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INSIGHTS INTO THE MECHANISM OF NATURAL TERPENOIDS AS NF-κB INHIBITORS: AN OVERVIEW ON THEIR ANTICANCER POTENTIAL

H. Jain[1], N. Dhingra[2], T. Narsinghani[1], R. Sharma[1]*
[1]*School of Pharmacy, Devi Ahilya University, Takshashila Campus, Indore (Madhya Pradesh) 452001, India*
[2]*School of Life Science, Devi Ahilya University, Takshashila Campus, Indore (Madhya Pradesh) 452001, India*

The transcription factor, nuclear factor kappa B (NF-kB) is one of the principal inducible protein in mammals known to control the gene expression in many critical physiological responses such as oxidative stress, inflammation etc. and has been shown to play an important role in the pathogenesis of cancer. Terpenoids are major constituents present in nutritionally used fruits, vegetables and different spices which possess various pharmacological action including anticancer activity. Various terpenoids, *viz.* monoterpenoids, sesquiterpenoids, diterpenoids, sesterterpenoids, triterpenoids, tetraterpenoids and polyterpenoids inhibit NF-kB signaling pathway through IkB phosphorylation, DNA binding, p65 translocation etc. Keeping in mind these facts, the present review revealed the anti-cancer potential of naturally occurring terpenoids highlighting their mechanism of NF-kB inhibition. This review also focuses on some of the naturally occurring terpenoids belonging to various chemical categories with potential inhibitory effects on NF-kB and their role in the treatment of cancer.

Key Words: **Nuclear factor kappa B (NF-kB), terpenoids, cancer.**

Nuclear factor kappa B (NF-κB) is one of the most important transcription factors in mammals which is responsible for controlling gene expression linked with physiological responses, *viz*. oxidative stress, inflammation etc., and has been shown to play a pivotal role in the mechanism of cancer development. Therefore, the signaling pathway involving this transcriptional factor has opened a new way for pharmacologists, mainly in the field of oncology, where this pathway could prove to be of utmost importance in the treatment of cancer [1].

Naturally occurring plant components from traditional herbs are a significant source of potential therapeutic compounds for cancer treatment. Today several drugs used in clinics are discovered from natural sources. Safety and toxicity of modern drugs are very often questionable. Because of this apprehension, there is tremendous increase in the interest in natural medicines that are considered to be safe. Active constituents such as phenolic, flavonoids, glycosides and alkaloids of plants are well known for their medicinal values [2, 3]. Plant derived natural products provide a source for potent molecules to combat many diseases including cancer. Several promising molecules have been identified as anticancer agents, but there are still hurdles to overcome before they can be accepted as modern drugs [4].

Phenolic compounds and terpenoids are major constituents present in nutritionally used fruits, vegetables and different spices which possess various pharmacological activities including anticancer activity. Reports revealed that terpenoids that contain variable isoprene units have shown potential anticancer activity. Many of terpenoids which are extensively used for medical purpose have already been studied. Previous reports revealed that natural terpenoids were found to have cytotoxicity against variety of tumor cells. This observation strongly suggests that plant derived therapeutic ingredients modulate NF-κB signaling, which has a major role in the pathogenesis of cancer [5–8].

The present review focuses on the anticancer potential of natural terpenoids of varied categories, *viz*. monoterpenoids, sesquiterpenoids, diterpenoids, sesterterpenoids, triterpenoids, tetraterpenoids and polyterpenoids as NF-κB inhibitors. The review also deals with the activation and inhibition mechanism of NF-κB signaling pathways.

STRUCTURE, FUNCTION AND REGULATION OF NF-κB

NF-κB protein comprises of homodimers and heterodimers of different subunits. NF-κB is related through deoxyribonucleic acid (DNA) binding domain called as Rel homology domain. NF-κB proteins belonging to Rel family consists of five members which includes: p65 (RelA), RelB, cRel, p50/p105 (NF-κB 1) and p52/p100 (NF-κB 2). NF-κB 1 and NF-κB 2 are synthesized as precursor p100 and p105. Rel or NF-κB transcription factor binds to 9–10 base pair DNA sites known as kB sites. All vertebrate Rel proteins can form homodimers or heterodimers, except RelB that can form only heterodimers [9–11].

Rel or NF-κB proteins can be divided into two classes based on the sequence C-terminal to RH domain. Members of one class have long C-terminal which contains multiple copies of ankyrin repeats (33 residue protein structure) and has transrepression activity. This class includes NF-κB proteins p105, p100, and *Drosophila* Relish. The second class (the Rel proteins)

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*Correspondence: E-mail: kashishnarsinghani@rediffmail.com
Abbreviations used: DNA – deoxyribonucleic acid; ERK – extracellular signal regulated kinases; JNK – c-Jun N-terminal kinases; IKK – enzyme IκB kinase; LPS – lipopolysaccharide; NEMO – non-enzymatic protein NF-κB essential modulator; NF-κB – nuclear factor kappa B; NIK – NF-κB inducing kinase; TNF-α – tumor necrosis factor α.

includes c-Rel (and its retroviral homologue v-Rel), RelB, RelA (p65). This second class of Rel proteins contains C-terminal transcription activation domains which is required for transport of active NF-κB complex into the nucleus. The subunits p50 and p52 do not contain transcription activation domain [12, 13].

The transcriptional activity of NF-κB is suppressed by interaction with IκB family of inhibitory proteins. Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor (IκB) proteins are family of related proteins containing six or more ankyrin units at their N-terminus. IκB proteins include the following members: IκBα, IκBβ, IκBγ, IκBε, Bcl-3, Cactus, and the precursor proteins p100, p105 which contains five to seven ankyrin repeats [14].

SIGNALING PATHWAY OF NF-κB

Activation of NF-κB. Two signaling pathways lead to the activation of NF-κB, known as the classical (canonical) pathway and the alternative (non-canonical) pathway. The common regulatory step in both of these pathways is activation of an enzyme IκB kinase (IKK) which is present in complex form that consist of catalytic kinase subunits (IKKα/IKKβ) and the regulatory non-enzymatic protein NF-κB essential modulator (NEMO) also known as IKKγ. Activation of NF-κB dimers due to IKK involves phosphorylation which leads to proteasomal degradation of IκB, enabling the active NF-κB transcription factor for cytoplasmic translocation into the nucleus, thereby inducing target gene expression [14].

In the classical or canonical pathway proinflammatory cytokine tumor necrosis factor α (TNFα) stimulates and activates NF-κB, which in turns activates the subunit of IKK complex and leads to phosphorylation and degradation of IκB inhibitors. The canonical pathway activates NF-κB dimers comprising of RelA, c-Rel, RelB and p50. This pathway plays major role in the control of innate immunity and inflammation (Fig. 1) [15, 16].

p100/Re1B complexes are activated by non-canonical pathway and this pathway seems to involve an IKK complex consisting of two IKKα subunits (Fig. 2). Non-canonical pathway works on the mechanism of ligand induced activation which results in the activation of central signaling component of the pathway, i.e., NF-κB-inducing kinase (NIK). NIK phosphorylates and activates a downstream kinase, IκB kinase-α (IKKα) which further phosphorylates p100. Phosphorylation of p100 causes the translocation of NF-κB to the nucleus, which subsequently binds to specific target genes for processing [17].

Inhibition of NF-κB. In inactivated form, NF-κB remains in cytoplasm by family of inhibitors known as IκB proteins. This protein contains ankyrin repeats and masks the nuclear localization signals of NF-κB proteins and makes them inactivated and remains in the cytoplasm.

IKK complex consist of three subunits, IKKα, IKKβ, IKKγ also known as NEMO. IKKα plays an important role in NF-κB regulation, and also in epidermal differentiation independent of NF-κB pathway. IKKβ plays important function in the phosphorylation. NEMO is also known as inhibitor of IKKγ and this activates NF-κB [18, 19].

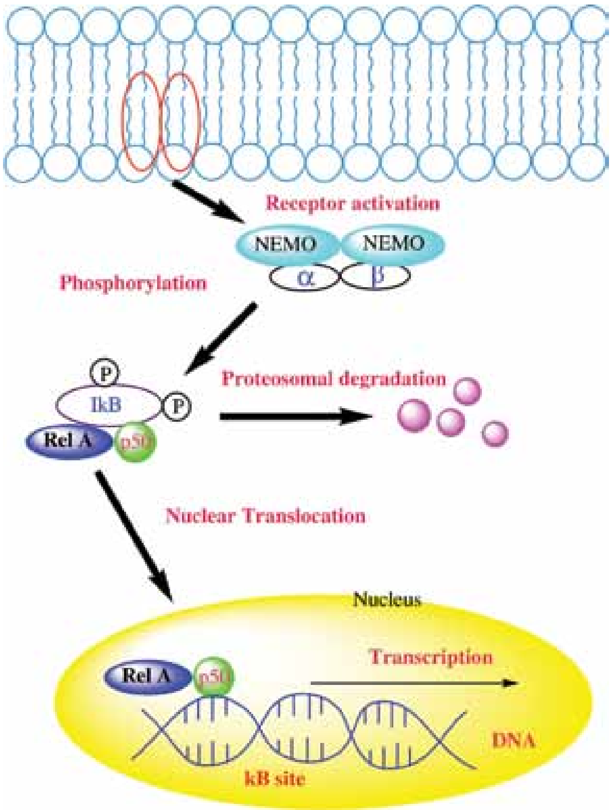


Fig. 1. Canonical pathway of NF-κB signaling

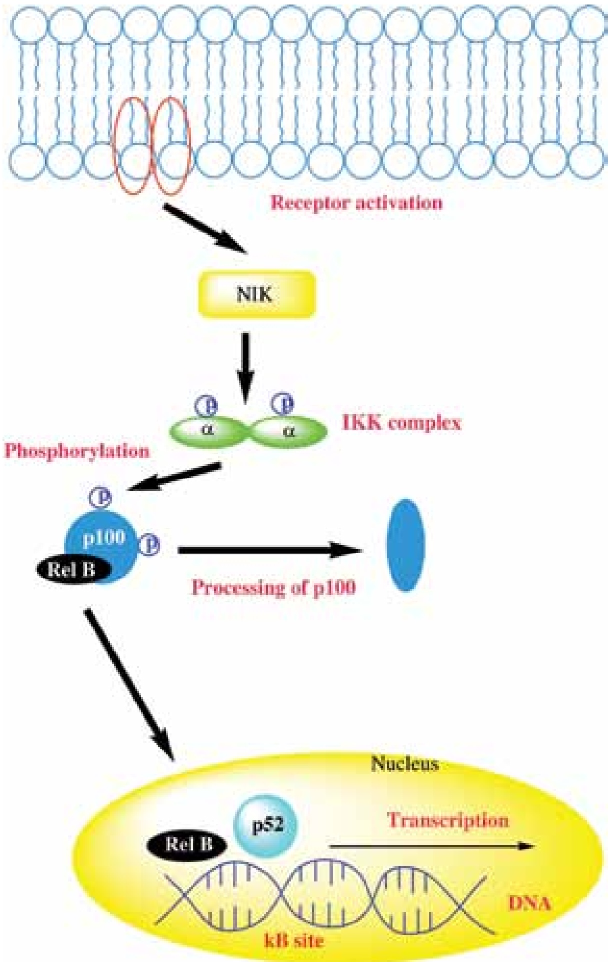


Fig. 2. Non-canonical pathway of NF-κB signaling

MECHANISM OF NF-κB ACTION IN MALIGNANT TRANSFORMATION

It was found that inactive NF-κB dimers are located in cell cytoplasm and are unable to bind with DNA as this inhibition of binding is associated with IκB proteins. This IκB proteins form complex with NF-κB. IκBα or IκBβ proteins of IκB family, selectively bind to the p50/p65 heterodimers and masks their nuclear localization signal, preventing nuclear translocation of NF-κB. Activation of NF-κB can occur by acetylation of p65 (RelA). Acetylated NF-κB is active and resistant from inhibitory action of IκB protein. Activation of NF-κB requires phosphorylation of IκB proteins by external inducers which activate enzyme IKK. This IKK phosphorylates the IκB protein resulting in dissociation of NF-κB from IκB protein and degradation of IκB by proteasome. The enzyme IKK is composed of heterodimers of catalytic IKKα and IKKβ and a regulatory protein NEMO. The NF-κB is then translocated to nucleus to activate target genes. The DNA/NF-κB complex then recruits other proteins that transcribe DNA into mRNA and then translate into proteins which result in change in cell function and may cause cancer (Fig. 3) [1–3, 13, 14].

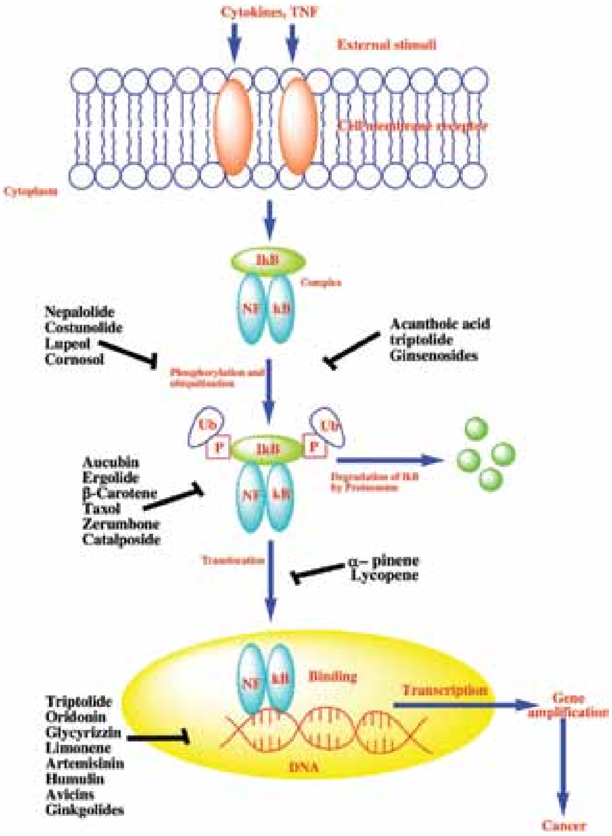


Fig. 3. Inhibition by different terpenoids in NF-κB signaling pathways (Ub — ubiquitination; P — phosphorylation)

TERPENOIDS: CHEMISTRY AND SYNTHESIS

Origination of term terpene came from word turpentine (lat. *Balsamum terebinthinae*). Terpenes are a large and varied class of natural products, produced primarily by a wide variety of plants, insects, microorganisms, and animals. More than 55,000 terpenoid molecules have been discovered so far. Different chemical and biological studies have proved that terpenoids possess variety of chemical, physical and biological activities due to their rich diversity in structural classes with varying degrees of unsaturation, functional groups, and ring closures [20].

Chemistry of terpenoids. Terpenoids are formed by 2-methylbutane residues, less precisely but usually also referred to as isoprene units (C_5H_8) and called as isoprenoids known to build up the carbon skeleton of terpenes. Terpenoids are broadly classified on the basis of the number of isoprene units present in the molecule. Depending on the number of 2-methylbutane (isoprene) subunits one differentiates between hemi- (C_5), mono- (C_{10}), sesqui- (C_{15}), di- (C_{20}), sester- (C_{25}), tri- (C_{30}), tetraterpenes (C_{40}) and polyterpenes $(C_5)_n$ with $n > 8$ [20].

Biosynthesis of terpenoids. Terpenoids are the secondary metabolites obtained naturally; these terpenoids are synthesized from isopentyl pyrophosphate and its isomer dimethylallyl pyrophosphate. Synthesis of terpenoids involves an enzyme known as terpene synthase. During the synthesis, firstly geranyl pyrophosphate, farnesyl pyrophosphate, geranylgeranyl pyrophosphate are synthesized. The prenyl pyrophosphate acts as precursor for different terpenoids such as monoterpenoids, diterpenoids, sesqueterpenoids. In triterpenoid synthesis oxidosqualene cyclase converts oxidosqualene into cyclic triterpene alcohols. Tetraterpenoids are synthesized from phytoene pathway in which phytoene synthases catalyzes the conversion of geranylgeranyl pyrophosphate into phytoene via condensation [21–23].

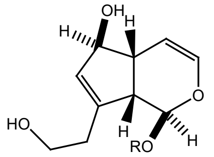
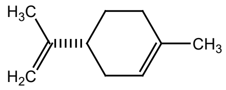
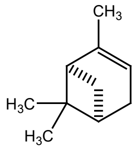
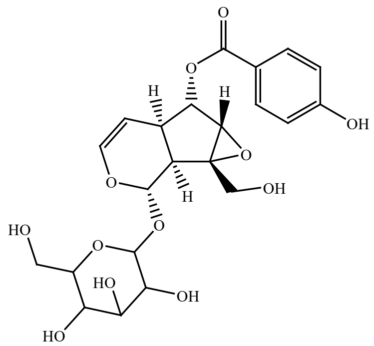
NATURAL TERPENOIDS AS NF-κB SIGNALING INHIBITORS

Terpenoids of natural origin can inhibit the signaling of NF-κB, the major regulator in the pathogenesis of inflammation and cancer. Various pathways were found to be involved in the anticancer activity of terpenoids, including activation of apoptosis. The terpenoids from natural sources are well known inhibitors of NF-κB signaling (Fig. 3). Some therapeutic indications on various terpenoids are described in the subsequent section.

Monoterpenoids. Monoterpenes (Table 1) are composed of isoprene units (two in number) with a general molecular formula of $C_{10}H_{16}$. They exist in acyclic, monocyclic or bicyclic forms. Naturally, monoterpenoids are found as terpene derivatives and modifications resulting from oxidation, methylation and glycosylation and most of them are volatile in nature [21, 22]. Some of the monoterpenoids act as NF-κB signaling inhibitors through IκB degradation, DNA binding or p65 translocation [24–26]. Some of the monoterpenoids are described below.

Aucubin. The glycoside derivatives irinoids are a class of monoterpenoids. The most common irinoid glycoside is aucubin. According to some studies, IκBα degradation is prevented by aucubin. Aucubin also prevents the nuclear translocation of p65 subunit

Table 1. Natural monoterpenoids as inhibitors of NF-κB pathways

Name	Structure	Site of NF-κB inhibition	Therapeutic Indication	References
Aucubin		IκBα degradation	Inflammation, hepatotoxicity, cancer	[24–26]
Limonene		DNA binding	Lymphoma and metastasis of gastric cancer	[27–29]
α-Pinene		P65 translocation	Inflammation	[30]
Catalposide		IκBα degradation	Inflammation	[31, 32]

of NF-κB complex in stimulated mast cells. It has been revealed through different studies that aucubin could be useful agent in prevention of inflammation, cancer, and hepatotoxicity [24–26].

Limonene. Limonenes are cyclic aromatic monoterpenes. The derivatives of limonene are perillic acid, perillyl alcohol and menthol. It has observed that menthol and perillyl alcohol have ability to induce NF-κB dependent apoptosis. In lymphoma cells, these compounds may inhibit NF-κB signaling. Also, in some studies the capability of limonene and perillyl alcohols to inhibit proliferation and metastasis of gastric cancer has been revealed; also it has been shown that dietary monoterpenes, limonene and perillyl alcohols have an inhibitory effect on mammary and pancreatic tumors in animal models [27–29].

α-Pinene. Pinene, a bicyclic monoterpene, is a powerful inhibitor of NF-κB system and is usually obtained from conifer trees. It has been reported that α-pinene inhibit NF-κB/p65 protein translocation in lipopolysaccharide (LPS) stimulated THP-1 cells. The inhibition of NF-κB signaling increased the expression of IκBα protein in the cells pretreated with α-pinene. It could be inferred from the studies that NF-κB signaling is inhibited by several flavoring monoterpenoids which are found in essential oils and spices. These flavoring monoterpenoids can also be used in inflammatory diseases and cancer [30].

Catalposide. Catalposide is an iridoid glycoside that inhibit NF-κB system. Catalposide inhibit degradation of IκBα protein and also translocation of p65 subunit [31].

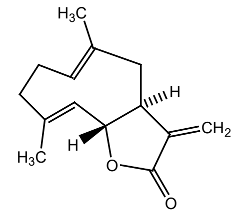
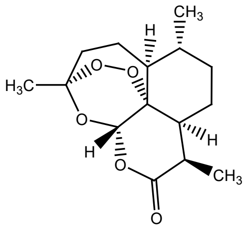
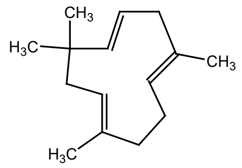
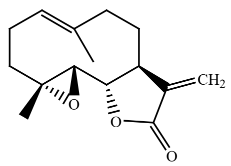
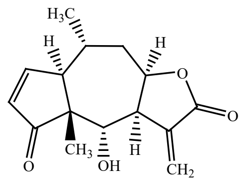
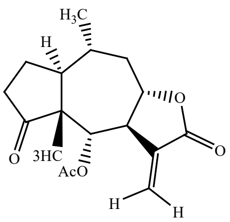
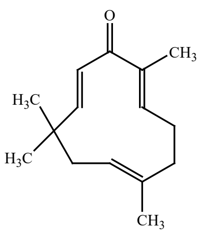
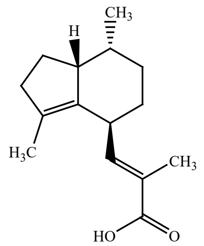
Genipin. Genipin is a monoterpenoid that inhibit degradation of IκBβ protein thus inhibiting NF-κB signaling. Genipin is the metabolite product of geniposide. Genipin inhibits the expression of iNOS and NO production in LPS stimulated cells [24, 32].

Sesquiterpene. Sesquiterpenes (Table 2) are derived from three isoprene units. Hence, they are C_{13} compounds and biosynthesized from farnesyl pyrophosphate. They have wide occurrence in nature and are mainly found in plants and fungi. The carbon skeleton of sesquiterpenes is found in highly diverse forms as compared to other terpenes. Sesquiterpene lactones contain α-methylene, γ-lactone system. Some of them also contain α-β-unsaturated carbonyls and epoxides. A number of sesquiterpene lactones show antitumor properties [32, 33].

Costunolide. Costunolide is a sesquiterpene lactone and a popular folk remedy in India. The most common source of costunolide is the root of medicinal plant *Saussurea costus* and it is also isolated from other medicinal plants such as *Magnolia grandiflora*. The mechanism of inhibition of NF-κB signaling by cosutnolide is the prevention of phosphorylation of IκB proteins. It also inhibits LPS induced basic inflammatory signaling pathway by inhibition of NF-κB activation and by prevention of downstream gene expression. Though some studies have presented it as an agent having anticancer, anti-inflammatory, anti-microbial, anti-ulcer properties but still these effects need more verification [34–37].

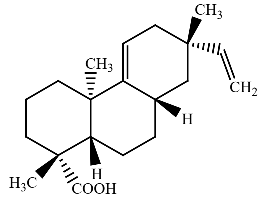
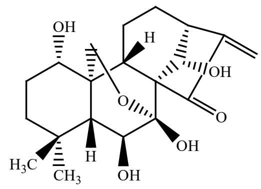
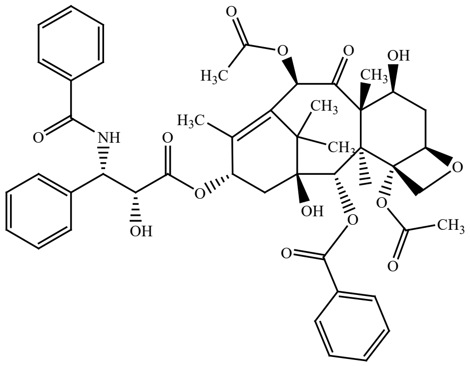
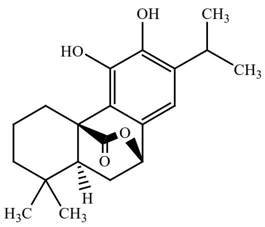
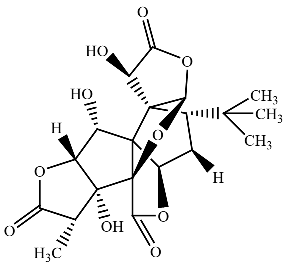
Artemisinin. Artemisinin, a sesquiterpene lactone, is a traditional Chinese medicine and is also called qinghaosu. Artemisinin is obtained from leaves

Table 2. Natural sesquiterpenes as inhibitors of NF-κB pathways

Name	Structure	Site of NF-κB inhibition	Therapeutic Indication	References
Costunolide		IκB phosphorylation	Leukemia, inflammation	[33–35]
Artemisinin		DNA binding	Malaria, cancer	[36–38]
Humulene		DNA binding	Inflammation	[40]
Parthenolide		Alkylation of p65	Arthiritis, lung cancer	[33, 59–61]
Helenalin A		p65 alkylation	Inflammation, infection	[62, 63]
Ergolide		IκB degradation	Inflammation, cancer	[64, 65]
Zerumbone		IκBα degradation	Inflammation, metastasis	[66, 67]
Valerenic acid		Reporter assay	Insomnia	[68]

of *Artemisia annua*. Artemisinin is very popular for the treatment of multidrug resistant malaria. Some studies have revealed its anticancer, immunosuppressive, anti-fungal and anti-angiogenesis properties. Chemically, artemisinin is endoperoxide sesquiterpenoid lactone containing complex polycyclic rings which function through alkylation of protein (a typical mechanism of sesquiterpene lactones). In cells, there

Table 3. Natural diterpenoids as inhibitors of NF-κB pathways

Name	Structure	Site of NF-κB inhibition	Therapeutic Indication	References
Acanthoic acid		IκB phosphorylation	Inflammation	[42, 43]
Oridonin		DNA binding	Leukemia, immunosuppresion	[44–46]
Taxol		Degradation of IKK complex	Inflammation	[47, 48]
Cornosol		IκBα phosphorylation	Inflammation, metastasis	[69, 70]
Ginkgolides		DNA binding	Neuroprotection, inflammation	[59, 71–73]

are many targets for alkylation, even NF-κB transcription system may be one, as artemisinin inhibits activation of NF-κB signaling induced by LPS. In a study of TNFα treated human synoviocytes, it was found that a synthetic derivative of artemisinin, artesunate, inhibited NF-κB signaling activation and proinflammatory cytokines production. Though the exact mechanism of artemisinin is unclear, but still it is an important agent as DNA binding of NF-κB complex which has been reported in some studies [38–40].

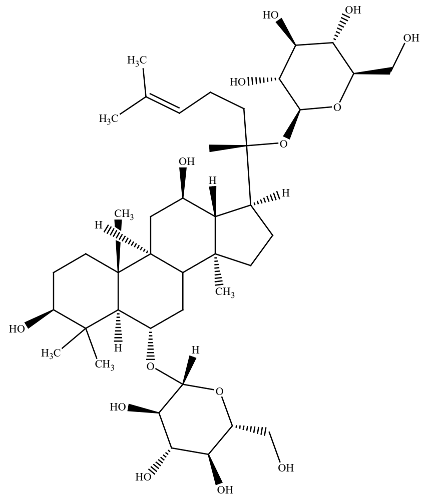
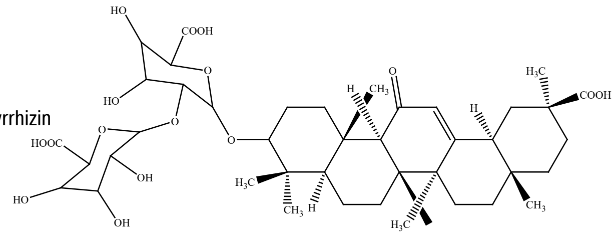
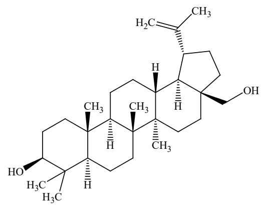
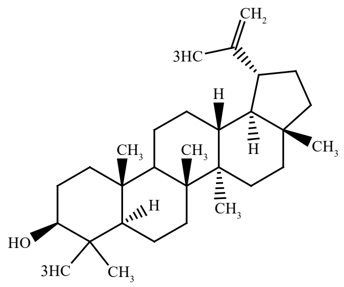
Nepalolide A. A plant of Chinese traditional medicine *Carpesium nepalense* is a source of sesquiterpene lactone nepalolide A. In C_6 glioma cells, nepalolide A is found to suppress signaling induced by LPS and cytokine and inhibit IκB protein phosphorylation [41].

Humulene. A source of monocyclic sesquiterpene humulene is *Humulus lupulus*, which is chemically α-caryophyllene. It was observed that activation of NF-κB system by LPS and the inflammatory response in rat paw edema assay could be effectively reduced by humulene. Even, it is more specific in properties, in comparison to other sesquiterpenes, as there is no modification in activation of extracellular signal regulated kinases (ERK), c-Jun N-terminal kinases (JNK) and p38 by humulene [42].

Parthenolide. Parthenolide is known to be the most powerful NF-κB signaling inhibitor. Parthenolide inhibits nuclear translocation of p65 subunit and also inhibit DNA binding of NF-κB complex. It is also used in the treatment of arthritis and other inflammatory diseases [36, 43–45].

Helenalin A. Helenalin A is a sesquiterpene that inhibits NF-κB signaling. Helenalin alkylates p65 subunit thus inhibiting the DNA binding of NF-κB complex.

Table 4. Natural triterpenoids as inhibitors of NF-κB pathways

Name	Structure	Site of NF-κB inhibition	Therapeutic Indication	References
Ginsenosides		IκBα phosphorylation, and degradation	Neurodegenerative diseases, cancer, inflammation	[50–53]
Glycyrrhizin		DNA binding	Inflammation	[54–56]
Betulin		IKKα inhibition	Arthritis, cancer metastasis	[74, 75]
Lupeol		IκBα phosphorylation	Metastasis, skin cancer	[76–78]

In addition to its anti-inflammatory properties, this terpene is also potent against many infections [46, 47].

Ergolide. Ergolide comes under the category of sesquiterpenoid isolated from *Innula britannica*. Ergolide possesses anti-inflammatory and anticancer properties exerted via apoptosis induction. It inhibits translocation of NF-κB complex and degradation of IκB proteins [48, 49].

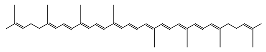
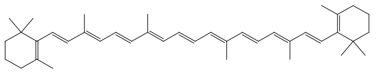
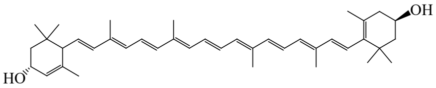
Zerumbone. It is a cyclic sesquiterpene isolated from *Zingiber zerumbet*. It induces phosphorylation of IκB proteins and thus blocks the function of IKK complex as a result of phosphorylation and degradation of IκB proteins. It leads to reduction of nuclear translocation of NF-κB complex [50, 51].

Valerenic acid. Valerenic acid is an effective sesquiterpene used against cancer and inflammation. Valerenic acid is obtained from *Valeriana officinalis*. It is a powerful inhibitor of NF-κB activation and cytokine activation. It is also used in sleep disorders [52].

Diterpenoids. Diterpenoids (Table 3) are C_{20} compounds, derived from four isoprene units and generally non-volatile in nature. They are biosynthesized from geranyl pyrophosphate. Diterpenoids may be acyclic, but generally they appear as monocyclic, bicyclic or tetracyclic compounds. Usually, diterpenoids show antitumor properties by indirectly inhibiting NF-κB signaling [22]. Some of the compounds with antitumor properties and of therapeutic importance are as follows:

Acanthoic acid. The mechanism of action of acanthoic acid and its analogues is reduction in activation of LPS induced IκBα phosphorylation along with inhibition of nuclear DNA binding of NF-κB system. Its property to prevent cytokine synthesis and pro-inflammatory response was also revealed. Some studies reported the

Table 5. Natural carotenoid tetraterpenoids as inhibitors of NF-κB pathways

Name	Structure	Site of NF-κB inhibition	Therapeutic Indication	References
Lycopene		NF-kB translocation	Inflammation	[80–83]
β-Carotene		IκBα degradation, DNA binding	Cancer, inflammation	[84, 85]
Lutein		IκBα degradation	Cataract, uveitis	[86, 87]

ability of acanthoic acid to prevent fibrosis and nodular formation [53, 54].

Oridonin. Oridonin is a kaurane diterpenoid which is obtained from *Rabsodia rubescens*. Oridonin affects the cancerous cells proliferation by inducing phagocytosis of apoptotic cells by macrophages and trigger apoptotic cell death as well. *In vitro* and *in vivo* studies have revealed immunosuppressive properties of oridonin. Unlike other diterpenoids, which suppress TNFα-induced IκBα protein degradation and nuclear translocation of NF-κB complex, oridonin inhibits NF-κB signaling by reversibly inhibiting DNA binding of NF-κB complex [55–57].

Taxol. Taxus brevifolia, a pacific yew tree, is a source of taxol which is chemically a complex polyoxygenated diterpenoid. Paclitaxel (generic name of taxol) is a popular and powerful drug used in cancer chemotherapy. The anticancer property of taxol is due to its binding to the β-tubulin protein present in microtubules. This results in suppression of microtubular dynamics and it also raised acetylation level of α-tubulin protein. This increase in stability of microtubules inhibits mitosis and thus results in cell death of proliferating cells. Some studies reveal the capacity of taxol in activation of NF-κB signaling via activation of TLR4 receptor (a receptor responsible for LPS induced NF-κB signaling) by taxol. The binding of taxol to CD18 protein also activates TLR4 system [58, 59].

Cornosol. Cornosol is a diterpenoid, obtained from *Rosmarinus officinalis* that inhibits IκBα phosphorylation and iNOS and NO production. Cornosol inhibits NF-κB signaling via its antioxidant capacity [60, 61].

Ginkgolide is biological active diterpenoid extracted from *Ginkgo biloba*. Ginkgolides inhibits the DNA binding of NF-κB complex and iNOS activation, and is therapeutically efficient in variety of inflammatory disorders [59, 62–65, 71–73].

Triterpenoids. Triterpenoids (Table 4) are formed by six isoprene units with 30 carbon atoms, and are structurally similar as steroidal compounds. Triterpenoids are present either in free state or as ester or glycosides and are classified as tetracyclic and pentacyclic triterpenoids. Various triterpenoids exhibiting NF-κB inhibiting properties are listed below [66].

Ginsenosides. Ginsenosides are steroids chemically similar to triterpene saponins. These compounds are obtained from roots of *Panax ginseng* (Korean ginseng), *Panax notoginseng* (Chinese ginseng), *Panax quinquefolium* (American ginseng) and other species of perennial plant Panax. Ginsenosides are widely used therapeutically as anti-inflammatory and anticancer agents and are also found useful in treatment of neurodegenerative disorders. Ginsenosides have many targets in cells and some studies have revealed their anti-cancer and anti-inflammatory activities via regulating signaling pathways. Inhibition of NF-κB signaling may be direct or indirect, and it is due to suppression of IκBα protein degradation as well as IKKα kinase activation. Some studies also showed the effect of ginsenosides in the DNA binding of NF-κB system. Ginsenosides also inhibit JNK pathway and AP-1 binding activity which shows that it can affect the upstream components of NF-κB signaling [67–70].

Glycyrrhizin. Glycyrrhizin is chemically a triterpenoid saponin glycoside and is widely used in Chinese and Egyptian medicine for treatment of cardiovascular, gastrointestinal and respiratory disorders. Glycyrrhizin is an active chemical constituent of licorice obtained from roots and stolons of *Glycyrrhiza glabra*. Glycyrrhizin is chemically composed of glycyrrhizic acid. Glycyrrhizic acid is widely studied and is shown to be capable to inhibit NF-κB signaling. Studies have also revealed the ability of glycyrrhizic acid to inhibit glutamate induced excitotoxicity in primary neurons and calcium mediated activation of NF-κB system [71–73].

Betulin is pentacyclic triterpenoid extracted from the bark of *Betula alba*. Derivatives of betulin are more therapeutically active against HIV and inflammation and act through inhibition of IKKα and NF-κB dependent gene expression [74, 75].

Lupeol is very common terpenoid found in many fruits and vegetables. The structure of lupeol is pentacyclic. Lupeol exhibits anticancer property by inhibiting NF-κB signaling including phosphorylation of IκB proteins [76–78].

Avicins are the plant stress metabolites obtained from the *Acacia victoriae*. Avicins inhibit DNA binding of NF-κB complex. Avicins do not affect degradation of IκB proteins [79].

Carotenoid tetraterpenoids. Carotenoid terpenoids (Table 5) are the pigmented tetrapenes containing eight isoprene units. These compounds are found to have antioxidative activity with therapeutic effects in cardiovascular disorders and osteoporosis; they also exhibit anticancer activity by regulating NF-κB signaling pathway.

Lycopene is an acyclic tetraterpenoid that is most commonly found in human body. Major dietary source include tomato and other fruits. Lycopene has powerful antioxidant activity. Lycopene can inhibit NF-κB signaling, nuclear translocation of NF-κB complex as well as its DNA binding [80–83].

β-Carotene. These compounds are the cyclic carotenes. β-Carotene is stored in liver and converted into vitamin A. β-Carotene suppresses LPS induced NF-κB signaling. It also degrades IκB protein and inhibits nuclear translocation of p65 subunit and DNA binding of NF-κB complex. β-Carotene by virtue of its proxidant characteristic inhibits cancer growth [84, 85].

Lutein is a cyclic tetraterpenoid present in fruits, vegetables and egg yolk. It inhibits nuclear localization of p65 subunits and IκBα protein degradation. It also inhibits activation of NF-κB signaling. Lutein pigment can protect from oxidative stress and cataract [86, 87].

CONCLUSION

Chemically diverse class of terpenoids represented with monoterpenoids, sesquiterpenoids, diterpenoids, sesterterpenoids, triterpenoids, tetraterpenoids and polyterpenoids, is capable to inhibit signaling *via* NF-κB pathway through different mechanisms, in particular, through IκB phosphorylation, DNA binding, p65 translocation etc. This provides promising possibilities for the use of terpenoids as NF-κB inhibitors from natural sources, for treatment of various human pathologies including cancer.

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