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Review

Terpenoids: natural inhibitors of NF-κB signaling with anti-inflammatory and anticancer potential

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Abstract. Traditional medicine has been a fertile source for revealing novel lead molecules for modern drug discovery. In plants, terpenoids represent a chemical defense against environmental stress and provide a repair mechanism for wounds and injuries. Interestingly, effective ingredients in several plant-derived medicinal extracts are also terpenoid compounds of monoterpenoid, sesquiterpenoid, diterpenoid, triterpenoid and carotenoid groups. Inflammatory diseases and cancer are typical therapeutic indications of traditional medicines. Thus folk medicine supports the studies which have demonstrated that plant-derived terpenoid ingredients can suppress nuclear factor-κB (NF-κB) signaling, the major regulator in the pathogenesis of inflammatory diseases and cancer. We review the extensive literature on the different types of terpenoid molecules, totalling 43, which have been verified both inhibiting the NF-κB signaling and suppressing the process of inflammation and cancer. It seems that during evolution, plants have established a terpene-based host defense which also represents a cornucopia of effective therapeutic compounds for common human diseases.

Keywords. Inflammation, innate immunity, phytochemistry, review, signal transduction, traditional medicine.

Introduction

Traditional medicine has been a fertile source for revealing novel lead molecules which are then subjected to investigation using the techniques of the modern drug discovery [1]. There are several success stories of modern drugs originating from medicinal plant remedies, such as aspirin and digoxin. Modern isolation and screening technologies have enhanced the search for new lead molecules and increased interest in folk medicinal plant extracts in drug companies [1]. Simultaneously, the enthusiasm for medicinal herbs and natural products has increased among the general public [2, 3]. There may be some safety concerns with traditional remedies, although they have been utilized in practise for hundreds of years. Only a few clinical studies have been performed

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to verify the potency of traditional remedies against common diseases. However, plant-derived natural products provide an interesting source for isolating and screening potent molecules to combat inflammatory diseases and cancer [1]. Several promising molecules have been recently identified, but there are still hurdles to overcome before they become accepted as modern drugs [3].

Phenolic compounds and terpenoids are major constituents present in nutritionally used fruits, vegetables and different spices [4]. Interestingly, the effective ingredients in several plant-derived medicinal extracts are also flavonoids and terpenoids (see below). These compounds have common properties, such as antioxidative activities, but they also possess a variety of specific properties since they undergo distinct interactions with several regulatory proteins. Generally, typical therapeutic indications of traditional medicinal products have been various inflammatory diseases and cancers. This observation strongly suggests that plant-derived therapeutic ingredients modulate NF-κB signaling, which has a major role in the pathogenesis of inflammatory diseases and cancer. Here we will focus on terpenoids and collate the vast literature to emphasize that during evolution plants have established terpene-based host armaments to protect themselves, but these chemicals may provide effective therapeutic compounds also for defence against pathogens and disease in humans. This principle has been tested over the millennia but still needs to be translated to molecular terms and modern drugs.

Chemistry and biology of terpenoids in plants

Terpenoids are formed from five-carbon isoprene units (C_5H_8) and also called isoprenoids. Terpenoids are plant secondary metabolites along with alkaloids and flavonoids. Terpenoids are evolutionarily the oldest of this group, and today they represent a highly diversified group of small molecules synthesized by plants [5–7]. Bouvier et al. [5] have extensively reviewed the isoprenoid synthesis pathways and the enzymes involved both in the synthesis of skeleton structures and their cyclization. There are more than 20,000 different natural terpene metabolites which are known to be synthesized from isopentenyl pyrophosphate (IPP) and its isomer dimethylallyl pyrophosphate (DMAPP) (Fig. 1). Terpene synthases are a large family of enzymes which are involved in the synthesis of diverse and complex terpenoid molecules [5–7]. Initially, three prenyltransferases synthesize linear prenyl pyrophosphates: GPP (geranyl pyrophosphate), FPP (farnesyl pyrophosphate) and GGPP (geranylgeranyl pyrophosphates) (Fig. 1). These prenyl pyrophosphates are the precursors for different terpene synthases involved in the catalysis of monoterpenoids, sesquiterpenoids and diterpenoids. The synthesis of triterpenoids requires oxidosqualene cyclases to convert oxidosqualene into cyclic triterpene alcohols (Fig. 1). One family of oxidosqualene cyclases can produce single products, such as lupeol cyclases, but there are also multifunctional oxidosqualene cyclases which use dammarenyl cation intermediates [5]. Phytoene synthases catalyze the conversion of GGPP into phytoene via condensation with a GGPP acceptor [5]. The tetraterpenoid carotenoids are synthesized via this phytoene pathway (Fig. 1).

The amazing variety of terpenoids in plants is due to the expansion of the terpene synthase superfamily during evolution [6, 7]. Over 100 terpene synthases are currently recognized, all of which seem to have originated from an ancestral diterpene synthase. Terpenoid synthases are present in all plant organs and are expressed either constitutively or via their induction during biotic stress [7]. The circadian rhythm also regulates the expression of terpene synthases, especially those producing volatile mono- and sesquiterpenes. Terpenoids undertake a multitude of ecological and physiological functions. Their major function in plants is the chemical defence against insects and environmental stress, but they are also involved in the repair of wounds and injuries [5, 6, 8]. In particular, the trees of the long-lived conifer lineage have established effective terpenoid-based chemical defenses, either as constitutive or inducible systems. The resin-based defenses in conifers are well known and have been reviewed in detail [6, 8]. The inducible terpene-based defenses of conifers involve the induction of different terpene synthases to produce many terpenoid compounds which provide flexibility to withstand a pathogen attack or to repair damage and wounding. Oleoresin is a complex mixture of monoterpenes, sesquiterpenes and diterpenoid acids which can be induced by insect attack or by traumatic wounding. The plant-derived resins and terpenoids present in different plant organs have a variety of uses in traditional medicine. In this review we will focus on the capacity of terpenoids to inhibit nuclear factor-κB (NF-κB) signaling and hence to represent sources of therapeutic drugs for inflammatory diseases and cancer.

NF-κB signaling: master regulator of innate immunity and inflammation-associated diseases

Sen and Baltimore [9] discovered the NF-κB transcription factors in 1986 when they used the EMSA technique to study protein complexes which were able

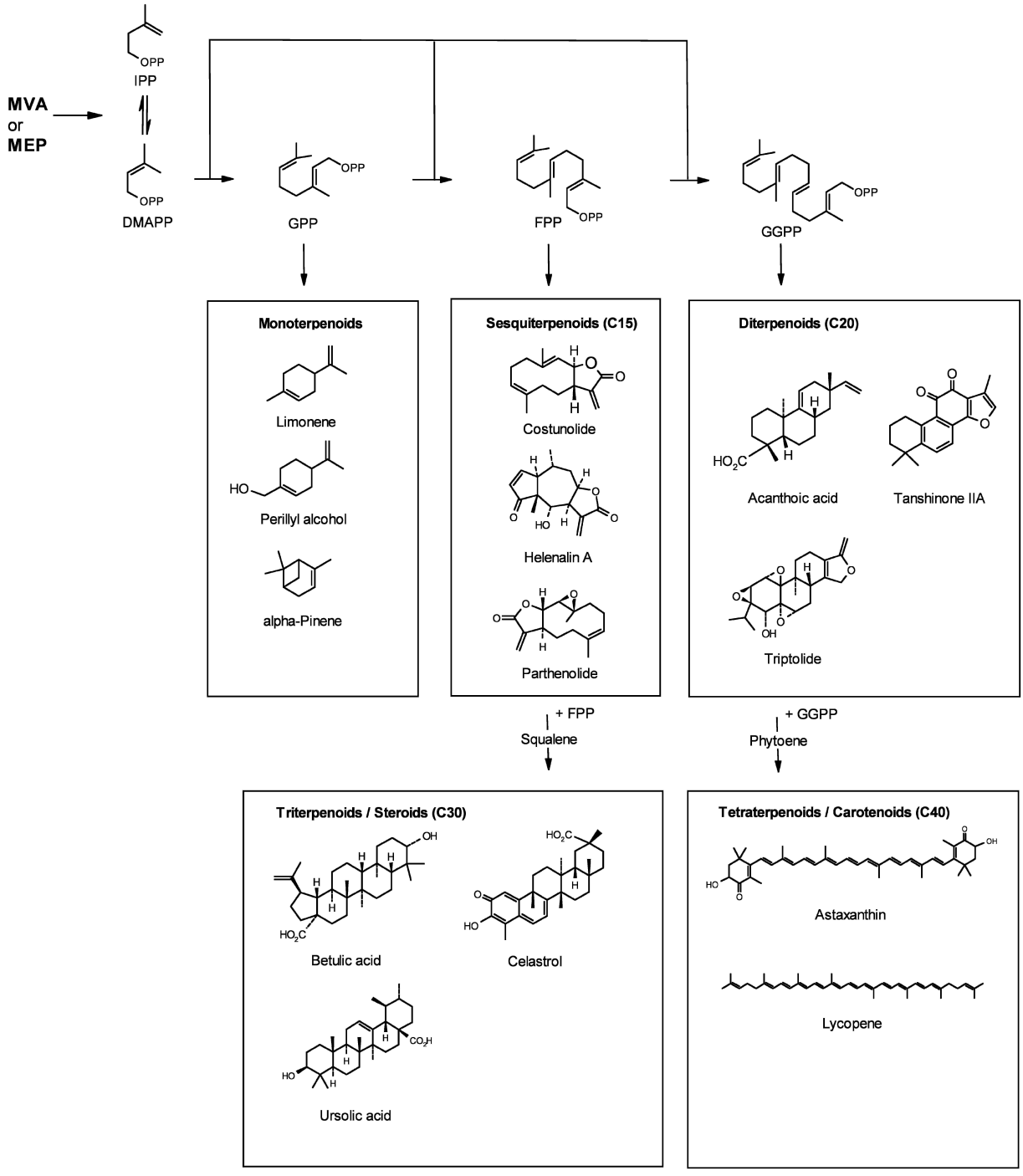

Figure 1. There are two alternative metabolic pathways of isoprenoid biosynthesis (MVA and MEP) leading to the formation of IPP and DMAPP. They are the precursors of isoprene, monoterpenoids (10-carbon), sesquiterpenoids (15-carbon), diterpenoids (20-carbon), triterpenoids (30-carbon) and carotenoids (40-carbon). Synthesis of all higher terpenoids proceeds via formation of GPP, FPP, and GGPP. MVA (mevalonate pathway, also known as HMG-CoA reductase pathway), MEP (non-mevalonate pathway, also known as MEP/DOXP pathway), -OPP (pyrophosphate), IPP (isopentenyl pyrophosphate), DMAPP (dimethylallyl pyrophosphate), GPP (geranyl pyrophosphate), FPP (farnesyl pyrophosphate) and GGPP (geranylgeranyl pyrophosphates).

to bind to the enhancer sequences of the immunoglobulin heavy chain and the kappa light chain genes. Over the next 20 years, the NF-κB signaling system has turned out to be a pleiotrophic mediator of inducible and tissue-specific gene control, also in non-immune cells. Its structure-function relationships and interactions with other signaling networks, as well as with inducers, inhibitors and target genes have been

extensively reviewed over these years [10–13]. Briefly, the NF-κB/REL complexes contain either homo- or heterodimers of the protein components of NF-κB and Rel families. The Rel family contains RelA/p65, c-Rel and RelB proteins, whereas the NF-κB family consists of p50 (p105) and p52 (p100) proteins. Generally, NF-κB complexes are trapped in the cytoplasm by binding to the inhibitory IκB proteins (IκBα, IκBß, IκBγ, IκBε and Bcl3). Activating signals, either external or internal in origin, phosphorylate the IκB proteins, which are subsequently ubiquitinated and degraded in the proteasomes. The release of IκB protein from the RHD domain of Rel protein reveals the NLS domain, and the NF-κB complex is translocated into the nucleus where it activates the transcription of a number of genes, especially inflammatory genes [11, 12].

There are numerous variations not only in the signaling pathways upstream of the activation of the NF-κB complex [10], but also in the modifications of the transactivation efficiency of NF-κB complexes at the transcription level. The major protein kinases phosphorylating IκB proteins are the IKKs (IκB kinases α and β), which are regulated by several interacting proteins linking the IKK complex to the canonical NF-κB signaling pathway [12, 13]. NEMO, an essential NF-κB modulator and the regulatory subunit of the IKK complex, regulates the activation of the IKK complex, especially in immune responses and genotoxic stress [12, 13]. NIK, an NF-κB-inducing kinase, activates another, non-canonical NF-κB pathway which mediates signals from CD40, lymphotoxin and BAFF/BLys receptors [10–12]. This pathway is IKK-dependent but IκB-independent and it regulates the NF-κB activation via the p100 (NF-κBp52) subunit processing. The NF-kB system and interacting signaling pathways are described in detail with diagrams in [10, 12].

The NF-κB system is the master regulator of immune responses and an ancient signaling pathway in the host defense of multicellular organisms [11]. Most cells, either immune or non-immune cells, contain a variety of pattern recognition receptors (PRRs) which identify different pathogen-associated molecular patterns, so-called PAMPs. Toll-like receptors (TLRs), NOD-like receptors (NLRs) and RIG-like receptors (RLRs) are the most general PRRs [e.g. 14]. All of these pattern recognition receptors are linked to the NF-κB signaling network, either directly or via cytokine signaling. TLRs are linked to the NF-κB system via different adapter proteins and protein kinases [14]. However, the IKKα/IKKβ kinase complex is the nodal point in NF-κB-mediated inflammatory signaling. Several cytokine receptors are also linked to NF-κB signaling in order to enhance and specify the inflammatory responses.

The NF-κB system is a cytoplasmic sensor responding not only to immune assaults but also to a variety of external and internal danger signals, such as oxidative stress, hypoxia and genotoxic stress [11, 12]. There are several kinases upstream from the IKKs, such as ATM, TAK1, MEKK3, NAK but also PI-3K/AKT which links several growth factor receptors to the activation of IKKα [10, 12, 13]. IKKα and IKKβ are also involved in different upstream signaling pathways and they have specific downstream targets. In general, IKKβ mediates the innate immunity responses, as well as cancer signals, whereas IKKα is involved in the transduction of growth and developmental signals [12, 13]. The inflammatory response genes are the most common target genes participating in the activation of NF-κB signaling [11]. The NF-κB signaling also has a major role in anti-apoptotic signaling and the development of cellular resistance against apoptosis [15]. Inhibition of apoptosis is mediated by the increased expression of IAPs (inhibitor proteins of apoptosis), such as c-FLIP, Bcl-xL, c-IAP1, c-IAP2 and XIAP. The resistance against apoptosis can expose dividing cells to tumorigenesis. Thus, NF-κB signaling represents the link between inflammation and cancer development and progression [11].

NF-κB factors are essential for the development and function of T and B lymphocytes, and the dysregulation of these cells causes many diseases [16]. Kumar et al. [16] have listed the genes the expression of which are regulated by NF-κB, as well as the major diseases associated with functional changes in the NF-κB system. Most of those diseases are chronic and aging-associated degenerative diseases, such as atherosclerosis, osteoporosis, rheumatoid arthritis and neuropathological diseases. It is known that inflammation plays an important role in the pathogenesis of these degenerative diseases. Interestingly, many anti-inflammatory drugs, such as corticosteroids, aspirin and some other non-steroidal anti-inflammatory drugs, can inhibit NF-κB activity and suppress the degeneration process. Currently, the IKK and NF-κB complexes are considered as promising targets for drug discovery programs [17]. Selective inhibition of IKKβ, the mediator of both innate immunity responses and cancer, has been a popular strategy to suppress NF-κB signaling. Several potent lead molecules have been discovered and are currently undergoing clinical trials [17].

Table 1. Inhibition of NF-κB signaling and some examples of therapeutic indications for monoterpenoids.

Compound	NF-κB inhibition	Therapeutic indications
Aucubin	IκBα degradation [21]	Inflammation [21], hepatotoxicity [22], cancer [23]
Catalposide	IκBα degradation [24]	Intestinal inflammation [24]
Genipin	IκBß degradation [25]	Cancer cell growth [23], inflammation [25]
Limonene	DNA binding [26]	Lymphoma [26], growth and metastasis of gastric cancer [27]
Perillyl alcohol	DNA binding [26]	Lymphoma [26], mammary and pancreatic tumors [28]
α-Pinene	p65 translocation [29]	Inflammation [29]

Inhibition of NF-κB signaling and some therapeutic indications of distinct terpenoids

Medicinal plant extracts have been used for centuries to alleviate inflammatory diseases and cancer. A plethora of terpenes have been characterized as being present in traditional, plant-derived natural remedies [4]. Several powerful inhibitors of NF-κB signaling are natural terpenes, e.g. helenalin A and parthenolide sesquiterpene lactones (see below). Moreover, several herbal remedies are claimed to be potent drugs against several inflammatory diseases and cancer, which are NF-κB-associated diseases (see above). Bremner and Heinrich [18] and Nam [19] have reviewed the effects of natural products, such as polyphenols and terpenes, on the function of the NF-κB system. Most of the terpenes isolated from natural sources, e.g. from plants and microbes, are terpene derivatives, i.e. terpenoids. Sesquiterpenoids are well-known inhibitors of NF-κB signaling, but the diterpenoid and triterpenoid classes also contain several potent inhibitors of NF-κB signaling (see Tables 1–5). The different terpenoids based upon the number of isoprene units incorporated into the basic molecular skeleton are classified below. Due to the reference limitation, only some therapeutic indications on each terpenoid have been listed.

Monoterpenoids (Table 1)

There have been more than 1000 monoterpenoids identified in natural products. Monoterpenes are formed from two isoprene units, the general molecular formula is $C_{10}H_{16}$, and they can appear as acyclic, monocyclic or bicyclic forms [5]. In nature, most monoterpenes occur as terpene derivatives, which can be modified by oxidation, methylation and glycosylation. Many monoterpenes are also volatile in nature. Conifer resins are rich natural sources of terpenoids, as well as monoterpenoids [6]. The literature describes very few studies of the effects of monoterpenoids on the function of the NF-κB system, although several pharmaceutical studies with monoterpenoids indicate that they may have some therapeutic potential. Table 1 shows the monoterpenoids which have been verified to be inhibitors of NF-κB signaling and some of their therapeutic indications.

Aucubin

Iridoids are a class of monoterpenoids which occur as glycoside derivatives in plants. Dinda et al. [20] have extensively reviewed naturally occurring iridoids, both their molecular structures and some of their properties. Aucubin is a common iridoid glycoside in several oriental medicinal plants. Jeong et al. [21] have observed that aucubin inhibits the degradation of IκBα protein and prevents the nuclear translocation of the p65 subunit of NF-κB complex in stimulated mast cells. Several other studies have also shown that aucubin can act as an anti-inflammatory compound and be protective against hepatotoxicity [21, 22]. Aucubin has also antitumoral activity [23].

Catalposide

Catalposide is another iridoid glycoside which inhibits the activation of NF-κB system in inflammatory models [24]. The degradation of IκBα protein was inhibited as well as the translocation of the p65 subunit to the nuclei. The anti-inflammatory target of catalposide may be upstream to the cytokine signaling since catalposide also attenuated TNF-α -induced p38 and ERK phosphorylation [24].

Genipin

Genipin is the metabolically hydrolyzed aglycone product of geniposide which is classified as belonging to the iridoid glycoside monoterpenes [20]. Geniposide is the major ingredient in the fruits of *Gardenia jasminoides* Ellis, which has been used in traditional medicine to treat inflammation, headache, fever and hepatic disorders. Recent studies have shown that genipin is an effective anti-inflammatory compound in RAW264.7 macrophages [25]. Molecular studies have indicated that genipin could inhibit the expression of iNOS and NO production in LPS(lipopolysaccharide)-stimulated RAW264.7 cells [25]. Simultaneously, genipin blocked the degradation of IκBβ protein, which is evidence of the inhibition of NF-κB signaling.

Table 2. Inhibition of NF-κB signaling and some examples of therapeutic indications for sesquiterpenoid compounds.

Compound	NF-κB inhibition	Therapeutic indications
Artemisinin	DNA binding [44]	Malaria and cancer [43], arthritis [45]
Artemisolide	IKKβ inhibition on Cys-179 [47]	Inflammation [46, 47]
Costunolide	IκB phosphorylation [42]	Angiogenesis, leukemia and ulcers [41], inflammation [42]
Elephantopins	IKK inhibition [50]	Inflammation, metastasis and osteoclastogenesis [see 50]
Ergolide	IκB degradation [48]	Inflammation [48], cancer [49]
Helenalin A	p65 alkylation [38]	Inflammation [37, 39], infections [40]
Huperzine A	IκBα phosphorylation [57]	Alzheimer's disease [56], inflammation [57]
Humulene	DNA binding [58]	Inflammation in rat paws [58]
Parthenolide	Alkylation of Cys-38 in p65 [34, 36]	Arthritis [2], cystic fibrosis [32], lung cancer [33]
Nepalolide	IκB phosphorylation [51]	Inflammation [51]
Valerenic acid	Reporter assay [59]	Insomnia [2], excitotoxicity [59]
Zerumbone	IκB degradation [52]	Inflammation [53], metastasis [52]

Furthermore, geniposide has been verified to be an effective antitumor compound [23].

Limonene

Limonene and its derivatives perillyl alcohol, perillic acid and menthol are cyclic aromatic monoterpenes. Berchtold et al. [26] observed that limonene, menthol and especially perillyl alcohol inhibit NF-κB signaling in lymphoma cells and induce NF-κB-dependent apoptosis. Several studies have shown that limonene and perillyl alcohols can inhibit the proliferation and metastasis of gastric cancer [27]. The dietary monoterpenes, limonene and perillyl alcohols have been claimed to have an inhibitory effect on mammary and pancreatic tumors in animal models [28]. Numerous other aromatic monoterpenoids and their derivatives present in spices, fruits, vegetables and plants are included in traditional medicine extracts, and many of them, such as linalool, have verified therapeutic effects in inflammatory diseases and cancer. But their role in NF-κB inhibition has not been scientifically proven.

α-Pinene

Conifer trees are a rich source of pinene, a bicyclic monoterpene, which is a powerful inhibitor of the NF-κB system. Zhou et al. [29] observed that α-pinene exposure clearly inhibited the translocation of NF-κB/p65 protein into nuclei in LPS-stimulated THP-1 cells. The pre-treatment of cells with α-pinene increased the expression of IκBα protein, which may have been attributable to the inhibition of LPS-induced NF-κB signaling. In conclusion, it seems that several flavouring monoterpenoids in essential oils and spices can inhibit NF-κB signaling and affect inflammatory diseases and cancer.

Sesquiterpenoids (Table 2)

Sesquiterpenes consist of three isoprene units generally forming mono-, bi- or tricyclic compounds (Fig. 1). Several traditional natural remedies contain compounds which are modified and structurally rearranged sesquiterpene structures, called sesquiterpenoids. Fraga [30] has reviewed the structural properties of the sesquiterpenoids isolated from nature products. More than 7000 sesquiterpene structures have been characterized, but sesquiterpene lactones are the ones most frequently found in natural remedies [31]. Robles et al. [31] have reviewed the recent pharmacological and ethnobotanical studies on some medicinal sesquiterpene lactones. Sesquiterpene lactones are a diverse group of plant compounds which have both medicinal activities but also toxic effects, such as allergic and neurotoxic effects [31]. Their medicinal properties include the prevention of inflammatory diseases and cancer. Their molecular mechanisms are far less specified, but recent studies indicate that inhibition of NF-κB signaling would represent one potential molecular mechanism.

Parthenolide

Parthenolide is the most widely studied of the sesquiterpene lactones (Fig. 1) and is known as a powerful natural inhibitor of NF-κB signaling. Parthenolide is an abundant ingredient in the medicinal herb feverfew (*Tanacetum parthenium*). The herb is a popular remedy for migraine and some inflammatory diseases, such as arthritis [2]. Several cell culture experiments have shown that the anti-inflammatory response by parthenolide is due to inhibition of NF-κB signaling [e.g. 32]. Parthenolide also seems to have anticancer and antimetastatic [33] activities, apparently mediated via NF-κB signaling in certain cancer models. Sesquiterpene lactones have been intensively

studied to understand the molecular mechanism of their inhibition of NF-B signaling [34–36]. Studies have revealed that parthenolide alkylates cysteine-38 in the p65 subunit of NF-κB and inhibits DNA binding of NF-κB complex [34, 36]. The inhibition mechanisms of NF-κB signaling caused by terpenoids will be discussed in more detail in the next section.

Helenalin A

Helenalin A is a sesquiterpene lactone (Fig. 1) which has been prepared from *Arnica flos*, mountain flowers [37]. Arnica-based herbal tincture has been used locally to treat haematoma, rheumatic diseases and skin inflammation. Lyss et al. [38] have shown that the anti-inflammatory potency of helenalin A is due to the inhibition of NF-κB signaling. They observed that helenalin A can alkylate the p65 subunit of NF-κB complex and hence inhibit the DNA binding of that complex and the transcription of NF-κB-dependent genes [38]. However, the alkylation properties of helenalin A are indiscriminate, and it can also target other proteins, such as 5-lipoxygenase and leukotriene C4 synthase [39] which affect inflammatory responses, too. In addition to its anti-inflammatory efficiency, helenalin A is also potent against infections [40]. Helenalin A, as well as the other sesquiterpene lactones, have toxic effects which may limit its therapeutic use.

Costunolide

Costunolide is the effective sesquiterpene lactone ingredient in the root product prepared from the medicinal *Saussurea costus* plant [41]. This product is a well-known folk remedy in India. Costunolide, a parthenolide-related sesquiterpene lactone, is also present in several other medicinal plant products isolated, e.g. from *Magnolia grandiflora* [42]. Like a number of other sesquiterpene lactones [35], costunolide can inhibit NF-κB signaling [42], but the mechanism seems to be different from that of helenalin A or parthenolide (see above) although the direct effect of costunolide on IKK complex has not been studied. Costunolide inhibits the phosphorylation of IκB proteins and thereby inhibits the nuclear localization of NF-κB complex. Costunolide inhibits the basic inflammatory signaling pathway induced by LPS by inhibiting NF-κB activation and downstream gene expression [42]. Pandey et al. [41] have reviewed the plethora of pharmacological effects observed using Saussurea root products, including anti-inflammatory, anticancer, antimicrobial, antiulcer and hepatoprotective properties. However, the role of costunolide in all of these effects has not been verified.

Artemisinin

Some of the sesquiterpene lactones are effective ingredients in traditional Chinese herbal remedies. Artemisinin, also known as Qinghaosu, was isolated from the leaves of *Artemisia annua*, a Chinese folk medicine product [43]. Artemisinin is a promising antimalarial drug, especially against multidrug-resistant malaria [43]. Artemisinin has also anticancer, antiangiogenesis, antifungal and immunosuppressive properties [43]. The molecular action of artemisinin and its derivatives, such as artesunate, has not been identified. However, it seems that artemisinin, an endoperoxide sesquiterpene lactone with complex polycyclic rings, also functions via protein alkylation, a typical property of sesquiterpene lactones. There are a large number of alkylation targets in cells. Some appear to be specific only for distinct sesquiterpene lactones, and hence the lactones are effective only in certain diseases. The NF-κB transcription system may be one of the targets, since artemisinin inhibits the LPS-induced activation of NF-κB signaling [44]. Artesunate, a synthetic artemisinin derivative, also inhibits activation of NF-κB signaling and the production of proinflammatory cytokines induced by TNF-α treatment in human synoviocytes [45]. The exact mechanism is still unclear, but artemisinin has been reported to inhibit the DNA binding of NF-κB complex [44]. The production of artemisinin is still a problem, and the search for new botanical sources continues, simultaneously with clinical trials.

Artemisolide

Artemisia species is a rich source of terpenes and a traditional plant preparation in Chinese folk medicine. Artemisolide, a sesquiterpene-monoterpene lactone, is present in several *Artemisia* species [46]. Artemisolide has been shown to inhibit the LPS-induced activation of NF-κB signaling in RAW 264.7 macrophages [46, 47]. Molecular studies have revealed that artemisolide targets the IKKβ subunit at the cysteine-179 residue in the IKK complex and inhibits proinflammatory signaling [47]. It seems that the molecular target of artemisolide is different from those of helenalin A and parthenolide [36, 38], and hence the therapeutic responses may also be different.

Ergolide

A number of structurally different sesquiterpene lactones have been isolated from plant extracts used as folk remedies around the world. One of these sesquiterpene lactones is ergolide, isolated from the flowers of *Inula britannica*, including the Asteraceae family. Ergolide is a powerful anti-inflammatory compound [48]. Ergolide also has anticancer efficiency due to its capacity to induce apoptosis [49].

Ergolide has inhibited NF-κB activation in LPS-stimulated RAW 264.7 macrophages [48]. Nuclear translocation of NF-κB complex was inhibited, as well as the degradation of IκB protein. Since these effects were blocked by cysteine supplementation, this points to the involvement of alkylation of the IκB kinases.

Elephantopins

The elephantopins isodeoxyelephantopin and deoxyelephantopin are sesquiterpene lactones isolated from *Elephantous scaber* (Elephant's foot), including the Asteraceae family [50]. Isodeoxyelephantopin is an anti-inflammatory compound, but it also potentiates apoptosis and inhibits osteoclastogenesis via the suppression of NF-κB activation. Interestingly, isodeoxyelephantopin inhibited cytokine-induced NF-κB activation via suppression of the action of IKK complex [50].

Nepalolide A

Nepalolide A is a sesquiterpene lactone isolated from the *Carpesium nepalense* plant used in Chinese traditional medicine e.g. for the inhibition of hepatitis [51]. Nepalolide A has inhibited the LPS- and cytokine-induced activation of NF-κB signaling in C6 glioma cells [51]. The suppression of NF-κB signaling appeared as the inhibition of the IκB protein phosphorylation in stimulated cells.

Zerumbone

Zerumbone is a cyclic sesquiterpene lactone isolated from *Zingiber zerumbet* Smith, a Hawaiian and Polynesian ginger. Several studies have shown that zerumbone is an effective inhibitor of NF-κB signaling and a potent anti-inflammatory and anticancer compound [52, 53]. Zerumbone blocked the function of the IKK complex as a result of reduced protein phosphorylation and degradation of IκB proteins, subsequently leading to a decrease in the nuclear translocation of NF-κB complex and gene expression [52, 53].

Siedle et al. [35] have investigated the potency of different sesquiterpene lactones to inhibit the TNF-α-induced DNA-binding intensity of nuclear NF-κB complex. Different sesquiterpene lactones with different structural groups, such as germacranolides (parthenolide and costunolide), heliangolides, guaianolides and pseudo-guaianolides (helenalin A) have been evaluated. Several compounds evoked the total (100 %) block of the nuclear DNA binding of NF-κB complex in concentrations ranging from 5 to 20 μM [35]. Anti-inflammatory capacities were not evaluated, but Koch et al. [54] have shown that inhibition of inflammatory cytokine production correlates with inhibition of NF-κB activation. Furthermore, it seems likely that these compounds possess several NF-κB-independent therapeutic properties, such as antiparasitic, antimicrobial and fungicidal activities.

Huperzine A

In addition to sesquiterpene lactones, sesquiterpene alkaloids have the potential to inhibit NF-κB signaling. Huperzine A is a sesquiterpene alkaloid isolated from *Huperzia serrata*, which has been used in China for centuries in the treatment of contusions, swellings and schizophrenia [55]. Recently, huperzine A has received much attention since it was shown to be a potent and highly specific inhibitor of acetylcholinesterase [55, 56]. Clinical studies have shown that huperzine A may be a potential drug for the treatment of Azheimer's disease [55]. Acetylcholinesterase is not the only enzyme inhibited, since several other molecular targets have been revealed [56, 57]. For instance, huperzine A can inhibit NF-κB signaling and it can suppress inflammatory responses [57]. The molecular mechanism needs to be clarified. Huperzine A has relatively few toxic side effects, and hence it may be a safe sesquiterpene for therapeutic studies [55].

Humulene

Humulene (α-caryophyllene) is a monocyclic sesquiterpene isolated from the oils of *Humulus lupulus*. Humulene has anti-inflammatory properties both in topical and systemic models. Medeiros et al. [58] observed that humulene could effectively reduce both the LPS-induced NF-κB activation and the inflammatory response in the rat paw. Humulene did not modify the activation of ERK, p38 and JNK, indicating that it is more specific in its properties than several other sesquiterpenoids, which also inhibit MAPK-mediated inflammatory signaling.

Valerenic acid

Valerenic acid is the effective ingredient in Valerian oil obtained from *Valeriana officinalis*. Valerian is a traditional remedy for sleep disorders [2], but a recent study showed that valerenic acid is a powerful inhibitor of NF-κB activation and cytokine expression [59]. Valerenic acid may be an effective herbal remedy in inflammatory diseases with mild, if any, side-effects [2].

In conclusion, sesquiterpenoids, especially lactone derivatives, are powerful NF-κB-dependent anti-inflammatory compounds. However, they are generally very toxic due to their alkylation capabilities. There are also several interesting sesquiterpenoids, such as farnesol, juvenile hormone and longifolene, but their effects on the NF-κB signaling need to be clarified. Furthermore, some sesquiterpenoids, such as thapsi-

Table 3. Inhibition of NF-κB signaling and some examples of therapeutic indications for diterpenoid compounds.

Compound	NF-κB inhibition	Therapeutic indications
Acanthoic acid	IκBα phosphorylation [60]	Hepatic fibrosis [61], inflammation [60, 61]
Andalusol	IKKβ and NIK inhibition [78]	Inflammation [78]
Carnosol	IκBα phosphorylation [62]	Metastasis [63], inflammation [62]
Ginkgolides	DNA binding [66]	Neuroprotection [65], ovarian cancer [64], inflammation [66]
Hypoestoxide	IKKβ inhibition [79]	Inflammation and edema [79], colorectal cancer [80]
Kahweol	IKK inhibition, IκB degradation [69]	Cancer [70], inflammation [68, 69]
Kamebakaurin	p50 protein modification [81]	Arthritis [82], lymphocytic leukemia [83]
Oridonin	DNA binding [87]	Leukemia [85], immunosuppression [86]
Ponicidin	DNA binding [87]	Breast cancer [84], inflammation [87]
Tanshinone IIA	IKKα/β and NIK inhibition [72]	Breast cancer [71], inflammation [72]
Triptolide	IκBα phosphorylation, DNA binding [73]	Inflammatory diseases [2, 74, 75]

gargin and vomitoxin, can cause toxic effects in cells, and this side-effect can activate NF-κB signaling.

Diterpenoids (Table 3)

Diterpenes contain four isoprene units and have the basic structure of $C_{20}H_{32}$. However, medicinal compounds in natural remedies are generally modified and structurally rearranged diterpene structures, called diterpenoids (Fig. 1). Diterpenoids can be acyclic, but generally they appear as mono-, bi-, tri-, tetra- or macrocyclic compounds. Oleoresin from the conifer species is a rich source of diterpenoids [6, 8], and diterpenoids are also ingredients in many plant remedies. Physiologically active diterpenoids include aphidicolin, forskolin, gibberellins, phorbols, retinol derivatives and taxanes. The molecular targets and functional mechanisms of these compounds are well known, but they do not directly affect the NF-κB system, although they can have indirect effects on NF-κB signaling. For instance, taxol can activate NF-κB signaling via the TLR4 receptor complex. Furthermore, there are diterpenoid compounds, such as abietic acid, which have both anti-inflammatory and other therapeutic effects, but involvement of the NF-κB system has still to be verified.

Acanthoic acid

Acanthoic acid, a pimarane diterpene (Fig. 1), has been isolated from the root bark of *Acanthopanax koreanum* Nakai, which has been used as a sedative and antirheumatic remedy in Korean folk medicine. Chao et al. [60] synthesized a series of acanthoic acid analogues. They observed that these novel diterpenes inhibited the LPS-induced activation of IκBα phosphorylation and the nuclear DNA binding of NF-κB complex in Raw 264.7 cells. Furthermore, acanthoic acid and its analogues reduced LPS-induced cytokine synthesis and pro-inflammatory response. The low toxicity of these compounds increases their potential as promising anti-inflammatory molecules. Kang et al. [61] have shown that acanthoic acid can prevent fibrosis and nodular formation in rat lung.

Carnosol

Carnosol and carnosic acid are an abundant abietane type of diterpene constituents in Rosemary extracts (*Rosmarinus officinalis*), a well-known traditional herb remedy. Rosemary extract and its constituents carnosol and ursolic acid have anticancer and anti-inflammatory potential [62, 63]. Lo et al. [62] observed that carnosol could inhibit activation of the NF-κB system in LPS-activated RAW 264.7 macrophages. Inhibition of IκBα phosphorylation as well as the reduction in the expression of iNOS and NO production was dose-dependent. Carnosol also suppresses the metastatic potential of mouse melanoma cells [63]. It seems that this property is due to the suppression of metalloproteinase-9 expression via downregulation of NF-κB and c-Jun -mediated signaling [63]. The antioxidant capacity of carnosol may be the mechanism of inhibition of NF-κB signaling [62].

Ginkgolides

Ginkgolides are biologically active diterpene trilactones found in extracts from *Ginkgo biloba* leaves. Ginkgo biloba extracts contain several flavonoids and terpenoids: ginkgolides A, B and C, which are diterpenes, and bilobalide, which is an active sesquiterpene [2, 65]. The Ginkgo extract is one of the traditional Chinese plant remedies, and it has been claimed to have therapeutic efficiency in a variety of diseases, such as inflammatory diseases, vascular insufficiencies, ovarian cancer and several neuronal disorders [2, 64–66]. Several studies with Ginkgo extract EGb 761 have shown that this extract can inhibit NF-κB signaling and reduce the level of

inflammatory response [e.g. 66]. However, ginkgolides and biloba induced changes similar to those of EGb extract by inhibiting the DNA binding of NF-κB complex and iNOS activation [66]. Clearly, the exact mechanism of inhibition needs to be clarified.

Kahweol

Kahweol and cafestol are coffee-specific diterpenoids isolated from the beans of *Coffea arabica.* These two diterpenoids, along with caffeine and some polyphenols, are effective constituents in unfiltered coffee, but not in filtered coffee, and they can affect cholesterol metabolism, blood pressure, inflammation and the metabolic syndrome [67]. Only a few studies have been focused on the specific effects of these diterpenoids in coffee. Several cell culture experiments have revealed that kahweol and cafestol can inhibit inflammatory responses in macrophages [68, 69]. In reporter gene assays with LPS-induced macrophages, kahweol suppressed the NF-κB-dependent transcriptional activation, probably due to inhibition of the nuclear DNA binding of NF-κB complex [68]. It seems that kahweol can inhibit IKK activity in LPS-activated macrophages and prevent the degradation of IκB proteins [69]. This type of regulation may be responsible for the anti-inflammatory and anticarcinogenic effects of kahweol [68–70]. However, the therapeutic effects of kahweol and cafestol have been much less studied than those of caffeine.

Tanshinone IIA

Tanshinone IIA is the major active diterpene quinone (Fig. 1) in the herbal product from the roots of *Salvia miltiorrhiza.* Tanshinone is a commonly used Chinese plant remedy which seems to have some activity against immunological disorders, osteoporosis, cardiovascular diseases and breast cancer [71, 72]. Several studies have shown that tanshinone IIA can inhibit NF-κB signaling and inflammatory responses [e.g. 72]. Tanshinone IIA suppresses NF-κB signaling, inhibiting both the IKKα/β and NIK activation, and subsequently phosphorylation of IκBα protein and the nuclear translocation of NF-κB complex [72]. Tanshinone IIA does not suppress NF-κB signaling in a specific manner but inhibits signaling via the ERK1/2, p38 and JNK pathways [72].

Triptolide

Triptolide, a diterpenoid triepoxide (Fig. 1), is the effective constituent in extracts from *Tripterygium wilfordii* Hook F, a traditional Chinese herbal remedy. Extracts from the 'Thunder of God Vine' have been used to treat several autoimmune and inflammatory diseases, such as rheumatoid arthritis and polycystic kidney disease [2]. Currently, triptolide is the focus of intensive medicinal research in an attempt to develop a powerful drug for inflammatory diseases and possibly also for cancer therapy [3]. New derivatives have been synthesized to reduce the toxic side-effects and improve the pharmacokinetic profile of triptolide [3]. Much research has focused on finding the target molecule(s) of triptolide and understanding its therapeutic mechanisms. Several studies have verified that triptolide can inhibit NF-κB signaling [73, 74]. In experiments on inflammation, triptolide inhibited the phosphorylation of IκBα protein, translocation of the NF-κB complex into nuclei and finally DNA binding of the complex [73]. However, the molecular target needs to be clarified. Triptolide also inhibited NF-κB signaling in T-lymphocytes via upregulation of IκBα protein expression [74]. This kind of triptolide-induced inhibition of NF-κB signaling could account for the inflammatory and immunosuppressive responses, such as rheumatoid arthritis, and cause apoptosis of cancer cells [75].

Kaurane types of cyclized diterpenoids, mostly of the *ent*-series, are common constituents in traditional herbal remedies. Garcia et al. [76] have reviewed in detail the occurrence and biological activities of kaurane diterpenes and their glycosides. Several kaurane diterpenoids are known to inhibit NF-κB signaling and to suppress inflammatory responses. The *Sideritis* species contains several labdane diterpenoids, such as andalusol, foliol and linearol [77], which have anti-inflammatory properties and are used in traditional remedies.

Andalusol

Andalusol is a tetracyclic kaurene diterpene which inhibits NF-κB signaling and inflammatory responses [78]. Andalusol inhibited the activation of IKKβ and NIK kinases, as well as the nuclear DNA binding of the NF-κB complex in LPS-stimulated macrophages [78]. However, andalusol did not inhibit DNA binding of the NF-κB complex *in vitro.* It seems that andalusol affects upstream signaling, inhibiting activation of the IKK complex.

Hypoestoxide

Hypoestoxide, a cyclic diterpene from *Hypoestes rosea*, has also been reported to inhibit the IKKβ activation and inflammatory responses [79] as well as colorectal cancer [80].

Kamebakaurin

Plant extracts of *Isodon japonicus*, common remedies in traditional oriental folk medicine, contain kaurane diterpenes, such as kamebakaurin, kamebanin, kamebacetal and excisanin A [81]. Kamebakaurin inhibits inflammatory responses both in several cell culture

Table 4. Inhibition of NF-κB signaling and some examples of therapeutic indications for triterpenoid compounds.

Compound	NF-kB inhibition	Therapeutic indications
Avicins	DNA binding [121, 122]	Cancer and inflammation [see 121]
Betulinic acid	IKKα inhibition [101]	Melanoma, leukemia, malaria, HIV, inflammation [see 100]
Boswellic acid	IKKα/β inhibition [99]	Arthritis [97], atherosclerosis [98]
CCDO-Me/Im	IKKβ inhibition on Cys-179 [109, 110]	Melanoma, leukemia, tumor growth, inflammation [107, 108]
Celastrol	IKKβ inhibition [92]	Arthritis [3], ALS [90], metastasis [91]
Ginsenosides	IkBα phosphorylation and degradation [115, 116]	Neurodegeneration, cancer, inflammation, [see 113, 114]
Glycyrrhizin	DNA binding [118, 119]	Excitotoxicity [118], inflammation [119],
Lupeol	IkBα phosphorylation [102]	Skin cancer [102], metastasis [103], inflammation [104]
Saikosaponins	IκBα phosphorylation [124, 125]	Inflammatory diseases [123, 125], hepatoma [124]
Ursolic acid	IKKα inhibition, DNA binding [106]	Carcinogenesis, hyperlipidemia, inflammation [see 105]

models [e.g. 81] and in animal models *in vivo* [82]. Lee et al. [81] studied the mechanism of the effects of kamebakaurin on NF-κB signaling. They observed that kamebakaurin modifies the Cys62 residue in p50 protein in the NF-κB complex. This covalent interaction of kamebakaurin with p50-Cys62 could interfere with the DNA-binding activity of the NF-κB complex and subsequently with the transactivation of NF-κB-dependent genes, e.g. c-IAP1 and Bfl-1/A1 [81]. Kamebakaurin also accelerates apoptosis in chronic lymphocytic leukemia [83].

Ponicidin

Ponicidin, an *ent*-kaurane diterpenoid isolated from *Rabdosia rubescens*, is an important traditional Chinese herbal remedy used especially in the treatment of malignant cancers. Cell culture experiments have indicated that ponicidin inhibits cell cycle progression and induces apoptosis in tumour cells [84].

Oridonin

Another kaurane diterpenoid isolated from *Rabdosia rubescens*, oridonin, can also inhibit the proliferation of cancerous cells and trigger their apoptotic cell death as well as enhance the phagocytosis of apoptotic cells by macrophages [84, 85]. Oridonin has also immunosuppressive properties both *in vitro* and *in vivo* [86]. Ponicidin and oridonin are effective inhibitors of NF-κB signaling [86, 87]. Leung et al. [87] have observed that these diterpenoids do not significantly suppress TNF-α-induced IκBα protein degradation and nuclear translocation of NF-κB complex but reversibly inhibit DNA binding of NF-κB complex. The exact mechanism of the inhibition is not known, but these kaurane types of diterpenoids may interfere either with the NF-κB complex formation or its binding to DNA.

Taxol

Taxol is a complex polyoxygenated diterpenoid originally isolated from the bark of the Pacific yew tree, *Taxus brevifolia*. Taxol is a powerful anticancer compound which has been used clinically to combat several cancer diseases with the generic name of paclitaxel [88]. Taxol binds to the β-tubulin protein in microtubules, which increases the acetylation level of α-tubulin and suppresses microtubular dynamics. The excessive stabilization of the microtubules blocks mitosis, and this leads to the apoptotic cell death of proliferating cancer cells. Interestingly, taxol has other targets in cells which can activate NF-κB signaling and induce the expression of pro-inflammatory genes [89]. Fitzpatrick and Wheeler [89] have reviewed in detail these immunopharmacological effects of taxol. It seems that taxol activates TLR4, the same receptor which is stimulated by bacterial LPS. Taxol binds to the CD18 protein, which in turn activates the multiprotein TLR4 complex and downstream signaling cascades including the NF-κB signaling [89]. In conclusion, it seems that plant-derived diterpenoids have several target proteins in cells. But most of the studied effects involve the inhibition of NF-κB signaling, although the diterpenoid target may be located at the NF-κB or IKK complexes, or at sites upstream in the signaling cascade.

Triterpenoids (Table 4)

Triterpenes are formed from six isoprene units with 30 carbons, but in nature, triterpenes occur as complex cyclic structures called triterpenoids (Fig. 1). Pentacyclic triterpenoids, with either a hopane or lupane skeleton, are abundant natural products [5]. Triterpenoids are the major substituents in several Chinese herbal remedies, such as ginseng and *Platycodon* (see below).

Celastrol

Celastrol, a quinone methide triterpenoid (Fig. 1), isolated from the Chinese Thunder of God Vine (*Tripterygium wilfordii* Hook F.), as well as triptolide (see above), is currently being investigated in the search for novel treatment of inflammatory diseases, such as rheumatoid arthritis [3] and amyotrophic lateral sclerosis [90]. There are also several other therapeutic possibilities, such as prevention of tumour cell invasion [91]. The molecular mechanisms of celastrol to prevent inflammation and cancer still need to be clarified. Lee et al. [92] observed that celastrol could inhibit the activation of NF-κB by different stimuli both in human Jurkat and U937 cells. Interestingly, they observed that celastrol inhibited the constitutively active IKKβ kinase in a dose-dependent manner. A mutation of cysteine-179 in the activation loop of IKKβ abolished the effect of celastrol in NF-κB signaling. This is an interesting observation since recent studies have shown that inhibition of IKKβ can suppress both inflammation and tumour angiogenesis [93]. Westerheide et al. [94] have revealed the second mechanism, *i.e.* celastrol can activate the heat shock transcription factor 1 (HSF1) and induce the expression of HSP70 protein. Zhang and Sarge [95] have observed that celastrol could inhibit polyglutamine aggregation due to induction of the heat shock response. This observation is interesting since the heat shock response and the induction of HSP70 can inhibit the function of IKK complex and suppress both inflammation and tumorigenesis, a topic we have recently reviewed in detail [96]. It seems that the IKK complex is the target, either direct or indirect, of celastrol.

Boswellic acid

Boswellic acid, a pentacyclic triterpenic acid, or its derivatives, such as acetyl-11-keto-β-boswellic acid, are components of an Ayurvedic therapeutic plant, *Boswellia serrata.* Boswellic acid has therapeutic action against different kinds of chronic inflammatory diseases, such as rheumatoid arthritis [97] and atherosclerosis [98]. Several studies have shown that boswellic acid and its derivatives inhibit NF-κB signaling [98, 99]. Syrovets et al. [99] observed that boswellic acid can bind and inhibit IKKα and IKKβ kinases and subsequently modulate downstream NF-κB signaling.

Betulin

Betulin is a pentacyclic triterpenoid which is present at high concentration in the bark of the white birch tree (*Betula alba*). The derivative of betulin, betulinic acid (Fig. 1), is pharmacologically more active than betulin. Alakurtti et al. [100] have reviewed the pharmacological properties of betulin and betulinic acid. Betulinic acid and its derivatives have therapeutic potential against different cancers, such as melanoma, and against infections, such as HIV, and against different kinds of inflammation [100, 101]. Takada and Aggarwal [101] observed that betulinic acid could suppress the activation of IKKα induced by a variety of typical NF-κB activators. Betulinic acid also down-regulated NF-κB-dependent gene expression [101]. Due to the inhibition of IKKα, the use of betulinic acid may have toxic effects during pregnancy (see below).

Lupeol

Lupeol is a pentacyclic triterpenoid which is a major constituent of many common fruits and vegetables, e.g. olives, mango and fig, and in several medicinal herbs. Lupeol has therapeutic effects in some cancers [102, 103] and inflammation [104]. Several studies have shown that lupeol inhibits NF-κB signaling, including phosphorylation of IκBα protein, DNA binding of NF-κB complex and NF-κB-dependent reporter gene activity [102, 103]. It seems that lupeol could inhibit several signaling pathways, such as Akt-dependent pathways, and in this way it may possess anti-cancer and anti-inflammatory properties [102, 104].

Ursolic acid

Ursolic acid (Fig. 1) and its isomer, oleanolic acid, are pentacyclic triterpenes which are active ingredients of several plant-derived folk remedies, e.g. they are present in the extracts from rosemary leaves [105]. They are reported to have therapeutic effects, for instance, against inflammation, carcinogenesis and hyperlipidemia [105, 106]. Shishodia et al. [106] have observed that ursolic acid inhibited the activation of NF-κB signaling induced by a variety of carcinogenic agents in several cell lines. Ursolic acid inhibited IκBα kinase activation, IκBα protein phosphorylation and degradation, p65 nuclear translocation and the DNA binding of NF-κB complex, as well as the NF-κB-dependent gene expression [106]. Ursolic acid is one of the promising terpenoid-based drug candidates.

CDDO-Me/Im

The synthetic derivatives of oleanolic and ursolic acid triterpenoids, 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid (CDDO), and its C-28 methyl ester (CDDO-Me) and C28 imidazole (CDDO-Im) are potent anti-inflammatory and antitumor agents [107, 108]. The inhibition of NF-κB signaling seems to be an essential molecular mechanism underpinning the therapeutic effects of CDDO and its derivatives. Shishodia et al. [108] observed that CDDO-Me inhibited, more potently than CDDO or CDDO-Im, NF-κB signaling activated by a variety of stimulating

agents in human leukemia cells. Interestingly, they showed that CCDO-Me inhibited IKKα kinase and subsequently IκBα protein phosphorylation and degradation, as well as NF-κB-dependent transactivation of the reporter gene. Later, Ahmad et al. [109] and Yore et al. [110] showed that CDDO-Me and CDDO-Im could inhibit IKKβ kinase by directly binding to Cys-179 and inhibiting the enzymatic activity of IKKβ. A similar mechanism is probably responsible for inhibition of IKK complex by oleanolic and ursolic acid (see above).

Saponins, the glycosides of triterpenes or steroids, are common substituents in traditional herbal remedies. Vincken et al. [111] have thoroughly reviewed the chemistry and occurrence of plant-derived saponins. Saponins can be toxic, so-called sapotoxins, but they have a variety of therapeutic properties, e.g. in cholesterol metabolism, in immune defense, in cancer therapy and in antimicrobial protection. Francis et al. [112] have reviewed the biological activities and therapeutic potential of plant-derived triterpenoid saponins.

Ginsenosides

Ginseng is probably the best known of the traditional Chinese herbal remedies in the West. There are different types of ginseng root products, but all refer to the perennial plant of *Panax* species. Ginsenosides are steroid-like triterpene saponins and found exclusively in *Panax* species, mostly growing in Asian countries. There is an extensive literature on the structural diversity of ginsenosides and the pharmacology of ginseng products [113, 114]. Ginsenosides have multiple targets in cells and a multitude of therapeutic effects, e.g. being used in inflammatory diseases, cancer and neurodegenerative disorders. Hofseth and Wargovich [114] have reviewed the interactions of ginseng with the signaling pathways regulating the inflammation-to-cancer cascades. Ginseng and ginsenosides inhibit NF-κB signaling, either directly or indirectly [114–116]. Different ginsenosides seem to suppress the activation of IKKα kinase and the phosphorylation and degradation of IκBα protein, as well as DNA binding of the NF-κB complex. It is likely that ginsenosides can affect the upstream components of the NF-κB signaling cascade since the JNK pathway and AP-1 binding activity are also inhibited by ginsenosides [115, 116].

Glycyrrhizin

Glycyrrhizin, a triterpenoid glycosidic saponin, is an active constituent in licorice, the root extract from *Glycyrrhiza glabra*. Licorice is an ancient remedy found in traditional Chinese and Egyptian herbal medicines. Fiore et al. [117] have reviewed the therapeutic use of licorice from ancient times to the present. Licorice has been used to treat several diseases of the cardiovascular, gastrointestinal and respiratory systems [117] as well as its use as a flavouring sweetener. Hypertension can be a side-effect of the excessive use of licorice. The major constituent of glycyrrhizin is glycyrrhizic acid, which can inhibit NF-κB signaling [118, 119]. Glycyrrhizic acid has been shown to inhibit glutamate-induced excitotoxicity in primary neurons [118]. The calcium-mediated activation of the NF-κB system was suppressed by glycyrrhizic acid. A similar compound, 18-β-glycyrrhetinic acid, can inhibit inflammatory responses in human colonic epithelial cells [119].

Avicins

Avicins are an interesting family of triterpenoid saponins isolated from *Acacia victoriae* (Leguminosae). Avicins are plant stress metabolites which have been reported to induce cellular stress adaptation and suppress innate immunity responses [120]. Avicin G can inhibit DNA binding of NF-κB complex and the expression of N-kB-dependent genes [121]. Interestingly, avicin G did not affect the degradation of IκBα protein. Moreover, the treatment of cells with dithiothreitol (DTT) could reverse the avicin G-induced inhibition in DNA binding of NF-κB complex. This is due to the ability of avicins to cause thioesterification, also called avicinylation, of the cysteine residue in the DNA-binding domain of the NF-κB protein [122]. The amount of avicin in plants is dependent on stress insults, and hence different stress models in *in vitro* cultures have been established to achieve biomass production of avicins.

Saikosaponins

Saikosaponins are biologically active triterpenoid saponins present in a variety of plant families, such as *Bupleurum* (Umbelliferae), and in several herbal remedies. Saikosaponins have been shown to possess anti-inflammatory and anti-cancer properties in different *in vitro* and *in vivo* systems [123–125]. Saikosaponin D can inhibit NF-κB signaling, which is associated with inhibition of T cell activation [125] and apoptosis of cancer cells [124]. Saikosaponin D inhibits the phosphorylation of IκBα protein, but saikosaponin also increases the protein level of inhibitory IκBα protein. Saikosaponin D also inhibits activation of JNK signaling, suggesting that the molecular target of saikosaponin would be upstream from the IKK and NF-κB complexes. It seems that triterpenoids, especially triterpenoid saponins, are widely represented in plant-derived medicinal products, and these agents possess a multitude of NF-κB-dependent therapeutic effects.

Table 5. Inhibition of NF-κB signaling and some examples of therapeutic indications for carotenoid tetraterpenes.

Compound	NF-κB inhibition	Therapeutic indications
Astaxanthin	IKKα inhibition, IκBα degradation [140]	Inflammation [139, 140], hypertension [139], uveitis [141]
ß-Carotene	IκBα degradation, DNA binding [132, 133]	Cancer [126, 133], inflammation [132]
Lutein	IκBα degradation, p65 translocation [136, 137]	Macular degeneration [136], cataract [126, 135], uveitis [137]
Lycopene	NF-κB translocation [129, 130]	Atherosclerosis, arthritis, prostate cancer [see 127]

Carotenoid tetraterpenes (Table 5)

Carotenoid terpenes are pigmented tetraterpenes typically containing eight isoprenoid units with conjugated double bonds which provide the strong light absorption and bright colour of the compounds. Plant carotenoids play an important role in maintaining human health. There have been numerous reviews concerned with the therapeutic effects of carotenoids in the prevention of disease, but some controversies exist, e.g. the consequences of excessive use of carotenoids [126]. Carotenoids are powerful antioxidants which have therapeutic effects in several chronic illnesses, such as in cardiovascular disease and osteoporosis. Carotenoids can also protect against inflammatory responses and cancer, suggesting that carotenoids can modulate redox-sensitive signaling pathways, such as NF-κB signaling.

Lycopene

Lycopene is an acyclic tetraterpene containing several conjugated carbon double bonds (Fig. 1) which endow it with a typical bright red colour. Lycopene is the most common carotenoid in the human body. Tomato and other red vegetables and fruits are the major dietary sources of lycopene. Lycopene is a powerful antioxidant, better than vitamin E, and hence it can prevent free radical attack during oxidative stress. Heber and Lu [127] have reviewed the molecular mechanisms involved in the action of lycopene and its therapeutic indications. Lycopene has been claimed to decrease the risk for some chronic diseases, such as cardiovascular and inflammatory diseases, e.g. atherosclerosis and rheumatoid arthritis. Furthermore, lycopene seems to promote prostate health, especially preventing the development of prostate cancer. Lycopene is an effective antioxidant due to the numerous double bonds present in its structure. Reactive oxygen species (ROS) and oxidative stress activate NF-κB signaling, and hence all antioxidants, e.g. phytochemicals [128], can prevent NF-κB-dependent signaling. Moreover, the inflammatory signaling induced by LPS and TNF cytokines is mediated via ROS-dependent signaling [128]. Several studies have demonstrated that lycopene can inhibit NF-κB signaling [129, 130]. Lycopene, for instance, can inhibit nuclear localisation and DNA binding of NF-κB complex, as well as reducing macrophage activation [129]. It seems that these properties are due to the antioxidative activity of lycopene, e.g. lycopene may prevent ROS-mediated NF-κB signaling, such as that observed in inflammation and cancer cell proliferation.

β-Carotene

Carotenes are cyclic tetraterpenes including several isomers of which β-carotene is the most common in nature. The orange colour of carrots and many other fruits and vegetables is due to their β-carotene content. β-Carotene is stored in liver and can be converted to vitamin A. The therapeutic actions of β-carotene have been widely studied, but there are still some controversies [126, 131]. Some studies indicate that β-carotene may reduce the risk for cancer and cardiovascular diseases. The effect of β-carotene on inflammation and immune responses has been much less frequently studied. β-Carotene has been reported to suppress LPS-induced NF-κB signaling and the expression of inflammatory genes in RAW264.7 macrophages [132]. β-Carotene blocked the degradation of IκBα protein, the nuclear translocation of the p65 protein and the DNA binding of NF-κB complex, as well as LPS-induced expression of iNOS, COX-2, TNF-α and IL-1β expression [132]. Interestingly, in cancer cells, ß-carotene increased the production of ROS and simultaneously the DNA binding of NF-κB complex [133]. It seems that in tumour cells, β-carotene can have pro-oxidant characteristics, and in this way it causes growth inhibition. This may be due to the oxidation of β-carotene and carotenoid-derived aldehyde production, which induces oxidative stress and apoptotic cell death, as has been observed in RPE cells [134].

Lutein

Lutein is a cyclic tetraterpene carotenoid with several conjugated double bonds which absorb blue light and endow a yellow-orange colour to the molecule. This lipophilic xanthophyll is a dihydroxy derivative of β-carotene and widely present in fruits and vegetables but also in egg yolks. Clinical studies suggest that lutein has the potential to prevent several diseases, but the final conclusion still awaits more evidence [126, 135]. Lutein is also called a macula pigment since in

the human body it is located at high concentrations in the macula area of retina, which takes care of fine vision. Dietary supplementation with lutein can elevate the macular lutein pigment concentration. There is evidence to indicate that lutein pigments can protect against oxidative stress and prevent age-related macular degeneration and cataract [126, 135]. Izumi-Nagai et al. [136] showed in a mouse model that lutein supplementation could significantly suppress choroidal neovascularization, which is the most severe form of macular degeneration. Lutein pre-treatment significantly inhibited macrophage infiltration and the inflammatory response. Interestingly, lutein treatment reduced *in vivo* the nuclear localization of p65 protein and IκBα protein degradation [136]. Lutein treatment also dose-dependently inhibited endotoxin-induced uveitis and activation of NF-κB signaling in the rat [137]. However, high supplementation of lutein has induced aldehyde formation and oxidative stress and subsequently apoptotic cell death in cultured human retinal pigment epithelial cells [134].

Zeaxanthin

Zeaxanthin is a structural isomer to lutein. Lutein and zeaxanthin are the only carotenoids present in the retina, zeaxanthin being especially present in the central part of the macula [135]. Dietary supplementation has elevated the serum concentration of zeaxanthin and macular pigment density in humans [138]. Zeaxanthin has therapeutic effects similar to lutein, especially in the protection of the eye against age-related macular degeneration and cataract, probably due to its antioxidant capacity [135]. The effects of zeaxanthin on NF-κB signaling still need to be established, although most likely they are similar to those of lutein described above.

Astaxanthin

Astaxanthin is a tetraterpenoid xanthophyll (Fig. 1) which is a common red colouring compound, e.g. in salmon, shrimp and crabs. Astaxanthin is the most powerful antioxidant of all the carotenoids and cannot be converted to vitamin A in the human body. Hussein et al. [139] have reviewed the literature concerning the therapeutic effects of astaxanthin. It seems that the strong antioxidant properties of astaxanthin could be behind many of the reported therapeutic actions, such as anti-inflammatory effects, antihypertensive and neuroprotective potential, and benefits to cardiovascular health [139]. Lee et al. [140] observed that astaxanthin is a powerful inhibitor of NF-κB signaling in LPS-stimulated RAW264.7 cells and primary macrophages. Astaxanthin inhibited the activation of IKKα kinase, and blocked IκBα protein degradation and the nuclear translocation of the NF-κB p65 subunit [140]. Moreover, astaxanthin suppressed the expression of inflammatory NF-κB-dependent genes. Suzuki et al. [141] observed that astaxanthin could suppress endotoxin-induced uveitis by inhibiting NF-κB signaling in the rat. The antioxidative properties of astaxanthin seem to be the molecular mechanism behind these anti-inflammatory responses.

In conclusion, the literature contains a plethora of therapeutic effects induced by the carotenoid terpenes. However, there are only a few prospective clinical studies for carotenoids. In the future, the effects of carotenoids need to be evaluated separately under controlled conditions with larger human populations.

Molecular mechanisms of terpenoid-induced NF-κB inhibition: distinct targets but potent remedies for common diseases

Natural terpenoids are powerful inhibitors of NF-κB signaling and subsequently could represent suppressive agents for inflammatory diseases and cancer (see above). However, the molecular target is unknown in nearly all cases, a common feature for many plant-derived medicinal compounds. This is a challenge for drug development since many of the natural terpenoids have toxic side-effects, which means that they hit several targets, wanted and unwanted, in the human body. Unknown molecular targets prevent specific drug design. Moreover, NF-κB signaling, the master regulator of inflammation, stress and cancer, provides an excellent example of the multitude of signaling interactions related to the function of the NF-κB system. Most studies have focused on recording the changes in (1) the activity level of IKK complex proteins, (2) the phosphorylation and degradation levels of IκB proteins, (3) the translocation of NF-κB or p65 protein into the nuclei, (4) the DNA-binding activity of NF-κB complex, or finally changes in (5) the transactivation level of NF-κB-driven reporter genes. These are all reliable markers for demonstrating the inhibition of NF-κB signaling, but they do not identify the target molecule, which may be located upstream in the integrated signaling cascades leading to the activation of the NF-κB complex. Kawai and Akira [14] have reviewed the complexity of signal regulation from the Toll-like receptors to the NF-κB complex. Evidently, a number of terpenoids affect some upstream targets, since simultaneously with inhibition of the NF-κB pathway they also inhibit the MAPK pathway (see above) and the activation of AP-1, which further potentiates the suppression of inflammatory responses [14].

Sesquiterpene lactones have been the most widely studied of all terpenoids as inhibitors of the NF-κB system. The DNA binding of NF-κB complex is dependent on the cysteine residues of p50 and p65 subunits. Several studies have demonstrated that especially Cys-38 in the p65 subunit is a sensitive alkylation target, e.g. for parthenolide [34]. Quantitative structure-activity relationships (QSARs) with a variety of sesquiterpene lactones have demonstrated the role of a number of alkylating centers, e.g. methylene lactone moieties, in the inhibition of DNA binding of NF-κB complex [35]. Self-organizing neural networks using a counterpropagation network (CPGNN) verified the importance of α-methylene-γ-lactone with its α,β-unsaturated carbonyl structure in the reaction with Cys-38 of p65 protein [142]. In addition to the NF-κB subunits, the protein kinases of the IKK complex may be the targets of alkylation by sesquiterpene lactones. For instance, artemisolide targets IKKβ at Cys-179 and inhibits kinase activity [47]. Interestingly, triterpenoid CDDO-Me (see above) can also interact and oxidize Cys-179 of IKKβ and inhibit NF-κB signaling [109, 110].

Terpenoids such as celastrol and costunolide can induce the expression of heat shock proteins, especially the HSP70 chaperone [94, 143, 144]. Celastrol can also disrupt the HSP90-Cdc37 interaction [144]. It is well established that the heat shock response can suppress the activation of NF-κB signaling and the inflammatory response. We have recently reviewed this phenomenon in detail [96]. An increase in the level of HSP70 protein as well as a decrease in the HSP90-Cdc36 complexes can disturb the function of the IKK complex and hence suppress innate immunity signaling via the NF-κB system [144]. Celastrol induces the heat shock response by activating the transcription factor 1 (HSF1) [94]. Celastrol is currently a promising drug candidate, a so-called HSP-inducer drug.

The NF-κB signaling pathway is an ancient signaling system which has gained different network connections and functions during evolution. Currently, there is a huge number of compounds, both natural and synthetic molecules, which have been demonstrated to inhibit the NF-κB system [145]. The Gilmore Lab [145] has collected an enormous amount of information on Rel/NF-κB transcription factors, such as inhibitors, target genes and diseases associated with NF-κB system. However, the molecular mechanism of the inhibition of NF-κB signaling has been clarified in only a few cases. The NF-κB signaling system is a redox-dependent network [128, 146]. Both the Rel/NF-κB proteins themselves and the signaling kinases upstream can be regulated by the balance between the ROS and antioxidants. Several phytochemicals can act as antioxidants and modulate the responses mediated by NF-κB signaling, such as inflammation [128]. Terpenoids in general are not ideal natural antioxidants, but the carotenoid tetraterpenes are potent antioxidants and they can regulate NF-κB signaling (see above). Interestingly, the presence of antioxidants in the cytoplasm can inhibit the activation of NF-κB signaling induced by oxidative stress or cytokines. But in the nuclei, on the contrary, antioxidants prevent the oxidation of cysteine residues in the DNA-binding domain of the NF-κB proteins, and by this way they maintain NF-κB signaling during oxidative stress [128, 146].

Conclusions

There is a vast literature indicating that plant-derived terpenoids can inhibit signaling via the NF-κB system and hence possess beneficial therapeutic effects against inflammatory diseases and cancer. However, we should be cautious and aware that plants do not synthesize terpenoids for our benefit but for their own defense against insects [147] and environmental threats. Some of the terpenoids are agricultural pesticides, such as juvenile hormone, and many of them can have toxic side-effects, as with the sesquiterpene lactones. One interesting question is why plants might have devised the terpenoids, and attempt to suppress NF-κB signaling, as a way of combating hostile insects. One novel answer could be that terpenoids are intended to destroy the immune system of the invaders and probably also to disrupt morphogenesis mediated via NF-κB signaling.

One alarming example of the dangers which may lie in the use of natural NF-κB inhibitors is the case of thalidomide, a sedative and antinausea drug which turned out to cause severe birth defects. Thalidomide has been shown to be an inhibitor of NF-κB signaling in several experimental models [e.g. 148], although the molecular mechanism still needs to be clarified. Inhibition of NF-κB signaling, especially via IKKα kinase, could be dangerous during pregnancy, since it has been convincingly demonstrated that IKKα kinase regulates mammalian development and its deficiency induces abnormalities in organogenesis, e.g. those of limbs and skin [149]. However, thalidomide is recognized as a potent therapy in several serious diseases, such as in multiple myeloma [150]. While it is relatively straightforward to show that terpenoids can inhibit NF-κB signaling, the identification and verification of the exact molecular target is much more difficult, especially because terpenoids can be metabolized in mammalian tissues [151]. However, this knowledge is necessary for drug

discovery using either *in silico* techniques or high-throughput screening, although high-content screening with cell cultures does permit screening based on NF-κB signaling. On the other hand, potent NF-κB inhibitors targeting the general function of the IKK or NF-κB complex may induce too drastic changes at the transcriptional level and evoke toxic side-effects. Hence the specific inhibitors focusing on the distinct targets upstream from the IKK and NF-κB complexes might block the signals in a more specific manner and only partially suppress NF-κB-dependent responses. It does appear that the exact molecular target of several plant-derived terpenoids is not the IKK or NF-κB complex but some target upstream, for instance at the receptor level, since several terpenoids also inhibit the JNK pathway (see above). This provides promising possibilities for drug discovery to identify specific inhibitors from traditional medicinal plant extracts.

Only a few plant-derived remedies have been clinically tested in larger scientific population-based studies. In some cases the results in clinical studies have been contradictory, as in the case of β-carotene effects on lung cancer [152]. It is essential that compounds in plant extracts identified as being effective *in vitro* should be tested separately in clinical studies. Currently, therapeutic indications mostly emerge from cell culture studies but increasingly also from animal experiments. Plant-derived terpenoids provide a challenging field to identify new potent natural NF-κB inhibitors for the therapy of inflammatory diseases and cancer.

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