Anti-Cancer Effects of Dietary Polyphenols

Subjects: Food Science & Technology

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Consumption of coffee, tea, wine, curry, and soybeans has been linked to a lower risk of cancer in epidemiological studies. Several cell-based and animal studies have shown that dietary polyphenols like chlorogenic acid, curcumin, epigallocatechin-3-*O*-gallate, genistein, quercetin and resveratrol play a major role in these anticancer effects. Several mechanisms have been proposed to explain the anticancer effects of polyphenols. Depending on the cellular microenvironment, these polyphenols can exert double-faced actions as either an antioxidant or a prooxidant, and one of the representative anticancer mechanisms is a reactive oxygen species (ROS)-mediated mechanism. These polyphenols can also influence microRNA (miR) expression. In general, they can modulate the expression/activity of the constituent molecules in ROS-mediated anticancer pathways by increasing the expression of tumor-suppressive miRs and decreasing the expression of oncogenic miRs.

dietary polyphenols cancer ROS

1. Introduction

Human epidemiological studies have shown that diets high in plant polyphenols have beneficial effects on various diseases including cancer [1][2]. Researchers have discussed the anticancer effects of coffee, tea, wine, and curry based on recent evidence from human studies, in which chlorogenic acid (CGA), (-)-epigallocatechin gallate (EGCG), resveratrol (RES), and curcumin (CUR), respectively, are believed to be major contributors to the activity [3] (**Figure 1** and **Table 1**).

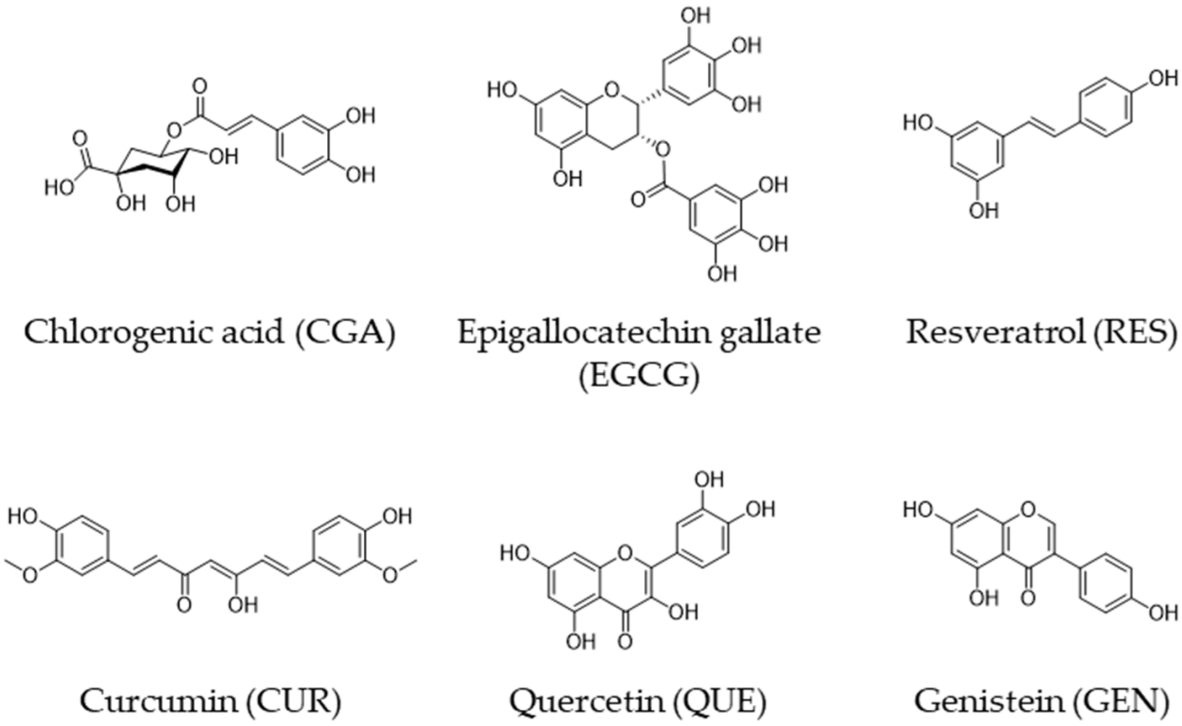

Figure 1. Chemical structures of CGA, EGCG, RES, CUR, QUE, and GEN.

Table 1. Major food sources of polyphenols.

Polyphenol	Major Food Source
Chlorogenic acid (CGA)	Coffee bean
(−)-Epigallocatechin gallate (EGCG)	Green tea
Resveratrol (RES)	Red wine
Curcumin (CUR)	Curry
Quercetin (QUE)	Onion
Genistein (GEN)	Soy

Quercetin (QUE) is a flavonol found in a variety of fruits and vegetables including apples, grapes, broccoli, green tea, and onions [4][5] (**Figure 1**), and several human studies have shown that QUE-rich diets have anticancer effects [5][6][7][8]. For example, Ekström et al. [7] discovered that QUE intake had a strong inverse association with the risk of noncardia gastric adenocarcinoma, with an adjusted odds ratio (OR) of 0.57 (95% confidence interval [CI] = 0.40–0.83) when the highest quintile (≥11.9 mg/day) was compared to the lowest quintile (<4 mg).

Epidemiologic studies have also shown that a soy-rich diet reduces the risk of various diseases, including cancer, and one of the main contributors is thought to be genistein (GEN), a phenolic compound [9][10][11] (**Figure 1**). Wang et al. [12] discovered a lower risk of papillary macrocarcinomas in women who consumed 1860–3110 µg/day of GEN (OR = 0.26, CI = 0.08–0.85) compared to women who consumed <760 µg/day in a population-based case-

control study in Connecticut from 2010 to 2011. A meta-analysis conducted by Applegate et al. [13] revealed that the pooled relative risk for GEN in the risk of prostate cancer was 0.90 (CI: 0.84–0.97).

Many epidemiological studies, on the other hand, have found that these foods have no anticancer effects [1][14]. The inconsistent results could be due to a number of confounding factors, including the quantity and quality of plant foods consumed, as well as residual pesticides and acrylamide formed during preparation, cigarette smoking, alcohol consumption, differences in ingredients, hormonal activities, microbiota, and genetic background [1][14][15]. Human intervention studies that are well-designed could provide significant evidence for the anticancer effects of dietary foods containing these polyphenols.

The anticancer properties of these polyphenols have been demonstrated in a large number of cell-based and animal studies, and their possible anticancer mechanisms have been proposed. Of them, one involving reactive oxygen species (ROS) appears to be the most likely, in which these polyphenols can act as both an ROS-generator and an ROS-scavenger [16].

2. Anticancer Mechanism of Tumor Suppressor miRs Upregulated by Polyphenols

Table 2 summarizes the available data for tumor-suppressor miRs that are commonly upregulated by at least three different polyphenols in cancer cells. **Figure 2** shows that several molecules involved in the anticancer mechanism are found in ROS-mediated pathways. **Table 2** also provides information on the modulatory effects of miRs upregulated by these polyphenols on these molecules.

Table 2. Tumor-suppressor miRs upregulated by polyphenols, cell types examined, and effects of miR upregulation.

miR	CUR	EGCG	GEN	QUE	RES	Effects of miRs Upregulated by Polyphenols on Molecules in the ROS-Mediated Pathway: ↑, Upregulation; ↓ Downregulation
miR-16	MCF-7 (breast cancer) (Yang, et al.) [17]	HepG2 (liver cancer) (Tsang, et al.) [18]		A549 (lung cancer) (Sonoki, et al.) [19] HSC-6 SCC-9 (oral	MCF7-ADR MCF10A MDA-MB-231-luc-D3H2LN (breast cancer) (Hagiwara, et al.) [21] CCRF-CEM	↓Bcl-2 [17][18]

miR	CUR	EGCG	GEN	QUE	RES	Effects of miRs Upregulated by Polyphenols on Molecules in the ROS-Mediated Pathway: ↑, Upregulation; ↓ Downregulation
				cancer) (Zhao, et al.) [20]	(acute lymphoblastic leukemia) (Azimi, et al.) [22]	
miR-22	BxPC-3 (pancreatic carcinoma) (Sun, et al.) [23] Y79 (retinoblastoma) (Sreenivasan, et al.) [24] *Downregulated * MyLa2059, SeAx* (*malignant cutaneous lymphoma*) (Sibbesen, et al.) [25]	CNE2 (nasopharyngeal carcinoma) (Li, et al.) [26]		Tca8113 SAS (oral squamous cell carcinoma) (Zhang, et al.) [27]		↓VEGF via↓Sp1 [23]
miR-34a	MDA-MB-231 MDA-MB-435 (breast cancer) (Guo, et al.) [28] SGC-7901 (gastric cancer) (Sun, et al.) [29] HCT116 (colorectal cancer) (Toden, et al.) [30] BxPC-3 (pancreatic cancer) (Sun, et al.) [23] *Downregulated * TE-7* (*esophageal adenocarcinoma*)	SK-N-BE2 IMR-32 (malignant neuroblastoma) (Chakrabarti, et al.) [32] SH-SY5Y SK-N-DZ (malignant neuroblastoma) (Chakrabarti, et al.) [33] HCT116 HCT116-5FUR (colorectal cancer, 5FU resistant) (Toden, et al.) [34] CNE2	HNC-TICs (tumor-initiating cells of head and neck cancer) (Hsieh, et al.) [36] DU145 (prostate cancer) (Chiyomaru, et al.) [37] AsPC-1 MiaPaCa-2 (pancreatic cancer) (Xia, et al.) [38]		MDA-MB-231-luc-D3H2LN (breast cancer) (Hagiwara, et al.) [21] DLD-1 (colon cancer) (Kumazaki, et al.) [39] MCF-7 (breast cancer) (Otsuka, et al.) [40] SKOV-3 OV-90 (ovarian cancer) (Yao, et al.) [41]	↓Bcl-2 [28][29][30][41] ↓NF-κB via Notch-1 [38]

miR	CUR	EGCG	GEN	QUE	RES	Effects of miRs Upregulated by Polyphenols on Molecules in the ROS-Mediated Pathway: ↑, Upregulation; ↓ Downregulation
	(Subramaniam, et al.) [31]	(nasopharyngeal carcinoma) (Li, et al.) [26] HepG2 (hepatocellular carcinoma) (Mostafa, et al.) [35]				
miR-141	HCT116-5FUR (colorectal cancer, 5FU resistant) (Toden, et al.) [42]	*Downregulated * MM1.s* (*multiple myeloma*) (Gordon, et al.) [43]	786-O ACHN (renal carcinoma) (Chiyomaru, et al.) [44]		MCF7-ADR MCF-7 MCF10A MDA-MB-231-luc-D3H2LN (breast cancer) (Hagiwara, et al.) [21]	
miR-145	U-87 MG (glioblastoma) Mirgani, et al.) [45] DU145 22RV1 (prostate cancer) (Liu, et al.) [46]	HCT116 HCT116-5FUR (colorectal cancer, 5FU resistant) (Toden, et al.) [34]	Y79 (retinoblastoma) (Wei, et al.) [47]	SKOV-3 A2780 (ovarian cancer) (Zhou, et al.) [48]	BT-549 MDA-MB-231 MCF-7 (breast cancer) (Sachdeva, et al.) [49]	↑Caspase-3 [48]
miR-146a	U-87 MG (glioblastoma) (Wu, et al.) [50] AsPC-1 (pancreatic cancer) [19] CDF (analog) (Bao, et al.) [51]	[18] [20]	Colo357 Panc-1 (pancreatic cancer) G2535 (mixture of genistein and other isoflavones) (Li, et al.) [52]	MCF-7 MDA-MB-231 (breast cancer) (Tao, et al.) [53]	[3][57][58]	↓NF-κB [50] ↑Caspase-3 [53] ↓EGFR [53]
miR-200c	HCT116-5FUR SW480-5FUR (colorectal cancer, 5FU resistant)	HCT116-5FUR (colorectal cancer, 5FU resistant)			Cancer stem cells of nasopharyngeal carcinoma (Shen, et al.)	↑PTEN [54]

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CUR, EGCG, and QUE have been shown to upregulate miR-22, which may downregulate specificity protein 1 (Sp1), estrogen receptor 1 (ESR1) [23], erythoblastic leukemia viral oncogene homolog 3 (Erbb3) [24], and nuclear receptor coactivator 1 (NCoA1) [25]. Sun et al. [23] discovered that CUR increased miR-22 expression in PxBC-3 pancreatic cancer cells using oligonucleotide microarray analysis. Transfection with miR-22 mimetics reduced expression of the target genes Sp1 and ESR1, whereas antisense inhibition of miR-22 increased Sp1 and ESR1

[59]

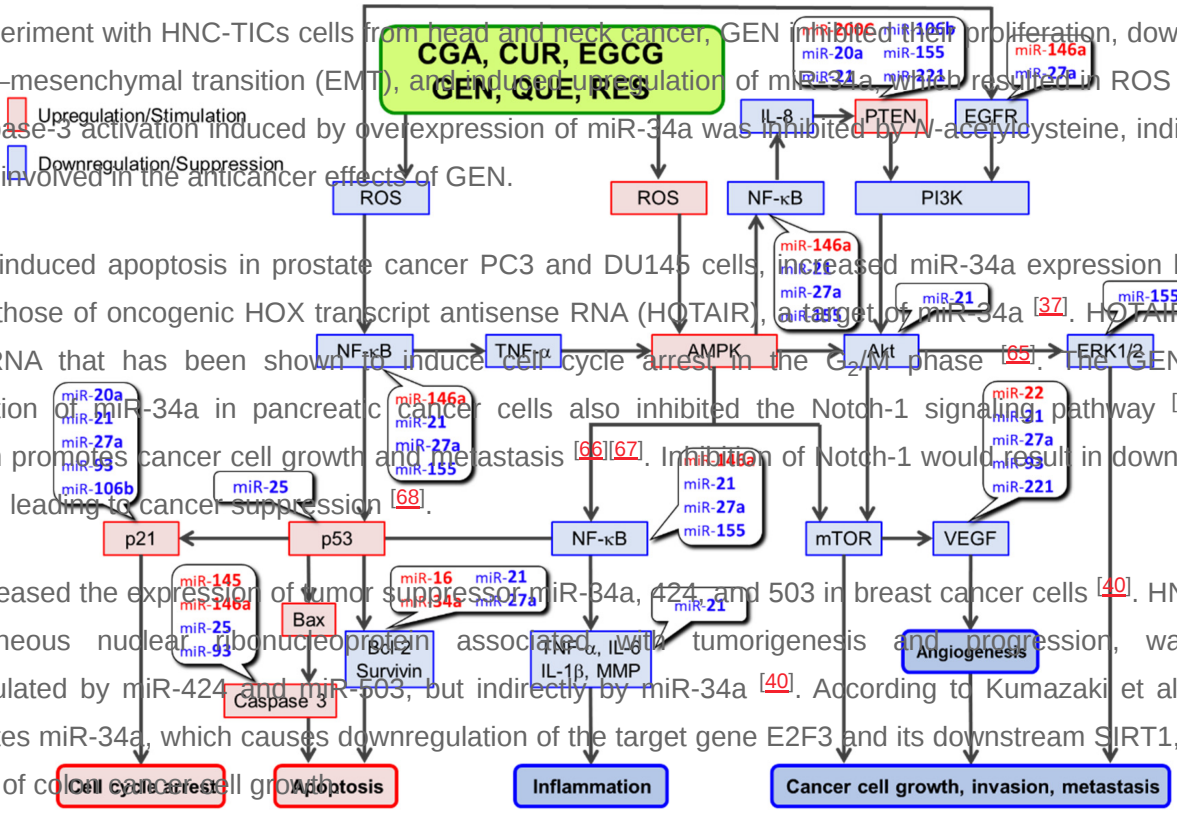
miR	CUR	EGCG	GEN	QUE	RES	Effects of miRs Upregulated by Polyphenols on Molecules in the ROS-Mediated Pathway: ↑, Upregulation; ↓ Downregulation
	[25]				[62]	
	(Toden, et al.) [42] MiaPaCa-2 MiaPaCa-2-GR BxPC-3 (pancreatic cancer) CDF (analog) (Soubani, et al.) [54]	(Toden, et al.) [34]		[64]	[55] [63] MCF7-ADR MCF-7 MCF10A MDA-MB-231-luc-D3H2LN (breast cancer) (Hagiwara, et al.) [21] HCT116 (colorectal cancer) (Dermani, et al.) [56]	

CUR upregulation of miR-34 resulted in Bcl-2 downregulation, cell cycle arrest, and/or c-Myc downregulation [28][29][30]. RES increased apoptosis and miR-34a expression in ovarian cancer cells [41]. miR-34a inhibition experiments revealed that miR-34a downregulates Bcl-2, upregulates Bax, and activates caspase-3.

* The items shown in italics are different findings from other reported results (see Text).

EGCG has been shown to exert anticancer effects by upregulating tumor-suppressing miRs including miR-34a and downregulating oncogenic miRs such as miR-92, miR-93, and miR-106b [31].

Figure 2. ROS-mediated anti-cancer activities associated with miRs regulated by polyphenols.



In an experiment with HNC-TICs cells from head and neck cancer, GEN inhibited their proliferation, downregulated epithelial–mesenchymal transition (EMT), and induced upregulation of miR-34a, which resulted in ROS production [36]. Caspase-3 activation induced by overexpression of miR-34a was inhibited by *N*-acetylcysteine, indicating that ROS are involved in the anticancer effects of GEN.

In, GEN induced apoptosis in prostate cancer PC3 and DU145 cells, increased miR-34a expression levels, and reduced those of oncogenic HOX transcript antisense RNA (HOTAIR), a target of miR-34a [37]. HOTAIR is a non-coding RNA that has been shown to induce cell cycle arrest in the G_2/M phase [65]. The GEN-mediated upregulation of miR-34a in pancreatic cancer cells also inhibited the Notch-1 signaling pathway [38], whose activation promotes cancer cell growth and metastasis [66][67]. Inhibition of Notch-1 would result in down regulation of NF-κB, leading to cancer suppression [68].

RES increased the expression of tumor suppressor miR-34a, 424, and 503 in breast cancer cells [40]. HNRNPA1, a heterogeneous nuclear ribonucleoprotein associated with tumorigenesis and progression, was directly downregulated by miR-424 and miR-503, but indirectly by miR-34a [40]. According to Kumazaki et al. [39], RES upregulates miR-34a, which causes downregulation of the target gene E2F3 and its downstream SIRT1, leading to inhibition of colon cancer cell growth.

Thus, polyphenols appear to upregulate miR-34 in general, but Subrama-niam et al. [31] found that CUR decreased expression of miR-34a in esophageal cancer TE-7 cells. One possible explanation for the difference is that the p53 status of different cell lines differs, as TE-7 cells are p53-deficient and p53 is an upstream regulator of miR-34a.

2.4. miR-141

CUR upregulated the expression of EMT-suppressing miRs such as miR-34a, 101, 141, 200c, and 429 in 5-fluorouracil (5FU)-resistant HCT116 cells, but not in 5FU-resistant SW480 cells [42]. EMT is a crucial step in the generation of cancer stem cells and the progression of cancer. The extent to which miR-141 contributes to EMT suppression is not known.

Chiyomaru et al. [44] discovered that treatment of renal carcinoma cells with GEN increased miR-141 expression and decreased HOTAIR, which is known to promote malignancy. HOTAIR expression was reduced in cells transfected with pre-miR-141. By increasing the expression of a number of tumor-suppressive miRs, including miR-16, 141, 143, and 200c, RES reduced the viability of breast cancer cells and inhibited cancer stem-like cell characteristics [21]. The miR-141 inhibitor reduced the efficacy of RES's inhibitory effect against cancer invasion, implying that miR-141 plays a role in RES' anticancer effect.

Gordon et al. [43] reported that treatment of multiple myeloma, MM1.s cells, with the carcinogen benzo[a]pyrene upregulated the expression of miR-15a, 16, 25, 92, 125b, 141, and 200a, all of which are p53 targets. EGCG inhibited the expression of tumor-suppressive miR-141 which upregulates p53. The finding appears inconsistent with EGCG's anticancer activity. It is possible that EGCG's downregulation of oncogenic miR-25 may be more effective in the anticancer effect than downregulation of miR-141 in these cells.

2.5. miR-145

Curcumin encapsulated in a non-toxic nanocarrier inhibited the proliferation of glioblastoma U-87 MG cells, increased miR-145 expression, and decreased the expression of transcription factors Oct4, SOX-2, and Nanog, all of which are upregulated and result in increased metastasis, invasion, and recurrence [45][69].

CUR inhibited the proliferation, invasion, and tumorigenicity of prostate cancer stem cells HuPCaSCs ($CD44^+/CD133^+$ subpopulation isolated from prostate cancer cell lines Du145 and 22RV1) by increasing the expression of miR-145, which prevents cell proliferation by decreasing Oct4 expression [46]. In colorectal cancer cells, EGCG increased apoptosis and cell cycle arrest, and upregulated miR-145 [34].

In GEN-treated retinoblastoma Y79 cells, miR-145 was found to be significantly upregulated [47]. The siRNA downregulated miR-145 and the target of miR-145 has been identified as ABCE1 which has oncogene-like properties. By increasing the expression of miR-145, QUE was found to induce apoptosis in human ovarian carcinoma cells. The increased expression levels of cleaved caspase-3 induced by QUE were further increased by overexpression of miR-145 [48].

2.6. miR-146a

CUR upregulated miR-146a in human U-87 MG glioblastoma cells, and overexpression of miR-146a increased apoptosis and decreased NF-κB activation in cells treated with the anticancer drug temozolomide [50]. miR-146a expression is lower in pancreatic cancer cells compared to normal human pancreatic duct epithelial cells. GEN treatment increased miR-146a expression with decreasing EGFR and NF-κB expression in these cancer cells. Transfection of miR-146a inhibited these cells' invasive ability by downregulating EGFR and NF-κB, implying that upregulation of miR-146a is involved in the anticancer effect of GEN [52]. The results of experiments with or without transfection of miR-146a mimic or anti-miR-146a revealed that QUE increased miR-146a, leading to apoptosis induction through downregulation of EGFR and activation of caspase-3 in a study of QUE's anticancer effect [53].

2.7. miR-200c

Experiments on overexpression or silencing of miR-200c in pancreatic cancer MiaPaCa-2 cells showed that a CUR analog upregulated PTEN expression, increased levels of MT1-MMP, and reduced tumor cell aggressiveness through upregulation of miR-200c [54]. Toden et al. [42] discovered that CUR improved the efficacy of 5-FU in suppressing tumor growth and EMT in 5FU-resistant colorectal cancer cells. miR-200c, a key EMT-suppressing miR, was upregulated by CUR, and miR-200c was found to downregulate BMI1, SUZ12, and EZH2 in a transfection experiment.

Upregulation of miR-200c was also observed in RES-treated nasopharyngeal carcinoma cancer stem cells [55], EGCG-treated 5FU-resistant colorectal cancer cells [34], and RES-treated breast cancer cells [21]. Dermani et al. [56] discovered that RES increased the expression of miR-200c and decreased the viability of colorectal cancer cells. Transfection with anti-miR-200c increased vimentin and ZEB1 expression, while decreasing E-cadherin expression and apoptosis. These changes were reversed by RES, indicating that RES induces apoptosis and inhibits EMT in colorectal cancer by regulating miR-200c.

References

1. Wahle, K.W.J.; Brown, I.; Rotondo, D.; Heys, S.D. Plant Phenolics in the Prevention and Treatment of Cancer. Adv. Exp. Med. Biol. 2010, 698, 36–51.
2. Kumar, N.; Goel, N. Phenolic Acids: Natural Versatile Molecules with Promising Therapeutic Applications. Biotechnol. Rep. 2019, 24, e00370.
3. Ohishi, T.; Hayakawa, S.; Miyoshi, N. Involvement of MicroRNA Modifications in Anticancer Effects of Major Polyphenols from Green Tea, Coffee, Wine, and Curry. Crit. Rev. Food Sci. Nutr. 2022, 1–32.
4. Tanabe, H.; Pervin, M.; Goto, S.; Isemura, M.; Nakamura, Y. Beneficial Effects of Plant Polyphenols on Obesity. Obes. Control Ther. 2017, 4, 1–16.

5. Lam, T.K.; Rotunno, M.; Lubin, J.H.; Wacholder, S.; Consonni, D.; Pesatori, A.C.; Bertazzi, P.A.; Chanock, S.J.; Burdette, L.; Goldstein, A.M.; et al. Dietary Quercetin, Quercetin-Gene Interaction, Metabolic Gene Expression in Lung Tissue and Lung Cancer Risk. Carcinogenesis 2010, 31, 634–642.
6. Bandera, E.V.; Williams, M.G.; Sima, C.; Bayuga, S.; Pulick, K.; Wilcox, H.; Soslow, R.; Zauber, A.G.; Olson, S.H. Phytoestrogen Consumption and Endometrial Cancer Risk: A Population-Based Case-Control Study in New Jersey. Cancer Causes Control 2009, 20, 1117–1127.
7. Ekström, A.M.; Serafini, M.; Nyrén, O.; Wolk, A.; Bosetti, C.; Bellocco, R. Dietary Quercetin Intake and Risk of Gastric Cancer: Results from a Population-Based Study in Sweden. Ann. Oncol. Off. J. Eur. Soc. Med. Oncol. 2011, 22, 438–443.
8. Woo, H.D.; Kim, J. Dietary Flavonoid Intake and Smoking-Related Cancer Risk: A Meta-Analysis. PLoS ONE 2013, 8, e75604.
9. Hwang, Y.W.; Kim, S.Y.; Jee, S.H.; Kim, Y.N.; Nam, C.M. Soy Food Consumption and Risk of Prostate Cancer: A Meta-Analysis of Observational Studies. Nutr. Cancer 2009, 61, 598–606.
10. Spagnuolo, C.; Russo, G.L.; Orhan, I.E.; Habtemariam, S.; Daglia, M.; Sureda, A.; Nabavi, S.F.; Devi, K.P.; Loizzo, M.R.; Tundis, R.; et al. Genistein and Cancer: Current Status, Challenges, and Future Directions. Adv. Nutr. 2015, 6, 408–419.
11. Yamagata, K.; Yamori, Y. Potential Effects of Soy Isoflavones on the Prevention of Metabolic Syndrome. Molecules 2021, 26, 5863.
12. Wang, Q.; Huang, H.; Zhao, N.; Ni, X.; Udelsman, R.; Zhang, Y. Phytoestrogens and Thyroid Cancer Risk: A Population-Based Case-Control Study in Connecticut. Cancer Epidemiol. Biomarkers Prev. 2020, 29, 500–508.
13. Applegate, C.C.; Rowles, J.L.; Ranard, K.M.; Jeon, S.; Erdman, J.W. Soy Consumption and the Risk of Prostate Cancer: An Updated Systematic Review and Meta-Analysis. Nutrients 2018, 10, 40.
14. Yang, C.S.; Wang, X.; Lu, G.; Picinich, S.C. Cancer Prevention by Tea: Animal Studies, Molecular Mechanisms and Human Relevance. Nat. Rev. Cancer 2009, 9, 429–439.
15. Shahinfar, H.; Jayedi, A.; Khan, T.A.; Shab-Bidar, S. Coffee Consumption and Cardiovascular Diseases and Mortality in Patients with Type 2 Diabetes: A Systematic Review and Dose-Response Meta-Analysis of Cohort Studies. Nutr. Metab. Cardiovasc. Dis. 2021, 31, 2526–2538.
16. Slika, H.; Mansour, H.; Wehbe, N.; Nasser, S.A.; Iratni, R.; Nasrallah, G.; Shaito, A.; Ghaddar, T.; Kobeissy, F.; Eid, A.H. Therapeutic Potential of Flavonoids in Cancer: ROS-Mediated Mechanisms. Biomed. Pharmacother. 2022, 146, 112442.

17. Yang, J.; Cao, Y.; Sun, J.; Zhang, Y. Curcumin Reduces the Expression of Bcl-2 by Upregulating MiR-15a and MiR-16 in MCF-7 Cells. Med. Oncol. 2010, 27, 1114–1118.
18. Tsang, W.P.; Kwok, T.T. Epigallocatechin Gallate Up-Regulation of MiR-16 and Induction of Apoptosis in Human Cancer Cells. J. Nutr. Biochem. 2010, 21, 140–146.
19. Sonoki, H.; Sato, T.; Endo, S.; Matsunaga, T.; Yamaguchi, M.; Yamazaki, Y.; Sugatani, J.; Ikari, A. Quercetin Decreases Claudin-2 Expression Mediated by Up-Regulation of MicroRNA MiR-16 in Lung Adenocarcinoma A549 Cells. Nutrients 2015, 7, 4578–4592.
20. Zhao, J.; Fang, Z.; Zha, Z.; Sun, Q.; Wang, H.; Sun, M.; Qiao, B. Quercetin Inhibits Cell Viability, Migration and Invasion by Regulating MiR-16/HOXA10 Axis in Oral Cancer. Eur. J. Pharmacol. 2019, 847, 11–18.
21. Hagiwara, K.; Kosaka, N.; Yoshioka, Y.; Takahashi, R.-U.; Takeshita, F.; Ochiya, T. Stilbene Derivatives Promote Ago2-Dependent Tumour-Suppressive MicroRNA Activity. Sci. Rep. 2012, 2, 314.
22. Azimi, A.; Hagh, M.F.; Talebi, M.; Yousefi, B.; Hossein pour feizi, A.A.; Baradaran, B.; Movassaghpour, A.A.; Shamsasenjan, K.; Khanzedeh, T.; Ghaderi, A.H.; et al. Time-and Concentration-Dependent Effects of Resveratrol on MiR 15a and MiR16-1 Expression and Apoptosis in the CCRF-CEM Acute Lymphoblastic Leukemia Cell Line. Asian Pac. J. Cancer Prev. 2015, 16, 6463–6468.
23. Sun, M.; Estrov, Z.; Ji, Y.; Coombes, K.R.; Harris, D.H.; Kurzrock, R. Curcumin (Diferuloylmethane) Alters the Expression Profiles of MicroRNAs in Human Pancreatic Cancer Cells. Mol. Cancer Ther. 2008, 7, 464–473.
24. Sreenivasan, S.; Thirumalai, K.; Danda, R.; Krishnakumar, S. Effect of Curcumin on MiRNA Expression in Human Y79 Retinoblastoma Cells. Curr. Eye Res. 2012, 37, 421–428.
25. Sibbesen, N.A.; Kopp, K.L.; Litvinov, I.V.; Jønson, L.; Willerslev-Olsen, A.; Fredholm, S.; Petersen, D.L.; Nastasi, C.; Krejsgaard, T.; Lindahl, L.M.; et al. Jak3, STAT3, and STAT5 Inhibit Expression of MiR-22, a Novel Tumor Suppressor MicroRNA, in Cutaneous T-Cell Lymphoma. Oncotarget 2015, 6, 20555–20569.
26. Li, B.-B.; Huang, G.-L.; Li, H.-H.; Kong, X.; He, Z.-W. Epigallocatechin-3-Gallate Modulates MicroRNA Expression Profiles in Human Nasopharyngeal Carcinoma CNE2 Cells. Chin. Med. J. 2017, 130, 93–99.
27. Zhang, C.; Hao, Y.; Sun, Y.; Liu, P. Quercetin Suppresses the Tumorigenesis of Oral Squamous Cell Carcinoma by Regulating MicroRNA-22/WNT1/β-Catenin Axis. J. Pharmacol. Sci. 2019, 140, 128–136.
28. Guo, J.; Li, W.; Shi, H.; Xie, X.; Li, L.; Tang, H.; Wu, M.; Kong, Y.; Yang, L.; Gao, J.; et al. Synergistic Effects of Curcumin with Emodin against the Proliferation and Invasion of Breast

Cancer Cells through Upregulation of MiR-34a. Mol. Cell. Biochem. 2013, 382, 103–111.

29. Sun, C.; Zhang, S.; Liu, C.; Liu, X. Curcumin Promoted MiR-34a Expression and Suppressed Proliferation of Gastric Cancer Cells. Cancer Biother. Radiopharm. 2019, 34, 634–641.
30. Toden, S.; Okugawa, Y.; Buhrmann, C.; Nattamai, D.; Anguiano, E.; Baldwin, N.; Shakibaei, M.; Boland, C.R.; Goel, A. Novel Evidence for Curcumin and Boswellic Acid-Induced Chemoprevention through Regulation of MiR-34a and MiR-27a in Colorectal Cancer. Cancer Prev. Res. 2015, 8, 431–443.
31. Subramaniam, D.; Ponnurangam, S.; Ramamoorthy, P.; Standing, D.; Battafarano, R.J.; Anant, S.; Sharma, P. Curcumin Induces Cell Death in Esophageal Cancer Cells through Modulating Notch Signaling. PLoS ONE 2012, 7, e30590.
32. Chakrabarti, M.; Khandkar, M.; Banik, N.L.; Ray, S.K. Alterations in Expression of Specific MicroRNAs by Combination of 4-HPR and EGCG Inhibited Growth of Human Malignant Neuroblastoma Cells. Brain Res. 2012, 1454, 1–13.
33. Chakrabarti, M.; Ai, W.; Banik, N.L.; Ray, S.K. Overexpression of MiR-7-1 Increases Efficacy of Green Tea Polyphenols for Induction of Apoptosis in Human Malignant Neuroblastoma SH-SY5Y and SK-N-DZ Cells. Neurochem. Res. 2013, 38, 420–432.
34. Toden, S.; Tran, H.-M.; Tovar-Camargo, O.A.; Okugawa, Y.; Goel, A. Epigallocatechin-3-Gallate Targets Cancer Stem-like Cells and Enhances 5-Fluorouracil Chemosensitivity in Colorectal Cancer. Oncotarget 2016, 7, 16158–16171.
35. Mostafa, S.M.; Gamal-Eldeen, A.M.; Maksoud, N.A.E.; Fahmi, A.A. Epigallocatechin Gallate-Capped Gold Nanoparticles Enhanced the Tumor Suppressors Let-7a and MiR-34a in Hepatocellular Carcinoma Cells. An. Acad. Bras. Cienc. 2020, 92, e20200574.
36. Hsieh, P.-L.; Liao, Y.-W.; Hsieh, C.-W.; Chen, P.-N.; Yu, C.-C. Soy Isoflavone Genistein Impedes Cancer Stemness and Mesenchymal Transition in Head and Neck Cancer through Activating MiR-34a/RTCB Axis. Nutrients 2020, 12, 1924.
37. Chiyomaru, T.; Yamamura, S.; Fukuhara, S.; Yoshino, H.; Kinoshita, T.; Majid, S.; Saini, S.; Chang, I.; Tanaka, Y.; Enokida, H.; et al. Genistein Inhibits Prostate Cancer Cell Growth by Targeting MiR-34a and Oncogenic HOTAIR. PLoS ONE 2013, 8, e70372.
38. Xia, J.; Duan, Q.; Ahmad, A.; Bao, B.; Banerjee, S.; Shi, Y.; Ma, J.; Geng, J.; Chen, Z.; Rahman, K.M.W.; et al. Genistein Inhibits Cell Growth and Induces Apoptosis through Up-Regulation of MiR-34a in Pancreatic Cancer Cells. Curr. Drug Targets 2012, 13, 1750–1756.
39. Kumazaki, M.; Noguchi, S.; Yasui, Y.; Iwasaki, J.; Shinohara, H.; Yamada, N.; Akao, Y. Anti-Cancer Effects of Naturally Occurring Compounds through Modulation of Signal Transduction and MiRNA Expression in Human Colon Cancer Cells. J. Nutr. Biochem. 2013, 24, 1849–1858.

40. Otsuka, K.; Yamamoto, Y.; Ochiya, T. Regulatory Role of Resveratrol, a MicroRNA-Controlling Compound, in HNRNPA1 Expression, Which Is Associated with Poor Prognosis in Breast Cancer. Oncotarget 2018, 9, 24718–24730.
41. Yao, S.; Gao, M.; Wang, Z.; Wang, W.; Zhan, L.; Wei, B. Upregulation of MicroRNA-34a Sensitizes Ovarian Cancer Cells to Resveratrol by Targeting Bcl-2. Yonsei Med. J. 2021, 62, 691–701.
42. Toden, S.; Okugawa, Y.; Jascur, T.; Wodarz, D.; Komarova, N.L.; Buhrmann, C.; Shakibaei, M.; Boland, C.R.; Goel, A. Curcumin Mediates Chemosensitization to 5-Fluorouracil through MiRNA-Induced Suppression of Epithelial-to-Mesenchymal Transition in Chemoresistant Colorectal Cancer. Carcinogenesis 2015, 36, 355–367.
43. Gordon, M.W.; Yan, F.; Zhong, X.; Mazumder, P.B.; Xu-Monette, Z.Y.; Zou, D.; Young, K.H.; Ramos, K.S.; Li, Y. Regulation of P53-Targeting MicroRNAs by Polycyclic Aromatic Hydrocarbons: Implications in the Etiology of Multiple Myeloma. Mol. Carcinog. 2015, 54, 1060–1069.
44. Chiyomaru, T.; Fukuhara, S.; Saini, S.; Majid, S.; Deng, G.; Shahryari, V.; Chang, I.; Tanaka, Y.; Enokida, H.; Nakagawa, M.; et al. Long Non-Coding RNA HOTAIR Is Targeted and Regulated by MiR-141 in Human Cancer Cells. J. Biol. Chem. 2014, 289, 12550–12565.
45. Tahmasebi Mirgani, M.; Isacchi, B.; Sadeghizadeh, M.; Marra, F.; Bilia, A.R.; Mowla, S.J.; Najafi, F.; Babaei, E. Dendrosomal Curcumin Nanoformulation Downregulates Pluripotency Genes via MiR-145 Activation in U87MG Glioblastoma Cells. Int. J. Nanomedicine 2014, 9, 403–417.
46. Liu, T.; Chi, H.; Chen, J.; Chen, C.; Huang, Y.; Xi, H.; Xue, J.; Si, Y. Curcumin Suppresses Proliferation and in Vitro Invasion of Human Prostate Cancer Stem Cells by CeRNA Effect of MiR-145 and LncRNA-ROR. Gene 2017, 631, 29–38.
47. Wei, D.; Yang, L.; Lv, B.; Chen, L. Genistein Suppresses Retinoblastoma Cell Viability and Growth and Induces Apoptosis by Upregulating MiR-145 and Inhibiting Its Target ABCE1. Mol. Vis. 2017, 23, 385–394.
48. Zhou, J.; Gong, J.; Ding, C.; Chen, G. Quercetin Induces the Apoptosis of Human Ovarian Carcinoma Cells by Upregulating the Expression of MicroRNA-145. Mol. Med. Rep. 2015, 12, 3127–3131.
49. Sachdeva, M.; Liu, Q.; Cao, J.; Lu, Z.; Mo, Y.-Y. Negative Regulation of MiR-145 by C/EBP-β through the Akt Pathway in Cancer Cells. Nucleic Acids Res. 2012, 40, 6683–6692.
50. Wu, H.; Liu, Q.; Cai, T.; Chen, Y.-D.; Wang, Z.-F. Induction of MicroRNA-146a Is Involved in Curcumin-Mediated Enhancement of Temozolomide Cytotoxicity against Human Glioblastoma. Mol. Med. Rep. 2015, 12, 5461–5466.
51. Bao, B.; Ali, S.; Banerjee, S.; Wang, Z.; Logna, F.; Azmi, A.S.; Kong, D.; Ahmad, A.; Li, Y.; Padhye, S.; et al. Curcumin Analogue CDF Inhibits Pancreatic Tumor Growth by Switching on Suppressor

MicroRNAs and Attenuating EZH2 Expression. Cancer Res. 2012, 72, 335–345.

52. Li, Y.; Vandenboom, T.G.; Wang, Z.; Kong, D.; Ali, S.; Philip, P.A.; Sarkar, F.H. MiR-146a Suppresses Invasion of Pancreatic Cancer Cells. Cancer Res. 2010, 70, 1486–1495.
53. Tao, S.-F.; He, H.-F.; Chen, Q. Quercetin Inhibits Proliferation and Invasion Acts by Up-Regulating MiR-146a in Human Breast Cancer Cells. Mol. Cell. Biochem. 2015, 402, 93–100.
54. Soubani, O.; Ali, A.S.; Logna, F.; Ali, S.; Philip, P.A.; Sarkar, F.H. Re-Expression of MiR-200 by Novel Approaches Regulates the Expression of PTEN and MT1-MMP in Pancreatic Cancer. Carcinogenesis 2012, 33, 1563–1571.
55. Shen, Y.-A.; Lin, C.-H.; Chi, W.-H.; Wang, C.-Y.; Hsieh, Y.-T.; Wei, Y.-H.; Chen, Y.-J. Resveratrol Impedes the Stemness, Epithelial-Mesenchymal Transition, and Metabolic Reprogramming of Cancer Stem Cells in Nasopharyngeal Carcinoma through P53 Activation. Evid. Based Complement. Alternat. Med. 2013, 2013, 590393.
56. Karimi Dermani, F.; Saidijam, M.; Amini, R.; Mahdavinezhad, A.; Heydari, K.; Najafi, R. Resveratrol Inhibits Proliferation, Invasion, and Epithelial-Mesenchymal Transition by Increasing MiR-200c Expression in HCT-116 Colorectal Cancer Cells. J. Cell Biochem. 2017, 118, 1547–1555.
57. Hayakawa, S.; Ohishi, T.; Miyoshi, N.; Oishi, Y.; Nakamura, Y.; Isemura, M. Anti-Cancer Effects of Green Tea Epigallocatchin-3-Gallate and Coffee Chlorogenic Acid. Molecules 2020, 25, 4553.
58. Khan, F.; Niaz, K.; Maqbool, F.; Ismail Hassan, F.; Abdollahi, M.; Nagulapalli Venkata, K.C.; Nabavi, S.M.; Bishayee, A. Molecular Targets Underlying the Anticancer Effects of Quercetin: An Update. Nutrients 2016, 8, 529.
59. Vellingiri, B.; Iyer, M.; Devi Subramaniam, M.; Jayaramayya, K.; Siama, Z.; Giridharan, B.; Narayanasamy, A.; Abdal Dayem, A.; Cho, S.-G. Understanding the Role of the Transcription Factor Sp1 in Ovarian Cancer: From Theory to Practice. Int. J. Mol. Sci. 2020, 21, 1153.
60. Huang, C.; Xie, K. Crosstalk of Sp1 and Stat3 Signaling in Pancreatic Cancer Pathogenesis. Cytokine Growth Factor Rev. 2012, 23, 25–35.
61. Su, F.; Geng, J.; Li, X.; Qiao, C.; Luo, L.; Feng, J.; Dong, X.; Lv, M. SP1 Promotes Tumor Angiogenesis and Invasion by Activating VEGF Expression in an Acquired Trastuzumab-resistant Ovarian Cancer Model. Oncol. Rep. 2017, 38, 2677–2684.
62. Wang, Q.; Wang, J.; Xiang, H.; Ding, P.; Wu, T.; Ji, G. The Biochemical and Clinical Implications of Phosphatase and Tensin Homolog Deleted on Chromosome Ten in Different Cancers. Am. J. Cancer Res. 2021, 11, 5833–5855.
63. Lee, Y.-S.; Lim, K.-H.; Guo, X.; Kawaguchi, Y.; Gao, Y.; Barrientos, T.; Ordentlich, P.; Wang, X.-F.; Counter, C.M.; Yao, T.-P. The Cytoplasmic Deacetylase HDAC6 Is Required for Efficient

Oncogenic Tumorigenesis. Cancer Res. 2008, 68, 7561–7569.

64. Qin, L.; Wu, Y.-L.; Toneff, M.J.; Li, D.; Liao, L.; Gao, X.; Bane, F.T.; Tien, J.C.-Y.; Xu, Y.; Feng, Z.; et al. NCOA1 Directly Targets M-CSF1 Expression to Promote Breast Cancer Metastasis. Cancer Res. 2014, 74, 3477–3488.
65. Jiang, J.; Wang, S.; Wang, Z.; Cai, J.; Han, L.; Xie, L.; Han, Q.; Wang, W.; Zhang, Y.; He, X.; et al. HOTAIR Promotes Paclitaxel Resistance by Regulating CHEK1 in Ovarian Cancer. Cancer Chemother. Pharmacol. 2020, 86, 295–305.
66. Yu, L.; Li, W. Abnormal Activation of Notch 1 Signaling Causes Apoptosis Resistance in Cervical Cancer. Int. J. Clin. Exp. Pathol. 2022, 15, 11–19.
67. Cui, L.; Dong, Y.; Wang, X.; Zhao, X.; Kong, C.; Liu, Y.; Jiang, X.; Zhang, X. Downregulation of Long Noncoding RNA SNHG1 Inhibits Cell Proliferation, Metastasis, and Invasion by Suppressing the Notch-1 Signaling Pathway in Pancreatic Cancer. J. Cell Biochem. 2019, 120, 6106–6112.
68. Kiesel, V.A.; Stan, S.D. Modulation of Notch Signaling Pathway by Bioactive Dietary Agents. Int. J. Mol. Sci. 2022, 23, 3532.
69. Alemohammad, H.; Asadzadeh, Z.; Motafakker Azad, R.; Hemmat, N.; Najafzadeh, B.; Vasefifar, P.; Najafi, S.; Baradaran, B. Signaling Pathways and MicroRNAs, the Orchestrators of NANOG Activity during Cancer Induction. Life Sci. 2020, 260, 118337.