Available online at www.sciencedirect.com

ScienceDirect

Journal of Nutritional Biochemistry 99 (2022) 108841

Journal of Nutritional Biochemistry

REVIEW ARTICLE

Vitamin D in autophagy signaling for health and diseases: Insights on potential mechanisms and future perspectives

Sujit Kumar Bhutia*

Cancer and Cell Death Laboratory, Department of Life Science, National Institute of Technology Rourkela, Rourkela, 769008, India

Received 6 December 2020; received in revised form 8 June 2021; accepted 10 August 2021

Abstract

Vitamin D regulates the pleiotropic effect to maintain cellular homeostasis and epidemiological evidence establishes an association between vitamin D deficiency and various human diseases. Here, the role of autophagy, the cellular self-degradation process, in vitamin D-dependent function is documented in different cellular settings and discussed the molecular aspects for treating chronic inflammatory, infectious diseases, and cancer. Vitamin D activates autophagy through a genomic and non-genomic signaling pathway to influence a wide variety of physiological functions of different body organs along with bone health and calcium metabolism. Moreover, it induces autophagy as a protective mechanism to inhibit oxidative stress and apoptosis to regulate cell proliferation, differentiation, and immune modulation. Furthermore, vitamin D and its receptor regulate autophagy signaling to control inflammation and host immunity by activating antimicrobial defense mechanisms. Vitamin D has been revealed as a potent anticancer agent and induces autophagy to increase the response to radiation and chemotherapeutic drugs for potential cancer therapy. Increasing vitamin D levels in the human body through timely exposure to sunlight or vitamin D supplements could activate autophagy as part of the homeostasis mechanism to prevent multiple human diseases and aging-associated dysfunctions.

Keywords: Autophagy; Cancer; Inflammation; Immunity; Vitamin D; Oxidative stress.

1. Introduction

Vitamin D deficiency is a major global health issue. It is considered a potential pandemic, and about 1 billion people have vitamin D deficiency worldwide. However, vitamin D deficiency individuals are asymptomatic and highly prevalent in aged, obese, and home resident individuals with less exposure to sunlight. Vitamin D deficiency is also related to the population with higher melanin content in the skin, including Indians. Vitamin D is a fat-soluble steroid hormone that has long been known for its calcium homeostasis and bone metabolism [1-3]. Moreover, vitamin D regulates pleiotropic non-calcemic cellular functions, including immune regulation, inflammation, antioxidant defense, differentiation, and cell death to maintain homeostasis [4,5]. Vitamin D deficiency has been associated with different human diseases, including infection and inflammatory disease [6-8], neural disorder, kidney dysfunction, aging [1,2], and cancer [9-12], indicating its importance in health benefits in humans.

Autophagy is an evolutionary conserved catabolic process to engulf cytoplasmic materials and dysfunctional organelles through the formation of double-layered autophagosome that fuses with lysosome for degradation and recycling of nutrients to maintain cellular homeostasis. Autophagy induces stress response and triggers by starvation, infection, and toxin exposure to protect cells. The housekeeping function of autophagy recycles metabolic substrates, including free amino acids, carbohydrates, nucleotides, and lipids for the biosynthetic process and ATP generation for maintenance and cell survival. Furthermore, autophagy functions as a protective mechanism by eliminating dysfunctional organelles, protein aggregates and invading intracellular microbes through lysosomal degradation [13,14]. Autophagy primarily serves as a cytoprotective mechanism, and excessive autophagy leads to cell death, known as autophagy-dependent cell death. Autophagy plays a crucial role in maintaining body homeostasis, and its impairment is associated with neural disorders, developmental abnormities, inflammatory diseases, aging, and cancer [15,16].

This review highlights the potential role of autophagy in the health-promoting effect of vitamin D in different diseases. Moreover, it aims to discuss autophagy signaling by activating the vitamin D receptor (VDR)-dependent pathway to control cellular functions and treat chronic inflammatory, infectious diseases, and cancer. Furthermore, it highlights the role of vitamin D in autophagy activation through a genomic and non-genomic signaling

* Corresponding author at: Sujit Kumar Bhutia, Cancer and Cell death Laboratory, Department of Life Science, National Institute of Technology Rourkela, Rourkela 769008, Odisha, India. Tel.: +91 661 2462686; fax: +91 661 2472926.

E-mail address: sujitb@nitrkl.ac.in.

https://doi.org/10.1016/j.jnutbio.2021.108841
0955-2863/

pathway to influence a wide variety of physiological processes in different tissue to maintain homeostasis. More importantly, this review discusses the potential function of vitamin D and its receptor to induce autophagy to promote antimicrobial defense mechanisms to control inflammation and host immunity. In addition, it showed that vitamin D exhibits as a potent anticancer agent and potentiates the effect of radiation and chemotherapeutic drug through modulation of autophagy for potential therapy. Lastly, the review focuses on the protective role of vitamin D-induced autophagy by preventing oxidative stress and apoptosis to control aging and age-related diseases as a part of the homeostasis mechanism.

2. Vitamin D, biosynthesis, and receptor

Vitamin D, a fat-soluble, seco-steroid prohormone, controls multiple biological functions to maintain cellular homeostasis [17,18]. The natural process of generating vitamin D_3 is through UV-B exposure of the skin under direct sunlight with a restricted number of foods, including cod liver oil, fatty fish, salmon, tuna, meat [19-21], and mackerel. However, mushrooms contain a high amount of vitamin D_2 which is also known as ergocalciferol. The synthesis of vitamin D consists of complex reactions in different tissues in the human body. In the presence of UV-B from sunlight, the cholesterol precursor 7-hydrocholesterol photolyzes through a non-enzymatic process to generate previtamin D_3 that subsequently undergoes thermal isomerization to form vitamin D_3 (cholecalciferol) in the skin. Similarly, plants, particularly fungus, synthesize ergocalciferol (vitamin D_2) from ergosterol. The endogenous vitamin D_3 and dietary supplements, as well as vitamin D_2 from fungus, are transferred to the liver and converted to 25-hydroxyvitamin D_3 [25(OH)D3] (calcidiol) through the addition of hydroxyl group at C-25 position by vitamin D hydroxylates (encode by CYP27A1). The 25(OH)D3 (refer as vitamin D hereafter) represents the serum concentration of vitamin D and functions as a biomarker for vitamin D status of a person. This vitamin D metabolite is transported in the blood to the kidney as well to cells of different tissue and converted to 1,25 (OH)2D3 through mitochondrial enzyme 25(OH)D3-1α hydroxylase (encode by CYP27B1) and is the active form of vitamin D_3 to regulate various cellular functions. Interestingly, as a feedback mechanism, 1α 25(OH)2 24 hydroxylase (encode by CYPB24A1), another enzyme present in mitochondria, converts 25(OH)D3 or 1α 25 (OH)2D3 to 24, 25 (OH)$2D_3$ or 1, 24, 25 (OH)$2D_3$ through 24-hydroxylation for degradation and excretion in bile [3,6,7,18] (Fig. 1).

Vitamin D functions through the genomic and non-genomic pathways (Fig. 1). In the genomic mechanism, vitamin D binds to its receptor known VDR, widely distributed in many different cell types to regulate gene transcription [3,5]. Like classical transcription factors, VDR forms a heterodimer with retinoid-X receptor (RXR) through the DNA-binding domain and α-helical ligand-binding domain leading to transport into the nucleus. The complex binds to vitamin D response elements (VDREs) in the regulatory part of target genes. It showed that VDREs generally are located close to the promoter region, but a recent study revealed that VDREs could find a distant site of about 75 kb to regulate transcription of about 1,000 genes indicating the potential influence of vitamin D to regulate the transcriptome. Vitamin D target genes includes nuclear factor erythroid 2-related factor 2 (NRF2), GSTA4, CYP1A1, CYP3A4, CYP24A1 for antioxidant and detoxification; MYC, JUN, FOS, CCND1, CDKN1A, CDKN1B, G0S2, CST5, DKK1 for proliferation and cell cycle control; CDH1, CDH2, OCLN, CLD2, TJP1, CASR, FLNA for cellular differentiation; BCL2, BAK, BAG, BIRC5, BAX, G0S2, IGFBPs for apoptosis; HIF1A, VEGF, DKK4 for angiogenesis; NFKB1A, RELA, IL1B, IL6, IL8, IL10, IL17, IL23, CL2, CCL11, CCL13, CYTL1 for immunoregulation [2,4,22]. Furthermore, VDR controls the epigenetic mechanism through DNA methylation, histone modification, and chromatin remodeling to contribute vitamin D-dependent phenotypic stability and cellular processes [2,3,17]. For example, vitamin D controls the methylation state of its gene promoters for gene activation. It showed that vitamin D response gene methylation and genome-wide methylation were correlated with vitamin D deficiency. The VDR/RXR complex activates lysine demethylase 6B and histone acetyltransferases (HATs), including p300/CBP and steroid receptor coactivators 1 and 2 (SRC-1 and SRC-2) to regulate gene-related functions [23-26].

In non-genomic action, vitamin D functions through membrane binding receptor known as rapid response steroid-binding proteins to control various signaling molecules, including catalase, superoxide dismutase, phosphatidylinositol-3-kinase (PI3K)/protein kinase B (AKT), protein kinases A and C, adenylyl cyclase, phospholipases Ca^{2+} ion channels, and generation of secondary messengers without affecting gene transcription [3,27].

3. Autophagy: the self-degradative mechanism

Autophagy is a self-digestion process, and the word autophagy is derived from the Greek word auto means self, and phagia means eating. Autophagy is regulated by autophagy-related proteins (ATG) and comprises the following steps: (1) phagophore nucleation, (2) phagophore initiation, (3) phagophore elongation to form autophagosome, and (4) autolysosome formation and degradation of cargo. Autophagy initiates by different stress signals, including starvation, protein aggregates, hypoxia, oxidative, and endoplasmic reticulum (ER) stress (Fig. 2). Autophagy induces the formation of sack-like structures known as phagophore in yeast and omegasome to a specific subcellular location known as phagophore assembly site on ER, and other organelles, as recently reported [28,29]. Autophagy stimulates through activation of Unc-51 like kinase (ULK1) complex consists of ULK1, ATG13, and FIP200. Autophagy promotes through multiple signaling complexes that control the cellular energy and nutrients through the mammalian target of rapamycin (mTOR). mTOR is found in two distinct forms, mTORC1 and mTORC2, but mTORC1 is predominated over mTOR2 for autophagy induction. ULK1 and ATG13 form complex and phosphorylated by mTOR in nutrient-rich conditions and remain inactive, switching off autophagy. During starvation, ULK1 is dissociated from the active site of mTORC1 and hypophosphorylated. ULK1 is self-activated through autophosphorylation leading to phosphorylation of ATG13 and FIP200 to initiate autophagy [30,31]. Autophagy also induces in response to energy depletion through a decrease in ATP/AMP ratio by activation of 5′ AMP-activated protein kinase (AMPK) and inhibition of mTOR as well as direct phosphorylation of ULK1 [32]. ULK1 complex activates the Class III phosphoinositide 3-kinase (PI3K; VPS34) complex to produce a pool of phosphatidylinositol 3-phosphate (PI3P) to expand the phagophore at the ER site. In the mammalian system, VPS34 complex consists of VPS34, Beclin-1, ATG14, pseudokinase p150, ultraviolet irradiation resistance-associated gene and Autophagy And Beclin 1 Regulator 1 which are recruited onto omegasome to increase catalytic activity for autophagosome biogenesis [13,33]. Furthermore, the ULK1 complex regulates the activity of ATG9, a transmembrane protein to deliver phospholipid to phagophore from different cellular membranes, including ER, Golgi complex, recycling endosome, and plasma membrane to expand the autophagic membrane. PI3P on omegasome recruits PI3K effector proteins, including WD repeat domain phosphorylation regulating protein and its partner ATG2; zinc finger FYVE domain contains protein 1 to phagophore through interaction with PI3K binding creating a platform for the association of ubiquitination conjugation system [34].

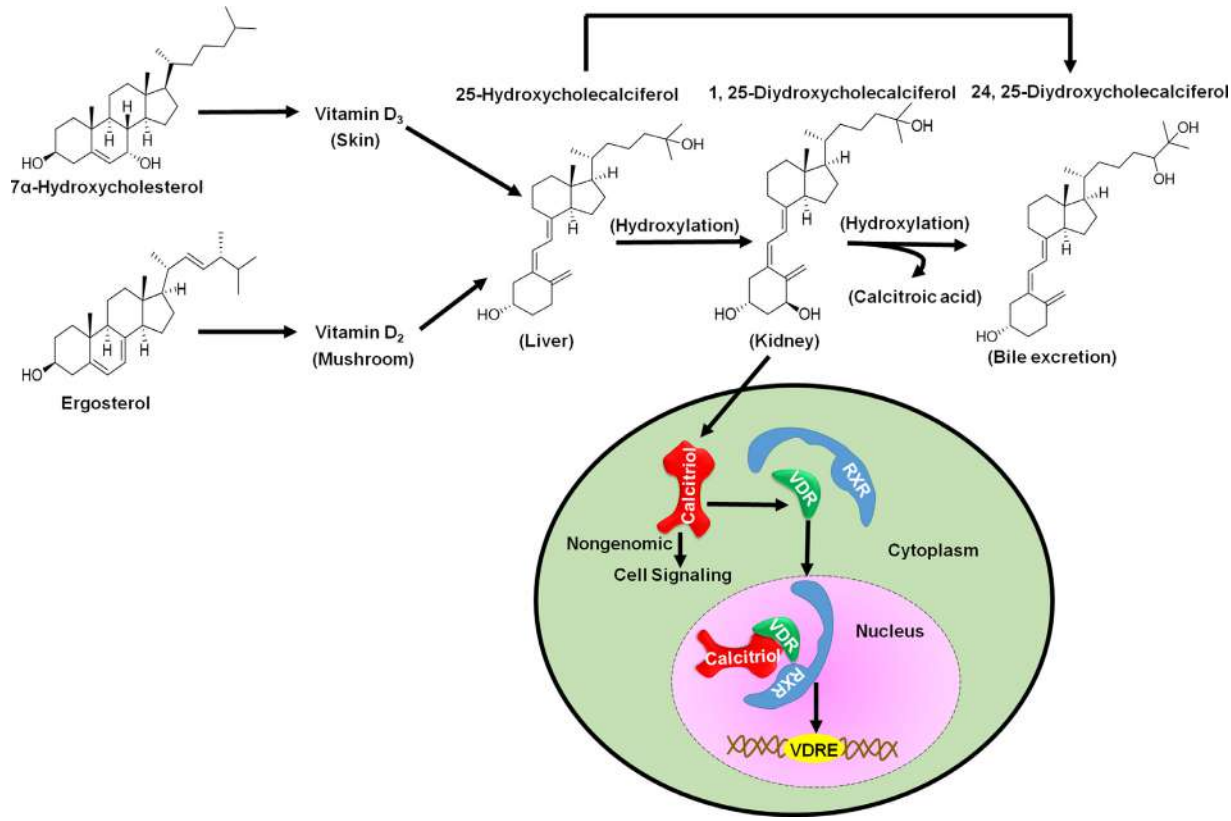

Fig. 1. . Vitamin D synthesis and signaling. The synthesis of vitamin D initiates from the 7-hydrocholesterol in the presence of UV-B to produce vitamin D_3 (cholecalciferol) in the skin, and fungus synthesizes ergocalciferol (vitamin D_2) from ergosterol. The vitamin D_3 and vitamin D_2 are transferred to the liver and converted to 25(OH)D3, which carries in the blood to the kidney and cells of different tissue and converted to 1,25 (OH)2D3 to regulate diverse cellular functions. Interestingly, as a feedback mechanism, 1α 25(OH)2 24 hydroxylase (encode by CYPB24A1), another enzyme presents in mitochondria, convert 25(OH)D3 and 1α 25 (OH)2 D3 to 24, 25 (OH)2 D3 and 1, 24, 25 (OH)2D3 through 24-hydroxylation to degrade and excrete in bile. Vitamin D functions through the genomic and non-genomic pathways. In the genomic mechanism, vitamin D binds to its receptor known as the vitamin D receptor (VDR) and form a heterodimer with retinoid-X receptor and translocate to the nucleus to activate target genes of vitamin D response element (VDREs). In non-genomic action, vitamin D functions through membrane binding receptors known as rapid response steroid-binding proteins to control various signaling molecules, including enzyme, kinases, phosphatases, ion channels, and generation of secondary messengers without affecting gene transcription.

The ubiquitination conjugation system is part of the elongation process which is essential to close the phagophore to form mature autophagosome [35,36]. Initially, ATG7 (E1 ubiquitin-activating enzyme) activates ATG12, and simultaneously, ATG10 (E1; ubiquitin-activating enzyme) activates ATG5 followed to form ATG12–ATG5 binary complex. Then ATG16L1 is conjugated with binary complex ATG12–ATG5 to form ATG12–ATG5–ATG16L1 ternary complex (E3 ubiquitin-like ligase). In the second ubiquitin system, ATG4, the cysteine protease cleaves LC3 family proteins to produce LC3 I with a glycine residue. The ternary complex is then recruited to phagophore through the interaction of ATG16L1 with WIPP2. ATG7 activates LC3 I to conjugate with phosphatidyl ethanolamine to form membrane anchor lipidated LC3 II through ATG3 and ternary complex E3 ligase at the omegasome on the outer and inner membrane of phagophore to promote phagophore elongation. Although autophagy is considered a bulk degradation process of cytoplasmic cargo, highly selective autophagic degradation occurs inside the cells. The selective autophagy induces through the LC3 interacting region in an ubiquitin-dependent and independent manner. The ubiquitin proteins bind to adaptor protein p62, which interacts with LC3 to selectively engulf the cargo. On the other hand, many receptors, including BNIP3 and BNIP3L, PUMA, directly interact with LC3 to induce selective autophagy and degradation of cellular organelles. The maturation process involves the fusion of the autophagosome with the lysosome to form an autolysosome. In the final step for fusion, SNARE proteins are inserted on the autophagosome, leading to HOPS complex recruitment. For example, an autophagosomal protein SNARE syntaxin 17 interacts with SNAP29 and VAMP8 on the endosome or lysosome involved in fusion process for autolysosome. The outer membrane of autophagosome fuses with the lysosomal membrane to form autolysosome to degrade the cargo with acid hydrolases in the lysosomal lumen [37]. Autophagy is associated with the development of proto-lysosome from autolysosome through autophagic lysosomal reformation to maintain the lysosomal pool as a feedback mechanism. The newly formed proto-lysosomes are then matured to form the active functional lysosome to continue autophagy to attain cellular homeostasis [38].

4. Vitamin D, vitamin D receptor, and autophagy signaling

Vitamin D and its receptor regulate autophagy through a different signaling pathway (Fig. 3). VDR promotes the expression of ATG16L1 at the transcriptional level to induce autophagy. Moreover, a low level of VDR in intestinal epithelial cells correlates with a decrease in the expression of ATG16L1 and impaired autophagy, leading to an increased risk for inflammatory bowel disease [39]. In another study, VDR constitutively represses LC3B expression, and knockdown of VDR results in a 100-fold increase in LC3B as compared to vitamin D-induced LC3B to promote autophagy. In this setting, vitamin D treatment dismisses the constitutive inhibition of the MAP1LC31B gene by VDR [40]. Furthermore, LC3

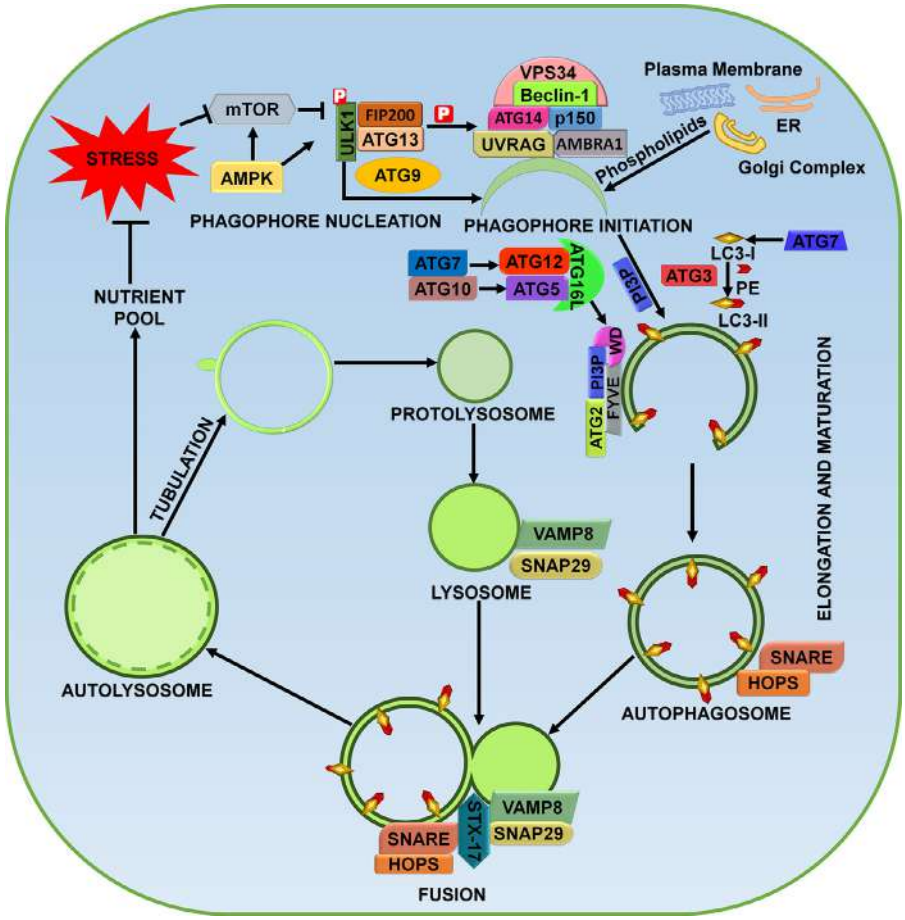

Fig. 2. . Mechanism of autophagy. Autophagy induces through inhibition of mTOR by the stress response. It results in the phosphorylation of the ATG13 and FIP200 by ULK1 followed by activation of Class III PI3K VPS34 complex to produce a pool of PI3P to expand the phagophore at the ER site. Moreover, ULK1 regulates the activity ATG9 helps in membrane extraction from other sources. PI3P on omegasome recruits PI3K effector proteins through interaction with PI3K binding creating a platform for the association of ubiquitination conjugation system. Further, the membrane gets elongated with the conjugation machinery to form a mature autophagosome, which gets fused with the lysosome to form an autolysosome. Autolysosomes degrade the cargos and help in nutrient recycling and/or undergo tubulation to form proto-lysosomes. The proto-lysosomes further matured to form the functional lysosomes available for the other cellular processes, including autophagy.

directly functions as a VDR ligand and promotes VDR/RXR heterodimer formation in the nucleus. Mechanistically, LC3 binds to VDR through its ligand-binding domain and transports to the nucleus to interact with RXR to regulate downstream signaling [41].

Vitamin D activates autophagy as a protective mechanism to inhibit oxidative stress and apoptosis. After UV exposure, vitamin D activates autophagy to conserve energy to inhibit AKT/GSK3/mTOR pathway in keratinocytes. Moreover, vitamin D activates PINK1/PARKIN-dependent mitophagy to inhibit reactive oxygen species (ROS) generation resulting in promoted post-UV DNA repair to inhibit oxidative DNA damage [42]. Vitamin D activates pro-survival autophagy through the up-regulation of Beclin-1 and inactivation of ERK1.2-AKT pathway in endothelial cells [43]. Moreover, vitamin D modulates MEK/ERK and PTEN/PI3K/AKT/mTOR signaling to activate autophagy in hepatocytes, and inhibition of the signaling pathway reduces the protective effect of vitamin D from hepatic injury [44]. In addition, in cardiomyocytes, vitamin D modulates autophagy through inhibition of β-catenin/TCF4/GSK-3β and mTOR signaling to protect from myocardial hypertrophy [45]. Vitamin D activates protein tyrosine phosphatase non-receptor type 6 by recruiting VDR–RXRA complex and NCOA1 to induce autophagy through modulation of MAPK and STAT3, leading to the degradation of accumulated lipids inside the macrophages to inhibit the formation of foam cells and atherosclerosis [46]. Vitamin D induces autophagy in osteoclast through RANKL to promote osteoclastogenesis for bone homeostasis [47]. Another study showed that vitamin D activates autophagy through AMPK/mTOR signaling pathway to inhibit osteoarthritis-associated inflammation in chondrocyte cells [48].

Vitamin D induces autophagy as an antibacterial defense mechanism. Vitamin D increases human cathelicidin/LL-37 peptide expression to promote autophagy through transcriptional up-regulation of Beclin-1 and ATG5. Moreover, vitamin D-induced cathelicidin increases autophagosome–lysosome fusion leading to the restoration of *Mycobacterium tuberculosis* (Mtb) containing phagosome maturation and degradation [49-51]. In addition, vitamin D activates PDIA3 membrane receptor and drives PDIA3-STAT3 complex to nucleus leading to increase in the expression of MCLN3 gene to enhance Ca^{2+} release from the lysosome to normalize acidification to eliminate *H. pylori* infection in autolysosomal degradation pathway [52]. Interestingly, in response to influenza A virus infection, vitamin D upregulates fusion proteins, including syntaxin 17 and V-type proton ATPase subunit, through the VDR signaling pathway to restore autophagic flux and inhibit apoptosis and tissue damage [53].

Vitamin D regulates different signaling pathways to induce autophagy in various cancers. Vitamin D activates Ca^{2+} signaling to induce autophagy and generates massive autophagosomes in a

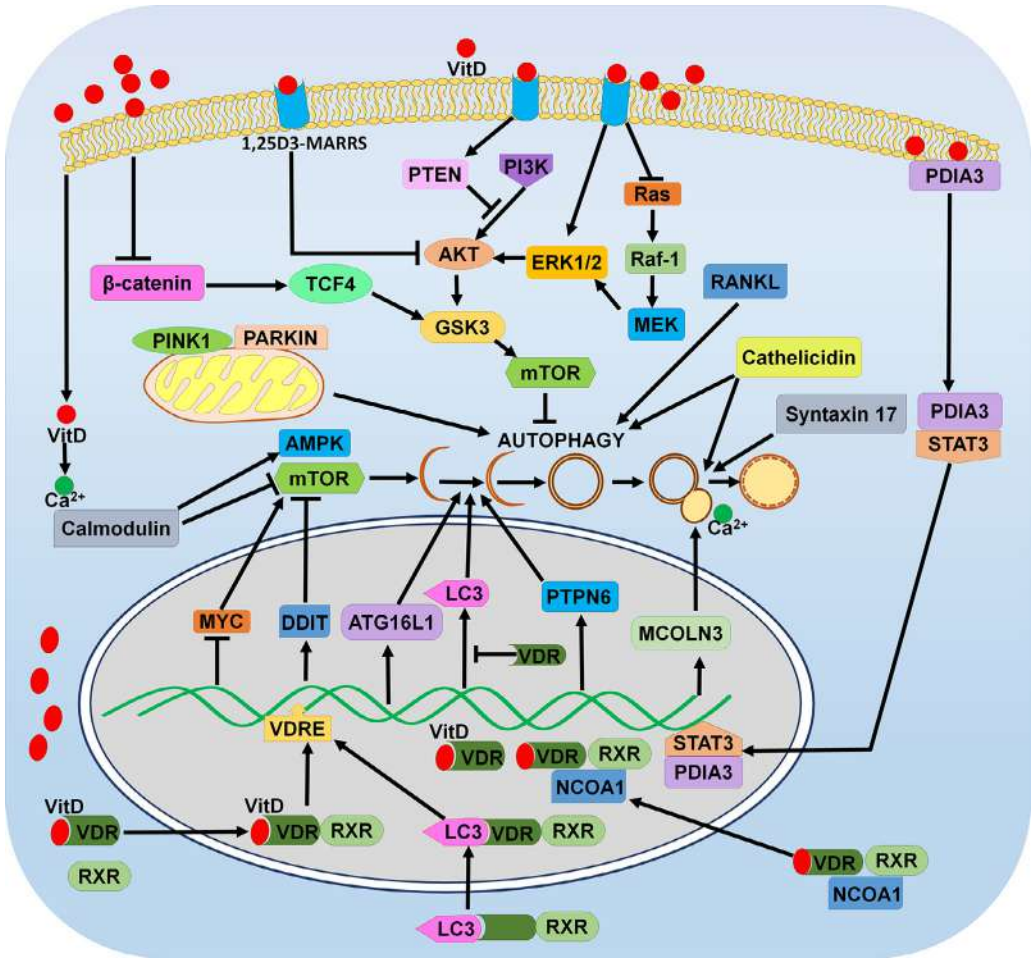

Fig. 3. . Vitamin D and its receptor in autophagy signaling. Vitamin D inhibits mTOR to induce autophagy through Ca^{2+}/calmodilun-dependent activation of AMPK and inhibition of β-catenin/TCF4/GSK-3β signaling. It also activates pro-survival autophagy through activation of ERK1/2-AKT pathway and up-regulation of Beclin-1. Vitamin D modulates MEK/ERK and PTEN/PI3K/AKT/mTOR signaling to activate autophagy. Furthermore, vitamin D activates PINK1/PARKIN-dependent mitophagy to control ROS production and remove damaged mitochondria. Vitamin D also induces autophagy by targeting RANKL. As an antibacterial defense mechanism, vitamin D induces autophagy through cathelicidin and triggers autophagosome–lysosome fusion leading to phagosome maturation and degradation. In addition, vitamin D treatment stimulates PDIA3 membrane receptor and drives PDIA3-STAT3 complex activation and nuclear translocation leading to increased MCLN3 expression. It enhances Ca^{2+} release from the lysosome to normalize acidification and promotes autolysosomal degradation pathway. Interaction of the autophagic protein LC3 with VDR potentiates its nuclear translocation to promote VDR-retinoid-X receptor heterodimer and activate VDR signaling. Vitamin D treatment also promotes DDIT4 expression through VDR signaling to activate autophagy by targeting mTOR signaling.

Beclin-1- and ATG-7-dependent pathway [54]. This process triggers Ca^{2+}/calmodulin-dependent kinase kinase β activation of AMPK and inhibition of mTOR to stimulate autophagy in cancer cells. Interestingly, vitamin D downregulates MYC expression, leading to mTOR inactivation and hence, autophagy activation to promote myeloid differentiation [55]. In addition, vitamin D treatment promotes DNA damage-inducible transcript 4 (DDIT4) expressions through VDR signaling to activate autophagy in mTOR signaling as an anticancer mechanism [56] (Fig. 3).

5. Vitamin D in health and diseases: the role of autophagy

5.1. Vitamin D-induced autophagy in maintaining cellular homeostasis

5.1.1. Skin and vitamin D: the complex relationship

With the site for synthesis, vitamin D also plays a crucial role in skin protection and involves the growth, repair, and metabolism of skin cells [57]. Here, I have discussed the role of vitamin D in maintaining skin cells through the modulation of autophagy. Vitamin D and its analogs induce autophagy in keratinocytes to protect them from different skin diseases [58]. UV exposure causes DNA damage in skin keratinocytes, and it is shown that vitamin D has a protective effect on UV-induced DNA damage. Treatment of vitamin D increases glycolysis and autophagy through inhibition of AKT/GSK3/mTOR pathway to conserve energy for repairing pyrimidine dimer after UV exposure (Table 1). Furthermore, vitamin D activates PINK1/PARKIN-dependent mitophagy to inhibit ROS and to repair mitochondrial damage leading to apurinic/apyrimidinic site generation for DNA repair to protect the development of skin cancer [42]. Similarly, vitamin D exhibits an antioxidant response against H_2O_2 through modulation of autophagy in melanocytes. It is showed that calcipotriol regulates the velocity of melanocyte dendrites, increases superoxide dismutase activity, reduces mitochondrial membrane potential (MMP), and restores calcium homeostasis to manage oxidative stress [59]. In another study, vitamin D and calcium modulate sebocyte morphology, enhance cell number, and decrease lipogenesis with significantly higher autophagy in young acne patients indicating that vitamin D could have therapeutic importance in maintaining calcium in skin ep-

Table 1
Effect of vitamin D-induced autophagy signaling in cellular homeostasis in different cell and tissue types

	Cell/tissue type	Autophagy signaling	Function of vitamin D-induced autophagy signaling	References
Skin	Keratinocytes	Inhibit AKT/GSK3/mTOR and activate of PINK1/PARKIN pathway	Protect from UV-induced DNA damage and inhibit apoptosis	[42]
	Melanocytes	Increase expression of Beclin–1, LC3-II/LC3-I, Mfn2, and Drp1	Protect against H_2O_2-induced oxidative stress and restores the dendritic morphology	[59]
	Sebocytes	Activate lipophagy	Maintain morphology, increase cell numbers, decrease sebaceous lipogenesis	[60]
	M2 macrophage	Activate KLF4-PPARγ pathway	Protect from UV-induced acute skin injury and inflammation	[61]
Bone	Chondrocytes	Activate AMPK/mTOR signaling	Inhibit of osteoarthritis associated with inflammation	[48]
	Synovial fibroblast	Activate VDR and PPARγ to restore autophagic flux	Prevent inflammation in rheumatoid arthritis	[63]
	Osteoclast	Increase expression of RANKL	Promote osteoclastogenesis	[47]
Heart and blood vessel	Cardiomyocytes	Restore autophagic flux	Protect from myocardial injury by inhibiting ER stress and mitochondrial dysfunction	[68]
	Cardiomyocytes	Inhibit β-catenin/TCF4/GSK-3β and mTOR signaling	Reduce diabetic cardiomyopathy	[45]
	Cardiomyocytes	Inhibit the translocation of FOXO1 to nucleus through VDR activation	Attenuate diabetic heart-related cardiac autophagy and apoptosis	[69]
	Cardiomyocytes	Modulate autophagy dysfunction and promote flux	Inhibit apoptosis and inflammation in experimental autoimmune myocardiatisis	[70]
	Endothelial cells	Upregulate Beclin-1/ERK1.2/AKTKT pathway	Inhibit apoptosis caused by H_2O_2 and maintain mitochondria function	[43]
Nervous system	Neural cells	Activate AMPK-associated pro-survival signaling	Attenuate rotenone-induced neurotoxicity	[72]
	Neural cells	Activate VDR expression and restores autophagic activity	Attenuate autophagy dysfunction-mediated cell death in traumatic brain injury	[74]
	Neural cells	High LC3-II/LC3-I	Attenuate tyrosine hydroxylase expression in Parkinson's disease	[75]
Gastrointestinal	Paneth cells	Transcriptional activation of ATG16L1 through VDR	Maintain intestinal homeostasis and prevent gut inflammation	[39,77,78]
	Peritoneal macrophage	Autophagy mediated NLPRP3 degradation	Inhibit ulcerative colitis-associated inflammation	[79]
	Gastric epithelial cells	Translocate PDIA3-STAT3 complex to nucleus leading to increase expression of MCLN3 to enhance Ca^{2+} release from the lysosome to normalized acidification	Autolysosomal degradation of *Helicobacter pylori* leading to inhibit its pathogenicity in the stomach	[52]
Liver	Hepatocytes	Activate MEK/ERK and PTEN/PI3K/AKT/mTOR pathway	Inhibit oxidative stress in hepatic ischemia–reperfusion	[44]
	HepG2 cells	Activate ATG16L1 through VDR	Decrease lipid accumulation and modulate liver inflammation in hepatic steatosis	[83]
Pancreas and kidney	Pancreatic-β cells	Increase expression levels of LC3 and Beclin–1	Protect from oxidative damage and increases insulin secretion in diabetic model	[84,85]

(*continued on next page*)

Table 1 (*continued*)

	Cell/tissue type	Autophagy signaling	Function of vitamin D-induced autophagy signaling	References
	HK-2	Activate autophagy through binding of VDR to LC3	Renoprotective through inhibition of fibrotic genes against angiotensin-induced renal injury	[41]
	Podocytes	Regulate of aberrant autophagy	Inhibit autoantibody-induced injury in lupus nephritis	[88]
	Kidney cells	Increase expression of Beclin–1, LC3-II/LC3-I	Anti-inflammatory and anti-apoptotic effect in diabetic nephropathy	[90,91]
Lungs	BEAS-2B, THP1 cells	Promote formation of autophagosome formation	Activate NRF2 signaling to inhibit particles-induced pulmonary injury and tissue repair	[92]
	A549, THP1 cells	Activate VDR and cathelicidin through p-38/MAPK- and STAT4-dependent pathway	Inhibit intracellular mycobacterial growth	[95]
Ovary	*Ovary cells*	Increase LC3II level and AKT phosphorylation	Promote ovary maturation in testosterone-induced polycystic ovarian syndrome in rats	[96]
	Placenta cells	Modulate VDR signaling genes, including CYP24A1, ATG4B, mTOR signaling	Maintain placenta morphology, function, and pregnancy outcome in mice	[100]

ithelium [60]. Interestingly, vitamin D exhibits anti-inflammatory activity to promote tissue repair and inhibits apoptosis in M2 polarized macrophage in UV-induced acute skin injury in a murine model [61]. More importantly, vitamin D activates autophagy to polarized macrophages through activation of the KLF4-PPARγ pathway, and inhibition of autophagy prevents down-regulation of tumor necrosis factor α (TNFα) and MMP (Table 1), leading to inflammation in the skin.

5.1.2. Maintaining healthy bone, periodontal health, and muscle function

Vitamin D is essential for bone growth and remodeling. Vitamin D deficiency affects bone density and is associated with osteoporosis [3]. A population study is showed that ATG7 and SOD2 gene expression is significantly decreased in the osteoporotic group compared to the osteoporosis-free group indicating that vitamin D could be correlated with autophagy and oxidative stress in osteoporosis [62]. Interestingly, vitamin D promotes autophagy in chondrocytes and suppresses osteoarthritis associated with inflammation through AMPK/mTOR signaling in the mouse model [48]. Furthermore, the combination of arsenic trioxide and vitamin D activates VDR and PPARγ to restore defective autophagy to alleviate inflammation in synovial fibroblast in rheumatoid arthritis [63]. Interestingly, vitamin D shows a dual role in osteoclastogenesis. Vitamin D can directly inhibit autophagy to suppress osteoclast proliferation and induces differentiation. On the other side, vitamin D induces autophagy through RANKL to promote osteoclastogenesis regulating osteoporosis [47]. Vitamin D supplements showed a decrease in cytotoxic T cells, pro-inflammatory cytokines, and increased autophagy-related proteins in peripheral blood mononuclear cells in periodontitis patients [64]. However, different metabolites of vitamin D induce opposing effects. For example, vitamin D activates autophagy and protects muscle cells through AKT signaling from pro-cachectic cytokines TNFα, interferon γ (IFN-γ) or interleukin (IL)-6 and cachexia condition-induced atrophy in myocytes [65]. On the other hand, active vitamin D promotes atrophagic activity through activation of FOXO3 and atrogens by blocking autophagic flux. The contrasting vitamin D activity is due to differential expression of CYP24A1 present in mitochondria to convert vitamin D to the inactive form [47].

5.1.3. Heart and blood vessel abnormalities

Vitamin D plays a critical role in maintaining the function of the heart, and its deficiency is associated with cardiovascular diseases [66,67]. Vitamin D-activated receptors prevent myocardial reperfusion (MI/R) by inhibiting ER stress and mitochondrial dysfunction-dependent apoptosis [68]. Furthermore, VRD activation suppresses MI/R-induced autophagy dysfunction and restores autophagic flux. Moreover, vitamin D administration significantly reduces myocardial hypertrophy and intestinal fibrosis and concomitantly restores dysfunctional autophagy in streptozotocin-induced diabetic rats [45]. At the molecular level, vitamin D modulates autophagy by inhibiting β-catenin/TCF4/GSK-3β and mTOR signaling in cardiomyocytes (Table 1). Cardiovascular dysfunction is associated with diabetes through excessive autophagy and result in apoptosis. Vitamin D supplements decrease cardiac autophagy and damage through VDR activation to inhibit the translocation of FOXO1 to the nucleus in Zucker diabetic fatty rat [69]. Interestingly, it is showed that the administration of vitamin D decreases experimental autoimmune myocardiatisis in mice through improved cardiac function, suppressed myocardial apoptosis, and cell infiltration. It is correlated with a reduced number of autophagosomes and decreased LC3 and Beclin-1 expression indicating the role of vitamin D on autophagy differs in different tissues and diseases [70].

Vitamin D prevents endothelial cell death by promoting the expression of the autophagy genes and re-establishes the MMP that arises from oxidative stress. Vitamin D activates pro-survival autophagy through the up-regulation of Beclin-1 and inactivation of ERK1.2-AKT pathway [43]. Vitamin D has been shown to enhance random skin flap survival in rats through increased angiogenesis, decreased oxidative stress, and inflammation. It is revealed that higher autophagic activity in skin flaps might involve modulation of oxidative stress and warrants further studies [71].

5.1.4. Nervous system and neurological disorder

Vitamin D regulates the development of neurons, their maintenance, and survival. Vitamin D attenuates rotenone-induced cell death in neural cells by activating AMPK-associated pro-survival autophagy [72]. The effect of vitamin D on locomotory recovery after spinal cord injury is studied in rats [73]. It is showed that vitamin D treatment increases antioxidant activity with higher autophagy leading to functional recovery in damaged neurons as compared to the control. Furthermore, vitamin D activates VDR expression and restores autophagic activity with decreased apoptosis, leading to diminished traumatic brain injury in rats [74]. Moreover, vitamin D protects neural cells from 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced Parkinson's disease through autophagic modulation [75]. Furthermore, vitamin D inhibits experimental autoimmune encephalomyelitis in mice with autophagy modulation (Table 1) [76], indicating vitamin D can be a promising treatment for multiple sclerosis.

5.1.5. Gastrointestinal system and gut microbiome

In intestinal homeostasis, VDR plays an essential role in vitamin D-activated autophagy signaling. It is showed that VDR knockout in the intestine results in dysfunctional autophagy and lysosomes, leading to the impaired antibacterial function of Paneth cells (Table 1). Furthermore, VDR transcriptionally regulates ATG16L1 to induce autophagy and prevent risk factors for inflammatory bowel disease [39]. The VDR knockout mice are susceptible to dextran sulfate sodium-induced colitis, and butyrate administration increases VDR expression along with the inhibition of inflammation. Interestingly, VDR knockout shows a change in intestinal microbiome function and imbalanced bacterial profiles in mice. Interestingly, vitamin D activates ATG16L1-dependent autophagy and suppresses IL-1β expression to clear *Salmonella* infection in intestinal epithelial cells to maintain gut homeostasis [77]. Another study is showed that VDR deficiency increases cell death through induction of Bax along with a decrease in ATG16L1 and Beclin-1 expression in intestinal cells of mice [78]. Moreover, Beclin-1 is shown to interact with Bcl-2, inhibiting autophagy in VDR deficient epithelial cells in mice with a high label of bacterial endotoxin in serum. Besides, vitamin D treatment increases VDR and ATG16L1 expression in the organoid *in vitro* and colitis IL-10$^{-/-}$ mice, indicating that imbalance of autophagy and apoptosis in VDR deficiency leads to inflammation and inflammation-associated diseases. A recent study has revealed that vitamin D exhibits anti-inflammatory activity by inhibiting inflammasome activation, leading to diminish caspase-1 action and IL-1β through VDR signaling pathway in macrophage with DSS-induced ulcerative colitis mice [79]. Mechanistically, vitamin D promotes NLRP3 ubiquitination and degradation through autophagy. Furthermore, it is showed that 3-methyladenine reduces the NLRP3 degradation caused by vitamin D. Administration of probiotic prevents intestinal epithelial cells from *Salmonella* infection through induction of autophagy and VDR signaling pathway [80,81]. *Helicobacter pylori* invade gastric epithelium and residing in the autophagosomes. It is showed that *H. pylori* infection impairs the acidification of autolysosomes resulting inability to fuse with lysosomes, leading to the survival of bacteria in the stomach. Vitamin D treatment reactivates autolysosomal degradation in the PDIA3 membrane receptor-dependent pathway. Vitamin D drives PDIA3-STAT3 complex for nuclear translocation leading to increase expression of MCLN3 to augment Ca^{2+} release from the lysosome to control acidification and eliminate *Helicobacter pylori* infection in the autophagosomal degradation pathway [52]. Another study is indicated that the combined effect of vitamin D and alginates regulates acidity and antioxidant activity in gastric epithelial cells [82]. This gastro-protective effect has also been demonstrated to enhanced autophagic activity with inhibition of ROS-induced apoptosis, although detail needs to be investigated.

5.1.6. Liver and inflammation

Vitamin D-induced autophagy prevents the liver from oxidative stress and inflammation. The protective role of vitamin D through the modulation of autophagy to inhibit oxidative stress in hepatic ischemia–reperfusion was studied in mice [44]. It is observed that vitamin D activates MEK/ERK and PTEN/PI3K/AKT/mTOR signaling to promote autophagy in hepatocytes and inhibition of autophagy signaling pathway reduces the protective effect of vitamin D from liver damage. The protective effect of vitamin D-dependent autophagy in hepatic steatosis is studied in mice [83]. The data have found that vitamin D treatment decreases lipid accumulation and modulates liver inflammation by activating ATG16L1 in mice.

5.1.7. Pancreas, kidney, and diabetes pathogenesis

Vitamin D increases cell viability and insulin secretion and protects from oxidative stress through autophagy activation in INS-1 cells in streptozotocin-induced diabetics in rats [84]. Vitamin D treatment promotes autophagy in pancreatic-β cells and increases insulin secretion in streptozotocin-induced type-1 diabetes mellitus in the mouse model [85]. It is observed that vitamin D attenuated glucose-induced autophagy inhibition in peritoneal mesothelium through mTOR signaling in mice models, indicating a potential therapy of vitamin D for peritoneal injury [86]. In high glucose exposure conditions, autophagic protein LC3 binds with VDR independent of LC3 interacting region and transports to the nucleus to promote VDR-RXR heterodimer to activate VDR signaling (Table 1). This nuclear transport of LC3 exerts a renoprotective effect regulating fibrogenic gene expression in high glucose-induced HK-2 cells [41]. Administration of vitamin D is reported to be renoprotective against angiotensin-induced renal injury through inhibition of pro-fibrotic and pro-inflammatory cytokines and mitochondrial dysfunction. Furthermore, vitamin D modulates angiotensin-induced autophagy dysfunction in mice [87]. Another study has reported that vitamin D reduces podocyte injury caused by autoantibody isolated from lupus nephritis patients' serum. The data have indicated that vitamin D regulates aberrant autophagy activation and decreased expression of nephrin [88], indicating a novel approach to manage lupus nephritis. Interestingly, 22-oxacalcitrol, vitamin D analog promotes the renoprotective effect and inhibits pro-inflammatory immune response through attenuation of fasting sugar, serum IL-16, toll-like receptor 4 (TLR-4), and IFN-γ gene with up-regulation of autophagy genes and down-regulation of apoptotic genes in diabetic nephropathy [89]. Moreover, 22-oxacalcitrol has showed a renoprotective effect in acute kidney injury in rats by decreasing apoptosis and fibrosis, with an increase in autophagy, leading to an anti-inflammatory response for cell survival [90]. In combination with insulin, vitamin D exhibits a renoprotective response with antioxidant and anti-inflammatory effects in diabetic nephropathy rats. Moreover, this combination shows down-regulation of mTOR and stimulation of autophagy as compared to the control groups [91].

5.1.8. Lungs and pulmonary diseases

It is reported that fine particulate matters induce chronic pulmonary disease, and the effect of vitamin D was studied in feed particulate-induced tissue damage both *in vitro* and *in vivo* [92]. Interestingly, vitamin D administration inhibits inflammation through regulation of TGF-β signaling in NRF2-dependent manner (Table 1). Furthermore, vitamin D activates autophagy leading to degradation of p62 and its partner Keap1, which causes reduced NRF2 ubiquitination hence, increases stability, and protects tissue injury in the lung. Interestingly, vitamin D protects *Aspergillus*

fumigatus infected mice through the regulation of inflammation. Moreover, vitamin D increases the cellular function of the lung through modulation of autophagy and NF-kB activity in infected mice, although the detailed role of autophagy needs to be identified to control pulmonary aspergillosis [93,94]. Another study has indicated that a combination of innate cytokines (IL-1 and IL-18) inhibits mycobacterial growth through activation of VDR, cathelicidin, and autophagy in p-38/MAPK- and STAT4-dependent pathways in macrophage and lung epithelial cells [95].

5.1.9. Ovary and gynecological disorder

Polycystic ovarian syndrome (PCOS) is a complex and metabolic disorder in a reproductive woman with increased cardiovascular risks. Vitamin D deficiency decreases LC3II level and increases AKT phosphorylation with reduced insulin receptor signaling ovaries of the testosterone-induced (PCOS) in rats [96]. Interestingly vitamin D supplements promote autophagy and ovary maturation, indicating the beneficial effect of vitamin D on PCOS treatment. The data are showed that vitamin D treatment in PCOS induced by chronic dihydrotestosterone administration in C57BL/6J mice rescues cardiac dysfunction and inhibits cardiomyocytes apoptosis with improved cardiac function (Table 1). At the cellular level, vitamin D activates autophagy through mTOR-AMPK signaling to prevent cardiac remodeling [97]. Interestingly, vitamin D treatment attenuates placental ischemia through modulation of apoptosis and autophagy. The data are showed that vitamin D improves the impaired heart, kidney, and placenta of ischemia in rats by decreasing oxidative stress-induced apoptosis [98]. In comparison to normal individuals, patients with pre-eclampsia showed a decrease in vitamin D in serum and VDR, LC3B, and Beclin-1 in placental tissues affecting trophoblast survival capacity through inactivation of autophagy [99]. VDR null placenta in C57BL/6 mice exhibits a differential expression of VDR signaling genes, including CYP24A1, ATG4B, mTOR signaling PRR5 compared to wild type without showing any change in placenta morphology, function, and pregnancy outcome in mice [100]. This study indicates maternal vitamin D status might be crucial in determining pregnancy outcome through genomic and non-genomic signaling, although a detailed analysis and role of autophagy in this connection need to be identified.

5.2. Vitamin D-induced lethal autophagy controls cellular transformation and cancer

As part of the anticancer mechanism, vitamin D regulates cancer growth and proliferation in the autophagy-dependent pathway. Vitamin D induces an increase in intracellular Ca^{2+} to activate autophagy and accumulates massive autophagosomes in a Beclin-1- and ATG7-dependent pathway. This mechanism involves Ca^{2+}/calmodilun-dependent protein kinase kinase β activation of AMPK and inhibition of mTOR to induce autophagy in MCF-7 cells [54]. Moreover, vitamin D treatment increases in expression of autophagy-related genes signature in luminal breast cancer cells, which is lost from mammary gland cells during cancer progression. Mechanistically, VDR constitutively inhibits autophagy through repressor of LC3B expression, and exposure to vitamin D de-represses the expression of LC3B to promote autophagy. Furthermore, inhibition of vitamin D-induced autophagosome maturation with chloroquine potentiates anti-breast cancer therapy in MCF-7 xenograft mice [40]. Interestingly, microarray data have indicated that the genome signature of vitamin D exposure in normal mammary tissue distinct from that of the breast cancer cells [101]. Moreover, many unique genes, including pathways of autophagy genes, are identified, which could be valuable for the biomarker of vitamin D treatment in breast cancer.

EB1089, a synthetic analog of vitamin D, induces cell death through autophagy in breast cancer MCF-7 cells [102]. In this setting, knockdown of Beclin-1 inhibits cell death and tumor proliferation in a caspase-independent manner. Interestingly, vitamin D triggers autophagic cell death through the modulation of Beclin-1-associated complex along with differentiation in leukemia cells in apoptosis deficient conditions. [103]. Interestingly, DDIT4 expression inhibits human cutaneous squamous cell carcinoma with decreased autophagy flux. In this connection, vitamin D treatment promotes DDIT4 expression through VDR signaling to activate autophagy through mTOR signaling pathway and exhibits potent antitumor activity *in vitro* and *in vivo* [56]. In another study, vitamin D and its analogs inhibit PI3K/AKT/mTOR signaling and activate autophagy through Beclin-1 as a part of the anticancer mechanism of action in Kaposi's sarcoma cells [104]. Moreover, vitamin D inhibits the translocation of phosphorylated AKT to the nucleus in VDR and NF-kB-dependent mechanism to induce cell death.

EB1089 potentiates the effect of radiation to promote autophagic cell death and inhibits cell proliferation in breast cancer cells. Vitamin D induces cytostatic autophagy to radio-sensitize through VDR, TP53 AMPK pathway in non-small cell lung cancer. The combined effect promotes growth arrest and proliferation recovery without affecting increased DNA damage, decreased DNA repair, or an increase in apoptosis, necrosis, or senescence but through the conversion of protective autophagy to cytostatic autophagy in non-small cell lung cancer cells. Vitamin D radio-sensitizes the breast cancer cells and switches cytoprotective to cytotoxic autophagy to inhibit cancer growth in apoptosis-independent manner. Interestingly, vitamin D failed to radio-sensitize and unable to induce cytostatic autophagy in low expressing VDRs in BT474 cells [105-109]. Interestingly, vitamin D inhibits proliferation and induces cell cycle arrest and autophagy in Pfeiffer diffuse large B lymphoma cell lines through AKT/mTOR/PI3K signaling pathway [110]. In this connection, the expression of CYP24A1 that degrades vitamin D is found increased in a grade-wise manner in this cancer. Furthermore, rapamycin blocks the expression of CYP24A1 and VDR, leading to inhibit degradation of vitamin D and combination with vitamin D promotes cell cycle arrest and anticancer effect in this cancer. Likely, temozolomide combined with vitamin D inhibits the growth of glioblastoma C6 cells through activation of cytotoxic autophagy, and it has indicated that the presence of 3-methyladenine significantly reduces the anticancer activity of the combined effect. In addition, the *in vivo* study has exhibited profound tumor regression with prolonged survival time in the combined group compared only to temozolomide [111]. Vitamin D, in combination with 1-asparaginase which is involved in amino acid depletion, induces myeloid differentiation. It is observed that the combination treatment induces MYC down-regulation, leading to mTOR inactivation and autophagy activation to promote differentiation. Moreover, I-asparaginase administration increases *in vivo* effect of vitamin D with prolonged survival time in the xenograft model, suggesting the combined treatment may be a promising approach for acute myeloid leukemia [55]. The combined effect of vitamin D and metformin exhibits antiproliferative effects in p53-dependent ways in colon cancer cells. Furthermore, vitamin D-metformin in combination also induces autophagy through the AMPK-mTOR-dependent pathway in wild p53 status HCT116 cells [112]. Moreover, high doses of vitamin D supplementation suppress high fat-associated tumorigenesis through a decrease in pro-inflammatory cytokine production, leading to inhibition of the Wnt signaling pathway in APC mutant mice [113]. Similarly, the addition of sulforaphane to high dose vitamin D reduces histone deacetylase activity and promotes autophagy to inhibit colorectal cancer. Combinations of vitamin D with plant polyphenol Carnosic

acid potentiate the antitumor activity of sorafenib on hepatocellular carcinoma [114]. It is showed that the combined treatment increases autophagy and apoptosis to induce cell death. Moreover, it is indicated that the combined approach promotes inhibition of autophagosome and lysosome fusion to cause cell death. Vitamin D and its analogs inhibit the hepatitis C virus with altered gene expression-related autophagy, and the detailed role of autophagy needs to be studied in hematoma cells [115].

5.3. Vitamin D-induced autophagy in immunity and infection

Vitamin D has a crucial role in controlling immunity through autophagy. For example, autophagy activity in the peripheral blood mononuclear cells and T cells from severe vitamin D deficiency and vitamin D insufficient individuals are compared in systemic lupus erythematous patients [116]. It is showed that autophagy signature molecules mTOR, LC3, and p62 expression are altered in the severe deficiency group compared to the insufficient group indicating that vitamin D deficiency affects autophagy. Interestingly, the transcriptome pattern is analyzed in vitamin D-treated monocytes exposed to bacterial lipopolysaccharides (LPS) [117]. The data are directed that LPS in the presence of vitamin D results in the up-regulation of antibacterial activity and autophagy pathway with down-regulation of the pro-inflammatory response gene compared to only the LPS treated group. Vitamin D promotes autophagy as an antibacterial defense mechanism against Mtb through cathelicidin/LL-37 peptide by transcriptional up-regulation of Beclin-1 and ATG5. It is showed that mycobacterial phagosomes are localized with autophagosome in a cathelicidin-dependent manner to degrade bacteria in macrophages [36]. Interestingly, the IFN-γ promotes antibacterial activity through vitamin D signaling-induced autophagy in human macrophages [51,118]. Furthermore, vitamin D-upregulated cathelicidin/DEFB4 triggers autophagosome–lysosome fusion leading to restoration of Mtb phagosome maturation and degradation. More importantly, mycobacterial lipoprotein induces TLR2/1/CD14-Ca^{2+}-AMPK-p38-MAPK pathway to contribute vitamin D-dependent activation to promote antibacterial autophagy [119]. In another study, vitamin D causes interleukin IL-1β, which activates through inflammasome in macrophages. The IL-1β promotes antibacterial signaling on neighboring epithelial cells to inhibit Mtb infection in macrophages in an autophagy-independent manner [120]. Vitamin D supplements in pulmonary tuberculosis patients are shown to increase immune response to control the growth of mycobacteria in macrophages through activation of the mannose receptor, DS SIGN, and autophagy genes [121]. Prostaglandin E2, a lipid mediator, inhibits vitamin D-induced cathelicidin and autophagy during Mtb infection and promotes intracellular Mtb growth and survival in macrophages [122]. Vitamin D also inhibits *Mycobacterium marinum* infection through the antibacterial activity of cathelicidin-induced autophagy in THP1 cells [50].

Vitamin D, at the physiological level, inhibits HIV-1 infection replication through autophagy in human macrophages in a cathelicidin-independent manner [123]. The TLR-8 induces vitamin D-dependent autophagic response triggering human expression of cathelicidin antibacterial peptide, VDR, and CY27A to inhibit replication of HIV-1 [124]. Interestingly, the physiological concentration of vitamin D induces cathelicidin antibacterial peptide to induce autophagy flux in HIV-Mtb co-infected macrophages to impede growth and replication. Furthermore, vitamin D restores the impaired Mtb-mediated TNF releases in HIV-positive macrophages through TLR signaling [125]. Influenza A virus infection induces apoptosis and tissue damage to humans. Vitamin D supplementation inhibits apoptosis through VDR-dependent mechanism. Interestingly, vitamin D restores autophagic flux inhibited by viral infection through up-regulation of fusion protein, including syntaxin 17 and V-type proton ATPase subunit, to prevent apoptosis [53], suggesting that vitamin D can be a preventive, therapeutic agent through modulation of autophagy in viral infections. Pre- and post-treatment of vitamin D are shown to decrease inflammation in response to influenza A infection in human epithelial cells [126], although the role of autophagy in regulating this phenotype is still need to be investigated. Rotavirus infection is associated with severe diarrhea in young children. The data have directed that vitamin D treatment increases the expression of Beclin-1, LC3, and decreases expression of p62 with higher expression of cathelicidin, leading to inhibit the viral infection in pigs and porcine small intestine epithelial cells [127].

Vitamin D, in combination with retinoic acid, increases the uptake of Mtb through ROS-induced autophagy [128]. The combined effect increases antigen presentation with marked change phenotypes of macrophage, leading to promotes persistent Mtb. Further, the combined effect of vitamin D with primaquine increases the number of monocytes, suppresses pro-inflammatory cytokines, nitric oxide synthase, and enhances antioxidant genes, antibacterial peptides, and autophagic protein against *Pneumocystis* pneumonia in C57BL/6 mice [129]. Artesunate treatment attenuates sepsis-induced immunosuppression in *Pseudomonas aeruginosa* infected mice and enhances pro-inflammatory cytokines with decreased bacterial load in mice. At the molecular level, the Artesunate interacts with the VDR to inhibit nuclear translocation to increase autophagy through ATG16L1. Moreover, it promotes VDR and NF-kB interaction, leading to nuclear translocation of NF-kB to synthesize pro-inflammatory cytokines to inhibit bacterial growth in macrophages [130].

5.4. Vitamin D, autophagy, and aging: does it have a role in controlling COVID-19?

Autophagy, the cytoprotective mechanism, is inactivated with aging leading to the accumulation of reactive mitochondria, dysfunctional organelles, and protein aggregates [131]. Similarly, vitamin D levels are reduced with aging, and vitamin D deficiency accelerates aging and age-related diseases in humans [132-137]. For example, it is observed that the expression of VDR is decreased with age, as shown in rats associated with intervertebral disc degeneration pathogenesis. Furthermore, activation of VDR attenuates apoptosis and mitochondrial dysfunction along with reduced autophagy in cells of annulus fibrous through inhibition of mTOR/p70S6K signal pathway [138]. Interestingly, vitamin D also reported to protect form viral infection including HIV [123], rotavirus [127], influenza [53,126], and hepatitis [115,139]. Does vitamin D status associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection cause COVID-19 in humans? Recently, the Israeli population study has established a link between low vitamin D in serum and COVID-19 positive patients. In this study, 7,800 people are analyzed for viral infection, and 782 patients are COVID-19 positive. The COVID-19 positive patients are associated with low plasma vitamin D levels compared to COVID-19 negative patients [140]. Another study has suggested that circulating vitamin D levels are significantly and inversely associated with SARS-CoV-2 nucleic acid amplification testing, and this correlation is highly relevant in different demographic factors including latitudes, ethnicities, both sexes, and age ranges in the United States [141]. In addition, the individuals have vitamin D deficiency at the time of COVID-19 test are at high risk than the individuals with sufficient vitamin D levels. Furthermore, it is found that COVID-19 patients with deficient vitamin D levels have improved with supplement ware not found to have a high risk for COVID-19 compared with patients with likely sufficient vitamin

D status [142]. Interestingly, a pilot randomized clinical study has revealed that treatment with vitamin D significantly decreases the need for ICU for COVID-19 patients indicating vitamin D controls the severity of the disease [143]. Moreover, vitamin D level has been shown to regulate lung function to determine the clinical outcome in COVID-19 patients [144]. Vitamin D has been documented as an anti-inflammatory hormone to control cytokine storms and protect from cellular dysfunction and infection in elderly adults with COVID-19 [145]. In this setting, it can be hypothesized that aged individuals with a deficiency in vitamin D and autophagy are more susceptible to viral infections, including SARS-CoV-2, and older adults associated with different diseases could aggravate the COVID-19, leading to death. Autophagy is reported to inhibit viral infection through a process known as virophagy, a mechanism for removing viruses through autophagy [146]. On the contrary, autophagy fusion inhibitors, including chloroquine, have indicated a promising effect in controlling viral growth by inhibiting endosome-containing viruses with the lysosome to release the viral particle to the cytoplasm during infection [147]. The detailed role of autophagy in COVID-19 disease and its role in controlling SARS-CoV-2 need to be further studied.

6. Conclusion and future perspectives

Vitamin D has been documented as a vital hormone to control cellular homeostasis and protects from different diseases. Here, vitamin D-activated autophagy signaling contributes to preventing cellular dysfunction and establishes the fine-tuning to maintain a healthy life. Vitamin D functions as an antioxidant through autophagy to control cell death, inflammation, and inflammation-associated diseases. The genomic and non-genomic function of vitamin D promotes autophagy to establish gut microbiome homeostasis and prevents gut-associated inflammatory disease. Moreover, it regulates both pro-inflammatory and anti-inflammatory responses through autophagy modulation, suggesting utilizing this seco-steroid for two opposing functions, including autoimmune disease and immunosuppression. In addition, vitamin D exhibits a potent anticancer agent and potentiates the effect of radiation and chemotherapeutic drugs through modulation of autophagy for potential therapy. Although autophagy signaling through the supplement of vitamin D regulates multiple cellular functions, the detailed role of autophagy in contributing vitamin D activity warrants further study in different models. Identification of critical molecules and associated signaling pathways through proteomics approaches could widen vitamin D-based therapy or supplement and classical drugs for multiple human diseases. What is the genetic and epigenetic basis of vitamin D-associated autophagy activity in modulating cellular functions that need to be deciphered to understand the contribution of conflicting roles at different cells, tissues, and systems? In conclusion, increasing vitamin D level in human body through timely exposure to sunlight or vitamin D supplements could activate autophagy as part of the homeostasis mechanism to prevent multiple human diseases and aging-associated dysfunctions.

Declaration of Competing Interest

The author declares that there are no conflicts of interest assocaited with this publication.

Acknowledgments

Research support was partly provided by the Indian Council of Medical Research (ICMR), [Number:5/13/20/2020/NCD-III] Govt. of India. I would like to acknowledge Kewal K. Mahapatra, Srimanta Patra, and Soumya R. Mishra for helping me for preparing the figures and other technical support.

References

[1] Berridge MJ. Vitamin D, reactive oxygen species and calcium signalling in ageing and disease. Philos Trans R Soc Lond B Biol Sci 2016;371:20150434.
[2] Christakos S, Dhawan P, Verstuyf A, Verlinden L, Carmeliet G. Vitamin D: metabolism, molecular mechanism of action, and pleiotropic effects. Physiol Rev 2016;96:365–408.
[3] Berridge MJ. Vitamin D cell signalling in health and disease. Biochem Biophys Res Commun 2015;460:53–71.
[4] Carlberg C, Molnár F. Vitamin D receptor signaling and its therapeutic implications: genome-wide and structural view. Can J Physiol Pharmacol 2015;93:311–18.
[5] Carlberg C, Muñoz A. An update on vitamin D signaling and cancer. Semin Cancer Biol. (In press).
[6] Chetcuti Zammit S, Ellul P, Girardin G, Valpiani D, Nielsen KR, Olsen J, et al. Vitamin D deficiency in a European inflammatory bowel disease inception cohort: an Epi-IBD study. Eur J Gastroenterol Hepatol 2018;30:1297–303.
[7] Schrumpf JA, van der Does AM, Hiemstra PS. Impact of the Local inflammatory environment on mucosal vitamin D metabolism and signaling in chronic inflammatory lung diseases. Front Immunol 2020;11:1433.
[8] Fakhoury HMA, Kvietys PR, AlKattan W, Anouti FA, Elahi MA, Karras SN, et al. Vitamin D and intestinal homeostasis: barrier, microbiota, and immune modulation. J Steroid Biochem Mol Biol 2020;200:105663.
[9] Li W, Peregrina K, Houston M, Augenlicht LH. Vitamin D and the nutritional environment in functions of intestinal stem cells: Implications for tumorigenesis and prevention. J Steroid Biochem Mol Biol 2020;198:105556.
[10] Avenell A, MacLennan GS, Jenkinson DJ, McPherson GC, McDonald AM, Pant PR, et al. Long-term follow-up for mortality and cancer in a randomized placebo-controlled trial of vitamin D(3) and/or calcium (RECORD trial). J Clin Endocrinol Metab 2012;97:614–22.
[11] Lope V, Castelló A, Mena-Bravo A, Amiano P, Aragonés N, Fernández-Villa T, et al. Serum 25-hydroxyvitamin D and breast cancer risk by pathological subtype (MCC-Spain). J Steroid Biochem Mol Biol 2018;182:4–13.
[12] Grant WB. Review of recent advances in understanding the role of vitamin D in reducing cancer risk: breast, colorectal, prostate, and overall cancer. Anticancer Res 2020;40:491–9.
[13] Dikic I, Elazar Z. Mechanism and medical implications of mammalian autophagy. Nat Rev Mol Cell Biol 2018;19:349–64.
[14] Mukhopadhyay S, Panda PK, Sinha N, Das DN, Bhutia SK. Autophagy and apoptosis: where do they meet? Apoptosis 2014;19:555–66.
[15] Saha S, Panigrahi DP, Patil S, Bhutia SK. Autophagy in health and disease: a comprehensive review. Biomed Pharmacother = Biomed Pharmacother 2018;104:485–95.
[16] Mahapatra KK, Panigrahi DP, Praharaj PP, Bhol CS, Patra S, Mishra SR, et al. Molecular interplay of autophagy and endocytosis in human health and diseases. Biol Rev 2019;94:1576–90.
[17] Hanel A, Carlberg C. Vitamin D and evolution: pharmacologic implications. Biochem Pharmacol 2020;173:113595.
[18] Carlberg C, Haq A. The concept of the personal vitamin D response index. J Steroid Biochem Mol Biol 2018;175:12–17.
[19] Crowe FL, Steur M, Allen NE, Appleby PN, Travis RC, Key TJ. Plasma concentrations of 25-hydroxyvitamin D in meat eaters, fish eaters, vegetarians and vegans: results from the EPIC-Oxford study. Public Health Nutr 2011;14:340–6.
[20] Liu J, Arcot J, Cunningham J, Greenfield H, Hsu J, Padula D, et al. New data for vitamin D in Australian foods of animal origin: impact on estimates of national adult vitamin D intakes in 1995 and 2011-13. Asia Pacific J Clin Nutr 2015;24:464–71.
[21] Liu J, Greenfield H, Strobel N, Fraser DR. The influence of latitude on the concentration of vitamin D3 and 25-hydroxy-vitamin D3 in Australian red meat. Food Chem 2013;140:432–5.
[22] Kutuzova GD, DeLuca HF. 1,25-Dihydroxyvitamin D3 regulates genes responsible for detoxification in intestine. Toxicol Appl Pharmacol 2007;218:37–44.
[23] Pereira F, Barbáchano A, Silva J, Bonilla F, Campbell MJ, Muñoz A, et al. KDM6B/JMJD3 histone demethylase is induced by vitamin D and modulates its effects in colon cancer cells. Hum Mol Genet 2011;20:4655–65.
[24] Zhu H, Wang X, Shi H, Su S, Harshfield GA, Gutin B, et al. A genome-wide methylation study of severe vitamin D deficiency in African American adolescents. J Pediatr 2013;162:1004–9 e1.
[25] Zhou Y, Zhao L-J, Xu X, Ye A, Travers-Gustafson D, Zhou B, et al. DNA methylation levels of CYP2R1 and CYP24A1 predict vitamin D response variation. J Steroid Biochem Mol Biol 2014;144:207–14 Pt A.
[26] Beckett EL, Duesing K, Martin C, Jones P, Furst J, King K, et al. Relationship between methylation status of [26]vitamin D-related genes, vitamin D levels, and methyl-donor biochemistry. J Nutr Intermed Metab 2016;6:8–15.
[27] Larriba MJ, González-Sancho JM, Bonilla F, Muñoz A. Interaction of vitamin D with membrane-based signaling pathways. Front Physiol 2014;5:60.
[28] Abada A, Elazar Z. Getting ready for building: signaling and autophagosome biogenesis. EMBO Rep 2014;15:839–52.

[29] Nishimura T, Tamura N, Kono N, Shimanaka Y, Arai H, Yamamoto H, et al. Autophagosome formation is initiated at phosphatidylinositol synthase-enriched ER subdomains. EMBO J 2017;36:1719–35.
[30] Park JM, Jung CH, Seo M, Otto NM, Grunwald D, Kim KH, et al. The ULK1 complex mediates MTORC1 signaling to the autophagy initiation machinery via binding and phosphorylating ATG14. Autophagy 2016;12:547–64.
[31] Saxton RA, Sabatini DM. mTOR signaling in growth, metabolism, and disease. Cell 2017;168:960–76.
[32] Kim J, Kundu M, Viollet B, Guan K-L. AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1. Nat Cell Biol 2011;13:132–41.
[33] Su H, Yang F, Wang Q, Shen Q, Huang J, Peng C, et al. VPS34 acetylation controls its lipid kinase activity and the initiation of canonical and non-canonical autophagy. Mol Cell. 2017;67:907–21 e7.
[34] Bakula D, Müller AJ, Zuleger T, Takacs Z, Franz-Wachtel M, Thost A-K, et al. WIPI3 and WIPI4 β-propellers are scaffolds for LKB1-AMPK-TSC signalling circuits in the control of autophagy. Nat Commun 2017;8:15637.
[35] Slobodkin MR, Elazar Z. The Atg8 family: multifunctional ubiquitin-like key regulators of autophagy. Essays Biochem 2013;55:51–64.
[36] Tsuboyama K, Koyama-Honda I, Sakamaki Y, Koike M, Morishita H, Mizushima N. The ATG conjugation systems are important for degradation of the inner autophagosomal membrane. Science (New York, NY) 2016;354:1036–41.
[37] Itakura E, Kishi-Itakura C, Mizushima N. The hairpin-type tail-anchored SNARE syntaxin 17 targets to autophagosomes for fusion with endosomes/lysosomes. Cell 2012;151:1256–69.
[38] Chen Y, Yu L. Recent progress in autophagic lysosome reformation. Traffic (Copenhagen, Denmark) 2017;18:358–61.
[39] Wu S, Zhang YG, Lu R, Xia Y, Zhou D, Petrof EO, et al. Intestinal epithelial vitamin D receptor deletion leads to defective autophagy in colitis. Gut 2015;64:1082–94.
[40] Tavera-Mendoza LE, Westerling T, Libby E, Marusyk A, Cato L, Cassani R, et al. Vitamin D receptor regulates autophagy in the normal mammary gland and in luminal breast cancer cells. Proc Natl Acad Sci 2017;114:E2186 E94.
[41] Li A, Zhang H, Han H, Zhang W, Yang S, Huang Z, et al. LC3 promotes the nuclear translocation of the vitamin D receptor and decreases fibrogenic gene expression in proximal renal tubules. Metab: Clin Exp 2019;98:95–103.
[42] Rybchyn MS, De Silva WGM, Sequeira VB, McCarthy BY, Dilley AV, Dixon KM, et al. Enhanced repair of UV-induced DNA damage by 1,25-dihydroxyvitamin D(3) in skin is linked to pathways that control cellular energy. J Invest Dermatol 2018;138:1146–56.
[43] Uberti F, Lattuada D, Morsanuto V, Nava U, Bolis G, Vacca G, et al. Vitamin D protects human endothelial cells from oxidative stress through the autophagic and survival pathways. J Clin Endocrinol Metab 2014;99:1367–74.
[44] Yang J, Chen Q, Tian S, Song S, Liu F, Wang Q, et al. The role of 1,25-dyhydroxyvitamin D3 in mouse liver ischemia reperfusion injury: regulation of autophagy through activation of MEK/ERK signaling and PTEN/PI3K/Akt/mTORC1 signaling. Am J Transl Res 2015;7:2630–45.
[45] Wei H, Qu H, Wang H, Ji B, Ding Y, Liu D, et al. 1,25-Dihydroxyvitamin-D3 prevents the development of diabetic cardiomyopathy in type 1 diabetic rats by enhancing autophagy via inhibiting the β-catenin/TCF4/GSK-3β/mTOR pathway. J Steroid Biochem Mol Biol 2017;168:71–90.
[46] Kumar S, Nanduri R, Bhagyaraj E, Kalra R, Ahuja N, Chacko AP, et al. Vitamin D3-VDR-PTPN6 axis mediated autophagy contributes to the inhibition of macrophage foam cell formation. Autophagy 2020;24:1–17.
[47] Ji L, Gao J, Kong R, Gao Y, Ji X, Zhao D. Autophagy exerts pivotal roles in regulatory effects of 1α,25-(OH)2D3 on the osteoclastogenesis. Biochem Biophys Res Commun 2019;511:869–74.
[48] Kong C, Wang C, Shi Y, Yan L, Xu J, Qi W. Active vitamin D activates chondrocyte autophagy to reduce osteoarthritis via mediating the AMPK-mTOR signaling pathway. Biochem Cell Biol = Biochim Biol Cell 2020;98:434–42.
[49] Yuk JM, Shin DM, Lee HM, Yang CS, Jin HS, Kim KK, et al. Vitamin D3 induces autophagy in human monocytes/macrophages via cathelicidin. Cell Host Microbe 2009;6:231–43.
[50] Sato E, Imafuku S, Ishii K, Itoh R, Chou B, Soejima T, et al. Vitamin D-dependent cathelicidin inhibits *Mycobacterium marinum* infection in human monocytic cells. J Dermatol Sci 2013;70:166–72.
[51] Fabri M, Stenger S, Shin DM, Yuk JM, Liu PT, Realegeno S, et al. Vitamin D is required for IFN-gamma-mediated antimicrobial activity of human macrophages. Sci Transl Med 2011;3:104ra2.
[52] Hu W, Zhang L, Li MX, Shen J, Liu XD, Xiao ZG, et al. Vitamin D3 activates the autolysosomal degradation function against *Helicobacter pylori* through the PDIA3 receptor in gastric epithelial cells. Autophagy 2019;15:707–25.
[53] Godbole NM, Sinha RA, Tiwari S, Pawar SD, Dhole TN. Analysis of influenza virus-induced perturbation in autophagic flux and its modulation during vitamin D3 mediated anti-apoptotic signaling. Virus Res 2020;282:197936.
[54] Høyer-Hansen M, Bastholm L, Szyniarowski P, Campanella M, Szabadkai G, Farkas T, et al. Control of macroautophagy by calcium, calmodulin-dependent kinase kinase-beta, and Bcl-2. Mol Cell 2007;25:193–205.
[55] Song JH, Park E, Kim MS, Cho KM, Park SH, Lee A, et al. l-Asparaginase-mediated downregulation of c-Myc promotes 1,25(OH)(2) D(3)-induced myeloid differentiation in acute myeloid leukemia cells. Int J Cancer 2017;140:2364–74.
[56] Zhang X, Luo F, Li J, Wan J, Zhang L, Li H, et al. DNA damage-inducible transcript 4 is an innate guardian for human squamous cell carcinoma and an molecular vector for anti-carcinoma effect of 1,25(OH)(2) D(3). Exp Dermatol 2019;28:45–52.
[57] Bikle D, Christakos S. New aspects of vitamin D metabolism and action – addressing the skin as source and target. Nat Rev Endocrinol 2020;16:234–52.
[58] Wang RC, Levine B. Calcipotriol induces autophagy in HeLa cells and keratinocytes. J Invest Dermatol 2011;131:990–3.
[59] Gong Q, Li X, Sun J, Ding G, Zhou M, Zhao W, et al. The effects of calcipotriol on the dendritic morphology of human melanocytes under oxidative stress and a possible mechanism: is it a mitochondrial protector? J Dermatol Sci 2015;77:117–24.
[60] Zouboulis CC, Seltmann H, Abdel-Naser MB, Hossini AM, Menon GK, Kubba R. Effects of extracellular calcium and 1,25 dihydroxyvitamin D3 on sebaceous gland cells in vitro and in vivo. Acta Dermato-venereol 2017;97:313–20.
[61] Das LM, Binko AM, Traylor ZP, Peng H, Lu KQ. Vitamin D improves sunburns by increasing autophagy in M2 macrophages. Autophagy 2019;15:813–26.
[62] Ezzat S, Louka ML, Zakaria ZM, Nagaty MM, Metwaly RG. Autophagy in osteoporosis: relation to oxidative stress. J Cell Biochem 2019;120:2560–8.
[63] Wang W, Li C, Zhang Z, Zhang Y. Arsenic trioxide in synergy with vitamin D rescues the defective VDR-PPAR-γ functional module of autophagy in rheumatoid arthritis. PPAR Res 2019;2019:6403504.
[64] Meghil MM, Hutchens L, Raed A, Multani NA, Rajendran M, Zhu H, et al. The influence of vitamin D supplementation on local and systemic inflammatory markers in periodontitis patients: a pilot study. Oral Dis 2019;25:1403–13.
[65] Sustova H, De Feudis M, Reano S, Alves Teixeira M, Valle I, Zaggia I, et al. Opposing effects of 25-hydroxy- and 1α,25-dihydroxy-vitamin D3 on pro-cachectic cytokine-and cancer conditioned medium-induced atrophy in C2C12 myotubes. Acta Physiol 2019;226:e13269.
[66] Patel U, Yousuf S, Lakhani K, Raval P, Kaur N, Okafor T, et al. Prevalence and outcomes associated with vitamin D deficiency among indexed hospitalizations with cardiovascular disease and cerebrovascular disorder—a nationwide study. Medicines 2020;7:72.
[67] Kusunose K, Okushi Y, Okayama Y, Zheng R, Abe M, Nakai M, et al. Association between vitamin D and heart failure mortality in 10,974 hospitalized individuals. Nutrients 2021;13:335.
[68] Yao T, Ying X, Zhao Y, Yuan A, He Q, Tong H, et al. Vitamin D receptor activation protects against myocardial reperfusion injury through inhibition of apoptosis and modulation of autophagy. Antioxid Redox Signal 2015;22:633–50.
[69] Guo X, Lin H, Liu J, Wang D, Li D, Jiang C, et al. 1,25-Dihydroxyvitamin D attenuates diabetic cardiac autophagy and damage by vitamin D receptor-mediated suppression of FoxO1 translocation. J Nutr Biochem 2020;80:108380.
[70] Hu F, Yan L, Lu S, Ma W, Wang Y, Wei Y, et al. Effects of 1, 25-dihydroxyvitamin D3 on experimental autoimmune myocarditis in mice. Cell Physiol Biochem 2016;38:2219–29.
[71] Zhou KL, Zhang YH, Lin DS, Tao XY, Xu HZ. Effects of calcitriol on random skin flap survival in rats. Sci Rep 2016;6:18945.
[72] Jang W, Kim HJ, Li H, Jo KD, Lee MK, Song SH, et al. 1,25-Dyhydroxyvitamin D attenuates rotenone-induced neurotoxicity in SH-SY5Y cells through induction of autophagy. Biochem Biophys Res Commun 2014;451:142–7.
[73] Zhou KL, Chen DH, Jin HM, Wu K, Wang XY, Xu HZ, et al. Effects of calcitriol on experimental spinal cord injury in rats. Spinal Cord 2016;54:510–16.
[74] Cui C, Cui J, Jin F, Cui Y, Li R, Jiang X, et al. Induction of the vitamin D receptor attenuates autophagy dysfunction-mediated cell death following traumatic brain injury. Cell Physiol Biochem 2017;42:1888–96.
[75] Li H, Jang W, Kim HJ, Jo KD, Lee MK, Song SH, et al. Biochemical protective effect of 1,25-dihydroxyvitamin D3 through autophagy induction in the MPTP mouse model of Parkinson's disease. Neuroreport 2015;26:669–74.
[76] Zhen C, Feng X, Li Z, Wang Y, Li B, Li L, et al. Suppression of murine experimental autoimmune encephalomyelitis development by 1,25-dihydroxyvitamin D3 with autophagy modulation. J Neuroimmunol 2015;280:1–7.
[77] Lu R, Zhang Y-G, Xia Y, Sun J. Imbalance of autophagy and apoptosis in intestinal epithelium lacking the vitamin D receptor. FASEB J 2019;33:11845–56.
[78] Huang F-C. Vitamin D differentially regulates *Salmonella*-induced intestine epithelial autophagy and interleukin-1β expression. World J Gastroenterol 2016;22:10353–63.
[79] Cao R, Ma Y, Li S, Shen D, Yang S, Wang X, et al. 1,25(OH)2D3 alleviates DSS-induced ulcerative colitis via inhibiting NLRP3 inflammasome activation. J Leukocyte Biol 2020;108:283–95.
[80] Lu R, Shang M, Zhang YG, Jiao Y, Xia Y, Garrett S, et al. Lactic acid bacteria isolated from Korean Kimchi activate the vitamin D receptor-autophagy signaling pathways. Inflamm Bowel Dis 2020;26:1199–211.
[81] Lai WT, Huang FC. Probiotics exert reciprocal effects on autophagy and interleukin-1β expression in *Salmonella*-infected intestinal epithelial cells via autophagy-related 16L1 protein. Beneficial Microb 2019;10:913–22.
[82] Uberti F, Bardelli C, Morsanuto V, Ghirlanda S, Molinari C. Role of vitamin D(3) combined to alginates in preventing acid and oxidative injury in cultured gastric epithelial cells. BMC Gastroenterol 2016;16:127.
[83] Li R, Guo E, Yang J, Li A, Yang Y, Liu S, et al. 1,25(OH)2 D3 attenuates hepatic steatosis by inducing autophagy in mice. Obesity (Silver Spring) 2017;25:561–71.
[84] He D, Wang Y, Liu R, He A, Li S, Fu X, et al. 1,25(OH)(2)D(3) activates autophagy to protect against oxidative damage of INS-1 pancreatic beta cells. Biol Pharm Bull 2019;42:561–7.

[85] Wang Y, He D, Ni C, Zhou H, Wu S, Xue Z, et al. Vitamin D induces autophagy of pancreatic β-cells and enhances insulin secretion. Mol Med Rep 2016;14:2644–50.
[86] Yang L, Fan Y, Zhang X, Liu J, Ma J. Effect of 1,25(OH)2D3 on high glucose-induced autophagy inhibition in peritoneum. Mol Med Rep 2017;16:7080–5.
[87] Shen Q, Bi X, Ling L, Ding W. 1,25-Dihydroxyvitamin D3 attenuates angiotensin II-induced renal injury by inhibiting mitochondrial dysfunction and autophagy. Cell Physiol Biochem 2018;51:1751–62.
[88] Yu Q, Qiao Y, Liu D, Liu F, Gao C, Duan J, et al. Vitamin D protects podocytes from autoantibodies induced injury in lupus nephritis by reducing aberrant autophagy. Arthritis Res Ther 2019;21:19.
[89] Hamzawy M, Gouda SAA, Rashid L, Attia Morcos M, Shoukry H, Sharawy N. The cellular selection between apoptosis and autophagy: roles of vitamin D, glucose and immune response in diabetic nephropathy. Endocrine 2017;58:66–80.
[90] Hamzawy M, Gouda SAA, Rashed L, Morcos MA, Shoukry H, Sharawy N. 22-Oxacalcitriol prevents acute kidney injury via inhibition of apoptosis and enhancement of autophagy. Clin Exp Nephrol 2019;23:43–55.
[91] Khodir SA, Samaka RM, Ameen O. Autophagy and mTOR pathways mediate the potential renoprotective effects of vitamin D on diabetic nephropathy. Int J Nephrol 2020:7941861.
[92] Tao S, Zhang H, Xue L, Jiang X, Wang H, Li B, et al. Vitamin D protects against particles-caused lung injury through induction of autophagy in an Nrf2-dependent manner. Environ Toxicol 2019;34:594–609.
[93] Dai J, Liang Y, Li H, Zhou W, Wang B, Gong A, et al. Vitamin D enhances resistance to *Aspergillus fumigatus* in mice via inhibition of excessive autophagy. Am J Transl Res 2018;10:381–91.
[94] Hu S, Dai J, Chen X. Vitamin D reduces autophagy by regulating NF-κB resistance to *Aspergillus fumigatus* infection. Gene 2020;753:144819.
[95] Yang R, Yang E, Shen L, Modlin RL, Shen H, Chen ZW. IL-12+IL-18 cosignaling in human macrophages and lung epithelial cells activates cathelicidin and autophagy, inhibiting intracellular mycobacterial growth. J Immunol 2018;200:2405–17.
[96] Lajtai K, Nagy CT, Tarszabó R, Benkő R, Hadjadj L, Sziva RE, et al. Effects of vitamin D deficiency on proliferation and autophagy of ovarian and liver tissues in a rat model of polycystic ovary syndrome. Biomolecules 2019;9:471.
[97] Gao L, Cao JT, Liang Y, Zhao YC, Lin XH, Li XC, et al. Calcitriol attenuates cardiac remodeling and dysfunction in a murine model of polycystic ovary syndrome. Endocrine 2016;52:363–73.
[98] Tian X, Ma S, Wang Y, Hou L, Shi Y, Yao M, et al. Effects of placental ischemia are attenuated by 1,25-dihydroxyvitamin D treatment and associated with reduced apoptosis and increased autophagy. DNA Cell Biol 2016;35:59–70.
[99] Hutabarat M, Wibowo N, Obermayer-Pietsch B, Huppertz B. Impact of vitamin D and vitamin D receptor on the trophoblast survival capacity in preeclampsia. PLOS ONE 2018;13:e0206725.
[100] Wilson RL, Buckberry S, Spronk F, Laurence JA, Leemaqz S, O'Leary S, et al. Vitamin D receptor gene ablation in the conceptus has limited effects on placental morphology, function and pregnancy outcome. PLOS ONE 2015;10:e0131287.
[101] Simmons KM, Beaudin SG, Narvaez CJ, Welsh J. Gene signatures of 1,25-dihydroxyvitamin D3 exposure in normal and transformed mammary cells. J Cell Biochem 2015;116:1693–711.
[102] Høyer-Hansen M, Bastholm L, Mathiasen IS, Elling F, Jäättelä M. Vitamin D analog EB1089 triggers dramatic lysosomal changes and Beclin 1-mediated autophagic cell death. Cell Death Differ 2005;12:1297–309.
[103] Wang J, Lian H, Zhao Y, Kauss MA, Spindel S. Vitamin D3 induces autophagy of human myeloid leukemia cells. J Biol Chem 2008;283:25596–605.
[104] Suares A, Tapia C, González-Pardo V. VDR agonists down regulate PI3K/Akt/mTOR axis and trigger autophagy in Kaposi's sarcoma cells. Heliyon 2019;5:e02367 -e.
[105] Demasters G, Di X, Newsham I, Shiu R, Gewirtz DA. Potentiation of radiation sensitivity in breast tumor cells by the vitamin D3 analogue, EB 1089, through promotion of autophagy and interference with proliferative recovery. Mol Cancer Therap 2006;5:2786–97.
[106] Gewirtz DA, Hilliker ML, Wilson EN. Promotion of autophagy as a mechanism for radiation sensitization of breast tumor cells. Radiother Cncol 2009;92:323–8.
[107] Wilson EN, Bristol ML, Di X, Maltese WA, Koterba K, Beckman MJ, et al. A switch between cytoprotective and cytotoxic autophagy in the radiosensitization of breast tumor cells by chloroquine and vitamin D. Horm Cancer 2011;2:272–85.
[108] Bristol ML, Di X, Beckman MJ, Wilson EN, Henderson SC, Maiti A, et al. Dual functions of autophagy in the response of breast tumor cells to radiation: cytoprotective autophagy with radiation alone and cytotoxic autophagy in radiosensitization by vitamin D 3. Autophagy 2012;8:739–53.
[109] Sharma K, Goehe RW, Di X, Hicks 2nd MA, Torti SV, Torti FM, et al. A novel cytostatic form of autophagy in sensitization of non-small cell lung cancer cells to radiation by vitamin D and the vitamin D analog, EB 1089. Autophagy 2014;10:2346–61.
[110] Han J, Tang Y, Zhong M, Wu W. Antitumor effects and mechanisms of 1,25(OH)2D3 in the Pfeiffer diffuse large B lymphoma cell line. Mol Med Rep 2019;20:5064–74.
[111] Bak DH, Kang SH, Choi DR, Gil MN, Yu KS, Jeong JH, et al. Autophagy enhancement contributes to the synergistic effect of vitamin D in temozolomide-based glioblastoma chemotherapy. Exp Therap Med 2016;11:2153–62.
[112] Abu El Maaty MA, Strassburger W, Qaiser T, Dabiri Y, Wölfl S. Differences in p53 status significantly influence the cellular response and cell survival to 1,25-dihydroxyvitamin D3-metformin cotreatment in colorectal cancer cells. Mol Carcinogen 2017;56:2486–98.
[113] Li J, Frederick A-LM, Jin Y, Guo C, Xiao H, Wood RJ, et al. The prevention of a high dose of vitamin D or its combination with sulforaphane on intestinal inflammation and tumorigenesis in Apc1638N mice fed a high-fat diet. Mol Nutr Food Res 2019;63:1800824.
[114] Wu Q, Wang X, Pham K, Luna A, Studzinski GP, Liu C. Enhancement of sorafenib-mediated death of Hepatocellular carcinoma cells by carnosic acid and vitamin D2 analog combination. J Steroid Biochem Mol Biol 2020;197:105524.
[115] Abdel-Mohsen MA, El-Braky AA, Ghazal AAE, Shamseya MM. Autophagy, apoptosis, vitamin D, and vitamin D receptor in hepatocellular carcinoma associated with hepatitis C virus. Medicine 2018;97:e0172.
[116] Zhao M, Duan XH, Wu ZZ, Gao CC, Wang N, Zheng ZH. Severe vitamin D deficiency affects the expression of autophagy related genes in PBMCs and T–cell subsets in active systemic lupus erythematosus. Am J Clin Exp Immunol 2017;6:43–51.
[117] Kariuki SN, Blischak JD, Nakagome S, Witonsky DB, Di Rienzo A. Patterns of transcriptional response to 1,25-dihydroxyvitamin D3 and bacterial lipopolysaccharide in primary human monocytes. G3 (Bethesda) 2016;6:1345–55.
[118] Klug-Micu GM, Stenger S, Sommer A, Liu PT, Krutzik SR, Modlin RL, et al. CD40 ligand and interferon-γ induce an antimicrobial response against *Mycobacterium tuberculosis* in human monocytes. Immunology 2013;139:121–8.
[119] Shin DM, Yuk JM, Lee HM, Lee SH, Son JW, Harding CV, et al. Mycobacterial lipoprotein activates autophagy via TLR2/1/CD14 and a functional vitamin D receptor signalling. Cell Microbiol 2010;12:1648–65.
[120] Verway M, Bouttier M, Wang T-T, Carrier M, Calderon M, An B-S, et al. Vitamin D induces interleukin-1β expression: paracrine macrophage epithelial signaling controls *M. tuberculosis* infection. PLOS Pathog 2013;9:e1003407.
[121] Afsal K, Selvaraj P. Effect of 1,25-dihydroxyvitamin D3 on the expression of mannose receptor, DC-SIGN and autophagy genes in pulmonary tuberculosis. Tuberculosis (Edinburgh, Scotland) 2016;99:1–10.
[122] Wan M, Tang X, Rekha RS, Muvva SSVJR, Brighenti S, Agerberth B, et al. Prostaglandin E2 suppresses hCAP18/LL-37 expression in human macrophages via EP2/EP4: implications for treatment of Mycobacterium tuberculosis infection. FASEB J 2018;32:2827–40.
[123] Campbell GR, Spector SA. Vitamin D inhibits human immunodeficiency virus type 1 and *Mycobacterium tuberculosis* infection in macrophages through the induction of autophagy. PLoS Pathog 2012;8:e1002689.
[124] Campbell GR, Spector SA. Toll-like receptor 8 ligands activate a vitamin D mediated autophagic response that inhibits human immunodeficiency virus type 1. PLOS Pathog 2012;8:e1003017.
[125] Anandaiah A, Sinha S, Bole M, Sharma SK, Kumar N, Luthra K, et al. Vitamin D rescues impaired *Mycobacterium tuberculosis*-mediated tumor necrosis factor release in macrophages of HIV-seropositive individuals through an enhanced toll-like receptor signaling pathway in vitro. Infect Immunity 2013;81:2–10.
[126] Khare D, Godbole NM, Pawar SD, Mohan V, Pandey G, Gupta S, et al. Calcitriol [1, 25[OH]2 D3] pre- and post-treatment suppresses inflammatory response to influenza A (H1N1) infection in human lung A549 epithelial cells. Eur J Nutr 2013;52:1405–15.
[127] Tian G, Liang X, Chen D, Mao X, Yu J, Zheng P, et al. Vitamin D3 supplementation alleviates rotavirus infection in pigs and IPEC-J2 cells via regulating the autophagy signaling pathway. J Steroid Biochem Mol Biol 2016;163:157–63.
[128] Estrella J, Kan-Sutton C, Gong K, Eissa T, Rajagopalan M, Lewis D, et al. A novel in vitro human macrophage model to study the persistence of *Mycobacterium tuberculosis* using vitamin D3 and retinoic acid activated THP-1 macrophages. Front Microbiol 2011;2:67.
[129] Lei G-S, Zhang C, Cheng B-H, Lee C-H. Mechanisms of action of vitamin D as supplemental therapy for pneumocystis pneumonia. Antimicrob Agents Chemother 2017;61 e01226-17.
[130] Shang S, Wu J, Li X, Liu X, Li P, Zheng C, et al. Artesunate interacts with the vitamin D receptor to reverse sepsis-induced immunosuppression in a mouse model via enhancing autophagy. Br J Pharmacol 2020;177:4147–65.
[131] Barbosa MC, Grosso RA, Fader CM. Hallmarks of aging: an autophagic perspective. Front Endocrinol 2019;9:790.
[132] Berridge MJ. Vitamin D deficiency accelerates ageing and age-related diseases: a novel hypothesis. J Physiol 2017;595:6825–36.
[133] Cao X, Ying Z, Li X, Zhang J, Hoogendijk EO, Liu Z. Serum 25-hydroxyvitamin D in relation to disability in activities of daily living, mobility, and objective physical functioning among Chinese older adults. Exp Gerontol 2021;148:111290.
[134] Nakamura K, Kitamura K, Watanabe Y, Saito T, Takahashi A, Kobayashi R, et al. Predictors of decline in vitamin D status in middle-aged and elderly individuals: a 5-year follow-up study. Br J Nutr 2020;124:729–35.
[135] Jin X, Xiong S, Ju SY, Zeng Y, Yan LL, Yao Y. Serum 25-hydroxyvitamin D, albumin, and mortality among chinese older adults: a population-based longitudinal study. J Clin Endocrinol Metab 2020;105:dgaa349.
[136] Gilani A, Ramsay SE, Welsh P, Papacosta O, Lennon LT, Whincup PH, et al. Vitamin D deficiency is associated with orthostatic hypotension in older men:

a cross-sectional analysis from the British Regional Heart Study. Age Ageing 2021;50:198–204.
[137] Pan T, Banerjee R, Dasgupta A, Paul B. Vitamin D status among women aged 40 years and above in a rural area of West Bengal: a community-based study. J Fam Med Prim Care 2018;7:1263–7.
[138] Tong T, Liu Z, Zhang H, Sun J, Zhang D, Wang F, et al. Age-dependent expression of the vitamin D receptor and the protective effect of vitamin D receptor activation on H(2)O(2)-induced apoptosis in rat intervertebral disc cells. J Steroid Biochem Mol Biol 2019;190:126–38.
[139] Gutierrez JA, Jones KA, Flores R, Singhania A, Woelk CH, Schooley RT, et al. Vitamin D metabolites inhibit hepatitis C virus and modulate cellular gene expression. J Virol Antivir Res 2014;3. doi:10.4172/2324-8955.1000129.
[140] Merzon E, Tworowski D, Gorohovski A, Vinker S, Golan Cohen A, Green I, et al. Low plasma 25(OH) vitamin D level is associated with increased risk of COVID-19 infection: an Israeli population-based study. FEBS J 2020;287:3693–702.
[141] Kaufman HW, Niles JK, Kroll MH, Bi C, Holick MF. SARS-CoV-2 positivity rates associated with circulating 25-hydroxyvitamin D levels. PLOS ONE 2020;15:e0239252.
[142] Meltzer DO, Best TJ, Zhang H, Vokes T, Arora V, Solway J. Association of vitamin D status and other clinical characteristics with COVID-19 test results. JAMA Netw Open 2020;3:e2019722.
[143] Entrenas Castillo M, Entrenas Costa LM, Vaquero Barrios JM, Alcalá Díaz JF, López Miranda J, Bouillon R, et al. Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: a pilot randomized clinical study. J Steroid Biochem Mol Biol 2020;203:105751.
[144] Abrishami A, Dalili N, Mohammadi Torbati P, Asgari R, Arab-Ahmadi M, Behnam B, et al. Possible association of vitamin D status with lung involvement and outcome in patients with COVID-19: a retrospective study. Eur J Nutr 2020:1–9.
[145] Meftahi GH, Jangravi Z, Sahraei H, Bahari Z. The possible pathophysiology mechanism of cytokine storm in elderly adults with COVID-19 infection: the contribution of “inflame-aging”. Inflamm Res 2020;69:825–39.
[146] Mijaljica D, Klionsky DJ. Autophagy/virophagy: a “disposal strategy” to combat COVID-19. Autophagy 2020;16:2271–2.
[147] Bonam SR, Muller S, Bayry J, Klionsky DJ. Autophagy as an emerging target for COVID-19: lessons from an old friend, chloroquine. Autophagy 2020;16:2260–6.