Frontiers in Bioscience Landmark

Front. Biosci. (Landmark Ed) **2022**; 27(6): 192
https://doi.org/10.31083/j.fbl2706192

Review

The Role and Mechanisms of Action of Natural Compounds in the Prevention and Treatment of Cancer and Cancer Metastasis

Yunqiao Wang[1,†], Mingtai Chen[1,2,†], Hao Yu[1,†], Gang Yuan[1,3,†], Li Luo[4], Xiongfei Xu[1,5], Yanneng Xu[1,3], Xinbing Sui[6,7,*], Elaine Lai-Han Leung[8,*], Qibiao Wu[1,9,10,*]

[1]Faculty of Chinese Medicine and State Key Laboratory of Quality Research in Chinese Medicine, Macau University of Science and Technology, 999078 Macau, China
[2]Department of Cardiovascular Disease, Shenzhen Traditional Chinese Medicine Hospital, 518020 Shenzhen, Guangdong, China
[3]Department of Intervention, Traditional Chinese Medicine Hospital Affiliated to Southwest Medical University, 646000 Luzhou, Sichuan, China
[4]Education Evaluation and Faculty Development Center, Guangxi Medical University, 530021 Nanning, Guangxi, China
[5]Department of Vascular Surgery, The Affiliated Hospital of Southwest Medical University, 646000 Luzhou, Sichuan, China
[6]College of Pharmacy, Hangzhou Normal University, 310030 Hangzhou, Zhejiang, China
[7]Department of Medical Oncology, The Affiliated Hospital of Hangzhou Normal University, College of Medicine, Hangzhou Normal University, 310030 Hangzhou, Zhejiang, China
[8]Faculty of Health Sciences, University of Macau, Taipa, 999078 Macau, China
[9]Guangdong-Hong Kong-Macao Joint Laboratory for Contaminants Exposure and Health, 510000 Guangzhou, Guangdong, China
[10]Zhuhai MUST Science and Technology Research Institute, 51900 Zhuhai, Guangdong, China
*Correspondence: qbwu@must.edu.mo (Qibiao Wu); laihanl@gmail.com (Elaine Lai-Han Leung); hzzju@hznu.edu.cn (Xinbing Sui)
[†]These authors contributed equally.

Academic Editors: Antonio Barbieri and Francesca Bruzzese
Submitted: 2 April 2022 Revised: 13 May 2022 Accepted: 26 May 2022 Published: 15 June 2022

Abstract

Cancer has emerged as one of the world's most concerning health problems. The progression and metastasis mechanisms of cancer are complex, including metabolic disorders, oxidative stress, inflammation, apoptosis, and intestinal microflora disorders. These pose significant challenges to our efforts to prevent and treat cancer and its metastasis. Natural drugs have a long history of use in the prevention and treatment of cancer. Many effective anti-tumor drugs, such as Paclitaxel, Vincristine, and Camptothecin, have been widely prescribed for the prevention and treatment of cancer. In recent years, a trend in the field of antitumor drug development has been to screen the active antitumor ingredients from natural drugs and conduct in-depth studies on the mechanisms of their antitumor activity. In this review, high-frequency keywords included in the literature of several common Chinese and English databases were analyzed. The results showed that five Chinese herbal medicines (Radix Salviae, Panax Ginseng C. A. Mey, Hedysarum Multijugum Maxim, Ganoderma, and Curcumaelongae Rhizoma) and three natural compounds (quercetin, luteolin, and kaempferol) were most commonly used for the prevention and treatment of cancer and cancer metastasis. The main mechanisms of action of these active compounds in tumor-related research were summarized. Finally, we found that four natural compounds (dihydrotanshinone, sclareol, isoimperatorin, and girinimbin) have recently attracted the most attention in the field of anti-cancer research. Our findings provide some inspiration for future research on natural compounds against tumors and new insights into the role and mechanisms of natural compounds in the prevention and treatment of cancer and cancer metastasis.

Keywords: Chinese medicine; bioactive compounds; cancer; tumor; molecular mechanisms

1. Introduction

Cancer is one of the most concerning health problems facing mankind. The progression and metastasis mechanisms of cancer are complex, including metabolic disorders, oxidative stress, inflammation, apoptosis, and intestinal microflora disorders. These pose a significant challenges to our efforts to prevent and treat cancer and its metastases. Natural drugs have a long history of use in the prevention and treatment of cancer. Many effective anti-tumor drugs, such as Paclitaxel, Vincristine, and Camptothecin, have been widely prescribed for the prevention and treatment of cancer [1]. In recent years, a trend in the field of antitumor drug development has been to screen effective and safe antitumor ingredients from natural drugs and to conduct in-depth studies on the mechanisms of their antitumor activity.

In this review, we searched Chinese and English electronic databases including the CNKI database, Wanfang Data Knowledge Service Platform, VIP Chinese Science and Technology Journal Database, PubMed Database, and Web of Science Database, for relevant studies. All research results from 2000 to the present were selected to obtain the three most commonly used Chinese herbal medicines through screening. The active compounds from the selected medicines were identified using the Traditional Chinese Medicine Systems Pharmacology Database (TCMSP)

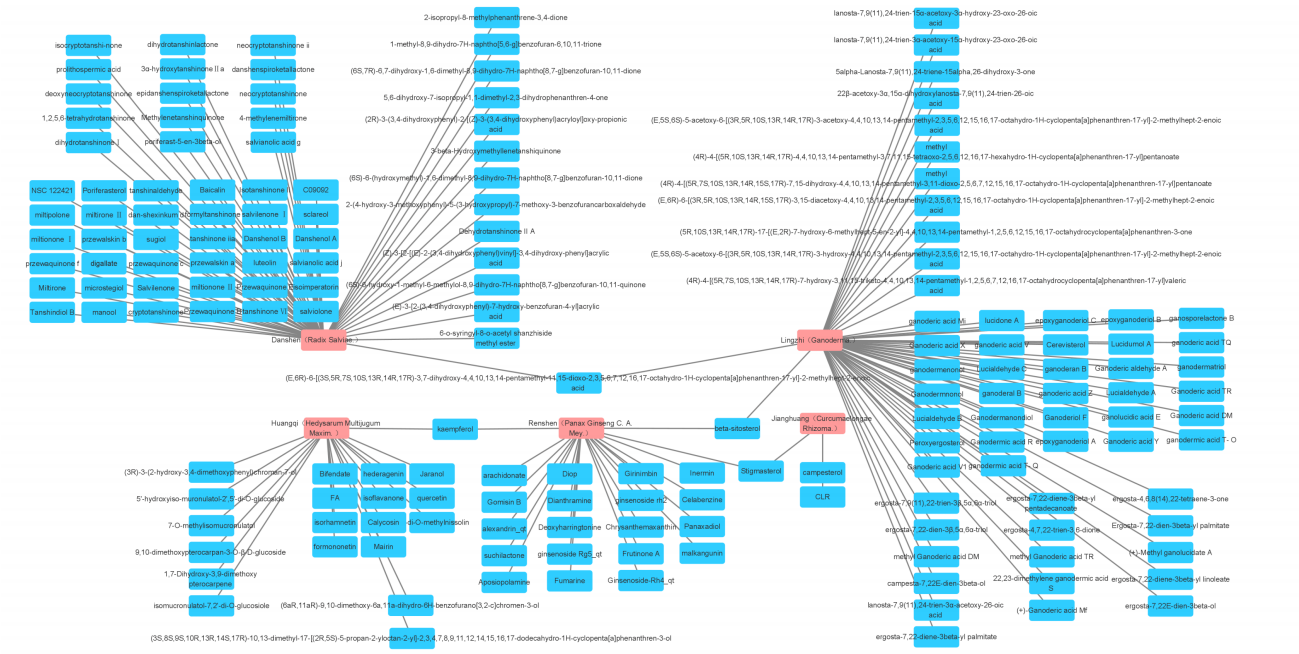

Fig. 1. The five most widely used single drugs in cancer and their active ingredients.

by analyzing oral bioavailability and drug similarity index. Subsequently, we searched the databases (PubMed and Web of Science) using the keywords for one of the compounds from the TCMSP and "Cancer" or "Tumor" "Carcinoma" or "Malignancy" to obtain articles published from January 2000 to the present.

Finally, we comprehensively analyzed and summarized the literature on the pharmacological effects and molecular mechanisms of these natural compounds against cancer and cancer metastasis. This article presents some new insights into the role of natural compounds in the prevention and treatment of cancer and cancer metastasis.

2. Materials and Methods

Common Chinese and English databases, including CNKI Database, Wanfang Data Knowledge Service Platform, VIP Chinese Science and Technology Journal Database, PubMed, and Web of Science, were searched, screening for relevant literature published in China and abroad from January 2000 to November 2021. The databases were searched using the following terms: ["traditional Chinese medicine (TCM)" OR "Chinese medicine" OR "herbal medicine" AND "cancer" OR "tumor" OR "carcinoma" OR "malignancy"]. According to the interface of each database, the comprehensive retrieval of subject words combined with keywords and free words was carried out to ensure the systematic integrity of the literature retrieval.

We searched all the basic studies on the mechanism of antitumor action of natural compounds and gathered all proven targets. To ensure the authenticity and stability of the results, only relevant studies with cell samples were selected.

3. Results

A total of 31,878 articles were retrieved, after excluding review articles, studies on TCM formulas, active ingredients of herb combinations, and other articles not related to a single drug. 1793 single-drug articles were included in our study, involving 39 commonly used Chinese herbal medicines. The most commonly used five traditional Chinese medicines were Radix Salviae (Danshen, 162 articles), Panax Ginseng C. A. Mey (Renshen, 159 articles), Hedysarum Multijugum Maxim (Huangqi, 131 articles), Ganoderma (Lingzhi, 123 articles) and Curcumaelongae Rhizoma (Jianghuang, 96 articles). We then searched the active compounds of these five drugs separately through TCMSP. The active compounds of each herb were sorted by the screening criteria with oral bioavailability $\geq$30% and drug-likeness $\geq$0.18 for the ADME (absorption, distribution, metabolism, and excretion) evaluation system. A total of 172 active compounds were obtained, excluding duplicates, and a total of 168 were identified (Fig. 1). We searched our five databases using the keywords for one of the natural compounds from the TCMSP and "cancer" or "tumor" or "carcinoma" or "malignancy". A total of 32,783 unscreened articles were obtained. Among them, the 3 active compounds in the literature with more than 1000 articles were quercetin (11427 articles), luteolin (2996), and kaempferol (2702) (Fig. 2). Herein, we focused on evaluating these three active compounds by comprehensively

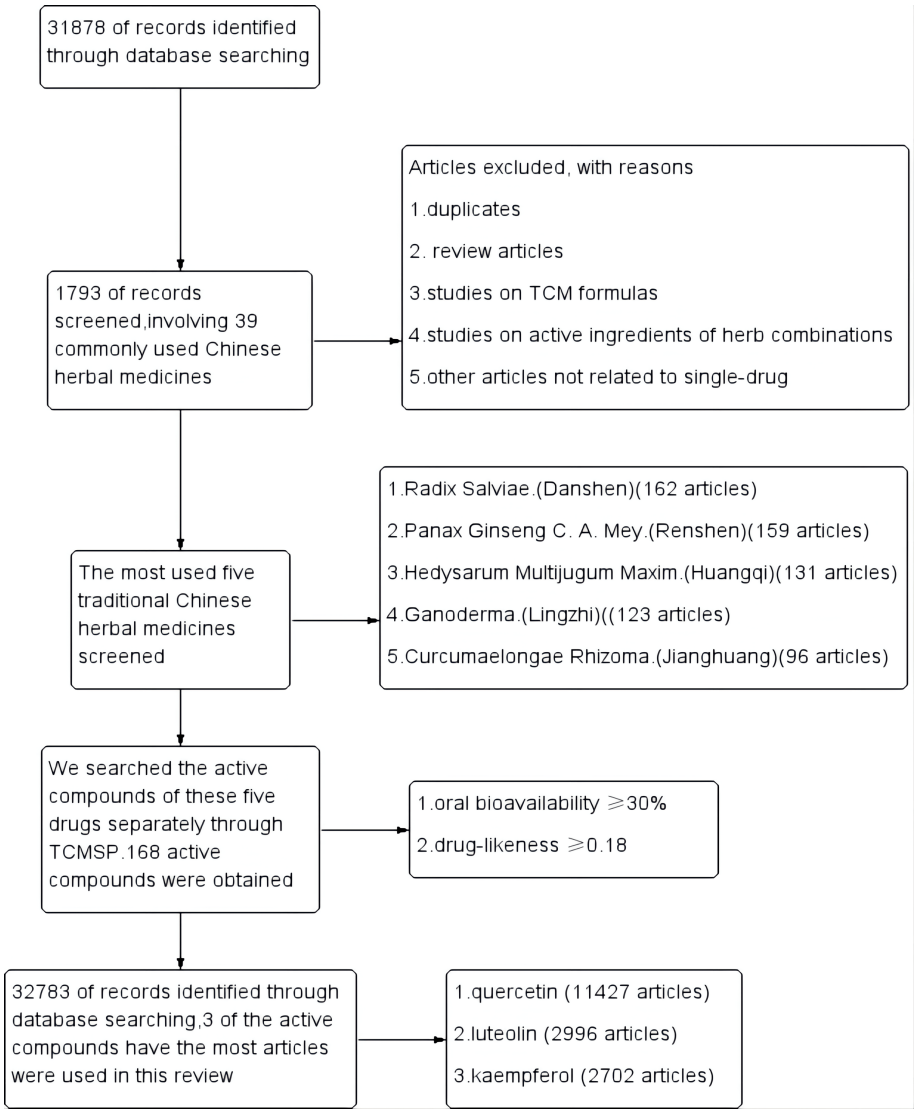

Fig. 2. Study flow diagram.

reviewing the relevant articles and determined that they have great anticancer potential, and also found that four natural compounds (dihydrotanshinone, sclareol, isoimperatorin, and girinimbin) have recently attracted most attention in the field of anti-cancer therapy. At the same time, we predicted the potential targets of these four compounds through the SwissTargetPrediction database.

3.1 The Main Targets and Mechanisms of Quercetin in Cancer Prevention and Cancer Metastasis

We summarized the reported targets of quercetin in the articles, which involving 36 different cancer cells (Table 1, Ref. [2–130]).

In breast cancer, the action of quercetin involves modulating SOD enzyme activity, the selective inhibition of *CYP1B1*, *CYP2*, and *CYP3* family of enzymes, G2/M arrest, and apoptosis [5]. A study on human breast cancer showed that quercetin triggered cell death of MDA-MB-231 cells via mitochondrial- and *caspase-3*-dependent pathways [7]. In studies on MCF-7 cells, quercetin not only induced cell cycle arrest but also induced significant apoptosis; the induction of apoptosis could be blocked by antisense *p21 CIP1/WAF1* expression [16]. Quercetin regulated MCF-7 cell apoptosis through the *AMPK-mTOR* signaling pathway [19] and promoted apoptosis by inducing G0/G1 phase arrest [23].

In lung cancer, quercetin induced autophagy and apoptosis in lung cancer cells through the *SIRT1/AMPK* signaling pathway [32]. Quercetin also inhibited the metastasis of lung cancer by modulating the *Akt/MAPK* signaling pathway and reduced the nuclear translocation of *β-catenin* [33]. Some studies have also found that quercetin induced apoptosis of A549 cells, mainly through down-regulating the *IL-6/STAT-3* signaling and the activation of *MEK-ERK* [40,43].

In liver cancer, quercetin could enhance the effect of *interferon-α* in hepatocellular carcinoma cells and reduce the proliferation ability of hepatocellular carcinoma cells

Table 1. The model cell and reported targets of quercetin.

Model cell	Reported targets
MDA-MB-468	cyclin B1 [2] TNF alpha, CCL28 [3] p53, Bcl2 [4] SOD, CYP1B1, CYP2, and CYP3 [5]
MDA-MB-231	*Cx43* [6] caspase-3, -8 and -9 [7] MMP-3 [8] alpha5- and alpha9-nAChR [9] Skp2, p27, FoxO1 [10] p53, p21, Bcl-xL, cyclin B1 [11] Skp2 [12] miR-146a, EGFR, bax, and caspase-3 [13] aldehyde dehydrogenase 1A1, C-X-C chemokine receptor type 4, mucin 1, and epithelial cell adhesion molecules [14] NF-κB , Hsp27, Hsp70 and Hsp90 [15]
MCF-7	p21CIP1/WAF1 [16] PKC, ERK, AP-1 [17] p53, p57, CDK2, cyclins A and B, Bcl-2, DeltaPsi(m), caspase-6, -8 and -9 [18] AMPK, mTOR [19] AMPK, mTOR, HIF-1 [20] Bcl-2, Bax [21,22] survivin [23] RAGE, HMGB1, NF-κB [24] PTEN, Akt [25] CyclinD1, p21, Twist, and phospho p38MAPK [26] CDK6 [27] TGF-β, Lef1, ABCG2, Vim, and Cav1 [28] MMP-2/-9 [29]
SkBr3	HIF-1alpha, VEGF [30]
A549	Bax, Bcl-2 and caspase-3 [31] SIRT1, AMPK p62, LC3-II, beclin 1, Atg5, Atg7 and Atg12 [32] TIMP-2, Akt, MAPK, β-catenin, and EMT [33] *Bax*, *Bcl2* [34,35] PDK3 [36] aurora B [37] nm23-H1, TIMP-2, MMP-2 [38] MMP-9, TGF-β1 [39] Bcl2, Bax, IL-6, STAT3, NF-κB [40] *p53* [41] caspase-3 [42] Bcl-2, Bcl-x, Bax, caspase-3, caspase-7 and PARP, ERK, MEK1/2, PI3k, p38, Akt [43] p53, p21, survivin [44] COX-2, iNOS [45] *Hsp72* [46] Hsp27 [47]
H1299	SIRT1, AMPK, p62, LC3-II, beclin 1, Atg5, Atg7, and Atg12 [32] p53, p21, survivin [44] DR5, caspase-10/3, p300 [48]
H69	Bax, Bcl-2, and caspase-3 [31]

Table 1. Continued.

Model cell	Reported targets
HepG2	*PDK3* [36] ABCC6 [49] p53, cyclin D1 [50,51] m-TOR, Nrf-2 [52] MEK1/ERK1/2, p38 MAPK, and JNK [53] cyclin D1 [54] SHP2, IFN-α, STAT1 [55] Bad, Bax, Bcl-2, and Survivin [56] BAX, BCL-2 [57] miR-34a, p53, SIRT1 [58] *Sp1* [59] PI3K, PKC, COX-2 and ROS, p53, and BAX [60] *FASN* [61] Nrf2, ARE [62] p38-MAPK, Nrf2 [63] NF-κB, COX-2 [64] P53, caspase-3, caspase-9, survivin ,and Bcl-2 [65] Nrf2, Keap1 [66] caspase-3, caspase -9, Bcl-xL, Bcl-xS, Bax, Akt, ERK [67]
Huh-7	p53, cyclin D1 [50] MEK1/ERK1/2, p38 MAPK, and JNK [53] SHP2, IFN-α, STAT1 [55] BAX, BCL-2 [57]
HeLa	*Hsp72* [46] Hsp27 [47] MMP2, ezrin, METTL3, and P-Gp [68] Bax, Bcl-2, Cyclin D1, Caspase-3, GRP78, CHOP IRE1, p-Perk, and c-ATF6 [69] DNMTs, HDACs, HAT, HMTs and TSGs [70] LC3-I/II, Beclin 1, active caspase-3, and S6K1 [71] *Rac1* [72] ROS, cytochrome-c, bcl-2, Bax, PI3K, and p-Akt [73] *HPA* [74] AKT, Bcl-2, p53 and caspase-3 [75] Bcl-2, Bcl-xL, Mcl1, Bax, Bad, p-Bad, cytochrome C, Apaf-1, caspases, surviving, p53, p21, cyclin D1, p50, p65, IκB, p-IκB-α, IKKβ and ubiquitin ligase [76] AMPK, ACC, AICAR, HSP70, caspase 3, PP2a and SHP-2 [77]
Caski	*HPA* [74]
SiHa	MMP2, ezrin, METTL3 and P-Gp [68] β-tubulin [78]
Hep-2	*Hsp72* [46] Hsp27 [47]
TFK-1	BAX, BCL-2 [57]
LNCaP	PI3K, Akt [79] Bcl-2, VEGF, Akt, PI3K [80] Bax, Bcl-2, caspase-3, AKT, VEGF [81] PI3K, Akt, AR [82] *HSP27* [83] Bcl-2, Bax [84] PARP, Bad, Bcl-xL, Bax, procaspases-3, -8 and -9 [85] HIF-1 alpha, VEGF [30] caspase, PARP, IAP and Bcl-2 [86] Sp1, AR [87] AR, PSA, NKX3.1, ODC,, and hK2 [88] *hsp70* [89]

Table 1. Continued.

Model cell	Reported targets
PC-3	Bcl-2, VEGF, Akt, PI3K [80] Bax, Bcl-2, caspase-3, AKT, VEGF [81] Cyclin D1, ErbB-2, ErbB-3, c-Raf, MAPK kinase 1/2 (MEK1/2), MAPK, Elk-1, and Akt-1 [90] *hsp70* [89] LC3, Beclin-1, PI3K, Akt, mTOR, LC3-II, LC3-I [91] PI3K, Akt [92] P53, PI3K, AKT, MMP-2, and MMP-9 [93] *TSP-1* [94] TGF-β, vimentin, N-cadherin, E-cadherin, Twist, Snail, and Slug [95] ATF, GRP78, GADD153, CDK2, cyclins E and D, Bcl-2, Bax, caspase-3, -8, and -9 [96] N-cadherin, vimentin, E-cadherin, Snail, Slug, Twist, EGFR, PI3K, Akt, ERK 1/2 [97] uPA, uPAR, EGF, EGF-R, β-catenin, NF-κB, p-EGF-R, N-Ras, Raf-1, c.Fos, c.Jun, and p-c.Jun [98] Bad, IGFBP-3, cytochrome C, caspase-9, caspase-10, PARP, caspase-3, IGF-IRβ, PI3K, p-Akt, cyclin D1, IGF-I, II, and IGF-IR [99,100] PLC, PKC, and MEK1/2 [101] Bcl-2, Bcl-x(L), and Bax [102] *MMP-2* and *MMP-9* [103] Cdc2/Cdk-1, cyclin B1, cyclin A, p21/Cip1, pRb, pRb2/p130, Bcl-2, Bcl-X(L), Bax, and caspase-3 [104] *HSP72* [105]
LAPC-4	PI3K, Akt, miR-21, miR-19b, miR-148a, AR [82]
RWPE-1	*HSP27* [83]
TSU-Pr1	*HSP27* [83]
DU-145	caspase, PARP, IAP , and Bcl-2 [86] *HSP72* [105] DR 5, PARP, caspase-3, and caspase-9 [106]
JCA-1	*hsp70* [89]
SW480	AIF and Caspase-3 [107] TGF-β1, Twist1 [108] cyclin D(1) and survivin [109] beta-catenin and Tcf-4 [110] ErbB2, ErbB3, Akt, Bax , and Bcl-2 [111]
HT-29	ErbB2, ErbB3, Akt, Bax, and Bcl-2 [111] Bcl-2, mTOR, Akt, p53, Bax, p38 MAPK, and PTEN [112] Akt, CSN6, Myc, p53, Bcl-2, and Bax [113] ROS, AMPK, p38, and sestrin 2 [114] GSTA1, GSTM1, GSTP1, GSTT1, and UGT1 [115] *AMPK*, *p53*, and *p21* [116] AMPK, COX-2 [117]
Caco-2	GSTA1, GSTM1, GSTP1, GSTT1, and UGT1 [115] TNF-α, Cox-2, IL-6, MMP-2, MMP-9, E-cadherin, TLR4, and NF-κB p65 [118] NF-κB, Bax, and Bcl-2 [119] *hOGG1* [120] CDC6, CDK4, cyclin D1, beta-catenin, TCF and MAPK [121] *Ki67* [122]
SW-620	NF-κB, Bax and Bcl-2 [119]
HuTu 80	GSTA1, GSTM1, GSTP1, GSTT1 and UGT1 [115] *Ki67* [122]
CX-1	HIF-1alpha, VEGF [30]
Eca109	VEGF-A, MMP9 and MMP2 [123] NF-κB, pIκBα

Table 1. Continued.

Model cell	Reported targets
EC9706	NF-κB, pIκBα [124]
KYSE-510	miR-1-3p, TAGLN2 [125]
TE-7	miR-1-3p, TAGLN2 [125]
SKMEL-103	AKT, AXL, PIM-1, ABLK, HSP90, HSP70, and GAPDH [126]
SKMEL-28	AKT, AXL, PIM-1, ABLK, HSP90, HSP70, and GAPDH [126]
PANC-1	c-Myc, TGF-β1, Gli2 Smad2/3, Zeb2, and Snail1 [127] STAT3, EMT, and MMP [128] Grp78/Bip, p-PERK, PERK, ATF4, ATF6, and GADD153/CHOP [129]
Patu8988	c-Myc, TGF-β1, Gli2 Smad2/3, Zeb2, and Snail1 [127] STAT3, EMT, and MMP [128]
BGC823	uPAR, NF-κb, PKC, and ERK1/2 [130]

by activating the *JAK/STAT* pathway [55]. Quercetin induced apoptosis in hepatocellular carcinoma cells by regulating *Bcl-2*, activating *caspases*, and inhibiting the *ERK* and *PI3K/Akt* pathways [67].

In cervical cancer, quercetin reactivation suppressed genes associated with cervical cancer by modulating epigenetic marks [70]. At the same time, quercetin induced apoptosis via the *PI3k/Akt* pathway [73], leading to the accumulation of ROS and upregulation of apoptosis of cervical cancer cells [75]. Quercetin suppressed the viability of cervical cancer cells in a dose-dependent manner [76].

In prostatic cancer, the combined use of metformin and quercetin exerted significant anticancer effects through the *VEGF/Akt/PI3K* pathway [80]. Quercetin increased the heat-induced prostatic cancer cell toxicity, possibly related to *hsp70* [89]. Quercetin directly activated the caspase via the mitochondrial pathway, leading to apoptosis in prostate cancer cells [96].

In colon cancer, the anticancer effect of quercetin on colon cancer cells was associated with the down-regulation of survivin and cyclin D(1) expression [109]. The anticancer effect of quercetin was also correlated with the *Akt* and *ErbB2/ErbB3* signaling pathways [111]. Quercetin induced apoptosis via the *Akt-CSN6-Myc* signaling axis in colon cancer cells [113].

In esophageal cancer, quercetin reduced the invasion and proliferation of esophageal cancer cells, which is related to *MMP9*, *MMP2*, and *VEGF-A* [123]. Meanwhile, inhibition of *miR-1-3p* could reduce the anticancer effect of quercetin, resulting in the restoration of esophageal cancer cell proliferation [125].

In pancreatic ductal adenocarcinoma, quercetin inhibited tumor cell proliferation and induced tumor cell apoptosis, which is associated with the *SHH* and *TGF-β/Smad* signaling pathways [127].

3.2 The Main Targets and Mechanisms of Luteolin in Cancer Prevention and Cancer Metastasis

We summarized the reported targets of luteolin in the articles, which involving 24 different cancer cells (Table 2, Ref. [131–186]).

In lung cancer, luteolin reduced the invasive ability of lung cancer cells, which is associated with *Src/FAK*-related targets [134]. Luteolin demonstrated antitumor effects through the *MEK-ERK* pathway [140] and reduced cell invasion via *Sirt1*-mediated apoptosis [146].

In cervical cancer, the expression of some proapoptotic genes, such as *FAS*, *BOK*, *BAK1*, *BAD*, *BAX*, *FADD*, *TRADD,* and *Caspases 9* and *3*, was increased by luteolin treatment. At the same time, it was also found that the expression of some anti-apoptotic genes, such as *NAIP*, *MCL-1*, and *BCL-2*, was significantly reduced. These results confirm that luteolin has strong anti-proliferative and pro-apoptotic effects, and this function is likely to be achieved by inhibiting *AKT* and *MAPK* pathways [150].

In gastric cancer, luteolin could reduce the proliferative capacity of gastric cancer cells by reducing *VEGF* production [160]. Luteolin could also cause cell death through the *MAPK* and *PI3K* pathways [161].

In breast cancer, luteolin reduced breast cancer cell proliferation and induced breast cancer cell apoptosis in two different breast cancer cell studies [165]. The antitumor effect of luteolin is related to the *STAT3*, *MAPK*, and *PI3K* signaling pathways [166]. The inhibitory effect of luteolin on breast cancer cell invasion might be related to the reduction of *VEGF* production [174].

In colon cancer, alterations in the protein levels and enzymatic activities of *HDACs* and *DNMTs* were also found in luteolin-treated colon cancer cells [180].

In liver cancer, luteolin affected the *AMPK-NF-κB* signaling pathway by increasing the production of ROS. The study also showed that *AMPK* was likely to be a new regulator of *NF-κB* in the process of luteolin promoting the apoptosis of liver cancer cells [186].

Table 2. The model cell and reported targets of luteolin.

Model cell	Reported targets
H929	isoQC, CD47 and SIRPα [131]
H1975	cyclin D1, caspase-3, Ki-67, p-LIMK and p-cofilin [132] JNK, DR5, Drp1 [133]
H1650	cyclin D1, caspase-3, Ki-67, p-LIMK and p-cofilin [132]
A549	*JNK*, *DR5*, *Drp1* [133] pFAK, pSrc, Rac1, Cdc42, RhoA [134] AIM2, caspase-1 and IL-1β [135] p-PDK1 [136] miR-34a-5p, Bcl-2, MDM4, p53, p21, Bax, caspase-3 and caspase-9 [137] MEK, ERK, c-Fos , PI3K, Akt, NF-κB [138] Tyro3, Axl and MerTK [139] caspases-3 and -9, Bcl-2, Bax, MEK, ERK, Akt [140] *Nrf2* [141,142] E-cadherin, TGF-β1 [143] TRAIL [144] JNK, Bax, pro caspase-9, caspase-3, TNFα, NF-κB [145]
H460	AIM2, caspase-1 and IL-1β [135] miR-34a-5p, Bcl-2, MDM4, p53, p21, Bax, caspase-3 and caspase-9 [137] *Axl* and *Tyro3* [139] Bad, Bcl-2, Bax, caspase-3 and Sirt1 [146] Bcl-2, caspase-3, -8, and -9, MAPK and ROS [147] Beclin-1, LC3II [148]
H1299	Bcl-2, caspase-3, -8, and -9, MAPK and ROS [147]
LNM35	caspase-3 and -7 [149]
HeLa	*TRAIL* [144] APAF1, BAX, BAD, BID, BOK, BAK1, TRADD, FADD, FAS, Caspases 3 and 9, NAIP, MCL-1, BCL-2, CCND1, 2 and 3, CCNE2, CDKN1A, CDKN2B, CDK4, and CDK2, TRAILR2/DR5, TRAILR1/DR4, Fas/TNFRSF6/CD95, TNFR1/TNFRSF1A, and Cytochrome C, HIF1α, BCL-X, MCL1, AKT1 and 2, ELK1, PIK3C2A, PIK3C2B, MAPK14, MAP3K5, MAPK3 and MAPK1, GSK3b, PRAS 40, PTEN, AKT, ERK2, RISK2, P70S6k, PDK1, ERK1, MTOR, P53 and P27 [150] PKA, Jak1, Tyk2, STAT1/2, SHP-2 [151] E6, E7, pRb, p53, E2F5, Fas/FasL, DR5/TRAIL, FADD, caspase-3, caspase-8, Bcl-2, and Bcl-xL [152] caspase-8, caspase-3, XIAP, PKC [153] TNFα, NF-kappa B, JNK, JNKK1, JNKK2 [154]
AGS	Bcl-2, Cdc2, Cyclin B1, Cdc25C Caspase-3, Caspase-6, Caspase-9, Bax, and p53 [155]
CRL-1739	MUC1, ADAM-17, IL-8, IL-10 and NF-κB. [156]
SGC-7901	*FOXO1* [157] cMet, MMP9, Ki-67, caspase-3, PARP-1, Akt and ERK [158] VEGF, HIF-1 alpha, Bcl-2, PGE2, caspase-3 and -9 [159]
Hs-746T	VEGF, Notch1 [160]
BGC-823	Bax, Bcl-2, MAPK, pi3k, caspase-3, caspase-9 and cytochrome c [161] VEGF-A and MMP-9 [162]
MKN45	cMet, MMP9, Ki-67, caspase-3, PARP-1, Akt and ERK [158]
MCF-7	caspase-3, caspase -8, caspase -9, Bcl-2, Bax, miR-16, miR-21 and miR-34a [163] Bax, Bcl-2, Caspase-3, EMT, Vimentin, Zeb1, N-cadherin, E-cadherin, miR-203 [164] Sp1, NF-κB, DNMT1 and OPCML [165] EGFR, PI3K, Akt, MAPK, Erk 1/2, STAT3 [166] *Bcl-2*, ROS [167] DR5, caspase-8/-9/-3, PARP, cytochrome c, Bax, Bcl-2 [168] Bcl-2, Bcl-2, AEG-1 and MMP-2 [169] Erα, IGF-1 [170] GTF2H2, NCOR1, TAF9, NRAS, NRIP1, POLR2A, DDX5, NCOA3, CCNA2, PCNA, CDKN1A, CCND1, PLK1 [171] caspase-3 and -7 [149]

Table 2. Continued.

Model cell	Reported targets
MDA-MB-453	Bax, Bcl-2, Caspase-3, EMT, Vimentin, Zeb1, N-cadherin, E-cadherin, miR-203 [164]
BT474	Sp1, NF-κB, DNMT1 and OPCML [165]
MDA-MB-231	EGFR, PI3K, Akt, MAPK, Erk 1/2, STAT3 [166] caspase-3 and -7 [149] OPCML [172] hTERT, NF-κB, c-Myc [173] *VEGF* [174] Notch-1 [175] caspase-8, caspase-3, Fas, STAT3 [176] AKT, PLK1, cyclin B(1), cyclin A, CDC2, CDK2, Bcl-xL and Bax [177]
MDA-MB-435	*VEGF* [174]
SW620	LC3B-I/II, Atg5, Bcl-2, Bax, caspase-3, PARP, ERK1/2, FOXO3a [178]
HCT116	*p53* [179] Nrf2, ARE, DNMTs, HDACs [180]
HT29	caspase-8, caspase-3, XIAP, PKC [153] *caspase-3* and -7 [149] Nrf2, ARE, DNMTs, HDACs [180]
HepG2	PKA, Jak1, Tyk2, STAT1/2, SHP-2 [151] caspase-8, caspase-3, XIAP, PKC [153] caspase-3 and -7 [149] *p21*, *p53* [181] USP47, p62 [182] *AMPK*, *NF-κB*, ROS [183,186] HGF, ERK1/2, Akt, JNK1/2, MEK, PI3K [184] p53, CDK, p21 [185]
CNE1	caspase-8, caspase-3, XIAP, PKC [153]

3.3 The Main Targets and Mechanisms of Kaempferol in Cancer Prevention and Cancer Metastasis

We summarized the reported targets of kaempferol in the articles, which involving 25 different cancer cells (Table 3, Ref. [187–213]).

In lung cancer, kaempferol promoted the apoptosis of lung cancer cells by inhibiting *Nrf2* [187]. Kaempferol exerted antitumor effects through the *PTEN*, *miR-340* and *PI3K/AKT* pathways, thus inhibiting the growth of lung cancer cells and inducing the death of lung cancer cells [188].

In breast cancer, kaempferol reduced the invasive effect of breast cancer cells in both MCF-7 cells and MDA-MB-231 cells, which might be related to the activation of *Rac1* and *RhoA* [191]. At the same time, some studies have shown that the antitumor effect of kaempferol is independent of the *ER*-dependent pathway [193]. Kaempferol could block the signaling pathways related to *MMP-9*, thus affecting the expression of *MMP-9* to reduce the migration ability of breast cancer cells [195].

In gastric cancer, kaempferol could induce gastric cancer cell apoptosis by affecting the *JNK-CHOP* signaling pathway [197]. A study found that the expression of *miR-181a* increased in gastric cancer cells treated with kaempferol. This may be one of the mechanisms of kaempferol's antitumor effect [198].

In cervical cancer, kaempferol promoted cervical cancer cell death by affecting the *hTERT* and *PI3K/AKT* pathways [200]. Kaempferol had an obvious regulatory effect on ovarian cancer cell apoptosis, indicating that kaempferol has the potential to be a promising drug for ovarian cancer [203].

In colon cancer, kaempferol could reduce ROS production and affect *NF-κ*, *MAPK*, *PI3K/AKT*, and *BJAK/STAT3* signaling pathways [208]. More in-depth research has shown that kaempferol plays an antitumor effect by inducing cell cycle arrest in colon cancer [210].

In liver cancer, kaempferol reduced *AKT* phosphorylation in human liver cancer cells and has been shown to affect *PARP*, *caspase-3*, *caspase-7,* and *caspase-9* [212]. Studies have also shown that kaempferol can significantly affect the invasion and growth of liver cancer cells; this process may be related to *PTEN* and *miR-21*, as well as the *PI3K* pathway [213].

Table 3. The model cell and reported targets of kaempferol.

Model cell	Reported targets
A549	ROS, *Nrf2*, *NQO1*, *HO1*, *AKR1C1* and *GST* [187] miR-340, PTEN, PI3K, AKT [188] ROS, SOD, *GPx*, *CAT* [189] TGF-β1, EMT, E-cadherin, Smad3, Smad4, Snail, Akt1 [190]
NCIH460	ROS, *Nrf2*, *NQO1*, *HO1*, *AKR1C1* and *GST* [187]
MCF-7	ROS, SOD, *GPx*, *CAT* [189] *ER*, *PR*, *HER2*, *RhoA*, and *Rac1* [191] IRS-1, AKT, MEK1/2 [192] *ER*, *E2* [193]
MDA-MB-231	*ER*, *PR*, *HER2*, *RhoA,* and *Rac1* [191] γH2AX, caspase 9, caspase 3, p-ATM [194] AP-1, MAPK, PKCδ, MMP-9 [195] CYP1A1, CYP1B1, AHR, ERα [196]
BT474	γH2AX, caspase 9, caspase 3, p-ATM [194]
SK-BR-3	*ER*, *PR*, *HER2*, *RhoA*, and *Rac1* [191]
BT-549	CYP1A1, CYP1B1, AHR, ERα [196]
AGS	bcl-2, PARP, caspase 3, caspase 9, LC3-I, LC3-II, β-actin [197]
SGC-7901	ROS, SOD, *GPx*, *CAT* [189]
SNU-216	cyclin D1, bcl-2, bax, caspase 3, caspase 9, autophagy-related gene 7, LC3-I, LC3-II, Beclin 1, p62, MAPK, ERK, PI3K, miR-181a [198] bcl-2, PARP, caspase 3, caspase 9, LC3-I, LC3-II, β-actin [197]
MKN28	cyclin B1, Cdk1 and Cdc25C, Bcl-2, Bax, caspase-3 and -9, PARP, p-Akt, p-ERK, and COX-2 [199]
MKN-74	bcl-2, PARP, caspase 3, caspase 9, LC3-I, LC3-II, β-actin [197]
NCI-N87	bcl-2, PARP, caspase 3, caspase 9, LC3-I, LC3-II, β-actin [197]
NUGC-3	bcl-2, PARP, caspase 3, caspase 9, LC3-I, LC3-II, β-actin [197]
SGC7901	cyclin B1, Cdk1 and Cdc25C, Bcl-2, Bax, caspase-3 and -9, PARP, p-Akt, p-ERK, and COX-2 [199]
Hela	ROS, SOD, *GPx*, *CAT* [189] *PI3K*, *AKT*, and *hTERT* [200]
A2780	GRP78, PERK, ATF6, IRE-1, LC3II, beclin 1, and caspase 4 [201] Chk2, Cdc25C, Cdc2 [202] Bcl-x(L), p53, Bad, and Bax [203]
CP70	Bcl-x(L), p53, Bad, and Bax [203]
HCT116	hnRNPA1, PTBP1, miR-339-5p [204] *AP-1* [205] PARP, caspase-8, caspase-9, caspase-3, phospho-p38 MAPK, p53, and p21 [206] caspase-3, Bcl-2, PUMA, ATM, and H2AX [207]
LS174-R	ROS, *JAK*, *STAT3*, *MAPK*, *PI3K*, *AKT*, and *NF-κB* [208]
DLD1	hnRNPA1, PTBP1, miR-339-5p [204]
HT29	*AP-1* [205] IGF-II, IGF-IR, ErbB3, Akt, and ERK-1/2 [209] CDK2, CDK4, cyclins D1, cyclin E, and cyclin A [210]
HCT15	hnRNPA1, PTBP1, miR-339-5p [204] *AP-1* [205] PARP, caspase-8, caspase-9, caspase-3, phospho-p38 MAPK, p53, and p21 [206]
SW480	*DR5* [211]
HepG2	AKT, caspase-9, caspase-7, caspase-3, and PARP [212] miR-21, PTEN, PI3K, AKT, mTOR [213]

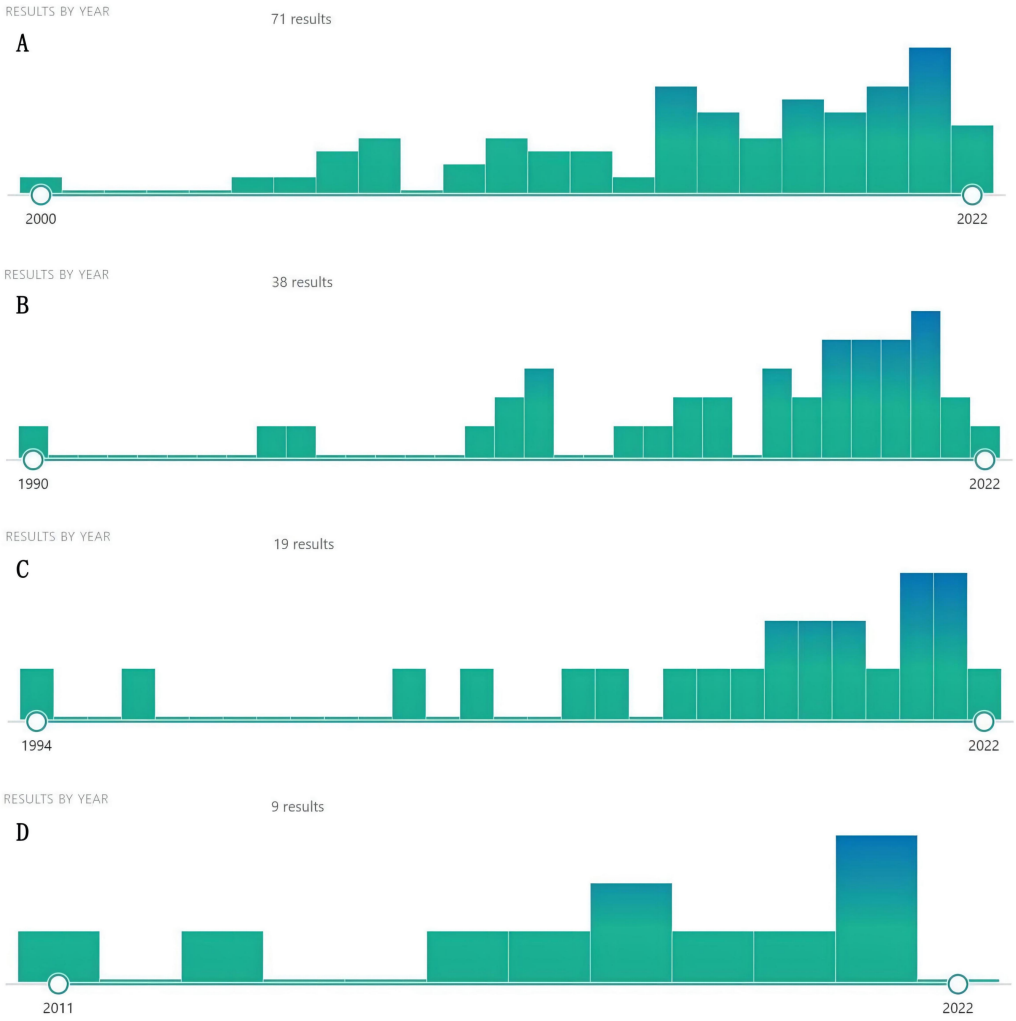

Fig. 3. Increasing literature about dihydrotanshinone (A), Sclareol (B), Isoimperatorin (C), and girinimbin (D) (From PubMed).

3.4 Other Potential Natural Compounds in Cancer Prevention and Cancer Metastasis

Using the name of natural compounds and "cancer" OR "tumor" OR "carcinoma" OR "malignancy" as keywords to search PubMed, we found a number of natural compounds with the potential to treat cancer and cancer metastasis. Although there were few studies on these natural compounds against cancer, they recently proliferated, indicating that natural compounds, such as dihydrotanshinone, sclareol, isoimperatorin, and girinimbin have a great anticancer potential, warranting further research (Fig. 3). At the same time, we predicted the potential targets of these four natural compounds through the SwissTargetPrediction database and screened out the top ten targets with a probability score greater than 0 (Table 4).

4. Discussion

Malignant tumors are common diseases with biological characteristics such as cell differentiation, abnormal proliferation, infiltration, and metastasis, and have become a worldwide problem. Western medicine treatments have a significant effect on eliminating malignant tumors, but are often accompanied by a variety of toxic and adverse effects such as gastrointestinal reactions, myelosuppression, and decreased immunity. Traditional Chinese medicine has a history of more than 2000 years in the prevention and treatment of tumors. It has played an important role in the treatment of cancers: increasing evidence has shown that TCM, usually combined with western medicine, can improve response to western medicine, reduce the toxic and side effects, improve the quality of life of patients, stabilize the tumor body, prevent tumor recurrence and metastasis, prolong the survival period, and increase the survival rate. Accordingly, the anti-tumor effects and mechanisms of TCM have become focal points of research. The development of modern science and technology, and the complementary advantages of multi-disciplinary and multi-field modalities help promite TCM's broad prospects in anti-cancer field. In anticancer treatment, the application of TCM is limited due to the complex composition, difficult dosage control,

Table 4. Other potential targets of potential natural compounds.

Potential natural compounds	Potential targets	Probability score
Dihydrotanshinone	*AKR1B1*	1
	ACHE	1
	CES1	1
	PTPN6	1
	CES2	1
	PTPN11	1
	STAT3	0.114337559
	IDO1	0.114337559
	MALT1	0.106099949
	KDM4E	0.097874534
Sclareol	*UGT2B7*	0.206265233
	HSD11B1	0.182601417
	PTGS1	0.174646372
	NR1H3	0.111501865
	AR	0.111501865
	CYP19A1	0.111501865
	NR3C2	0.111501865
	TRPV1	0.111501865
	IDO1	0.111501865
	CNR2	0.111501865
Isoimperatorin	*BACE1*	0.149732594
	KCNA3	0.108770969
	SRD5A1	0.108770969
	CA12	0.100578902
	CA9	0.100578902
	KCNA5	0.100578902
	MAOA	0.100578902
	ALOX5	0.100578902
	MAOB	0.100578902
	ALOX15	0.100578902
Girinimbin	*DYRK1A*	0.100578902
	BCHE	0.100578902
	CLK4	0.100578902
	HTR2B	0.100578902
	HTR2C	0.100578902
	SLC6A3	0.100578902
	HTR6	0.100578902
	AKT1	0.100578902
	CLK2	0.100578902
	DYRK3	0.100578902

and unclear mechanisms of action. With the standardization and modernization of TCM, through the multi-field and multi-level objective, accurate, qualitative, and quantitative research on the anti-cancer efficacy of TCM, the shortcomings of TCM (such as complex composition), unclear mechanisms, and unclear targets have been gradually overcome. Traditional Chinese medicine played an increasingly important role in the field of anti-cancer treatment.

With the continuous research on the natural ingredients of TCM, we found that these ingredients can exert anti-tumor activities in various stages of tumor growth, reflected in the following aspects: Improve the immune activity of the body, reduce the immunosuppressive effect of tumor cells, and inhibit the growth of tumor cells; regulate specific signaling pathways, inhibit tumor cell proliferation, and promote their apoptosis and autophagy; inhibit tumor angiogenesis; inhibit cancer cell invasion and metastasis ability; induce cancer cell cycle arrest, promoting its apoptosis, etc.

In this review, we found five commonly used anti-cancer Chinese herbal medicines and 168 qualified natural compounds extracted from them (oral bioavailability $\geq$30% and drug-likeness $\geq$0.18). In our analysis, we found that, based on TCM, natural active ingredients still have many contents worthy of in-depth exploration in the prevention and treatment of cancer and cancer metastasis. They have multiple targets and complex but effective mechanisms. Some natural compounds have been widely used in clinical practice and have attracted increasing attention in recent years. Traditional Chinese medicines and their active compounds have provided inspiration and options for the treatment of cancer, both in the past and in the future. Among the three most deeply studied natural compounds (quercetin, luteolin, and kaempferol), we should pay more attention to how to expand the curative effect and specific application research. For the natural compounds (dihydrotanshinone, sclareol, isoimperatorin, and girinimbin) that have recently garnered increased attention, we still need to strengthen basic research as we anticipate better natural drugs for cancer.

Although this paper searched and screened the relevant literature to the greatest extent possible, there are still certain limitations. In order to ensure the stability and reliability of the results, we selected human-related cell experiments and excluded clinical studies and animal experiments, but this did not ensure the comprehensive inclusion of all eligible studies. Further, we only provided a preliminary summary of the mechanisms and targets, and did not perform a systematic analysis.

5. Conclusions

Within the five most widely used anti-cancer Chinese herbal medicines,168 effective natural compounds were identified. The three most common natural compounds and their main mechanisms of action in the prevention and treatment of cancer and cancer metastasis were reviewed and summarized. In addition, our review found that four natural compounds have recently attracted the most attention in the field of anti-cancer study, indicating they are worthy of further research. Our findings provide some inspiration for future research on natural compounds against tumors and new insights into the role and mechanisms of natural compounds in the prevention and treatment of cancer and cancer metastasis.

Author Contributions

QW, YW, and ELHL designed the research study. YW, HY, XS, MC, and GY performed the research. LL provided advice on data collection. HY analyzed the data. XX, YX, and GY retrieved and collected the data. YW wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Acknowledge the support of the Science and Technology Development Fund, Macau SAR, the National Natural Science Foundation of China; 2020 Young Qihuang Scholar funded by the National Adminstation of Traditional Chinese Medicine; Guangdong Medical Science and technology research foundation project, the Zhejiang province science and technology project of TCM, Shenzhen Science and Technology Program.

Funding

This study was funded by the Science and Technology Development Fund, Macau SAR (file No.: 0098/2021/A2, 130/2017/A3, and 0099/2018/A3), National Natural Science Foundation of China (grant No. 81874380, 82022075, 81730108, and 81973635), 2020 Young Qihuang Scholar funded by the National Adminstation of Traditional Chinese Medicine, the Science and Technology Planning Project of Guangdong Province (2020B1212030008), Guangdong Medical Science and technology research foundation project (No. C2021102), and Shenzhen Science and Technology Program (No. JCYJ20210324111213038).

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Muntean DM, Sturza A, Pavel IZ, Duicu OM. Modulation of Cancer Metabolism by Phytochemicals - A Brief Overview. Anti-Cancer Agents in Medicinal Chemistry. 2018; 18: 684–692.

[2] Balabhadrapathruni S, Thomas TJ, Yurkow EJ, Amenta PS, Thomas T. Effects of genistein and structurally related phytoestrogens on cell cycle kinetics and apoptosis in MDA-MB-468 human breast cancer cells. Oncology Reports. 2000; 7: 3–12.

[3] Buchanan TF, Bauer D, Soliman KF. Quercetin inhibition of TNFα-induced CCL28 release from human triple negative breast cancer (MDA-MB-468) cells. The FASEB Journal. 2017; 31: 809-4.

[4] Baksi R, Rana R, Nivsarkar M. Chemopreventive potential of plant-derived epigenetic inhibitors silibinin and quercetin: an involvement of apoptotic signaling cascade modulation. Future Journal of Pharmaceutical Sciences. 2021; 7: 69.

[5] Sharma R, Gatchie L, Williams IS, Jain SK, Vishwakarma RA, Chaudhuri B, *et al*. Glycyrrhiza glabra extract and quercetin reverses cisplatin resistance in triple-negative MDA-MB-468 breast cancer cells via inhibition of cytochrome P450 1B1 enzyme. Bioorganic & Medicinal Chemistry Letters. 2017; 27: 5400–5403.

[6] Conklin CMJ, Bechberger JF, MacFabe D, Guthrie N, Kurowska EM, Naus CC. Genistein and quercetin increase connexin43 and suppress growth of breast cancer cells. Carcinogenesis. 2007; 28: 93–100.

[7] Chien S, Wu Y, Chung J, Yang J, Lu H, Tsou M, *et al*. Quercetin-induced apoptosis acts through mitochondrial- and caspase-3-dependent pathways in human breast cancer MDA-MB-231 cells. Human & Experimental Toxicology. 2009; 28: 493–503.

[8] Phromnoi K, Yodkeeree S, Anuchapreeda S, Limtrakul P. Inhibition of MMP-3 activity and invasion of the MDA-MB-231 human invasive breast carcinoma cell line by bioflavonoids. Acta Pharmacologica Sinica. 2009; 30: 1169–1176.

[9] Shih Y, Liu H, Chen C, Hsu C, Pan M, Chang H, *et al*. Combination Treatment with Luteolin and Quercetin Enhances Antiproliferative Effects in Nicotine-Treated MDA-MB-231 Cells by down-regulating Nicotinic Acetylcholine Receptors. Journal of Agricultural and Food Chemistry. 2010; 58: 235–241.

[10] Huang HC, Lin CL, Lin JK. 1,2,3,4,6-penta-O-galloyl-β-D-glucose, quercetin, curcumin and lycopene induce cell-cycle arrest in MDA-MB-231 and BT474 cells through downregulation of Skp2 protein. Journal of Agricultural and Food Chemistry. 2011; 59: 6765–6775.

[11] Seo H, Ju J, Jang K, Shin I. Induction of apoptotic cell death by phytoestrogens by up-regulating the levels of phospho-p53 and p21 in normal and malignant estrogen receptor α–negative breast cells. Nutrition Research. 2011; 31: 139–146.

[12] Huang C, Lee SY, Lin CL, Tu TH, Chen LH, Chen YJ, *et al*. Co-treatment with quercetin and 1,2,3,4,6-penta-O-galloyl-β-D-glucose causes cell cycle arrest and apoptosis in human breast cancer MDA-MB-231 and AU565 cells. Journal of Agricultural and Food Chemistry. 2013; 61: 6430–6445.

[13] Tao S, He H, Chen Q. Quercetin inhibits proliferation and invasion acts by up-regulating miR-146a in human breast cancer cells. Molecular and Cellular Biochemistry. 2015; 402: 93–100.

[14] Wang R, Yang L, Li S, Ye D, Yang L, Liu Q, *et al*. Quercetin Inhibits Breast Cancer Stem Cells via Downregulation of Aldehyde Dehydrogenase 1A1 (ALDH1A1), Chemokine Receptor Type 4 (CXCR4), Mucin 1 (MUC1), and Epithelial Cell Adhesion Molecule (EpCAM). Medical Science Monitor. 2018; 24: 412–420.

[15] Kıyga E, Şengelen A, Adıgüzel Z, Önay Uçar E. Investigation of the role of quercetin as a heat shock protein inhibitor on apoptosis in human breast cancer cells. Molecular Biology Reports. 2020; 47: 4957–4967.

[16] Choi JA, Kim JY, Lee JY, Kang CM, Kwon HJ, Yoo YD, *et al*. Induction of cell cycle arrest and apoptosis in human breast cancer cells by quercetin. International Journal of Oncology. 2001; 19: 837–844.

[17] Lin CW, Hou WC, Shen SC, Juan SH, Ko CH, Wang LM, *et al*. Quercetin inhibition of tumor invasion via suppressing PKC delta/ERK/AP-1-dependent matrix metalloproteinase-9 activation in breast carcinoma cells. Carcinogenesis. 2008; 29: 1807–1815.

[18] Chou C, Yang J, Lu H, Ip S, Lo C, Wu C, *et al*. Quercetin-mediated cell cycle arrest and apoptosis involving activation of a caspase cascade through the mitochondrial pathway in human breast cancer MCF-7 cells. Archives of Pharmacal Research. 2010; 33: 1181–1191.

[19] Lee Y-K, Park SY, Kim Y-M, Lee W-S, Park OJ. Regulation of MCF-7 cell apoptosis by phytochemical quercetin through AMPK-mTOR signaling pathway. Journal of Cancer Prevention. 2010; 15: 320–325.

[20] Lee Y-K, Park OJ. Involvement of AMPK/mTOR/HIF-1α in anticancer control of quercetin in hypoxic MCF-7 cells. Food Science and Biotechnology. 2011; 20: 371–375.
[21] Duo J, Ying GG, Wang GW, Zhang L. Quercetin inhibits human breast cancer cell proliferation and induces apoptosis via Bcl-2 and Bax regulation. Molecular Medicine Reports. 2012; 5: 1453–1456.
[22] Soufi L, Farasat A, Ahmadpour-Yazdi H, Zolghadr L, Gheibi N. The effects of the esterified Quercetin with omega3 and omega6 fatty acids on viability, nanomechanical properties, and BAX/BCL-2 gene expression in MCF-7 cells. Molecular Biology Reports. 2021; 48: 5161–5169.
[23] Deng X, Song H, Zhou Y, Yuan G, Zheng F. Effects of quercetin on the proliferation of breast cancer cells and expression of survivin in vitro. Experimental and Therapeutic Medicine. 2013; 6: 1155–1158.
[24] Dhumale SS, Waghela BN, Pathak C. Quercetin protects necrotic insult and promotes apoptosis by attenuating the expression of RAGE and its ligand HMGB1 in human breast adenocarcinoma cells. IUBMB Life. 2015; 67: 361–373.
[25] Li S, Qiao S, Zhang J, Li K. Quercetin Increase the Chemosensitivity of Breast Cancer Cells to Doxorubicin via PTEN/Akt Pathway. Anti-Cancer Agents in Medicinal Chemistry. 2015; 15: 1185–1189.
[26] Ranganathan S, Halagowder D, Sivasithambaram ND. Quercetin Suppresses Twist to Induce Apoptosis in MCF-7 Breast Cancer Cells. PLoS ONE. 2015; 10: e0141370.
[27] Yousuf M, Khan P, Shamsi A, Shahbaaz M, Hasan GM, Haque QMR, *et al*. Inhibiting CDK6 Activity by Quercetin is an Attractive Strategy for Cancer Therapy. ACS Omega. 2020; 5: 27480–27491.
[28] Prieto-Vila M, Shimomura I, Kogure A, Usuba W, Takahashi RU, Ochiya T, *et al*. Quercetin Inhibits Lef1 and Resensitizes Docetaxel-Resistant Breast Cancer Cells. Molecules. 2020; 25: 2576.
[29] Ozkan E, Bakar-Ates F. Potentiation of the Effect of Lonidamine by Quercetin in MCF-7 human breast cancer cells through down-regulation of MMP-2/9 mRNA Expression. Anais da Academia Brasileira de Ciencias. 2020; 92: e20200548.
[30] Lee DH, Lee YJ. Quercetin suppresses hypoxia-induced accumulation of hypoxia-inducible factor-1alpha (HIF-1alpha) through inhibiting protein synthesis. Journal of Cellular Biochemistry. 2008; 105: 546–553.
[31] Zhaorigetu, Farrag IM, Belal A, Badawi MHA, Abdelhady AA, Galala F, *et al*. Antiproliferative, Apoptotic Effects and Suppression of Oxidative Stress of Quercetin against Induced Toxicity in Lung Cancer Cells of Rats: In vitro and In vivo Study. Journal of Cancer. 2021; 12: 5249–5259.
[32] Guo H, Ding H, Tang X, Liang M, Li S, Zhang J, *et al*. Quercetin induces pro-apoptotic autophagy via SIRT1/AMPK signaling pathway in human lung cancer cell lines A549 and H1299 in vitro. Thoracic Cancer. 2021; 12: 1415–1422.
[33] Elumalai P, Ezhilarasan D, Raghunandhakumar S. Quercetin Inhibits the Epithelial to Mesenchymal Transition through Suppressing Akt Mediated Nuclear Translocation of β-Catenin in Lung Cancer Cell Line. Nutrition and Cancer. 2022; 74: 1894–1906.
[34] Alam S, Mohammad T, Padder RA, Hassan MI, Husain M. Thymoquinone and quercetin induce enhanced apoptosis in non-small cell lung cancer in combination through the Bax/Bcl2 cascade. Journal of Cellular Biochemistry. 2022; 123: 259–274.
[35] Klimaszewska-Wiśniewska A, Hałas-Wiśniewska M, Izdebska M, Gagat M, Grzanka A, Grzanka D. Antiproliferative and antimetastatic action of quercetin on a549 non-small cell lung cancer cells through its effect on the cytoskeleton. Acta Histochemica. 2017; 119: 99–112.
[36] Dahiya R, Mohammad T, Roy S, Anwar S, Gupta P, Haque A, *et al*. Investigation of inhibitory potential of quercetin to the pyruvate dehydrogenase kinase 3: towards implications in anticancer therapy. International Journal of Biological Macromolecules. 2019; 136: 1076–1085.
[37] Xingyu Z, Peijie M, Dan P, Youg W, Daojun W, Xinzheng C, *et al*. Quercetin suppresses lung cancer growth by targeting Aurora B kinase. Cancer Medicine. 2016; 5: 3156–3165.
[38] Chuang C, Yeh C, Yeh S, Lin E, Wang L, Wang Y. Quercetin metabolites inhibit MMP-2 expression in a549 lung cancer cells by PPAR-γ associated mechanisms. The Journal of Nutritional Biochemistry. 2016; 33: 45–53.
[39] Zhao X, Zhang J. Mechanisms for quercetin in prevention of lung cancer cell growth and metastasis. Zhong Nan Da Xue Xue Bao Yi Xue Ban. 2015; 40: 592–597.
[40] Mukherjee A, Khuda-Bukhsh AR. Quercetin down-regulates IL-6/STAT-3 Signals to Induce Mitochondrial-mediated Apoptosis in a Nonsmall- cell Lung-cancer Cell Line, a549. Journal of Pharmacopuncture. 2015; 18: 19–26.
[41] Chan ST, Yang NC, Huang CS, Liao JW, Yeh SL. Quercetin enhances the antitumor activity of trichostatin A through upregulation of p53 protein expression in vitro and in vivo. PLoS ONE. 2013; 8: e54255.
[42] Wen C, Ying B, Zhang Y, Zhang J, Fan H. Effect of quercetin on the expression and growth of caspase-3 in lung adenocarcinoma cancer cell line A549. Zhongguo Fei Ai Za Zhi. 2008; 11: 194–197.
[43] Nguyen TT, Tran E, Nguyen TH, Do PT, Huynh TH, Huynh H. The role of activated MEK-ERK pathway in quercetin-induced growth inhibition and apoptosis in A549 lung cancer cells. Carcinogenesis. 2004; 25: 647–659.
[44] Kuo P, Liu H, Chao J. Survivin and p53 Modulate Quercetin-induced Cell Growth Inhibition and Apoptosis in Human Lung Carcinoma Cells. Journal of Biological Chemistry. 2004; 279: 55875–55885.
[45] Banerjee T, Van der Vliet A, Ziboh VA. Downregulation of COX-2 and iNOS by amentoflavone and quercetin in a549 human lung adenocarcinoma cell line. Prostaglandins, Leukotrienes and Essential Fatty Acids. 2002; 66: 485–492.
[46] Jakubowicz-Gil J, Paduch R, Gawron A, Kandefer-Szerszeń M. The effect of cisplatin, etoposide and quercetin on Hsp72 expression. Polish Journal of Pathology. 2002; 53: 133–137.
[47] Jakubowicz-Gil J, Paduch R, Gawron A, Kandefer-Szerszeń M. The effect of heat shock, cisplatin, etoposide and quercetin on Hsp27 expression in human normal and tumour cells. Folia Histochemica et Cytobiologica. 2002; 40: 31–35.
[48] Chuang C, Chan S, Chen C, Yeh S. Quercetin enhances the antitumor activity of trichostatin a through up-regulation of p300 protein expression in p53 null cancer cells. Chemico-Biological Interactions. 2019; 306: 54–61.
[49] Abruzzese V, Matera I, Martinelli F, Carmosino M, Koshal P, Milella L, *et al*. Effect of Quercetin on ABCC6 Transporter: Implication in HepG2 Migration. International Journal of Molecular Sciences. 2021; 22: 3871.
[50] Liu Z, Xu W, Han J, Liu Q, Gao L, Wang X, *et al*. Quercetin induces apoptosis and enhances gemcitabine therapeutic efficacy against gemcitabine-resistant cancer cells. Anti-Cancer Drugs. 2020; 31: 684–692.
[51] Tanigawa S, Fujii M, Hou D. Stabilization of p53 is Involved in Quercetin-Induced Cell Cycle Arrest and Apoptosis in HepG2 Cells. Bioscience, Biotechnology, and Biochemistry. 2008; 72: 797–804.
[52] Yarahmadi A, Khademi F, Mostafavi-Pour Z, Zal F. In-Vitro Analysis of Glucose and Quercetin Effects on m-TOR and Nrf-2 Expression in HepG2 Cell Line (Diabetes and Cancer Connection). Nutrition and Cancer. 2018; 70: 770–775.

[53] Ding Y, Chen X, Wang B, Yu B, Ge J, Shi X. Quercetin suppresses the chymotrypsin-like activity of proteasome via inhibition of MEK1/ERK1/2 signaling pathway in hepatocellular carcinoma HepG2 cells. Canadian Journal of Physiology and Pharmacology. 2018; 96: 521–526.
[54] Zhou J, Fang L, Liao J, Li L, Yao W, Xiong Z, *et al*. Investigation of the anti-cancer effect of quercetin on HepG2 cells in vivo. PLoS ONE. 2017; 12: e0172838.
[55] Igbe I, Shen X, Jiao W, Qiang Z, Deng T, Li S, *et al*. Dietary quercetin potentiates the antiproliferative effect of interferon-α in hepatocellular carcinoma cells through activation of JAK/STAT pathway signaling by inhibition of SHP2 phosphatase. Oncotarget. 2017; 8: 113734–113748.
[56] Dai W, Gao Q, Qiu J, Yuan J, Wu G, Shen G. Quercetin induces apoptosis and enhances 5-FU therapeutic efficacy in hepatocellular carcinoma. Tumor Biology. 2016; 37: 6307–6313.
[57] Brito AF, Ribeiro M, Abrantes AM, Mamede AC, Laranjo M, Casalta-Lopes JE, *et al*. New Approach for Treatment of Primary Liver Tumors: the Role of Quercetin. Nutrition and Cancer. 2016; 68: 250–266.
[58] Lou G, Liu Y, Wu S, Xue J, Yang F, Fu H, *et al*. The p53/miR-34a/SIRT1 Positive Feedback Loop in Quercetin-Induced Apoptosis. Cellular Physiology and Biochemistry. 2015; 35: 2192–2202.
[59] Lee RH, Cho JH, Jeon Y, Bang W, Cho J, Choi N, *et al*. Quercetin Induces Antiproliferative Activity against Human Hepatocellular Carcinoma (HepG2) Cells by Suppressing Specificity Protein 1 (Sp1). Drug Development Research. 2015; 76: 9–16.
[60] Maurya AK, Vinayak M. Anticarcinogenic action of quercetin by downregulation of phosphatidylinositol 3-kinase (PI3K) and protein kinase C (PKC) via induction of p53 in hepatocellular carcinoma (HepG2) cell line. Molecular Biology Reports. 2015; 42: 1419–1429.
[61] Zhao P, Mao J, Zhang S, Zhou Z, Tan Y, Zhang Y. Quercetin induces HepG2 cell apoptosis by inhibiting fatty acid biosynthesis. Oncology Letters. 2014; 8: 765–769.
[62] Saw CLL, Guo Y, Yang AY, Paredes-Gonzalez X, Ramirez C, Pung D, *et al*. The berry constituents quercetin, kaempferol, and pterostilbene synergistically attenuate reactive oxygen species: Involvement of the Nrf2-are signaling pathway. Food and Chemical Toxicology. 2014; 72: 303–311.
[63] Granado-Serrano AB, Martín MA, Bravo L, Goya L, Ramos S. Quercetin modulates Nrf2 and glutathione-related defenses in HepG2 cells: Involvement of p38. Chemico-Biological Interactions. 2012; 195: 154–164.
[64] Granado-Serrano AB, Martín M, Bravo L, Goya L, Ramos S. Quercetin Attenuates TNF-Induced Inflammation in Hepatic Cells by Inhibiting the NF-κB Pathway. Nutrition and Cancer. 2012; 64: 588–598.
[65] Tan J, Wang B, Zhu L. Regulation of Survivin and Bcl-2 in HepG2 Cell Apoptosis Induced by Quercetin. Chemistry & Biodiversity. 2009; 6: 1101–1110.
[66] Tanigawa S, Fujii M, Hou D. Action of Nrf2 and Keap1 in are-mediated NQO1 expression by quercetin. Free Radical Biology and Medicine. 2007; 42: 1690–1703.
[67] Granado-Serrano AB, Martín MA, Bravo L, Goya L, Ramos S. Quercetin Induces Apoptosis via Caspase Activation, Regulation of Bcl-2, and Inhibition of PI-3-Kinase/Akt and ERK Pathways in a Human Hepatoma Cell Line (HepG2). The Journal of Nutrition. 2006; 136: 2715–2721.
[68] Xu W, Xie S, Chen X, Pan S, Qian H, Zhu X. Effects of Quercetin on the Efficacy of Various Chemotherapeutic Drugs in Cervical Cancer Cells. Drug Design, Development and Therapy. 2021; 15: 577–588.
[69] He C, Lu X, Li J, Shen K, Bai Y, Li Y, *et al*. The effect of quercetin on cervical cancer cells as determined by inducing tumor endoplasmic reticulum stress and apoptosis and its mechanism of action. American Journal of Translational Research. 2021; 13: 5240–5247.
[70] Kedhari Sundaram M, Hussain A, Haque S, Raina R, Afroze N. Quercetin modifies 5′CpG promoter methylation and reactivates various tumor suppressor genes by modulating epigenetic marks in human cervical cancer cells. Journal of Cellular Biochemistry. 2019; 120: 18357–18369.
[71] Wang Y, Zhang W, Lv Q, Zhang J, Zhu D. The critical role of quercetin in autophagy and apoptosis in HeLa cells. Tumor Biology. 2016; 37: 925–929.
[72] Chakerzehi A, Arvanagh N, Saedi S, Hematti M, Ardakani J, Moradi A, *et al*. Effect of Quercetin on RAC1 Gene Expression as a Marker of Metastasis in Cervical Cancer Cells. Zahedan Journal of Research in Medical Sciences. 2015; 17.
[73] Xiang T, Fang Y, Wang S. Quercetin suppresses HeLa cells by blocking PI3K/Akt pathway. Journal of Huazhong University of Science and Technology [Medical Sciences]. 2014; 34: 740–744.
[74] Zhang WT, Zhang W, Zhong YJ, Lü QY, Cheng J. Impact of quercetin on the expression of heparanase in cervical cancer cells. Zhonghua Fu Chan Ke Za Zhi. 2013; 48: 198–203.
[75] Bishayee K, Ghosh S, Mukherjee A, Sadhukhan R, Mondal J, Khuda-Bukhsh AR. Quercetin induces cytochrome-c release and ROS accumulation to promote apoptosis and arrest the cell cycle in G2/M, in cervical carcinoma: signal cascade and drug-DNA interaction. Cell Proliferation. 2013; 46: 153–163.
[76] Vidya Priyadarsini R, Senthil Murugan R, Maitreyi S, Ramalingam K, Karunagaran D, Nagini S. The flavonoid quercetin induces cell cycle arrest and mitochondria-mediated apoptosis in human cervical cancer (HeLa) cells through p53 induction and NF-κB inhibition. European Journal of Pharmacology. 2010; 649: 84–91.
[77] Jung JH, Lee JO, Kim JH, Lee SK, You GY, Park SH, *et al*. Quercetin suppresses HeLa cell viability via AMPK-induced HSP70 and EGFR down-regulation. Journal of Cellular Physiology. 2010; 278: 408–414.
[78] Olazarán-Santibañez F, Rivera G, Vanoye-Eligio V, Mora-Olivo A, Aguirre-Guzmán G, Ramírez-Cabrera M, *et al*. Antioxidant and Antiproliferative Activity of The Ethanolic Extract of Equisetum Myriochaetum and Molecular Docking of Its Main Metabolites (Apigenin, Kaempferol, and Quercetin) on β-Tubulin. Molecules. 2021; 26: 443.
[79] Lu X, Yang F, Chen D, Zhao Q, Chen D, Ping H, *et al*. Quercetin reverses docetaxel resistance in prostate cancer via androgen receptor and PI3K/Akt signaling pathways. International Journal of Biological Sciences. 2020; 16: 1121–1134.
[80] Sun S, Gong F, Liu P, Miao Q. Metformin combined with quercetin synergistically repressed prostate cancer cells via inhibition of VEGF/PI3K/Akt signaling pathway. Gene. 2018; 664: 50–57.
[81] Yang F, Song L, Wang H, Wang J, Xu Z, Xing N. Combination of Quercetin and 2-Methoxyestradiol Enhances Inhibition of Human Prostate Cancer LNCaP and PC-3 Cells Xenograft Tumor Growth. PLoS ONE. 2015; 10: e0128277.
[82] Wang P, Phan T, Gordon D, Chung S, Henning SM, Vadgama JV. Arctigenin in combination with quercetin synergistically enhances the antiproliferative effect in prostate cancer cells. Molecular Nutrition & Food Research. 2015; 59: 250–261.
[83] Yu F, Jiang LL, Di YC. Effect of quercetin on heat shock protein 27 expression in prostate cancer cells. Zhongguo Yi Xue Ke Xue Yuan Xue Bao Acta Academiae Medicinae Sinicae. 2014; 36: 506–509.
[84] Wang G, Song L, Wang H, Xing N. Quercetin synergizes with 2-methoxyestradiol inhibiting cell growth and inducing apopto-

sis in human prostate cancer cells. Oncology Reports. 2013; 30: 357–363.
[85] Lee D, Szczepanski M, Lee YJ. Role of Bax in quercetin-induced apoptosis in human prostate cancer cells. Biochemical Pharmacology. 2008; 75: 2345–2355.
[86] Kim Y, Lee YJ. TRAIL apoptosis is enhanced by quercetin through Akt dephosphorylation. Journal of Cellular Biochemistry. 2007; 100: 998–1009.
[87] Yuan H, Gong A, Young CY. Involvement of transcription factor Sp1 in quercetin-mediated inhibitory effect on the androgen receptor in human prostate cancer cells. Carcinogenesis. 2005; 26: 793–801.
[88] Xing N. Quercetin inhibits the expression and function of the androgen receptor in LNCaP prostate cancer cells. Carcinogenesis. 2001; 22: 409–414.
[89] Nakanoma T, Ueno M, Iida M, Hirata R, Deguchi N. Effects of quercetin on the heat-induced cytotoxicity of prostate cancer cells. International Journal of Urology. 2001; 8: 623–630.
[90] Huynh H, Nguyen TT, Chan E, Tran E. Inhibition of ErbB-2 and ErbB-3 expression by quercetin prevents transforming growth factor alpha (TGF-alpha)- and epidermal growth factor (EGF)-induced human PC-3 prostate cancer cell proliferation. International Journal of Oncology. 2003; 23: 821–829.
[91] Song J, Bai J, Wang S, Liu L, Zhao Z. Effects of Quercetin on Autophagy and Phosphatidylinositol 3-kinase/Protein Kinase B/Mammalian Target of Rapamycin Signaling Pathway in Human Prostate Cancer PC-3 Cells. Zhongguo Yi Xue Ke Xue Yuan Xue Bao. 2020; 42: 578–584.
[92] Lu X, Chen D, Yang F, Xing N. Quercetin Inhibits Epithelial-to-Mesenchymal Transition (EMT) Process and Promotes Apoptosis in Prostate Cancer via Downregulating lncRNA MALAT1. Cancer Management and Research. 2020; 12: 1741–1750.
[93] Su Z, Liu T, Hong G. Engineering T. Quercetin Suppress Prostatic Cancer Biological Activity In Vitro and Vivo Study. Journal of Biomaterials and Tissue Engineering. 2018; 8: 949–961.
[94] Yang F, Jiang X, Song L, Wang H, Mei Z, XU Z, *et al*. Quercetin inhibits angiogenesis through thrombospondin-1 upregulation to antagonize human prostate cancer PC-3 cell growth in vitro and in vivo. Oncology Reports. 2016; 35: 1602–1610.
[95] Baruah MM, Khandwekar AP, Sharma N. Quercetin modulates Wnt signaling components in prostate cancer cell line by inhibiting cell viability, migration, and metastases. Tumor Biology. 2016; 37: 14025–14034.
[96] Liu K, Yen C, Wu RS, Yang J, Lu H, Lu K, *et al*. The roles of endoplasmic reticulum stress and mitochondrial apoptotic signaling pathway in quercetin-mediated cell death of human prostate cancer PC-3 cells. Environmental Toxicology. 2014; 29: 428–439.
[97] Bhat FA, Sharmila G, Balakrishnan S, Arunkumar R, Elumalai P, Suganya S, *et al*. Quercetin reverses EGF-induced epithelial to mesenchymal transition and invasiveness in prostate cancer (PC-3) cell line via EGFR/PI3K/Akt pathway. The Journal of Nutritional Biochemistry. 2014; 25: 1132–1139.
[98] Senthilkumar K, Arunkumar R, Elumalai P, Sharmila G, Gunadharini DN, Banudevi S, *et al*. Quercetin inhibits invasion, migration and signalling molecules involved in cell survival and proliferation of prostate cancer cell line (PC-3). Cell Biochemistry and Function. 2011; 29: 87–95.
[99] Senthilkumar K, Elumalai P, Arunkumar R, Banudevi S, Gunadharini ND, Sharmila G, *et al*. Quercetin regulates insulin like growth factor signaling and induces intrinsic and extrinsic pathway mediated apoptosis in androgen independent prostate cancer cells (PC-3). Molecular and Cellular Biochemistry. 2010; 344: 173–184.
[100] Vijayababu MR, Arunkumar A, Kanagaraj P, Arunakaran J. Effects of quercetin on insulin-like growth factors (IGFs) and their binding protein-3 (IGFBP-3) secretion and induction of apoptosis in human prostate cancer cells. Journal of Carcinogenesis. 2006; 5: 10.
[101] Bandyopadhyay S, Romero JR, Chattopadhyay N. Kaempferol and quercetin stimulate granulocyte-macrophage colony-stimulating factor secretion in human prostate cancer cells. Molecular and Cellular Endocrinology. 2008; 287: 57–64.
[102] Vijayababu MR, Kanagaraj P, Arunkumar A, Ilangovan R, Dharmarajan A, Arunakaran J. Quercetin Induces p53-Independent Apoptosis in Human Prostate Cancer Cells by Modulating Bcl-2-Related Proteins: a Possible Mediation by IGFBP-3. Oncology Research Featuring Preclinical and Clinical Cancer Therapeutics. 2006; 16: 67–74.
[103] Vijayababu MR, Arunkumar A, Kanagaraj P, Venkataraman P, Krishnamoorthy G, Arunakaran J. Quercetin downregulates matrix metalloproteinases 2 and 9 proteins expression in prostate cancer cells (PC-3). Molecular and Cellular Biochemistry. 2006; 287: 109–116.
[104] Vijayababu MR, Kanagaraj P, Arunkumar A, Ilangovan R, Aruldhas MM, Arunakaran J. Quercetin-induced growth inhibition and cell death in prostatic carcinoma cells (PC-3) are associated with increase in p21 and hypophosphorylated retinoblastoma proteins expression. Journal of Cancer Research and Clinical Oncology. 2005; 131: 765–771.
[105] Asea A, Ara G, Teicher BA, Stevenson MA, Calderwood SK. Effects of the flavonoid drug quercetin on the response of human prostate tumours to hyperthermia in vitro and in vivo. International Journal of Hyperthermia. 2001; 17: 347–356.
[106] Jung Y, Heo J, Lee YJ, Kwon TK, Kim Y. Quercetin enhances TRAIL-induced apoptosis in prostate cancer cells via increased protein stability of death receptor 5. Life Sciences. 2010; 86: 351–357.
[107] Özgöçmen M, Bayram D, Armağan İ, Türel GY, Sevimli M, Şenol N. Is Quercetin Beneficial for Colon Cancer? A Cell Culture Study, Using the Apoptosis Pathways. Anti-Cancer Agents in Medicinal Chemistry. 2022; 22: 193–200.
[108] Feng J, Song D, Jiang S, Yang X, Ding T, Zhang H, *et al*. Quercetin restrains TGF-β1-induced epithelial–mesenchymal transition by inhibiting Twist1 and regulating E-cadherin expression. Biochemical and Biophysical Research Communications. 2018; 498: 132–138.
[109] Shan BE, Wang MX, Li RQ. Quercetin inhibit human SW480 colon cancer growth in association with inhibition of cyclin D1 and survivin expression through Wnt/beta-catenin signaling pathway. Cancer Investigation. 2009; 27: 604–612.
[110] Park CH, Chang JY, Hahm ER, Park S, Kim HK, Yang CH. Quercetin, a potent inhibitor against beta-catenin/Tcf signaling in SW480 colon cancer cells. Biochemical and biophysical research communications. 2005; 328: 227–234.
[111] Kim WK, Bang MH, Kim ES, Kang NE, Jung KC, Cho HJ, *et al*. Quercetin decreases the expression of ErbB2 and ErbB3 proteins in HT-29 human colon cancer cells. The Journal of Nutritional Biochemistry. 2005; 16: 155–162.
[112] Erdoğan MK, Ağca CA, Aşkın H. Quercetin and Luteolin Improve the Anticancer Effects of 5-Fluorouracil in Human Colorectal Adenocarcinoma In Vitro Model: A Mechanistic Insight. Nutrition and Cancer. 2022; 74: 660–676.
[113] Yang L, Liu Y, Wang M, Qian Y, Dong X, Gu H, *et al*. Quercetin-induced apoptosis of HT-29 colon cancer cells via inhibition of the Akt-CSN6-Myc signaling axis. Molecular Medicine Reports. 2016; 14: 4559–4566.
[114] Kim GT, Lee SH, Kim JI, Kim YM. Quercetin regulates the sestrin 2-AMPK-p38 MAPK signaling pathway and induces apoptosis by increasing the generation of intracellular ROS in a p53-independent manner. International Journal of Molecular Medicine. 2014; 33: 863–869.

[115] Odenthal J, van Heumen BWH, Roelofs HMJ, te Morsche RHM, Marian B, Nagengast FM, *et al*. The Influence of Curcumin, Quercetin, and Eicosapentaenoic Acid on the Expression of Phase II Detoxification Enzymes in the Intestinal Cell Lines HT-29, Caco-2, HuTu 80, and LT97. Nutrition and Cancer. 2012; 64: 856–863.
[116] Kim H, Kim S, Kim B, Lee S, Park Y, Park B, *et al*. Apoptotic Effect of Quercetin on HT-29 Colon Cancer Cells via the AMPK Signaling Pathway. Journal of Agricultural and Food Chemistry. 2010; 58: 8643–8650.
[117] Lee Y, Park SY, Kim Y, Lee WS, Park OJ. AMP kinase/cyclooxygenase-2 pathway regulates proliferation and apoptosis of cancer cells treated with quercetin. Experimental and Molecular Medicine. 2009; 41: 201.
[118] Song Y, Han M, Zhang X. Quercetin suppresses the migration and invasion in human colon cancer Caco-2 cells through regulating toll-like receptor 4/Nuclear Factor-kappa B pathway. Pharmacognosy Magazine. 2016; 12: 237.
[119] Zhang X, Zhang S, Yin Q, Zhang J. Quercetin induces human colon cancer cells apoptosis by inhibiting the nuclear factor-kappa B Pathway. Pharmacognosy Magazine. 2015; 11: 404.
[120] Min K, Ebeler SE. Quercetin inhibits hydrogen peroxide-induced DNA damage and enhances DNA repair in Caco-2 cells. Food and Chemical Toxicology. 2009; 47: 2716–2722.
[121] van Erk MJ, Roepman P, van der Lende TR, Stierum RH, Aarts JMMJG, van Bladeren PJ, *et al*. Integrated assessment by multiple gene expression analysis of quercetin bioactivity on anticancer–related mechanisms in colon cancer cells in vitro. European Journal of Nutrition. 2005; 44: 143–156.
[122] Ackland ML, van de Waarsenburg S, Jones R. Synergistic antiproliferative action of the flavonols quercetin and kaempferol in cultured human cancer cell lines. In vivo. 2005; 19: 69–76.
[123] Liu Y, Li C, Xu Q, Cheng D, Liu K, Sun Z. Quercetin inhibits invasion and angiogenesis of esophageal cancer cells. Pathology - Research and Practice. 2021; 222: 153455.
[124] Chuang-Xin L, Wen-Yu W, Yao C, Xiao-Yan L, Yun Z. Quercetin enhances the effects of 5-fluorouracil-mediated growth inhibition and apoptosis of esophageal cancer cells by inhibiting NF-κB. Oncology Letters. 2012; 4: 775–778.
[125] Wang Y, Chen X, Li J, Xia C. Quercetin Antagonizes Esophagus Cancer by Modulating miR-1-3p/TAGLN2 Pathway-Dependent Growth and Metastasis. Nutrition and Cancer. 2022; 74: 1872–1881.
[126] Rocha-Brito KJP, Clerici SP, Cordeiro HG, Scotá Ferreira AP, Barreto Fonseca EM, Gonçalves PR, *et al*. Quercetin increases mitochondrial proteins (VDAC and SDH) and downmodulates AXL and PIM-1 tyrosine kinase receptors in NRAS melanoma cells. Biological Chemistry. 2022; 403: 293–303.
[127] Guo Y, Tong Y, Zhu H, Xiao Y, Guo H, Shang L, *et al*. Quercetin suppresses pancreatic ductal adenocarcinoma progression via inhibition of SHH and TGF-β/Smad signaling pathways. Cell Biology and Toxicology. 2021; 37: 479–496.
[128] Yu D, Ye T, Xiang Y, Shi Z, Zhang J, Lou B, *et al*. Quercetin inhibits epithelial-mesenchymal transition, decreases invasiveness and metastasis, and reverses IL-6 induced epithelial-mesenchymal transition, expression of MMP by inhibiting STAT3 signaling in pancreatic cancer cells. OncoTargets and Therapy. 2017; 10: 4719–4729.
[129] Lee JH, Lee H, Jung GO, Oh JT, Park DE, Chae KM. Effect of quercetin on apoptosis of PANC-1 cells. Journal of the Korean Surgical Society. 2013; 85: 249.
[130] Li H, Chen C. Quercetin has Antimetastatic Effects on Gastric Cancer Cells via the Interruption of uPA/uPAR Function by Modulating NF-κb, PKC-δ, ERK1/2, and AMPKα. Integrative Cancer Therapies. 2018; 17: 511–523.
[131] Li Z, Gu X, Rao D, Lu M, Wen J, Chen X, *et al*. Luteolin promotes macrophage-mediated phagocytosis by inhibiting CD47 pyroglutamation. Translational Oncology. 2021; 14: 101129.
[132] Zhang M, Wang R, Tian J, Song M, Zhao R, Liu K, *et al*. Targeting LIMK1 with luteolin inhibits the growth of lung cancer in vitro and in vivo. Journal of Cellular and Molecular Medicine. 2021; 25: 5560–5571.
[133] Wu B, Xiong J, Zhou Y, Wu Y, Song Y, Wang N, *et al*. Luteolin enhances TRAIL sensitivity in non-small cell lung cancer cells through increasing DR5 expression and Drp1-mediated mitochondrial fission. Archives of Biochemistry and Biophysics. 2020; 692: 108539.
[134] Masraksa W, Tanasawet S, Hutamekalin P, Wongtawatchai T, Sukketsiri W. Luteolin attenuates migration and invasion of lung cancer cells via suppressing focal adhesion kinase and non-receptor tyrosine kinase signaling pathway. Nutrition Research and Practice. 2020; 14: 127.
[135] Yu Q, Zhang M, Ying Q, Xie X, Yue S, Tong B, *et al*. Decrease of AIM2 mediated by luteolin contributes to non-small cell lung cancer treatment. Cell Death & Disease. 2019; 10: 218.
[136] Wang Y, Zhang Y, Chen X, Hong Y, Wu Z. Combined treatment with myo-inositol and luteolin selectively suppresses growth of human lung cancer A549 cells possibly by suppressing activation of PDK1 and Akt. Nan Fang Yi Ke Da Xue Xue Bao. 2018; 38: 1378–1383.
[137] Jiang ZQ, Li MH, Qin YM, Jiang HY, Zhang X, Wu MH. Luteolin Inhibits Tumorigenesis and Induces Apoptosis of Non-Small Cell Lung Cancer Cells via Regulation of MicroRNA-34a-5p. International Journal of Molecular Sciences. 2018; 19: 447.
[138] Sonoki H, Tanimae A, Endo S, Matsunaga T, Furuta T, Ichihara K, *et al*. Kaempherol and Luteolin Decrease Claudin-2 Expression Mediated by Inhibition of STAT3 in Lung Adenocarcinoma A549 Cells. Nutrients. 2017; 9: 597.
[139] Lee YJ, Lim T, Han MS, Lee S, Baek S, Nan H, *et al*. Anticancer effect of luteolin is mediated by downregulation of TAM receptor tyrosine kinases, but not interleukin-8, in non-small cell lung cancer cells. Oncology Reports. 2017; 37: 1219–1226.
[140] Meng G, Chai K, Li X, Zhu Y, Huang W. Luteolin exerts pro-apoptotic effect and anti-migration effects on a549 lung adenocarcinoma cells through the activation of MEK/ERK signaling pathway. Chemico-Biological Interactions. 2016; 257: 26–34.
[141] Chian S, Thapa R, Chi Z, Wang XJ, Tang X. Luteolin inhibits the Nrf2 signaling pathway and tumor growth in vivo. Biochemical and Biophysical Research Communications. 2014; 447: 602–608.
[142] Tang X, Wang H, Fan L, Wu X, Xin A, Ren H, *et al*. Luteolin inhibits Nrf2 leading to negative regulation of the Nrf2/are pathway and sensitization of human lung carcinoma a549 cells to therapeutic drugs. Free Radical Biology and Medicine. 2011; 50: 1599–1609.
[143] Chen K, Chen C, Lin C, Yang T, Chen T, Wu L, *et al*. Luteolin attenuates TGF-β1-induced epithelial–mesenchymal transition of lung cancer cells by interfering in the PI3K/Akt–NF-κB–Snail pathway. Life Sciences. 2013; 93: 924–933.
[144] Yan J, Wang Q, Zheng X, Sun H, Zhou Y, Li D, *et al*. Luteolin enhances TNF-related apoptosis-inducing ligand's anticancer activity in a lung cancer xenograft mouse model. Biochemical and Biophysical Research Communications. 2012; 417: 842–846.
[145] Cai X, Ye T, Liu C, Lu W, Lu M, Zhang J, *et al*. Luteolin induced G2 phase cell cycle arrest and apoptosis on non-small cell lung cancer cells. Toxicology in Vitro. 2011; 25: 1385–1391.
[146] Ma L, Peng H, Li K, Zhao R, Li L, Yu Y, *et al*. Luteolin exerts an anticancer effect on NCI-H460 human non-small cell lung cancer cells through the induction of Sirt1-mediated apoptosis. Molecular Medicine Reports. 2015; 12: 4196–4202.

[147] Cho H, Ahn K, Choi JY, Hwang S, Kim W, Um H, *et al*. Luteolin acts as a radiosensitizer in non-small cell lung cancer cells by enhancing apoptotic cell death through activation of a p38/ROS/caspase cascade. International Journal of Oncology. 2015; 46: 1149–1158.
[148] Park S, Park HS, Lee JH, Chi GY, Kim G, Moon S, *et al*. Induction of endoplasmic reticulum stress-mediated apoptosis and non-canonical autophagy by luteolin in NCI-H460 lung carcinoma cells. Food and Chemical Toxicology. 2013; 56: 100–109.
[149] Attoub S, Hassan AH, Vanhoecke B, Iratni R, Takahashi T, Gaben A, *et al*. Inhibition of cell survival, invasion, tumor growth and histone deacetylase activity by the dietary flavonoid luteolin in human epithelioid cancer cells. European Journal of Pharmacology. 2011; 651: 18–25.
[150] Raina R, Pramodh S, Rais N, Haque S, Shafarin J, Bajbouj K, *et al*. Luteolin inhibits proliferation, triggers apoptosis and modulates Akt/mTOR and MAP kinase pathways in HeLa cells. Oncology Letters. 2021; 21: 192.
[151] Tai Z, Lin Y, He Y, Huang J, Guo J, Yang L, *et al*. Luteolin sensitizes the antiproliferative effect of interferon α/β by activation of Janus kinase/signal transducer and activator of transcription pathway signaling through protein kinase a-mediated inhibition of protein tyrosine phosphatase SHP-2 in cancer cells. Cellular Signalling. 2014; 26: 619–628.
[152] Ham S, Kim KH, Kwon TH, Bak Y, Lee DH, Song YS, *et al*. Luteolin induces intrinsic apoptosis via inhibition of E6/E7 oncogenes and activation of extrinsic and intrinsic signaling pathways in HPV-18-associated cells. Oncology Reports. 2014; 31: 2683–2691.
[153] Shi R, Ong C, Shen H. Protein Kinase C Inhibition and X-Linked Inhibitor of Apoptosis Protein Degradation Contribute to the Sensitization Effect of Luteolin on Tumor Necrosis Factor–Related Apoptosis-Inducing Ligand–Induced Apoptosis in Cancer Cells. Cancer Research. 2005; 65: 7815–7823.
[154] Shi R, Ong C, Shen H. Luteolin sensitizes tumor necrosis factor-α-induced apoptosis in human tumor cells. Oncogene. 2004; 23: 7712–7721.
[155] Wu B, Zhang Q, Shen W, Zhu J. Anti-proliferative and chemosensitizing effects of luteolin on human gastric cancer AGS cell line. Molecular and Cellular Biochemistry. 2008; 313: 125–132.
[156] Radziejewska I, Borzym-Kluczyk M, Leszczyńska K. Luteolin alters MUC1 extracellular domain, sT antigen, ADAM-17, IL-8, IL-10 and NF-κB expression in Helicobacter pylori-infected gastric cancer CRL-1739 cells: A preliminary study. Biomedical Reports. 2021; 14: 19.
[157] Ding J, Li D, Li Q, He S, Xie J, Liang X, *et al*. Luteolin-loading of her-2-poly (lactic-co-glycolic acid) nanoparticles and proliferative inhibition of gastric cancer cells via targeted regulation of forkhead box protein O1. Journal of Cancer Research and Therapeutics. 2020; 16: 263.
[158] Lu J, Li G, He K, Jiang W, Xu C, Li Z, *et al*. Luteolin exerts a marked antitumor effect in cMet-overexpressing patient-derived tumor xenograft models of gastric cancer. Journal of Translational Medicine. 2015; 13: 42.
[159] Zhang Q, Wan L, Guo Y, Cheng N, Cheng W, Sun Q, et al. Radiosensitization effect of luteolin on human gastric cancer SGC-7901 cells. Journal of Biological Regulators and Homeostatic Agents. 2009; 23: 71–78.
[160] Zang M, Hu L, Zhang B, Zhu Z, Li J, Zhu Z, *et al*. Luteolin suppresses angiogenesis and vasculogenic mimicry formation through inhibiting Notch1-VEGF signaling in gastric cancer. Biochemical and Biophysical Research Communications. 2017; 490: 913–919.
[161] Lu X, Li Y, Li X, Aisa HA. Luteolin induces apoptosis in vitro through suppressing the MAPK and PI3K signaling pathways in gastric cancer. Oncology Letters. 2017; 14: 1993–2000.
[162] Lu XY, Li YH, Xiao XW, Li XB. Inhibitory effects of luteolin on human gastric carcinoma xenografts in nude mice and its mechanism. Zhonghua Yi Xue Za Zhi. 2013; 93: 142–146.
[163] Magura J, Moodley R, Mackraj I. The effect of hesperidin and luteolin isolated from Eriocephalus africanus on apoptosis, cell cycle and miRNA expression in MCF-7. Journal of Biomolecular Structure & Dynamics. 2022; 40: 1791–1800.
[164] Gao G, Ge R, Li Y, Liu S. Luteolin exhibits anti-breast cancer property through up-regulating miR-203. Artificial Cells, Nanomedicine, and Biotechnology. 2019; 47: 3265–3271.
[165] Dong X, Zhang J, Yang F, Wu J, Cai R, Wang T, *et al*. Effect of luteolin on the methylation status of the OPCML gene and cell growth in breast cancer cells. Experimental and Therapeutic Medicine. 2018; 16: 3186–3194.
[166] Sui JQ, Xie KP, Xie MJ. Inhibitory effect of luteolin on the proliferation of human breast cancer cell lines induced by epidermal growth factor. Sheng Li Xue Bao. 2016; 68: 27–34.
[167] Sato Y, Sasaki N, Saito M, Endo N, Kugawa F, Ueno A. Luteolin Attenuates Doxorubicin-Induced Cytotoxicity to MCF-7 Human Breast Cancer Cells. Biological & Pharmaceutical Bulletin. 2015; 38: 703–709.
[168] Park S, Ham S, Kwon TH, Kim MS, Lee DH, Kang J, *et al*. Luteolin Induces Cell Cycle Arrest and Apoptosis through Extrinsic and Intrinsic Signaling Pathways in MCF-7 Breast Cancer Cells. Journal of Environmental Pathology, Toxicology and Oncology. 2014; 33: 219–231.
[169] Jiang Y, Xie KP, Huo HN, Wang LM, Zou W, Xie MJ. Inhibitory effect of luteolin on the angiogenesis of chick chorioallantoic membrane and invasion of breast cancer cells via down-regulation of AEG-1 and MMP-2. Sheng Li Xue Bao. 2013; 65: 513–518.
[170] Wang L, Xie K, Huo H, Shang F, Zou W, Xie M. Luteolin Inhibits Proliferation Induced by IGF-1 Pathway Dependent ERα in Human Breast Cancer MCF-7 Cells. Asian Pacific Journal of Cancer Prevention. 2012; 13: 1431–1437.
[171] Markaverich BM, Shoulars K, Rodriguez MA. Luteolin Regulation of Estrogen Signaling and Cell Cycle Pathway Genes in MCF-7 Human Breast Cancer Cells. International Journal of Biomedical Science. 2011; 7: 101–111.
[172] Dong X, Zheng T, Zhang Z, Bai X, Li H, Zhang J. Luteolin reverses OPCML methylation to inhibit proliferation of breast cancer MDA-MB-231 cells. Nan Fang Yi Ke Da Xue Xue Bao. 2020; 40: 550-555.
[173] Huang L, Jin K, Lan H. Luteolin inhibits cell cycle progression and induces apoptosis of breast cancer cells through down-regulation of human telomerase reverse transcriptase. Oncology Letters. 2019; 17: 3842–3850.
[174] Cook MT, Liang Y, Besch-Williford C, Hyder SM. Luteolin inhibits lung metastasis, cell migration, and viability of triple-negative breast cancer cells. Breast Cancer. 2017; 9: 9–19.
[175] Sun D, Zhang H, Mao L, Mao C, Chen W, Cui M, *et al*. Luteolin Inhibits Breast Cancer Development and Progression in Vitro and in Vivo by Suppressing Notch Signaling and Regulating MiRNAs. Cellular Physiology and Biochemistry. 2015; 37: 1693–1711.
[176] Yang M, Wang C, Chen N, Ho W, Lu F, Tseng T. Luteolin enhances paclitaxel-induced apoptosis in human breast cancer MDA-MB-231 cells by blocking STAT3. Chemico-Biological Interactions. 2014; 213: 60–68.
[177] Lee E, Oh S, Sung M. Luteolin exerts anti-tumor activity through the suppression of epidermal growth factor receptor-mediated pathway in MDA-MB-231 ER-negative breast cancer cells. Food and Chemical Toxicology. 2012; 50: 4136–4143.
[178] Potočnjak I, Šimić L, Gobin I, Vukelić I, Domitrović R. Antitumor activity of luteolin in human colon cancer SW620 cells is

mediated by the ERK/FOXO3a signaling pathway. Toxicology in Vitro. 2020; 66: 104852.
[179] Yoo HS, Won SB, Kwon YH. Luteolin Induces Apoptosis and Autophagy in HCT116 Colon Cancer Cells via p53-Dependent Pathway. Nutrition and Cancer. 2022; 74: 677–686.
[180] Zuo Q, Wu R, Xiao X, Yang C, Yang Y, Wang C, *et al*. The dietary flavone luteolin epigenetically activates the Nrf2 pathway and blocks cell transformation in human colorectal cancer HCT116 cells. Journal of Cellular Biochemistry. 2018; 119: 9573–9582.
[181] Lee Y, Kwon YH. Regulation of apoptosis and autophagy by luteolin in human hepatocellular cancer Hep3B cells. Biochemical and Biophysical Research Communications. 2019; 517: 617–622.
[182] Chang TL, Liou PS, Cheng PY, Chang HN, Tsai PJ. Borneol and Luteolin from Chrysanthemum morifolium Regulate Ubiquitin Signal Degradation. Journal of Agricultural and Food Chemistry. 2018; 66: 8280–8290.
[183] Alnahdi A, John A, Raza H. Augmentation of Glucotoxicity, Oxidative Stress, Apoptosis and Mitochondrial Dysfunction in HepG2 Cells by Palmitic Acid. Nutrients. 2019;11(9):1979.
[184] Lee W, Wu L, Chen W, Wang C, Tseng T. Inhibitory effect of luteolin on hepatocyte growth factor/scatter factor-induced HepG2 cell invasion involving both MAPK/ERKs and PI3K–Akt pathways. Chemico-Biological Interactions. 2006; 160: 123–133.
[185] Su Bog Y, Jung Hwa L, Hae Young C, Kwang Sik I, Song Ja B, Jae Soo C, *et al*. Inhibitory effects of luteolin isolated fromixeris sonchifolia hance on the proliferation of hepg2 human hepatocellular carcinoma cells. Archives of Pharmacal Research. 2003; 26: 151–156.
[186] Hwang JT, Park OJ, Lee YK, Sung MJ, Hur HJ, Kim MS, *et al*. Anti-tumor effect of luteolin is accompanied by AMP-activated protein kinase and nuclear factor-κB modulation in HepG2 hepatocarcinoma cells. International Journal of Molecular Medicine. 2011; 28: 25–31.
[187] Fouzder C, Mukhuty A, Kundu R. Kaempferol inhibits Nrf2 signalling pathway via downregulation of Nrf2 mRNA and induces apoptosis in NSCLC cells. Archives of Biochemistry and Biophysics. 2021; 697: 108700.
[188] Han X, Liu CF, Gao N, Zhao J, Xu J. RETRACTED: Kaempferol suppresses proliferation but increases apoptosis and autophagy by up-regulating microRNA-340 in human lung cancer cells. Biomedicine & Pharmacotherapy. 2018; 108: 809–816.
[189] Liao W, Chen L, Ma X, Jiao R, Li X, Wang Y. Protective effects of kaempferol against reactive oxygen species-induced hemolysis and its antiproliferative activity on human cancer cells. European Journal of Medicinal Chemistry. 2016; 114: 24–32.
[190] Jo E, Park SJ, Choi YS, Jeon W, Kim B. Kaempferol Suppresses Transforming Growth Factor-β1–Induced Epithelial-to-Mesenchymal Transition and Migration of a549 Lung Cancer Cells by Inhibiting Akt1-Mediated Phosphorylation of Smad3 at Threonine-179. Neoplasia. 2015; 17: 525–537.
[191] Li S, Yan T, Deng R, Jiang X, Xiong H, Wang Y, *et al*. Low dose of kaempferol suppresses the migration and invasion of triple-negative breast cancer cells by downregulating the activities of RhoA and Rac1. OncoTargets and Therapy. 2017; 10: 4809–4819.
[192] Kim S, Hwang K, Choi K. Treatment with kaempferol suppresses breast cancer cell growth caused by estrogen and triclosan in cellular and xenograft breast cancer models. The Journal of Nutritional Biochemistry. 2016; 28: 70–82.
[193] Oh SM, Kim YP, Chung KH. Biphasic effects of kaempferol on the estrogenicity in human breast cancer cells. Archives of Pharmacal Research. 2006; 29: 354–362.
[194] Zhu L, Xue L. Kaempferol Suppresses Proliferation and Induces Cell Cycle Arrest, Apoptosis, and DNA Damage in Breast Cancer Cells. Oncology Research Featuring Preclinical and Clinical Cancer Therapeutics. 2019; 27: 629–634.
[195] Li C, Zhao Y, Yang D, Yu Y, Guo H, Zhao Z, *et al*. Inhibitory effects of kaempferol on the invasion of human breast carcinoma cells by downregulating the expression and activity of matrix metalloproteinase-9. Biochemistry and Cell Biology. 2015; 93: 16–27.
[196] MacPherson L, Matthews J. Inhibition of aryl hydrocarbon receptor-dependent transcription by resveratrol or kaempferol is independent of estrogen receptor α expression in human breast cancer cells. Cancer Letters. 2010; 299: 119–129.
[197] Kim TW, Lee SY, Kim M, Cheon C, Ko S. Kaempferol induces autophagic cell death via IRE1-JNK-CHOP pathway and inhibition of G9a in gastric cancer cells. Cell Death & Disease. 2018; 9: 875.
[198] Zhang F, Ma C. Kaempferol suppresses human gastric cancer SNU-216 cell proliferation, promotes cell autophagy, but has no influence on cell apoptosis. Brazilian Journal of Medical and Biological Research. 2019; 52: e7843.
[199] Song H, Bao J, Wei Y, Chen Y, Mao X, Li J, *et al*. Kaempferol inhibits gastric cancer tumor growth: an in vitro and in vivo study. Oncology Reports. 2015; 33: 868–874.
[200] Kashafi E, Moradzadeh M, Mohamadkhani A, Erfanian S. Kaempferol increases apoptosis in human cervical cancer HeLa cells via PI3K/AKT and telomerase pathways. Biomedicine & Pharmacotherapy. 2017; 89: 573–577.
[201] El-Kott AF, Shati AA, Al-Kahtani MA, Alharbi SA. Kaempferol Induces Cell Death in A2780 Ovarian Cancer Cells and Increases Their Sensitivity to Cisplatin by Activation of Cytotoxic Endoplasmic Reticulum-Mediated Autophagy and Inhibition of Protein Kinase B. Folia Biologica. 2020; 66: 36–46.
[202] Gao Y, Yin J, Rankin GO, Chen YC. Kaempferol Induces G2/M Cell Cycle Arrest via Checkpoint Kinase 2 and Promotes Apoptosis via Death Receptors in Human Ovarian Carcinoma A2780/CP70 Cells. Molecules. 2018; 23: 1095.
[203] Luo H, Rankin GO, Li Z, DePriest L, Chen YC. Kaempferol induces apoptosis in ovarian cancer cells through activating p53 in the intrinsic pathway. Food Chemistry. 2011; 128: 513–519.
[204] Wu H, Cui M, Li C, Li H, Dai Y, Cui K, *et al*. Kaempferol Reverses Aerobic Glycolysis via miR-339-5p-Mediated PKM Alternative Splicing in Colon Cancer Cells. Journal of Agricultural and Food Chemistry. 2021; 69: 3060–3068.
[205] Park J, Lee G, An H, Lee C, Cho ES, Kang HC, *et al*. Kaempferol sensitizes cell proliferation inhibition in oxaliplatin-resistant colon cancer cells. Archives of Pharmacal Research. 2021; 44: 1091–1108.
[206] Choi J, Kim J, Lee H, Pak J, Shim BS, Kim S. Reactive Oxygen Species and p53 Mediated Activation of p38 and Caspases is Critically Involved in Kaempferol Induced Apoptosis in Colorectal Cancer Cells. Journal of Agricultural and Food Chemistry. 2018; 66: 9960–9967.
[207] Li W, Du B, Wang T, Wang S, Zhang J. Kaempferol induces apoptosis in human HCT116 colon cancer cells via the Ataxia-Telangiectasia Mutated-p53 pathway with the involvement of p53 Upregulated Modulator of Apoptosis. Chemico-Biological Interactions. 2009; 177: 121–127.
[208] Riahi-Chebbi I, Souid S, Othman H, Haoues M, Karoui H, Morel A, *et al*. The Phenolic compound Kaempferol overcomes 5-fluorouracil resistance in human resistant LS174 colon cancer cells. Scientific Reports. 2019; 9: 195.
[209] Lee HS, Cho HJ, Kwon GT, Park JHY. Kaempferol Downregulates Insulin-like Growth Factor-i Receptor and ErbB3 Signaling in HT-29 Human Colon Cancer Cells. Journal of Cancer Preven-

tion. 2014; 19: 161–169.
[210] Cho HJ, Park JHY. Kaempferol Induces Cell Cycle Arrest in HT-29 Human Colon Cancer Cells. Journal of Cancer Prevention. 2013; 18: 257–263.
[211] Yoshida T, Konishi M, Horinaka M, Yasuda T, Goda AE, Taniguchi H, et al. Kaempferol sensitizes colon cancer cells to TRAIL-induced apoptosis. Biochemical and Biophysical Research Communications. 2008; 375: 129–133.
[212] Wang J, Fang X, Ge L, Cao F, Zhao L, Wang Z, *et al*. Antitumor, antioxidant and anti-inflammatory activities of kaempferol and its corresponding glycosides and the enzymatic preparation of kaempferol. PLoS ONE. 2018; 13: e0197563.
[213] Zhu G, Liu X, Li H, Yan Y, Hong X, Lin Z. Kaempferol inhibits proliferation, migration, and invasion of liver cancer HepG2 cells by down-regulation of microRNA-21. International Journal of Immunopathology and Pharmacology. 2018; 32: 2058738418814341.