Chapter 10
Fruits and Vegetables in Cancer

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S. M. Jafari et al. (eds.), *Nutraceuticals and Cancer Signaling*, Food Bioactive Ingredients, https://doi.org/10.1007/978-3-030-74035-1_10

Abstract Cancer diseases have been widely recognized as a significant global public health problem and their incidence, morbidity and mortality are high in worldwide. There is a lot of evidence that fruit and vegetables could provide health benefits and reduce the risk of cancer. The anticancer properties of fruit and vegetables are attributed to their composition rich in phytochemicals or phytonutrients. This chapter will summarize the role of phytochemicals of fruit and vegetables namely quercetin, resveratrol, carotenoids and dietary fibers in cancer prevention. A large number of *in vivo* and *in vitro* experiments has demonstrated the beneficial effects of these compounds. These phytochemicals are also capable of increasing the effectiveness of drugs already established in treatments, reinforcing the importance of indicating the consumption of fruit and vegetables by the population.

Keywords Cancer prevention · Quercetin · Resveratrol · Carotenoids · Dietary fibers

Abbreviations

ABC transporter	ATP-binding cassette transporter
ADR	Adriamycin
AHR	Aryl hydrocarbon receptor (transcript factor)
Akt	Serine/threonine-specific protein kinase also known as protein kinase B
AMP	Adenosine mono phosphate
AMPK	Activated protein kinase
Bad gene	Inhibit the apoptosis-preventing activity of Bcl-2
Bax	BCL2 associated X, apoptosis regulator gene
Bcl-2	B-cell lymphoma 2 gene
BCRP	Breast cancer resistance protein
BET	Bromodomain extraterminal domain
CACO-2	Colon cancer cells lines
CDK	Cyclin-dependent kinases
CDK4	Cyclin-dependent kinase 4
cFLIPL	Cellular FLICE-like inhibitory protein
Chk2	Checkpoint kinase 2
cIAP-2	Cellular inhibitor of apoptosis protein 2
CK19	Citoqueratina 19
CK8/18	Cytokeratin 8/18
c-met	Tyrosine-protein kinase-met
COX-2	Cyclooxygenase-2
Cyclin D1	Regulator of cell cycle progression
DHT	Dihydrotestosterone
E-cadherin	Cell adhesion molecule
EGFR	Epidermal growth factor receptor

EGR1	Early growth response 1
ER1α	Estrogen receptor alpha (ERα)
ERK1/2	Extracellular signal-regulated protein kinases 1 and 2
FAK	Focal adhesion kinase
Fas-L/Fas	Fas ligand/first apoptosis signal (cell surface receptor induces apoptosis)
FOS	Fos proto-oncogene
FOSL1	FOS-related antigen 1 (oncogene)
Gefitinib	EGFR-specific tyrosine kinase inhibitor
HGPIN	High-grade prostatic intraepithelial neoplasia
hnRNPA1	Heterogeneous nuclear ribonucleoprotein A1
HOXA10	Homeobox A10
Hsp27	Heat shock protein 27
Hsp70	Heat shock protein 70
Hsp90	Heat shock protein 90
HUVECs	Human umbilical vein endothelial cells
ICAM-1	Cell adhesion molecule
IGF-1	Insulin-like growth factor-1
IGFBP3	Insulin-like growth factor binding protein-3
ILK	Integrin-linked kinase
ITGA5	Gene expression of integrin α5
ITGB1	Integrin β1
JAK2/STAT3	Janus kinase 2/signal transducer and activator of transcription 3 pathway
JNK	c-Jun N-terminal kinase
JUN	Proto-oncogene
MAPKs	Mitogen-activated protein kinases
Maspin	Mammary serine protease inhibitor
MCF-7/adr	Adriamycin-resistant human breast cancer cells
MDR1	Multi-drug resistance gene 1
miR-16	microRNA 16
MMP9	Matrix metalloproteinase 9
MOLT-4	Human T lymphoblast; acute lymphoblastic leukemia
MRP1	Multi-drug resistance associated protein
mTOR	Mechanistic target of rapamycin
N-cadherin	Cell surface protein related to cell adhesion
NF-κB	Factor nuclear kappa B
p53	Tumor suppressor gene protein 53
PDCD4	Programmed cell death 4
P-gp	P-glycoprotein
PLGA	Poly lactic-co-glycolic acid
PPARγ	Peroxisome proliferator-activated receptor gamma
RAR	Retinoic acid receptor
Ras/MEK/ERK	Signaling pathway involved in the proliferation of the cancer cells

RASSF-1α	Ras associated domain family-1α
RAW 264.7	Murine macrophage **cell** line
SIRT1	Sirtuin-1
Snall	EMT- inducible transcription factor
SOD	Superoxide dismutase
SRT501	Micronized resveratrol
STAT3	Signal transducer and activator of transcription 3
Survivin	Anti-apoptotic protein
TNF-α	Tumor necrosis factor alpha
Trans-RESV	Trans-resveratrol
VASP	Vasodilator-stimulated phosphoprotein
VCAM-1	Cell adhesion molecule
VEGF	Vascular endothelial growth factor
Vimentin	Characteristic mesenchymal marker of EMT (intermediate filament)
Wnt signaling pathway	Regulate cell proliferation and differentiation
α-V-β3	Integrin receptor

1 Introduction

Hippocrates, medicine father (460-377 BC) already said: "Let food be your medicine" (Arai 2005). Nowadays, several bioactive compounds from dietary sources promote potential health benefits and chronic disease prevention in addition to the nutrition function (Da Silveira et al. 2020). Therefore, the consumption of suitable foods ratifies Hippocrates prediction.

Over the last decades, cancer diseases have been widely recognized as a significant public health problem worldwide which incidence vary by age and race (Fitzmaurice et al. 2019; Force et al. 2019; Prager et al. 2018). The etiology of cancer is associated to intrinsic components (mutations in oncogenes and suppressor genes), and extrinsic causes including environment exposure and lifestyle such as smoking, diet, obesity, and physical inactivity (Islami et al. 2018; Siegel et al. 2019).

The intrinsic risk factors range to 10–30% to all cancer diseases while the extrinsic factors reach to 70–90% being potentially risk for carcinogenesis in most common cancer types (Wu et al. 2016). On the other hand, cancer is a preventable disease, which requires lifestyle changes mainly adoption of healthy dietary habits (Anand et al. 2008; Pedersen et al. 2016).

A global study analyzed the food consumption of populations in 195 countries, listing the main dietary factors that influence population health. This systematic analysis revealed that the diet is responsible for more deaths than other risks such as tobacco smoking. The non-optimal intake of whole grains, fruit and vegetables (F&V), in addition to other inappropriate eating habits was responsible for mortality

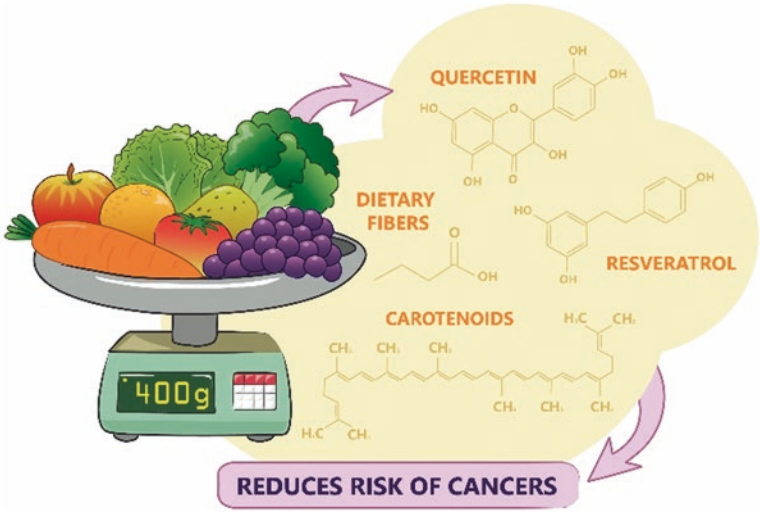

Fig. 10.1 Five servings per day of fruit and vegetables is beneficial to cancer prevention. A healthy diet for cancer prevention involves an adequate daily intake of fruit and vegetables (~400 g) to provide phytochemicals such as quercetin, resveratrol, carotenoids and dietary fibers with chemopreventive potential

by cancer across those countries (Afshin et al. 2019). Thus, the suitable diet with higher intakes of fruits and vegetables could be beneficial for cancer prevention (Stepien et al. 2016; Turner 2014).

In this way, the consumption at least five servings per day of fruit and vegetables (400 g/day) which provide a higher intake of phytonutrients and fiber (Fig. 10.1), was recommended as a healthy diet for cancer prevention (WCRF/AICR 2018). Moreover, epidemiological studies reported that a diet rich in fruits and vegetables was associated with a reduced risk of several types of cancer such as breast, prostate, colorectal, gastrointestinal, and other ones (Madigan and Karhu 2018; Ranjan et al. 2019).

It's known, that the anticancer properties of fruit and vegetables are attributed to their composition rich in phytochemicals or phytonutrients such as phenolic compounds (*e.g.,* flavonoids, stilbenes, lignans, and phenolic acids), terpenoids (*e.g.,* carotenoids), alkaloids, terpenes, organosulfur compounds and dietary fibers (De Silva and Alcorn 2019; Fraga et al. 2019; Meybodi et al. 2017; Tang et al. 2019).

Among the phytochemicals, the polyphenols are the most important bioactive compounds known as potential anticancer agents, and their biological effects depend on their bioavailability as well as biotransformation through gut microbiota (Poe 2017; Sajadimajd et al. 2020). Most of them have ability to inhibit cancer cell proliferation by cellular, molecular, and genetic levels through stimulating multiple cell-signaling pathways (Desai et al. 2018; Manayi et al. 2020).

This great deal of anticancer activity of substances derived from natural sources as dietary phytochemicals make them a potential target for use as new and more

effective strategy to minimize adverse impacts and resistance to conventional treatments or can be stablished as a complementary treatment in a safe way (Mitra and Dash 2018).

The aim of the present chapter is to review the role of phytochemicals from fruit and vegetables, namely quercetin, resveratrol, carotenoids and dietary fibers on cancer.

2 Quercetin

Quercetin (QE) is a biologically active polyphenolic flavonoid, belonging to flavanol subclass, widely distributed among fruit and vegetables such as apples, red grapes, raspberries, cherries, onions, broccoli, tomatoes, citrus fruits and green leafy vegetables (Brito et al. 2015; Hashemzaei et al. 2017). The beneficial effect of quercetin on health has been extensively studied due to perform several pharmacological effects such as antioxidant, anti-inflammatory and anticancer (David et al. 2016).

Plant quercetins are mainly found as glycosides but the aglycone also promotes biological effects (D'Andrea 2015). Intestinal β-glucosidases from gut microbiota catalyze the hydrolysis of glycosidic bonds, releasing quercetin conjugates prior to enterocytes absorption. So, the bioavailability could be affected, which could also reflect in systemic effects explaining the differences between the pharmacological activities *in vitro* and *in vivo* (Guo and Bruno 2015; Kawabata et al. 2015).

The anticancer effects of quercetin have been confirmed *in vitro* and *in vivo* assays that reveal anticancer activity against different tumors such as oral, breast, gastric, prostate and colon, among others (Kee et al. 2016; Li et al. 2019; Liu et al. 2017b; Shu et al. 2018; Srinivasan et al. 2015; Wu et al. 2019; Zeng et al. 2018; Zhao et al. 2019). It must be highlighted that quercetin may act as antioxidant promoting chemopreventive effects as well as pro-oxidant revealing chemotherapeutic effects. Indeed, it must be pointed that the anticancer effect of quercetin is exerted through multiple intracellular molecular targets (Fig. 10.2), that are involved in carcinogenesis (Neuwirthová et al. 2018).

Although there is a wide variety of quercetin preclinical trials concerning cancer disease, few reports assessing its clinical effects are available. Thereby, the steady increase in information about quercetin anticancer properties is sure to stimulate further research in humans.

2.1 Quercetin and Colorectal Cancer

The potential of flavonoids to modulate risk cancer comes from strong evidences of epidemiologic studies that recommend increasing flavonoid-rich foods consumption (Bondonno et al. 2019; He and Sun 2016). In this way, a long-follow up

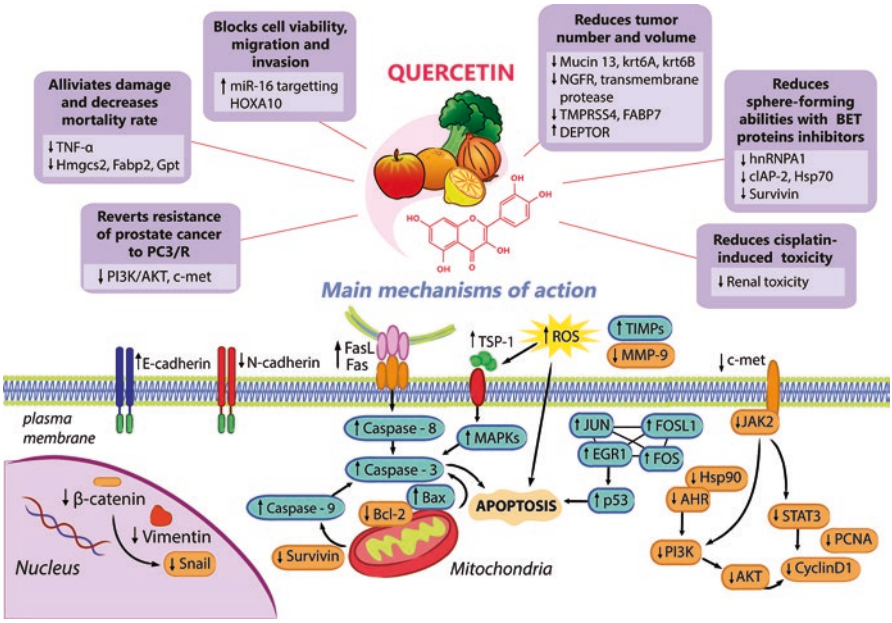

Fig. 10.2 Main molecular mechanisms triggered by quercetin to exert the anti-cancer effect. Quercetin has multiple intracellular targets in a cancer cell, triggering several cellular signals modulating carcinogenic genes and proteins. These anti-cancer effects include to promote the loss of cell viability with induction of caspases or ROS production, autophagy through MAPKs, PI3K/AKT, JAK2/STAT3 pathway or Fas activation, leading to apoptosis, and causing cell cycle arrest. Quercetin can regulate TSP-1, miR-16, matrix metalloproteinases, E-cadherin, N-cadherin, β-catenin and snail expression to reduce metastasis. The tumor growth can be delayed by modulation of PCNA, Bax, hnRNPA1, Hsp70 and Survivin expression by quercetin treatment

prospective cohort study with 56,048 participants revealed that a moderate and habitual intake of total flavonoids (~500 mg/day) and individual flavonoid subclasses including flavanols was associated with a lower risk of all-cause mortality, included cancer-related (Bondonno et al. 2019).

The colorectal cancer (CRC) is the fourth most diagnosed in the world (Lucente 2018). The quercetin protective effects in CRC were reported *in vitro*, *in vivo* and in human studies. These researches reveal that QE effects depend on the amount of quercetin dietary intake and involve mechanisms related to inflammatory pathways, inhibition of enzymes responsible for carcinogenesis as well as apoptosis induction and metastases inhibition (Bondonno et al. 2019; Djuric et al. 2012; Darband et al. 2018; Kee et al. 2016; Qi et al. 2019).

In vitro results showed QE potential to suppress colorectal metastasis (Kee et al. 2016). This flavanol inhibited the cell viability of colon 26 (CT26) and colon 38 (MC38) inducing apoptosis through mitogen-activated protein kinases (MAPKs) pathway in CT26 cells. Moreover, QE inhibited CT26 cells migration and invasion

through matrix expression metalloproteinases (MMPs) and tissue regulation inhibitor of metalloproteinases (TIMPs).

In addition, *in vivo* studies showed QE positive effects in CRC when mice were supplemented with alternated QE and β-glucan diet which alleviated colon damage and reduced the mortality rate in mice. This treatment significantly caused changes in the inflammatory pattern by decreasing TNF-α level and downregulating three kvv genes (Hmgcs2, Fabp2, and Gpt) associated to inflammation and the cancer (Qi et al. 2019).

A large case-control study included a total of 1163 cases and 1501 control participants, between 45 and 80 years, aimed to assess the QE consumption and the risk to both proximal and distal colon cancers. The authors found that the high intake of fruits rich in QE corresponded to a significant reduced risk for proximal colon cancer (Djuric et al. 2012).

In general, QE can display a wide variety of anticancer mechanisms in colon cancer, including cell cycle arrest, inhibition of cell proliferation, inflammation, angiogenesis, and metastasis as well as apoptosis and autophagy inductions which could be associated to positive results in humans' studies (Darband et al. 2018).

2.2 Quercetin and Breast Cancer

Breast cancer (BC) accounts for 30% of all new cancer diagnoses and is one of the tumors that causes more mortality in women (Siegel et al. 2019). Some observational studies have showed the association of lower incidence of breast cancer in population with a diet rich in flavonoid-rich foods (Desai et al. 2019; Hui et al. 2013).

In a meta-analysis conducted to examine the correlation between flavonoids intake and the breast cancer risk, it was verified that it significantly decreased in women with high intake of flavanols. Also, it was observed that flavanols, flavones or flavan-3-ols intake was correlated with a significant reduced risk of breast cancer in post-menopausal women (Hui et al. 2013).

Garlic and onion are consumed by Puerto Rican women which have a lower breast cancer rate compared to Europe and other countries. The combined effect of their intake was investigated in a population case-control study involving 314 breast cancer cases women and 346 controls from Puerto Rico. These vegetables were associated with a reduced risk of breast cancer, and the authors suggested that their moderate or high consumption are protective against breast cancer risk (Desai et al. 2019). These vegetables are rich in flavanols as quercetin as well as others natural compounds that could explain the referred results.

The lower risk of breast cancer with flavonoids intake could be correlated with pre-clinical experiments results which reiterate the great QE potential in breast cancer (Ezzati et al. 2020).

Triple Negative Breast Cancer (TNBC) do not express hormone receptivity or HER-2, tends to be more aggressive than others subtype of breast cancer and has a

high recurrence rates due metastatic lesions in distant sites (Watkins et al. 2019). The invasion ability is related to epithelial mesenchymal transition (EMT) that can be target of inhibition by flavonoids contributing to suppress cancer metastasis. The anti-tumor and anti-invasive ability of QE was investigated in TNBC cells *in vitro* (Srinivasan et al. 2015). QE induced the anti-tumor activity by inhibiting the migratory ability of TNBC cells as well as EMT markers modulation in a mesenchymal-to-epithelial transition. Furthermore, QE up-regulated E-cadherin and downregulated vimentin levels (Srinivasan et al. 2015).

The dose-dependent QE supplementation effects on mammary tumorigenesis were investigated in triple negative C3(1)/SV40Tag transgenic mouse model for 16 weeks to determine the optimal dose and to establish a novel mRNA expression profile (Steiner et al. 2014). This study demonstrated that the benefits in tumorigenesis capable to elicit an anti-neoplastic response can be reach with moderate doses of dietary quercetin (0.2%). The results showed tumor growth reduction (78%) and genes differential expression (31 down-regulated/9 up-regulated). The tumorigenesis reduction was mainly correlated with Mucin 13 downregulation, keratin 6A (krt6a) and keratin 6B (krt6b), nerve growth factor receptor (NGFR), transmembrane protease, serine 4 (TMPRSS4) and fatty acid binding protein-7 (FABP7) genes. In addition, the tumorigenesis reduction was also associated with DEP domain containing mTOR-interacting protein (DEPTOR) increased expression. Thus, the moderate QE treatment induced specific gene expression on mammary cells that could be responsible by anti-carcinogenic actions in breast cancer (Steiner et al. 2014).

QE associated to cisplatin can act synergistically to improve the efficacy against breast cancer cells. This effect is due to cancer growth inhibition and oxidative damage reduction, which leads to a decrease in the renal toxicity caused by cisplatin in EMT6 breast tumor-bearing mice (Liu et al. 2019b).

Additionally, QE has a great potential for use as natural compound in a complementary way or alternative treatment for breast cancer. This is confirmed by its anticancer effects that involves several anticancer mechanisms such as those described above and others including apoptosis induction, cell cycle progression inhibition, cell morphology alteration, inhibition of migration and as antiproliferative through the modulation of several metabolic pathways (Ezzati et al. 2020).

2.3 Quercetin and Prostate Cancer

Prostate cancer (PC) is a malignant disease within male population. The incidence worldwide is increasing, and the affected people can develop metastasis to bone or other organs.

QE was also assayed as prostate anticancer and successfully inhibited human prostate cancer cell xenograft tumor growth by preventing angiogenesis *in vitro* and *in vivo*. The QE treatment inhibited PC-3 and human umbilical vein endothelial

cells (HUVECs) metastasis, including proliferation, migration and invasion in a dose-dependent manner. Furthermore, QE inhibited PC-3 cell xenograft tumor growth in BALB/c mice without toxic reactions and reduced angiogenesis through TSP-1 upregulation (Yang et al. 2016).

A case-control study was developed in Western New York, involving 433 men with primary prostate cancer and 538 population-based controls correlating selected nutrients intake (including quercetin) to the risk of prostate cancer. The food frequency questionnaire analysis revealed that higher intakes of vitamin C, α- and β-carotene, lutein, lycopene, lignans, and quercetin significantly reduced PC risk. Since QE plays an important role in the antioxidant metabolism, which prevents carcinogenesis, QE intakes must be fundamental in reducing cancer risk (McCann et al. 2005).

The quercetin-doxorubicin combined treatment reversed the PC cell line resistant (PC3/R) to doxorubicin. Quercetin was able to downstream the phosphoinositide 3-kinase/protein kinase-B (PI3K/AKT) pathway, increasing the cell sensitivity to apoptosis *in vitro*, through tyrosine-protein kinase-met (c-met) downregulated expression (Shu et al. 2018).

2.4 Quercetin and Gastric Cancer

Gastric cancer (GC) remains one of the most common and deadly cancers in the world (Rawla and Barsouk 2019). Therefore, several studies were taken into account for quercetin potential in GC and several assays *in vitro*, *in vivo* and clinical trials were performed in order to establish an ideal protocol.

Human NCI-N87 gastric cancer cells were treated with QE and its DNA was isolated. Bioinformatic analysis revealed several target genes differentially expressed compared to control cells revealing four transcript factors upregulated (EGR1, FOSL1, FOS, and JUN) and one downregulated (AHR). These factors were involved with extracellular signal-regulated kinases 1/2-EGR1 pathway modulation and phosphatidylinositol-3-kinase/Akt signaling (Zeng et al. 2018).

QE inhibited cell growth and induced apoptosis, necrosis and autophagy in cancer cells (Haghi et al. 2017). In addition, *in vivo*, QE induced p53-dependent apoptosis by increasing expression of cleaved forms of caspase-3, -9 in xenograft mice models with human gastric carcinoma (Lee et al. 2016).

A study involving 505 Swedish patients, including men and women aged from 40 to 79 years, was carried out to assess the correlation between inclusion of QE in the diet and the risk of noncardia gastric adenocarcinoma. It was found that high dietary QE intake protected those from this adenocarcinoma and the effect was stronger for women exposed to oxidative stress, such as tobacco smoking (Ekström et al. 2011).

2.5 Quercetin and Oral Cancer

Oral cancer (OC) is one of the most frequent malignant diseases contributing for death and poor prognosis worldwide (Zhao et al. 2019). Since the conventional treatment for OC has several side effects, the search for new biomolecules and the use of new technology delivery system to improve the natural compounds effectiveness is fundamental. For this purpose, QE has been studied and has shown excellent results in several studies.

In OC cells from tumor tissues collected from patients, QE inhibit cell viability, cell migration as well as cell invasion by enhanced miR-16 expression. Indeed, the knockdown of miR-16 gene reversed the effect of QE on OC progression (Zhao et al. 2019). Further assays revealed that QE induced morphological cell changes and cell viability reduction (50%) in human OC cells. The last mechanisms occur by inducing apoptosis via cell surface receptor (Fas-L/Fas) and mitochondria-dependent pathways. The cell death mechanism also involves an early ROS production as well as increased levels of caspases 3, 9 and 8 in a time dependent way (Ma et al. 2018a).

QE performed a chemopreventive effect in oral squamous cell carcinoma in hamster's model. The QE treatment (12.5–50 mg/kg via oral gavage daily for 14 weeks), mainly in high doses, was able to induce tumor reduction as well as apoptosis through suppression of factor nuclear kappa-B (NF-κB) signaling and its target gene Bcl-2. Furthermore, the QE treatment induced an increase in the expression of the Bax gene. Other effects observed included significant reduction in the severity of hyperplasia, dysplasia and in the body-weight loss (Zhang et al. 2017a).

Currently, there are 15 studies listed in the ClinicalTrials.gov database (http://www.clinicaltrials.gov) that involve quercetin and cancer. The main studies include the following cancers: prostate, colorectal, pancreatic, lung, oral, renal, kidney, and lymphoma. Among these, one study characterized as phase 1 and phase 2, had a status of completed (Kooshyar et al. 2017). Since oral mucositis (OM) is one of the significant problems in chemotherapy, a protocol was designed to evaluate the quercetin role in this condition. Although the mucositis incidence was lower in the quercetin group (n = 10), further research must be recommended to support this result (Kooshyar et al. 2017).

2.6 Quercetin and Other Cancers

In vitro assays revealed the QE anticancer activity in several tumor cell lines as acute lymphoblastic leukemia MOLT-4T-cells, human myeloma U266B1 cells, human lymphoid Raji cells and ovarian cancer CHO cells, with various IC_{50} values (50–120 μM, 24 h) (Hashemzaei et al. 2017).

In human papillary thyroid cancer cells (B-CPAP) QE was able to induce cell death. The treatment resulted in cell proliferation decrease and apoptosis rate

increased by caspases-3 activation and arrested cells in S phase. These effects were triggered by Hsp90 (heat shock protein) downregulation that is involved in the decrease of chymotrypsin-like proteasome activity which causes the reduction of cell growth and induces cell death in thyroid cancer cells (Mutlu et al. 2016).

Indeed, *in vitro* and *in vivo* assays, with liver cancer cells, QE revealed tumor progression inhibition by apoptosis, metastasis, and autophagy (Wu et al. 2019). In hepatocellular carcinoma LM3 cells, both cell migration and cell invasion inhibition were associated with the regulation of N-cadherin, E-cadherin, vimentin, and matrix metalloproteinase-9 (MMP9) expression. *In vivo*, the treatment with QE affected the tumor growth significantly and showed proliferating cell nuclear antigen (PCNA) downregulation and Bax upregulation, both of them related to apoptosis induction and tumor cell proliferation (Wu et al. 2019).

As already well showed above, the anticancer effects of QE against different tumors such as colon, breast, prostate, gastric, oral, among others were confirmed *in vitro* and *in vivo* assays. There are several studies demonstrating the effect of QE treatment on cell lines, however, the corresponding effect in clinical trials in humans still is scarce.

3 Resveratrol

Resveratrol (RESV) is a polyphenol stilbene (3,5,40-trans-trihydroxystilbene) found in grapes, peanuts and berries (Xiao et al. 2019). The application of grape extracts for human health can be dated over 2000 years in Ayurvedic medicine (Paul et al. 1999). However, the benefits of RESV became famous from the observation of a reduced rate of coronary heart disease among followers of the Mediterranean diet who habitually consume red wine between meals (Renaud and Gueguen 1998). For investigate this issue, a large prospective epidemiologic study in Eastern France was carried out with 34,014 middle-aged men, showing that the moderate red wine intake was really associated with a reduced mortality rate including deaths from cancer (Renaud et al. 1998). These effects were attributed to high content of polyphenol antioxidants in red wine in which resveratrol is considered one of the main constituents. Nevertheless, one of the highest concentrations of resveratrol in nature is found at the *Polygonum cuspidatum* root, a plant used in traditional Chinese and Japanese medicine been referred as green anti-cancer drug (Guo et al. 2018).

The phytochemical RESV was isolated in 1939 and after its discovery RESV was object of several researches including its activities related to cancer chemoprevention and other applications to human health (Paul et al. 1999; Pezzuto 2019; Ramírez-Garza et al. 2018; Takaoka 1939). The anticancer potential of RESV was demonstrated on the cyclooxygenase-1 (COX-1) inhibition, human promyelocytic leukemia cell inhibition, phase II enzymes induction, preneoplastic lesions and tumorigenesis inhibition without cytotoxicity (Jang et al. 1997).

Nowadays, RESV exhibits extraordinary potential associated with life extension in addition to anticancer properties (Fig. 10.3), including anti-inflammatory (Hu

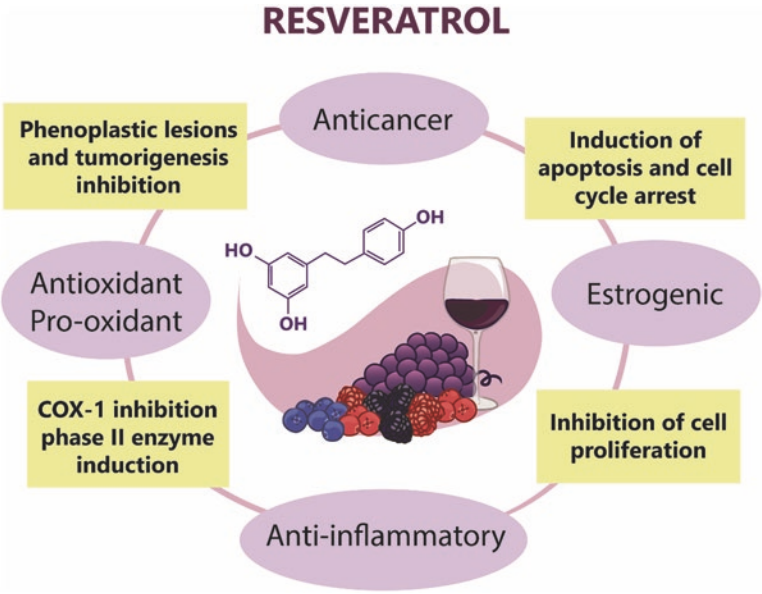

Fig. 10.3 Main biological activities of resveratrol involved on its anticancer effectiveness. The anticancer properties of resveratrol are associated with its anti-inflammatory and estrogenic attributes and it has a dual effect acting as an antioxidant or pro-oxidant in a dose-dependent manner. In antioxidant activity can decrease ROS and modulate antioxidant enzymes while in transient prooxidant effect it induces both ROS production and cytoprotective oxidative stress-activated enzyme NAD(P)H dehydrogenase expression. The anti-inflammatory properties have been demonstrated by its ability to downregulate COX-2 and prostaglandin E-2. Furthermore, resveratrol also has a dual estrogenic activity of block and activate estrogen receptors, such as α-V-β3 integrin receptor that induces pro-apoptotic genes and anti-proliferation

et al. 2010), and antioxidant activities, autophagy and apoptosis process (Sirerol et al. 2016), and others multiple intracellular pathways (Chottanapundet al. 2014; Honari et al. 2019; Liu et al. 2014; Moosavi et al. 2018; Zhou et al. 2018). Moreover, RESV has estrogenic effects which have been tested in several *in vitro* and *in vivo* carcinogenesis assays with different types of cancers (Chin et al. 2015; Hasan and Bae 2017; Martínez et al. 2014; Salehi et al. 2018; Zhao et al. 2018).

The autophagy has a dual role in cancer biology, however under stress conditions, this process can trigger the tumor cell death and therefore its regulation has significance in the treatment of cancer (Kocaturk et al. 2019). RESV can be autophagy an inducer of autophagy in different cancer cells (Andreadi et al. 2014; Russo and Russo 2018) by signaling pathways such as AMPK and SIRT1 activation and directly inhibiting the mechanistic target of rapamycin (mTOR) which contributes for reverse multidrug resistance in cancer cells (Tian et al. 2019).

Informationon the chemotherapeutic effect of RESV in humans is increasing due to the large number of anti-cancer activities demonstrated in preclinical evidences.

Thus, epidemiologic and clinical trials have been carried out in different cancer types to show additional evidence of resveratrol. Here we highlighted the main outcomes of resveratrol in different levels of evidence as well as its synergic, adverse, and controversial effects in some cancers.

3.1 Resveratrol and Colorectal Cancer

Regarding the anticancer properties of resveratrol on gastrointestinal system, there are promising results on the prevention of CRC. A study with colon cancer cell lines (CACO-2) revealed cells susceptibility to RESV, which in a dose-dependent manner increased apoptosis-promoting effects predominantly through cell cycle arrest by caspase-dependent and cyclin-CDK pathways (Liu et al. 2014). A phase I study in patients with CRC and hepatic metastases, analyzed the micronized RESV (SRT501) effects in hepatic tissue after after administration of 5.0 g daily, for 14 days. This concentration induced an increase in cleaved caspase 3 (Howells et al. 2011).

Wnt signaling pathway is associated with colon cancer initiation. The RESV-containing freeze-dried grape powder (GP) effects were studied through the administration of GP (80 g/day containing 0.07 mg of resveratrol) for a fortnight. The results showed that Wnt target gene expression was inhibited only in the normal colonic mucosa, with no effects on cancerous mucosa. The authors suggest that resveratrol may act preventing colon cancer through the inhibition of the Wnt pathway (Nguyen et al. 2009). Indeed, Patel et al. (2010) studied 20 patients with CRC treated with RESV (eight daily doses of resveratrol at 0.5 or 1.0 g before surgical resection). The RESV consumption reduced tumor cell proliferation suggesting anticarcinogenic effects.

As previously cited, RESV presents antioxidant and anti-inflammatory properties. In a study using CRC Apc^{Min} mice, low RESV dose reduced tumor growth. This corresponded to ROS *in vitro* increase detected in patients' samples with resectable CRC who received RESV capsules (5 mg or 1.0 g for 6 days). In this condition, RESV-prooxidant activity was related with its anticancer efficacy. In addition, low RESV dose supplementation increased the expression of cytoprotective oxidative stress-activated enzyme NAD(P)H dehydrogenase, quinone 1 (NQO1) regulated by Nrf-2 in human CRC cells (Cai et al. 2015).

As a matter of fact, in response to intestinal mucosa stress, there was an increase in adenosine mono phosphate activated protein kinase (AMPK) expression followed by autophagy which may contribute for tumor-suppressing mechanism. Thus, it was highlighted that a low RESV dose promoted anticancer effect mediated by transient prooxidant activity and autophagy induction (Cai et al. 2015).

Indeed, remembering the inflammatory process reported in intestinal cancers, RESV also revealed an anti-inflammatory effect in CACO-2 cells by downregulation of both COX-2 and prostaglandin E-2 (PGE-2) associated to NF-kB inhibition (Cianciulli et al. 2012) as well as COX-2 mRNA expression reduction due to superoxide and peroxide suppression in human CRC cells (Gong et al. 2017).

3.2 *Resveratrol and Breast Cancer*

Breast cancer has been intensively studied and there are some evidences that RESV might be an important ally in the treatment.

RESV can act as a phytoestrogen once it is capable of blocking and activate estrogen receptors (ER) and due to this reason, it is considered as potential anti-cancer adjuvant (BHAT et al. 2001). On the other hand, it is known that dihydrotestosterone (DHT) is a strong promoter of the breast cancer for binding in ER. Interestingly, the receptor for DHT also exists on α-V-β3 integrin receptor that also binds to RESV, inducing pro-apoptotic genes and anti-proliferation (Chin et al. 2015). Although both RESV and DHT signals are transduced by ERK1/2, the responses are different. Chin et al. (2015) studied the effects of both RESV and DHT in ER-α-positive and negative breast cancer cells. In both types of cells, RESV bound to integrin α-V-β3, promoting nuclear accumulation of COX-2 and p53-dependent action, inducing anti-proliferation. This inhibition of apoptosis by DHT in RESV-treated cells was showed to be due to the binding of DHT to the integrin receptor on the cell surface for the hormone. This fact promoted suppression of the nuclear interaction of COX-2 protein and activated ERK1/2, which are related with decrease in inflammatory molecules as well as is essential to the pro-apoptotic action of RESV.

Recently, the resistance to chemotherapy on the breast cancer treatment became an issue on the therapy effectiveness. To overcome this situation, many studies were developed with RESV in combination with other chemotherapeutic agents or drug-delivery systems to decrease resistance to treatment, improve its metabolization and bioavailability as well as to reduce the related side effects in anticancer therapy (Castillo-Pichardo and Dharmawardhane 2012; Kim et al. 2014a; Lee et al. 2019a, Redondo-Blanco et al. 2017; Sheu et al. 2015; Zhao et al. 2016).

RESV also showed promisors results on the reduction of multidrug resistance when co-encapsulated with paclitaxel (Meng et al. 2016). Furthermore, this interesting molecule plays a role in the sensibilization to gefitinib (an epidermal growth factor receptor specific tyrosine kinase inhibitor), reduce metastasis as well as tumor burden (Castillo-Pichardo and Dharmawardhane 2012). In addition, new drug-delivery systems increased the efficacy and delivery rate of RESV in human breast cancer (MCF-7) cell line when conjugated with gold nanoparticles (Lee et al. 2019a).

The treatment with both RESV and doxorubicin (DOX) combined notably increased the cellular accumulation of DOX. This action occurred due the down-regulation of the expression levels of ABC transporter genes, MDR1, and MRP1 and due the inhibition of drug-resistant in human breast cancer (MCF-7/adr) and MDA-MB-231 mice cell line. Thus, RESV was able to enhance the DOX-induced cytotoxicity (Kim et al. 2014a). Indeed, another study suggested the co-encapsulation of both RESV and DOX in a modified PLGA nanoparticle (NPS) to overcome the DOX-resistance *in vitro* and *in vivo* (Zhao et al. 2016). The complex DOX-RESV-NPS could overcome DOX resistance by inhibiting the expression of P-gp,

MRP-1 and BCRP, and induce apoptosis through down-regulating the expression of NF-κB and BCL-2. In tumor-bearing mice, the complex DOX-RES-NPS mainly delivered DOX and RES to tumor tissue. Compared with free DOX, the complex DOX-RESV-NPS inhibited the DOX-resistant tumor growth in mice, do not presenting expressive systemic toxicity.

In cancer chemotherapy, RESV reduced the intracellular ROS level and increased the SOD level in a co-treatment with doxorubicin in breast cancer cells demonstrating its efficacy in decrease the cardiotoxicity in doxorubicin-mediated chemotherapy (Sheu et al. 2015).

A case-control study carried out on 369 cases vs. 602 controls of Swiss women with follow up for 10 years demonstrated that dietary intake of RESV from grapes is inversely related to the risk of breast cancer (Levi et al. 2005). At the treatment with trans-RESV (5 or 50 mg twice a day for 12 weeks), 39 adult women with increased breast cancer risk presented a decrease in the fraction of methylated RASSF-1α DNA, a tumor suppressor gene associated with breast cancer. Furthermore, it was observed an increased level of trans-RESV in the circulation and a decreased (Zhu et al. 2012).

3.3 Resveratrol and Prostate Cancer

Regarding prostate carcinoma (PC), RESV inhibits cell proliferation and induces apoptosis of human (PC) DU-145 cell lines (Agarwal et al. 2000). This effect occurs due the induction of cell cycle arrest in PC3 and DU145 androgen-insensitive cells (Lin et al. 2002; Sgambato et al. 2001). MicroRNA-21 levels (miR-21) are frequently elevated in PC contributing for the invasiveness. Thus, the strategy to inhibit miR-21 by gene therapy could be useful on cancer treatment (Zennami et al. 2019). *In vitro*, RESV revealed miR-21 expression decrease in PC-3 M-MM2 cells and increased expression of PDCD4 and Maspin genes, which are negatively regulated by miR-21 (Sheth et al. 2012). The *in vitro* results were corroborated by *in vivo* model of PC since RESV reduced PC growth and metastasis. The authors pointed in evidence that the Akt/miR-21 pathway is responsible for anticancer actions of resveratrol in prostate cancer (Sheth et al. 2012).

In a phase I clinical study, 35 μg of resveratrol contained in 4000 mg of pulverized muscadine grape extract was daily administrated in patients with prostate cancer and delayed the recurrence by prolonging the prostate specific antigen doubling time by 5.3 months (Paller et al. 2015). RESV has also been shown to be effective in improving chemotherapy in prostate cancer cells. The association between docetaxel (DTX) and RESV induced upregulation on pro-apoptotic genes and downregulation on anti-apoptotic genes (Singh et al. 2017).

3.4 Resveratrol and Other Cancers

RESV has demonstrated its effectiveness also in lung cancer. Several studies have been performed to evaluate its effect and mechanism. The main findings are related to the induction of apoptosis (Thomas et al. 2016; Whyte et al. 2007; Zhang et al. 2015a, b), increasing in cell cycle arrest (Han et al. 2012; Whyte et al. 2007; Zhao et al. 2009), and reduction of tumor cells proliferation (Han et al. 2012; Thomas et al. 2016; Wu et al. 2010; Zhao et al. 2009). The mechanisms involved on the findings include mainly the induction of caspase-3 and caspase-9 (Lucas and Kolodziej 2015; Yousef et al. 2017; Zhao et al. 2009; Zhang et al. 2015a) and upregulation of p53 expression (Luo et al. 2013; Whyte et al. 2007; Yuan et al. 2015). The reduction of tumor cells was also verified *in vivo* studies (Savio et al. 2016; Wu et al. 2010; Zhao et al. 2009). Furthermore, the action against lung metastatic cancer may be maybe related to its anti-angiogenic activity (Savio et al. 2016) as well as the ability of reduce tumor suppressor genes levels (miR-21 and elevated PDCD4) as occurs in prostate cancer (Sheth et al. 2012).

A study with oral squamous cancer cell lines revealed a dose-dependent action of RESV on both inhibition of cell proliferation and cell cycle arrest in the G2/M phase. Furthermore, REVS induced an increase in phospho-CDC2 and cyclins A2 and B1 expression by oral squamous cell carcinoma (Yu et al. 2016). *In vitro* studies using human esophageal cancer cell line TE-1 demonstrated that high concentrations of RESV inhibited cell growth (Dun et al. 2015). In addition, the anti-angiogenic effects of RESV were evidenciated when it was used in combined treatment with 5-fluorouracil (5-FU) on B16 murine melanoma tumors models. The co-treatment induced downregulation of COX-2, VEGF and VASP levels while occurred an upregulation of AMPK. *In vivo*, this effects resulted in an antiproliferative activity. On the other hand, *in vivo* occurred a reduction in microvessel density, angiogenesis inhibition and consequently reduction in tumor size (Lee et al. 2015).

The dietary pattern rich in RESV and other phytochemicals was associated with the low risk of esophageal cancer development in a case–control study. In this investigation, 181 cases of esophageal adenocarcinoma, 158 cases of esophageal squamous-cell carcinoma, 255 cases of gastro-esophageal junctional adenocarcinoma and 806 controls were enrolled. The results demonstrated that RESV may act synergistically with dietary phytochemicals in prevention of all types of esophageal cancer evaluated (Lin et al. 2014). These results emphasize the idea that natural dietary agents are good options on ~~the~~ cancer prevention.

The effects of RESV and the mechanisms involved in pancreatic and ovarian cancer are similar to the others *in vitro* and *in vivo* models discussed above. The pretreatment with resveratrol showed an antineoplastic effect on ovarian cancer cells with tumor growth suppression after the treatment with cisplatin, suggesting a prolonged disease-free survival (Tan et al. 2016). A synthetic analog of resveratrol, DHS (Trans-4,4′-Dihydroxystilbene), enhances the sensitivity of pancreatic and ovarian cancer cells to chemotherapeutic agents *in vitro*. This action occurs via inhibition of ribonucleotide reductase regulatory subunit M2 (RRM2), a potent inhibitor

of DNA replication. In murine models of tumor xenografts, DHS was efficient against pancreatic, ovarian, and colorectal cancer cells (Cheng et al. 2018). In addition, a study on pancreatic cancer demonstrated the effect of resveratrol *in vitro* and *in vivo* on the downregulation of NF-kB and NF-kB dependent gene expression and suppression of proliferation, metastasis and angiogenesis markers (Harikumar et al. 2010).

4 Carotenoids

Carotenoids represent a diverse group of phytochemicals tetraterpenoids that include pigments such as lycopene, β-carotene, α-carotene, lutein, zeaxanthin, and cryptoxanthin (Rowles and Erdman 2020). In plants, these pigments contribute to the visible colors and vary in range from light yellow through orange to red (Krinsky and Johnson 2005). Fruit and vegetables are the primary sources of carotenoids, in which its concentration vary widely (Khoo et al. 2011). In human diet, they are primarily derived from crop plants, in edible leaves, flowers, and fruits such as banana, acerola, apple, mango, orange, tomato and papaya (Cardoso et al. 2017; Lemmens et al. 2014; Namitha and Negi 2010). In vegetables, they are found in carrots, pumpkins as well as spinach, broccoli, and green leafy vegetables (Namitha and Negi 2010).

Epidemiological studies showed a correlation between carotenoids rich diet and preventive actions such as low incidence of specific types of cancer, improved efficiency of treatment and decreased aggressiveness (Abar et al. 2016; Baglietto et al. 2011; Boggs et al. 2010; Chen et al. 2001, 2013; De et al. 2004; Giovannucci 2002; Kim et al. 2018; Liu et al. 2003; Rowles et al. 2017, 2018). The main mechanisms by which carotenoids are involved in anti-cancer action are associated with processes of cell growth and death as well as that related to the antioxidant effect (Liu et al. 2003; Namitha and Negi 2010; Niranjana et al. 2015; Rowles and Erdman 2020).

Studies *in vitro* and *in vivo* have reported several biological properties from carotenoids, among them chemopreventive in a wide range of cancer types (Fig. 10.4) (Milani et al. 2017; Saini and Keum 2018). Lycopene shows potential to interfere in the process of carcinogenesis in different cancer types such as (Rowles et al. 2017; Wang et al. 2015), breast (Aune et al. 2012), oral cavity (Leoncini et al. 2016), pharynx (Kubo and Corley 2007), digestive tract (Yang et al. 2013), and lung (Abar et al. 2016; Gallicchio et al. 2008). β-Carotene showed biological activities against several cancer types such as leukaemia (Upadhyaya et al. 2007), colon cancer (Palozza et al. 2002), gastric cancer (Jang et al. 2009), adenocarcinoma (Palozza et al. 2001), neuroblastoma (Kim et al. 2014b), hepatocarcinoma (Chen et al. 2012, 2013), skin tumours (Mathews-Roth 1982) and prostate cancer (Chen et al. 2012; Soares et al. 2013; Wan et al. 2014). α-Carotene was associated to hepatocarcinoma (Chen et al. 2013). In addition, lutein, zeaxanthin, and cryptoxanthin were also associated with low skin cancer incidence (Heinen et al. 2007; Juin et al. 2018; Logozzi et al. 2019).

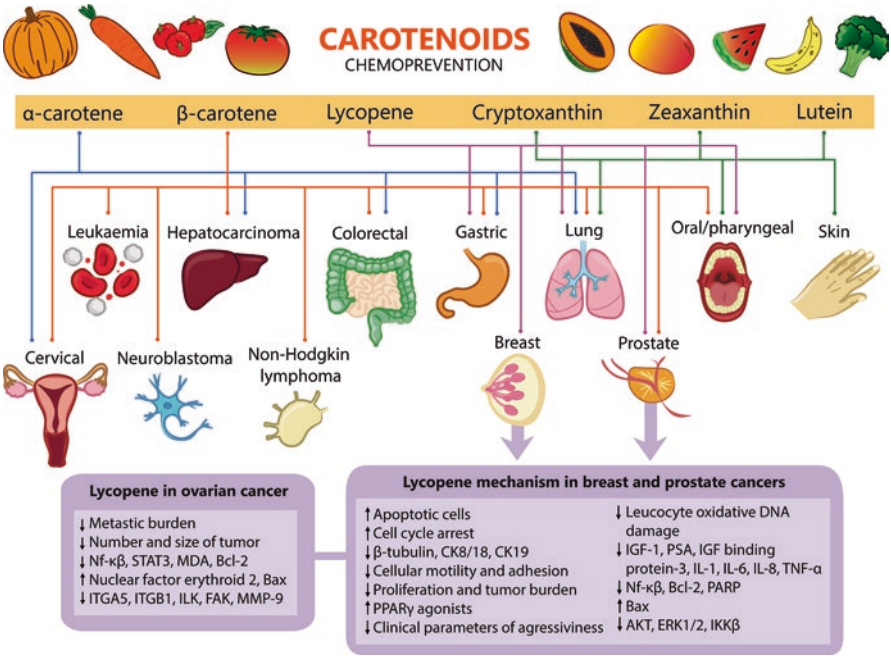

Fig. 10.4 Carotenoids as chemopreventive against cancer and action mechanisms of lycopene in breast, prostate and ovarian cancer. Different carotenoids are involved in the prevention of various types of cancer. Lycopene (Lyc) presents anti-inflammatory effect by reduction of cytokines (IL-1, IL-6, IL-8, TNF-α), by modulating NF-κB signaling pathway, anti-proliferative effect (PPARγ, b-tubulin, CK8/18, CK19), modulates biomarkers of growth and differentiation (IGF-1, IGF-3) and promotes arrest cell cycle. Moreover, reduces oxidative stress (DNA damage) and PSA levels, inhibits motility and cell adhesion leading a reduced metastasis and induction of apoptosis (Bcl-2, PARP, Bax), reducing tumor burden and cancer aggressiveness in breast, ovarian and prostate

Contrarily, there is a great variation in the action of these substances in different types of cancer and many researches present inconclusive or controversial results (Botterweck et al. 2000; Lai et al. 2014; Petimar et al. 2017; Takachi et al. 2010; Umesawa et al. 2014;). This section will focus on studies that show an association between the consumption of carotenoids and their anti-cancer effect, in particular lycopene, which is the most studied carotenoid, but it also includes studies with β-carotene, α-carotene, zeaxanthin, lutein and cryptoxanthin.

4.1 Lycopene and Prostate Cancer

Prostate cancer is one of the most common cancers in men and it is considered a global public health problem. Clinical and epidemiological studies indicate that diet plays a key essential in prevention and development of prostate cancer (Gathirua-Mwangi and Zhang 2014; Mokbel et al. 2019).

A clinical trial that involved prostate carcinoma patients (32 men) which received tomato sauce (30 mg lycopene/day) for 3 weeks before prostatectomy showed that its consumption increased apoptotic cells in benign prostatic hyperplasia (BPH) and in carcinomas (Kim et al. 2003). In first time, in carcinomas the results showed that tomato sauce consumption did not alter Bcl-2 expression and reduced Bax expression. However, in subsequently experiment with prostate carcinoma biopsies was verified the overexpression of genes related to apoptosis (Bcl-2 and Bax), when compared to controls cells (Kim et al. 2003).

These findings were corroborated by *in vitro* studies with lycopene modulating the transcriptional expression levels of Bax and Bcl-2 and this up-regulated process was correlated with the apoptotic effect in cancer cells but no in BPH cells (Soares et al. 2013, 2017). *In vitro*, lycopene induced inhibitory effect on primary prostate epithelial cell (PEC) (Barber et al. 2006). In addition, lycopene reduced the numbers of cells in G0/G1 phase and raised in S and G2/M phases in metastatic prostate cancer cell lineages and promoted cell cycle arrest in G0/G1 phase in a primary cancer cell line (Soares et al. 2013).

In vitro, lycopene presents several properties as reduction of cellular motility and promotes the blocking of cancer cell adhesion (Elgass et al. 2014), reduction of inflammatory cytokines levels, including interleukin-1 (IL-1), IL-6, IL-8, and tumor necrosis factor-alpha (TNF-α) (Jiang et al. 2019). Indeed, lycopene decreased proliferation on prostate cancer (PC-3) cells, alteration of growth and apoptosis associated to biomarkers expression (Rafi et al. 2013). It is worth mentioning that in prostate cancer lycopene reduced the tumor burden (Jiang et al. 2019), and increased the anti-proliferative effect of peroxisome proliferator-activated receptor gamma (PPARγ) agonists, however, neither Doxorubicin or Taxol, were able to do so (Rafi et al. 2013).

Several clinical trials were performed to evaluate the effect of lycopene supplementation on prostate cancer. Lycopene supplementation (30 mg/day), either in the form of tomato sauce or oleoresin tablets, for a short period before radical prostatectomy (36 men) increased lycopene concentrations in prostate tissue and modulated biomarkers of growth and differentiation (insulin-like growth factor-1) (IGF-1), IGF binding protein-3, prostate-specific antigen (PSA)), and decreased clinical parameters of cancer prostate aggressiveness (Kucuk et al. 2001). Analogously, the intervention with tomato sauce based pasta dishes for 3 weeks (30 mg of lycopene per day) on patients with localized prostate adenocarcinoma (32 men) increased serum and prostate lycopene levels and reduced leukocyte oxidative DNA damage, and serum PSA levels (Chen et al. 2001). Confirming previous findings, another pilot phase II clinical study with lycopene dietary supplementation (10 mg/day) reduced cancer prostate progression (Cap) (Barber et al. 2006). In a double-blind crossover study, 30 healthy adults daily consumed 160 g of a high-lycopene tomato sauce which evidenced the putative role of lycopene in the prevention of oxidative stress related diseases (Abete et al. 2013). Thus, there are sufficient evidences that lycopene in diet is inversely associated with risk of prostate cancer and draws attention for potentially prevent cancer.

On the other hand, some studies do not support these evidences. In a multicenter study the association between intake of lycopene and specific tomato products and prostate cancer risk (29,361 men) in a follow-up of 4.2 years with 1338 cases of CaP identified, the reduced risks were not found (Kirsh et al. 2006). In a double-blind, randomized, placebo-controlled trial of 105 African American men veterans, no significant changes in the 8-oxodeoxyguanosine or the lipid peroxidation product malondialdehyde were observed in prostate tissue or plasma, respectively, as a result of 30 mg/day lycopene as a tomato oleoresin supplementation (Van Breemen et al. 2011).

In another phase II randomized, double-blind, placebo-controlled trial carried out in Chicago, the participants consumed lycopene (30 mg/day) for 6 months, but no effect were detected on serum PSA, IGF-1, or IGFBP3 concentrations, neither any effect on proliferation or cell cycle inhibition in benign tissue of men with high grade prostatic intraepithelial neoplasia (HGPIN) was observed (Gann et al. 2015). However, lycopene supplementation increases its levels in serum and prostate tissue (Van Breemen et al. 2011), increases atrophy and decreases in extensive HGPIN (Gann et al. 2015).

Other randomized trials revealed a decreases in prostate cancer risk (Peisch et al. 2017; Perez-Cornago et al. 2017), even if other studies did not demonstrate strong associations between prostate cancer risk and dietary factors (Lane et al. 2017).

4.2 Lycopene and Breast Cancer

Among women, the breast tumour is the most common type. Several factors are related to the risk of developing breast cancer, including diet (Hauner and Hauner 2010; Sauter 2018). In a systematic review, the results suggest that the dietary patterns that include vegetables may reduce breast cancer risk (Dandamudi et al. 2018). Studies indicate that lycopene presents anticancer properties that could be associated to reduced breast cancer risk (Sesso et al. 2005; Yan et al. 2016).

Regarding breast cancer, it has been proposed that carotenoids play a similar role to prostate cancer, such as decrease of the anti-apoptotic protein, Bcl-2, poly ADP-ribose polymerase (PARP), pro-inflammatory and survival protein NF-kB expressions, and activation of the growth signaling proteins, Akt and ERK1/2, where some of them show a clear association with clinical studies (Aune et al. 2012; Rowles and Erdman 2020).

On human breast cancer cells lycopene inhibited cell proliferation through the modulation of cell cycle proteins such as beta tubulin, CK8/18, CK19 (Uppala et al. 2013), arrested cell cycle that can be related to cellular type, time and dose-dependent (Teodoro et al. 2012). Lycopene inhibited the activity of IκB kinase β (IKKβ) (Assar et al. 2016) that consequently modulated the NF-κB signaling pathway and then promoted suppression of TNF-α, a proinflammatory cytokine (Assar et al. 2016), presenting anti-inflammatory effect.

The results of a pilot case-control study performed in Chicago among African, American, and Caucasian women suggest that the plasma lycopene level may be associated with the reduction of reduction of breast cancer risk (Simon et al. 2000). On the other hand, in a prospective cohort study conducted with 39,876 women, the reduced risks to breast cancer development were not found with high dietary lycopene or plasma lycopene levels (Sesso et al. 2005).

4.3 Lycopene and Ovarian Cancer

Ovarian cancer (OvCa) is a leading cause of death among women worldwide. It has been suggested that one of the mechanisms for preventing ovarian cancer is the reduction of oxidative stress. Among carotenoids, lycopene is a well-known natural antioxidant with anti-cancer properties. Considering that fruit and vegetables are a main source of carotenoids, studies were carried out to characterize and analyze dietary patterns in relation to OvCa risk.

The human studies with carotenoids still remain controversy although preclinical studies have been showed promissor findings. A clinical study investigated the plasma carotenoids levels related to ovarian cancer risk in Korean women. The results showed that among antioxidants levels, lycopene was capable to reduce 90% the OvCa risk in the Korean population (Jeong et al. 2009). However, a meta-analysis that included 678,892 subjects and 6127 cases displayed an insignificant inverse association between dietary lycopene consumption and ovarian cancer risk (OR, 0.963; 95% CI, 0.859–1.080) and although the findings are not significantly the authors suggested the importance of lycopene in the diet for OvCa prevention between postmenopausal women (Li and Xu 2014).

In OvCa intraperitoneal animal model the lycopene acted in the mechanisms involved in the development and progression of the tumor. When combined with paclitaxel and carboplatin, it reduced the tumour and metastatic burden of OvCa in vivo. This study shows the relevance of lycopene in the prevention and treatment of OvCa (Holzapfel et al. 2017). The lycopene supplementation reduced ovarian tumour incidence, as well as the number and the size of the tumours in Laying Hens. In this case, lycopene reduced NF-κB expression, increased nuclear factor erythroid 2 expressions, decreased STAT3 expression, which characterize anti-inflammatory mechanisms, and decreased serum malondialdehyde levels, which shows antioxidant effect (Sahin et al. 2018). *In vitro* lycopene inhibits the proliferation of ovarian cancer cells and enhances their apoptosis possibly mediated by up-regulating Bax expression and down-regulating Bcl-2 expression (Xu et al. 2019).

Recently, Zhang et al. (2017b) reported an important study using lycopene nanoparticles associated with low dose of trichostatin A, a chemotherapy agent, and showed positive results against human ovarian cancer cells (SKOV3). The authors showed that their combinatory effects caused excellent cytotoxicity and induced greater apoptosis in SKOV3 cells through regulation of various mechanisms. They

suggested that it could be an alternative in cancers that cannot be submitted to radiation therapy or surgical treatment.

4.4 Other Carotenoids and Cancers

Although *in vivo* and *in vitro* studies suggest differential mechanisms of carotenoid action to protect against prostate cancer (Rafi et al. 2013; Soares et al. 2013; Wan et al. 2014), epidemiological studies are still confusing and controversial. According to Petimar et al. (2017) there is no association between total tomato consumption and reduced risk of prostate cancer. On the other hand, results of a meta-analysis study estimate a 9% reduction in the risk of prostate cancer for every 10 g of cooked tomato/week, due to the combination of lycopene with other carotenoids and their bioavailability through the cooking process (Rowles et al. 2017). In another meta-analysis study, consumption of α-carotene, but not β-carotene, reduced the risk of prostate cancer by 13% and the dose-response association decreased by 2% for each 0.2 mg of α-carotene consumed (Wang et al. 2015). In addition, a correlation was observed between high concentrations of β-carotene serum and low risk of prostate cancer (Karppi et al. 2012).

The relationship between high rates of α-carotene and β-carotene serum demonstrated an inverse association with the risk of cervical cancer in women (Guo et al. 2015). In addition, a review study showed a similar association between 1 mg β-carotene consumption (1000 Kcal dietary) and lower risk (12%) of endotmetrial cancer (Okuyama et al. 2014) and a decrease 16% the ovarian cancer risk with higher consumption of β-carotene (Huncharek et al. 2001).

Diets rich in β-carotene have been associated with a 5% reduction in the rate of breast cancer for every additional 5 mg consumed. Also, blood α-carotene and lutein levels were associated with a decrease in breast cancer (Aune et al. 2012). Another study revealed that plasma α-carotene level seems to be related to a lower rate of invasive breast cancer in the post-menopausal period. Hence, it was associated with a 37% decreased risk of invasive estrogen receptor-positive breast cancer (Wang et al. 2015). Besides, high levels of β-carotene could be involved in reduced risk of breast cancer in women while high levels can also reduce the breast cancer risk (Eliassen et al. 2012). In vitro, the treatment with β-carotene inhibited cell proliferation, arrests cell cycle, and increased apoptosis in human breast cell lines (Gloria et al. 2014).

A higher intake or serum concentrations of total carotenoids (lycopene, β-cryptoxanthin, α and β -carotene, and lutein/zeaxanthin) were strongest associated with a significant decrease in lung cancer risk than individual carotenoids (Gallicchio et al. 2008). It was observed through a meta-analysis study an increase in blood concentrations of lycopene (10 μg/100 mL), β-carotene (20 μg/100 mL), α-carotene (5 μg/100 mL) related to a decreasing in relative risk for lung cancer. Indeed, lower blood concentrations of β-cryptoxanthin (5 μg/100 mL) showed association with lung cancer risk in a non-linear relationship (Abar et al. 2016). In fact,

some animal studies show that β-cryptoxanthin, zeaxanthin and lycopene appear to prevent various types of cancer through NF-κB, RAR/PPARs, RAR/PPARs, SIRT1 signaling pathways and p53 tumor suppressor pathways mediated by their oxidative metabolites (Lim and Wang 2020).

The consumption of β-carotene can decrease the risk of lung cancer by 2% for each extra mg consumed per day and 1% for each 10 μg of β-cryptoxanthin consumed per day as well as 3% for additional consumption of lycopene(mg) per day (Abar et al. 2016; Gallicchio et al. 2008). These data are intriguing because this association only occurred with smokers. On the other hand, supplementation with high doses of β-carotene (about 10–20 times higher than normal dose) increases the risk of lung cancer in smokers and people exposure to asbestos (Goodman et al. 2004; Omenn et al. 1996; Virtamo et al. 2000). In addition, β-carotene in similar doses, can function as a pro-oxidant and/or co-carcinogenic substance (Rowles and Erdman 2020). High levels of β-carotene activate cytochrome P450 enzymes leading to increased activation of tobacco smoke pre-carcinogens and the formation of alternate, harmful, β-carotene and retinol metabolites (Goralczyk 2009). Indeed, it is accepted that while β-carotene and retinol are protective at physiologic doses and derived from fruit and vegetables consumption, high-dose supplementation is harmful particularly in the context of cigarette smoke exposure (Hada et al. 2019).

The carotenoids also showed chemopreventive effects in colorectal cancer. *In vitro* β-carotene had a positive effect against human adenocarcinoma colon cancer cells (Niranjana et al. 2015). In human studies, serum carotenoids including lutein, zeaxanthin, alfa-carotene, β-carotene was inversely associated with a reduced risk of colorectal cancer among Japanese women (Okuyama et al. 2014). Subsequently, in a case-control study performed with Korean population, a high dietary lutein and zeaxanthin intake reduced significantly the colorectal cancer risk (Kim et al. 2019). The possible protective role of xanthophylls especially lutein against carcinogenesis includes the selective modulation of apoptosis, inhibition of cellular differentiation and effects on angiogenesis as well as anti-oxidative activity decreasing reactive oxygen species (ROS) and consequently oxidative stress (Madaan et al. 2017; Ribaya-Mercado and Blumberg 2004).

In general, the consumption of two or more carotenoids associated such as α-carotene, β-carotene, β-cryptoxanthin, zeaxanthin, lutein, lycopene and food rich carotenoids are also involved with a reduced risk of head and neck cancer, oral and pharyngeal cancer, non-Hodgkin lymphoma, skin cancer and gastric cancer (De et al. 2004; Heinen et al. 2007; Kim et al. 2018; Kubo and Corley 2007; Larsson et al. 2007; Leoncini et al. 2015; Lissowska et al. 2004; Pelucchi et al. 2008; Ward et al. 2019). It is known that the consumption of phytochemicals triggers multiple mechanisms, and the phytochemical combinations may have synergistic effects. Additionally, cancer treatments combined with a diet rich in carotenoids may potentiate their anticancer effects and improve prognosis. One study suggests that the combined therapy of 5-FU and β-carotene exerted antitumor effects in vivo and in vitro, in a synergistic way and could mean an innovative therapeutic treatment for ESCC (Zhang et al. 2016). Thus, further research is needed to confirm the applicability of this suggestion.

5 Dietary Fibers

Although the role of dietary fibers (DFs) had been studied a long time ago, regarding their health benefits, only in the last few years, the action mechanisms of DFs have been related to the prevention of different types of cancer (Carlson et al. 2018; Chen et al. 2016b; Conti et al. 2018; de Silva and Alcorn 2019; Encarnação et al. 2018; Grosso et al. 2017; Moen et al. 2016; Navarro et al. 2016; Tajaddini et al. 2015; Trefflich et al. 2020; Xu et al. 2018).

DFs comprises nondigestible carbohydrates, including polysaccharides, oligosaccharides, resistant starch (RS), and noncarbohydrate residues, such as polyphenols, classified according their structure and solubility (Dai and Chau 2017; Slavin 2013). Considering water solubility, dietary fibers can be classified as soluble dietary fiber (SDF) including pectin, inulin, gum, mucilage and insoluble dietary fiber (IDF) that consists mainly of cellulose, hemicellulose, and lignin (Dhingra et al. 2012). DFs from fruits and vegetables have a considerably proportion of SDF which is highly fermented by the human microbiota (Moen et al. 2016).

Lignans comprise a vast group of non-flavonoid polyphenols widespread in plant kingdom (Das and Devi 2019). They share chemical characteristics with some IDFs, such as lignins, but are not classified as dietary fiber, being often found in association with them (Peterson et al. 2010).

Secoisolariciresinol diglycoside (SDG) is one of the most abundant dietary lignans found in flaxseed (Touré and Xueming 2010). When ingested, SDG undergoes hydrolysis to form the aglycone, secoisolariciresinol (SECO) (Adolphe et al. 2010). It has biological activities such as antioxidant and anticancer effect (Alphonse and Aluko 2015). Pinoresinol (PINO) is a high-value plant-derived lignan that can be found in rich concentration in olive oil, with reported antifungal, anti-inflammatory, antioxidant and hypoglycemic activities (López-Biedma et al. 2016). Matairesinol (MAT) is a dibenzyl-butyrolactone lignan found in seeds, vegetables and fruits. It has biological activities such as anti-angiogenic and anti-cancer (Choi et al. 2014; Yamawaki et al. 2011). Lariciresinol (LAR) is a tetrahydrofuran lignan present in Açai Brazilian berry fruits (*Euterpe Oleracea*) and cashew nuts (Chin et al. 2008; Rodríguez-García et al. 2019).

Sesamin is a lignan isolated from sesame seed oil that wields several biological properties, including antitumor activities (Akl et al. 2013; Kong et al. 2014). Another constituent of sesame oil with biological importance is sesamol, a water-soluble lignan with antioxidant, antimutagenic, anti-hepatotoxic, anti-inflammatory, anti-aging and chemopreventive properties (Majdalawieh and Mansour 2019).

Plant lignans and their glycosides are metabolized by gut microbiota to produce different substances that exhibit several biological properties, including anti-inflammatory, antioxidant, estrogenic and anticancer activities (Fig. 10.5), (Kiyama 2016). They are known as enterolignans or mammalian lignans, namely enterolactone (ENL) and enterodiol (END). Several *in vivo* and *in vitro* studies have provided strong evidence that ENL exhibits potent anti-cancer and/or protective properties against different cancers (Mali et al. 2019).

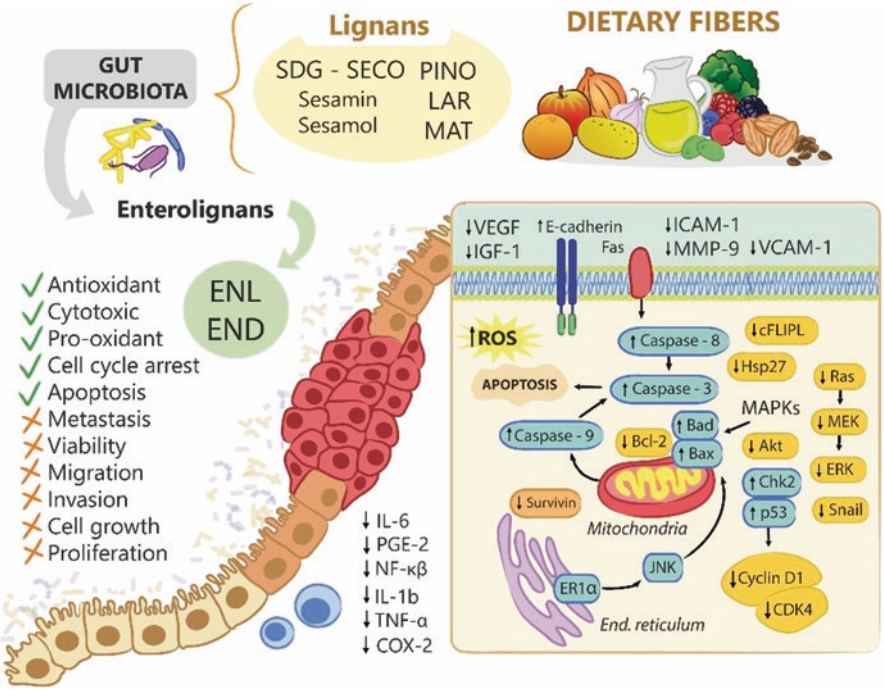

Fig. 10.5 The main anticancer effects and mechanisms of dietary fiber (lignans). Lignans, namely secoisolariciresinol diglycoside (SDG), its aglycone form (SECO), pinoresinol (PINO), Matairesinol (MAT), Lariciresinol (LAR), sesamin and sesamol are associated components of dietary fibers. They are metabolized by gut microbiota to produce actives metabolites, enterolignans known as enterolactone (ENL) and enterodiol (END). These compounds exerts beneficial effects against cancer by several actions mechanisms, such as regulation of enzymes and pro-inflammatory cytokines (COX-2, IL-6, TNF-α), modulation of Bax/Bcl-2 ratio, p53 NF-kb, MMPs and E-cadherin expression, through MAPKs, JNK/ER1a and Ras/ERK pathways. All these anticancer activities (✓) and targets pathways of dietary lignans contribute to inhibitory effect (×) in cancer prevention

Aside from fruits and vegetables, lignans can be found mainly in seeds and its oils (*e.g.,* flax and sesame), also in olive fruit, whole grains and nuts (*e.g.,* almonds and cashew nut). The quantity varies according its food source (Barreca et al. 2020; Chin et al. 2008; de Souza et al. 2017; Durazzo et al. 2018; Kristo et al. 2016; Rodríguez-García et al. 2019).

Rodríguez-García et al. (2019) reported that lignan consumption varies according to the region food-pattern around the world. The major source of lignan ingestion in Latin American diet is flax seed (e.g. secoisolariciresinol); as to Asia, mainly China and India, one has spices, vegetables and Sesame seeds with its oils (e.g. sesamin), whereas in European regions one finds berries (e.g. lariciresinol e matairesinol). Besides, the main lignan sources in the Mediterranean diet are garlic, onions, vegetables, whole grains, virgin olive oil (VOO), and seasonal fruit (Pounis

et al. 2016). Indeed, Offringa et al. (2019) suggested that there is a connection among plant-based diets which contain naturally enriched food of lignans and health benefits, including decrease in cancer risks.

In the last decades, the potential effects of lignans have been the targets of several studies associated with breast, ovarian, prostate, colorectal, cervical, and esophageal cancers as well as hepatocellular carcinoma (Jung et al. 2013). Therefore, this section will focus on lignans effects on different aspects of cancer.

5.1 Lignans and Breast Cancer

In animal studies, it has been observed that SDG supplementation in mice reduces tumor growth in E0771 model of triple-negative breast cancer (TNBC), probably via mechanism involving inhibition of NF-kB. The authors also analyzed an enterolactone (ENL) treatment *in vitro*, which inhibited cell viability, survival, and NF-kB activity (Bowers et al. 2019). Certain tumors have a greater capacity to spread to other organs, which contributes to the difficulty of treatment. In this sense, ENL also has antimetastatic potential activity against TNBC, through inhibition of TGF-β-induced epithelial to mesenchymal transition (EMT) and blocking ERK/NF-κB/Snail signaling pathway *in vitro* (Mali et al. 2018). Another study showed that ENL and SECO enhanced the anticancer activity of therapeutic drugs, such as docetaxel, against breast cancer cell lines, which in combination with ENL could have their doses reduced and still maintain the same effectiveness (Di et al. 2018). Furthermore, ENL could also work on enhancement of radio sensitivity of breast cancer by abrogating X-ray, inducing G2/M arrest, impairing DNA repair processes and increasing apoptosis (Bigdeli et al. 2016). PINO behaved as cytotoxic, anti-proliferative and pro-oxidant in human breast tumor cells (MDA-MB-231; MCF7), without regard to estrogen-receptor expression levels. Indeed, it revealed an antioxidant role preventing DNA damage in MCF10A cells (López-Biedma et al. 2016). In a study with breast cancer cells (SKBr3), LAR and PINO, increased apoptosis induction as well as cell growth, survival and proliferation decrease (Soltani et al. 2020).

In a bioinformatics analysis, MAT had the best binding energy with ER+ receptor for breast cancer cells, compared to PINO, LAR and SECO. It was revealed similar interactions compared to the drug tamoxifen, that could suggest promising biological activity in this type of cancer (Mohamadyar-Toupkanlou et al. 2017). Siao et al. (2015) showed that breast cancer cells (MCF-7), treated with sesamin reduced cell viability by necrosis, apoptosis and cell cycle arrest, promoted by an increase of Bax and caspase-3 expression and sub-G1 arrest related with increased tumor suppressor p53 and Chk2 expression. Indeed, sesamol was able to exert, maintain and augment cytotoxicity on MCF-7 breast cancer cell due association with oleic acid-conjugated gelatin nanoparticles that enhanced sesamol uptake in transdermal delivery through albino mice skin (Elmasry et al. 2018). Both encapsulated and free form of sesamol administration remarkably decreased skin tumor

burden by bcl-2 downregulation and Bax upregulation, inducing apoptosis (Bhardwaj et al. 2016).

In a cross-sectional study, the consumption of phytoestrogens (isoflavones and lignans) by breast cancer patients in different menopausal status was associated with their diet and survival (Boucher et al. 2017). The results showed that the phytoestrogens intake was higher in premenopausal than in postmenopausal consumers, and lignans intake were significantly higher than isoflavones. Among lignans, foods assessed were flaxseed, flaxseed bread, sesame seeds that were associated to provide SECO, PINO, LAR and MAT lignans in diet. Indeed, SECO was the major contributor of diet for all patients. The authors suggested that higher phytoestrogens intake may affect postmenopausal breast cancer survival. In a similar study, no associations were found for SECO intake and breast prognosis (Swann et al. 2013).

In a case-control study, the consumption of flaxseed was associated with a significant reduction in breast cancer risk (OR 0.82, 95% CI 0.69–0.97) among premenopausal women which was attributed to LAR and PINO intake (Lowcock et al. 2013). In addition, evidence for a better prognosis in postmenopausal breast cancer patients who have high estimated enterolignan (ENL and END), dietary intake of lignan-rich foods, and dietary fiber intake exposures was revealed in a large German cohort (Buck et al. 2011). The associations of estimated enterolignans and dietary fiber intake with survival were independent of ER status of the tumour.

Lignans can also act through hormone-independent mechanisms. A population based prospective cohort with 1743 cancer patients revealed that the higher mean ENL concentrations and lower CRP concentrations were inversely associated with mortality and survival (Jaskulski et al. 2018). On the other hand, the association of prognosis with circulating ENL and inflammatory markers changes in post-menopausal breast cancer reveals that enterolignans levels changed over time and were not associated with prognosis (Jaskulski et al. 2019). Thus, these clinical trials show controversy for ENL.

5.2 Lignans and Gastrointestinal Cancers

Lariciresinol lignan has antioxidant and cytoprotective activities and was capable of modulate antioxidant enzymes and up-regulate Nrf-2 via p38 activation pathway in RAW 264.7 (Bajpai et al. 2017). LAR anti-tumor activity was assessed against hepatocellular carcinoma (HepG2 cells) and induced mitochondrial-mediated apoptosis pathway S-phase arrest that contributed to growth inhibition and downregulated Hsp27 expression, a protein that is correlated to chemotherapeutic drugs resistance (Ma et al. 2016, 2018b). LAR also denotes growth inhibition and cell cycle arrest activities against human gastric cancer cells by apoptosis induction through increased Bax/Bcl-2 ratios, ROS generation and decreased MMP (Zhang et al. 2015b). PINO was also associated with mitochondrial apoptosis in hepatocarcinoma cells (HepG2) as well as Fas death receptor pathways, inhibiting migration and invasion through E-cadherin increased expression with VCAM-1, ICAM-1, and

decreasing of MMP-9 expression (Zhang et al. 2018). In hepatocellular carcinoma *in vitro* and *in vivo*, sesamol revealed its anticancer effects by directly altering mitochondrial metabolism, interrupting the S-phase cell cycle and inducing the activation of apoptosis by intrinsic and extrinsic routes (Liu et al. 2017c). In silico analysis with molecular docking suggests that phytoestrogens as SECO, LAR, MAT, and PINO among others, can be considered potential drug candidates for hepatocellular carcinoma while targeting β-catenin in the *Wnt* signaling (Kanahaiya et al. 2017).

Evidence indicates that SDG chemopreventive colon cancer effects may have associated with type 2 diabetes mellitus once it was able to inhibit CDK4 and increase GLUT-1 expression, controlling glycemic parameters. Also, it reduced IL-1b, TNF-a levels and inhibited IGF-1, suggesting action on preventing cell proliferation and cancer progression (Shah and Patel 2016). SDG also presents strong anti-inflammatory properties decreasing IL-6, NF-kB activity, and PGE-2 on human intestinal Caco-2 cells, probably due to its furofuran structure and its intestinal metabolism (During et al. 2012). For instance, Shin et al. (2018) evaluated *in vitro* activity of END on CRC cells. This lignan induced apoptosis mechanism through MAPK signaling pathway and reduced metastatic capacity, exhibiting cytotoxic effect to cancer cells. Sesamol induced apoptosis in human colon HCT116 cells, exerted both antioxidant and pro-oxidant activities, and suppressed cell viability through S-phase arrest (Khamphio et al. 2016).

A Spanish case-control study showed that the lignans and total flavonoids intake were inversely related to CRC risk (Zamora-Ros et al. 2013). In the other hand, the results of EPIC Cohort showed no significant association between total polyphenol intake and CRC risk (Zamora-Ros et al. 2018). It could be said that polyphenols have multiple targets and different actions such as immunomodulation, anti-angiogenesis, anti-proliferative, apoptosis induction and metastasis suppression that depend on gut-microbiota-modulation for therapeutic potential promoting in CRC (Cueva et al. 2020).

Lignans are safe (Bedell et al. 2014), however, clinical studies should be developed in order to identify therapeutically relevant doses to understand their role in cancer prevention (De Silva and Alcorn 2019).

5.3 Lignans and Lung Cancer

Radiotherapy is a treatment widely used in patients with the most diverse types of cancer. However, it causes several adverse effects on the patient. SDG demonstrated a potential protective activity against radiation-induced oxidative damage to non-malignant lung cells, mediated by free-radical scavenging or increasing of endogenous antioxidant defenses, like trans-resveratrol (Velalopoulou et al. 2016). Similar result was obtained where SDG successfully scavenged active chlorine species (ACS) preventing radiation-induced DNA damage (Mishra et al. 2016). These findings may present SDG as a novel radioprotective agent in cancer therapy, which has already been patented (Christofidou-Solomidou 2018).

In lung cancer cells, ENL was able to suppress metastases through disruption of F-actin cytoskeleton dynamics, inhibition of the focal adhesion kinase and steroid receptor coactivator/paxillin signaling cascade and expression of motility regulators. It was also observed cycle arrest activity in the G1 and downregulation of cyclin D1 and CDK4 mRNA (Chikara et al. 2017a, b). In a brand new study by Chen et al. (2020), sesamin suppressed cell proliferation in non-small cell lung cancer (NSCLC) by induction of cell cycle arrest via inhibiting cyclin D1 expression, up-regulated p53 expression and Akt activity inhibition, both *in vitro* and *in vivo*, without severe side effects. As a matter of fact, sesamin also ameliorates the survival of cardiac muscle cells impaired by doxorubicin, an important chemotherapy drug and sesamin combined with cisplatin synergistically suppressed lung cancer cells (H460) proliferation (Liu et al. 2019a; Su et al. 2014).

5.4 Lignans and Other Cancers

In both *in vitro* and *in vivo* assays PINO inhibited ovarian cancer cell growth by autophagy via MMP levels reduction, cell invasion inhibition and Ras/MEK/ERK signaling pathway (Ning et al. 2019).

Not only that, high concentrations of both END and ENL could inhibit ovarian cancer cell proliferation, as well as viability, migration and invasiveness i*n vitro* and *in vivo*, but ENL was considered more effective particularly in *the in vivo* analysis (Liu et al. 2017a). On cervical cancer cells (HeLa cells) sesamin inhibits proliferation and migration dose-dependently, inducing cell autophagy, and modulated apoptosis with increased expressions of Bax/Bcl-2 ratio and ER-stress related proteins through IRE1α/JNK pathway (Dou et al. 2018). In prostate cancer (PC3 cells) under LPS stimulation, sesamin significantly decreased TNF-α, IL-6, cyclin D1, COX-2, Bcl-2 and Survivin expressions. Other effects of sesamin included decreasing in MMP-9, ICAM-1 and VEGF proteins through p38-MAPK signaling pathway, NF-κB activation and inhibition of tumor growth *in vivo* (Xu et al. 2015).

Indeed, PINO sensitized glioblastoma cancer cells against TNF-related apoptosis-inducing ligand (TRAIL) therapy, increasing apoptosis, caspase-8 and downregulation of FLICE-inhibitory protein ($cFLIP_L$) by a mechanism involving *de novo* protein synthesis (Lee et al. 2019b). In the light of these results, PINO has potential to enhance the effectiveness of usual anticancer drugs. MAT had promising effects on C6 glioma cells on rats, reducing proliferation and inducing apoptosis without affect astrocytes, as does arctigenin (ARC), another lignan (Baetas et al. 2018).

Furthermore, PINO promoted a doxorubicin resistance-reversing effect on human myelogenous leukemia cells with low cytotoxicity (González et al. 2017). In T-cell lymphoma, MAT and ARC caused antiproliferative effects with selective cytotoxicity. Importantly, they cause cell cycle arrest in the S phase and apoptosis activation, mainly by upregulation of Bax (MAT), Bad (ARC), and caspase-9 (Both) expressions, besides increasing intracellular ROS levels. (Su et al. 2015).

6 Evidences in Focus

The consistent protective effects of fruits and vegetables should reflect the fact that they are the largest source of fiber and contain several phytochemicals with anticancer properties. There are many studies that show the anticancer effects of phytochemicals (quercetin, resveratrol, carotenoids and dietary fiber) and some of these studies are summarized in Tables 10.1, 10.2, 10.3 and 10.4.

The data listed in Tables 10.1, 10.2, 10.3, and 10.4 show that phytochemicals from fruits and vegetables exert their anticancer protective effects through different mechanisms and may act in a synergic way been strongly related to prevent several cancers. There are many evidences in cancer research that suggest quercetin, resveratrol, carotenoids and dietary fibers (lignans) as anticancer agents. This represents the advance on acknowledgment on chemopreventive role fruits and vegetables besides their functional properties, already well established.

The search for scientific work carried out *in vitro*, *in vivo* and in human studies brings together a wide range of evidence to ratify the role of these natural compounds envisaging cancer combat. Furthermore, published pre-clinical trials represent an endless search to information. However, despite positive associations in epidemiological studies, there are still limitations of clinical studies.

In fact, the evidence from clinical trials is advantageous because in intervention studies, the results represent controlled approaches; on the other hand, epidemiological studies have strengths and limitations (WCRF/AICR 2018).

All these researches results show the diet importance in order to maintain a healthy life associated to fruits and vegetables intake. Indeed, particularly this chapter emphasizes bioactive phytochemicals role in cancer prevention. Furthermore, these phytochemicals could be used as a tool to be associated to traditional cancer treatments searching alleviate the side effects (Clinton et al. 2019).

7 Final Remarks

Despite the technological and pharmaceutical advances, cancer remains to be a global concern. Herbal medicine or phytotherapics has been used for a long time as complementary therapy to cancer treatment. In addition, the side effects caused by the chemotherapy are well known and the search for new natural agents that decrease these effects is fundamental. In this sense, natural compounds, such as quercetin, resveratrol, carotenoids and dietary fibers, have been gaining attention of scientists and community.

Quercetin is considered the most abundant antioxidant in the human diet and its easy accessibility, great efficacy and low toxicity make it a promising biological compound that can be used alone or in combination with other chemotherapeutic drugs in the treatment of cancer, including colorectal, breast, prostate, gastric, oral

Table 10.1 *In vitro* evidences of phytochemicals from fruit and vegetables in cancer prevention

Phytochemical	Treatment	Anticancer effect	Reference
Quercetin	Mouse colon cancer cells (CT26; MC38) and human colon adenocarcinoma cell (HT29) [10–100 μM] 24–72 h	Inhibition of cell viability by induction of intrinsic apoptosis through the ERK, JNK and p38 MAPKs pathway in CT26 cells. Inhibition of metastasis by decreasing MMP-2 and MMP-9 activity and regulating expression of EMT markers, such as E-cadherin (increased) and N-cadherin, β-catenin and snail (decreased).	Kee et al. (2016)
Quercetin	Human oral cancer SAS cells [40 μM] 12–48 h	Reduction of cell viability due ROS and Ca^{2+} production increase and decrease of mitochondrial membrane potential ($\Delta\Psi m$) levels. The treatment also increased Fas, FasLigand, caspase 8, ATF6β and gastrin releasing peptide78.	Ma et al. (2018a)
Quercetin	Human prostate cancer cell line (PC3) and doxorubicin-resistant PC3 cells (PC3/R) [10 μM] for 48 h in combination with doxorubicin	Induction of apoptosis in PC3/R cells through mitochondrial/ROS pathway by inhibition of c-met expression and PI3K/AKT pathway downstream.	Shu et al. (2018)
Resveratrol	Human Intestinal cell Caco-2 [10–50 μM] 1 h	Reduction, in a concentration-dependent manner, the induction of COX-2. Cells treated with 50 μM, exhibited a less evident reduction of COX-2 expression.	Cianciulli et al. (2012)
Resveratrol	Oral squamous cancer cells (OSCC: SCC-VII, SCC-25, and YD-38) [0.1–1.5 μg/mL] 24–48 h	Induction of cell cycle arrest in the G2/M phase and enhanced expression of phospho-cdc2 (Tyr 15), cyclin A2, and cyclin B1 in the (OSCC) cells.	Yu et al. (2016)
Resveratrol	Breast cancer cell with different ER status (MCF-7 and MDA-MB-231) [10 μM] 96 h	DHT interfered with RESV-induced anti-proliferation in both ER-α-positive MCF-7 and ER-α-negative MDA-MB-231 cells.	Chin et al. (2015)
Lycopene	Prostate and Breast cancer cells (PC3 and MDA-MB-231) [0.5–5 μM] 20–48 h	Suppression PC3 and MDA-MB-231 with proliferation inhibition. Inhibits IκB phosphorylation and inhibits TNFα-induced NF-κB p65 nuclear translocation in PC3 and MDA-MB-231 cells	Assar et al. (2016)
Lycopene	Human prostate cancer cells and benign prostate hyperplastic cells Bone metastasis-derived PCA human cells (PC-3), and brain metastasis-derived PCA human cells (DU-145) [0.5–20 μM] 48–96 h	Decreased the percentage of cells in G0/G1 phase and increased in S and G2/M phases in metastatic prostate cancer cell lineages; cell cycle arrest in G0/G1 phase in a primary cancer cell line; apoptosis in prostate cancer cells with altered gene expression of Bax and Bcl-2.	Soares et al. (2013)

β-carotene	Rat melanoma cells and rat aortic ring assay (in vitro angiogenesis study model) (1–10 μg/mL) for 6 days	A significant and dose-dependent inhibition of microvessel outgrowth from the rat aorta ring induced by the conditioned medium from B16F-10 cells with the microvessel outgrowth totally stopped at 10 μg/mL	Guruvayoorappan and Kuttan (2007)
Lycopene + Beta-carotene	Human breast cell lines (0.5–10 μM) for 48 and 96 h.	Inhibition of cell proliferation; cell cycle arrest in different phases, induction of apoptosis. Decrease the expression of antiapoptotic protein Bcl-2 and PARP130 decrease the activation of the growth signaling protein Akt and ERK1/2.	Gloria et al. (2014)
END	Mouse colon adenocarcinoma cells (CT26) [0.1–100 μM] 24–72 h	Increase 40% of apoptosis rate in CT26 cells and reduced metastatic capacity of the cells in a concentration-dependent manner. Down-regulation of phosphorylation of ERK, JNK, and p38.	Shin et al. (2018)
SECO ENL	Breast cancer cell with different ER status (SKBR3 and MDA-MB-231) [50 μM] 72 h in combination with chemotherapeutic agents	SECO with docetaxel, presented moderate antiproliferative properties against metastatic cancer cells lines. ENL with docetaxel, increased 50% cytotoxicity to MDA-MB-231 more efficiently than SECO. SECO with ENL and Metformin, increased fourfold the cytotoxicity in a concentration dependent-response.	Di et al. (2018)
Pectin-rich in phenolics extracts	Colon carcinoma (Caco-2) and the leukemia monocytic (THP-1) cell lines Caco-2 (7 days treatment) THP-1 (4 days treatment) Pectolivs and MCP [0.37–10 mg/mL]	Pectolivs rich in phenolics, inhibit cells proliferation in both models of cancerous cells and the inhibitory effect was higher than control MCP. Caco-2 cells were more susceptible to inhibition of proliferation than THP-1 cells. Pectolivs induced apoptosis as determined by activation of caspase-3, and inhibited agglutination of red blood cells by galectin-3.	Bermúdez-Oria et al. (2019)

COX-2 cyclooxygenase-2, *END* enterodiol, *ENL* enterolactone, *ERK* extracellular signal-regulated kinase, *EMT* epithelial-mesenchymal transition, *JNK* jun N-terminal kinase, *IκB* inhibitor of kappa B, *MAPKs* mitogen-activated protein kinases, *MMP-2* matrix metalloproteinases 2, *MCP* modified citrus pectin, *Pectolivs* pectin-rich olive extracts, *SECO* secoisolariciresinol, *ATF6β* transcription factors-6β, *TNFα* transcription necrosis factor-α

Table 10.2 *In vivo* evidences of phytochemicals from fruits and vegetables in cancer prevention

Phytochemical	Type of cancer	Model	Rout/dose/duration	Effects observed	Mechanism	Reference
Quercetin	Pancreatic cancer	nu/nu mice	40 mg/kg (v.o.) daily Mon–Fri for 3 weeks	Suppress tumor growth	Increase pro-apoptotic effects of BET inhibitors by decreasing hnRNPA1 and downregulated protein levels of cIAP-2, Hsp70 and Survivin.	Pham et al. (2019)
Quercetin	Lung cancer	C57 mice	50, 100 and 200 μg/mL (v.o.) daily for 15 days	Decrease of tumor volume	Upregulation of apoptosis related genes including p53, Bax and Fas and the ratio of Bax/Bcl-2 increase.	Li et al. (2019)
Quercetin	Gastric carcinoma	NOD/SCID mice	30 mg/kg (v.o.) daily for 2 weeks	Decrease of tumor volume	Induction of p53-dependent apoptosis by increasing expression of the cleaved forms of caspase-3, -9, and Parp.	Lee et al. (2016)
Resveratrol	Breast cancer	BALB/c nude mice	RESV-loaded NPS (30 mg/kg) (i.v.) with DOX (5 and 10 mg/kg), every 5th day, for 25 days.	Suppress tumor growth	Effects in dose-dependent manner, pro-apoptotic effects via caspase-3 activity and cytotoxicity.	Zhao et al. (2016)
Resveratrol	Ovarian cancer	nu/nu mice	Cisplatin (6 mg/kg) RESV (160 mg/kg) (i.p.) for 25 days.	Antineoplastic effect	Inhibition of glucose uptake.	Tan et al. (2016)
Resveratrol	Pancreatic cancer	nu/nu mice	RESV (40 mg/kg), (p.o.) once daily or/with gemcitabine (25 mg/kg) (i.p.) twice weekly	Potentiate the cytotoxic effects of gemcitabine	Downregulation of Ki-67 and the micro vessel density CD31 markers of proliferation index. Suppressed NF-κB activation and expression of cyclin D1, COX-2, ICAM-1, MMP-9 and surviving.	Harikumar et al. (2010)
Lycopene	Breast cancer	Rats	LYC (50 mg/Kg) alone or combined with melatonin (SC) (2.5 mg/kg) for 120 days	Decreases the tumor number and suppress tumor growth	Antioxidant mechanism with inhibition of lipid peroxidation and decreased SOD, CAT and GPx activities.	Moselhy and Al Mslmani (2008)

(continued)

Table 10.2 (continued)

Phytochemical	Type of cancer	Model	Rout/dose/duration	Effects observed	Mechanism	Reference
Lycopene	Ovarian cancer	NOD/SCID mice	15 mg/kg (v.o) Preventative effects: 2 weeks PI of OV-MZ-6 cells in mice Therapeutic effects:4 weeks AS	Anti-metastatic Antiproliferative	Downregulated of ITGA5, ITGB1, ILK, FAK and MMP9 expression in metastatic tissue. Decreased levels of CA125 in serum and ascites.	Holzapfel et al. (2017)
Lycopene	Prostate cancer	Rat	4 g lycopene/kg diet for 4-week	Antiproliferative Suppress tumor growth	Downregulation of 5-a-reductase, reduced steroid target genes expression and prostatic insulin-like growth factor-1 (IGF-1) and interleukin-6.	Siler et al. (2004)
END ENL	Ovarian cancer	BALB/c nude mice Xenograft model	END/ENL (0.1 mg/kg or 1 mg/kg) Once per 2 days for 32 days	Antiproliferative Suppress tumor growth	END performed estrogenic activity at lower concentration, while in higher concentration cause side effects on weight loss. ENL at higher dose was more effective as anti-cancer agent than END	Liu et al. (2017a)
SDG	Breast cancer	C57BL/6 mice	100 mg SDG/kg diet for 7 weeks	Suppress tumor growth	Significant decrease in phosphorylated (Ser276) p65 as well as NF-κB target gene expression in the tumors.	Bowers et al. (2019)
Sesamol	Hepato-carcinoma	BALB/c nude mice Xenograft model	100 mg/kg or 200 mg/kg via i.p. every day from day 10 thru day 44	Suppress tumor growth	The Bcl-2/Bax ratio in tumor tissues decreased and levels of the cell proliferation marker Ki76 were down-regulated, while levels of the cell apoptosis marker cleaved-caspase 3 were increased. The expression of LC3 protein was remarkably decreased by sesamol in a dose-dependent manner.	Liu et al. (2017c)

AS after surgery, *CAT* catalase, *GPx* glutathione peroxidase, *HCC* human hepatocellular carcinoma cells, *i.g* intragastrically, *i.p* intraperitoneally, *LYC* lycopene, *v.o.* via oral, *PI* prior implantation, *SC* subcutaneously, *TNBC* triple-negative breast cancer, *RESV* resveratrol, *SOD* superoxide dismutase

Table 10.3 Clinical evidences of phytochemicals from fruits and vegetables in cancer prevention

Phytochemical	Cancer type	Study design	Subjects	Intervention treatment/ duration	Outcomes	Reference
Quercetin	Colorectal cancer	Observational prospective	5 patients with FAP (men and women) aging 21–54 years	Quercetin 20 mg and curcumin 480 mg orally 3 times a day for 6 months	Decrease polyp number and size of ileal and rectal adenomas with minimal adverse side effects	Cruz-Correa et al. (2006)
Quercetin	Blood malignancies	Double-blind, randomized placebo controlled	20 adult patients who underwent high dose chemotherapy for blood malignancies	250 mg quercetin capsules twice daily for 4 weeks	Lower oral mucositis incidence in treated group	Kooshyar et al. (2017)
Trans-resveratrol	Breast	Placebo-controlled	39 adult women at increased breast cancer risk	5 or 50 mg, twice daily, 12 weeks	Decrease in the fraction of methylated RASSF-1α DNA Decrease in the expression of PGE2 in the breast	Zhu et al. (2012)
Resveratrol	Colorectal	Intervention	20 patients with confirmed colorectal cancer	0.5 or 1.0 g, eight daily doses, before surgical resection	Reduced tumor cell proliferation	Patel et al. (2010)
Plant-derived resveratrol	Colon	Clinical Trial phase I	8 patients diagnosed with colon cancer	80 g/day containing 0.07 mg of resveratrol, 2 weeks	Inhibition of Wnt target gene expression in normal colonic mucosa, with no effect on cancerous mucosa	Nguyen et al. (2009)
Lycopene	Prostate adenocarcinoma	Clinical Trial phase I	32 patients with localized prostate adenocarcinoma	Tomato sauce-based pasta dishes for the 3 weeks (30 mg of lycopene per day) preceding radical prostatectomy	Serum PSA levels decreased, from 10.9 ng/mL (95% CI = 8.7–13.2 ng/mL) to 8.7 ng/mL (95% CI = 6.8–10.6 ng/mL) (P < .001).	Chen et al. (2001)
Lycopene	Prostate	Randomized clinical trial	Benign prostate Hyperplasia patients	Administration of 15 mg lycopene every day for 6 months	Reduced disease progression with decreased serum PSA concentration	Schwarz et al. (2008)

(continued)

Table 10.3 (continued)

Phytochemical	Cancer type	Study design	Subjects	Intervention treatment/ duration	Outcomes	Reference
Flaxseed	Breast cancer	Randomized Intervention Placebo controlled	24 postmenopausal women (ER^+) BC	25 g/day ground (FS) with 1 mg/day anastrozole (AI) 13–16 days	FS + AI treatments decrease 40% the ERβ expression and reduce serum steroid hormone DHEA production, as well as urinary lignan excretion	McCann et al. (2014)

AI aromatase inhibitor, *BC* breast cancer, *ER* estrogen receptor, *FS* flaxseed, *FAP* familial adenomatous polyposis, *PGE2* prostaglandina-2

Table 10.4 Observational epidemiology evidences of phytochemicals from fruit and vegetables in cancer prevention

Phytochemical	Population	Cancer type	Aim	Methods	Outcomes	Reference
Quercetin	505 cases and 1116 controls (40–79 years)	Gastric cancer	To study the impact of the dietary antioxidant quercetin on risk of gastric adenocarcinoma	FFQ	High dietary quercetin intake protects to this adenocarcinoma, and the effect is stronger for women exposed to oxidative stress, such as tobacco smoking	Ekström et al. (2011)
Quercetin	1163 cases and 1501 controls participants, between 45 and 80 years	Colon canscer	Associate the dietary quercetin with proximal colon cancer risk	FFQ	Protective effect of quercetin on risk of proximal colon cancer were significant only to high fruit intake, or low tea intake.	Djuric et al. (2012)
Resveratrol	Patients over 18 years diagnosed with cancer in the first 6 months of 2018 vs. healthy individuals	Head and neck cancer	Evaluate the relationship between traditional Mediterranean diet and the risk of developing head and neck cancer	Mediterranean Diet Adherence Screener questionnaire	The consistent medium-high adherence to Mediterranean diet is associated with a decrease in the risk of developing head and neck cancer	Salvatore Benito et al. (2019)
Resveratrol	181 cases of oesophageal adenocarcinoma, 158 cases of oesophageal squamous-cell carcinoma, 255 cases of gastro-oesophageal junctional adenocarcinoma and 806 controls from a Swedish nationwide population-based case–control study	Oesophageal adenocarcinoma, oesophageal squamous-cell carcinoma and gastro-oesophageal junctional adenocarcinoma	To verify the association of a dietary pattern rich in lignans, quercetin, and resveratrol with the risk of oesophageal cancer development.	FFQ	Lignans, quercetin, and resveratrol synergistically act to prevent the development of all types of esophageal cancer investigated	Lin et al. (2014)

(continued)

Table 10.4 (continued)

Phytochemical	Population	Cancer type	Aim	Methods	Outcomes	Reference
Lycopene	39 women with breast cancer and 31 control women. Evaluation of the relationship between plasma micronutrient levels and breast cancer risk.	Breast cancer	To evaluate the potential for accrual to a study of the association of plasma levels of b-carotene, retinol, lycopene, a-tocopherol, and g-tocopherol with breast cancer risk among African American and Caucasian women	FFQ and micronutrients plasma levels	Among the lowest lycopene tertile, the risk of breast cancer among Caucasian women was 0.76 and the risk of breast cancer among African American women was 2.29, although these odds ratios were not statistically significant.	Simon et al. (2000)
Lycopene	43,851 PCa cases reported from 692,012 participants (32 studies in North America), 6 from Europe, 2 from Australia, 2 from Asia (China and Singapore) and 1 from South America (Uruguay).	Prostate cancer	To determine the impact of dietary and circulating concentrations of lycopene on PCa risk and to investigate potential dose response associations.	Meta-analysis using randomized control trials, cohort, cross-sectional, retrospective, prospective and case–control studies	Higher dietary and circulating lycopene concentrations are inversely associated with PCa risk	Rowles et al. (2017)
β-carotene	9 studies including 5 in USA and 3 in Europe	Pancreatic cancer	To evaluate the association between antioxidants intake and pancreatic cancer risk	Meta-analysis with relevant articles retrieved from PUBMED and EMBASE databases and standard methods	It was significantly associated with reduced pancreatic cancer risk	Chen et al. (2016b)
Flaxseed and flax bread	2999 cases and 3370 controls (25–74 years)	Breast cancer	To investigate associations between phytoestrogens-containing foods and BC	FFQ	Dietary lignans intake was associated with 20–30% reductions in BC risk in postmenopausal	Lowcock et al. (2013)

BC breast cancer, *FFQ* food frequency questionnaire

and others. Thus, the variety of published evidence suggests that quercetin is a flavonoid with great anticancer potential.

In vitro, *in vivo*, clinical and epidemiological studies reveal that resveratrol is a promising molecule with anticancer activity, in prevention and treatment, especially in synergisms with other chemotherapeutic agents, in addition to reducing the associated side effect during treatment. It is well tolerated at low doses, but its beneficial effects remain controversial in humans or have only been shown to a limited extent so far, due to several factors such as achieving consensus on dose-response profiles, biomarker or conclusive result, since a small number of patients included in clinical studies and the diversity of resveratrol doses used. Further clinical trials should be carried out to clarify the effects of resveratrol in cancer patients and to determine its therapeutic and chemopreventive potential.

Researches indicate that different carotenoids such as lycopene and beta-carotene are involved in the anticancer action. Despite this, there are still controversial studies for some types of cancer. Thus, this analysis requires attention and important aspects need to be considered such as the availability of these carotenoids, their processing before ingestion and the interaction with other phytochemicals present in the tested foods. Those factors can influence the presence or absence of anticancer properties, as well as side effects of this combination, and influence the results of research since little is known about phytochemical/phytochemical interactions. Another subject that deserves attention is the role of bacteria microflora involved in the biotransformation of these phytochemicals, changing the nutrition and the functions of these molecules in human organisms. In general, a diet rich in fruits and vegetables, important sources of carotenoids, is recommended to maintain health and prevent diseases like cancer.

Dietary fibers provide a beneficial physiological effect through their functional mechanisms besides to playing a protective role in various types of cancer. Among them, lignans stand out, whose ingestion in the diet produces bioactive metabolites related to the prevention of carcinogenesis through the efficiency of the intestinal microbiota in the metabolism of these components. Thus, lignans can interfere directly or indirectly in various metabolic pathways, acting as antioxidants/pro-oxidants, phytoestrogenic agents in various types of cancer, mainly gastrointestinal, breast and lung cancer.

The main phytochemicals agents presented in this chapter reveal their anti-cancer mechanisms through multiple intracellular targets, triggering metabolic pathways and molecular signals that modulate genes and proteins associated to inflammatory, antioxidant/pro-oxidant, and carcinogenic processes.

These phytochemicals are also capable of increasing the effectiveness of drugs already established in treatments, without toxicity, reinforcing the importance of indicating the consumption of fruits by the population. However, further clinical studies must be developed to identify therapeutically relevant doses to prevent cancer.

References

Abar L, Vieira AR, Aune D et al (2016) Blood concentrations of carotenoids and retinol and lung cancer risk: an update of the WCRF-AICR systematic review of published prospective studies. Cancer Med 5:2069–2083

Abete I, Perez-Cornago A, Navas-Carretero S et al (2013) A regular lycopene enriched tomato sauce consumption influences antioxidant status of healthy young-subjects: a crossover study. J Funct Foods 5:28–35. https://doi.org/10.1016/j.jff.2012.07.007

Adolphe JL, Whiting SJ, Juurlink BHJ et al (2010) Health effects with consumption of the flax lignan secoisolariciresinol diglycoside. Br J Nutr 103:929–938. https://doi.org/10.1017/S0007114509992753

Afshin A, Sur PJ, Fay KA et al (2019) Health effects of dietary risks in 195 countries, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 393:1958–1972. https://doi.org/10.1016/S0140-6736(19)30041-8

Agarwal C, Sharma Y, Agarwal R (2000) Anticarcinogenic effect of a polyphenolic fraction isolated from grape seeds in human prostate carcinoma DU145 cells: modulation of mitogenic signaling and cell-cycle regulators and induction of G1 arrest and apoptosis. Mol Carcinog. 28: 129–38. https://doi.org/10.1002/1098-2744(200007)28:3<129::AID-MC1>3.0.CO;2-0.

Akl MR, Ayoub NM, Abuasal BS et al (2013) Sesamin synergistically potentiates the anticancer effects of γ-tocotrienol in mammary cancer cell lines. Fitoterapia 84:347–359. https://doi.org/10.1016/j.fitote.2012.12.013

Alphonse P, Aluko R (2015) A review on the anti-carcinogenic and anti-metastatic effects of flax seed lignan secolariciresinol diglucoside (SDG). Discov Phytomed 2:12–17. https://doi.org/10.15562/phytomedicine.2015.24

Anand P, Kunnumakkara AB, Sundaram C et al (2008) Cancer is a preventable disease that requires major lifestyle changes. Pharm Res 25:2097–2116. https://doi.org/10.1007/s11095-008-9661-9

Andreadi C, Britton RG, Patel KR, Brown K (2014) Resveratrol-sulfates provide an intracellular reservoir for generation of parent resveratrol, which induces autophagy in cancer cells. Autophagy 10:524–525. https://doi.org/10.4161/auto.27593

Arai S (2005) Functional food science. J Sci Food Agric 85:1603–1605. https://doi.org/10.1002/jsfa.2248

Assar EA, Vidalle MC, Chopra M, Hafizi S (2016) Lycopene acts through inhibition of IκB kinase to suppress NF-κB signaling in human prostate and breast cancer cells. Tumor Biol 37:9375–9385. https://doi.org/10.1007/s13277-016-4798-3

Aune DS, Chan AR, Vieira DA et al (2012) Dietary compared with blood concentrations of carotenoids and breast cancer risk: a systematic review and meta-analysis of prospective studies. Am J Clin Nutr 96:356–373

Baetas AC, Fábio L, Paula A, et al (2018) In vitro cytotoxicity of lignans isolated from Ficus citrifolia P. Miller (Moraceae) on C6 glioma cell line. Glo. Adv. Res. J. Med. Med. Sci. 7:77–84

Baglietto L, Krishnan K, Severi G et al (2011) Dietary patterns and risk of breast cancer. Br J Cancer 104:524–531

Bajpai VK, Alam MB, Quan KT et al (2017) Antioxidant efficacy and the upregulation of Nrf2-mediated HO-1 expression by (+)-lariciresinol, a lignan isolated from Rubia philippinensis, through the activation of p38. Sci Rep 7:46035. https://doi.org/10.1038/srep46035

Barber NJ, Zhang X, Zhu G et al (2006) Lycopene inhibits DNA synthesis in primary prostate epithelial cells in vitro and its administration is associated with a reduced prostate-specific antigen velocity in a phase II clinical study. Prostate Cancer Prostatic Dis 9:407–413. https://doi.org/10.1038/sj.pcan.4500895

Barreca D, Nabavi SM, Sureda A et al (2020) Almonds (Prunus Dulcis Mill. D. A. Webb): a source of nutrients and health-promoting compounds. Nutrients 12:672. https://doi.org/10.3390/nu12030672

Bedell S, Nachtigall M, Naftolin F (2014) The pros and cons of plant estrogens for menopause. J Steroid Biochem Mol Biol 139:225–236. https://doi.org/10.1016/j.jsbmb.2012.12.004

Bermúdez-oria A, Rodríguez-gutiérrez G, Alaiz M, et al (2019) Function proliferation of Caco-2 and THP-1 cells. Food & function, 10(8),4844-4853. https://doi.org/10.1039/c9fo00917e

Bhardwaj R, Sanyal S, Vaiphei K et al (2016) Sesamol induces apoptosis by altering expression of Bcl-2 and Bax proteins and modifies skin tumor development in Balb/c mice. Anti Cancer Agents Med Chem 17:726–733. https://doi.org/10.2174/1871520616666160819103249

Bhat KPL, Kosmeder JW II, Pezzuto J (2001) Biological effects of resveratrol. Antioxid Redox Signal 3:1041–1064. https://doi.org/10.1089/152308601317203567

Bigdeli B, Goliaei B, Masoudi-Khoram N et al (2016) Enterolactone: a novel radiosensitizer for human breast cancer cell lines through impaired DNA repair and increased apoptosis. Toxicol Appl Pharmacol 313:180–194. https://doi.org/10.1016/j.taap.2016.10.021

Boggs DA, Palmer JR, Wise LA et al (2010) Fruit and vegetable intake in relation to risk of breast cancer in the black women's health study. Am J Epidemiol 172:1268–1279. https://doi.org/10.1093/aje/kwq293

Bondonno NP, Dalgaard F, Kyrø C et al (2019) Flavonoid intake is associated with lower mortality in the Danish diet cancer and health cohort. Nat Commun 10:3651. https://doi.org/10.1038/s41467-019-11622-x

Botterweck AA, Van den Brandt PA, Goldbohm RA (2000) Vitamins, carotenoids, dietary fiber, and the risk of gastric carcinoma: results from a prospective study after 6.3 years of follow-up. Cancer 88:737–748

Boucher BA, Wanigaratne S, Harris SA, Cotterchio M (2017) Post-diagnosis isoflavone and lignan intake in newly diagnosed breast cancer patients: cross-sectional survey shows considerable intake from previously unassessed high lignan foods. Curr Dev Nutr 2:cdn.117.002063. https://doi.org/10.3945/cdn.117.002063

Bowers LW, Lineberger CG, Ford NA et al (2019) The flaxseed lignan secoisolariciresinol diglucoside decreases local inflammation, suppresses NFκB signaling, and inhibits mammary tumor growth. Breast Cancer Res Treat 173:545–557. https://doi.org/10.1007/s10549-018-5021-6

Brito AF, Ribeiro M, Abrantes AM et al (2015) Quercetin in cancer treatment, alone or in combination with conventional therapeutics? Curr Med Chem 22:3025–3039. https://doi.org/10.2174/0929867322666150812145435

Buck K, Zaineddin AK, Vrieling A et al (2011) Estimated enterolignans, lignan-rich foods, and fibre in relation to survival after postmenopausal breast cancer. Br J Cancer 105:1151–1157. https://doi.org/10.1038/bjc.2011.374

Cai H, Scott E, Kholghi A et al (2015) Cancer chemoprevention: evidence of a nonlinear dose response for the protective effects of resveratrol in humans and mice. Sci Transl Med 7(298):298ra117. https://doi.org/10.1126/scitranslmed.aaa7619

Cardoso LAC, Kanno KYF, Karp SG (2017) Microbial production of carotenoids a review. Afr J Biotechnol 16:139–146

Carlson JL, Erickson JM, Lloyd BB, Slavin JL (2018) Health effects and sources of prebiotic dietary fiber. Curr Dev Nutr 2(3):nzy005. https://doi.org/10.1093/CDN/NZY005

Castillo-Pichardo L, Dharmawardhane SF (2012) Grape polyphenols inhibit Akt/mammalian target of rapamycin signaling and potentiate the effects of gefitinib in breast cancer. Nutr Cancer 64:1058–1069. https://doi.org/10.1080/01635581.2012.716898

Chen L, Stacewicz-Sapuntzakis M, Duncan C et al (2001) Oxidative DNA damage in prostate cancer patients consuming tomato sauce-based entrees as a whole-food intervention. J Natl Cancer Inst 93:1872–1879

Chen HY, Huang SM, Yang CM et al (2012) Diverse effects of β-carotene on secretion and expression of VEGF in human hepatocarcinoma and prostate tumor cells. Molecules 17:3981–3988

Chen JY, Song Y, Zhang LS (2013) Lycopene/tomato consumption and the risk of prostate cancer: a systematic review and meta-analysis of prospective studies. J Nutr Sci Vitaminol (Tokyo) 59:213–223

Chen J, Jiang W, Shao L et al (2016a) Association between intake of antioxidants and pancreatic cancer risk: a meta-analysis. Int J Food Sci Nutr 67(7):744–753. https://doi.org/10.1080/09637486.2016.1197892

Chen S, Chen Y, Ma S et al (2016b) Dietary fibre intake and risk of breast cancer: a systematic review and meta-analysis of epidemiological studies. Oncotarget 7:80980–80989. https://doi.org/10.18632/oncotarget.13140

Chen Y, Li H, Zhang W et al (2020) Sesamin suppresses NSCLC cell proliferation and induces apoptosis via Akt/p53 pathway. Toxicol Appl Pharmacol 387:114848. https://doi.org/10.1016/j.taap.2019.114848

Cheng L, Yan B, Chen K et al (2018) Resveratrol-induced downregulation of NAF-1 enhances the sensitivity of pancreatic cancer cells to gemcitabine via the ROS/Nrf2 signaling pathways. Oxidative Med Cell Longev 2018:9482018. https://doi.org/10.1155/2018/9482018

Chikara S, Lindsey K, Borowicz P et al (2017a) Enterolactone alters FAK-Src signaling and suppresses migration and invasion of lung cancer cell lines. BMC Complement Altern Med 17:1–12. https://doi.org/10.1186/s12906-016-1512-3

Chikara S, Lindsey K, Dhillon H et al (2017b) Enterolactone induces G1-phase cell cycle arrest in nonsmall cell lung cancer cells by downregulating cyclins and cyclin-dependent kinases. Nutr Cancer 69:652–662. https://doi.org/10.1080/01635581.2017.1296169

Chin YW, Chai HB, Keller WJ, Kinghorn AD (2008) Lignans and other constituents of the fruits of Euterpe oleracea (Açai) with antioxidant and cytoprotective activities. J Agric Food Chem 56:7759–7764. https://doi.org/10.1021/jf801792n

Chin YT, Yang SH, Chang TC et al (2015) Mechanisms of dihydrotestosterone action on resveratrol induced anti-proliferation in breast cancer cells with different ER status. Oncotarget 6:35866–35879. https://doi.org/10.18632/oncotarget.5482

Choi SW, Park KI, Yeon JT et al (2014) Anti-osteoclastogenic activity of matairesinol via suppression of p38/ERK-NFATc1 signaling axis. BMC Complement Altern Med 14:35. https://doi.org/10.1186/1472-6882-14-35

Chottanapund S, Van Duursen MBM, Navasumrit P et al (2014) Anti-aromatase effect of resveratrol and melatonin on hormonal positive breast cancer cells co-cultured with breast adipose fibroblasts. Toxicol Vitr 28:1215–1221. https://doi.org/10.1016/j.tiv.2014.05.015

Christofidou-Solomidou (2018) Use of secoisolariciresinol diglucosides (SDGS) and related compounds for protection against radiation damage. US patent. US 2018/0243327 A1, 30 Aug 2018

Cianciulli A, Calvello R, Cavallo P et al (2012) Modulation of NF-κB activation by resveratrol in LPS treated human intestinal cells results in downregulation of PGE2 production and COX-2 expression. Toxicol Vitr 26:1122–1128. https://doi.org/10.1016/j.tiv.2012.06.015

Clinton SK, Giovannucci EL, Hursting SD (2019) The World Cancer Research Fund/American Institute for Cancer Research third expert report on diet, nutrition, physical activity, and cancer: impact and future directions. J Nutr 150(4):663–671. https://doi.org/10.1093/jn/nxz268

Conti S, Vexler A, Hagoel L et al (2018) Modified citrus pectin as a potential sensitizer for radiotherapy in prostate cancer. Integr Cancer Ther 17:1225–1234. https://doi.org/10.1177/1534735418790382

Cruz-Correa M, Shoskes DA, Sanchez P et al (2006) Combination treatment with curcumin and quercetin of adenomas in familial adenomatous polyposis. Clin Gastroenterol Hepatol 4(8):1035–1038. https://doi.org/10.1016/j.cgh.2006.03.020

Cueva C, Silva M, Pinillos I et al (2020) Interplay between dietary polyphenols and oral and gut microbiota in the development of colorectal cancer. Nutrients 12:1–19. https://doi.org/10.3390/nu12030625

D'Andrea G (2015) Quercetin: a flavonol with multifaceted therapeutic applications? Fitoterapia 106:256–271. https://doi.org/10.1016/j.fitote.2015.09.018

Da Silveira VM, de Oliveira LMN, Mota EF et al (2020) Consumption of rich/enrich phytonutrients food and their relationship with health status of population. In: Nabavi SM, Suntar I, Barreca D, Khan H (eds) Phytonutrients in food. Woodhead Publishing, Duxford, pp 67–101. https://doi.org/10.1016/B978-0-12-815354-3.00006-X

Dai FJ, Chau CF (2017) Classification and regulatory perspectives of dietary fiber. J Food Drug Anal 25:37–42. https://doi.org/10.1016/j.jfda.2016.09.006

Dandamudi A, Tommie J, Nommsen-Rivers L, Couch S (2018) Dietary patterns and breast cancer risk: a systematic review. Anticancer Res 38:3209–3222. https://doi.org/10.21873/anticanres.12586

Darband SG, Kaviani M, Yousefi B et al (2018) Quercetin: a functional dietary flavonoid with potential chemo-preventive properties in colorectal cancer. J Cell Physiol 233:6544–6560. https://doi.org/10.1002/jcp.26595

Das M, Devi KP (2019) A mini review on the protective effect of lignans for the treatment of neurodegenerative disorders. J Nutr Food Lipid Sci 2019:40–53. https://doi.org/10.33513/nfls/1901-06

David AVA, Arulmoli R, Parasuraman S (2016) Overviews of biological importance of quercetin: a bioactive flavonoid. Pharmacogn Rev 10(20):84. https://doi.org/10.4103/0973-7847.194044

De Silva SF, Alcorn J (2019) Flaxseed lignans as important dietary polyphenols for cancer prevention and treatment: chemistry, pharmacokinetics, and molecular targets. Pharmaceuticals 12:21–38. https://doi.org/10.3390/ph12020068

De Souza PAL, Marcadenti A, Portal VL (2017) Effects of olive oil phenolic compounds on inflammation in the prevention and treatment of coronary artery disease. Nutrients 9(10):1087. https://doi.org/10.3390/nu9101087

De SE, Correa P, Boffetta P et al (2004) Dietary patterns and risk of gastric cancer: a case-control study in Uruguay. Gastric Cancer 7:211–220

Desai SJ, Prickril B, Rasooly A (2018) Mechanisms of phytonutrient modulation of cyclooxygenase-2 (COX-2) and inflammation related to cancer. Nutr Cancer 70:350–375. https://doi.org/10.1080/01635581.2018.1446091

Desai G, Schelske-Santos M, Nazario CM et al (2019) Onion and garlic intake and breast cancer, a case-control study in Puerto Rico. Nutr Cancer 12:1–10. https://doi.org/10.1080/01635581.2019.1651349

Dhingra D, Michael M, Rajput H, Patil RT (2012) Dietary fibre in foods: a review. J Food Sci Technol 49:255–266. https://doi.org/10.1007/s13197-011-0365-5

Di Y, De Silva F, Krol ES, Alcorn J (2018) Flaxseed lignans enhance the cytotoxicity of chemotherapeutic agents against breast cancer cell lines MDA-MB-231 and SKBR3. Nutr Cancer 70:306–315. https://doi.org/10.1080/01635581.2018.1421677

Djuric Z, Severson RK, Kato I (2012) Association of dietary quercetin with reduced risk of proximal colon cancer. Nutr Cancer 64(3):351–360. https://doi.org/10.1080/01635581.2012.658950

Dou H, Yang S, Hu Y et al (2018) Sesamin induces ER stress-mediated apoptosis and activates autophagy in cervical cancer cells. Life Sci 200:87–93. https://doi.org/10.1016/j.lfs.2018.03.003

Dun J, Chen X, Gao H et al (2015) Resveratrol synergistically augments anti-tumor effect of 5-FU in vitro and in vivo by increasing S-phase arrest and tumor apoptosis. Exp Biol Med 240:1672–1681. https://doi.org/10.1177/1535370215573396

Durazzo A, Lucarini M, Camilli E et al (2018) Dietary lignans: definition, description and research trends in databases development. Molecules 23:1–14. https://doi.org/10.3390/molecules23123251

During A, Debouche C, Raas T, Larondelle Y (2012) Among plant lignans, pinoresinol has the strongest antiinflammatory properties in human intestinal Caco-2 cells. J Nutr 142:1798–1805. https://doi.org/10.3945/jn.112.162453

Ekström AM, Serafini M, Nyrén O et al (2011) Dietary quercetin intake and risk of gastric cancer: results from a population-based study in Sweden. Ann Oncol 22(2):438–443. https://doi.org/10.1093/annonc/mdq390

Elgass S, Cooper A, Chopra M (2014) Lycopene treatment of prostate cancer cell lines inhibit adhesion and migration properties of the cells. Int J Med Sci 11:948–954. https://doi.org/10.7150/ijms.9137

Eliassen AH, Hendrickson SJ, Brinton LA et al (2012) Circulating carotenoids and risk of breast cancer: pooled analysis of eight prospective studies. J Natl Cancer Inst 104:1905–1916

ElMasry SR, Hathout RM, Abdel-Halim M, Mansour S (2018) In vitro transdermal delivery of sesamol using oleic acid chemically modified gelatin nanoparticles as a potential breast cancer medication. J Drug Deliv Sci Technol 48:30–39. https://doi.org/10.1016/j.jddst.2018.08.017
Encarnação JC, Pires AS, Amaral RA et al (2018) Butyrate, a dietary fiber derivative that improves irinotecan effect in colon cancer cells. J Nutr Biochem 56:183–192. https://doi.org/10.1016/j.jnutbio.2018.02.018
Ezzati M, Yousefi B, Velaei K, Safa A (2020) A review on anti-cancer properties of quercetin in breast cancer. Life Sci 248:117463. https://doi.org/10.1016/j.lfs.2020.117463
Fitzmaurice C, Abate D et al (2019) Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer groups, 1990 to 2017: a systematic analysis for the global burden of disease study. JAMA Oncol 5(12):1749–1768. https://doi.org/10.1001/jamaoncol.2019.2996
Force LM, Abdollahpour I, Advani SM et al (2019) The global burden of childhood and adolescent cancer in 2017: an analysis of the Global Burden of Disease Study 2017. Lancet Oncol 20:1211–1225. https://doi.org/10.1016/S1470-2045(19)30339
Fraga CG, Croft KD, Kennedy DO, Tomás-Barberán FA (2019) The effects of polyphenols and other bioactives on human health. Food Funct 10:514–528. https://doi.org/10.1039/c8fo01997e
Gallicchio L, Boyd K, Matanoski G et al (2008) Carotenoids and the risk of developing lung cancer: a systematic review. Am J Clin Nutr 88:372–383
Gann PH, Deaton RJ, Rueter EE et al (2015) A phase II randomized trial of lycopene-rich tomato extract among men with high-grade prostatic intraepithelial neoplasia. Nutr Cancer 67:1104–1112. https://doi.org/10.1080/01635581.2015.1075560
Gathirua-Mwangi WG, Zhang J (2014) Dietary factors and risk for advanced prostate cancer. Eur J Cancer Prev 23:96–109. https://doi.org/10.1097/CEJ.0b013e3283647394
Giovannucci E (2002) A review of epidemiologic studies of tomatoes, lycopene, and prostate cancer. Exp Biol Med 227(10):852–859. https://doi.org/10.1177/153537020222701003
Gloria NF, Soares N, Brand C et al (2014) Lycopene and beta-carotene induce cell-cycle arrest and apoptosis in human breast cancer cell lines. Anticancer Res 34:1377–1386
Gong WH, Zhao N, Zhang ZM et al (2017) The inhibitory effect of resveratrol on COX-2 expression in human colorectal cancer: a promising therapeutic strategy. Eur Rev Med Pharmacol Sci 21:1136–1143
González ML, Mariano D, Laiolo J et al (2017) Mechanism underlying the reversal of drug resistance in P-glycoprotein-expressing leukemia cells by pinoresinol and the study of a derivative. Front Pharmacol 8:1–19. https://doi.org/10.3389/fphar.2017.00205
Goodman GE, Thornquist MD, Balmes J et al (2004) The beta-carotene and retinol efficacy trial: incidence of lung cancer and cardiovascular disease mortality during 6-year follow-up after stopping β-carotene and retinol supplements. JNCI 96:1743–1750
Goralczyk R (2009) ß-Carotene and lung cancer in smokers: review of hypotheses and status of research. Nut Cancer 61(6):767–774. https://doi.org/10.1080/01635580903285155
Grosso G, Godos J, Lamuela-Raventos R et al (2017) A comprehensive meta-analysis on dietary flavonoid and lignan intake and cancer risk: level of evidence and limitations. Mol Nutr Food Res 61:1600930. https://doi.org/10.1002/mnfr.201600930
Guo Y, Bruno RS (2015) Endogenous and exogenous mediators of quercetin bioavailability. J Nutr Biochem 26:201–210. https://doi.org/10.1016/j.jnutbio.2014.10.008
Guo L, Zhu H, Lin C et al (2015) Associations between antioxidant vitamins and the risk of invasive cervical cancer in chinese women: a case–control study. Sci Rep 5:13607
Guo C, Bai M, Miao M, Miao Y (2018) Analysis of the chemical, pharmacological and clinical applications of Polygonum Cuspidatum. IOP Conf Ser Mater Sci Eng 301:012062. https://doi.org/10.1088/1757-899X/301/1/012062
Guruvayoorappan C, Kuttan G (2007) β-Carotene inhibits tumor-specific angiogenesis by altering the cytokine profile and inhibits the nuclear translocation of transcription factors in B16F-10 melanoma cells. Integr Cancer Ther 6(3):258–270. https://doi.org/10.1177/1534735407305978

Hada M, Mondul AM, Weinstein SJ et al (2019) Serum retinol and risk of overall and site-specific cancer in the alpha-tocopherol, beta-carotene cancer prevention (ATBC) study. Am J Epidemiol 189(6):532–542

Haghi A, Azimi H, Rahimi R (2017) A comprehensive review on pharmacotherapeutics of three phytochemicals, curcumin, quercetin, and allicin, in the treatment of gastric cancer. J Gastrointest Cancer 48:314–320. https://doi.org/10.1007/s12029-017-9997-7

Han Z, Yang Q, Liu B et al (2012) MicroRNA-622 functions as a tumor suppressor by targeting K-Ras and enhancing the anticarcinogenic effect of resveratrol. Carcinogenesis 33:131–139. https://doi.org/10.1093/carcin/bgr226

Harikumar KB, Kunnumakkara AB, Sethi G et al (2010) Resveratrol, a multitargeted agent, can enhance antitumor activity of gemcitabine in vitro and in orthotopic mouse model of human pancreatic cancer. Int J Cancer 127:257–268. https://doi.org/10.1002/ijc.25041

Hasan MM, Bae H (2017) An overview of stress-induced resveratrol synthesis in grapes: perspectives for resveratrol-enriched grape products. Molecules 22(2):294. https://doi.org/10.3390/molecules22020294

Hashemzaei M, Delarami FA, Yari A et al (2017) Anticancer and apoptosis-inducing effects of quercetin in vitro and in vivo. Oncol Rep 38(2):819–828. https://doi.org/10.3892/or.2017.5766

Hauner H, Hauner D (2010) The impact of nutrition on the development and prognosis of breast cancer. Breast Care 5:377–381. https://doi.org/10.1159/000322648

He X, Sun LM (2016) Dietary intake of flavonoid subclasses and risk of colorectal cancer: evidence from population studies. Oncotarget 7(18):26617

Heinen MM, Hughes MC, Ibiebele TI et al (2007) Intake of antioxidant nutrients and the risk of skin cancer. Eur J Cancer 43:2707–2716. https://doi.org/10.1016/j.ejca.2007.09.005

Holzapfel NP, Shokoohmand A, Wagner F et al (2017) Lycopene reduces ovarian tumor growth and intraperitoneal metastatic load. Am J Cancer Res 7:1322–1336

Honari M, Shafabakhsh R, Reiter RJ et al (2019) Resveratrol is a promising agent for colorectal cancer prevention and treatment: focus on molecular mechanisms. Cancer Cell Int 19:180. https://doi.org/10.1186/s12935-019-0906-y

Howells LM, Berry DP, Elliott PJ et al (2011) Phase I randomised double-blind pilot study of micronized resveratrol (SRT501) in patients with hepatic metastases—safety, pharmacokinetics and pharmacodynamics. Cancer Prev Res 4(9):1419–1425. https://doi.org/10.1158/1940-6207.CAPR-11-0148

Hu R, Saw CLL, Yu R, Kong ANT (2010) Regulation of NF-E2-related factor 2 signaling for cancer chemoprevention: antioxidant coupled with anti-inflammatory. Antioxidants Redox Signal 13:1679–1698. https://doi.org/10.1089/ars.2010.3276

Hui C, Qi X, Qianyong Z et al (2013) Flavonoids, flavonoid subclasses and breast cancer risk: a meta-analysis of epidemiologic studies. PLoS One 8(1):e54318. https://doi.org/10.1371/journal.pone.0054318

Huncharek M, Klassen H, Kupelnick B (2001) Dietary beta-carotene intake and the risk of epithelial ovarian cancer: a meta-analysis of 3,782 subjects from five observational studies. In Vivo 15(4):339–343

Islami F, Goding Sauer A, Miller KD et al (2018) Proportion and number of cancer cases and deaths attributable to potentially modifiable risk factors in the United States. CA Cancer J Clin 68:31–54. https://doi.org/10.3322/caac.21440

Jang M, Cai L, Udeani GO et al (1997) Cancer chemopreventive activity of resveratrol, a natural product derived from grapes. Science (80-) 275:218–220. https://doi.org/10.1126/science.275.5297.218

Jang SH, Lim JW, Kim H (2009) Mechanism of β-carotene-induced apoptosis of gastric cancer cells: involvement of ataxia-telangiectasia-mutated. Ann N Y Acad Sci 1171:156–162

Jaskulski S, Jung AY, Behrens S et al (2018) Circulating enterolactone concentrations and prognosis of postmenopausal breast cancer: assessment of mediation by inflammatory markers. Int J Cancer 143:2698–2708. https://doi.org/10.1002/ijc.31647

Jaskulski S, Jung AY, Huebner M et al (2019) Prognostic associations of circulating phytoestrogens and biomarker changes in long-term survivors of postmenopausal breast cancer. Nutr Cancer 72(7):1155–1169. https://doi.org/10.1080/01635581.2019.1672762

Jeong NH, Song ES, Lee JM et al (2009) Plasma carotenoids, retinol and tocopherol levels and the risk of ovarian cancer. Acta Obstet Gynecol Scand 88:457–462. https://doi.org/10.1080/00016340902807215

Jiang L-N, Liu Y-B, Li B-H (2019) Lycopene exerts anti-inflammatory effect to inhibit prostate cancer progression. Asian J Androl 21:80. https://doi.org/10.4103/aja.aja_70_18

Juin C, de Oliveira Junior RG, Fleury A et al (2018) Zeaxanthin from Porphyridium purpureum induces apoptosis in human melanoma cells expressing the oncogenic BRAF V600E mutation and sensitizes them to the BRAF inhibitor vemurafenib. Braz J Pharmacogn 28:457–467. https://doi.org/10.1016/j.bjp.2018.05.009

Jung S, Spiegelman D, Baglietto L et al (2013) Fruit and vegetable intake and risk of breast cancer by hormone receptor status. J Natl Cancer Inst 105:219–236. https://doi.org/10.1093/jnci/djs635

Kanahaiya D, Senthilraja P, Manivel G (2017) In silico analysis on phytoestrogens from dried fruits as beta- catenin inhibitors in liver cancer. Res J Life Sci Bioinform Pharm Chem Sci 2(5):52

Karppi J, Kurl S, Laukkanen JA et al (2012) Serum beta-carotene in relation to risk of prostate cancer: the kuopio ischaemic heart disease risk factor study. Nutr Cancer 64:361–367

Kawabata K, Mukai R, Ishisaka A (2015) Quercetin and related polyphenols: new insights and implications for their bioactivity and bioavailability. Food Funct 6:1399–1417. https://doi.org/10.1039/c4fo01178c

Kee JY, Han YH, Kim DS et al (2016) Inhibitory effect of quercetin on colorectal lung metastasis through inducing apoptosis, and suppression of metastatic ability. Phytomedicine 23:1680–1690. https://doi.org/10.1016/j.phymed.2016.09.011

Khamphio M, Barusrux S, Weerapreeyakul N (2016) Sesamol induces mitochondrial apoptosis pathway in HCT116 human colon cancer cells via pro-oxidant effect. Life Sci 158:46–56. https://doi.org/10.1016/j.lfs.2016.06.017

Khoo H-E, Prasad KN, Kong KW et al (2011) Carotenoids and their isomers: color pigments in fruits and vegetables. Molecules 16:1710–1738. https://doi.org/10.3390/molecules16021710

Kim H-S, Bowen P, Chen L et al (2003) Effects of tomato sauce consumption on apoptotic cell death in prostate benign hyperplasia and carcinoma. Nutr Cancer 47:40–47. https://doi.org/10.1207/s15327914nc4701_5

Kim TH, Shin YJ, Won AJ et al (2014a) Resveratrol enhances chemosensitivity of doxorubicin in multidrug-resistant human breast cancer cells via increased cellular influx of doxorubicin. Biochim Biophys Acta - Gen Subj 1840:615–625. https://doi.org/10.1016/j.bbagen.2013.10.023

Kim YS, Lee HA, Lim JY et al (2014b) β-Carotene inhibits neuroblastoma cell invasion and metastasis in vitro and in vivo by decreasing level of hypoxia-inducible factor-1α. J Nutr Biochem 25:655–664

Kim JH, Lee J, Choi J et al (2018) Dietary carotenoids intake and the risk of gastric cancer: a case—control study in Korea. Nutrients 10:8. https://doi.org/10.3390/nu10081031

Kim J, Lee J, Oh J et al (2019) Dietary lutein plus zeaxanthin intake and DICER1 rs3742330 A > G polymorphism relative to colorectal cancer risk. Sci Rep 9:3406

Kirsh VA, Mayne ST, Peters U et al (2006) A prospective study of lycopene and tomato product intake and risk of prostate cancer. Cancer Epidemiol Biomark Prev 15:92–98. https://doi.org/10.1158/1055-9965.EPI-05-0563

Kiyama R (2016) Biological effects induced by estrogenic activity of lignans. Trends Food Sci Technol 54:186–196. https://doi.org/10.1016/j.tifs.2016.06.007

Kocaturk NM, Akkoc Y, Kig C et al (2019) Autophagy as a molecular target for cancer treatment. Eur J Pharm Sci 134:116–137. https://doi.org/10.1016/j.ejps.2019.04.011

Kong X, Ma M, Zhang Y et al (2014) Differentiation therapy: sesamin as an effective agent in targeting cancer stem-like side population cells of human gallbladder carcinoma. BMC Complement Altern Med 14:254. https://doi.org/10.1186/1472-6882-14-254

Kooshyar MM, Mozafari PM, Amirchaghmaghi M et al (2017) A randomized placebo-controlled double-blind clinical trial of quercetin in the prevention and treatment of chemotherapy-induced oral mucositis. J Clin Diagn Res 11(3):ZC46–ZC50. https://doi.org/10.7860/JCDR/2017/23975.9571

Krinsky NI, Johnson EJ (2005) Carotenoid actions and their relation to health and disease. Mol Asp Med 26:459–516

Kristo AS, Klimis-zacas D, Sikalidis AK (2016) Protective role of dietary berries in cancer. Antioxidants (Basel) 5(4):37. https://doi.org/10.3390/antiox5040037

Kubo A, Corley DA (2007) Meta-analysis of antioxidant intake and the risk of esophageal and gastric cardia adenocarcinoma. Am J Gastroenterol 102:2323–2330

Kucuk O, Sarkar FH, Sakr W et al (2001) Phase II randomized clinical trial of lycopene supplementation before radical prostatectomy. Cancer Epidemiol Biomark Prev 10:861–868

Lai GY, Weinstein SJ, Taylor PR et al (2014) Effects of alpha-tocopherol and beta-carotene supplementation on liver cancer incidence and chronic liver disease mortality in the atbc study. Br J Cancer 111:2220–2223

Lane JA, Oliver SE, Appleby PN et al (2017) Prostate cancer risk related to foods, food groups, macronutrients and micronutrients derived from the UK Dietary Cohort Consortium food diaries. Eur J Clin Nutr 71:274–283. https://doi.org/10.1038/ejcn.2016.162

Larsson SC, Bergkvist L, Näslund I et al (2007) Vitamin A, retinol, and carotenoids and the risk of gastric cancer: a prospective cohort study. Am J Clin Nutr 85:497–503

Lee SH, Koo BS, Park SY, Kim YM (2015) Anti-angiogenic effects of resveratrol in combination with 5-fluorouracil on B16 murine melanoma cells. Mol Med Rep 12:2777–2783. https://doi.org/10.3892/mmr.2015.3675

Lee HH, Lee S, Shin YS, et al (2016) Anti-cancer effect of quercetin in xenograft models with EBV-associated human gastric carcinoma. Molecules 21(10). pii: E1286. https://doi.org/10.3390/molecules21101286

Lee DG, Go EB, Lee M et al (2019a) Gold nanoparticles conjugated with resveratrol induce cell cycle arrest in MCF-7 cell lines. Appl Biol Chem 62 (1), 1-6. https://doi.org/10.1186/s13765-019-0440-6

Lee SR, Quan KT, Byun HS et al (2019b) Accelerated degradation of cFLIPL and sensitization of the TRAIL DISC-mediated apoptotic cascade by pinoresinol, a lignan isolated from Rubia philippinensis. Sci Rep 9:1–13. https://doi.org/10.1038/s41598-019-49909-0

Lemmens L, Colle I, Van Buggenhout S et al (2014) Carotenoid bioaccessibility in fruit- and vegetable-based food products as affected by product (micro)structural characteristics and the presence of lipids: a review. Trends Food Sci Technol 38:125–135. https://doi.org/10.1016/J.TIFS.2014.05.005

Leoncini E, Nedovic D, Panic N et al (2015) Carotenoid intake from natural sources and head and neck cancer: a systematic review and meta-analysis of epidemiological studies. Cancer Epidemiol Biomark Prev 24:1003–1011. https://doi.org/10.1158/1055-9965.EPI-15-0053

Levi F, Pasche C, Lucchini F et al (2005) Resveratrol and breast cancer risk. Eur J Cancer Prev 14(2):139–142. https://doi.org/10.1097/00008469-200504000-00009

Li X, Xu J (2014) Meta-analysis of the association between dietary lycopene intake and ovarian cancer risk in postmenopausal women. Sci Rep 4:1–9. https://doi.org/10.1038/srep04885

Li B, Hou D, Guo H et al (2017) Resveratrol sequentially induces replication and oxidative stresses to drive p53-CXCR2 mediated cellular senescence in cancer cells. Sci Rep 7:1–12. https://doi.org/10.1038/s41598-017-00315-4

Li H, Tan L, Zhang JW et al (2019) Quercetin is the active component of Yang-Yin-Qing-Fei-Tang to induce apoptosis in non-small cell lung cancer. Am J Chin Med 47(4):879–893. https://doi.org/10.1142/S0192415X19500460

Lim JY, Wang XD (2020) Mechanistic understanding of β-cryptoxanthin and lycopene in cancer prevention in animal models. Biochim Biophys Acta Mol Cell Biol Lipids 1865(11):158652. https://doi.org/10.1016/j.bbalip.2020.158652

Lin HY, Shih A, Davis FB et al (2002) Resveratrol induced serine phosphorylation of p53 causes apoptosis in a mutant p53 prostate cancer cell line. J Urol 168:748–755. https://doi.org/10.1016/S0022-5347(05)64739-8

Lin Y, Yngve A, Lagergren J et al (2014) A dietary pattern rich in lignans, quercetin and resveratrol decrease the risk of oesophageal cancer. Br J Nutr 112(12):2002–2009. https://doi.org/10.1017/S0007114514003055

Lissowska J, Gail MH, Pee D et al (2004) Diet and stomach cancer risk in Warsaw, Poland. Nutr Cancer 48:149–159

Liu C, Lian F, Smith DE et al (2003) Lycopene supplementation inhibits lung squamous metaplasia and induces apoptosis via up-regulating insulin-like growth factor-binding protein3 in cigarette smoke-exposed ferrets. Cancer Res 63:3138–3144

Liu B, Zhou Z, Zhou W et al (2014) Resveratrol inhibits proliferation in human colorectal carcinoma cells by inducing G1/S-phase cell cycle arrest and apoptosis through caspase/cyclin-CDK pathways. Mol Med Rep 10:1697–1702. https://doi.org/10.3892/mmr.2014.2406

Liu H, Liu J, Wang S et al (2017a) Enterolactone has stronger effects than enterodiol on ovarian cancer. J Ovarian Res 10:1–9. https://doi.org/10.1186/s13048-017-0346-z

Liu Y, Tang ZG, Lin Y et al (2017b) Effects of quercetin on proliferation and migration of human glioblastoma U251 cells. Biomed Pharmacother 92:33–38. https://doi.org/10.1016/j.biopha.2017.05.044

Liu Z, Ren B, Wang Y et al (2017c) Sesamol induces human hepatocellular carcinoma cells apoptosis by impairing mitochondrial function and suppressing autophagy. Sci Rep 7:1–12. https://doi.org/10.1038/srep45728

Liu B, Chen Y, Li H (2019a) Effect and mechanism of sesamin combined with cisplatin on anti-lung cancer cell line H460. J Guangdong Pharm Univ 35 (2):252–255.

Liu H, Lee JI, Ahn TG (2019b) Effect of quercetin on the anti-tumor activity of cisplatin in EMT6 breast tumor-bearing mice. Obstet Gynecol Sci 62(4):242–248. https://doi.org/10.5468/ogs.2019.62.4.242

Logozzi M, Mizzoni D, Di Raimo R et al (2019) Oral administration of fermented papaya (FPP®) controls the growth of a murine melanoma through the in vivo induction of a natural antioxidant response. Cancers (Basel) 11(1):118. https://doi.org/10.3390/cancers11010118

López-Biedma A, Sánchez-Quesada C, Beltrán G et al (2016) Phytoestrogen (+)-pinoresinol exerts antitumor activity in breast cancer cells with different oestrogen receptor statuses. BMC Complement Altern Med 16:1–14. https://doi.org/10.1186/s12906-016-1233-7

Lowcock EC, Cotterchio M, Boucher BA (2013) Consumption of flaxseed, a rich source of lignans, is associated with reduced breast cancer risk. Cancer Causes Control 24:813–816. https://doi.org/10.1007/s10552-013-0155-7

Lucas I, Kolodziej H (2015) Trans-resveratrol induces apoptosis through ROS-triggered mitochondria-dependent pathways in A549 human lung adenocarcinoma epithelial cells. Planta Med 81:1038–1044. https://doi.org/10.1055/s-0035-1546129

Lucente P (2018) Primary care for survivors of colorectal cancer. J Am Acad Physician Assist 31:20–25. https://doi.org/10.1097/01.JAA.0000547743.54815.a0

Luo H, Yang A, Schulte BA et al (2013) Resveratrol induces premature senescence in lung cancer cells via ROS-mediated DNA damage. PLoS One 8(3):e60065. https://doi.org/10.1371/journal.pone.0060065

Ma ZJ, Wang XX, Su G et al (2016) Proteomic analysis of apoptosis induction by lariciresinol in human HepG2 cells. Chem Biol Interact 256:209–219. https://doi.org/10.1016/j.cbi.2016.07.011

Ma YS, Yao CN, Liu HC et al (2018a) Quercetin induced apoptosis of human oral cancer SAS cells through mitochondria and endoplasmic reticulum mediated signaling pathways. Oncol Lett 15:9663–9672. https://doi.org/10.3892/ol.2018.8584

Ma ZJ, Lu L, Yang JJ et al (2018b) Lariciresinol induces apoptosis in HepG2 cells via mitochondrial-mediated apoptosis pathway. Eur J Pharmacol 821:1–10. https://doi.org/10.1016/j.ejphar.2017.12.027

Madaan T, Choudhary AN, Gyenwalee S et al (2017) Lutein, a versatile phyto-nutraceutical: an insight on pharmacology, therapeutic indications, challenges and recent advances in drug delivery. PharmaNutrition 5:64–75. https://doi.org/10.1016/j.phanu.2017.02.005

Madigan M, Karhu E (2018) The role of plant-based nutrition in cancer prevention. JUMD 3:9. https://doi.org/10.20517/2572-8180.2018.05

Majdalawieh AF, Mansour ZR (2019) Sesamol, a major lignan in sesame seeds (Sesamum indicum): anti-cancer properties and mechanisms of action. Eur J Pharmacol 855:75–89. https://doi.org/10.1016/j.ejphar.2019.05.008

Mali AV, Joshi AA, Hegde MV, Kadam SS (2018) Enterolactone modulates the ERK/NF-κB/Snail signaling pathway in triple-negative breast cancer cell line MDA-MB-231 to revert the TGF-β-induced epithelial-mesenchymal transition. Cancer Biol Med 15:137–156. https://doi.org/10.20892/j.issn.2095-3941.2018.0012

Mali AV, Padhye SB, Anant S et al (2019) Anticancer and antimetastatic potential of enterolactone: clinical, preclinical and mechanistic perspectives. Eur J Pharmacol 852:107–124. https://doi.org/10.1016/j.ejphar.2019.02.022

Manayi A, Vazirian M, Hadjiakhoondi A (2020) Disease modifying effects of phytonutrients at gene levels. In: Nabavi SM, Suntar I, Barreca D, Khan H (eds) Phytonutrients in food. Woodhead Publishing, Duxford, pp 103–116. https://doi.org/10.1016/B978-0-12-815354-3.00005-8

Martínez V, Mitjans M, Vinardell MP (2014) Cytoprotective effects of polyphenols against oxidative damage. In: Polyphenols in human health disease, vol 1. Elsevier, Amsterdam, pp 275–288. https://doi.org/10.1016/B978-0-12-398456-2.00022-0

Mathews-Roth MM (1982) Antitumor activity of beta-carotene, canthaxanthin and phytoene. Oncology 39:33–37

McCann SE, Ambrosone CB, Moysich KB et al (2005) Intakes of selected nutrients, foods, and phytochemicals and prostate cancer risk in western New York. Nutr Cancer 53(1):33–41. https://doi.org/10.1207/s15327914nc5301_4

McCann SE, Edge SB, Hicks DG, et al. (2014) A pilot study comparing the effect of flaxseed, aromatase inhibitor, and the combination on breast tumor biomarkers. Nutr Cancer. 66(4):566–575. https://doi.org/10.1080/01635581.2014.894097

Meng J, Guo F, Xu H et al (2016) Combination therapy using co-encapsulated resveratrol and paclitaxel in liposomes for drug resistance reversal in breast cancer cells in vivo. Sci Rep 6:1–11. https://doi.org/10.1038/srep22390

Meybodi NM, Mortazavian AM, Monfared AB et al (2017) Phytochemicals in cancer prevention: a review of the evidence. Int J Cancer Manag 27(5):599–612. https://doi.org/10.17795/ijcp-7219

Milani A, Basirnejad M, Shahbazi S et al (2017) Carotenoids: biochemistry, pharmacology and treatment. Br J Pharmacol 174:1290–1324. https://doi.org/10.1111/bph.13625

Mishra OP, Popov AV, Pietrofesa RA, Christofidou-Solomidou M (2016) Gamma-irradiation produces active chlorine species (ACS) in physiological solutions: secoisolariciresinol diglucoside (SDG) scavenges ACS—a novel mechanism of DNA radioprotection. Biochim Biophys Acta 1860:1884–1897. https://doi.org/10.1016/j.bbagen.2016.05.037

Mitra S, Dash R (2018) Natural products for the management and prevention of breast cancer. Evid Based Complement Alternat Med 2018:8324696. https://doi.org/10.1155/2018/8324696

Moen B, Henjum K, Måge I et al (2016) Effect of dietary fibers on cecal microbiota and intestinal tumorigenesis in azoxymethane treated A/J Min/+ mice. PLoS One 11:1–20. https://doi.org/10.1371/journal.pone.0155402

Mohamadyar-Toupkanlou F, Esfandiari M, Kashef-Saberi MS et al (2017) The structural bioinformatics analysis of biophenolic lignan-estrogen receptor interaction. Curr Cancer Drug Targets 17:1–8. https://doi.org/10.2174/1568009617666170623121446

Mokbel K, Wazir U, Mokbel K (2019) Chemoprevention of prostate cancer by natural agents: evidence from molecular and epidemiological studies. Anticancer Res 39:5231–5259. https://doi.org/10.21873/anticanres.13720

Moosavi MA, Haghi A, Rahmati M et al (2018) Phytochemicals as potent modulators of autophagy for cancer therapy. Cancer Lett 424:46–69. https://doi.org/10.1016/j.canlet.2018.02.030

Moselhy SS, Al Mslmani MAB (2008) Chemopreventive effect of lycopene alone or with melatonin against the genesis of oxidative stress and mammary tumors induced by 7,12 dimethyl(a) benzanthracene in Sprague Dawely female rats. Mol Cell Biochem 319:175–180. https://doi.org/10.1007/s11010-008-9890-6

Mutlu AE, Kasacı T, Yılmaz AM et al (2016) Quercetin-induced cell death in human papillary thyroid cancer (B-CPAP) cells. J Thyroid Res 2016:9843675. https://doi.org/10.1155/2016/9843675

Namitha KK, Negi PS (2010) Chemistry and biotechnology of carotenoids. Crit Rev Food Sci Nutr 50(8):728–760. https://doi.org/10.1080/10408398.2010.499811

Navarro SL, Neuhouser ML, Cheng TYD, Tinker LF, Shikany JM, Snetselaar L et al (2016) The interaction between dietary fiber and fat and risk of colorectal cancer in the women's health initiative. Nutrients 8(12):779. https://doi.org/10.3390/nu8120779

Neuwirthová J, Gál B, Smilek P, Urbánková P (2018) Potential of the flavonoid quercetin to prevent and treat cancer—current status of research. Klin Onkol 31(3):184–190. https://doi.org/10.14735/amko2018184

Nguyen AV, Martinez M, Stamos MJ et al (2009) Results of a phase I pilot clinical trial examining the effect of plant-derived resveratrol and grape powder on Wnt pathway target gene expression in colonic mucosa and colon cancer. Cancer Manag Res 1:25–37. https://doi.org/10.2147/cmar.s4544

Ning Y, Fu YL, Zhang QH et al (2019) Inhibition of in vitro and in vivo ovarian cancer cell growth by pinoresinol occurs by way of inducing autophagy, inhibition of cell invasion, loss of mitochondrial membrane potential and inhibition Ras/MEK/ERK signalling pathway. J BUON 24:709–714

Niranjana R, Gayathri R, Mol SN et al (2015) Carotenoids modulate the hallmarks of cancer cells. J Funct Foods 18:968–985

Offringa LC, Stanton MV, Hauser ME, Gardner CD (2019) Fruits and vegetables versus vegetables and fruits: rhyme and reason for word order in health messages. Am J Lifestyle Med 13:224–234. https://doi.org/10.1177/1559827618769605

Okuyama Y, Ozasa K, Oki K et al (2014) Inverse associations between serum concentrations of zeaxanthin and other carotenoids and colorectal neoplasm in Japanese. Int J Clin Oncol 19:87–97

Omenn GS, Goodman GE, Thornquist MD et al (1996) Risk factors for lung cancer and for intervention effects in CARET, the beta-carotene and retinol efficacy trial. J Natl Cancer Inst 88:1550–1559

Paller CJ, Rudek MA, Zhou XC et al (2015) A phase I study of muscadine grape skin extract in men with biochemically recurrent prostate cancer: safety, tolerability, and dose determination. Prostate 75(14):1518–1525. https://doi.org/10.1002/pros.23024

Palozza P, Calviello G, Serini S et al (2001) β-carotene at high concentrations induces apoptosis by enhancing oxy-radical production in human adenocarcinoma cells. Free Radic Biol Med 30:1000–1007

Palozza P, Serini S, Maggiano N et al (2002) Induction of cell cycle arrest and apoptosis in human colon adenocarcinoma cell lines by β-carotene through down-regulation of cyclin A and Bcl-2 family proteins. Carcinogenesis 23:11–18

Patel KR, Brown VA, Jones DJL et al (2010) Clinical pharmacology of resveratrol and its metabolites in colorectal cancer patients. Cancer Res 70(19):7392–7399. https://doi.org/10.1158/0008-5472.CAN-10-2027

Paul B, Masih I, Deopujari J, Charpentier C (1999) Occurrence of resveratrol and pterostilbene in age-old darakchasava, an ayurvedic medicine from India. J Ethnopharmacol 68:71–76

Pedersen JK, Engholm G, Skytthe A et al (2016) Cancer and aging: epidemiology and methodological challenges. Acta Oncol 55(Suppl 1):7–12. https://doi.org/10.3109/0284186X.2015.1114670

Peisch SF, Van Blarigan EL, Chan JM et al (2017) Prostate cancer progression and mortality: a review of diet and lifestyle factors. World J Urol 35:867–874. https://doi.org/10.1007/s00345-016-1914-3

Pelucchi C, Tramacere I, Bertuccio P et al (2008) Dietary intake of selected micronutrients and gastric cancer risk: an Italian case-control study. Ann Oncol 20:160–165

Perez-Cornago A, Travis RC, Appleby PN et al (2017) Fruit and vegetable intake and prostate cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC). Int J Cancer 141:287–297. https://doi.org/10.1002/ijc.30741

Peterson J, Dwyer J, Adlercreutz H et al (2010) Dietary lignans: physiology and potential for cardiovascular disease risk reduction. Nutr Rev 68:571–603. https://doi.org/10.1111/j.1753-4887.2010.00319.x

Petimar J, Wilson KM, Wu K et al (2017) A pooled analysis of 15 prospective cohort studies on the association between fruit, vegetable, and mature bean consumption and risk of prostate cancer. Cancer Epidemiol Biomarkers Prev 26:1–12

Pezzuto JM (2019) Resveratrol: twenty years of growth, development and controversy. Biomol Ther 27:1–14. https://doi.org/10.4062/biomolther.2018.176

Pham TND, Stempel S, Shields MA, et al (2019) Quercetin enhances the anti-tumor effects of BET inhibitors by suppressing hnRNPA1. Int J Mol Sci 20(17). pii: E4293. https://doi.org/10.3390/ijms20174293

Poe K (2017) Plant-based diets and phytonutrients: potential health benefits and disease prevention. Arch Med 9:6–7. https://doi.org/10.21767/1989-5216.1000249

Pounis G, Di Castelnuovo A, Bonaccio M, Costanzo S, Persichillo M et al (2016) Flavonoid, lignan intake in a Mediterranean population: proposal for a holistic approach in polyphenol dietary analysis, the Moli-sani Study. Eur J Clin Nutr 70:338–345. https://doi.org/10.1038/ejcn.2015.178

Prager GW, Braga S, Bystricky B et al (2018) Global cancer control: responding to the growing burden, rising costs and inequalities in access. ESMO open 3:1–10. https://doi.org/10.1136/esmoopen-2017-000285

Qi J, Yu J, Li Y et al (2019) Alternating consumption of β-glucan and quercetin reduces mortality in mice with colorectal cancer. Food Sci Nutr 7(10):3273–3285. https://doi.org/10.1002/fsn3.1187

Rafi MM, Kanakasabai S, Reyes MD et al (2013) Lycopene modulates growth and survival associated genes in prostate cancer. J Nutr Biochem 24:1724–1734

Ramírez-Garza SL, Laveriano-Santos EP, Marhuenda-Muñoz M et al (2018) Health effects of resveratrol: results from human intervention trials. Nutrients 10:1–18. https://doi.org/10.3390/nu10121892

Ranjan A, Ramachandran S, Gupta N et al (2019) Role of phytochemicals in cancer prevention. Int J Mol Sci 20:1–17. https://doi.org/10.3390/ijms20204981

Rawla P, Barsouk A (2019) Epidemiology of gastric cancer: global trends, risk factors and prevention. Prz Gastroenterol 14:26–38. https://doi.org/10.5114/pg.2018.80001

Redondo-Blanco S, Fernández J, Gutiérrez-del-Río I et al (2017) New insights toward colorectal cancer chemotherapy using natural bioactive compounds. Front Pharmacol 8:1–22. https://doi.org/10.3389/fphar.2017.00109k

Renaud S, Gueguen R (1998) The French paradox and wine drinking. Novartis Found Symp 216:208–217. https://doi.org/10.1002/9780470515549.ch13

Renaud SC, Guéguen R, Schenker J et al (1998) Alcohol and mortality in middle-aged men from Eastern France. Epidemiology 9(2):184–188

Ribaya-Mercado JD, Blumberg JB (2004) Lutein and zeaxanthin and their potential roles in disease prevention. J Am Coll Nutr 23:567S–587S. https://doi.org/10.1080/07315724.2004.10719427

Rodríguez-García C, Sánchez-Quesada C, Toledo E et al (2019) Naturally lignan-rich foods: a dietary tool for health promotion? Molecules 24(5):917. https://doi.org/10.3390/molecules24050917

Rowles JL, Erdman JW (2020) Carotenoids and their role in cancer prevention. Biochim Biophys Acta Mol Cell Biol Lipids 1865(11):158613. https://doi.org/10.1016/j.bbalip.2020.158613

Rowles JL, Ranard KM, Smith JW et al (2017) Increased dietary and circulating lycopene are associated with reduced prostate cancer risk: a systematic review and meta-analysis. Prostate Cancer Prostatic Dis 20:361–377

Rowles JL, Ranard KM, Applegate CC et al (2018) Processed and raw tomato consumption and risk of prostate cancer: a systematic review and dose–response meta-analysis. Prostate Cancer Prostatic Dis 21(3):319–336

Russo M, Russo GL (2018) Autophagy inducers in cancer. Biochem Pharmacol 153:51–61. https://doi.org/10.1016/j.bcp.2018.02.007

Sahin K, Yenice E, Tuzcu M et al (2018) Lycopene protects against spontaneous ovarian cancer formation in laying hens. J Cancer Prev 23:25–36. https://doi.org/10.15430/jcp.2018.23.1.25

Saini RK, Keum Y-S (2018) Significance of genetic, environmental, and pre- and postharvest factors affecting carotenoid contents in crops: a review. J Agric Food Chem 66:5310–5324. https://doi.org/10.1021/acs.jafc.8b01613

Sajadimajd S, Bahramsoltani R, Iranpanah A et al (2020) Advances on natural polyphenols as anticancer agents for skin cancer. Pharmacol Res 151:104584. https://doi.org/10.1016/j.phrs.2019.104584

Salehi B, Mishra AP, Nigam M et al (2018) Resveratrol: a double-edged sword in health benefits. Biomedicine 6:1–20. https://doi.org/10.3390/biomedicines6030091

Salvatore Benito A, Valero Zanuy MÁ, Alarza Cano M et al (2019) Adherence to Mediterranean diet: a comparison of patients with head and neck cancer and healthy population. Endocrinol Diabetes Nutr [Internet] 66(7):417–424. https://doi.org/10.1016/j.endinu.2018.12.002

Sauter ER (2018) Breast cancer prevention: current approaches and future directions. Eur J Breast Health 14(2):64–71. https://doi.org/10.5152/ejbh.2018.3978

Savio M, Ferraro D, MacCario C et al (2016) Resveratrol analogue 4,4′-dihydroxy-trans-stilbene potently inhibits cancer invasion and metastasis. Sci Rep 6:1–12. https://doi.org/10.1038/srep19973

Schwarz S, Obermüller-Jevic UC, Hellmis E, Koch Wet al. (2008) Lycopene inhibits disease progression in patients with benign prostate hyperplasia. J Nutr 138(1):49–53. https://doi.org/10.1093/jn/138.1.49

Sesso HD, Buring JE, Zhang SM et al (2005) Dietary and plasma lycopene and the risk of breast cancer. Cancer Epidemiol Biomark Prev 14:1074–1081. https://doi.org/10.1158/1055-9965.EPI-04-0683

Sgambato A, Ardito R, Faraglia B et al (2001) Resveratrol, a natural phenolic compound, inhibits cell proliferation and prevents oxidative DNA damage. Mutat Res Genet Toxicol Environ Mutagen 496:171–180. https://doi.org/10.1016/S1383-5718(01)00232-7

Shah NR, Patel BM (2016) Secoisolariciresinol diglucoside rich extract of L. usitatissimum prevents diabetic colon cancer through inhibition of CDK4. Biomed Pharmacother 83:733–739. https://doi.org/10.1016/j.biopha.2016.07.041

Sheth S, Jajoo S, Kaur T et al (2012) Resveratrol reduces prostate cancer growth and metastasis by inhibiting the Akt/MicroRNA-21 pathway. PLoS One 7(12):e51655. https://doi.org/10.1371/journal.pone.0051655

Sheu MT, Jhan HJ, Hsieh CM et al (2015) Efficacy of antioxidants as a complementary and alternative medicine (CAM) in combination with the chemotherapeutic agent doxorubicin. Integr Cancer Ther 14(2):184–195. https://doi.org/10.1177/1534735414564425

Shin M, Jeon Y, Jin J (2018) Apoptotic effect of enterodiol, the final metabolite of edible lignans, in colorectal cancer cells. J Sci Food Agric 99(5):2411–2419. https://doi.org/10.1002/jsfa.9448

Shu Y, Xie B, Liang Z, Chen J (2018) Quercetin reverses the doxorubicin resistance of prostate cancer cells by downregulating the expression of c-met. Oncol Lett 15(2):2252–2258. https://doi.org/10.3892/ol.2017.7561

Siao AC, Hou CW, Kao YH, Jeng KC (2015) Effect of sesamin on apoptosis and cell cycle arrest in human breast cancer MCF-7 cells. Asian Pacific J Cancer Prev 16:3779–3783. https://doi.org/10.7314/APJCP.2015.16.9.3779

Siegel RL, Miller KD, Jemal A (2019) Cancer statistics, 2019. CA Cancer J Clin 69:7–34. https://doi.org/10.3322/caac.21551

Siler U, Barella L, Spitzer V et al (2004) Lycopene and vitamin E interfere with autocrine/paracrine loops in the Dunning prostate cancer model. FASEB J 18(9):1019–1021. https://doi.org/10.1096/fj.03-1116fje

Simon MS, Djuric Z, Dunn B et al (2000) An evaluation of plasma antioxidant levels and the risk of breast cancer: a pilot case control study. Breast J 6:388–395. https://doi.org/10.1046/j.1524-4741.2000.20067.x

Singh SK, Banerjee S, Acosta EP et al (2017) Resveratrol induces cell cycle arrest and apoptosis with docetaxel in prostate cancer cells via a p53/p21WAF1/CIP1 and p27KIP1 pathway. Oncotarget 8:17216–17228. https://doi.org/10.18632/oncotarget.15303

Sirerol JA, Rodríguez ML, Mena S et al (2016) Role of natural stilbenes in the prevention of cancer. Oxid Med Cell Longev 2016:3128951. https://doi.org/10.1155/2016/3128951

Slavin J (2013) Fiber and prebiotics: mechanisms and health benefits. Nutrients 5:1417–1435. https://doi.org/10.3390/nu5041417

Soares CN, Teodoro AJ, Oliveira FL et al (2013) Borojevic, influence of lycopene on cell viability, cell cycle, and apoptosis of human prostate cancer and benign hyperplastic cells. Nutr Cancer 65:1076–1085

Soares N d CP, Machado CL, Trindade BB et al (2017) Lycopene extracts from different tomato-based food products induce apoptosis in cultured human primary prostate cancer cells and regulate TP53, Bax and Bcl-2 transcript expression. Asian Pacific J Cancer Prev 18:339–345. https://doi.org/10.22034/APJCP.2017.18.2.339

Soltani M, Ahmadian Chashmi N et al (2020) Investigating the cytotoxic effect of pinoresinol and lariciresinol on breast cancer cell line SKBr3. JMBS 11(1):13–20

Srinivasan A, Thangavel C, Liu Y et al (2015) Quercetin regulates β-catenin signaling and reduces the migration of triple negative breast cancer. Mol Carcinog 55:743–756. https://doi.org/10.1002/mc.22318

Steiner JL, Davis JM, McClellan JL et al (2014) Dose-dependent benefits of quercetin on tumorigenesis in the C3(1)/SV40Tag transgenic mouse model of breast cancer. Cancer Biol Ther 15(11):1456–1467. https://doi.org/10.4161/15384047.2014.955444

Stepien M, Chajes V, Romieu I (2016) The role of diet in cancer: the epidemiologic link. Salud Publica Mex 58:261–273. https://doi.org/10.21149/spm.v58i2.7795

Su S, Li Q, Liu Y et al (2014) Sesamin ameliorates doxorubicin-induced cardiotoxicity: involvement of Sirt1 and Mn-SOD pathway. Toxicol Lett 224:257–263. https://doi.org/10.1016/j.toxlet.2013.10.034

Su S, Cheng X, Wink M (2015) Cytotoxicity of arctigenin and matairesinol against the T-cell lymphoma cell line CCRF-CEM. J Pharm Pharmacol 67:1316–1323. https://doi.org/10.1111/jphp.12426

Swann R, Perkins KA, Velentzis LS et al (2013) Maturitas the DietCompLyf study: a prospective cohort study of breast cancer survival and phytoestrogen consumption. Maturitas 75:232–240. https://doi.org/10.1016/j.maturitas.2013.03.018

Tajaddini A, Pourzand A, Sanaat Z, Pirouzpanah S (2015) Dietary resistant starch contained foods and breast cancer risk: a case-control study in northwest of Iran. Asian Pac J Cancer Prev 16:4185–4192. https://doi.org/10.7314/apjcp.2015.16.10.4185

Takachi R, Inoue M, Sawada N et al (2010) Fruits and vegetables in relation to prostate cancer in Japanese Men: the Japan public health center-based prospective study. Nutr Cancer Int J 62:30–39

Takaoka M (1939) Resveratrol, a new phenolic compound, from Veratrum grandiflorum. J Chem Soc Jpn 60:1090–1100

Tan L, Wang W, He G et al (2016) Resveratrol inhibits ovarian tumor growth in an in vivo mouse model. Cancer 122:722–729. https://doi.org/10.1002/cncr.29793

Tang GY, Meng X, Gan RY et al (2019) Health functions and related molecular mechanisms of tea components: an update review. Int J Mol Sci 20(24):6196. https://doi.org/10.3390/ijms20246196

Teodoro AJ, Oliveira FL, Martins NB et al (2012) Effect of lycopene on cell viability and cell cycle progression in human cancer cell lines. Cancer Cell Int 12(1):36. https://doi.org/10.1186/1475-2867-12-36

Thomas E, Gopalakrishnan V, Hegde M et al (2016) A novel resveratrol-based tubulin inhibitor induces mitotic arrest and activates apoptosis in cancer cells. Sci Rep 6:1–13. https://doi.org/10.1038/srep34653

Tian Y, Song W, Li D et al (2019) Resveratrol as a natural regulator of autophagy for prevention and treatment of cancer. Onco Targets Ther 12:8601–8609. https://doi.org/10.2147/OTT.S213043

Touré A, Xueming X (2010) Flaxseed lignans: source, biosynthesis, metabolism, antioxidant activity, bio-active components, and health benefits. Compr Rev Food Sci Food Saf 9:261–269. https://doi.org/10.1111/j.1541-4337.2009.00105

Trefflich I, Marschall HU, Di Giuseppe R et al (2020) Associations between dietary patterns and bile acids—results from a cross-sectional study in vegans and omnivores. Nutrients 12(1):47. https://doi.org/10.3390/nu12010047

Turner ND (2014) Human nutrition: cancer health concerns. Encyclopedia of meat sciences. Elsevier, Amsterdam, pp 100–104. https://doi.org/10.1016/B978-0-12-384731-7.00176-8

Umesawa M, Iso H, Mikami K et al (2014) Relationship between vegetable and carotene intake and risk of prostate cancer: the JACC study. Br J Cancer 110:792–796. https://doi.org/10.1038/bjc.2013.1685

Upadhyaya KR, Radha KS, Madhyastha HK (2007) Cell cycle regulation and induction of apoptosis by β-carotene in U937 and HL-60 leukemia cells. BMB Rep 40(6):1009–1015. https://doi.org/10.5483/bmbrep.2007.40.6.1009

Uppala PT, Dissmore T, Lau BHS et al (2013) Selective inhibition of cell proliferation by lycopene in mcf-7 breast cancer cells in vitro: a proteomic analysis. Phytother Res 27:595–601. https://doi.org/10.1002/ptr.4764

Van Breemen RB, Sharifi R, Viana M et al (2011) Antioxidant effects of lycopene in African American men with prostate cancer or benign prostate hyperplasia: a randomized, controlled trial. Cancer Prev Res 4:711–718. https://doi.org/10.1158/1940-6207.CAPR-10-0288

Velalopoulou A, Tyagi S, Pietrofesa RA et al (2016) The flaxseed-derived lignan phenolic secoisolariciresinol diglucoside (SDG) protects non-malignant lung cells from radiation damage. Int J Mol Sci 17:1–15. https://doi.org/10.3390/ijms17010007

Virtamo J, Edwards BK, Virtanen M et al (2000) Effects of supplemental -tocopherol and -carotene on urinary tract cancer. Cancer Causes Control 11:933–939

Watkins EJ (2019) Overview of breast cancer. J. Am. Acad. Physician Assist. 32(10):13–7. https://doi.org/10.1097/01.JAA.0000580524.95733.3d

Wan L, Tan HL, Thomas-Ahner JM et al (2014) Dietary tomato and lycopene impact androgen signaling- and carcinogenesis-related gene expression during early TRAMP prostate carcinogenesis. Cancer Prev Res (Phila) 7:1228–1239

Wang Y, Gapstur SM, Gaudet MM et al (2015) Plasma carotenoids and breast cancer risk in the Cancer Prevention Study II Nutrition Cohort. Cancer Causes Control 26:1233–1244

Ward EM, Sherman RL, Henley SJ et al (2019) Annual report to the nation on the status of cancer, featuring cancer in men and women age 20–49 years. J Natl Cancer Inst 111(12):1279–1297

Whyte L, Huang YY, Torres K, Mehta RG (2007) Molecular mechanisms of resveratrol action in lung cancer cells using dual protein and microarray analyses. Cancer Res 67:12007–12017. https://doi.org/10.1158/0008-5472.CAN-07-2464

World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) (2018) Diet, nutrition, physical activity and cancer: a global perspective: continuous update project expert report. https://www.wcrf.org/sites/default/files/Wholegrains-veg-and-fruit.pdf. Accessed 18 Feb 2020

Wu JY, Tsai KW, Shee JJ et al (2010) 4'-Chloro-3,5-dihydroxystilbene, a resveratrol derivative, induces lung cancer cell death. Acta Pharmacol Sin 31:81–92. https://doi.org/10.1038/aps.2009.182

Wu S, Powers S, Zhu W, Hannun YA (2016) Substantial contribution of extrinsic risk factors to cancer development. Nature 529:43–47. https://doi.org/10.1038/nature16166

Wu L, Li J, Liu T et al (2019) Quercetin shows anti-tumor effect in hepatocellular carcinoma LM3 cells by abrogating JAK2/STAT3 signaling pathway. Cancer Med 8(10):4806–4820. https://doi.org/10.1002/cam4.2388

Xiao Q, Zhu W, Feng W et al (2019) A review of resveratrol as a potent chemoprotective and synergistic agent in cancer chemotherapy. Front Pharmacol 9:1–10. https://doi.org/10.3389/fphar.2018.01534

Xu P, Cai F, Liu X, Guo L (2015) Sesamin inhibits lipopolysaccharide-induced proliferation and invasion through the p38-MAPK and NF-κB signaling pathways in prostate cancer cells. Oncol Rep 33:3117–3123. https://doi.org/10.3892/or.2015.3888

Xu H, Ding Y, Xin X et al (2018) Dietary fiber intake is associated with a reduced risk of ovarian cancer: a dose-response meta-analysis. Nutr Res 57:1–11. https://doi.org/10.1016/j.nutres.2018.04.011

Xu J, Li Y, Hu H (2019) Effects of lycopene on ovarian cancer cell line SKOV3 in vitro: suppressed proliferation and enhanced apoptosis. Mol Cell Probes 46:101419. https://doi.org/10.1016/j.mcp.2019.07.002

Yamawaki M, Nishi K, Nishimoto S et al (2011) Immunomodulatory effect of (−)-matairesinol in vivo and ex vivo. Biosci Biotechnol Biochem 75:859–863. https://doi.org/10.1271/bbb.100781

Yan B, Lu MS, Wang L et al (2016) Specific serum carotenoids are inversely associated with breast cancer risk among Chinese women: a case-control study. Br J Nutr 115:129–137. https://doi.org/10.1017/S000711451500416X

Yang T, Yang X, Wang X, Wang Y, Song Z (2013) The role of tomato products and lycopene in the prevention of gastric cancer: a meta-analysis of epidemiologic studies. Med Hypotheses 80(4):383–388. https://doi.org/10.1016/j.mehy.2013.01.005

Yang F, Jiang X, Song L et al (2016) Quercetin inhibits angiogenesis through thrombospondin-1 upregulation to antagonize human prostate cancer PC-3 cell growth in vitro and in vivo. Oncol Rep 35(3):1602–1610. https://doi.org/10.3892/or.2015.4481

Yousef M, Vlachogiannis IA, Tsiani E (2017) Effects of resveratrol against lung cancer: in vitro and in vivo studies. Nutrients 9:1–14. https://doi.org/10.3390/nu9111231

Yu XD, Yang JL, Zhang WL, Liu DX (2016) Resveratrol inhibits oral squamous cell carcinoma through induction of apoptosis and G2/M phase cell cycle arrest. Tumor Biol 37:2871–2877. https://doi.org/10.1007/s13277-015-3793-4

Yuan L, Zhang Y, Xia J et al (2015) Resveratrol induces cell cycle arrest via a p53-independent pathway in A549 cells. Mol Med Rep 11:2459–2464. https://doi.org/10.3892/mmr.2014.3100

Zamora-Ros R, Not C, Guinó E et al (2013) Association between habitual dietary flavonoid and lignan intake and colorectal cancer in a Spanish case-control study (the Bellvitge Colorectal Cancer Study). Cancer Causes Control 24:549–557. https://doi.org/10.1007/s10552-012-9992-z

Zamora-Ros R, Cayssials V, Jenab M et al (2018) Dietary intake of total polyphenol and polyphenol classes and the risk of colorectal cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. Eur J Epidemiol 33:1063–1075. https://doi.org/10.1007/s10654-018-0408-6

Zeng Y, Shen Z, Gu W, Wu M (2018) Bioinformatics analysis to identify action targets in NCI-N87 gastric cancer cells exposed to quercetin. Pharm Biol 56(1):393–398. https://doi.org/10.1080/13880209.2018.1493610

Zennami K, Choi SM, Liao R et al (2019) PDCD4 is an androgen-repressed tumor suppressor that regulates prostate cancer growth and castration resistance. Mol Cancer Res 17:618–627. https://doi.org/10.1158/1541-7786.MCR-18-0837

Zhang L, Dai F, Sheng PL et al (2015a) Resveratrol analogue 3,4,4′-trihydroxy-trans-stilbene induces apoptosis and autophagy in human non-small-cell lung cancer cells in vitro. Acta Pharmacol Sin 36:1256–1265. https://doi.org/10.1038/aps.2015.46

Zhang L, Si J, Li G et al (2015b) Umbelliprenin and lariciresinol isolated from a long-term-used herb medicine Ferula sinkiangensis induce apoptosis and G0/G1 arresting in gastric cancer cells. RSC Adv 5:91006–91017. https://doi.org/10.1039/c5ra11335k

Zhang Y, Zhu X, Huang T et al (2016) β-Carotene synergistically enhances the anti-tumor effect of 5-fluorouracil on esophageal squamous cell carcinoma in vivo and in vitro. Toxicol Lett 261:49–58

Zhang W, Yin G, Dai J et al (2017a) Chemoprevention by quercetin of oral squamous cell carcinoma by suppression of the NF-κB signaling pathway in DMBA-treated hamsters. Anticancer Res 37(8):4041–4049. https://doi.org/10.21873/anticanres.11789

Zhang XF, Huang FH, Zhang GL et al (2017b) Novel biomolecule lycopene-reduced graphene oxide-silver nanoparticle enhances apoptotic potential of trichostatin A in human ovarian cancer cells (SKOV3). Int J Nanomedicine 12:7551–7575. https://doi.org/10.2147/IJN.S144161

Zhang Y, Zhao H, Di Y et al (2018) Antitumor activity of pinoresinol in vitro: inducing apoptosis and inhibiting HepG2 invasion. J Funct Foods 45:206–214. https://doi.org/10.1016/j.jff.2018.04.009

Zhao W, Bao P, Qi H, You H (2009) Resveratrol down-regulates survivin and induces apoptosis in human multidrug-resistant SPC-A-1/CDDP cells. Oncol Rep 23:1265–1270. https://doi.org/10.3892/or_00000634

Zhao Y, Huan ML, Liu M et al (2016) Doxorubicin and resveratrol co-delivery nanoparticle to overcome doxorubicin resistance. Sci Rep 6:1–15. https://doi.org/10.1038/srep35267

Zhao Y, Tang H, Zeng X et al (2018) Resveratrol inhibits proliferation, migration and invasion via Akt and ERK1/2 signaling pathways in renal cell carcinoma cells. Biomed Pharmacother 98:36–44. https://doi.org/10.1016/j.biopha.2017.12.029

Zhao J, Fang Z, Zha Z et al (2019) Quercetin inhibits cell viability, migration and invasion by regulating miR-16/HOXA10 axis in oral cancer. Eur J Pharmacol 847:11–18. https://doi.org/10.1016/j.ejphar.2019.01.006

Zhou X, Zhao Y, Wang J et al (2018) Resveratrol represses estrogen-induced mammary carcinogenesis through NRF2-UGT1A8-estrogen metabolic axis activation. Biochem Pharmacol 155:252–263. https://doi.org/10.1016/j.bcp.2018.07.006

Zhu W, Qin W, Zhang K et al (2012) Trans-resveratrol alters mammary promoter hypermethylation in women at increased risk for breast cancer. Nutr Cancer 64(3):393–400. https://doi.org/10.1080/01635581.2012.654926