Chapter 10

Health Benefits of Phenolic Compounds Against Cancers

Abdelkader Basli, Nassim Belkacem and Iman Amrani

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/67232

Abstract

Phenolic compounds are the biggest group of phytochemicals, and many of them have been found in plant-based foods. Polyphenol-rich diets have been linked to many health benefits including cancer. The potential anti-carcinogenic mechanisms of action that have been so far identified for phenolic compounds, as well as the feasibility reports occurred *in vivo*. In general terms, under the oxidative stress, polyphenols could act in those cellular mechanisms by participating in the modulation of the redox status and on multiple key elements in intracellular signal transduction pathways related to cell proliferation, differentiation, apoptosis, inflammation, angiogenesis and metastasis. A protective role of polyphenols against carcinogenesis is supported by many studies carried out on animal models and different mechanisms of action have been proposed to explain such protective effects. Studies performed in animals have demonstrated that phenolic components can prevent and/or slow down the initiation-progression of different types of cancers. They act through the regulation of cell signal transduction and gene expression and exhibit either up or down regulation of genes controlling tumor development.

Keywords: phenolic compounds, carcinogenesis, apoptosis induction, tumor metastasis and angiogenesis

1. Introduction

Cancer is a broad term used to describe a large group of disorders characterized by an uncontrolled growth of abnormal cells. These cells have the ability to escape surveillance by the immune system, to multiply indefinitely, to invade nearby tissues and to spread to distant sites of the body forming metastases [1]. Most cancers fall into one of the four main groups: carcinomas, sarcomas, leukemias or lymphomas. Carcinomas are cancers of epithelial origin. They represent approximately 90% of human malignancies. Sarcomas, which are rare

in humans, refer to solid tumors deriving from connective tissues, such as muscle, bone, cartilage and fibrous tissue. Cancers arising from the blood cells precursors and from cells of the immune system are called leukemias and lymphomas, respectively. Together, these two account for about 8% of human malignancies. Cancers can further be classified according to the topography of the primary tumor into several types, such as colon cancer, breast cancer, lung cancer, etc. [2].

1.1. Worldwide cancer incidence and mortality

Cancer ranks among the leading causes of morbidity in the world. According to GLOBOCAN 2012, the latest online database produced by the International Agency for Research on Cancer (IARC): 14.1 million new cancer cases occurred in 2012 worldwide. About 8 million (57%) were in economically developing countries, in which about 82% of the world's population reside [3]. The global incidence of cancer is expected to increase to 22.2 million by 2030 (an increase of 57% from 2012), based only on projected demographic changes and unchanged cancer incidence rates [4]. The most common malignancy worldwide is lung cancer accounting for 1.8 million new cases in 2012, followed by breast cancer (1.7 million new cases), colorectal cancer (1.4 million new cases), prostate cancer (1.1 million new cases), stomach cancer (951,000 new cases) and liver cancer (782,000 new cases) [5].

The overall age standardized cancer incidence rate in 2012 was almost 25% higher in men than in women, with rates of 205 and 165 per 100,000, respectively [3]. Lung, prostate, colorectal, stomach and liver cancer are the most common types of cancer in men, while breast, colorectal, lung, cervix and stomach cancer are the most common among women [5].

In terms of mortality, cancer is the second most common cause of death worldwide after cardiovascular diseases. The total number of cancer deaths in 2012 was 8.2 million, of these 2.9 million (35%) occurred in economically developed countries and 5.3 million (65%) in less developed countries [3]. Lung cancer remains the leading cause of death worldwide with 1.6 million deaths in 2012, followed by liver cancer (745,000 deaths), stomach cancer (723,000 deaths), colorectal cancer (694,000 deaths) and breast cancer (522,000 deaths) [5].

1.2. Cancer development process and prevention

Cancer is a multifactorial disease; many exogenous factors (such as poor diet, tobacco smoking, chemicals, radiation and infectious organisms) and endogenous factors (such as inherited mutations, hormones and immune conditions) contribute to its aetiology [6–8]. These factors may act together or in sequence to trigger and/or promote cancer development. The latter, also known as “carcinogenesis” or “tumorigenesis”, is a complex multistep process resulting from the progressive accumulation and functional cooperation of genetic and epigenetic alterations that eventually allow cells to break free from the tight network of regulation systems that maintain the homeostatic balance between proliferation and programmed cell death [1].

The genetic alterations can be the result of endogenous processes, such as errors in DNA replication, intrinsic chemical instabilities of certain DNA bases or attacks by free radicals gen-

erated during metabolism. DNA damage can also result from interactions with exogenous agents, such as radiation and chemical carcinogens. Under normal conditions, human cells have the ability to overcome these alterations thanks to DNA repair genes, apoptosis and cell buffer systems. Whenever these cell protection mechanisms are constitutionally altered or the DNA attack overtake the capacities of a normal cell, permanent mutations occur. These mutations could activate genes involved in cell growth and proliferation (oncogenes) or inactivate genes involved in cell senescence and apoptosis (tumour suppressor genes). If the permanent mutations occur in DNA repair genes as well, they will facilitate the acquisition of additional mutations [9, 10].

Cancers are also a consequence of epigenetic alterations, which are by definition, persistent and heritable changes in gene expression that result from modifications of chromatin structure without modification of the cell's DNA sequence. This can occur with DNA methylation and histone modifications [11]. This type of alterations along with the genetic ones lead to the transformation of a normal cell into a neoplastic cell with six essential physiological dysfunctions that collectively dictate its malignant growth: self-sufficiency in growth signals, insensitivity to growth inhibitory (antigrowth) signals, evasion of programmed cell death (apoptosis), limitless replicative potential, sustained angiogenesis and tissue invasion and metastasis [1].

The multistage nature of the carcinogenesis process, the presence of precursor lesions at the intermediate stages between normal and malignant cells, the slow growth of tumors and, the long latency, generally for decades before the diagnosis is established indicate that the carcinogenic process could be blocked or delayed and that the development of invasive cancers could be prevented [12].

Many scientists are focusing their researches on finding new strategies for cancer prevention. One strategy with promising potential is “chemoprevention” that has been defined by Sporn in 1976 as “the use of natural, synthetic or biological agents to reverse, suppress or prevent either the initial phases of carcinogenesis or the progression of premalignant cells to invasive disease” [13, 14].

Several epidemiologic studies suggest that regular consumption of fruits and vegetables significantly reduces the risk of different cancers. The beneficial effects of this type of diet are in part attributed to their content of phenolic compounds, which have shown promising antitumour properties in both *in vitro* and *in vivo* studies [15–17].

2. Phenolic compounds

2.1. Classification

Phenolic compounds, widely distributed secondary metabolites in plants, form a group of molecules with highly diversified chemical structures. They can be classified according to their carbon skeleton into the following main classes: simple phenols, phenolic acids, flavonoids, tannins, lignans, lignins, curcuminoids, coumarins and stilbenes as shown in **Figure 1**.

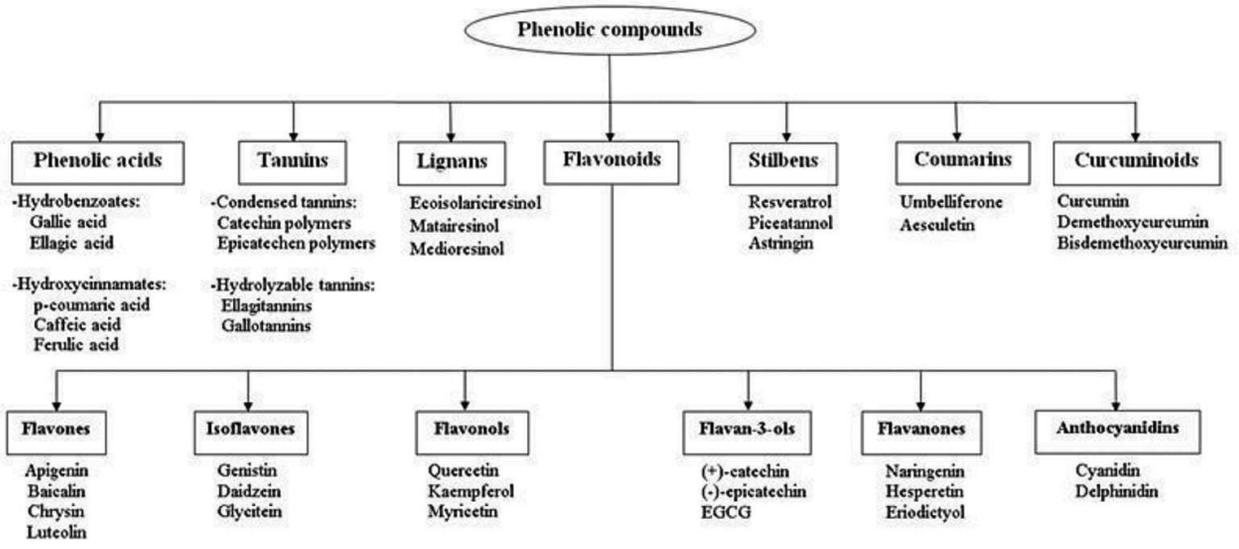

Figure 1. Main classes of phenolic compounds.

Phenolic acids include hydroxybenzoates (C6–C1) and hydroxycinammates (C6–C3). Hydroxybenzoic acids are represented mainly by gallic and ellagic acids, whereas the major hydroxycinnamic acids are caffeic and ferulic acids.

Flavonoids are the largest group of phenolic compounds containing two aromatic rings linked by a three atoms of carbon bridge (C6–C3–C6). They include mainly flavones, isoflavones, flavonols, flavans, flavanones and anthocyanidins [18]. Rutin, quercetin-3-O-rutinoside, is the glycoside of the flavonol quercetin. Epigallocatechin-3-gallate (EGCG), a type of the flavanol catechin, is the ester of epigallocatechin and gallic acid. Silymarin is a flavonolignan composed mainly by silybin (A and B), isosilybin (A and B), silychristin (A and B) and silydianin [19].

Tannins are divided into two different chemical groups, hydrolysable tannins that are polymers of gallic or ellagic acids and condensed tannins that are polymers of catechins or epicatechins.

Curcumin (C6–C7–C6) is a diferuloylmethane belonging to the group of curcuminoids [20].

2.2. Food sources of phenolic compounds

Phenolic compounds are widespread in food. Fruits and vegetables, such as apples, cherries, oranges, citrus, grapes, berries, peaches, cereals and tomatoes are particularly rich in polyphenols as shown in **Table 1**.

2.3. Phenolic compounds as antioxydants

Phenolic compounds have received increasing interest in the human health due to their benefit effects against several diseases like cancers attributed in particular to their antioxidant activity [29, 30]. Multiple investigations support that oxidative stress plays a key role in the cancer occurrence and other health problems induced by the excess production of the reactive

oxygen species (ROS) that includes many radicals, such as superoxide (O-2), hydroxyl (OH—), hydroperoxyl (OOH—), peroxyl (ROO—), alkoxyl (RO—), nitric oxide (NO—) and peroxynitrite anion (ONOO—). The ROS may cause oxidative damage to vital biomolecules, such as DNA, lipids and proteins [31].

Phenolic compound	Carbon skeleton	Food source	References
Phenolic acids Gallic acid Ellagic acid Hydroxybenzoates *p*-Hydroxybenzoic acid protocatechuic acid Vanillic acid Syringic acids	C6–C1	Berries, particularly raspberries, strawberries, and blackberries, grape juice and cereals	[19–21]
Hydroxycinammates *p*-Coumaric, caffeic, ferulic acids Hydroxycinnamic derivatives Chlorogenic acid Curcumin	C6–C3	Blueberry, cherry, sweet pear, apples (chlorogenic acid), orange, potato, grape fruit, coffee beans, plum, tomatoes, grape, wheat bran, kiwis, cereal grains (ferulic acid), apricots, carrots, cereals, citrus fruits, oilseeds, peaches and spinach	[20–23]
Flavonols Quercetin Kaempferol Myricetin Isorhamnetin	C6–C3–C6	Onions *Allium cepa,* apples, plums, cranberries, strawberries, grapes, kale, broccoli, celery stalks, tomatoes, buckwheat, endive, leeks, lettuce, olive, pepper, red wine, green tea and grape juice	[19–27]
Flavones Apigenin Luteolin	C6–C3–C6	Celery, parsley, artichoke, green olive, sweet peppers, onion, garlic, chamomile tea, Thai chili, citrus fruits, celery and spinach	[19–21, 23, 24, 26]
Flavan-3-ols (+)-Catechin (-)-Epicatechin	C6–C3–C6	Tea, apricots, sour cherries, grapes and blackberries, apples, peaches nectarines, barley (cereal), plums, nuts, red wine and chocolate	[19–27]
Flavanones Naringenin Hesperetin Eriodictyol Minor compounds Sakuranetin Isosakuranetin	C6–C3–C6	Citrus fruits: orange, lemons, grapes and tomatoes (Naringenin)	[19, 21, 23, 24, 26, 27]
Anthocyanidins Cyanidin Delphinidin Petunidin Peonidin Pelargonidin Malvidin	C6–C3–C6	The most widespread anthocyanidin in fruits is cyanidin-3 glucoside Grapes, blueberry, red onions, blood oranges and red wine Blackcurrant, blackberry, and elderberry (only cyanide)	[19, 21, 23, 24, 26, 27]
Isoflavones Genistin Daidzein Glycitein	C6–C3–C6	Soybeans and soy products are almost the sole dietary source of isoflavones Found also in small amounts in chickpeas	[19–24, 26, 27]

Phenolic compound	Carbon skeleton	Food source	References
Stilbenes Resveratrol	C6–C2–C6	Red wine and peanuts Also found in berries, red cabbage, spinach, grapes, berries, plums and pine nuts	[19, 21–23]
Piceatannol Astringin		Brazilian red wines	[19]
Lignan Secoisolariciresinol Matairesinol Medioresinol Pinoresinol Lariciresinol	$(C_6–C_3)_2$	Flaxseed is the richest source Buckwheat, sesame seed, rye and wheat	[21–23]
Tannins Condensed tannins Catechin polymers Epicatechin polymers	$(C6–C3–C6)_n$	Lentils, pear, grapes, peaches, plums, mangosteens, pears, red and white wine and apple juice	[22, 30]
Hydrolyzable tannins Ellagitannins Punicalagin Casuarictin		Strawberries, blackberries, raspberries, walnuts, pecans pomegranate bark, leaf and the fruit husk	[20, 21, 23, 28]
Gallotannins		Mangoes	
Coumarins Umbelliferone Aesculetin	C6–C3	Carrots, celery, citrus fruits, parsley and parsnips	[21]

Table 1. Food sources of some phenolic compounds.

Phenolic compounds may suppress ROS formation by different mechanisms, such as inhibiting some enzymes like xanthine oxidase responsible for superoxide ion production; chelating trace elements like metals, such as free iron and copper ions involved in the formation of radicals and scavenging radical species by hydrogen donation. The antioxidant capacity is related to the number and the position of hydroxyl groups in the phenolic compound [24, 25].

3. Polyphenols in prevention of cancer

Natural polyphenols are naturally occurring compounds found largely in the fruits, vegetables and are the most antioxidants in human diets, and their radical scavenging activities are related to substitution of hydroxyl groups in the aromatic rings of phenolic. They have been considered powerful antioxidants *in vitro* and proved to be more potent antioxidants than Vitamin C and E and carotenoids [32]. Phenolic compounds are also capable of scavenging free superoxide radicals, reducing the risk of cancer and protecting biological systems against the harmful effects of oxidative processes on macromolecules, such as carbohydrates, proteins, lipids and DNA [33]. It was found that in addition to their primary antioxidant activity, this group of compounds displays a wide variety of biological functions which are

mainly related to modulation of carcinogenesis. Furthermore, prevention of cancer is one of the most documented biological properties of the polyphenols. The effects of polyphenols on human cancer cell lines are protection and reduction of the number of tumors or their growth [34]. Mechanisms of anti-cancer effects of polyphenols, found in fruits, vegetables and spices representing parts of daily nutrition, have been considered. These compounds may be the basis for development of cancer preventive preparations. Several studies in extracts or isolated polyphenols from different plant food reported in a number of cancer cell lines including different evolutionary stages of cancer. Extracts prepared from blackberry, raspberry, blueberry, cranberry, strawberry as well as the isolated polyphenols from strawberry mainly like anthocyanins, kaempferol, quercetin, esters of coumaric acid and ellagic acid, have nutraceutical properties against tumor growth and cancer. They have revealed to be more effective to inhibit the growth of human oral (KB, CAL-27), breast (MCF-7), colon (HT-29, HCT-116) and prostate (LNCaP, DU-145) tumor cell lines in a dose-dependent manner with various sensitivity between cell lines [35, 36]. Many studies have focused on the antioxidative effects of phenolic compounds and it is suggested that its potential physiological effects for the protection and treatment of cancer and cardiovascular diseases come from its antioxidant activity. According to Ref. [37], phenolic compounds can block carcinogenesis initiation by inactivation of exogenous or endogenous genotoxic molecules including reactive oxygen species. Another mechanism consists in inhibition of activity and synthesis of carcinogen-metabolizing enzymes. Polyphenols activate phase I enzymes (cytochrome P450) to detoxify molecules procancérogènes [38, 39]. Many polyphenols, such as quercetin, catechins, isoflavones, lignans, flavanones, ellagic acid, red wine polyphenols, resveratrol or curcumin, showed protective effects in some cancerous models by different mechanisms. All the mechanisms of action of phenolic compounds against cancer are summarized in **Table 2**.

Dietary polyphenols	Protective effects and mechanisms	Conditions	Level
Hydroxytyrosol	Inhibiting cell proliferation	In human promyelocytic	*In vitro*
	Inducing apoptosis by arresting the cells in the G0/G1 phase with a concomitant decrease in the cell percentage in the S and G2/M phases		
Resveratrol	Inhibiting cell proliferation and down regulating telomerase activity	In human colon tumor cells	*In vitro*
	Inducing apoptosis mediated by p53-dependent pathway	In HepG2 cells	*In vitro*
	Inhibiting cell proliferation by interfering with an estrogen receptor-α-associated PI3K pathway	In estrogen-responsive MCF-7 human breast cancer cells	*In vitro*
	Suppressing COX-2 expression by blocking the activation of MAPKs and AP-1	In dorsal skin of female ICR mice	*In vitro*
	Decreasing the expression of COX-1, COX-2, c-myc, c-fos,c-jun, transforming growth factor-β-1 and TNF-α	In mouse skin	*Ex vivo*
	Inhibiting oncogenic disease through the inhibition of protein kinase CKII activity	In HeLa cell lysates	*In vitro*

Dietary polyphenols	Protective effects and mechanisms	Conditions	Level
	Inhibiting the Ca(2+)-dependent activities of PKCα and PKCβI	On the activities of PKC isozymes	*In vitro*
	Inhibiting nitrobenzene(NB)-DNA adducts	In male Kunming mice adducts	*In vivo*
Chlorogenic acid	Inhibiting the formation of DNA single strand breaks	In supercoiled pBR322 DNA	*In vitro*
Quercetin Luteolin	Blocking EGFR tyrosine kinase activity	In MiaPaCa-2 cancer cells	*In vitro*
Myricetin Apigenin Quercetin Kaempferol	Inhibiting human CYP1A1 activities Inhibiting the formation of diolepoxide 2(DE2) and B[a]P activation	On 7-ethoxyresorufin *o*-deethylation	*In vitro*
Silymarin Hesperetin Quercetin Daidzein	Interacting with *p*-glycoprotein and modulating the activity of ATP-binding cassette transporter, breast cancer resistance protein (BCRP/ABCG2)	In two separate BCRP-overexpressing cell lines	*In vitro*
EGCG	Inhibiting telomerase	In human cancer cells	*In vitro*
		In nude mice models	*In vivo*

Table 2. Anti-mutagenic/anti-carcinogenic properties of polyphenols [40].

3.1. Natural polyphenols and apoptosis targeting in cancer cells

In chemoprevention, suppression of cell proliferation and induction of differentiation and apoptosis are important strategies, with the induction of programmed cell death currently considered as one relevant target in a preventive track. Apoptosis (programmed cell death) is the process by which cells trigger their self-destruction in response to a signal. It is defined by a set of characteristic morphological features such cell shrinkage, chromatin condensation and DNA fragmentation due to endonuclease activation, cell budding and apoptotic body formation and loss of the membrane integrity [41]. Programmed cell death plays an important role in the maintenance of biological cells and systems. Apoptosis can be triggered through two main pathways: extrinsic and intrinsic. Extrinsic factors could act in the activation of cell surface receptors, such as tumor necrosis factor (TNF)-alpha that leads to the induction of caspase-8. Intrinsic pathways involved internal cell signaling primarily through the mitochondria. Regulation system of apoptosis are also induced in the mitochondria on the intrinsic pathway by several families of proteins, including small mitochondrial-derived activator of caspases (SMACs), inhibitor of apoptosis proteins (IAPs) and the B-cell lymphoma 2 protein (Bcl-2) family, as well as membrane polarity and integrity [42]. Other key molecule in apoptosis regulation is the transcription factor p53. The main role of p53 is the protection against genomic instability and tumorigenesis. Functionally promotes survival by activating checkpoints and facilitating damage repair, sustained proliferation blocking and apoptosis [43]. Many dietary phenolic compounds, including quercetin, EGCG [(-)-epigallocatechin-3-gallate], apigenin, chrysin, silymarin, curcumin, ellagic acid and resveratrol, may block carcinogenesis through induction of apoptosis. They may induce apoptosis via multiple mechanisms.

In vitro studies show that EGCG, curcumin or resveratrol sensitize LNCaP prostate cancer cells to TNF-related apoptosis-inducing ligand (TRAIL)-mediated apoptosis through modulation of the extrinsic apoptotic pathway [44, 45]. Furthermore, apoptosis intrinsic pathway could be triggered by phenolic compounds. Resveratrol induces apoptosis through the intrinsic pathway in prostate cancer-derived cell lines by activating caspases-9/3 and by changing the Bax/Bcl-2 ratio [46]. Apoptosis may be also induced through activation of proapoptotic proteins (e.g. caspases, proapoptotic Bcl-2 family members) and/or inhibition of antiapoptotic proteins (e.g. Bcl-2, Bcl-xL and survivin) [41]. Interestingly, a synergistic effect has been reported to induce apoptosis by combination of drugs and/or natural phenolics. In this line, (-)-epicatechin (EC) showed a major synergistic effect on the induction of apoptosis in gastric cancer MKN-45 cells treated with epigallocatechin-3-gallate [47]. Similarly, the combination of curcumin with (-)-epicatechin increased the inhibition of cell growth as compared to curcumin or EC alone, as well as the apoptosis rate and the expression of related genes to the programmed cell death, such as growth arrest DNA damage 153/45 (GADD153/45) in PC-9 cells [48]. Hexameric procyanidins inhibited the deoxycholic acid (DOC)-induced cytotoxicity and partly delayed the DOC-induced Caco-2 cell apoptosis [49]. In the same way, curcumin suppresses Caco-2 proliferation partially via activation of the mitochondrial apoptotic pathway and cell cycle retardation [50].

3.2. Antiproliferative effect

Suppression of cell proliferation and induction of differentiation and apoptosis are relevant strategies in preventive approaches. Deregulated cell cycle and resistance to apoptosis are hallmarks of cancer. The activity of the transcription factor nuclear factor-kappa B (NF-κB), responsible for the activation of many genes involved in cell proliferation, is closely linked to the redox status of cells. Indeed, NF-κB is part of a family of dimeric proteins (p50/p65). In the absence of stimulation, NF-kB is localized in the cytoplasm and is associated with its natural inhibitor IκB (inhibitor of NF-κB). ROS production (H_2O_2, superoxide anion and the hydroxyl radical) induces phosphorylation of IκB causing its ubiquitination and degradation by the proteasome. NF-κB is activated and translocated into the nucleus. At this stage, many genes (about 200) will be active [51]. Moreover, a number of human cancers, including breast cancer, non-small cell lung carcinoma, thyroid cancer, T- or B-lymphocyte leukemia, melanoma, colon cancer, bladder cancer and several virally induced tumors have been characterized by constitutive NF-κB activity and the inhibition of NF-κB abrogates tumor cell proliferation [52, 53]. Indeed, it has been postulated that some natural plant product anticancer effects are due to its capacity to inactivate NF-κB-dependent signaling. Many phenolic compounds including resveratrol [54], curcumin [55] and (-)-epigallocatechin-3-gallate [56] inhibit IKK-mediated IκB phosphorylation by stimulating the retention of NF-κB in the cytosol and its subsequent inactivation. Other studies demonstrate the ability of flavonoids as NF-κB inhibitors and their role in preventing NF-κB signaling pathway-mediated disorders. It is identified that apigen, quercetin, kaempferol, rutin is a potent inhibitor of NF-κB, which may perform a pivotal function in the regulation of cell growth, apoptosis and the regulation of the cell cycle [57–59]. Overall, the results indicated that flavonoids suppress the activation of NF-κB and NF-κB-regulated gene expression, leading to enhancement of apoptosis. This provides the molecular basis for the ability of polyphenols to act as an anticancer.

3.3. Effects on angiogenesis and metastasis

Angiogenesis, the formation and growth of new blood vessels from preexisting microvasculature, is a key stage in tumor growth, invasion and metastasis [41], many proteins have been identified in humans as activators of angiogenesis, among them, fibroblast growth factor (FGF), interleukin 8 (IL-8), the platelet-derived epidermal growth factor, transforming growth factor α (TGFα), the vascular endothelial growth factor (VEGF) and small molecules, such as adenosine, prostaglandin E and tetrahydrofolate (THF) [60]. According to many *in vitro* studies, VEGF and FGF-β appear to be the most important factors responsible for tumor growth and are produced by many types of cancer cells as well as normal cells [61]. Polyphenols can act as suppressing agents and inhibit the formation and growth of tumors from initiated cells; they inhibit cell proliferation *in vitro* [62]. Moreover, polyphenols, such as those of green tea, can also inhibit angiogenesis and, therefore, limit the growth of the tumors [63] or prevent tumor invasion through inhibition of the matrix metalloproteinases [64]. (+)-Catechin-inhibited tumour-specific angiogenesis by regulating the production of pro- and anti-angiogenic factors, such as pro-inflammatory cytokines, nitric oxide, VEGF, IL-2 and tissue inhibitor of metalloproteinase-1 [65]. Several studies report a selective effect of phenolic compounds in inhibiting angiogenesis in cancer cells. Thus curcumin, baicalin and resveratrol can also inhibit the angiogenic factor VEGF in tumor cells in culture [66–68]. On the other hand, quercetin inhibits angiogenesis through multiple mechanisms, including interaction with the cox-2 and lipoxygenase-5 enzymes, EGFR, the HER2 intracellular signalling pathway and the NF-κB nuclear transcription protein [69]; furthermore, it has been shown that proanthocyanidins added to mice with tumor xenografts reduced VEGF secretion, which resulted in reduced intratumoral microvasculature [70]. Previous studies reported that the chemical modification of (-)-epicatechin by its acylation improved the anti-cancer and anti-angiogenic activities of this flavanol [71].

The tissue invasion and metastasis formation require that tumor cells acquire the ability to migrate to other tissue and to invade them. This involves changing some cellular functions (cell adhesion) and the modification of the expression of certain genes, such as those encoding metalloproteinases degrading the extracellular matrix (MMP) or molecules adhesion [72]. Because metastasis occurs through a multistep process, dietary polyphenols have also been reported to interfere with cancer cell adhesion and movement processes through various mechanisms. Polyphenols, such as curcumin, apigenin, quercetin and catechin, have been reported to be chemopreventive through their anti-proliferative, anti-metastatic and/or anti-invasive properties [73, 74]. Resveratrol has been shown to inhibit cell migration/invasion and metastasis in several types of cancer, including breast cancer [75]. In addition, it was reported that Interleukin 6 (IL-6) and its major effector, the signal transducer and activator of transcription 3 (STAT3), are part of an important inflammation-associated pathway in malignancies [76] and metastasis [77] in different types of cancer. Resveratrol might be a potential agent chemosensitization on several types of cancer. This ability would be explained by the regulation of many signaling molecules including drug transporters, cell proliferation regulators, members of the NF-κB signal transducer and activator of transcription 3 (STAT3) signaling pathways [78]. CD44 and CD54 played an important role in tumor metastasis by the mutual adhesion

and interaction between cancer cells and vascular endothelial cells [79]. Tea polyphenols, known as catechins, have effects on cancer prevention, inhibition and anti-metastasis. Recent studies reported their role in the blockage of adhesion of lung carcinoma cell lines to endothelial cells is related to CD44 and CD54. The mechanism of tea polyphenol prevention of human lung carcinoma metastasis might be through inhibiting adhesion molecule expression to block cancer cell adhesion [80]. In breast cancer, curcumin exerts a strong anti-invasive effect on estrogen receptor (ER)-negative MDAMB231 cells through the down regulation of nuclear factor κB and activator protein-1 (NF-kB/AP 1) transcription factors dependent MMP-1 and -2 expression, the up regulation of TIMP-1 (metallopeptidase inhibitor-1), and the inhibition of VEGF and b-FGF [81]. In addition, caffeic acid is a widespread phenolic acid exerts an effective inhibition of the *in vitro* invasion of PC3 cells in prostate cancer [82]. Quercetin has also been widely investigated for its potential to inhibit both cellular migration and the invasion of cancer cells. Mechanistically, quercetin may inhibit cellular migration and invasion through the deactivation of matrix metalloproteinases-2 (MMP-2) and/or matrix metalloproteinases-9 (MMP-9) [83]. Recent study showed that polyphenol enrichment of a blueberry preparation by fermentation increases its chemopreventive potential by protecting mice against tumor development, inhibiting the formation of cancer stem cells and reducing lung metastasis [84]. Indeed, the cytoprotective and anticancer action of dietary in-taken natural polyphenols has for long been attributed only to their direct radical scavenging activities. Quercetin has been reported to possess anticancer property against benzo-pyrene-induced lung carcinogenesis in mice, an effect attributed to its free radical scavenging activity [85]. The anti-carcinogenic effects of resveratrol appear also to be closely associated with its antioxidant activity [86].

4. Conclusion

Cancer has become in the recent decades one of the leading causes of death worldwide. The search for effective prevention has become a priority for the basic and clinical science. Polyphenols have been proposed as alternative therapy and shown effective in cancer treatment especially when consumed in synergistic mixtures. It has been already demonstrated that polyphenols are able to exert differential effects on tumor cells. Their action can be attributed not only to their ability to act as antioxidants but also to their ability to interact with basic cellular mechanisms. Polyphenols, such as resveratrol, EGCG, curcumin and quercetin, have been shown to promote extrinsic and intrinsic apoptosis induction in different types of cancers (e.g. colon, lung, prostate, breast, melanoma or leukemia). Others studies performed in animals reported that phenolic components can prevent and/or slow down the initiation-progression of different types of cancers, such as cancer of prostate, liver, colon, leukemia, etc. Polyphenols can also act as suppressing agents, and inhibit the formation and growth of tumors from initiated cells; they inhibit cell proliferation *in vitro.* However, the exact mechanisms of actions are not fully understood and many properties remain unclear, require further consideration. These experimental and hypothetical data evince the need to perform further studies to understand the differential mechanisms of the polyphenols on cancer cells, which could contribute to find selective targets in cancer treatment.

Author details

Abdelkader Basli[1]*, Nassim Belkacem[2] and Iman Amrani[3]

*Address all correspondence to: mbasli@yahoo.fr

1 Research Laboratory of Biochemistry, Biophysics, Biomathematics and Scientometrics "L3BS" Faculty of Natural Sciences and Life, University of Bejaia, Bejaia, Algeria

2 Plant Biotechnology Laboratory and Ethnobotany, Faculty of Natural Sciences and Life, University of Bejaia, Bejaia, Algeria

3 Laboratory of Constitutional and Acquired Genetic Diseases, Faculty of Medicine, University of Batna 2, Algeria

References

[1] Hanahan D, Weinberg R.A. The hallmarks of cancer. Cell. 2000;100:57–70.

[2] Cooper GM. The Cell: A Molecular Approach. 2nd ed. Sunderland (MA): Sinauer Associates; 2000.

[3] Ferlay J SI, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. GLOBOCAN 2012. Cancer Incidence and Mortality Worldwide: IARC Cancer Base No. 11. Lyon, France: International Agency for Research on Cancer; 2013.

[4] Bray F, Jemal A, Grey N, Ferlay J, Forman D. Global cancer transitions according to the Human Development Index (2008–2030): a population-based study. The Lancet Oncology. 2012;13(8):790–801.

[5] Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: Sources methods and major patterns in GLOBOCAN 2012. International Journal of Cancer. 2015;136:359–386.

[6] Fedewa SA, Sauer AG, Siegel RL, Jemal A. Prevalence of major risk factors and use of screening tests for cancer in the United States. Cancer Epidemiology, Biomarkers & Prevention. 2015;24:637–652.

[7] Danaei G, Vander Hoorn S, Lopez AD, Murray CJ, Ezzati M. Causes of cancer in the world: Comparative risk assessment of nine behavioural and environmental risk factors. Lancet. 2005;366:1784–1793.

[8] Anand P, Kunnumakkara AB, Sundaram C, Harikumar KB, Tharakan ST, Lai OS, et al. Cancer is a preventable disease that requires major lifestyle changes. Pharmaceutical Research. 2008;25:2097–2116.

[9] Bertram JS. The molecular biology of cancer. Molecular Aspects of Medicine. 2000; 21:167–223.

[10] Pedraza-Farina LG. Mechanisms of oncogenic cooperation in cancer initiation and metastasis. Yale Journal of Biology and Medicine. 2006;79:95–103.

[11] Sharma S, Kelly TK, Jones PA. Epigenetics in cancer. Carcinogenesis. 2010;31:27–36.

[12] Turrini E, Ferruzzi L, Fimognari C. Potential effects of pomegranate polyphenols in cancer prevention and therapy. Oxidative Medicine and Cellular Longevity. 2015;2015:938475.

[13] Sporn MB. Approaches to prevention of epithelial cancer during the paraneoplastic period. Cancer Research. 1976;36:2699–2702.

[14] Sporn MB. The war on cancer. Annals of the New York Academy of Sciences.1997; 833:137–146.

[15] Benetou V, Orfanos P, Lagiou P, Trichopoulos D, Boffetta P, Trichopoulou A. Vegetables and fruits in relation to cancer risk: Evidence from the Greek EPIC cohort study. Cancer Epidemiology, Biomarkers & Prevention. 2008;17:387–392.

[16] Feskanich D, Ziegler RG, Michaud DS, Giovannucci EL, Speizer FE, Willett WC, et al. Prospective study of fruit and vegetable consumption and risk of lung cancer among men and women. Journal of National Cancer Institute. 2000;92:1812–1823.

[17] Carocho M, Ferreira IC. The role of phenolic compounds in the fight against cancer. Anti-cancer Agents in Medicinal Chemistry. 2013;13:1236–1258.

[18] Giada M. Food phenolic compounds: Main classes, sources and their antioxidant power. In: Gonzalez JAM editor. Oxidative Stress and Chronic Degenerative Diseases—A Role for Antioxidants. Rijeka: InTech; 2013. pp. 87–112.

[19] Abouzid S. Silymarin, natural flavonolignans from milk thistle. In: Rao V editor. Phytochemicals: A Global Perspective of Their Role in Nutrition and Health. InTech; 2012. pp. 255–273.

[20] Fraga CG. Plant phenolics and human health: Biochemistry, nutrition and pharmacology. John Wiley & Sons. 2009; 471–489.

[21] King A, Young G. Characteristics and occurrence of phenolic phytochemicals. Journal of the American Dietetic Association. 1999;99(2):213–218.

[22] Naczk M, Shahidi F. Phenolics in cereals, fruits and vegetables: Occurrence, extraction and analysis. Journal of Pharmaceutical and Biomedical Analysis. 2006;41(5):1523–1542.

[23] Yang CS, Landau JM, Huang MT, Newmark H. Inhibition of carcinogenesis by dietary polyphenolic compounds. Annual Review of Nutrition. 2001;21(1):381–406.

[24] Fantini M, Benvenuto M, Masuelli L, Frajese GV, Tresoldi I, Modesti A, Bei R. *In vitro* and *in vivo* antitumoral effects of combinations of polyphenols, or polyphenols and anticancer drugs: Perspectives on cancer treatment. International Journal of Molecular Sciences. 2015;16(5):9236–9282.

[25] Duthie GG, Duthie SJ, Kyle JAM. Plant polyphenols in cancer and heart disease: Implications as nutritional antioxidants. Nutrition Research Reviews. 2000;13(1):79–106.

[26] Hahn M, Baierle M, Mariele F, Charão Guilherme B, Bubols F, Gravina S, Zielinsky P, Marcelo DA, Solange CG. Polyphenol-rich food general and on pregnancy effects. Drug and Chemical Toxicology. 2016;1–7.

[27] Duthie GG, Gardner PT, Kyle JAM. Plant polyphenols: Are they the new magic bullet? Proceedings of the Nutrition Society. 2003;62(3):599–603.

[28] Scalbert A, Williamson G. Dietary intake and bioavailability of polyphenols. The Journal of Nutrition. 2000;130(8):2073S–2085S.

[29] Bakkalbasi E, Mentes Z, Artik N. Food ellagitannins-occurrence, effects of processing and storage. Critical Reviews in Food Science and Nutrition. 2008;49(3):283–298.

[30] Hollman PCH. Evidence for health benefits of plant phenols: Local or systemic effects? Journal of the Science of Food and Agriculture. 2001;81(9):842–852.

[31] Zujko ME, Witkowska AM. Antioxidant potential and polyphenol content of selected food. International Journal of Food Properties. 2011;14(2):300–308.

[32] Lee KW, Lee HJ. The roles of polyphenols in cancer chemoprevention. Biofactors. 2006;26(2):105–121.

[33] Rice-Evans CA, Miller NJ, Bolwell PG, Bramley PM, Pridham JB. The relative antioxidant activities of plant-derived polyphenolic flavonoids. Free Radical Research. 1995;22:375–383.

[34] Halliwell B, Gutteridge JMC. Role of free radicals and catalytic metal ions in human disease: An overview. Methods in Enzymology. 1990;186:80–85.

[35] Yang CS, Landau JM, Huang MT, Newmark HL. Inhibition of carcinogenesis by dietary polyphenolic compounds. Annual Review of Nutrition. 2001;21:381–406.

[36] Seeram NP, Adams LS, Zhang Y, Lee R, Sand D, Scheuller HS, Heber D. Blackberry, black raspberry, blueberry, cranberry, red raspberry, and strawberry extracts inhibit growth and stimulate apoptosis of human cancer cells in vitro. Journal of Agricultural and Food Chemistry. 2006;54:9329–9339.

[37] Zhang Y, Seeram NP, Lee R, Feng L, Heber D. Isolation and identification of strawberry phenolics with antioxidant and human cancer cell antiproliferative properties. Journal of Agricultural of Food Chemistry. 2008;56:670–675.

[38] Zinoveva VN, Spasov AA. Mechanisms of plant polyphenols anti-cancer effects. I. Blockade of carcinogenesis initiation. Biomeditsinskaia Khimiia. 2012;58:160–175.

[39] Cragg GM, Newman DJ. Plants as a source of anti-cancer agents. Journal of Ethnopharmacology. 2005;100:72–79.

[40] Manach C, scalbert A, Morand C. Resmesy C, Jimenez L. Polyphenols: Food source and bioavailability. The American Journal of Clinical Nutrition. 2004;79(5):727–747.

[41] Ramos S. Cancer chemoprevention and chemotherapy: Dietary polyphenols and signalling pathways. Molecular Nutrition & Food Research. 2008;52:507–526.

[42] Wang L, Du F, Wang X. TNF-alpha induces two distinct caspase-8 activation pathways. Cell. 2008;133:693–703.

[43] Lavin MF, Gueven N. The complexity of p53 stabilization and activation. Cell Death & Differentiation. 2006;13:941–950.

[44] Shankar S, Chen Q, Sarva K, Siddiqui I, Srivastava RK. Curcumin enhances the apoptosis-inducing potential of TRAIL in prostate cancer cells: Molecular mechanisms of apoptosis, migration and angiogenesis. Journal of Molecular Signaling. 2007;2:10.

[45] Siddiqui IA, Malik A, Adhami VM, Asim M, Hafeez BB, et al. Green tea polyphenol EGCG sensitizes human prostate carcinoma LNCaP cells to TRAIL-mediated apoptosis and synergistically inhibits biomarkers associated with angiogenesis and metastasis. Oncogene. 2008;27:2055–2063.

[46] Benitez DA, Pozo-Guisado E, Alvarez-Barrientos A, Fernandez-Salguero PM, Castellón EA. Mechanisms involved in resveratrol-induced apoptosis and cell cycle arrest in prostate cancer-derived cell lines. Journal of Andrology. 2007;28:282–293.

[47] Horie N, Hirabayashi N, Takahashi Y, Miyauchi Y, Taguchi H, Takeishi K. Synergistic effect of green tea catechins on cell growth and apoptosis induction in gastric carcinoma cells. Biological and Pharmaceutical Bulletin. 2005;28:574–579.

[48] Saha A, Kuzuhara T, Echigo N, Suganuma M, Fujiki H. New role of (-)-epicatechin in enhancing the induction of growth inhibition and apoptosis in human lung cancer cells by curcumin. Cancer Prevention Research. 2010;3:953–962.

[49] Da Silva M, Jaggers GK, Verstraeten SV, Erlejman AG, Fraga CG, Oteiza PI. Large procyanidins prevent bile-acid-induced oxidant production and membrane-initiated ERK1/2, p38, and Akt activation in Caco-2 cells. Free Radical Biology & Medicine. 2012;52:151–159.

[50] Satoru S, Chisato M, Tetsuya K, Yohko F. Curcumin inhibit the proliferation of a human colorectal cancer cell line Caco-2 partially by both apoptosis and G2/M cell cycle arrest. IJPR. 2014;4:84–90.

[51] Bowie A, O'Neill LAJ. Oxidative stress and nuclear factor-kB activation. Biochemical Pharmacology. 2000;59:13–23.

[52] Rath PC, Aggarwal BB. Antiproliferative effects of IFN-alpha correlate with the down-regulation of nuclear factor-kappa B in human Burkitt lymphoma Daudi cells. Journal of Interferon and Cytokine Research. 2001;21:523–528.

[53] Bharti AC, Donato N, Singh S, Aggarwal BB. Curcumin (diferuloyl-methane) down-regulates the constitutive activation of nuclear factor-kappa B and I-kappa B alpha kinase in human multiple myeloma cells, leading to suppression of proliferation and induction of apoptosis. Blood. 2003;101:1053–1062.

[54] Roy P, Madan E, Kalra N, Nigam N, George J, et al. Resveratrol enhances ultraviolet B-induced cell death through nuclear factor-kappaB pathway in human epidermoid carcinoma A431 cells. Biochemical and Biophysical Research Communications. 2009;384:215–220.

[55] Deeb D, Jiang H, Gao X, Al-Holou S, Danyluk AL, et al. Curcumin [1,7-bis(4-hydroxy-3-methoxyphenyl)-1-6-heptadine-3,5-dione; C21H20O6] sensitizes human prostate cancer cells to tumor necrosis factor-related apoptosis-inducing ligand/Apo2L-induced apoptosis by suppressing nuclear factor-kappaB via inhibition of the prosurvival Akt signaling pathway. Journal of Pharmacology and Experimental Therapeutics. 2007;321:616–625.

[56] Ahmad N, Gupta S, Mukhtar H. Green tea polyphenol epigallocatechin-3-gallate differentially modulates nuclear factor kappaB in cancer cells versus normal cells. Archives of Biochemistry and Biophysics. 2000;376:338–346.

[57] Yoon MS, Lee JS, Choi BM, Jeong YI, Lee CM, Park JH, Moon Y, Sung SC, Lee SK, Chang YH, Chung HY, Park YM. Apigenin inhibits immunostimulatory function of dendritic cells: Implication of immuno-therapeutic adjuvant. Molecular Pharmacology, 2006;70:1033–1044.

[58] García-Mediavilla V, Crespo I, Collado PS, Esteller A, Sánchez-Campos S, Tuñón MJ, González-Gallego J. The anti-inflammatory flavones quercetin and kaempferol cause inhibition of inducible nitric oxide synthase, cyclooxygenase-2 and reactive C-protein, and down-regulation of the nuclear factor kappa B pathway in Chang liver cells. European Journal of Pharmacology. 2007;557:221–229.

[59] Ren W, Qiao Z, Wang H, Zhu L, Zhang L, Lu Y, Zhang Z, Wang Z. Molecular basis of Fas and cytochrome c pathways of apoptosis induced by tartary buckwheat flavonoid in HL-60 cells. Methods and Findings in Experimental and Clinical Pharmacology. 2003;25:431–436.

[60] Folkman J. Fundamental concepts of the angiogenic process. Current Molecular Medicine. 2003;3:643–651.

[61] Aggarwal BB, Shishodia S. Molecular targets of dietary agents for prevention and therapy of cancer. Biochemical Pharmacology. 2006;71:1397–1421.

[62] Kuntz S, Wenzel U, and Daniel H. Comparative analysis of the effects of flavonoids on proliferation, cytotoxicity, and apoptosis in human colon cancer cell lines. European Journal of Nutrition. 1999;38:133–142.

[63] McCarty MF. Polyphenol-mediated inhibition of AP-1 transactivating activity may slow cancer growth by impeding angiogenesis and tumor invasiveness. Medical Hypotheses. 1998;50:511–514.

[64] Demeule M, Brossard M, Page M, Gingras D, Beliveau R. Matrix metalloproteinase inhibition by green tea catechins. Biochimica et Biophysica Acta. 2000;1478:51–60.

[65] Guruvayoorappan C, Kuttan G. (+)-Catechin inhibits tumour angiogenesis and regulates the production of nitric oxide and TNF-alpha in LPS-stimulated macrophages. Innate Immunity. 2008;14:160–174.

[66] Arbiser JL, Klauber N, Rohan R, et al. Curcumin is an in vivo inhibitor of angiogenesis. Molecular Medicine. 1998;4:376–383.

[67] Lin MT, Yen ML, Lin CY, Kuo ML. Inhibition of vascular endothelial growth factor-induced angiogenesis by resveratrol through interruption of src dependent vascular endothelial cadherin tyrosine phosphorylation. Molecular Pharmacology. 2003;64:1029–1036.

[68] Liu JJ, Huang TS, Cheng WF, Lu FJ. Baicalein and baicalin are potent inhibitors of angiogenesis: Inhibition of endothelial cell proliferation, migration and differentiation. International Journal of Cancer. 2003;106:559–565.

[69] Huynh H, Nguyen TT, Chan E, Tran E. Inhibition of ErbB-2 and ErbB-3 expression by quercetin prevents transforming growth factor alpha (tgf-α)- and epidermal growth factor (egf)-induced human pc-3 prostate cancer cell proliferation. International Journal of Oncology. 2003;23:821–829.

[70] Singh RP, Tyagi AK, Dhanalakshmi S, Agarwal R, Agarwal C. Grape seed extract inhibits advanced human prostate tumor growth and angiogenesis and upregulates insulin-like growth factor binding protein-3. International Journal of Cancer. 2004;108:733–740.

[71] Matsubara K, Saito A, Tanaka A, Nakajima N, Akagi R, Mori M, Mizushina Y. Epicatechin conjugated with fatty acid is a potent inhibitor of DNA polymerase and angiogenesis. Life Sciences. 2007; 80:1578–1585.

[72] Yilmaz M, Christofori G, Lehembre F. Distinct mechanisms of tumor invasion and metastasis. Trends in Molecular Medicine. 2007;13:535–541.

[73] Menon LG, Kuttan R, Kuttan G. Anti-metastatic activity of curcumin and catechin. Cancer Letters. 1999;141:159–165.

[74] Caltagirone S, Rossi C, Roggi A, Ranelletti FO, Natali PG, Brunetti M, Aiello FB, Oiantelli M. Flavonoids apigenin and quercetin inhibit melanoma growth and metastatic potential. International Journal of Cancer. 2000;87:595–600.

[75] Szekeres T, Saiko P, Fritzer-Szekeres M, Djavan B, Jager W. Chemopreventive effects of resveratrol and resveratrol derivatives. Annals of the New York Academy of Sciences. 2011;1215:89–95.

[76] Lamy S, Akla N, Ouanouki A, Lord Dufour S, Beliveau R. Diet derived polyphenols inhibit angiogenesis by modulating the interleukin 6/STAT3 pathway. Experimental Cell Research. 2012;318:1586–1596.

[77] Chang Q, Bournazou E, Sansone P, Berishaj M, Gao SP, Daly L, et al. The IL 6/JAK/Stat3 feed forward loop drives tumorigenesis and metastasis. Neoplasia. 2013;15:848–862.

[78] Gupta SC, Kannappan R, Reuter S, Kim JH, Aggarwal BB. Chemosensitization of tumors by resveratrol. Annals of the New York Academy of Sciences. 2011;1215:150–160.

[79] Grothey A, Heistermann P, Philippou S, Voigtmann R. Serum levels of soluble intercellular adhesion molecule-1 (ICAM-1, CD54) in patients with non-small-cell lung cancer: Correlation with histological expression of ICAM-1 and tumour stage. British Journal of Cancer. 1998;77:801–807.

[80] Zheng FJ, Shi L, Yang J, Deng XH, Wu YQ, Yan XQ, Huang N. Effect of tea polyphenols on the adhesion of highly metastatic human lung carcinoma cell lines to endothelial cells in vitro. Asian Pacific Journal of Cancer Prevention. 2012;13:3751–3755.

[81] Bachmeier B, Nerlich AG, Iancu CM, et al. The chemopreventive polyphenol curcumin prevents hematogenous breast cancer metastases in immunodeficient mice. Cell Physiology and Biochemistry. 2007;19:137–152.

[82] Lansky EP, Harrison G, Froom P, Jiang WG. Pomegranate (Punica granatum) pure chemicals show possible synergistic inhibition of human PC-3 prostate cancer cell invasion across Matrigel. Investigational New Drugs. 2005;23:121–122.

[83] Lai WW, Hsu SC, Chueh FS, Chen YY, Yang JS, Lin JP, et al. Quercetin inhibits migration and invasion of SAS human oral cancer cells through inhibition of NF-kappaB and matrix metalloproteinase-2/-9 signaling pathways. Anticancer Research. 2013;33:1941–1950.

[84] Vuong T, Mallet JF, Ouzounova M, Rahbar S, Hernandez-Vargas H, Zdenko H, Matar C. Role of a polyphenol-enriched preparation on chemoprevention of mammary carcinoma through cancer stem cells and inflammatory pathways modulation. Journal of Translational Medicine. 2016;14:13.

[85] Kamaraj S, Vinodhkumar R, Anandakumar P, Jagan S, Ramakrishnan G, Devaki T. The effects of quercetin on antioxidant status and tumor markers in the lung and serum of mice treated with benzo(a)pyrene. Biological and Pharmaceutical Bulletin. 2007;30:2268–2273.

[86] Athar M, Back JH, Tang X, Kim KH, Kopelovich L, Bickers DR, Kim AL. Resveratrol: A review of preclinical studies for human cancer prevention. Toxicology Applied Pharmacology. 2007;224:274–283.