v1: 23 April 2025

Review Article

Vitamin D Deficiency in Smokers: A Major Risk Factor in Lung Carcinogenesis

Peer-approved: 23 April 2025

Qeios, Vol. 7 (2025)
ISSN: 2632-3834

Subendu Sarkar[1], Manas Kamal Sen[2], Rajender Pal Singh[3], Gorachand Bhattacharya[4]

1. Central Research Laboratory, ESIC Medical College and Hospital, Faridabad, India; 2. Department of Respiratory Medicine, ESIC Medical College and Hospital, Faridabad, India; 3. Department of Experimental Medicine and Biotechnology, Postgraduate Institute of Medical Education and Research (PGIMER), India; 4. Apollo Multispecialty Hospitals, India

Worldwide prevalence and mortality of lung cancer are gradually increasing. Tobacco smoking is the major cause of lung carcinogenesis. Smoking causes a remarkable reduction in vitamin D concentration. Moreover, vitamin D deficiency is associated with lung carcinogenesis. In this context, vitamin D is effective in reducing lung cancer mortality. However, the underlying molecular mechanisms are poorly understood. A comprehensive literature survey has been conducted to search for studies associated with lung cancer, tobacco smoking, vitamin D, and molecular mechanisms. PubMed, Google Scholar, Web of Science, Embase, and Scopus were used to search for articles up to November 2024. Peer-reviewed full articles written only in the English language were taken into consideration. VDR gene polymorphism is one of the important reasons of vitamin D deficiency in smokers. Smoking increases Ca^{2+} influx in vascular smooth muscle cells, which is correlated with lung carcinogenesis. However, vitamin D reduces Ca^{2+} via decreasing HRC. Smoking enhances genetic/epigenetic alterations, gene mutations, SNPs, inflammation, oxidative stress, and activation of signaling pathways related to lung cancer. Vitamin D reduces gene expressions of HIF-1α, Ki-67, HTERT, NF1, CYP1A1, EPHX1, and VEGF. Additionally, it increases the survival of lung cancer patients with p53, KRAS, and EGFR mutations. Besides, vitamin D reduces inflammation and increases B and NK-cell counts. It decreases ROS and reactive oxygen. Lung cancer-associated signal transduction of TGF-β, Wnt, Hedgehog, Notch, PI3K/AKT/mTOR, MAPK, ERK1, ERK2, and NF-κB are also reduced. The present study highlights the therapeutic role of vitamin D to control and prevent the smoking-induced progression of lung cancer.

Corresponding author: Subendu Sarkar, drsubendus@gmail.com

Introduction

As per the World Health Organization, lung cancer is the leading cause of cancer-related death worldwide. Lung cancer is the second most common cancer globally. According to the last update, around 1.8 million deaths have been recorded in the year 2020 [1]. According to the Global Cancer Statistics (GLOBOCAN 2020), the lung cancer incidence rate in men is high (37.5 in 100,000) in higher HDI (Human Development Index) countries such as North America, North and West Europe, New Zealand, and Australia, and less (10.3 in 100,000) in lower HDI countries of Africa and South-Central Asia [2]. However, the cases of lung cancer are increasing in many countries. Around 14% of lung cancer deaths can be

 doi.org/10.32388/02IGML.3

correlated with air pollution with PM2.5 (particulate matter). However, most cases of lung cancer deaths (two-thirds) in the worldwide population are due to tobacco smoking.

Two major types of lung cancer are found: non-small cell lung cancer (NSCLC) (85%) and small cell lung cancer (10-15%). NSCLC can be further classified into large cell carcinoma, adenocarcinoma, and squamous cell carcinoma [3]. Whereas small cell lung cancer can be sub-divided into lung carcinoid tumor and other lung cancers [4]. Lung cancer, or bronchogenic carcinoma, can be characterized by tumor development in lung parenchyma or bronchi. It is already mentioned that tobacco smoking is the leading cause of lung cancer mortality. Smoking develops dysplasia in the lung epithelium [5]. Tobacco smoking activates the PI3K/Akt/mTOR signaling pathway, which in turn initiates tumorigenesis [6]. Tobacco smoking contains multiple carcinogenic compounds such as nitrosamines, polycyclic aromatic hydrocarbons, and aldehydes, which may lead to certain mutations in genes such as KRAS, TP53, EGFR, BRAF, MEK, MET, PIK3CA, etc. [7]. Besides, the addictive tobacco compound nicotine induces the progression of the cell cycle, epithelial-to-mesenchymal transition, migration, invasion, angiogenesis, and evasion of apoptosis [8]. Mutations, including genetic/epigenetic modifications (promoter methylation), transcriptomic changes including inflammation and apoptosis pathways, lead to premalignant alterations such as dysplasia and clonal patches [9].

It is extensively studied that vitamin D is less in tobacco smokers [10]. Smoking significantly affects vitamin D and calcium metabolism and reduces the serum 25(OH)D below the normal value and parathyroid hormone [11]. As per previous studies, the serum/plasma vitamin D level of <20 ng/ml is considered vitamin D deficiency [12][13]. However, the exact molecular mechanism behind the reduction of vitamin D in smokers is poorly understood. Besides, lung cancer patients carry remarkably low levels of vitamin D in their blood [14]. Hence, inadequate vitamin D levels may be potentially associated with lung cancer pathophysiology.

Therefore, this study aims to elucidate the molecular mechanisms and pathways linking tobacco-induced lung carcinogenesis and vitamin D deficiency, and to explore the potential therapeutic role of vitamin D in lung cancer.

Data curation

A comprehensive literature survey has been conducted to search for studies associated with lung cancer, tobacco smoking, vitamin D, and molecular mechanisms. The key-words used for search strategy include lung cancer, cigarette, tobacco, smoking, and Vitamin D. PubMed, Google Scholar, Web of Science, Embase, and Scopus were used to search for articles up to November 2024. Peer reviewed full articles, original research and reviews, case studies, and clinical trials written only in English language are taken into consideration.

Vitamin D and tobacco smoking

Vitamin D is a potent micronutrient required for various biological functions in the body. Its low level is widely associated with numerous disease pathogenesis and improper molecular functions [15]. Vitamin D is synthesized by the epidermis using direct exposure to sunlight on the skin. It is of two types- Vitamin D_2 or ergocalciferol and vitamin D_3 or cholecalciferol. Vitamin D_2 and D_3, after several hydroxylation processes, form intermediates 25-hydroxyvitamin D or 25(OH) D in the liver and 1,25-dihydroxyvitamin D or calcitriol in the kidney (Fig. 1). Serum 25(OH) D is an active hormone and a good parameter for measuring vitamin D in serum.

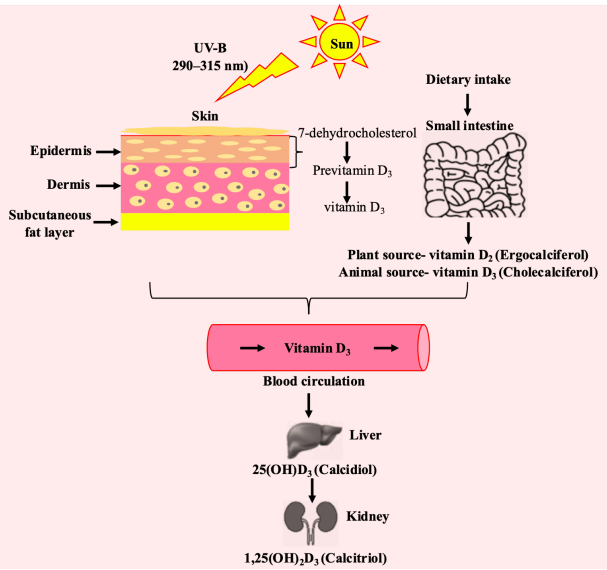

Figure 1. Vitamin D_3 synthesis in the skin using sunlight and vitamin D_2 and D_3 synthesis in the small intestine using dietary intake. Vitamin D3, after successive hydroxylation, produces 25(OH) D_3 (Calcidiol) in the liver and 1,25$(OH)_2D_3$ (Calcitriol) in the kidney.

doi.org/10.32388/02IGML.3

A study conducted on the US population over the period from 2001 to 2014 revealed that both active and passive tobacco smoking are associated with 25(OH) D deficiency [16]. It is reported that the serum concentration of vitamin D in active smokers is comparatively less than the non-smokers [17]. An effect of smoking on VDR gene polymorphism is already reported [18]. A previous study on cigarette smoke exposure in a male Wistar rat model has reported lung injury with a reduction of the vitamin D receptor (VDR). Depletion of VDR is associated with activation of the mitogen-activated protein kinase (MAPK) [19]. Activation of the MAPK signaling pathway is observed in lung cancer, especially in NSCLC [20][21]. VDR has an important role in calcium and inorganic phosphate (Pi) homeostasis [22]. Cigarette smoking significantly increases calcium and Pi [23][24] (Fig. 2). It is reported that nicotine binds to α3 and α7 nAChR (nicotinic acetylcholine receptor) present on vascular smooth muscle cells and promotes intracellular Ca_2^+ influx [25]. It is in this context that increased levels of calcium and Pi are associated with lung cancer [23][26][27]. However, vitamin D supplementation is quite useful in reducing increased calcium and Pi levels. A study on a mice model has revealed that vitamin D maintains calcium homeostasis by downregulating the histidine-rich calcium-binding (HRC) protein and inhibits tumor growth, proliferation, and migration [28]. On the other hand, it is reported that 30% of the Pi absorption in the human intestine is vitamin D-dependent [29]. It is reported that parathyroid hormone (PTH) induces lung cancer in patients having hypercalcemia [30]. However, vitamin D supplementation is effective in reducing serum PTH levels [31]. In addition to the VDR gene polymorphism, various toxic compounds of cigarette smoke may have a potential effect on vitamin D metabolism [32]. Increased levels of carcinogenic polycyclic aromatic hydrocarbons are correlated with decreased levels of vitamin D [33]. Another study shows that a high level of benzene is associated with a low level of vitamin D [34].

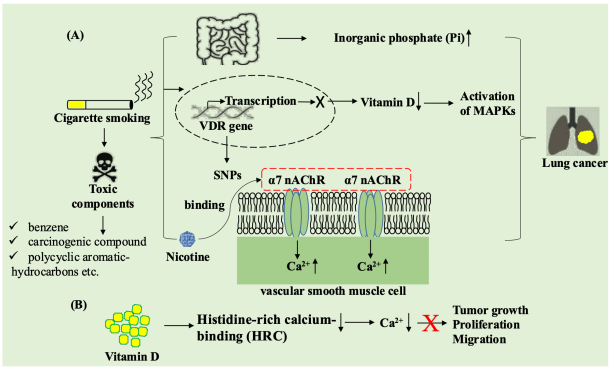

Figure 2. (A) Reduction of vitamin D concentration due to toxic and carcinogenic components of cigarette smoking. Smoking promotes elevation of Ca^{2+} influx in smooth muscle cells, which is associated with lung cancer pathogenesis (B) Supplementation of vitamin D leads to the decrease of Ca^{2+} influx, which may be beneficial to control tumor growth, proliferation, and migration.

Molecular aspects of smoking and lung cancer

It is reported that around 15% of smokers develop lung carcinoma [35]. Whereas, 80% - 90% of cases of lung cancers are caused by smoking [36]. The molecular mechanisms of smoking-induced lung cancer are complex to establish and poorly explored. However, frequent gene mutations, polymorphisms, gene overexpression, inflammation, etc. may explain the disease pathogenesis as described here (Fig. 3).

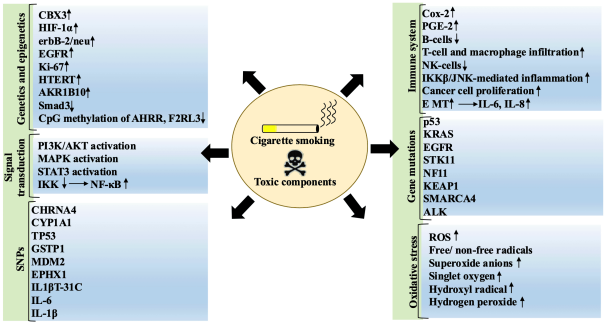

Figure 3. Toxic components of cigarette smoking effects on various biological events such as genetic/epigenetic alterations, gene mutations, SNPs, the immune system, oxidative stress, and signaling pathways related to lung cancer. Symbols "↓" and "↑" represent "low" and "high," respectively.

doi.org/10.32388/02IGML.3

It is demonstrated that smoking causes overexpression of the oncogene chromobox homolog 3 (CBX3), which promotes lung cancer progression [37]. A study conducted on NSCLC patients shows that lifetime cigarette smoking is closely associated with p53 tumor suppressor mutation. This study has reported that 47% of the tumor samples represent G:C→T:A transversion [38]. In addition to p53 mutation, cigarette smoking is also associated with K-ras mutation and overexpression of the erbB-2/neu oncogene in lung adenocarcinoma [39]. It is demonstrated that smokers having lung adenocarcinoma exhibit higher expressions of *EGFR*, *Ki-67*, and *HTERT* compared to nonsmokers [40]. Besides, it is reported for lung cancer patients that AKR1B10 (Aldo-Keto Reductase Family 1, Member B10) is overexpressed in smokers than in nonsmokers [41]. AKR1B10 is reported to promote cancer cell survival and the initiation of lung carcinoma [42]. Similarly, overexpression of the epidermal growth factor receptor (EGFR) is associated with NSCLC (40%-80%) [43]. Besides, EGFR mutation is a good biomarker and a potential target in lung cancer [43]. It is reported that EGFR expression is high in current smokers [44]. However, smoking is less associated with EGFR mutation rates and decreased overall survival of NSCLC patients [45]. Current smoking is closely associated with a reduction in the methylation of CpG islands compared to former and never smokers [46]. It is in this context that CpG island promoter methylation is pivotal to regulate gene expression. Smoking-induced methylation of several genes is already reported [46]. Especially, hypomethylation of CpG sites of *AHRR* and *F2RL3* is associated with lung cancer risk [47]. DNA methylation is catalyzed by DNA methyltransferases (DNMTs). It is shown that DNMT1 gene expression is significantly higher in smokers than in nonsmokers, which depicts the low expression of target genes [48]. An in vitro study using the lung adenocarcinoma cell line A549 shows that cigarette smoking decreases transforming growth factor beta (TGF-β)-mediated suppression of tumors via lowering the expression of SmaD3 (SMAD Family Member 3) [49].

In addition to the epigenetic regulations, tobacco smoking results in 1,000 to 10,000 mutations in a somatic cell [50]. In smokers, 25% of the cells get driver mutations. It is reported for NSCLC that former as well as current smokers show mutations in KRAS, STK11, NF1, KEAP1, and SMARCA4 [51]. Studies conducted on NSCLC patients reveal that 35% of smokers show EGFR mutations [52]. Similarly, transversion mutations (G→T or G→C) can be found in KRAS in 25% of lung adenocarcinomas associated with cigarette smoking [53] [54]. However, different studies have been conducted, which suggest that EGFR and KRAS mutations are frequent in smokers having lung cancer [55][56]. It is reported that smokers with advanced lung adenocarcinoma show mutations in the anaplastic lymphoma receptor tyrosine kinase (ALK) gene. Studies conducted on 9,575 patients have shown ALK mutations in 6.8%, out of which 70.9% of lung adenocarcinoma patients are smokers [57].

Similar to gene expressions and mutations, smoking significantly causes gene polymorphisms in lung cancer. Single nucleotide polymorphisms in smokers having lung cancer are documented for nicotinic acetylcholine receptor alpha 4 subunits (CHRNA4) (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6636285/) cytochrome P450 family 1 subfamily A member 1 (CYP1A1) [58], cytochrome P450 2A6 (CYP2A6) [59], tumor suppressor *TP53* (*p53*) [60], glutathione S-transferase P1 (GSTP1) [61], murine double minute-2 (MDM2) [62], and epoxide hydrolase 1 (EPHX1) [63].

Smoking-induced SNPs are also documented in inflammatory genes interleukin-*1β* T-31C [64], Il-6 [65], IL-1β [66]. However, IL-6 and IL-1β polymorphisms are important in the development of lung cancer [67][68]. In addition to the gene expressions, mutations, and SNPs, smoking-induced inflammation causes a tremendous effect to exacerbate lung cancer pathogenesis [69]. In this context, pulmonary disorders such as chronic obstructive pulmonary disease (COPD) can be correlated with an abnormal inflammatory response [70]. Cigarette smoking promotes the overexpression of cyclooxygenase-2 (COX-2) and prostaglandin (PGE2) E2 [71]. Elevation of COX-2 and PGE2 plays an important role in promoting the inflammation-induced development of lung cancer [72]. It is important to mention that smoking reduces B-cell frequency. Depletion of B-cells results in the repression of T-cell and macrophage infiltration towards lung tumors [73]. Besides, smoking impacts the tumor immune environment to induce a subset of Treg cells for immunosuppression in lung cancer [74]. However, the elevation of Treg cells and the reduction of NK-cells in smokers having a high risk of lung cancer are also reported [75]. In vivo studies show that smoking induces lung tumorigenesis through developing IKKβ and JNK1-mediated inflammatory responses [76]. Smoking promotes cancer stem cell proliferation, which in turn induces epithelial-mesenchymal transition (EMT) and

increases the production of inflammatory cytokines such as IL-6, IL-8 [77].

Hypoxia and angiogenesis are two major factors in lung cancer carcinogenesis. Hypoxia leads to the activation of transcription factors and promotes the high expression of proinflammatory genes, which causes profound inflammation [78]. It is demonstrated that nicotine results in the overexpression of Hypoxia-inducible factor-1α (HIF-1α) and vascular endothelial growth factor (VEGF) in NSCLC [79]. HIF-1α is responsible for antiapoptosis and cancer cell proliferation [80]. Whereas the increased expression of VEGF causes angiogenesis, tumorigenesis, and metastasis [81]. Besides, signal transducer and activator of transcription 3 (STAT3) is shown to be overactivated in tobacco-induced lung tumors with reduced immunosuppression [82]. In vitro studies show that myeloid cell leukemia-1 (Mcl-1) through STAT3 is overexpressed due to nicotine exposure. It suggests that the downregulation of Mcl-1 and inhibition of the STAT3 pathway may be potential targets in lung cancer [83]. Nicotine has been shown to activate phosphoinositide 3-kinases/ protein kinase B (PI3K/AKT), mitogen-activated protein kinases (MAPK), and c-src survival pathways in lung cancer progression [84]. Additionally, PI3K/AKT is also activated by nicotine via α7-nAChR [85]. In vitro studies show that cigarette smoke condensate phosphorylates and degrades IκBα kinase (IKK), which in turn activates nuclear factor-κB (NF-κB) and enhances lung carcinogenesis [86].

Oxidative damage due to smoking plays an important role in lung cancer pathogenesis. Reactive oxygen species (ROS) can be generated directly from smoke itself and indirectly from other carcinogens or their metabolites [87]. Free radicals and non-free radicals such as superoxide anions, singlet oxygen, hydroxyl radical, and hydrogen peroxide cause significant damage to tissue by the oxidation of nucleic acids, lipids, and proteins. However, the quinone/hydroquinone complex of the tar phase of cigarette smoke induces ROS generation. Oxidative damage to DNA/RNA results in the breaking of nucleic acid strands followed by improper gap filling, which can lead to gene mutation and lung cancer [88][89]. Oxidative stress can further activate the transcription factor NF-κB to initiate the inflammatory cascade to trigger lung cancer [90].

Vitamin D in lung cancer

Supplementation of vitamin D is reported to ameliorate lung carcinogenesis in different ways (Fig. 4). It is reported that vitamin D deficiency (<20 ng/mL, 75.9%) is associated with the advanced stage of NSCLC, where smokers (61.1%) show vitamin D concentrations <10 ng/mL [91]. Another study has shown that 46% of the stage-IV lung cancer patients, including NSCLC, have vitamin D deficiency compared to normal [92]. However, supplementation of vitamin D with 30,000 IU/day for 14 days is effective in achieving the target of 25(OH) D level in lung cancer patients (44%) having vitamin D deficiency [93]. A systematic review and meta-analysis including 12 randomized clinical trials with 72,669 participants has revealed the association of vitamin D intake with a reduction in lung cancer mortality [94]. In addition to nicotine, a potential carcinogen nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) promotes the nicotinic acetylcholine receptor (nAChR)/ proto-oncogene tyrosine-protein kinase (Src)/STAT3-mediated lung tumorigenesis and activates the renin-angiotensin system and insulin-like growth factor-1 receptor (IGF-1R) signaling [95].

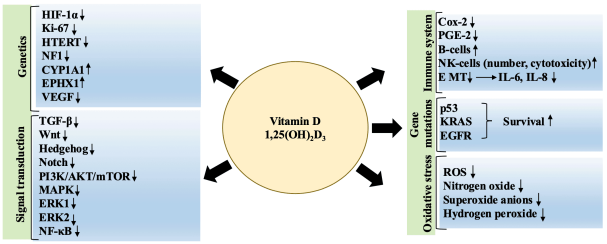

Figure 4. Effect of vitamin D on various biological events such as genetic/epigenetic alterations, survival of gene mutations, immune system, oxidative stress, and signaling pathways related to lung cancer. Symbols "↓" and "↑" represent "low" and "high," respectively.

It is reported that VDR knockout mice exhibit decreased metastatic growth of lung cancer cells [96]. VDR knockout mice show increased 1α,25$(OH)_2D_3$ levels in serum due to the absence of vitamin D-dependent calcium activity. In this study, wild-type VDR+/+ and knockout VDR-/- mice have been injected with cloned metastatic variant LLC cells tagged with GFP. It has been observed after day 18 that VDR+/+ mice develop more metastatic nodules and tumors compared to VDR-/- mice. Another study shows that vitamin D downregulates HRC protein and inhibits tumor growth, proliferation, and migration in lung cancer [97]. In this study, H460 lung cancer cells with or without supplementation of calcitriol (2×10^{-8} M) are studied for HRC expression and other cancerous properties. It is

doi.org/10.32388/02IGML.3

noticed that HRC expression, as well as cell migration and proliferation, are inhibited and apoptosis is initiated.

Molecular targets of vitamin D in lung cancer in relation to smoking

As mentioned earlier, mutations in the oncogenic suppressor p53 play a major role in lung cancer progression. However, a study has reported that vitamin D at the dose of 2000 IU/d can reduce the risk of death in p53 immunoreactive patients by increasing the survival rate up to 80.9% in gastrointestinal cancer [98]. Kras mutations are associated with smokers in NSCLC [99]. KRAS itself, or through the RAS/RAF/MEK/ERK canonical pathway, functions in cytoskeleton organization, cell survival, proliferation, and vesicle trafficking [100]. It is reported that Kras mutations are significantly correlated with VDR overexpression [101]. Mutations in EGFR are also reported in smokers (23.4%), however, they are more common in never-smokers (60.3%) [52]. It has been shown that activation of EGFR-tyrosine kinases (TK) plays an important role in lung cancer progression [102]. However, EGFR mutations, such as T790M mutations in EGFR, can resist drugs such as EGFR-TK inhibitors (gefitinib and erlotinib). Reduced levels of vitamin D are associated with EGFR mutations, as reported in pulmonary adenocarcinoma [103]. In this context, vitamin D may be useful for the progression-free survival of lung adenocarcinoma patients having EGFR mutations [104]. Similar to EGFR, Ki-67 is also associated with vitamin D levels. Ki-67 is a prognostic marker, and its staining is useful to measure the tumor proliferative fraction [105]. It is reported that 1,25 dihydroxyvitamin D concentration in serum is inversely associated with Ki-67 [106]. In this context, vitamin D_3 supplementation in a dose-dependent manner is useful to reduce Ki-67 levels [107]. Additionally, hTERT has been shown to enhance epithelial-mesenchymal transition in lung cancer cells by increasing cMET (receptor tyrosine kinase) [108]. It has been shown that $1,25(OH)_2D_3$ downregulates hTERT mRNA expression and suppresses cancer growth in ovarian cancer cells [109]. However, the function of vitamin D to suppress lung cancer is yet to be explored. Additionally, hypomethylation of smoking-related genes is already mentioned earlier, which is linked to lung cancer. In this context, a higher concentration of serum 25(OH) D is linked to increased methylation, as reported in breast cancer [110]. However, the effect of vitamin D in the regulation of smoking-induced epigenetic modification in lung cancer is yet to be unfurled. Neurofibromatosis 1 (NF1) is a tumor suppressor and is shown to downregulate RAS activity. NF1 mutations are common in lung cancer [111]. However, the serum concentration of vitamin D is inversely associated with NF1 [112]. It further states the therapeutic efficacy of vitamin D to suppress tumor development in patients with NF1. As previously stated, SNPs in CYP1A1 is reported in smokers having lung cancer[113]. In this context, vitamin D-induced expression of CYP1A1 has been reported using *in vitro* studies [60]. Besides, mutations and SNPs in epoxide hydrolase 1 (EPHX1) are linked to lung cancer and various diseases [114][115]. EPHX1 is an enzyme involved in the hydrolysis of epoxides from aromatic hydrocarbons and amines released by cigarette smoke [116]. This process leads to the production of carcinogens and enhances the pathogenesis of lung cancer. In vivo studies show that $1,25(OH)_2D_3$ results in the overexpression of EPHX1 in vitamin D-deficient rats [117]. However, this mechanism is not explored in lung cancer. IL-6 and IL-1B polymorphisms are associated with lung cancer pathogenesis [118].

Apart from these, vitamin D is known to regulate the immune system. Vitamin D has been shown to downregulate the proinflammatory cytokines IL-6 and IL-8 [119][120]. Additionally, cyclooxygenase-2 (COX-2) overexpression is associated with cigarette smoking-induced NSCLC [121]. However, vitamin D is shown to be effective in reducing COX-2 and prostaglandins (PGs) in a dose-dependent manner [122]. Vitamin D is also reported to inhibit PGE2 [123]. Moreover, $1,25(OH)_2D_3$ has been shown to be involved in activated B-cell proliferation and the improvement of regulatory B-cell function [124] [125]. It is reported that NK cells exhibit the first line of defense against lung tumors. They generally activate both innate and adaptive immune responses. Therefore, NK cells are used as immunotherapy to treat tumors. In this context, $1,25(OH)_2D_3$ directly affects the function and cytotoxicity of NK cells, which is supported by in vivo studies [126][127]. Additionally, vitamin D targets cancer stem cell-associated signal transduction pathways such as TGF-β, Wnt, Hedgehog, Notch, and prevents cancer stem cell proliferation [128]. As mentioned earlier, EMT is associated with lung cancer progression. Hence, targeting EMT may be a potential therapeutic strategy in lung cancer [129]. It is shown that vitamin D $1,25(OH)_2D_3$ prevents EMT by inhibiting proliferation [130].

It is already mentioned earlier that overexpression of HIF-1α and VEGF is associated with lung cancer

pathogenesis. Besides, vitamin D level is negatively correlated with serum HIF-1α level in diabetic nephropathy [131]. However, this correlation is not unfurled in the case of lung cancer. It is reported that vitamin D has the potential to reduce VEGF gene expression as well as the serum level of VEGF [132][133]. It is reported that vitamin D inactivates the PI3K/AKT/mTOR signaling pathway and inhibits the progression of NSCLC through suppressing the Warburg effect and stemness of NSCLC cells [134]. It has been shown that vitamin D is capable of suppressing MAPK signaling in colon cancer [135]. However, vitamin D targeting potential signaling pathways related to lung cancer needs to be studied in more detail. As stated previously, NF-κB aggravates lung cancer by promoting lung tumorigenesis and metastasis [136]. Additionally, JAK–STAT signaling also contributes to lung adenocarcinoma, which may be correlated with cigarette smoking [137]. It is reported that inhibition of JAK1/2 may be a therapeutic strategy in K-RAS-mediated lung adenocarcinoma [138]. In this context, an *in vivo* study with *Drosophila melanogaster* reveals significant downregulation of genes associated with NF-κB and JAK/STAT signaling pathways [139]. Cigarette smoking, especially nicotine, significantly contributes to activating extracellular signal-regulated kinase 1/2 (ERK1/2) through phosphorylation, which can be correlated with lung cancer [140][141]. It is reported that administration of vitamin D can result in the downregulation of the ERK1/2 activation pathway and attenuates chemokine secretion in myocardial injury [142]. However, the correlation between vitamin D and ERK needs to be studied in lung cancer patients.

Vitamin D supplementation is reported to downregulate reactive oxygen species (ROS) [143][144]. Vitamin D plays a central role in modulating mitochondrial oxidative metabolism by lowering fusion/fission and oxidative phosphorylation [145]. Vitamin D upregulates glutathione, which converts hydrogen peroxide (H2O2) to water. Additionally, vitamin D activates glucose-6-phosphate dehydrogenase and downregulates nitrogen oxide and converts O^{2-} to H_2O_2 [146]. However, vitamin D increases superoxide dismutase in muscle, which suggests vitamin D as a potential antioxidant [144][147].

Conclusion

The number of lung cancer cases and deaths is increasing. Clinicians are concerned about proper and targeted therapeutics. Tobacco smoking is the leading cause of lung cancer-related mortality. In this context, smoking causes a significant reduction in vitamin D concentration in both active and passive smokers. It is also studied that vitamin D deficiency is associated with lung carcinogenesis in smokers. Besides, vitamin D supplementation has been shown to be effective in the reduction of lung cancer mortality. However, the underlying molecular mechanisms are poorly understood. The present study has shown the plausible molecular targets and biochemical interactions through which vitamin D can act as a supplementation therapy to control and prevent lung cancer pathogenesis.

Extensive literature study and data compilation have revealed that smoking remarkably decreases the vitamin D level in lung cancer patients. The reasons for reducing vitamin D in lung cancer may be due to VDR gene polymorphism and VDR depletion because of the toxic and carcinogenic component of cigarette smoking such as nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone. Smoking also heightens Ca^{2+} influx in vascular smooth muscle cells, which further aggravates lung cancer pathogenesis. In this context, vitamin D may lower the Ca^{2+} influx through decreasing HRC, which in turn inhibits cancer cell proliferation and migration. Smoking significantly overexpresses genes related to lung cancer pathogenesis. It also results in epigenetic alterations such as hypomethylation and genetic alterations such as gene mutations and polymorphisms. Smoking potentially increases inflammation and reduces vital immune cells such as B-cells and NK-cells. Smoking predominantly increases ROS and activates various signaling pathways related to lung cancer progression. However, existing literature shows the importance of vitamin D in targeting smoking-induced biochemical alterations as mentioned. Vitamin D potentially targets and reduces the gene expressions of HIF-1α, Ki-67, HTERT, NF1, CYP1A1, EPHX1, and VEGF, which are significantly associated with lung cancer pathogenesis. Additionally, vitamin D increases the survival of lung cancer patients having p53, KRAS, and EGFR gene mutations. Supplementation of vitamin D may reduce lung cancer-related inflammation and increase B and NK-cell counts. Vitamin D has been shown to reduce ROS and reactive oxygen species to control oxidative damage to nucleic acids. Nevertheless, vitamin D targets various signaling pathways such as TGF-β, Wnt, Hedgehog, Notch, PI3K/AKT/mTOR, MAPK, ERK1, ERK2, and NF-κB, which may control lung cancer progression. This study highlights the potential of vitamin D as an adjunct therapeutic agent in mitigating smoking-induced lung carcinogenesis. However, extensive research in the concerned field is required for an in-depth understanding of the underlying molecular mechanisms and target-specific pathways.

Statements and Declarations

Authors' contributions

SS was involved in the literature search, study design, data compilation, conceptualization, interpretation, original draft writing, formatting, editing, and review. MKS performed original draft editing and review. RPS performed the original draft editing and review. GB performed the original draft editing and review.

Conflicts of interest

No potential conflict of interest was reported by the authors.

Funding

Authors did not receive any funding associated with this study.

Data Availability

No new data were generated in this study. Data sharing is not applicable to this article.

References

1. ^*Cancer. World Health Organization (2024). Available from: https://www.who.int/news-room/fact-sheets/detail/cancer.*
2. ^*Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F (2021) Global Cancer Statistics 2020: GLOBOCAN Estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71:209-249. https://doi.org/10.3322/caac.21660.*
3. ^*Gridelli C, Rossi A, Carbone DP, Guarize J, Karachaliou N, Mok T, Petrella F, Spaggiari L, Rosell R (2015) Non-small-cell lung cancer. Nat Rev Dis Primers 1:15009. doi: 10.1038/nrdp.2015.9.*
4. ^*Fernandez-Cuesta L, Sexton-Oates A, Bayat L, Foll M, Lau SCM, Leal T (2023) Spotlight on small-cell lung cancer and other lung neuroendocrine neoplasms. 2023. ASCO Educational Book. https://doi.org/10.1200/ EDBK_390794.*
5. ^*Siddiqui F, Vaqar S, Siddiqui AH. Lung cancer (2024) Available from: https://www.ncbi.nlm.nih.gov/books/NBK482357/.*
6. ^*Sanaei MJ, Razi S, Pourbagheri-Sigaroodi A, Bashash D (2022) The PI3K/Akt/mTOR pathway in lung cancer; oncogenic alterations, therapeutic opportunities, challenges, and a glance at the application of nanoparticles. Transl Oncol 18:101364. https://doi.org/10.1016/j.tranon.2022.101364.*
7. ^*Cooper WA, Lam DC, O'Toole SA, Minna JD (2013) Molecular biology of lung cancer. J Thorac Dis 5:S479-S490. https://doi.org/10.3978/j.issn.2072-1439.2013.08.03.*
8. ^*Schaal C, Chellappan SP (2014) Nicotine-mediated cell proliferation and tumor progression in smoking-related cancers. Mol Cancer Res 12:14-23. https://doi.org/10.1158/1541-7786.MCR-13-0541.*
9. ^*Herbst RS, Heymach JV, Lippman SM (2008) Lung cancer. N Engl J Med 359:1367-1380. https://doi.org/10.1056/NEJMra0802714.*
10. ^*Yang L, Zhao H, Liu K, Wang Y, Liu Q, Sun T, Chen S, Ren L (2021) Smoking behavior and circulating vitamin D levels in adults: A meta-analysis. Food Sc Nutr 9: 5820-5832. https://doi.org/10.1002/fsn3.2488.*
11. ^*Brot C, Rye Jorgensen N, Helmer Sorensen O (1999) The influence of smoking on vitamin D status and calcium metabolism. Eur J Clin Nutr 53:920-926 https://doi.org/10.1038/sj.ejcn.1600870.*
12. ^*Yodoshi T, Orkin S, Arce-Clachar AC, Bramlage K, Liu C, Fei L, El-Khider F, Dasarathy S, Xanthakos SA, Mouzaki M (2020) Vitamin D deficiency: prevalence and association with liver disease severity in pediatric nonalcoholic fatty liver disease. Eur J Clin Nutr 74:427-435. https://doi.org/10.1038/s41430-019-0493-y.*
13. ^*Gad AI, Elmedames MR, Abdelhai AR, Marei AM (2020) The association between vitamin D status and non-alcoholic fatty liver disease in adults: a hospital-based study. Egypt Liver J 10. https://doi.org/10.1186/s43066-020-00033-z.*
14. ^*Zhang L, Wang S, Che X, Li X (2015) Vitamin D and lung cancer risk: a comprehensive review and meta-analysis. Cell Physiol Biochem 36:299-305. https://doi.org/10.1159/000374072.*
15. ^*Wang H, Chen W, Li D, Yin X, Zhang X, Olsen N, Zheng SG (2017) Vitamin D and chronic diseases. Aging Dis 8:346-353. https://doi.org/10.14336/AD.2016.1021.*
16. ^*Yuan L, Ni J (2022) The association between tobacco smoke exposure and vitamin D levels among US general population, 2001–2014: temporal variation and inequalities in population susceptibility. Environ Sci Pollut Res 29:32773-32787. https://doi.org/10.1007/s11356-021-17905-5.*
17. ^*Jiang CQ, Chan YH, Xu L, Jin YL, Zhu T, Zhang WS, Cheng KK, Lam TH (2016) Smoking and serum vitamin D in older Chinese people: cross-sectional analysis based on the Guangzhou Biobank Cohort Study. BMJ Open 6:e010946. https://doi.org/10.1136/bmjopen-2015-010946.*
18. ^*Suchanecka A, Chmielowiec K, Chmielowiec J, Trybek G, Masiak J, Michałowska-Sawczyn M, Nowicka R, Grocholewicz K, Grzywacz A (2020) Vitamin D receptor gene polymorphisms and cigarette smoking impact on oral*

health: A case-control study. Int J Environ Res Public He alth 17:3192. https://doi.org/10.3390/ijerph17093192.

19. ^*Okrit F, Chantranuwatana P, Werawatganon D, Chaya nupatkul M, Sanguanrungsirikul S (2021) Changes of vi tamin D receptors (VDR) and MAPK activation in cytop lasmic and nuclear fractions following exposure to ciga rette smoke with or without filter in rats. Heliyon 7:e05 927. https://doi.org/10.1016/j.heliyon.2021.e05927.*
20. ^*Greenberg AK, Basu S, Hu J, Yie T, Tchou-Wong KM, Ro m WN, Lee TC (2002) Selective p38 activation in huma n non–small cell lung cancer. Am J Respir Cell Mol Biol 26:558-64, https://doi.org/10.1165/ajrcmb.26.5.4689.*
21. ^*Jain AS, Prasad A, Pradeep S et al (2021) Everything ol d is new again: Drug repurposing approach for non-sm all cell lung cancer targeting MAPK signaling pathway. Front Oncol 11:741326. https://doi.org/10.3389/fonc.2021. 741326.*
22. ^*Akimbekov NS, Digel I, Sherelkhan DK, Razzaque MS (2022) Vitamin D and phosphate interactions in health and disease. Adv Exp Med Biol 1362:37-46. https://doi.or g/10.1007/978-3-030-91623-7_5. PMID: 35288871.*
23. a, b*Nemr S, Alluri S, Sundaramurthy D, Landry D, Brade n G (2017) Hypercalcemia in lung cancer due to simulta neously elevated PTHrP and ectopic calcitriol productio n: First case report. Case Rep Oncol Med 2017. https://do i.org/10.1155/2017/2583217.*
24. ^*Haglin L.M, Tornkvist B, Backman LO (2014) High ser um phosphate and triglyceride levels in smoking wome n and men with CVD risk and type 2 diabetes. Diabetol Metab Syndr 6:39. https://doi.org/10.1186/1758-5996-6-39.*
25. ^*Petsophonsakul P, Burgmaier M, Willems B et al (202 2) Nicotine promotes vascular calcification via intracell ular Ca2+-mediated, Nox5-induced oxidative stress, an d extracellular vesicle release in vascular smooth muscl e cells. Cardiovasc Res 118:2196-2110. https://doi.org/10.1 093/cvr/cvab244.*
26. ^*Khanna A, Periwal P, Talwar D (2015) Small cell carci noma lung presenting as life-threatening hypercalcemi a- A rare association. Lung India 32:671-673. https://doi. org/10.4103/0970-2113.168101.*
27. ^*Nemr S, Alluri S, Sundaramurthy D, Landry D, Braden G (2017) Hypercalcemia in lung cancer due to simultan eously elevated PTHrP and ectopic calcitriol productio n: First case report. Case Rep Oncol Med 2017:1-3. http s://doi.org/10.1155/2017/2583217.*
28. ^*Jin H, Xu CX, Lim HT et al (2009) High dietary inorga nic phosphate increases lung tumorigenesis and alters Akt signaling. Am J Respir Crit Care Med 179:59-68. htt ps://doi.org/10.1164/rccm.200802-306OC.*
29. ^*Liua N, Lib X, Fua Y, Lia Y, Lua W, Pana Y, Yanga J, Kon g J (2021) Inhibition of lung cancer by vitamin D depen ds on downregulation of histidine-rich calcium-bindin g protein. J Adv Res 29:13-22. https://doi.org/10.1016/j.jar e.2020.08.013.*
30. ^*Jacquillet G, Unwin RJ (2019) Physiological regulation of phosphate by vitamin D, parathyroid hormone (PT H) and phosphate (Pi). Pflugers Arch 471:83-98. https:// doi.org/10.1007/s00424-018-2231-z.*
31. ^*Uchimura K, Mokuno T, Nagasaka A et al (2002) Lung cancer associated with hypercalcemia induced by conc urrently elevated parathyroid hormone and parathyroi d hormone-related protein levels. Metabolism 51:871-5. https://doi.org/10.1053/meta.2002.33341.*
32. ^*Lotito A, Teramoto M, Cheung M, Becker K, Sukumar D (2017) Serum parathyroid hormone responses to vita min D supplementation in overweight/obese adults: A s ystematic review and meta-analysis of randomized cli nical trials. Nutrients 9:241. https://doi.org/10.3390/nu9 030241.*
33. ^*Yang L, Zhao H, Liu K, Wang Y, Liu Q, Sun T, Chen S, Re n L (2021) Smoking behavior and circulating vitamin D levels in adults: A meta-analysis. Food Sci Nutr 9:5820-5832. https://doi.org/10.1002/fsn3.2488.*
34. ^*Chen S, Li S, Li H, Du M, Ben S, Zheng R, Zhang Z, Wan g M (2023) Effect of polycyclic aromatic hydrocarbons on cancer risk causally mediated via vitamin D levels. E nviron Toxicol 38:2111-2120. https://doi.org/10.1002/tox. 23835.*
35. ^*Rahman A, Elmi A (2021) Air pollutants are negatively associated with vitamin D-synthesizing UVB radiation intensity on the ground. Sci Rep 11:21480. https://doi.or g/10.1038/s41598-021-00980-6.*
36. ^*Kusnierczyk P (2023) Genetic differences between sm okers and never-smokers with lung cancer. Front Immu nol 14:1063716. https://doi.org/10.3389/fimmu.2023.1063 716.*
37. ^*Hammouz RY, Kostanek JK, Dudzisz A, Witas P, Orzech owska M, Bednarek AK (2020) Differential expression o f lung adenocarcinoma transcriptome with signature o f tobacco exposure. J Appl Genet 61:421-437. https://doi.o rg/10.1007/s13353-020-00569-1.*
38. ^*Jin X, Zhang B, Zhang H, Yu H (2022) Smoking-associ ated upregulation of CBX3 suppresses ARHGAP24 expr ession to activate Rac1 signaling and promote tumor pr ogression in lung adenocarcinoma. Oncogene 41:538-5 49. https://doi.org/10.1038/s41388-021-02114-8.*
39. ^*Suzuki H, Takahashi T, Kuroishi T, Suyama M, Ariyosh i Y, Takahashi T, Ueda R (1992) p53 mutations in non-s mall cell lung cancer in Japan: association between mu tations and smoking. Cancer Res 52:734-736.*
40. ^*Bongiorno PF, Whyte RI, Lesser EJ, Moore JH, Orringer MB, Beer DG (1994) Alterations of K-ras, p53, and erbB-*

2/neu in human lung adenocarcinomas. J Thorac Cardiovasc Surg 107:590-595.

41. ^Dutu T, Michiels S, Fouret P et al (2005) Differential expression of biomarkers in lung adenocarcinoma: a comparative study between smokers and never-smokers. Ann Oncol 16:1906-1914, https://doi.org/10.1093/annonc/mdi408.
42. ^Cubillos-Angulo JM, Fukutani ER, Cruz LAB, Arriaga MB, Lima JV, Andrade BB, Queiroz ATL, Fukutani KF (2020) Systems biology analysis of publicly available transcriptomic data reveals a critical link between AKR1B10 gene expression, smoking and occurrence of lung cancer. PLoS One 15:e0222552. https://doi.org/10.1371/journal.pone.0222552.
43. a, bArteaga CL (2003) ErbB-targeted therapeutic approaches in human cancer. Exp Cell Res 284:122-130. https://doi.org/10.1016/s0014-4827(02)00104-0.
44. ^da Cunha Santos G, Shepherd FA, Tsao MS (2011) EGFR mutations and lung cancer. Annu Rev Pathol 6:49-69. https://doi.org/10.1146/annurev-pathol-011110-130206.
45. ^Kumar B, Cordell KG, Lee JS et al (2007) Response to therapy and outcomes in oropharyngeal cancer are associated with biomarkers including human papillomavirus, epidermal growth factor receptor, gender, and smoking. Int J Radiat Oncol Biol Phys 69:S109-11. https://doi.org/10.1016/j.ijrobp.2007.05.072.
46. a, bTseng CH, Chiang CJ, Tseng JS et al (2017) EGFR mutation, smoking, and gender in advanced lung adenocarcinoma. Oncotarget 8:98384-98393. https://doi.org/10.18632/oncotarget.21842.
47. ^Harlid S, Xu Z, Panduri V, Sandler DP, Taylor JA (2014) CpG sites associated with cigarette smoking: analysis of epigenome-wide data from the Sister Study. Environ Health Perspect 122:673-678. https://doi.org/10.1289/ehp.1307480.
48. ^Baglietto L, Ponzi E, Haycock P et al (2017) DNA methylation changes measured in pre-diagnostic peripheral blood samples are associated with smoking and lung cancer risk. Int J Cancer 140:50-61. https://doi.org/10.1002/ijc.30431.
49. ^Kwon YM, Park JH, Kim H, Shim YM, Kim J, Han J, Park J, Kim DH (2007) Different susceptibility of increased DNMT1 expression by exposure to tobacco smoke according to histology in primary non-small cell lung cancer. J Cancer Res Clin Oncol 133:219-226. https://doi.org/10.1007/s00432-006-0160-2.
50. ^Samanta D, Gonzalez AL, Nagathihalli N, Ye F, Carbone DP, Datta PK (2012) Smoking attenuates transforming growth factor-β-mediated tumor suppression function through downregulation of SmaD3 in lung cancer. Cancer Prev Res (Phila) 5:453-463. https://doi.org/10.1158/1940-6207.
51. ^Yoshida K, Gowers KHC, Lee-Six H et al (2020) Tobacco smoking and somatic mutations in human bronchial epithelium. Nature 578:266-272. https://doi.org/10.1038/s41586-020-1961-1.
52. a, bWang X, Ricciuti B, Nguyen T, Li X, Rabin MS, Awad MM, Lin X, Johnson BE, Christiani DC (2021) Association between smoking history and tumor mutation burden in advanced non-small cell lung cancer. Cancer Res 81:2566-2573. https://doi.org/10.1158/0008-5472.CAN-20-3991.
53. ^Zhang X, Guo X, Gao Q, Zhang J, Zheng J, Zhao G, Okuda K, Tartarone A, Jiang M (2023) Association between cigarette smoking history, metabolic phenotypes, and EGFR mutation status in patients with non-small cell lung cancer. J Thorac Dis 15:5689-5699. https://dx.doi.org/10.21037/jtd-23-1371.
54. ^Riely GJ, Kris MG, Rosenbaum D, Marks J, Li A, Chitale DA, Nafa K, Riedel ER, Hsu M, Pao W, Miller VA, Ladanyi M (2008) Frequency and distinctive spectrum of KRAS mutations in never smokers with lung adenocarcinoma. Clin Cancer Res 14:5731-5734. https://doi.org/10.1158/1078-0432.CCR-08-0646.
55. ^Takamochi K, Oh S, Suzuki K (2013) Differences in EGFR and KRAS mutation spectra in lung adenocarcinoma of never and heavy smokers. Oncol Lett 6:1207-1212.
56. ^Dogan S, Shen R, Ang DC et al (2012) Molecular epidemiology of EGFR and KRAS mutations in 3,026 lung adenocarcinomas: higher susceptibility of women to smoking-related KRAS-mutant cancers. Clin Cancer Res 18:6169-6177. https://doi.org/10.1158/1078-0432.CCR-11-3265.
57. ^Masykura N, Zaini J, Syahruddin E, Andarini SL, Hudoyo A, Yasril R, Ridwanuloh A, Hidajat H, Nurwidya F, Utomo A (2019) Impact of smoking on frequency and spectrum of K-RAS and EGFR mutations in treatment naive Indonesian lung cancer patients. Lung Cancer (Auckl) 10:57-66. https://doi.org/10.2147/LCTT.S180692.
58. ^Zheng ZR, Ku HY, Chen KC et al (2023) Association of smoking and ALK tyrosine-kinase inhibitors on overall survival in treatment-naïve ALK-positive advanced lung adenocarcinoma. Front Oncol 13:1063695. https://doi.org/10.3389/fonc.2023.1063695.
59. ^Song N, Tan W, Xing D, Lin D (2001) CYP 1A1 polymorphism and risk of lung cancer in relation to tobacco smoking: a case-control study in China. Carcinogenesis 22:11-16. https://doi.org/10.1093/carcin/22.1.11.
60. a, bAriyoshi N, Miyamoto M, Y. Umetsu, Kunitoh H, Dosaka-Akita H, Sawamura Y, Yokota J, Nemoto N, Sato K, Kamataki T (2002) Genetic polymorphism of CYP2A6 gene and tobacco-induced lung cancer risk in male smokers, Cancer Epidemiol. Biomarkers Prev 11:890-894.

61. ^Aldakheel FM, Abuderman AA, Alali BH, Mateen A, Al duraywish SA, Jamil K, Alqahtani MS, Syed R (2021) Sm oking and P53 polymorphism association with chromo somal aberration in lung cancer. J King Saud Univ – Sci 33:101533. https://doi.org/10.1016/j.jksus.2021.101533.
62. ^Miller DP, Neuberg D, de Vivo I, Wain JC, Lynch TJ, Su L, Christiani DC (2003) Smoking and the risk of lung canc er: susceptibility with GSTP1 polymorphisms. Epidemio logy 14:545-551. https://doi.org/10.1097/01.ede.0000073 120.46981.24.
63. ^Liu G, Wheatley-Price P, Zhou W, Park S, Heist RS, Aso maning K, Wain JC, Lynch TJ, Su L, Christiani DC (2008) Genetic polymorphisms of MDM2, cumulative cigarette smoking and nonsmall cell lung cancer risk. Epidemiol ogy 122:915-918. https://doi.org/10.1002/ijc.23178.
64. ^Walia HK, Singh N, Sharma S (2021) Genetic polymorp hisms in the mEH gene in relation to tobacco smoking: Role in lung cancer susceptibility and survival in north Indian patients with lung cancer undergoing platinum-based chemotherapy. Future Oncol 17:4925-4946. http s://doi.org/10.2217/fon-2021-0412.
65. ^Nishida Y, Hara M, Sakamoto T et al (2016) Japan mul ti-Institutional collaborative cohort (J-MICC) study gro up. Influence of cigarette smoking and inflammatory g ene polymorphisms on glycated hemoglobin in the Jap anese general population. Prev Med Rep 3:288-295. htt ps://doi.org/10.1016/j.pmedr.2016.03.010.
66. ^Shin K, Jang Y, Koh SJ, Chae JS, Kim OY, Park S, Choi D, Shin D, Kim HJ, Lee JH (2007) Influence of the IL-6 -572 C > G polymorphism on inflammatory markers accordi ng to cigarette smoking in Korean healthy men. Cytoki ne 39:116-122.
67. ^Nishida Y, Hara M, Nanri H et al (2015) Interaction bet ween interleukin1-β gene polymorphism and cigarette smoking on HbA1c in a Japanese general population. In t J Epidemiol 44:i193–i194, https://doi.org/10.1093/ije/dy v096.304.
68. ^Metwally YF, Elsaid AM, Elsadda RR, Refaat S, Zahran RF (2023) Impact of IL-6 and IL-1β gene variants on no n-small-cell lung cancer risk in Egyptian patients. Bioc hem Genet 62:3367-3388. https://doi.org/10.1007/s10528 -023-10596-2.
69. ^Eaton KD, Romine PE, Goodman GE, Thornquist MD, Barnett MJ, Petersdorf EW (2018) Inflammatory gene p olymorphisms in lung cancer susceptibility. J Thorac On col 13:649-659. https://doi.org/10.1016/j.jtho.2018.01.022.
70. ^Walser T, Cui X, Yanagawa J, Lee JM, Heinrich E, Lee G, Sharma S, Dubinett SM (2008) Smoking and lung canc er: the role of inflammation. Proc Am Thorac Soc 5:811-815. https://doi.org/10.1513/pats.200809-100TH.
71. ^Schneyer AL, Sluss PM, Whitcomb RW, Hall JE, Crowle y Jr WF, Freeman RG (1991) Development of a radioliga nd receptor assay for measuring follitropin in serum: a pplication to premature ovarian failure. Clin Chem 37:5 08-514.
72. ^Martey CA, Pollock SJ, Turner CK, O'Reilly KMA, Baglo le CJ, Phipps RP, Sime PJ (2004) Cigarette smoke induce s cyclooxygenase-2 and microsomal prostaglandin E2 s ynthase in human lung fibroblasts: implications for lun g inflammation and cancer. Am J Physiol Lung Cell Mol Physiol 287:L981-L991. https://doi.org/10.1152/ajplung.0 0239.2003.
73. ^Liu X, Zhang J, Sun W, Cao J, Ma Z (2024) COX-2 in lun g cancer: Mechanisms, development, and targeted ther apies. Chronic Dis Transl Med 1-12. https://doi.org/10.10 02/cdt3.120.
74. ^Wu H, Chen C, Gu L et al (2022) B cell deficiency prom otes the initiation and progression of lung cancer. Front Oncol 12:1006477. https://doi.org/10.3389/fonc.2022.100 6477.
75. ^Hu Y, Xu C, Ren J, Zeng Y, Cao F, Fang H, Jintao G, Zhou Y, Li Q (2022) Exposure to tobacco smoking induces a s ubset of activated tumor-resident tregs in non-small cel l lung cancer. Transl Oncol 15:101261. https://doi.org/10.1 016/j.tranon.2021.101261.
76. ^Elisia I, Lam V, Cho B et al (2020) The effect of smokin g on chronic inflammation, immune function and bloo d cell composition. Sci Rep 10:19480. https://doi.org/10.1 038/s41598-020-76556-7.
77. ^Takahashi H, Ogata H, Nishigaki R, Broide DH, Karin M (2010) Tobacco smoke promotes lung tumorigenesis by triggering IKKβ- and JNK1-dependent inflammatio n. Cancer Cell 17:89-97. https://doi.org/10.1016/j.ccr.200 9.12.008.
78. ^Hirata N, Horinouchi T, Kanda Y (2022) Effects of ciga rette smoke extract derived from heated tobacco produ cts on the proliferation of lung cancer stem cells. Toxico l Rep 9:1273-1280. https://doi.org/10.1016/j.toxrep.2022.0 6.001.
79. ^Hussain MS, Tripathi V (2018) Smoking under hypoxic conditions: a potent environmental risk factor for infla mmatory and autoimmune diseases. Mil Med Res 5:11. https://doi.org/10.1186/s40779-018-0158-5.
80. ^Zhang Q, Tang X, Zhang Z, Velikina R, Shi S, Le AD (20 07) Nicotine induces hypoxia-inducible factor-1α expres sion in human lung cancer cells via nicotinic acetylchol ine receptor–mediated signaling pathways. Clin Cancer Res 13:4686-4694. https://doi.org/10.1158/1078-0432.CC R-06-2898.
81. ^Takasaki C, Kobayashi M, Ishibashi H, Akashi T, Okub o K (2016) Expression of hypoxia-inducible factor-1α aff ects tumor proliferation and antiapoptosis in surgically resected lung cancer. Mol Clin Oncol 5:295-300. https:// doi.org/10.3892/mco.2016.937.

82. ^Ngaha TYS, Zhilenkova AV, Essogmo FE et al (2023) Angiogenesis in lung cancer: understanding the roles of growth factors. Cancers (Basel) 15:4648. https://doi.org/10.3390/cancers15184648.
83. ^Njatcha C, Farooqui M, Almotlak AA, Siegfried JM (2020) Prevention of tobacco carcinogen-induced lung tumor development by a novel STAT3 decoy inhibitor. Cancer Prev Res (Phila) 13:735-746. https://doi.org/10.1158/1940-6207.
84. ^Zhou M, Zhao J, Zhang Q, Jin X, Liao M, Zhang L, Wang J, Yang M (2020) Nicotine upregulates the level of Mcl-1 through STAT3 in H1299 Cells. J Cancer 11:1270-1276. https://doi.org/10.7150/jca.35453.
85. ^Chen RJ, Wang YJ, Ho YS (2006) Rapid activation of Stat3 and ERK1/2 by nicotine modulates the cells proliferation and apoptosis of human bladder cancer cells. Epidemiology 17:S305.
86. ^He Z, Xu Y, Rao Z, Zhang Z, Zhou J, Zhou T, Wang H (2024) The role of α7-nAChR-mediated PI3K/AKT pathway in lung cancer induced by nicotine. Sci Total Environ 912:169604. https://doi.org/10.1016/j.scitotenv.2023.169604.
87. ^Anto RJ, Mukhopadhyay A, Shishodia S, Gairola CG, Aggarwal BB (2002) Cigarette smoke condensate activates nuclear transcription factor-κB through phosphorylation and degradation of IκBα: correlation with induction of cyclooxygenase-2. Carcinogenesis 23:1511-1518. https://doi.org/10.1093/carcin/23.9.1511.
88. ^Caliri AW, Tommasi S, Besaratinia A (2021) Relationships among smoking, oxidative stress, inflammation, macromolecular damage, and cancer. Mutat Res Rev Mutat Res 787:108365. https://doi.org/10.1016/j.mrrev.2021.108365.
89. ^Dutta J, Singh S, Jaiswal A, Ray A, Das P, Mabalirajan U (2022) Role of oxidative stress and DNA damage/repair in lung cancer. In: Chakraborti S, Ray BK, Roychoudhury S (ed) Handbook of oxidative stress in cancer: Mechanistic aspects, Springer, Singapore, pp 937-956, https://doi.org/10.1007/978-981-15-9411-3_57.
90. ^Stefanou DT, Kouvela M, Stellas D, Voutetakis K, Papadodima O, Syrigos K, Souliotis VL (2022) Oxidative stress and deregulated DNA damage response network in lung cancer patients. Biomedicines 10:1248. https://doi.org/10.3390/biomedicines10061248.
91. ^Arul Jothi KN, Kumaran K, Senthil S, Nidhu AB, Munaff N, Janitri VB, Kirubakaran R, Singh SK, Gupt G, Dua K, Krishnan A (2023) Implications of reactive oxygen species in lung cancer and exploiting it for therapeutic interventions. Med Oncol 40:43. https://doi.org/10.1007/s12032-022-01900-y.
92. ^Ma K, Xu W, Wang C, Li B, Su K, Li W (2017) Vitamin D deficiency is associated with a poor prognosis in advanced non-small cell lung cancer patients treated with platinum-based first-line chemotherapy. Cancer Biomark 18:297-303. https://doi.org/10.3233/CBM-161687.
93. ^McFarland DC, Fernbach M, Breitbart WS, McFarland DC, Fernbach M, Breitbart WS, Nelson C (2022) Prognosis in metastatic lung cancer: vitamin D deficiency and depression - a cross-sectional analysis. BMJ Support Palliat Care 12:339-346. https://doi.org/10.1136/bmjspcare-2020-002457.
94. ^Hoffer LJ, Robitaille L, Swinton N, Agulnik J, Cohen V, Small D, Pepe C, Eintracht S (2015) Appropriate vitamin D loading regimen for patients with advanced lung cancer. Nutr J 15(1):84. https://doi.org/10.1186/s12937-016-0203-8.
95. ^Zhang R, Zhang Y, Liu Z et al (2022) Association between vitamin D supplementation and cancer mortality: A systematic review and meta-analysis. Cancers (Basel) 14:3717. https://doi.org/10.3390/cancers14153717.
96. ^Boo HJ, Min HY, Hwang SJ, Lee H, Lee J, Oh S, Park C, Park J, Lee YM, Lee H (2023) The tobacco-specific carcinogen NNK induces pulmonary tumorigenesis via nAChR/Src/STAT3-mediated activation of the renin-angiotensin system and IGF-1R signaling. Exp Mol Med 55:1131-1144. https://doi.org/10.1038/s12276-023-00994-2.
97. ^Nakagawa K, Kawaura A, Kato S, Takeda E, Okano T (2004) Metastatic growth of lung cancer cells is extremely reduced in Vitamin D receptor knockout mice. J Steroid Biochem Mol Biol 89-90:545-547. https://doi.org/10.1016/j.jsbmb.2004.03.066.
98. ^N. Liu, X. Li, Y. Fu, Y. Li, W. Lu, Y. Pan, J. Yang, J. Kong (2021) Inhibition of lung cancer by vitamin D depends on downregulation of histidine-rich calcium-binding protein, J Adv Res 29:13-22. https://doi.org/10.1016/j.jare.2020.08.013.
99. ^Kanno K, Akutsu T, Ohdaira H, Suzuki Y, Urashima M (2023) Effect of vitamin D supplements on relapse or death in a p53-immunoreactive subgroup with digestive tract cancer: Post hoc analysis of the AMATERASU randomized clinical trial. JAMA Netw Open 6:e2328886. https://doi.org/10.1001/jamanetworkopen.2023.28886.
100. ^Wang X, Ricciuti B, Nguyen T, Li X, Rabin MS, Awad MM, Lin X, Johnson BE, Christiani DC (2021) Association between smoking history and tumor mutation burden in advanced non-small cell lung cancer. Cancer Res 81:2566-2573. https://doi.org/10.1158/0008-5472.CAN-20-3991.
101. ^Westcott PM, To MD (2013) The genetics and biology of KRAS in lung cancer. Chin J Cancer 32:63-70. https://doi.org/10.5732/cjc.012.10098.
102. ^Kure S, Nosho K, Baba Y et al (2009) Vitamin D receptor expression is associated with PIK3CA and KRAS mutations in colorectal cancer. Cancer Epidemiol. Biomarke

rs Prev 18:2765-2772. https://doi.org/10.1158/1055-9965.EPI-09-0490.

103. ^*Liu TC, Jin X, Wang Y, Wang K (2017) Role of epiderma l growth factor receptor in lung cancer and targeted the rapies. Am J Cancer Res 7:187-202.*
104. ^*Shin D, Kim S, Park S, Koh JS, Kim CH, Baek H, Yang S H, Na II (2014) Serum 25-hydroxyvitamin D levels corre late with EGFR mutational status in pulmonary adenoc arcinoma. Endocr Relat Cancer 21:715-721. https://doi.or g/10.1530/ERC-14-0259.*
105. ^*Shaurova T, Dy GK, Battaglia S et al (2020) Vitamin D 3 metabolites demonstrate prognostic value in EGFR-m utant lung adenocarcinoma and can be deployed to op pose acquired therapeutic resistance. Cancers 12:675. ht tps://doi.org/10.3390/cancers12030675.*
106. ^*Chirieac LR (2016) Ki-67 expression in pulmonary tu mors. Transl Lung Cancer Res 5:547-551. http://dx.doi.or g/10.21037/tlcr.2016.10.13.*
107. ^*Rosenberg A, Nettey OS, Gogana P, Sheikh U, Macias V, Kajdacsy-Balla A, Sharifi R, Kittles RA, Murphy AB (201 9) Physiologic serum 1,25 dihydroxyvitamin D is invers ely associated with prostatic Ki67 staining in a diverse s ample of radical prostatectomy patients. Cancer Causes Control 30:207-214. https://doi.org/10.1007/s10552-019-1 128-2.*
108. ^*Wagner D, Trudel D, Van der Kwast T et al (2013) Rand omized clinical trial of vitamin D3 doses on prostatic vit amin D metabolite levels and ki67 labeling in prostate c ancer patients. J Clin Endocrinol Metab 98:1498-1507. h ttps://doi.org/10.1210/jc.2012-4019.*
109. ^*Prasad RR, Mishra DK, Kumar M, Yadav PK (2022) Hu man telomerase reverse transcriptase promotes the epi thelial to mesenchymal transition in lung cancer cells b y enhancing c-MET upregulation. Heliyon 8:e08673. htt ps://doi.org/10.1016/j.heliyon.2021.e08673.*
110. ^*Kasiappan R, Shen Z, Tse AK, Jinwal U, Tang J, Lungch ukiet P, Sun Y, Kruk P, Nicosia SV, Zhang X, Bai W (2012) 1,25-Dihydroxyvitamin D3 suppresses telomerase expre ssion and human cancer growth through microRNA-49 8. J Biol Chem 287:41297-41309. https://doi.org/10.1074/j bc.M112.407189.*
111. ^*O'Brien KM, Sandler DP, Xu Z, Kinyamu HK, Taylor JA, Weinberg CR (2018) Vitamin D, DNA methylation, and b reast cancer. Breast Cancer Res 20:70. https://doi.org/10. 1186/s13058-018-0994-y.*
112. ^*Redig AJ, Capelletti M, Dahlberg SE, Sholl LM, Mach S, Fontes C, Shi Y, Chalasani P, Janne PA (2016) Clinical an d molecular characteristics of NF1-mutant lung cancer. Clin Cancer Res 22:3148-3156. https://doi.org/10.1158/10 78-0432.CCR-15-2377.*
113. ^*Lammert M, Friedman JM, Roth HJ, Friedrich RE, Klu we L, Atkins D, Schooler T, Mautner VF (2006) Vitamin D deficiency associated with number of neurofibromas in neurofibromatosis 1. J Med Genet 43:810-813. https:// doi.org/10.1136/jmg.2006.041095.*
114. ^*Matsunawa M, Akagi D, Uno S, Endo-Umeda K, Yama da S, Ikeda K, Makishima M (2012) Vitamin D receptor activation enhances benzo (a) pyrene metabolism via C YP1A1 expression in macrophages. Drug Metab Dispos 40:2059-2066. https://doi.org/10.1124/dmd.112.046839.*
115. ^*Walia HK, Singh N, Sharma S (2021) Genetic polymorp hisms in the mEH gene in relation to tobacco smoking: Role in lung cancer susceptibility and survival in north Indian patients with lung cancer undergoing platinum-based chemotherapy. Future Oncol 17: 4925-4946. http s://doi.org/10.2217/fon-2021-0412.*
116. ^*Vaclavikova R, Hughes DJ, Soucek P (2015) Microsoma l epoxide hydrolase 1 (EPHX1): Gene, structure, functio n, and role in human disease. Gene 571:1-8. https://doi.o rg/10.1016/j.gene.2015.07.071.*
117. ^*Zhang P, Zhang Y, Yang H, Li W, Chen X, Long F (2015) Association between EPHX1 rs1051740 and lung cancer susceptibility: a meta-analysis. Int J Clin Exp Med 8:179 41-17949.*
118. ^*O'Brien KM, Sandler DP, Xu Z, Kinyamu HK, Taylor JA, Weinberg CR (2018) Vitamin D, DNA methylation, and b reast cancer. Breast Cancer Res 20:70. https://doi.org/10. 1186/s13058-018-0994-y.*
119. ^*Shin KK, Jang Y, Koh SJ, Chae JS, Kim OY, Park S, Choi D, Shin DJ, Kim HJ, Lee JH (2007) Influence of the IL-6 - 572C>G polymorphism on inflammatory markers acco rding to cigarette smoking in Korean healthy men. Cyto kine 39:116-122. https://doi.org/10.1016/j.cyto.2007.06.0 05.*
120. ^*Ashtari F, Madanian R, Zarkesh SH, Ghalamkari A (20 22) Serum levels of interleukin-6 and Vitamin D at the onset of multiple sclerosis and neuromyelitis optica: A p ilot study. J Res Med Sci 27:67. https://doi.org/10.4103/jr ms.jrms_796_21.*
121. ^*O'Brien MB, McLoughlin RM, Roche C, Nelson CD, Me ade KG (2021) Effect of IL-8 haplotype on temporal prof ile in circulating concentrations of interleukin 8 and 25 (OH) vitamin D in Holstein-Friesian calves. Vet Immuno l Immunopathol 238:110287.*
122. ^*Sandler AB, Dubinett SM (2004) COX-2 inhibition and lung cancer. Semin Oncol 31:45-52. https://doi.org/10.105 3/j.seminoncol.2004.03.045.*
123. ^*Wang Q, He Y, Shen Y, Zhang Q, Chen D, Zuo C, Qin J, W ang H, Wang J, Yu Y (2014) Vitamin D inhibits COX-2 exp ression and inflammatory response by targeting thioes terase superfamily member 4. J Biol Chem 289:11681-11 694. https://doi.org/10.1074/jbc.M113.517581.*
124. ^*Liu X, Nelson A, Wang X, Farid M, Gunji Y, Ikari J, Iwas awa S, Basma H, Feghali-Bostwick C, Rennard SI (2014)*

Vitamin D modulates prostaglandin E2 synthesis and degradation in human lung fibroblasts. Am J Respir Cell Mol Biol 50:40-50. https://doi.org/10.1165/rcmb.2013-0211OC.

125. ^*Chen S, Sims GP, Chen XX, Gu YY, Chen S, Lipsky PE (2007) Modulatory effects of 1,25-dihydroxyvitamin D3 on human B cell differentiation. J Immunol 179:1634-1647. https://doi.org/10.4049/jimmunol.179.3.1634.*
126. ^*Rolf L, Muris AH, Hupperts R, Damoiseaux J (2016) Illuminating vitamin D effects on B cells--the multiple sclerosis perspective. Immunology 147:275-284. https://doi.org/10.1111/imm.12572.*
127. ^*Ota K, Dambaeva S, Kim MW, Han A, Fukui A, Gilman-Sachs A, Beaman K, Kwak-Kim J (2015) 1,25-Dihydroxy-vitamin D3 regulates NK-cell cytotoxicity, cytokine secretion, and degranulation in women with recurrent pregnancy losses. Eur J Immunol 45:3188-3199. https://doi.org/10.1002/eji.201545541.*
128. ^*Oh M, Jung S, Kim Y, Lee GY, Han SN (2024) Dietary vitamin D3 supplementation enhances splenic NK cell activity in healthy and diabetic male mice. Nutr Res 127:144-155. https://doi.org/10.1016/j.nutres.2024.06.004.*
129. ^*So JY, Suh N (2015) Targeting cancer stem cells in solid tumors by vitamin D. J Steroid Biochem Mol Biol 148:79-85. https://doi.org/10.1016/j.jsbmb.2014.10.007.*
130. ^*Nam MW, Kim CW, Choi KC (2022) Epithelial-mesenchymal transition-inducing factors involved in the progression of lung cancers. Biomol Ther (Seoul) 30:213-220. https://doi.org/10.4062/biomolther.2021.178.*
131. ^*Ricca C, Aillon A, Viano M, Bergandi L, Aldieri E, Silvagno F (2019) Vitamin D inhibits the epithelial-mesenchymal transition by a negative feedback regulation of TGF-β activity. J Steroid Biochem Mol Biol 187:97-105.*
132. ^*Gharib AF, Askary AE, Almehmadi M, Etewa RL, Althobaiti BB, Allam HH, Elsayyad LK, Shafie A (2022) Vitamin D and hypoxia-inducible factor (HIF-1α) serum levels as markers for progression of nephropathy in type 2 diabetic patients. Clin Lab 68. https://doi.org/10.7754/Clin.Lab.2021.210540.*
133. ^*Liu J, Han P, Li M et al (2015) The histidine-rich calcium binding protein (HRC) promotes tumor metastasis in hepatocellular carcinoma and is upregulated by SATB1. Oncotarget 6:6811-6824. https://doi.org/10.18632/oncotarget.3049.*
134. ^*Zhao J, Ping J, Wang Y, Liu X, Li N, Hu Z, Ming L (2020) Vitamin D suppress the production of vascular endothelial growth factor in mast cell by inhibiting PI3K/Akt/p38 MAPK/HIF-1α pathway in chronic spontaneous urticarial. Clin Immunol 215:108444.*
135. ^*Yiyan SY, Yang S, Li D, Li W (2022) Vitamin D affects the Warburg effect and stemness maintenance of non- small-cell lung cancer cells by regulating the PI3K/AKT/mTOR signaling pathway. Curr Cancer Drug Targets 22:86-95. https://doi.org/10.2174/1568009621666210729100300.*
136. ^*Meeker S, Seamons A, Paik J, Treuting PM, Brabb T, Grady WM, Maggio-Price L (2014) Increased dietary vitamin D suppresses MAPK signaling, colitis, and colon cancer. Cancer Res 74:4398-4408. https://doi.org/10.1158/0008-5472.CAN-13-2820.*
137. ^*Rasmi RR, Sakthivel KM (2020) NF-κB inhibitors in treatment and prevention of lung cancer. Biomed Pharmacother 130:110569.*
138. ^*Yoo W, Jung HY, Lim S, Sung JS, Park KH, Ryu JS, Shin SW, Kim JS, Seo JH, Kim YH (2011) An association study of polymorphisms in JAK3 gene with lung cancer in the Korean population. Cancer Res Treat 43:108-116. https://doi.org/10.4143/crt.2011.43.2.108.*
139. ^*Mohrherr J, Haber M, Breitenecker K et al (2019) JAK-STAT inhibition impairs K-RAS-driven lung adenocarcinoma progression. Int J Cancer 145:3376-88. https://doi.org/10.1002/ijc.32624.*
140. ^*Hardiyanti W, Djabir YY, Fatiah D, Pratama MR, Putri TZAD, Chaeratunnisa R, Latada NP, Mudjahid M, Asri RM, Nainu F (2024) Evaluating the impact of vitamin D3 on NF-κB and JAK/STAT signaling pathways in drosophila melanogaster. ACS Omega 9:20135-20141. https://doi.org/10.1021/acsomega.4c00134.*
141. ^*Chen RJ, Ho YS, Guo HR, Wang YJ (2008) Rapid activation of Stat3 and ERK1/2 by nicotine modulates cell proliferation in human bladder cancer cells. Toxicol Sci 104:283-293. https://doi.org/10.1093/toxsci/kfn086.*
142. ^*Crosbie PAJ, Crosbie EJ, Aspinall-O'Dea M, Walker M, Harrison R, Pernemalm M, Shah R, Joseph L, Booton R, Pierce A, Whetton AD (2016) ERK and AKT phosphorylation status in lung cancer and emphysema using nanocapillary isoelectric focusing. BMJ Open Respir Res 3:e000114. https://doi.org/10.1136/bmjresp-2015-000114.*
143. ^*Habooby NGSA, Yousif NG, Hadi NR, Al-Baghdadi JJ (2018) Vitamin D attenuates myocardial injury by reduces ERK phosphorylation induced by I/R in mice model. Curr Chem Genom Transl Med 12:27-38. https://doi.org/10.2174/2213988501812010027.*
144. ^a, ^b*Gu JC, Wu YG, Huang WG, Fan XJ, Chen XH, Zhou B, Lin ZJ, Feng XL (2022) Effect of vitamin D on oxidative stress and serum inflammatory factors in the patients with type 2 diabetes. J Clin Lab Anal 36:e24430. https://doi.org/10.1002/jcla.24430.*
145. ^*Bhat M, Ismail A (2015) Vitamin D treatment protects against and reverses oxidative stress induced muscle proteolysis. J Steroid Biochem Mol Biol 152:171-179. https://doi.org/10.1016/j.jsbmb.2015.05.012.*
146. ^*Quigley M, Rieger S, Capobianco E, Wang Z, Zhao H, Hewison M, Lisse TS (2021) Vitamin D modulation of mit*

ochondrial oxidative metabolism and mTOR enforces s tress adaptations and anticancer responses. JBMR Plus 6:e10572. https://doi.org/10.1002/jbm4.10572.

147. ^*Wimalawansa SJ (2019) Vitamin D deficiency: Effects on oxidative stress, epigenetics, gene regulation, and ag ing. Biology 8:30. https://doi.org/10.3390/biology80200 30.*

Declarations

Funding: No specific funding was received for this work.
Potential competing interests: No potential competing interests to declare.