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Plant Natural Products as Potential Modulators of the Transcription Factor NF-κB

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ABSTRACT

Nuclear factor-κB (NF-κB) is an inducible transcription factor which plays important role in the regulation of the immune, inflammatory and carcinogenic responses. Partial NF-κB activation is necessary for normal cell survival and immunity; however the deregulated NF-κB expression is associated with cancer development, metastasis, and in several inflammatory disorders with a resistant phenotype and poor prognosis. Therefore, NF-κB has become an interesting target for drug discovery and several natural and synthetic products have been screened for their ability to inhibit NF-κB pathway. This review surveys the plant natural products with significant NF-κB inhibitory activity focusing on their potential mechanism of action and their implications for cancer therapy.

Keywords: cancer, inflammation, NF-κB inhibition, plant natural products

Abbreviations: COX-2, cyclooxygenase-2; **EGF**, epidermal growth factor; **ELAM-1**, endothelial leukocyte adhesion molecule-1; **IAP**, inhibitor of apoptosis; **ICAM-1**, intercellular adhesion molecule-1; **IKK**, IκB kinase complex; **IL-1β**, interleukin-1β, **iNOS**, inducible nitric oxide synthase; **IκB**, inhibitor of NF-κB; **MMP**, matrix metalloproteinase; **NF-κB**, Nuclear factor-κB; **NLS**, nuclear localization signal; **PDGF**, platelet-derived growth factor; **PGE2**, prostaglandin E2; **PMA**, phorbol 12-myristate 13-acetate; **RHD**, Rel-homology domain; **TNF-α**, tumor necrosis factor-α; **uPA**, urokinase type of plasminogen activator; **VCAM-1**, vascular cell adhesion molecule-1; **VEGF**, vascular endothelial growth factor

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INTRODUCTION

Transcription factor NF-κB was initially identified in 1986 by Sen and Baltimore as a mediator enhancing the expression of the kappa light-chain gene in the nuclei of murine mature B cell lines and plasmacytomas, but has subsequently found in about all animal cell types (Sen and Baltimore 1986; Aggarwal 2004; Luqman and Pezzuto 2010). NF-κB family members have been shown to regulate the expression of multiple genes which play important roles in cell survival, proliferation, host responses to injury and infection, and development of various diseases, including cancer and inflammation (Van Waes 2007). However, normal activity of NF-κB is required for cell survival and immunity, the deregulated activation of NF-κB is associated with serious inflammatory disorders, malignancies, and a wide range of other pathologies with strong manifestations and poor prognosis (Folmer *et al*. 2009).

In mammalian cells, NF-κB family have been differentiated into five members, namely NF-κB1 (p105/p50), NF-κB2 (p100/p52), RelA (p65), cRel, and RelB, which combine to form various homo- and heterodimeric associations. Each member of NF-κB family features a conserved amino-terminal region called the Rel-homology domain (RHD), comprising the DNA-binding, and dimerization domains, and the nuclear localization signal (NLS) (Sun and Andersson 2002). Two different NF-κB activation pathways have been recognized, a canonical pathway initiated by NF-κB1

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and a noncanonical pathways initiated by NF-κB2. Before the NF-κB complex is translocated into the nucleus, NF-κB1 and NF-κB2 are cleaved to the active p50 and p52 subunits, respectively. In the cytoplasm of the non-stimulated cells, NF-κB resides in an inactive form, bound to the NF-κB inhibitor IκB (Karin *et al*. 2004). NF-κB may be activated in response to various stimuli, including exposure to cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β), to carcinogens, to bacterial or viral antigens, or to free radicals (Garg and Aggarwal 2002). The extracellular signals converge on the TNF-α receptor1 (TNFR1), and initiate the recruitment of the TNFR1-associated death domain protein (TRADD) and of the TNF-receptor-associated factor 2 protein (TRAF2) to TNFR1. This leads to the ubiquitination of the receptor-interacting protein (RIP) and to the activation of the transforming growth factor β (TGEβ)-activated kinase 1 (TAK1) and of the IκB kinase complex (IKK). IκB is rapidly degraded upon phosphoryaltion by IKK and uncovers NLS of NF-κB enabling its translocation to the nucleus, where it initiates its target gene transcriptions (Baud and Karin 2001; Sun and Andersson 2002).

In many cancers, including both haematologic and solid malignancies, an aberrant NF-κB activation has been observed (Rayet and Gelinas 1999; Karin *et al*. 2002; Kim *et al*. 2006). Some of the reasons for the abnormal NF-κB activity are aberrant IKK activity and a shorter half-life of IκBα in B-cell lymphoma, mutated IκBα in Hodgkin's lymphoma, IL-1β production in acute myelogenous leukemia, and TNF-α production in cutaneous T-cell lymphoma and Brukitt's lymphoma (Grag and Aggarwal 2002). NF-κB can modulate the transcription of genes involved in cell proliferation, angiogenesis, metastasis, tumor promotion, inflammation and suppression of apoptosis (Basseress and Baldwin 2006; Dutta *et al*. 2006; Cilloni *et al*. 2007; Jost and Ruland 2007; Melisi and Chiao 2007).

Aberrant activation of NF-κB and the signaling pathways controlling its activity has been shown to play important role in cancer development and progression, in addition to drug resistance, particularly during chemo- and radiotherapies. Therefore, blocking NF-κB can force cancer cells to cease proliferation or to be sensitized to the action of antitumor therapy (Karin 2006). Based on these findings, NF-κB has become an interesting subject for intense studies aiming at developing new therapeutic protocols for cancer. A large number of natural and synthetic compounds are currently being investigated for NF-κB inhibitory activity (Bremner and Heinrich 2002; Zambre *et al*. 2006; Folmer *et al*. 2008). In this review, we survey in particular plant natural products capable of functioning in this capacity with promising activity.

ROLE OF NF-κB IN CANCER

NF-κB has been proven to play critical roles in different stages of tumorigenesis including cell survival, cell proliferation, inflammation, angiogenesis, tumor promotion, and metastasis. The roles of NF-κB at different stages of cancer development will be discussed below.

NF-κB activation promotes cell survival

NF-κB can negatively regulate apoptosis in tumor cells through production of several inhibitors of apoptosis (IAPs) (Ahn and Aggarwal 2005). IAPs inhibit caspase-3 and caspase-9 (Kawamura *et al*. 2003), and FLICE inhibitory protein (FLIP) inhibits caspase-8 (Matta *et al*. 2002). NF-κB has been connected to the inhibition of apoptosis in multiple cancers including T-cell lymphoma, melanoma, pancreatic cancer, bladder cancer, and breast cancer and in tumor-related cell types such as B cells, T cells, granulocytes, macrophages, neuronal cells, smooth muscle cells, and osteoclasts (Aggarwal 2004).

NF-κB activation mediates cell proliferation

Several NF-κB-regulated cytokines are tumor growth factors such as TNF-α, IL-1β, and interleukin-6 (IL-6) (Ahn and Aggarwal 2005). For example, TNF-α was found to be a growth factor for glioblastoma (Aggarwal *et al*. 1996; Mukhopadhyay *et al*. 2002) and cutaneous T-cell lymphoma (Giri and Aggarwal 1998); IL-1β, a growth factor for acute myelogenous leukemia (Estrov *et al*. 1998); and IL-6, a growth factor for multiple myeloma (Bharti *et al*. 2003) and head and neck squamous cell carcinoma (Kato *et al*. 2000). Other growth factors such as epithelial growth factor (EGF) and platelet-derived growth factor (PDGF) induce proliferation of tumor cells through NF-κB activation (Romashkova and Makarov 1999; Habib *et al*. 2001). In addition to growth factors, certain cell-cycle regulatory proteins such as cyclin D1 involved in transition from G1 to S phase in cell cycle are also regulated by NF-κB (Mukhopadhyay *et al*. 2002). In some cells, prostaglandin E2 (PGE2) has been shown to induce proliferation of tumor cells. PGE2 synthesis is mediated through cyclooxygenase-2 (COX-2), and the latter is also regulated by NF-κB activation (Yamamoto *et al*. 1995).

NF-κB activation mediates tumor invasiveness and angiogenesis

Tumor invasiveness is influenced by several NF-κB-regulated proteases, including matrix metalloproteinases (MMPs), urokinase type of plasminogen activator (uPA), and interleukin-8 (IL-8) (Novak *et al*. 1991; Bond *et al*. 1998). MMPs regulate the invasiveness and migration of cancer cells by degrading the structural extracellular matrix (ECM) components through cleaving laminin-5 (Sethi *et al*. 2008). MMPs induce tumor growth by the interaction of ECM molecules and integrins, cleaving insulin-like growth factors, and shedding transmembrane precursors of growth factors (e.g. transforming growth factor-β (TGF-β)). In addition MMPs promote angiogenesis through raising the bioavailability of proangiogenic growth factors (Sethi *et al*. 2008), whereas uPA, a crucial protease involved in tumor invasiveness and metastasis, has been reported to be transcriptionally activated by phorbol 12-myristate 13-acetate (PMA), IL-1β, and TNF-α through the induction of NF-κB activity and the degradation of its short-lived inhibitor protein, IκBα (Novak *et al*. 1991). In 1999, Wang and co-workers reported that the overexpression of uPA in pancreatic cancer cells was mediated through constitutive RelA (p65) activity and the uPA promoter comprises an NF-κB binding site that directly induces uPA expression by RelA (Wang *et al*. 1999a). In conclusion, a significant protocol to hinder the tumor invasiveness is to target NF-κB and thus its regulated genes.

Angiogenesis is critical for tumor progression and it has been shown to be regulated by chemokines such as monocyte chemoattractant protein-1 (MCP-1) and IL-8; and growth factors (e.g. vascular endothelial growth factor (VEGF)) produced by neutrophils, macrophages, and other inflammatory cells (Aggarwal 2004). The production of these angiogenic factors is regulated by NF-κB activation (Chilov *et al*. 1997). NF-κB mediates the the upregulation of IL-8 and VEGF expression in bombesin-stimulated PC-3 cells (Levine *et al*. 2003). NF-κB expression has been implicated in VEGF expression and the regulation of microvessel density in human colorectal cancer (Yu *et al*. 2003). It was also reported that the inhibition of NF-κB activity is associated with suppression of tumor angiogenesis, invasiveness, and metastasis (Huang *et al*. 2001). Cylcooxygenase-2 (COX-2), elevated in aggressive variants of colorectal carcinomas, is shown to be transcriptionally activated by NF-κB and promote angiogenesis (Tsujii *et al*. 1998). These studies further highlight the role of NF-κB activation in mediating angiogenesis.

NF-κB activation can mediate tumor metastasis

Metastasis involves a complex series of steps mediating the migration of tumor cells both into and out of the vessel walls of blood or lymphatic systems, and thus, transports them from the original tumor site to other parts of the body. The ability to penetrate through vessel walls is mediated by specific molecules expressed on the endothelial cells of blood vessels in response to a number of signals from inflammatory cells and tumor cells. Among those specific molecules are intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and endothelial leukocyte adhesion molecule-1 (ELAM-1) which in turn have been recognized to be regulated by NF-κB (van de Stolpe *et al*. 1994). Helbig and co-workers have demonstrated that NF-κB can regulate the migration of breast cancer cells by directly upregulating the expression of the chemokine receptor CXCR4 (Helbig *et al*. 2003). These findings indicate the importance of inhibiting NF-κB activation in reducing the metastasis of tumor cells to other body organs and tissues.

NF-κB activation induces chemo- and radio-resistance

NF-κB inhibits the apoptosis induced by a variety of DNA-damaging chemotherapeutic agents and ionizing radiation in addition to TNF-α-induced apoptosis. NF-κB activity in tumor cells is elevated upon exposure to radiation or certain chemotherapeutic agents combined with the fact that many tumors reveal increased NF-κB activity without treatment. Therefore, NF-κB activity may significantly oppose an effective cancer therapy and its inhibition enhances apoptotic responses to chemo- (Wang *et al*. 1999b) and radiotherapies (Shao *et al*. 1997; Yamagishi *et al*. 1997).

NATURAL PRODUCTS WITH NF-κB INHIBITION: ROLE IN CANCER THERAPY

The pivotal role of the NF-κB signaling pathway in the inhibition of apoptosis, cancer cell proliferation and progression, together with the observation that NF-κB is aberrantly activated in a variety of epithelial and haematologic malignancies. These findings strongly supported the assumption that NF-κB inhibitors would help in cancer therapy.

To date, more than 120 plant natural products are considered as important anticancer drugs used as such or as simple synthetic derivatives of the naturally occurring substances. Some examples include paclitaxel (Taxol®), vincristine (Oncovin®), vinblastine (Velban®) and camptothecin (Campto®) which are already well-established cancer chemotherapeutic agents in the pharmaceutical market. An excellent review was recently published summarizing the action mechanism(s) of anticancer pharmaceuticals that modulate NF-κB activity (Luqman and Pezzuto 2010).

Recently, NF-κB was proven to regulate COX-2 and iNOS expression, and hence several chemopreventive natural products have in turn been shown to inhibit COX-2 and iNOS through inhibiting NF-κB activity. Some potential cancer chemopreventive phytochemicals regulating NF-κB activity have been listed in **Table 1** where they are chemically classified into polyphenols, anthraquinones, benzophenones, iridoids, monoterpenes, sesquiterpene lactones, di-, and triterpenes. **Table 1** indicates also the corresponding sources and the reported actions or mechanisms.

Polyphenols

This group of NF-κB-regulating compounds comprise a vast array of dietary phytochemicals such as flavonoids, curcumin, resveratrol, and other stilbene derivatives (Soobrattee *et al*. 2006). Some studies reported that the cancer chemopreventive properties of quercetin, resveratrol, and myricetin may be mediated through downregulation of the NF-κB pathway (Cao *et al*. 2002; Santangelo *et al*. 2007). These studies supported the hypothesis that NF-κB is a functionally relevant target of cancer chemopreventive agents and dietary compounds, indicating its role in the earliest stages of carcinogenesis. Genistein, a natural isoflavone firstly isolated from *Genista tinctoria* and found in many other soyabean products, significantly inhibits NF-κB DNA-binding and hence it can be implemented together with other anticancer drugs such as docetaxel or cisplatin as a novel protocol for the treatment of pancreatic cancer (Gong *et al*. 2003; Li *et al*. 2004).

Polyphenols from green tea (*Camellia sinensis*) are another example of dietary phytochemicals proved significant inhibition of NF-κB signaling pathway by blocking IKK activity leading to subsequent inhibition of phosphorylation and degradation of IκBα, thus preventing nuclear translocation and DNA-binding of RelA (p65). Taken together, potentiate apoptosis, inhibit cellular invasion, and induce cell cycle arrest (Aktas *et al*. 2004; Na *et al*. 2006; Wahyudi and Sargowo 2007; Locatelli *et al*. 2008). Natural polyphenols from *Scutellaria baicalensis*, namely wogonin, baicalein, and oroxylin A, exhibited potent inhibitory activity of NF-κB signaling pathway by blocking IκBα degradation and suppressing the phosphorylation of RelA (p65), and consequently inhibiting the DNA-binding of NF-κB leading to induction of apoptosis (Chen *et al*. 2000; Ma *et al*. 2005; Piao *et al*. 2008; Li-Weber 2009; Yang *et al*. 2011).

Rottlerin, a polyphenol also named mallotoxin or kamala, was isolated from an ancient Indian remedy for tapeworms (*Mallotus philippinenesis*) and it was known as an inhibitor of protein kinases as PKCδ, Akt/PKB and CaMKs (Gschwendt *et al*. 1994; Davies *et al*. 2000). Rottlerin was identified as an inhibitor of NF-κB pathway activated by either phorbol esters or H_2O_2 through different paths including the antioxidant activity, lowering the levels of phosphorylated-IκBα, and preventing p65 nuclear migration provoking cellular arrests via down-regulating the gene inducing cyclin-D1 expression (Luo *et al*. 2005; Torricelli *et al*. 2008; Maioli *et al*. 2009).

Sesquiterpene lactones

Natural sesquiterpene lactones from different plant resources revealed potent inhibitory activity on NF-κB signaling pathway such as parthenolide (*Tanacetum parthenium*), andrographolide (*Andrographis paniculata*), helenalin (*Arnica montana*), isohelenin (*Artemisia ludoviciana*), andrographolide (*Andrographis paniculata*), zedoarondiol (*Curcuma heyneana*), and rugulactone (*Cryptocarya rugulosa*). Amongst these natural sesquiterpene lactones, parthenolide and zedoarondiol suppress NF-κB activation by inhibiting IKK and the subsequent phosphorylation and degradation of IκBα which in turn lead to blocking the gene expression of iNOS, COX-2, and pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 (Steele *et al*. 2006; Chao *et al*. 2009; Gunn *et al*. 2011). In addition, isohelenin and rugulactone suppress NF-κB activation by stabilizing (Bork *et al*. 1997; Mazor *et al*. 2000) and inducing (Meragelman *et al*. 2009) its cytoplasmic negative regulator IκBα, respectively. Whereas, helenalin and andrographolide inhibit NF-κB activity by interacting with RelA (p65) (Lyss *et al*. 1997) and NF-κB1 (p50) (Xia *et al*. 2004; Gunn *et al*. 2011), respectively.

Di- and triterpenes

NF-κB-regulating diterpenes and triterpenes comprise several dietary phytochemicals which are widely spread in different genera belonging to different plant families such as rosmanol (*Rosmarinus officinalis*), glycyrrhizin and glycyrrhetinic acid (*Glycyrrhiza glabra*), oleandrin (*Nerium oleander*). In addition, styaxoside A, isolated from *Styrax japonica*, and natural products from *Isodon japonicus*, namely kamebakaurin, kanebanin, kamebacetal A, and excisanin A, suppress the activity of NF-κB signaling pathway through inhibting its DNA binding and target gene expressions

Table 1 Natural products modulating NF-κB activity.

Class	Examples	Source	Action/Mechanism reported	Reference
Polyphenol	Apigenin		Block the LPS-induced activation of NF-κB through the prevention of inhibitor κB (IκB) degradation. Inhibit NF-κB-dependent transcriptional activity.	Gerritsen *et al*. 1995; Liang *et al*. 1999
	Baicalein	*Scutellaria baicalensis*	Block IκBα degradation.	Ma *et al*. 2005
	Caffeic acid phenethyl ester		Decrease nuclear localization of the p65 subunit of NF-κB; however, their repressor, IκBα was not modified.	Montpied *et al*. 2003; Carrasco-Legleu *et al*. 2004
	Cardamonin	*Artemisia absinthium*	Suppress NF-κB through direct inhibition of its DNA binding in both LPS-stimulated cells and nuclear extracts of the cells (*in vitro*).	Hatziieremia *et al*. 2006
	Cudraflavone B	*Morus alba*	Block nuclear translocation of NF-κB, thereby inhibiting gene expression and secretion of TNF-α and COX-2 in THP-1 human monocyte cell line.	Hošek *et al*. 2011
	Curcumin (diferuloyl methane) and derivatives	*Curcuma longa*	Highly pleiotropic molecule inhibiting NF-κB activation induced by various agents through suppression of Toll-like receptor (TLR) -4, inhibition of RelA (p65) nuclear translocation and prevention of IκBα degradation, hence suppressing cell proliferation and induces apoptosis.	Chan *et al*. 1998; Surh *et al*. 2001; Han *et al*. 2002; Divya and Pillai 2006; Singh and Khar 2006; Lubbad *et al*. 2009; Zhou *et al*. 2011
	Deguelin	Three genera from family Fabaceae (*Lonchocarpus*, *Derris* or *Tephrosia*)	Inhibit NF-κB activation by suppressing IKK activity leading to sequential suppression of IκBα phosphorylation, degradation, p65 nuclear translocation and NF-κB-regulated gene expression. Taken together, potentiate apoptosis, inhibit cellular invasion, and induce cell cycle arrest.	Murillo *et al*. 2002; Nair *et al*. 2006; Geeraerts *et al*. 2007
	5,3'-Dihydroxy-3,6,7,8,4'-pentamethoxyflavone (PMF)	*Gardenia obtusifolia*	Inhibit IKK, leading to suppression of phosphorylation and degradation of IκBα, and consequent nuclear translocation of RelA (p65), thus abrogating NF-κB-dependent gene expression.	Phromnoi *et al*. 2011
	(–)-Epigallocatechin-3-gallate	*Camellia sinensis*	Supress phosphorylation and degradation of IκB-α through inhibiting IKK, preventing subsequent nuclear translocation of RelA (p65). Block the induction of NOS by down-regulating LPS-induced activity of NF-κB. Inhibit TNF-α through NF-κB pathway in HUVECs.	Surh *et al*. 2001; Yang *et al*. 2001; Kazi *et al*. 2002; Afaq *et al*. 2003; Aktas *et al*. 2004; Wahyudi and Sargowo 2007
	Gallates (gallic acid esters), 4-*O*-methylgallic acid	*Camellia sinensis*	Inhibit NF-κB activation induced by cytokines, induce apoptosis, and suppress mitochondrial and cytoplasmic glutathione (GSH) depletion. Suppress inflammation-associated gene expression by blocking NF-κB activation through inhibiting IκB kinase (IKK) activity.	Murase *et al*. 1999; Na *et al*. 2006; Locatelli *et al*. 2008
	Gigantol	*Cymbidium goeringii*	Inhibit NF-κB inactivation through a dose-dependent inhibition of DNA binding of RelA (p65), hence suppressing the lipopolysaccharide (LPS)-induced expression of iNOS, COX-2, the release of cytokines (TNF-α, IL-1β, and IL-6).	Won *et al*. 2006
	Hypericin	*Hypericum perforatum*	Inhibit NF-κB induction via suppressing upstream kinases of the NF-κB pathway, particularly protein kinase C.	Bork *et al*. 1999; Lallena *et al*. 1999
	Quercetin Luteolin	grapes and peanuts vegetables and fruits	Block NF-κB activation by inhibiting the degradation of IκBα and the nuclear translocation of p65 subunit of NF-κB. Taken together, decrease the expression of proinflammatory cytokines (TNF-α, IL-1β, IL-6, and IL-8), iNOS, and COX-2.	Wadsworth *et al*. 2001; Cao *et al*. 2002; Santangelo *et al*. 2007
	Luteolin-7-glucoside	*Glossogyne tenuifolia*	Reduce the activation of NF-κB and MAPK family members, including the ERK1/2 and p38 pathways.	Wu *et al*. 2004
	Oroxylin A	*Scutellaria baicalensis*	Inhibit NF-κB in LPS-stimulated macrophages	Chen *et al*. 2000
	Piceatannol	*Euphorbia lagascae*	Suppress LPS- and TNF-α-induced NF-κB activation through inhibiting IκBα phosphorylation, RelA (p65) phosphorylation and its nuclear translocation but no significant effect on IκBα degradation.	Ashikawa *et al*. 2002; Islam *et al*. 2004; Son *et al*. 2010
	Pterostilbene 3'-Hydroxypterostilbene	*Pterocarpus marsupium*	Suppress LPS-induced NF-κB activation and nuclear translocation of its subunit by blocking the phosphorylation of IκBα and its subsequent degradation. Taken together, inhibit iNOS, COX-2 gene expressions and induce apoptosis.	Heynekamp *et al*. 2006; Pan *et al*. 2008
	Resveratrol	*Polygonum cuspidatum*	Suppress reactive oxygen species (ROS), inhibit IKK activity, and degradation of IκBα, thus preventing nuclear translocation of RelA (p65) subunit of NF-κB.	Surh *et al*. 2001; Asou *et al*. 2002; Estrov *et al*. 2003; Heynekamp *et al*. 2006; Cheeke *et al*. 2006
	Silymarin	*Silybum marianum*	Inhibit NO production and iNOS gene expression by inhibiting NF-κB/ReI activation in RAW 264.7 macrophages.	Saliou *et al*. 1998; Manna *et al*. 1999; Kang *et al*. 2002

Table 1 (Cont.)

Class	Examples	Source	Action/Mechanism reported	Reference
	Wogonin	*Scutellaria baicalensis*	Block TNF-α-induced NF-κB activation through inhibiting phosphorylation on RelA (p65) and consequently the DNA binding of NF-κB and induce apoptosis.	Nakamura *et al*. 2003; Piao *et al*. 2008; Li-Weber 2009; Yang *et al*. 2011
	Rottlerin	*Mallotus philippnenesis*	Inhibit TNF-α-induced NF-κB activation in MCF-7 and HT-29 cells via its antioxidant property against DPPH, H_2O_2, and menadione in culture cells.	Luo *et al*. 2005; Torricelli *et al*. 2008; Maioli *et al*. 2009
Anthraquinone	Rhein (4,5-dihydroxyanthraquinone -2-carboxylic acid)	*Cassia alata*	Inhibit NF-κB activation by inhibiting the phosphorylation of IκB and its subsequent degradation, which altogether suppresses the nuclear translocation of RelA (p65).	Fernand *et al*. 2011
Benzophenone	Garcinol	*Garcinia indica*	Inhibit LPS-induced NF-κB activation through suppressing the phosphorylation of IκBα and p38 mitogen-activated kinase (MAPK), and lowering LPS-induced increase of ROS. Suppress the expression of iNOS.	Liao *et al*. 2004
Iridoids	Aucubin	*Aucuba japonica*	Block both the IκBα degradation and the translocation of NF-κB from the cytosol fraction to the nuclear fraction which lead to inhibition of TNF-α and IL-6 production in RBL-2H3 mast cells.	Saleem *et al*. 2002; Jeong *et al*. 2002
Monoterpene	α-pinene		Inhibit the nuclear translocation of NF-κB due to the upregulation of IκB alpha expression.	Zhou *et al*. 2004
	Syringopicroside	*Folium syringae*	Suppress NF-κB activation through inhibiting the expression of p65 subunit, TNF-α, and IL-6.	Liu and Wang 2011
Sesquiterpene lactone	Andrographolide	*Andrographis paniculata*	Forms a covalent adduct with reduced cysteine 62 of NF-κB1 (p50), and blocking the binding of NF-κB oligonucleotide to nuclear protein.	Xia *et al*. 2004; Gunn *et al*. 2011
	Artemisinin	*Artemisia annua*	Inhibit the activation of the nuclear factor NF-κB and suppress nitric oxide synthesis in cytokine-stimulated human astrocytoma T67 cells.	Aldieri *et al*. 2003
	4',6-Dihydroxy-4-methoxyisoaurone	*Trichosanthes kirilowii*	Inhibit NF-κB activation (mechanism not clarified).	Dat *et al*. 2010
	2β,5-Epoxy-5,10-dihydroxy-6α-angeloyloxy-9β-isobutyloxy -germacran-8α,12-olide	*Carpesium divaricatum*	Inhibit NF-κB activation via stabilization of the NF-κB/IκB complex and reduce nuclear translocation of subunit p65 of NF-κB.	Kim *et al*. 2001
	Helenalin	*Arnica montana*	Inhibit NF-κB through alkylation of p65 subunit.	Lyss *et al*. 1997
	Isohelenin	*Artemisia ludoviciana*	Stabilize cytoplasmic IκBα leads to inhibition of NF-κB nuclear translocation. Inhibit nuclear translocation of NF-κB and inhibit degradation of the NF-κB inhibitory protein.	Bork *et al*. 1997; Mazor *et al*. 2000
	Parthenolide	*Tanacetum parthenium*	Supress NF-κB nuclear translocation by inhibiting IKK activity and the subsequent phosphorylation of IκBα.	Kang *et al*. 2001; Zingarelli *et al*. 2002; Steele *et al*. 2006; Gunn *et al*. 2011
	Rugulactone	*Cryptocarya rugulosa*	Suppress NF-κB activation through the induction of its negative regulator IκBα.	Meragelman *et al*. 2009
	Zedoarondiol	*Curcuma heyneana*	Suppress NF-κB activation by inhibiting IKK and the subsequent phosphorylation and degradation of the inhibitor IκBα which lead to inhibiting the expression of iNOS, COX-2, and pro-inflammatory cytokine such as TNF-α, IL-1β, and IL-6.	Cho *et al*. 2009
Diterpene	Andalusol	*Siderites foetens*	Inhibit iNOS by inhibition of NF-κB.	de las Heras *et al*. 1999
	Hypoestoxide	*Hypoestes rosea*	Inhibit NF-κB activation through direct inhibition of IκB kinase (IKK) activity	Ojo-Amaize *et al*. 2001
	Kamebakaurin Kamebanin Kamebacetal A Excisanin A	*Isodon japonicus*	Inhibit of NF-κB activation by targeting DNA-binding activity of p50 and block the expression of antiapoptotic NF-κB target genes. It did not prevent either stimuli-induced degradation of IκBα or nuclear translocation of NF-κB.	Hwang *et al*. 2001; Lee *et al*. 2002
	Foliol Linearol *ent*-Kaurenoic acid	*Sideritis* spp.	Inhibit NF-κB and IκB kinase (IKK) activation *in vivo* through interference with downstream IKK phosphorylation.	Castrillo *et al*. 2001
	Rosmanol	*Rosmarinus officinalis*	Reduce nuclear translocation of NF-κB subunits by prevention of the phosphorylation and the subsequent degradation of the inhibitor IκB resulting in downregulation of iNOS and COX-2.	Lai *et al*. 2009
	Styraxoside A	*Styrax japonica*	Inhibit NF-κB pathway by inhibiting its DNA binding and gene expressions of proinflammatory enzymes (iNOS, COX-2, TNF-α and IL-1β).	Yun *et al*. 2007
Triterpene	Avicin G	*Acacia victoriae*	Inhibit NF-κB in TNF-α Jarket cells via suppressing the P65 subunit and NF-κB's binding to the DNA.	Haridas *et al*. 2001

Table 1 (Cont.)

Class	Examples	Source	Action/Mechanism reported	Reference
	Bruguierin A	*Bruguiera gymnorrhiza*	Inhibit PMA-induced NF-κB activation and selectively inhibit COX-2 with IC_{50} values of 1.4 and 0.37 μM, respectively.	Homhual *et al*. 2006
	Corosolic acid		Block NF-κB and STAT3 activation, and induce caspase activation.	Fujiwara *et al*. 2011
	Cucurbitacin B	*Cucurbita maxima*	Inhibit TNF-α-induced NF-κB activation, suppress phosphorylation of Ser536 in RelA (p65) necessary for transactivation activity. Taken together, inhibit the expression of NF-κB-dependent anti-apoptotic proteins (mechanism not clarified).	Dat *et al*. 2010; Jin *et al*. 2011
	Glycyrrhizin Glycyrrhetinic acid	*Glycyrrhiza glabra*	Inhibit nuclear factor NF-κB	Wang *et al*. 1998
	Lupeol		Inhibit of TPA-induced, activation of PI3K, phosphorylation of Akt at Thr(308), activation of NF-κB and IKK-α, and degradation and phosphorylation of IκBα.	Saleem *et al*. 2004
	Maslinic acid	*Olea europaea*	Suppress TNF-α-induced NF-κB activation by inhibiting IκBα degradation, phosphorylation, nuclear translocation of RelA (p65), and its downstream gene expressions. Significantly suppress tumor growth, angiogenesis, and induce tumor apoptosis.	Li *et al*. 2010
	Oleandrin	*Nerium oleander*	Inhibit NF-κB via the IKK complex and IκBα phosphorylation.	Manna *et al*. 2000
	Oleanolic acid		Stimulate NO and TNF-α production and upregulate iNOS and TNF-α expressions via NF-κB transactivation in both peritoneal macrophages and RAW264.7 cells at high dose.	Choi *et al*. 2001
Miscellaneous	S-allylcysteine	*Allium sativum*	Inhibit NF-κB activation.	Geng *et al*. 1997; Ho *et al*. 2001; Ide and Lau 2001
	Anacardic acid	*Anacardium occidentale*	Inhibit NF-κB activation through inhibiting IκBα and abrogating its phosphorylation and its subsequent degradation leading to inhibition of nuclear translocation of p65 and potentiation of apoptosis. Taken together, suppress NF-κB-regulated gene products involved in cell survival, proliferation, invasion, and inflammation.	Sung *et al*. 2008
	Capsaicin	*Capsicum annuum*	Both block TNF-α-induced NF-κB activation in a dose-dependent manner with IC_{50} values of 0.68 (capsaicin) and 4.2 (capsazepine) μM.	Luqman *et al*. 2011
	Cryptocaryone	*Cryptocarya rugulosa*	Suppress NF-κB activation through the induction of its negative regulator IκBα.	Meragelman *et al*. 2009
	Harmine	*Peganum harmala*	Block NF-κB activation and other transcription factors involved in tumor development and angiogenesis.	Hamsa and Kuttan 2010
	Pristimerin		Inhibit NF-κB activation (mechanism not clarified and cytotoxicity is noticed at higher dose).	Dirsch *et al*. 1997

(Hwang *et al*. 2001; Lee *et al*. 2002; Yun *et al*. 2007), whereas hypoestoxide, foliol, linearol, and oleandrin inhibit NF-κB signaling pathway through direct inhibition of IκB kinase (IKK) complex (Manna *et al*. 2000; Castrillo *et al*. 2001; Ojo-Amaize *et al*. 2001).

PRECLINICAL AND CLINICAL ADVANCES

Recently, suppression of NF-κB was marked as an important mechanism of action of many therapeutic and preventive pharmaceuticals with acceptable safety profiles such as steroids, non-steroidal anti-inflammatory drugs (NSAID), and natural and synthetic compounds. In addition, newer agents targeting the proteasome, IKK, and other upstream kinases involved in NF-κB activation revealed anticancer activity in clinical or preclinical studies.

Corticosteroids in cancer therapy

The cytotoxic effects of corticosteroids exhibited in combination with other DNA-damaging agents led to the use of steroid-based regimens as a treatment protocol of certain leukemias, lymphomas, and myelomas. Corticosteroids mediate their anti-inflammatory and cytotoxic effects through the inhibition of NF-κB pathways (Nakanishi and Toi 2005). Corticosteroids have met a significant place in current cancer therapy, with supportive measures to manage the hematopoietic and immunosuppressive side effects expected with agents with broad effects on NF-κB, DNA replication, and other functions.

NSAIDs in cancer chemoprevention

NSAIDs, such as aspirin, sulindac, ibuprofen, and COX-2 inhibitors (celecoxib), have been shown to inhibit NF-κB activation by suppressing IKK activation and IκBα (Yin *et al*. 1998; Palayoor *et al*. 1999; Yamamoto *et al*. 1999; Takada *et al*. 2004). NSAIDs have been shown to reduce adenoma and colon cancer development in patients with inflammatory bowel disease and hereditary colon cancer, and long-term NSAID use has also been associated with a reduction in risk of colon, breast, and prostate cancer in population-based studies (Hoffmeister *et al*. 2006; Blair *et al*. 2007). Further studies are still demanded to define the NF-κB-dependent and -independent mechanisms of action of synthetic and dietary NSAIDs. Moreover, the possible risks of gastrointestinal and cardiovascular side effects must be judged in comparison to the beneficial outcomes of the synthetic NSAIDs.

IKK inhibitors

IKKβ and RelA (p65) knockouts were proven to sensitize cells to apoptosis and cytotoxic therapies. Therefore, the implementation of IKKβ antagonists in cancer therapy has been the subject of intensive developmental and preclinical studies (Karin *et al*. 2004; Luo *et al*. 2005). PS-1145 or ML120b derivatives (Millennium Pharmaceuticals), IKKβ-selective angtagonists, exhibited antiproliferative activity in preclinical studies against multiple myeloma cells, diffuse large B-cell lymphoma, chronic myelogenous leukemia, and prostate carcinoma cells (Lam *et al*. 2005; Yemelyanov *et al*. 2006; Cilloni *et al*. 2006). However, recent studies revealed that IKKα and IKKβ in addition to casein kinase 2 (CK2) contribute to NF-κB activation (Yu *et al*. 2006). These findings pointed out the need to re-evaluate the IKKβ antagonist and distinguish inhibitors of IKKα, IKKβ, CK2, and other kinases regulating NF-κB activity.

Proteasome inhibitors

Proteasome inhibitors represent a new developing class of therapeutic agents, which regulate the degradation of IκB and subsequently inhibit NF-κB (Richardson *et al*. 2006). The proteasome inhibitor bortezomib (Velcade®, Millennium Pharmaceuticals, Cambridge, MA) has been shown to have significant preclinical and clinical activity and is now approved by Food and Drug Administration (FDA) for the treatment of patients with advanced multiple myeloma (Sánchez-Serrano 2006). Preclinical and clinical studies revealed that combining bortezomib with other cytotoxic therapies, or inhibitors of other prosurvival pathways, may enhance its antitumor activity in some cancers such as head and neck squamous cell carcinoma (Van Waes *et al*. 2005).

CONCLUDING REMARKS AND FUTURE PERSPECTIVES

NF-κB transcription factor family comprises regulators of a vast array of genes involved in development of serious diseases such as cancer and inflammation. Although inhibition of NF-κB signaling pathway seems beneficial, some studies indicated that NF-κB activation can be pro-apoptotic in certain conditions, depending on the type of stimulus to which cells are exposed (Campbell *et al*. 2004).

In this review, we focused on the role of NF-κB in tumorigenesis and chemoresistance, and how NF-κB-inhibitory phytochemicals can be implemented in cancer treatment protocols. According to the action of some cancer chemopreventive agents, inhibition of NF-κB reveals a promising way to prevent carcinogenesis at an early stage. Looking at the overall NF-κB signaling pathway as a potential target for cancer treatment, many possible interventions have been developed such as IKK-specific inhibitors and proteasome inhibitors. However, the major drawback of IKK-specific inhibitors that they do not affect IKK-independent NF-κB activity (Tergaonkar *et al*. 2003), proteasome inhibitors can overcome this drawback and block both IKK-dependent and -independent NF-κB activity (Cusack *et al*. 2001). The proteasome inhibitor bortezomib (Velcade®, Millennium) represents a success story for the development of a cancer chemotherapeutic agent based on the inhibition of NF-κB activity.

Nevertheless, more studies are still needed to develop more NF-κB-inhibitory pharmaceuticals that can be indicated for treatment of serious human diseases such as cancer and other inflammatory disorders. It is also important to identify many agents and closely investigate them taking into consideration that these agents function by a plethora of mechanisms of action and thereby behave in an unpredictable ways. Furthermore, many factors can affect and modulate the efficacy of those agents such as absorption, distribution, and metabolism, hence extensive *in vitro*, *in vivo*, and finally clinical trials are required to distinguish and establish the full behavior of these agents.

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