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REVIEW

Targeting NF-κB signaling pathway in cancer by dietary polyphenols

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ABSTRACT

Being a transcription factor, NF-κB regulates gene expressions involving cell survival and proliferation, drug resistance, metastasis, and angiogenesis. The activation of NF-κB plays a central role in the development of inflammation and cancer. Thus, the down-regulation of NF-κB may be an exciting target in prevention and treatment of cancer. NF-κB could act as a tumor activator or tumor suppressant decided by the site of action (organ). Polyphenols are widely distributed in plant species, consumption of which have been documented to negatively regulate the NF-κB signaling pathway. They depress the phosphorylation of kinases, inhibit NF-κB translocate into the nucleus as well as interfere interactions between NF-κB and DNA. Through inhibition of NF-κB, polyphenols downregulate inflammatory cascade, induce apoptosis and decrease cell proliferation and metastasis. This review highlights the anticancer effects of polyphenols on the basis of NF-κB signaling pathway regulation.

KEYWORDS

Dietary polyphenols; cancer; signaling pathway; nuclear factor-κB; phosphorylation

Introduction

Cancer, also known as neoplasm or malignant tumor, is a multifactorial disease caused by alteration of gene expression and cell signaling pathways (Rajagopal et al. 2018b). It is characterized by abnormal and endless cell divisions, which form growths called tumors, invade nearby tissues, spread to distant organs and can be life threatening (https://www.cancer.gov/about-cancer/understanding/what-is-cancer). In 2018, cancer is accountable to 9.6 million deaths with an incidence of 1 in 6 deaths all around the world (WHO 2018, 12 September). In addition to environmental factors and cell mutations, recent studies have shown that the epigenetic changes such as DNA methylation may cause cellular transformation, which eventually lead to cancer (Rajagopal et al. 2018b). In particular, the involvement of NF-κB (nuclear factor-κB) pathway in inflammation processes and cancer development, have been widely reported (DiDonato, Mercurio, and Karin 2012; De Simone et al. 2015; Zhang et al. 2015, 2018). The clinical evidences illustrated that NF-κB pathway components are essential players in the cancer onset and progression, which regulate gene expressions related to cell survival and proliferation, drug resistance, metastasis, and angiogenesis (Zhang, Lenardo, and Baltimore 2017).

In light of these assumptions, NF-κB is a molecular target in cancer. In this perspective, several phytochemicals were identified and revealed to have significant targeting and inhibitory effects on NF-κB signaling (Sethi and Tergaonkar 2009; Gupta et al. 2011; Shanmugam et al. 2016). Among these polyphenols, resveratrol (Ryu et al. 2011; Tsai et al. 2012; Aravindan et al. 2013; Ren et al. 2013; Jiao et al. 2015; Zhang et al. 2015), curcumin (Gupta, Kismali, and Aggarwal 2013; Marquardt et al. 2015; Puliyappadamba et al. 2015; Basha et al. 2016; Bisht et al. 2016; De Porras et al. 2016; Kunnumakkara et al. 2017), epigallocatechin gallate (Qin et al. 2012; Zhang et al. 2012; Zhou et al. 2012, 2014; Chung

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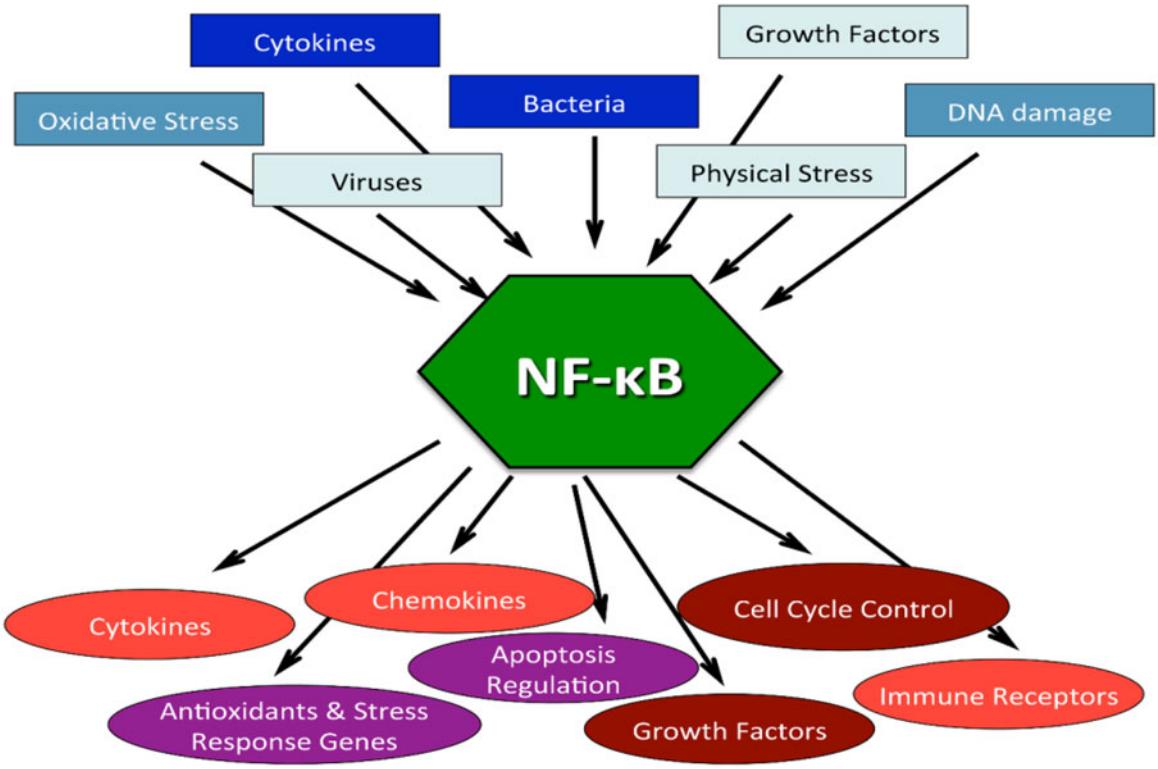


Figure 1. NF-κB transcriptionally regulates hundreds of genes, when getting stimulated by numerous stimuli.

and Vadgama 2015; Li et al. 2015), genistein (Pan et al. 2012; Yamasaki et al. 2013; Du et al. 2016), and cardamonin (James et al. 2017) are the most studied for their capabilities to inhibit cancer cell proliferation by blocking the nuclear translocation of NF-κB or reducing NF-κB activation (Rajagopal et al. 2018a this paper cannot be found in the references).

The objective of the manuscript is to review research progress on the significant roles of polyphenols in modulating NF-κB and anticancer effects. Additionally, the chemistry, food sources and bioavailability of the representative polyphenols are also reported. Electronic databases including PubMed, WOS and Scopus were searched using the topics ("NF-κB polyphenols" OR "NF-κB flavonoids" OR "NF-κB phenolic acids" OR "NF-κB stilbenoids" OR "NF-κB anthocyanins"). Datasets were outlined from 2000 to 2018.

NF-κB: what, when, where?

NF-κB is a group of dimeric transcription factors, whose family in mammal contains five genes, namely NF-κB1 (p50/p105), NF-κB2 (p52/p100), RelA (p65), RelB and c-Rel (Karin and Ben-Neriah 2000; Barroso et al. 2016). Their proteins are characterized by a 300-amino acid conserved Rel Homology Domain (RHD) locating toward the N terminus, which is involved in the dimerization process, interaction with their specific inhibitors, and DNA binding (Hayden and Ghosh 2004). Without stimulation, NF-κB dimers bind to IκB and keep in an inactive state. Once stimulated, NF-κB regulates gene expressions that impact many life processes, including cell growth, proliferation, inflammatory, immune responses, and neoplastic transformations in many tumors (Figure 1) (Rao et al. 2011; Jana et al. 2017).

As reported, NF-κB can be activated *via* different molecular pathways (Figure 2). The first one is known as the canonical or classical activation pathway, which refers to dimmers composed of p65, c-Rel, and p50. Pro-inflammatory cytokines and infections trigger this pathway by activating the β unit of IκB kinase (IKK) complex (IKKβ), which then phosphorylates IκB proteins, degrades IκB and liberates NF-κB dimmers. Free NF-κB dimmers then translocate to the nucleus, bind to specific sequences and activate the transcription of 100 genes involved in biological processes (Hayden and Ghosh 2004). The second pathway called alternative activation pathway applies to dimmers consisting of RelB and p100 subunits. Tumor necrosis factor (TNF) family members regulate this pathway by activating the IKKα catalytic subunit. The activated IKKα phosphorylates p100, which subsequently undergoes proteolysis and releases p52, the latter then translocates to the nucleus and activates transcription of specific target genes (Dolcet et al. 2005). It is suggested that the activated NF-κB is bound to κB sites in order to modify gene expression and encode various proteins (Hayden and Ghosh 2011).

The NF-κB signaling pathway can also be activated by oxidative stress and stimuli like IL-1 and TNF-α (Chen et al. 2011). Studies reported the involvement of NF-κB mediated upregulation of HIF-1 (hypoxia-inducible factor-1) in oxidative stress. Elevated level of ROS (reactive oxygen species) can trigger NF-κB, which results in increasing HIF-1α and plays a vital role in the pathogenesis of cardiovascular disorders and tumor progression (Bonello et al. 2007). In tumors, NF-κB and HIF-1α are regularly activated and concerned

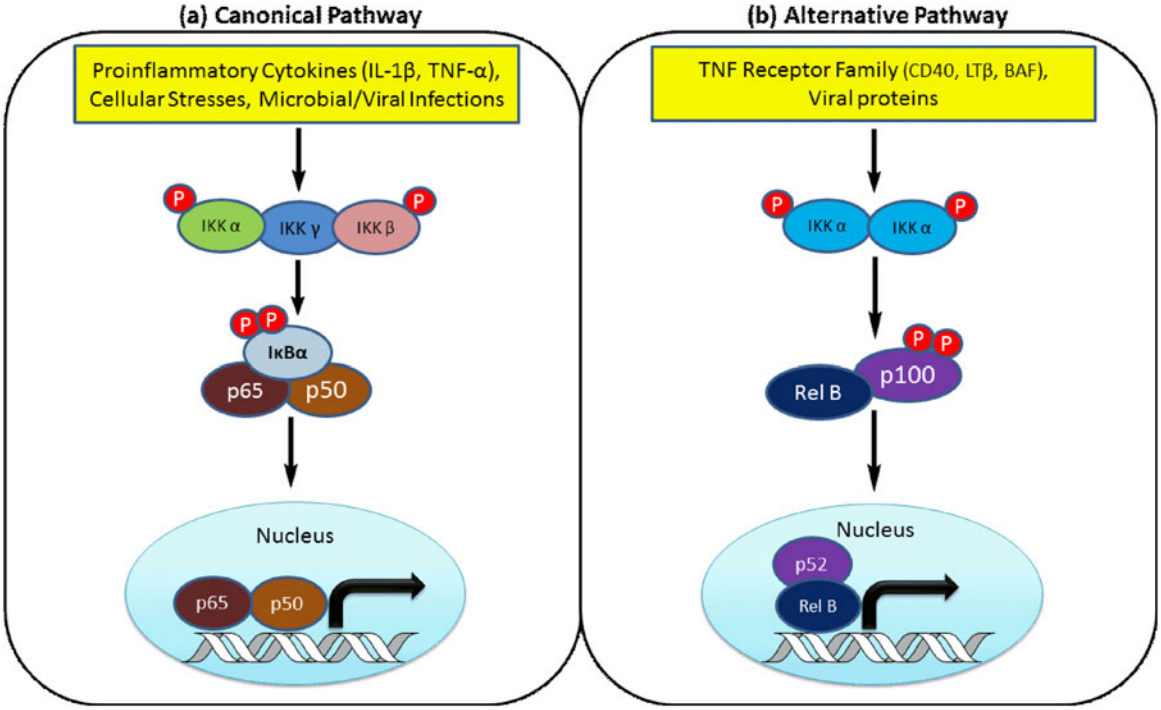


Figure 2. Molecular pathways of NF-κB activation. The conical pathway is triggered by proinflammatory cytokines, a variety of cellular stresses, microbial or viral infections by activating IKK complex. IKK phosphorylates IkB in serine residues leading to the degradation of Iκ B and liberation of NF-κB dimmers, with the latter subsequently translocating to the nucleus. The alternative pathway is mediated by TNF receptor family and viral proteins such as LMP-1 from Epstein Barr virus (EBV), which activate the IKKα subunit. IKKα phosphorylates p100 which is then proteolysed to produce the p52 mature form. The dimmers then translocated to the nucleus to induce the transcription of specific target genes. Interleukin 1 beta (IL-1β); Tumor necrosis factor alpha (TNF-α); Cluster of differentiation 40 (CD40); Lymphotoxin beta (LTβ); B-cell activating factor (BAF).

with tumor development, progression and resistance to chemotherapy (Tafani et al. 2013). The upregulation of NF-κB in diabetes and its complications has been documented. According to available literature, hyperglycemia increases NF-κB gene expression and causes insulin resistance in adipose tissues as a pro-inflammatory agent (Khosravi et al. 2018). Viruses target components of the NF-κB signaling pathway to facilitate cell survival and replication. Frequent activation of NF-κB in chronic viral infections may lead to carcinogenesis (Hiscott, Kwon, and Génin 2001).

NF-κB transcription factor works as an endogenous tumor promoter, as it plays a central role in carcinogenesis of several types of B-cell tumors, such as multiple myeloma (MM) (Allavena et al. 2008; Demchenko and Kuehl 2010). NF-κB gives a critical connection between cancer and inflammation. Inflammatory environment, especially in malignant progression, can lead to NF-κB activation in cancers. Moreover, NF-κB enhances the expression of TNF-α, IL-6, and Bcl-X_L. IL-6 and TNF-α are famous tumor promoting cytokines, whereas Bcl-X_L is a survival gene (Karin 2009). Receptor activator of NF-κB (RANK), RANKL (a ligand of RANK) and osteoprotegerin (OPG, a decoy receptor of RANKL) regulate osteoclasts formation and activity, which leads to bone remodeling. It has been suggested that the RANK/RANKL/OPG pathway can predict bone diseases, including bone metastasis recurrence and prognosis (Santini et al. 2011). To prevent carcinogenesis, the NF-κB signaling pathway could be considered as a target. However, before initiating NF-κB inhibition approaches for cancer prevention, the role of NF-κB in the cancer pathogenesis should be carefully evaluated because in different organs NF-κB may either promote (colon and liver) or suppress (skin and liver) tumor formation (Lin et al. 2010).

NF-κB and inflammation

Inflammation is a tissue process consisting of a series of molecular, cellular and vascular phenomena with defensive purpose against physical, chemical or biological aggressions (Kumar et al. 2015). It is an immediate and nonspecific response, although it may facilitate the development of a specific response. As a consequence of the inflammation, vasodilatation and enhanced permeability occur near the inflammatory focus in order to facilitate the arrival and translocation of leukocytes, as well as other inflammatory mediators (Geering et al. 2013; Kumar et al. 2015). The ultimate goal of inflammation is to eliminate or inhibit infections or cell damage, help the body recovering to normal conditions and restore the function of affected tissues or organs (Medzhitov 2008). However, inflammation that should be an acute and self-limiting process can become chronic due to a non-resolution or incorrect resolution of the acute inflammatory response. One of the most common reasons for this type of inflammation is usually associated with metabolic diseases such as metabolic syndromes and cancers (Minihane et al. 2015). In this sense, chronic and persistent inflammation substantially increases the risk of malignant transformation of cells (Kundu and Surh 2008; Hoesel and Schmid 2013). Within the inflammatory process, long-standing activation of NF-κB is linked with pro-

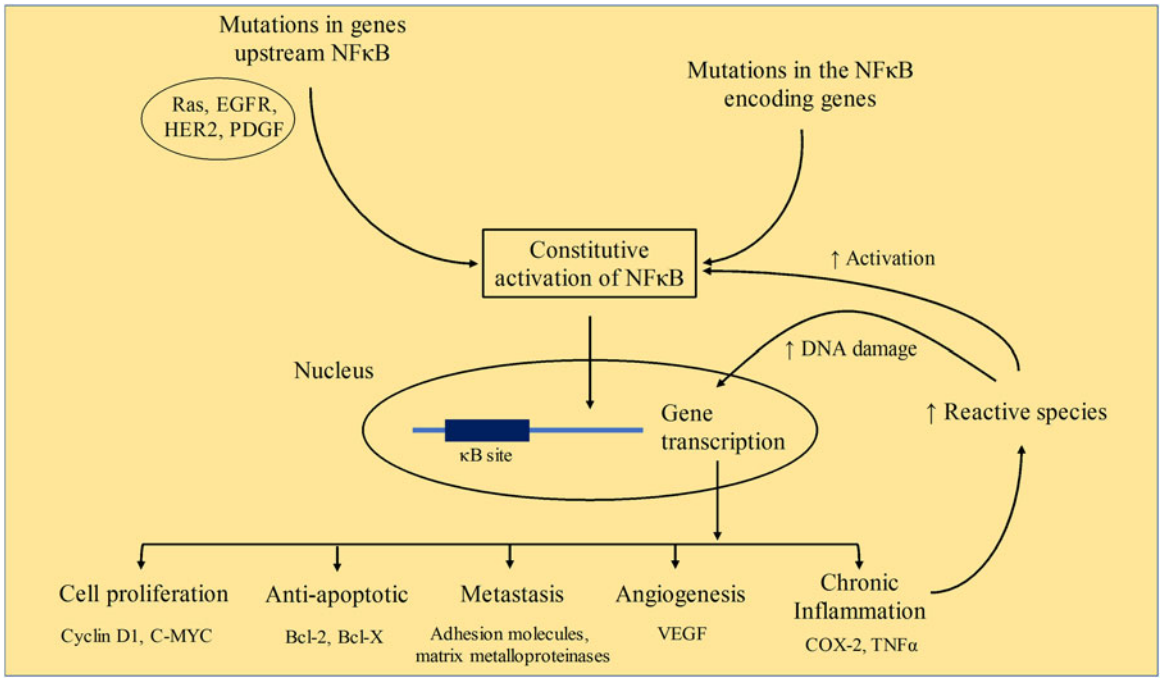


Figure 3. The relation between NF-κB activation and cancer. Mutations in NF-κB, but mostly in upstream activators can lead to excessive activation of NF-κB and the induction of genes related to chronic inflammation, cell proliferation, metastasis, and angiogenesis. Cyclooxygenase-2 (COX-2); Epidermal growth factor receptor (EGFR); Human epidermal growth factor receptor-2 (HER2); Platelet-derived growth factor (PDGF); Tumor necrosis factor alpha (TNF-α); Vascular endothelial growth factor (VEFG).

tumorigenic results. It has been suggested that subjects suffering from chronic inflammatory diseases, including chronic hepatitis and pancreatitis, gastric inflammation induced by Helicobacter pylori, and inflammatory bowel diseases, present increasing risk of some cancers (Grivennikov 2013; Hausmann et al. 2014; Wang et al. 2014).

The NF-κB pathway is essential in modulation of the inflammatory processes since its activation leads to enhanced expression of pro-inflammatory cytokines, chemoattractant proteins, and their specific receptors. Furthermore, NF-κB transcription cascade can also be activated by increased levels of pro-inflammatory cytokines (Perkins 2004). During chronic inflammation, immune cells generate reactive nitrogen species (RNS) and reactive oxygen species (ROS), which can mediate the carcinogenic process. Excessive production of RNS and ROS in the inflamed tissue can lead to tumorigenesis by inducing DNA damage and mutations, which correspondingly result in the activation and/or inactivation of oncogenes and tumor suppressor genes, respectively (Grivennikov, Greten, and Karin 2010). Besides, excess of ROS produced by immune cells also reinforces the inflammatory responses mediated by NF-κB in the microenvironment of the tumor.

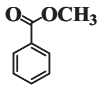
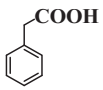
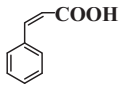
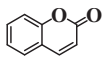
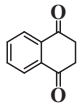
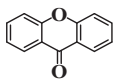
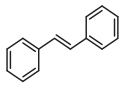
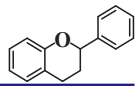
Another factor responsible to carcinogenesis is the possible appearance of mutations in the NF-κB genes (Figure 3). Although mutations in the NF-κB encoding genes related with inflammatory pathway have been reported in B-cells lymphoid tumors, their presence in the solid tumor is not familiar (Sun et al. 2014). The existence in solid malignancies of mutations in genes upstream of the NF-κB signaling pathway include Ras, EGFR, PDGF or human epidermal growth factor receptor-2 (HER2), which can direct the constitutive activation of NF-κB (Chaturvedi et al. 2011). NF-κB can also induce transcription of genes related with cell proliferation like C-MYC and cyclin D1 (Guttridge et al. 1999; Yuan et al. 2016), with angiogenesis and metastasis like adhesion molecules, VEGF, matrix metalloproteinases, and with anti-apoptosis like Bcl-2 and Bcl-X (Xie et al. 2010; Acharyya et al. 2012).

NF-κB and polyphenols

Being a regulator of 100 target genes, NF-κB could be a molecular target to treat diseases, including but not limited to inflammatory disorders, such as asthma, arthritis and auto-immune diseases. Newly, many plant-derived compounds have been identified as potential modulators of the NF-κB signaling pathway (Miao et al. 2019; Zhao et al. 2019). Natural polyphenols are considered as the most important bioactive natural products (Devi et al. 2015; Curti et al. 2017; Chen et al. 2018) as well as most widely distributed dietary phytochemicals, which exhibit various pharmacological and physiological functions (Xiao and Högger 2015; Xiao et al. 2016; Xiao 2017; Khan et al. 2018, 2019). In this review, we shall focus on the medicinal chemistry of polyphenols regarding their NF-κB inhibition capacity (Table 1). Bellik et al. (2012) reviewed the anti-inflammatory activities of phytochemicals, their target pathways, mechanisms and clinical efficiency. The anti-inflammatory effects of polyphenols are generally attributed to the suppression of canonical NF-κB pathway, which degraded IKK complex to release NF-κB.

In the respect of targeting the NF-κB pathway, some polyphenols are reported to inhibit the phosphorylation of kinases, which prevent NF-κB translocation and thus inhibit

Table 1. Classification of phenolic compounds according to structure.

Phytochemicals	Classification	Skeleton	Basic structure
Gallic acid	Phenolic acids	C6-C1	
Gallacetophenone	Acetophenones	C6-C2	
p-Hydroxyphenyl-acetic acid	Phenylacetic acid	C6-C2	
p-Coumaric acid	Hydroxycinnamic acids	C6-C3	
Esculetin	Coumarins	C6-C3	
Juglone	Naphthoquinones	C6-C4	
Mangiferin	Xanthones	C6-C1-C6	
Resveratrol	Stilbenoids	C6-C2-C6	
Naringenin	Flavanoids	C6-C3-C6	

the transcription of pro-inflammatory mediators. In addition, polyphenols also inhibit interactions between NF-κB and its targeted DNA (Ruiz and Haller 2006). Both mechanisms can finally inhibit the expression of several pro-inflammatory proteins and enzymes regulated by NF-κB.

Phenolic acids

Delay in the onset of inflammatory diseases with consumption of hydroxycinnamic acid derivatives is reported through antioxidant (AOX) and antiradical properties, by acting on pathways of activation of enzymes and expression of genes. The ester of caffeic acid, chlorogenic acid, with quinic acid, having distinct pharmacological profile has been described to exert potent anti-inflammatory, immunoprotective, antioxidant and anti-bacterial properties.

Recently, Ye et al. (2017) explored the mechanism of chlorogenic acid in acute kidney injury and demonstrated that chlorogenic acid dose-dependently suppresses LPS-induced creatinine and pro-inflammatory cytokines including IL-6, and IL-1β and TNF-α in serum and tissue. As reported from *in vivo* studies, chlorogenic acid suppressed serum BUN and creatinine levels and LPS-induced IL-6, IL-1β and TNF-α production in both kidney tissues and serum. It also attenuated LPS-induced kidney histopathologic changes. Chlorogenic acid as a significant component in *Cymbopogon citratus* was described to decrease in NF-κB-dependent NO production in murine macrophages (Francisco et al. 2013). Oleuropein and hydroxyl tyrosol interfere with tau protein and amyloid Aβ aggregation which results in neuroprotection. St-Laurent-Thibault et al. (2011) linked reduction in Aβ-induced toxicity by these compounds in cultured neuroblastoma cells with modulation of NF-κB signaling.

Curcumin

The extensive literature on the health benefit of curcumin, including many clinical studies, has been recently reviewed by Hewlings and Kalman (2017). Curcumin suppresses IL-1, -2, -6, -8, -12 and TNF-α and decreases the expression levels of iNOS, LPO and COX-2 (Abe, Hashimoto, and Horie 1999). It has also been indicated to inhibit the NF-κB pathway in nonalcoholic fatty liver disease (Jiménez-Flores et al. 2014).

Curcumin was reported to block the translocation of p65 subunits to nucleus by suppression of phosphorylation and degradation of IκBα, which thus intervened the NF-κB signaling pathway. Curcumin was also shown to inhibit IKK activation (Shakibaei et al. 2007). Despite having potent antioxidant and anti-inflammatory properties, curcumin is not much effective against systemic diseases because of its poor bioavailability. Curcumin has not been successful in any clinical trials, and several papers involving it with cancer treatment have been retracted (Prasad et al. 2017).

Stilbenoids

Resveratrol interferes with NF-κB signaling in diverse different cell types, such as H4 cells, Jurkat, U-937 and HeLa (Manna, Mukhopadhyay, and Aggarwal 2000). Several studies illustrated that resveratrol suppressed NF-κB activation in U-937 cells after stimulation with PMA (Aggarwal and Shishodia 2006), okadaic acid, H_2O_2, TNF-α, ceramide or LPS (Harikrishnan et al. 2018). Resveratrol modulates the NF-κB signaling pathway in an unspecific manner. It also inhibits the activation of c-Jun kinase and MAPK kinase induced by TNF-α in U-937 cells. Some specificity was found as it inhibits the translocation of the p65 NF-κB subunit into the nucleus. Several studies showed that resveratrol suppressed the production and expression of IL-6, nitric oxide in LPS-stimulated RAW264.7 cells. Furthermore, resveratrol also suppresses the phosphorylation of IκB-α (Kumar and Sharma 2010; Ma et al. 2015).

Flavonoids

Devi, Kiruthiga, and Pandian (2009) described the inhibitory capability of flavonoids against NF-κB signaling pathway and reviewed the effects of various flavonols (such as quercetin and kaempferol) and flavones (like flavone, chrysin, and baicalin) on ICAM-1 expression, which is stimulated by TNF-α. Amongst the given flavonoids, apigenin, kaempferol, luteolin, and chrysin are negative regulators for ICAM-1 expression. Besides this, other experiments recommended that various activities like IκB kinase activity, NF-κB DNA-

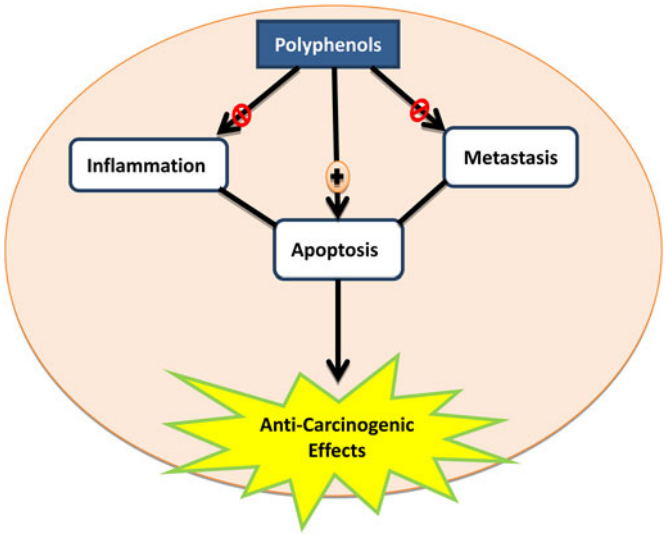


Figure 4. Effects of polyphenols on inflammation, apoptosis and metastasis.

protein binding activity, IκB degradation, and NF-κB luciferase activity were actively inhibited by luteolin and apigenin (Hashimoto et al. 2017).

Hispidulin inhibits the activation of p38 and JNK induced by RANKL (Nepal et al. 2013). Kaempferol suppresses the phosphorylation of IRS-1, IKKα, and IKKβ with a decreased NF-κB level and thus lowers IL-6 and TNF-α levels in diabetic mice (Luo et al. 2015). Quercetin has been indicated to downregulate the expression of NF-κB in non-alcoholic fatty liver disease (Porras et al. 2017). Amrutha et al. (2014) explored the structure-activity relationships of flavonoids on inhibiting NF-κB signaling in MDA-MB-231 cells. It was found that the multi-methyl flavonoids such as chrysoeriol, diosmetin, and acacetin showed higher inhibition ability than non-methyl flavonoids (Amrutha et al. 2014).

Anthocyanins

Enhancement of cognitive and motor function during aging has also been documented with the use of anthocyanins from berries due to their antioxidant and neuroprotective properties (Poulose, Carey, and Shukitt-Hale 2012). Down-regulation of pro-inflammatory cytokines by anthocyanins (100 mg/kg) in multiple sclerosis rats could protect against oxidative stress caused by demyelination (Carvalho et al. 2015). The modulation of Nrf2 and NF-κB signaling pathways by anthocyanins are also linked with their neuroprotective effects against oxidative and inflammatory damages (de Pascual-Teresa 2014). A blueberry anthocyanin decreased the expression of iNOS, COX2 and NO (Lau et al. 2009).

Catechins

Catechin suppressed NF-κB signaling pathway in allergic rhinitis mice by reducing p-NF-κBp65 and NF-κBp65 levels, suppressing the degradation of IκB-α, and inhibiting nuclear translocation of NF-κBp65 (Pan et al. 2018). Catechin 7-*O*-β-D-glucopyranoside could inhibit intestinal inflammation in colitic rats by prevention of the phosphorylation of p38 MAPK, IκB-α, and DNA-NF-κB binding (Kook et al. 2015). EGCG downregulated the expression of COX-2 *via* restraining NF-κB signaling pathway in colon cancer cells (Peng et al. 2006). EGCG can also suppress the expressions of P38 and nuclear NF-κB in human RASFs, whereas EC and EGC did not show any inhibition effects (Fechtner et al. 2017).

Ellagitannins

A class of polyphenols, i.e. ellagitannins and ellagic acid conjugates are mostly found in pomegranates, raspberries, strawberries, blackberries, nuts, and grapes. Anti-inflammatory activities of pomegranate ellagitannins at the gastrointestinal level has been reported from various studies (Colombo, Sangiovanni, and Dell'Agli 2013). The ellagitannins from raspberries and blackberries suppress NF-κB transcription and nuclear translocation. It also diminished the secretion of IL-8 at minute concentrations, which was induced by IL-1β and TNF-α (Sangiovanni et al. 2013). Agrimoniin, a dimeric ellagitannin from the *Rosaceae* family, is one of the main phenolic compounds found in strawberries and other plants. Agrimoniin inhibited IL-8 secretion mostly due to negative regulation of NF-κB signaling pathway (Grochowski et al. 2017).

Polyphenols targeting NF-κB in cancers

Polyphenols inhibit inflammatory processes, induce apoptosis and decrease cell proliferation and metastasis through targeting NF-κB signaling pathway (Figure 4).

Effect on inflammation

As documented in various studies, several polyphenols exert anti-inflammatory effects by negative regulation of NF-κB, which contribute to their chemopreventive and chemoprotective activities (Surh et al. 2001). Curcumin downregulates the expression of inflammation and cancer-related genes, including TNF-α, IL-1β, and NF-κB (Duvoix et al. 2005). Curcumin-mediated suppression of NF-κB result in blocking the pro-metastatic positive feedback loop. Metastases in breast and prostate cancer animals was obviously repressed by curcumin (Pfeffer et al. 2015). While investigating the anti-inflammatory activities of capsaicin in LPS-stimulated macrophages, Park et al. concluded from an experimental study in 2004 that consumption of capsaicin inhibited the production of pro-inflammatory cytokines by inactivation of NF-κB (Park et al. 2004).

An extract rich in procyanindins inhibits the expression of iNOS and the translocation of NF-κB, and thus modulates inflammatory response in activated macrophages (Terra et al. 2007). Along with NF-κB, another transcription factor HIF1-α plays a key role in controlling vital cellular processes including inflammatory reparative response. Resveratrol and other members of sirtuins are known for regulation of both these transcription factors (Tafani et al. 2013). Wheeler et al.

(2004) concluded that EGCG from green tea could restrain IL-8-mediated activation of NF-κB signaling pathway and suppress IL-8 gene expression *via* inhibiting the phosphorylation of p65 subunit.

Effect on apoptosis

Chemopreventive agents including polyphenols can inhibit tumor growth by arresting cell cycle and inducing cell apoptosis (Lin 2002). Tea polyphenols possess antiproliferative and apoptotic effects having anticancer capacities against various cancer cells. EGCG and theaflavins induce apoptosis in human cervical cancer cells by suppressing the activation of NF-κB and Akt via blocking phosphorylation of κBα and κBβ subunits, thus down-regulating COX-2 (Singh et al. 2011). Other molecular mechanisms of apoptosis induction by tea polyphenols include upregulating the expression levels of p53, p21, p73, caspase-3, caspase-9, caspase-8, and Bax; while down-regulating the expression levels of Bcl-2 and Bcl-xL (Zhao et al. 2014; Wang et al. 2018). Synergistic anticancer effects of bleomycin and tea polyphenols in human cervical cancer cells *via* induction of apoptotic pathways were studied, and it was suggested that both of these agents might provide an effective combination therapy for cervical cancer (Alshatwi et al. 2016).

In 2004, Gupta et al. (2004) reported that tea polyphenols EGCG induced apoptosis and inhibited cell proliferation in a dose-dependent fashion by negative regulation of translocation of NF-κB. Hafeez et al. (2008) demonstrated that delphinidin induced cell growth arresting and apoptosis by restraining NF-κB binding to DNA in prostate cancer cells. Curcumin can induce apoptosis by blocking the NF-κB activation in cervical cancer cells (Divya and Pillai 2006). The expression levels of Bcl-2 involved in apoptosis was up-regulated by curcuminoids (Duvoix et al. 2005). Intake of resveratrol has been reported to induce apoptosis, inhibit cell proliferation and decrease chemoresistance *via* suppressing STAT3 and NF-κB pathways (Benitez et al. 2007).

Effect on tumor metastasis

Several phenolic compounds such as curcumin, resveratrol, gallic acid, caffeic acid, carnosol have potential effects on cancer invasion and metastasis (Weng and Yen 2012). Proanthocyanidins from grape seeds decrease the expression of MMP in human prostate carcinoma cells, which is associated with the inhibition of MAPK activation and NF-κB signaling pathway. MMP has been recognized to facilitate tumor cell invasion and metastasis of prostate cancer (Vayalil, Mittal, and Katiyar 2004). In oral cancers, anthocyanins have been demonstrated to decrease cell proliferation, metastasis through negatively regulating NF-κB pathway, inhibiting MMP expression and down-regulating MAPK pathway (Fan et al. 2015). In 2004, Chung et al. (2004) successfully studied the anticancer and anti-metastatic activities of caffeic acid and its phenethyl ester on hepatocarcinoma cells. These two compounds were found to suppress tumor growth *in vitro* as well as *in vivo* by decreasing NF-κB and MMP activities (Chung et al. 2004).

Conclusion

The transcription factor NF-κB exerts an essential function in regulating gene expression of many biological processes including cell growth, metabolic reprograming, inflammation, and cancer. When getting stimulated, it promotes nuclear translocation and activates the target genes transcription. NF-κB may be tumor promoting or tumor suppressing depending upon the site of carcinogenesis. Genetic modification regulating NF-κB activation may enhance NF-κB activity. It also links inflammation with cancer. Down-regulating NF-κB signaling pathway could be a molecular target for treating inflammation, age-related diseases, and cancer prevention. Polyphenols can negatively regulate NF-κB signaling pathway, induce apoptosis, decrease cell proliferation and metastasis, and possess anti-inflammatory effects. Polyphenols prevent NF-κB translocation into the nucleus through inhibition of phosphorylation of kinases. They also interfere the binding of activated NF-κB with target DNA. Considering the central role in regulating the NF-κB signaling pathway by polyphenols, there is the possibility to develop more specific agents with higher success rates that can modulate molecular pathway by acting on different steps.

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