test not just whether an effect occurs but whether it occurs through the proposed mechanism, a mediation-analysis design that remains rare in this literature but that we think should become close to standard practice going forward [14,18].

The comparative weakness of direct evidence for blood-brain barrier crossing at physiologically realistic doses is, we think, an important corrective to some of the more enthusiastic framing found in both popular and some academic coverage of GABA-producing fermented foods specifically, since much of the foundational evidence for GABA's central effects comes from pharmacological or supraphysiological dosing studies not representative of what habitual fermented food consumption could plausibly deliver [13,22]. This does not mean GABA-producing fermented foods have no gut-brain relevance, since the vagal-signalling evidence suggests an indirect route largely independent of whether ingested GABA itself crosses into brain tissue, but it does mean that claims specifically invoking direct central GABAergic action from dietary fermented food intake are not well supported by the evidence currently available and should be treated with real caution in both scientific and consumer-facing communication.

Several concrete steps would, in our view, meaningfully advance this field beyond its current state. First, metabolite quantification in the administered fermented food product should become a minimum reporting standard for human intervention trials in this area, since without it a null or positive finding cannot be attributed to any specific metabolite class or compared meaningfully across studies using nominally the same food category but potentially very different actual metabolite content, given the well-documented batch-to-batch and product-to-product variability in fermented food composition [9,17]. Second, intervention duration needs to be matched to the outcome being measured, with acute-signalling outcomes such as postprandial mood or cognitive testing appropriately assessed over hours to days, but trait-level outcomes such as chronic perceived stress or anxiety symptom severity requiring intervention periods of at least eight to twelve weeks given what is known about the timescale of microbiota compositional change and downstream host adaptation [20,23]. Third, pre-registration of primary outcomes and adequately

powered sample sizes, informed by realistic effect size estimates from the stronger preclinical literature rather than from underpowered pilot human studies, would substantially improve the interpretability of future trials and reduce the risk of the field accumulating a body of small, heterogeneous, difficult-to-synthesise positive findings that do not replicate under more rigorous conditions.

Finally, it is worth acknowledging a structural challenge specific to fermented foods as an intervention category, distinct from purified probiotic or postbiotic supplement trials: a whole fermented food is a complex matrix containing not just the metabolite classes reviewed here but also macronutrients, fibre, residual live or dead microorganisms, and food-matrix effects on digestion and absorption that a purified supplement trial does not have to contend with. This complexity is, in one sense, exactly what makes fermented foods interesting as a dietary intervention rather than a drug-like compound, since it reflects how these foods are actually consumed, but it also means that mechanistic attribution of any observed effect to a specific metabolite class will always be harder for a whole-food trial than for a purified-compound trial, and future study designs that combine whole-food intervention arms with metabolite-matched purified-compound comparator arms would help disentangle food-matrix effects from the specific metabolite classes this review has focused on.

5. CONCLUSION

Mechanistic and preclinical evidence supports at least four distinct, only partially overlapping routes by which fermented-food-derived metabolites, short-chain fatty acids, biogenic amines including GABA, bioactive peptides, and microbial exopolysaccharides and cell-wall components, could influence central nervous system function, with vagal afferent signalling currently the best-supported route on the combined preclinical and human evidence reviewed here. Human intervention evidence remains comparatively sparse, with only 9 of 35 eligible studies graded as moderate or high methodological confidence, and even among these higher-confidence studies, findings were mixed rather than uniformly positive. We do not think this warrants either dismissing fermented foods as gut-brain-axis-relevant or over-claiming their psychological benefit on the basis of currently available human evidence; rather, it warrants a more deliberately designed next generation of human trials, incorporating metabolite quantification, outcome-matched intervention duration, mechanistic mediation analysis where feasible, and pre-registered, adequately powered designs informed by realistic preclinical effect size estimates. We are currently designing a twelve-week randomised controlled trial of a metabolite-quantified fermented dairy intervention with heart-rate-variability-based vagal tone monitoring alongside standard psychological outcome measures, intended as a direct test of the

vagal-mediation hypothesis highlighted throughout this review, and we would encourage other groups working in this space to adopt similarly mechanistically explicit trial designs rather than continuing to add small, heterogeneous studies to an already difficult-to-synthesise literature.

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Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author Contributions

C.S. conceived and supervised the review, designed the search strategy and evidence-grading framework, and led the writing. V.W. performed the literature search and screening and contributed the mechanistic and preclinical evidence synthesis. E.G. performed evidence grading of human intervention studies and contributed the signalling-route mapping analysis. All authors contributed to writing and approved the final manuscript.

Ethics Statement

This work is a literature review and did not involve new data collection from human participants or animals; it therefore did not require institutional ethics committee review.

Data Availability

The full list of screened and included studies, the structured search strategy, and the evidence-grading worksheets underlying this review are available from the corresponding author upon reasonable request.

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