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Review Article

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Vitamin D and The Gut Microbiota: a Narrative Literature Review

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ABSTRACT

Recently several studies have attempted to investigate the association between vitamin D and microbiota. However, studies have reported inconsistent results. This narrative review aimed to investigate the potential association between vitamin D and microbiota population in the gut by pooling together the results from observational studies and clinical trials. We considered animal and human studies in this field. Several studies have shown the correlation of vitamin D deficiency with microbiota. Furthermore, interventional studies were emerging that vitamin D change the microbiota composition in which leads to an increase in beneficial bacteria, such as *Ruminococcaceae*, *Akkermansia*, *Faecalibacterium*, and *Coprococcus* while decreases in *Firmicutes*. Vitamin D could change the microbiota toward decreasing in *Firmicutes* and increasing in *Bacteroidetes*. At genera level, vitamin D may connect to some genera of *Lachnospiaceae* family (e.g., *Blautia*, *Rosburia*, *Dorea*, and *Coprococcus*). It seems that adequate level of vitamin D is an important factor in improving the composition of the gut microbiota. More studies are needed to confirm possible underling mechanisms.

Keywords: Microbiome; Microbiota; Intestines; Vitamin D

INTRODUCTION

Vitamin D deficiency is described as a public health concern globally, which has health consequences in more than one billion people [1,2]. Vitamin D is known for its role in calcium-phosphorus homoeostasis and bone metabolism [2]. Recent evidences have shown the association between hypovitaminosis D and autoimmune disorders [3], cancers [4,5], cardiovascular disease [6], diabetes mellitus [7], and infections [8,9]. Furthermore, vitamin D deficiency is highly associated with gastrointestinal diseases, including inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), and colon cancer [10,11]. The presence of vitamin D receptor (VDR) in almost every tissue highlights the importance of vitamin D in biological functions. VDR is expressed in many cells, including muscle, intestinal epithelium, kidney and also in the immune cells [12,13]. As VDR is widely expressed in various immune cells, including B cells, T cells and antigen presenting cells, it may demonstrate the immunomodulatory role of vitamin D in different organs such as gut [13].

Conflict of Interest
The authors declare that they have no competing interests.

Human gut is a host of numerous numbers of microorganisms (about 10^{13}–10^{14}) known as microbiota [14]. Evidence has supported the roles of microbiota in human's immunity and metabolism [15]. The microbiota includes bacteria, fungi, archaea, protozoa and viruses that act in the human gut as symbiotic or pathogenic [15,16]. More than 1,000 different bacterial species have been determined in human gut. The 4 major phyla composed the gut microbiota are at first *Bacteroidetes* and *Firmicutes* and then *Actinobacteria*, and *Proteobacteria* [17]. The alteration in the diversity of gut microbiota, called dysbiosis, can negatively influence gut health. The change in the composition and diversity of gut microbiota depends on many factors like host genetics, environmental factors, diet, antibiotics, pregnancy, and infection [18-21]. Among these factors, dietary elements responsible for up to 57% changes in gut microbiota [22].

Considering that vitamin D deficiency can cause gastrointestinal disease through its immunomodulatory role, recently, a hypothesis has been suggested on an association between vitamin D and gut microbiota. Recent human and animal investigations have shown that vitamin D could alter microbiota composition through increasing the maintenance of gut homeostasis [23] and decreasing permeability [24]. However, it is not clear how vitamin D could shift gut microbial communities to achieve these goals. Therefore, the present study reviewed the association between vitamin D and gut microbiota composition. The characteristics of studies are presented in details in **Tables 1** and **2**.

VITAMIN D AND MICROBIOTA: ANIMAL STUDIES

In a study by Assa et al. [26], a relatively high quantity of Bacteroidetes was found in vitamin D deficient mice. The researchers showed that vitamin D through preserving gut barrier homeostasis and tight-junction building reduces dysbiosis and adherent-invasive *Escherichia coli* colonization. Assa et al. [24] also reported the similar results in another study in which vitamin D deficient mice were more vulnerable to infectious and predisposed to epithelial barrier dysfunction that leads to increasing gut permeability. Jahani et al. [25] indicated supplementation with vitamin D_3 during pregnancy and lactation had different effects

Table 1. Summary of animal studies

Author	Population	Sex	Intervention	Duration (day)	Microbiome identification	Results
Jahani et al. [25]	Female and male CD-1 mice	M/F	5,000 IU D3/kg diet	During pregnancy, lactation and 3-mon aged	qRT-PCR targeting 16S rRNA gene	VDR expression was 50% higher in the offspring in high vitamin D feeding group. Lower vitamin D levels was correlated with increased pro-inflammatory genes expression at 3-mon age, low vitamin D diet fed mice had lower *Bacteroides*/*Prevotella* ratio count at PND 21 although this difference disappeared at adulthood. Higher level of LPS concentration were seen in vitamin D deficient diet group at adulthood.
Assa et al. [24]	C57BL/6 mice	F	Vitamin D deficient diet	5 wk	qPCR targeting 16S rRNA gene	Higher relative quantities of *Bacteroidetes*, *Firmicutes*, *Actinobacteria* and *Gammaproteobacteria*: vitamin D deficient mice. After 10-day injection of *Citrobacter rodentium*, relative abundance of *Gammaproteobacteria* and *Actinobacteria* in vitamin D deficient group.
Assa et al. [26]	C57BL/6 mice	F	Vitamin D deficient diet	5 wk	qPCR targeting 16S rRNA gene	Higher abundance of *Bacteroidetes*: vitamin D deficient mice. Relative increase in *Gammaproteobacteria* was observed in infected mice with LF82.
Ooi et al. [23]	Cyp KO & VDR KO C57BL/6 mice	Sex-matched	1.25 mg/100 g diet	NR	qRT-PCR targeting 16S rRNA gene	Higher abundance of *Bacteroidetes* and *Proteobacteria* and lower bacteria from *Firmicutes* and *Deferribacteres* phyla was reported in Cyp KO and VDR KO mice compared with wild-type.

qRT-PCR, quantitative real time polymerase chain reaction; qPCR, quantitative polymerase chain reaction; VDR, vitamin D receptor; PND, postnatal days; LPS, lipopolysaccharides; KO, knockout; Cyp, cytochrome P; rRNA, ribosomal ribonucleic acid; NR, not reported.

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Table 2. Summary of interventional and observational human studies

Author	Country	Study type	Population	Sex	Number	Dose (IU/day)	Duration (day)	Microbiome identification	Results
Schäffler et al. [27]	Germany	Interventional	Patients with Crohn's disease	M/F	17	20,000 IU daily from day 1 to day 3, then every second day	30	PCR targeting 16S rRNA gene	Grater abundance of *Alistipes*, *Barnesiella*, unclassified *Porphyromonadaceae*, *Roseburia*, *Anaerotruncus*, *Subdoligranulum* and an unclassified *Ruminococcaceae* was seen after vitamin D supplementation.
Garg et al. [28]	London	Interventional	Patients with ulcerative colitis	M/F	25	40,000 IU D3 weekly	60	PCR targeting 16S rRNA gene	*Enterobacteriaceae* increased significantly after vitamin D supplementation.
Kanhere et al. [29]	USA	Interventional	Adults with cystic fibrosis	M/F	41	50,000 IU D3 weekly	90	PCR targeting 16S rRNA gene	*Lactococcus* was increased, while *Veillonella* and *Erysipelotrichaceae* were decreased.
Sordillo et al. [30]	USA	Interventional	Infants 3–6 mons whose parents had allergies/asthma	M/F	333	4,000 or 400 IU/day D3 + prenatal vitamins	NR	Sequencing of bacterial 16S rRNA gene	Greater levels of *Lachnospiraceae*/*U. Clostridales*, higher frequency of *Lachnobacterium*, and lower frequency of *Lactococcus*.
Gominak et al. [17]	USA	Interventional	Neurology patient	M/F	90	Individualized dose of vitamin D to guarantee a blood level of 60–80 ng/mL	Over 1,000	NR	NR
Ciubotaru et al. [31]	USA	Interventional	Prediabetes and hypovitaminosis	M/F	115	50,000 IU/week D3	Over 365	PCR targeting 16S rRNA gene	Lower relative abundance of genera belonging to the *Lachnospiraceae* (e.g., *Ruminococcus*, *Roseburia*, *Blautia*, and *Dorea*). Lower abundance of members of *Clostridia* class.
Cantarel et al. [3]	USA	Interventional	Women with or without relapsing-remitting multiple sclerosis	F	-	5,000 IU/day D3	90	PCR targeting 16S rRNA gene	Greater abundance of *Faecalibacterium* and *Enterobacteriaceae*, and lower abundance of *Ruminococcus*. MS patients (untreated): higher *Akkermansia*, *Faecalibacterium*, and *Coprococcus* genera. MS patients (treated by GA): higher *Janthinobacterium*, lower *Eubacterium* and *Ruminococcus*.
Talsness et al. [32]	The Netherlands	Observational	One month old infants	M/F	913	-	-	RT-PCR targeting 16S rRNA gene	A significant negative linear trend between maternal vitamin D supplementation and plasma 25(OH) D concentration and *Bifidobacterium* spp. was seen. There was a positive linear trend between quintile groups and *Bacteroides fragilis* group counts. In some breast-fed infants vitamin D supplementation leads to lower abundance of *Clostridium difficile*.
Luthold et al. [33]	Brazil	Observational	Healthy individual	M/F	150	-	-	PCR targeting 16S rRNA gene	Higher abundance of *Provotella* and lower abundance of *Haemophilus* and *Veillonella*. Lower abundance of *Coprococcus* and *Bifidobacterium*.
Mandal et al. [34]	Norway	Observational	Pregnant women	F	60	-	-	PCR targeting 16S rRNA gene	Increased *Actinobacteria*/*Proteobacteria* ratio, *Actinobacteria*/*Bacteroidetes* ratio, *Proteobacteria*/*Firmicutes* ratio, and other *Bacteroides*.
Thomas et al. [35]	USA	Observational	Older men	M	567	-	-	PCR targeting 16S rRNA gene	Higher levels of $1,25(OH)_2$ D were more related to butyrate producing bacteria that are associated with better gut microbial health.
Kassem et al. [36]	USA	Observational	Infants	M/F	580	-	-	PCR targeting 16S rRNA gene	Prenatal and cord blood vitamin D levels were associated with early life (up to 1 mon) gut microbiota.

PCR, polymerase chain reaction; rRNA, ribosomal ribonucleic acid; NR, not reported; RT-PCR, reverse transcription polymerase chain reaction.

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on offspring at different life span. Lower vitamin D levels were related with increased pro-inflammatory genes expression, reduction in VDR at 3-month-aged offspring, lower *Bacteroides/Prevotella* ratio at day 21 and higher level of lipopolysaccharides (LPS) concentration in adults. In addition, lower bacteria count was reported in the mice received low vitamin D in comparison to high vitamin D diet. Dysbiosis and increasing of injury in gut following VDR or 1, 25$(OH)_2D_3$ deficiency has been also reported by Ooi et al. [23]. They found that vitamin D could regulate the intestinal microbiota while *Bacteroidetes* and *Proteobacteria* were more abundant in fecal sample of cytochrome P (Cyp) knockout (KO) and VDR KO mice in comparison to wild-type mice. In contrast, *Firmicutes* were less abundant in Cyp KO and VDR KO mice. The results of Ooi et al. [23] is similar to Assa et al. [24] about the abundance of *Bacteroidetes* as Assa et al. [25] reported the relatively high quantity of *Bacteroidetes*, *Firmicutes*, *Actinobacteria* and *Gammaproteobacteria* observed in vitamin D deficient mice in one study and in another one higher relative abundance of *Bacteroidetes*.

VITAMIN D AND MICROBIOTA: HUMAN STUDIES

Cantarel et al. [3] conducted a clinical trial on women with or without relapsing-remitting multiple sclerosis (MS) who were vitamin D insufficient. They reported that after 3 months of vitamin D supplementation (5,000 IU/day), the relative abundance of *Faecalibacterium* and *Enterobacteriaceae* increased, while in overall the relative abundance of *Ruminococcus* decreased. Moreover, after supplementation with vitamin D, untreated MS participants had an increased abundance of *Akkermansia*, *Faecalibacterium*, and *Coprococcus* genera, in comparison with healthy controls and glatiramer acetate-treated MS subjects. Those treated with glatiramer acetate compared to other groups had increases in *Janthinobacterium* and decreases in *Eubacterium* and *Ruminococcus* after vitamin D supplementation [3]. In a 3-month uncontrolled trial, 1,000 neurological patients received individualized doses of vitamin D to guarantee a blood level of 60–80 ng/mL plus B100 (B complex of 100 mg of all B vitamins except 100 mcg of cyanocobalamin, 100 mcg of biotin, and 400 mcg of folic acid). The authors concluded that these patients did not experience the IBS symptoms during 3 years after stopping the supplementation. Supplementing vitamin D plus all 8 B vitamins led to a change in the intestinal microbiome to normal status in 3 months. This result showed the role of normal intestinal microbiome in reducing pain, sleep disorders, and IBS symptoms through increasing vitamin D and B vitamins level [17].

In another study, Ciubotaru et al. [31] conducted a double-blind placebo-controlled randomized trial in men with pre-diabetes and vitamin D deficiency for more than one year. Supplementation with 50,000 IU/week ergocalciferol reduced the relative abundance of several genera of the *Lachnospiraceae* (e.g., *Ruminococcus*, *Roseburia*, *Blautia*, and *Dorea*) in high vitamin D quartiles. Another clinical trial also investigated the association between vitamin D supplementation and gut microbiome composition on 333 infants 3 to 6-month-aged. After vitamin D supplementation in pregnant women in 2 different doses of 4,000 IU vitamin D + prenatal vitamins or 400 IU vitamin D + prenatal vitamins, fecal samples from infants were collected and analyzed. In infants with higher cord blood vitamin D levels, the relative abundance of *Lachnospiraceae*/*U. Clostridales* and *Lachnobacterium* was higher, while the relative abundance of *Lactococcus* was lower [30].

According to the study recently published by Garg et al. [28] *Enterobacteriaceae* were significantly increased in patients with ulcerative colitis following 40,000 IU D3/week

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supplementation for 8 weeks. In another controlled trial on patients with Crohn's disease, 20,000 IU D3 were given for one month. Greater abundance of *Alistipes*, *Barnesiella*, unclassified *Porphyromonadaceae*, *Roseburia*, *Anaerotruncus*, *Subdoligranulum* and an unclassified *Ruminococcaceae* was reported after vitamin D supplementation [27]. In a double-blind, randomized, placebo-controlled clinical trial on adults with cystic fibrosis, *Lactococcus* was increased, while *Veillonella* and *Erysipelotrichaceae* were decreased after 12-week supplementation with 50,000 IU D3/week [29]. In another study 62 fecal sample from healthy infants were collected that thirty-five of them were supplemented with 400 IU of vitamin D per day. Comparative metagenomic analysis was done to investigate the distribution and diversity of infant gut microbiota. The researchers found that vitamin D plays an important role in modifying the infant gut microbiota, especially increase the probiotics types [37].

Observational studies have also been conducted in this field. In a cross-sectional study designed on 150 healthy individuals, authors demonstrated that higher vitamin D intake was associated with higher abundance of *Provotella* and lower abundance of *Haemophilus* and *Veillonella*. Moreover, the abundance of *Coprococcus* and *Bifidobacterium* was inversely related to the vitamin D intake [33]. Another study was conducted to find the correlation between some dietary nutrients and microbiota composition in 60 women, during the second trimester of pregnancy. Results showed that higher vitamin D intake is associated with increased ratio of *Actinobacteria/Proteobacteria*, *Actinobacteria/Bacteroidetes*, *Proteobacteria/Firmicutes*, and other *Bacteroides* in pregnant women [34]. Another cohort study by Talsness et al. [32] aimed to evaluate the effect of vitamin D supplementation of infant and maternal subject on microbiota composition. A significant negative linear trend between maternal vitamin D supplementation and plasma 25(OH) D concentration and *Bifidobacterium* spp. was seen. In some breast-fed infants, vitamin D supplementation leads to lower abundance of *Clostridium difficile*. In a cross-sectional study of 567 old men, higher levels of $1,25(OH)_2$ D were more related to butyrate producing bacteria that are associated with better gut microbial health [35]. In a birth cohort study, prenatal and cord blood vitamin D levels were associated with early life (up to 1 month) gut microbiota [36]. Recently, a review highlighted the therapeutic potential of vitamin D/VDR in the gut microbiota modulation and anti-inflammatory effects in IBD [38].

CRITICAL APPRAISAL OF EVIDENCE

Reviewing the studies showed that the normal microbiota makes up of 4 main phyla (*Bacteroidetes, Firmicutes, Proteobaceria,* and *Actinobacteria*) [17] in which many factors including diet could change their balance [39]. Gut microbiota plays an important role in health and disease and now is considered as a separate human organ that affect the other organs [40]. The 2 main bacteria phyla in human feces are *Bacteroidetes* and *Firmicutes*. Other dominant phyla with less relative abundance are *Proteobaceria,* and *Actinobacteria* [17,41]. To make a better view about the results, we considered microbiota in the phylum to genus level. In this section of review, we discuss the probable effect of vitamin D on gut microbiome in the phylum to genus level.

In phyla level, one study has shown that supplementation with vitamin D may change the microbiota composition with reducing in phylum *Firmicutes* [31]. Two other interventional studies have reported inconsistence results in which *Firmicutes* genus increased in one study while, the population of *Firmicutes* decreased in the other study [3,30]. Although some studies showed increased *Firmicutes* genus, it has been reported that this genus is known as butyrate producers and anti-inflammatory [42]. In an observational study, Luthold et al. [33], have

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shown a reduction in *Firmicutes* phyla while Mandal et al. [34], have reported an increase in *Proteobaceria/Firmicutes* ratio. However, in both studies, the population of phylum *Bacteroidetes* increased. There is a hypothesis in which changing in microbiota composition to higher level of *Bacteroidetes* and lower level of *Firmicutes* would benefit the host while increasing in *Firmicutes* may leads to gut barrier dysfunction [43,44].

The other 2 dominant phyla are *Proteobaceria*, and *Actinobacteria*, which seems to present pro-inflammatory and anti-pathogenic properties. One study has reported increase in *Proteobaceria* after vitamin D supplementation [3] and the other showed increase in *Actinobacteria/Proteobaceria*, *Actinobacteria/Bacteroidetes,* and *Proteobaceri/Firmicutes* ratio with higher dietary intake of vitamin D [34] while Luthold et al. [33] showed inverse relationship between some *Proteobaceria* and *Actinobacteria* genus and serum levels of vitamin D. This controversy may be explained by differences in study design. Luthold et al. [33], conducted his study in a cross-sectional design which is not strong for identifying causal relationships.

In genus level, all genera that their changes have been reported in the studies were as follows: *Lactococcus*, *Blautia*, *Rosburia*, *Ruminococcus*, *Dorea*, *Faecalibacterum*, *Coprococcus*, *Veillonella*, *Subdoligranulum*, *Erysipelotrichaceae*, *Eubacterium*, *Anaerotruncus*, *C. difficile* (phylum *Firmicutes*), *Provotella*, *Alistipes*, *Barnesiella*, *Porphyromonadaceae* (phylum *Bacteroidetes*), *Haemophilus*, *Janthinobacterium*, *Enterobacteriaceae* (phylum *Proteobaceria*), *Bifidobacterium* (phylum *Actinobacteria*), and *Akkermansia* (phylum *Verrucomicrobia*). Among these genera *Blautia*, *Rosburia*, *Dorea*, and *Coprococcus* are all from family *Lachnospiaceae*. One study showed significant reduction in abundance of *Blautia*, *Rosburia*, *Ruminococcus*, and *Dorea* after vitamin D supplementation [31] which all are associated with increasing gut permeability and inflammation [45]. In another study by Cantarel et al. [3] supplementation with vitamin D_3 in MS women lead to increase in abundance of *Akkermansia*, *Faecalibacterum*, and *Coprococcus* (family *Lachnospiaceae*) which *Coprococcus* and *Faecalibacterum* have known as butyrate producers and may be anti-inflammatory [42]. *Akkermansia*, another increased genus is a mucin-degrading bacteria [46]. Sordillo et al. [30] concluded that higher vitamin D level is correlated with higher abundance of *Lachnospiaceae/U. Clostridales*. Multivariate analysis showed increasing *Lachnobacterium* and decreasing *Lactococcus* abundance. According to this research, low vitamin D level is associated with dysbiosis and inflammation progression. Contrary to the results of this study about *Lactococcus*, 2 studies reported an increase in *Lactococcus*, which related to positive gut health, after supplementation with vitamin D [29,33]. On the other hand, based on Luthold et al. [33], the abundance of *Bifidobacterium* inversely related to the vitamin D intake. In line with this finding, the abundance of *Bifidobacterium* spp. was inversely related to maternal plasma 25(OH) D concentration in observational study by Talsness et al. [32]. *Bifidobacterium* and lactic acid bacteria like *Lactococcus* are both known for their potential probiotic effects. Although the results of this review are partly associated with the prebiotic properties of vitamin D, are not confirmed by the contradictory nature of the studies and there is a need for further studies focusing on probiotic bacteria.

Luthold et al. [33] showed higher abundance of *Provotella* and lower abundance of *Coprococcus*, *Haemophilus* and *Veillonella* in the highest vitamin D intake tertile which is consistent with Kanhere et al.'s study [47] on the *Veillonella* which was known as cause of many infections [47]. Results about *Coprococcus* are inconsistent with *Cantarel* study which could be due to its cross-sectional design or the other factors for example the probable effect of MS on intestinal microbiota. Moreover, results of this research showed the lowest tertile of vitamin D intake correlated with increasing in LPS level that likely due to increase in gram negative bacteria (*Haemophilus* & *Proteobacteria*) which have LPS in their outer membrane. As mentioned above,

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in the Mandal et al.'s research [34], vitamin D intake was associated with increasing the *Actinobacteria/Proteobacteria*, *Actinobacteria/Bacteroidetes*, *Proteobacteria/Firmicutes* ratio, and other *Bacteroides* in pregnant women. On the other hand, higher vitamin D intake may decreases microbiome diversity. It has been known that reduction in microbiota variety is related to some diseases including IBD [48], obesity [20], autism [49], and allergy [50]. Besides higher intake of vitamin D changes the microbiome toward increasing *Actinobacteria* and *Proteobacteria* abundance at phyla levels. These 2 phyla presented anti-pathogenic properties [34]. To be noted that meat and other animal products are important sources of vitamin D and several publications have reported the effect of meat on microbiota [51]. These relationships may be explained with antimicrobial characteristics of vitamin D that encompass certain groups of bacteria. Therefore, higher intake of vitamin D might cause an increase in probable pathogens [34]. The observed contradiction in findings may be the result of inaccurate vitamin D assessment method (food frequency questionnaire) used in this research.

Suggested mechanisms for the role of vitamin D in gut health is shown in **Figure 1**. Generally, vitamin D effects are as follows: gene expression modulation of anti-microbial peptides like

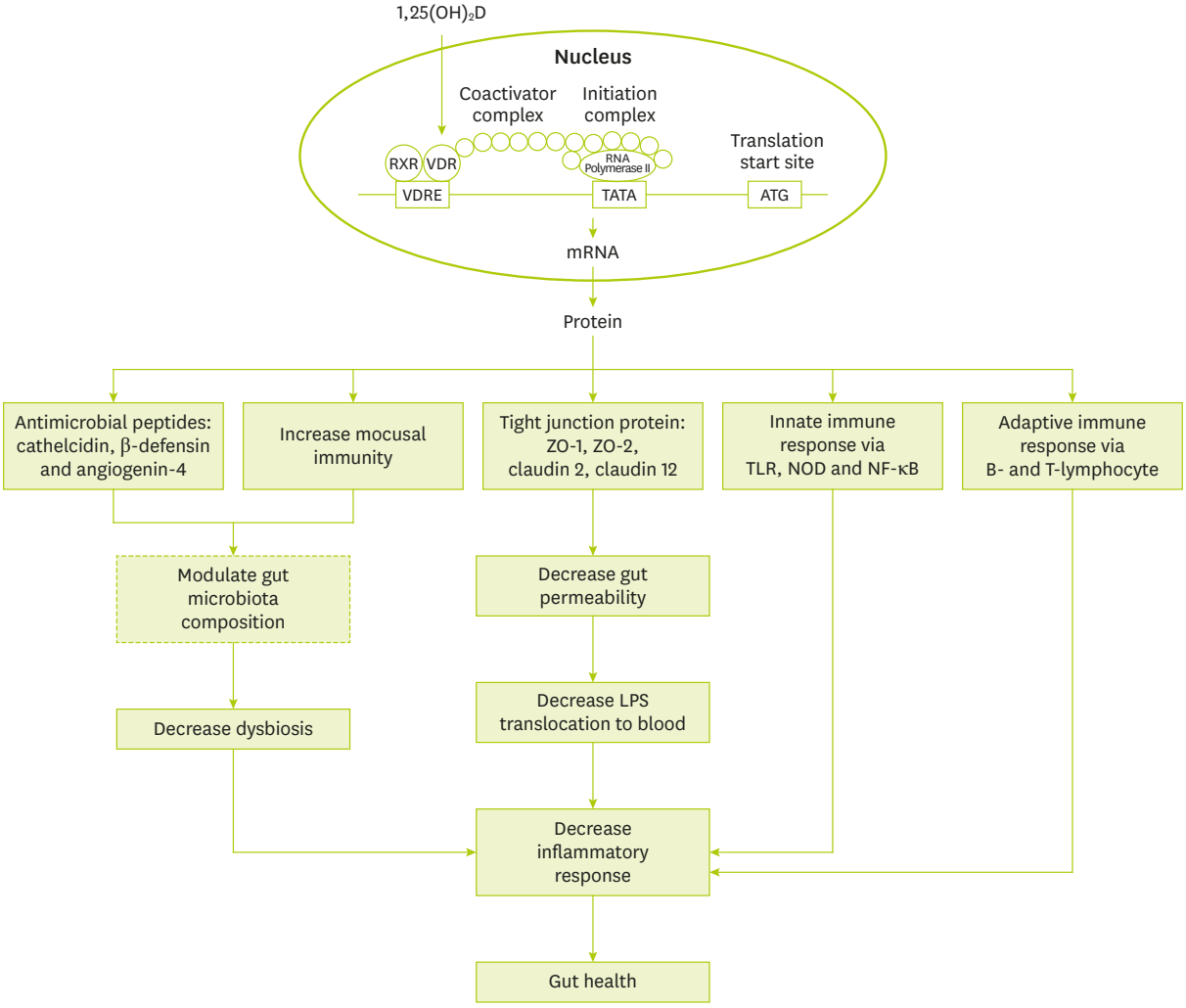

Figure 1. Suggested mechanisms for the association of vitamin D and microbiota.
RXR, retinoid X receptor; VDR, vitamin D receptor; VDRE, vitamin D response element; ZO, zonula occludens; TLR, Toll-like receptor; NOD, nucleotide oligomerization domain; NF-κB, nuclear factor kappa B; LPS, lipopolysaccharides.

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cathelicidin and β-defensin [52], gene expression modulation of tight junction proteins like zonulin occluden-1, zonulin occluden-2, claudin 2, and 12 [53], regulation of innate immune system via gene expression modulation of toll-like receptor 2 and nucleotide-binding oligomerization domain 2 and adaptive immune system via modulation of B- and T-lymphocyte function [52,54].

CONCLUSION

This study reviewed the data of literatures that investigated the association between vitamin D and gut microbiota. In observational studies, the association of vitamin D deficiency with dysbiosis has been reported. Furthermore, interventional studies were emerging that vitamin D change the microbiota composition in which leads to increase in beneficial bacteria, such as *Ruminococcaceae*, *Akkermansia*, *Faecalibacterium*, *Lactococcus*, and *Coprococcus* while decreases in some genera from *Firmicutes*.

There is scarcity of research on the association between vitamin D and microbiota composition. It seems appropriate dose of vitamin D can alter the gut microbiota with increase in *Bacteroidetes* and decrease in *Firmicutes.* At genera level, vitamin D may connect to some genera of *Lachnospiaceae* family (e.g., *Blautia*, *Rosburia*, *Dorea*, and *Coprococcus*). Therefore, maintaining the appropriate amount of vitamin D in the body seems to have beneficial effects on the composition of the gut microbiota.

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