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NARRATIVE REVIEW – OPEN ACCESS

Impact of Polyphenolic Compounds on the MAPK Signaling Pathway against Carcinogenesis

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ABSTRACT

The mitogen-activated protein kinase (MAPK) signaling pathway is one of the signaling pathways involved in cellular life. Dysregulation of the MAPK signaling pathway is implicated in the emergence of diverse stages of carcinogenesis, including metastasis, angiogenesis, apoptosis, invasion, proliferation and cell differentiation. Therefore, it contributes significantly to the process of carcinogenesis. The mitogen-activated protein kinase signaling pathway presents numerous molecular components that can be regulated against carcinogenesis. Many studies have shown that polyphenols in various dietary sources have important contributions to the regulation of this pathway. This contribution occurs by inducing cell death, altering immunity, blocking angiogenesis and suppressing cancerous cell growth. Numerous studies have been conducted on this aspect of polyphenolic compounds, with encouraging outcomes. Its clinical efficacy against cancer is also being investigated. This study focuses on the importance of mitogen-activated protein kinase signaling pathway in carcinogenesis by emphasizing the properties of polyphenolic compounds. The study aims to research the clinical effectiveness of polyphenolic compounds in regulating the MAPK signaling pathway against cancer.

Keywords: MAPK signaling pathway, carcinogenesis, polyphenols, cancer, tumor

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INTRODUCTION

Carcinogenesis begins when cells proliferate indefinitely, migrate, avoid apoptotic cell death, generate signals for autonomic proliferation and maturation, become immune to growth inhibitory signals and disrupt the extracellular matrix (1). Normal cells must undergo abnormal cell changes, hyperplasia and dysplasia to transform into malignant cells. Hyperplasia causes a tremendous increase in the number of normal cells, whereas dysplasia causes cells to exhibit peculiar phenotypic features. However, these changes may not always result in carcinogenesis (2, 3). Early detection of carcinogenesis significantly increases the survival and recovery rates of patients. Depending on the phase and type of tumor, surgery, radiation therapy or chemotherapy may be recommended. The highest level of efficacy and positive results are achieved by using appropriate treatment combinations (4, 5). On the other hand, these therapeutic approaches can lead to various health problems that reduce the general standard of living. Clinical research recommendations to avoid such problems are lacking (6).

Polyphenolic compounds, characterized by aromatic rings containing a hydroxyl (OH) moiety, can be used in combination with other medications in the therapy of patients with cancer to increase efficacy and safety (7, 8). Polyphenols, which have a wide range of structurally simple to very complex compounds, play a significant role in the defense mechanisms of herb (9, 10). Polyphenols have potential anticancer effects in the intrinsic mitochondrial pathway, apoptotic perforin granzyme pathways and extrinsic death receptor pathway. The mitogen-activated protein kinase (MAPK) signaling pathway is interrelated in cell cycle metabolism, progression or cell senescence (11). Polyphenols regulate the MAPK signaling pathway to produce anticancer effects in diverse types of cancer, along with the induction of the apoptotic response. In addition, numerous studies have demonstrated that the MAPK signaling pathway is frequently mutated in some cell cultures with cancer, emphasizing its essential function (12).

Understanding the actions involved in modulating signaling pathways by polyphenolic compounds provides useful information for disease prevention and treatment. The MAPK signaling pathway is dysregulated in 40 of 100 patients with malignant tumors located in the axis of the signaling cascade. In light of this, the keywords "MAPK signaling pathway," "carcinogenesis" and "polyphenols" were searched in scientific databases such as Scopus, Institute for Scientific Information-Web of Science, Google Scholar, Science Direct and PubMed. This study presents the anti-tumor effect of dietary polyphenolic compounds for the regulation of MAPK signaling pathways through preclinical and clinical studies involving various types of cancer.

MAPK

The MAPK signaling pathway is composed of serine-threonine kinases that are significant components of one of the main signaling cascades that regulate cell death, survival, differentiation and growth. MAPKs, activated in response to extracellular and intracellular signals, activate tyrosine kinase receptor-type transmembrane glycoproteins, resulting in the regulation of target points. The three main players of the MAPK signaling pathway are stress-activated protein kinase 2 [p38, stress-activated protein kinase 2 (SAPK2)], stress-activated protein kinase c-Jun amino group (NH2) terminal kinase and extracellular signal-regulated protein kinases (p44/s42). p38 and c-Jun NH2 terminal kinase are activated by oxidative stress, cytokines, genotoxicity and hypoxia, while p44/s42 is activated by cytokines and mitogens (13). Inflammation, immunity, apoptosis, differentiation, proliferation or differentiation are all regulated by the MAPK signaling pathway, which plays a role in carcinogenesis (14, 15) The schematic diagram of the MAPK signaling pathway is presented in Figure 1.

Dysregulation of the MAPK signaling pathway can lead to cellular transformation. This signaling pathway is dysregulated in 40 out of every 100 patients with a malignant tumor in the signaling cascade axis, particularly in rat sarcoma (RAS) (30%) (16). RAS represents the initial actors in the MAPK/extracellular signal-regulated protein kinase phosphorylation cascade and is a family of guanosine triphosphatases (GTPases) with 150 G-protein (17). Activation of RAS results in extracellular signal-regulated protein kinase phosphorylation. Therefore, extracellular signal-regulated protein kinase moves into the nucleus and encourages transcription factor activation (18).

A stress-activated protein kinase called Jun NH2 terminal kinase moves from the cytosol to the nucleus and causes c-Jun activation (19). c-Jun NH2-terminal kinase plays an important role in the development of carcinogenesis because it has numerous targets involved in various cellular regulatory systems (20).

There are four p38 isoforms involved in the MAPK signaling pathway or expressed by different genes. The gama, sigma and beta isoforms are tissue-specific, while the alpha (α) isoform is found in all tissues. The absence of the α isoform is fatal (21). P38 can phosphorylate 200-300 substrates, including kinases implicated in gene regulation and cytoplasmic substrates such as cyclin D1 (22). P38a participates in a number of interesting processes, including the regulation of extracellular signal-regulated kinase and c-Jun NH2-terminal kinase signaling by preventing RAS transformation, which causes cell aging and cell cycle arrest (23). The stimulation of p38 dependent apoptosis results from the inhibition of carcinogenesis in the breast, lung, liver and colon via reactive oxygen species formation in response to oncogene activation (24). But its role in neutralizing carcinogenesis is revealed only in the early stages (25).

Curcumin

Curcumin is a natural polyphenolic compound found in the spice turmeric. One of the most effective anti-cancer medicines, curcumin, has demonstrated various regulatory mechanisms in MAPK. In the Ishikawa cell line involved in endometrial carcinoma, curcumin supplementation induces phase S cell cycle arrest, downregulation of the p-extracellular signal-regulated kinase-2/c-Jun pathway, downregulation of extracellular signal-regulated kinase and Jun messenger ribonucleic acid (mRNA) and induces apoptosis. Interestingly, curcumin reduces cell invasion and decreases activator protein 1 (AP-1) synthesis by downregulation of p-extracellular signal regulated kinase-c-Jun, thereby reducing matrix metalloproteinase 2/9 (MMP2/9) transcription (26). Curcumin has effects on mitogen-activated protein kinase pathways that go beyond in vitro. Turmeric supplementation showed a reduction in tumor growth in a xenograft prostate tumor model. The related mechanism in reducing prostate cancer with turmeric is its association with the decrease of phosphorylated Jun protein (p-Jun) NH2-terminal kinase. In addition, curcumin is also effective in reducing p-Jun and leads to a reduction in anti-apoptotic proteins (Bcl-xL and Bcl-2) mRNA values (27).

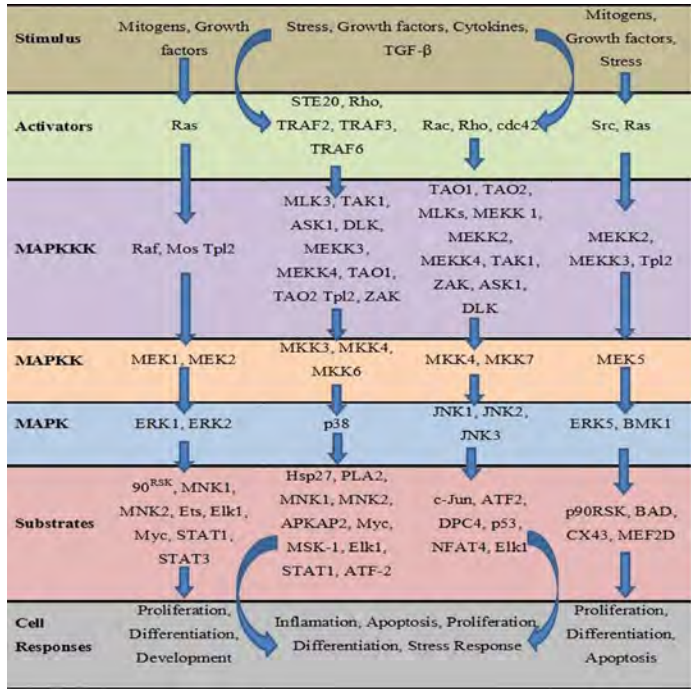

Figure 1. Impact of polyphenolic compounds on MAPK signaling pathway against carcinogenesis

Stilbenoids

Stilbenoids are natural polyphenolic compounds produced in various plants that have been shown to inhibit mitogen-activated protein kinase in different tumors. Resveratrol, a stilbenoid found in grapes, has been identified as a potent tumor growth inhibitor that also increases phosphorylated p38 (p-p38) levels, which decreases B-cell lymphoma 2 (Bcl-2) (28). Urological malignancies are a serious problem and treatment with resveratrol inhibits kidney cancer cells' capacity to proliferate and spread. Resveratrol modulates extracellular signal-regulated kinase1/2 signaling pathways by changing the expression of matrix metalloproteinases (MMP-9 and MMP-2), E-cadherin, p-extracellular signal regulated kinase1/2 and extracellular signal-regulated kinase1/2 (29).

Apigenin

Apigenin is a natural polyphenolic compound found in many plants. Supplementation of melanoma cells C8161 and A375 with apigenin inhibits their growth by inhibiting p-extracellular signal-regulated kinase1/2, protein kinase B (AKT) and mammalian target of rapamycin (mTOR), causing growth arrest (29).

Table 1. Effects of polyphenolic compounds on the MAPK pathway and carcinogenesis

Polyphenols	MAPK	Carcinogenesis
Curcumin (26, 27)	Down regulation of the kinase-2/c-Jun pathway regulated by β-extracellular signaling Down regulation of extracellular signal-regulated kinase and Jun mRNA	Endometrial carcinoma
	Reduction of p-Jun NH2-terminal kinase	Prostate cancer
Resveratrol (28)	Increases p-p38 levels	Different tumors
Apigenin (29)	Inhibition of p-extracellular signal-regulated kinase 1/2	Melanoma cells C8161 and A375
Epigallocatechin 3-gallate and sunitinib (30)	Suppressing extracellular signal-regulated kinase	Cancer cell lines
Quercetin (31)	Modulation of the c-Jun NH2-terminal kinase	Colon tumor
Kaempferol (32)	Modulation of the protein expression	Colorectal tumor
Gallic acid (33)	Down regulation the phosphorylation of the Ras	Glioma

MAPK: Mitogen-activated protein kinase

Epigallocatechin 3-Gallate And Sunitinib

Epigallocatechin 3-gallate and sunitinib, known as tea polyphenolic compounds, have strong anti-cancer effects both on their own and when combined with other treatments. In cancer cell lines, epigallocatechin 3-gallate and sunitinib have demonstrated synergy. They reduce cell viability and suppress the extracellular signal-regulated kinase signaling pathway (30).

Quercetin and Kaempferol

Quercetin is a polyphenolic compound found especially in capers, red onions and cabbage. Kaempferol is a natural flavonol, a type of flavonoid found in a variety of herbs and plant-derived foods, such as beans, cabbage, spinach, broccoli and tea. Quercetin and kaempferol are two of the most promising polyphenolic compounds for tumor therapy. Quercetin inhibits colon tumor with mutant Kirsten rat sarcoma viral oncogene homolog (KRAS) through modulation of the c-Jun NH2-terminal kinase pathway. Quercetin activates the p-Jun NH2-terminal kinase/c-Jun axis, which inhibits protein kinase B specifically. Caspase-3 is then activated, resulting in apoptosis (31). In fact, polyphenols can act as chemo-sensitizers. Kaempferol has been shown to increase the effectiveness of fluorouracil-resistant colon tumor cell treatment. Concomitant therapy leads to increased cell cycle arrest, apoptosis and modulateion of protein expression, MAPK, phosphatidylinositol-3-kinase/AKT and nuclear factor-kappa β, which are involved in the growth and evolution of colorectal tumor (32).

Gallic Acid

Gallic acid is a polyphenol found in walnuts, sumac, witch hazel, tea leaves, oak bark and other plants. Gallic acid has been reported to down-regulate the phosphorylation of the Ras/MAPK signaling pathway involved in invasion, cellular proliferation and survival in human glioma (33).

All these regulatory activities on MAPK signaling pathways highlight the pharmacological significance that polyphenolic compounds can have for cancer therapy by inhibiting these pathways (Table 1). However, further study is required to properly understand the mechanisms involved in these pathways.

Polyphenols and MAPK in Carcinogenesis

The anti-inflammatory and anticancer activities of some dietary polyphenols such as curcumin, quercetin, apigenin, gallic acid and resveratrol are due to their regulatory impacts on pathways, such as the mitogen-activated protein kinase signaling pathway (34). An in vivo study was conducted to assess the apoptosis of acute monocytic leukemia SHI-1 cell line treated with curcumin. Interestingly, mitogen-activated protein kinase phosphorylation was activated after curcumin supplementation, while phosphorylation of nuclear factor-kappa β and extracellular signal-regulated kinase1 and extracellular signal-regulated kinase 2 was suppressed (35). Another study noticed that curcumin supplementation down-regulated p44/p42 MAPK phosphorylation in breast tumors. The research concluded that curcumin suppresses growth and activates caspase-induced apoptosis of cells via the MAPK signaling pathway (36). It has also been noticed that the anti-cancer activity of turmeric-mediated modulation of breast carcinogenesis is mainly dependent on its activity on nuclear factor-kappa β, MAPK, phosphatidylinositol-3-kinase/AKT/mTOR, Wnt/β-catenin and Janus kinase 2/Signal transducer and activator of transcription 3 signaling pathway (JAK2/STAT3) signaling networks (37). In addition to triggering the c-Jun NH2-terminal kinase/MAPK signaling pathway, quercetin has been found to reduce the growth of HepG2 cells by suppressing many signaling proteins, including extracellular signal-regulated kinase or MAPK, which are important for cell survival (38). Apigenin exhibited important chemopreventive properties by preventing the progression and metastasis of choriocarcinoma by modulating the MAPK signaling pathway (39). Resveratrol has been shown to significantly down-regulate the p38 MAPK/nuclear factor-kappa β pathway (40).

CONCLUSION

This review provides an overview of the potential of the most effective polyphenols in regulating the MAPK signaling pathway, which plays a major role in carcinogenesis and controls a variety of cellular processes such as cell proliferation, differentiation and apoptosis. Current cancer treatments often result in serious side effects, reducing patients' quality of life. Polyphenols are gaining interest due to their numerous bioactivities and may present an intriguing alternative as therapeu-

tic agents for the treatment of cancer because they are more potent and less toxic. However, bioavailability is a crucial factor to consider when using them therapeutically in cancer patients due to biotransformation processes that modify their structure and bioactivity during passage through the intestine and hepatic metabolism. Polyphenolic compounds have been found to regulate a variety of signaling pathways, including significant tumor suppressors like mitogen-activated protein kinase and onco-proteins such as RAS isoforms. Numerous polyphenolic compounds can alter the expression of important compounds in this signaling pathway in a variety of tumor types through a variety of distinct methods of action. All these aspects make polyphenolic compounds a promising therapeutic resource for tumor therapy. Overall, the ability of polyphenolic compounds to affect cell signaling pathways may contribute to their potential ability to prevent or treat illnesses related to cell growth and survival.

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