Antimicrobial and Immune-Modulatory Effects of Vitamin D Provide Promising Antibiotics-Independent Approaches to Tackle Bacterial Infections – Lessons Learnt from a Literature Survey

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Antimicrobial multidrug-resistance (MDR) constitutes an emerging threat to global health and makes the effective prevention and treatment of many, particularly severe infections challenging, if not impossible. Many antibiotic classes have lost antimicrobial efficacy against a plethora of infectious agents including bacterial species due to microbial acquisition of distinct resistance genes. Hence, the development of novel anti-infectious intervention strategies including antibiotic-independent approaches is urgently needed. Vitamins such as vitamin D and vitamin D derivates might be such promising molecular candidates to combat infections caused by bacteria including MDR strains. Using the Pubmed database, we therefore performed an in-depth literature survey, searching for publications on the antimicrobial effect of vitamin D directed against bacteria including MDR strains. In vitro and clinical studies between 2009 and 2019 revealed that vitamin D does, in fact, possess antimicrobial properties against both Gram-positive and Gram-negative bacterial species, whereas conflicting results could be obtained from in vivo studies. Taken together, the potential anti-infectious effects for the antibiotic-independent application of vitamin D and/or an adjunct therapy in combination with antibiotic compounds directed against infectious diseases such as tuberculosis, *H. pylori* infections, or skin diseases, for instance, should be considered and further investigated in more detail.

Keywords: vitamin D, vitamin D derivates, antimicrobial effects, novel antimicrobial therapies, antimicrobial peptides, host defense peptides, multidrug-resistant bacteria

Introduction

Antimicrobial Resistance. Antimicrobial resistance (AMR) poses a serious threat to human health, limiting the effective treatment and prevention of many infections caused by bacteria, viruses, parasites, or fungi due to the emerging acquisition of resistance genes by infectious agents. Thus, AMR is a global problem that has to be addressed effectively at regional, national, and international levels [1]. Genes causing AMR can be transmitted via plasmids or acquired by chromosomal incorporation into the genome of the infectious target cell. Transfer of distinct AMR genes might result in the following events, subsequently hampering effective antimicrobial treatment: (i) mutations of the binding site, preventing the attachment of the antimicrobial compound to the infectious target cell (e.g., against beta-lactam antibiotics, streptomycin, tetracycline, and erythromycin); (ii) chemical/conformational changes of the ribosomal molecules, subsequently blocking the binding sites of or reducing the affinity for the antimicrobial compound (e.g., the enzymatic methylation of the 23S rRNA against erythromycin); (iii) chemical/conformational changes in the antimicrobial molecule, leading to reduced or even complete loss of its efficacy (e.g., following acetylation of chloramphenicol by an acetyltransferase); (iv) expression of antimicrobial enzymes,

inactivating the antimicrobial compound intracellularly (e.g., beta-lactamases); (v) expression of protective proteins, actively removing antimicrobials from the ribosome by energy deprivation (e.g., ribosome protecting proteins against tetracycline); and (vi) proactive expulsion of the antimicrobial out of the infectious cell (e.g., by a tetracycline efflux pump) [2].

In particular, multi-drug resistant (MDR) bacterial strains constitute major obstacles on the course of a rational, goal-directed treatment of infected and particularly severely compromised patients with immune-suppressive comorbidities, making a curative outcome for the patient utmost challenging, if not impossible. Recently, the World Health Organization (WHO) has published a list of the 12 most critical MDR bacterial groups. At the top of the list can be found *Pseudomonas aeruginosa* (particularly carbapenem-resistant strains), followed by Enterobacteriaceae (carbapenem-resistant or extended spectrum beta-lactamase (ESBL)-producing strains) and *Acinetobacter baumannii* (carbapenem-resistant). Also, a high priority of awareness require emerging *Enterococcus faecium* (vancomycin-resistant enterococci [VRE]), *Staphylococcus aureus* (methicillin-resistant [MRSA], vancomycin-intermediate [VISA], and vancomycin-resistant strains), *Helicobacter pylori* (clarithromycin-resistant), *Campylobacter* including *C. jejuni* (fluoroquinolone-resistant and macrolide-resistant), *Salmonella* (fluoroquinolone-resistant), and *Neisseria gonorrhoeae* (third-generation cephalosporin-resistant and fluoroquinolone-resistant). Resistance of the following bacterial infectious agents is considered to be of medium priority: *S. pneumoniae* (penicillin-non-susceptible),

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Haemophilus influenzae (ampicillin-resistant) and *Shigella* (fluoroquinolone-resistant). Hence, the emergence of MDR bacterial strains (particularly of those that have acquired plasmid encoded resistance genes) on one side and the lack of novel antimicrobial molecules in the pharmaceutical pipelines on the other contribute to this serious global threat to human health [3]. Hence, one reasonable approach to tackle this issue is to identify antibiotic-independent candidates with antimicrobial properties that might be alternative or adjunct options to combat infections by bacterial pathogens including MDR strains. Given that vitamins including vitamin D are well known for their health-beneficial properties [4, 5, 6, 7, 8, 9, 10, 11, 12], a comprehensive literature survey was performed addressing the potential antimicrobial effects of vitamin D with a focus on bacterial including MDR pathogens.

Antimicrobial and Immune-Modulatory Effects of Vitamin D. Natural rich sources of vitamin D such as cod liver oil or sun exposure were used in the pre-antibiotic era for the therapy of tuberculosis or scrofula, for instance [13, 14]. After the discovery of synthetic antibiotics, the anti-infectious value of vitamin D was rather ignored for a while until the increasing cost of antibiotics and particularly the rise in antibiotic resistance led to the need to search for alternative and/or adjunct antibiotic-independent therapeutic strategies, with vitamin D supplementation as a promising option [13, 14].

Ultraviolet light exposure stimulates the production of vitamin D in the skin from 7-dehydrocholesterol. After catabolizing steps in defined tissues, including the liver, the biologically active form of vitamin D, 25(OH)-vitamin D, is secreted into the circulation. In the kidneys, the enzyme CYP27B1 further metabolizes 25(OH)-vitamin D to $1,25(OH)_2$-vitamin D, which is the main biologically active hormonal form of vitamin D [15, 16]. Three hormones, namely, parathormone (PTH), fibroblast growth factor 23 (FGF23), and $1,25(OH)_2$-vitamin D itself, are involved in the control of CYP27B1 activity in the renal proximal convoluted tubule, providing, to some extent, a quick response to changes in the ambient calcium and phosphate levels. Calcitonin regulates CYP27B1 activity in the proximal straight tubule. While PTH is stimulating CYP27B1 production, FGF23 is inhibiting its expression. Due to the fact that calcium and phosphate regulate the secretion of PTH and FGF23 from the parathyroid glands and bone, they also indirectly regulate CYP27B1 activity in the kidneys [17].

Previous reports documented health-beneficial effects of vitamins in general [4, 5, 6, 7, 8, 9, 10, 11, 12]. Among these, vitamin D has been shown to alleviate several morbidities, including bacterial infections caused by *Mycobacterium tuberculosis* and *S. aureus* [8, 18, 19, 20, 21, 22]. In addition, vitamin D has been shown to support clearance of *P. aeruginosa* by macrophages [8, 23] and to exert direct bactericidal activity against *Helicobacter pylori* [6, 7, 24], as well as against *Streptococcus mutans* [4]. Notably, in vitro studies revealed that the expression of distinct virulence factors in *Porphyromonas gingivalis*, as well as bacterial growth, could be inhibited by vitamin D application [25].

The immune-modulatory properties of vitamin D are exerted following binding to the vitamin D receptor (VDR) that is expressed by numerous innate and adaptive immune cell subsets, including monocytes, macrophages, dendritic cells, naïve CD4+ T cells, T helper (Th) 1 cells and Th2 cells [26]. The VDR constitutes a nuclear hormone receptor, and its activation leads to the induction of chromatin remodeling, resulting in either activated or suppressed expression of distinct genes [26]. After binding on VDR, vitamin D causes hetero-dimerization with the retinoic acid receptor (RXR),

affecting gene expression either through binding of the VDR/RXR complex to vitamin D response elements (VDREs) of the target genes or association with other transcription factors, preventing binding and activation of target genes [26, 27]. Immune-related genes, such as CD14 [28], β-defensin (DEFB4) [29], TNF-α [30], Toll-like receptor (TLR)-4 [28], hepcidin (HAMP) [31], co-stimulatory molecules involved in antigen presentation such as CD86, CD80, and CD40 [32], Th1 cytokines (IL-2, IL-12, and IFN-γ), and Th2 cytokines (IL-4, IL-5 and IL-10) [33, 34, 35], represent all vitamin D target genes. The action of vitamin D is not restricted to the modulation of respective gene expression. The VDR activation further stimulates the differentiation of monocytes into mature macrophages and induces macrophage chemotactic ability and phagocytosis of *M. tuberculosis* [36, 37, 38, 39]. Furthermore, $1,25(OH)_2$-vitamin D has been shown to modulate cathelicidin antimicrobial peptide (CAMP) gene expression in innate immune cells such as monocytes and macrophages. CAMP can be found in the lysosomes of macrophages, as well as neutrophils. Hence, in addition to acting as chemo-attractants of other immune cells, $1,25(OH)_2$-vitamin D as the main active hormonal form of vitamin D [15, 40] exerts pivotal roles in innate immunity with broad antimicrobial effects [31, 41].

The molecular mechanisms underlying the antimicrobial effects of vitamin D involve distinct antimicrobial peptides (AMPs) [42], also known as host defense peptides (HDPs), and will be more comprehensively addressed later on. In brief, these relatively small (<10 kDa) AMPs are known for their net positive charge and amphipathicity of the cell [43, 44] and can be divided into two groups, namely, cathelicidins and defensins [45, 46, 47]. Many pathogenic bacteria, such as, *N. gonorrhoeae, Vibrio cholerae*, enterotoxigenic *Escherichia coli* and *Shigella flexneri* have been shown to be tackled by HDPs [48, 49, 50, 51]. Previous studies further revealed that induction of endogenous HDP production exerted enhanced antimicrobial capacities in rabbits and chicken [52, 53, 54, 55, 56]. On the other hand, infections and injuries lead to an increased expression of HDPs with an unwanted exaggerated immune response harming the vertebrate host. Vitamin D3 and the short chain fatty acid butyrate, however, are capable of inducing HDPs without provoking inflammatory responses due to an orchestrated and well-balanced interaction with commensal microbes [55, 57].

Methods

Inclusion and Exclusion Criteria. The main inclusion criteria for the literature survey were in vitro and in vivo, such as clinical infection studies with bacterial strains and antimicrobial effects of vitamin D (active form) and its derivates. In vitro and in vivo studies addressing anti-viruses and anti-fungi properties of vitamin D were excluded.

Searching Strategy. Using the MEDLINE database PubMed, we performed an online literature survey of publications investigating the antibacterial effect of vitamin D directed against bacteria including MDR strains. Publications of the past 10 years (i.e., between 2009 and 2019) were considered, and the following steps (as summarized in Table 1) were carried out using Boolean logic through the advance search history option on the PubMed database.

Firstly, using the Boolean operator OR, which ensured that synonyms were included, the literature was searched for publications with the key words "Vitamin D OR vitamin D3 OR Cholecalciferol OR Calciol". By using the MeSH term, this method was further enhanced in order to find publications with any possible variations of the name of vitamin D.

Table 1. Boolean logic search results on PubMed

Search	Add to builder	Query	Items found	Time
#7	Add	Search ((vitamin d or vitamin d3 or cholecalciferol or calciol)) AND ((antimicrobial or antibiotic)) AND ((antibiotic resistance)) Filters: published in the last 10 years	29	08:42:35
#6	Add	Search ((vitamin d or vitamin d3 or cholecalciferol or calciol)) AND ((antimicrobial or antibiotic)) AND ((antibiotic resistance))	46	08:42:09
#5	Add	Search antibiotic resistance	192750	08:41:25
#4	Add	Search ((vitamin d or vitamin d3 or cholecalciferol or calciol)) AND ((antimicrobial or antibiotic))	3337	08:39:31
#3	Add	Search antimicrobial or antibiotic	1751536	08:37:43
#2	Add	Search vitamin d OR vitamin d3 OR cholecalciferol OR calciol	82904	08:36:59
#1	Add	Search vitamin d	80994	08:35:17

Secondly, the search term "antimicrobial or antibiotic" was employed to identify studies that centered and focused on antibiotic properties. Thirdly, the term "antibiotic resistance" was included to assure that investigations on resistant bacteria were also contained. Finally, in order to limit the results, all three search terms were combined through the Boolean operator "AND".

Thereby, 46 items could be found. Studies published within the previous 10 years were searched for yielding 29 articles, all of which were carefully evaluated, considering the above-mentioned inclusion and exclusion criteria. Some of the articles were withdrawn because they were relating to viruses or fungi; others did not focus on the antimicrobial effect of vitamin D. Finally, 6 articles remained. Nevertheless, withdrawn articles provided helpful information for the understanding of the immune-modulatory functions of vitamin D, in particular, and were included in the discussion.

Data Extraction. In order to provide a systematic literature search, all the information gained from the studies was carefully evaluated and selected, considering the defined inclusion and exclusion criteria in the first line. The type of the study, the characteristics of the populations participating in the study, the main findings of each publication, how relevant the findings were related to the addressed topic, and how the different parameters were measured, as well as possible study errors or derived inconsistencies, were additionally taken into consideration.

Ethics Statement. Not applicable (literature survey).

Results

Searching Results. An *E. coli* strain with a K1 capsule was isolated from a neonate suffering from meningitis and further used in an in vitro study. Microglia were prepared from vitamin D-deficient mice and from wild-type counterparts, incubated with the *E.coli* isolate, and stimulated with synthetic TLR-1/-2, TLR-3, TLR-4, or TLR-9 agonists. In both vitamin D-deficient and wild-type mice, the *E. coli* eradication rates increased upon stimulation with different TLR agonists in a dose-dependent manner. The study further revealed that high dose stimulations of incubated microglia with TLR-3, TLR-4, and TLR-9 ligands, but not with TLR-1/-2 agonists, cause significant increases in the *E. coli* phagocytosis rates in the microglia derived from wild-type but not from vitamin D-deficient mice, supporting the anti-microbial effects of vitamin D [5].

Another study addressed the antibacterial effect of exogenous vitamin D against *Helicobacter pylori* Sydney strain 1 both in vitro and in vivo. Firstly, the pathogen was used to induce chronic gastritis in the stomach of mice that were either subjected to vitamin D or placebo treatment. Furthermore, in order to investigate the antimicrobial action of vitamin D on intracellular *H. pylori* replication, healthy human gastric epithelial cells (HFE145) were infected with *H. pylori* for 72 h. Two months post-infection, gastric *H. pylori* burdens were lower in vitamin D mice, as compared to placebo-treated mice. In support, the intracellular *H. pylori* replication could be dampened upon $1,25(OH)_2$-vitamin D application, as compared to placebo stimulation in vitro [6].

In a clinical study including 150 *H. pylori*-infected patients from Egypt, the pathogen-eradicating effects of vitamin D were assessed. Before the start of a 14-day triple therapy (with clarithromycin, amoxicillin, and omeperazole) and 4 weeks thereafter, the 25(OH)-vitamin D serum concentrations were measured in each patient. Of note, vitamin D levels were significantly higher in the successfully *H. pylori* eradicated cohort as compared to the triple therapy non-responders. Whereas two thirds of patients from the failed treatment group suffered from overt vitamin D deficiency, this held true for only 9.5% of the *H. pylori*-negative patients. Remarkably, a 25(OH)-vitamin D serum deficiency could be found in more than 25% of all patients included in the survey [7].

In an observational study from Japan, however, the antimicrobial effects of vitamin D could not be confirmed, given that even a negative correlation between vitamin D-rich diet/ serum-vitamin D levels and anti-*H. pylori* effects could be assessed. Three-hundred-eighty-nine *H. pylori* infected patients with diagnosed gastritis received a triple *H. pylori* eradication therapy, consisting of two antibiotics, namely, amoxicillin with clarithromycin or metronidazole, and a proton pump inhibitor (PPI). The daily vitamin D intake of the participants was determined applying a food-frequency questionnaire. The results revealed that the estimated daily intake of vitamin D was significantly lower in the successfully treated group than in the triple therapy non- responding cohort [58].

A screening series of 853 drugs approved by the Food and Drug Administration (FDA) revealed that 126 compounds, which turned out to be vitamin D analogues, displayed antimicrobial activities directed against *S. mutans* due to planktonic cell lysis. In a further in-depth evaluation of the structure of the respective compounds, the 3 compounds with the most potent antibacterial activities were the vitamin D analogues, namely, alpha-calcidol and doxercalciferol, and vitamin D. Antimicrobial susceptibility assays with *S. mutans* cultures revealed minimal inhibitory concentrations (MICs) of 16 µg/mL of the vitamin D derivates under investigation [4].

Lipid-soluble compounds including vitamin D have been found to cause changes in the fluidity of the bacterial membrane, facilitating the penetration of synthetic substances, including antibiotics [59, 60]. Therefore, a recent in vitro study addressed the antibacterial activity and antibiotic-modifying effects of vitamin D directed against clinical MDR *P. aeruginosa*, *E. coli*, and *S. aureus* strains. Measurement of the MICs of the aminoglycosides amikacin, neomycin, and gentamicin applying the broth microdilution assay revealed that vitamin D alone did not exhibit antimicrobial effects against the 3 MDR bacterial isolates. Addition of vitamin D to amikacin or

gentamicin, however, could lower the MIC of the respective aminoglycosides against the clinical MDR *P. aeruginosa* strain by a factor <0.25 and hence improve the antimicrobial susceptibility more than four times. Notably, the combination of vitamin D and neomycin even had an antagonistic effect, thus, reducing the effectiveness of the antibiotics. The synergistic antimicrobial effects of vitamin D with the aminoglycosides against the *E. coli* strain were less pronounced as compared to those against *P. aeruginosa* and virtually missing in case of *S. aureus* [8].

Further Findings from Studies Providing Useful Knowledge Regarding the Multifaceted Properties of Vitamin D in Health and Disease. As aforementioned, the antibacterial effects of vitamin D are also due to the induced expression of antimicrobial peptides such as cathelicidin and β-defensin, further providing synergistic antimicrobial properties [61]. A recent study revealed positive associations between synthetic calcium channel blockers, expression of cathelicidin and β-defensin, and intracellular 1,25(OH)$_2$-vitamin D concentrations in immune-compromised patients during sepsis [62]. The authors hypothesized that septic patients suffering from infections by antibiotic-resistant pathogens making the channels sensitive might benefit from calcium channel-blocking medications [62]. However, the specific relationship between intracellular calcium concentrations, vitamin D, and calcium channel blockers still needs to be investigated in more detail.

Further studies addressed potential associations between sepsis, vitamin D concentrations, kidney function, and mortality. In a study published in 2009, 24 septic patients admitted to the intensive care unit (ICU), 5 non-septic ICU control patients, and 11 healthy subjects were included and subjected to comparative analyses of vitamin D serum concentrations, kidney function, and mortality. Results revealed a positive correlation between 25(OH)-vitamin D serum concentrations and of the antimicrobial peptide cathelicidin (LL-37) [63]. Other reports hypothesized that kidney failure might be considered a risk factor for infection and that the retention of phosphorus with lowering calcium levels were associated with higher mortality [64, 65]. A potential mechanistic explanation for this association might be the following:

25(OH)-vitamin D is filtered in complex with the vitamin D binding protein and can be reabsorbed from the glomerular filtrate [66]. After filtration, in which the megalin protein plays a major role, the binding protein is degraded, the 25(OH)-vitamin D is converted into 1,25(OH)$_2$-vitamin D, and both 25(OH)-vitamin D and 1,25(OH)$_2$-vitamin D are reabsorbed into the circulation [65, 66]. Some knowledge of renal failure as a risk factor for infection could be obtained by studying the response to phosphorus retention in the combined effects of PTH, FGF23, and Klotho [67]. Kidney failure with vitamin D deficiency stimulates the release of FGF23, which cooperates with the anti-aging protein Klotho for elimination of retained phosphorus if vitamin D is replaced [64, 67, 68]. PTH and FGF 23 are in the position to increase, at the proximal tubular site, the phosphate transport to decrease phosphorus reabsorption. However, while PTH contributes to activation of 1-alpha-hydroxylase, FGF23 (in competition) inhibits activation of this enzyme hampering, at the same time, the formation of the active form of vitamin D. This leads to adverse, if not even fatal, consequences, pointing towards the pivotal role of active vitamin D within this pathophysiological scenario [64, 67]. Considering the link between phosphorus and calcium [64, 65], as well as the relationship between vitamin D and phosphorus [64, 67, 68], this could further support the orchestrated interaction between vitamin D, calcium, and host defense peptides to protect from human infections.

A previous publication addressed the correlation between shigellosis and antimicrobial peptides [69]. *Shigella* infections usually cause fever together with mucoid and hemorrhagic stool. In response to *Shigella* infection, gut epithelial cells induce mucosal secretion of AMPs, which exert antibacterial lytic effects and recruit immune cells to the site of the infection [50]. AMPs further share important roles in chemotaxis, angiogenesis, and immune cell activation [70]. It is hypothesized that deficiencies in Th17 cells, which are important for epithelial immunity against pathogens, lead to deficiency in AMPs resulting in reduced pathogenic antigen presentation at epithelial surfaces [69, 71, 72, 73, 74]. If this hypothesis is correct, compounds with the ability to induce epithelial AMP expression (such as butyrate, phenyl-butyrate and vitamin D, for instance) could "by-pass" a deficient Th17-cell compartment and be used as a novel adjunct and antibiotic-independent strategy to combat infections [69].

To date, a potential link between vitamin D deficiency and susceptibility towards tuberculosis could be found in several studies. An epidemiological study revealed that the incidence of tuberculosis was two times lower in white populations with increased levels of vitamin D than in black populations [75]. Higher incidences of tuberculosis during spring and early summer also support an inverse correlation between vitamin D levels and tuberculosis [76, 77]. Other studies, however, showed that both lower and higher circulating levels of vitamin D might impact the progression of active tuberculosis [78, 79]. Furthermore, an in vitro study revealed that vitamin D stops the entry of *M. tuberculosis* into and the bacterial survival within the cell [80] by promoting the fusion of phagosomes and lysosomes in macrophages and subsequently reducing the viability of *M. tuberculosis* [81]. In addition, vitamin D induces the transcription of AMPs, further restricting the intracellular growth of *M. tuberculosis* [61, 82, 83]. Moreover, high intracellular concentrations of iron have been reported to enhance the mycobacterial growth and survival [31, 84], given that vitamin D down-regulates the HAMP expression, leading to decreased intracellular iron concentrations resulting in suppressed survival of intracellular bacteria including *M. tuberculosis* [85]. Furthermore, vitamin D modulates both innate and adaptive immune responses resulting in dampened inflammatory sequelae of infection [86, 87, 88, 89, 90]. Several clinical trials have used vitamin D supplements as an adjuvant supplementation for the therapy of tuberculosis. Whereas some studies revealed better treatment responses [91, 92, 93, 94], others did not [79, 95]. Therefore, well-designed studies should further unravel potential antibiotic-independent approaches including vitamin D supplementation as an adjunct treatment option to combat tuberculosis particularly caused by MDR strains.

Discussion

Main Findings of the Literature Survey. The performed literature survey revealed potent antibacterial effects of vitamin D directed against a multitude of both Gram-positive and Gram-negative bacterial strains including *S. mutans*, *P. aeruginosa*, *E. coli*, *M. tuberculosis*, *H. pylori,* and *Shigella* as shown in vitro and in vivo. Of note, potent synergistic antibacterial effects of vitamin D in combination with aminoglycosides against clinical MDR *P. aeruginosa* and *E. coli* strains could also be found.

One in vivo study, however, revealed rather contrasting results given an even negative relationship between high dietary vitamin D intake and successful eradication of *H. pylori* in Japanese patients. There are several limitations that need to be taken into consideration and that might explain discrepant

results. For instance, in this study, antibiotic resistance of *H. pylori* was not assessed in the Japanese study cohort [58]. Furthermore, besides study design many dependent and independent variables might be responsible for inconsistencies in the assessed parameters, defined outcome, ethnicity, and genetic, as well as the epigenetic factors within the respective study populations among many others. Nevertheless, overall, there is a strong body of evidence supporting the health-beneficial roles of exogenous vitamin D opening novel avenues for the treatment and even prevention of many human morbidities including infections with (resistant) bacterial strains.

Open Questions and Areas for Future Research. In the present literature survey, the antimicrobial effects of vitamin D were demonstrated in very heterogeneous in vitro and in vivo studies of limited numbers. Due to this heterogeneity a definitive conclusion about the antimicrobial effects of vitamin D cannot be drawn. The molecular mechanisms underlying the effects of vitamin D in patients with distinct morbidities caused by bacteria including MDR strains needs to be further unraveled. Moreover, in the past 10 years, only one single in vitro study addressing synergistic antibacterial properties of vitamin D in combination with synthetic antibiotic compounds against MDR bacterial strains exists to date [8]. Hence, more well-designed studies should be conducted to explore the interaction between vitamin D, antibiotics, and eradication therapies of MDR pathogens in more detail. Considering the dynamics in the emergence and spread of MDR bacterial strains, the lack of novel antimicrobial molecules in the pharmaceutical pipelines and, hence, the progressive global threat due to more and more limited options to combat potentially life-threatening infectious diseases in the near future should further emphasize that this innovative step of research and clinical application is urgently needed.

Limitations of the Literature Survey. Due to different factors during the research or due to mistakes in the studies that were carried out and published, wrong conclusions may arise. Therefore, it is important to carefully consider and review the information taken from the studies. The fact that some clinical trials have been carried out in a very distinct population (e.g., Japanese population) or in a limited cohort (low numbers of samples or patients) constitutes a profound limitation. It should be also mentioned that the present work has methodological limitations. Although the effort to reach a search strategy has been made, which would be as sensitive as possible, there might be relevant studies that have not been included. Of note, the quality assessment of the included studies was performed by a single investigator.

Antimicrobial Peptides and Vitamin D – Future Perspectives as Treatment Options. HDPs including AMPs are molecules with immune-modulatory properties, competent to regulate innate and adaptive immune responses, and lyse a broad range of microorganisms such as bacteria, fungi, parasites, and viruses [44, 45, 96, 97]. Interestingly, AMPs exert potent antagonistic effects directed against lipopolysaccharide (LPS), the main important cell wall constituent and pathogenicity factor of Gram-negative bacteria [98]. In addition, it has been shown that AMPs act as potent inhibitors of microbial biofilms with antibiotic tolerance [99, 100]. Furthermore, AMPs stimulate cell proliferation, promote wound healing, and kill cancer cells [44, 45, 96]. Thus, AMPs play primary roles in host protection against microbial infections. In support, the beneficial anti-inflammatory effects of AMPs in skin infections diseases such as psoriasis [101], atopic dermatitis [102], rosacea [103], Kostmann's syndrome [104], severe congenital neutropenia [105], lupus erythematodes [106], acne vulgaris [107], folliculitis [108],

scleroderma [109], cutaneous T-cell lymphoma [110], or basal cell carcinoma [111], in autoimmune disorders [112, 113], respiratory infectious diseases [114], and cancer [115, 116, 117, 118] have been shown in several studies. The underlying antimicrobial mechanism might be explained by the fact that the AMPs are cationic and have an affinity to the negatively charged bacterial membrane resulting in its disruption and bacterial cell lysis [69]. Thus, stimulation of endogenous AMP production represents a promising approach for treating human morbidities including infections. The link between AMPs and vitamin D might be due to the following mechanisms: vitamin D is known to synergize with 4-phenylbuturate (PBA), a substance competent to induce expression of AMPs [119]. In addition, vitamin D itself can also up-regulate the expression of the AMP cathelicidin LL-37 [120]. An adjuvant therapy of PBA and $1,25(OH)_2$-vitamin with first line anti-mycobacterial compounds, such as rifampicin, isoniazid, ethambutol, and pyrazinamide, revealed positive effects in tuberculosis treatment [121]. This further provides strong evidence that AMP induction or modulation in combination with conventional antibiotics might be reasonable options to combat many infections. Therefore, the dietary modulation of HDP synthesis through increasing daily vitamin D intake, for instance, might be a novel promising, antibiotics-independent approach for antimicrobial therapy [122, 123]. Although this scientific research field has yet to be elucidated in more detail, the studies that have been already done set the bases for novel developments and open the door for the use of AMP inducers as dietary supplements to treat infections and other human diseases including skin diseases, autoimmune disorders, and cancer [111, 112, 113, 114, 115, 122].

List of Abbreviations

AMP: antimicrobial peptide
AMR: antimicrobial resistance
CAMP: Cathelicidin antimicrobial peptide
DEFB4: beta-defensin
ESBL: extended spectrum beta-lactamase
FGF23: fibroblast growth factor 23
FDA: Food and Drug Administration
HAMP: hepcidin
HDP: host defense peptides
ICU: intensive care unit
LPS: lipopolysaccharide
MRSA: methicillin-resistant *Staphylococcus aureus.*
MIC: minimal inhibitory concentration
MDR: multi-drug resistant
PTH: parathormone
PBA: 4-phenylbuturate
PPI: proton pump inhibitor
RXR: retinoic acid receptor
Th: T helper
TLR: Toll-like receptor
VISA: vancomycin-intermediate *Staphylococcus aureus*
VRE: vancomycin-resistant enterococci
VDR: vitamin D receptor
VDRE: vitamin D response element
WHO: World Health Organization

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Authors' Contributions

AG conceived and designed the survey, wrote the paper. SB provided critical advise in design of the survey, edited paper. MMH supervised the survey, co-wrote the paper.

Conflict of Interests

SB and MMH are Editorial Board members.

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