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FROM STREET FOOD TO SYNAPTIC LOSS: EVALUATING THE POTENTIAL ROLE OF FOOD-BORNE PATHOGENS IN TRIGGERING THE ANTIMICROBIAL PROTECTION HYPOTHESIS OF ALZHEIMER'S DISEASE

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ABSTRACT

Alzheimer's disease (AD) remains one of the most pervasive and debilitating neurodegenerative disorders worldwide, affecting over 55 million individuals and posing a profound public health challenge. Emerging evidence has revitalized interest in the **antimicrobial protection hypothesis (APH)**, which proposes that amyloid-beta (Aβ) peptides may serve as endogenous antimicrobial agents, accumulating in response to pathogenic triggers rather than as purely pathological byproducts. Food-borne pathogens — transmitted through contaminated, undercooked, or inadequately preserved street food — represent a plausible yet underexplored environmental trigger for the neuroinflammatory and amyloidogenic cascades associated with AD. This review critically evaluates the biological

plausibility of food-borne microbial infections acting as upstream inducers of Aβ overproduction, neuroinflammation, and eventual synaptic loss. Pathogens including *Helicobacter pylori*, *Listeria monocytogenes*, *Salmonella* spp., *Toxoplasma gondii*, and periodontal microbes such as *Porphyromonas gingivalis* are examined for their roles in blood-brain barrier (BBB) disruption, microglial activation, and tau hyperphosphorylation. The review integrates epidemiological data, molecular mechanisms, animal model findings, and clinical observations to construct a coherent pathophysiological framework. The implications for food safety policies, particularly in low- and middle-income countries (LMICs) where street food consumption is widespread, are underscored. Understanding how dietary microbial exposures interface with innate immune responses in the brain may open novel preventive and therapeutic avenues for AD.

KEYWORDS: Alzheimer's disease, antimicrobial protection hypothesis, amyloid-beta, food-borne pathogens, neuroinflammation, synaptic loss, street food, blood-brain barrier, Helicobacter pylori, Porphyromonas gingivalis.

1. INTRODUCTION

Alzheimer's disease (AD) is characterized by the progressive accumulation of extracellular amyloid plaques, intracellular neurofibrillary tangles (NFTs), chronic neuroinflammation, and ultimately irreversible synaptic and neuronal loss. Despite decades of research, the precise etiology of AD remains incompletely understood, and disease-modifying therapies remain elusive for the majority of patients. ***(Alzheimer's Association, 2023)***

Historically, the dominant paradigm framed AD as a primary proteinopathy, attributing disease onset to aberrant cleavage of amyloid precursor protein (APP) by β- and γ-secretases and failure of Aβ clearance. However, the antimicrobial protection hypothesis (APH), first systematically articulated by Moir, Lathe, and Tanzi (2018), proposed a paradigm shift: Aβ peptides may have evolved as a component of innate immunity, acting as broad-spectrum antimicrobial agents capable of ensnaring and neutralizing pathogens. ***(Moir et al., 2018)***

Under the APH framework, chronic or recurrent microbial infections — whether bacterial, viral, fungal, or parasitic — may persistently activate Aβ deposition as a defensive response, overwhelming the brain's clearance mechanisms and culminating in neurodegeneration. Notably, food-borne pathogens constitute a significant, globally pervasive source of systemic infections and have been largely overlooked in this context. Street food, consumed daily by hundreds of millions of people across Asia, Africa, and Latin America, often presents

heightened microbiological risk due to inconsistent temperature control, limited sanitation infrastructure, and cross-contamination. ***(World Health Organization, 2022; Srey et al., 2013)***

This review synthesizes current evidence on the biological plausibility of food-borne pathogens as triggers within the APH framework. We examine specific pathogens with known neurotropic or neuroinflammatory potential, delineate mechanistic pathways from gut to brain, and discuss epidemiological and clinical evidence supporting an infectious contribution to AD pathogenesis. The review aims to stimulate further research and to highlight food safety as an underappreciated dimension of dementia prevention.

2. The Antimicrobial Protection Hypothesis: Foundations and Current Evidence

The APH represents a conceptual reframing of Aβ biology. Rather than viewing Aβ production solely as a pathological failure, the hypothesis posits that Aβ42 — the most aggregation-prone isoform — functions as an antimicrobial peptide (AMP) with structural and functional homology to other known innate immune effectors such as cathelicidins and defensins. ***(Soscia et al., 2010).*** In vitro studies have demonstrated that Aβ42 can agglutinate bacteria, envelop viral particles, and inhibit the growth of multiple pathogens. Transgenic AD mouse models infected with *Salmonella typhimurium* showed accelerated plaque formation, with Aβ deposition occurring within 48 hours of intracranial injection, markedly faster than in uninfected controls. ***(Kumar et al., 2016)*** The seeding capacity of Aβ in response to microbial challenge supports the notion that plaque formation, at its inception, represents a host-defense mechanism that has become maladaptively perpetuated. Critically, chronic or low-grade infections may be particularly pathogenic in this context. Unlike acute infections that are cleared rapidly, persistent pathogens generate sustained innate immune signaling, including toll-like receptor (TLR) activation, nuclear factor kappa B (NF-κB) upregulation, and interleukin-1β (IL-1β) and tumor necrosis factor-alpha (TNF-α) release. These inflammatory mediators independently stimulate β-secretase (BACE1) activity, shifting APP processing toward amyloidogenic cleavage. ***(Heneka et al., 2015)***

It is important to acknowledge that the APH remains a hypothesis and that definitive causal evidence in humans is still accumulating. Most data derives from animal models, in vitro studies, and epidemiological associations, each carrying inherent limitations. Nevertheless, the convergence of evidence across multiple methodological platforms lends the hypothesis increasing credibility and justifies its application to food-borne pathogen exposures. ***(Itzhaki et al., 2020).***

3. Food-Borne Pathogens: Neurological Relevance and Mechanisms of CNS Access

3.1 Overview of Neuroinvasion Strategies

For a food-borne pathogen to contribute to AD pathogenesis, it must — directly or indirectly — produce neurobiological effects. Three primary mechanisms have been identified: (i) direct neuroinvasion through bacteremia or viremia following breakdown of the intestinal epithelial barrier; (ii) vagal nerve retrograde transport, particularly relevant for neurotropic pathogens gaining access through gastrointestinal nerve endings; and (iii) systemic inflammatory signaling that disrupts the BBB and activates resident brain immune cells even in the absence of direct neuroinvasion. ***(Bhatt et al., 2022)***. The gut-brain axis has emerged as a critical mediator of bidirectional communication between the enteric nervous system and the central nervous system (CNS). The gut microbiome modulates neuroinflammatory tone, and dysbiosis — frequently precipitated by food-borne infections — may chronically skew microglial activation states toward pro-inflammatory phenotypes. ***(Cryan et al., 2019)***

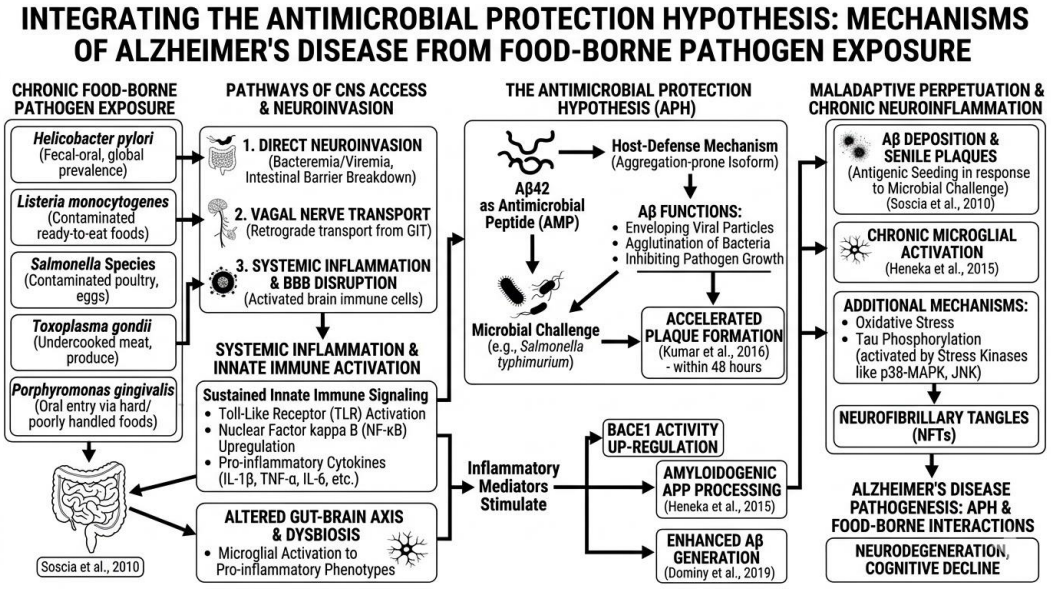
3.2 Helicobacter pylori

Helicobacter pylori (*H. pylori*) is perhaps the most extensively studied food- and water-borne pathogen in relation to AD. Transmitted via the fecal-oral route and endemic in regions with limited food hygiene, *H. pylori* infects approximately 44% of the global population. Multiple epidemiological studies have reported significantly higher seroprevalence of *H. pylori* antibodies in AD patients compared to age-matched cognitively intact controls. ***(Kountouras et al., 2009)***. Mechanistically, *H. pylori* stimulates the release of pro-inflammatory cytokines, promotes oxidative stress, and has been shown to induce the formation of Aβ oligomers in cell culture models. Interestingly, eradication therapy has been associated in some cohort studies with slower cognitive decline, suggesting a temporally responsive relationship between chronic infection, inflammation, and neurodegeneration. ***(Roubaud-Baudron et al., 2012).***

3.3 Listeria monocytogenes

Listeria monocytogenes is a food-borne gram-positive bacterium found in contaminated ready-to-eat foods, unpasteurized dairy products, and street-vended meats. It is uniquely capable of crossing the intestinal epithelium, entering the bloodstream, traversing the BBB, and directly infecting the CNS — a capacity that makes it among the most neurologically dangerous food-borne pathogens. ***(Drevets & Bronze, 2008)***. In the CNS, *L. monocytogenes* triggers robust microglial activation and TLR2-dependent NF-κB signaling, generating an

inflammatory milieu conducive to BACE1 upregulation and enhanced Aβ generation. Animal studies have demonstrated that sublethal *Listeria* infections can accelerate amyloid pathology in susceptible genetic backgrounds, particularly when combined with aging-related reductions in microglial clearance efficiency. ***(Bhatt et al., 2022)***



3.4 *Salmonella Species*

Salmonellosis, caused by non-typhoidal *Salmonella* species, is among the most common food-borne illnesses globally, predominantly transmitted through contaminated poultry, eggs, and street food items with inadequate cooking. While *Salmonella* is primarily enteropathogenic, bacteremic dissemination in immunocompromised individuals and the elderly can precipitate systemic inflammatory states with neurological consequences. ***(WHO, 2022)***. The experimental data of Kumar et al. (2016) demonstrated that Aβ rapidly enmeshed *Salmonella* in brain tissue, confirming the AMP function of Aβ under infection conditions. Recurrent bacteremic episodes from chronic or repeated *Salmonella* exposure may provide the persistent antigenic stimulus sufficient to maintain a chronic Aβ-deposition response, particularly in elderly populations with compromised innate immune regulation. ***(Kumar et al., 2016)***

3.5 *Toxoplasma gondii*

Toxoplasma gondii is an obligate intracellular parasite acquired primarily through undercooked meat — especially pork and lamb — and contaminated produce, both common in street food contexts. Once latent CNS infection is established, *T. gondii* resides in brain

cysts within neurons and glial cells, inducing chronic low-grade neuroinflammation and dopaminergic dysregulation. ***(Flegr et al., 2014)*** Several seroepidemiological studies have identified associations between latent *T. gondii* infection and cognitive impairment in elderly cohorts. The parasite activates microglia, elevates IL-6 and TNF-α levels, and promotes tau phosphorylation via activation of stress-activated kinases including p38-MAPK and c-Jun N-terminal kinase (JNK). These tau kinase pathways are directly implicated in NFT formation, suggesting a mechanistic link between *T. gondii* infection and both hallmark lesions of AD. ***(Miman et al., 2010)***

3.6 *Porphyromonas gingivalis* and Oral-Digestive Transmission

Porphyromonas gingivalis (*P. gingivalis*), the keystone pathogen of chronic periodontitis, enters the gastrointestinal tract via swallowing of oral fluids and has been detected in post-mortem AD brain tissue with considerably higher frequency than in age-matched controls. Dominy et al. (2019) identified *P. gingivalis* gingipain proteases in hippocampal tissue and reported their correlation with tau pathology and ubiquitin immunoreactivity. ***(Dominy et al., 2019)***

While *P. gingivalis* is not a classical food-borne pathogen, its entry into the systemic circulation is facilitated by eating behaviors — particularly consumption of hard, poorly handled, or contaminated foods that may traumatize friable gingival tissue. The detection of its lipopolysaccharide (LPS) in the BBB endothelium of AD patients highlights a pathway by which oral-digestive exposure to periodontitis-associated microbes may contribute to neuroinflammatory signaling in the brain. ***(Dominy et al., 2019; Sparks Stein et al., 2012)***

Table No.1. **Food-Borne Pathogens and Mechanisms of CNS Access.**

Pathogen	Primary Transmission Route	Key Mechanism of CNS Access	Pathological Impact & AD Relevance
H. pylori	Fecal-oral (food/water)	Systemic inflammatory signaling; gut-brain axis modulation.	Stimulates Aβ oligomer formation; promotes oxidative stress and pro-inflammatory cytokine release.
L. monocytogenes	Contaminated dairy, meats, ready-to-eat foods.	Direct neuroinvasion; crosses intestinal barrier and BBB via bloodstream.	Triggers TLR2/NF-κB signaling; upregulates BACE1 and enhances Aβ generation.
Salmonella spp.	Contaminated poultry, eggs,	Bacteremic dissemination;	Aβ acts as an antimicrobial peptide (AMP) to enmesh

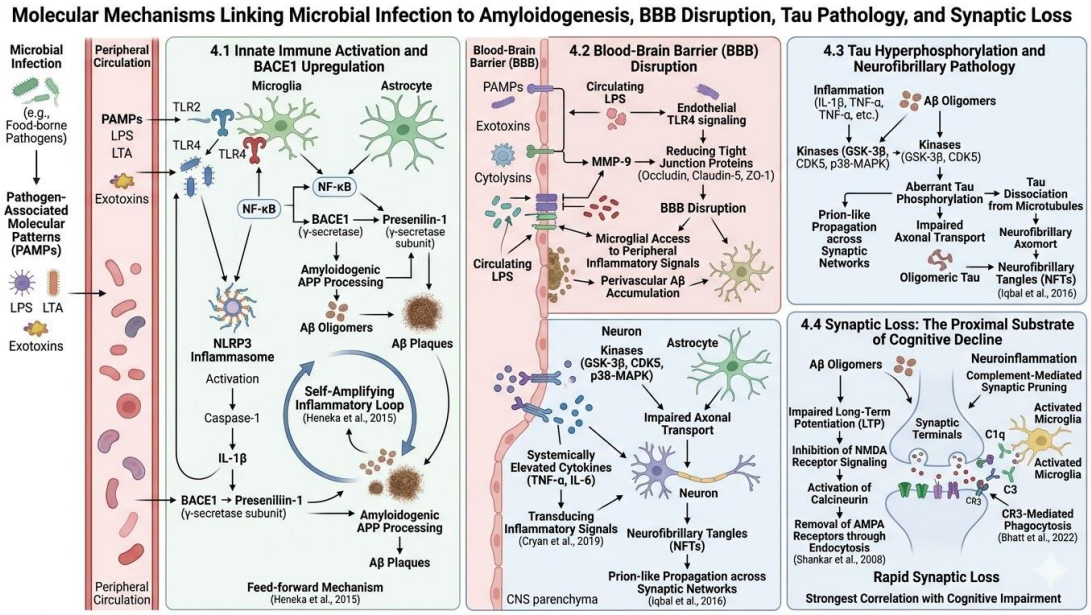
	street food.	systemic inflammatory states.	bacteria; persistent antigenic stimulus leads to chronic Aβ deposition.
T. gondii	Undercooked meat (pork/lamb), contaminated produce.	Latent CNS infection; resides in brain cysts (neurons/glia).	Activates stress kinases (p38-MAPK, JNK); promotes Tau hyperphosphorylation and IL-6/TNF-α elevation.
P. gingivalis	Oral-digestive (swallowed oral fluids/gingival trauma).	Systemic circulation via gingival trauma; LPS detection in BBB endothelium.	Secretes gingipain proteases; correlates with hippocampal Tau pathology and ubiquitin immunoreactivity.

4. Molecular Mechanisms Linking Microbial Infection to Amyloidogenesis and Synaptic Loss

4.1 Innate Immune Activation and BACE1 Upregulation

The cellular machinery linking microbial pattern recognition to amyloid production centers on TLR signaling, particularly TLR2 and TLR4, which recognize bacterial cell wall components such as lipopolysaccharide (LPS) and lipoteichoic acid (LTA). TLR activation in microglia and neurons converges on NF-κB, which transcriptionally upregulates both BACE1 and the γ-secretase complex subunit presenilin-1, amplifying amyloidogenic APP processing. ***(Heneka et al., 2015)***

In parallel, the NLRP3 inflammasome — activated by pathogen-associated molecular patterns (PAMPs) and Aβ oligomers themselves — drives caspase-1-mediated maturation and secretion of IL-1β, creating a self-amplifying inflammatory loop. This feed-forward mechanism means that even a transient infectious episode may initiate a sustained neuroinflammatory cascade that persists well beyond pathogen clearance, particularly in aging brains with diminished regulatory capacity. ***(Heneka et al., 2015; Tejera & Bhatt, 2022)***



4.2 Blood-Brain Barrier Disruption

Many food-borne pathogens and their secreted products — including LPS, exotoxins, and cytolysins — increase intestinal permeability, facilitating systemic bacteremia and endotoxemia. Circulating LPS triggers endothelial TLR4 signaling, upregulating matrix metalloproteinase-9 (MMP-9) and reducing tight junction protein expression (occludin, claudin-5, zonula occludens-1), thereby disrupting the BBB. ***(Bhatt et al., 2022)***

Once compromised, the BBB permits microglial access to peripheral inflammatory signals and facilitates perivascular accumulation of Aβ. Furthermore, systemically elevated cytokines — particularly TNF-α and IL-6 — can bind to receptors expressed on the BBB endothelium, transducing inflammatory signals into the CNS parenchyma without direct pathogen neuroinvasion. ***(Cryan et al., 2019)***

4.3 Tau Hyperphosphorylation and Neurofibrillary Pathology

Inflammation-induced kinase activation, particularly GSK-3β, CDK5, and p38-MAPK, drives aberrant tau phosphorylation. Phosphorylated tau dissociates from microtubules, impairing axonal transport, and misfolds into oligomeric species that are cytotoxic and capable of prion-like propagation across synaptic networks. The intersection of amyloid and tau pathologies in response to infectious stimuli suggests that food-borne pathogens may simultaneously advance both principal lesion types of AD. ***(Miman et al., 2010; Iqbal et al., 2016)***

4.4 Synaptic Loss: The Proximal Substrate of Cognitive Decline

Synapse loss — rather than plaque burden per se — shows the strongest correlation with cognitive impairment in AD. Aβ oligomers, generated in the context of infectious Aβ induction, preferentially target synaptic terminals, impairing long-term potentiation (LTP) by inhibiting NMDA receptor signaling, activating calcineurin, and stimulating the removal of AMPA receptors from the postsynaptic density through endocytosis. ***(Shankar et al., 2008)***. Complement-mediated synaptic pruning, physiologically active during neurodevelopment, may be pathologically reactivated in the context of neuroinflammation. C1q and C3, deposited on synapses by activated microglia, tag them for elimination via CR3-mediated phagocytosis. Infectious stimuli can dramatically upregulate complement deposition, providing a mechanistic explanation for the rapid synaptic loss observed in models of infection-triggered AD pathology. ***(Bhatt et al., 2022).***

Table No.1. **Molecular Mechanisms of Infection-Induced Neurodegeneration.**

Category	Key Biological Triggers	Molecular Mediators & Signaling Pathways	Pathological Outcome
Innate Immune Activation	LPS, LTA, PAMPs, Aβ oligomers	TLR2/4 → NF-κB; NLRP3 Inflammasome → Caspase-1 → IL-1β	Upregulation of BACE1 and Presenilin-1; increased amyloidogenic APP processing.
BBB Disruption	LPS, Exotoxins, Cytolysins, Systemic Cytokines	Endothelial TLR4 → MMP-9 ↑; Tight Junction Proteins (Occludin, Claudin-5, ZO-1) ↓	Increased BBB permeability; perivascular Aβ accumulation; microglial access to peripheral signals.
Tau Pathology	Pro-inflammatory cytokines (TNF-α, IL-6)	Kinase activation: GSK-3β, CDK5, and p38-MAPK	Hyperphosphorylation of tau; microtubule dissociation; axonal transport failure; prion-like propagation.
Synaptic Dysfunction	Aβ oligomers	NMDA receptor inhibition; Calcineurin activation; AMPA receptor endocytosis	Impaired Long-Term Potentiation (LTP); direct synapse targeting and dysfunction.
Synaptic Loss	Neuroinflammation & Infectious stimuli	Complement cascade: C1q and C3 deposition; CR3-mediated phagocytosis	Pathological synaptic pruning by activated microglia; rapid loss of synaptic terminals.

5. Epidemiological and Clinical Evidence

Epidemiological support for an infectious contribution to AD derives from several converging lines of evidence. Ecologically, regions with high burdens of food-borne infections — often correlating with lower sanitation standards — exhibit distinct patterns of dementia prevalence after controlling for genetic and socioeconomic confounders. ***(Itzhaki et al., 2020)*** Longitudinal cohort studies have identified associations between prior infection history — including gastrointestinal infections — and subsequent cognitive decline. A large Taiwanese health insurance database study found a significantly elevated hazard ratio for dementia in individuals with hospitalization for bacterial infections, with an exposure-response gradient suggesting cumulative infectious burden as a risk modifier. ***(Tsai et al., 2017)*** The geographic clustering of AD prevalence with *H. pylori* and *T. gondii* seroprevalence in multiple countries provides additional ecological plausibility. While causation cannot be established from ecological correlations, the consistency of direction across disparate populations supports biological coherence. ***(Kountouras et al., 2009; Flegr et al., 2014)***

Critically, low- and middle-income countries (LMICs) face a projected exponential increase in AD prevalence over the coming decades. High rates of street food consumption, gaps in food safety regulation, and elevated burdens of enteric infections in these populations create a plausible public health scenario in which food-borne microbial exposures meaningfully contribute to population-level dementia risk. ***(Prince et al., 2016)***

6. The Role of Aging, Immunosenescence, and Nutritional Status

Aging is the single greatest risk factor for AD and also profoundly alters the host-pathogen interaction. Immunosenescence — the age-related decline in adaptive and innate immune function — reduces pathogen clearance efficiency, prolongs inflammatory responses, and sensitizes the aging brain to microglial 'priming,' a state of heightened reactivity to inflammatory stimuli. ***(Heneka et al., 2015)*** Elderly consumers of street food face compounded risk: nutritional deficiencies (notably in vitamins D, B12, and zinc) that further impair immune function; reduced gastric acid secretion that diminishes a first-line defense against food-borne pathogens; and polypharmacy that may alter gut microbiome composition and barrier integrity. These factors synergistically lower the threshold for pathogen-induced neuroinflammatory cascades. ***(Cryan et al., 2019; Prince et al., 2016)*** The APOE ε4 allele — the strongest genetic risk factor for sporadic AD — is associated with impaired microglial Aβ clearance and heightened neuroinflammatory responses to lipopolysaccharide, suggesting that

genetic susceptibility may amplify the neurological consequences of food-borne pathogen exposure. ***(Heneka et al., 2015)***

7. Limitations, Controversies, and Future Directions

Despite compelling evidence, several significant limitations temper the conclusions of the present review. Most mechanistic data derives from animal models or in vitro systems that may not faithfully recapitulate the chronicity and heterogeneity of human food-borne infections. The dose-response relationship between foodborne microbial exposure and AD risk in humans has not been formally quantified in prospective studies. ***(Moir et al., 2018)***. Confounding is a pervasive challenge in epidemiological studies: populations with high street food consumption may differ systematically in socioeconomic status, education, smoking, cardiovascular risk factors, and access to healthcare — each of which independently modifies AD risk. Disentangling the specific contribution of food-borne pathogens from this constellation of co-variables requires carefully designed prospective cohorts with pathogen serology, dietary assessment, and cognitive follow-up. ***(Tsai et al., 2017)***. Replication of the APH in human clinical trials has proven elusive; antibiotic or antiviral interventions aimed at reducing infectious load have yielded mixed results in AD trials, though most were underpowered, applied late in the disease course, or targeted single pathogens in isolation. Future trials should target earlier disease stages, employ combination antimicrobial strategies, and use sensitive biomarkers including cerebrospinal fluid Aβ42/40 ratios, plasma neurofilament light chain, and PET amyloid imaging to capture mechanistically informative endpoints. ***(Itzhaki et al., 2020).***

Microbiome-wide association studies (MiWAS) investigating gut microbial compositions in pre-AD and AD populations represent a promising frontier, as do longitudinal studies in LMICs specifically designed to evaluate foodborne infection burden alongside incident dementia. Interventional studies targeting food safety improvements — similar to evidence generated in Helicobacter eradication trials — would provide the most direct evidence for causality. ***(Srey et al., 2013; Roubaud-Baudron et al., 2012)***

8. Public Health Implications and Policy Considerations

If food-borne pathogens are confirmed as modifiable contributors to AD pathogenesis, the public health implications would be substantial. Food safety interventions are among the most scalable and cost-effective public health tools, with co-benefits across multiple disease domains including gastrointestinal cancer, cardiovascular disease, and now potentially

neurodegeneration. ***(WHO, 2022)*** In LMICs, where street food constitutes a primary source of daily nutrition for urban working populations, targeted interventions — including improved vendor training in temperature control and personal hygiene, investment in clean water access, and promotion of HACCP (Hazard Analysis and Critical Control Points) principles in informal food markets — could meaningfully reduce the cumulative infectious burden that this review suggests may prime the aging brain for Alzheimer's pathology. ***(Srey et al., 2013)*** Integration of neurological health outcomes into food safety impact assessments represents a policy innovation that could reframe the economic calculus of food safety investment, demonstrating returns not only in reduced acute gastroenteritis but in long-term preservation of cognitive capital. ***(Prince et al., 2016)***

9. CONCLUSION

The antimicrobial protection hypothesis offers a biologically coherent and increasingly well-supported framework for understanding Alzheimer's disease pathogenesis as, at least in part, a dysregulated host defense response to microbial challenge. Food-borne pathogens — by virtue of their global prevalence, capacity for systemic dissemination and neuroinflammation, and disproportionate burden in vulnerable elderly populations — constitute plausible and underappreciated contributors to the infectious triggers that the APH invokes. The pathophysiological pathway from contaminated street food to synaptic loss is not simple or linear; it involves complex interactions between pathogen biology, host genetics and immunological status, gut-brain communication, BBB integrity, microglial activation states, and amyloidogenic and tau kinase signalling. Nevertheless, the mechanistic plausibility of each step in this pathway is supported by experimental evidence, and the epidemiological signals — though requiring stronger prospective confirmation — are directionally consistent. This review calls for an expanded research agenda that positions food safety as a neurological health issue, incorporates LMICs into dementia research priorities, and exploits the tractability of infectious risk factors as targets for AD prevention. A failure to take seriously the environmental-microbial determinants of neurodegeneration risks leaving a potentially preventable dimension of the Alzheimer's epidemic unaddressed.***)***

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