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# Synergistic Anticancer Effects of Vitamin D and Plant-Derived Compounds: Molecular Mechanisms, Therapeutic Potential, and Nanotechnology-Enabled Delivery Approaches

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**Abstract**

Vitamin D is widely recognized for its pivotal role in the prevention and treatment of various cancers. The active compounds derived from plants have garnered significant attention due to their multi-faceted anticancer properties. Given the complexity and heterogeneity of cancer, monotherapies often fall short in effectiveness. As a result, combinatorial pharmacological strategies, which utilize multiple drug agents, are increasingly being employed globally. Notably, emerging evidence highlights the potent synergistic anticancer effects of vitamin D in combination with certain phytochemicals against a variety of cancers. This review explores the cooperative mechanisms through which vitamin D and phytochemicals enhance cancer prevention and therapy. In addition to examining their synergistic effects, this review also discusses recent advancements in nanotechnology-based delivery systems for vitamin D, which hold promise for optimizing its therapeutic potential. Collectively, these findings underscore the potential of combining vitamin D with phytochemicals and innovative delivery methods as a promising strategy in the fight against cancer, paving the way for more effective, multi-targeted therapeutic approaches.

**Keywords:** vitamin D; plant-derived compounds; phytochemicals; synergism; cancer

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## 1. Introduction

Despite significant advances in our understanding of vitamin D and its medicinal applications, its full role in numerous biological processes remains incompletely understood. More than a decade ago, we published a review examining the biological activities of vitamin D and its analogues, with particular emphasis on bone metabolism, diabetes, cancer, skin diseases, and delivery and targeting strategies [1]. Since that time, a growing number of studies have focused on the anticancer properties of vitamin D [2], driven in part by the continued recognition of cancer as a leading cause of mortality worldwide [3]. This growing recognition has spurred further investigation into the potential of vitamin D as an anticancer agent.

However, cancer is a complex, heterogeneous disease with diverse etiologies, and conventional monotherapies often exhibit limited efficacy in its treatment and prevention [4]. Numerous experimental studies, both in vitro and in vivo, suggest that combining vitamin D with other therapeutic agents can enhance its anticancer effects. For instance,

the antibiotic salinomycin is a polyether ionophore of natural origin with anticancer properties against many cancer cell lines [5]. Vitamin $D_3$ and salinomycin synergy resulted in inhibiting the proliferation of MCF-7 breast carcinoma cells; a possible mechanism is endoplasmic reticulum stress transcriptional upregulation of genes (ATF6, GADD153, GADD45G, EIF2AK3, and HSPA5), which are related to this stress [6]. Combining vitamin D with repurposed drugs such as metformin and auranofin has demonstrated enhanced efficacy compared to monotherapy [7]. Another interesting example is cisplatin (a chemotherapeutic drug). The combination of vitamin D and this drug provides a better anti-proliferative property and is less toxic than cisplatin alone in the T24 bladder cancer cell line [8]. The interaction between Vitamin D and arsenic trioxide (chemotherapeutic drug) was estimated for acute promyelocytic leukemia in vitro; isobologram analysis showed a strong synergistic effect [9].

The prospect of combining vitamin D with plant-derived bioactive compounds has become particularly intriguing. Several plant extracts have been shown to enhance the anticancer effects of vitamin D [10,11]. One key advantage of such combinations is that they may offer greater efficacy and lower toxicity compared to traditional anticancer therapies. Plants are a rich source of compounds with well-established anticancer properties, including alkaloids, polyphenols (e.g., phenolic acids, stilbenes, lignans, and flavonoids), carotenoids, terpenoids, quinones, saponins, polysaccharides, and peptides. These bioactive compounds exhibit various pharmacological effects such as anti-inflammatory, antioxidant, and antidiabetic activities, all of which are critical for cancer prevention and treatment [12]. In fact, over 60% of the anticancer drugs currently in use were developed from plant sources [13]. Moreover, many plant-derived compounds are readily available, cost-effective, and less toxic than conventional anticancer agents. Their anticancer activity can partially be attributed to their antioxidant properties, as oxidative stress caused by an imbalance between reactive oxygen species (ROS) and antioxidant defenses is closely linked to cancer and other diseases [14]. ROS, including superoxide, hydrogen peroxide, hydroxyl radicals, and singlet oxygen, are highly reactive molecules that can damage cellular structures, leading to carcinogenesis [15]. Environmental stressors, such as radiation, pollution, and xenobiotics, contribute to ROS overproduction, further complicating cancer pathogenesis [16].

ROS exert a well-recognized dual role in cancer biology. At moderate levels, ROS function as pro-tumorigenic signaling molecules that promote genomic instability, activate oncogenic pathways, and support metabolic adaptations favorable to tumor growth [17,18]. Conversely, when ROS levels exceed the antioxidant buffering capacity of the cell, they induce oxidative damage and trigger cell death pathways, including apoptosis, thereby exerting tumor-suppressive effects [19]. This balance between pro-survival and pro-apoptotic ROS underscores the importance of cellular redox context, tumor type, and microenvironmental conditions in determining the net biological outcome of ROS signaling.

Phytochemicals with antioxidant activity may mitigate the formation of free radicals, regulate ROS-scavenging enzymes, and influence numerous cellular processes by modulating various molecular targets and signaling pathways [20,21]. These pathways are involved in vital biological processes, including cell survival, proliferation, apoptosis, migration, angiogenesis, hormonal regulation, and immune responses [22].

A comprehensive analysis of scientific literature reveals substantial overlaps in the anticancer mechanisms of vitamin D and plant-derived bioactive compounds. Although the synergistic anticancer effects of vitamin D and phytochemicals represent a promising strategy for cancer prevention and treatment, several challenges—including limited bioavailability, stability, and targeted delivery—have hindered their clinical translation. This review addresses these limitations by integrating current evidence on shared molecular pathways, synergistic therapeutic effects, and recent advances in delivery strategies, with

particular emphasis on nanotechnology-based systems designed to enhance the efficacy and safety of vitamin D. Collectively, after many years of scarce attention [23], this work aims to provide an updated and integrated perspective on the role of vitamin D in cancer prevention and therapy, its delivery approaches, and the therapeutic potential of its synergistic interactions with phytochemicals.

## 2. Overview of the Anticancer Activity of Vitamin D

Vitamin D exists in several vitamers. Figure 1 demonstrates the most active vitamers, 1,25-dihydroxyvitamin $D_3$ and vitamin $D_3$. Vitamin $D_1$ is known as a mixture of ergocalciferol and lumisterol. Vitamin $D_2$ is ergocalciferol, vitamin $D_3$ is cholecalciferol, vitamin $D_4$ is 22-dihydroergocalciferol and vitamin $D_5$ (sitocalciferol), with vitamin $D_2$ and $D_3$ being the most biologically relevant and widely studied forms [1,24]. Vitamin D is synthesized in the skin from 7-dehydrocholesterol upon exposure to ultraviolet radiation and can also be obtained from dietary sources or supplementation [25]. Its biological effects are mediated primarily through binding to the vitamin D receptor (VDR), which activates both genomic and non-genomic signaling pathways [26]. VDRs are expressed in a broad range of tissues and cell types, including skin, skeletal muscle, adipose tissue, pancreatic endocrine cells, immune cells, and vascular endothelium [27]. Although VDR activation has been reported to promote certain cancer types under specific conditions [28], it is more commonly associated with protective effects, particularly in maintaining cellular redox balance and limiting excessive ROS production [29].

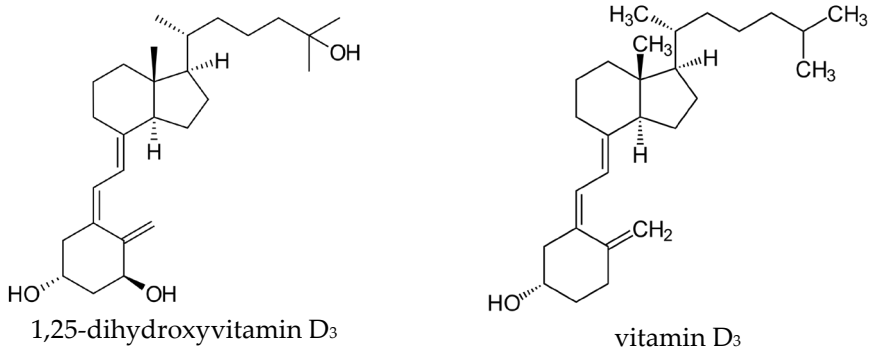



**Figure 1.** Molecular structure of 1,25-dihydroxyvitamin $D_3$ and vitamin $D_3$.

Genomic vitamin D signaling involves the formation of a heterodimer between the ligand-activated VDR and the retinoid X receptor (RXR). This complex binds to vitamin D response elements within target genes, leading to transcriptional modulation [30]. These genomic effects develop over hours to days and regulate a wide array of biological processes, including innate and adaptive immunity, energy metabolism, cell proliferation and differentiation, calcium–phosphate homeostasis, and neuroprotection [31,32]. Importantly, the expression of CYP24A1, an enzyme responsible for vitamin D catabolism into inactive calcitroic acid, has emerged as a predictive marker of vitamin D efficacy in cancer patients and is frequently upregulated in tumor cells [33].

In contrast, non-genomic vitamin D signaling occurs independently of direct gene transcription and involves rapid activation of intracellular signaling cascades [31,32]. Cancer progression is closely linked to VDR-mediated signaling [34], and accumulating evidence suggests that vitamin D can exert anticancer effects even in the absence of functional VDRs, indicating the involvement of alternative pathways [35].

Clinical and epidemiological studies consistently associate vitamin D deficiency with an increased risk of multiple malignancies. Low serum vitamin D levels have been correlated with a higher incidence of colorectal, ovarian, lung, breast, and prostate cancers [36].

At the cellular level, vitamin D regulates numerous interconnected processes (Figure 2), including the stabilization of calcium signaling and redox homeostasis, thereby limiting ROS-mediated cellular damage [37].

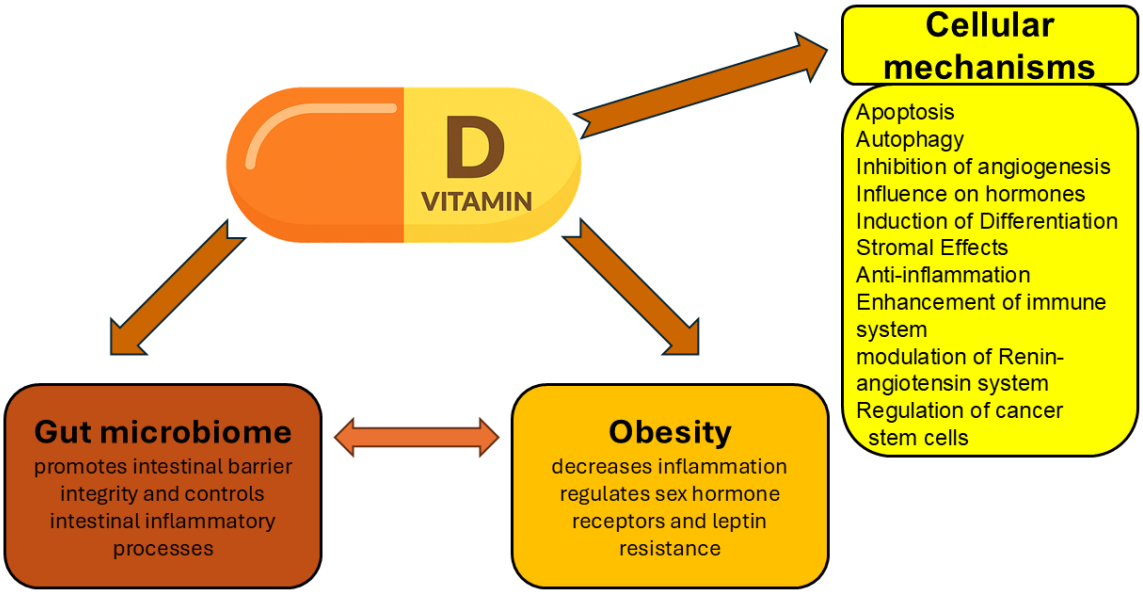



**Figure 2.** Mechanisms of anticancer action of vitamin D. The influence of vitamin D on gut microbiome, obesity and various cellular mechanisms.

Vitamin D exerts multiple anticancer effects, including the suppression of tumor cell proliferation [38,39], induction of apoptosis [40], modulation of autophagy [41], suppression of angiogenesis [42], regulation of hormone signaling [43], promotion of cellular differentiation, inhibition of epithelial-to-mesenchymal transition [44], antagonism of Wnt/β-catenin signaling [45], stromal remodeling [46], regulation of cancer stem cells [47], enhancement of antitumor immunity [48], anti-inflammatory effects [49], modulation of the gut microbiome [50], regulation of the renin–angiotensin system [51], and protection against oxidative stress-induced DNA damage [52].

Among these mechanisms, inhibition of cancer cell proliferation is partly mediated by the ability of vitamin D to suppress the Warburg effect, characterized by enhanced aerobic glycolysis, which is a hallmark of many cancer types [53]. Vitamin D also induces apoptosis through cancer-type-specific mechanisms, regulating key apoptotic mediators such as caspases and Bcl-2 family proteins [54]. For example, vitamin D upregulates caspase activity in non-malignant MCF-12A cells but not in malignant MCF-7 breast cancer cells, highlighting context-dependent responses [55].

Autophagy, a tightly regulated self-degradative process controlled by autophagy-related genes (ATGs), plays a dual role in cancer progression and therapy. The process involves phagophore initiation, autophagosome formation, fusion with lysosomes, and cargo degradation [56]. Vitamin D has been reported to modulate autophagy, contributing to its therapeutic efficacy in cancer treatment [57].

Angiogenesis, the formation of new blood vessels, is essential for tumor growth and metastasis [58]. Several in vivo studies have demonstrated that vitamin D can suppress angiogenesis, thereby limiting tumor progression [59–61]. In addition, vitamin D exerts immunomodulatory effects by activating immune cells, inducing pro-apoptotic proteins [62], and upregulating cyclin-dependent kinase inhibitors [63]. Notably, VDR is expressed in nearly all leukocyte populations, including macrophages, dendritic cells, activated $CD4^+$ and $CD8^+$ T cells, and B cells, underscoring its role in immune regulation [64].

Vitamin D also interacts with key oncogenic signaling pathways, including Wnt/β-catenin, NF-κB, PI3K/Akt, and p53, thereby influencing tumor growth, invasion, and metastasis [65]. Beyond direct cellular effects, vitamin D contributes to cancer prevention through modulation of the gut microbiome, enhancement of intestinal barrier integrity, and regulation of intestinal inflammation [66]. Vitamin D has a positive effect on the gut microbiota; enhances the growth of beneficial bacteria such as *Ruminococcaceae*, *Akkermansia*, *Faecalibacterium* and *Coprococcus*; and suppresses *Firmicutes* (*Staphylococcus aureus*, *Streptococcus pneumoniae*, *Listeria* and *Bacillus anthracis*) activity [67].

Obesity is a recognized risk factor for cancer incidence and mortality, particularly in breast and colorectal cancers [68]. Chronic low-grade inflammation associated with obesity promotes carcinogenesis and tumor progression [69]. Vitamin D may mitigate these pro-carcinogenic effects by reducing inflammation [70], regulating sex hormone receptor signaling, and improving leptin sensitivity, thereby exerting protective metabolic and immunological effects [71].

## 3. Synergy Between Vitamin D and Phytochemicals

Many phytochemicals possess intrinsic anticancer properties capable of preventing tumor initiation and inhibiting cancer cell proliferation [72]. Figure 2 provides the main mechanisms of anticancer action of vitamin D. Anticancer compounds of plant origin not only encompass all modes of action of vitamin D (Figure 2) but also take actions on multiple signaling pathways and have various mechanisms that are not characteristic of vitamin D [73]. This is also true with regard to several phytochemicals in the context of breast cancer [74]. Other examples are polyphenols that may modulate signal transduction pathways and induce apoptosis [75] even as alkaloids such as vincristine, vinblastine, colchicine, vindesine and vincamine disturb mitotic spindle assembly and consequently break cell division [76]. As already mentioned, obesity is one of the most prominent factors driving the development of cancer. Many compounds of plant origin may be beneficial in obesity management, and molecular mechanisms of their activities include adipose tissue mass reduction by increasing fat cell apoptosis, hindering precursor cell proliferation, regulation of lipid metabolism, and enhancement of energy expenditure; inhibiting triglyceride absorption by decreasing pancreatic lipase and suppressing appetite [77].

When combined with vitamin D, these plant-derived compounds can potentiate their anticancer effects through multiple mechanisms, including modulation of ROS-scavenging enzymes, inhibition of cell cycle progression, induction of apoptosis and autophagy, suppression of angiogenesis, and inhibition of metastasis. Vitamin D and phytochemicals share overlapping therapeutic targets, and certain combinations demonstrate synergistic anticancer activity.

Experimental studies suggest that some phytochemicals interact directly with the vitamin D receptor [78]. For instance, the alkaloids coclaurine and reticuline upregulated VDR expression and inhibited colorectal cancer progression in vitro [79]. Similarly, vitexin was shown to target VDR and modulate macrophage polarization, thereby preventing colorectal cancer [80], while asperuloside enhanced colonic VDR expression, alleviating colitis symptoms and reducing tumor burden [81]. Isoflavones such as genistein, biochanin A, and formononetin suppressed CYP24A1 induction in Huh7 cancer cells under both normoxic and hypoxic conditions [82]. These findings suggest that additional plant-derived compounds capable of direct VDR binding remain to be discovered and characterized.

Combination therapies involving vitamin D and phytochemicals have shown promising results, particularly because they target common apoptotic and cell survival pathways. Original studies evaluating these synergistic interactions are summarized in Table 1, with phytochemicals listed alphabetically. However, the anticancer potential of many phyto-

chemicals has not been studied in sufficient depth to allow direct comparison with vitamin D. Among well-characterized compounds, the polyphenol resveratrol has been extensively investigated and serves as a model for comparison. Resveratrol, found in wine, chocolate, cocoa, and various fruits and juices [83], exhibits broad anticancer activity, functioning as both a chemopreventive [84] and therapeutic agent [85].

Vitamin D and resveratrol share numerous mechanistic similarities. Both regulate critical processes in cell proliferation, differentiation, and apoptosis [86] and modulate key signaling molecules, including NF-κB, Akt, MAPK, Fas antigen receptors, TNF-α, Bcl-2, Bcl-xL, and p53 [87]. Glutathione has been shown to mediate the anticarcinogenic effects of both resveratrol [88] and vitamin D [89]. The superoxide dismutase family is important for the reduction in deleterious effects of reactive oxygen species [90]. Regulation of the enzyme superoxide dismutase is performed by both vitamin D [91] and resveratrol [92]. Both agents influence caspase-3 activity, an effector of apoptotic pathways [93,94]. Similarly to vitamin D [95], resveratrol activates protein kinases involved in cell proliferation, differentiation, apoptosis, and malignant transformation [96]. Furthermore, vitamin D and resveratrol inhibit tumor angiogenesis through downregulation of vascular endothelial growth factor (VEGF) [97–99]. The combination of vitamin D with flavonoids has also been associated with reduced risk of obesity-related breast cancer [100].

As mentioned throughout the paper, since cancer is so complex in its etiology, combining vitamin D with other active agents is effective but only at a specific concentration and ratio. The mechanism responsible for synergistic antioxidant activity has not been explained perfectly yet due to the challenging nature of the phytochemicals. The problem of anticancer effect in a mixture of vitamin D and plant compounds is very difficult to solve because it depends on the chemical structure of the compounds, their concentrations and molecular ratio, applied solvent, the reaction time and treatment of the sample [101].

Isobologram analysis gives the possibility to estimate the interaction between two or more drugs as synergistic, additive, or antagonistic mathematically based on the combination index [102]. Thus far, only a few studies have been undertaken to evaluate the synergism of vitamin D with some drugs [103,104], but not with phytochemicals.

Combinations of vitamin D and plant active components were not used in clinical trials. Although these combinations mediate their anticancer effects by modulating multiple signaling pathways, many challenges are connected with their inadequate bioavailability, pharmacokinetics, metabolism and toxicity. One of the important obstacles to successful clinical feasibility is a lack of pharmacodynamic biomarkers allowing to estimate anticancer effect in a proper form [105].

**Table 1.** Vitamin $D_3$ and phytochemicals synergistically contribute to anticancer effect.

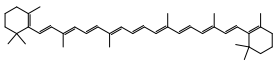
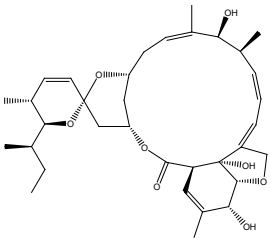
| Compound and Source | Structure | Cancer Model | Mechanism | References |
|---|---|---|---|---|
| β-carotene<br>Fungi, plants, fruits |  | Esophageal cancer in vitro | Induction of apoptosis in EC9706 cells | [106] |
| Aglycon<br>Agave species |  | Prostate cancer in vitro | Synergistically decreases cell viability and proliferation. | [107,108] |

**Table 1.** *Cont.*

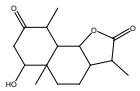
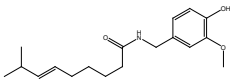
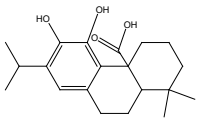
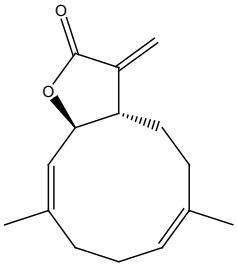
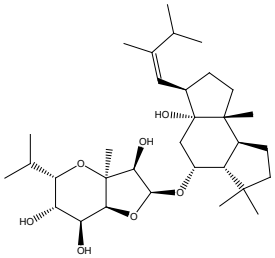
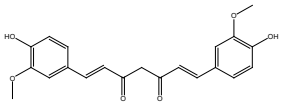
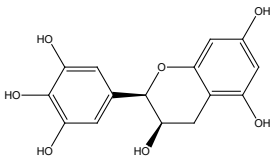
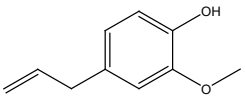
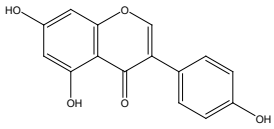
| Compound and Source | Structure | Cancer Model | Mechanism | References |
|---|---|---|---|---|
| Arsantin<br>*Artemisia santolina* |  | Leukemia in vitro | HL-60 cells differentiation | [109] |
| Capsaicin<br>Chili peppers |  | Leukemia in vitro | HL-60 cells differentiation | [110] |
| Carnosic acid<br>Rosemary, common sage |  | Leukemia in vitro | Inhibits proliferation and augments differentiation of human leukemic cells | [111] |
| Costunolide<br>*Saussurea costus* |  | Leukemia in vitro | HL-60 leukemia cell differentiation | [112] |
| Cotylenin A<br>*Cladosporium* spp. |  | AML<br>in vitro | Inducing the monocytic differentiation of AML cells | [113] |
| Curcumin<br>*Curcuma longa* |  | Prostate cancer, leukemia in vitro | Inhibition of proliferation of HL-60 cells<br>Effect and inhibitory metastatic characteristics in prostate cancer cells | [114]<br>[115] |
| Epigallocatechin<br>Green tea |  | Uterine myoma Clinical research | The total myoma volume decreased by 34.7% | [116] |
| Eugenol<br>Clove oil |  | Leukemia in vitro | Inhibition of proliferation of HL-60 cells | [117] |
| Genistein<br>Soybeans |  | Prostate cancer in vitro | Inhibition of proliferation of $1,25(OH)_2D_3$ in DU145 cells | [118] |

**Table 1.** *Cont.*

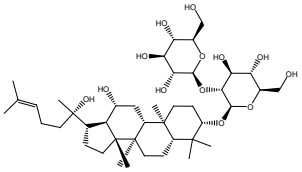
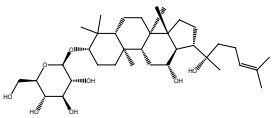
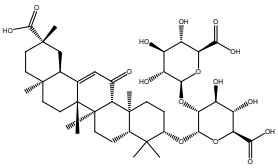
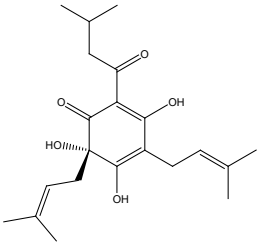
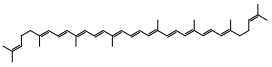
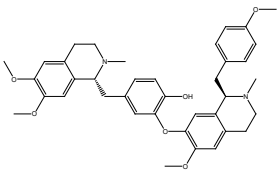
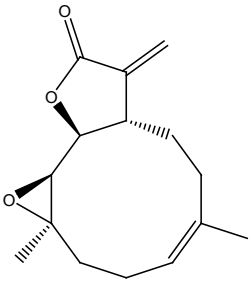
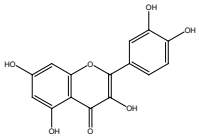
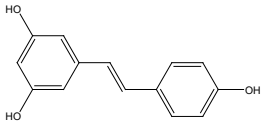
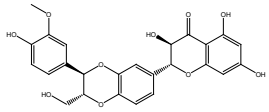
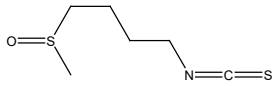
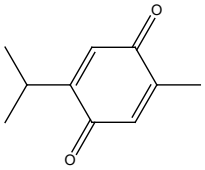
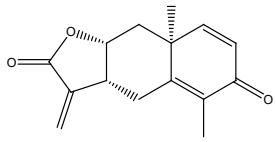
| Compound and Source | Structure | Cancer Model | Mechanism | References |
|---|---|---|---|---|
| Ginsenoside Rg3<br>*Panax ginseng* |  | Prostate cancer in vivo and in vitro | Induces apoptosis and reduces cell proliferation | [119] |
| Ginsenoside Rh2<br>*Panax ginseng* |  | Prostate cancer in vitro | Stimulating apoptosis and reduced cell proliferation | [120] |
| Glycyrrhizin<br>*Glycyrrhiza glabra* |  | Prostate cancer in vivo and in vitro | Inhibits growth of LNCaP and C4-2 PCa cells | [107,121] |
| Humulone<br>*Humulus lupulus* |  | Leukemia in vitro | HL-60 cells differentiation | [122] |
| Lycopene<br>Tomatoes, vegetables and fruits |  | Leukemia in vitro | Inhibition of cell cycle progression and induction of differentiation in HL-60 cells | [123] |
| Neferine<br>Green seed embryo of the lotus plant |  | Colorectal cancer in vitro | Inhibition of metastasis | [124] |
| Parthenolide<br>*Tanacetum* spp. |  | Leukemia in vitro | Induced HL-60 cell differentiation into monocytes via the inhibition of NF-κB activity | [125] |
| Quercetin<br>Many plants |  | Breast cancer in vitro and in vivo | Inhibition of cell cycle progression | [126] |

**Table 1.** *Cont.*

| Compound and Source | Structure | Cancer Model | Mechanism | References |
|---|---|---|---|---|
| Resveratrol<br>Grape, berries, peanuts |  | Lung cancer<br>in vitro | Influence on cell proliferation, inhibition, cell cycle, apoptosis, and expression of cytokines and proteins. Affect VDR and other nuclear receptors indirectly | [127,128] |
| Silibinin<br>*Silybum marianum* |  | AML<br>in vitro | Anti-proliferative and anti-migratory effects Differentiation of AML Cells | [129,130] |
| Sulforaphane<br>Cruciferous vegetables |  | Prostate cancer in vitro and in vivo | Modulate the JNK/MAPK signaling pathway and suppress intestinal Wnt-signaling and tumorigenesis in obese mice. | [131,132] |
| Thymoquinone<br>*Nigella sativa* |  | Colon cancer<br>in vitro | Anti-tumorigenic effects | [133] |
| Yomogin<br>*Artemisia iwayomogi* |  | Leukemia<br>in vitro | Differentiation of HL-60 cells | [134] |

## 4. Co-Delivery Systems for the Prevention and Treatment of Cancer

### *4.1. Importance of Co-Delivery Systems*

Co-delivery systems are spectacular strategies because of the opportunity to achieve synergistic therapeutic effects, which are more effective in overcoming the multidrug resistance in many cancer cells. These combined therapies can provide better outcomes than separate delivery approaches carrying either phytochemicals or vitamin D. Liposomes, emulsions and nanosystems are widespread delivery systems for vitamin D and phytochemicals [135].

The synergistic effect of vitamin D and phytochemicals relates to various biological mechanisms that enhance their combined impact, for example, their molecular targets, enzymatic pathways and so on.

Herein, designing novel nano-scale platforms to deliver vitamin D and anticancer active compounds of plant origin is also discussed.

### *4.2. Approaches to Vitamin D Delivery*

Although the anticancer properties of vitamin D have been extensively documented in the prevention and treatment of colorectal, prostate, and breast cancers [136,137], significant challenges continue to limit its clinical application. Administration of vitamin D at high doses is often ineffective and may lead to adverse effects such as hypervitaminosis D, hypercalcemia, and hyperphosphatemia. Moreover, serious side effects have been reported

when vitamin D is combined with other anticancer drugs in cancer patients [121]. Consequently, the therapeutic and chemopreventive potential of vitamin D has not yet been fully realized in clinical oncology. An additional limitation is its relatively short half-life in the bloodstream, which further restricts sustained therapeutic efficacy [138].

Globally, a substantial proportion of the population fails to meet the recommended daily vitamin D intake due to insufficient sunlight exposure [139]. Furthermore, vitamin D is highly susceptible to degradation during storage and food processing, and upon exposure to heat, light, and moisture, resulting in reduced stability and bioavailability [140]. Its poor water solubility and limited intestinal absorption further compromise its anticancer effectiveness. To address these limitations, targeted delivery strategies have emerged as a promising approach to enhance vitamin D bioavailability and therapeutic performance. As illustrated in Figure 3, advanced delivery systems including nanoencapsulation, nanoemulsions, complexation, mixed micelle systems, conjugation strategies, carbon quantum dots, and crosslinking techniques have been explored to overcome these barriers [141,142]. Notably, such formulations have been shown to enhance vitamin D bioavailability by two- to eight-fold, with encapsulation techniques significantly improving its bioaccessibility [143,144]. A recent review is devoted to the targeted delivery of vitamins in the context of gastrointestinal disorders, including colorectal cancer [145].

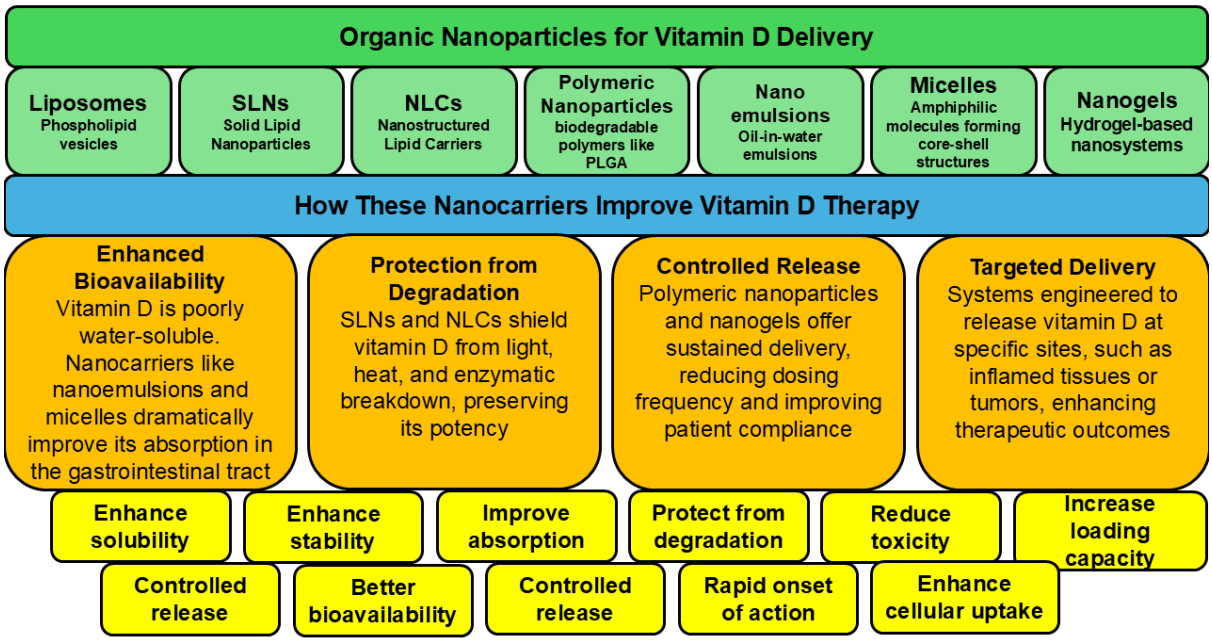



**Figure 3.** The targeted delivery of vitamin D. The image depicts various organic nanoparticles used for vitamin D delivery and their properties.

Encapsulation strategies offer additional advantages by protecting vitamin D from environmental degradation and improving its stability under adverse conditions [146]. In vivo studies have demonstrated that encapsulated vitamin D improves key physiological parameters, including circulating vitamin D levels, intestinal calcium and phosphorus absorption, and glycemic control in experimental models [147]. For example, vitamin $D_3$ encapsulated in gum Arabic exhibited superior absorption and bioavailability compared with its free form [148]. While nanoemulsions based on gum Arabic have been developed for vitamin D delivery, further investigation of their physicochemical properties, stability, and biological activity remains necessary [149]. Alternative approaches include the use of non-toxic, long-term Pickering emulsions based on zein–chitosan complex particles, which have shown promise for the encapsulation and sustained delivery of vitamin

$D_3$ [150]. The development of a complex nanoemulsion by combining pea protein and Tween 80 together gave the possibility to enhance vitamin D uptake and its transport efficiency significantly [151].

Targeted nanocarrier systems have also been explored to enhance the anticancer efficacy of vitamin D in drug-resistant tumors. Epidermal growth factor receptor (EGFR)-targeted liposomal nanoparticles co-encapsulating vitamin D and the 24-sulfoxamine derivative of 1,25-dihydroxyvitamin $D_3$ (CTA091) demonstrated improved cellular uptake and more effective inhibition of colony formation in drug-resistant lung cancer models compared with free compounds [152]. Similarly, targeted delivery of vitamin D-loaded nanoparticles to drug-resistant C6 glioma cells significantly reduced cell proliferation and increased sensitivity to chemotherapeutic agents such as doxorubicin, epirubicin, and docetaxel ($p < 0.05$) [153]. Importantly, evidence suggests that targeted vitamin D delivery is more effective during early stages of carcinogenesis than in advanced disease [154].

Carbon Nanofiber–Sodium Alginate Composite Aerogels effectively delivered vitamin D to human colorectal cancer cells, improved their bioavailability, and significantly decreased cancer cell proliferation and migration [155].

Combination delivery systems have further expanded the therapeutic potential of vitamin D. Sodium caseinate micelles co-loaded with vitamin D and etoposide exhibited enhanced anticancer activity against human MDA-MB-231 and MCF-7 breast cancer cell lines compared with free vitamin D [156]. Similarly, micellar formulations co-encapsulating paclitaxel and vitamin D have been developed for intravenous or intratumoral administration in pancreatic cancer models, demonstrating improved therapeutic outcomes [157].

The proliferation of melanoma cells (B16 F10 cell line) was suppressed by liposomal vitamin D and free vitamin D; however, the former had a better antiproliferative effect and the most pronounced decrease in the expression of AKT1, BCL2, and PI3K genes [158].

In addition, nanoliposomal encapsulation of vitamin D using thin-film hydration and sonication methods has been shown to markedly enhance its solubility, cellular uptake in Caco-2 cells, storage stability (even at 25 °C), and stability in aqueous and gastrointestinal environments [159]. Collectively, these advances highlight the critical role of innovative delivery systems in overcoming the physicochemical and biological limitations of vitamin D, thereby unlocking its full potential as an anticancer agent.

### *4.3. Lymphatic Transport of Vitamin D*

The lymphatic system harbors numerous potential therapeutic targets that may influence various types of cancer [160]. For drugs to be effectively transported via the lymphatic route, they must exhibit significant lipophilicity. Specifically, a log $p$ value greater than 5 and triglyceride solubility exceeding 50 mg/mL have been suggested as critical physicochemical thresholds for efficient lymphatic transport. Vitamin $D_3$, known for its high lipophilicity (with a log $p$ value around 9), relies on this pathway for its oral bioavailability [161].

As illustrated in Figure 4, the sequential assembly of chylomicrons within enterocytes involves several key steps: the formation of primordial lipoproteins in the rough endoplasmic reticulum (RER), the synthesis of large triglyceride-rich droplets in the smooth endoplasmic reticulum (SER), and the subsequent biosynthesis of chylomicrons through core expansion.

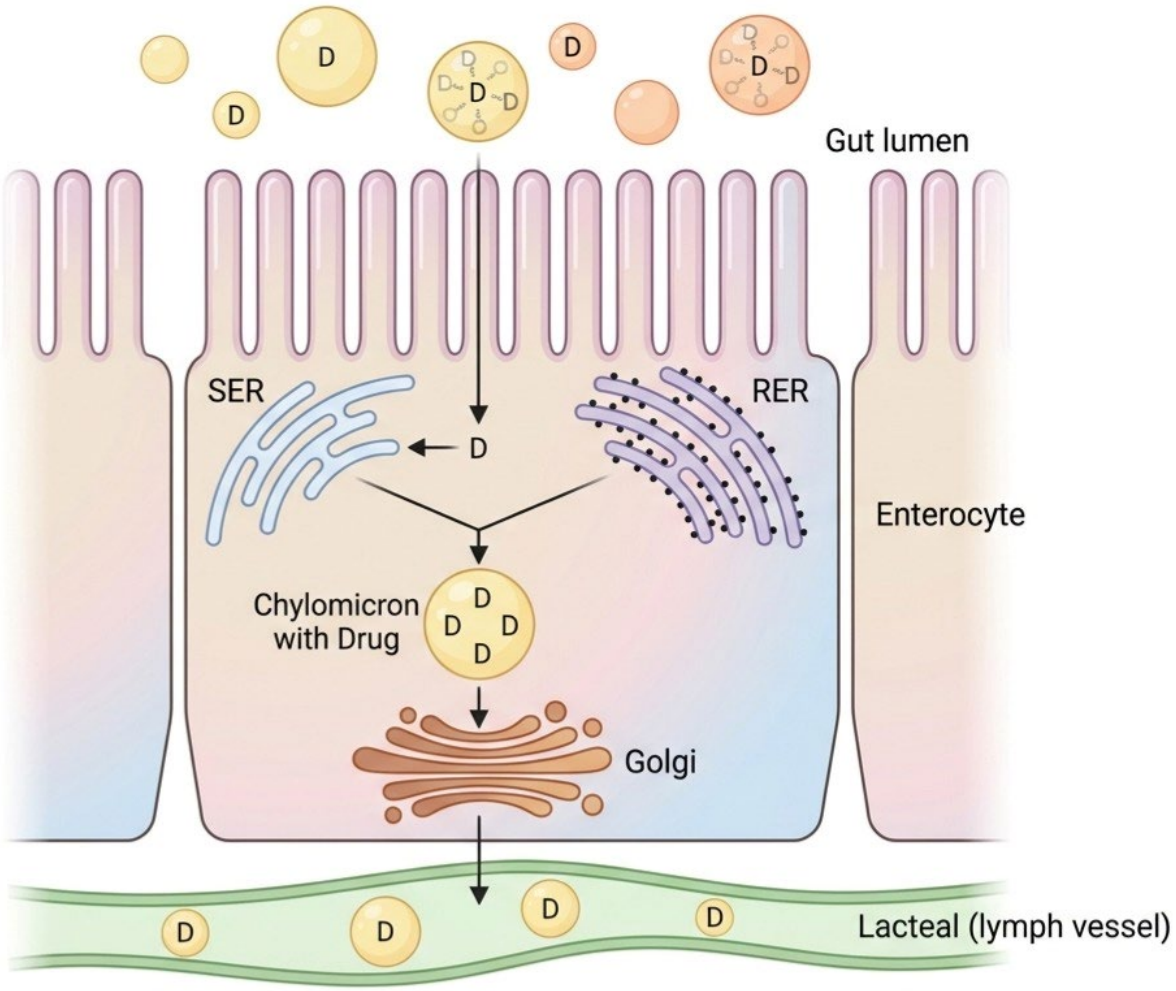



**Figure 4.** Lymphatic transport of vitamin D. The three events in the sequential assembly of chylomicrons within the enterocyte are presented: (1) formation of primordial lipoproteins in the rough endoplasmic reticulum (RER); (2) synthesis of large triglyceride-rich droplets in the smooth endoplasmic reticulum (SER); (3) biosynthesis of chylomicrons in the core expansion process. It was demonstrated that most of the dose (75%) of lipophilic vitamin D gains access to the lymphatic system by incorporating into the lipidic core of the chylomicrons.

Lymphatic transport of vitamin D is particularly critical for preventing metastasis, as the lymphatic system plays an essential role in the metastatic dissemination of cancer cells [162].

### *4.4. Formulations Combining Vitamin D with Plant-Derived Compounds*

A major limitation in the therapeutic use of phytochemicals lies in their inherent properties, including low bioavailability due to rapid metabolism, poor cellular uptake, and inadequate targeting [163]. These factors restrict their effectiveness, particularly when combined with vitamin D for cancer treatment. This highlights the critical need for the development of innovative drug delivery systems that enhance the pharmacokinetic profile, cellular uptake, and therapeutic efficacy of vitamin D in combination with plant-derived compounds.

Several phytochemicals have been identified as bioenhancers, known to improve the solubility and bioavailability of vitamin D [164]. However, the mechanisms underlying their bioenhancing effects remain poorly understood, and research into their modes of action is limited. Despite the importance of co-delivery systems, relatively few studies have investigated formulations combining vitamin D with phytochemicals. One such study explored the co-encapsulation of vitamin D and rutin in chitosan–zein microparticles

using hydrophobic interactions, hydrogen bonding, Van der Waals forces, and nonspecific electrostatic neutralization between the oppositely charged polymers [165,166].

In addition, curcumin and vitamin D have been co-encapsulated in nanoliposomes [167] and nanoemulsions [168], resulting in enhanced solubility, stability, and bioavailability compared to their free forms. Similarly, cinnamon essential oil, which contains several anticancer compounds such as monoterpenes and terpenoids [169], has been studied in combination with vitamin D, though not extensively. A recent study demonstrated that a vitamin D-encapsulated cinnamon oil nanoemulsion induced G0/G1 cell cycle arrest in A549 lung carcinoma cells, increased the expression of pro-apoptotic markers (Bax, caspase-3, and caspase-9), and decreased anti-apoptotic Bcl-2 levels [170]. This highlights the significant potential of combined vitamin D–phytochemical formulations while also emphasizing the substantial gaps in current knowledge that necessitate further investigation.

In experimental in vitro studies, micellization significantly enhanced the uptake of vitamin D by buccal and intestinal cells. While curcuma extract further improved the uptake of micellated vitamin D, its bioefficacy remained unchanged [171].

The health benefits of vegetables are well-documented, and the concept of using vegetable-derived systems for vitamin D delivery is particularly intriguing. Notably, a study demonstrated that vitamin D-loaded tomato-derived extracellular vesicles effectively reduced the growth, spread, and survival of colon cancer cells [172]. This innovative approach underscores the potential of plant-based delivery systems in enhancing the therapeutic effects of vitamin D in cancer treatment.

## 5. Conclusions

The synergistic interactions between vitamin D and phytochemicals hold considerable promise for cancer prevention and therapy by modulating multiple cellular and molecular pathways. However, the majority of potential combinations remain largely unexplored, representing a significant opportunity for future research.

To fully realize this therapeutic potential, future studies should prioritize the identification of novel, effective vitamin D–phytochemical combinations and the development of advanced drug delivery systems to enhance bioavailability and stability. Unfortunately, the effect of various factors on the bioavailability of vitamin D was not estimated in any clinical studies [173]. Moreover, there is a pressing need for comprehensive in vivo studies and well-designed clinical trials to establish standardized protocols and evaluate the efficacy of these combinations in cancer treatment. Addressing these challenges will be critical for translating preclinical findings into practical, safe, and effective anticancer strategies.

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## Abbreviations

The following abbreviations are used in this manuscript:

| | |
|---|---|
| Akt | Protein kinase B |
| AML | Acute Myeloid Leukemia |
| ATGs | Autophagy-related genes |
| BCL-2 | B-cell lymphoma 2 |
| Bcl-xL | B-cell lymphoma—extra large |
| CYP24A1 | Cytochrome P450 family 24 subfamily A member 1 |
| EGFR | Epidermal growth factor receptor |
| MAPK | Mitogen-Activated Protein Kinase |
| NF-κB | Nuclear Factor kappa-light-chain-enhancer of activated B cells |
| NLCs | Nanostructured lipid carriers |
| PI3K | Phosphoinositide 3-kinase |
| RER | Rough Endoplasmic Reticulum |
| ROS | Reactive oxygen species |
| RXR | Retinoid X receptor |
| SER | Smooth Endoplasmic Reticulum |
| SLNs | Solid Lipid Nanoparticles |
| TNF-α | Tumor Necrosis Factor-alpha |
| VDR | Vitamin D receptor |
| VEGF | Vascular endothelial growth factor |

## References


1. Sintov, A.C.; Yarmolinsky, L.; Dahan, A.; Ben-Shabat, S. Pharmacological Effects of Vitamin D and Its Analogs: Recent Developments. *Drug Discov. Today* **2014**, *19*, 1769–1774. [CrossRef] [PubMed]
2. Seretis, K.; Bounas, N.; Sioka, C. The Association of Vitamin D with Non-Melanoma Skin Cancer Risk: An Umbrella Review of Systematic Reviews and Meta-Analyses. *Medicina* **2023**, *59*, 2130. [CrossRef] [PubMed]
3. Norton, W.E.; Kennedy, A.E.; Mittman, B.S.; Parry, G.; Srinivasan, S.; Tonorezos, E.; Vanderpool, R.C.; Jacobsen, P.B. Advancing Rapid Cycle Research in Cancer Care Delivery: A National Cancer Institute Workshop Report. *J. Natl. Cancer Inst.* **2023**, *115*, 498–504. [CrossRef]
4. Mokhtari, R.B.; Homayouni, T.S.; Baluch, N.; Morgatskaya, E.; Kumar, S.; Das, B.; Yeger, H. Combination Therapy in Combating Cancer. *Oncotarget* **2017**, *8*, 38022–38043. [CrossRef]
5. Antoszczak, M.; Huczyński, A. Salinomycin and Its Derivatives—A New Class of Multiple-Targeted "Magic Bullets". *Eur. J. Med. Chem.* **2019**, *176*, 208–227. [CrossRef] [PubMed]
6. Marques, L.A.; Semprebon, S.C.; Biazi, B.I.; Felicidade, I.; Zanetti, T.A.; Baranoski, A.; Concato, V.M.; Pavanelli, W.R.; Mantovani, M.S. Vitamin D3 and Salinomycin Synergy in MCF-7 Cells Cause Cell Death via Endoplasmic Reticulum Stress in Monolayer and 3D Cell Culture. *Toxicol. Appl. Pharmacol.* **2022**, *452*, 116178. [CrossRef]
7. Abu el Maaty, M.; Wölfl, S. Effects of 1,25$(OH)_2D_3$ on Cancer Cells and Potential Applications in Combination with Established and Putative Anti-Cancer Agents. *Nutrients* **2017**, *9*, 87. [CrossRef]
8. Özgen, Ö.; Özen Eroğlu, G.; Küçükhüseyin, Ö.; Akdeniz, N.; Hepokur, C.; Kuruca, S.; Yaylım, İ. Vitamin D Increases the Efficacy of Cisplatin on Bladder Cancer Cell Lines. *Mol. Biol. Rep.* **2023**, *50*, 697–706. [CrossRef]
9. Lashkari, M.; Fatemi, A.; Farsinejad, A.; Valandani, H.M.; Khalilabadi, R.M. Vitamin D3, Arsenic Trioxide, or Combination Therapy for Acute Promyelocytic Leukemia. *Gene Rep.* **2022**, *27*, 101576. [CrossRef]
10. Shabtay, A.; Sharabani, H.; Barvish, Z.; Kafka, M.; Amichay, D.; Levy, J.; Sharoni, Y.; Uskokovic, M.R.; Studzinski, G.P.; Danilenko, M. Synergistic Antileukemic Activity of Carnosic Acid-Rich Rosemary Extract and the 19-nor Gemini Vitamin D Analogue in a Mouse Model of Systemic Acute Myeloid Leukemia. *Oncology* **2008**, *75*, 203–214. [CrossRef]
11. Sharabani, H.; Izumchenko, E.; Wang, Q.; Kreinin, R.; Steiner, M.; Barvish, Z.; Kafka, M.; Sharoni, Y.; Levy, J.; Uskokovic, M.; et al. Cooperative Antitumor Effects of Vitamin $D_3$ Derivatives and Rosemary Preparations in a Mouse Model of Myeloid Leukemia. *Int. J. Cancer* **2006**, *118*, 3012–3021. [CrossRef]
12. Telang, N.T. Natural Bioactive Agents: Testable Stem Cell-Targeting Alternatives for Therapy-Resistant Breast Cancer. *Int. J. Mol. Sci.* **2025**, *26*, 2529. [CrossRef]
13. Greenwell, M.; Rahman, P.K.S.M. Medicinal Plants: Their Use in Anticancer Treatment. *Int. J. Pharm. Sci. Res.* **2015**, *6*, 4103–4112. [CrossRef]

14. Arfin, S.; Jha, N.K.; Jha, S.K.; Kesari, K.K.; Ruokolainen, J.; Roychoudhury, S.; Rathi, B.; Kumar, D. Oxidative Stress in Cancer Cell Metabolism. *Antioxidants* **2021**, *10*, 642. [CrossRef] [PubMed]
15. Zhang, J.; Wang, X.; Vikash, V.; Ye, Q.; Wu, D.; Liu, Y.; Dong, W. ROS and ROS-Mediated Cellular Signaling. *Oxid. Med. Cell. Longev.* **2016**, *2016*, 4350965. [CrossRef] [PubMed]
16. Brewer, M.S. Natural Antioxidants: Sources, Compounds, Mechanisms of Action, and Potential Applications. *Compr. Rev. Food Sci. Food Saf.* **2011**, *10*, 221–247. [CrossRef]
17. Sabharwal, S.S.; Schumacker, P.T. Mitochondrial ROS in Cancer: Initiators, Amplifiers or an Achilles' Heel? *Nat. Rev. Cancer* **2014**, *14*, 709–721. [CrossRef]
18. Sena, L.A.; Chandel, N.S. Physiological Roles of Mitochondrial Reactive Oxygen Species. *Mol. Cell* **2012**, *48*, 158–167. [CrossRef]
19. Trachootham, D.; Alexandre, J.; Huang, P. Targeting Cancer Cells by ROS-Mediated Mechanisms: A Radical Therapeutic Approach? *Nat. Rev. Drug Discov.* **2009**, *8*, 579–591. [CrossRef]
20. Milkovic, L.; Zarkovic, N.; Saso, L. Controversy about Pharmacological Modulation of Nrf2 for Cancer Therapy. *Redox Biol.* **2017**, *12*, 727–732. [CrossRef]
21. Yahfoufi, N.; Alsadi, N.; Jambi, M.; Matar, C. The Immunomodulatory and Anti-Inflammatory Role of Polyphenols. *Nutrients* **2018**, *10*, 1618. [CrossRef]
22. Li, F.; Li, S.; Li, H.-B.; Deng, G.-F.; Ling, W.-H.; Wu, S.; Xu, X.-R.; Chen, F. Antiproliferative Activity of Peels, Pulps and Seeds of 61 Fruits. *J. Funct. Foods* **2013**, *5*, 1298–1309. [CrossRef]
23. Danilenko, M.; Studzinski, G.P. Enhancement by Other Compounds of the Anti-Cancer Activity of Vitamin $D_3$ and Its Analogs. *Exp. Cell Res.* **2004**, *298*, 339–358. [CrossRef]
24. Radlović, N.; Mladenović, M.; Simić, D.; Radlović, P. Vitamin D in the Light of Current Knowledge. *Srp. Arh. Celok. Lek.* **2012**, *140*, 110–114. [CrossRef] [PubMed]
25. Bikle, D.D. Vitamin D Metabolism, Mechanism of Action, and Clinical Applications. *Chem. Biol.* **2014**, *21*, 319–329. [CrossRef] [PubMed]
26. Voltan, G.; Cannito, M.; Ferrarese, M.; Ceccato, F.; Camozzi, V. Vitamin D: An Overview of Gene Regulation, Ranging from Metabolism to Genomic Effects. *Genes* **2023**, *14*, 1691. [CrossRef] [PubMed]
27. Carlberg, C. Molecular Endocrinology of Vitamin D on the Epigenome Level. *Mol. Cell. Endocrinol.* **2017**, *453*, 14–21. [CrossRef]
28. Campbell, M.J.; Trump, D.L. Vitamin D Receptor Signaling and Cancer. *Endocrinol. Metab. Clin. N. Am.* **2017**, *46*, 1009–1038. [CrossRef]
29. Ricca, C.; Aillon, A.; Bergandi, L.; Alotto, D.; Castagnoli, C.; Silvagno, F. Vitamin D Receptor Is Necessary for Mitochondrial Function and Cell Health. *Int. J. Mol. Sci.* **2018**, *19*, 1672. [CrossRef]
30. Pike, J.W.; Meyer, M.B. The Vitamin D Receptor: New Paradigms for the Regulation of Gene Expression by 1,25-Dihydroxyvitamin $D_3$. *Endocrinol. Metab. Clin. N. Am.* **2010**, *39*, 255–269. [CrossRef]
31. Kamei, Y.; Ohizumi, H.; Fujitani, Y.; Nemoto, T.; Tanaka, T.; Takahashi, N.; Kawada, T.; Miyoshi, M.; Ezaki, O.; Kakizuka, A. PPARγ Coactivator 1β/ERR Ligand 1 Is an ERR Protein Ligand, Whose Expression Induces a High-Energy Expenditure and Antagonizes Obesity. *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 12378–12383. [CrossRef] [PubMed]
32. Stanisic, T.; Ewing, E.U.; Lindell, A.; Al-Jaberi, F.; Kongsbak-Wismann, M. Vitamin D3-VDR and Vitamin A-RAR Affect IL-13 and IFNγ Secretion from Human CD4+ T Cells Directly and Indirectly via Competition for Their Shared Co-Receptor RXR. *Scand. J. Immunol.* **2025**, *101*, e13429. [CrossRef] [PubMed]
33. King, A.N.; Beer, D.G.; Christensen, P.J.; Simpson, R.U.; Ramnath, N. The Vitamin D/CYP24A1 Story in Cancer. *Anti-Cancer Agents Med. Chem.* **2010**, *10*, 213–224. [CrossRef]
34. 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. [CrossRef] [PubMed]
35. Khanal, R.; Nemere, I. The ERp57/GRp58/1,25D3-MARRS Receptor: Multiple Functional Roles in Diverse Cell Systems. *Curr. Med. Chem.* **2007**, *14*, 1087–1093. [CrossRef]
36. Lappe, J.M.; Travers-Gustafson, D.; Davies, K.M.; Recker, R.R.; Heaney, R.P. Vitamin D and Calcium Supplementation Reduces Cancer Risk: Results of a Randomized Trial. *Am. J. Clin. Nutr.* **2007**, *85*, 1586–1591. Erratum in *Am. J. Clin. Nutr.* **2008**, *87*, 794. https://doi.org/10.1093/ajcn/87.3.794. [CrossRef]
37. Berridge, M.J. Vitamin D, Reactive Oxygen Species and Calcium Signalling in Ageing and Disease. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **2016**, *371*, 20150434. [CrossRef]
38. Wade, W.N.; Willingham, M.C.; Koumenis, C.; Cramer, S.D. P27Kip1 Is Essential for the Antiproliferative Action of 1,25-Dihydroxyvitamin D3 in Primary, but Not Immortalized, Mouse Embryonic Fibroblasts. *J. Biol. Chem.* **2002**, *277*, 37301–37306. [CrossRef]
39. Chang, S.; Gao, L.; Yang, Y.; Tong, D.; Guo, B.; Liu, L.; Li, Z.; Song, T.; Huang, C. MiR-145 Mediates the Antiproliferative and Gene Regulatory Effects of Vitamin D3 by Directly Targeting E2F3 in Gastric Cancer Cells. *Oncotarget* **2015**, *6*, 7675–7685. [CrossRef]

40. Guzey, M.; Kitada, S.; Reed, J.C. Apoptosis Induction by 1alpha,25-Dihydroxyvitamin D3 in Prostate Cancer. *Mol. Cancer Ther.* **2002**, *1*, 667–677.
41. Zhang, X.; Luo, F.; Li, J.; Wan, J.; Zhang, L.; Li, H.; Chen, A.; Chen, J.; Cai, T.; He, X.; 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 $1,25(OH)_2D_3$. *Exp. Dermatol.* **2019**, *28*, 45–52. [CrossRef] [PubMed]
42. Anisiewicz, A.; Pawlik, A.; Filip-Psurska, B.; Turlej, E.; Dzimira, S.; Milczarek, M.; Gdesz, K.; Papiernik, D.; Jarosz, J.; Kłopotowska, D.; et al. Unfavorable Effect of Calcitriol and Its Low-Calcemic Analogs on Metastasis of 4T1 Mouse Mammary Gland Cancer. *Int. J. Oncol.* **2018**, *52*, 103–126. [CrossRef] [PubMed]
43. Kasiappan, R.; Sun, Y.; Lungchukiet, P.; Quarni, W.; Zhang, X.; Bai, W. Vitamin D Suppresses Leptin Stimulation of Cancer Growth through MicroRNA. *Cancer Res.* **2014**, *74*, 6194–6204. [CrossRef] [PubMed]
44. Yeung, C.-Y.; Chiang Chiau, J.-S.; Cheng, M.-L.; Chan, W.-T.; Jiang, C.-B.; Chang, S.-W.; Liu, C.-Y.; Chang, C.-W.; Lee, H.-C. Effects of Vitamin D-Deficient Diet on Intestinal Epithelial Integrity and Zonulin Expression in a C57BL/6 Mouse Model. *Front. Med.* **2021**, *8*, 649818. [CrossRef]
45. Jeong, Y.; Swami, S.; Krishnan, A.V.; Williams, J.D.; Martin, S.; Horst, R.L.; Albertelli, M.A.; Feldman, B.J.; Feldman, D.; Diehn, M. Inhibition of Mouse Breast Tumor-Initiating Cells by Calcitriol and Dietary Vitamin D. *Mol. Cancer Ther.* **2015**, *14*, 1951–1961. [CrossRef]
46. Ferrer-Mayorga, G.; Gómez-López, G.; Barbáchano, A.; Fernández-Barral, A.; Peña, C.; Pisano, D.G.; Cantero, R.; Rojo, F.; Muñoz, A.; Larriba, M.J. Vitamin D Receptor Expression and Associated Gene Signature in Tumour Stromal Fibroblasts Predict Clinical Outcome in Colorectal Cancer. *Gut* **2017**, *66*, 1449–1462. [CrossRef]
47. Fernández-Barral, A.; Costales-Carrera, A.; Buira, S.P.; Jung, P.; Ferrer-Mayorga, G.; Larriba, M.J.; Bustamante-Madrid, P.; Domínguez, O.; Real, F.X.; Guerra-Pastrián, L.; et al. Vitamin D Differentially Regulates Colon Stem Cells in Patient-Derived Normal and Tumor Organoids. *FEBS J.* **2020**, *287*, 53–72. [CrossRef]
48. Lathers, D.M.R.; Clark, J.I.; Achille, N.J.; Young, M.R.I. Phase 1B Study to Improve Immune Responses in Head and Neck Cancer Patients Using Escalating Doses of 25-Hydroxyvitamin D3. *Cancer Immunol. Immunother.* **2004**, *53*, 422–430. [CrossRef]
49. Muñoz, A.; Grant, W.B. Vitamin D and Cancer: An Historical Overview of the Epidemiology and Mechanisms. *Nutrients* **2022**, *14*, 1448. [CrossRef]
50. Su, D.; Nie, Y.; Zhu, A.; Chen, Z.; Wu, P.; Zhang, L.; Luo, M.; Sun, Q.; Cai, L.; Lai, Y.; et al. Vitamin D Signaling through Induction of Paneth Cell Defensins Maintains Gut Microbiota and Improves Metabolic Disorders and Hepatic Steatosis in Animal Models. *Front. Physiol.* **2016**, *7*, 498. [CrossRef]
51. Dougherty, U.; Mustafi, R.; Sadiq, F.; Almoghrabi, A.; Mustafi, D.; Kreisheh, M.; Sundaramurthy, S.; Liu, W.; Konda, V.J.; Pekow, J.; et al. The Renin-Angiotensin System Mediates EGF Receptor-Vitamin d Receptor Cross-Talk in Colitis-Associated Colon Cancer. *Clin. Cancer Res.* **2014**, *20*, 5848–5859. [CrossRef] [PubMed]
52. Sheeley, M.P.; Andolino, C.; Kiesel, V.A.; Teegarden, D. Vitamin D Regulation of Energy Metabolism in Cancer. *Br. J. Pharmacol.* **2022**, *179*, 2890–2905. [CrossRef]
53. Yiyan, S.; Yang, S.; Li, D.; Li, W. 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* **2022**, *22*, 86–95. [CrossRef]
54. Azhar, A.; Naseem, Z.; Haider, G.; Farooqui, N.; Farhat, S.; Rehman, R. PCOS Model: Apoptotic Changes and Role of Vitamin D. *Electron. J. Gen. Med.* **2022**, *19*, em398. [CrossRef] [PubMed]
55. Brosseau, C.M.; Pirianov, G.; Colston, K.W. Involvement of Stress Activated Protein Kinases (JNK and P38) in 1,25 Dihydroxyvitamin D3-Induced Breast Cell Death. *Steroids* **2010**, *75*, 1082–1088. [CrossRef] [PubMed]
56. Mahapatra, K.K.; Panigrahi, D.P.; Praharaj, P.P.; Bhol, C.S.; Patra, S.; Mishra, S.R.; Behera, B.P.; Bhutia, S.K. Molecular Interplay of Autophagy and Endocytosis in Human Health and Diseases. *Biol. Rev. Camb. Philos. Soc.* **2019**, *94*, 1576–1590. [CrossRef]
57. Bristol, M.L.; Di, X.; Beckman, M.J.; Wilson, E.N.; Henderson, S.C.; Maiti, A.; Fan, Z.; Gewirtz, D.A. 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*, 739–753. [CrossRef]
58. Olejarz, W.; Kubiak-Tomaszewska, G.; Chrzanowska, A.; Lorenc, T. Exosomes in Angiogenesis and Anti-Angiogenic Therapy in Cancers. *Int. J. Mol. Sci.* **2020**, *21*, 5840. [CrossRef]
59. Chung, I.; Han, G.; Seshadri, M.; Gillard, B.M.; Yu, W.; Foster, B.A.; Trump, D.L.; Johnson, C.S. Role of Vitamin D Receptor in the Antiproliferative Effects of Calcitriol in Tumor-Derived Endothelial Cells and Tumor Angiogenesis In Vivo. *Cancer Res.* **2009**, *69*, 967–975. [CrossRef]
60. Mantell, D.J.; Owens, P.E.; Bundred, N.J.; Mawer, E.B.; Canfield, A.E. $1\alpha,25$-Dihydroxyvitamin $D_3$ Inhibits Angiogenesis In Vitro and In Vivo. *Circ. Res.* **2000**, *87*, 214–220. [CrossRef]
61. Wei, Q.; Zhang, Y.-H. Flavonoids with Anti-Angiogenesis Function in Cancer. *Molecules* **2024**, *29*, 1570. [CrossRef]
62. Welsh, J. Function of the Vitamin D Endocrine System in Mammary Gland and Breast Cancer. *Mol. Cell. Endocrinol.* **2017**, *453*, 88–95. [CrossRef] [PubMed]

63. Chauss, D.; Freiwald, T.; McGregor, R.; Yan, B.; Wang, L.; Nova-Lamperti, E.; Kumar, D.; Zhang, Z.; Teague, H.; West, E.E.; et al. Autocrine Vitamin D Signaling Switches off Pro-Inflammatory Programs of TH1 Cells. *Nat. Immunol.* **2022**, *23*, 62–74. [CrossRef]
64. Musavi, H.; Abazari, O.; Barartabar, Z.; Kalaki-Jouybari, F.; Hemmati-Dinarvand, M.; Esmaeili, P.; Mahjoub, S. The Benefits of Vitamin D in the COVID-19 Pandemic: Biochemical and Immunological Mechanisms. *Arch. Physiol. Biochem.* **2023**, *129*, 354–362. [CrossRef] [PubMed]
65. Prasanth, D.; Khan, P.A.; Jamal-E-Fatima; Durgawale, T.P.; Siddique, F.A.; Khan, S.L.; Farhana, A.; Panigrahy, U.P.; Shahid, M.A.A.; Sayeed, M.; et al. Vitamin D-Induced Mechanisms in Cancer Prevention and Therapy: Recent Advances and Future Opportunities. *Anim. Models Exp. Med.* **2025**, *8*, 1935–1946. [CrossRef] [PubMed]
66. Assa, A.; Vong, L.; Pinnell, L.J.; Avitzur, N.; Johnson-Henry, K.C.; Sherman, P.M. Vitamin D Deficiency Promotes Epithelial Barrier Dysfunction and Intestinal Inflammation. *J. Infect. Dis.* **2014**, *210*, 1296–1305. [CrossRef]
67. Tangestani, H.; Boroujeni, H.K.; Djafarian, K.; Emamat, H.; Shab-Bidar, S. Vitamin D and the Gut Microbiota: A Narrative Literature Review. *Clin. Nutr. Res.* **2021**, *10*, 181–191. [CrossRef]
68. Grant, W. Cancer Incidence Rates in the US in 2016–2020 with Respect to Solar UVB Doses, Diabetes and Obesity Prevalence, Lung Cancer Incidence Rates, and Alcohol Consumption: An Ecological Study. *Nutrients* **2024**, *16*, 1450. [CrossRef]
69. Taylor, E.B. The Complex Role of Adipokines in Obesity, Inflammation, and Autoimmunity. *Clin. Sci.* **2021**, *135*, 731–752. [CrossRef]
70. Liu, W.; Zhang, L.; Xu, H.-J.; Li, Y.; Hu, C.-M.; Yang, J.-Y.; Sun, M.-Y. The Anti-Inflammatory Effects of Vitamin D in Tumorigenesis. *Int. J. Mol. Sci.* **2018**, *19*, 2736. [CrossRef]
71. Tarasiuk, A.; Mosińska, P.; Fichna, J. The Mechanisms Linking Obesity to Colon Cancer: An Overview. *Obes. Res. Clin. Pract.* **2018**, *12*, 251–259. [CrossRef] [PubMed]
72. Nayak, B.; Liu, R.H.; Tang, J. Effect of Processing on Phenolic Antioxidants of Fruits, Vegetables, and Grains—A Review. *Crit. Rev. Food Sci. Nutr.* **2015**, *55*, 887–918. [CrossRef] [PubMed]
73. Aljabali, A.A.A.; Obeid, M.A.; Bashatwah, R.M.; Qnais, E.; Gammoh, O.; Alqudah, A.; Mishra, V.; Mishra, Y.; Khan, M.A.; Parvez, S.; et al. Phytochemicals in Cancer Therapy: A Structured Review of Mechanisms, Challenges, and Progress in Personalized Treatment. *Chem. Biodivers.* **2025**, *22*, e202402479. [CrossRef] [PubMed]
74. Kodali, N.; Madu, C.O.; Lu, Y. Phytochemicals in Breast Cancer Prevention and Therapy: Mechanisms, Efficacy, and Future Prospects. *Curr. Issues Mol. Biol.* **2025**, *47*, 527. [CrossRef]
75. Kogut, Ł.; Puchalski, C.; Katryńska, D.; Zaguła, G. The Multidirectional Biological Activity of Resveratrol: Molecular Mechanisms, Systemic Effects and Therapeutic Potential-A Review. *Nutrients* **2026**, *18*, 313. [CrossRef]
76. Dhyani, P.; Quispe, C.; Sharma, E.; Bahukhandi, A.; Sati, P.; Attri, D.C.; Szopa, A.; Sharifi-Rad, J.; Docea, A.O.; Mardare, I.; et al. Anticancer Potential of Alkaloids: A Key Emphasis to Colchicine, Vinblastine, Vincristine, Vindesine, Vinorelbine and Vincamine. *Cancer Cell Int.* **2022**, *22*, 206. [CrossRef]
77. Rao, P.P. Phytochemicals in Obesity Management: Mechanisms and Clinical Perspectives. *Curr. Nutr. Rep.* **2025**, *14*, 17. [CrossRef]
78. Huang, Y.-Q.; Liu, J.-L.; Chen, G.-X.; Shen, D.-T.; Zhu, W.; Chen, X.-L.; Liu, F.-B.; Hou, Q.-K. Berberine Enhances Intestinal Mucosal Barrier Function by Promoting Vitamin D Receptor Activity. *Chin. J. Integr. Med.* **2024**, *30*, 143–151. [CrossRef]
79. Alghamdi, H.A.; Alghamdi, S.S.; Al-Zahrani, M.H.; Trivilegio, T.; Bahattab, S.; AlRoshody, R.; Alhaidan, Y.; Alghamdi, R.A.; Matou-Nasri, S. Reticuline and Coclaurine Exhibit Vitamin D Receptor-Dependent Anticancer and Pro-Apoptotic Activities in the Colorectal Cancer Cell Line HCT116. *Curr. Issues Mol. Biol.* **2025**, *47*, 810. [CrossRef]
80. Chen, Y.; Liang, J.; Chen, S.; Lin, N.; Xu, S.; Miao, J.; Zhang, J.; Chen, C.; Yuan, X.; Xie, Z.; et al. Discovery of Vitexin as a Novel VDR Agonist That Mitigates the Transition from Chronic Intestinal Inflammation to Colorectal Cancer. *Mol. Cancer* **2024**, *23*, 196. [CrossRef]
81. Lu, Y.; Guan, T.; Xu, S.; Chen, Y.; Shen, Q.; Zhu, S.; Liu, Y.; Liang, J.; Hou, S. Asperuloside Inhibited Epithelial-Mesenchymal Transition in Colitis Associated Cancer via Activation of Vitamin D Receptor. *Phytomedicine* **2022**, *101*, 154070. [CrossRef]
82. Angeli-Terzidou, A.E.; Gkotinakou, I.-M.; Pazaitou-Panayiotou, K.; Tsakalof, A. Inhibition of Calcitriol Inactivating Enzyme CYP24A1 Gene Expression by Flavonoids in Hepatocellular Carcinoma Cells under Normoxia and Hypoxia. *Arch. Biochem. Biophys.* **2021**, *704*, 108889. [CrossRef]
83. Burns, J.; Yokota, T.; Ashihara, H.; Lean, M.E.J.; Crozier, A. Plant Foods and Herbal Sources of Resveratrol. *J. Agric. Food Chem.* **2002**, *50*, 3337–3340. [CrossRef] [PubMed]
84. Jang, M.; Cai, L.; Udeani, G.O.; Slowing, K.V.; Thomas, C.F.; Beecher, C.W.W.; Fong, H.H.S.; Farnsworth, N.R.; Kinghorn, A.D.; Mehta, R.G.; et al. Cancer Chemopreventive Activity of Resveratrol, a Natural Product Derived from Grapes. *Science* **1997**, *275*, 218–220. [CrossRef] [PubMed]
85. Ko, J.-H.; Sethi, G.; Um, J.-Y.; Shanmugam, M.K.; Arfuso, F.; Kumar, A.P.; Bishayee, A.; Ahn, K.S. The Role of Resveratrol in Cancer Therapy. *Int. J. Mol. Sci.* **2017**, *18*, 2589. [CrossRef]
86. Norman, A.W. From Vitamin D to Hormone D: Fundamentals of the Vitamin D Endocrine System Essential for Good Health. *Am. J. Clin. Nutr.* **2008**, *88*, 491S–499S. [CrossRef] [PubMed]

87. Shukla, Y.; Singh, R. Resveratrol and Cellular Mechanisms of Cancer Prevention. *Ann. N. Y. Acad. Sci.* **2011**, *1215*, 1–8. [CrossRef]
88. Sengottuvelan, M.; Senthilkumar, R.; Nalini, N. Modulatory Influence of Dietary Resveratrol during Different Phases of 1,2-Dimethylhydrazine Induced Mucosal Lipid-Peroxidation, Antioxidant Status and Aberrant Crypt Foci Development in Rat Colon Carcinogenesis. *Biochim. Biophys. Acta* **2006**, *1760*, 1175–1183. [CrossRef]
89. Goto, R.L.; Tablas, M.B.; Prata, G.B.; Espírito Santo, S.G.; Fernandes, A.A.H.; Cogliati, B.; Barbisan, L.F.; Romualdo, G.R. Vitamin D3 Supplementation Alleviates Chemically-Induced Cirrhosis-Associated Hepatocarcinogenesis. *J. Steroid Biochem. Mol. Biol.* **2022**, *215*, 106022. [CrossRef]
90. Griess, B.; Tom, E.; Domann, F.; Teoh-Fitzgerald, M. Extracellular Superoxide Dismutase and Its Role in Cancer. *Free Radic. Biol. Med.* **2017**, *112*, 464–479. [CrossRef]
91. Capobianco, E.; McGaughey, V.; Seraphin, G.; Heckel, J.; Rieger, S.; Lisse, T.S. Vitamin D Inhibits Osteosarcoma by Reprogramming Nonsense-Mediated RNA Decay and SNAI2-Mediated Epithelial-to-Mesenchymal Transition. *Front. Oncol.* **2023**, *13*, 1188641. [CrossRef] [PubMed]
92. Robb, E.L.; Stuart, J.A. The Stilbenes Resveratrol, Pterostilbene and Piceid Affect Growth and Stress Resistance in Mammalian Cells via a Mechanism Requiring Estrogen Receptor Beta and the Induction of Mn-Superoxide Dismutase. *Phytochemistry* **2014**, *98*, 164–173. [CrossRef] [PubMed]
93. Alkhalaf, M.; El-Mowafy, A.; Renno, W.; Rachid, O.; Ali, A.; Al-Attyiah, R. Resveratrol-Induced Apoptosis in Human Breast Cancer Cells Is Mediated Primarily through the Caspase-3-Dependent Pathway. *Arch. Med. Res.* **2008**, *39*, 162–168. [CrossRef] [PubMed]
94. Ebrahim, A.R.; El-Mesery, M.; El-Karef, A.; Eissa, L.A. Vitamin D Potentiates Anti-Tumor Activity of 5-Fluorouracil via Modulating Caspase-3 and TGF-B1 Expression in Hepatocellular Carcinoma-Induced in Rats. *Can. J. Physiol. Pharmacol.* **2018**, *96*, 1218–1225. [CrossRef]
95. Iglesias González, P.A.; Mori, C.; Valdivieso, Á.G.; Santa Coloma, T.A. Vitamin D and Retinoic Acid Require Protein Kinase C Activity and Reactive Oxygen Species as Opposing Signals Regulating PEIG-1/GPRC5A Expression in Caco-2 and T84 Colon Carcinoma Cells. *Biomolecules* **2025**, *15*, 711. [CrossRef]
96. Fulda, S.; Debatin, K.-M. Resveratrol Modulation of Signal Transduction in Apoptosis and Cell Survival: A Mini-Review. *Cancer Detect. Prev.* **2006**, *30*, 217–223. [CrossRef]
97. Nakanishi, K.; Hiramoto, K.; Ooi, K. High-Dose Vitamin C Exerts Its Anti-Cancer Effects in a Xenograft Model of Colon Cancer by Suppressing Angiogenesis. *Biol. Pharm. Bull.* **2021**, *44*, 884–887. [CrossRef]
98. Hu, W.-H.; Duan, R.; Xia, Y.-T.; Xiong, Q.-P.; Wang, H.-Y.; Chan, G.K.-L.; Liu, S.-Y.; Dong, T.T.-X.; Qin, Q.-W.; Tsim, K.W.-K. Binding of Resveratrol to Vascular Endothelial Growth Factor Suppresses Angiogenesis by Inhibiting the Receptor Signaling. *J. Agric. Food Chem.* **2019**, *67*, 1127–1137. [CrossRef]
99. Tseng, S.-H.; Lin, S.-M.; Chen, J.-C.; Su, Y.-H.; Huang, H.-Y.; Chen, C.-K.; Lin, P.-Y.; Chen, Y. Resveratrol Suppresses the Angiogenesis and Tumor Growth of Gliomas in Rats. *Clin. Cancer Res.* **2004**, *10*, 2190–2202. [CrossRef]
100. Sergeev, I. The Novel Role of Vitamin D and Flavonoids in Reducing Risk of Obesity-Associated Breast Cancer. *FASEB J.* **2015**, *29*, 602.11. [CrossRef]
101. Olszowy-Tomczyk, M. Synergistic, Antagonistic and Additive Antioxidant Effects in the Binary Mixtures. *Phytochem. Rev.* **2020**, *19*, 63–103. [CrossRef]
102. Huang, R.-Y.; Pei, L.; Liu, Q.; Chen, S.; Dou, H.; Shu, G.; Yuan, Z.-X.; Lin, J.; Peng, G.; Zhang, W.; et al. Isobologram Analysis: A Comprehensive Review of Methodology and Current Research. *Front. Pharmacol.* **2019**, *10*, 1222. [CrossRef] [PubMed]
103. Yu, W.-D.; Ma, Y.; Flynn, G.; Muindi, J.R.; Kong, R.-X.; Trump, D.L.; Johnson, C.S. Calcitriol Enhances Gemcitabine Antitumor Activity in Vitro and in Vivo by Promoting Apoptosis in a Human Pancreatic Carcinoma Model System. *Cell Cycle* **2010**, *9*, 3094–3101. [CrossRef]
104. Moffatt, K.A.; Johannes, W.U.; Miller, G.J. 1Alpha,25dihydroxyvitamin D3 and Platinum Drugs Act Synergistically to Inhibit the Growth of Prostate Cancer Cell Lines. *Clin. Cancer Res.* **1999**, *5*, 695–703. [PubMed]
105. Hierro, C.; Azaro, A.; Argilés, G.; Elez, E.; Gómez, P.; Carles, J.; Rodon, J. Unveiling Changes in the Landscape of Patient Populations in Cancer Early Drug Development. *Oncotarget* **2017**, *8*, 14158–14172. [CrossRef]
106. Wang, S.-K.; Yang, L.; Wang, T.-T.; Huang, G.-L.; Yang, L.-G.; Sun, G.-J. Inhibition of Proliferation and Induction of Apoptosis by the Combination of β-Carotene and 1,25-Dihydroxyvitamin D3 in Human Esophageal Cancer EC9706 Cells. *Asian Pac. J. Cancer Prev.* **2012**, *13*, 6327–6332. [CrossRef]
107. Ben-Eltriki, M.; Hassona, M.; Meckling, G.; Adomat, H.; Deb, S.; Tomlinson Guns, E.S. Pharmacokinetic Interaction of Calcitriol with 20(S)-Protopanaxadiol in Mice: Determined by LC/MS Analysis. *Eur. J. Pharm. Sci.* **2019**, *130*, 173–180. [CrossRef]
108. Ben-Eltriki, M.; Deb, S.; Adomat, H.; Tomlinson Guns, E.S. Calcitriol and 20(S)-Protopanaxadiol Synergistically Inhibit Growth and Induce Apoptosis in Human Prostate Cancer Cells. *J. Steroid Biochem. Mol. Biol.* **2016**, *158*, 207–219. [CrossRef]
109. Kweon, S.H.; Song, J.H.; Kim, H.J.; Kim, T.S.; Choi, B.G. Induction of Human Leukemia Cell Differentiation via PKC/MAPK Pathways by Arsantin, a Sesquiterpene Lactone from Artemisia Santolina. *Arch. Pharm. Res.* **2015**, *38*, 2020–2028. [CrossRef]

110. Kang, S.N.; Chung, S.W.; Kim, T.S. Capsaicin Potentiates 1,25-Dihydoxyvitamin D3- and All-Trans Retinoic Acid-Induced Differentiation of Human Promyelocytic Leukemia HL-60 Cells. *Eur. J. Pharmacol.* **2001**, *420*, 83–90. [CrossRef]
111. Steiner, M.; Priel, I.; Giat, J.; Levy, J.; Sharoni, Y.; Danilenko, M. Carnosic Acid Inhibits Proliferation and Augments Differentiation of Human Leukemic Cells Induced by 1,25-Dihydroxyvitamin D3 and Retinoic Acid. *Nutr. Cancer* **2001**, *41*, 135–144. [CrossRef]
112. Kim, S.H.; Kang, S.N.; Kim, H.J.; Kim, T.S. Potentiation of 1,25-Dihydroxyvitamin $D_3$-Induced Differentiation of Human Promyelocytic Leukemia Cells into Monocytes by Costunolide, a Germacranolide Sesquiterpene Lactone. *Biochem. Pharmacol.* **2002**, *64*, 1233–1242. [CrossRef]
113. Yamada, K.; Honma, Y.; Asahi, K.; Sassa, T.; Hino, K.; Tomoyasu, S. Differentiation of Human Acute Myeloid Leukaemia Cells in Primary Culture in Response to Cotylenin A, a Plant Growth Regulator. *Br. J. Haematol.* **2001**, *114*, 814–821. [CrossRef]
114. Liu, Y.; Chang, R.L.; Cui, X.X.; Newmark, H.L.; Conney, A.H. Synergistic Effects of Curcumin on All-Trans Retinoic Acid- and 1 Alpha,25-Dihydroxyvitamin D3-Induced Differentiation in Human Promyelocytic Leukemia HL-60 Cells. *Oncol. Res.* **1997**, *9*, 19–29.
115. Bartik, L.; Whitfield, G.K.; Kaczmarska, M.; Lowmiller, C.L.; Moffet, E.W.; Furmick, J.K.; Hernandez, Z.; Haussler, C.A.; Haussler, M.R.; Jurutka, P.W. Curcumin: A Novel Nutritionally Derived Ligand of the Vitamin D Receptor with Implications for Colon Cancer Chemoprevention. *J. Nutr. Biochem.* **2010**, *21*, 1153–1161. [CrossRef] [PubMed]
116. Porcaro, G.; Santamaria, A.; Giordano, D.; Angelozzi, P. Vitamin D plus Epigallocatechin Gallate: A Novel Promising Approach for Uterine Myomas. *Eur. Rev. Med. Pharmacol. Sci.* **2020**, *24*, 3344–3351. [CrossRef] [PubMed]
117. Oh, M.K.; Park, S.J.; Kim, N.H.; Cho, J.K.; Jin, J.Y.; Kim, I.S. Cooperative Induction of HL-60 Cell Differentiation by Combined Treatment with Eugenol and 1α,25-Dihydroxyvitamin $D_3$. *J. Life Sci.* **2007**, *17*, 1191–1196. [CrossRef]
118. Swami, S.; Krishnan, A.V.; Peehl, D.M.; Feldman, D. Genistein Potentiates the Growth Inhibitory Effects of 1,25-Dihydroxyvitamin D3 in DU145 Human Prostate Cancer Cells: Role of the Direct Inhibition of CYP24 Enzyme Activity. *Mol. Cell. Endocrinol.* **2005**, *241*, 49–61. [CrossRef]
119. Ben-Eltriki, M.A.M. Preclinical Evaluation of Vitamin D and Ginsenoside Metabolites in Combination for Prostate Cancer Therapy: Pharmacokinetic and Pharmacodynamic Interactions. Ph.D. Thesis, University of British Columbia, Vancouver, BC, Canada, 2018.
120. Ben-Eltriki, M.; Deb, S.; Guns, E.S.T. 1α,25-Dihydroxyvitamin D3 Synergistically Enhances Anticancer Effects of Ginsenoside Rh2 in Human Prostate Cancer Cells. *J. Steroid Biochem. Mol. Biol.* **2021**, *209*, 105828. [CrossRef]
121. Ben-Eltriki, M.; Deb, S.; Guns, E.S.T. Calcitriol in Combination Therapy for Prostate Cancer: Pharmacokinetic and Pharmacodynamic Interactions. *J. Cancer* **2016**, *7*, 391–407. [CrossRef]
122. Tobe, H. Biological Activities of Humulone. In *Beer in Health and Disease Prevention*; Elsevier: Amsterdam, The Netherlands, 2009; pp. 695–702.
123. Amir, H.; Karas, M.; Giat, J.; Danilenko, M.; Levy, R.; Yermiahu, T.; Levy, J.; Sharoni, Y. Lycopene and 1,25-Dihydroxyvitamin D3 Cooperate in the Inhibition of Cell Cycle Progression and Induction of Differentiation in HL-60 Leukemic Cells. *Nutr. Cancer* **1999**, *33*, 105–112. [CrossRef]
124. Yang, J.; Zhang, Q.; Huang, G.; Cong, J.; Wang, T.; Zhai, X.; Zhang, J.; Qi, G.; Zhou, L.; Jin, J. Combined Effects of Vitamin D and Neferine on the Progression and Metastasis of Colorectal Cancer. *J. Cancer Res. Clin. Oncol.* **2023**, *149*, 6203–6210. [CrossRef]
125. Kang, S.N.; Kim, S.H.; Chung, S.W.; Lee, M.H.; Kim, H.J.; Kim, T.S. Enhancement of 1 Alpha,25-Dihydroxyvitamin $D_3$-Induced Differentiation of Human Leukaemia HL-60 Cells into Monocytes by Parthenolide via Inhibition of NF-Kappa B Activity. *Br. J. Pharmacol.* **2002**, *135*, 1235–1244. [CrossRef]
126. Sannappa Gowda, N.G.; Shiragannavar, V.D.; Puttahanumantharayappa, L.D.; Shivakumar, A.T.; Dallavalasa, S.; Basavaraju, C.G.; Bhat, S.S.; Prasad, S.K.; Vamadevaiah, R.M.; Madhunapantula, S.V.; et al. Quercetin Activates Vitamin D Receptor and Ameliorates Breast Cancer Induced Hepatic Inflammation and Fibrosis. *Front. Nutr.* **2023**, *10*, 1158633. [CrossRef] [PubMed]
127. Maj, E.; Maj, B.; Bobak, K.; Gos, M.; Chodyński, M.; Kutner, A.; Wietrzyk, J. Differential Response of Lung Cancer Cells, with Various Driver Mutations, to Plant Polyphenol Resveratrol and Vitamin D Active Metabolite PRI-2191. *Int. J. Mol. Sci.* **2021**, *22*, 2354. [CrossRef] [PubMed]
128. Dampf Stone, A.; Batie, S.F.; Sabir, M.S.; Jacobs, E.T.; Lee, J.H.; Whitfield, G.K.; Haussler, M.R.; Jurutka, P.W. Resveratrol Potentiates Vitamin D and Nuclear Receptor Signaling. *J. Cell. Biochem.* **2015**, *116*, 1130–1143. [CrossRef] [PubMed]
129. Bhatia, V.; Falzon, M. Restoration of the Anti-Proliferative and Anti-Migratory Effects of 1,25-Dihydroxyvitamin D by Silibinin in Vitamin D-Resistant Colon Cancer Cells. *Cancer Lett.* **2015**, *362*, 199–207. [CrossRef]
130. Wassermann, R.; Novik, V.; Danilenko, M. Cell-Type-Specific Effects of Silibinin on Vitamin D-Induced Differentiation of Acute Myeloid Leukemia Cells Are Associated with Differential Modulation of RXRα Levels. *Leuk. Res. Treat.* **2012**, *2012*, 401784. [CrossRef]
131. Li, J.; Frederick, A.-L.M.; Jin, Y.; Guo, C.; Xiao, H.; Wood, R.J.; Liu, Z. 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*, e1800824. [CrossRef]

132. Tuttis, K.; Machado, A.R.T.; Santos, P.W.d.S.; Antunes, L.M.G. Sulforaphane Combined with Vitamin D Induces Cytotoxicity Mediated by Oxidative Stress, DNA Damage, Autophagy, and JNK/MAPK Pathway Modulation in Human Prostate Tumor Cells. *Nutrients* **2023**, *15*, 2742. [CrossRef]
133. Idris, S.; Refaat, B.; Almaimani, R.A.; Ahmed, H.G.; Ahmad, J.; Alhadrami, M.; El-Readi, M.Z.; Elzubier, M.E.; Alaufi, H.A.A.; Al-Amin, B.; et al. Enhanced in Vitro Tumoricidal Effects of 5-Fluorouracil, Thymoquinone, and Active Vitamin D3 Triple Therapy against Colon Cancer Cells by Attenuating the PI3K/AKT/MTOR Pathway. *Life Sci.* **2022**, *296*, 120442. [CrossRef]
134. Kim, S.H.; Kim, T.S. Synergistic Induction of 1,25-Dihydroxyvitamin $D_3$- and All-*Trans*-Retinoic Acid-Induced Differentiation of HL-60 Leukemia Cells by Yomogin, a Sesquiterpene Lactone from *Artemisia princeps*. *Planta Med.* **2002**, *68*, 886–890. [CrossRef] [PubMed]
135. Aydın, Ö.K.; Baysan, U.; Altay, Ö.; Baysan, I.İ.; Ertekin, F.K.; Jafari, S.M. Vitamin Delivery Systems by Spray-Drying Encapsulation within Plant Protein-Based Carriers: A Review. *Food Biosci.* **2023**, *56*, 103341. [CrossRef]
136. Holick, M.F. Vitamin D: Its Role in Cancer Prevention and Treatment. *Prog. Biophys. Mol. Biol.* **2006**, *92*, 49–59. [CrossRef] [PubMed]
137. Pandolfi, F.; Franza, L.; Mandolini, C.; Conti, P. Immune Modulation by Vitamin D: Special Emphasis on Its Role in Prevention and Treatment of Cancer. *Clin. Ther.* **2017**, *39*, 884–893. [CrossRef]
138. Ramalho, M.J.; Loureiro, J.A.; Gomes, B.; Frasco, M.F.; Coelho, M.A.N.; Pereira, M.C. PLGA Nanoparticles as a Platform for Vitamin D-Based Cancer Therapy. *Beilstein J. Nanotechnol.* **2015**, *6*, 1306–1318. [CrossRef]
139. Sahota, O. Understanding Vitamin D Deficiency. *Age Ageing* **2014**, *43*, 589–591. [CrossRef]
140. Jakobsen, J.; Knuthsen, P. Stability of Vitamin D in Foodstuffs during Cooking. *Food Chem.* **2014**, *148*, 170–175. [CrossRef]
141. Villamayor, N.; Villaseñor, M.J.; Ríos, Á. Selective Dual Sensing Strategy for Free and Vitamin D3 Micelles in Food Samples Based on S,N-GQDs Photoinduced Electron Transfer. *Anal. Bioanal. Chem.* **2024**, *416*, 4173–4191. [CrossRef]
142. Hussain, M.; Xu, J.; Ahmad, I.; Hussain, K.; Qayum, A.; Xiaoqin, L.; Zhong, H.; Guan, R. Efficacy of Nano-Based Strategies on the Safe Delivery and Bioavailability of Vitamin D: Review. *Food Rev. Int.* **2024**, *40*, 1581–1599. [CrossRef]
143. Bashir, I.; Wani, S.M.; Bhat, A.A.; Khan, A.A.; Hussain, S.Z.; Ganai, S.A.; Anjum, N. Effect of Freeze Drying and Spray Drying on Physical Properties, Morphology and in Vitro Release Kinetics of Vitamin D3 Nanoparticles. *Powder Technol.* **2024**, *432*, 119164. [CrossRef]
144. Maurya, V.K.; Bashir, K.; Aggarwal, M. Vitamin D Microencapsulation and Fortification: Trends and Technologies. *J. Steroid Biochem. Mol. Biol.* **2020**, *196*, 105489. [CrossRef] [PubMed]
145. Nowacka, A.; Śniegocki, M.; Bożiłow, D.; Ziółkowska, E.A. CYP24A1 in Small Intestinal Vitamin D Metabolism and Clinical Implications. *Nutrients* **2025**, *17*, 3348. [CrossRef] [PubMed]
146. Park, S.J.; Garcia, C.V.; Shin, G.H.; Kim, J.T. Development of Nanostructured Lipid Carriers for the Encapsulation and Controlled Release of Vitamin D3. *Food Chem.* **2017**, *225*, 213–219. [CrossRef] [PubMed]
147. Jannasari, N.; Fathi, M.; Moshtaghian, S.J.; Abbaspourrad, A. Microencapsulation of Vitamin D Using Gelatin and Cress Seed Mucilage: Production, Characterization and in Vivo Study. *Int. J. Biol. Macromol.* **2019**, *129*, 972–979. [CrossRef]
148. Lamsen, M.R.L.; Wang, T.; D'Souza, D.; Dia, V.; Chen, G.; Zhong, Q. Encapsulation of Vitamin $D_3$ in Gum Arabic to Enhance Bioavailability and Stability for Beverage Applications. *J. Food Sci.* **2020**, *85*, 2368–2379. [CrossRef]
149. Bashir, I.; Wani, S.M.; Jan, N.; Ali, A.; Rouf, A.; Sidiq, H.; Masood, S.; Mustafa, S. Optimizing Ultrasonic Parameters for Development of Vitamin D3-Loaded Gum Arabic Nanoemulsions—An Approach for Vitamin D3 Fortification. *Int. J. Biol. Macromol.* **2024**, *278*, 134894. [CrossRef]
150. Shah, B.R.; Xu, W.; Mráz, J. Formulation and Characterization of Zein/Chitosan Complex Particles Stabilized Pickering Emulsion with the Encapsulation and Delivery of Vitamin $D_3$. *J. Sci. Food Agric.* **2021**, *101*, 5419–5428. [CrossRef]
151. Walia, N.; Zhang, S.; Wismer, W.; Chen, L. A Low Energy Approach to Develop Nanoemulsion by Combining Pea Protein and Tween 80 and Its Application for Vitamin D Delivery. *Food Hydrocoll. Health* **2022**, *2*, 100078. [CrossRef]
152. Liu, C.; Shaurova, T.; Shoemaker, S.; Petkovich, M.; Hershberger, P.A.; Wu, Y. Tumor-Targeted Nanoparticles Deliver a Vitamin D-Based Drug Payload for the Treatment of EGFR Tyrosine Kinase Inhibitor-Resistant Lung Cancer. *Mol. Pharm.* **2018**, *15*, 3216–3226. [CrossRef]
153. Maleklou, N.; Allameh, A.; Kazemi, B. Targeted Delivery of Vitamin D3-Loaded Nanoparticles to C6 Glioma Cell Line Increased Resistance to Doxorubicin, Epirubicin, and Docetaxel in Vitro. *In Vitro Cell. Dev. Biol. Anim.* **2016**, *52*, 989–1000. [CrossRef]
154. Feldman, D.; Krishnan, A.V.; Swami, S.; Giovannucci, E.; Feldman, B.J. The Role of Vitamin D in Reducing Cancer Risk and Progression. *Nat. Rev. Cancer* **2014**, *14*, 342–357. [CrossRef] [PubMed]
155. Bingol Ozakpinar, O.; Dastan, H.; Gurboga, M.; Sayin, F.S.; Ozsavci, D.; Caliskan Salihi, E. Carbon Nanofiber-Sodium Alginate Composite Aerogels Loaded with Vitamin D: The Cytotoxic and Apoptotic Effects on Colon Cancer Cells. *Gels* **2023**, *9*, 561. [CrossRef] [PubMed]

156. Agwa, M.M.; Abu-Serie, M.M.; Abdelmonsif, D.A.; Moussa, N.; Elsayed, H.; Khattab, S.N.; Sabra, S. Vitamin D3/Phospholipid Complex Decorated Caseinate Nanomicelles for Targeted Delivery of Synergistic Combination Therapy in Breast Cancer. *Int. J. Pharm.* **2021**, *607*, 120965. [CrossRef]
157. Peixoto, D.; Ravasco, J.M.; Blanco-Fernandez, B.; Veiga, F.; Concheiro, A.; Conde, J.; Paiva-Santos, A.C.; Alvarez-Lorenzo, C. Enzyme-Responsive Vitamin D-Based Micelles for Paclitaxel-Controlled Delivery and Synergistic Pancreatic Cancer Therapy. *Mater. Today Bio* **2025**, *31*, 101555. [CrossRef] [PubMed]
158. Bahrami, A.; Farasat, A.; Zolghadr, L.; Sabaghi, Y.; Gheibi, N. Vitamin D and Inhibition of Melanogenesis: Examination of Liposomal Vitamin D Nanocarrier Anti-Melanogenesis Activity on B16 F10 Cell Line. *Food Sci. Nutr.* **2025**, *13*, e70302. [CrossRef]
159. Landi, C.; Landucci, E.; Mazzantini, C.; Castellacci, R.; Bergonzi, M.C. Vitamin D Nanoliposomes to Improve Solubility, Stability, and Uptake Across Intestinal Barrier. *Pharmaceutics* **2025**, *17*, 1244. [CrossRef]
160. Li, Y.; Liu, R.; Ji, Z.; Gao, L.; Wang, X.; Zhang, J.; Hu, L.; Qu, Y.; Bai, J.; Wu, D.; et al. Predicting Lymphatic Transport Potential Using Graph Transformer Based on Limited Historical Data from in Vivo Studies. *J. Control. Release* **2025**, *384*, 113847. [CrossRef]
161. Dahan, A.; Hoffman, A. Use of a Dynamic in Vitro Lipolysis Model to Rationalize Oral Formulation Development for Poor Water Soluble Drugs: Correlation with in Vivo Data and the Relationship to Intra-Enterocyte Processes in Rats. *Pharm. Res.* **2006**, *23*, 2165–2174. [CrossRef]
162. Li, J.; Luco, A.-L.; Camirand, A.; St-Arnaud, R.; Kremer, R. Vitamin D Regulates CXCL12/CXCR4 and Epithelial-to-Mesenchymal Transition in a Model of Breast Cancer Metastasis to Lung. *Endocrinology* **2021**, *162*, bqab049. [CrossRef]
163. Bajalia, E.M.; Azzouz, F.B.; Chism, D.A.; Giansiracusa, D.M.; Wong, C.G.; Plaskett, K.N.; Bishayee, A. Phytochemicals for the Prevention and Treatment of Renal Cell Carcinoma: Preclinical and Clinical Evidence and Molecular Mechanisms. *Cancers* **2022**, *14*, 3278. [CrossRef] [PubMed]
164. Imam, S.S.; Alshehri, S.; Ghoneim, M.M.; Zafar, A.; Alsaidan, O.A.; Alruwaili, N.K.; Gilani, S.J.; Rizwanullah, M. Recent Advancement in Chitosan-Based Nanoparticles for Improved Oral Bioavailability and Bioactivity of Phytochemicals: Challenges and Perspectives. *Polymers* **2021**, *13*, 4036. [CrossRef] [PubMed]
165. Tchuenbou-Magaia, F.L.; Tolve, R.; Anyadike, U.; Giarola, M.; Favati, F. Co-Encapsulation of Vitamin D and Rutin in Chitosan-Zein Microparticles. *J. Food Meas. Charact.* **2022**, *16*, 2060–2070. [CrossRef]
166. Debotton, N.; Dahan, A. Applications of Polymers as Pharmaceutical Excipients in Solid Oral Dosage Forms. *Med. Res. Rev.* **2017**, *37*, 52–97. [CrossRef]
167. Chaves, M.A.; Baldino, L.; Pinho, S.C.; Reverchon, E. Co-Encapsulation of Curcumin and Vitamin D3 in Mixed Phospholipid Nanoliposomes Using a Continuous Supercritical $CO_2$ Assisted Process. *J. Taiwan Inst. Chem. Eng.* **2022**, *132*, 104120. [CrossRef]
168. Marques, M.; Gonçalves, R.F.S.; Madalena, D.A.; Abrunhosa, L.; Vicente, A.A.; Pinheiro, A.C. Co-Encapsulation of Vitamin $D_3$ and Curcumin in Plant Protein-Based Nanoemulsions: Formulation Optimization, Characterization, and in Vitro Digestion. *Sustain. Food Technol.* **2025**, *3*, 2204–2214. [CrossRef]
169. Denkova-Kostova, R.; Teneva, D.; Tomova, T.; Goranov, B.; Denkova, Z.; Shopska, V.; Slavchev, A.; Hristova-Ivanova, Y. Chemical Composition, Antioxidant and Antimicrobial Activity of Essential Oils from Tangerine (*Citrus reticulata* L.), Grapefruit (*Citrus paradisi* L.), Lemon (*Citrus lemon* L.) and Cinnamon (*Cinnamomum zeylanicum* Blume). *Z. Naturforschung C* **2021**, *76*, 175–185. [CrossRef]
170. Meghani, N.; Patel, P.; Kansara, K.; Ranjan, S.; Dasgupta, N.; Ramalingam, C.; Kumar, A. Formulation of Vitamin D Encapsulated Cinnamon Oil Nanoemulsion: Its Potential Anti-Cancerous Activity in Human Alveolar Carcinoma Cells. *Colloids Surf. B Biointerfaces* **2018**, *166*, 349–357. [CrossRef]
171. Steinbauer, S.; Wallner, M.; Karl, L.-M.; Gramatte, T.; Essl, K.; Iken, M.; Weghuber, J.; Blank-Landeshammer, B.; Röhrl, C. Differential Enhancement of Fat-Soluble Vitamin Absorption and Bioefficacy via Micellization in Combination with Selected Plant Extracts In Vitro. *Nutrients* **2025**, *17*, 359. [CrossRef]
172. Sarwareddy, K.K.; Singh, A.D.; Patnam, S.; Sesuraj, B.A.; Ponamgi, S.; Thakur, B.K.; Manda, V.S. Harnessing Tomato-Derived Small Extracellular Vesicles as Drug Delivery System for Cancer Therapy. *Future Sci. OA* **2025**, *11*, 2461956. [CrossRef]
173. Naravejsakul, K.; Cholamjiak, W.; Yajai, W.; Inpun, J.; Waratamrongpatai, W. Development of a Machine Learning-Based Predictive Model for Urinary Tract Infection Risk in Patients with Vitamin D Deficiency: A Multidimensional Clinical Data Analysis. *BioMedInformatics* **2025**, *5*, 57. [CrossRef]


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