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Targeting PI3K/Akt/mTOR signaling pathway by polyphenols: Implication for cancer therapy

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Abstract

Cancer is one of the biggest challenges facing medicine and its cure is regarded to be the Holy Grail of medicine. Therapy in cancer is consisted as various artificial cytotoxic agents and radiotherapy, and recently immunotherapy. Recently much attention has been directed to the use of natural occurring agents in cancer therapy. One of the main group of agents utilized in this regard is polyphenols which are found abundantly in berries, fruits and vegetables. Polyphenols show to exert direct and indirect effects in progression of cancer, angiogenesis, proliferation and enhancing resistance to treatment. One of the cellular pathways commonly affected by polyphenols is PI3K/Akt/mTOR pathway, which has far ranging effects on multiple key aspects of cellular growth, metabolism and death. In this review article, evidence regarding the biology of polyphenols in cancer via PI3K/Akt/mTOR pathway is discussed and their application on cancer pathophysiology in various types of human malignancies is shown.

Key words: Polyphenols; Natural compounds; PI3K, Akt; Chemoprevention.

Abbreviation: PI3K, Phosphoinositide 3-kinase; mTOR, mammalian target of rapamycin; PDK-1; phosphoinositide-dependent protein kinase-1; miRNA, micro RNA; NF-κB, nuclear factor kappa B; IGF, insulin-like growth factor; PIP2, phosphatidylinositol 4,5 bisphosphate; EGFR, epidermal growth factor receptor; PARP, Poly (ADP-ribose) polymerase; CDK, cyclin-dependent kinases; EGCG, Epigallocatechin-3-gallate; VEGF, vascular endothelial growth factor; PTEN, phosphatase and tensin homologue, COX-2, cyclooxygenase-2; NSCLC, non-small-cell lung cancer; MMP, matrix metalloproteinase; GSK-3, glycogen synthase kinase-3; PKC, protein kinase C; PAK, P21 activated kinase 1; HIF, hypoxia-inducible factor; CTGF, connective tissue growth factor; EMT, epithelial to mesenchymal transition.

1. Introduction

Therapeutic potential of various natural products including polyphenols has gained interest in recent years. They are one of the most abundant sources of anti-oxidants in human diet such as tea, beans, herbal plants, various barriers, wines and more (1, 2). Because of their abundance and their anti-oxidative role, researchers have speculated that these agents can have wide reaching effects on multiple human pathologies including age related neurodegeneration, and cellular stress caused by accumulation of toxins (3-6). It is demonstrated by studies showing the beneficial effects of rich sources of polyphenols on the aforementioned conditions (7). One of the fields in which the use of polyphenols has been indicated is in human malignancies (8). Because carcinogenesis is a multistep process in which multiple cell signaling pathways show abnormalities. It has been hypothesized that the use of agents, natural or synthetic which can alter these signaling cascades could be influential in reversing the process of carcinogenesis. One of these signaling pathways is PI3K/Akt/mTOR pathway. Multiple *in vitro* and *in vivo* studies have shown that this pathway has direct effects on multiple cellular functions such as proliferation, migration, apoptosis, autophagy and more. Further, studies have shown that downstream effects of this cascade determines important hallmarks of malignancy such as initiation/progression, angiogenesis, metastasis and resistance to treatment (9). Therefore, as mentioned before, this cascade is targeted in numerous studies performed on various cell lines (10) including various synthetic inhibitors of molecules such as PI3K and natural products (11). One group of natural agents used in this regard is the members of polyphenols. Polyphenols are able to alter the function of multiple molecules effective in PI3K signaling such as Akt, mammalian target of rapamycin (mTOR) and phosphoinositide-dependent protein kinase-1 (PDK-1). Further, these agents interfere with other signaling cascades effective on

PI3K/Akt/mTOR signaling such as inflammatory signaling, angiogenesis and metabolic pathways and exert their anti-carcinogenic effect (Figure 1 and 2) (12, 13). In addition, Polyphenols can directly affect the downstream signaling cascades of PI3K pathway, decreasing the pro-carcinogenic function of this signaling. The pro-apoptotic and anti-proliferative futures of some polyphenols are examples of this (14, 15). In this review article, the significance of polyphenols in targeting PI3K/Akt/mTOR pathway is discussed in detail and their precise effect regarding carcinogenesis is shown (Figure 2).

2. Polyphenols

Polyphenols are a group of chemicals with a vast diversity formed by the combination of multiple aromatic rings and hydroxyl groups with adjacent glycosides and other acetylated chemical groups. They are considered as secondary metabolites, synthesized only in plant kingdom, assuming that they are not essential for plants in cellular levels (16). Phenols and polyphenol terms are used interchangeably through scientific literature and can be misleading. The definition of polyphenols is always confusing and vague even to researchers (17). Historically, the first definition of polyphenols was introduced by White–Bate-Smith–Swain–Haslam (WBSSH) (18). The most recent definition is proposed by Quideau as following: “The term “polyphenol” should be used to define compounds exclusively derived from the shikimate/phenylpropanoid and/or polyketide pathway, featuring more than one phenolic unit and deprived of nitrogen-based functions” (19). The latter definition covers more polyphenols such as Ellagic acid, thus a core molecule in many natural phenolic compounds is not considered a polyphenol itself by WBSSH definition. More than 8000 compounds are enlisted in this group, however, they can be categorized into several major subgroups including flavonoids, Chalcones, Phenolic acids, lignans, curcumoids and stillbenoids (20, 21). Polyphenols are found abundantly

in cereals, legumes, fruits and juices and beverages (especially barley, black gram, black currant, apple juice, red wine) (22). As mentioned earlier, polyphenols are all composed of phenol molecules, which are supplemented with various motifs and molecular groups such as hydroxyl groups conferring a structure-activity relationship to these molecules. Moreover, polyphenols vary in the number of double bonds existent in their phenolic or oxo functional groups, enabling them to show wide ranging physical characteristics (23). The aforementioned structures enables polyphenols to show a great amount of resistance towards environmental stress, yielding them the ability to absorb ultra-violet light (a beneficial characteristic) giving the constant exposure of plants to UV light (the latter is mostly caused by the existence of a carbonyl or a propenoyl ester group) (24). Importantly, the structural variation in polyphenols seem to justify various characteristics of polyphenols (at least to some extend). For example, the existence of catecholic B ring and unglycosylation on C ring enables flavonoids to show optimal anti-oxidative capabilities, whereas the existence of a monohydroxylated B ring in some flavonols make them have an abysmal anti-oxidative effect compared to other polyphenols. Interestingly, the structural variations may directly have clinical applications. Some in vivo studies have shown that certain polyphenols show pro-oxidative characteristics, making them hazardous to administer in living non-plant organisms. Biochemical analysis has shown that these polyphenols are rich in pyrogallol and catechol motifs, enabling them to reduce chelated iron and copper (25). Quideau et al. has discussed the complex structural variation of polyphenols and their significance in cellular function (25). Table 1 summarizes different subgroups of polyphenols as the most notable members of each subgroup and common dietary sources for them. Figure 3 demonstrates the common structure of each major group of polyphenols.

Flavonoids are common micronutrients in daily diet, thus over 8000 natural flavonoids have been described. They are found ubiquitously in plants as an important part of plant pigments especially in flowers (26-28). Flavonoids are significant among other polyphenols for their dominant abundance in dietary and their proved role in prevention of many oxidation-related diseases (29). These low molecular-weight compounds consist of 3 phenolic rings (A,B,C or C6-C3-C6 rings) while subcategorized according to the presence of oxy and hydroxyl groups and a double bond at particular positions of molecule (30). The presence of these groups determines the molecule's biologic activities and the maximum absorption wave length (27, 30). At least 10 subgroups have been defined with flavonols as the most common group (31). Flavones are made up from a common structure including carbon back bone of 2-phenylchromen-4-one (2-phenyl-1-benzopyran-4-one), on which residual groups are deposited. Flavonols are made up from an alteration to a core consisting of 3-hydroxy-2-phenylchromen-4-one. Flavonols include forms in which the core structure is supplemented with glucoside groups such as Kaempferol. Flavanones are composed of a basic 2,3-dihydroflavone structure with the exception of lacking a double bond between C2 and C3 (32). Flavanols possess a 2-phenyl-3,4-dihydro-2H-chromen-3-ol skeleton such as catechin. Isoflavones closely resemble flavones except for the location of one of phenyl groups (33). Anthocyanins (glycosides of anthocyanidins) which are located at the end of cluster of enzymes and forms the flavonoids are pigment molecules with alternative structure based on environmental PH . They are composed from a similar carbon skeleton (like other flavonoids) with alternative supplementary groups (34). Chalcones are the second major group of polyphenols including a constant trans-1, 3-diaryl-2-propen-1-ones structure. These molecules contain two aromatic rings with wide ranging substituents. Naturally, trans isomers of these molecules are more stable and commonly found in vegetables and fruits with a molecule yielding

a “bronzed” color to its host plant (35). Phenolic acids are the next major group of polyphenols. These molecules are all made up of a phenolic ring attached to a varying carboxylic group. Based on the carbon back bone (C1-C6 and C3-C6), these molecules are further classified in two groups of hydroxybenzoic acids and hydroxycinnamic acids (36). Liganas, which are the most abundant polyphenols in flaxseed, are composed of two phenylpropene molecules which are joined by a complementary structure either a C3 side chain or by a connection between C3 ring and an aromatic ring (37). International Union of Pure and Applied Chemistry (IUPAC) identifies lignans as “dimeric C_6C_3 coupled motifs which are connected to carbons 8 and 8′ “ (not including neolignans which are chained at other motifs) (38). Curcuminoids are derivatives of curcuminoid as a linear molecule composed of a skeleton of two aromatic rings which are chained by a seven carbon chain (diarylheptanoid) (39). The most prominent member of this group is curcumin found in Turmeric (root from a member of Zingiberaceae) (40). Stilbenoids are close polyphenol derivatives of chalcones, which are all composed of a central skeleton called stilbene and two phenolic groups joined via an ethylene motif (41). These agents are further classified into five subgroups including oligostilbenes, bibenzyls, bisbibenzyls, stilbenes and phenanthrenes (42). This structural variability potentiates the use of polyphenols in many human pathologies. The biologic effect of polyphenols in human body depends on their intake amount, intestinal absorption and bioavailability (21, 43). Dark chocolate, red wine, berries and green tea are rich sources of flavonoids (44). It is estimated a daily intake of 189.7 mg flavonoids by adults in U.S (45). The bioavailability of flavonoids varies greatly in each subgroup of polyphenols and vast variety of these compounds has made it a challenging task to study their biologic effect and therapeutic efficacy. However, most reviews agree on their minimal bioavailability in contrast to vitamin supplements (21, 46). Many polyphenols are shown to

inhibit the intracellular inflammation pathways at different points, thus reducing the oxidative stress (47). A clinical study on micro RNA (miRNA) expression in mononuclear cells followed an acute intake of olive oil has shown drastic transcriptional changes switching these cells to a less inflammatory phenotype which may reduce the incidence of cardiovascular and neoplastic diseases in long term (4, 48). Natural isoflavone, genistein is shown to play a significant anti-osteoporosis role by its interactions with estrogen receptors (49). In vivo studies have shown a significant potency for polyphenols in reducing the oxidation of LDL, their plasma levels and atherogenicity (50, 51). Therefore, clinical trials show that polyphenol-rich diets (mostly isoflavones) have a significant role in controlling of metabolic risk factors of cardiovascular diseases (52-55). Various types of polyphenols are proved to possess strong bactericidal efficacy against gram-positives such as methicilin-resistant staphylococcus aureus (MRSA) and enterococcus (50, 56). Some are found to be active against oral cariogenic gram-positive bacterium, Porphyromonas gingivalis (57). The flavonoids from bergamot peel are found to be highly active against some important gram-negative pathogens (58). The protective and therapeutic functions of these natural compounds are commonly reported in various cardiovascular disease, neurodegenerative diseases and cancer.

Currently, our knowledge regarding the structural classification of polyphenols and their probable role in functionality is limited, while evidence suggests that some motifs of polyphenols may have unique functional characteristics, as mentioned previously. One example is the difference between anti-oxidant capacity of polyphenols, which may depend on glycosylation patterns or the abundance of 3-hydroxy group found in flavonols. Furthermore, some polyphenols may act as metal chelation molecules and limit the rate of Fenton reaction (59). Importantly, in vivo studies have shown that most of anti-oxidative roles of polyphenols are

exerted via regulating inflammation modulators and enzymes, thus the significance of polyphenol structure has not been well understood (17). It is also thought that some of anti-tumor effects of certain polyphenols may depend on their chemical structure, and their resemblance to agents which activate certain receptors such as the effects of curcumin which may be mediated by direct bonding to vitamin D receptors (60). Another example is the structural similarity between members of flavonoids and certain synthetic chemical agents such as homology between quercetin and LY294002, a PI3K inhibitor (61). However, it is important to remind that the structural variations of polyphenols are not the only effective factor in their binding capacities because not all proteins show constant binding affinity to these molecules. It is proposed that proline rich proteins better bind to polyphenols rich in galloyl groups such as EGCG (25).

3. Therapeutic application of polyphenols in cancer

Antioxidant functions of polyphenols are discussed thoroughly over the past three decades and their therapeutic potential in prevention of cancers has received large attention (62), which is followed by the study of Polyphenols isolated and enriched by many different nutrients (62-65). The neoplasia-predisposing effect of chronic inflammation is a known fact (66). Several pathways are suggested for polyphenols' intracellular anti-inflammatory activity and all of them lead to downregulation of transcription factor nuclear factor kappa B (NF-κB) (67-69). A cohort study on elderly Italian population has shown that a polyphenol-rich diet could not affect all-cause mortality, cardiovascular diseases, cancers or inflammatory cytokine levels after a 9 year follow-up (70). A recent trial has shown that one month administration of high-dose resveratrol has brought significant immunomodulatory effects by increasing the circulating regulatory T cells and reducing pro-inflammatory cytokines (71). Safety, pharmacokinetics of resveratrol has

been studied in healthy volunteers. The study has also shown a decrease in circulatory insulin-like growth factor (IGF) and its receptor, which is contributed to its cancer preventive function (72). Reviews on the clinical applications of resveratrol have concluded that a high-dose intake of this polyphenol may be beneficial in preventing prostate, breast and colorectal cancers (73). In vitro studies have shown promising antineoplastic efficacy for resveratrol against numerous cancer models such as skin, breast, prostate, lung, colon and liver cancers. Resveratrol achieves this function by inducing apoptosis, inhibiting angiogenesis and reducing cell proliferation (74). However, its benefits against prostate cancer are questioned by some studies. Prostate cancer has a special place in studies of cancer prevention by nutritional antioxidants. SELECT trial has previously shown no preventive benefits from vitamin E or selenium supplements against this cancer (75). This made a profound effect on the collective opinion regarding their benefits in prevention of prostate cancer and is an important reference in FDA's statement at 2009 against benefits of supplementary antioxidants. A clinical trial has shown only intracellular anti-inflammatory changes in the reduction of NF-κB levels, following administration of green tea but not black tea, however, this finding has not been reflected into any histological changes (76, 77). On the other hand, a trial on men with prostate cancer has revealed a significant slower increment in Prostate-Specific Antigen (PSA) among men taking polyphenol-rich diets, however, this finding has not been investigated to be associated with other disease progression criteria (78). A trial on men with rising PSA and following primary treatment has shown that pomegranate juice can prolong PSA doubling time, induce apoptosis and reduce cell proliferation (79). Non-clinical studies have suggested anti-proliferative properties for polyphenols found naturally in grumixama against several lines of breast cancer cells by arresting cell cycle at mitosis checkpoints (80, 81). Resveratrol from grape is shown to have a

protective role against breast cancer (82). Studies have concluded that a polyphenol-rich diet can be beneficial in chemoprevention of colorectal cancers (83-85). Although most studies agree with the benefits of polyphenols in chemoprevention of cancers, they cannot provide adequate clinical support for health-care decision makers (e.g., FDA) to approve polyphenols for therapeutic or supplemental use. Various studies have suggested numerous mechanisms underlying potent anticancer effects of polyphenols, say clearance of toxic carcinogenic agents, regulation of major signal transduction pathways, modulation of cell cycle checkpoints, promotion of apoptosis, and regulation of enzymatic activities. Table 2 shows the different polyphenols used in *in vivo* and *in vitro* studies and their effect on selected cancer cells. The most prominent effect in each study is mentioned in Table 2. Dosage has been reported either as the concentration which is attained in studies, or as the amount administered to cell cultures (in micro-grams).

4. Targeting PI3K signaling in cancer

PI3Ks are a special group of kinases with three subtypes, in which type one is the most important phosphorylate phosphatidylinositol 4,5 bisphosphate (PIP2) at the 3rd position and forms PIP3. This leads to the modifications in the activity of downstream proteins sensitive to the intracellular PIP3 levels (86, 87). This kinase is bound to different membrane receptors and the common core ending of its signaling makes cross-talks and networks of signaling possible while explaining its role in different categories of diseases including cancers and type 2 diabetes mellitus (86, 88). The reason behind targeting PI3K pathway in cancer is raised from the studies showing that PI3K signaling with regard to mutations and alter the function of various mediators of pathway are the most common pathway involved in cancer. As mentioned earlier, PI3K signaling is able to affect every step of carcinogenesis. Moreover, the involvement of this

pathway is proved to be a prognostic factor and also a predictor of response to chemotherapy (89). However, targeting this pathway is not without challenges align with the studies showing the promising results aspired because of the reasons, say a) Targeting PI3K is rarely cytotoxic, b) cancer cells have gained intrinsic methods to resist therapy against PI3K signaling inhibition, c) therapy has not shown sufficient inhibition, and d) therapy has caused increased levels of insulin because of PI3Ks effect on metabolism and causing hyperglycemia and more (90). Concerning all, there are six classes of drugs, particularly target PI3K signaling including Pan – class I PI3K inhibitors, Isoform-selective PI3K inhibitors, PI3K inhibitors, mTOR kinase inhibitors, panPI3K/mTOR inhibitors and Akt inhibitors (91). Among various agents belonging to the mentioned six groups, only everolimus, idelalisib, copanlisib and temsirolimus are approved for clinical usage (92). Apart from treatment of lymphoma, a single therapy with PI3K pathway inhibitors has shown efficiency (93). A recent major trend in the aforementioned agents is the combination therapy with agents affecting other major pathways of cancer progression. Combining with epidermal growth factor receptor (EGFR), poly (ADP-ribose) polymerase (PARP), HER2, BRAF, and MEK inhibitors are examples of such strategies. Further combination therapy with multiple agents targeting PI3K pathway activity has also deemed possible (11). These strategies have been tested on HER2-positive breast cancer (combination of trastuzumab and paclitaxel with everolimus), Head and neck squamous cell carcinoma (Alpelisib and cetuximab), non-small cell lung carcinoma (buparlisib with erlotinib) and glioblastoma multiforme (Buparlisib with temozolomide) (94).

5. Polyphenols-targeting of PI3K signaling in cancer

5.1. Inhibition of cell proliferation

Unregulated cellular proliferation is one of the main hallmarks of cancer. Cell proliferation is controlled by a series of serine tyrosine kinases termed cyclin-dependent kinases (CDK). These molecules are activated in specific intervals of cell cycle while acting as a checkpoint to control if cells are qualified to undergo division (95, 96). Various agents affect different molecules involved in cell cycle regulation, say polyphenols. Epigallocatechin-3-gallate (EGCG) as a polyphenol enriched from green tea has shown anti-proliferative effects in bladder cancer T24 and 5637 cell lines. This effect is exerted via the decreased expression of phosphorylated PI3K and Akt. The addition of EGCG to mice implanted with tumor has resulted a significant decrease in tumor size and weight (97). EGCG is also found to have anti proliferative effects on PC-3 prostate cancer cell lines mediated by inhibiting PI3K signaling that causes ERK1/2 activation. Noteworthy, this effect is independent from MEK and its downstream mediators (98). EGCG has another novel property as its interaction with STAT3 pathway. Administration of EGCG to keloids shows an inhibition in STAT3 signaling which causes a reduction in proliferation, collagen formation and deposition (99) (Figure 4). Pomegranate, rich by polyphenols, is exhibited to have anti-tumor effects on colorectal cancers. Banerjee et al. has supplemented Sprague-Dawley rats with pomegranate juice (2504.74 mg gallic acid) and found that it causes a reduction in cellular proliferation and aberrant foci of colorectal cells. Alongside these histologic changes, phosphorylation of PI3K/Akt is inhibited, and an increase is shown in the expression of miR-126. Another part of this study has shown that this led to a strong anti-inflammatory effect in colon HT-29 cancer cell lines (100). Myricetin, a flavonoid found in berries and grapes, has anti-proliferative effects on U-87 glioblastoma multiform cells. Myricetin has the ability to bind

multiple molecules such as PI3K, ROCK-2, JNK and more while reducing signaling of PI3K/Akt and JNK pathways (101) (Figure 4). Fisetin (a flavonoid) shows favorable effects in reducing the proliferation of mammary carcinomas 4T1, MCF-7 and MDA-MB-231. These effects are mediated by inhibition of PI3K/Akt/mTOR signaling. This study has been performed both in vivo and in vitro, thus the results were consistent in both, however, in vivo experiment shows that fisetin has a low bioavailability, possibly questioning its beneficence in clinical contexts (102). Oroxylum indicum as a traditional Chinese medicinal plant has high contents of Oroxin B (a polyphenol from flavonoids). Li et al. has investigated the role of this flavonoid on SMMC-7721 cells and found that Oroxin B has dose dependent effects in reducing the expression of PI3K, p-Akt and vascular endothelial growth factor (VEGF). It also increased phosphatase and tensin homologue (PTEN) expression.

Another significant effect of this agent was inhibiting cyclooxygenase (COX)-2 (expressed in the next sections of article (103). Non-small-cell lung cancer (NSCLC) is one of the most common cancers worldwide with a rather grim prognosis. Various research initiatives have tried to find a way to inhibit tumor growth, which decrease T score of tumors and make them operable. A study by Lu et al. has focused on the effects of Baicalein on A549 and H460 cell lines and found that it inhibited its growth and increased sensitivity to cisplatin. These effects are the result of down regulated miR-424-3p, PI3K and p-Akt and upregulated PTEN expression profiles (104). Baicalein downregulates a specific long non coding RNA. This downregulation has resulted a reduced PI3K/Akt signal output, and proliferation reduction (105) (Figure 4). Luteoloside is another polyphenol with anti-cancer activity. Zhou et al. has found that it is able to reduce proliferation by activating the G0/G1 cellular arrest. The effects are dependent on Akt/mTOR/p70S6K signaling (106). Apigenin, a polyphenol from flavonoids found in most

vegetables, is shown to have anti-proliferative effects in A549 human lung cancer cell lines with Akt while playing a major role in its function. Apigenin reduces the expression of Akt and thus modulates PI3K/Akt signaling. Interestingly, other than Akt, this agent has negative effects on the levels of expression of genes such as matrix metalloproteinase (MMP)-9, glycogen synthase kinase (GSK)-3 and HEF1(107). Apigenin is also tested on prostate cancer cells, and shows the same beneficial effects of anti-proliferation coupled with a significant increase in p21 and p27 levels (108). Apigenin has also shown promise in the prevention of skin cancer. UVB has cancerous effects on the skin, and Apigenin is able to reverse the proliferative effects shown after UVB administration, which is mediated by increased mTOR signaling and resulted in keratinocyte proliferation and progression of cancer (109). Isoquercitrin, another polyphenol, shows beneficial effects on bladder cancer cell lines. In therapeutic doses, it is able to cause G1 arrest in these cells. It also inhibits PI3K signaling and reduces the expression of protein kinase C (PKC) (110). Isoangustone A, a compound extracted from licorice, is shown to be effective in reducing proliferation in melanoma. Melanoma is a skin cancer, and its prognosis directly related to the depth of tumor progression, which partially is dependent on cellular proliferation. Isoangustone A is to reduce proliferation in SK-MEL-28 cells by targeting PI3K signaling and decreasing the phosphorylation of Akt, GSK-3β, and JNK1/2. It also reduces the expression of cyclins D1 and E. The collective effect of these actions is arrest in G1 cell stop (111, 112). Some polyphenols have shown effects on the induction of melanogenesis in melanoma cancer cells. Isosakuranetin is able to inhibit PI3K signaling coupled with an induction in melanogenesis (113). Methyl 3,5-dicaffeoyl quinate a flavonoid found in herbal plants with proven anti-oxidant activities is shown to have anti-proliferative effects on colon cancer cell lines HT-29. It induces G0 to G1 arrest in these cells caused by an increase in p27 levels and a decrease in cyclin D1 and

p53, along with inhibited phosphorylation of PI3K/Akt. This agent is also able to induce apoptosis by altering the balance between BAX and BCL-2 (114). Quercetin is another flavonoid with much capability in stopping proliferation of colon cancer cells. It has anti-proliferative effects by reducing the signaling of PI3K/Akt/mTOR. It also exerts its effect via interaction with CB1-R, an estrogen receptor (115). Further, quercetin reduces migration of cancer cells by inhibiting TNF-alpha signaling dependent on PI3K pathway (116). Scutellaria flavonoids are a group of polyphenols extracted from the leaves of Scutellaria Ocmulgee showing anti-proliferative effects on gliomas. An in vivo study performed on F344 rats harboring F98 glioma has shown that the inhibition of activation of Akt, GSK-3α/β and NF-κB has caused a significant reduction in the proliferation of glioma cells (117). Pancreatic cancer is one of the cancers with the worst prognosis, with virtually no cure in high stages. It has been sought that limiting the proliferation of cancer cells has the capability to limit the spread of tumor in abdomen while decreasing the possibility of involving major vessels, thus increasing the chance of curative surgery (118). A study conducted by Yamaguchi et al. has found that p-hydroxycinnamic acid (a flavonoid) has anticancer effect on MIA PaCa-2 pancreatic cancer. It induces G1 and G2 cell cycle arrest by inhibiting NF-κB, ERK and PI3K signaling and discussed that this flavonoid is comparable and has not better results than gemcitabine as a potent chemotherapy agent (119).

5.2. Induction of apoptosis

Apoptosis is defined as programmed cell death, which happens in order to sustain the normal physiology and function of a tissue. It has been shown that cells that accumulate extensive DNA damage and cannot be repaired by DNA repair pathways initiate apoptosis. However, malignant cells have developed strategies to evade apoptosis including mutations in p53 and reduced expression of molecules termed caspases which are the key mediators and effectors of apoptosis

while impair the external signaling and alter the balance between pro and anti-apoptotic molecules (120). Clinical studies in the field of cancer have shown that targeting apoptosis is an effective strategy in fighting cancer. One strategy in targeting apoptosis is the targeting peripheral pathways effective in cell survival and apoptosis, say Akt and its downstream signaling namely P13K-Akt-FOxO axis (121, 122). Theoretically, as polyphenols are able to target this pathway, they can have beneficial effects in altering apoptosis as well. However, this axis may be altered independently from some mediators and dependent on some others. A study has shown that silibinin is able to induce apoptosis with a decreased FoxM1 expression, which is dependent on PI3K , but independent from Akt functional status (123). A study conducted by Yan et al. has found that adding Oleuropein (a polyphenol found in olive oil) is able to increase apoptosis in hepatic cancer cells HepG2 by activating the caspase pathway and altering the balance between Bax and BCL-2. This is witnessed along inhibited Akt phosphorylation. Oleuropein also induces reactive oxygen species and likely involved in its function (124). Similar effects are seen between calycopterin and HepG2 cells. Calycopterin increases the expression of mitochondrial apoptotic proteins. Interestingly, this treatment reduces the levels of caspases 3 and 9 (125). Herbacetin also has similar effects on apoptosis by PI3K/Akt pathway inhibition (126). Phloroglucinol is tested on HT-29 colon cancer cells. The results have shown that this agent has the ability of adversely regulating IGF-1 signaling. Inhibition of IGF-1 is resulted in the inactivation of downstream signaling cascades like PI3K/Akt/mTOR (127). The concept of apoptosis looks at the chemoprevention of cancers. In a study conducted by Wang et al. the combination of arctigenin (a green tea polyphenol) and curcumin have been used in order to reverse the effects of carcinogenesis on prostate and breast cancer cells. According to the results, this combination therapy has significantly increased the amount of Bax2 compared to

Bcl-2, then promoting apoptosis. This is achieved along the inhibition of NF-κB, PI3K/Akt and Stat3 signaling (128). Mulberry leaf is rich in polyphenols and its extract is an inducer of apoptosis in hepatocellular carcinoma HEP3B cells. These cells are negative for P53 which is a key tumor suppressor, thus the extract is able to induce apoptosis via decreasing the amounts of anti-apoptotic molecules and AMPK/PI3K/Akt signaling. Interestingly, transfection of p53 resulted in autophagy could cite a role for p533 in determining methods of cellular extermination (129). Isoliquiritigenin is a flavonoid with anti-oxidant and anti-inflammatory effects. Chen et al. has studied the effect of this agent on U2OS Osteosarcoma cells, resulting that it causes a reduction in levels of Akt and mTOR phosphorylation. It is also led to a decreased Bcl-2 and increased caspase 3 activity (130). Another study has shown that Isoliquiritigenin plays its pro-apoptotic role in prostate cancer by inhibiting ErbB3 signaling (Figure 4) (which is a member of epidermal growth factor receptor tyrosine kinases) (131). As mentioned before, glioblastoma multiform is a target of polyphenols in various studies. Subsequently, Lee et al. has reported that the effects of an extract produced from Artocarpus communis is studied on glioblastoma U87 and U118 cells. The extract is able to induce apoptosis via the mitochondrial pathway, and by the release of cytochrome c would increase the levels of Bad and Bax while decrease Bcl-2. The study has found that at least in mitochondrial pathway, ROS is produced in mitochondria and causes PI3K/Akt/ERK1/2-induced cell death (132). Mitochondrial pathway is also affected by Naringenin (a flavonoid) utilized on endometriosis cells. Naringenin depolarized the mitochondrial membrane potential and induced pro-apoptotic molecules such as Bax and Bak in VK2/E6E7 and End1/E6E7 endometriosis cell lines (133). Mitochondrial pathway is also involved in the pro-apoptotic effects of *Cotinus coggygria* on glioblastoma cells (134) and effects of Didymin on hepatoma cells (135). Naringenin is also involved in increasing apoptosis

in prostate cancer cell lines via targeting both PI3K/Akt signaling by reducing the phosphorylation of proteins such as ERK1/2, P53, P38, and JNK, also mitochondrial pathway by affecting mitochondrial membrane potential (136). Furthermore, Naringenin suppressed carcinogenesis mediated by 12-O-Tetradecanoylphorbol-13-acetate along with inhibition of NF-κB and inhibition of activator protein (AP)-1 (Fig 4) (137). Gold nanoparticles-conjugated quercetin inhibited signaling of epidermal growth factor and its downstream molecules including PI3K/Akt/mTOR/GSK-3<beta> in breast cancer cells (MCF-7 and MDA-MB-231). In addition, the expression levels of Bax and Bcl-2 were increased, hence as an increased apoptosis (138). Triticuside A and LYG-202 also had similar effects on the same cell lines (139, 140). Further, the effects of quercetin is shown on glioma cells by Pan et al. It is suggested that quercetin is able to induce apoptosis via reducing the expression of molecules such as MMP-9, Bcl-2, p-ERK and p-Akt accompanied by suppressed Ras/MAPK/ERK and PI3K/Akt signaling (141). Phloretin is able to exert pro-apoptotic effects on glioma cells by the generation of ROS and modulating PI3K signaling (142). Kaempferol as a natural flavonol is found in various herbs and plants and tested on CML k562 and human leukemia U937 cell lines to examine its anti-cancer effects. It is shown that apoptosis is induced via phosphorylation of Akt and inactivation of Bax (143). Further, Kaempferol induces apoptosis in bladder cancer cells by inducing PTEN (a key tumor suppressor) (144). In another study, Kaempferol has decreased the viability of HeLa cervical cancer cells via inducing apoptosis by PI3K/Akt and hTERT pathways (145). Butein as another polyphenol has similar effects to kaempferol.(146) N101-2 is another flavonoid with similar anti-apoptotic effects. However, this agent has a unique ability of inducing apoptosis via Fas extrinsic pathway (147). As mentioned before, Apigenin is a flavonoid with extensive effects in battling carcinogenesis. One important target of Apigenin is the cell cycle and apoptosis pathways (148).

Apigenin suppressed mitochondrial potential in JAR and JEG3 choriocarcinoma cells is coupled with a decreased phosphorylation of Akt. This study also has shown that the effects of Apigenin are comparable with pharmacologic inhibitors of PI3K/Akt like LY294002 (149). It is also shown that Apigenin induces apoptosis and autophagy in hepatocellular carcinoma cells by affecting PI3K/Akt/mTOR pathway (150). Wogonin (a O-methylated flavone) usually is found in Baikal skullcap and shown to induce apoptosis in HL-60 leukemia cells by inhibiting PI3K/Akt signaling. An increases in apoptosis is mediated both by mitochondrial and caspase pathways. Further, it is able to activate a specific chain of signaling termed the stress signaling of endoplasmic reticulum including IRE1α, PERK-eIF2α, CHOP, GRP94 and GRP78 (151). This is important because a new series of studies have suggested that a third way exists for induction of apoptosis via the stress signaling of endoplasmic reticulum (152). Future studies might show a role for polyphenols in this regard as well. Another study examining Wogonin on MCF-7 cells has found that beside the affecting on PI3K signaling, it reduces survivin in these cells to promote further apoptosis (153). Centipedegrass extract is rich of maysin (a flavonoid) and shown to be effective in induction of apoptosis in mouse (B16F1) and human (SKMEL-5) skin cancer lines. This is mediated by downregulation of p-Akt and GSK-3. It also induces cellular arrest in G2/M interval (154). Isoorientin (a polyphenol) is mainly extracted, but not exclusively from Phyllostachys pubescens and Drosophyllum, which is shown effective in promoting apoptosis in hepatoblastoma cells via the mitochondrial based regulated by MAPK signaling (155). This effect is mediated itself by the ROS generated by isorientin and later affects apoptosis by PI3K pathway (156). Isoorientin is also shown to activate the mitochondrial pathway of apoptosis by its effect on PI3K/Akt signaling in HepG2 cells (157). Myricetin (a flavonoid found mostly in vegetables, nuts and fruits) is shown to be able to cause apoptosis in

pancreatic cancer cells via inhibition of PI3K. In vivo treatment also causes a notable decrease in tumor size and reduces metastasis (158). It is also able to increase apoptosis via inhibiting P21 activated kinase 1 (PAK1) singling as the component of RAS signaling. This is achieved by concurrent affecting on two signaling pathways, MAPK/ERK and PI3K/Akt (159). Licochalcone A, another flavonoid is tested on BGC-823 cells (gastric cancer), finding that this agent causes apoptosis via inducing ROS generation. ROS increment is accompanied with an interference with MAPK and PI3K/Akt signaling (160). Artocarpin (a flavonoid) is administered to non-small cell lung cancer cells in order to study its effects on apoptosis in these cells. The results have shown an increase in the phosphorylation of main mediators of PI3K and Erk1/2 signaling led to an increased NF-κB activity. These effects happened in both ERK/ p38/ p53 dependent and independent manners (161). Another polyphenol with proven pro-apoptotic characteristics is Quercetin. Numerous studies have been performed on cell lines consisting of melanoma, lung, breast, prostate and adenocarcinoma cell lines showing that Quercetin induces apoptosis in these cells by increasing the levels of caspases 9 ,8 , 3 while increasing the levels of Bax, reducing the levels of Bcl-2, increasing the release of cytochrome c, and reducing heath shock proteins (162). These effects are mediated via multiple different signaling pathways, while in vitro studies have shown that some of them are in part mediated by the effect of this polyphenol on PI3K/Akt signaling pathway. Shen et al. has shown that the pro-apoptotic effects of Quercetin are because of the alteration in mitochondrial membrane potential while accompanied by a reduction in the levels of phosphorylated Akt. Interestingly, pre-treatment of malignant cells with a Akt activator is able to reverse the effects of Quercetin (163). Similar results are also reported by Kuhar et al. in H-520 cancer cells (164).

5.3. Inhibition of angiogenesis

Angiogenesis is defined as the creation of new vessels from the previously existed ones. This phenomenon is occurring in both physiologic and pathologic processes. In this case, the most important pathologic process is carcinogenesis. Various studies have shown that angiogenesis is a key factor in tumor proliferation and cellular migration and metastasis (165). The process of angiogenesis is driven by multiple signaling pathways including hypoxia response pathway with the inflammation pathway, signaling of growth factors, pathway(s) of this article, and PI3K/Akt/mTOR pathway (166). Studies have shown that this signaling pathway is able to promote angiogenesis via an increase in the levels of vascular endothelial growth factor (VEGF), both dependent and independent from hypoxia-inducible factor (HIF)-1α. VEGF and HIF-1 α are the mediators active in hypoxia signaling, also preventing their optimum function by any means is effective in reducing angiogenesis (167). Other pathways such as PI3K and certain growth factors also lead to their activation. PI3K signaling also increases the amount of other molecules important in angiogenesis such as NO and Angiopoietins (168). This integration of PI3K signaling and angiogenesis has encouraged researchers to target this pathway to halt angiogenesis (169). Ellagic acid inhibits the proangiogenic effect of VEGF by directly inhibiting the tyrosine kinase activity of VEGF receptor-2 in MDA-MB-231 breast cell lines. The downstream signaling of VEGF including PI3K/Akt and MAPK signaling are also inhibited (170). Hispidulin (a miniature flavonoid molecule) has the same effects on human pancreatic cell lines (171). The same mechanism of action has been shown for epigallocatechin gallate (EGCG a polyphenol found in tea) especially Chinese grown. Interestingly, the concentration that is enough to inhibit VEGF function has no inhibitory effect on nitric oxide synthase (172). Moreover, in another study performed on endometrial cancer cell lines, adding pro-EGCG is

associated with reduced VEGFA secretion. This reduction is shown to be associated with inhibited PI3K/Akt/mTOR/HIF1α signaling (173). EGCG reduces the expression of mediators of angiogenesis such as CD31, VEGF and HIF-1 alpha in PANC-1 cells through inhibition of PI3K signaling (174). Inhibition of this signaling cascade is also seen with Delphinidin supplementation on A549 lung cancer cells. Delphinidin is able to reduce the signaling caused by hypoxia generated by CoCL2. Noteworthy, p38 mediated pathways are spared.(175, 176) Similar results are shown with Kaempfrerol usage on human umbilical vein endothelial cells and Oligomer procyanidins (F2) on astrocytoma U25 cell lines (177, 178). Balakrishnan et al. has studied the effects of Gold nanoparticle-conjugated quercetin on MCF-7 and MDA-MB-231 and found that the expression of various proteins such as VEGF, MMP2and9, p-PI3K and Akt has been decreased. This is accompanied with reduced tube formation and angiogenesis (179). Luteolin is another polyphenol which exerts anticancer effects. A study by Lu et al. has found that Luteolin has effects similar to anti- Akt agent LY294002. It also reduces the expression of MMP-9 as a key MMP effective in angiogenesis. It also is able to reduce the proliferation of cancer cells (180). Another study has shown that this agent increases the survival of endothelial cells by inhibiting PI3K signaling (181). It is shown that Procyanidin B2 3,3″-di-O-gallate has both the ability to target VEGF-PI3K/Akt pathway and integrin signaling (182). It was found that glyceollins, a pterocarpan which is a subgroup of isoflavonoids, exerted its anti-HIF-1 effect via PI3K pathway. It was found that another mechanism for its action was that it blocked the binding activity of Hsp90 (183). Likewise, Apigenin as a dietary flavonoid is able to inhibit VEGF and HIF-1 alpha expression via PI3K/Akt/p70S6K1 pathway (184).

Genistein as an isoflavone from the group flavonoids is an agent found in soy products. It is suggested that this agent is able to reduce angiogenesis associated with carcinogenesis. It is able

to increase the anti-angiogenic properties of agents such as arsenic trioxide in human hepatocellular carcinomas by inhibiting Akt and NF-κB signaling (185). Wogonin (a flavonoid like compound found in *Scutellaria baicalensis*) also inhibites NF-Kb signaling besides PI3K. It is able to reverse the proangiogenic effects of LPS in MCF-7 cells by the mentioned functions (186). Similar results have been shown in a separate study examining the effects of wogonin in preventing angiogenesis in HUVECs being effected by H202.(187) Thus, Wogonin also inhibites IGF-1 signaling mediated via PI3K pathway (188). Chang et al. has examined the effects of extracts of *Nelumbo nucifera Gaertn* leaves on breast cancer cell lines MDA-MB-231 and found that treatment successfully reduces tumor weight and capillary density. The mechanism of this action is the reduction of PI3K signaling coupled with reduced connective tissue growth factor (CTGF) activity. A reduction in VEGF and MMP2 levels are also seen (189). Shakya et al. has studied the effect of wheatgrass extract, which is rich in polyphenols on Hep-2 cell lines and found that compounds in the extract interferes with residues on PI3K and Akt. Besides, these upstream changes, a reduction in levels of VEGF, MMP-9 and COX-2 is shown (190). The association between COX-2 and tumor angiogenesis has been already demonstrated because some of its products such as thromboxane A (2) are active promotors of angiogenesis (191), and the role of PI3K signaling is also shown in COX-2 induction. The negative regulatory effects of polyphenols on arachidonic acid metabolic network is also demonstrated in MCF-7 and MDA-MB-231cells (192, 193). Considering the fact that studies have shown some polyphenols like the aforementioned wheatgrass and Licochalcone can suppress induction of COX-2 by PI3K, an indirect effect of PI3K on angiogenesis via COX-2 could be one of the strategies utilized and studied in future (194, 195). Another set of molecules linked to angiogenesis are the FOXO transcription factors. Resveratrol which is found in grapes and products derived from grapes

induced anti-angiogenic effects via the inhibition of PI3K/Akt signaling, which is led to FOXO transcriptional activity and cause diminished angiogenesis (196). Fisetin (a flavonoid) is another polyphenol with investigated roles in cancer. In a study conducted by Pal et al. therapy with Fisetin and sorafenib which is a RAF inhibitor in melanoma cancer cells inhibites PI3K/Akt/mTOR signaling which grants favorable outcomes such as reduced angiogenesis (197). A minor group of polyphenols are lignans. Studies have shown that a member of polyphenols family named Magnolol has shown effects in inhibiting angiogenesis via PI3K/Akt/mTOR signaling in endothelial cells. This effect was in part mediated via inhibition of RAS signaling and regulation of ROS mediated apoptosis (198, 199).

5.4. Inhibition of metastasis

Metastasis is perhaps the most important event determining the outcome of cancer and the main result of failure of treatment (200). Various signaling pathways have been shown to take part in the promotion of metastasis such as PI3K/Akt/mTOR pathway. Various articles have underlined the role of this pathway in various cancers' metastasis including glioblastomas, osteosarcoma, prostate cancer, colorectal carcinoma, laryngeal carcinoma and more. PI3K signaling is able to promote metastasis by inducing angiogenesis, epithelial-mesenchymal transition inducing cellular proliferation and migration and altering tumor environment (201) that is discussed later in this article beside epithelial to mesenchymal transition (EMT). EMT is a process in which epithelial cells undergo functional and morphologic changes, and acquire the qualities of mesenchymal cells resulting tumor aggressiveness. Various pathways including PI3K/Akt, TGF-β signaling, NF-κB, Ras and Wnt/β-catenin are shown to mediate the process. This process is hallmarked by decreased levels of E-cadherin, B-catenin, CK18, CK 8 and increased expression

of N-cadherin, Vimentin, Fibronectin and SMA (202). As PI3K has shown significant roles in ECM and other preliminary events in promoting apoptosis, scholars have aimed at targeting this signaling pathway in order to limit the rates of metastasis. As mentioned, one of the most invasive cancers are pancreatic cancers. Li W has found that Curcumin is able to inhibit epithelial-to-mesenchymal transition induced by superoxide dismutase and produced H202 to induce invasive behavior in cancer cells. Curcumin also reduces p-Akt levels, thus blocks PI3K/Akt/NF-κB signaling pathway (203). Curcumin is able to induce the expression of certain Micro-RNAs affecting EMT (204). Luteolin is shown to suppress breast cancer metastasis by broad alterations in angiogenesis, proliferation and invasion. It reduces levels of VGEF, decreased EMT, increased apoptosis and reduced proliferation. Many of these effects are shown to be concomitant with the reduction of PI3K signaling. Luteolin has direct effects on the interaction of PI3K with Akt, and Ras with ERK, and Akt with GSK3β, limiting the output of their downstream pathways (205). Considering the above mentioned studies, Luteolin is able to stop the pro-metastatic effects of IGF-1 by interrupting its interactions with PI3K/Akt/mTOR signaling (206). Further, Luteolin is able to inhibit metastasis of U-87 MG and T98G cells by downregulating Cdc42 through altering PI3K/Akt activity (207). In another study, Luteolin inhibits the invasion of PC3 prostate cells by regulating E-cadherin through Akt/mdm2 pathway (208). Breast cancer is one of the malignancies with frequent metastasis to bone. Patients with metastasis harboring breast cancer are deemed un-treatable. p-hydroxycinnamic acid (a flavonoid) has shown positive anti-metastatic effects on MDA-MB-231 cells. Invasion to the bone tissue requires the recruitment of osteoclasts and osteoblasts, which secret growth factors necessary for the invasion of another cancerous cell. This agent is able to limit these actions in a co-culture of MDA-MB-231 with bone marrow cells. These effects are suggested to be edited by

p-hydroxycinnamic effects on NF-κB and PI3K signaling (209). Similar results are shown with the use of LFG-500 as a flavonoid with strong anti-cancer effects (210). Lung adenocarcinoma is another cancer with vicious metastatic capabilities. A flavonoid extracted from Murraya paniculata (a Chinese herb) decreases the expression of markers of EMT and upregulated E-Cadherin. These effects are shown to be related with the interruption of EGFR/PI3K/Akt and STAT3/NF-κB/COX-2 signaling (211). Glabridin is another agent shows efficacy in fighting metastasis in lung cancer by inhibiting FAK signaling pathway in A549 lung cancer cells. Inhibited FAK function is led to a decreased Akt activity, resulting a reduced Rho-A activity, thus reduced phosphorylation of myosin light chain (212). Notably, myosin phosphorylation by myosin light chain kinase has a role in regulating invasiveness of cancer cells (213). Rho pathway is also affected by Glabridin in MDA-MB-231 breast cancer cells in a similar fashion (214). Hispidulin (4', 5, 7-trihydroxy-6-methoxyflavone) found in various Chinese herbs induces changes such as reduced HIF-1alpha expression by modulation of PTEN/PI3K/Akt, reduced E-cadherin downregulation and blockade of transcription factors involved in EMT such as Snail, Slug and Twist in HT29 colorectal cancer cell lines (215, 216). LYG-202 inhibits the activation and angiogenesis caused by endothelial cells in a breast cancer model. This is mediated by a decrease of CXCL12 secretion. CXCL12 is a chemokine able to activate downstream signaling pathways including Akt/NF-κB signaling, thus reducing its secretion and preventing its pro-antigenic is led to pro-metastatic effects (217).

Tricetin is tested on osteosarcoma U2OS cells. Osteosarcomas are tumors occurred in young ages as one of the cancers with frequent metastasis, specially to lungs (218). It is shown that Tricetin reduces Akt signaling led to a decreased expression of MMP-9 and p38 (219). Fisetin also shows anti-metastatic capabilities with similar reductions in levels of MMP-2 and -9 (220).

Apigenin also has these effects on SW480 colorectal cancer cell lines (221) and ovarian tumor model (222, 223). Quercetin is the next agent that has shown anti-metastatic effects. A study on PC-3 cells has found that Quercetin inhibits EMT in these cells by reversing the effects of EGF through EGFR/PI3K/Akt pathway (224). Quercetin also shows more diverse effects on cell cycle and apoptosis of cancer stem cells in MCF-7 cells. Quercetin causes G1 arrest, CyclinD1 decrement and Bcl-2-like protein-4 expression increment (225). Genistein is another important flavonoid with anti-metastatic properties. Various related studies and review articles have suggested that this agent inhibits metastasis by a reduction of cellular proliferation, apoptosis increment, expression of MMPs reduction and cell invasion decrement. Human clinical trials in stages 1 and 2 are conducted, thus reported a potential for future use of this flavonoid in clinical contexts (226). Alpinumisoflavone (a natural flavonoid) is explored for its effect in renal cell carcinomas. It is found that this agent is able to suppress Akt signaling, increasing the expression of miR-101 shown to be inversely related to TNM staging (227).

5.5. Overcoming drug resistance

Drug resistance is one of the major issues concerning cancers, especially in higher stages and grades of cancer (228). Various mechanisms have been introduced as the backbone of developing drug resistance including inactivation of drugs, changing the target of drugs, drug efflux, activation of DNA damage repair, inhibition of apoptosis and other less discussed ones such as epigenetic alterations in DNA (229). It is shown that PI3K/Akt is one of the cellular signaling pathways directly involved in the emergence of drug resistance. As mentioned earlier, this pathway is able to inhibit metastasis, modulate tumor environment, and connect with other signaling pathways like DNA damage response, thus increasing tolerance to the cytotoxic effects of chemotherapy agents (230). Further, many in vitro, in vivo and human studies have shown

that cancers with high resistance to chemotherapy or radiation have high levels of phosphorylation of mediators active in this signaling pathway (231). Either with specific synthetic inhibitors or by natural agents such as polyphenol, that is why targeting PI3K/Akt/mTOR pathway seems to be reasonable and tested in multiple studies (10). Baicalein is shown to increase sensitivity of A549 and H460 lung cancer cells to cisplatin as a common agent used in chemotherapy of multiple cancers, which acts by interfering with DNA replication and causing DNA damage led to the activation of apoptosis pathways (232). Baicalein exertes this effect via increasing the expression of PTEN mediated by a decrease in synthesis of miR-424-3p as a negative regulator of PTEN. Further, it decreases the signal output of PI3K/Akt pathway. These effects are seen with minimal toxicity to normal lung cells (104). Another study has found that inhibition of NF-κB has a role in the effects of Baicalein. This study has shown that this agent reversed EMT and caused a reduction in anti-apoptotic molecules regulated by NF-KB (233). The benefits of combining polyphenols with conventional chemotherapy in lung cancer is further shown in a study which examined the effect of Alpinetin on NSCLC cells that are drug resistant. Adding polyphenol causes an increase in response to cis-diammined dichloridoplatium by modulating PI3K/Akt signaling pathway (234). 3,6,2',4',5'-Pentahydroxyflavone administration is able to overcome gefitinib resistance in NSCLC cells in a similar fashion (235). Apigenin is also shown to have effects on sensitivity to cisplatin on human CD44+ prostate cells by suppressing the phosphorylation of PI3K and Akt, and inhibiting NF-KB. There also is a decrease in SNAIL expression (236). Apigenin is also used in laryngeal carcinoma and the results have shown that it decreases resistance to radiotherapy by inhibiting the expression of GLUT-1 and PI3K/Akt signaling (237). Tangeretin is administered to cisplatin resistant human ovarian cancer cells lines to assess its effects on their sensitivity to treatment.

Pretreatment has resulted a reduction in activation of downstream molecules of PI3K/Akt signaling such as GSK-3beta and NF-κB. Apoptosis is increased and cellular arrest is induced in G2/M interval (238). Paeonol increases sensitivity to radiation in ovarian cancer cell lines of SKOV-3 and OVCAR-3 by altering the regulation of PI3K/Akt pathway. It also inhibits the expression of VEGF and HIF-1alpha (239). Isoxanthohumol (a flavonoid found in hops) is administered as co-therapy to melanoma B16 and A375. It is witnessed that this mediation increases the anti-tumor activity of paclitaxel by modulating PI3K/Akt and MEK-ERK signaling. Also, this agent is able to suppress the effects of ROS created by paclitaxel (240). Baicalein has similar effects on B16F10 Mouse Melanoma Cells by reducing the signaling of PI3K/Akt (241). Bladder cancer is one of the most common urological cancers, which resistance to chemotherapy and radiotherapy and creates much difficulty in efficient treatment (242). A study conducted by Krajnović et al. has found that adding silybin to regimens of therapy of bladder cancer causes a significant better response by inhibiting an increased activation of NF-κB and PI3K pathways through radiotherapy (243). Genistein is shown effective in increasing the sensitivity of osteosarcoma to gemcitabine by downregulation of Akt and NF-κB (244). Wogonin is also tested on multidrug resistant cell lines in order to assess its capability in reducing resistance in cancer cell lines. Human myelogenous leukemia K562/A02 cells undergone Wogonin treatment are resulted to an inhibited expression of MRP1 which is mediated by decreased Nrf-2 signaling. Interestingly, Nrf-2 itself is regulated by PI3K/Akt pathway. Wogonin also has indirect transcriptional effects on Nrf-2 by increasing specific DNA-PKcs (245). ABT-737 is an inhibitor of Bcl-xL, Bcl-2 and Bcl-w, and one of the agents used in treatment of chronic lymphocytic leukemia. Resistance to this agent has been reported and scholars such as Russo et al. has suggested that quercetin may play a role in increasing sensitivity to ABT-737 by down regulation

of Mcl-1 which itself is mediated by the inhibition of PI3K/Akt signaling (246). Similar results are shown for the co-therapy of glycolytic inhibitors and selected group of polyphenols in human acute myeloid leukemia cell lines (247). In a study conducted by Dirican et al. it is shown that combination of docetaxel and thymoquinone is able to induce apoptosis via modulating PI3K-Akt pathway. Adding these two agents shows a synergistic effect on DU-145 human prostate cancer cells. Authors have suggested that routinely administering these two agents together could justify a decrease in docetaxel dosage which is led to reducing its side effects (248). Another example of significant co-therapy is shown between Chloroquine and Luteolin in Squamous Cell Carcinoma (249).

5.6.Other effects

Beside the aforementioned effects, some novel observations have shown the role of PI3K pathway in more unconventional matters. One of the effects of PI3K pathway is the alteration in cellular metabolism. Cancer cells purposely direct their metabolic pathway to anabolism so that they can meet the increased demand for nutrients necessary for tumor proliferation and growth (250). One of the pathways important in the programming of needed changes in metabolism is PI3K/Akt /mTOR pathway. This pathway has direct effects on Warburg effect, Nucleotide biosynthesis, lipid synthesis, glutamine metabolism and possibly more not understood yet (250, 251). Because of these broad effects, it has been suggested that poly phenols can influence cellular metabolism in cancer. A study conducted by Yeh et al. has shown that tea polyphenols are able to exert anti-lipidemic effects on MCF-7 breast cancer cells achieved by blocking the stimulatory effect of EGF on fatty acid synthetize on these cells by effecting PI3k/Akt/SP-1 and MAPK/ERK/ELK pathways (252). This effect has been further shown on AU565 cell lines. Other studies suggest that polyphenols may inhibit the uptake of necessary nutrient in cancer cell

(253). These studies suggest that tea polyphenols might have a role in chemoprevention of breast carcinoma based on the hypothesis that tumor FAS has a role in tumor progression (254, 255). Another important function of PI3K pathway is the regulating glucose metabolism and Warburg effect. Various studies have shown that polyphenols such as Apigenin, Cyanidin, Daidzein, Curcumin, Epigallocatechin gallate, Genistein and more have effect on glucose uptake and enzyme regulation in cancer cells. These polyphenols can cause a reduction in glucose uptake by affecting GLUT1 and 4 (256, 257). Further, one interesting crosslink that enables polyphenols to target is the one between HIF-1alpha and glucose metabolism cascade of enzymes. Reducing the stabilization of HIF-1alpha, by any means possible, is able to reduce the expression of some of its target genes including pyruvate kinase and lactate dehydrogenase and two last enzymes active in turning glucose to lactate (258). Another cellular process of interest regarding the role of polyphenols on PI3K signaling is autophagy. Autophagy is a process in which cells remove unneeded or misfolded proteins via lysosomes. The main regulator of apoptosis is mTOR kinase that exerts regulatory effects on ATG1/Ulk-1/-2 complexes in the initial steps of starting autophagy. Growth factor signaling, specially via PI3K/Akt, is able to activate mTOR that leads to inhibited autophagy, but stimuli such as stress and hypoxia done by JNK pathway in term of phosphorylates Bcl-2 and facilitates the interaction of Beclin-1 with VPS34 (259). Fisetin is shown to inhibit mTOR kinase signaling pathway by activating TSC2 by deactivating Akt in prostate cancer cells PC3 (260). Dihydromyricetin has similar effects with a similar mechanism on HepG2 cells (261). Wogonoside (a flavonoid) has shown beneficial effects in human glioblastoma cells. Its administration has resulted an increased autophagy and apoptosis which is mediated by an inhibition in PI3K/Akt/mTOR/p70S6K signaling. The increase in autophagy is demonstrated by an increase in punctate microtubule associated protein 1 light chain 3 (LC3)

(262). Honokiol has similar effects on neuroblastoma cells through activating endoplasmic stress and inhibiting PI3K/Akt/mTOR signaling (263). Noteworthy, the relation between endoplasmic reticulum stress and autophagy and cellular death is a complicated one (264). Accordingly, Epigallocatechin-3-Gallate (EGCG) is able to induce survival via altering the activation of mTOR-AMPK Pathways by influencing the endoplasmic reticulum (265). Further, inhibiting autophagy is seen with some polyphenols, which is effective in reducing tolerance to some medication. One example is the effect of tea polyphenols on castration-resistant prostate cancer. Docetaxel is the first line therapy for these cancers, and induction of autophagy is a method of resistance to this agent. Tea polyphenols are able to increase the activity of mTOR signaling and reduce autophagy and thus increasing toxicity of docetaxel (266). Similar results are shown on the effect of polyphenols in reducing resistance to Epirubicin in bladder cancer (267). A metabolite of Ellagitannins is shown to induce apoptosis in sw620 colorectal cancer cells. These effects are concomitant with reduced cell proliferation, delayed migration, and decreased MMP9 expression. The occurrence of these effects simultaneously elicits the integrated network governing of all these functions (268). Such diverse effects were also seen with administration of Honokiol in lung cancer cells (269). One method of autophagy induction is the restriction of energy and amino acids, which could have clinical applications as it alters the characteristics of cancer cells (270, 271). A study performed by Ferraresi et al. has found that Resveratrol has a similar effect and even more potent that amino acid starvation. It is led to the entry of cancer cells to a dormant phase resulted in less aggressive behavior. The effects are mediated by mTOR signaling, which interrupts the interruption of BECLIN1-BCL-2 complex (272).

Polyphenols also alter energy hemostasis in cells via directly and indirectly affecting of mitochondria. Agents such as Resveratol are able to induce or inhibit complex 1 in mitochondrial

respiration chain (based on dosage), which is in part mediated by binding to F1 subunit of F0F1-ATP synthase (273). Resveratol is also able to induce mitochondrial cell death by overloud of calcium ions, and induction of caspase cascade. These effects are done in high concentrations. Curcumin, altered mitochondrial function via affecting AMPK/SIRT1/PGC-1α signaling pathway, causes an upregulation in the function of members of mitochondrial respiration chain. Curcumin is also able to increase the number of mitochondria in cells by upregulating NRF-1 and TFAM (274). Another effect of polyphenols exerted via altering the function of mitochondria is thermogenesis and fatty acids oxidation via increasing the expression of UCP1 and PGC-1α. Studies have shown that these effects may be clinically useful in weight loss and reducing the adverse effects of metabolic diseases such as diabetes (275). The usefulness of these effects is not well understood in human cancers, however, some in vitro and in vivo studies have reported positive results. In vitro studies of human breast cancer cells have shown that polyphenols from the group flavonoids can decrease glucose uptake and its conversion to pyruvate and lactate. This is particularly important as neoplastic cells depend heavily on glucose sustenance and reduction of its supply can reduce their proliferative abilities. Polyphenols also inhibit glycolytic enzymes such as PFK, pyruvate carboxylase, acylphosphatase, and aldehyde dehydrogenase (276-278). Table 3 summarizes anti-cancer effects of different groups of polyphenols discussed, their most significant members and specific anti-cancer effects of each sub-group.

6. **Targeting PI3K in human trials: Current status and challenges ahead**.

As mentioned before, polyphenols are indicated to treat various malignancies in different organs, as they are able to affect some of key signaling pathways which are altered in malignant transformation of cells, most notably PI3K/Akt pathway (279). Although convincing evidence

are existed regarding the possible role of agents targeting PI3K/Akt in fighting human malignancies, no large scale clinical trial has yet been initiated to study the agents affecting PI3K/Akt pathway. Currently, phase I/II trials are conducted on the possibility of utilizing m-TOR inhibitors, dual inhibitors, Akt inhibitors and selective and non-selective Pi3k inhibitors in treating solid tumors in human subjects. More recently, phase 3 trials have been initiated, in which cancers of the breast, liver, kidney and neuroendocrine tumors and sarcomas are targeted (280). Initial reports of these trials have shown that therapy with the aforementioned inhibitors of PI3K/Akt signaling pathway has resulted an increased overall survival and progression free survival, but not significantly improve treatment compared to prior established targeted therapy in use of those solid tumors such as VEGF inhibitors, hormone therapy and conventional cytotoxic chemotherapy agents (281-283).

The clinical trials conducted so far have shown that the aforementioned agents have considerable toxicity associated with their prolonged use, and patients frequently complain of nausea, diarrhea, fatigue, rash and anorexia. Laboratory follow ups have also shown elevation in liver enzymes and blood glucose levels (284). Another important factor not routinely discussed in clinical studies has been the most optimal routes of deliver for these agents, and currently little evidence exists to enable clinicians to consider these agents for wide spread use (285).

The same could also be said about polyphenols, agents with little evidence concerning their use in human studies. Currently, most of human studies examining anti-cancer effects of polyphenols are performed on patients with prostate, breast, lung or colorectal cancers, and therapy has been provided mostly in the form of nutritional supplements alongside conventional treatments such as surgery and chemotherapy in early phase trials (286, 287). However, there is potential for further studies, examining the wide array of agents available in polyphenol family, and studying

their anti-cancer effects alongside other beneficial effects on metabolism, inflammation and reduction of adverse effects of cancer therapy (288, 289). Table 4 summarizes clinical trials initiated in which polyphenols are studied as anti-cancer agents in human subjects.

7. Conclusion

The present review study has looked into different roles of polyphenols in cancer pathology and clinical applications, which are mediated by PI3K/Akt/mTOR pathway (Table 2). It is shown that polyphenols are able to alter tumor growth, proliferation, angiogenesis, migration, metastasis, mostly directs to the fact that polyphenols show potential in terms of chemo-preventive agents and as an adjunctive therapy in multiple cancer for reducing resistance to treatment or enhancing the overall outcome. Currently, the use of polyphenols in human subjects is limited to some extend because researchers are not able to fully witness the beneficial effects of polyphenols in *in vivo* studies, and also because of the dubious role of polyphenols in some aspects of carcinogenesis such as generation of ROS. Currently no clinical trials exist for most of these agents, and probably lack of evidence regarding their safety and efficacy in human subjects is the reason for their limited application in clinical contexts. It is suggested that various specialist investigate the role of polyphenols in human cancer by conducting more clinical trials, respectively, the beneficial effects of polyphenols are more utilized in cancer medicine.

Conflict of interests

The authors declared no conflict of interests.

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Fig 1. schematic represents PI3k signaling pathway on the pathogenesis of cancer. Briefly, tyrosine kinase receptor stimulated by EGF, shh, IGF-1, insulin and CAM. Consequently, PI3k activated and converted PIP2 into PIP3. Afterward, PIP3, PI3K, PDK1 and mTORC2 phosphorylate and activate AKT. AKT increases cell proliferation by activating CREB and inhibiting p27. Also AKT by effect on mTORC1 and their downstream pathways inhibits expression of P70 and 4EBP1 genes and increases critical cellular processes such as protein synthesis, growth and angiogenesis.

Moreover, FOXO phosphorylation prevents interning of it into the nucleus. This process suppresses the expression of p27 and p21 genes.

Fig 2. Different classes of drugs through targeting PI3K signaling pathway lead to anti-cancer outcomes which limits tumor progression.

Fig 3. Molecular structures of polyphenol subgroups. Note that although all flavonoids share a rather common skeleton, differences in various motifs makes them biochemically different.

Fig 4 represents multiple functions of polyphenol components on downstream signaling pathways. As shown in (A) some of polyphenol components through effect on different molecular signaling pathways exert the inhibition of cell proliferation, whereas as shown in (B) several of polyphenol components induce apoptosis by effect on different types of signaling molecular pathways.

Table1. The classification and natural sources of various polyphenols.

Group of polyphenol		Examples	Natural Source	Clinical use in cancer
Flavonoids	Flavones	Apigenin, Baicalein, Fisetin, luteolin, Myricetin, Luteoloside (cynaroside), wogonin, Tangeretin, isoorientin, Hispidulin, Tricetin	carrots, peppers, celery, olive oil, peppermint, thyme, rosemary and oregano, Scutellaria baicalensis , citrus peels, Phyllostachys pubescens, Patrinia, and Drosophyllum lusitanicum, Artemisia vestita, Tasmanian bluegum	Lung cancer, Choriocarcinoma, Prostate cancer (and the related stem cells), Colorectal cancer, Hepatocellular carcinoma, Cervical cancer, Melanoma, Breast cancer, Glioblastoma, Gastric cancer, Pancreatic cancer, metastatic skin SCC, Ovarian cancer, Hepatoblastoma, Osteosarcoma, kin cancer
	Flavonols	Quercetin, Calycopterin, Isoquercitrin, Herbacetin, Kaempferol	Fruits, vegetables, red onions, Dracocephalum kotschyi Boiss (Labiatae), Tea, mango,	Colon cancer, Hepatoblastoma, Bladder cancer, Cervical cancer
	Flavanones	Alpinetin, flavonoid N101-2, Naringenin, Didymin	Grape fruit, citrus fruits	Lung cancer, Cervical cancer, HCC, Prostate cancer
	Flavanols	Dihydromyricetin	stems and leaves of *Ampelopsis grossedentata*	HCC
	Isoflavone	Alpinumisoflavone, Isoangustone, Genistein, Glabridin, Alpinumisoflavone	Licorice root, lupin, fava beans, soybeans, Rinorea welwitschii	Renal cell carcinoma, Melanoma, Colorectal cancer, Breast cancer, Lung cancer, Osteosarcoma, HCC, clear renal cell carcinoma
	Anthocyanidines	Delphinidin	pigmented fruits and vegetables	Lung cancer

Chalcones	Butein, Isoliquiritigenin, Phloretin, isoxanthohumol, Licochalcone A, Ellagic acid	licorice, soy beans, shallots, apple tree leaves, Manchurian apricot, hops, beer, fruits (walnuts, pecans, cranberries, raspberries, stra wberries, and grapes)	Cervical cancer, HCC, Breast cancer, Prostate cancer, Osteosarcoma, Glioblastoma, Gastric cancer,
Phenolic Acids	p-hydroxycinnamic, Phloroglucinol	burdock, hawthorn, artichoke, pear, basil, thyme, oregano, apple, echinacea, strawberries, pineapple, coffee, sunflower, blueberries	Breast cancer, Pancreatic cancer, Colon cancer
Lignans	Silibinin (a mixture of flavonolignans), arctigenin, Honokiol, Magnolol	milk thistle, great burdock, Saussurea heteromalla, green tea, Magnolia	Multiple myeloma, acute myeloblastic leukemia, lung cancer, prostatic cancer, colon cancer, breast cancer, bladder cancer and hepatocellular carcinoma, neuroblastoma
Curcumoids	curcumin	turmeric	Breast cancer, Prostate cancer
Stillbenoids	Resveratrol	grapes, blueberries, raspberries, mulberries	Breast cancer, Ovarian cancer, Prostate cancer

Table 2. Polyphenols targeting PI3K/Akt/mTOR signaling

Agent	Study	Cell lines	Dosage	Anti-cancer effect mediated via Pi3k signaling	Ref.
Myricetin	In vitro	Glioblastoma	-	Anti-proliferative	(101)
	In vitro	PaCa-2, Panc-1, S2-013	12.5–200μM	Induction of apoptosis	(158)
	In vivo and in Vitro	HepG2 Wistar rats	20μ 100mg	Induction of apoptosis	(159)
Fisetin	In vitro and in Vivo	4T1, MCF-7 and MDA-MB-231 In vivo study was done on tumor bearing mice	20, 40 and 80 μM in in vitro 223 mg/kg in vivo	Induction of apoptosis – suppressing proliferation	(102)
	in vitro and in raft cultures	A375 and SK-MEL-28 melanoma cells	20 μM in vitro, three times a week fisetin 45 mg/kg	Reduction of invasion and metastasis	(197)
	In vitro	PC-3	1 mg/ml as a solution with DMSO	Anti-metastasis effect	(220)
	In vitro	PC3, DU145 and LNCaP	40, 80 and 120 microM	Induction of autophagy	(260)
Oroxin B	In vitro	SMMC-7721	0.34, 1.01 and 1.68 microM	Inhibition of proliferation	(260)
Baicalein	In vitro	A549 and H460	40 and 80 microM/L	Increased sensitivity to cisplatin	(104)
	In vitro	HeLa, SiHa, ME-180, and Caski	25, 50, 100 and 200 microM	Down regulation of a non coding RNA resulting in inhibited proliferation	(105)
	In Vitor	A549	12.5, 25, 50, 100 and 200 microM	Increased cisplatin sensitivity	(233)
	In vitro	B16F10 Mouse Melanoma	100, 150 and 200 mM	Decreased migration, invasion and cellular viability	(241)
Luteoloside	In vitro	A549 and H292	10, 30, 60 microM	Induction of cellular arrest	(106)
Apigenin	In Vitro	A549	20, 40, 60, 80 and 100 microM	Inhibition of proliferation, migration and invasion	(107)
	In vitro	PC3 and DU145	25 μM	Reduction of survival and migration	(108)
	In vitro	JAR and JEG3 choriocarcinoma cells	5, 10, 20 ,50 and 100 microM	Induction of apoptosis	(149)
	In vitro	HepG2	10, 20 and 40 microM	Induction of autophagy and apoptosis	(150)
	In vitro	OVCAR-3 and	2.5, 5, 10 and	Inhibition of	(184)

		A2780/CP70	25 microM	angiogenesis	
	In Vitro	SW480, DLD-1 and LS174T	20, 40, 80 and 120 microM	Inhibition of migration and invasion	(221)
	In vivo	Nude mouse model implemented with Hep-2 laryngeal cancer cells	50 and 100 micrograms	Increase of radio sensitivity	(237)
Isoquercitrin	In vitro	5637 and T24 bladder cancer cell lines	100, 200, 400 and 800 microM	Increase in apoptosis in inhibiting proliferation	(110)
methyl 3,5-dicaffeoyl quinate	In vitro	HT-29	6.25, 12.5, 25, 50, 100 and 200 micrM	Induction of cell cycle arrest and apoptosis	(114)
Quercetin	In vitro	Caco2 and DLD-1	50 microM	Induction of apoptosis and decrease in cellular proliferation	(115)
	In vitro	JB6 P+	20 and 40 microM	Inhibition in migration and invasion	(116)
	In vitro	MCF-7 and MDA-MB-231	25, 50, 75, 100 and 125 microM	Induction of apoptosis	(179)
	In vitro	U87-MG	50, 100 and 200 microM	Induction of apoptosis and inhibition of migration and invasion	(141)
	In Vitro and in vivo	MCF- 7, MDA-MB- 2 Chick embryo as the in Vivo model	25, 50,75, 100 and 125	Inhibition of epithelial mesenchymal transition	(179)
	In vitro	PC-3	100 microM	Inhibition of epithelial mesenchymal transition	(224)
	In vitro	MCF-7	25, 50, 75, 100, 125, 150, 175 and 200 microM	Inhibition of proliferation	(290)
	In Vitro	K562, U937, HBP-ALL	10 and 20 microM	Reduced resistance to ABT-737	(246)
p-hydroxycinnamic acid	In vitro	Pt45P1 and PaCa-2	10, 100, 250, 500 and 1000	Anti-proliferative	(119)
	In Vitro	MDA-MB-231	10, 100, 250, 500 and 1000	Anti-proliferative	(209)
Silibinin	In vitro	U87 and U251 glioma cells	200 μM	Induction of apoptosis	(123)
Oleuropein	In vitro	HepG2 and Huh7	20, 40, 60, 80 or 100 μM	Induction of apoptosis	(124)
calycopterin	In vitro	HepG2	10, 25, 50, 100, 150 and 200 microM	Induction of apoptosis and cell cycle arrest	(125)
Herbacetin	In vitro	HepG2	25, 50, 100 and 200	Induction of apoptosis	(126)
Artigenin	In vitro	MCF-7 and LNCaP	1 μM	Induction of apoptosis	(128)
Curcumin	In vitro	BxPC-3 and Panc-1	20 μM	Inhibition of epithelial mesenchymal	(291)

				transition	
	In Vitro and In Vivo	L1210, 4T1, B16 and CT26	10μM	Inhibition of ATP synthase	(251)
	In vitro	MCF-7	5 and 10 μM	Reversing the Warburg effect.	(257)
Isoliquiritigenin	In vitro	U2OS	10 and 20 microM	Inhibition of invasion and proliferation	(130)
	In vitro	MDA-MB-231 and BT-549	10, 20 and 40 microM	Prevention of metastasis	(193)
Naringenin	In vitro	VK2/E6E7 and End1/E6E7 endometriosis cells	20, 50 and 100	Induction of apoptosis	(133)
	In vitro	PC3 and LNCaP	5, 10, 20, 50 and 100 microM	Induction of apoptosis	(136)
	In vitro	HepG2, Huh-7, and HA22T	12.5, 25, 50 and 100 microM	Inhibition of invasion	(137)
Didymin	In vitro	HepG2	25 microM	Induction of apoptosis	(135)
Phloretin	In vitro	U87 and U251	200 microM	Induction of cell cycle arrest	(142)
Kaempferol	In vitro	K562	50 microM	Induction of apoptosis	(143)
	In vitro	EJ and T24 bladder cancer cells	20, 40, 80 and 160 microM	Induction of apoptosis	(144)
	In vitro	HeLa	12-100μM	Induction of apoptosis	(145)
Burein	In vitro	HeLa	15, 25 and 50 microM	Inhibition of proliferation and increase in ROS generation	(146)
N101-2	In vitro	SiHa and CaSki human cervical cancer cells	5, 10 and 15 microM	Induction of apoptosis	(147)
Wogonin	In Vitro	HL-60 leukemia cells	Up to 150 microM	Induction of apoptosis and endoplasmic reticulum stress	(151)
	In vitro	MCF-7	10, 20, 40, 80 , 160 and 320	Induction of apoptosis	(153)
	In vitro and in vivo	MCF-7, MDA-MB-231 HepG2 and HCT116	10, 20 and 40 microM	Inhibition of angiogenesis	(186)
	In vitro and in vivo	human umbilical vein endothelial cells	1, 10 and 100 microM	Inhibition of angiogenesis	(187)
	In vitro and in vivo	MCF-7 and chick chorioallantoic membrane	Undetermined	Inhibition of proliferation and angiogenesis	(185)
	In vitro	K562/A02	20-200 microM	Reduction of multidrug resistance	(245)
Isoorientin	In vitro	HepG2	10,20,40, 80 and 100 microM	Induction of apoptosis	(157)
Licochalcone A	In vitro	BGC-823	20, 40, 60, 80 and 100	Induction of apoptosis	(160)
	In vitro	HaCaT human keratinocytes	5 and 10 microM	Suppresion of COX-2	(195)
Artocarpin	In vitro and In vivo	A549, H1299 and H226	0.1, 1,5 and 10	Induction of apoptosis and inhibition of	(161)

				proliferation	
Ellagic acid	In vivo and In vitro	MDA-MB-23	2.5, 5, 10, 15 and 20	Inhibition of angiogenesis	(170)
Hispidulin	In vitro and in vivo	PANC-1, PANC-28 and BxPC-3	1-200 microM	Inhibition of angiogenesis and proliferation	(171)
	In vitro	HT29	12.5, 25 and 50 microM	Prevention of epithelial-mesenchymal transition	(215)
epigallocatechin gallate	In vitro	Human umbilical vein endothelial cells	1 microM	Inhibition of angiogenesis	(172)
Delphinidin	In vitro and in vivo	A549	20-200 microM	Inhibition of angiogenesis	(175)
	In vitro	B16-F10 mouse melanoma	10 microgr/ml	Inhibition of proliferation	(176)
Procyanidins	In vitro and in vivo	U251	10, 30, 60 and 100 microM	Inhibition of angiogenesis and invasion	(178)
	In vitro	Human umbilical vein endothelial cells	40 microM	Inhibition of angiogenesis	(172)
Luteolin	In vitro and in vivo	HUVECs	2,5,10 and 50	Inhibition of angiogenesis	(181)
	In Vitro	U251MG and U87MG	5-100 microM	Reduction of migration	(206)
	In vitro	U-87 MG and T98G	10, 20, 30, 40, 50 microM	Reduction of migration	(207)
	In vitro and in vivo	PC3	10, 20 and 40 microM	Inhibition of invasion	(208)
	In vitro and in vivo	MET1 and MET4	10-100 microM	Increase I drug sensitivity	(249)
Procyanidin B2 3,3″-di-O-gallate	In vitro	LNCaP and PC3 and HUVECS	10,20,30 and 40 microM	Inhibition of migration	(182)
Resveratrol	In vitro	HUVECs	20 microM	Anti-angiogenic effect	(196)
	In vitro	NIH-OVCAR-3 o	100 μM	Induction of autophagy	(272)
Magnolol	In vitro	HUVECs	o.5 and 1 microM	Inhibition of angiogenesis	(198)
	In vitro	Mouse D3 ES cells	20 microM	Inhibition of angiogenesis	(199)
Glabridin	In vitro	A549	1,2.5,5 and 10 microM	Inhibition of migration, invasion and angiogenesis	(212)
	In viro	MDA-MB-231	1, 2,5, 5 and 10 microM	Inhibition of migration, invasion and angiogenesis	(214)
Tricetin	In vitro	U2OS and HOS	Up to 80 microM	Inhibition of metastasis	(219)
Alpinumisoflavone	In vitro	786-O and Caki1	2.5, 5 and 1o microM	Inhibition of metastasis	(227)
Alpinetin	In vitro	A549, SK-MES-1, NCI-H292, and A549/cis-diammined dichloridoplatium (CDDP)	50, 100, 200 and 400 microM	Induction of apoptosis	(234)

3, 6, 2′, 4′, 5′-Pentahydroxyflavone	In vitro	MRC-5, A549, H1299, H1650, and HCC827 human lung cell lines	5 and 20 microM	Reduction in resistance to Gefitinib	(235)
Tangeretin	In vitro	A2780 and A2780/CP70	150 micro-mol/L	Reduction in cisplatin sensitivity	(238)
isoxanthohumol	In vivo	A375 Murine melanoma B16	11.5, 23 and 46 microM	Increase in paclitaxel sensitivity	(240)
Silybin	In vitro	MB49	40, 60 and 80 microM	Improvement in response to radiotherapy	(243)
thymoquinone	In vitro	DU-145	1-120 microM	Induction of apoptosis	(248)
Wogonoside	In vitro	SHG44 glioblastoma cell line and U251MG, U87MG and A172	250 micoM	Induction of apoptosis	(262)
Honokiol	In vitro	NB41A3 cells	25, 50 and 100 microM	Induction of autophagy	(263)
Honokiol	In vitro	H460, A549, H358, H2122, BEAS-2B, NIH3T3, CCD19-Lu	20, 40 and 60 microM	Induction of apoptosis and cellular arrest	(269)

Table.3. Anticancer effects of different subgroups of polyphenols, with the corresponding agents.

Polyphenol classification		Anticancer effects	Agents
Flavonoids	Flavones	Induction of apoptosis, increased sensitivity to platinum agents, decreased cell proliferation, induction of cell cycle arrest, inhibition of angiogenesis, induction of autophagy, inhibition of Epithelial mesenchymal transition, reduction in cellular migration.	Myricetin, Oroxin B, *Baicalein, Luteoloside, Apigenin , Silibinin, Wogonin, Isoorientin, Artocarpin, Hispidulin, Luteolin, Tricetin,*
	Flavonols	Inhibition of metastasis, induction of autophagy and apoptosis, reduction in cellular proliferation.	Fisetin , Herbacetin, Kaempferol,
	Flavanones	Induction of apoptosis	Naringenin, Didymin, N101-2, Alpinetin
	Flavanols	Induction of apoptosis, reduction of cellular invasion, decreased cellular proliferation, inhibition of epithelial mesenchymal transformation.	Quercetin, Isoquercitrin,
	Isoflavone	Inhibition of angiogenesis, inhibition of cellular migration, inhibition of metastasis	Glabridin, Alpinumisoflavone,
	Anthocyanidine	Inhibition of angiogenesis and cellular proliferation.	Delphinidin
Chalcones		Prevention of metastasis, induction of cell cycle arrest, increase in ROS generation, suppression of COX-II, inhibition of angiogenesis, induction of apoptosis	Isoliquiritigenin, Phloretin , Butein, Licochalcone, Ellagic acid, Isoxanthohumol,
Phenolic Acids		Reduction of cellular proliferation, induction of apoptosis.	p-hydroxycinnamic
Lignans		Induction of apoptosis, inhibition of angiogenesis, induction of apoptosis and cell cycle arrest	Arctigenin, Magnolol, Honokiol,
Curcuminoids		Reversing the Warburg effect, reduction of ATP synthesis, inhibition of epithelial mesenchymal transformation.	Curcumin
Stillbenoids		Induction of apoptosis and autophagy, inhibition of angiogenesis.	Resveratrol

Type of polyphenol	Polyphenol route of administration	Cancer type	Number of patients	Aim	Number
Not specified.	Oral supplementation (474 mg phenolics/day)	Breast cancer	40	Metabolic Profiling of Dietary Polyphenols	***NCT03482401***
Quercetin, green tea polyphenols	Oral supplementation	Prostate cancer	31	To assess alteration in expression of COMT, DNMT1, MRP1	***NCT01912820***
Walnut polyphenols	Oral supplementation (2 ounces of walnuts daily for 4-10 weeks)	Prostate cancer	50	Alteration in the expression of Ki67	NCT03824652
Polyphenon E (EGCG)	Oral supplementation as 4 capsules daily with a meal for the duration of the study	Prostate cancer	33	Alteration in serum prostate specific antigen levels and serum levels of VEGF and HGF.	NCT00676780
Blueberry polyphenols	Oral supplementation of blueberry powder, 30-45 grams per day for 4 cycles of 21 days	Non-Small Cell Lung Cancer	4	Evaluation of clinical response using the Response Evaluation Criteria in Solid Tumor (RECIST) Guidelines	***NCT01426620***
Pomegranate polyphenol	Oral supplementation of Pomegranate extract	Colorectal cancer	60	Gene expression profiling of IGF-1 and CEA	***NCT01916239***
Tea polyphenols	Oral supplementation of 300mg Bid for 6 months	Squamous cell carcinoma of the esophagus (chemoprevention)	600	Occurrence of high grade dysplasia	***NCT01496521***
Tea polyphenol	Oral supplementatio	Colorectal adenomas	1001	Incidence of	***NCT01360320***

(EGCG)	n of 150mg tea poly phenol Bid			colorectal adenomas in a time span of 3 years	
Quercetin	Oral supplementation of 400 mg daily quercetin for 24 months	Oral SCC in Fanconi anemia patients (chemoprevention)	55	Reduction of buccal micronuclei	***NCT03476330***
Resveratrol (combination with bortezomib)	5.0 grams of Resveratrol for 20 consecutive days in a 21 day cycle	Multiple Myeloma	24	Response rate and adverse events	***NCT00920556***
Resveratrol (combination with sirolimus)	250 mg daily for 8 weeks, then 500 mg daily for 8 weeks, then 800 mg Bid for 8 weeks	lymphangioleiomyomatosis (LAM)	25	Serum VEGF-D levels and pulmonary function tests	***NCT03253913***
Resveratrol	80 mg daily	Colon cancer	11	Assess Wnt signaling pathway	***NCT00256334***
Resveratrol	1 -1/3 lb/ day of red grapes	Colon cancer chemoprevention	30	Localization of β-catenin	***NCT00578396***
Resveratrol	5 gm/day	Low Grade Gastrointestinal Tumors	7	Notch activation in post treatment biopsies	***NCT01476592***
Resveratrol	Not specified	Colon cancer	20	M-G1 and COX-II expression in circulating WBCs	***NCT00433576***
Apigenin	20 mg	Colon cancer (chemoprevention)	382	Recurrence rate of neoplasia	***NCT00609310***

Table.4. List of clinical trials assessing the beneficence of polyphenols in human cancer subjects