

Review

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Review

# Hydrogen and Ozone Therapies as Adjunctive Strategies for Gastrointestinal Health in Geriatric Populations

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## Abstract

Aging is accompanied by progressive gastrointestinal structural and functional decline, increased intestinal permeability, dysbiosis, and impaired mucosal immunity, collectively elevating susceptibility to infections, chronic inflammation, and multimorbidity. These age-related changes are further exacerbated by polypharmacy, metabolic disorders, and lifestyle factors, positioning the gastrointestinal tract as a central driver of systemic physiological decline. Gut-centered interventions have emerged as critical strategies to mitigate these vulnerabilities and support healthy ageing. Dietary modulation, prebiotic and probiotic supplementation, and microbiota-targeted approaches have demonstrated efficacy in improving gut microbial diversity, enhancing short-chain fatty acid production, restoring epithelial integrity, and modulating immune signaling in older adults. Beyond nutritional strategies, non-nutritional interventions such as molecular hydrogen and medical ozone offer complementary mechanisms by selectively neutralizing reactive oxygen species, reducing pro-inflammatory signaling, modulating gut microbiota, and promoting mucosal repair. Hydrogen-based therapies, administered via hydrogen-rich water or inhalation, confer antioxidant, anti-inflammatory, and cytoprotective effects, while ozone therapy exhibits broad-spectrum antimicrobial activity, enhances tissue oxygenation, and stimulates epithelial and vascular repair. Economic considerations further differentiate these modalities, with hydrogenated water positioned as a premium wellness product and ozonated water representing a cost-effective, scalable option for geriatric gastrointestinal care. Although preclinical and early clinical studies are promising, evidence in older adults remains limited, emphasizing the need for well-designed, age-specific trials to establish safety, dosing, and efficacy. Integrating dietary, microbiota-targeted, and emerging non-nutritional gut-centered interventions offers a multimodal framework to preserve gut integrity, immune competence, and functional health, potentially mitigating age-related decline and supporting overall healthspan in older populations.

**Keywords:** aging; gastrointestinal health; gut microbiota; hydrogen therapy; ozone therapy; dysbiosis; immunosenescence; inflammaging; geriatric care; interventions

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## 1. Introduction

Aging represents one of the most pressing global public health challenges, affecting an approximately 50–65% of community-dwelling adults over the age of 65 with projections indicating a doubling of this population by 2050 [1]. Progressive decline in age, being accompanied with other conditions [1], such as metabolic, cardiovascular, and musculoskeletal conditions [2] significantly affect the quality of life in high-income populations and increase healthcare burden worldwide [3].

Older adults with existing comorbidities, especially those co-diagnosed with cardiovascular disease, pulmonary and renal dysfunctions, as well as diabetes, due to compromised immune functions and necessity to frequently require hospitalization have elevated risk of infections [3,4] and mortality [3]. This heightened susceptibility to infections reflects a convergence of metabolic dysregulation, and age-related deterioration of systemic immune system, known as immuno-senescence, characterized by chronic low-grade inflammation (“inflammaging”) [5].

Immunosenescence negatively influences both innate and adaptive immune responses, that is demonstrated as reduced phagocytic activity and antibody production, as well as weakened T-cell function [6,7]. In parallel, inflammaging driven by persistent activation of inflammatory pathways in metabolic and cardiovascular disease further compromises immune resilience and reduce tissue repair capacity [8]. Metabolic disturbances common for obesity and type 2 diabetes as contributors to systemic inflammation have been shown to accelerate immune aging and exacerbate the infection risk in older populations [6,8]. For example, pneumococcal disease have been linked to the fivefold higher risk of death in in older adults with comorbidities compared to those without (16% vs. 3.2%) [4]. Similarly, seasonal respiratory infections, such as influenza and norovirus have been linked with increased hospitalization and mortality, particularly among institutionalized older adults [9]. Interestingly, an higher risk was also observed for gastrointestinal infections, among those caused by *Clostridioides difficile* represents the leading cause of healthcare-associated diarrhea in aging individuals with kidney, liver, or cardiovascular disease [10,11]. Of special interest are also immunocompromised older patients diagnosed with infections attributed to the presence of other pathogens, including *Helicobacter pylori* and parasites, in particular *Blastocystis spp.*, and *Dientamoeba fragilis* [12], as they may have increased prevalence of non-specific gastrointestinal symptoms, like irritable bowel syndrome (IBS) and chronic diarrhea [13].

Although progressive aging and immunosenescence seem to be a key factor linked with increasing infection risk, also the changes in gut physiology present in older populations may play an important role in the infection, vulnerability and immunity among older populations [14,15]. Use of multiple types of medications, particularly proton pump inhibitors and antibiotics, additionally affects the composition of the gut microbiota, reduce microbial diversity, and promotes dysbiosis [16]. Also, accompanied with polypharmacy reduced gastric acid secretion, may influence intestinal motility, and disturb mucus layer integrity, loosen epithelial tight junctions, consequently increase risk of pathogen translocation [14,17]. This might be of special interest in the aging populations, as gastrointestinal dysfunction itself affects up to 40–50% of adults over 80 years of age and significantly contributes to functional decline, loss of independence, and institutionalization [18]. In addition, these individuals frequently present the changes in the gut microbiota composition, characterized by depletion of anti-inflammatory bacteria involved in short chain acid (SCFA) production, such as *Akkermansia*, *Bifidobacterium*, *Faecalibacterium*, and *Lactobacillus*, in expense of pro-inflammatory taxa [19,20]. This shift in the gut microbiome is considered as additional disturber of the integrity of intestinal barrier, that further promote the endotoxemia and translocation of inflammatory mediators, such as lipopolysaccharides (LPS)[17]. The increased pro-inflammatory environment associated with trimethylamine N-oxide accumulation, may additionally contribute to systemic manifestations, reflecting in increased severity of cardiovascular and neurodegenerative conditions, as well as impaired glucose regulation and malnutrition [19,21,22].

Given these complex mechanisms how progressive aging by influencing the immune function and microbiota composition can influence on the health and infection in older populations, the interventions supporting the gastrointestinal competence are of increased interest. Although many dietary approaches, including supplementation with microbial preparations have been tested, other alternatives with immunomodulatory properties are of interest. Hydrogen and ozone-based interventions, represent emerging adjunctive approaches with potential to support gut-immune axis regulation in aging populations [23].

Therefore, given the potential of using hydrogen and ozone-based interventions, thus still limited knowledge and implications in gut-centered care in geriatric patients [5,24], the key aim of

this explorative review is to present the existing knowledge from human studies on potential health benefits of using hydrogen- and ozone-based therapies in improving gastrointestinal health among older adults. In addition, the economic advantages for public healthcare systems will be justified with key purpose to reduce burden of costs linked with progressive aging worldwide.

## 2. Aging and Gastrointestinal Multimorbidity

As populations age, the prevalence of multimorbidity having multiple chronic diseases increases, including gastrointestinal conditions. This significantly affects the quality of life of older populations, therefore understanding the effects of acquired conditions on aging on the gut health is of interest, with main purpose of developing effective prevention and management strategies. Epidemiological studies focused on the multimorbidity patterns and GI vulnerability consistently demonstrated that disorders affecting GI are considered as an important factor contributing to diagnosis of additional comorbid conditions, with metabolic, cardiovascular, and musculoskeletal diseases in Asian countries [25–27].

Although gastrointestinal manifestations are common in aging populations, they are considered as early indicators of other chronic conditions. In older adults, gut-related issues were reported to be less stable over time as many individuals progress from the GI-dominant disorders to cardiovascular or multi-system disease as they age [26,28,29]. Factors such as advanced age, female gender, low socioeconomic status, poor childhood health, presence of obesity, along with unhealthy lifestyle habits, low physical activity substance use, were linked to higher comorbidity risk associated with chronic inflammatory gut diseases [26]. Additionally, in older adults, the poor gut health was associated with increased healthcare utilization, functional decline, and, when combined with other chronic conditions, higher mortality and risk of complications [28,30], including gastrointestinal bleeding [31]. Notably, the chronic gastrointestinal diseases are often reported alongside arthritis or metabolic dysfunction, what all together may additionally elevate the risk of functional and mental health decline in these individuals [32,33]. Although there are many possible mechanisms, these elevated risks are often attributed to structural and functional changes within the gastrointestinal system, including impaired motility, reduced mucosal defense, and altered gut microbiota, all of which increase susceptibility to malnutrition and infection [20,34]. Notably, progressive aging has been associated with decreased esophageal, gastric, and colonic motility, often resulting in slower transit, constipation, and dysphagia, that may reduce nutrient absorption and increase the risk of malnutrition and related complication [34,35]. In addition, subsequent changes within the composition of the gut microbiota may result in the reduced microbial diversity, characterized by lower counts of beneficial bacteria [19] including *Akkermansia*, however an increase in pro-inflammatory or opportunistic organisms [36]. These changes promote a persistent state of "inflammaging", which have been associated with frailty, infection, and poor nutritional status [19]. The limited availability of essential nutrients over time may lead to malnutrition that further increase the risks for the development of a range of conditions associated with neurological musculoskeletal, cardiovascular, immune and skin conditions [16].

Taken together, these structural and functional shifts illustrate how aging transforms the gut into a more prone system that contributes to multimorbidity and amplifies the impact of existing chronic diseases. As gastrointestinal homeostasis seem to be compromised due to progressive aging, the immune competence and ability to defend against infections can be significantly affected.

## 3. Age-Related Immunological Disturbances and Their Effect on the Gut Physiology

Progressive ageing has significant impact on the gut physiology, including the mucosal immunity, intestinal barrier integrity and microbial ecology [35,37]. These age-induced immune disturbances may further promote increased intestinal permeability, dysbiosis, and impaired immune homeostasis [37], that all together promote systemic immune ageing along with increased

development of age-associated diseases [38], including obesity, diabetes, cardiovascular disease, and dementia that collectively contribute to increased infection risk and disease severity among older adults [35,39].

Immunosenescence, characterized as the gradual deterioration of immune function associated with age [5,40], significantly compromises host defense against pathogens [37] and opportunistic microorganisms [5]. Quantitative and qualitative defects in innate and adaptive immunity, including reduced T- and B-cell diversity, impaired phagocytic activity, and a persistent pro-inflammatory environment ultimately lead to immune exhaustion, that is reflected in suboptimal vaccine responses and increased susceptibility to infections in aging populations [5]. In addition, immunosenescence frequently coexists with inflammaging, a chronic low-grade inflammatory state with increased sustained production of pro-inflammatory mediators such as interleukin-6 (IL-6), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and C-reactive protein (CRP), that further lead to thymic involution, T-cell exhaustion, and reduced availability of naïve lymphocytes [40,41]. These systemic alterations impair immune resilience which also affect the gut-associated lymphoid tissue (GALT) involved in maintaining mucosal homeostasis, antigen sampling, immunoglobulin A (IgA) production, and localized immune surveillance at the intestinal surface [42,43]. As progressive ageing may lead to reduced lymphocyte repertoire diversity and dysregulated cytokine signaling, may compromise the effective immune responses against pathogenic and opportunistic microorganisms within GALT. Following alterations may have serious consequences, thus the gastrointestinal tract is continuously exposed to many antigens and requires tightly regulated balance between immune tolerance and acute responses against pathogens. Nevertheless, the persistent inflammaging and disruptions in redox systems attributed to progressive aging have been shown to activate innate immune pathways and promote the release of pro-inflammatory cytokines such as IL-6 and TNF- $\alpha$  through the senescence-associated secretory phenotype (SASP) [42,44]. Furthermore, there is growing evidence to demonstrate the role of ageing in disrupting intestinal morphology and function, that can contribute to perturbed integrity of epithelial tight junction, along with reduced mucus production, and lower secretion of antimicrobial peptides [41]. An increased intestinal permeability promote the translocation of pro-inflammatory microbial products into systemic circulation, what may promote systemic inflammation and accelerate thymic involution and T-cell exhaustion [45]. Notably, older individuals are reported with lower microbial diversity what may favors the expansion of pathogenic and opportunistic microorganisms and diminishing the beneficial commensals linked with SCFAs production and immunoregulatory bioactives. Consequently, these age-associated changes within the composition of gut microbiota promote establishment of inflammatory luminal environment, that exaggerate mucosal immune activation and inflammaging [46].

Taken together, the age-induced changes within immune system along with immunosenescence, should be considered as intestinal barrier dysfunction, and age-associated dysbiosis positions the gastrointestinal tract as a central therapeutic target in geriatric care. This framework supports the exploration of gut-centered interventions capable of modulating oxidative stress, microbial composition, and immune responses, thereby addressing key drivers of inflammation and gastrointestinal conditions in aging populations.

#### 4. Gut-Centered Therapeutic Strategies in Aging

Progressive aging is accompanied by significant physiological changes within physiology involving multiple organs, among which immune and the gastrointestinal systems have emerged as one of the most vulnerable. Although many mechanisms have been implicated, the aging impact on the gut microbiota, that is a key regulator of metabolic homeostasis, immune function, and neuroendocrine signaling, seem to have the most profound impact on the susceptibility to chronic disease, frailty, cognitive impairment, and chronic low-grade systemic inflammation in older adults. Importantly, age-related alterations in gut function and microbial ecology are increasingly recognized not as passive consequences of aging, but as active contributors to biological aging trajectories.

Given these implications, the gut microbiome has emerged as central therapeutic target in geriatric care and aging prevention. Gut-centered strategies, including dietary interventions and microbiota-directed supplementation, lifestyle interventions offer a unique opportunity to mitigate inflammaging, preserve metabolic resilience, and support healthy longevity. Understanding the drivers of microbiota disruption in older adults is therefore essential for the development of effective, personalized interventions aimed at maintaining gut integrity and systemic health across the aging continuum.

Research to date demonstrated that changes within the gut microbiota associated with aging can be induced by both intrinsic biological factors as well as by modifiable external factors, including dietary habits, medications, and physical activity. In particular, long-term use of multiple medications, such as antibiotics, proton pump inhibitors (PPIs), and laxatives prescribed for management of coexisting chronic conditions has been shown to significantly disrupt the gut homeostasis and promote dysbiosis further leading to impaired gut barrier function and immune dysregulation, that reinforce inflammaging and increase vulnerability to infections and systemic complications [47].

Fibre-rich dietary patterns and microbiota-centered interventions have emerged as promising strategies to counteract age-related dysbiosis and promote healthy ageing. Early evidence demonstrate that interventions with prebiotic fibre, such as inulin and resistant starch, as well as synbiotic formulations targeting butyrate-producing taxa including *Faecalibacterium* and *Roseburia*, may restore SCFAs availability, improve epithelial barrier integrity, and shift immune signaling toward anti-inflammatory profiles [47]. In addition, evidence from human studies further supports the clinical relevance of gut-focused interventions in modifying ageing-induced conditions, including frailty, sarcopenia, cognition, impaired glycaemic control, and biological ageing markers. Among the most successful strategies, plant-based interventions with rich in fibre foods have associated with favorable microbial profiles and improved health outcomes within musculoskeletal, immune, vascular, and neurocognitive systems. Interestingly, lifestyle programs incorporating Mediterranean- or DASH-like dietary models through promoting favourable gut microbiota profiles were associated with benefits for cognitive function and systemic inflammation reduction in older or at-risk populations, that is consistent with observational data suggesting such dietary patterns in later life with slower cognitive decline and reduced frailty, likely mediated in part through microbiome-associated reductions in systemic inflammation [48,49].

Accordingly, there is evidence to support the role of gut-focused supplementation in management of the ageing-related outcomes. A recent study involving community-dwelling adults aged  $\geq 65$  years, have shown that daily intervention with a prebiotic blend composed of inulin and oligofructose through favorable shifts in the gut microbiota toward higher proportions of bifidogenic taxa and SCFAs producers may improve frailty status and physical function compared with placebo [50]. Similarly, the "Gut Feelings" study which involved adults with moderate psychological distress and low dietary prebiotic intake, a 8-week long intervention with a high-prebiotic diet, combined with probiotic supplementation, indicated that increasing intake of plant-based foods, such as legumes, whole grains, onions, garlic, leeks, and resistant starch may improve the total mood, and reduce anxiety, stress, and sleep disturbances compared with placebo [46]. The observed clinically considerable effect on mental health outcomes seem to be attributed to the increased fermentable fibre intake following intervention that may contribute to increased microbial diversity, and higher fecal SCFAs levels, resultant from regular intake of food-based fibre [51]. Furthermore, results of a recent meta-analysis further support the potential role of probiotic supplementation in ageing-related functional outcomes. Across trials interventions with *Lactobacillus* and *Bifidobacterium* ranging from 8 to 24 weeks at doses of approximately  $10^9$ – $10^{11}$  CFU/day, have associated with moderate improvements in inflammatory markers including CRP IL-6 [52]. Interestingly, supplementation with a probiotic-based nutritional supplement for 8 weeks, through increasing the abundance of beneficial taxa such as *Bifidobacterium*, lead to improvements in cognitive and neuromuscular function among individuals with early symptomatic Alzheimer's disease [52,53].

Although dietary modulation and microbiota-targeted therapies represent core components of gut-centered care in ageing populations, they more recently are supplemented with other interdisciplinary strategies capable of modulating redox balance, epithelial regeneration, immune signaling, and microbial ecology through non-nutritional mechanisms. Within this context, molecular hydrogen-based and ozone-based interventions have gained attention due to their favorable effects on redox status along with ability to improve mitochondrial metabolism and immune function, that seem to be affected in older individuals. Given the promising effects of these therapeutic strategies will be further explored to justify their suitability for multimorbidity, chronic inflammation and infection management among aging populations.

#### 4.1. Hydrogen-Based Interventions in Gastrointestinal Health

Building on the rationale for gut-centered strategies in ageing, molecular hydrogen has emerged as a promising non-nutritional intervention targeting oxidative stress, inflammation, and mucosal integrity within the gastrointestinal tract. Age-related dysbiosis, impaired barrier function, and persistent inflammaging disrupt redox homeostasis and mitochondrial function, that lead to microbial imbalance followed by intestinal impairment [47]. Consequently, hydrogen-based interventions such as hydrogen-rich water (HRW), hydrogen-saline, or inhalation have been shown potential to selectively neutralize ROS, modulate pro-inflammatory signaling, and protect epithelial cells from oxidative damage [54]. In addition, early evidence obtained from both experimental and clinical studies indicate that molecular hydrogen can upregulate endogenous antioxidant defenses through activation of the Nrf2 pathway, enhancing expression of cytoprotective enzymes such as heme oxygenase-1 (HO-1) and superoxide dismutase (SOD), that protect intestinal tissues from oxidative injury [47]. In the same time, hydrogen have been shown to downregulate pro-inflammatory pathways, including NF- $\kappa$ B signalling and induce reduced production of proinflammatory mediators, such as TNF- $\alpha$  and IL-6, that were reported to be elevated in aging and chronic GI disorders [18]. In addition, human studies suggest that HRW may also reduce apoptosis in immune cells and have modulatory role on the inflammatory gene networks especially in adults over 30 years of age, what may indicate benefits of molecular hydrogen in mitigating age-related immune dysregulation [18].

Furthermore, interventions with molecular hydrogen demonstrate potential to confer direct gut-specific benefits. HRW have been shown beneficial properties on intestinal tissues that may help in strengthening tight junction proteins, maintaining epithelial integrity, that all together improve permeability and protect the intestinal tissues against inflammation and barrier dysfunction [47]. These effects were attributed to favorable shifts within the gut microbiota composition, including increased abundance of Bifidobacterium, enhanced microbial diversity, and upregulation of butyrate-producing taxa, all of which reinforce gut and systemic health [47]. Notably, studies in older adults indicate that six months long intervention including daily intake of HRW can increase telomere length and influence DNA methylation patterns, suggesting molecular anti-aging effects [47].

Furthermore, small human trial conducted in adults with inflammatory bowel disease or functional gastrointestinal disorders indicated that intervention with HRW (1–2 L/day, 0.5–1.6 ppm H<sub>2</sub>) has potential to improve disease activity indices, reduce CRP and oxidative stress markers, as well as enhance the stool frequency, abdominal comfort, and quality of life [42]. Similarly, inhaling hydrogen (1–4% H<sub>2</sub> in oxygen or air) for 30–60 minutes, 1–2 times daily has been shown to improve gastrointestinal symptoms and ameliorate ileus, as well as improve bowel motility, and reduce oxidative and inflammatory gut markers in critically ill or perioperative patients [55].

Although the results of these studies may suggest hydrogen-based therapies as an adjunctive, redox-modulating therapy that may improve homeostasis of gastrointestinal mucosa, support barrier integrity, and mitigate low-grade inflammation, the robust clinical evidence retrieved from older adults being older than  $\geq 60$ –65-year-old with gastrointestinal endpoints is lacking. The existing trials

include either wide range of age groups or focus on non-GI outcomes, thus the meaning clinical use in geriatrics is currently extrapolative and experimental.

In summary, hydrogen-based interventions represent a complementary, gut-centered strategy capable of restoring redox homeostasis, modulating inflammation, and protecting mucosal integrity in older adults. When integrated with dietary and microbiota-targeted strategies, molecular hydrogen offers a multi-modal approach to maintaining gastrointestinal health and promoting healthy ageing. Despite mechanistic promise and early clinical evidence, implementation in geriatric practice remains limited, highlighting the need for larger, well-controlled trials to define optimal dosing, duration, and long-term benefits.

#### 4.2. Ozone-Based Therapies in GI and Infection Control

Ozone therapy has emerged as a promising gut-centered, non-nutritional intervention for ageing populations, particularly in the context of dysbiosis, impaired mucosal immunity, and compromised gut barrier integrity, which increase susceptibility to infections and systemic inflammation [47]. Ozonated water administered via gaseous insufflation or rectal/colonic application, ozone demonstrated antimicrobial, immunomodulatory, and tissue-regenerative properties, while enhancing oxygenation and redox balance in intestinal tissues. Preclinical studies demonstrate that ozone can reduce microbial pathogenicity, stimulate epithelial repair, and modulate inflammatory signaling, thereby mitigating inflammation and supporting mucosal immune competence. These mechanisms position ozone as a logical adjunct to dietary and microbiota-targeted therapies, offering a multi-modal strategy to improve gastrointestinal resilience and systemic homeostasis in older adults.

Ozone therapy also exerts systemic benefits relevant to geriatric care, particularly through effects on the vascular system. By enhancing red blood cell glycolysis and improving oxygen delivery to hypoxic tissues, ozone improves microcirculation, vascular elasticity, and tissue oxygenation, supporting the renal–cardiovascular axis and reducing thrombosis risk [56].

Activation of antioxidant pathways, including Nrf2-mediated upregulation of superoxide dismutase, catalase, and glutathione peroxidase, improves mitochondrial function, endothelial health, and redox homeostasis [57].

Ozone additionally promotes vasculogenic and angiogenesis via hypoxia-inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ) signaling, contributing to tissue repair and neurovascular support [42]. These properties have potential relevance for cognitive function and rehabilitation in older adults experiencing age-related vascular and metabolic decline.

Clinical evidence underscores ozone's utility in wound and ulcer management, particularly in ischemic or refractory lesions. In systemic sclerosis, adjunctive oxygen–ozone therapy significantly increased digital ulcer healing rates (92% vs. 42%;  $p = 0.01$ ) and improved disability scores compared with standard care alone [58]. Ozonated oil formulations reduced chronic venous ulcer surface area by up to 73% over 30 days, with 25% achieving complete healing, highlighting combined antimicrobial and pro-repair effects [59]. In diabetic foot ulcers (DFUs), ozone therapy effectively reduced bacterial colony counts, emphasizing its role in infection control even when structural healing outcomes were not significantly altered [60]. Adjunctive topical hyaluronic acid further supports tissue hydration and extracellular matrix integrity, enhancing healing rates in chronic ulcers [61]. These findings suggest broader applicability of ozone in geriatric care, offering low-risk, non-pharmacological interventions for tissue repair and functional recovery.

Ozone also addresses the critical challenge of infection control in geriatric chronic wounds, particularly given the high prevalence of multidrug-resistant organisms (MDROs) such as MRSA, MDR Acinetobacter, and ESBL-producing Enterobacteriaceae [6,62,63]. Chronic wounds in elderly populations often harbor polymicrobial biofilms that resist conventional antibiotics [39,64,65]. Ozone exhibits broad-spectrum antimicrobial properties, that combined with its tissue-regenerative effects, provide a dual benefit including reducing pathogen load while promoting epithelial and vascular repair.

Experimental studies also suggest a potential influence of ozone on the gut–brain axis. Low-dose ozone exposure in animal models reduced amyloid-beta accumulation and improved cognitive performance, consistent with a response in which mild oxidative stress activates protective cellular pathways [4]. Although these findings are limited to preclinical studies and have no direct clinical application, they indicate that ozone’s redox-modulating effects may extend beyond local gastrointestinal action, with systemic implications for aging tissues.

Collectively, these data indicate that ozone-based therapies offer multifaceted benefits in older adults: enhancing mucosal barrier function, controlling infection, promoting tissue regeneration, improving vascular and microcirculatory function, and potentially supporting neuromuscular and cognitive outcomes. Despite promising early evidence, implementation in routine geriatric practice remains limited, highlighting the need for further clinical trials to establish standardized protocols, dosing, and long-term safety in aging populations.

## 5. Economic and Accessibility Considerations of Hydrogen- and Ozone-Based Interventions in Geriatric Gastrointestinal Care

Beyond clinical rationale, the practical adoption of hydrogenated and ozonated water therapies in older adults depends on economic accessibility, technological scalability, and consumer behavior. These factors are particularly relevant in geriatric care, where affordability and feasibility strongly influence the implementation of non-pharmacological interventions for gastrointestinal health.

Hydrogenated water is produced by dissolving molecular hydrogen ( $H_2$ ) into water via electrolysis or specialized cartridges. This process requires advanced equipment and energy input, resulting in higher retail prices that may limit widespread use in geriatric populations [66].

In contrast, ozonated water is generated by dissolving ozone gas ( $O_3$ ) into water using relatively simple and inexpensive ozone generators. These devices are widely available and already employed in hospitals, food processing, and municipal water systems [67] offering a more cost-efficient solution for routine application. Furthermore, ozonated water demonstrated a well-established role as a disinfectant and antimicrobial agent, efficiently eliminating bacteria, viruses, and other contaminants without chemical residues, supporting its cost-effective use in healthcare and institutional settings [68]. For gut-centered applications in older adults, this suggests that ozone may provide immediate, economically defensible benefits through infection control and mucosal protection, while hydrogen’s value is more speculative and likely justified only in niche, high-end wellness contexts.

Beyond gastrointestinal health, research has explored potential relevance to age-related oxidative stress and inflammation, which contribute to neurodegeneration and mucosal vulnerability [69]. Molecular hydrogen may offer neuroprotective and anti-inflammatory effects, but evidence is limited to small-scale human studies and animal models [70]. Ozonated water, although primarily used for microbial control, may indirectly support systemic health and gut function in older adults by reducing microbial load and improving tissue oxygenation [71]. However, neither intervention is currently validated for direct treatment of cognitive decline or dementia, and further research is required to clarify clinical utility.

Comparing these modalities illustrates a clear trade-off between innovation appeal and practical scalability. Hydrogenated water, with higher production costs and luxury positioning, targets consumers willing to pay a premium for potential health benefits. Ozonated water, by contrast, represents an accessible, affordable technology with demonstrated utility for infection control and mucosal protection. Its economic advantage is particularly relevant in institutional and clinical settings where broad adoption is required. The choice between these interventions therefore depends on context, as hydrogen may suit individualized wellness programs, while ozone offers measurable cost-effectiveness for larger-scale geriatric care focused on gut health.

Hydrogenated and ozonated water therapies exemplify the intersection of scientific promise, economic feasibility, and consumer behavior. In the context of geriatric gastrointestinal care, cost, accessibility, and scalability are key determinants of real-world implementation. While hydrogenated water may serve as a high-value adjunct in personalized wellness strategies, ozonated water provides

a more practical, evidence-backed option for infection control, mucosal support, and systemic resilience in older adults. These economic considerations are critical when evaluating the integration of non-nutritional gut-centered interventions alongside dietary and pharmacological strategies in aging populations.

## 6. Conclusions

Aging is accompanied by complex, interrelated changes in gastrointestinal structure, function, and immunity, which collectively amplify vulnerability to infection, chronic inflammation, and systemic multimorbidity. Declines in gut barrier integrity, microbial diversity, and mucosal immune function influenced by multiple medications use, metabolic disorders, and lifestyle factors, that position the gastrointestinal tract as both a driver and amplifier of age-related physiological decline. These alterations underscore the critical need for gut-centered interventions that go beyond conventional dietary strategies to support immune competence, microbial homeostasis, and tissue resilience in older adults.

Evidence from preclinical and early clinical studies highlights the potential of hydrogen- and ozone-based therapies as adjunctive, non-nutritional interventions targeting key mechanisms of ageing-related gut vulnerability. Molecular hydrogen exerts selective antioxidant and anti-inflammatory effects, preserves epithelial integrity, and modulates gut microbiota, while ozone demonstrates broad antimicrobial, immunoregulatory, and tissue-reparative properties, with additional benefits for vascular function and systemic redox balance. Both modalities show promise in supporting mucosal health, reducing infection risk, and mitigating oxidative stress, although rigorous, age-specific clinical trials remain limited.

Economic and practical considerations further differentiate these interventions. Hydrogenated water, though mechanistically promising, is often positioned as a premium wellness product, whereas ozonated water offers a more accessible, scalable, and cost-effective approach for broader geriatric care. In both cases, integration into routine practice requires careful evaluation of feasibility, evidence strength, and target populations.

In summary, gut-centered care in aging should encompass a multimodal framework that combines dietary and microbiota-targeted strategies with emerging non-nutritional therapies, such as molecular hydrogen and medical ozone. These approaches hold potential not only to preserve gastrointestinal integrity and immune resilience but also to improve functional outcomes, quality of life, and overall health span in older adults. Future research should prioritize well-designed, age-specific trials to clarify optimal dosing, long-term safety, and clinical efficacy, thereby translating mechanistic promise into practical interventions that support healthy ageing.

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## References

1. S. R. Chowdhury, D. Chandra Das, T. C. Sunna, J. Beyene, and A. Hossain, 'Global and regional prevalence of multimorbidity in the adult population in community settings: a systematic review and meta-analysis', *eClinicalMedicine*, vol. 57, p. 101860, Mar. 2023, doi: 10.1016/j.eclinm.2023.101860.
2. R. Ofori-Asenso, K. L. Chin, A. J. Curtis, E. Zomer, S. Zoungas, and D. Liew, 'Recent Patterns of Multimorbidity Among Older Adults in High-Income Countries', *Popul. Health Manag.*, vol. 22, no. 2, pp. 127–137, Apr. 2019, doi: 10.1089/pop.2018.0069.
3. M. L. Cristina, A. M. Spagnolo, L. Giribone, A. Demartini, and M. Sartini, 'Epidemiology and Prevention of Healthcare-Associated Infections in Geriatric Patients: A Narrative Review', *Int. J. Environ. Res. Public Health*, vol. 18, no. 10, p. 5333, May 2021, doi: 10.3390/ijerph18105333.
4. L. Björkhem-Bergman, T. Schultz, and P. Strang, 'Age and co-morbidities as independent risk factors of infections leading to hospital admission in the last year of life among the elderly: A retrospective registry-based study', *Ups. J. Med. Sci.*, vol. 129, p. e10504, Mar. 2024, doi: 10.48101/ujms.v129.10504.
5. Z. Liu *et al.*, 'Immunosenescence: molecular mechanisms and diseases', *Signal Transduct. Target. Ther.*, vol. 8, no. 1, p. 200, May 2023, doi: 10.1038/s41392-023-01451-2.
6. A. Panda *et al.*, 'Human innate immunosenescence: causes and consequences for immunity in old age', *Trends Immunol.*, vol. 30, no. 7, pp. 325–333, July 2009, doi: 10.1016/j.it.2009.05.004.
7. E. Grebenciucova and J. R. Berger, 'Immunosenescence: the Role of Aging in the Predisposition to Neuro-Infectious Complications Arising from the Treatment of Multiple Sclerosis', *Curr. Neurol. Neurosci. Rep.*, vol. 17, no. 8, p. 61, Aug. 2017, doi: 10.1007/s11910-017-0771-9.
8. A. Moskalev, I. Stambler, and C. Caruso, 'Innate and Adaptive Immunity in Aging and Longevity: The Foundation of Resilience', *Aging Dis.*, vol. 11, no. 6, p. 1363, 2020, doi: 10.14336/AD.2020.0603.
9. R. E. Thomas, 'Pneumococcal Pneumonia and Invasive Pneumococcal Disease in Those 65 and Older: Rates of Detection, Risk Factors, Vaccine Effectiveness, Hospitalisation and Mortality', *Geriatrics*, vol. 6, no. 1, p. 13, Feb. 2021, doi: 10.3390/geriatrics6010013.
10. J. Eeuwijk, G. Ferreira, J. P. Yarzabal, and M. Robert-Du Ry Van Beest Holle, 'A Systematic Literature Review on Risk Factors for and Timing of Clostridioides difficile Infection in the United States', *Infect. Dis. Ther.*, vol. 13, no. 2, pp. 273–298, Feb. 2024, doi: 10.1007/s40121-024-00919-0.
11. S. Kassem, N. Hijazi, N. Stein, A. Zaina, and M. Ganaim, 'Clinical outcomes of clostridioides difficile infection in the very elderly', *Intern. Emerg. Med.*, vol. 19, no. 4, pp. 1041–1049, June 2024, doi: 10.1007/s11739-024-03580-0.
12. M. Ganci, H. Butt, J. Tyrrell, E. Suleyman, and M. Ball, 'The effect of Blastocystis sp. and Dientamoeba fragilis on psychological symptom severity in a sample of clinically diverse males and females', *Curr. Psychol.*, vol. 42, no. 5, pp. 4017–4030, Feb. 2023, doi: 10.1007/s12144-021-01700-z.
13. J. Caudet, M. Trelis, S. Cifre, J. M. Soriano, H. Rico, and J. F. Merino-Torres, 'Interplay between Intestinal Bacterial Communities and Unicellular Parasites in a Morbidly Obese Population: A Neglected Trinomial', *Nutrients*, vol. 14, no. 15, p. 3211, Aug. 2022, doi: 10.3390/nu14153211.
14. Y. Xu *et al.*, 'The Roles of the Gut Microbiota and Chronic Low-Grade Inflammation in Older Adults With Frailty', *Front. Cell. Infect. Microbiol.*, vol. 11, p. 675414, July 2021, doi: 10.3389/fcimb.2021.675414.
15. F. L. Iber, P. A. Murphy, and E. S. Connor, 'Age-Related Changes in the Gastrointestinal System: Effects on Drug Therapy', *Drugs Aging*, vol. 5, no. 1, pp. 34–48, July 1994, doi: 10.2165/00002512-199405010-00004.
16. D. Rémond *et al.*, 'Understanding the gastrointestinal tract of the elderly to develop dietary solutions that prevent malnutrition', *Oncotarget*, vol. 6, no. 16, pp. 13858–13898, June 2015, doi: 10.18632/oncotarget.4030.
17. D. Rémond *et al.*, 'Understanding the gastrointestinal tract of the elderly to develop dietary solutions that prevent malnutrition', *Oncotarget*, vol. 6, no. 16, pp. 13858–13898, June 2015, doi: 10.18632/oncotarget.4030.
18. Y. Wu, J. Xu, X. Rong, F. Wang, H. Wang, and C. Zhao, 'Gut microbiota alterations and health status in aging adults: From correlation to causation', *AGING Med.*, vol. 4, no. 3, pp. 206–213, Sept. 2021, doi: 10.1002/agm2.12167.
19. K. Schütte *et al.*, 'Impact of healthy aging on active bacterial assemblages throughout the gastrointestinal tract', *Gut Microbes*, vol. 13, no. 1, p. 1966261, Jan. 2021, doi: 10.1080/19490976.2021.1966261.

20. Y. Wu, J. Xu, X. Rong, F. Wang, H. Wang, and C. Zhao, 'Gut microbiota alterations and health status in aging adults: From correlation to causation', *AGING Med.*, vol. 4, no. 3, pp. 206–213, Sept. 2021, doi: 10.1002/agm2.12167.
21. A. M. Fretts *et al.*, 'Association of Trimethylamine *N* -Oxide and Metabolites With Mortality in Older Adults', *JAMA Netw. Open*, vol. 5, no. 5, p. e2213242, May 2022, doi: 10.1001/jamanetworkopen.2022.13242.
22. E. M. Brunt, C. G. Janney, A. M. Di Bisceglie, B. A. Neuschwander-Tetri, and B. R. Bacon, 'Nonalcoholic steatohepatitis: a proposal for grading and staging the histological lesions', *Am. J. Gastroenterol.*, vol. 94, no. 9, pp. 2467–2474, Sept. 1999, doi: 10.1111/j.1572-0241.1999.01377.x.
23. L. Gould *et al.*, 'Chronic wound repair and healing in older adults: Current status and future research', *Wound Repair Regen.*, vol. 23, no. 1, pp. 1–13, Jan. 2015, doi: 10.1111/wrr.12245.
24. J. K. Abankwah *et al.*, 'Gut aging: A wane from the normal to repercussion and gerotherapeutic strategies', *Heliyon*, vol. 10, no. 19, p. e37883, Oct. 2024, doi: 10.1016/j.heliyon.2024.e37883.
25. X. Xue *et al.*, 'Multimorbidity patterns and influencing factors in older Chinese adults: a national population-based cross-sectional survey', *J. Glob. Health*, vol. 15, p. 04051, Feb. 2025, doi: 10.7189/jogh.15.04051.
26. A. Kumar and S. Yadav, 'Towards a new perspective: Exploring the variability of conditional risk factors for multimorbidity susceptibility among older adults in India', *PLOS One*, vol. 20, no. 6, p. e0323890, June 2025, doi: 10.1371/journal.pone.0323890.
27. W. Liu *et al.*, 'Oxidative Stress Factors Mediate the Association Between Life's Essential 8 and Accelerated Phenotypic Aging: NHANES 2005–2018', *J. Gerontol. Ser. A*, vol. 79, no. 1, p. glad240, Jan. 2024, doi: 10.1093/gerona/glad240.
28. Q. Liu *et al.*, 'Identification and trajectory of multimorbidity patterns among older people in China: a longitudinal study based on the China health and retirement longitudinal study 2011–2020 data', *Front. Public Health*, vol. 13, p. 1597224, July 2025, doi: 10.3389/fpubh.2025.1597224.
29. H.-C. Hsu, 'Trajectories of multimorbidity and impacts on successful aging', *Exp. Gerontol.*, vol. 66, pp. 32–38, June 2015, doi: 10.1016/j.exger.2015.04.005.
30. B. Ahmadi *et al.*, 'Multimorbidity: Epidemiology and Risk Factors in the Golestan Cohort Study, Iran A Cross-Sectional Analysis', *Medicine (Baltimore)*, vol. 95, no. 7, p. e2756, Feb. 2016, doi: 10.1097/MD.0000000000002756.
31. M. V. Lenti *et al.*, 'Mortality rate and risk factors for gastrointestinal bleeding in elderly patients', *Eur. J. Intern. Med.*, vol. 61, pp. 54–61, Mar. 2019, doi: 10.1016/j.ejim.2018.11.003.
32. H.-G. Zhang, J.-F. Wang, A. Jialin, X.-Y. Zhao, C. Wang, and W. Deng, 'Relationship between multimorbidity burden and depressive symptoms in older Chinese adults: A prospective 10-year cohort study', *J. Affect. Disord.*, vol. 389, p. 119714, Nov. 2025, doi: 10.1016/j.jad.2025.119714.
33. S. Zhang *et al.*, 'Six-Year Change in QT Interval Duration and Risk of Incident Heart Failure — A Secondary Analysis of the Atherosclerosis Risk in Communities Study —', *Circ. J.*, vol. 85, no. 5, pp. 640–646, Apr. 2021, doi: 10.1253/circj.CJ-20-0719.
34. S. Soenen, C. K. Rayner, K. L. Jones, and M. Horowitz, 'The ageing gastrointestinal tract', *Curr. Opin. Clin. Nutr. Metab. Care*, vol. 19, no. 1, pp. 12–18, Jan. 2016, doi: 10.1097/MCO.0000000000000238.
35. M. Camilleri, 'The aging gastrointestinal tract: digestive and motility problems', in *Yamada's Textbook of Gastroenterology*, 1st edn, T. C. Wang, M. Camilleri, B. Leibold, A. S. Lok, W. J. Sandborn, K. K. Wang, and G. D. Wu, Eds, Wiley, 2022, pp. 505–511. doi: 10.1002/9781119600206.ch26.
36. Z. Ling, X. Liu, Y. Cheng, X. Yan, and S. Wu, 'Gut microbiota and aging', *Crit. Rev. Food Sci. Nutr.*, vol. 62, no. 13, pp. 3509–3534, May 2022, doi: 10.1080/10408398.2020.1867054.
37. N. Bosco and M. Noti, 'The aging gut microbiome and its impact on host immunity', *Genes Immun.*, vol. 22, no. 5–6, pp. 289–303, Oct. 2021, doi: 10.1038/s41435-021-00126-8.
38. L. S. Hohman and L. C. Osborne, 'A gut-centric view of aging: Do intestinal epithelial cells contribute to age-associated microbiota changes, inflammaging, and immunosenescence?', *Aging Cell*, vol. 21, no. 9, p. e13700, Sept. 2022, doi: 10.1111/acel.13700.
39. F. Sanada *et al.*, 'Source of Chronic Inflammation in Aging', *Front. Cardiovasc. Med.*, vol. 5, p. 12, Feb. 2018, doi: 10.3389/fcvm.2018.00012.

40. N. Theodorakis *et al.*, 'Immunosenescence: How Aging Increases Susceptibility to Bacterial Infections and Virulence Factors', *Microorganisms*, vol. 12, no. 10, p. 2052, Oct. 2024, doi: 10.3390/microorganisms12102052.
41. H. Zheng, C. Zhang, Q. Wang, S. Feng, Y. Fang, and S. Zhang, 'The impact of aging on intestinal mucosal immune function and clinical applications', *Front. Immunol.*, vol. 13, p. 1029948, Nov. 2022, doi: 10.3389/fimmu.2022.1029948.
42. X. Li, C. Li, W. Zhang, Y. Wang, P. Qian, and H. Huang, 'Inflammation and aging: signaling pathways and intervention therapies', *Signal Transduct. Target. Ther.*, vol. 8, no. 1, p. 239, June 2023, doi: 10.1038/s41392-023-01502-8.
43. T. Teissier, E. Boulanger, and L. S. Cox, 'Interconnections between Inflammageing and Immunosenescence during Ageing', *Cells*, vol. 11, no. 3, p. 359, Jan. 2022, doi: 10.3390/cells11030359.
44. H. Y. Chung *et al.*, 'Molecular inflammation: Underpinnings of aging and age-related diseases', *Ageing Res. Rev.*, vol. 8, no. 1, pp. 18–30, Jan. 2009, doi: 10.1016/j.arr.2008.07.002.
45. J. Conway *et al.*, 'Age-related loss of intestinal barrier integrity plays an integral role in thymic involution and T cell ageing', *Aging Cell*, vol. 24, no. 3, p. e14401, Mar. 2025, doi: 10.1111/accel.14401.
46. M. E. Caetano-Silva *et al.*, 'Aging amplifies a gut microbiota immunogenic signature linked to heightened inflammation', *Aging Cell*, vol. 23, no. 8, p. e14190, Aug. 2024, doi: 10.1111/accel.14190.
47. S. Donati Zeppa *et al.*, 'Interventions on Gut Microbiota for Healthy Aging', *Cells*, vol. 12, no. 1, p. 34, Dec. 2022, doi: 10.3390/cells12010034.
48. S. L. Crowder *et al.*, 'Cancer-Related Cognitive Impairment and the Potential of Dietary Interventions for the Prevention and Mitigation of Neurodegeneration', *Cancer Res.*, vol. 85, no. 2, pp. 203–217, Jan. 2025, doi: 10.1158/0008-5472.CAN-24-3041.
49. J. Lee, S. Kim, Y. Lee, Y.-J. Kwon, and J.-W. Lee, 'Higher Adherence to the Mediterranean Diet Is Associated with a Lower Risk of Steatotic, Alcohol-Related, and Metabolic Dysfunction-Associated Steatotic Liver Disease: A Retrospective Analysis', *Nutrients*, vol. 16, no. 20, p. 3551, Oct. 2024, doi: 10.3390/nu16203551.
50. J. Yang *et al.*, 'Prebiotics improve frailty status in community-dwelling older individuals in a double-blind, randomized, controlled trial', *J. Clin. Invest.*, vol. 134, no. 18, p. e176507, Sept. 2024, doi: 10.1172/JCI176507.
51. T. M. Freijy *et al.*, 'Effects of a high-prebiotic diet versus probiotic supplements versus synbiotics on adult mental health: The "Gut Feelings" randomised controlled trial', *Front. Neurosci.*, vol. 16, p. 1097278, Feb. 2023, doi: 10.3389/fnins.2022.1097278.
52. Y. S. Handajani, Y. Turana, A. Hengky, G. Hamid, E. Schroeder-Butterfill, and K. Kristian, 'Probiotics supplementation or probiotic-fortified products on sarcopenic indices in older adults: systematic review and meta-analysis from recent randomized controlled trials', *Front. Aging*, vol. 5, p. 1307762, Feb. 2024, doi: 10.3389/fragi.2024.1307762.
53. E. H. Lee *et al.*, 'Effects of the multidomain intervention with nutritional supplements on cognition and gut microbiome in early symptomatic Alzheimer's disease: a randomized controlled trial', *Front. Aging Neurosci.*, vol. 15, p. 1266955, Nov. 2023, doi: 10.3389/fnagi.2023.1266955.
54. S. Wu, X. Liu, R. Jiang, X. Yan, and Z. Ling, 'Roles and Mechanisms of Gut Microbiota in Patients With Alzheimer's Disease', *Front. Aging Neurosci.*, vol. 13, p. 650047, May 2021, doi: 10.3389/fnagi.2021.650047.
55. H. Sakata *et al.*, 'Inhaled hydrogen ameliorates endotoxin-induced bowel dysfunction', *Acute Med. Surg.*, vol. 4, no. 1, pp. 38–45, Jan. 2017, doi: 10.1002/ams2.218.
56. J. D. Reynolds *et al.*, 'Pharmacologic Targeting of Red Blood Cells to Improve Tissue Oxygenation', *Clin. Pharmacol. Ther.*, vol. 104, no. 3, pp. 553–563, Sept. 2018, doi: 10.1002/cpt.979.
57. E. Ogut, 'Mechanisms and therapeutic potential of ozone therapy in enhancing vasculogenesis and angiogenesis through growth factor activation and oxidative signaling pathways', *Discov. Med.*, vol. 2, no. 1, p. 240, Sept. 2025, doi: 10.1007/s44337-025-00491-7.
58. S. Kaymaz *et al.*, 'Efficacy of local oxygen–ozone therapy for the treatment of digital ulcer refractory to medical therapy in systemic sclerosis: A randomized controlled study', *Mod. Rheumatol.*, vol. 32, no. 6, pp. 1102–1107, Oct. 2022, doi: 10.1093/mr/roab117.
59. L. G. Solovăstru, A. Stîncanu, A. De Ascentii, G. Capparé, P. Mattana, and D. Vâță, 'Randomized, Controlled Study of Innovative Spray Formulation Containing Ozonated Oil and  $\alpha$ -Bisabolol in the Topical

- Treatment of Chronic Venous Leg Ulcers', *Adv. Skin Wound Care*, vol. 28, no. 9, pp. 406–409, Sept. 2015, doi: 10.1097/01.ASW.0000470155.29821.ed.
60. K. Kadir, Y. Syam, S. Yusuf, and M. Zainuddin, 'Ozone Therapy on Reduction of Bacterial Colonies and Acceleration of Diabetic Foot Ulcer Healing', *Home Healthc. Now*, vol. 38, no. 4, pp. 215–220, July 2020, doi: 10.1097/NHH.0000000000000889.
  61. P. Humbert, J. Mikosinki, H. Benchikhi, and F. Allaert, 'Efficacy and safety of a gauze pad containing hyaluronic acid in treatment of leg ulcers of venous or mixed origin: a double-blind, randomised, controlled trial', *Int. Wound J.*, vol. 10, no. 2, pp. 159–166, Apr. 2013, doi: 10.1111/j.1742-481X.2012.00957.x.
  62. V. Papadopoulou *et al.*, 'Overcoming biological barriers to improve treatment of a Staphylococcus aureus wound infection', *Cell Chem. Biol.*, vol. 30, no. 5, pp. 513–526.e5, May 2023, doi: 10.1016/j.chembiol.2023.04.009.
  63. V. Puca *et al.*, 'Microbial Species Isolated from Infected Wounds and Antimicrobial Resistance Analysis: Data Emerging from a Three-Years Retrospective Study', *Antibiotics*, vol. 10, no. 10, p. 1162, Sept. 2021, doi: 10.3390/antibiotics10101162.
  64. M. C. B. Ammons, L. S. Ward, S. T. Fisher, R. D. Wolcott, and G. A. James, 'In vitro susceptibility of established biofilms composed of a clinical wound isolate of Pseudomonas aeruginosa treated with lactoferrin and xylitol', *Int. J. Antimicrob. Agents*, vol. 33, no. 3, pp. 230–236, Mar. 2009, doi: 10.1016/j.ijantimicag.2008.08.013.
  65. K. Raziyeva, Y. Kim, Z. Zharkinbekov, K. Kassymbek, S. Jimi, and A. Saparov, 'Immunology of Acute and Chronic Wound Healing', *Biomolecules*, vol. 11, no. 5, p. 700, May 2021, doi: 10.3390/biom11050700.
  66. S. Shirahata *et al.*, 'Electrolyzed-Reduced Water Scavenges Active Oxygen Species and Protects DNA from Oxidative Damage', *Biochem. Biophys. Res. Commun.*, vol. 234, no. 1, pp. 269–274, May 1997, doi: 10.1006/bbrc.1997.6622.
  67. B. L. Loeb, 'Ozone: Science & Engineering Thirty Years of Progress', *Ozone Sci. Eng.*, vol. 31, no. 5, pp. 379–392, Sept. 2009, doi: 10.1080/01919510903091854.
  68. H. Hong, M. F. Rizzi, D. Wang, L. McLandsborough, and J. Lu, 'A Meta-Analysis on the Antimicrobial Effectiveness of Ozonated Water Treatments for Fresh Produce Washing—Effect of Ozonation Methods', *Foods*, vol. 13, no. 23, p. 3906, Dec. 2024, doi: 10.3390/foods13233906.
  69. J. C. Park, L. Chang, H.-K. Kwon, and S.-H. Im, 'Beyond the gut: decoding the gut-immune-brain axis in health and disease', *Cell. Mol. Immunol.*, vol. 22, no. 11, pp. 1287–1312, Aug. 2025, doi: 10.1038/s41423-025-01333-3.
  70. W. Chen, H.-T. Zhang, and S.-C. Qin, 'Neuroprotective Effects of Molecular Hydrogen: A Critical Review', *Neurosci. Bull.*, vol. 37, no. 3, pp. 389–404, Mar. 2021, doi: 10.1007/s12264-020-00597-1.
  71. Q. Wang *et al.*, 'Ozone controls the metabolism of tryptophan protecting against sepsis-induced intestinal damage by activating aryl hydrocarbon receptor', *World J. Gastroenterol.*, vol. 31, no. 17, May 2025, doi: 10.3748/wjg.v31.i17.105411.

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