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Review Article

Role of natural products in tumor therapy from basic research and clinical perspectives

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ABSTRACT

Cancer is the leading cause of morbidity and mortality worldwide and is an important barrier to lengthening life expectancy in every country. Natural products are receiving increased attention from researchers globally and increasing numbers of natural products are approved for clinical studies involving cancer in recent years. To gain more insight into natural products that have undergone clinical trials for cancer treatment, a comprehensive search was conducted. The https://clinicaltrials.gov website was searched for relevant clinical trials and natural product information up to December 2022. The search terms included different types of cancers, such as colorectal, lung, breast, gynecologic, kidney, bladder, melanoma, pancreatic, hepatocellular, gastric and haematologic. Then, PubMed and Web of Science were searched for relevant articles up to February 2024. Hence, we listed existing clinical trials about natural products used in the treatment of cancers and discussed the preclinical and clinical studies of some promising natural products and their targets, indications, and underlying mechanisms of action. Our intent was to provide basic information to readers who are interested or majoring in natural products and obtain a deeper understanding of the progress and actions of natural product mechanisms of action.

Keywords: Natural products, cancer, clinical trial

1. INTRODUCTION

Cancer is a major public health problem worldwide. According to an estimate from the World Health Organization (WHO) in 2019, cancer ranks as the first or second leading cause of death in many countries [1]. In the past few decades, significant advances have been made in the treatment of cancer, such as surgical resection, chemotherapy, radiotherapy, immunotherapy, biotherapy, and molecular-targeted therapy [2]. However, current treatments are still not achieving the expected optimal outcomes. In recent years numerous natural products have been approved by the United States (US) Food and Drug Administration (FDA) for cancer treatment. Natural products refer to the compounds extracted and/or optimized from nature and have a wide range of sources, including plants, animals, marine organisms, and microorganisms. Natural products play an important role and have an irreplaceable status in drug development and design. Notably, there are > 10,000 species of Chinese materia medica with a one thousand year-long history of clinical use with a strong theoretical basis in Chinese Medicine. In the clinical setting Chinese medicine is sometimes used to treat cancer with an unexpected good curative effect but the results are difficult to explain and repeat. As such, the identification of the active ingredients in these Chinese materials not only contribute to the research and promotion of Chinese medicine but is also an important component of drug research in China. In contrast, natural products are an important source of dietary supplements and this industry is growing very rapidly, with annual sales now in the multi-billions of dollars [3]. In the US nearly one-half of patients begin taking new dietary supplements when they are diagnosed with cancer [4]. Although these dietary supplements are marketed and used by

patients with cancer, dietary supplements have not been approved by the US FDA for preventing cancer, stopping cancer growth, or preventing cancer recurrence. Dietary supplements may help to improve health but may also be ineffective or risky. In the future the ongoing research involving natural products will facilitate the accumulation of substantial evidence to support the use of dietary supplements. Indeed, in recent years many natural products have been extensively investigated to cure different types of cancer (Figure 1). However, few studies have systematically collated and analyzed clinical trial results with respect to the use of natural products for the treatment of cancer. In this paper we comprehensively collected and summarized existing clinical trial data about natural products used in the treatment of cancer and discussed the preclinical and clinical studies of some promising natural products, the targets, indications for use, and detailed mechanisms of action (Figure 2). This review is intended to provide basic information to readers who are interested or majoring in natural products and obtain a deeper understanding of the progress and mechanisms of actions underlying natural products.

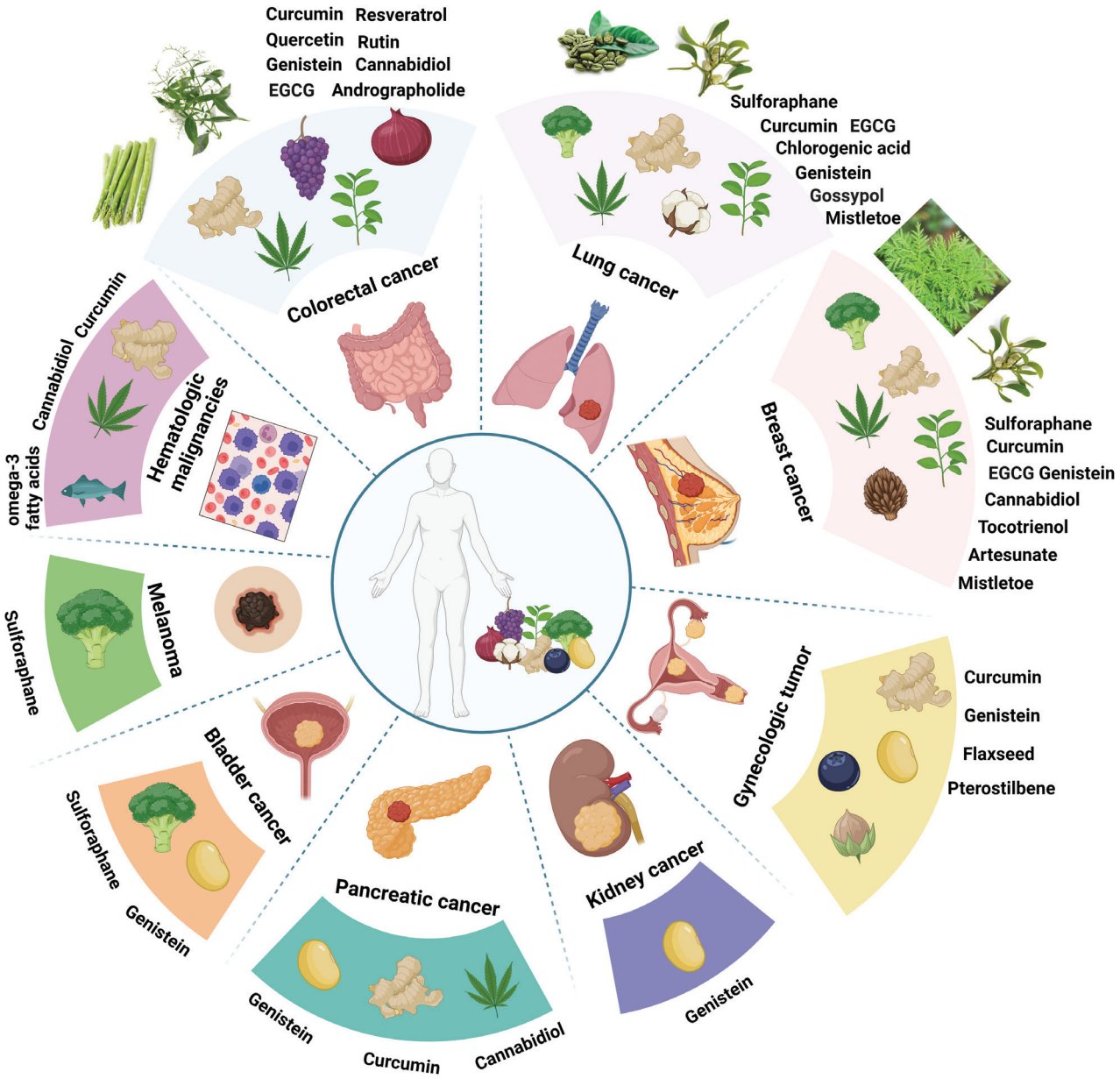

Figure 1 | Schematic representation of the typical natural products in different types of cancers. This figure is created with BioRender.com.

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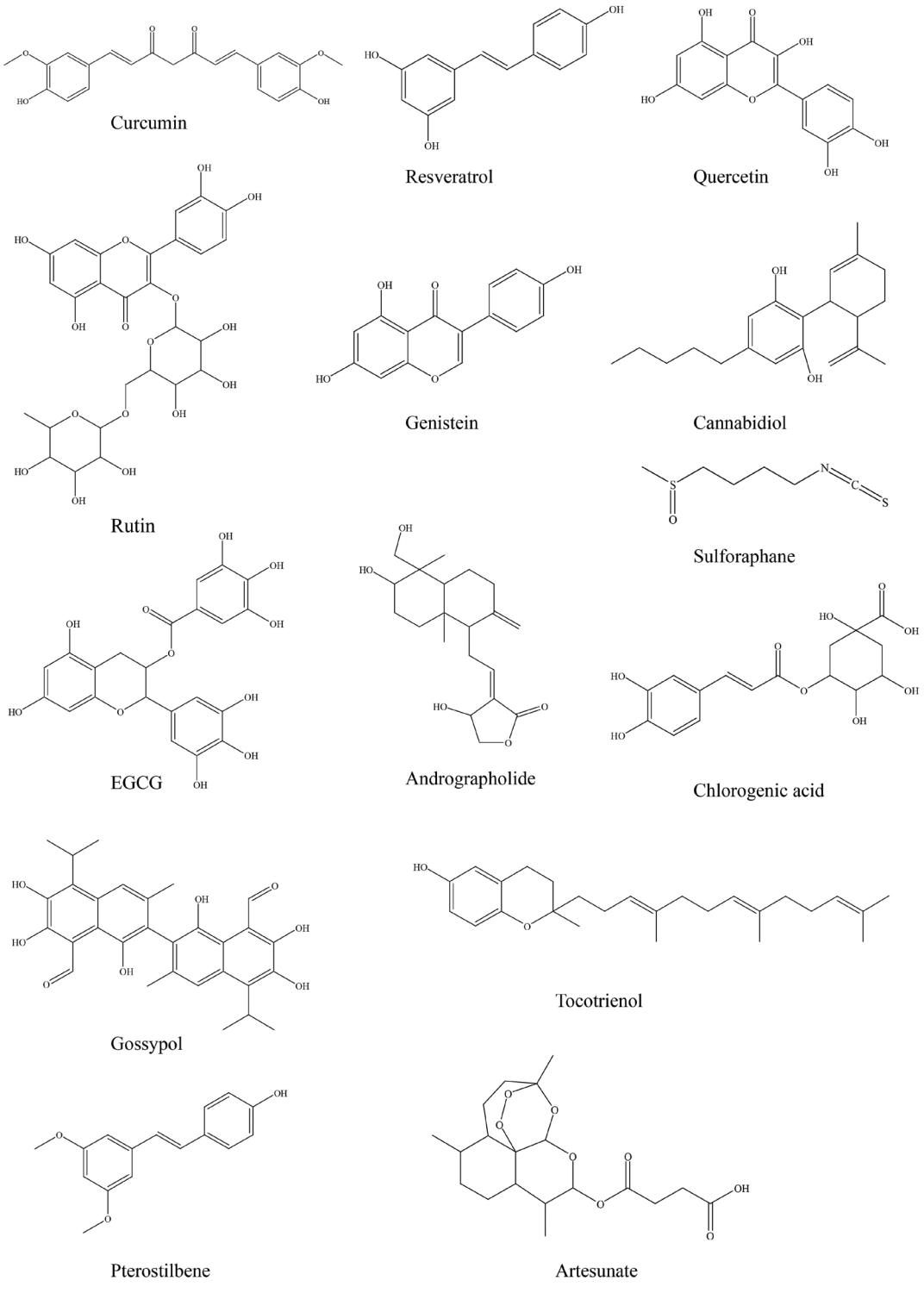

Figure 2 | The chemical structure of typical natural products.

2. COLORECTAL CANCER

Colorectal cancer (CRC) is the second most significant cause of cancer-related mortality worldwide [5, 6]. Currently, surgical resection, chemotherapy, and adjuvant therapy are common treatment strategies for CRC. Nevertheless, side effects, such as cytotoxicity and resistance, limit utilization of these treatment modalities. There is a clear need to develop new drugs and/or new therapeutic combinations for CRC patients. **Table 1** lists the preclinical studies involving natural products and their derivatives in the context of CRC. **Table 2** further clarifies the clinical trials involving natural products in different types of cancers.

2.1 Curcumin

Curcumin is a natural polyphenolic compound isolated from *Curcuma longa* L. Ginger plant has been widely used clinically in Chinese medicine for many years. In recent years, numerous studies have demonstrated the potential of curcumin to modulate the development and progression of several cancers, including CRC. A prospective, observational, single-group analysis showed that curcumin in combination with bevacizumab/folinic acid, fluorouracil (5-FU), and irinotecan (FOLFIRI)in patients with CRC had comparable long-term survival outcomes with acceptable toxicity outcomes (NCT02439385) [7]. Another double-group phase IIa trial showed that curcumin combined with folinic acid, 5-FU, and oxaliplatin (FOLFOX)) chemotherapy exhibited a longer overall survival (OS) than the FOLFOX alone group (NCT01490996) [8]. However, in patients with colorectal adenomas undergoing surgery, the administration of a combination of curcumin and anthocyanin did not directly modulate inflammatory and metabolic biomarkers [9]. In CRC cell and animal studies, curcumin was shown to activate the ROS/KEAP1/NRF2/miR-34a/b/c cascade, thereby suppressing epithelial-mesenchymal transition (EMT) and metastasis, and inducing apoptosis and senescence [10]. The curcumin analog, DMC-BH, has also shown promising anti-tumor effects via inactivation of the PI3K/AKT/mTOR signaling pathway [11]. The synergistic anti-tumor effects of curcumin have also attracted much attention. For example, curcumin enhanced the therapeutic efficacy of radiotherapy and augmented the radiotherapy-induced abscopal effect in mice with CRC by acting as an immunomodulator [12]. Similarly, the combination of curcumin and luteolin synergistically inhibited colon cancer by reducing the Notch1 and TGF-β signaling pathways [13]. Remarkably, a low concentration of curcumin potentiated the anti-cancer effect of 5-FU against CRC, which inhibited p-ERK, STAT1, and L1 expression [14]. Curcuminoid WZ26 augments the anti-cancer effect of cisplatin by regulating the TrxR1/ROS/JNK pathway [15]. These results further indicated that curcumin is a promising compound for the treatment of CRC. However, the use of curcumin in the pharmaceutical field has been hindered due to its bioavailability and stability. Therefore, it is essential to explore better curcumin derivatives or new dosage forms.

2.2 Resveratrol

Resveratrol is a non-flavonoid polyphenol that is widely distributed in the leaves and skins of grapes. Resveratrol has been marketed as a dietary supplement and commonly used to treat high cholesterol, cancer, and heart disease but there is no substantial scientific evidence to support these application. Of importance, the mechanism underlying the resveratrol effect in cancer prevention and management has garnered increasing attention [16]. Brockmueller et al. [17] verified that higher resveratrol concentrations *in vitro* boosts CRC cell apoptosis by mediating a negative regulatory loop between p53 and Sirt-1. To overcome the low bioavailability of resveratrol, researchers have conducted related studies on resveratrol analogues. For example, resveratrol derivatives (CS and DMU-281) exert a marked anti-cancer activity on CRC cells, effectively inducing apoptosis and cell cycle arrest [18, 19]. Similarly, the 3-β-D-glucoside of trans-resveratrol exerts anti-proliferative and pro-apoptotic effects on CRC cells by regulating modulation of the tumor microenvironment [20]. Additionally, Lin et al. [21] reported that oxyresveratrol inhibits CRC cell migration by regulating EMT and microRNA (miRNAs). Resveratrol also has an important role in overcoming drug resistance in CRC. For example, resveratrol increases the chemosensitivity of CRC cells to 5-FU by targeting the β1-integrin/HIF-1α axis [22]. Moreover, resveratrol inhibits drug-related metabolic enzyme (CYP3A4 and glutathione-S-transferase [GST]) activity [23]. Previously, we reported that PD-1/PD-L1 interaction blockade is an effective cancer immunotherapy [24-27] but the response rate of patients to anti-PD-1/PD-L1 immunotherapy may be affected by PD-L1 expression. Thus, identifying drugs that modulate PD-L1 expression is warranted. Notably, Lucas et al. [28] showed that resveratrol plus piceatannol upregulated the expression of PD-L1 in CRC cells. These results indicated that resveratrol may be a potential compound in cancer immunotherapy that may expand indications and enhance the efficiency of cancer vaccines.

2.3 Quercetin

Quercetin is a natural flavonoid molecule frequently found in fruits and vegetables (e.g., onions). Quercetin is also marketed as a dietary supplement used for heart and blood vessels, cancer, arthritis, bladder infections and diabetes but there is a lack of scientific evidence to support most of these uses. A randomized clinical trial is underway to assess the efficacy of sulindac, curcumin, rutin, and quercetin in preventing colon cancer but the results have not been announced (NCT00003365). Mechanistic studies showed that quercetin inhibits the migration and invasion of colon cancer cells by regulating the JNK signaling pathway [29]. Fosso et al. [30]

Table 1 | Preclinical studies of natural products and their derivatives in colorectal cancer.

Compounds	Source	Experiments		Effects and mechanisms	Ref.
		In vivo	*In vitro*		
Curcumin	*Curcuma longa* L.	Xenograft NOD/SCID mice model for SW620-Luc2	HCT116, RKO, SW48, CCD18Co, SW620-Luc2	ROS↑, KEAP1↑, NRF2↑, ARE↑, miR-34a/b/c↑, apoptosis↑, senescence↑; EMT↓, metastasis↓	[10]
		Xenograft BALB/c nude mice for CT26	CT26	BAX↑, cleaved caspase 3↑, granzyme B↑, IL-6↑, IL-1β↑; NF-κB↓, PD-L1↓; immunomodulation	[12]
		Xenograft BALB/c nude mice for CL-188	CL-188, DLD-1	Tumor necrosis↑; Notch1↓, TGF-β↓, proliferation↓, metastasis↓	[13]
		Xenograft nude mice for SW620	SW620	Apoptosis↑; proliferation↓, p-ERK↓, STAT1↓, L1↓; enhancing the anti-cancer effect of 5-FU	[14]
Analogue DMC-BH		Xenograft nude mice for HCT116 and HT-29	HCT116, HT29	Apoptosis↑; PI3K↓, AKT↓, mTOR↓; proliferation↓, invasion↓	[11]
Analogue WZ26		Xenograft BALB/c nude mice for HCT116	HCT116, RKO	ROS↑, JNK↑, DNA damage↑, cisplatin-induced cell death↑; TrxR1↓	[15]
Resveratrol	Grapes, peanuts, blueberries, and *Reynoutria japonica*	(-)	HCT116 WT, HCT116 $p53^{-/-}$, MRC-5	p53↑, p21↑, BAX↑, cytochrome C↑, cleaved caspase 3↑, apoptosis↑; Sirt-1↓	[17]
		(-)	HCT116, 5-FU-resistant HCT116R, MRC-5	Caspase 3↑, chemosensitisation to 5-FU↑; β1-integrin receptors↓, NF-κB↓, VEGF↓, HIF-1α↓, CD44↓, CD133↓, ALDH1↓	[22]
		(-)	Caco2, CEM/ADR5000	caspase 3/8/6/9↑; P-gp↓, MRP1↓, BCRP↓, CYP3A4↓, GST↓, hPXR↓	[23]
Analogue DMU-218		(-)	DLD-1, LOVO	Caspase 3, Smac/Diablo, Fadd, Hsp60↑; Hsp27, Bcl-2, Bcl-xL↓; inducing cell cycle arrest and apoptosis	[19]
Analogue CS		(-)	HCT116, CCD-112	p53↑, p21↑, Fas death receptor↑, FADD↑, caspase 3/8/9↑, cleaved PARP↑, cell cycle arrest↑, apoptosis↑	[18]
Oxyresveratrol		(-)	HT29, HCT116	miR-3612↑, E-cadherin↑; snail↓, miR-3687↓, miR-301a-3p↓, migration↓	[21]
3-β-D-glucoside of trans-resveratrol		(-)	HT29, SW480, Caco2, HUVEC	IL-10↓, IL-8↓, E-selectin↓, VCAM-1↓, producing anti-proliferative and pro-apoptotic effects	[20]
Quercetin	Onions, asparagus, red leaf lettuce, and *Ginkgo biloba* L.	Xenograft BALB/c nude mice for RKO	RKO, SW480, HCT116	E-cadherin↑, p38↑, p-JNK↑, p-ERK↑; N-cadherin↓, vimentin↓	[29]
		(-)	HCT116, HT29	Sprouty2↑, PTEN↑, SFRP1↑, ZBTB10↑; Sp1↓, miR-27a↓, miR-23a↓, miR- 24-2↓	[30]
		DMH-exposed Wistar rats	(-)	BAX↑, PARP↑, APC↑; Bcl-2↓, β-catenin↓	[31]
		$APC^{Min/+}$ mice	(-)	Wnt/β-catenin pathway inhibition	[32]

Table 1 | Continued

Compounds	Source	Experiments		Effects and mechanisms	Ref.
		In vivo	*In vitro*		
		(-)	HT29	ESR2↑, GPR30 genes↑; inducing cell cycle arrest in the G0/G1 phase, inhibiting BPA-exposed HT29 cells viability	[33]
		Xenograft BALB/c nude mice for HCT116	HCT116	Oxaliplatin-induced ROS production↑, oxaliplatin-mediated proliferation suppression↑; GSH↓	[34]
		(-)	COLO 320, MCF7, 3T3-L1	Caspase 3↑, cell death↑, mitochondrial depolarization↑; controlling the growth of cells, arresting cell cycle	[35]
Rutin	Hedyotis diffusa Wild	(-)	HT29	BAX↑, p53↑, caspases 3/8/9↑, MAPK↑; NF-κB↓, IKK-α↓, IKK-β↓	[36]
Genistein	Soy	(-)	HT29, SW620	H_2O_2↑, oxidative stress↑, inflammation↑; cell viability↓	[39]
Cannabidiol	*Cannabis sativa* L.	Xenograft C57BL/6 mice for MC38	MC38	M1-like macrophages↑; M2-like macrophages↓, PI3K/AKT signaling↓	[43]
		(-)	HT29, SW480, HCT116, HCT15	Cleaved caspase 3↑, BAX↑, p-p53↑, ATF4↑, CHOP↑, endoplasmic reticulum stress↑, Atg7↑, p-Beclin-1↑, LC3-II↑, p- JNK↑, p-p38↑, p-ERK↑; Bcl-xL↓, IAP-1↓, survivin↓, Alix↓	[44]
		Xenograft SCID mice for HCT116 p53wt and HCT116 $p53^{-/-}$	HCT116 p53wt, LS174T p53wt), HCT116 $p53^{-/-}$, SW480 p53mut	ROS↑, cleaved PARP1↑, p21↑; CDK2↓; inducing autophagy, Hsp70 and KEAP1-NRF2 signaling pathway	[45]
		(-)	LoVo, SW480	MTs↑, MT2A↑	[46]
		(-)	HCT116, SW480, SW620, Caco2, CCD18CO	cleavage PARP↑, BiP↑, IRE1α↑, eIF2α↑, ATF3↑, ATF4↑, cell arrest↑, apoptosis↑, endoplasmic reticulum stress↑; cyclin D1↓, cyclin D3↓, CDK2↓, CDK4↓, CDK6↓; cell viability↓	[47]
EGCG	Tea	Xenograft BALB/c nude mice for SW480; azoxymethane-induced and dextran sulfate sodium-promoted mouse model	HCT116, SW480, HCT15, HT29, LoVo, Caco2, HEK293	ESE-1↑	[53]
		(-)	HCT116, RKO, SW620, HEK293T	YAP↑, CTGF↑, CYR61↑, ABCB1↑, ABCC1↑, vimentin↑, Slug↑; LATS1/2↓, p-LATS1/2↓; the activation of YAP promoted proliferation, EMT and drug exportation transporters	[55]
		(-)	HT29, SW480, HCT15, HCT116, Caco2	NOX1↓, MMP-2↓, MMP-9↓; inhibiting the activation of the EGFR and downstream of NF-κB, AKT, and ERK1/2	[54]
		(-)	CT-26	Plasminogen↑; tetranectin↓; proliferation↓	[51]

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Table 1 | Continued

Compounds	Source	Experiments		Effects and mechanisms	Ref.
		In vivo	*In vitro*		
Andrographolide	*Andrographis paniculata*	Xenograft nude mice for HCT116/5-FUR	HCT116, HCT116/5-FUR	BAX↑, PARP↑, caspase 3↑	[62]
		Xenograft BALB/c mice for CT26	CT26	IFN-γ↑, FasL↑, perforin↑, Granzyme B↑; COX2↓, PGE2↓;	[63]
		(-)	HT29, HCT15, HCT116	IRE-1↑, PERK↑, ATF6↑; VEGFR1↓, FoxM1↓, PTTG1↓;	[60]
		Xenograft 002019-NU/J nude mice for HT29	HT29, HCT15, HCT116	ROS↑; β-catenin↓, cyclin D1↓, c-Myc↓, TCF4↓, LGR5↓, LEF1↓, Axin-1↓, mitochondrial membrane potential↓, ATP level↓	[61]
Analogue AGS-30		Xenograft nude mice for HT29	HT29, HCT116,	ROS↑, p-JNK1/2↑, cleaved caspase 3/9↑, cleaved PARP↑	[57]
		Transgenic zebrafish model, rat aortic ring model, mouse Matrigel plug model, and xenograft nude mice for HT29	HT29, HUVECs	VEGF↓, p-ERK1/2↓, p-AKT↓, p-VEGFR2↓, p-mTOR↓, p-MEK1/2↓, p-p38↓, inhibiting blood vessel formation, AKT/mTOR and ERK-dependent pathways, as well as VEGF signaling	[59]

further found that quercetin exhibits anti-proliferative and pro-apoptotic effects by counteracting the Sp1-miR-27a axis in CRC cells. It is known that 1,2-dimethyl hydrazine (DMH) is a cogent environmental toxicant. In a DMH-exposed colon cancer rat model, quercetin was shown to ameliorate ROS formation, inflammation, and hyperproliferation by targeting the adenomatous polyposis coli (APC) and β-catenin pathways [31]. This finding is consistent with the results from Benito et al. [32], who demonstrated that micro-encapsulated probiotics in combination with quercetin inhibit the development of CRC in $APC^{Min/+}$ mice by inhibition of the Wnt/β-catenin signaling pathway. Similarly, recent studies have reported that bisphenol A (BPA) may have toxic effects on the body and colon. Quercetin and its fermented extract exhibited excellent inhibitory effect on the viability of BPA-exposed HT29 colon cancer cells [33]. Additionally, quercetin enhanced the chemotherapeutic impact of oxaliplatin in HCT116 cells by increasing intracellular ROS through its suppressive action on glutathione levels [34]. Moreover, amalgamation of quercetin with anastrozole and capecitabine induce activation of caspase 3 expression *in vitro* [35]. These results indicate that quercetin is a promising chemotherapeutic intervention in the treatment of CRC.

2.4 Rutin

Rutin, which is extracted from *Hedyotis diffusa* Wild, has also been a focus of CRC treatment. Nafees et al. [36] showed that rutin in combination with silibinin produces synergistic anti-cancer effects on HT29 CRC cells by regulating expression of apoptosis, inflammation, and MAPK pathway proteins. Recently, a new colonic delivery method for rutin was studied by formulating rutin into frankincense-based compression-coated tablets and showed that the anti-cancer effect was improved [37]. Interestingly, network pharmacology and analysis of gene biological information showed that the potential intracellular signaling pathways of rutin in human SW480 cells may be associated with miRNAs-long non-coding RNAs (lncRNAs)-messenger RNAs-transcription factors [38]. Further research is required to validate the anti-cancer effect of rutin on CRC *in vivo*.

2.5 Genistein

Genistein, a polyphenolic isoflavone compound, is abundantly present in soy or soy-based products. People residing in Asian countries usually have a high intake of genistein in the daily diet because many traditional foods are made from soybeans [39]. Recently, the anti-cancer activity of genistein has undergone extensive research. A phase I/II pilot study showed that genistein in combination with FOLFOX or FOLFOX–bevacizumab is safe and well-tolerated [40]. Moreover, genistein in combination with FOLFOX or FOLFOX–bevacizumab enhanced response rates and progression-free survival (PFS) in the treatment of metastatic CRC (NCT01985763) [40]. Another nested case-control study determined that high

Table 2 | Clinical trials of natural products in different types of cancers.

Types of cancers	Natural products	Group	Clinical status/Study type	Study population	Sample size	Experiments results	Ref.
Colorectal cancer	Lipid carrier containing curcumin	Curcumin plus bevacizumab/FOLFIRI (folinic acid, 5-FU, irinotecan)	A prospective, observational, single-group analysis	Colorectal cancer patients	44	OS 30.7 months, median PFS 12.8 months, none of the patients achieved a CR, 9 patients achieved a PR, presenting comparable long-term survival outcomes with acceptable toxicity outcomes	[7]
	Curcumin	Curcumin plus FOLFOX (folinic acid, 5-FU, oxaliplatin) or FOLFOX group	A phase IIa Trial	Colorectal cancer patients	28	CXCL1, PFS (-); OS↑	[8]
		Curcumin plus anthocyanin or placebo group	A randomized, double-blind, placebo-controlled, phase II presurgical trial	Colorectal adenomas patients	35	IGF-1, 25OHD, IL-10, IL-6, TNFα, IGFBP-3, Leptin, Adiponectin, L/A, hs-CRP, HOMA-index (-); did not directly modulate inflammatory and metabolic biomarkers	[9]
	Genistein	Genistein plus FOLFOX or genistein plus FOLFOX–bevacizumab	A phase I/II pilot study	Metastatic colorectal cancer patients	13	BOR, 61.5%; median PFS, 11.5 months	[40]
	EGCG	GTE group or placebo group	A single-center prospective randomized open-labelled study	Patients with complete removal of colorectal adenomas by endoscopic polypectomy	176	The number of relapsed adenomas↓; body mass index, dietary intake, serum lipid profiles, fasting serum glucose, and serum C-reactive protein level (-)	[49]
		GTE (standardized to contain 150 mg EGCG) group or placebo group	A prospective, randomized, double-blind, placebo-controlled, multicentre trial	50 and 80 years and had ≥1 histologically confirmed colorectal adenoma(s) removed within 6 months	1001	The GTE and placebo groups did not have a statistically significant difference in the adenoma rate and adverse events	[50]
Lung cancer	EGCG	Prophylactic EGCG or therapeutic EGCG group after the occurrence of esophagitis or conventional therapy group	A prospective, three-arm, randomized trial	Medically inoperable stage IIIA or IIIB or limited stage small cell lung cancer patients	83	Adjusted esophagitis index (AEI)↓, pain index (API)↓, dysphagia index (ADI)↓	[84]
		EGCG or conventional therapy group	The 5-year survival analysis of phase II study	Lung cancer patients	83	Objective response rate (ORR) was higher in the EGCG group; PFS (-), OS (-)	[83]
	Genistein	1.8-2.0 Gy radiation therapy, concurrent weekly paclitaxel/carboplatin, plus BIO 300 (cohort 1, 500 mg/d; cohort 2, 1000 mg/d; cohort 3, 1500 mg/d)	A open-label, single-arm, ascending dose phase Ib/IIa study	Stage II-IV NSCLC patients	21	Tumor response rate was 65%, CR rate was 20%, a dose-dependent decrease in the serum TGF-β1 level, no serious AEs or dose-limiting toxicities; low toxicity rates	[101]
	Gossypol	Gossypol plus docetaxel and cisplatin or docetaxel and cisplatin alone group	A randomized, double-blind, placebo-controlled study	Advanced NSCLC patients with high APE1 expressio.	62	PFS (-), OS (-), serious adverse events (-)	[106]

Table 2 | Continued

Types of cancers	Natural products	Group	Clinical status/Study type	Study population	Sample size	Experiments results	Ref.
	Mistletoe	*Viscum album* L. treatment	A real-world data study	Lung cancer patients	112	Improved poor quality of life, especially in combination with radiation; pain, nausea, and vomiting were reduced	[112]
		Viscum album L. plus chemotherapy or chemotherapy alone group	A non-controlled, non-randomized observational multicenter cohort study	Stage IV NSCLC patients	158	Median survival (17.0 months vs. 8 months), OS prolonged, 1- and 3-year OS rates were greater	[113]
		Viscum album extract (Helixor-M) was instilled via pleural catheter	A prospective observational study	Lung cancer with malignant pleural effusions patients	52	Recurrence rate, 81% (42/52); 1-month recurrence rate, 48% (20/42); adverse events included pain medication, 13 (25%); fever > 38 °C, 8 (15%); oxygen demand, 6 (12%); pneumothorax, 2 (4%)	[111]
Breast cancer	Sulforaphane	Sulforaphane supplement by dietary cruciferous vegetable intake	A randomized controlled trial	Women had abnormal mammogram findings and were scheduled for breast biopsy	54	Total cruciferous vegetable intake was inversely associated with Ki-67 protein expression; other biomarkers (HDAC3, HDAC6, H3K9, H3K18, and p21) had no correlation	[118]
		ITC-rich broccoli sprout extract (BSE) (200 μmol ITC per day) or placebo group	A randomized pilot intervention study	Postmenopausal breast cancer patients	30	High compliance (100%) and low toxicity (no grade 4 adverse events), increased trend in cleaved caspase 3, decreased trend in Ki-67, NQO1, and ER-α were observed but the differences were not statistically significant	[119]
	Curcumin	Paclitaxel plus curcumin or paclitaxel plus placebo	A randomized, double-blind, placebo-controlled, parallel-group comparative clinical study	Breast cancer patients	150	ORR↑, reduced fatigue, the self-assessed overall physical performance was significantly higher	[126]
	EGCG	EGCG or placebo group	A double-blind, placebo-controlled, phase II randomized clinical trial	Breast cancer patients receiving postoperative radiotherapy	180	The occurrence of grade 2 or worse RID was significantly lower in the EGCG group, RID index↓, symptom indexes↓, 4 patients (3.6%) had adverse events	[138]
		Daily intake of GTE 1315 mg (EGCG 800 mg) or placebo group	A randomized, double-blinded, placebo-controlled phase II clinical trial	Healthy postmenopausal women	1075	Both percent MD and absolute MD were not changed in all women; percent MD was decreased in younger women (50–55 years)	[136]
		Daily intake of GTE 1315 mg (EGCG 800 mg) or placebo group	A placebo-controlled double-blind randomized clinical trial	Healthy postmenopausal women	1075	Did not reduce sex steroid hormones; increased estradiol concentration	[137]

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Table 2 | Continued

Types of cancers	Natural products	Group	Clinical status/Study type	Study population	Sample size	Experiments results	Ref.
	Genistein	Isoflavone (containing 137.5 mg genistein) or placebo group	A phase I double-blind clinical trial	Healthy postmenopausal women	30	There were no significant changes in estrogenic effects, DNA strand breakage, apurinic/apyrimidinic sites, or apoptosis	[146]
		Isoflavones (containing 11.57% genistein) or placebo group	A double-blind, randomized, placebo-controlled intervention study	Breast cancer patients (n=66) and high-risk women (n=29)	95	No statistically significant impact on mammographic density and fibroglandular tissue volume	[147]
	Tocotrienol	Standard neoadjuvant treatment alone or in combination with delta-tocotrienol	A open-label, randomized phase II trial	Newly diagnosed, histologically verified breast cancer patients	80	There was no difference in OS, IDFS, and adverse events, and no association between ctDNA status and pathological treatment response	[160]
		Tocotrienol-rich fraction (TRF) plus tamoxifen or placebo plus tamoxifen	A double-blinded, placebo-controlled pilot trial	Breast cancer patients with ER-positive tumors	240	There was no difference in BC-specific survival, disease-free survival, cancer recurrence; mortality was decreased but no statistical significant difference was detected	[161]
	Artesunate	Artesunate dose group:100 mg/d, 150 mg/d, 200 mg/d	Open uncontrolled phase I Study	Patients with metastatic breast cancer	13	No major safety concerns	[167]
		Artesunate administered at doses of 150-300 mg daily for 1.5 years	A case report	Patients with metastatic breast cancer	1	The patient experienced a stabilization of her disease for 1.5 years, causing no or minimal side-effects	[168]
	Mistletoe	Targeted therapy or targeted therapy plus *Viscum album* L.	A real-world data observational cohort study	Breast and gynecological cancer patients	242	No adverse events, improving targeted therapy adherence, does not negatively alter the safety profile of targeted therapies	[179]
		Two different European mistletoe extract groups or a control group	A prospective, randomized, open-label clinical trial	Breast cancer patients	95	Fewer fever symptoms; improved pain and appetite loss scores; no significant differences in relapse or metastasis	[180]
Cervical cancer/ Endometrial cancer	Curcumin	IDC, pembrolizumab	An investigator-initiated, non-randomized, open-label, multicohort, non-comparative, multisite, phase II study	Cervical cancer patients (n = 18), endometrial cancer patients (n = 25)	43	irORR was 11.1% in cervical cancer and 12% in endometrial cancer, grade≥3 adverse events were 10 (55.6%) in cervical cancer patients and 9 (36.0%) in endometrial cancer patients	[183]
Cervical cancer	Bryostatin-1	Bryostatin-1 and cisplatin	A multi-institutional, prospective, single-arm trial	Metastatic or recurrent cervical cancer patients	14	80% (8/10) patients had progressive disease and 20% (2/10) had stable disease; there were no treatment responses	[191]

Table 2 | Continued

Types of cancers	Natural products	Group	Clinical status/Study type	Study population	Sample size	Experiments results	Ref.
	Polyphenon E	Polyphenon E or placebo group	A phase II randomized, double-blind, placebo-controlled trial	Women with persistent high-risk HPV infection and low-grade cervical intraepithelial neoplasia	98	Polyphenon E vs. placebo group: Progression, 6 (14.6%) vs. 3(7.7%; CR, 7 (17.1%) vs. 6 (14.6%)	[192]
Ovarian cancer	Bryostatin-1	Bryostatin-1 in combination with cisplatin	A multi-centered phase II study	Recurrent or persistent epithelial ovarian cancer patients	8	Median PFS (3 months) and median OS (8.2 months); all patients experienced grade 3 or 4 adverse events	[196]
Endometrial cancer	Curcumin	Curcumin phytosome orally for 2 weeks	A open-label, non-randomized phase II study	Endometrial cancer patients	7	Minor immunomodulatory effects, a non-significant trend to improved quality of life	[197]
	Genistein	Dietary exposures were divided into quintiles for legumes, tofu, total isoflavones, glycitein, daidzein, and genistein for all women in the cohort	A longitudinal multiethnic Cohort Study	Non-hysterectomized postmenopausal women	46027	A reduced risk of cancer was associated with the intake of total isoflavone, daidzein, or genistein (highest vs. lowest quintile)	[200]
Kidney cancer	Isoquercetin	Administration of isoquercetin and sunitinib	A phase I trial	kidney cancer patients	12	A statistically significant improvement in fatigue score	[207]
Pancreatic cancer	Curcumin	Gemcitabine and Meriva®, a patented preparation of curcumin complexed with phospholipids	A single centre, single arm prospective phase II trial	Pancreatic cancer patients	52	Response rate, 27.3%; cases with stable disease, 34.1%; total disease control rate, 61.4%, median PFS, 8.4 months, median OS, 10.2 months; grade 3/4 toxicity (neutropenia, 38.6%; anemia, 6.8%); no significant changes in quality of life	[210]
	Genistein	AXP107-11 in combination with standard gemcitabine treatment	A phase Ib, single site, open-label, clinical study	Pancreatic cancer patients	16	No hematologic or non-hematologic toxicity; median overall survival time, 4.9 months (range 1.5-19.5 months); 44% (7/16) survived longer > 6 months; 19% were alive at the 1-year follow-up evaluation	[216]
Melanoma	SFN	Three dosage groups (50, 100, or 200 μmol of oral sprout extract (SFN) daily for 28 days	A phase II study	Melanoma patients had at least 2 clinically atypical nevi ≥ 4 mm	17	No dose-limiting toxicities; the levels of SFN dose-dependent increase in plasma and skin, IP-10↓, MCP-1↓, MIG↓, MIP-1β↓	[233]
Multiple myeloma	Curcumin	MPC group (melphalan, prednisone, and curcumin) or MP group (melphalan, prednisone, and placebo)	A randomized, single-blind & parallel design of the study	Multiple myeloma patients	33	Improving overall remission, NF-κB↓, VEGF↓, TNF-α ↓, and IL-6	[253]
	Curcumin and piperine	Newly diagnosed patients were divided into control or treatment group (curcumin/piperine); pCR patients were the chemotherapy group	A clinical trial	Newly diagnosed MM (n=20) and pCR patients (n=12)	32	OCT-4A↓, NANOG↓,SOX2↓, cell cycle S and G0/G1 phases↓, cell cycle G2/M phases↑, inhibition of multiple myeloma CSC proliferation	[258]

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Table 2 | Continued

Types of cancers	Natural products	Group	Clinical status/Study type	Study population	Sample size	Experiments results	Ref.
Hepatocellular carcinoma	Huaier granule	Huaier granule or non-huaier treatment	A multicentre, randomised, controlled, phase IV trial	After curative resection of hepatocellular carcinoma patients	1044	Prolonging RFS; reducing extrahepatic recurrence	[260]
		Huaier granule or non-huaier treatment	A propensity score analysis	After curative resection of hepatocellular carcinoma patients	1111	Prolonging overall survival >5 years	[261]
		Huaier granule or non-huaier treatment	A single-center cohort study	Hepatocellular carcinoma patients	826	Improving OS rate	[262]
		SRL-based therapy or tacrolimus-based therapy	A single center experience	HCC patients who underwent liver transplantation (LT)	36	α-fetoprotein↓, $FoxP3^+$ Treg↓, $CD8^+$/$CD3^+$ T cells↑, longer recurrence and survival times	[263]

Complete response (CR), partial response (PR), best overall response rate (BOR), progression-free survival (PFS), overall survival (OS), objective response rate (ORR), invasive disease-free survival (IDFS), recurrence-free survival (RFS), complete response (pCR) 1 year after chemotherapy.

plasma levels of isoflavones (genistein and daidzein) are associated with a decreased risk of CRC [41]. Alorda-Clara et al. [39] demonstrated that high concentrations of genistein decrease cell viability depending on the regulation of oxidative stress and inflammation in colon cancer cells. Network pharmacology and bioinformatics analyses further uncovered the molecular mechanisms underlying genistein against CRC [42]. The potential drug targets associated with autophagy, including epidermal growth factor receptor (EGFR) and estrogen receptor (ER) [42]. Hence, genistein is a promising natural compound that may become a drug and supplement in cancer treatment. While some researchers have studied the anti-cancer activity of genistein, the precise mechanism by which genistein might prevent cancer has not been established.

2.6 Cannabidiol

Cannabidiol (CBD), which is isolated from the *Cannabis sativa* L., has been approved as a drug in the US and is utilized for controlling seizures among patients with Lennox-Gastaut syndrome. Cin recent years several clinical trials have attempted to determine whether CBD provides benefits to patients with CRC and breast cancer (BC) in recent years (NCT03607643; NCT04398446; NCT04482244; NCT05016349; NCT04754399). Single-cell analyses revealed that CBD inhibits alternative activation of macrophages and shifts metabolic processes by inhibiting the PI3K-AKT pathway, which rewires the tumor microenvironment and restores the intrinsic anti-tumor properties of macrophages. Accordingly, CBD enhances the response of anti-PD-1 immunotherapy to CRC *in vivo* [43]. Cannabidiol was shown to induce apoptosis and autophagy *in vitro* by activating the JNK/p38/ERK MAPK pathway [44]. Further research revealed that CBD-induced ROS production is dependent on the p53 pathway. An Hsp70 inhibitor was shown to contribute to shifting CBD-induced autophagy toward apoptosis, which improved programmed tumor cell death in p53wt CRC cells [45]. Additionally, metallothionein family proteins, as regulators of zinc, have an important role in facilitating the anti-cancer effects of CBD [46]. CBD-induced cycle cell arrest and apoptosis are dependent on the activation of cannabinoid receptor type 2 (CB2) but not cannabinoid receptor type 1 (CB1) [47]. A corollary study should determine the impact of CBD in combination with another chemotherapy agent in animal and clinical trials.

2.7 Epigallocatechin-3-gallate (EGGG)

Tea, as one of the most widely consumed beverages worldwide, is generally thought to have health benefits. Most studies involving tea and cancer prevention have focused on green tea. EGCG is the most active and abundant catechins in green tea. The other catechins include epigallocatechin (EGC), epicatechin-3-gallate (ECG), and epicatechin. The catechins have the capacity to scavenge free radicals, which may protect cells

from ROS-induced DNA damage [48]. At present the chemoprophylaxis effects of EGCG or green tea extract (GTE) in CRC patients are receiving attention in clinical trials (NCT02891538; NCT01239095; NCT01360320; NCT02321969). One clinical trial reported that a GTE supplement decreased the number of relapsed adenomas and exhibited a favorable outcome for the prevention of colorectal adenomas (NCT02321969) [49]. Conversely, another randomized, placebo-controlled clinical trial reported that GTE is well-tolerated but no statistically significant difference was detected in the adenoma rate (NCT01360320) [50-52]. Additional mechanistic studies showed that EGCG was an activator of epithelial-specific E26 transformation-specific sequence (ETS) transcription factor-1 (ESE-1), and overexpression of ESE-1 suppressed tumor development and cell migration/invasion [53]. Another study reported that the ECG and EGCG dimers inhibit CRC cell invasion and metastasis by downregulating MMP-2 and MMP-9 expression via a NOX1/EGFR-dependent mechanism [54]. Moreover, Iram et. al [51] demonstrated that EGCG suppressed CRC cell proliferation by targeting tetranectin. Interestingly, the activation of Yes associated protein (YAP) protein induced by EGCG may impede the anti-tumor effect of EGCG [55]. Although EGCG has been shown to inhibit CRC tumorigenesis in laboratory and animal studies, the results of human epidemiologic and clinical studies have been inconclusive.

2.8 Andrographolide

Andrographolide is a natural product from the traditional Chinese medicine, *Andrographis paniculata*. In the past several decades, researchers have focused on the potential role of andrographolide and its derivatives in inflammatory diseases and cancer treatment [56]. However, a phase II clinical trial investigating the efficacy and safety of andrographolide plus capecitabine in CRC patients was terminated due to a low accrual rate (NCT01993472). Nevertheless, several researchers have synthesized a series of andrographolide derivatives that exhibit favorable anti-cancer effects [57, 58]. Specifically, the andrographolide derivative, AGS-30, was shown to induce apoptosis in CRC cells by activating the ROS-dependent JNK signaling pathway [57]. Another study showed that AGS-30 suppresss tumor growth and angiogenesis by inhibiting AKT/mTOR and ERK-dependent pathways, as well as interrupting VEGF signaling [59]. Alternatively, a series of studies demonstrated that andrographolide and melatonin had a synergistic effect on promoting the death of CRC cells by inducing endoplasmic reticulum stress and suppressing angiogenic activity [60]. Similarly, the combined action synergized to inhibit the colospheroid phenotype by targeting the Wnt/β-catenin signaling pathway [61]. We previously demonstrated andrographolide reversed 5-FU resistance in human CRC by elevating BAX expression [62]. Moreover, andrographolide potentiated PD-1 blockade immunotherapy by inhibiting COX2-mediated PGE2 release [63]. Overall, these findings indicate that andrographolide and its derivatives inhibit the development of CRC *in vivo* and *in vitro.* A clinical trial of andrographolide derivatives merits further investigation. We look forward to more experiments to determine the role of andrographolide in regulating the immunologic microenvironment and immunosuppression in CRC [64]. Natural products have an important role in the treatment of CRC, of which quercetin, resveratrol, and CBD have been marketed as drugs and supplements. Mechanistic studies have shown that quercetin, resveratrol, and CBD hinder the progression of CRC via multiple signaling pathways. Well-designed, rigorous clinical studies are needed to optimize dosage, formulations, and the appropriate target population.

3. LUNG CANCER

Lung cancer is the most common cancer and the leading cause of cancer-related deaths worldwide [65]. Lung cancer is categorized as small cell lung cancer (SCLC) or non-small cell lung cancer (NSCLC) based on the main histotype, prognosis, and therapy. Although significant progress has been made in the diagnosis and treatment of lung cancer in recent years, the prognosis for patients remains unsatisfactory. Efforts are currently underway to examine natural products for treating the possibility of lung cancer, many of which have proceeded to clinical trials (**Table 3**).

3.1 Sulforaphane

Sulforaphane (SFN) is a primary isothiocyanate (ITC) derived from cruciferous vegetables, especially broccoli and cauliflower [66]. SFN is metabolized into SFN-N-acetyl-cysteine (SFN-NAC) and SFN-cysteine (SFN-Cys) in the blood. A mechanistic study showed that SFN-Cys inhibits NSCLC cell invasion by microtubule-mediated claudin dysfunction, while SFN-NAC inhibits invasion by microtubule-mediated inhibition of autolysosome formation [67]. Similarly, SFN triggers NSCLC cell apoptosis by downregulating fatty acid synthase and inhibiting microtubule-mediated mitophagy [68, 69]. SFN intervention suppresses tobacco smoke-induced cancer stem cell (CSC)-like properties of human bronchial epithelial (HBE) cells via the IL-6/ΔNp63α/Notch axis *in vivo*, [70]. The synergistic anti-tumor effects of SFN with other drugs have also attracted much attention. SFN in combination with the allyl, ITC, produces superior protective effects against carcinogenesis [71]. SFN metabolites decrease the resistance of NSCLC cells to paclitaxel in usual doses by activating caspase 3-induced microtubule disruption [72]. A higher level of EGFR showed resistance to SFN induced ROS-mediated apoptosis [73]. These findings indicate that the antitumor effects of SFN and its metabolites involved in multiple targets and pathways. A future study may determine SFN function in the lung cancer immunologic microenvironment.

Table 3 | Preclinical studies of natural products and their derivatives in lung cancer.

Compounds	Source	Experiments		Effects and mechanisms	Ref.
		In vivo	*In vitro*		
Sulforaphane	Broccoli, cauliflower	(-)	A549, SK-1	p-ERK1/2↑, claudin-7↑; claudin-5↓; SFN-Cys inhibited invasion via microtubule-mediated claudin dysfunction, SFN-NAC inhibited invasion via microtubule-mediated inhibition of autolysosome formation	[67]
		(-)	A549, SK-1	Proteasomes↑, LC3 II/I↑; FASN↓, ACACA↓, ACLY↓, SREBP1↓, Bnip3↓, NIX↓, α/β-tubulin↓	[68]
		Xenograft BALB/c nude mice for CSE-transformed HBE	HBE	IL-6↓, ΔNp63α↓, Notch↓, Hes1↓, CD133↓, Nanog↓	[70]
		(-)	A549	p53↑, cleaved caspase 3↑, cleaved PARP↑, apoptosis↑, cell cycle arrest↑, ROS↑; survivin↓, cell growth↓	[71]
		(-)	A549, taxol-resistant A549	p-ERK1/2↑; βIII-tubulin↓, XIAP↓, tau↓, stathmin1↓, α-tubulin↓	[72]
		Xenograft BALB/c nude mice for CL1-5; 24 lung tissues samples of lung cancer patients	CL1-0, CL1-5	γH2AX↑, ROS↑	[73]
Curcumin	*Curcuma longa* L.	32 specimens of lung cancer tissue and the corresponding healthy tissues	H1299, A549	TAp63α↑, E-cadherin↑, ZO-1↑; miR-19↓, vimentin↓, N-cadherin↓	[78]
		(-)	A549, HepG2	Caspase 3↑, apoptosis↑; p-PI3K↓, AKT↓, proliferation↓, migration↓	[80]
		(-)	A549, docetaxel/vincristine-resistant A549	p-p38↑, p-ERK↑, cleaved PARP↑, p-eIF2α↑, ROS↑, apoptosis↑	[79]
Analogue EF24		Xenograft BALB/c nude mice for A549	A549, SPC-A1, H460 and H520	ROS↑, apoptosis↑, mitochondrial fssion↑, autophagy↑; proliferation↓	[75]
Analogue EB30		(-)	A549, NCI-H292, HBE	AIF↑, BAX↑, cleaved PARP↑, cleaved caspase-3/9↑, p-ERK↑, p-90RSK↑, apoptosis↑, cell cycle arrest↑, ROS↑; Bcl-2↓, Bcl-xL↓, p-AKT↓, p-P70S6K↓, proliferation↓, migration↓	[74]
Analogue MS13		(-)	NCI-H520, NCI-H23, MRC-9	Caspase 3↑, anti-proliferative activity↑, apoptosis↑; Bcl-2↓	[76]
Curcumin mono-carbonyl analog 2c		Xenograft BALB/c nude mice for NCI–H460	NCI–H460, HepG2, HT-1080, A549, MRC-5	BAX↑, caspase-3/9↑; GPX4↓, Bcl-2↓, TrxR↓; inducing ROS-dependent apoptosis and ferroptosis	[77]
Diarylheptanoid 35d		Xenograft SCID mice for HCC827	H460, H1299, H1650, HCC827, H1975	Hsp70↑, bag3↑, p62↑; EGFR↓	[81]
Derivative 35d		Xenograft SCID mice for HCC827	HCC827	CPTI↑, CPTII↑, Hsp60↑, long-chain acylcarnitines↑, mitochondrial dysfunction↑; short-chain acylcarnitines↓, Tom20↓, fatty acyl metabolism↓	[82]

Table 3 | Continued

Compounds	Source	Experiments		Effects and mechanisms	Ref.
		In vivo	*In vitro*		
EGCG	Tea	Multi-dose urethane-induced C57BL/6J mice lung tumorigenesis with high-fat diet	A549, RAW264.7	STAT1↓, SLC7A11↓; apoptosis↑, ferroptosis↑, leptin-induced proliferation↓, invasion↓, migration↓	[91]
		Xenograft BALB/c nude mice for NCI-H1975 or AR	EGFR-mutant NCI-H1975, H1975 AR cell, HEK293	AMPK pathway↑, mitochondrial membrane depolarization↑, apoptosis↑; AKT/mTOR and MAPK/ERK pathways↓, altering cancer energy metabolism	[92]
Chlorogenic acid	Green coffee, apples, artichoke, and *Lonicera japonica* Thunb	Xenograft BALB/c nude mice for A549	A549	cIAP1↓, cIAP2↓, proliferation↓, inhibiting the binding of ANXA2 to p50	[93]
		Xenograft NOD/SCID mice for Huh7 and H446	NCI-H446, Huh7, Bel-7402, HEK293T, HCT116, U87MG, M059J, CCC-HEL-1, NCI-H358, WI-38, MRC-5, A549-5FU, SK-LU-1, MIHA, iPS, HH, rat C6 and mouse G422 glioma cells	SUMO1↑, p21↑, Tuj1↑, GFAP↑, p53↑, KHSRP↑, cell differentiation↑; miR-17 family↓, p-c-Myc↓, EPCAM↓, CD44↓, proliferation rate↓, migration↓, invasion↓, mitochondrial ATP production↓	[94]
		Xenograft BALB/c nude mice for LAC-1	(-)	IL-6↓, alleviating cancer-related neurological complications	[95]
Genistein	soy	(-)	BEAS-2B	Reducing ROS and DNA damage, upregulating p-NRF2 nuclear translocation and catalase activity	[104]
		Xenograft BALB/c nude mice for A549	H292, A549, 16HBE	Apoptosis↑; circ_0031250↓, miR-873-5p↓, FOXM1↓, cell viability↓, proliferation↓ migration↓, invasion↓	[102]
		(-)	A549, 95D	FOXO3a↑, PUMA↑, ROS↑, cytochrome c↑, BAX↑; mitochondrial membrane potential↓, mitochondrial activity↓, Bcl-2↓	[103]
Gossypol	Cotton seeds (*Gossypium herbaceum* L.)	(-)	A549, NCI H460	LC3-II↑, ROS↑, autophagy↑, apoptosis↑; p62↓	[108]
		(-)	H1975 (EGFR L858R/T790 M), H441, A549	Apoptosis↑; YAP↓, TAZ↓, p-EGFR↓, p-ERK1/2↓; cell growth↓	[109]
Gossypol acetate		Xenograft BALB/c nude mice for A549	HEK-293FT, H1944, H1299, A549, H460, H23	E2F1↓, LRPPRC↓, CDK6↓; suppressing cell cycle G1/S transition, oxidative phosphorylation, cancer stem cells	[107]
Mistletoe	*Viscum album* L.	Xenograft NU/J nude mice for H82	H82, H69, H196, SHP77	Apoptosis↑; cleaved PARP↑, C-myc↓, N-myc↓, cell growth↓	[114]

3.2 Curcumin

Accumulating evidence has shown that curcumin has anti-cancer effects by inhibiting lung cancer cell growth and inducing apoptosis [74-78]. Xie et al. [78] demonstrated that curcumin suppresses tobacco smoke-induced EMT progress by increasing TAp63α expression and reducing miR-19 expression. Recently, a series of curcumin derivatives (EF24, EB30, and MS13) were synthesized by researchers and showed excellent anti-cancer effects on lung cancer. The underlying mechanism includes suppression of the PI3K/AKT pathway, activation of ERK1/2, and accumulation of ROS [74-76]. Another curcumin analog (2c) has been designed that exhibits selective ROS generation compared to normal cells through the inhibition of intracellular TrxR, thereby mitigating side effects and improving the safety profile [77]. In addition, existing evidence indicates that curcumin promotes apoptosis of chemoresistant lung cancer cells via ROS-regulated p38 MAPK phosporylation [79]. A triple combination (curcumin, thymoquinone, and 3, 3′-diindolylmethane) better attenuates lung and liver cancer progression compared to a double combination [80]. Moreover, diarylheptanoid 35d was shown to overcome EGFR tailored tyrosine kinase inhibitor (TKI) resistance in EGFR-mutant lung adenocarcinoma by inducing Hsp70-mediated lysosomal degradation of EGFR [81]. Similarly, Hsieh et al. [82] further demonstrated that the curcumin derivative, 35d, enhanced the sensitivity of osimertinib (a TKI inhibitor) to lung cancer cells by disrupting fatty acyl metabolism and inducing mitochondrial stress. These results from *in vivo* and *in vitro* experiments are encouraging and we anticipate publication of additional clinical outcomes involving curcumin and its analogues.

3.3 EGCG

Accumulating evidence reveals that EGCG has a strong protective effect against lung cancer. Several clinical studies showed that EGCG is a radioprotective agent, prevents radiation-induced esophagitis, and enhances objective response rate (ORR) but without significantly prolonging PFS and OS in lung cancer patients [83, 84]. A number of *in vitro* and *in vivo* studies have confirmed that EGCG inhibits CSC-like properties and self-renewal ability of lung cancer [85-88]. Moreover, EGCG has been shown to inhibit lung cancer cell proliferation and migration by suppressing EGFR signaling [89-90]. Alternatively, Li et al. [91] reported that EGCG alleviates obesity-exacerbated lung cancer progression. The underlying mechanism is associated with the STAT1/SLC7A11-mediated ferroptosis pathway and gut microbiota. EGCG also has a critical role in overcoming drug resistance in tumors. According to Zhou et al. [92], EGCG circumvents drug-induced resistance in NSCLC by modulating glucose metabolism and the AMPK/AKT/MAPK axis. Overall, EGCG may be a potential anti-cancer agent. The potential research direction in the future may involve examining the role of EGCG in regulating the lung cancer immunologic microenvironment.

In addition, polyphenon E serves as a standardized, highly reproducible green tea polyphenol mixture containing 60% EGCG. Polyphenon E is the recommended form of green tea for clinical chemoprevention trials and has entered multiple phase I/II lung cancer clinical studies (NCT00363805; NCT00707252). Currently, a limited number of studies have been conducted to determine the anti-cancer mechanism underlying polyphenon E in lung cancer. The components of green tea are complex and the study of single component EGCG or multiple components of polyphenol E are necessary, which are more conducive to understand the mechanism underlying the green tea anti-cancer effect.

3.4 Chlorogenic acid

Chlorogenic acid (CGA) is a phenolic acid that is widely distributed in green coffee, apples, artichoke, and *Lonicera japonica* Thunb. Green coffee is used for obesity, diabetes, high blood pressure, and high cholesterol but there remains a lack of good scientific evidence. Recently, a phase I/II study was conducted to investigate the safety and efficacy of injected anCGA in the treatment of advanced lung cancer (NCT03751592). A mechanistic study verified that CGA inhibits binding of annexin A2 (ANXA2) to p50 and attenuates related anti-apoptotic genes, thereby suppressing the proliferation of A549 *in vivo* and *vitro* [93]. It is known that inducing cancer differentiation is a promising approach to treat cancer. Further studies demonstrated that CGA treatment prevents the development of lung cancer by inducing lung cancer differentiation [94]. Alternatively, orally administered dietary *Ilex paraguariensis* led to a dose-dependent brain accumulation of CGA and quercetin in mice with lung adenocarcinoma, in different neuroprotective effects occurred in the telencephalon and diencephalon [95]. These findings support plant-based strategies to improve prognosis in lung cancer.

3.5 Soy isoflavone and genistein

Soy isoflavone, a type of flavonoid, is classified as a plant estrogen extracted from soybeans, which consists of genistein, daidzein, and glycitein. Chei et al. [96, 97] conducted a pooled analysis of four cohort studies from Japan and China that revealed a significant association between higher intake of isoflavone and soy food and a reduced risk of lung cancer among individuals who have never smoked. These findings were consistent with several meta-analyses that concluded higher intake of soy and soy isoflavone are inversely associated with the risk of lung cancer incidence and mortality [98-100]. Moreover, genistein, as one of the predominant soy isoflavones, has also entered clinical trials (NCT01628471; NCT00769990; NCT00533949). A multicenter phase Ib/IIa clinical trial demonstrated that the radioprotectant, BIO 300 oral suspension (synthetic genistein nanosuspension), is an effective radioprotector for patients

with NSCLC receiving concurrent chemoradiotherapy. BIO 300 oral suspension exhibits low toxicity rates, along with the pharmacodynamic results and high tumor response rates [101]. Additionally, Yu et al. [102] found that genistein induced apoptosis and repressed NSCLC progression by inhibiting circ_0031250/miR-873-5p/FOXM1axis. Chan et al. [103] found that genistein induced mitochondrial apoptosis and FOXO3a/PUMA expression in NSCLC cells. Interestingly, genistein and procyanidin B2 alleviate carcinogen-induced ROS and DNA damage by activating NRF2/ARE signaling in normal bronchial epithelial cells, which provided a research basis for cancer prevention through dietary modifications [104]. Hence, soy is considered to be a healthy diet component, but soy isoflavone and genistein as dietary supplements need additional supportive clinical data.

3.6 Gossypol

Gossypol is a natural polyphenolic compound extracted from cotton seeds, roots, and stems [105]. Use of gossypol acetate, as a gynecologic medicine, was discontinued owing to serious side effects but gossypol acetate is currently receiving attention again. Recently, a randomized, double-blind, placebo-controlled study showed that gossypol in combination with docetaxel and cisplatin was well-tolerated and had a better median PFS and OS than the control group. Because there were no significant differences between the gossypol, docetaxel, and cisplatin group and the control group, future studies with larger sample sizes should be conducted [106]. In the past few years gossypol has made significant progress in improving chemoradiotherapeutic sensitivity. For example, gossypol acetate was shown to enhance the sensitivity of CDK4/6 inhibitors (cancer therapeutic drugs) by inhibiting the LRPPRC-CDK6 loop in lung cancer cells. Gossypol acetate is considered to be a degrader of LRPPRC [107]. Gossypol can also enhance the cytotoxic effect of sorafenib in lung cancer by promoting autophagy and apoptosis [108]. In addition, gossypol overcomes TKI resistance in EGFR L858R/T790 mutation NSCLC cells by inhibiting YAP/TAZ and EGFR [109]. These findings suggest that gossypol is a potential natural product for the clinical management of lung cancer.

3.7 Mistletoe

European mistletoe (Santalaceae: *Viscum album L.*), commonly known as mistletoe, is frequently prescribed as an unconventional cancer therapy in central Europe [110]. Mistletoe is a universal name for various species of semi-parasitic plants which grow on host trees, such as apple, elm, oak, and pine [111]. A real-world data questionnaire-based study assessed the poor quality of life for lung cancer at first diagnosis and 12 months later. The results showed that add-on *Viscum album* L. therapy improved poor quality of life in lung cancer patients, especially when paired with radiation therapy. Specifically, the occurrence of pain, nausea, and vomiting decreased remarkably [112]. This finding is in agreement with Lee et al. [111] who showed that *Viscum album* extract is an effective and tolerable procedure for controlling malignant pleural effusions (MPEs) in lung cancer patients. Of note, another real-world observational multicenter analysis demonstrated that *Viscum album L.* in combination with chemotherapy significantly enhanced OS for stage IV NSCLC patients [113]. It was further shown that mistletoe lectin inhibits the growth of Myc-amplified SCLC [114]. Although mistletoe has entered clinical trials for the treatment of lung cancer patients, the anti-lung cancer mechanism is still unclear and more preclinical trials are needed to better define the tumor microenvironment. In conclusion, natural products with the unique advantages of multi-ingredient, multi-target, multi-pathway therapy have been widely investigated in lung cancer. In the absence of clinically ideal drugs for the prevention and treatment of lung cancer, it is a potential direction to explore natural products to prevent or delay the process of lung cancer, and dietary supplements are a good adjuvant treatment.

4. BREAST CANCER

BC is the most common cancer among women with a high incidence and prevalence. The four subtypes of BC are widely recognized: luminal A; luminal B; human epidermal growth factor (HER2)-positive; and triple negative [115]. Although treatment options have rapidly developed in recent years, relapse and metastasis remain the main causes of BC death. The advances in natural products, particularly in the field of cancer therapy, provide a promising research direction for the treatment of BC (**Table 4**).

4.1 Sulforaphane

In recent years the anti-BC effects of SFN have been widely investigated in preclinical and clinical trials [116, 117]. A clinical trial showed that dietary cruciferous vegetable intake (SFN supplement) is inversely associated with Ki-67 protein (a biomarker of cell proliferation) expression among women scheduled for breast biopsies. This finding indicated that SFN supplements from cruciferous vegetables have potent anti-BC activity (NCT00843167) [118]. Similarly, another randomized pilot intervention study found that ITC-rich broccoli sprout extract supplement has high compliance (100%) and low toxicity (no grade 4 adverse event) rates in BC patients. Large differences in biomarker expression of NQO1, ER-α, ER-β, and cleaved caspase 3 were observed but the differences were not statistically significant due to small sample sizes (NCT01753908) [119]. A mechanistic study demonstrated that SFN influences metabolism and methylation, alters the diversity of gut microbiota, and indirectly affects the activation of aryl hydrocarbon receptor (AHR) by tryptophan metabolism, thereby inhibiting the progression of BC [120]. Moreover, SFN suppresses TGF-β1-induced migration and invasion by

Table 4 | Preclinical studies of natural products and their derivatives in breast cancer.

Compounds	Source	Experiments		Effects and mechanisms	Ref.
		In vivo	*In vitro*		
Sulforaphane	Broccoli, cauliflower	Xenograft BALB/c nude mice for MCF7	MCF7	Sulfate-related metabolites↑, glutathione-related metabolites↑, genus *Lactobacillus*↑; tryptophan metabolites↓, methyl-purine metabolites↓, bacterium *Desulfovibrio*↓, inhibiting the activation of the AHR pathway and influencing microbial diversity	[120]
		C3(1)-SV40 Tag (FVB-Tg(C3-TAg) cJeg/JegJ) (C3) mice, FVB/N-Tg (MMTVneu) 202NK1/J-(HER2/neu) mice	ER(-) BC cell lines (MDA-MB-157 and MDA-MB-231), ER(+) BC cell lines (MCF7), MCF10A	DNMT3B↑, p16↑, p53↑, MYC↑; DNMT3A↓, HDAC1↓, HDAC6↓, KAT2A↓, EZH2↓, HDAC1↓, HDAC3↓, HDAC8↓, tumor growth↓	[123]
		(-)	MDA-MB-231, MDA-MB-157	paxillin↓, IQGAP1↓, FAK↓, PAK2↓, ROCK↓, p-ERK↓, p-MEK↓, inhibiting actin stress fiber formation	[121]
		Xenograft BALB/c nude mice for 4T1	4T1	NRF2↑, HO-1↑, GCLC↑; COX-2↓, PGE2↓; increasing cytotoxic CD8+ T cells	[122]
Curcumin	*Curcuma longa* L.	(-)	MCF7	Vimentin↓, α-SMA↓, fibronectin↓, CXCL12↓, CXCR4↓, NF-κB↓, SHH↓	[130]
		(-)	MCF7 (ER-positive), MDA-MB-231	MAPKAPK3, AKT3, CDK5, IGF1R, and MAPK11 may be potential therapeutic targets of curcumin	[135]
Analogue PAC		(-)	MCF7, MDA-MB-231	BAX↑, apoptosis↑; Bcl-2↓, migration↓, modulating the DNA repair gene expression	[131]
EGCG	Tea	(-)	ADMSC, MDA-MB-231	p-smad2↓, p-NF-κB↓, snail↓, slug↓, CCL2↓, CCL5↓, CXCL8↓, IL-1β↓, IL-6↓, VEGFα↓, HIF-1α↓, COX2↓, IDO↓	[141]
		Normal and breast cancer tissues, xenograft BALB/c nude mice for MDAMB-231 cells	T47D, MCF7, SKBR3, MDA-MB453, UACC-812, MDA-MB-231, BT-549, MDA-MB-468	Cytoplasmic YAP1 inhibition of cell proliferation and promotion of autophagic death; YAP1 promotion of autophagosome formation, autophagic death, assembly of the ESCRT-III complex subunits (CHMP2B and VPS4B) in the cytoplasm	[144]
		C3(1)-SV40 Tag (FVB-Tg(C3-1-TAg) cJeg/JegJ) (C3), FVB/N-Tg (MMTVneu)202NK1/J (HER2/neu)	ER(-) BC cell lines (MDA-MB-157 and MDA-MB-231), ER(+) BC cell line (MCF7)	p16↑, p53↑, MYC↑; BMI1↓, HDAC1↓, HDAC3↓, DNMT3A↓, HDAC3↓, changing the expression of tumor- and epigenetic-related proteins in C3 mice, preventing ER-negative mammary cancer in transgenic mice	[123]
		Xenograft nude mice for MCF7/ADR	MCF7/ADR, MCF7, H9c2	ATP↑, SOD↑, TNF-α↑, iFN-γ↑; IL-10↓, P-gp↓, HMGB1↓, MDA↓,	[145]
Genistein	soy	Preclinical patient-derived xenograft orthotopic mouse models	(-)	Cd74↓, Lp1↓, Sat1↓, Tap63↓, Dnmt3b↓, Tet2↓, Hdac2↓, Dnmts↓, changing genome-wide transcriptomic, DNA methylation, multiple epigenetic-related genes	[148]

Table 4 | Continued

Compounds	Source	Experiments		Effects and mechanisms	Ref.
		In vivo	*In vitro*		
		(-)	MCF7, T47D	HER2↑, p-ERK1/2↑, p-EZH2(Ser21)↑, IL-6↑, IL-8↑; H3K27me3↓	[150]
		(-)	MCF7, BJ	High concentrations of genistein (50 μM and higher) destroyed MCF7 BC cells, but it harmful to dermal fibroblasts at longer exposure times (48 h)	[151]
		(-)	HFF-1	Cleaved PARP↑, ER-β↑, androgen receptor↑; cyclin E↓, pro-caspase 7↓, Aromatase↓, ER-α↓	[149]
Cannabidiol	*Cannabis sativa* L.	Xenograft nude mice for MDAMB-231 cells	TNBC, MCF10A, MDA-MB-468, MDAMB-231	Caspase 9↑, GADD45-α↑, p-p38↑, p-p53↑; integrin-α5↓, integrin-β5↓, integrin-β1↓, fbronectin↓, vimentin↓, Beclin1↓, LOX↓	[153]
		(-)	MCF7, MDA-MB-231, T47D, SK-BR-3, MCF10A, HUVECs	VHL↑, HIF-1α↓, Src↓, proliferation↓, invasion↓, migration↓; suppressing angiogenesis and stem cell-like properties↓	[152]
		(-)	MDA-MB-231	CBD at low threshold concentration (5 μM) protected BC cells; above this concentration, CBD formed aggregates, anti-proliferation, arrested the cell cycle, and triggered autophagy; at higher doses, CBD caused bubbling cell death	[158]
		Xenograft nude mice for MCF7-derived malignant phenotype (6D cells)	(-)	p53↑; Ki67↓, Bcl2↓, CB1↓, p-AKT↓, BIRC3↓, ΔNP63α↓	[157]
		(-)	MCF7	Lactate dehydrogenase↑, apoptosis↑; ATP↓	[154]
		(-)	MCF7aro, HFF-1	Caspase 7/8/9↑, AR↑, apoptosis↑; ER-α↓, aromatase↓, EGR3↓, ERK1/2↓	[155]
Tocotrienol	Palm oil, rice bran, oat, wheat germ, barley and rye	(-)	MDA-MB-231, MCF7	Cytochrome C↑, cleaved PARP-1↑, BAX/Bcl-2↑, cleaved caspase 3↑; p-PI3K↓, p-GSK-3↓	[159]
		(-)	Doxorubicin resistant MCF7	mdr1↓, P-gp↓, inhibition of NF-κB activation and reduction of NF-κB transcriptional activity	[163]
		(-)	MDA-MB-231	Reducing lipid droplet biogenesis; potentiating lipophagy	[164]
		Xenograft BALB/c nude mice for 4TI	4T1	MIG-6↑, Cadherin 13↑, CD4+/CD127+ ↑, CD4+/CD25+↓, CD4+/CD25+/CD73+↓	[165]
Artesunate	*Artemisia annua* L.	Xenograft BALB/c nude mice for 4TI	L-929, 4 T1	MMP-9↓, MMP-2↓, MMP-14↓, FAP↓, fibronectin↓, vimentin↓, α-SMA↓, S100A4↓, p-Smad3↓,TGF-β1↓	[169]

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Table 4 | Continued

Compounds	Source	Experiments		Effects and mechanisms	Ref.
		In vivo	*In vitro*		
		A mammary hyperplasia model	MCF10A	BAX↑; p-AKT↓, p-NF-κB↓, COX-2↓, PCNA↓, proliferation↓, inflammation↓, fibrosis↓	[173]
	(-)		MCF7, HeLa, HCT116, HepG2, A549, MCF7/ADR, A549/*TAX*, A549/DDP	p62↑, LC3↑; m-cathepsin L↓, m-cathepsin D↓, inducing autophagosome accumulation but decreasing the formation of autolysosomes, inhibiting lysosomal function	[172]
		Xenograft BALB/*c* nude mice for 4T1	4T1	Cleaved caspase3↑, cleaved PARP↑, p-H2AX↑, p-p38↑; MMPs↓, uPA↓ p-STAT3↓, FOXM1↓, RAD51↓, survivin↓	[181]
	(-)		MCF7, 4T1, RAW 264.7	Artesunate influenced cell viability, ROS production, cell cycle arrest, and inflammatory responses in a fever-range hyperthermia-dependent manner	[182]

inhibiting the RAF/MEK/ERK pathway in BC cells [121]. Alternatively, the adjuvant administration of SFN enhances the therapeutic effects of doxorubicin against BC. This finding might be explained by blocking myeloid-derived suppressor cell (MDSC) accumulation and suppressive activities, increasing in cytotoxic CD8+ T cells [122]. Strikingly, Li et al. [123] verified that paternal exposure to combined SFN and EGCG synergistically increases tumor latency and prevents the growth of ER(-) BC in control-fed female offspring. These results indicated that SFN shows great promise as a cancer-fighting treatment in BC. Although SFN is not currently being marketed as a dietary supplement, SFN remains a promising natural product, the bioavailability and stability of which need further optimization.

4.2 Curcumin

Several recent studies have reported that curcumin is used for the treatment of BC [124, 125]. For example, a randomized, placebo-controlled clinical study reported that outcomes in BC patients treated with curcumin in combination with paclitaxel was superior to paclitaxel-placebo, exhibiting a higher ORR, improved physical performance, and reduced fatigue following a 12-week treatment period [126]. Additionally, curcumin was shown to reduce radiation-induced dermatitis (RID) in BC patients compared to placebo-treated groups, although this result has not been published (NCT01042938). Extensive *in vitro* and animal experiments have verified that curcumin and its analogs exhibit inhibitory effects on the proliferation, migration, and invasion of BC cells. These actions involve various molecular targets, including the lncRNA HCG11/Sp1 axis, hedgehog/Gli1 signaling pathway, and TGF-β signaling inhibition [127-129]. Furthermore, Jang et al. [130] reported that curcumin remodels the microenvironment of BC by interrupting a positive feedback loop between adipose-derived mesenchymal stem and cancer cells. This finding reflected inhibition of the CXCL12/CXCR4 axis [130]. The curcumin analog, PAC, was shown to inhibit BC by modulating DNA repair pathway gene expression [131]. Of note, a series of studies have demonstrated that curcumin has a pivotal role in augmenting the therapeutic efficiency of chemotherapy drugs in BC [132-134]. Additional high-throughput assays were performed to investigate the potential of MAPKAK3, p-AKT3, CDK5, IGF1R, and MAPK11 as prognostic markers and therapeutic targets for curcumin in treating BC patients [135]. Validation of these findings is necessary both *in vitro* and *in vivo*.

4.3 EGCG

A growing body of research has underscored the prospective role of EGCG or GTE, particularly genistein, in reducing the risk of BC. For example, a clinical trial has shown that supplementation with GTE (containing 64% EGCG) among healthy postmenopausal women did not exhibit significant effects on reduction of mammographic density (MD). However, supplementation

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with GTE did result in an elevation of circulating estradiol concentrations. Notably, a reduction in percent MD was observed among younger women [50-55 years of age] (NCT00917735) [136, 137]. Another double-blind, placebo-controlled, phase II randomized clinical trial revealed that topical EGCG solution is safe for external use on the skin and reduces the occurrence of RID compared to placebo groups (NCT02580279) [138]. Hence, GTE or EGCG may have a complex influence on the progression of BC, which requires more preclinical and clinical evidence. Some researchers have confirmed that EGCG exhibits suppressive effects on tumor growth in BC through diverse mechanisms. This effect encompasses attenuating MDSCs-mediated immunosuppression, halting the acquisition of cancer-associated adipocyte (CAA)-like phenotype, or inhibiting the expression of proline dehydrogenase [139-141]. Both green tea extract and EGCG inhibit BC cell migration [142, 143]. Guo et al. [144] reported that EGCG effectively maintains YAP1 within the cytoplasm, enabling assembly of the ESCRT-III complex and ultimately stimulating autophagic apoptosis in BC cells. Alternatively, polyethylene glycol-doxorubicin/EGCG/folic acid inhibits the expression of P-glycoprotein (P-gp) and reverses the multidrug resistance (MDR) of BC cells, thereby enhancing therapeutic efficacy of doxorubicin [145]. Remarkably, paternal consumption of combined botanicals (SFN or EGCG-rich) contribute to the prevention of ER-negative mammary cancer in transgenic mice [123]. Therefore, natural products as beneficial dietary components may facilitate cancer prevention.

4.4 Genistein

Recently, a phase I clinical trial reported that soy isoflavone, at a dose of 900 mg/day, is safe and well-tolerated among healthy postmenopausal women(NCT00099008) [146]. However, another intervention study concluded that a 12-month soy supplement did not exert a statistically significant impact on breast MRI fibroglandular tissue density or MD (NCT00290758; NCT01219075) [147]. Notably, the lifetime exposure to dietary genistein, starting at conception, decreases the risk of BC risk in mice by modulating epigenetic mechanisms [148]. Genistein was shown to enhance the anti-cancer properties of exemestane *in vitro* [149]. Paradoxically, long-term low-level genistein results in endocrine resistance in BC cells by suppressing H3K27 trimethylation, thus posing potential health risks [150]. Although genistein had high potential for use in the treatment of skin problems during and after BC treatment, genistein is not completely safe. High concentrations of genistein (≥50 μM) destroys MCF7 BC cells but is harmful to dermal skin fibroblasts at longer exposure times (48 h) [151]. These results indicate that genistein, as a partial agonist of ER-α, might be beneficial to tumor prevention under certain conditions but it may possess potential risks to BC patients in other cases, which may vary depending on the concentration, concurrent therapies, and BC subtype.

4.5 Cannabidiol

There have been several isolated reports on the anti-cancer function of CBD through distinct mechanisms. For example, Jo et al. [152] demonstrated that CBD inhibits angiogenesis and CSC properties of BC cells by regulating Src/VHL/HIF-1α signaling. Surapaneni et al. [153] discovered that CBD induces apoptosis, cell cycle G1 arrest, migration suppression, and doxorubicin sensitivity enhancement. The main mechanism of action for CBD involves activation of GADD45α/p38/p53, downregulation of integrin-α5, -β5, and -β1, and inhibition of autophagy [153]. A series of studies have highlighted the promising synergistic effects of combining CBD with exemestane, rimonabant, or photodynamic therapy *in vitro* in improving the treatment of BC. These findings endorse the therapeutic potential of CBD for cancer treatment [154-156]. Furthermore, CBD has been shown to effectively block *in vivo* development of BC [157]. Interestingly, D'Aloia et al. [158] found that the effect of CBD on cultured BC cells depended on a specific threshold concentration. At doses above this threshold, CBD exhibits a potent cytotoxic effect, ultimately inducing the bubbling cell death [158]. CBD not only exhibits anti-cancer effects on BC but may also improve chemotherapy-mediated complications and decrease drug resistance. We expect more clinical evidence to support the application of CBD in BC patients.

4.6 Tocotrienol

Vitamin E, a liposoluble micronutrient, is categorized into subgroups of tocopherols and tocotrienols, each containing four isoforms: α; β; γ; and δ. In general, tocotrienols are abundant in palm oil, rice bran, oats, wheat germ, barley, and rye, whereas tocopherols are mainly present in vegetable oils, such as corn, olive, and sunflower oils [159]. At present, the safety and effectiveness of tocotrienols in the treatment of BC are being evaluated in clinical trials (NCT04496492; NCT03855423). Regrettably, a recent clinical trial concluded that δ-tocotrienol does not improve the effectiveness of neoadjuvant BC treatment or mitigate the incidence of adverse effects (NCT02909751) [160]. This finding is consistent with the results from Nesaretnam et al. [161], who demonstrated that adjuvant tocotrienol therapy does not have an impact on BC-specific survival in women with early BC (NCT01157026). It is important to note that accruing evidence suggest the anti-cancer properties of tocotrienols *in vitro.* For example, based on label-free quantitative proteomics analysis, γ-tocotrienol is thought to be a potential proteasome inhibitor, the inhibitory action of which contributes to the induction of apoptosis [162]. In addition, γ-tocotrienol reverses MDR in doxorubicin-resistant BC cells by regulating the NF-κB-P-gp axis [163]. Moreover, omega 3-docosahexaenoic acid (DHA) together with δ-tocotrienol decreases lipid droplet biogenesis and potentiates lipophagy lipid droplets, possibly exerting a beneficial effect on inhibiting BC malignancy [164]. Conversely, *spirulina*

(Arthrospira) *platensis* plus γ-tocotrienol does not show any synergistic anti-cancer effects *in vivo*. Compared to combination groups, the γ-tocotrienol alone group induced more necrotic cells based on histopathologic analysis [165]. Interestingly, Idriss et al. [159] reported that β-tocotrienol exhibits more cytotoxic effects than γ-tocotrienol on BC cells and β-tocotrienol induces apoptosis via a P53-independent PI3K dependent pathway. These preclinical investigations suggest that tocotrienol may be a promising anti-cancer agent for BC. Furthermore, the four isoforms of tocotrienols may have distinct roles in the treatment of cancer. Future research, including additional animal studies and larger clinical trials, is necessary to fully evaluate the therapeutic potential of tocotrienols in BC.

4.7 Artesunate

Artesunate is a semi-synthetic derivative of the Chinese herb, *Artemisia annua L.*, that has an excellent safety profile in the treatment of malaria [166]. A recent phase I study demonstrated that chronic oral intake of artesunate (up to 200 mg/day [2.2-3.9 mg/kg/day]) over a period of 37 months did not elicit any significant safety concerns among patients with metastatic BC (NCT00764036) [167]. Another clinical case reported that in a patient with metastatic BC oral artesunate maintained disease stabilization for a duration of 1.5 years. Biomarker profiling revealed that carcinoembryonic antigen may be a potential target of artesunate [168]. A mechanistic study demonstrated that artesunate and dihydroartemisinin suppresses TGF-β signaling, subsequently inactivating cancer-associated fibroblasts, leading to inhibition of cancer growth and metastasis [169]. Other research showed that artesunate exhibits synergistic interactions with doxorubicin or TP-0903, a mesenchymal-epithelial transition and receptor tyrosine kinase inhibitor, and enhances the cytotoxic effect on BC cells [170, 171]. Recent evidence suggests a connection between enhanced lysosomal function and paclitaxel resistance in cancer cells. This resistance can be overcome with artesunate or other inhibitors of lysosomal function [172]. Simultaneously, artesunate was shown to effectively mitigate the proliferation of mammary hyperplasia by suppressing the NF-κB and AKT signaling pathways in a rat model of mammary hyperplasia [173]. Hence, artesunate is a potential natural product or dietary supplement. The effectiveness of artesunate in preventing BC needs to be supported by additional clinical data.

4.8 Mistletoe

Mistletoe, as a complementary and alternative medicine, has become increasingly popular among cancer patients [174-176]. Accumulating evidence indicates that mistletoe may have a positive impact on the quality of life among patients with BC, such as improving fatigue, insomnia, and physical function [177, 178]. Moreover, a real-world data study demonstrated that add-on *Viscum album* L. did not negatively impact the safety profile of targeted therapies in breast and gynecologic cancer patients [179]. Similarly, other clinical trials revealed that mistletoe is safe and decreases chemotherapy side effects but does not influence the frequency of relapse and metastasis within 5 years [180]. Cellular and animal experiments have demonstrated that mistletoe induces apoptosis and inhibits metastasis by targeting the STAT3-FOXM1 pathway in BC [181]. Mistletoe exerts distinct effects on BC cells and macrophages, influencing cell viability, ROS generation, cell cycle arrest, and inflammation, all of which are modulated by changing in fever-range hyperthermia [182]. Although clinical trials have been conducted to investigate the potential of mistletoe in mitigating the side effects and enhancing anti-cancer effects, only a few numbers of animal studies have delved into the underlying molecular targets and mechanisms of its actions.

5. GYNECOLOGIC TUMOR

Gynecologic tumors are common tumors in women, affecting the health of women worldwide. Cervical, ovarian, and endometrial cancer (EC) are common gynecologic tumors. In recent years, natural products used in the treatment of gynecologic tumors have also received attention (**Table 5**).

5.1 Cervical cancer

5.1.1 Curcumin. Recently, several clinical trials have commenced to assess the safety and effectiveness of curcumin in the treatment of cervical cancer, as well as its potential as a complementary medicine in conjunction with standard therapy (NCT02554344; NCT04294836). For example, a phase II study showed that the combination of pembrolizumab, stereotactic body radiotherapy, and low-dose cyclophosphamide, aspirin, lansoprazole, vitamin D, and curcumin (IDC) did not meet expected clinical activity in cervical and EC patients but some difficult-to-treat patients may have derived benefit from this therapeutic regimen, with durable responses (NCT03192059) [183]. Mechanistic studies found that curcumin exhibits a cytotoxic effect on cervical cancer cells *in vitro* through activation of p53 and p21 signaling [184, 185]. Similarly, in papillomavirus (HPV)-positive cervical cancer cells, curcumin suppresses proliferation and migration by directly targeting the viral oncoprotein E6 protein, subsequently activating p53 and p21 [186]. Interestingly, Lee et al. [187] discovered that the curcumin derivative, CLEFMA, triggers intrinsic and extrinsic apoptotic pathways by activating ERK1/2 and p38 signaling [187]. Conversely, EF24 suppresses cellular migration and MMP-9 expression by inhibiting p38 signaling [188]. While curcumin shows excellent anti-cancer effects based on preclinical evidence, more scientific evidence is required to determine whether curcumin can

Table 5 | Preclinical studies of natural products and their derivatives in other types of cancers.

Type of cancer	Compounds	Source	Experiments		Effects and mechanisms	Ref.
			In vivo	*In vitro*		
Cervical cancer	Curcumin	*Curcuma longa* L.	(-)	HeLa, CaSki	p53↑, p21↑, BAX↑, cleaved caspase 3↑, E-cadherin↑, Bcl-2↓, N-cadherin↓,vimentin↓, viral oncoproteins E6 and E7↓	[186]
			The laying hen develops ovarian cancer spontaneously, diet supplemented with whole flax seed, defatted flax meal or flax oil	(-)	CYP1A1↑, 2MeOE2↑, p-p38↑, p-ERK1/2↑, CYP3A4↓, a whole flaxseed supplemented diet decreased the onset and severity of ovarian cancer	[193]
			The laying hen develops ovarian cancer spontaneously, diet supplemented with whole flax seed, defatted flax meal or flax oil	BG1, HeyC2, TOV112D	2MeOE2↑, DHA↑, 2MeOE2 and DHA both have anti-angiogenic effects. 2MeOE2 has pro-apoptotic effects, anti-cancer actions of 2MeOE2 are dependent on p38-MAPK pathway	[194]
	Analogue CLEFMA		Xenograft SCID mice for HCC827	HCC827	CPTI↑, CPTII↑, Hsp60↑, long-chain acylcarnitines↑, mitochondrial dysfunction↑; short-chain acylcarnitines↓, Tom20↓; disrupting the fatty acyl metabolism	[187]
	Analogue EF-24		(-)	HeLa, SiHa	MMP-9↓, p-p38↓, migration↓	[188]
Endometrial cancer	Curcumin	*Curcuma longa* L.	Xenograft NOD-SCID mice for Ishikawa	Ishikawa, HEC-1B, VERO	Slit-2↑, ROS↑, apoptosis↑; SDF-1↓, CXCR4↓, MMP-2↓, MMP-9↓, CTGF↓, migration↓	[198]
	Analogue CP41		Xenograft BALB/c nude mice for HEC-1B	AN3CA, HEC-1B	H3F3A ↑,p-p38↑, p-ERK↑, p-JNK↑, BAX↑, cleaved caspase 3↑, ROS↑, mitochondrial impairment↑, endoplasmic reticulum stress↑; Bcl-2↓, proteasome↓	[199]
	Genistein	Soy	Xenograft BALB/c nude mice for Ishikawa, EC tissues of 51 patients aged<40 years	Ishikawa	PR↑, FOXO1↑, c-Jun↑, p-JNK↑, cleaved caspase 3↑, p-cdc2↑; p-histone H3↓,C/EBPβ↓, Ki-67↓, inducing cell cycle arrest in G2 and apoptosis	[201]
	Pterostilbene	Blueberries, grapes	EC tissues of 51 patients	HTB-111, Ishikawa	caspase 3/8/9↑, BCL2L14↑, miR-663b↓	[203]
Kidney cancer	Genistein	Soy	(-)	786-O, ACHN	Cleaved caspase 3/8/9↑, BAX↑; CD133↓, CD44↓, ALDH1A1↓, Oct4↓, Nanog↓, PCNA↓, cyclin D1↓, Bcl-2↓, renal CSCs↓	[206]
Pancreatic cancer	Curcumin	*Curcuma longa* L.	(-)	PANC1, AsPC-1	TFPI-2↑, E-cadherin↑; p-ERK↓, p-JNK↓, N-cadherin↓, vimentin↓	[213]
			(-)	p53Y220C mutant cancer line BxPC-3	Caspase 3↑, stabilizing p53Y220C mutant and restore its function	[215]
			(-)	p53Y220C mutant cancer line BxPC-3	Cleaved caspase 3/7↑, cleaved PARP↑, BAX↑; p-Bcl2↓, rescuing mutant p53Y220C	[214]

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Table 5 | Continued

Type of cancer	Compounds	Source	Experiments		Effects and mechanisms	Ref.
			In vivo	*In vitro*		
	Analogue FN2		(-)	PANC1	BAX↑, apoptosis↑; Bcl-2↓, p-p65↓, p-AKT↓, cell growth↓	[208]
	Analogue C66		(-)	HPNE, BxPC3, SW1990 PANC1	IL-1β↓, IL-6↓, IL-8↓, IL-15↓, TNF-α↓, COX2↓, p-JNK↓	[212]
	Genistein	Soy	Xenograft NOD/SCID nude mice for genistein-resistant PaCa and PANC1 cells	PANC1, PaCa	DEPTOR↑; ELK1↓; inhibiting PI3K/AKT/mTOR pathway, enhancing the sensitivity of PC cells to genistein	[218]
			(-)	MiaPaCa2 and PANC1, H6C7	Cytosolic cytochrome c↑, cleaved caspase 3/9↑, ROS↑; STAT3↓, survivin↓, mitochondrial membrane potential↓, cyclin D1↓,ALDH1A1↓, cell viability↓; triggering cell cycle arrest in G0/G1 phase	[219]
	Analogue AXP107-1		Patient-derived xenograft BALB/c) nude mice model	MiaPaCa2, PANC1	Cleaved PARP↑, cleaved caspase 3/9↑, GPER1↑; MUC1↓; reducing chemoresistance of gemcitabine	[217]
	Cannabidiol	*Cannabis sativa* L.	Xenograft PAK1 wild type and knockout C57BL6 mice for murine PC cells TB33117	PANC1, CFPAC1, Capan2, SW1990, HPAF11, MiaPaCa2, PSCs	PD-L1↓, PAK1↓, pPAK1↓; inhibiting the proliferation of PC, PSC, and PSC-stimulated PC cells	[220]
			Xenograft C57BL/6NTac mice for PANC02	PANC02	Enhancing radiation therapy treatment outcomes	[221]
			(-)	PANC1, MiaPaCa2	CBD increased the chemosensitivity of gemcitabine and paclitaxel; oxygen-ozone enhanced the cytotoxicity of CBD; the combination of CBD with oxygen-ozone resulted in an upregulation of the CDKN2A, MAP2K1, and ERBB2 genes, a downregulation of the BRAF, RHOA, AKT1, AKT2, PIK3CB, PIK3CD, PIK3R1, and PIK3R2 genes	[222]
			(-)	PANC1, U266	IL-2 determined the expression of CB2 receptor, CBD increased the cytotoxicity of CIK cells	[223]
Bladder cancer	SFN	Broccoli, cauliflower	32 bladder tumors and 20 adjacent non-tumor tissue samples; nitrosamine-induced bladder tumor model in C57BL/6 mice	RT4, T24, UMUC-3	HK2↓, PDH↓, AKT1↓, p-AKT↓, N-PKM2↓ SFN inhibited ATP production by inhibiting glycolysis and mitochondrial oxidative phosphorylation (OXPHOS)	[225]
	Genistein	Soy	(-)	SV-HUC-1	E-cadherin↑; vimentin↓, Snail↓, Slug↓, CD44↓, Cyclin D1↓, PCNA↓, p-ERK↓, p-AKT↓, p-STAT3↓	[230]

Table 5 | Continued

Type of cancer	Compounds	Source	Experiments		Effects and mechanisms	Ref.
			In vivo	*In vitro*		
Melanoma	SFN	Broccoli, cauliflower	The zebrafish embryos were exposed tp SFN and phenylthiourea	B16F10, A375	Tyrosinase↑, melanin biosynthesis↑; MITF↑, PKCβ1↑, PCNA↓	[234]
			(-)	A375	Anti-carcinogenic activities of sulforaphane are influenced by nerve growth factor	[235]
Leukemias	Curcumin	*Curcuma longa* L.	(-)	Jurkat	Cannabidiol, curcumin, and quercetin induced mitochondrial membrane potential loss and Ca^{2+} overload, curcumin, and quercetin caused direct mitochondrial uncoupling	[237]
			(-)	MOLT-4, BJ	The combination of curcumin, genistein, resveratrol, and quercetin has cooperative anti-neoplastic activity without a significant effect on non-tumor cells	[239]
			Xenograft BALB/c nude mice for HL-60	HL60	Cleaved caspase3↑, BAX↑, p27↑; HOTAIR↓, WT1↓,miR-20a-5p↓, Bcl-2↓	[240]
			Xenograft NOD/SCID mice for MOLM13	MOLM13, OCI-AML2, HL60	ROS↑, mitochondrial dysfunction↑, p21↑, p-JNK↑, p-p38↑, cleaved caspase 3↑, cleaved PARP↑; CHK1↓, RAD51↓, Cyclin-D↓, XIAP↓, c-Myc↓; enhancing cytarabine sensitivity	[241]
Lymphomas	Curcumin	*Curcuma longa* L.	(-)	CH12F3	γH2AX↑, PARP1↑, PCNA↑, caspase 3/9↑, Rad51↓, inducing DNA breaks, sensitizing lymphoma cells to various DNA damage drugs	[249]
			Xenograft BALB/c nude mice for Raji	U937, Raji	Cleaved caspase 3↑, cleaved caspase 9↑, BAX↑, E-cadherin↑; p-Smad3↓, N-cadherin↓, Bcl-2↓	[250]
			131 DLCBL tissue samples, xenograft BALB/C nude mice for Raji	OCI-LY8, Raji	CD59↓, pCREB↓, inhibiting the activation of NF-kB	[251]
Multiple myeloma	GZ17-6.02 (isovanillin, harmine and curcumin)	*Curcuma longa* L.	(-)	ALMC1, ANBL6, U266	p-ATG13↑, p-S318↑,Beclin1↑, ATG5↑, BAK↑, BIM↑; Bcl-XL↓, MCL1↓, HDACs1/2/3↓, causing autophagosome formation and autophagic flux, regulating histone H3 acetylation and methylation	[254]
	Cannabidiol	*Cannabis sativa* L.	(-)	KMS-12 PE, U266	CB2 receptor is highly expressed on CIK cells and MM cells	[259]

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be used as a dietary supplement for the prevention or treatment of cervical cancer.

5.1.2 Other natural products. Bryostatin1 is a putative anti-cancer compound derived from marine animals [189]. However, current clinical trials have not met expectations [190]. Nezhat et al. [191] reported that bryostatin-1 and cisplatin combination therapy is not effective in metastatic or recurrent cervical cancer patients (NCT00005965). Likewise, the clinical evaluation of polyphenol E was also disappointing. According to Garcia [192], the administration of polyphenol E did not promote the clearance of persistent high-risk HPV infection and low-grade cervical intraepithelial neoplasia among women, compared to the placebo groups (NCT00303823). Therefore, the underlying mechanisms of these natural products is seldom mentioned in recent studies.

5.2 Ovarian Cancer

5.2.1 Flaxseed. Flaxseed, isolated from *Linum usitatissimum L.*, is composed of total fat (polyunsaturated, monounsaturated, and saturated fatty acids), carbohydrate (total dietary fiber and sugars), protein, water, minerals, vitamins, and lignans. In the laying hen a whole flaxseed supplemented diet decreased the onset and severity of spontaneous ovarian cancer. This flaxseed-enriched diet stimulated the systemic production of 2-methoxyestradiol (2MeOE 2) and DHA, thereby promoting apoptosis and decreasing angiogenesis in ovarian tumors but not in normal ovarian tissues [193, 194]. Another LC-MS/MS metabolomics approach also demonstrated that flaxseed increased animal lifespan and reduced ovarian cancer severity [195]. These findings indicate that flaxseed may be a healthy dietary habit to weaken ovarian cancer severity.

5.2.2 Other natural products. Although bryostatin-1 and squalamine have been investigated in clinical trials of ovarian cancer, these clinical trial results have not been published. Moreover, current clinical trials are experiencing disappointment. For example, Morgan et al. [196] observed that bryostatin-1 in combination with cisplatin treatment of patients with recurrent or persistent ovarian cancer had a modest response rate, but toxicities were insufferable and precluded tolerability. Consequently, these two natural products have rarely been mentioned in recent clinical and animal research pertaining to ovarian cancer.

5.3 Endometrial Cancer

5.3.1 Curcumin. Recently, clinical investigations have been conducted on the potential therapeutic effect of curcumin for EC. Specifically, seven EC patients who consumed curcumin orally for 2 weeks exhibited minor immunomodulatory effects without a significant trend in quality of life improvement (NCT02017353) [197]. Curcumin was shown to inhibit cellular migration *in vivo* by inducing Slit-2 mediated downregulation of SDF-1 and CXCR4 [198]. Further research demonstrated that the curcumin analogue, CP41, induced apoptosis by activating the H3F3A/proteasome-MAPK signaling pathway and augmenting oxidative stress. Additionally, CP41 enhanced the sensitivity of EC to chemotherapeutic agents through mediation of H3F3A [199]. These findings suggest that curcumin holds considerable promise as a natural therapeutic agent for the treatment of EC.

5.3.2 Genistein. Previous research has revealed that soy isoflavone containing genistein, daidzein, and glycitein is safe and well-tolerated in healthy postmenopausal women. However, limited endometrial biopsy samples have prevented the trial from evaluating the effectiveness of isoflavone in preventing EC in this group (NCT00099008) [146]. Another multiethnic cohort study demonstrated that the highest intake of total isoflavones, daidzein, or genistein was associated with a decreased risk of EC in non-hysterectomized postmenopausal women [200]. Currently, there is a scarcity of prospective studies on overall or individual isoflavones, particularly genistein. Furthermore, immunohistochemistry analysis found that elevated progesterone receptor (PR) expression significantly increased rates of progression-free and OS among 31 young EC patients. Genistein was shown to increase long-time PR expression *in vivo* and inhibit cell proliferation in an ER-independent manner [201]. Although genistein has been assessed in different clinical trials, the precise mechanism by which genistein might help prevent EC has not been established. Additional laboratory and animal studies are clearly needed.

5.3.3 Pterostilbene. Pterostilbene, a resveratrol analog, is extracted mainly from blueberries and grapes. Existing evidence indicates that pterostilbene-mediated endometriotic cell apoptosis modulation has been confirmed to be more potent than resveratrol [202]. Of note, a clinical trial is presently underway to assess the effectiveness of megestrol acetate with or without pterostilbene in the treatment of patients with EC undergoing hysterectomy (NCT03671811). Furthermore, Wang et al. [203] concluded that EC patients with high miR-663b expression have a significantly poor prognosis. An *in vitro* study revealed that pterostilbene effectively suppresses cell viability and induces apoptosis via the miR-663b/BCL2L14 signaling pathway [203]. As a result, pterostilbene holds promising potential in the treatment of EC but further clinical and animal studies are imperative to validate the therapeutic effectiveness.

In conclusion, there are relatively few clinical studies on natural products for use in gynecologic tumors. Notably, Chinese medicine treats some chronic gynecologic diseases with good curative effect, employing theories that include preventive measures, the reinforcement of vital qi to eliminate pathogenic factors, and the enhancement of bodily resistance. The theoretical

guidance of Chinese medicine will greatly inspire the research of natural products. Targeting natural products may be a promising direction to enhance health management and prevention of gynecologic tumors.

6. KIDNEY CANCER

Kidney cancer is not a single disease. Kidney cancer represents several distinct types of cancer. Renal cell carcinoma (RCC) is the most common subtype, accounting for 85% of all cases [204]. In addition to surgery, there has been an explosion in target therapies that control tumor growth and the creation of blood vessels in the past decade [205]. In addition, the use of natural products for the treatment of kidney cancer has attracted attention.

6.1 Genistein

A recent clinical trial examined the impact of combining genistein with interleukin-2 (IL-2) in patients diagnosed with metastatic melanoma or kidney cancer (NCT00276835). Existing evidence demonstrated that genistein exhibits an interventional inhibitory effect on renal CSCs *in vitro* by suppressing the sonic hedgehog (Shh) pathway [206]. Although genistein has obtained attention in clinical trials of kidney cancer, mechanistic studies are lacking.

6.2 Other natural products

Sunitinib is recognized as the standard first-line therapy for advanced RCC. Nevertheless, sunitinib is associated with numerous side effects, one of which is fatigue, which occurs frequently. A recent phase I clinical trial has demonstrated that isoquercetin is safe and effective in reducing fatigue among kidney cancer patients receiving sunitinib treatment. This finding holds significant promise for improving the quality of life for these patients (NCT02446795) [207]. Other natural products contain shark cartilage (AE-941) and bryostatin 1. Shark cartilage has gradually lost interest among researchers. The anti-cancer effect of bryostatin 1 on kidney cancer has not been verified *in vivo* or *in vitro.* To date, natural product clinical trials in kidney cancer therapy are limited. It must be recalled that Chinese medicine has a thorough theoretical system with a focus on kidney disease in the ancient books of *Yellow Emperors Classic of Medicine*. Based on these rich theories and abundance of Chinese medicinal herbs, the search for compound Chinese medicine and monomers suitable for the treatment of kidney diseases and cancer has unique advantages.

7. PANCREATIC CANCER

Pancreatic cancer (PC) is a fatal malignant tumor with a 5-year survival rate of 5% [208]. PC has an extremely poor prognosis due to extensive local invasion, early systemic dissemination, and resistance to chemotherapeutic drugs. Surgery is the most effective treatment of PC, but 80%-85% of patients are diagnosed with advanced and unresectable disease [209]. Hence, considering natural products as a research direction is a promising breakthrough.

7.1 Curcumin

Presently, clinical trials exploring the therapeutic potential of curcumin in PC treatment have been conducted (NCT00192842, NCT00486460, NCT00094445). Of note, a prospective phase II trial has demonstrated that the phytosome complex of curcumin, as a complementary therapy in first-line therapy of advanced PC, had improved safety and efficacy compared to gemcitabine [210]. The curcumin analogue, FN2, also augmented the inhibitory effect of gemcitabine on PC cells [208, 211]. Another curcumin derivative, C66, has good anti-inflammatory activity. C66 was shown to inhibit the progression of PC cells via inhibition of JNK-mediated inflammation [212]. Curcumin inhibits ERK- and JNK-mediated EMT *in vitro* by upregulating TFPI-2, subsequently suppressing the migration and invasion of PC cells [213]. In addition, the p53Y220C mutation, a commonly identified variant in the p53 gene, results in the inactivation of the tumor suppressor protein, p53. This mutant p53Y220C is frequently observed in numerous tumors, including PC. Notably, curcumin has the potential to rescue mutant p53Y220C, thereby activating apoptosis [214, 215]. Therefore, curcumin possesses potential significance in the prevention and treatment of PC but additional clinical evidence is required to support its application.

7.2 Genistein

AXP107-1, a novel crystal form of genistein, has been demonstrated in a phase Ib clinical trial to be safe in patients with PC when used in combination with gemcitabine with no signs of hematologic or non-hematologic toxicity and with elevated serum levels [216]. The efficacy requires a larger sample size for verification. Of note, animal studies have verified that AXP107-1 in combination with gemcitabine has synergistic anti-cancer effects by activating GPER1 signaling [217]. In addition, Li et al. [218] showed that downregulation of ELK1 leads to upregulation of DEPTOR, which in turn enhances the sensitivity of PC cells to genistein through inhibition of mTOR signaling [218]. The anti-cancer effects of genistein *in vitro* are associated with induction of ROS-mediated mitochondrial apoptosis, cell cycle arrest, and regulation of STAT3 signaling [219]. In conclusion, these results predict that both curcumin and genistein are hot candidate adjuvant drugs for the treatment of PC. New delivery systems for genistein or curcumin contribute to improving bioavailability, stability, and application.

7.3 Cannabidiol

In recent years the treatment of CBD for PC has also attracted attention. For example, CBD was shown to inhibit the proliferation of PC, pancreatic stellate cell

(PSC), and PSC-stimulated PC cells by targeting the P-21 activated kinase 1 (PAK1)-dependent pathway. Furthermore, CBD also inhibits the expression of PD-L1 via downregulating PAK1 activity, thereby potentiating the immune checkpoint blockade of PC [220]. Additionally, Alfonzetti et al. [221] demonstrated that CBD augments the sensitivity of radiotherapy *in vivo* and *vitro*. Likewise, the combination of CBD and oxygen-ozone exhibited a synergistic augmentation in cytotoxic effects on PDAC cell lines [222]. It is known that cytokine-induced killer cells (CIKs) are pivotal cytotoxic immunologic effector cells and have shown encouraging synergistic effects when combined with cancer-associated inhibitors and blockade. Specially, a low dose of CBD was shown to significantly enhance the cytotoxic function of CIKs without exerting any associated mediators in pancreatic and myeloma cells [223]. CBD treatment may help increase the therapeutic response for non-responder patients by activation of CIK therapy. CBD is a promising adjuvant therapy medicine that can enhance the effectiveness of chemoradiotherapy in PC through various pathways and mechanisms.

8. BLADDER CANCER

Bladder cancer is the 10th most common cancer type worldwide with a 5-year survival rate of approximately 70% [224]. Huang et al. [225] showed that patients with stage T1 bladder cancer have unique glucose metabolic abnormalities. SFN significantly downregulates glucose metabolism by blocking the AKT1/HK2 axis [225]. Alternatively, Wang et al. [226] confirmed that upregulation of FAT atypical cadherin 1 (FAT1) is associated with a lower survival rate of patients with bladder cancer. *In vitro* studies further demonstrated that SFN inhibit FAT1 expression, thereby suppressing the viability and metastasis, and promoting apoptosis of bladder cancer cells [226]. In addition, a series of studies have indicated that SFN has a crucial role in overcoming drug resistance, particularly in the case of resistance to cisplatin, gemcitabine, or everolimus [227-229]. These laboratory and animal studies indicated that SFN has an important role in inhibiting the development of bladder cancer. However, the clinical trials of SFN or broccoli sprout extract in bladder cancer were terminated due to low accrual. Thus, a new delivery system for SFN may be necessary to improve bioavailability and decrease side effects, such as liposomes, cyclodextrin inclusion, and nanotechnologic approaches. Other natural compounds that have attracted attention in clinical trials for bladder cancer therapy include genistein and polyphenol E. Genistein has been shown to inhibit arsenic-induced EMT phenotype and CD44 expression *in vitro* by inhibiting HER2 phosphorylation [230]. Genistein and polyphenol E have received relatively little attention compared to SFN *in vitro* and *in vivo.*

9. MELANOMA

Melanoma is the most severe form of skin cancer [231]. The 5-year survival rate for cutaneous melanoma is 93% but patients with distant metastases have a 5-year survival rate of only 27% [232]. A clinical trial has demonstrated that the oral broccoli sprout extract, SFN, at a daily dose up to 200 μmol, is safe and well-tolerated in patients with melanoma and achieved dose-dependent levels in plasma and skin [233]. In a melanoma cell and zebrafish model, SFN has been shown to induce cell differentiation, melanogenesis, and inhibit proliferation by regulating the expression of MITF, PKCβ1, and tyrosinase [234]. However, when SFN combined with other biological elements, such as nerve growth factor, the anti-carcinogenic activities were partly reversed [235]. The next study should explore the role of SFN in combination with other chemotherapy drugs. Apart from SFN, other natural products include genistein and bryostatin-1 but have fewer clinical and animal results. In conclusion nrelatively few natural products have progressed to the clinical trial phase for the treatment of bladder cancer and melanoma.

10. HEMATOLOGIC MALIGNANCIES

10.1 Leukemia

Leukemia is a group of malignant disorders of the blood, bone marrow, and lymphoid system. Leukemia is further divided into four major types: acute myeloid leukemia (AML); acute lymphocytic leukemia (ALL); chronic myeloid leukemia (CML); and chronic lymphocytic leukemia (CLL) [236]. In recent years the potential of natural products in the treatment of hematologic tumors has garnered widespread interest. Specifically, curcumin has emerged as a promising candidate for clinical trials. In ALL cells, three phenolic compounds (curcumin, CBD, and quercetin) display anti-leukemic activity by promoting mitochondrial membrane potential loss and mitochondrial Ca2+ overload. Notably, curcumin and quercetin further facilitate mitochondrial uncoupling [237]. This mechanism may enable curcumin to reduce glucocorticoid resistance in ALL cells [238]. Similarly, further research showed that the "cocktail" of four phenolic compounds (curcumin, genistein, resveratrol, and quercetin) has a cooperative anti-neoplastic activity on ALL cells without a significant effect on non-tumor cells [239]. In the context of AML, curcumin was shown to attenuate adriamycin resistance by suppressing the HOTAIR/miR-20a-5p/WT1 pathway in AML cells [240]. Moreover, mitocurcumin utilized oxidative stress to upregulate JNK/p38 to lead to apoptosis and overcome cytarabine resistance via ROS/p21/CHK1 in AML [241]. Similarly, curcumin and its analogs also exhibit chemopotentiating properties in other leukemia subtypes, such as CLL and CML [242, 243]. In addition, a variety of curcumin analogues, including EF-24, C1206, C212, and DMC, have been shown to possess anti-leukemic properties in leukemia [244-247]. These results indicate that

curcumin is a promising anti-cancer medicine against various subtypes of leukemia. Conversely, other natural products exhibit limited clinical and animal-based results in the treatment of leukemias.

10.2 Lymphomas

Lymphomas arise from an aberrant clonal proliferation of lymphocytes and can present within any organ in the body. According to the WHO classification, mature lymphoid neoplasms are mainly divided into non-Hodgkin's lymphoma (NHL), which accounts for approximately 90% of all lymphomas, and Hodgkin's lymphoma (HL), which accounts for approximately 10% [248]. Curcumin triggers caspase 3-dependent apoptosis *in vitro* and induces DNA damage through impairing Rad51-dependent homologous recombination. More importantly, curcumin enhances the sensitivity of lymphoma cells to various DNA damage drugs, including hydroxyurea, camptothecin, and cisplatin [249]. Curcumin in combination with homoharringtonine synergistically inhibit lymphoma cell growth *in vivo* by inhibiting the TGF-β/Smad3 signaling pathway [250]. It is known that CD20 is a prerequisite for rituximab anti-tumor activity. Inhibiting the expression of CD59 is a good strategy for overcoming resistance [251]. Both curcumin and perillyl alcohol suppress activation of NF-κB and CREB, and subsequently restrain expression of CD59 but not CD20, thereby sensitizing rituximab-resistant B lymphoma cells [251]. In conclusion, curcumin may be a potential adjuvant drug to enhance the efficacy of chemotherapy drugs in leukemias and lymphomas but clinical application needs additional data support.

10.3 Multiple Myeloma

Multiple myeloma (MM) is described as an incurable malignant disease that accounts for approximately 10%-15% of all hematologic malignancies [252]. Currently, immunotherapy, particularly chimeric antigen receptor T cell therapy, has an increasingly significant role in the treatment of hematologic tumors, including MM. Natural products retain unique benefits in enhancing the potency of other drugs while mitigating adverse effects. A pilot randomized clinical trial demonstrated that the combination of curcumin with melphalan and prednisone is more effective on improving overall remission and reducing the levels of NF-κB, VEGF, TNF-α, and IL-6 among MM patients compared to the group receiving only melphalan and prednisone [253]. GZ17-6.02, a synthetically manufactured compound containing isovanillin, harmine, and curcumin, has been shown to enhance the toxicity of proteasome inhibitors to kill MM cells *in vitro* [254]. Additionally, a number of studies have demonstrated that omega-3 fatty acid derivatives of DHA or eicosapentaenoic acid (EPA) not only alleviate bortezomib resistance by facilitating glutathione degradation but also increase bortezomib cytotoxicity. More importantly the co-incubation time is also crucial in this process [255-257]. Furthermore, Mekkawy et al. [258] reported that bone marrow-derived MM CSCs exhibit potential as a prognostic indicator for predicting recurrent MM incidence among MM patients. Treatment with curcumin and piperine induce cell cycle arrest and apoptosis in MM CSCs [258]. Schmidt-Wolf et al. [259] verified that CB2 receptor is highly expressed on CIK cells as well as on MM cells. A low concentration of CBD could enhance the cytotoxic function of CIKs [259]. Hence, a thorough investigation into the precise mechanism by which CBD modulates CIKs in MM is imperative. In the future, we also look forward to more clinical data and application of natural products in the treatment of hematologic tumors.

11. OTHER TUMORS

Hepatocellular carcinoma (HCC) is among the most common and deadliest cancers and treatment options are limited. Huaier, a traditional herb, has enjoyed widespread application in Chinese medicine for approximately 1600 years. Multiple clinical trials have demonstrated that the administration of huaier granules extends recurrence-free survival (RFS) and OS after curative resection of HCC. Furthermore, this treatment also reduces extrahepatic recurrences [260-262]. Similarly, SRL therapy (sirolimus, thymalfasin, and huaier granules) has been shown to be safe and effective in preventing HCC recurrence following liver transplantatio, without significant adverse events [263]. These results suggest that huaier granules are a promising candidate natural product for the treatment of HCC. In addition to huaier granules, other natural products have been advanced to clinical trials, including icaritin, ginsenoside Rg3, artesunate, CBD, coriolus versicolor, and Xiang Sha Liu Jun Zi decoction. Gastric carcinoma accounts for approximately 6% of cancers worldwide and is the 3rd leading cause of cancer-related deaths [264]. Recently, huaier granules, ginsenoside Rg3, mistletoe, and bryostatin 1 have moved into clinical trials for gastric carcinoma but these results have not been published or completed.

12. CONCLUSION AND PERSPECTIVE

Natural products are structurally diverse and have a wide range of sources and unique pharmacologic and biological activities [265, 266]. Currently, natural product-based pharmaceuticals and diet supplement development strategies play an important role in modern new drug development, accounting for a significant share of the market. For example, resveratrol and quercetin have been marketed as dietary supplements. The development of natural products is driving more dietary supplements to market. Remarkably, arsenic, a traditional Chinese medicine, has demonstrated remarkable effectiveness in the treatment of relapsed acute promyelocytic leukemia, highlighting its significant medical value [267]. Other natural products, such

Table 6 | Natural products that have been tested in cancer treatment of clinical trials.

Disease	Natural product	References (https://clinicaltrials.gov)
Colorectal cancer	Curcumin, curcumin C3 complex	NCT02724202*, NCT00973869*, NCT01859858*, NCT01333917,NCT00027495*, NCT00003365*, NCT01294072*, NCT00295035, NCT05472753*, NCT02439385*, NCT01490996
	Resveratrol	NCT00256334, NCT00433576
	Quercetin	NCT00003365*
	Rutin	NCT00003365*
	Genistein	NCT01985763
	Cannabidiol	NCT03607643, NCT04398446
	Epigallocatechin gallate, green tea extract	NCT02891538, NCT01239095, NCT01360320*, NCT02321969*, NCT01606124
	Andrographolides	NCT01993472
	Mistletoe extract	NCT00049608*
	Oligofructose-enriched inulin	NCT00335504
	Topical menthol	NCT01855607
	Shark cartilage (BenFin)	NCT00026117
	Hydroxytyrosol	NCT05472753*
	Artesunate	NCT03093129, NCT02633098
Lung cancer	Sulforaphane, broccoli sprout extract	NCT03232138*, NCT00255775*
	Curcumin, curcumin C3 complex, Theracurmin 2X	NCT01048983, NCT03598309, NCT02321293*, NCT04871412*
	Epigallocatechin gallate, green tea extract, polyphenon E	NCT02577393, NCT04871412*, NCT01317953*, NCT00611650, NCT00573885, NCT00363805*, NCT00707252
	Coriolus Versicolor	NCT04871412*
	Chlorogenic acid	NCT03751592
	Soy isoflavones	NCT01958372*
	R-(-)-gossypol acetic acid, Gossypol	NCT00544596, NCT00397293, NCT00544960, NCT00934076, NCT00988169, NCT00773955, NCT01977209
	Mistletoe extract	NCT00052325*, NCT00079794, NCT00516022, NCT00049608*
	Genistein	NCT00769990*, NCT01628471
	Ginsenoside H dripping pills	NCT02714608
	Berry powder	NCT00681512*, NCT01426620*
	Shark cartilage extract AE-941	NCT00005838
	Flaxseed	NCT00955942*, NCT02475330*
	Lindera obtusiloba extract	NCT04348149*
	Antroquinonol	NCT02047344, NCT01134016
Breast cancer	Sulforaphane, broccoli sprout extract	NCT00894712, NCT03934905, NCT00982319, NCT00843167, NCT01753908, NCT03775525
	Curcumin, curcumin C3 complex	NCT03980509, NCT03847623*, NCT03072992, NCT03865992*, NCT01740323, NCT01975363*, NCT00852332*, NCT02556632, NCT01042938
	Epigallocatechin gallate, green tea extract, tea capsule, polyphenol	NCT02580279, NCT00516243, NCT00917735, NCT00949923*, NCT03482401*

Table 6 | Continued

Disease	Natural product	References (https://clinicaltrials.gov)
	Genistein, soy isoflavones	NCT00244933*, NCT00099008*, NCT00290758, NCT00036686*, NCT00200824*, NCT04880369*, NCT00513916*, NCT00343434*, NCT01219075*, NCT00204490*, NCT00769990*
	Cannabidiol	NCT04482244, NCT05016349, NCT04754399, NCT04398446
	Tocotrienol, tocotrienol-rich fraction (TRF)	NCT04496492, NCT02909751*, NCT03855423*, NCT01157026*
	Artesunate	NCT00764036
	Viscum album pini (mistletoe extract)	NCT00176046, NCT00049608*
	Omega-3 fatty acid, docosahexaenoic acid (DHA)	NCT00114296*, NCT02295059*, NCT01282580*, NCT01784042, NCT02101970*, NCT02278965, NCT02150525*, NCT05331807*, NCT00930527*, NCT02795572*, NCT02831582*, NCT01478477*, NCT02352779*, NCT01869764, NCT04268134*, NCT01881048*, NCT00627276*, NCT01849250, NCT01548534*, NCT01127867*, NCT01049295*, NCT03831178*, NCT03383835*
	Extra-virgin olive oil, hydroxytyrosol	NCT04174391*, NCT02068092
	Seaweed and soy protein	NCT01204957*
	Perillyl alcohol	NCT00003219, NCT00022425
	Shark cartilage (BenFin)	NCT00026117
	Black cohosh	NCT00060320*, NCT01628536*
	Flaxseed	NCT00612560*, NCT00956813*, NCT00010829*, NCT00794989*
	Crocin	NCT05504148
	Menthol	NCT05429814, NCT01855607
	White button mushroom extract	NCT00709020, NCT04913064
	FADA (active fraction of ficus septica leaf)	NCT05033925*
	Bryostatin 1	NCT00003205
	Huaier granule	NCT02627248, NCT02615457, NCT04790305
	IH636 grape seed proanthocyanidin extract	NCT00041223*, NCT00100893*
	QS21	NCT00004156, NCT00470574, NCT00030823, NCT00003357
	Capsaicin	NCT03794388
Cervical cancer	Curcumin	NCT03192059*, NCT02554344, NCT04294836
	Bryostatin 1	NCT00005965
	Green tea extract	NCT00303823*
Ovarian cancer	Flaxseed	NCT02324439
	Omega-3 fatty acid	NCT01821833*
	Bryostatin 1	NCT00004008, NCT00006942
	Squalamine lactate	NCT00021385
	Cannabidiol	NCT04398446

Table 6 | Continued

Disease	Natural product	References (https://clinicaltrials.gov)
Endometrial cancer	Genistein	NCT00099008*
	Flaxseed	NCT00010829*
	Curcumin	NCT02017353*, NCT03192059*
	Pterostilbene	NCT03671811
Pancreatic cancer	Curcumin	NCT00192842, NCT00486460, NCT00094445
	Genistein	NCT00376948*, NCT00882765*
	Cannabidiol	NCT03607643, NCT04398446
	Antroquinonol	NCT03310632
	Mistletoe extract (Iscador Qu)	NCT01448668, NCT02948309, NCT00049608*
	Perillyl alcohol	NCT00003769
	Bryostatin 1	NCT00031694
	Broccoli sprout grain	NCT01879878*
Bladder cancer	Sulforaphane, broccoli sprout extract	NCT03517995, NCT01108003
	Genistein	NCT01489813, NCT00118040
	Green tea extract, polyphenon E	NCT00666562*, NCT00088946*
Melanoma	Sulforaphane	NCT01568996
	Genistein	NCT00769990*, NCT00276835*
	Bryostatin 1	NCT00006022, NCT00112476
Leukemias	Curcumin	NCT05045443, NCT02100423
	Omega-3 fatty acid, docosahexaenoic acid (DHA) Eicosapentaenoic acid (EPA)	NCT00899353*, NCT02373579, NCT00003077*, NCT01051154*, NCT04006847
	Bryostatin 1	NCT00017342, NCT00003079, NCT00003174, NCT00087425, NCT00136461, NCT00002908, NCT00003171, NCT00003166, NCT00012376, NCT00005580
	Polyphenon E	NCT00262743
	Sheng-Yu-Tang	NCT02580071
	R-(-)-gossypol acetic acid (AT-101)	NCT01003769, NCT00275431
	Cordycepin	NCT00709215, NCT00003005
Lymphomas	Curcumin	NCT00969085, NCT02100423
	SGX301(synthetic hypericin)	NCT02448381, NCT05380635
	Genistein	NCT02624388
	Broken ganoderma lucidum spore powder	NCT04914143
	Omega-3 fatty acid	NCT00003077*
	Bryostatin 1	NCT00002725, NCT00022555, NCT00003993, NCT00058305, NCT00003936, NCT00003079, NCT00087425, NCT00002908, NCT00003166, NCT00005580
	Perillyl alcohol	NCT00002862
	R-(-)-gossypol acetic acid (AT-101)	NCT00891072, NCT05338931, NCT00440388, NCT00275431

Table 6 | Continued

Disease	Natural product	References (https://clinicaltrials.gov)
Multiple myelom	Curcumin	NCT01269203, NCT04731844, NCT00113841
	Omega-3 fatty acid	NCT00899353*, NCT00003077*
	Green tea extract	NCT00942422*
	Piperine	NCT04731844
	Bioperine	NCT00113841
	Bryostatin 1	NCT00002907, NCT00003166
	Shark cartilage extract AE-941	NCT00022282
	Psoralen	NCT00005092
	Agaricus blazei murill	NCT00970021*
	Cannabidiol	NCT03607643
Hepatocellular carcinoma	Huaier granule	NCT01760616, NCT03356236, NCT01770431
	Icaritin	NCT03236649, NCT01972672, NCT05594927, NCT03236636
	Ginsenoside Rg3	NCT04523467, NCT01717066
	Cannabidiol	NCT03607643
	Artesunate	NCT02304289
	Coriolus cersicolor	NCT01097083
	Xiang Sha Liu Jun Zi Decoction dry powder	NCT04562428
Gastric carcinoma	Huaier granule	NCT05498766
	Ginsenoside Rg3	NCT01757366
	Mistletoe extract	NCT01401075
	Bryostatin 1	NCT00006389, NCT00005599, NCT00006081
	Theracurmin 2X	NCT04871412*
	Green tea extract	NCT04871412*
	Coriolus Versicolor	NCT04871412*

*Natural products used in this clinical trial were dietary supplements.
The literature search conducted on the website https://clinicaltrials.gov this time covered data through December 2022.

as paclitaxel, vindesine, and homoharringtonine, have been effectively utilized in the clinical management of cancer. It follows that research on the active ingredients of Chinese materia medica and natural products contributes to inspiring more new cancer therapeutic drugs.

Apart from the natural products listed in **Table 6**, numerous emerging and well-known natural compounds, such as alfa-mangostin, garcinol, diosgenin, eugenol, xanthochymol, rosmarinic acid, and capsaicin, have demonstrated significant potential for entering clinical research in the treatment of cancers. For example, capsaicin has been used in clinical trials to assess its effectiveness in treating neuropathic pain among BC patients (NCT03794388, NCT05726929). These numerous emerging and well-known natural products provide a wide range of options for clinical trials of cancer treatments. In conclusion, natural products have great potential and market prospects in the field of new drug research. It is not only beneficial to the research and promotion of Chinese medicine but may also be developed as dietary supplements or adjuvant drugs for chemoradiotherapy. In this review, we have presented a comprehensive overview of the clinical trial progress in the field of natural product-relevant cancer therapy. The aim was to provide readers with a comprehensive resource of valuable information on natural drug candidates, deepen our understanding of the role of natural products in cancer treatment, and offer hope for the discovery of novel drug candidates for cancer therapy.

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CONFLICT OF INTEREST

All authors declare no conflicts of interest.

REFERENCES

[1] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al.: Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA: A Cancer Journal for Clinicians* 2021, 71:209–249.

[2] Liu Y, Yang S, Wang K, Lu J, Bao X, Wang R, et al.: Cellular Senescence and Cancer: Focusing on Traditional Chinese Medicine and Natural Products. *Cell Proliferation* 2020, 53:e12894.

[3] Pawar RS, Grundel E: Overview of Regulation of Dietary Supplements in the USA and Issues of Adulteration with Phenethylamines (PEAs). *Drug Testing and Analysis* 2016, 9:500–517.

[4] Patterson RE, Neuhouser ML, Hedderson MM, Schwartz SM, Standish LJ, Bowen DJ: Changes in Diet, Physical Activity, and Supplement use Among Adults Diagnosed with Cancer. *Journal of the American Dietetic Association* 2003, 103:323–328.

[5] Islam MR, Akash S, Rahman MM, Nowrin FT, Akter T, Shohag S, et al.: Colon Cancer and Colorectal Cancer: Prevention and Treatment by Potential Natural Products. *Chemico-Biological Interactions* 2022, 368:110170.

[6] Guo W, Sun Y, Liu W, Wu X, Guo L, Cai P, et al.: Small Molecule-Driven Mitophagy-Mediated NLRP3 Inflammasome Inhibition is Responsible for the Prevention of Colitis-Associated Cancer. *Autophagy* 2014, 10:972–985.

[7] Jeon Y, Sym SJ, Yoo BK, Baek JH: Long-Term Survival, Tolerability, and Safety of First-Line Bevacizumab and FOLFIRI in Combination With Ginsenoside-Modified Nanostructured Lipid Carrier Containing Curcumin in Patients With Unresectable Metastatic Colorectal Cancer. *Integrative Cancer Therapies* 2022, 21:15347354221105498.

[8] Howells LM, Iwuji COO, Irving GRB, Barber S, Walter H, Sidat Z, et al.: Curcumin Combined with FOLFOX Chemotherapy Is Safe and Tolerable in Patients with Metastatic Colorectal Cancer in a Randomized Phase IIa Trial. *The Journal of Nutrition* 2019, 149:1133–1139.

[9] Macis D, Briata IM, D'Ecclesiis O, Johansson H, Aristarco V, Buttiron Webber T, et al.: Inflammatory and Metabolic Biomarker Assessment in a Randomized Presurgical Trial of Curcumin and Anthocyanin Supplements in Patients with Colorectal Adenomas. *Nutrients* 2023, 15:3894.

[10] Liu C, Rokavec M, Huang Z, Hermeking H: Curcumin Activates a ROS/KEAP1/NRF2/miR-34a/b/c Cascade to Suppress Colorectal Cancer Metastasis. *Cell Death and Differentiation* 2023, 30:1771–1785.

[11] Liu G, Chen J, Bao Z: Promising Antitumor Effects of the Curcumin Analog DMC-BH on Colorectal Cancer Cells. *Aging* 2023, 15:2221–2236.

[12] Shih KC, Chan HW, Wu CY, Chuang HY: Curcumin Enhances the Abscopal Effect in Mice with Colorectal Cancer by Acting as an Immunomodulator. *Pharmaceutics* 2023, 15:1519.

[13] Aromokeye R, Si H: Combined Curcumin and Luteolin Synergistically Inhibit Colon Cancer Associated with Notch1 and TGF-beta Signaling Pathways in Cultured Cells and Xenograft Mice. *Cancers* 2022, 14:3001.

[14] Zheng X, Yang X, Lin J, Song F, Shao Y: Low Curcumin Concentration Enhances the Anticancer Effect of 5-Fluorouracil Against Olorectal Cancer. *Phytomedicine: International Journal of Phytotherapy and Phytopharmacology* 2021, 85:153547.

[15] Zhang T, Zheng P, Shen X, Shao R, Wang B, Shen H, et al.: Curcuminoid WZ26, a TrxR1 Inhibitor, Effectively Inhibits Colon Cancer Cell Growth and Enhances Cisplatin-Induced Cell Death through the Induction of ROS. *Free Radical Biology & Medicine* 2019, 141:93–102.

[16] Wu SX, Xiong RG, Huang SY, Zhou DD, Saimaiti A, Zhao CN, et al.: Effects and Mechanisms of Resveratrol for Prevention and Management of Cancers: An Updated Review. *Critical Reviews in Food Science and Nutrition* 2023, 63:12422–12440.

[17] Brockmueller A, Buhrmann C, Shayan P, Shakibaei M: Resveratrol Induces Apoptosis by Modulating the Reciprocal Crosstalk between p53 and Sirt-1 in the CRC Tumor Microenvironment. *Frontiers in Immunology* 2023, 14:1225530.

[18] Cheah FK, Leong KH, Thomas NF, Chin HK, Ariffin A, Awang K: Resveratrol Analogue, (E)-N-(2-(4-Methoxystyryl) Phenyl) Furan-2-Carboxamide Induces G(2)/M Cell Cycle Arrest through the Activation of p53-p21(CIP1/WAF1) in Human Colorectal HCT116 Cells. *Apoptosis: An International Journal on Programmed Cell Death* 2018, 23:329–342.

[19] Jozkowiak M, Skupin-Mrugalska P, Nowicki A, Borys-Wojcik S, Wierzchowski M, Kaczmarek M, et al.: The Effect of 4'-Hydroxy-3,4,5-Trimetoxystilbene, the Metabolite of Resveratrol Analogue DMU-212, on Growth, Cell Cycle and Apoptosis in DLD-1 and LOVO Colon Cancer Cell Lines. *Nutrients* 2020, 12:1327.

[20] De Gregorio A, Krasnowska EK, Zonfrillo M, Ravagnan G, Bordignon V, Bonmassar E, et al.: Influence of Polydatin on the Tumor Microenvironment In Vitro: Studies with a Colon Cancer Cell Model. *International Journal of Molecular Sciences* 2022, 23:8442.

[21] Lin TA, Lin WS, Chou YC, Nagabhushanam K, Ho CT, Pan MH: Oxyresveratrol Inhibits Human Colon Cancer Cell Migration through Regulating Epithelial-Mesenchymal Transition and microRNA. *Food & Function* 2021, 12:9658–9668.

[22] Brockmueller A, Girisa S, Kunnumakkara AB, Shakibaei M: Resveratrol Modulates Chemosensitisation to 5-FU via beta1-Integrin/HIF-1alpha Axis in CRC Tumor

Microenvironment. *International Journal of Molecular Sciences* 2023, 24:4988.

[23] El-Readi MZ, Eid S, Abdelghany AA, Al-Amoudi HS, Efferth T, Wink M: Resveratrol Mediated Cancer Cell Apoptosis, and Modulation of Multidrug Resistance Proteins and Metabolic Enzymes. *Phytomedicine: International Journal of Phytotherapy and Phytopharmacology* 2019, 55:269–281.

[24] Liu Q, Qu J, Zhao M, Xu Q, Sun Y: Targeting SHP2 as a Promising Strategy for Cancer Immunotherapy. *Pharmacological Research* 2020, 152:104595.

[25] Zhao M, Guo W, Wu Y, Yang C, Zhong L, Deng G, et al.: SHP2 Inhibition Triggers Anti-Tumor Immunity and Synergizes with PD-1 Blockade. *Acta Pharmaceutica Sinica B* 2019, 9:304–315.

[26] Pan J, Zhou L, Zhang C, Xu Q, Sun Y: Targeting Protein Phosphatases for the Treatment of Inflammation-Related Diseases: From Signaling to Therapy. *Signal Transduction and Targeted Therapy* 2022, 7:177.

[27] Deng G, Zhou L, Wang B, Sun X, Zhang Q, Chen H, et al.: Targeting Cathepsin B by Cycloastragenol Enhances Antitumor Immunity of CD8 T Cells via Inhibiting MHC-I Degradation. *Journal for Immunotherapy of Cancer* 2022, 10:e004874.

[28] Lucas J, Hsieh TC, Halicka HD, Darzynkiewicz Z, Wu JM: Upregulation of PD-L1 Expression by Resveratrol and Piceatannol in Breast and Colorectal Cancer Cells Occurs via HDAC3/p300-Mediated NF-kappaB Signaling. *International Journal of Oncology* 2018, 53: 1469–1480.

[29] Trinh NT, Nguyen TMN, Yook JI, Ahn SG, Kim SA: Quercetin and Quercitrin from Agrimonia pilosa Ledeb Inhibit the Migration and Invasion of Colon Cancer Cells through the JNK Signaling Pathway. *Pharmaceuticals* 2022, 15:364.

[30] Fosso E, Leo M, Muccillo L, Mandrone VM, Di Meo MC, Molinario A, et al.: Quercetin's Dual Mode of Action to Counteract the Sp1-miR-27a Axis in Colorectal Cancer Cells. *Antioxidants* 2023, 12:1547.

[31] Shree A, Islam J, Sultana S: Quercetin Ameliorates Reactive Oxygen Species Generation, Inflammation, Mucus depletion, Goblet Disintegration, and Tumor Multiplicity in Colon Cancer: Probable Role of Adenomatous Polyposis Coli, Beta-Catenin. *Phytotherapy Research: PTR* 2021, 35:2171–2184.

[32] Benito I, Encio IJ, Milagro FI, Alfaro M, Martinez-Penuela A, Barajas M, et al.: Microencapsulated Bifidobacterium Bifidum and Lactobacillus Gasseri in Combination with Quercetin Inhibit Colorectal Cancer Development in Apc(Min/+) Mice. *International Journal of Molecular Sciences* 2021, 22:4906.

[33] Garcia-Gutierrez N, Luna-Barcenas G, Herrera-Hernandez G, Campos-Vega R, Lozano-Herrera SJ, Sánchez-Tusié AA, et al.: Quercetin and Its Fermented Extract as a Potential Inhibitor of Bisphenol A-Exposed HT-29 Colon Cancer Cells' Viability. *International Journal of Molecular Sciences* 2023, 24:5604.

[34] Lee J, Jang CH, Kim Y, Oh J, Kim JS: Quercetin-Induced Glutathione Depletion Sensitizes Colorectal Cancer Cells to Oxaliplatin. *Foods* 2023, 12:1733.

[35] Rani Inala MS, Pamidimukkala K: Amalgamation of Quercetin with Anastrozole and Capecitabine: A Novel Combination to Treat Breast and Colon Cancers - An In Vitro Study. *Journal of Cancer Research and Therapeutics* 2023, 19(Supplement):S93–S105.

[36] Nafees S, Mehdi SH, Zafaryab M, Zeya B, Sarwar T, Rizvi MA: Synergistic Interaction of Rutin and Silibinin on Human Colon Cancer Cell Line. *Archives of Medical Research* 2018, 49:226–234.

[37] Ismail A, El-Biyally E, Sakran W: An Innovative Approach for Formulation of Rutin Tablets Targeted for Colon Cancer Treatment. *AAPS PharmSciTech* 2023, 24:68.

[38] Nasri Nasrabadi P, Zareian S, Nayeri Z, Salmanipour R, Parsafar S, Gharib E, et al.: A Detailed Image of Rutin Underlying Intracellular Signaling Pathways in Human SW480 Colorectal Cancer Cells Based on miRNAs-lncRNAs-mRNAs-TFs Interactions. *Journal of Cellular Physiology* 2019, 234:15570–15580.

[39] Alorda-Clara M, Torrens-Mas M, Morla-Barcelo PM, Roca P, Sastre-Serra J, Pons DG, et al.: High Concentrations of Genistein Decrease Cell Viability Depending on Oxidative Stress and Inflammation in Colon Cancer Cell Lines. *International Journal of Molecular Sciences* 2022, 23:7526.

[40] Pintova S, Dharmupari S, Moshier E, Zubizarreta N, Ang C, Holcombe RF: Genistein Combined with FOLFOX or FOLFOX-Bevacizumab for the Treatment of Metastatic Colorectal Cancer: Phase I/II Pilot Study. *Cancer Chemotherapy and Pharmacology* 2019, 84:591–598.

[41] Ko KP, Yeo Y, Yoon JH, Kim CS, Tokudome S, Ngoan LT, et al.: Plasma Phytoestrogens Concentration and Risk of Colorectal Cancer in Two Different Asian Populations. *Clinical Nutrition* 2018, 37:1675–1682.

[42] Liu X, Lan Y, Zhang L, Ye X, Shen Q, Mo G, et al.: Genistein Exerts Anti-Colorectal Cancer Actions: Clinical Reports, Computational and Validated Findings. *Aging* 2023, 15:3678–3689.

[43] Sun X, Zhou L, Wang Y, Deng G, Cao X, Ke B, et al.: Single-Cell Analyses Reveal Cannabidiol Rewires Tumor Microenvironment via Inhibiting Alternative Activation of Macrophage and Synergizes with Anti-PD-1 in Colon Cancer. *J Pharm Anal* 2023, 13:726–744.

[44] Kim NY, Mohan CD, Sethi G, Ahn KS: Cannabidiol Activates MAPK Pathway to Induce Apoptosis, Paraptosis, and Autophagy in Colorectal Cancer Cells. *Journal of Cellular Biochemistry* 2024, 125:e30537.

[45] Wang F, Dezfouli AB, Khosravi M, Sievert W, Stangl S, Schwab M, et al.: Cannabidiol-Induced Crosstalk of Apoptosis and Macroautophagy in Colorectal Cancer Cells Involves p53 and Hsp70. *Cell Death Discovery* 2023, 9:286.

[46] Kwon IS, Hwang YN, Park JH, Na HH, Kwon TH, Park JS, et al.: Metallothionein Family Proteins as Regulators of Zinc Ions Synergistically Enhance the Anticancer Effect of Cannabidiol in Human Colorectal Cancer Cells. *International Journal of Molecular Sciences* 2023, 24:16621.

[47] Lee HS, Tamia G, Song HJ, Amarakoon D, Wei CI, Lee SH: Cannabidiol Exerts Anti-Proliferative Activity via a Cannabinoid Receptor 2-Dependent Mechanism in Human Colorectal Cancer Cells. *International Immunopharmacology* 2022, 108:108865.

[48] Henning S, Niu Y, Lee N, Thames G, Minutti R, Wang H, et al.: Bioavailability and Antioxidant Activity of Tea Flavanols After Consumption of Green Tea, Black Tea, or a Green Tea Extract Supplement. *The American Journal of Clinical Nutrition* 2004, 80:1558–1564.

[49] Shin CM, Lee DH, Seo AY, Lee HJ, Kim SB, Son WC, et al.: Green Tea Extracts for the Prevention of Metachronous Colorectal Polyps Among Patients who Underwent Endoscopic Removal of Colorectal Adenomas: A

Randomized Clinical Trial. *Clinical Nutrition* 2018, 37:452–458.

[50] Seufferlein T, Ettrich TJ, Menzler S, Messmann H, Kleber G, Zipprich A, et al.: Green Tea Extract to Prevent Colorectal Adenomas, Results of a Randomized, Placebo-Controlled Clinical Trial. *The American Journal of Gastroenterology* 2022, 117:884–894.

[51] Iram S, Rahman S, Ali S, Kim J: Tetranectin Targeting by Epigallocatechin Gallate Suppresses Colon Cancer Cell Proliferation. *International Journal of Biological Macromolecules* 2022, 209:211–219.

[52] Kwon OS, Jung JH, Shin EA, Park JE, Park WY, Kim SH: Epigallocatechin-3-Gallate Induces Apoptosis as a TRAIL Sensitizer via Activation of Caspase 8 and Death Receptor 5 in Human Colon Cancer Cells. *Biomedicines* 2020, 8:84.

[53] Ha T, Lee J, Lou Z, Lee BS, Kim CH, Lee SH: Identification of Epithelial-Specific ETS-1 (ESE-1) as a Tumor Suppressor and Molecular Target of Green Tea Compound, EGCG. *Molecular Carcinogenesis* 2019, 58:922–932.

[54] Zhu W, Oteiza PI: NADPH Oxidase 1: A Target in the Capacity of Dimeric ECG and EGCG Procyanidins to Inhibit Colorectal Cancer Cell Invasion. *Redox Biology* 2023, 65:102827.

[55] Wang Y, Jin SS, Li DT, Jiang XC, Afrasiyab, Khalid A, et al.: Improving the Anti-Tumor Effect of EGCG in Colorectal Cancer Cells by Blocking EGCG-Induced YAP Activation. *American Journal of Cancer Research* 2023, 13:1407–1424.

[56] Qu J, Liu Q, You G, Ye L, Jin Y, Kong L, et al.: Advances in Ameliorating Inflammatory Diseases and Cancers by Andrographolide: Pharmacokinetics, Pharmacodynamics, and Perspective. *Medicinal Research Reviews* 2022, 42:1147–1178.

[57] Liu Z, Wu X, Dai K, Li R, Zhang J, Sheng D, et al.: The New Andrographolide Derivative AGS-30 Induces Apoptosis in Human Colon Cancer Cells by Activating a ROS-Dependent JNK Signalling Pathway. *Phytomedicine: International Journal of Phytotherapy and Phytopharmacology* 2022, 94:153824.

[58] Reabroi S, Chairoungdua A, Saeeng R, Kasemsuk T, Saengsawang W, Zhu W, et al.: A Silyl Andrographolide Analogue Suppresses Wnt/beta-Catenin Signaling Pathway in Colon Cancer. *Biomedicine & Pharmacotherapy* 2018, 101:414–421.

[59] Li J, Li F, Tang F, Zhang J, Li R, Sheng D, et al.: AGS-30, An Andrographolide Derivative, Suppresses Tumor Angiogenesis and Growth In Vitro and In Vivo. *Biochemical Pharmacology* 2020, 171:113694.

[60] Banerjee V, Sharda N, Huse J, Singh D, Sokolov D, Czinn SJ, et al.: Synergistic Potential of Dual Andrographolide and Melatonin Targeting of Metastatic Colon Cancer Cells: Using the Chou-Talalay Combination Index Method. *European Journal of Pharmacology* 2021, 897:173919.

[61] Sokolov D, Sharda N, Giri B, Hassan MS, Singh D, Tarasiewicz A, et al.: Melatonin and Andrographolide Synergize to Inhibit the Colospheroid Phenotype by Targeting Wnt/beta-Catenin Signaling. *Journal of Pineal Research* 2022, 73:e12808.

[62] Wang W, Guo W, Li L, Fu Z, Liu W, Gao J, et al.: Andrographolide Reversed 5-FU Resistance in Human Colorectal Cancer by Elevating BAX Expression. *Biochemical Pharmacology* 2016, 121:8–17.

[63] Liu W, Fan T, Li M, Zhang G, Guo W, Yang X, et al.: Andrographolide Potentiates PD-1 Blockade Immunotherapy by Inhibiting COX2-Mediated PGE2 Release. *International Immunopharmacology* 2020, 81:106206.

[64] Gao J, Wu Z, Zhao M, Zhang R, Li M, Sun D, et al.: Allosteric Inhibition Reveals SHP2-Mediated Tumor Immunosuppression in Colon Cancer by Single-Cell Transcriptomics. *Acta Pharmaceutica Sinica B* 2022, 12:149–166.

[65] Nicholson AG, Tsao MS, Beasley MB, Borczuk AC, Brambilla E, Cooper WA, et al.: The 2021 WHO Classification of Lung Tumors: Impact of Advances Since 2015. *Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer* 2022, 17:362–387.

[66] Yang F, Wang F, Liu Y, Wang S, Li X, Huang Y, et al.: Sulforaphane Induces Autophagy by Inhibition of HDAC6-Mediated PTEN Activation in Triple Negative Breast Cancer Cells. *Life Sciences* 2018, 213:149–157.

[67] Zheng Z, Lin K, Hu Y, Zhou Y, Ding X, Wang Y, et al.: Sulforaphane Metabolites Inhibit Migration and Invasion via Microtubule-Mediated Claudins Dysfunction or Inhibition of Autolysosome Formation in Human Non-Small Cell Lung Cancer Cells. *Cell Death & Disease* 2019, 10:259.

[68] Yan Y, Zhou Y, Li J, Zheng Z, Hu Y, Li L, et al.: Sulforaphane Downregulated Fatty Acid Synthase and Inhibited Microtubule-Mediated Mitophagy Leading to Apoptosis. *Cell Death & Disease* 2021, 12:917.

[69] Hu Y, Zhou Y, Yang G, Wang Y, Zheng Z, Li J, et al.: Sulforaphane-N-Acetyl-Cysteine Inhibited Autophagy Leading to Apoptosis via Hsp70-Mediated Microtubule Disruption. *Cancer Letters* 2018, 431:85–95.

[70] Xie C, Zhu J, Jiang Y, Chen J, Wang X, Geng S, et al.: Sulforaphane Inhibits the Acquisition of Tobacco Smoke-Induced Lung Cancer Stem Cell-Like Properties via the IL-6/DeltaNp63alpha/Notch Axis. *Theranostics* 2019, 9:4827–4840.

[71] Rakariyatham K, Yang X, Gao Z, Song M, Han Y, Chen X, et al.: Synergistic Chemopreventive Effect of Allyl Isothiocyanate and Sulforaphane on Non-Small Cell Lung Carcinoma Cells. *Food & Function* 2019, 10:893–902.

[72] Wang Y, Zhou Y, Zheng Z, Li J, Yan Y, Wu W: Sulforaphane Metabolites Reduce Resistance to Paclitaxel via Microtubule Disruption. *Cell Death & Disease* 2018, 9:1134.

[73] Wang TH, Chen CC, Huang KY, Shih YM, Chen CY: High Levels of EGFR Prevent Sulforaphane-Induced Reactive Oxygen Species-Mediated Apoptosis in Non-Small-Cell Lung Cancer Cells. *Phytomedicine: International Journal of Phytotherapy and Phytopharmacology* 2019, 64:152926.

[74] Fan J, Wu M, Wang J, Ren D, Zhao J, Yang G: 1,7-Bis(4-Hydroxyphenyl)-1,4-Heptadien-3-One Induces Lung Cancer Cell Apoptosis via the PI3K/Akt and ERK1/2 Pathways. *Journal of Cellular Physiology* 2019, 234:6336–6349.

[75] Chang M, Shang M, Yuan F, Guo W, Wang C: EF24 Exerts Cytotoxicity Against NSCLC via Inducing ROS Accumulation. *Cancer Cell International* 2021, 21:531.

[76] Wan Mohd Tajuddin WNB, Abas F, Othman I, Naidu R: Molecular Mechanisms of Antiproliferative and Apoptosis Activity by 1,5-Bis(4-Hydroxy-3-Methoxyphenyl)1,4-Pentadiene-3-One (MS13) on Human Non-Small Cell Lung Cancer Cells. *International Journal of Molecular Sciences* 2021, 22:7424.

[77] Liu X, Cui H, Li M, Chai Z, Wang H, Jin X, et al.: Tumor Killing by a Dietary Curcumin Mono-Carbonyl Analog that Works as a Selective ROS Generator via TrxR Inhibition. *European Journal of Medicinal Chemistry* 2023, 250:115191.

[78] Xie C, Zhu J, Yang X, Huang C, Zhou L, Meng Z, et al.: TAp63alpha Is Involved in Tobacco Smoke-Induced Lung Cancer EMT and the Anti-Cancer Activity of Curcumin via miR-19 Transcriptional Suppression. *Frontiers in Cell and Developmental Biology* 2021, 9:645402.

[79] Wu MF, Huang YH, Chiu LY, Cherng SH, Sheu GT, Yang TY: Curcumin Induces Apoptosis of Chemoresistant Lung Cancer Cells via ROS-Regulated p38 MAPK Phosphorylation. *International Journal of Molecular Sciences* 2022, 23:8248.

[80] Saddiq AA, El-Far AH, Mohamed Abdullah SA, Godugu K, Almaghrabi OA, Mousa SA: Curcumin, Thymoquinone, and 3, 3′-Diindolylmethane Combinations Attenuate Lung and Liver Cancers Progression. *Frontiers in Pharmacology* 2022, 13:936996.

[81] Hong X, Hsieh MT, Tseng TY, Lin HY, Chang HC, Yau ST, et al.: Diarylheptanoid 35d Overcomes EGFR TKI Resistance by Inducing hsp70-Mediated Lysosomal Degradation of EGFR in EGFR-Mutant Lung Adenocarcinoma. *The Journal of Biological Chemistry* 2023, 299:104814.

[82] Hsieh MT, Lee PC, Chiang YT, Lin HY, Lee DY: The Effects of a Curcumin Derivative and Osimertinib on Fatty Acyl Metabolism and Mitochondrial Functions in HCC827 Cells and Tumors. *International Journal of Molecular Sciences* 2023, 24:12190.

[83] Zhu W, Zhao Y, Zhang S, Li X, Xing L, Zhao H, et al.: Evaluation of Epigallocatechin-3-Gallate as a Radioprotective Agent During Radiotherapy of Lung Cancer Patients: A 5-Year Survival Analysis of a Phase 2 Study. *Frontiers in Oncology* 2021, 11:686950.

[84] Zhao H, Jia L, Chen G, Li X, Meng X, Zhao X, et al.: A Prospective, Three-Arm, Randomized Trial of EGCG for Preventing Radiation-Induced Esophagitis in Lung Cancer Patients Receiving Radiotherapy. *Radiotherapy and Oncology: Journal of the European Society for Therapeutic Radiology and Oncology* 2019, 137:186–191.

[85] Jiang P, Chen A, Wu X, Zhou M, Ul Haq I, Mariyam Z, et al.: NEAT1 Acts as an Inducer of Cancer Stem Cell-Like Phenotypes in NSCLC by Inhibiting EGCG-Upregulated CTR1. *Journal of Cellular Physiology* 2018, 233:4852–4863.

[86] Jiang P, Xu C, Chen L, Chen A, Wu X, Zhou M, et al.: Epigallocatechin-3-Gallate Inhibited Cancer Stem Cell-Like Properties by Targeting hsa-mir-485-5p/RXRalpha in Lung Cancer. *Journal of Cellular Biochemistry* 2018, 119:8623–8635.

[87] Jiang P, Xu C, Zhang P, Ren J, Mageed F, Wu X, et al.: Epigallocatechin-3-Gallate Inhibits Self-Renewal Ability of Lung Cancer Stem-Like Cells through Inhibition of CLOCK. *International Journal of Molecular Medicine* 2020, 46:2216–2224.

[88] Jiang P, Xu C, Chen L, Chen A, Wu X, Zhou M, et al.: EGCG Inhibits CSC-Like Properties through Targeting miR-485/CD44 Axis in A549-Cisplatin Resistant Cells. *Molecular Carcinogenesis* 2018, 57:1835–1844.

[89] Minnelli C, Cianfruglia L, Laudadio E, Mobbili G, Galeazzi R, Armeni T: Effect of Epigallocatechin-3-Gallate on EGFR Signaling and Migration in Non-Small Cell Lung Cancer. *International Journal of Molecular Sciences* 2021, 22:11833.

[90] Sun XL, Xiang ZM, Xie YR, Zhang N, Wang LX, Wu YL, et al.: Dimeric-(-)-Epigallocatechin-3-Gallate Inhibits the Proliferation of Lung Cancer Cells by Inhibiting the EGFR Signaling Pathway. *Chemico-Biological Interactions* 2022, 365:110084.

[91] Li F, Hao S, Gao J, Jiang P: EGCG Alleviates Obesity-Exacerbated Lung Cancer Progression by STAT1/SLC7A11 Pathway and Gut Microbiota. *The Journal of Nutritional Biochemistry* 2023, 120:109416.

[92] Zhou Y, Huang S, Guo Y, Ran M, Shan W, Chen WH, et al.: Epigallocatechin Gallate Circumvents Drug-Induced Resistance in Non-Small-Cell Lung Cancer by Modulating Glucose Metabolism and AMPK/AKT/MAPK axis. *Phytotherapy Research: PTR* 2023, 37:5837–5853.

[93] Wang L, Du H, Chen P: Chlorogenic Acid Inhibits the Proliferation of Human Lung Cancer A549 Cell Lines by Targeting Annexin A2 In Vitro and In Vivo. *Biomedicine & Pharmacotherapy* 2020, 131:110673.

[94] Huang S, Wang LL, Xue NN, Li C, Guo HH, Ren TK, et al.: Chlorogenic Acid Effectively Treats Cancers through Induction of Cancer Cell Differentiation. *Theranostics* 2019, 9:6745–6763.

[95] Cittadini MC, Repossi G, Albrecht C, Di Paola Naranjo R, Miranda AR, de Pascual-Teresa S, et al.: Effects of Bioavailable Phenolic Compounds from Ilex Paraguariensis on the Brain of Mice with Lung Adenocarcinoma. *Phytotherapy Research: PTR* 2019, 33:1142–1149.

[96] Shimazu T, Inoue M, Sasazuki S, Iwasaki M, Sawada N, Yamaji T, et al.: Isoflavone Intake and Risk of Lung Cancer: A Prospective Cohort Study in Japan. *The American Journal of Clinical Nutrition* 2010, 91:722–728.

[97] Chei CL, Sawada N, Khankari NK, Iwasaki M, Yamaji T, Cai H, et al.: Isoflavone and Soy Food Intake and Risk of Lung Cancer in Never Smokers: Report from Prospective Studies in Japan and China. *European Journal of Nutrition* 2022, 62:125–137.

[98] Nachvak SM, Moradi S, Anjom-Shoae J, Rahmani J, Nasiri M, Maleki V, et al.: Soy, Soy Isoflavones, and Protein Intake in Relation to Mortality from All Causes, Cancers, and Cardiovascular Diseases: A Systematic Review and Dose-Response Meta-Analysis of Prospective Cohort Studies. *Journal of the Academy of Nutrition and Dietetics* 2019, 119:1483–1500 e17.

[99] Fan Y, Wang M, Li Z, Jiang H, Shi J, Shi X, et al.: Intake of Soy, Soy Isoflavones and Soy Protein and Risk of Cancer Incidence and Mortality. *Frontiers in Nutrition* 2022, 9:847421.

[100] Yang WS, Va P, Wong MY, Zhang HL, Xiang YB: Soy Intake is Associated with Lower Lung Cancer Risk: Results from a Meta-Analysis of Epidemiologic Studies. *The American Journal of Clinical Nutrition* 2011, 94:1575–1583.

[101] Simone CB 2nd, Serebrenik AA, Gore EM, Mohindra P, Brown SL, Wang D, et al.: Multicenter Phase 1b/2a Clinical Trial of Radioprotectant BIO 300 Oral Suspension for Patients With Non-Small Cell Lung Cancer Receiving Concurrent Chemoradiotherapy. *International Journal of Radiation Oncology, Biology, Physics* 2024, 118:404–414.

[102] Yu Y, Xing Y, Zhang Q, Zhang Q, Huang S, Li X, et al.: Soy Isoflavone Genistein Inhibits hsa_circ_0031250/miR-873-5p/FOXM1 Axis to Suppress Non-Small-Cell Lung Cancer Progression. *IUBMB Life* 2021, 73:92–107.

[103] Chan L, Pang Y, Wang Y, Zhu D, Taledaohan A, Jia Y, et al.: Genistein-Induced Mitochondrial Dysfunction and FOXO3a/PUMA Expression in Non-Small Lung Cancer Cells. *Pharmaceutical Biology* 2022, 60:1876–1883.

[104] Suraweera TL, Merlin JPJ, Dellaire G, Xu Z, Rupasinghe HPV: Genistein and Procyanidin B2 Reduce Carcinogen-Induced Reactive Oxygen Species and DNA Damage through the Activation of Nrf2/ARE Cell Signaling in Bronchial Epithelial Cells In Vitro. *International Journal of Molecular Sciences* 2023, 24:3676.

[105] Zeng Y, Ma J, Xu L, Wu D: Natural Product Gossypol and its Derivatives in Precision Cancer Medicine. *Current Medicinal Chemistry* 2019, 26:1849–1873.

[106] Wang Y, Li X, Zhang L, Li M, Dai N, Luo H, et al.: A Randomized, Double-Blind, Placebo-Controlled Study of B-Cell Lymphoma 2 Homology 3 Mimetic Gossypol Combined with Docetaxel and Cisplatin for Advanced Non-Small Cell Lung Cancer with High Expression of Apurinic/Apyrimidinic Endonuclease 1. *Investigational New Drugs* 2020, 38:1862–1871.

[107] Zhou W, Wang W, Liang Y, Jiang R, Qiu F, Shao X, et al.: The RNA-Binding Protein LRPPRC Promotes Resistance to CDK4/6 Inhibition in Lung Cancer. *Nature Communications* 2023, 14:4212.

[108] Hussain Y, Meena A, Sinha RA: Gossypol Synergises Antiproliferative Effect of Sorafenib in Metastatic Lung Cancer Cells Following Chou-Talalay Algorithm. *Toxicol In Vitro* 2023, 93:105666.

[109] Xu J, Zhu GY, Cao D, Pan H, Li YW: Gossypol Overcomes EGFR-TKIs Resistance in Non-Small Cell Lung Cancer Cells by Targeting YAP/TAZ and EGFR(L858R/T790M). *Biomedicine & Pharmacotherapy* 2019, 115:108860.

[110] Bar-Sela G, Wollner M, Hammer L, Agbarya A, Dudnik E, Haim N: Mistletoe as Complementary Treatment in Patients with Advanced Non-Small-Cell Lung Cancer Treated with Carboplatin-Based Combinations: A Randomised Phase II Study. *European Journal of Cancer* 2013, 49:1058–1064.

[111] Lee YG, Jung I, Koo DH, Kang DY, Oh TY, Oh S, et al.: Efficacy and Safety of Viscum Album Extract (Helixor-M) to Treat Malignant Pleural Effusion in Patients with Lung Cancer. *Supportive Care in Cancer: Official Journal of the Multinational Association of Supportive Care in Cancer* 2019, 27:1945–1949.

[112] Schad F, Steinmann D, Oei SL, Thronicke A, Grah C: Evaluation of Quality of Life in Lung Cancer Patients Receiving Radiation and Viscum Album L.: A Real-World Data Study. *Radiation Oncology* 2023, 18:47.

[113] Schad F, Thronicke A, Steele ML, Merkle A, Matthes B, Grah C, et al.: Overall Survival of Stage IV Non-Small Cell Lung Cancer Patients Treated with Viscum Album L. in Addition to Chemotherapy, a Real-World Observational Multicenter Analysis. *PloS One* 2018, 13:e0203058.

[114] Shatat MA, Gauthier B, Yoon S, Yuan E, Yang P, Narla G, et al.: Mistletoe Lectin Inhibits Growth of Myc-Amplified Small-Cell Lung Cancer. *Cancer Medicine* 2023, 12:8378–8387.

[115] Barnard ME, Boeke CE, Tamimi RM: Established Breast Cancer Risk Factors and Risk of Intrinsic Tumor Subtypes. *Biochimica et Biophysica Acta* 2015, 1856:73–85.

[116] Sailo BL, Liu L, Chauhan S, Girisa S, Hegde M, Liang L, et al.: Harnessing Sulforaphane Potential as a Chemosensitizing Agent: A Comprehensive Review. *Cancers* 2024, 16:244.

[117] Shoaib S, Khan FB, Alsharif MA, Malik MS, Ahmed SA, Jamous YF, et al.: Reviewing the Prospective Pharmacological Potential of Isothiocyanates in Fight against Female-Specific Cancers. *Cancers* 2023, 15:2390.

[118] Zhang Z, Atwell LL, Farris PE, Ho E, Shannon J: Associations between Cruciferous Vegetable Intake and Selected Biomarkers Among Women Scheduled for Breast Biopsies. *Public Health Nutrition* 2016, 19:1288–1295.

[119] Wang Z, Tu C, Pratt R, Khoury T, Qu J, Fahey JW, et al.: A Presurgical-Window Intervention Trial of Isothiocyanate-Rich Broccoli Sprout Extract in Patients with Breast Cancer. *Molecular Nutrition & Food Research* 2022, 66:e2101094.

[120] Cao S, Hu S, Jiang P, Zhang Z, Li L, Wu Q: Effects of Sulforaphane on Breast Cancer Based on Metabolome and Microbiome. *Food Science & Nutrition* 2023, 11:2277–2287.

[121] Zhang Y, Lu Q, Li N, Xu M, Miyamoto T, Liu J: Sulforaphane Suppresses Metastasis of Triple-Negative Breast Cancer Cells by Targeting the RAF/MEK/ERK Pathway. *NPJ Breast Cancer* 2022, 8:40.

[122] Rong Y, Huang L, Yi K, Chen H, Liu S, Zhang W, et al.: Co-Administration of Sulforaphane and Doxorubicin Attenuates Breast Cancer Growth by Preventing the Accumulation of Myeloid-Derived Suppressor Cells. *Cancer Letters* 2020, 493:189–196.

[123] Li S, Wu H, Chen M, Tollefsbol TO: Paternal Combined Botanicals Contribute to the Prevention of Estrogen Receptor-Negative Mammary Cancer in Transgenic Mice. *The Journal of Nutrition* 2023, 153:1959–1973.

[124] Farghadani R, Naidu R: Curcumin as an Enhancer of Therapeutic Efficiency of Chemotherapy Drugs in Breast Cancer. *International Journal of Molecular Sciences* 2022, 23:2144.

[125] Barcelos KA, Mendonca CR, Noll M, Botelho AF, Francischini CRD, Silva MAM: Antitumor Properties of Curcumin in Breast Cancer Based on Preclinical Studies: A Systematic Review. *Cancers* 2022, 14:2165.

[126] Saghatelyan T, Tananyan A, Janoyan N, Tadevosyan A, Petrosyan H, Hovhannisyan A, et al.: Efficacy and Safety of Curcumin in Combination with Paclitaxel in Patients with Advanced, Metastatic Breast Cancer: A Comparative, Randomized, Double-Blind, Placebo-Controlled Clinical Trial. *Phytomedicine: International Journal of Phytotherapy and Phytopharmacology* 2020, 70:153218.

[127] Kunihiro AG, Brickey JA, Frye JB, Cheng JN, Luis PB, Schneider C, et al.: Curcumin Inhibition of TGFbeta Signaling in Bone Metastatic Breast Cancer Cells and the Possible Role of Oxidative Metabolites. *The Journal of Nutritional Biochemistry* 2022, 99:108842.

[128] Li M, Guo T, Lin J, Huang X, Ke Q, Wu Y, et al.: Curcumin Inhibits the Invasion and Metastasis of Triple Negative Breast Cancer via Hedgehog/Gli1 Signaling Pathway. *Journal of Ethnopharmacology* 2022, 283:114689.

[129] Duan Y, Chen HL, Ling M, Zhang S, Ma FX, Zhang HC, et al.: The Curcumin Analog EF24 Inhibits Proliferation and Invasion of Triple-Negative Breast Cancer Cells by Targeting the Long Noncoding RNA HCG11/Sp1 Axis. *Molecular and Cellular Biology* 2022, 42:e0016321.

[130] Jang BY, Shin MK, Han DH, Sung JS: Curcumin Disrupts a Positive Feedback Loop between ADMSCs and Cancer Cells in the Breast Tumor Microenvironment via the CXCL12/CXCR4 Axis. *Pharmaceutics* 2023, 15:2627.

[131] Almalki E, Al-Amri A, Alrashed R, Al-Zharani M, Semlali A: The Curcumin Analog PAC Is a Potential Solution for the Treatment of Triple-Negative Breast Cancer by Modulating the Gene Expression of DNA Repair Pathways. *International Journal of Molecular Sciences* 2023, 24:9649.

[132] Nayak D, Paul S, Das C, Bhal S, Kundu CN: Quinacrine and Curcumin in Combination Decreased the Breast Cancer Angiogenesis by Modulating ABCG2 via VEGF A. *Journal of Cell Communication and Signaling* 2023, 17:609–626.

[133] Petrova L, Gergov N, Stoup M, Zapryanova S, Van Damme EJM, Lebègue N, et al.: Jacalin-Curcumin Complex Sensitizes the Breast Cancer MDA-MB-231 Cell Line. *International Journal of Molecular Sciences* 2023, 24:17399.

[134] Afshari H, Noori S, Zarghi A: Curcumin Potentiates the Anti-Inflammatory Effects of Tehranolide by Modulating the STAT3/NF-kappaB Signaling Pathway in Breast and Ovarian Cancer Cell Lines. *Inflammopharmacology* 2023, 31:2541–2555.

[135] Wang R, Yu H, Chen P, Yuan T, Zhang J: Integrated Transcriptome and Molecular Docking to Identify the Hub Superimposed Attenuation Targets of Curcumin in Breast Cancer Cells. *International Journal of Molecular Sciences* 2023, 24:12479.

[136] Samavat H, Ursin G, Emory TH, Lee E, Wang R, Torkelson CJ, et al.: A Randomized Controlled Trial of Green Tea Extract Supplementation and Mammographic Density in Postmenopausal Women at Increased Risk of Breast Cancer. *Cancer Prevention Research* 2017, 10:710–718.

[137] Samavat H, Wu AH, Ursin G, Torkelson CJ, Wang R, Yu MC, et al.: Green Tea Catechin Extract Supplementation Does Not Influence Circulating Sex Hormones and Insulin-Like Growth Factor Axis Proteins in a Randomized Controlled Trial of Postmenopausal Women at High Risk of Breast Cancer. *The Journal of Nutrition* 2019, 149:619–627.

[138] Zhao H, Zhu W, Zhao X, Li X, Zhou Z, Meng X, et al.: Efficacy of Epigallocatechin-3-Gallate in Preventing Dermatitis in Patients With Breast Cancer Receiving Postoperative Radiotherapy: A Double-Blind, Placebo-Controlled, Phase 2 Randomized Clinical Trial. *JAMA Dermatology* 2022, 158:779–786.

[139] Xu P, Yan F, Zhao Y, Chen X, Sun S, Wang Y, et al.: Green Tea Polyphenol EGCG Attenuates MDSCs-Mediated Immunosuppression through Canonical and Non-Canonical Pathways in a 4T1 Murine Breast Cancer Model. *Nutrients* 2020, 12:1042.

[140] Lee WJ, Cheng TC, Yen Y, Fang CL, Liao YC, Kuo CC, et al.: Tea Polyphenol Epigallocatechin-3-Gallate Inhibits Cell Proliferation in a Patient-Derived Triple-Negative Breast Cancer Xenograft Mouse Model via Inhibition of Proline-Dehydrogenase-Induced Effects. *Journal of Food and Drug Analysis* 2021, 29:113–127.

[141] Gonzalez Suarez N, Fernandez-Marrero Y, Torabidastgerdooei S, Annabi B: EGCG Prevents the Onset of an Inflammatory and Cancer-Associated Adipocyte-like Phenotype in Adipose-Derived Mesenchymal Stem/Stromal Cells in Response to the Triple-Negative Breast Cancer Secretome. *Nutrients* 2022, 14:1099.

[142] Xie L, Yi J, Song Y, Zhao M, Fan L, Zhao L: Suppression of GOLM1 by EGCG through HGF/HGFR/AKT/GSK-3beta/beta-Catenin/c-Myc Signaling Pathway Inhibits Cell Migration of MDA-MB-231. *Food and Chemical Toxicology: An International Journal Published for the British Industrial Biological Research Association* 2021, 157:112574.

[143] Santos RA, Andrade EDS, Monteiro M, Fialho E, Silva JL, Daleprane JB, et al.: Green Tea (Camellia Sinensis) Extract Induces p53-Mediated Cytotoxicity and Inhibits Migration of Breast Cancer Cells. *Foods* 2021, 10:3154.

[144] Guo Y, Cui Y, Li Y, Jin X, Wang D, Lei M, et al.: Cytoplasmic YAP1-Mediated ESCRT-III Assembly Promotes Autophagic Cell Death and is Ubiquitinated by NEDD4L in Breast Cancer. *Cancer Commun (Lond)* 2023, 43:582–612.

[145] Zhang T, Li N, Wang R, Sun Y, He X, Lu X, et al.: Enhanced Therapeutic Efficacy of Doxorubicin Against Multidrug-Resistant Breast Cancer with Reduced Cardiotoxicity. *Drug Delivery* 2023, 30:2189118.

[146] Pop EA, Fischer LM, Coan AD, Gitzinger M, Nakamura J, Zeisel SH: Effects of a High Daily dose of Soy Isoflavones on DNA Damage, Apoptosis, and Estrogenic Outcomes in Healthy Postmenopausal Women: A Phase I Clinical Trial. *Menopause* 2008, 15:684–692.

[147] Wu AH, Spicer D, Garcia A, Tseng CC, Hovanessian-Larsen L, Sheth P, et al.: Double-Blind Randomized 12-Month Soy Intervention Had No Effects on Breast MRI Fibroglandular Tissue Density or Mammographic Density. *Cancer Prevention Research* 2015, 8:942–951.

[148] Sharma M, Arora I, Chen M, Wu H, Crowley MR, Tollefsbol TO, et al.: Therapeutic Effects of Dietary Soybean Genistein on Triple-Negative Breast Cancer via Regulation of Epigenetic Mechanisms. *Nutrients* 2021, 13:3944.

[149] Bezerra PHA, Amaral C, Almeida CF, Correia-da-Silva G, Torqueti MR, Teixeira N: In Vitro Effects of Combining Genistein with Aromatase Inhibitors: Concerns Regarding Its Consumption during Breast Cancer Treatment. *Molecules* 2023, 28:4893.

[150] Hu C, Wang M, Hu M, Ma S, Yang B, Xiao W, et al.: Genistein Induces Endocrine Resistance in Human Breast Cancer by Suppressing H3K27 Trimethylation. *Endocrine-Related Cancer* 2022, 30:e220191.

[151] Pawlicka MA, Zmorzynski S, Popek-Marciniec S, Filip AA: The Effects of Genistein at Different Concentrations on MCF-7 Breast Cancer Cells and BJ Dermal Fibroblasts. *International Journal of Molecular Sciences* 2022, 23:12360.

[152] Jo MJ, Kim BG, Kim WY, Lee DH, Yun HK, Jeong S, et al.: Cannabidiol Suppresses Angiogenesis and Stemness of Breast Cancer Cells by Downregulation of Hypoxia-Inducible Factors-1alpha. *Cancers* 2021, 13:5667.

[153] Surapaneni SK, Patel N, Sun L, Kommineni N, Kalvala AK, Gebeyehu A, et al.: Anticancer and Chemosensitization Effects of Cannabidiol in 2D and 3D Cultures of TNBC: Involvement of GADD45alpha, Integrin-alpha5, -beta5, -beta1, and Autophagy. *Drug Delivery and Translational Research* 2022, 12:2762–2777.

[154] Mokoena D, George BP, Abrahamse H: Cannabidiol Combination Enhances Photodynamic Therapy Effects on MCF-7 Breast Cancer Cells. *Cells* 2024, 13:187.

[155] Almeida CF, Teixeira N, Valente MJ, Vinggaard AM, Correia-da-Silva G, Amaral C: Cannabidiol as a Promising

Adjuvant Therapy for Estrogen Receptor-Positive Breast Tumors: Unveiling Its Benefits with Aromatase Inhibitors. *Cancers* 2023, 15:2517.

[156] Proto MC, Fiore D, Bifulco M, Gazzerro P: Rimonabant and Cannabidiol Rewrite the Interactions between Breast Cancer Cells and Tumor Microenvironment. *International Journal of Molecular Sciences* 2023, 24:13427.

[157] Garcia-Morales L, Mendoza-Rodriguez MG, Tapia Ramirez J, Meza I: CBD Inhibits In Vivo Development of Human Breast Cancer Tumors. *International Journal of Molecular Sciences* 2023, 24:13235.

[158] D'Aloia A, Ceriani M, Tisi R, Stucchi S, Sacco E, Costa B: Cannabidiol Antiproliferative Effect in Triple-Negative Breast Cancer MDA-MB-231 Cells Is Modulated by Its Physical State and by IGF-1. *International Journal of Molecular Sciences* 2022, 23:7145.

[159] Idriss M, Hodroj MH, Fakhoury R, Rizk S: Beta-Tocotrienol Exhibits More Cytotoxic Effects than Gamma-Tocotrienol on Breast Cancer Cells by Promoting Apoptosis via a P53-Independent PI3-Kinase Dependent Pathway. *Biomolecules* 2020, 10:577.

[160] Kjaer IM, Kahns S, Timm S, Andersen RF, Madsen JS, Jakobsen EH, et al.: Phase II trial of Delta-Tocotrienol in Neoadjuvant Breast Cancer with Evaluation of Treatment Response Using ctDNA. *Scientific Reports* 2023, 13:8419.

[161] Nesaretnam K, Selvaduray KR, Abdul Razak G, Veerasenan SD, Gomez PA: Effectiveness of Tocotrienol-Rich Fraction Combined with Tamoxifen in the Management of Women with Early Breast Cancer: A Pilot Clinical Trial. *Breast Cancer Research: BCR* 2010, 12:R81.

[162] Ramdas P, Radhakrishnan AK, Abdu Sani AA, Kumari M, Anandha Rao JS, Abdul-Rahman PS: Advancing the Role of Gamma-Tocotrienol as Proteasomes Inhibitor: A Quantitative Proteomic Analysis of MDA-MB-231 Human Breast Cancer Cells. *Biomolecules* 2019, 10:19.

[163] Ding Y, Fan J, Fan Z, Zhang K: gamma-Tocotrienol Reverses Multidrug Resistance of Breast Cancer Cells through the Regulation of the gamma-Tocotrienol-NF-kappaB-P-gp Axis. *The Journal of Steroid Biochemistry and Molecular Biology* 2021, 209:105835.

[164] Pizato N, Kiffer L, Luzete BC, Assumpcao JAF, Correa LH, Melo HAB, et al.: Omega 3-DHA and Delta-Tocotrienol Modulate Lipid Droplet Biogenesis and Lipophagy in Breast Cancer Cells: The Impact in Cancer Aggressiveness. *Nutrients* 2019, 11:1199.

[165] Subramaiam H, Chu WL, Radhakrishnan AK, Chakravarthi S, Selvaduray KR, Kok YY: Evaluating Anticancer and Immunomodulatory Effects of Spirulina (Arthrospira) Platensis and Gamma-Tocotrienol Supplementation in a Syngeneic Mouse Model of Breast Cancer. *Nutrients* 2021, 13:2320.

[166] Wen L, Liu L, Wen L, Yu T, Wei F: Artesunate Promotes G2/M Cell Cycle Arrest in MCF7 Breast Cancer Cells through ATM Activation. *Breast Cancer* 2018, 25:681–686.

[167] von Hagens C, Walter-Sack I, Goeckenjan M, Storch-Hagenlocher B, Sertel S, Elsässer M, et al.: Long-Term Add-on Therapy (Compassionate Use) with Oral Artesunate in Patients with Metastatic Breast Cancer after Participating in a Phase I Study (ARTIC M33/2). *Phytomedicine: International Journal of Phytotherapy and Phytopharmacology* 2019, 54:140–148.

[168] Saeed MEM, Drif AI, Efferth T: Biomarker Profiling Revealed Carcinoembryonic Antigen as a Target of Artesunate in a Ductal Breast Cancer Patient. *Anticancer Research* 2022, 42:3483–3494.

[169] Yao Y, Guo Q, Cao Y, Qiu Y, Tan R, Yu Z, et al.: Artemisinin Derivatives Inactivate Cancer-Associated Fibroblasts through Suppressing TGF-beta Signaling in Breast Cancer. *Journal of Experimental & Clinical Cancer Research: CR* 2018, 37:282.

[170] Terragno M, Vetrova A, Semenov O, Sayan AE, Kriajevska M, Tulchinsky E: Mesenchymal-Epithelial Transition and AXL Inhibitor TP-0903 Sensitise Triple-Negative Breast Cancer Cells to the Antimalarial Compound, Artesunate. *Scientific Reports* 2024, 14:425.

[171] Duarte D, Nunes M, Ricardo S, Vale N: Combination of Antimalarial and CNS Drugs with Antineoplastic Agents in MCF-7 Breast and HT-29 Colon Cancer Cells: Biosafety Evaluation and Mechanism of Action. *Biomolecules* 2022, 12:1490.

[172] Li Z, Zhu YT, Xiang M, Qiu JL, Luo SQ, Lin F: Enhanced Lysosomal Function is Critical for Paclitaxel Resistance in Cancer Cells: Reversed by Artesunate. *Acta Pharmacologica Sinica* 2021, 42:624–632.

[173] Li W, Zhao L, Li Y, Zhai Z: Artesunate Attenuates Proliferation of Epithelial Cells by Downregulating the NF-kappaB and AKT Signaling Pathways in Benign Mammary Gland Hyperplasia Rats. *Annals of Translational Medicine* 2021, 9:848.

[174] Steigenberger C, Schnell-Inderst P, Flatscher-Thoni M, Plank LM, Siebert U: Patient' and Social Aspects Related to Complementary Mistletoe Therapy in Patients with Breast Cancer: A Systematic Review Commissioned by the German Agency for Health Technology Assessment. *European Journal of Oncology Nursing* 2023, 65:102338.

[175] Stocker A, Mehnert-Theuerkauf A, Hinz A, Ernst J: Utilization of Complementary and Alternative Medicine (CAM) by Women with Breast Cancer or Gynecological Cancer. *PloS One* 2023, 18:e0285718.

[176] Staupe H, Buentzel J, Keinki C, Buentzel J, Huebner J: Systematic Analysis of Mistletoe Prescriptions in Clinical Studies. *Journal of Cancer Research and Clinical Oncology* 2023, 149:5559–5571.

[177] Oei SL, Thronicke A, Kroz M, von Trott P, Schad F, Matthes H: Impact of Oncological Therapy and Viscum album L Treatment on Cancer-Related Fatigue and Internal Coherence in Nonmetastasized Breast Cancer Patients. *Integrative Cancer Therapies* 2020, 19:1534735420917211.

[178] Loef M, Paepke D, Walach H: Quality of Life in Breast Cancer Patients Treated With Mistletoe Extracts: A Systematic Review and Meta-Analysis. *Integrative Cancer Therapies* 2023, 22:15347354231198074.

[179] Schad F, Thronicke A: Safety of Combined Targeted and Helixor((R))Viscum album L. Therapy in Breast and Gynecological Cancer Patients, a Real-World Data Study. *International Journal of Environmental Research and Public Health* 2023, 20:2565.

[180] Pelzer F, Troger W, Nat DR: Complementary Treatment with Mistletoe Extracts During Chemotherapy: Safety, Neutropenia, Fever, and Quality of Life Assessed in a Randomized Study. *Journal of Alternative and Complementary Medicine* 2018, 24:954–961.

[181] Kwon YS, Chun SY, Kim MK, Nan HY, Lee C, Kim S: Mistletoe Extract Targets the STAT3-FOXM1 Pathway to Induce Apoptosis and Inhibits Metastasis in Breast Cancer Cells. *The American Journal of Chinese Medicine* 2021, 49:487–504.

[182] Kozlowski HM, Pawlikowska M, Sobocinska J, Jedrzejewski T, Dzialuk A, Wrotek S: Distinct Modulatory Effects of Fever-Range Hyperthermia on the Response of Breast Cancer Cells and Macrophages to Mistletoe (Viscum album L.) Extract. *Pharmaceuticals* 2021, 14:551.

[183] De Jaeghere EA, Tuyaerts S, Van Nuffel AMT, Belmans A, Bogaerts K, Baiden-Amissah R, et al.: Pembrolizumab, Radiotherapy, and an Immunomodulatory Five-Drug Cocktail in Pretreated Patients with Persistent, Recurrent, or Metastatic Cervical or Endometrial Carcinoma: Results of the Phase II PRIMMO Study. *Cancer Immunology, Immunotherapy: CII* 2023, 72:475–491.

[184] Patino-Morales CC, Soto-Reyes E, Arechaga-Ocampo E, Ortiz-Sanchez E, Antonio-Vejar V, Pedraza-Chaverri J, et al.: Curcumin Stabilizes p53 by Interaction with NAD(P)H:quinone Oxidoreductase 1 in Tumor-Derived Cell Lines. *Redox Biology* 2020, 28:101320.

[185] Wang T, Wu X, Al Rudaisat M, Song Y, Cheng H: Curcumin Induces G2/M Arrest and Triggers Autophagy, ROS Generation and Cell Senescence in Cervical Cancer Cells. *Journal of Cancer* 2020, 11:6704–6715.

[186] Zhao X, Zhang R, Song Z, Yang K, He H, Jin L, et al.: Curcumin Suppressed the Proliferation and Apoptosis of HPV-Positive Cervical Cancer Cells by Directly Targeting the E6 Protein. *Phytotherapy Research: PTR* 2023.

[187] Lee CY, Hsiao YH, Chen PN, Wu HH, Lu CY, Yang SF, et al.: CLEFMA Induces Intrinsic and Extrinsic Apoptotic Pathways through ERK1/2 and p38 Signalling in Uterine Cervical Cancer Cells. *Journal of Cellular and Molecular Medicine* 2023, 27:446–455.

[188] Lee CY, Ho YC, Lin CW, Hsin MC, Wang PH, Tang YC, et al.: EF-24 Inhibits TPA-Induced Cellular Migration and MMP-9 Expression through the p38 Signaling Pathway in Cervical Cancer Cells. *Environmental Toxicology* 2023, 38:451–459.

[189] Mohanty S, Huang J, Basu A: Enhancement of Cisplatin Sensitivity of Cisplatin-Resistant Human Cervical Carcinoma Cells by Bryostatin 1. *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research* 2005, 11:6730–6737.

[190] Armstrong DK, Blessing JA, Rader J, Sorosky JI, Gynecologic Oncology Group S: A Randomized Phase II Evaluation of Bryostatin-1 (NSC #339555) in Persistent or Recurrent Squamous Cell Carcinoma of the Cervix: A Gynecologic Oncology Group Study. *Investigational New Drugs* 2003, 21:453–457.

[191] Nezhat F, Wadler S, Muggia F, Mandeli J, Goldberg G, Rahaman J, et al.: Phase II Trial of the Combination of Bryostatin-1 and Cisplatin in Advanced or Recurrent Carcinoma of the Cervix: A New York Gynecologic Oncology Group Study. *Gynecologic Oncology* 2004, 93:144–148.

[192] Garcia FA, Cornelison T, Nuno T, Greenspan DL, Byron JW, Hsu CH, et al.: Results of a Phase II Randomized, Double-Blind, Placebo-Controlled Trial of Polyphenon E in Women with Persistent High-Risk HPV Infection and Low-Grade Cervical Intraepithelial Neoplasia. *Gynecologic Oncology* 2014, 132:377–382.

[193] Dikshit A, Hales K, Hales DB: Whole Flaxseed Diet Alters Estrogen Metabolism to Promote 2-Methoxtestradiol-Induced Apoptosis in Hen Ovarian Cancer. *The Journal of Nutritional Biochemistry* 2017, 42:117–125.

[194] Pal P, Hales K, Petrik J, Hales DB: Pro-Apoptotic and Anti-Angiogenic Actions of 2-Methoxyestradiol and Docosahexaenoic Acid, the Biologically Derived Active Compounds from Flaxseed Diet, in Preventing Ovarian Cancer. *Journal of Ovarian Research* 2019, 12:49.

[195] Weston WC, Hales KH, Hales DB: Flaxseed Increases Animal Lifespan and Reduces Ovarian Cancer Severity by Toxically Augmenting One-Carbon Metabolism. *Molecules* 2021, 26:5674.

[196] Morgan RJ Jr, Leong L, Chow W, Gandara D, Frankel P, Garcia A, et al.: Phase II Trial of Bryostatin-1 in Combination with Cisplatin in Patients with Recurrent or Persistent Epithelial Ovarian Cancer: A California Cancer Consortium Study. *Investigational New Drugs* 2012, 30:723–728.

[197] Tuyaerts S, Rombauts K, Everaert T, Van Nuffel AMT, Amant F: A Phase 2 Study to Assess the Immunomodulatory Capacity of a Lecithin-Based Delivery System of Curcumin in Endometrial Cancer. *Frontiers in Nutrition* 2018, 5:138.

[198] Sirohi VK, Popli P, Sankhwar P, Kaushal JB, Gupta K, Manohar M, et al.: Curcumin Exhibits Anti-Tumor Effect and Attenuates Cellular Migration via Slit-2 Mediated Down-Regulation of SDF-1 and CXCR4 in Endometrial Adenocarcinoma Cells. *The Journal of Nutritional Biochemistry* 2017, 44:60–70.

[199] Zhang MJ, Shi M, Yu Y, Wang H, Ou R, Ge RS: CP41, a Novel Curcumin Analogue, Induces Apoptosis in Endometrial Cancer Cells by Activating the H3F3A/Proteasome-MAPK Signaling Pathway and Enhancing Oxidative Stress. *Life Sciences* 2024, 338:122406.

[200] Ollberding NJ, Lim U, Wilkens LR, Setiawan VW, Shvetsov YB, Henderson BE, et al.: Legume, Soy, Tofu, and Isoflavone Intake and Endometrial Cancer Risk in Postmenopausal Women in the Multiethnic Cohort Study. *Journal of the National Cancer Institute* 2012, 104:67–76.

[201] Yoriki K, Mori T, Aoyama K, Tarumi Y, Kataoka H, Kokabu T, et al.: Genistein Induces Long-Term Expression of Progesterone Receptor Regardless of Estrogen Receptor Status and Improves the Prognosis of Endometrial Cancer Patients. *Scientific Reports* 2022, 12:10303.

[202] Golabek-Grenda A, Kaczmarek M, Juzwa W, Olejnik A: Natural Resveratrol Analogs Differentially Target Endometriotic Cells into Apoptosis Pathways. *Scientific Reports* 2023, 13:11468.

[203] Wang YL, Shen Y, Xu JP, Han K, Zhou Y, Yang S, et al.: Pterostilbene Suppresses Human Endometrial Cancer Cells In Vitro by Down-Regulating miR-663b. *Acta Pharmacologica Sinica* 2017, 38:1394–1400.

[204] Motzer RJ, Jonasch E, Agarwal N, Alva A, Baine M, Beckermann K, et al.: Kidney Cancer, Version 3.2022, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network: JNCCN* 2022, 20:71–90.

[205] Owens B: Kidney Cancer. *Nature* 2016, 537:S97.

[206] Li E, Zhang T, Sun X, Li Y, Geng H, Yu D, et al.: Sonic Hedgehog Pathway Mediates Genistein Inhibition of Renal Cancer Stem Cells. *Oncology Letters* 2019, 18:3081–3091.

[207] Buonerba C, De Placido P, Bruzzese D, Pagliuca M, Ungaro P, Bosso D, et al.: Isoquercetin as an Adjunct Therapy in Patients With Kidney Cancer Receiving First-Line Sunitinib (QUASAR): Results of a Phase I Trial. *Frontiers in Pharmacology* 2018, 9:189.

[208] Wu P, Wang X, Ma Y, Xu X, Liu W, Sheng Z, et al.: (3E,5E)-3,5-Bis(Pyridin-3-Methylene)-Tetrahydrothiopyran-4-One Enhances the Inhibitory Effect of Gemcitabine on Pancreatic Cancer Cells. *Bioorganic Chemistry* 2020, 101:104022.

[209] Delitto D, Wallet SM, Hughes SJ: Targeting Tumor Tolerance: A New Hope for Pancreatic Cancer Therapy? *Pharmacology & Therapeutics* 2016, 166:9–29.

[210] Pastorelli D, Fabricio ASC, Giovanis P, D'Ippolito S, Fiduccia P, Soldà C, et al.: Phytosome Complex of Curcumin as Complementary Therapy of Advanced Pancreatic Cancer Improves Safety and Efficacy of Gemcitabine: Results of a Prospective Phase II Trial. *Pharmacological Research* 2018, 132:72–79.

[211] Liu P, Ying Q, Liu H, Yu SQ, Bu LP, Shao L, et al.: Curcumin Enhances Anti-Cancer Efficacy of Either Gemcitabine or Docetaxel on Pancreatic Cancer Cells. *Oncology Reports* 2020, 44:1393–1402.

[212] Chen H, Jiang Y, Liu R, Deng J, Chen Q, Chen L, et al.: Curcumin Derivative C66 Suppresses Pancreatic Cancer Progression through the Inhibition of JNK-Mediated Inflammation. *Molecules* 2022, 27:3076.

[213] Zhai LL, Li WB, Chen LJ, Wang W, Ju TF, Yin DL: Curcumin Inhibits the Invasion and Migration of Pancreatic Cancer Cells by Upregulating TFPI-2 to Regulate ERK- and JNK-Mediated Epithelial-Mesenchymal Transition. *European Journal of Nutrition* 2024, 63:639–651.

[214] Malhotra L, Sharma S, Hariprasad G, Dhingra R, Mishra V, Sharma RS, et al.: Mechanism of Apoptosis Activation by Curcumin Rescued Mutant p53Y220C in Human Pancreatic Cancer. *Biochimica et Biophysica Acta Molecular Cell Research* 2022, 1869:119343.

[215] Malhotra L, Goyal HKV, Jhuria S, Dev K, Kumar S, Kumar M, et al.: Curcumin Rescue p53Y220C in BxPC-3 Pancreatic Adenocarcinomas Cell Line: Evidence-Based on Computational, Biophysical, and In Vivo Studies. *Biochimica et Biophysica Acta General Subjects* 2021, 1865:129807.

[216] Lohr JM, Karimi M, Omazic B, Kartalis N, Verbeke CS, Berkenstam A, et al.: A Phase I dose Escalation Trial of AXP107-11, a Novel Multi-Component Crystalline form of Genistein, in Combination with Gemcitabine in Chemotherapy-Naive Patients with Unresectable Pancreatic Cancer. *Pancreatology: Official Journal of the International Association of Pancreatology* 2016, 16:640–645.

[217] Mesmar F, Dai B, Ibrahim A, Hases L, Jafferali MH, Jose Augustine J, et al.: Clinical Candidate and Genistein Analogue AXP107-11 has Chemoenhancing Functions in Pancreatic Adenocarcinoma through G Protein-Coupled Estrogen Receptor Signaling. *Cancer Medicine* 2019, 8:7705–7719.

[218] Li T, Kuang T, Yang Z, Zhang Q, Zhang W, Fan Y: Co-Treatment with Everolimus, an mTOR-Specific Antagonist, or Downregulation of ELK1 Enhances the Sensitivity of Pancreatic Cancer Cells to Genistein. *Frontiers in Cell and Developmental Biology* 2021, 9:633035.

[219] Bi YL, Min M, Shen W, Liu Y: Genistein Induced Anticancer Effects on Pancreatic Cancer Cell Lines Involves Mitochondrial Apoptosis, G(0)/G(1)Cell Cycle Arrest and Regulation of STAT3 Signalling Pathway. *Phytomedicine: International Journal of Phytotherapy and Phytopharmacology* 2018, 39:10–16.

[220] Yang Y, Huynh N, Dumesny C, Wang K, He H, Nikfarjam M: Cannabinoids Inhibited Pancreatic Cancer via P-21 Activated Kinase 1 Mediated Pathway. *International Journal of Molecular Sciences* 2020, 21:8035.

[221] Alfonzetti T, Moreau M, Yasmin-Karim S, Ngwa W, Avery S, Goia D: Phytoradiotherapy to Enhance Cancer Treatment Outcomes with Cannabidiol, Bitter Melon Juice, and Plant Hemoglobin. *Frontiers in Oncology* 2022, 12:1085686.

[222] Luongo M, Marinelli O, Zeppa L, Aguzzi C, Morelli MB, Amantini C, et al.: Cannabidiol and Oxygen-Ozone Combination Induce Cytotoxicity in Human Pancreatic Ductal Adenocarcinoma Cell Lines. *Cancers* 2020, 12:2774.

[223] Garofano F, Sharma A, Abken H, Gonzalez-Carmona MA, Schmidt-Wolf IGH: A Low Dose of Pure Cannabidiol Is Sufficient to Stimulate the Cytotoxic Function of CIK Cells without Exerting the Downstream Mediators in Pancreatic Cancer Cells. *International Journal of Molecular Sciences* 2022, 23:3783.

[224] Bilim V, Kuroki H, Shirono Y, Murata M, Hiruma K, Tomita Y: Advanced Bladder Cancer: Changing the Treatment Landscape. *Journal of Personalized Medicine* 2022, 12:1745.

[225] Huang L, He C, Zheng S, Wu C, Ren M, Shan Y: AKT1/HK2 Axis-Mediated Glucose Metabolism: A Novel Therapeutic Target of Sulforaphane in Bladder Cancer. *Molecular Nutrition & Food Research* 2022, 66:e2100738.

[226] Wang F, Liu P, An H, Zhang Y: Sulforaphane Suppresses the Viability and Metastasis, and Promotes the Apoptosis of Bladder Cancer Cells by Inhibiting the Expression of FAT-1. *International Journal of Molecular Medicine* 2020, 46:1085–1095.

[227] Justin S, Rutz J, Maxeiner S, Chun FK, Juengel E, Blaheta RA: Bladder Cancer Metastasis Induced by Chronic Everolimus Application Can Be Counteracted by Sulforaphane In Vitro. *International Journal of Molecular Sciences* 2020, 21:5582.

[228] Justin S, Rutz J, Maxeiner S, Chun FK, Juengel E, Blaheta RA: Chronic Sulforaphane Administration Inhibits Resistance to the mTOR-Inhibitor Everolimus in Bladder Cancer Cells. *International Journal of Molecular Sciences* 2020, 21:4026.

[229] Xie H, Rutz J, Maxeiner S, Grein T, Thomas A, Juengel E, et al.: Plant-Derived Sulforaphane Suppresses Growth and Proliferation of Drug-Sensitive and Drug-Resistant Bladder Cancer Cell Lines In Vitro. *Cancers* 2022, 14:4682.

[230] Zhou Q, Jin P, Liu J, Li S, Liu W, Xi S: HER2 Overexpression Triggers the IL-8 to Promote Arsenic-Induced EMT and Stem Cell-Like Phenotypes in Human Bladder Epithelial Cells. *Ecotoxicology and Environmental Safety* 2021, 208:111693.

[231] Guo W, Wang H, Li C: Signal Pathways of Melanoma and Targeted Therapy. *Signal Transduction and Targeted Therapy* 2021, 6:424.

[232] Siegel RL, Miller KD, Fuchs HE, Jemal A: Cancer Statistics, 2021. *CA: A Cancer Journal for Clinicians* 2021, 71:7–33.

[233] Tahata S, Singh SV, Lin Y, Hahm ER, Beumer JH, Christner SM, et al.: Evaluation of Biodistribution of Sulforaphane after Administration of Oral Broccoli Sprout Extract in Melanoma Patients with Multiple Atypical Nevi. *Cancer Prevention Research* 2018, 11:429–438.

[234] Eom YS, Shah FH, Kim SJ: Sulforaphane Induces Cell Differentiation, Melanogenesis and also Inhibit the Proliferation of Melanoma Cells. *European Journal of Pharmacology* 2022, 921:174894.

[235] Arcidiacono P, Stabile AM, Ragonese F, Pistilli A, Calvieri S, Bottoni U, et al.: Anticarcinogenic Activities of Sulforaphane are Influenced by Nerve Growth Factor in Human Melanoma A375 Cells. *Food and Chemical Toxicology: An International Journal Published for the British Industrial Biological Research Association* 2018, 113:154–161.

[236] Morceau F, Chateauvieux S, Orsini M, Trecul A, Dicato M, Diederich M: Natural Compounds and Pharmaceuticals Reprogram Leukemia Cell Differentiation Pathways. *Biotechnology Advances* 2015, 33:785–797.

[237] Olivas-Aguirre M, Torres-Lopez L, Pottosin I, Dobrovinskaya O: Phenolic Compounds Cannabidiol, Curcumin and Quercetin Cause Mitochondrial Dysfunction and Suppress Acute Lymphoblastic Leukemia Cells. *International Journal of Molecular Sciences* 2020, 22:204.

[238] Olivas-Aguirre M, Perez-Chavez J, Torres-Lopez L, Hernandez-Cruz A, Pottosin I, Dobrovinskaya O: Dexamethasone-Induced Fatty Acid Oxidation and Autophagy/Mitophagy Are Essential for T-ALL Glucocorticoid Resistance. *Cancers* 2023, 15:445.

[239] Koszalka P, Stasilojc G, Miekus-Purwin N, Niedzwiecki M, Purwin M, Grabowski S, et al.: The Cooperative Anti-Neoplastic Activity of Polyphenolic Phytochemicals on Human T-Cell Acute Lymphoblastic Leukemia Cell Line MOLT-4 In Vitro. *International Journal of Molecular Sciences* 2022, 23:4753.

[240] Liu JM, Li M, Luo W, Sun HB: Curcumin Attenuates Adriamycin-Resistance of Acute Myeloid Leukemia by Inhibiting the lncRNA HOTAIR/miR-20a-5p/WT1 Axis. *Laboratory Investigation; A Journal of Technical Methods and Pathology* 2021, 101:1308–1317.

[241] Gaur T, Ali A, Sharma D, Gupta SK, Gota V, Bagal B, et al.: Mitocurcumin Utilizes Oxidative Stress to Upregulate JNK/p38 Signaling and Overcomes Cytarabine Resistance in Acute Myeloid Leukemia. *Cell Signal* 2024, 114:111004.

[242] Bistue-Rovira A, Rico LG, Bardina J, Junca J, Granada I, Bradford JA, et al.: Persistence of Chronic Lymphocytic Leukemia Stem-like Populations under Simultaneous In Vitro Treatment with Curcumin, Fludarabine, and Ibrutinib: Implications for Therapy Resistance. *International Journal of Molecular Sciences* 2024, 25:1994.

[243] Feriotto G, Marchetti P, Rondanin R, Tagliati F, Aguzzi S, Beninati S, et al.: Cytotoxicity of Isoxazole Curcumin Analogs on Chronic Myeloid Leukemia-Derived K562 Cell Lines Sensitive and Resistant to Imatinib. *International Journal of Molecular Sciences* 2023, 24:2356.

[244] Hsiao PC, Chang JH, Lee WJ, Ku CC, Tsai MY, Yang SF, et al.: The Curcumin Analogue, EF-24, Triggers p38 MAPK-Mediated Apoptotic Cell Death via Inducing PP2A-Modulated ERK Deactivation in Human Acute Myeloid Leukemia Cells. *Cancers* 2020, 12:2163.

[245] Fan YJ, Zhou YX, Zhang LR, Lin QF, Gao PZ, Cai F, et al.: C1206, a Novel Curcumin Derivative, Potently Inhibits Hsp90 and Human Chronic Myeloid Leukemia Cells In Vitro. *Acta Pharmacologica Sinica* 2018, 39:649–658.

[246] Liu B, Shen Y, Huang H, Croce KD, Wu M, Fan Y, et al.: Curcumin Derivative C212 Inhibits Hsp90 and Eliminates both Growing and Quiescent Leukemia Cells in Deep Dormancy. *Cell Communication and Signaling: CCS* 2020, 18:159.

[247] Sawesi S, Malkaram SA, Abd Elmageed ZY, Fandy TE: Modulation of the Activity of Histone Lysine Methyltransferases and Demethylases by Curcumin Analog in Leukaemia Cells. *Journal of Cellular and Molecular Medicine* 2022, 26:5624–5633.

[248] Mugnaini EN, Ghosh N: Lymphoma. *Primary Care* 2016, 43:661–675.

[249] Zhao Q, Guan J, Qin Y, Ren P, Zhang Z, Lv J, et al.: Curcumin Sensitizes Lymphoma Cells to DNA Damage Agents through Regulating Rad51-Dependent Homologous Recombination. *Biomedicine & Pharmacotherapy* 2018, 97:115–119.

[250] Zhang Y, Xiang J, Zhu N, Ge H, Sheng X, Deng S, et al.: Curcumin in Combination with Homoharringtonine Suppresses Lymphoma Cell Growth by Inhibiting the TGF-beta/Smad3 Signaling Pathway. *Aging* 2021, 13:18757–18768.

[251] Ge X, Du Y, Chen J, Zhu N, Yao J, Zhang X, et al.: Herbal NF-kappaB Inhibitors Sensitize Rituximab-Resistant B Lymphoma Cells to Complement-Mediated Cytolysis. *Frontiers in Oncology* 2021, 11:751904.

[252] Kovacs Z, Guttman A: Utilization of Analytical Omics Tools in the Molecular Diagnostics of Multiple Myeloma. *Current Molecular Medicine* 2018, 18:260–272.

[253] Santosa D, Suharti C, Riwanto I, Dharmana E, Pangarsa EA, Setiawan B, et al.: Curcumin as Adjuvant Therapy to Improve Remission in Myeloma Patients: A Pilot Randomized Clinical Trial. *Caspian Journal of Internal Medicine* 2022, 13:375–384.

[254] Booth L, Roberts JL, West C, Dent P: GZ17-6.02 Interacts with Proteasome Inhibitors to Kill Multiple Myeloma Cells. *Oncotarget* 2024, 15:159–174.

[255] Chen J, Ruijtenbeek R, Garssen J, Redegeld FA: Esterified Derivatives of DHA and EPA Increase Bortezomib Cytotoxicity in Human Multiple Myeloma Cells. *European Journal of Pharmacology* 2022, 922:174883.

[256] Chen J, Garssen J, Redegeld F: The Efficacy of Bortezomib in Human Multiple Myeloma Cells is Enhanced by Combination with Omega-3 Fatty Acids DHA and EPA: Timing is Essential. *Clinical Nutrition* 2021, 40:1942–1953.

[257] Chen J, Zaal EA, Berkers CR, Ruijtenbeek R, Garssen J, Redegeld FA: Omega-3 Fatty Acids DHA and EPA Reduce Bortezomib Resistance in Multiple Myeloma Cells by Promoting Glutathione Degradation. *Cells* 2021, 10:2287.

[258] Mekkawy SA, Abdalla MS, Omran MM, Hassan NM, Abdelfattah R, Abdel-Salam IM: Cancer Stem Cells as a Prognostic Biomarker and Therapeutic Target Using Curcumin/Piperine Extract for Multiple Myeloma. *Asian Pacific Journal of Cancer Prevention: APJCP* 2022, 23:3507–3515.

[259] Garofano F, Schmidt-Wolf IGH: High Expression of Cannabinoid Receptor 2 on Cytokine-Induced Killer Cells

and Multiple Myeloma Cells. *International Journal of Molecular Sciences* 2020, 21:3800.

[260] Chen Q, Shu C, Laurence AD, Chen Y, Peng BG, Zhen ZJ, et al.: Effect of Huaier Granule on Recurrence after Curative Resection of HCC: A Multicentre, Randomised Clinical Trial. *Gut* 2018, 67:2006–2016.

[261] Luo S, Hu H: Huaier Granule Prolongs Overall Survival after Curative Resection of Hepatocarcinoma Carcinoma: A Propensity Score Analysis. *Journal of Ethnopharmacology* 2023, 301:115774.

[262] Shi K, Bi Y, Zeng X, Wang X: Effects of Adjuvant Huaier Granule Therapy on Survival Rate of Patients with Hepatocellular Carcinoma. *Frontiers in Pharmacology* 2023, 14:1163304.

[263] Zhou L, Pan LC, Zheng YG, Du GS, Fu XQ, Zhu ZD, et al.: Novel Strategy of Sirolimus Plus Thymalfasin and Huaier Granule on Tumor Recurrence of Hepatocellular Carcinoma Beyond the UCSF Criteria Following Liver Transplantation: A Single Center Experience. *Oncology Letters* 2018, 16:4407–4417.

[264] Gullo I, Grillo F, Mastracci L, Vanoli A, Carneiro F, Saragoni L, et al.: Precancerous Lesions of the Stomach, Gastric Cancer and Hereditary Gastric Cancer Syndromes. *Pathologica* 2020, 112:166–185.

[265] Zhu Y, Ouyang Z, Du H, Wang M, Wang J, Sun H, et al.: New Opportunities and Challenges of Natural Products Research: When Target Identification Meets Single-Cell Multiomics. *Acta Pharmaceutica Sinica B* 2022, 12:4011–4039.

[266] Li T, Pan J, Chen H, Fang Y, Sun Y: CXCR6-Based Immunotherapy in Autoimmune, Cancer and Inflammatory Infliction. *Acta Pharmaceutica Sinica B* 2022, 12:3255–3262.

[267] Wang ZY, Chen Z: Acute Promyelocytic Leukemia: From Highly Fatal to Highly Curable. *Blood* 2008, 111:2505–2515.