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Polyphenols as Tyrosine Kinase Inhibitors for the Treatment of Metastatic Cancers: Current and Future Perspective

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ABSTRACT

Cancer is the leading cause of death worldwide. The increased cancer mortality rate is due to metastasis, which is a key stumbling block in cancer treatment. Polyphenols are a broad group of antioxidant-rich natural chemicals that are frequently utilized as chemopreventives and adjuvants in cancer treatments. The tyrosine kinase pathway is one of many signaling pathways involved in the metastatic cascade. Tyrosine kinases are a class of enzymes that play a role in cancer progression. Despite a huge body of studies confirming their antimetastatic effects, polyphenols' significance in cancer metastasis remains underappreciated. To discover publications that emphasize the topic of this review study, a thorough literature search was undertaken in several electronic databases. PubMed Central, Google Scholar, Scopus, and Medline were among them. As a result, the current analysis outlines cancer metastasis signaling pathways, emphasizing the role of tyrosine kinases in the process. Polyphenols can decrease tyrosine kinase activity, which adds to their antimetastatic properties. This review also emphasizes the role of polyphenols in preventing cancer metastasis by interfering with the tyrosine kinase signaling cascade, which could lead to the development of future antimetastatic medications.

Keywords: polyphenols, cancer metastasis, tyrosine kinases, chemoprevention

INTRODUCTION

Cancer is the world's top cause of illness and mortality, accounting for a higher death rate. Cancer will be more prevalent in 2030, with an estimated 21.3 million new cases and 13.1 million deaths (Ferlay *et al*., 2019). Furthermore, the worldwide cancer burden is anticipated to rise by 47% between 2020 and 2040, with transitioning nations experiencing a bigger increase (64–95%) than transitioned countries (36–56%) due to demographic changes. This could be exacerbated by the increased risk factors linked with globalization and economic expansion (Sung *et al*., 2021). Despite rising cancer incidence and mortality rates, scientific efforts and improved research outputs have resulted in well-recognized advances in the diagnosis, prevention, and treatment of several cancers (Zugazagoitia *et al*. 2016). Cancer therapies available today include radiotherapy, surgery, chemotherapy, immunotherapy, and hormone therapy (Tsimberidou *et al*., 2020). The most typical trend in cancer eradication is the pharmacological strategy of employing chemotherapy medications to kill cancer cells. These medications, on the other hand, are not selective and may even be cytotoxic to non-cancer cells, resulting in a wide range of side effects (Fitzner *et al*., 2017). As a result, several efforts have been undertaken to evaluate the use of many naturally occurring chemicals that have shown exceptional efficacy in the prevention and treatment of certain malignancies. Despite a dearth of data and contradictory information on their role in cancer prevention and therapy, natural products may be an effective strategy to minimize cancer incidence and death (Qamar *et al*., 2019). Metastasis is an important component of cancer that allows neoplastic cells to spread to different places of the body from where they originated. It is the most hazardous aspect of cancer, accounting for more than 90% of cancer-related deaths (Summers *et al*., 2020).

Many studies are currently focusing on the mechanisms of cancer metastasis, such as gene expression (Park and Han, 2019) and changes in proteomics that regulate cell motility (Nikolaou and Machesky, 2020), matrix breakdown (Hamidi and Ivaska, 2018), angiogenesis (Haibe *et al*., 2020), and immune surveillance evasion (Gonzalez *et al*., 2018). In this context, activation or deactivation of several tyrosine kinases (TKs) has been shown to play a significant role across metastatic signaling cascades (Inan and Hayran, 2019). As a result, TKs may be exploited as therapeutic targets. On the other hand, there aren't many ways to stop cancer from spreading at the moment, if any at all. Given the premise that stopping a single phase of metastasis may halt the entire process, targeted interference with TKs and associated signaling cascades may be a reasonable strategy for reducing metastasis. A growing amount of evidence demonstrates that specific polyphenols can effectively target different stages of the TK cascades in several ways (Sakle *et al*., 2020). This study focuses on the most recent results (2000–2021) concerning the involvement of naturally occurring polyphenols in the modification of the TK signaling cascade. Importantly, *in vitro* and *in vivo* models have identified the molecular pathways by which polyphenols prevent the invasion and metastatic cascade.

Cancer metastasis: signaling mechanisms and drug targets

Cancer metastasis is a complex process caused by the interaction of numerous genes and signaling pathways. These processes cause cancer cells to migrate and more invasive (Pachmayr *et al*., 2017). Cancer cells must go through multiple stages before becoming metastatic and spreading from primary sites to distant secondary sites. The epithelial-mesenchymal transition (EMT) is the first step in the progression of cancer. Cancer cells undergo EMT, which causes them to lose epithelial traits and gain mesenchymal characteristics.

This process allows cancer cells to migrate away from their primary site. Cancer cells penetrate surrounding tissue after detachment and damage the extracellular matrix by secreting proteases such as matrix metalloproteinase -1, -2, and -9 (Chiang *et al*., 2016). Then, they travel into blood vessels (intravasation) and express numerous chemicals such as thrombin, cathepsin B, and cancer procoagulant to overcome the immune onslaught and bloodstream-induced shear stress. After that, initial cancer cells extravasate and form a premetastatic niche in the target tissue (Psaila and Lyden, 2009). The colonization step of the metastatic cascade involves the multiplication of micrometastatic cells into massive macrometastasis. Many signaling pathways influence the aforementioned processes, including:

The EGF/RAS/RAF/MEK/ERK pathway governs cell proliferation, differentiation, and motility as well as acting as an adaptor for extracellular stimuli transmission to the intracellular compartment. When a ligand interacts with growth factor receptors, the rat sarcoma virus oncogene (RAS) is activated, which activates the rapidly accelerated fibrosarcoma (RAF) isoforms (A-, B-, and C-RAF). RAF activates the mitogen-activated protein kinase (MAPK) and extracellular signal-regulated kinases (ERK 1 and 2). This pathway influences the metastatic cascade by suppressing apoptosis and increasing cellular migration (McCubrey *et al*., 2007). Many studies have established several targets in EGF/RAS/RAF/MEK/ERK signaling, and some of these targets, such as EGFR inhibitors (cetuximab, panitumumab), RAF inhibitors (vemurafenib and dabrafenib), and mitogen-activated kinase (MEK) inhibitors, have been successfully translated into FDA-approved medications (trametinib and selumetinib).

Similar to the previously stated system, the phosphoinositide 3-kinase (PI3K)/Akt/mTOR pathway promotes cell survival and migration. By interacting with the p70 S6 kinase (S6K1) and the eukaryotic initiation factor 4E-binding protein (4E-BP1), mTORC1 promotes tumor cell motility. Furthermore, mTORC2 modulates actin cytoskeleton dynamics via protein kinase C alpha (PKC), GTPases, and focal adhesion proteins, promoting cellular motility and invasion. Protein kinase B (Akt), on the other hand, maintains cellular viability by inhibiting pro-apoptotic proteins such as Bcl-2 and procaspase-9 (Zhou and Huang, 2011). The discovery of mTOR inhibition led to the development of temsirolimus and everolimus, two FDA-approved medicines used to treat advanced renal cell carcinoma and other malignancies (Baselga *et al*., 2012).

The HGF/Met pathway is crucial for metastasis. The binding of hepatocyte growth factor (HGF) to the MET proto-oncogene receptor tyrosine kinase (cMet RTK) increases cancer metastasis in a variety of ways. It activates intravasation by promoting neoangiogenesis, a process mediated by signal transducers and

activators of transcription 3 (STAT3), PI3K/Akt, and RAS signaling pathways, and activates local invasion by stimulating PI3K/Akt/mTOR (Zhang *et al*., 2016).

The Wnt/-Catenin pathway regulates E-cadherin transcription, which controls metastasis by generating EMT and invasiveness. Wnt ligands bind to the Frizzled receptor, which inhibits proteasomal degradation of catenin and regulates the expression of Wnt-related genes including E-cadherin and S100A4. Then, S100A4 boosts the RAS/RAF/MEK/ERK pathway and promotes tumor cell metastasis (by increasing cell motility and invasiveness), suggesting that S100A4 could be a promising target in cancer therapy (Boye and Maelandsmo, 2010).

The vascular endothelial growth factor (VEGF) pathway regulates angiogenesis, which is an important step in the metastatic cascade. The binding of VEGF to VEGF receptor TKs causes receptor autophosphorylation and signaling cascade activation. VEGFR-1 stimulates tumor cell proliferation, migration, and invasion by activating ERK-1/-2 and c-Jun NH2-terminal kinase (JNK). Additionally, activation of VEGFR-3 enhances cell survival, migration, and proliferation via inducing p42/p44, MAPK, and Akt signaling (Achen and Stacker, 2008). After extensive clinical trials, the FDA approved the anti-VEGF antibody (bevacizumab) and anti-VEGFR-2 antibody (ramucirumab) for the treatment of various cancers.

Role of protein kinases signaling in carcinogenesis

Many enzymes in the protein kinase system alter the activities of other proteins by adding phosphate groups to the tyrosine, serine, or threonine residues. As a result, the actions of a variety of regulatory proteins, which are critical in orchestrating a variety of cellular functions, are altered. The components of these systems are involved in various cellular processes, including metabolic regulation, cell cycle control, and cellular survival and differentiation. The function of the kinase system, on the other hand, is tightly controlled, and any change in this fine-tuning can lead to pathological changes like neoplastic transformation and cancer (Wilmes *et al*., 2020).

Common causes of kinase system dysregulation include overexpression, translocation, mutations, or dysregulation of the upstream signaling pathways. In this regard, many protein kinases are implicated in oncogenesis pathways; for example, the MAPK pathway governs most physiological functions such as cell proliferation, differentiation, and apoptosis. In mammals, the MAPK family includes the ERK, p38, and JNK kinases. Many upstream signaling pathways are dysregulated, including RAS/RAF/MAPK/ERK kinase and ERK1/2. This could cause MAPK signaling cascades to fail and lead to cancer development. Furthermore, mutations in genes encoding the RAS/RAF/MAPK pathway are implicated in the majority of well-known human malignancies (Alqahtani *et al*., 2019). When this pathway is activated, it sends out a signal to protein TK receptors such as the epidermal growth factor receptor (EGFR) and platelet-derived growth factor receptor (PDGR) (Zhang *et al*., 2020). Following that, intracellular second messengers translocate into the nucleus and govern the activation of a variety of transcription factors, several of which may be involved in cancer progression and oncogenesis. Furthermore, oxidative stress and DNA damage are key contributors to carcinogenesis when this signaling cascade is disrupted. Many studies have highlighted the role of activated MAP kinases ERK1/2 in the response to excessive cellular oxidative stress as well as their link to numerous neoplastic alterations (Liu *et al*., 2020).

Carcinogenesis is described as a breakdown in communication between various intercellular and extracellular signaling pathways, which disrupts multiple transcription factors and promotes incorrect expression of cancer-related genes. Several forms of cancer-related MAPK signaling pathway mutations in RAS and RAF components have been identified, and both have been shown to participate in the ERK signaling cascade (Kim and Choi, 2010). Much research has been conducted to elucidate the role of the kinase system in carcinogenesis, and oncogenic alterations in MAPK pathways primarily affect RAS and RAF activity.

Even though tyrosine phosphorylation contributes very little in comparison to serine and threonine phosphorylation, it is an important signaling step essential to sustain cellular activities. Phosphotyrosine signaling dysfunction can hasten the process of carcinogenesis. Disrupted TK signaling is widely implicated in many forms of cancer, with 51 of 90 TKs implicated in cancer by overexpression or mutation (Casaletto and McClatchey, 2012). The activity of TKs is endogenously modulated by another system known as protein tyrosine phosphatases (PTPs), which can be activated to dephosphorylate the

target proteins and consequently regulate phosphotyrosine signaling. In this regard, many investigations have found that PTPs, like PTKs, are linked to carcinogenesis. Only 22 of the 38 known classical PTPs have been described to play a tumor-suppressive role in diverse forms of cancer. Based on this, it is fair to speculate that cancer cells may contain somatic mutations and/or low PTP expression (Hendriks *et al*., 2013).

ROLE OF POLYPHENOLS IN CANCER CHEMOTHERAPY

Polyphenols are a diverse group of naturally occurring chemicals that can be easily obtained from a variety of plant-based ingredients. Chemically, they are distinguished by the presence of polyhydroxylated phenolic structures (Tsao, 2010). Polyphenols are divided into two general classes: flavonoids, which contain two phenolic rings connected by a carbon chain; and non-flavonoid polyphenols, which include three main subclasses, the majority of which are phenolic acids (benzoic acid derivatives and cinnamic acid derivatives), stilbenoids, and other polyphenols (Durazzo *et al*., 2019).

Polyphenols have anti-oxidative, anti-proliferative, apoptosis-inducing, and immune-modulatory properties that interfere with various signaling pathways in cancer cells, hinting that polyphenols could be effective in cancer prevention and treatment (Bian *et al*., 2020). Furthermore, the anti-neoplastic activities of polyphenols have been demonstrated in epidemiological studies, animal models, and various *in vitro* cell line reports (Reddivari *et al*., 2016; De Stefanis *et al*., 2019). Based on the aforementioned characteristics and the broad spectrum of the relevant processes, polyphenols are suggested as a prophylactic agent against carcinogenesis, as a potent chemotherapeutic agent (alone or in combination with other agents), and as a component of a palliative treatment approach.

Polyphenols in cancer chemoprevention

A considerable functional association exists between cancer and the type of nutrition consumed; an unsuitable diet can hasten the onset of many malignancies (Riboli and Norat, 2003). Many epidemiological studies show that eating fruits and vegetables daily helps to reduce the incidence of various forms of malignancies (Aune *et al*., 2011). Natural polyphenols have been shown to have chemopreventive benefits in a variety of *in vitro* and *in vivo* cancer models.

Chemoprevention largely works by altering multiple signaling pathways that regulate cancer cell proliferation and death (Kotecha *et al*., 2016). Many polyphenols derived from black and green tea, for example, have been proven in animal models to protect against UV radiation and 7,12-dimethylbenz[a] anthracene-induced skin cancer (Wang *et al*. 1994). Meanwhile, animal studies have revealed that resveratrol, the main polyphenol contained in grapes, has anti-cancer activities (Jang *et al*., 1997). The chemopreventive actions of polyphenols have been linked to a variety of their biological activities, including anti-oxidative, metabolic detoxification of xenobiotics, and apoptotic induction. They also stimulate the immune system and regulate the actions of several transcription factors, including NF-κB and the kinase system, both of which play significant roles in regulating gene expression in response to various stimuli (Lagoa *et al*., 2020).

Unfortunately, most of the available data focuses on each polyphenol alone, but in actuality, interactions with other natural or synthetic substances, both at the cellular and tissue levels, have a significant impact on the ultimate effects of these polyphenols (Khan *et al*., 2020). *In vitro* and *in vivo* evidence shows that combining two or three polyphenols is more efficient than employing a single polyphenol in preventing cancer growth (Tabrez *et al*., 2020). Liu *et al*. (2019) found that combining several phenols has pleiotropic effects because it changes many of the signaling pathways that are involved in the initiation and spread of cancer (Liu *et al*., 2019).

Polyphenols as adjuvants in cancer chemotherapy

Currently, the majority of treatment strategies rely on the use of combination medicines, which contain drugs with different molecular mechanisms and increased efficacy (Pathak *et al*., 2005). Various natural polyphenols, including resveratrol, genistein, and curcumin, have anticancer properties and have been proposed as chemopreventive drugs (Block *et al*. 2008). As a result, combining synthetic cytotoxic drugs with these natural substances may result in improved anticancer functions due to the synergistic activities as well as a reduction in chemotherapy-related side effects (Sarkar and Li, 2006). The benefits of using a drug combination approach in cancer treatment can be predicted because reducing doses can reduce the formation of resistance while retaining the same efficacy or

even higher efficacy due to synergistic effects (He *et al*., 2015). So, Lin et al. (2017) suggested that drug combinations with natural polyphenols could achieve the same results as traditional chemotherapeutic agents while having fewer side effects on the whole biological system (Lin *et al*., 2017).

Many experiments have been conducted to investigate the use of natural products as adjuvants in cancer chemotherapy and have discovered that they are beneficial in nasopharyngeal, breast, and pancreatic cancer therapies (Kim *et al*., 2015; Kuo *et al*., 2018). Their beneficial effects as adjuvant therapy can be attributed to a variety of reasons. For example, the natural substance can sensitize cancer cells to chemotherapeutic drugs or reduce cancer cell resistance to chemotherapy (Mileo *et al*., 2020; Hussain and Marouf, 2013). Furthermore, based on *in vitro* and animal studies, polyphenols have been proposed as adjuvant chemo/radiosensitizers of neoplastic cells, and their synergistic effects with various cancer therapy protocols have been adequately explored (Suganuma *et al*., 2011). However, clinical evidence supporting the potential use of polyphenols as adjuvants in cancer chemotherapy is limited, and more studies are needed to confirm these effects. Meanwhile, the anti-inflammatory and antioxidant properties of polyphenols have been related to a reduction in many of the systemic side effects of cancer chemotherapy (Wessner *et al*., 2007). As a result, polyphenols could be a viable cancer adjuvant therapy, as evidenced by their ability to increase anticancer outcomes while reducing the undesired side effects of currently available chemotherapies.

Tyrosine kinases as a target for polyphenols

In a growing number of studies, the anticancer activity of some polyphenols has been linked to the suppression of the TK signaling pathway (Figure 1). Many polyphenols have been thoroughly studied, including the flavonols 5-deoxykaempferol, kaempferol, fisetin, myricetin, and quercetin, which show direct inhibition of protein kinase-mediated carcinogenesis (Baek *et al*., 2013). In this context, 5-deoxykaempferol inhibits the phosphorylation of MKK3/6, MKK4, and Akt, and reduces the UVB-induced production of COX-2 and VEGF in mouse skin epidermal JB6 P+ cells (Bode and Dong, 2013). Other studies suggest that kaempferol suppresses cancer cell proliferation by directly targeting the RSK2 and PI3-K pathways (Baek *et al*., 2013; Bode and Dong, 2013). Furthermore, in the SKH-1 hairless mouse skin carcinogenesis model, myricetin suppresses PI3-K and decreases UVB-induced angiogenesis. Myricetin also suppresses the TK pathway by inhibiting Raf-1, MEK1, and Janus kinase/signal transducer and activator of transcription 3 (JAK1/STAT3) (Temviriyanukul *et al*., 2021).

According to these findings, myricetin may have a promising anticancer efficacy via the inhibition of multiple TK pathway targets. Quercetin, another polyphenol, was found to have potent anti-cancer properties in a variety of cell types. It works by inhibiting the activity of MEK1 and Raf-1 kinases, which are involved in TPA-induced malignancy (Russo *et al*., 2014). Other research has found that quercetin and other polyphenols inhibit both the MAPK and PI3-K pathways, both of which are involved in carcinogenesis (Feldman *et al*., 2010) (Figure 2).

Fisetin is a flavonol that targets CDK6, which is activated by cyclin binding and undergoes significant conformational changes. Fisetin and CDK6 create hydrogen bonds, which inhibit CDK6 activation and so have an anti-carcinogenic effect (Tadesse *et al*., 2015). Procyanidin B2 inhibits MEK1, which reduces AP-1 and NF-κB activation, resulting in a dose-dependent decrease in TPA-induced neoplastic transformation of JB6 P+ cells (Kang *et al*., 2008). Soybean isoflavone, one of the soybean metabolites, inhibits EGF and decreases neoplastic transformation and proliferation in a mouse epidermal cell culture (Lee *et al*., 2010). One of the positive effects of soybean isoflavone is the inhibition of cell progression in the G1 phase. Many investigations have demonstrated that this isoflavone influences phosphorylation processes controlled by many kinases, including CDK4 and CDK2 (Casagrande and Darbon, 2001). It also inhibits PI3-K, which reduces cyclin D1 expression (Hou and Kumamoto, 2010).

Another example is the polyphenol epigallocatechin gallate (EGCG), which is a major component of green tea and has been shown in many studies to have anti-cancer effects (Jung and Ellis, 2001). EGCG has been found to suppress EGF-induced malignant transformation in cancer cell lines by directly binding to the GST-Fyn-SH2 domain (He *et al*., 2008). It also blocks the Insulin-like Growth Factor-I (IGF-I) receptor, which has been linked to breast and cervical cancer cell lines (Adhami *et al*., 2006). Using polyphenols to target TKs could be a potential endeavor for the discovery and development of novel anticancer medicines in this field.

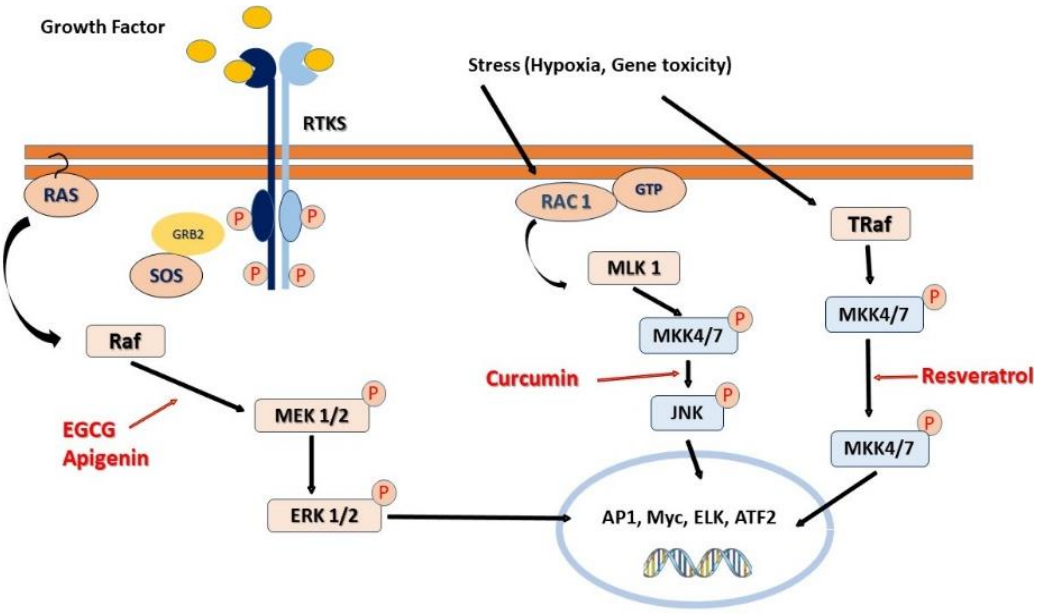

Figure 1: Potential sites of inhibitory actions of polyphenols in MAPK signaling pathways. ERK: extracellular signal-related kinases; JNK: c-Jun amino-terminal kinases.

Tyrosine kinases, polyphenols, and cancer metastasis

Natural polyphenols have been demonstrated to be helpful in a variety of cancers, including those that are metastatic. Their capacity to target PI3K/Akt/mTOR and other TK-based signaling pathways implicated in cell proliferation and metastasis is commonly linked to such effects (Figure 2). Because most of these polyphenols exhibit decreased toxicity over a wide dose range, evaluating their benefits as single agents or adjuvants with other drugs appears to be an appealing study topic. Many polyphenolic compounds (Table I) exhibit potent antimetastatic activity, which is mediated through interfering with a variety of metastasis-related mechanisms, including the TKs pathways (Weng and Yen, 2012). Many known targets in the TK signaling cascades, including the EGFR, JAK, Src, and VEGFR families, are blocked by specific types of polyphenols (Mahajan and Mahajan, 2015). Curcumin, for example, has been proven to inhibit the growth and metastasis of lung cancer, colorectal cancer, leukemia, colon cancer, and breast cancer cells by interfering with TK signaling.

Curcumin can disrupt the cell signaling pathway of EGFR, a receptor TK family implicated in cancer cell proliferation, adhesion, migration, and differentiation (Starok *et al*., 2015). As a result, blocking EGFR signaling looks to be a potential strategy for cancer prevention (Sun *et al*., 2012). Curcumin also inhibits the production of the pro-inflammatory cytokines CXCL1 and CXCL2 in metastatic breast cancer (Aggarwal *et al*., 2005). It has also been found in other studies to restrict cancer cell metastasis by lowering lncRNA-ROR and miR-145 levels (Liu *et al*., 2017). Additionally, curcumin can potentially restrict cancer spread in PC cells by reducing the expression of another lncRNA, the plasmacytoma variant translocation 1 (PVT1) (Mishra *et al*., 2019). Resveratrol and EGCG, on the other hand, inhibited metastasis by modulating lncRNAs (Hong *et al*., 2015).

Although numerous studies show that resveratrol can prevent cancer spread, the exact mechanism remains uncertain. Resveratrol has been demonstrated to activate autophagy in B16 melanoma cells by a method that involves ceramide buildup and suppression of the Akt/mTOR pathway (Wang *et al*., 2014; Bhattacharya *et al*., 2011). Furthermore, resveratrol suppresses cell migration and invasion as well as Akt/mTOR signaling in a range of malignant cell lines, according to several studies (Leo and Sivamani, 2014). *In vitro* experiments further revealed that resveratrol effectively prevents TGF-β1-induced EMT in A549 lung cancer cells (Wang *et al*., 2013). Resveratrol can prevent metastasis by lowering MALAT1 expression, which reduces the wnt/β-catenin signaling pathway (Ji *et al*., 2013).

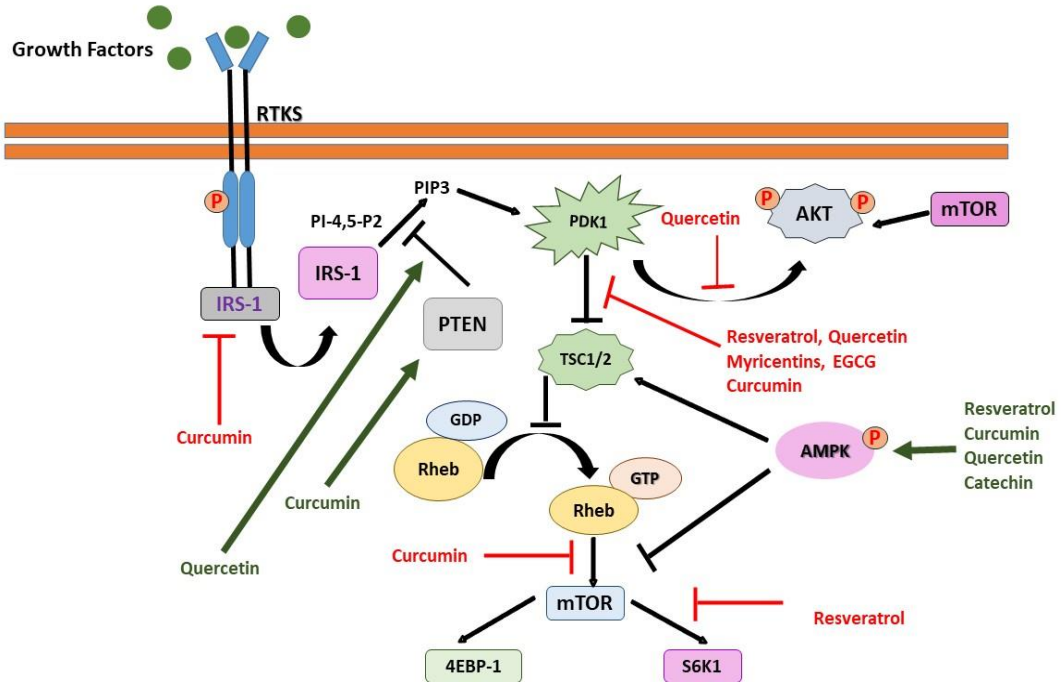

Figure 2: Polyphenols inhibit the PI3K/Akt/mTOR pathway in cancer. The phosphoinositide 3-kinase-AKT-mammalian target of rapamycin (PI3K/Akt/mTOR) pathway is overexpressed in a variety of cancers and is critical for tumor cell growth and survival. By activating RTKs such as the insulin-like growth factor-1 receptor (IGFR) with growth factors such as insulin, intracellular pathways can be activated. Akt is phosphorylated downstream of PI3K, and this phosphorylation has a variety of effects, one of which is the activation of mTOR. mTOR phosphorylates p70S6K and 4E-binding protein 1 (4EBP-1), resulting in increased mRNA translation and cell proliferation. Polyphenols inhibit this pathway by dephosphorylating several protein kinases involved in this signaling pathway. The green arrows indicate that the pathway is being activated, whereas the red arrows indicate that the pathway is being blocked by various polyphenols.

Table I. Examples of polyphenols that inhibit cancer invasion/metastasis through targeting the tyrosine kinases system *in vitro* and *in vivo*.

Polyphenol	Cell/animal model	Targets	Reference
Curcumin	Lung cancer A549/CL1-5	MEKK3; ERK:JNK; AP-1	Weng and Yen, 2012; Starok *et al.*, 2015
Resveratrol	Mouse lung cancer A549/CL1-5 Breast cancer MCF7/4T1	ERK/JNK/p38; PI3K/Akt; AP-1; NF-kB; FAK	Wang *et al.*, 2014; Bhattacharya *et al.*, 2011; Leo and Sivamani, 2014
Luteolin	Squamous cell carcinoma A431-III	Akt1; PI3K; pSTAT3; PKC/ERK/AP-1	Fan *et al.*, 2019; Yao *et al.*, 2019; Maruca *et al.*, 2019
Quercetin	Gastric cancer cell lines NSCLC-A549 xenograft	PKC-δ; ERK1/2; MAPKα	Kim *et al.*, 2018; Li & Chen, 2018; Chang *et al.*, 2017
Myricetin	Pulmonary mouse cancer 4T1 Breast cancer MDA-Mb-231Br Cholangiocarcinoma KKU-100	STAT3; PIM1/CXCR4	Ci *et al.*, 2018; Ye *et al.*, 2018
Kaempferol	Renal cancer cells Retinal pigment epithelial	AKT; FAK; ERK1/2	Hung *et al.*, 2017; Chien *et al.*, 2019

Furthermore, overexpression of the miR-17 family, which is related to the carcinogenic miRNA group, has been linked to metastasis (Li *et al*., 2014). In this respect, resveratrol has been shown in several epidemiological and preclinical investigations to lower the expression of PTEN-targeting members of the oncogenic miR-17 family, which are overexpressed in prostate cancer. Nonetheless, earlier research has demonstrated that resveratrol plays a role in increasing PTEN levels in prostate cancer (Dhar *et al*., 2015a). PTEN is deacetylated and inactivated as a result of metastasis-associated protein 1 (MTA1) suppression, which induces deacetylation and inactivation (Dhar *et al*., 2015b).

The flavonoid luteolin inhibited the metastasis of highly invasive A431-III squamous carcinoma cells by lowering the levels of phosphorylated p-Src and pSTAT3, which are implicated in cancer cell metastasis (Fan *et al*., 2019). In colorectal cancer cell lines, luteolin suppresses the migration and invasion processes by lowering the expression of MMP-2, MMP-3, MMP-9, and MMP-16. The downregulation of MMP-2 and MMP-9 is predominantly due to interference with the PI3K/AKT signaling pathway, as indicated by luteolin-induced suppression of phosphorylated Akt1 and PI3K (Yao *et al*., 2019). Luteolin can also efficiently block the PKC/ERK/AP-1 signaling pathway. This decreases the MMP-9 gene expression and limits the migration and invasion of colorectal cancer and human breast carcinoma cells (Maruca *et al*., 2019).

The most extensively studied flavonoid, quercetin, has been demonstrated to exhibit antimetastatic effects in stomach cancer cell lines (Kim and Park, 2018). This activity is predominantly mediated by interfering with the uPA/uPAR system, which controls NF-κB, PKC-δ, ERK1/2, and AMPKα and hence plays a significant role in cancer metastasis initiation and dissemination. Similarly, quercetin can diminish MMP-2 and MMP-9 expression by reducing Pak1-Limk1-cofilin signaling, which has been linked to the acceleration of cancer spread (Li and Chen, 2018). Furthermore, quercetin inhibits non-small cell lung cancer (NSCLC) metastasis in the A549 xenograft model as well as reduces the invasiveness of A549 and HCC827 cells via inhibiting AKT activation and MMP-9 expression (Chang *et al*., 2017). In the human colorectal adenocarcinoma cell line, quercetin can decrease the TGF-β1-induced EMT (Feng *et al*., 2018).

In the 4T1 animal model, myricetin, a polyphenolic flavonoid, inhibits lung metastasis as well as invasion and metastasis in the MDA-Mb-231Br breast cancer cell line. These effects are produced by the inhibition of MMP-2/MMP-9 expression, which is elevated in patients with metastatic cancer (Ci *et al*., 2018). Meanwhile, in cholangiocarcinoma KKU-100 cells, myricetin's antimetastatic effect was mediated in part by the STAT3 signaling pathway. Myricetin's tumor-suppressive actions are hypothesized to be mediated by PIM1 suppression and disruption of the PIM1/CXCR4 link. CXCR4 is critical in steering metastatic cancer cells to organs that produce CXCL12 and boosting the growth of malignant cells in distant metastases (Ye *et al*., 2018).

Kaempferol inhibits renal cancer cell invasion and migration via reducing MMP-2 protein levels and activity. This effect is associated with the downregulation of AKT phosphorylation and focal adhesion kinase (FAK). In a mouse cancer model, kaempferol also suppresses the spread of kidney cancer cells to the lungs (Hung *et al*., 2017). Furthermore, kaempferol inhibits human retinal pigment epithelial cell migration and invasion by decreasing MMP-2 synthesis and activity, which is mediated by increased levels of phosphorylated ERK1/2 (Chien *et al*., 2019). As a potential class for cancer-related angiogenesis, polyphenols offer a novel way to counteract VEGF-related cell signaling in cancer cells. Kaempferol inhibits cancer neovascularization in human cancer cell lines by inhibiting VEGF release. Many studies show that kaempferol reduces VEGF expression at the mRNA and protein synthesis stages (Luo *et al*., 2009).

Fisetin, a flavonoid, inhibits triple-negative breast cancer cell line metastasis by suppressing the PI3K-Akt-GSK-3β signaling pathway, which leads to EMT reversion. It reduces lung metastasis and affects the expression of EMT molecules and PTEN/Akt/GSK-3β in the metastatic breast cancer xenograft model similar to the in vitro model (Li *et al*., 2018). This polyphenol also inhibits human non-small cell lung cancer metastasis by reducing signaling proteins that function upstream of EMT and are involved in the maintenance of the mesenchymal phenotype (Tabasum and Singh, 2019). Fisetin also influences MMP activity and the levels of critical metastatic proteins in human osteosarcoma cells (Chen *et al*., 2019). Fisetin can also decrease a variety of human melanoma cell types by promoting EMT by targeting MAPK and NF-κB signaling (Pal *et al*., 2014).

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CONCLUSIONS

The significance of TKs in the metastatic cascade is well understood, and many polyphenols have demonstrated exceptional promise in inhibiting various targets within the TK signaling pathway to reduce cancer cell metastasis. Because some of these polyphenols inhibit multiple TK pathway targets, the precise antimetastatic mechanisms are still unknown. Despite numerous *in vitro* and *in vivo* preclinical studies, little is known about polyphenols' clinical usefulness in many forms of metastatic tumors, necessitating more research. On the other hand, the antimetastatic actions of specific polyphenols mentioned in this review could be a promising reference for the future development of natural or semi-synthetic anticancer medicines with the ability to inhibit various elements of the metastatic cascade, including the TK signaling pathway.

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