

Dietary Phytochemicals Targeting Nf- κ B Signalling Pathways: Potential Cancer Chemoprevention Strategy

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Abstract

Chemoprevention is an approach involving the use of natural or synthetic substances to prevent the risk of development many diseases including cancer. Nuclear factor- κ B (NF- κ B) signaling pathways is crucial in either inducing processes of inflammation and apoptosis. As a result, it is implicated in numerous stages of carcinogenesis through collaboration with several signaling pathways and molecules. This transcription factor may be regarded as key target for cancer chemoprevention. Phytochemicals available in food as well as green plants have been demonstrated to have cancer protection activities by modulating important cellular signaling pathways including NF- κ B pathway. Numerous phytochemicals, primarily components of edible vegetables and plants, have been reported in the literature to modulate NF- κ B. Suppressing NF- κ B may provide protection to the normal cells against development and spread of cancer. Majority of phytochemicals use various mechanisms to inhibit NF- κ B. Different phytochemicals combinations present in a natural food may enhance their modulating potential on NF- κ B and consequently elicit cancer prevention. This article reviews the current understanding of the potential effect of some phytochemicals and their combinations on NF- κ B activities.

Keywords: Phytochemicals, Cancer, Plants, Chemoprevention, Inhibition, Carcinogenesis

INTRODUCTION

Chemoprevention is an approach employed for the delaying, inhibition or reversing carcinogenesis in human via the synthetic natural or chemicals products. The name "chemoprevention" was introduced by Dr Michael B. Sporn to refer to the halting of cancer progression through the use of natural sources of vitamin A and by its synthetic form (Kwon *et al.*, 2007). Numerous findings have indicated that different naturally-occurring dietary compounds possess significant cancer preventive potentials and several experimental approaches have been performed to describe the mechanisms by which they exert their actions (Surh *et al.*, 2003). Several cancer cell lines and animal cancer models have been employed to assess the chemo-preventive potentials of many phytochemical constituents and evaluate the mechanisms by which they prevent cancer (Dinkova-Kostova *et al.*, 2005).

These researches have resulted in the identification of numerous novel phytochemicals possessing potential cancer-preventive properties, such as, polyphenols from flavonoids from soybeans green and black tea, and isothiocyanates from cruciferous vegetables (Chen *et al.*, 2005). These dietary phytochemicals have broad anti-cancer effect mediated by a number of

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cellular mechanisms (Dinkova-Kostova *et al.*, 2005). These include electrophilic or oxidative stresses that can lead to the stimulation of a wide range of cellular processes like increase in expression of phase II detoxifying enzymes (GST, UGT HO-1) (Shen *et al.*, 2006). Therefore, it can be concluded that the pleiotropic effects of these chemo-preventive agents can be deduced to be as a result of careful modulation of many signaling cascades within the cell by dietary phytochemicals. Cancer is an intricate heterogeneous disease with multiple etiologies. A wide range of foods found in our typical diets, including vegetables, fruits grains, seeds and spices have been indicated to be effective in cancer prevention (Dinkova-Kostova *et al.*, 2005). In addition to antioxidants, numerous plant-based organic chemical components, often known as phytochemicals possess strong chemo-preventive potential (Hu *et al.*, 2006).

Majority of dietary phytochemicals presumably combine a number of different approaches to achieve their chemo-preventive benefits. These include preventing carcinogens from binding to DNA and/or activating metabolic processes, promoting detoxification, stopping of cell proliferation and metastasis or angiogenesis, inducing apoptosis or differentiation of malignant or precancerous cells, repairing DNA damage, among other things (Singh and Aggarwal, 2000).

Evidence also exists that same phytochemicals have been reported as regulators of NF- κ B signaling pathway. Among the inhibitor of NF- κ B pathway in cancer cells, curcumin was the first extensively reported. Only a fraction of these phytochemicals had an impact on both the pathways (Haque *et al.*, 2021). NF- κ B transcription factors are directly engaged in many stages of carcinogenesis and their interaction with numerous other signaling molecules and pathways may eventually have an impact on cell differentiation and proliferation (Hoesel and Schmid, 2013). A number of human intervention trials are currently being examined using specific phytochemicals or using them in combination with well-known synthetic chemo-preventive agents.

Electronic literature was searched from Scopus, WOS and PubMed using the topics (“NF- κ B phytochemicals” OR “NF- κ B polyphenols” OR “NF- phenolic acids” OR “NF- κ B flavonoids” OR “NF- κ B phytochemicals”). Reports from 2000 to 2022 were considered. This review highlights the role of dietary products in the chemoprevention of cancer through inhibition of NF- κ B signaling pathway and provides an overview of the current understandings of molecular regulatory mechanism of NF- κ B, and effect of combining of phytochemicals in the chemoprevention of cancer.

Nuclear factor- κ B

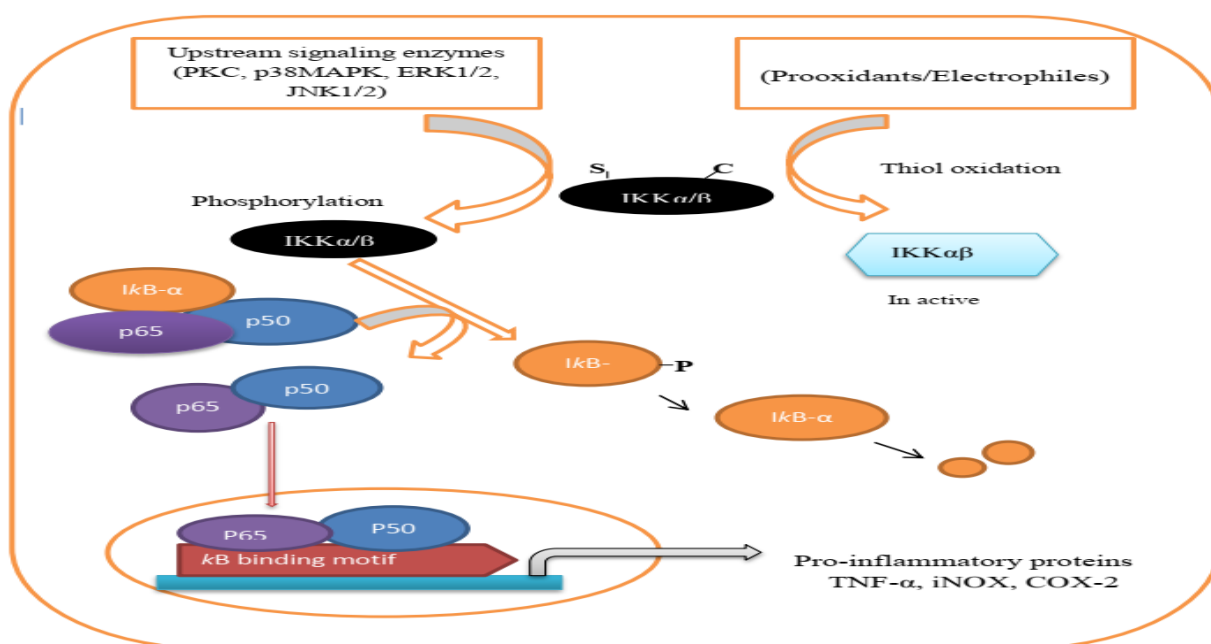
NF- κ B is a protein consisting of five-member family that are structurally related, including, RelB, RelA (p65), NF- κ B2 (p52), c-Rel and NF- κ B1 (p50) (Pires *et al.*, 2018). They function as distinct hetero- or homo-dimers κ B enhancer, a particular DNA element, to regulate the transcription of iNOS and COX-2, two of its main genes (Liu *et al.*, 2017). NF- κ B performs a significant role in eliciting inflammatory response that leads to the synthesis of pro-inflammatory molecules, such as cytokines (Pires *et al.*, 2018). It also plays role in enzymes production of like inducible nitric oxide synthetase (iNOS) and cyclooxygenase-2 (COX-2) (Shakibaei *et al.* 2007). Along with promoting angiogenesis, these enzymes also have a role in development of cancer (Chen *et al.*, 2005). NF- κ B is present in cells of immune system like neutrophils and is an essential transcription factor that inhibits apoptosis. Additionally, it is required for lymphocytes development (Sun *et al.*, 2016). The most prevalent activated form of NF- κ B is a dimer called p50/p65 (Giridharan and Srinivasan, 2018). The p50 subunit in this

complex simply assists in binding of NF- κ B to DNA while p65 subunit initiates transcription (Liu *et al.*, 2017).

NF- κ B Signaling Pathway

Under normal condition, inhibitory proteins, mostly family members of I κ B, sequester NF- κ B subunits in the cytoplasm, much like Nrf2, can be activated via different mechanisms (Sun *et al.*, 2016). NF- κ B variability and its occasionally conflicting functions as a pro- and anti-inflammatory mediator may be caused by a number of factors that affect activation of NF- κ B as well as its nuclear translocation (Pires *et al.*, 2018).

NF- κ B provides survival edge to cancer cells by enhancing anti-apoptotic genes (Giridharan and Sriniyasan, 2018). Additionally, in cancer, there exists an interaction between NF- κ B and autophagy (Verzella *et al.*, 2020). As a result, depending on the stimulus and the setting, NF- κ B can either facilitate or suppress the development of tumor. In this manner, Nrf2 lowers the levels of reactive oxygen species and inhibits I κ B- α mediated degradation of proteasome thereby stopping NF- κ B translocation into the nucleus. Additionally, increased Nrf2 levels increase the levels of heme oxygenase (HO-1), as well as a consequent increase in expression of phase II enzymes, and prevents I κ B- α degradation (Saha *et al.*, 2020).



**Figure 1: Schematic presentation of activation of NF- κ B signaling pathway
Potential chemo-preventive Phytochemicals targeting NF- κ B Signaling Pathways**

Curcumin

Curcumin is a pigment, obtained from *Curcuma longa* L. It is widely used in food preparation as a flavoring and coloring agent in most Asian countries (Verzella *et al.*, 2020). Several researches have demonstrated that curcumin exerts numerous biological effects like antioxidant, anti-inflammatory, chemotherapeutic and chemopreventive activities (Haroon *et al.*, 2020). Curcumin possess anti-inflammatory and antioxidant capabilities; however, because of its low absorption potential, it is less effective against systemic diseases. A report has shown that curcumin acts by blocking p65 subunits translocation into nucleus via suppressing the phosphorylation of I κ B α as well as degradation, thus interfering with the NF-

κ B signaling cascade (Chen *et al.*, 2005). Additionally, Curcumin blocks the activation of IKK (Shakibaei *et al.* 2007). Clinical investigations have demonstrated that curcumin inhibits TNF- α and interleukines (IL-1, IL-2, IL-6, IL-8, IL-12) and lowers COX-2, LPO and iNOS expression levels (Balogun *et al.*, 2003). In disease like nonalcoholic fatty liver, curcumin block NF- κ B pathway (Jimenez-Flores *et al.* 2014). Curcumin inhibits NF- κ B signaling pathway via p38MAPK and ERK1/2 blockage (Haroon *et al.*, 2020).

Resveratrol

Resveratrol is a well-known phytoalexin, mostly present in grapes and red wine (Harikrishnan *et al.* 2018). It exhibits numerous important functions in biological system such as anti-aging anti-inflammatory, neuroprotective and antioxidant potential (Aqeel *et al.*, 2012; Ballear *et al.*, 2014).

Through the blockage of IKK α and IKK β , resveratrol is capable of inhibiting phosphorylation of I κ B α induced by TPA and nuclear localization of p65 in skin of mouse (Kundu *et al.*, 2006). Resveratrol blocks NF- κ B pathway in various type of cells, including H4 cells, HeLa, U-937 and Jurkat (Manna and Mukhopadhyay, 2000). An unspecific mechanism is used by resveratrol regulates NF- κ B pathway. In some cells such as U-937, it also blocks the activation of c-Jun kinase MAPK kinase stimulated by TNF- α . In some instance, resveratrol inhibits the translocation of p65 NF- κ B subunit into the nucleus (Harikrishnan *et al.* 2018). Several scientific investigations have demonstrated the ability of resveratrol to suppress transcriptional capacity of p65 and inhibit IKK ubiquitination and NEMO-induce NF- κ B activation (Ren *et al.*, 2013). Numerous studies have shown that resveratrol protects PC12 cells against oxidative attack by inducing the expression of heme oxygenase-1 (HO-1) through Nrf2 regulatory pathway (Chen *et al.*, 2005). Resveratrol inhibits NF- κ B activation in U-937 cells following stimulation with okadaic acid, H₂O₂, LPS, ceramide, TNF- α (Harikrishnan *et al.* 2018) or PMA (Aggarwal and Shishodia, 2006) In RAW264.7 cells stimulated by LPS, resveratrol decrease expression and production of nitric oxide and IL-6. Additionally, resveratrol also decreases I κ B- α phosphorylation (Ma *et al.* 2015; Kumar and Sharma 2010).

Epigallocatechin gallate

Epigallocatechin gallate (EGCG) is found in large amount in green tea (*Camellia sinensis*) and white tea as catechin, where as seen in small amount in black tea (McKay and Blumberg, 2002). In mouse skin and MCF10A cell line, EGCG act by inhibiting activator protein-1 (AP-1) and NF- κ B activation in vivo (Kundu *et al.*, 2003; We *et al.*, 2006). EGCG increases antioxidant enzymes level via activation of Nrf2-ARE pathway, which in turn represses or activates NF- κ B signaling depending on the circumstance (Shen *et al.*, 2005; Wu *et al.*, 2006). EGCG can also inhibit I κ B α degradation, translocation of RelA into nucleus, as well as the binding affinity of NF- κ B to DNA (Joo *et al.*, 2012).

Quercetin

As the most extensively studied flavonoid, quercetin is present in many vegetables and fruits. It possesses many biological functions, such as, antioxidant, anti-tumor, and anti-inflammatory. Quercetin is also shown to lower the danger of cardiovascular disease (Anande *et al.*, 2016). Quercetin modulates NF- κ B pathway via several different mechanisms; it prevents phosphorylation of I κ B α , inhibits translocation of NF- κ B into the nucleus, and blocks the binding of NF- κ B to DNA and transcription of reporter gene in RAW264.7 cells (Endale *et al.*, 2013). Several studies have shown that quercetin can trigger apoptosis, partially as result of its ability to demethylate DNA, via HDAC inhibition and alteration of histone (H3ac and

H4ac). This initiates the transcription of genes to form products engaged in the process that lead to apoptosis (Endale *et al.*, 2013; De Prax, *et al.*, 2019).

Capsaicin

Capsaicin is a pungent ingredient mostly found in hot chili pepper (*Capsicum annuum* L.) (Han *et al.*, 2001). It has cancer preventing as well as anti-inflammatory potentials. Several studies have demonstrated that capsaicin decreases NF- κ B activation induced by TPA in cultured human promyelocytic leukemia HL-60, in mouse skin in vivo, and as well as in as human myeloid ML-1a cells (Surh and Na, 2008; Han *et al.*, 2002; Han *et al.*, 2001).

Silymarin

Silymarin, a bioflavonoid isolated from milk thistle or *Silybum marianum*. Wang *et al.* (2019) has indicated that it reduces binding effect of NF- κ B to DNA. In the HepG2 cell line, Silymarin inhibits okadaic acid-induced DNA binding potential of NF- κ B and its dependent gene expression. Report has shown that silymarin has no effect on induction of TNF-K by NF- κ B (Wang *et al.*, 2019).

Salidroside

Salidroside is a polyphenol present in *Rhodiola rosea* L. (Gao *et al.*, 2015). Salidroside has been reported to elicit many pharmacological effects, like anti-fatigue, anti-aging, antioxidant, anti-inflammatory and anti-cancer (Zhu *et al.*, 2011; Tan *et al.*, 2015). As observed in a rat model of Alzheimer's disease induced with d-galactose, salidroside modulated NF- κ B proteins expression, such as, I κ B α , NF- κ B p65, IKK and IKK α (Gao *et al.*, 2015; Wang *et al.*, 2019).

Lupeol

Many fruits and vegetables, like, cabbage, mangoes, strawberries olives, green and white pepper grapes contain a pentacyclic diterpenoid lupeol. It suppresses the phosphorylation of I κ B protein and prevents the activation of NF- κ B signaling (Lee *et al.*, 2007).

Betulin

Betulin is a triterpenoid with pentacyclic structure. It is isolated from *Betula alba* bark. It suppresses the IKK phosphorylation and degradation in cell, its localization in the nucleus, and p65 phosphorylation. Betulin derivatives exhibit anti-inflammation activity by regulating the expression of NF- κ B- and IKK α -dependent gene (Alakurtti *et al.*, 2016).

Lutein

Lutein is a cyclic tetraterpenoid which is abundant in leafy vegetables and fruits, like lettuce, broccoli, peas, spinach and kale. Lutein induces I κ B α protein degradation and blocks the translocation of p65 subunits into nucleus. Lutein inhibit the activation of NF- κ B (Majumdar *et al.*, 2009). This pigment provides protection against cataracts and oxidative stress (Izumi-Na *et al.*, 2007).

Lycopene

Lycopene is a tetraterpenoid that is present in tomatoes. It possesses strong antioxidant activity (Marti *et al.*, 2016). Lycopene has anti-cancer properties (Kelkel *et al.*, 2011), neuroprotective and anti-proliferative effects (Paul *et al.*, 2020). It mediates suppression of pro-inflammatory chemokines and chemokines of macrophages (Marcotorchino *et al.*, 2012; Lee *et al.*, 2012). Lycopene suppresses I κ B phosphorylation in cells and NF- κ B transcriptional potential. In MDA-MB-231 cells treated with lycopene, it inhibits translocation of p65 subunit mediated by TNF into the nucleus (Assar *et al.*, 2016).

β -Carotene

This cyclic carotene accumulates in liver cells and is transformed into vitamin A. The β -carotene inhibits NF- κ B signaling induced by LPS. It induces I κ B protein degradation and restrains translocation of p65 into the nucleus. It also suppresses NF- κ B binding potential to DNA. Due to its pro-oxidant effects, β -carotene suppresses metastasis of cancer (Kalariya *et al.*, 2008).

Isothiocyanates

Sulforaphane is a well-known isothiocyanate, predominantly found in cruciferous vegetables such as cabbage, cauliflower and broccoli (Surh and Na, 2008). It possesses the capacity to activate to phase 2 detoxification enzymes (Juge *et al.*, 2007; Surh and Na, 2008). Sulforaphane blocked the lipopolysaccharide- drive NF- κ B activation and expression of COX-2 in cultured mouse macrophages (Heiss *et al.*, 2001). It is interesting to note that sulforaphane directly binds to the crucial p50 thiol's groups, a potential active subunit present in NF- κ B, causing NF- κ B inactivation. This is neither related to the I κ B degradation nor translocation of NF- κ B in to nucleus. As opposed to these reports, treatment of epithelial cells of human mammary with sulforaphane prevented the expression of COX-2 drive by TPA through blocking the activities of IKK and subsequent phosphorylation and degradation of I κ B α , which lead to suppression of NF- κ B activation (Kim *et al.*, 2007).

Alternatively, this sulforaphane can interact with glutathione in its reduced form or any other redox regulators such as Ref-1 and thioredoxin, leading to the disruption of reducing environment important for the binding of NF- κ B to DNA (Heiss, and Gerhauser, 2005).

Table 1: Regulatory Effects of Some Phytochemical constituents on NF- κ B Signalling Pathway

Compound	Source	Mechanism of Action	Reference
Curcumin	<i>Curcuma longa</i> (Turmeric)	Inhibits I κ B α phosphorylation and degradation, and the translocation of p65 into the nucleus	Buhrmann <i>et al.</i> (2011)
Gallic acid	<i>Terminalia chebula</i> (Gallnut)	Decreases the acetylation of RelA	Choi <i>et al.</i> (2009) Kim <i>et al.</i> (2011)
[6]-Gingerol	<i>Zingiber officinale</i> (Ginger)	Inhibits p65 phosphorylation induced by TPA	Kim <i>et al.</i> (2005)
Quercetin	<i>Brassica oleracea</i> <i>var. italica</i> (Broccoli)	Suppresses phosphorylation of I κ B, nuclear translocation of NF- κ B, and Binding of NF- κ B to DNA.	Endale <i>et al.</i> (2013)
Resveratrol	<i>Vitis vinifera</i> (Grapes)	Reduces the p65 transcriptional activity, inhibits NEMO ubiquitination and NF- κ B activation mediated by IKK	Ren <i>et al.</i> (2013)
Epigallocatechin gallate	<i>Camellia sinensis</i> (Green tea)	Blocks degradation of I κ B α induced by LPS, translocation of RelA into the nucleus and the NF- κ B-DNA binding potential.	Joo <i>et al.</i> (2005)
Lutein	<i>Brassica oleracea</i> <i>var. sabellica</i> (Kale)	Inhibiting localization of p65 subunits in the nucleus and Degradation of I κ B α protein	Izumi-Nagai <i>et al.</i> (2007)
β -Carotene	<i>Daucus Carota</i> (Carrot)	I κ B protein degradation and prevents translocation of p65 subunit into the nucleus, as well as NF- κ B-DNA binding effect	Assar <i>et al.</i> (2016)
Lycopene	<i>Solanum lycopersicum</i> (Tomato)	Suppresses phosphorylation of I κ B in the cells and inhibits transcriptional activity of NF- κ B	Kalariya <i>et al.</i> (2008)

Combinatorial Effects of Phytochemical on NF- κ B Signaling Pathway

Generally minimal toxicity as well as ability of inducing or inhibiting signaling pathway such as NF- κ B, is a successful approach for cancer therapy and chemoprevention. Shortening feedback loops signaling, cellular cross communication between the signaling pathways and various cells types within the tumor may be beneficial (Surh and Na, 2008). The wide range of molecular approach exhibited by natural compounds encourages the development of synergistic combinatorial therapies (Lodi *et al.*, 2017). The reports from various *in vitro* investigations as well as *in vivo* to some extent, show that combinations of different phytochemical constituents may enhance their capacity for chemotherapeutic and chemopreventive, which can effectively target the signaling pathways associated with cell survival and proliferation. In cancer cells of pancreas, combinatorial effect of resveratrol and phenethyl isothiocyanate on the activation and expression of NF- κ B was studied. The combination of resveratrol and phenethyl isothiocyanate reduced the NF- κ B activation more effectively than using single compounds by decreasing NF- κ B p65- DNA binding and p65 gene expression. These results show that combinations of different phytochemicals which are present in natural diets may effectively regulate NF- κ B signaling pathway and decrease the survival and spread of pancreatic cancer cell (Majumdar *et al.*, 2009).

Table 2 presents different combinations of phytochemicals that modulate both NF- κ B and have more potent modulatory effects on these pathways than single compounds. It was reported that Epigallocatechin gallate and curcumin decrease phosphorylation of NF- κ B and reduce the levels of p-I- κ B in MCF-7 and LNca cells (Wang *et al.*, 2014). Combination of resveratrol, phenylisothiocyanate and quercetin synergistically reduced translocation of NF- κ B into nucleus in human pharyngeal carcinoma cells (Masuelli *et al.*, 2014). The examined phytochemicals were used in equimolar quantities in the majority of *in vitro* trial. Arbitrary selection applied only in a few instances (Majumdar *et al.*, 2009).

Regarding the mechanism of action or type of interaction that exists between different phytochemicals, the only effect observed was a synergy among different phytochemicals. But, determining the type of interaction based on Chou-Talalay method proved abortive. Combinations of different phytochemical constituents may be effective especially in chemoprevention (Hackman *et al.*, 2020).

Table 2: Modulatory Potentials of Phytochemicals Combination on NF- κ B Signalling Pathways

Phytochemical Combination	Interaction	Effect on NF- κ B	Reference
Resveratrol + Curcumin	Synergism	Decrease nuclear translocation of NF- κ B	Masuelli <i>et al.</i> (2014); Majumdar <i>et al.</i> (2009)
Phenylisothiocyanate + Sulforaphane	Synergism	Decrease expression of iNOS; COX-2; PGE2	Cheung <i>et al.</i> (2009)
Curcumin + Sulforaphane	Synergism	Decrease expression of iNOS; COX-2; PGE2	Cheung <i>et al.</i> (2009)
Epigallocatechin gallate + Curcumin	Synergism	Decrease phosphorylation NF- κ B; decrease p-I- κ B levels	Wang <i>et al.</i> (2014)
Resveratrol + Phenylisothiocyanate	Synergism	Increase the binding NF- κ Bp65 to DNA, and NF- κ B p65 and COX-2 expressions.	Krajka-Kuźniak <i>et al.</i> (2020); Cykowiak <i>et al.</i> (2021)

CONCLUSION

Numerous phytochemical constituents possessing anti-inflammatory effects inhibit activation of NF- κ B through multiple mechanisms. It's interesting to note that majority of phytochemicals used in cancer chemoprevention have both anti-oxidant and inflammatory capabilities. Additionally, this pathway plays an important role in the signaling network that controls cell proliferation and death. As a result, NF- κ B inhibitors are needed for cancer prevention.

Numerous phytochemicals have been characterized as NF- κ B inhibitors, but comparatively few have been demonstrated to function concurrently in the same experimental model. Numerous phytochemicals show synergistic effects when regulating NF- κ B pathway and their combinations may enhance this impact. Therefore, using phytochemical combinations to modulate NF- κ B and ultimately treat or prevent cancer looks to be a promising strategy.

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