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Gut-vitamin D interplay: key to mitigating immunosenescence and promoting healthy ageing

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Abstract

Background Immunosenescence is the loss and change of immunological organs, as well as innate and adaptive immune dysfunction with ageing, which can lead to increased sensitivity to infections, age-related diseases, and cancer. Emerging evidence highlights the role of gut-vitamin D axis in the regulation of immune ageing, influencing chronic inflammation and systemic health. This review aims to explore the interplay between the gut microbiota and vitamin D in mitigating immunosenescence and preventing against chronic inflammation and age-related diseases.

Main text Gut microbiota dysbiosis and vitamin D insufficiency accelerate immunosenescence and risk of chronic diseases. Literature data reveal that vitamin D modulates gut microbiota diversity and composition, enhances immune resilience, and reduce systemic inflammation. Conversely, gut microbiota influences vitamin D metabolism to promote the synthesis of active vitamin D metabolites with implications for immune health.

Conclusions These findings underscore the potential of targeting gut-vitamin D axis to modulate immune responses, delay the immune ageing, and mitigate age-related diseases. Further research is needed to integrate vitamin D supplementation and microbiome modulation into strategies aimed at promoting healthy ageing.

Keywords Gut microbiota, Vitamin D, Immune ageing, Immunosenescence, Healthy ageing

Introduction

Senescence, also known as biological ageing, is a key element in the development of chronic diseases due to diminished stress response and homeostasis. Age-related problems, including neurological diseases, malignancies, cardiovascular disorders, and bone and joint maladies, are mostly caused by immunological, metabolic, and circulatory function decline. As the proportion of people over 60 years old is growing worldwide, age-related illnesses become more prevalent [1]. Roy Walford termed a weak immune system as '*immunosenescence*', which is known to play a central role in ageing-associated diseases. Immunosenescence refers to the loss and modification of immunological organs, as well as innate and adaptive immune malfunction with ageing, which may lead to poor vaccination outcomes and increased vulnerability to infections, age-related diseases, and cancer [2]. Several changes associated with immunosenescence are being observed such as thymic involution, hematopoietic stem cell (HSC) dysfunction, disrupted naïve/memory ratio in T and B cells, mitochondrial dysfunction, inflammageing, accumulated senescent cells, genomic instability, and impaired new antigen response [3–5], though the full extent of biological changes is yet to know. Thymic

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involution is known to play a role in imbalanced immune cells proportions, in particular for T-cells. Thymic involution can be described by the disappearance of epithelial spaces in thymus as a result of thymic atrophies and gradual filling of perivascular spaces with elderly thymus, resulting in decreased naïve T cells, increased peripheral late-differentiated memory T-cells, and reduced migration of naïve T cells to the periphery [6–8]. Inflammageing, characterized by systemic, chronic low-grade inflammation, is regarded as a key hallmark of ageing. It is thought to arise from the accumulation of damaged macromolecules, with chronic tissue injury often linked to host-derived cellular debris [9]. Cellular senescence is central to inflammageing, as senescent cells adopt a unique senescence-associated secretory phenotype (SASP), releasing numerous soluble factors, including interleukins (IL-1, IL-6, IL-8, IL-13, and IL-18) and tumor necrosis factor (TNF-α) [10–13]. With the progressing ageing of immune system, metabolic system also undergoes certain changes including increased glycolysis, mitochondrial dysfunction, and oxidative stress [14, 15]. Altogether these features of immunosenescence are linked to increased mortalities and morbidities associated with age-related diseases [16, 17].

Vitamin D, '*the sunshine vitamin*' represents mainly two forms of sterols or prohormones including vitamin D3 (cholecalciferol) synthesized from a cholesterol precursor via ultraviolet activity and vitamin D2 (ergocalciferol) obtained from plant sterols or yeasts. Both of these prohormones require conversion to active form of vitamin D via two hydroxylation reactions for biological activities (Fig. 1). An adequate amount of vitamin D can be obtained from multiple sources such as fortified cereals, grains or dairy, fish (trout and salmon), fish liver oil, aquatic mammal liver, eggs, mushrooms, and margarines [18]. Biologically active form of vitamin D ($1,25(OH)_2D$) possess ability to modulate both innate and adaptive immune cells such as T and B cells, monocytes and macrophages, dendritic cells, neutrophils, and platelets, owing to the expression of vitamin D receptor (VDR) [19]. The $1,25(OH)_2D$ acts on target cells by binding to the VDR in the cytoplasm and heterodimerizing with the retinoid X receptor-α (RXR-α) in the nucleus. This forms the $1,25(OH)_2D$-RXR-VDR complex, which binds to vitamin D response elements (VDRE) on DNA, which allows it to regulate the expression of various genes involved in important physiological processes, like calcium and phosphate homeostasis, immune function, and cell differentiation [20]. Macrophages, neutrophils, or epithelial cells at regions exposed to the external environment absorb circulating 25(OH)D. While the vitamin D metabolism is predominantly carried out in the liver by CYP2R1, some immune cells, also express this enzyme, which allow them to produce $1,25(OH)_2D$, that functions as an intracrine hormone within the target cell. The $1,25(OH)_2D$ generated locally binds to VDR as well as the promoter of genes containing the VDRE, causing an increased production of uncleaved cathelicidin (hCAP18 in humans), which is then cleaved to active cathelicidin (LL37 in humans), which provides protection against bacterial infections. Invading microbes that trigger certain toll-like receptors (i.e., TLR 2/1) result in enhanced production of the VDR and CYP27B1, allowing vitamin D to improve the production of cathelicidin only in the presence of appropriate 25(OH)D substrate [21]. Gut epithelium VDR is also critical in maintaining mucosal barrier integrity and regulating gut innate immunity. The effect of vitamin D on immune cells is complex, as evidenced by the fact that VDR expression in immune cells varies depending on their activation level. For example, T-cells receive a larger concentration of VDR upon activation. Monocytes, on the other hand, decrease VDR expression as they differentiate into macrophages or dendritic cells. Immune cells have the same CYP27B1 enzyme as renal tubules, but it is not regulated by negative feedback from $1,25(OH)_2D$ itself. Because immune cells also express CYP24A1, $1,25(OH)_2D$ regulates it only weakly and is dependent on immune cell activation status. Essentially, vitamin D causes a shift in immunological status toward a more tolerogenic state [22]. Epidemiological studies have linked vitamin D deficiency to dysregulated immune function, resulting in increased vulnerability to infections and autoimmune diseases [23]. Larger systemic reviews showed a protective effects of vitamin D supplementation against acute respiratory infections, possibly due to enhanced cathelicidin expression, regulated cytokine release, and suppressed adaptive response via boosting the innate immune system [24, 25]. Other studies reported lower levels of 25(OH)D in patients with multiple sclerosis (MS), type 1 diabetes mellitus, and systemic lupus erythematosus (SLE) [26, 27].

The concept of human microbiota was first introduced to the scientific community by Joshua Lederberg as "*the ecological community of symbiotic and pathogenic microorganisms that literally share our body space and have been all but ignored as determinants of health and disease*" [28]. The idea that overall health is closely linked to the gut can be traced back to antiquity (400 BC), as reflected in Hippocrates' well-known assertion that "*all disease begins in the gut*", a perspective that continues to gain relevance with ongoing scientific advancements. Extensive research demonstrated that vast number of microorganisms (including bacteria, viruses, archaea, fungi, and protozoans) colonized the human body, particularly the parts exposed to the external environment such as skin, gastrointestinal, genitourinary, and respiratory tracts, whereas gastrointestinal tract is most heavily

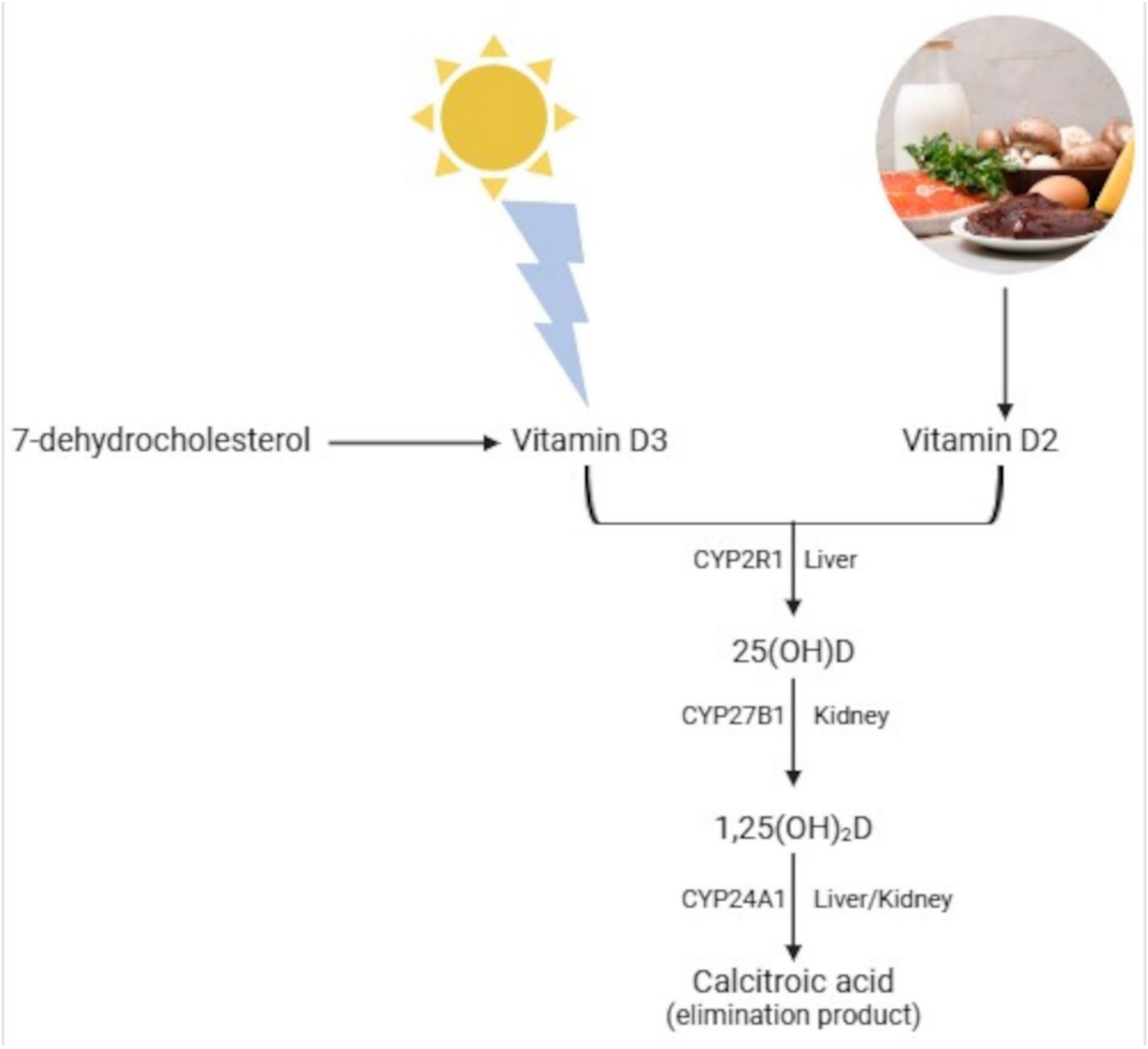

Fig. 1 Cytochrome P450-mediated metabolism of vitamin D

colonized with the microbes, with the colon containing around 70% of total microbes present in the body. Unlike other microbes, bacteria are most widely studied for their beneficial effects to the host, with 10^{14} bacterial cells normally present in human body [29]. Different phyla of gut microbiota have been identified to date, including *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, *Fusobacteria*, *Proteobacteria*, and *Verrucomicrobia* [29]. As evidenced by the literature data, gut microbiota offers numerous physiological benefits to the host such as strengthening the intestinal epithelium, protecting the gut barrier, regulating the mucosal immunity, and protection against pathogenic microbes. Other functions may include, like nutrient absorption, vitamin synthesis, digestion of dietary fibers to produce short chain fatty acids (SCFAs), and metabolism of xenobiotics [30]. Gut bacteria interact dynamically with the host's innate and adaptive immune systems to maintain intestinal homeostasis and suppress inflammatory responses. The metabolism of proteins and complex carbohydrates, synthesis of vitamins, and generation of a large variety of metabolic products can mediate a cross-talk between gut epithelium and immune cells [31]. Dysbiosis of gut microbiota could result in a disturbed interaction between gut bacteria and the mucosal immune system, causing dysregulated immune and inflammatory pathways, which may lead to gut leaky syndrome, increased susceptibility to infections, systemic inflammation and autoimmune reactions [29]. Growing evidence highlights the significant role of numerous dietary factors such as dietary fibers, prebiotics,

probiotics, micronutrients, and spices in shaping the intestinal microbiota, a critical foundation in the prevention of chronic and age-related diseases [32].

Considering that vitamin D deficiency might cause gastrointestinal disease due to its immunomodulatory role, a theory has been proposed regarding a link between vitamin D and gut microbiome. Recent human and animal studies have revealed that vitamin D can influence microbiota composition by promoting gut homeostasis [33] and lowering permeability [34]. However, it remains unclear whether this relationship between vitamin D and gut microbiome could help prevent or delay immune ageing, thereby providing protection against age-related diseases. This comprehensive review is designed to focus on the interplay between gut microbiota and vitamin D to impact the immune ageing, their potential therapeutic roles and implications for age-related diseases.

Interplay between vitamin D and gut microbiota

An association of vitamin D with gut health is well-established. Vitamin D influences disease risk factors through multiple mechanisms, including the modulation of gut microbiota composition and diversity. This modulation can enhance innate immunity, suppress inflammatory pathways, and maintain the intestinal barrier (Fig. 2). The active form of vitamin D ($1,25(OH)_2D$) selectively eliminates pathogenic microbes, creating a favourable environment for the colonization of beneficial bacteria [35]. Furthermore, vitamin D supports the mucosal barrier by promoting the expression of tight and adherent junction proteins and by reducing epithelial cell apoptosis [36]. Additionally, fermentation products generated by gut microbes can increase the expression of VDR in the intestine, which helps regulate pro-inflammatory pathways [37]. Literature data have suggested that vitamin D status and supplementation, both possess a significant impact on the composition of gut microbiota [38–41].

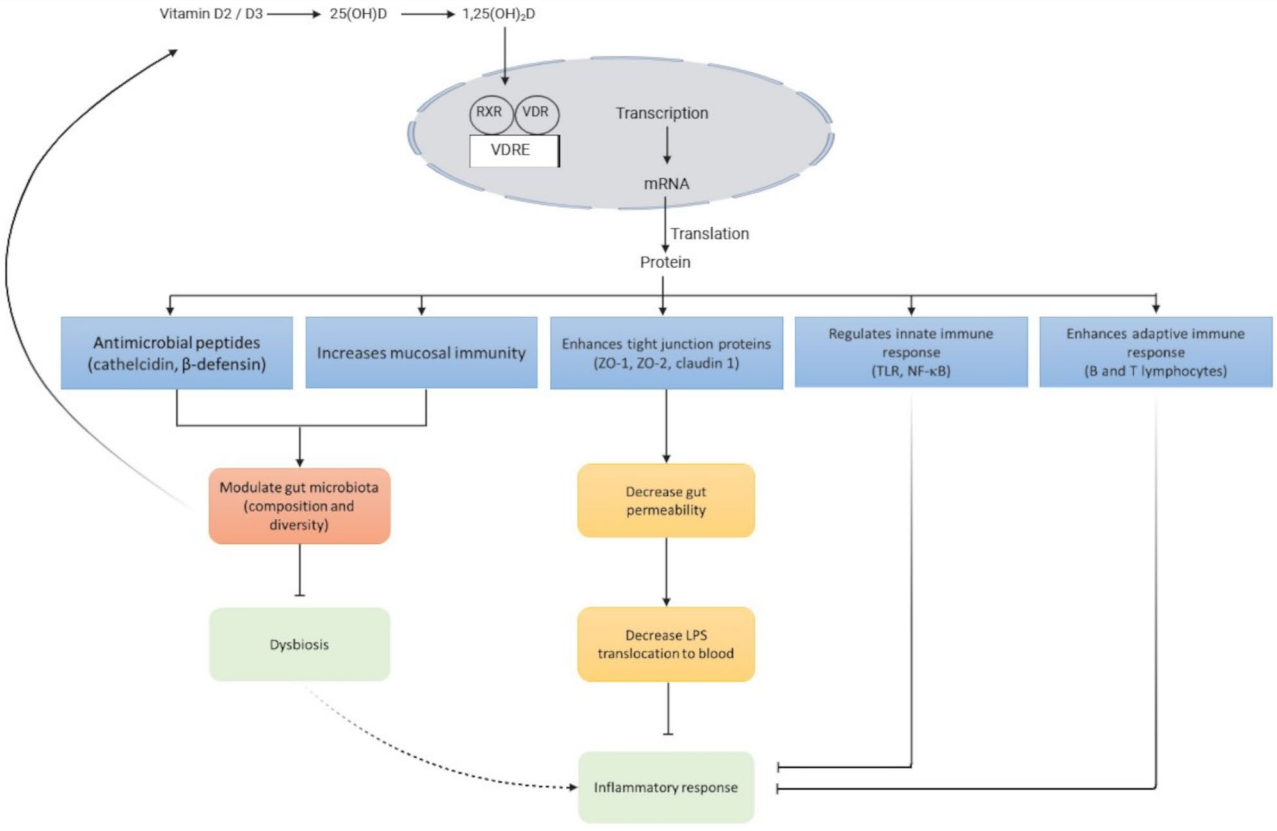

Fig. 2 Schematic representation of the interplay between vitamin D and gut microbiota, emphasizing its impact on immune responses. Vitamin D (both D2 and D3 isoforms) is metabolized into its active form, $1,25(OH)_2D$, which interacts with VDR and RXR to regulate transcription and translation of target genes. The downstream effects include increased production of antimicrobial peptides (e.g., cathelicidin and β-defensin), enhanced mucosal immunity, and improved epithelial barrier integrity through the upregulation of tight junction proteins (e.g., ZO-1, ZO-2, claudin-1). These actions modulate gut microbiota composition and diversity, decrease gut permeability, and reduce translocation of lipopolysaccharides (LPS) into the bloodstream. Additionally, vitamin D modulates both innate and adaptive immune responses, further mitigating inflammatory processes and restoring gut homeostasis, thereby preventing dysbiosis and systemic inflammation. VDR, vitamin D receptor; RXR, retinoid X receptor; VDRE, vitamin D response elements; mRNA, messenger RNA; ZO-1, zonula occludens-1; ZO-2, zonula occludens-2; TLR, toll-like receptors; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; LPS, lipopolysaccharide

Genome-wide association studies (GWAS) demonstrated a strong link of variations in human VDR gene with changes in gut microbiome [42], whereas animal studies have shown gut dysbiosis in case of VDR absence [33]. Wang et al. [42]. reported impact of VDR gene variations on *Parabacterioides*, as VDR knockout mice showed higher levels of genus *Parabacterioides* as compared to wild-type mice. An increase in *Proteobacteria* phyla and *Bacteroidetes* population has been observed proportionally to vitamin D deficiency, CYP27B1 deficiency (vitamin D metabolizing enzyme) or VDR depletion in experimental models [34]. On other hand, vitamin D supplementation had little effect on composition of gut microbiome at phyla level, though considerable impact has been noted on lower taxonomic level. Zhu et al. [43]. observed a reduction in colon mucosal size and enhanced accumulation of *Akkermansia muciniphila* in CYP27B1 knockout mice, attributed to a lack of the active form of vitamin D ($1,25(OH)_2D$). Consequently, this led to greater microbial infiltration into the intestinal mucosa, which triggered inflammation. These results are verified by bioinformatics analysis which showed that colon in VDR knockout mice is more prone to toxins with higher risk of infections and cancer [44].

A cross-sectional study of human subjects demonstrated a positive association of vitamin D intake with *Bacteroides* abundance and an inverse association with *Prevotella* abundance [45]. Another study conducted on overweight or obese individuals demonstrated a decreased abundance of *Ruminococcus*, with increased abundance of *Coprococcus* in subjects with sufficient serum level of vitamin D (>75 nmol/L) [46]. Vitamin D supplementation resulted in decreased levels of *Veillonella* and *Haemophilus* with increased abundance of *Prevotella* in stool samples of healthy subjects [47]. Additionally, serum vitamin D levels also affected bacterial enrichments at the genus level, as higher 25(OH) D levels were correlated with decreased *Veillonella* and *Haemophilus*, and increased *Megasphaera* abundance [47]. Contrarily, a study demonstrated an inverse effect of vitamin D supplementation on *Prevotella* abundance while a strong association was shown on *Bacteroides* in healthy participants [45]. Singh et al. [38]. reported that vitamin D supplementation had a notable impact on gut microbiota diversity, resulting in a higher proportion of *Bacteroidetes* relative to *Firmicutes* and an increased abundance of beneficial microbes, including *Akkermansia* and *Bifidobacterium*. Bashir et al. [41]. found that eight weeks of cholecalciferol supplementation increased *Bacteroidetes* and reduced *Proteobacteria* abundance in the upper gastrointestinal tract, as evidenced by stool samples, endoscopy, and colonoscopy biopsies. However, no significant change was observed in the microbial composition of the lower gastrointestinal tract or feces, indicating that fecal samples may not be appropriate for assessing its effects on microbial communities. Similarly, Seura et al. [48]. also failed to observe any considerable association of vitamin D supplementation and fecal microbial abundance. A study on the pediatric population showed a lower microbial diversity in children with vitamin D deficiency [49]. In particular, higher ratio of *Bacteroidetes* to *Firmicutes* and higher abundance of *Prevotella* than *Bacteroides* was observed in vitamin D deficient subjects. A systematic review of 25 human studies indicated that vitamin D supplementation led to more alterations in the composition of *Firmicutes*, *Bacteroidetes*, and *Actinobacteria* in the gut microbiota [50]. Moreover, both supplementation and higher levels of vitamin D resulted in a reduction in the families of *Oscillospiraceae* and *Veillonellaceae* [50].

The interaction of vitamin D with gut microbiota is not unidirectional, but is a dynamic, bidirectional relationship, as gut microbiota is also reported to play an important role in the metabolism of vitamin D. Numerous enzymes expressed by bacteria are involved in the hydroxylation of steroids including vitamin D [51]. For instance, the bacterial enzyme CYP105A1 expressed by *Streptomyces griseolus* converts cholecalciferol to biologically active form via two consecutive hydroxylations. This function of bacterial enzyme is corresponding to vitamin D metabolizing associated indigenous enzymes such as CYP27A1, CYP27B1, and CYP2R1 [52]. However, it is noteworthy that all enzymes involved in vitamin D metabolism require magnesium as a cofactor for their enzymatic activity in the liver and kidneys. Therefore, adequate magnesium intake is essential to maximize the physiological benefits of vitamin D [53].

The National Center for Biotechnology Information BioSystems database identified homologous proteins for CYP27A1 in *Ruminococcus torques* from the phylum *Firmicutes* and CYP27B1 in *Mycobacterium tuberculosis* [54]. A patent by Bora et al. [55]. (US5474923) details a technique for introducing hydroxyl groups to vitamin D compounds at the 1α-position in the kidney and/or at 25-position in the liver. The method utilizes a mixture containing microorganisms capable of hydroxylating vitamin D or enzymes produced by these microorganisms i.e., microbes from Actinomycetales, including *Nocardia*, *Streptomyces*, *Sphingomonas*, and *Amycolata*). Since FGF23, a pivotal regulator of vitamin D metabolism influenced by the microbiota, plays a critical role, further studies are essential to understand its effects [55, 56]. The mechanisms of vitamin D and gut microbiota interaction have been summarized in Table 1.

Table 1 Mechanisms of vitamin D and gut microbiota interaction

Mechanism	Vitamin D's role	Gut microbiota's role	Implications for health	References
Regulation of tight junction proteins	Enhances expression of proteins like occludin, claudin, and zonula occludens-1	Maintains epithelial barrier integrity by reducing permeability	Protects against leaky gut syndrome and systemic inflammation	[36, 115, 116]
Modulation of immune response	Shifts immune response toward anti-inflammatory pathways (e.g., IL-10 production)	Produces SCFAs to enhance Treg differentiation and reduce inflammation	Mitigates chronic inflammation and autoimmunity	[19, 37, 117]
Promotion of beneficial microbes	Selectively enhances growth of bacteria like *Akkermansia muciniphila* and *Bacteroides*	Produces metabolites that increase VDR expression and activity	Strengthens gut-immune homeostasis, reduces risk of dysbiosis	[42, 43, 50]
Hydroxylation of vitamin D	Provides substrate for microbial hydroxylation processes (e.g., 1α and 25-hydroxylation)	Microbial enzymes contribute to activation and recycling of vitamin D	Supports vitamin D metabolism and bioavailability	[52–54]
Suppression of pathogenic microbes	Reduces colonization of pathogens by improving mucosal defenses	Competes with pathogens and suppresses their virulence via SCFA production	Protects against gut infections and inflammation	[21, 36, 62]
Regulation of cytokine production	Balances pro- and anti-inflammatory cytokines (reduces TNF-α, IL-6; enhances IL-10)	Microbial metabolites modulate immune signaling pathways	Prevents overactive immune responses, supports immune tolerance	[37, 116, 117]
Metabolic cross-talk	Enhances gut microbial metabolism via improved substrate availability (e.g., SCFA synthesis)	Fermentation products promote VDR expression and immune modulation	Enhances gut-immune signaling, reduces inflammageing	[37, 38, 97]
Impact on gut microbial composition	Alters phylum-level abundance (e.g., increases *Bacteroidetes/Firmicutes* ratio)	Adjusts microbial diversity in response to vitamin D availability	Restores microbial balance, reduces dysbiosis	[38, 41, 50]

Gut-vitamin D axis and immune ageing

Vitamin D deficiency, gut dysbiosis, and immune ageing

Immune-mediated diseases are linked to vitamin D insufficiency, as the later can affect the gut microbiome and disturb the intestinal epithelial barrier. Vitamin D deficiency is one of the critical factors in gut dysbiosis that silently induces ageing of the immune system, particularly in old-age population. It compromises the mucosal barrier integrity of the intestinal tract, thus predisposing the individual to the risk of intestinal and extra-intestinal diseases [57]. Murine models with vitamin D deficiency showed dysbiosis, low antimicrobial activity, and increased susceptibility to intestinal inflammation [33, 58]. Vitamin D may impact mice's susceptibility to inflammation by altering gut microbiota and regulating the number of retinoid orphan receptor γt (RORγt)/forkhead box P3 $(FoxP3)^+$ regulatory T cells in the colon [59]. A study demonstrated the aggravated gut dysbiosis in the obese male offspring mice due to maternal vitamin D deficiency during pregnancy and lactation [60]. A significantly increased abundance of *Firmicutes* and *Firmicutes*/*Bacteroidetes* ratio, and decreased abundance of *Bacteroidetes* and *Verrucomicrobia*, with enhanced gene expressions of proinflammatory cytokines (CCL2, CCL4, and IL-1β) and reduced levels of intestinal barrier function (Occludin, Zonula Occludens-1 and Claudin-1) were observed in vitamin D deficient group. Vitamin D deficient mice challenged with *Citrobacter rodentium* showed increased colonic hyperplasia and epithelial barrier dysfunction due to altered fecal microbiome composition, as significant increase in the relative abundance of *Firmicutes*, *Bacteroidetes*, *Gammaproteobacteria*, and *Actinobacteria* was observed [34]. It resulted in the increased levels of pro-inflammatory cytokines such as IL-10, IL-17a, TNF-α, and transforming growth factor (TGF-β). A pilot study while assessing the association of gut microbiome and vitamin D deficiency in patients with knee arthritis showed that vitamin D deficiency affected the diversity of *Butyricimonas*, *Parabacteroides*, *Pseudobutyrivibrio*, *Gordonibacter*, and *Odoribacter* [61]. The mice with VDR-deficiency demonstrated depletion of *Lactobacillus* with enrichment of *Bacteroides* and *Clostridium* in the fecal samples, highlighting the potential role of VDR in the regulation of the composition and activity of the gut microbiome [62].

Gut dysbiosis or abnormal changes in gut microbial composition associated with vitamin D insufficiency, can disrupt immunological responses, resulting in inflammation, oxidative stress, and insulin resistance. Chronic dysbiosis and leakage of microbiota across the mucosal barrier can lead to higher risk of type 2 diabetes, cardiovascular disease, autoimmune illness, inflammatory bowel disease, and malignancies [31]. In healthy conditions, some commensal bacteria suppressed the growth of opportunistic infections by SCFAs production, which altered gut pH, as seen in the case of *Bifidobacterium* that lower gut pH during lactose fermentation, resulting in reduced *Escherichia coli* colonization [63, 64]. Commensal bacteria also restrict the growth and/or activity of pathogens by secreting bacterial metabolites, suppressing directly the virulence genes of pathogenic microbes. For example, members of *Enterobacteriaceae* family

consumed the residual oxygen, resulting in low levels of *Shigella* virulence in the gut lumen, where the later need oxygen for the competitive secretion of virulence factors [65]. Emerging evidence suggests that gut microbiome responds dynamically in order to adapt to a constantly changing environment with advancing age, modifying both bacterial species composition and metabolic function. This process is strictly regulated by the host-immune system, which acts as an architect in shaping the gut microbiome by allowing commensal bacteria to grow and occupy mucosal niches while selectively eradicating or neutralizing pathogenic bacteria. As immunological fitness gradually declines with age, surveillance of this dynamic host-microbial handshake is weakened, resulting in broad functional repercussions for host health and immunity, thus causing low-grade inflammation and immunosenescence, two important hallmarks of ageing [66]. Age-related dysbiosis, also known as microbe-ageing, is characterized by a reduction of *Bifidobacterium* and *Clostridiales*, an enrichment in *Proteobacteria*, and an overrepresentation of pathobionts such as *Enterobacteriaceae* [67–69]. In addition to environmental stresses, dietary factors, and certain medications, changes in mucosal niche at intestinal level with advancing age such as alterations in epithelial barrier formation, mucus layer composition, peristalsis, and regenerative capacity also contribute to the dysbiosis of gut microbiome [70, 71]. The present understanding of age-related changes in composition, function, and diversity of gut microbiota has been comprehensively reviewed [72–76].

Numerous preclinical models provide strong scientific evidence of microbe-ageing as the potential driver of immunosenescence and frailty. A study on *Drosophila melanogaster* demonstrated that gut dysbiosis not only lead to but also predicts the onset of age-related mucosal barrier dysfunction and immune activation [77]. Interestingly *D. melanogaster* kept under axenic conditions throughout life showed low rates of ageing [78], suggesting that preventing intestinal dysbiosis can prevent inflammageing while improving immune homeostasis and promoting healthy ageing [79]. While using *Nothobranchius furzeri* (a naturally short-lived vertebrate), Smith et al. [80]. demonstrated long-lasting beneficial systemic effects resulting in extension of life span as a result of heterochronic colonization of aged *N. furzeri* with microbiome from young donors. Colonization of microbiome from young donors led to increased abundance of bacteria that produces metabolites to support immune system health. Similarly, fecal microbiome transplantation (mainly *Akkermansia muciniphila*) improved overall health and lifespan of progeroid mice [81]. Another study showed impaired intestinal integrity and increased insulin resistance as a result of age-related decrease in abundance of *A. muciniphila*, primarily through microbiome-monocyte B cel axis [82]. *A. muciniphila* has also been reported to regulate antigen specific T-cell responses to modulate host immune cell function [83]. Alternatively, transfer of gut microbiome from older mice to young one resulted in leakage of microbial products to the circulation and onset of chronic low-grade inflammation, which led to enhanced T-cell activation in the systemic immune compartment [84]. Inflammageing in this study was further associated with dysregulated macrophage functioning. Donaldson et al. [85]. observed restoration of M-cells maturation in Peyer's patches, increased antigen uptake, and enhanced intestinal IgA responses with exposure of aged mice to microbiome from young donors. Moreover, age-related changes in the composition and diversity of intestinal microbiome may result in impaired hematopoiesis, increased susceptibility to infections and reduced response to vaccinations [86, 87]. Age-related changes in gut microbiome and their implications for immune ageing has been summarized in Table 2.

Gut microbiota, vitamin D, and chronic inflammatory diseases

Together, vitamin D and gut microbiome possess significant immunomodulatory properties and an impact on immune mediated diseases, including those associated with advancing age. Starting with vitamin D and, specifically, autoimmune processes, multiple pieces of evidence suggest that vitamin D insufficiency may be a risk factor for the development of autoimmune illnesses, as linked to altered self-tolerance of immune system in different cell-based models. Importantly, vitamin D deficiency can not only increase the likelihood of developing certain diseases, but it can also exacerbate their symptoms [26, 88]. Gut microbiome on the other hand is closely related with the regulation of host immune system, where dysbiosis of intestinal microbiota is involved in the etiopathogenesis of both intestinal and extra-intestinal diseases. For example, type 1 diabetes is frequently accompanied with a decreased abundance of *Lactobacilli*, *Bifidobacterium*, *Bacteroides*, *Akkermansia*, and *Faecalibacterium*, as these species are responsible for the regulation of glucose metabolism [89]. Similarly, a significant lower *Firmicutes*/*Bacteroidetes* ratio has been observed in SLE [90] and increased *Prevotella* covers has been reported in patients with rheumatoid arthritis [91]. *Firmicutes* are negatively correlated with the disease activity index in SLE [92] while *Prevotella* is known to synthesize Pc-p27 protein, that is responsible to trigger Th1-mediated immune response via binding to HLA-DR (Human Leukocyte Antigen– DR isotype) [91].

Vitamin D supplementation for four weeks resulted in significantly increased abundance of specific microbiota strains including *Alistipes*, *Anaerotruncus*, *Barnesiella*,

Table 2 Age-related changes in gut microbiota composition

Microbial changes with ageing	Contributing factors	Implications for immune ageing	References
Reduced *Bifidobacterium*	Decline in dietary fiber intake, increased oxidative stress	Decreased production of short-chain fatty acids (SCFAs), impaired gut barrier integrity	[66, 67, 71]
Increased *Proteobacteria*	Low-grade inflammation (inflammageing), immune surveillance decline	Enhanced pathobiont colonization, systemic inflammation	[65, 68, 76]
Enrichment of Pathobionts (e.g., *Enterobacteriaceae*)	Impaired immune regulation, changes in gut mucosal niche	Increased susceptibility to infections, gut dysbiosis	[66, 68, 81]
Reduced diversity of microbial species	Reduced mucus secretion, slower intestinal transit, dietary simplification	Weakened resilience against environmental stressors, impaired immune function	[69, 70, 74]
Altered *Firmicutes/Bacteroidetes* ratio	Changes in epithelial barrier integrity, chronic inflammation	Dysregulated immune responses, reduced SCFA production	[66, 69, 75]
Depletion of *Clostridiales*	Reduced dietary fiber fermentation, increased oxidative stress	Impaired Treg induction, increased inflammation	[67, 71, 79]
Reduction in SCFA-producing bacteria (e.g., *Faecalibacterium prausnitzii*)	Reduced metabolic cross-talk between gut and host	Weakened anti-inflammatory responses, enhanced leaky gut syndrome	[70, 74, 77]
Decreased *Akkermansia muciniphila*	Reduced mucin production, impaired intestinal epithelial repair	Increased intestinal permeability, systemic inflammation	[71, 78, 81]
Reduction in commensal bacteria (e.g., *Lactobacillus*)	Chronic inflammation, reduced immune surveillance	Reduced gut homeostasis, enhanced vulnerability to gut pathogens	[66, 67, 82]

Porphyromonadaceae, *Roseburia*, *Ruminococcaceae*, and *Subdoligranulum*, in patients with Chron's disease; however, no such effect was seen in healthy controls [93]. Another study showed a considerable richness of *Enterobacteriaceae* in patients with ulcerative colitis after eight weeks of vitamin D supplementation [94]. A randomized, placebo-controlled, clinical trial showed significant enrichment of *Lactococcus*, decreased *Erysipelotrichaceae* and *Veillonella* abundance, and improvement of cystic fibrosis in vitamin D insufficient patients, when supplemented with cholecalciferol for 12-weeks [40]. A randomized clinical trial conducted on subjects with prediabetes and vitamin D deficiency for more than one year demonstrated the reduction of the relative abundance of several genera of *Lachnospiraceae* i.e., *Blautia*, *Dorea*, *Roseburia*, and *Ruminococcus*, with vitamin D_2 supplementation (50,000 IU/week) [95].

Nevertheless, animal studies have shown that higher doses of vitamin D may not provide additional benefits to the host and can increase the risk of disease. Ghaly et al. [96]. reported that high-dose vitamin D supplementation led to adverse alterations in the fecal microbiome, predisposing mice to severe colitis. Specifically, the microbial composition in mice receiving 10,000 IU/kg of vitamin D closely resembled that of mice with dextran sodium sulfate (DSS)-induced colitis, indicating a shift towards a more pro-inflammatory microbiome profile. Notably, vitamin D was co-administered with calcium, which may have elevated the calcium-to-magnesium (Ca: Mg) ratio. This imbalance could potentially impair the synthesis of both the storage (25(OH)D) and active ($1,25(OH)_2D$) forms of vitamin D [97].

Based on the available evidence, the protective role of gut-vitamin D axis against immune-mediated diseases can be suggested through following mechanisms: (i) vitamin D insufficiency or supplementation could alter the intestinal microbiome and manipulate the bacterial composition or abundance, thus impacting disease manifestation; (ii) impaired physical and functional barrier integrity due to lack of vitamin D signaling, either due to dietary deficiency or genetically impaired VDR expression and/or activity, resulting in enhanced bacteria and host interaction that could lead to stimulate or inhibit immune responses; (iii) compromised innate immunological defenses in vitamin D deficiency settings [98]. Several in vivo studies also reported that butyrate may improve VDR signaling, and hence prokaryotes lack VDR expression, thus gut microbiota may play a central role in the host intestinal immune response related to vitamin D mechanisms [33, 62, 99].

The gut-brain-immune axis: vitamin D, microbiota, and neuroinflammation

The 'gut-brain' or 'microbiota-gut-brain' axis is a bidirectional signaling pathway that is important for maintaining both gastrointestinal health and brain functioning. Its communication is regulated at different levels by the central nervous system (CNS), autonomic nervous system (ANS), enteric nervous system (ENS), neuroendocrine system, hypothalamus-pituitary-adrenal (HPA) axis, and immune system, linking the emotional and cognitive centers of the brain with intestinal function [100–102]. Preclinical and clinical studies underscore that dysfunction along gut-brain axis could be implicated in cognitive and brain disorders, including neurodegenerative diseases [103]. The immune system influence or is influenced directly by both the CNS and the gut microbiome. The gut microbiota plays a vital role in shaping the peripheral

immune system, and supports the formation, maturation, and activation of microglia, the brain's innate immune cells. Microglia activation is thought to be influenced via SCFAs release by microbial metabolism, as demonstrated by the restoration of microglial shape and function in germ-free mice treated with bacterial extracts [104, 105]. According to Campbell et al. [106]., the gut microbiota also interacts with the brain via the systemic immune system and circulating cytokines. Changes in systemic immunity can affect immunological signaling in the brain, causing symptoms like loss of appetite, irritation, low mood, motivation, social disengagement, exhaustion, and reduced focus [107–110]. Brain-resident immune cells release cytokines and chemokines that directly cross the blood-brain barrier (BBB) and play a significant role in this interaction [111]. Research indicates that the gut microbiota affects BBB permeability, as shown in germ-free animals that had higher BBB permeability, possibly due to lower production of tight-junction proteins including occludin and claudin 5 [112]. The microbiota also plays a crucial role in the initial immune system maturation, affecting expression of TLRs and shaping antigen-specific immunity [113].

Dysbiosis of the gut microbiome, often exacerbated by vitamin D deficiency can disrupt the host-microbiome interaction, resulting in increased intestinal permeability, immunological dysregulation, and systemic inflammation. When the intestinal barrier is compromised, toxic chemicals like lipopolysaccharide (LPS) from Gram-negative bacteria can enter the bloodstream, leading to the upregulation of pro-inflammatory cytokines production. This, in turn, triggers microglial activation and neuroinflammatory signaling pathways [114, 115]. Moreover, during ageing, isoamylamine, a gut microbial metabolite, crosses the BBB and activates the S100 calcium-binding protein A8 (S100A8) signaling, leading to microglial death. Particularly, higher levels of *Ruminococcaceae* and lower levels of *Ruminococcaceae*-targeting bacteriophage *Myoviridae* were observed in the gut of aged rodents and humans, resulting in the increased isoamylamine levels, which disrupts the hairpin shape of S100A8's promoter region, allowing p53 access to it [116].

Both vitamin D and VDR regulate homeostasis in intestinal microbiome and brain health. Vitamin D supports the mucosal epithelial integrity, increases the tight junction proteins, prevents leaky gut syndrome, resulting in protection against systemic and neuro-inflammation [117, 118]. Vitamin D is also known to interfere in inflammatory and anti-inflammatory production balance, resulting in increased production of anti-inflammatory cytokines (i.e., IL-4 and IL-10) by regulatory T cells and decreased production of pro-inflammatory cytokines (i.e., IL-2, IL-17, TNF-α, and IFN-γ), thereby mitigating neuroinflammatory processes [119]. Studies have shown that vitamin D can modulate the gut microbiota by promoting the growth and activity of beneficial microbes that produce anti-inflammatory metabolites, which contributes to immune modulation and reinforces the gut-brain-immune axis [118]. Gominak et al. [39]. reported improvements in sleep, reductions in pain perception, and resolution of bowel symptoms in neurological patients supplemented with vitamins D and B complex over a three-month period. These benefits were attributed to the modulation of the intestinal environment, promoting the growth and activity of *Firmicutes*, *Bacteroidetes*, *Proteobacteria*, and *Actinobacteria*, collectively referred to as the "*healthy foursome*" that constitute the core of the normal human microbiome. Cantarel et al. [120]. conducted a clinical study on vitamin D insufficient female subjects with or without relapsing multiple sclerosis, who were treated with vitamin D (5,000 IU/day) for three months, with or without glatiramer-acetate (immuno-modulatory agent). Results showed an overall increased abundance of *Enterobacteriaceae* and *Faecalibacterium*, and decreased abundance of *Ruminococcus* after vitamin D supplementation. Moreover, vitamin D showed to modulate gut microbiota differently in treated and untreated patients, as higher levels of *Akkermansia*, *Faecalibacterium*, and *Coprococcus* were observed in untreated patients following vitamin D supplementation. While in glatiramer-acetate treated patients, vitamin D supplementation resulted in increased levels of *Janthinobacterium* with a decrease in *Eubacterium* and *Ruminococcus* levels [120].

Probiotics, prebiotics, and vitamin D supplementation: A synergistic approach for healthy ageing

Probiotics are microorganisms that improve health by modulating gut bacteria, offering benefits to the host health beyond basic nutrition. Probiotics can increase intestinal epithelial function, alter gastrointestinal mucosa immunity, protect gut barrier integrity, and limit growth and/or activity of pathogens. Probiotic supplementation possesses health benefits such as reducing oxidative stress, immune modulation, vitamin production (B group and K vitamins), and potentially preventing chronic disorders [121]. *Lactobacillius*, *Bifidobacterium*, *Saccharomyces*, some strains of *Escherichia coli*, and some Gram-positive cocci are the most commonly used probiotics [122–124]. Prebiotics, on the other hand, refers to food supplements or subclass of dietary fibers that can enhance the growth and/or activity of selective indigenous gut microbiota or probiotic strains [125]. Prebiotics enriched dietary sources include soybeans, raw oats, nondigestible carbohydrates, yacon, and unrefined wheat and barley [126]. Some of the most commonly using prebiotics are fructans [inulin, fructo-oligosaccharides

(FOS) and galacto-oligosaccharides (GOS)] [127]. Prebiotics undergo fermentation by gut microbiota strains to produce SCFAs such as acetate, propionate, and butyrate, which gain attention due to their central role in maintaining health and wellness. SCFAs, particularly butyrate, have shown promising immunomodulatory effects beyond their well-established role in gut health. With the availability of butyrate in postbiotic formulations, the incorporation of postbiotic agents into food supplements may serve as a valuable adjunct or alternative to current strategies targeting immune-regulatory pathways. Therefore, future recommendations should consider postbiotics, including SCFAs, as potential modulators of the immune system.

The immune-modulatory and anti-inflammatory activities of probiotic strains are well documented, as they affect bot humoral and cell-mediated immunity [128]. Peptidoglycan, teichoic acid, and lipoteichoic acid are cell wall components released by probiotics that play an important role in regulating immunity homeostasis [129–131]. Proteins secreted by *Lactobacillus reuteri* have been shown to downregulate the gene expression of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), leading to decreased cell proliferation and increased mitogen-activated protein kinase (MAPK) activity, which may ultimately lead to apoptosis [132]. Probiotic strains of *Bifidobacterium* species have been shown to reduce mRNA expression of TNF-α and IL-1β, released by macrophages in the intestinal inflammation [133]. Furthermore, *Enterococcus faecalis* induces IL-12 production from activated macrophages, which aids in the differentiation of $CD4^+$ T cells [134]. SCFAs (postbiotics) regulate host immunity via two main mechanisms including inhibition of histone deacetylase and activation of G-protein coupled receptors, which ultimately result in increased production of anti-inflammatory cytokines and decreased pro-inflammatory mediators [135]. Use of probiotics and prebiotics in old age is one of the cost-effective and widely-available intervention that provide shield against unhealthy ageing by improving homeostasis of intestinal microflora and immune-mediated processes [136, 137].

Vitamin D is well-known for its geroprotection potential via regulation of cellular and intracellular processes, that may drive immune responses towards immune protection against infections and age-related diseases [138]. Most of the immune cells, including T and B cells, dendritic cells, macrophages, and monocytes, express VDR and respond to vitamin D with fine-tuned modulations in cell signaling, path activation, and chemical synthesis, which have substantial implications for immune responses [139–146]. Adequate vitamin D levels in the elderly serve to prevent the normal decline in immunological surveillance through a finely orchestrated cascade of actions [138].

Hence, elder population is more prone to the risk of vitamin D deficiency and gut dysbiosis, integration of probiotics, prebiotics and vitamin D supplements offers a synergistic approach in mitigating age-related diseases while promoting healthy ageing. This integrative approach may not only restore gut microbial homeostasis but can also support immune-modulatory actions of vitamin D and amplify SCFAs production. While slowing down the process of immunosenescence, it may improve the overall wellbeing of elder population. A systematic review of randomized controlled trials assessed the health benefits of probiotics and vitamin D co-supplementation, which demonstrated greater health benefits as compared to their competitors (i.e., placebo, vitamin D or probiotics alone) [147]. The co-supplementation resulted in reduced disease severity, improved mental health and metabolic parameters (i.e., insulin sensitivity, dyslipidemia, low-grade inflammation, and oxidative capacity), and lower use of healthcare. A randomized, placebo-controlled study showed a significant increase in serum vitamin D levels and improvement of migraine headache parameters in adult subjects co-supplemented for 12-weeks with probiotic capsule (4.5×10^{11} CFU per day) and vitamin D (50,000 IU every 2 weeks) [148]. Probiotic capsule was comprised of *Lactobacillus plantarum*, *L. casei*, *L. acidophilus*, *L. bulgaricus*, *Bifdobacterium infantis*, *B. longum*, *B. breve*, and *Streptococcus thermophilus.* In another study, four weeks co-supplementation of probiotics (*Lactobacillus acidophilus* W22, *Lactococcus lactis* W58, *Levilactobacillus brevis* W63, *Bifidobacterium bifidum* W23, and *B. lactis* W51) and cholecalciferol resulted in altered diversity and composition of alpha and beta bacteria (i.e., *Lactobacillaceae* family, *Bacteroides* genus, *Roseburia inulinivorans*, and *Prevotella* genus) [149]. However, no significant effects were found on inflammatory mediators and SCFAs profile. Mohammadi et al. [150]. demonstrated significant improvement of cognitive function with decrease in total cholesterol and C-reactive protein levels in schizophrenic patients co-supplemented with probiotics (2×10^9 CFU of each, *Lactobacillus acidophilus*, *L. rhamnosus*, *L. reuteri*, *L. paracasei*, *Bifidobacterium longum*, and *Bacillus coagulans*) and vitamin D (400 IU/day) for 12-weeks. Animal study showed inhibition of chemically induced colorectal carcinogenesis in Wistar rats treated with a synergistic combination of probiotics (1×10^7 CFU) and vitamin D (250–2000 IU/day) [151]. Interestingly, supplementation of prebiotics (FOS and inulin) resulted in the modulation of gut microbiota (*Bacteroides thetaiotamicron* and *Faecalibacterium prausnitzii*) that contributed to the enhanced biosynthesis of provitamin D3 [152]. The hypothesis of this study was based on the assessment of

the potential role of gut microbiota to produce or modulate the precursors like cholesterol that can influence provitamin D3 levels. Thus, these results suggest a novel pathway that involved gut microbiota modulation by prebiotic supplementation to enhance the provitamin D3 levels and to address vitamin D deficiency.

Conclusions and future perspectives

In conclusion, the gut microbiome and immune system are intricately interconnected, with vitamin D serving as a pivotal intermediary in this dynamic relationship. This review provides a comprehensive discussion on the gut microbiota and vitamin D as an emerging and vital axis influencing immune ageing and age-related diseases. It highlights the dual role of gut microbiota in shaping host immunity and regulating vitamin D metabolism, alongside the significant immunomodulatory potential of vitamin D in maintaining intestinal homeostasis and barrier integrity. The findings suggest that vitamin D deficiency and gut dysbiosis synergistically accelerate immunosenescence and inflammageing, contributing to unhealthy ageing and increased risk of age-related diseases.

Current literature supports the potential of vitamin D supplementation, combined with prebiotics and probiotics, to restore gut microbial balance, improve vitamin D status, and reduce systemic inflammation. These interventions, when used together, may synergistically protect against gut dysbiosis and immune ageing in the elderly.

However, the existing body of research remains limited, necessitating more in-depth analysis to address unresolved questions before integrating vitamin D into routine clinical practice for promoting healthy ageing. While studies indicate that gut microbiota influence vitamin D metabolism through enzymatic pathways, the long-term effects of these interactions are not yet well understood. For example, how do variations in intestinal microflora composition impact vitamin D metabolism to synthesize active metabolites, and their immunomodulatory effects over time? Additionally, how does this interaction evolve with age, and what fundamental mechanisms underpin its role in resilience against chronic disorders? Environmental factors (such as diet and sun exposure), individual microbiome diversity, and genetic polymorphisms of VDR may also contribute to observed discrepancies, yet comprehensive analysis of these factors remains lacking in the literature.

Future research should focus on several key areas:

i. Conducting larger, robustly designed clinical trials to investigate the interplay between gut microbiota and vitamin D in protecting against immune ageing and age-related diseases at larger scale.
ii. Establishing dose-response relationships for vitamin D supplementation in the context of diverse gut microbiota profiles to establish personalized supplementation strategies.
iii. Investigating the role of microbial enzymatic hydroxylation pathways in vitamin D metabolism through advanced metabolomics and microbiome profiling techniques.
iv. Assessing the thresholds for vitamin D toxicity, especially in populations with varying baseline vitamin D levels, as excessive doses can lead to adverse outcomes such as hypercalcemia, kidney stones, or even an inflammatory shift in the microbiome.

These efforts are essential to fully elucidate the complex interactions among the gut microbiome, vitamin D, and immune ageing, ultimately enabling targeted interventions for promoting healthy ageing and mitigating the burden of age-related diseases.

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