Naturally Occurring NF-κB Inhibitors

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Abstract: NF-κB is a ubiquitous and well-characterised protein responsible for the regulation of complex phenomena, with a pivotal role in controlling cell signalling in the body under certain physiological and pathological conditions. Among other functions, NF-κB controls the expression of genes encoding the pro-inflammatory cytokines (e. g., IL-1, IL-2, IL-6, TNF-α, etc.), chemokines (e. g., IL-8, MIP-1α, MCP1, RANTES, eotaxin, etc.), adhesion molecules (e. g., ICAM, VCAM, E-selectin), inducible enzymes (COX-2 and iNOS), growth factors, some of the acute phase proteins, and immune receptors, all of which play critical roles in controlling most inflammatory processes. Since NF-κB represents an important and very attractive therapeutic target for drugs to treat many inflammatory diseases, including arthritis, asthma, and the auto-immune diseases, most attention has been paid in the last decade to the identification of compounds that selectively interfere with this pathway. Recently, a great number of plant-derived substances have been evaluated as possible inhibitors of the NF-κB pathway. These include a wide range of compound classess, such as lignans (manassantins, (+)-saucernetin, (-)-saucerneol methyl ether), sesquiterpenes (costunolide, parthenolide, celastrol, celaphanol A), diterpenes (excisanin, kamebakaurin), triterpenes (avicin, oleandrin), polyphenols (resveratrol, epigallocatechin gallate, quercetin), etc. In this mini-review we will discuss the medicinal chemistry of these compounds with regards to the NF-κB inhibition.

Keywords: NF-κB inhibitors, natural products, sesquiterpene lactones, curcumin, lignans.

INTRODUCTION

NF-κB is an inducible, ubiquitous and well-characterised protein responsible for the regulation of complex phenomena, with a pivotal role in controlling cell signalling in the body under certain physiological and pathological conditions. This transcription factor is one of the key regulators of genes involved in the immune and inflammatory response [1]. NF-κB is activated by pro-inflammatory stimuli such as tumor necrosis factor α (TNF-α), lipopolysaccharide (LPS). Among other functions, NF-κB controls the expression of genes encoding the pro-inflammatory cytokines (e. g., IL-1, IL-2, IL-6, TNF-α, etc.), chemokines (e.g., IL-8, MIP-1α, MCP1, RANTES, eotaxin, etc.), adhesion molecules (e. g., ICAM, VCAM, E-selectin), inducible enzymes (COX-2 and iNOS), growth factors, some of the acute phase proteins, and immune receptors, all of which play critical roles in controlling most inflammatory processes [2,3]. In unstimulated cells, NF-κB is sequestered in the cytoplasm by binding to an inhibitor protein and is present as an inactive heterodimer composed of two sub-units, p50 and p65 (also called relA). The heterodimer is complexed with inhibitory proteins IκB-α or IκB-β, preventing it from moving into the cell nucleus. When activated by certain inflammatory agents, specific protein kinases phosphorylate the IκB protein, causing its rapid degradation, and NF-κB becomes dissociated from IκB-α or IκB-β. Phosphorylated IκB is then rapidly degraded by the proteasome and NF-κB is translated into the nucleus, where it binds to specific DNA sequences present in the promoters of numerous target genes and induces transcriptional activation of genes encoding iNOS, inflammatory cytokines, and cell adhesion molecules [2-4]. Recently, it has been demonstrated that inhibition of NF-κB accounts also for the anti-inflammatory effects in *in vivo* experimental models [4]. Furthermore, it now seems that aberrant regulation of NF-κB could also underlie autoimmune diseases and different types of cancer [4].

Since NF-κB represents an important and very attractive therapeutic target for drugs to treat many inflammatory disorders, including arthritis, asthma, the auto-immune diseases, and different types of cancer, NF-κB and the signalling pathways that regulate its activity have become a focal point for intense drug discovery and development efforts. Extensive attention has been paid in the last decade to the identification of compounds that selectively interfere with this pathway. Several selective inhibitors of the NF-κB system have emerged from screening of combinatorial chemical libraries and rational drug design. In parallel, a great number of plant-derived substances has been evaluated as possible inhibitors of the NF-κB pathway. These plant-derived substances include several distinct classes of compounds such as phenols and polyphenols (curcumin, resveratrol, caffeic acid phenethyl ester (CAPE), quercetin, epigenin, epigallocatechin-3-gallate), lignans (manassantins, (+)-saucernetin, (-)-saucerneol methyl ether), sesquiterpenes (costunolide, parthenolide), diterpenes (helenalin, excisanin, kamebakaurin), triterpenes (avicin, oleandrin), etc. The majority of these compounds are anti-oxidants and act by blocking the protein kinase-mediated IκB degradation, thereby preventing NF-κB activation. In this mini-review we will discuss briefly the medicinal chemistry of these compounds with regards to the NF-κB inhibition.

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PLANT-DERIVED PHENOLS AND POLYPHENOLS AFFECTING NF-KB SYSTEM

Curcumin (**1**) (Fig. (**1**)), is a major component of turmeric (*Curcuma longa*), which is commonly used as a spice to give flavor and yellow color to curry and widely adopted as an anti-inflammatory compound in Eastern folklore medicine. It has been reported that in endothelial cells, curcumin inhibited NF-κB activation in a concentration-dependent manner [5]. The mechanism may be also related to its capacity to induce the heat shock response. In *in vitro* HeLa cells, curcumin induced expression of heat shock protein 70 *via* activation of the transcription enhancer heat shock factor-1 [6]. Gukovsky *et al*. [7] reported that curcumin ameliorates ethanol- and non-ethanol-induced experimental pancreatitis (causing pronounced inhibition of the serum amylase and lipase increase, reduction of neutrophil influx and inhibition of intrapancreatic trypsin activation). They found that the inhibition of NF-κB and AP-1, another important pro-inflammatory transcription factor, is largely responsible for this effect. The authors concluded that curcumin, which is currently in clinical trials for cancer prevention, has therapeutic potential for the management of pancreatitis.

Jobin *et al*. [8] demonstrated that curcumin blocks cytokine-induced pro-inflammatory gene expression in intestinal epithelial cells by inhibition of the signal leading to IKK activation, subsequent IκB phosphorylation/degradation, and NF-κB activation. Furthermore, evidence also indicates that curcumin is able to inhibit the IκB kinase 1 and IκB kinase 2 activities induced after stimulation with LPS [9]. Recently, Ukil *et al*. [10] showed that curcumin exerts beneficial effects on 2,4,6-trinitrobenzenesulphonic acid-induced colitis in mice, a model for inflammatory bowel disease. The anti-inflammatory effects of curcumin are associated with an inhibition of up-regulation of the pro-inflammatory Th1 cytokine response leading to the suppression of iNOS and attenuation of the recruitment of neutrophils and lipid peroxidation that in turn reduce tissue injury. The authors suggested that curcumin may be useful in the management of human inflammatory bowel disease [10].

The antioxidant compound caffeic acid phenethyl ester (CAPE) (**2**) (Fig. (**1**)) is an anti-carcinogenic, anti-inflammatory and immunomodulatory substance present in *Apis mellifera* propolis. CAPE has also been reported to prevent activation of the NF-κB pathway by a wide variety of inflammatory agents including TNF-α, phorbol ester, okadaic acid and H_2O_2 [11]. The action of CAPE is selective for the NF-κB pathway since other transcription factors were not affected. An *in vivo* study has revealed that CAPE also inhibits formation of the neointima by inhibiting NF-κB activation [11]. The mechanism by which CAPE inhibits the NF-κB pathway appears to be related to its ability to suppress the interaction of NF-κB with DNA, without affecting IκB degradation [11]. These findings further support the reported anti-inflammatory and anticancer properties of CAPE and could certainly account for the anti-inflammatory and immunomodulatory effects described for propolis extract [12].

Flavonoids are naturally occurring phenolic compounds that are ubiquitous in plants, and have been used to suppress inflammation, prevent the development of cancer and protect against vascular disease. Several studies demonstrate that flavonoids such as quercetin and apigenin mediate their effects by inhibiting NF-κB signalling [16,17]. The flavonoids quercetin and apigenin (**4,5**) (Fig. (**1**)) have also been shown to down-modulate the constitutive expression of NF-κB/p65 in the human prostate adenocarcinoma cell line LNCaP. Such data suggest that apigenin and quercetin have strong potential for the development of agents to prevent prostate cancer [18].

Resveratrol (**6**) (Fig. (**1**)), is one phenolic compound that has attracted a great deal of interests recently. A wide variety of biological activity has been described for resveratrol. Re-

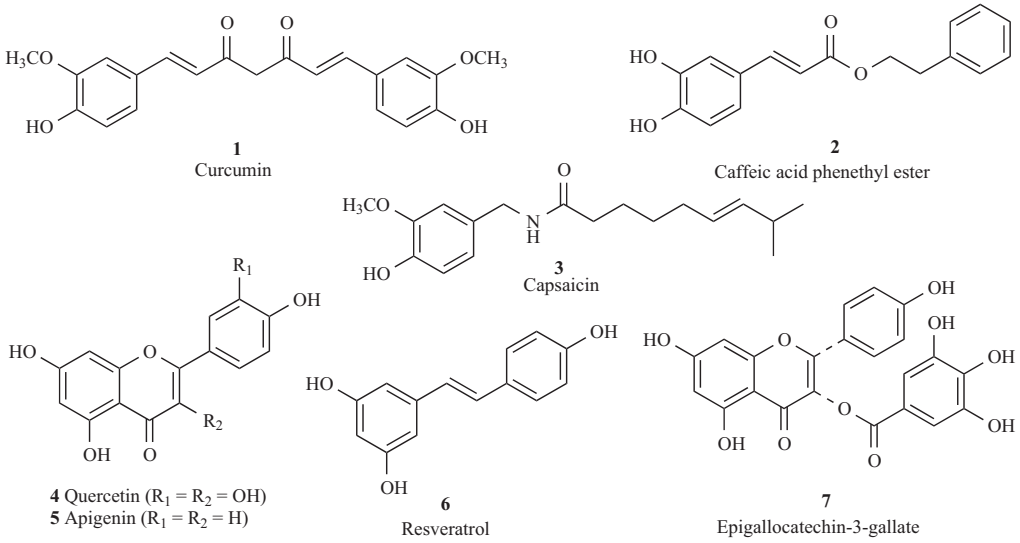

Fig. (1). Plant-derived phenols and polyphenols affecting NF-kB pathway.

garding the NF-κB system, resveratrol has been reported to inhibit expression of iNOS and to decrease nitric oxide production in activated macrophages, which is associated with inhibition of LPS-induced IκB-α phosphorylation and the NF-κB DNA-binding activity [16]. Resveratrol is also able to induce apoptosis in Rat-1 cells by inhibiting Ras-mediated activation of NF-κB [17]. These results indicate that at least some of the biological activities of resveratrol are mediated by inhibition of NF-κB pathways. It remains to be examined, however, whether resveratrol act as a direct IKK inhibitor.

Green tea is a common drink in many Eastern countries, and has been a subject of a number of scientific researches. Remarkable antiinflammatory and cancer chemopreventive effects in many animal tumor bioassays, cell culture systems, and epidemiologic studies have been demonstrated for green tea [19]. These biological effects of green tea are mediated by tea polyphenols, known also as tea catechins, which may inhibit NF-κB activation. Epigallocatechin 3-gallate (EGCG), the major polyphenol present in green tea, has been shown to inhibit TNF-α-induced degradation of IkB and activation of NF-κB in cancer and normal cells [20]. The impairment of NF-κB activity afforded by treatment with EGCG appears to be a sequential event of a depressed IKK activity. In cytosolic extracts of TNF-α-stimulated cells, EGCG specifically inhibited IKK activity, whereas antioxidants were ineffective [21]. The therapeutic effect of green tea has also been proven in *in vivo* experimental inflammatory processes; orally administered green tea polyphenols reduced TNF-α production and improved survival in a murine model of lipopolysaccharide-mediated lethality [22].

Since NF-κB plays a central role in most disease processes, and since it can regulate the expression of many key genes involved in inflammatory as well as in a variety of human cancers [13-15], NF-κB represents a relevant and promising target for the development of new chemopreventive and chemotherapeutic agents. And naturally occurring phenols and polyphenols like curcumin, CAPE, resveratrol, flavonoids quercetin and apigenin, or EGEG exerting inhibitory effects on the NF-κB activation may have potentials for this purpose. However, it should be aware that the ubiquitous nature of NF-κB suggests that such drugs would exhibit some undesirable side effects.

TERPENOIDS AS NF-KB INHIBITORS

Many herbal preparations from medicinal plants, e.g. flowers of some plants from the *Asteraceae* family, have been used as folk remedies for various inflammatory conditions, such as rheumatoid arthritis, asthma, psoriasis, and migraine [23,24]. Despite their currently popular use as natural alternative medicine in both Eastern and Western countries, only a few *in vivo* experimental studies have investigated their therapeutic potential as anti-inflammatory drugs in models of paw or ear edema, chronic arthritis [23, 25], gastritis, and colitis in rodents [26,27]. Recently, *in vitro* experiments have proposed that the antiinflammatory metabolites of these natural preparations are sesquiterpene lactones that are specific potent inhibitors of NF-κB pathway [28,29]. Some most frequently found sesquiterpene lactones include parthenolide, costunolide, and henenalin. Beside sesquiterpene lactones, a number of other terpenoids, including diterpenes and triterpenes, have also been reported to have inhibitory effects on NF-κB system.

Parthenolide (**8)** (Fig. (**2**)) is a sesquiterpene lactone present in several medicinal plants that have been used in folk medicine for their anti-inflammatory and analgesic properties. Several *in vitro* studies have shown that a great part of the anti-inflammatory action of this compound appears to be related to its ability to inhibit the NF-κB pathway. *In vitro* studies have proven that the sesquiterpene lactone parthenolide does not interfere with the generation of oxygen radicals [30], whereas it specifically inhibits activation of the NF-κB pathway by targeting IKK [29] and/or preventing the degradation of IκB-α and IκB-β [30]. Furthermore, parthenolide has recently been reported to exert beneficial effects during endotoxic shock in rats through inhibition of NF-κB DNA binding in the lung [31]. These effects of parthenolide may also accounts for its inhibition of proinflammatory mediator genes, such as the gene for the inducible nitric oxide synthase after endotoxin stimulation in rat smooth muscle cells [32] and the gene for IL-8 in immunostimulated human respiratory epithelial cells [33]. In addition, parthenolide has also been demonstrated to protect against myocardial ischemia and reperfusion injury in the rat by selective inhibition of IKK activation and IκBα degradation [34].

Costunolide (**9)** (Fig. (**2**)) is a closely related sesquiterpene lactone analogue of parthenolide present in several plants such as *Magnolia grandiflora*, *Tanacetum parthenium*. Koo *et al*. showed that costunolide also dose-dependently inhibited LPS-induced NF-κB activation. In this assay system, costunolide even exhibited more potent inhibitory activity than parthenolide. Detailed mechanism studies revealed that, similar to parthenolide, costunolide also significantly inhibited the degradation of IκB-α and IκB-β. In addition, costunolide also inhibited the phosphorylation of IκB-α. These accumulative results indicate that costunolide inhibits NF-κB activation by preventing the phosphorylation of IκB, and therefore, sequestering the complex in an inactive form [35].

Since different types of sesquiterpene lactones showed inhibition of NF-κB activation at similar concentrations, this effect seems to be characteristic for many of the sesquiterpene lactones with an exomethylene group like parthenolide and costunolide. Exomethylene groups of α,β-unsaturated carbonyl compounds can react by Michael type addition to sulfhydryl groups of cysteine residues in the DNA binding domain of the NF-κB subunit [36]. This may be also the case for helenalin [37]. Recently, Lyu *et al*. provided evidence that a sesquiterpene lactone, helenalin (**10)** (Fig. (**2**)), containing two functional groups, namely α,β-unsaturated carbonyl group and α-methylene-γ-lactone ring, exerts its effect by direct alkylation of the p65 subunit of NF-κB without inhibition of IκB degradation [37]. *In vitro* studies also demonstrated that helenalin selectively modifies the p-65 subunit of NF-κB at the nuclear level, therefore inhibiting its DNA binding [38]. However, costunolide differs from helenalin in a number of functional groups and inhibits degradation of IκB by inhibiting phosphorylation of IκB. Therefore, another functional group other than the exomethylene group and the molecular geometry of sesquiterpene lactone compounds appear to be important factors to determine the mode of NF-

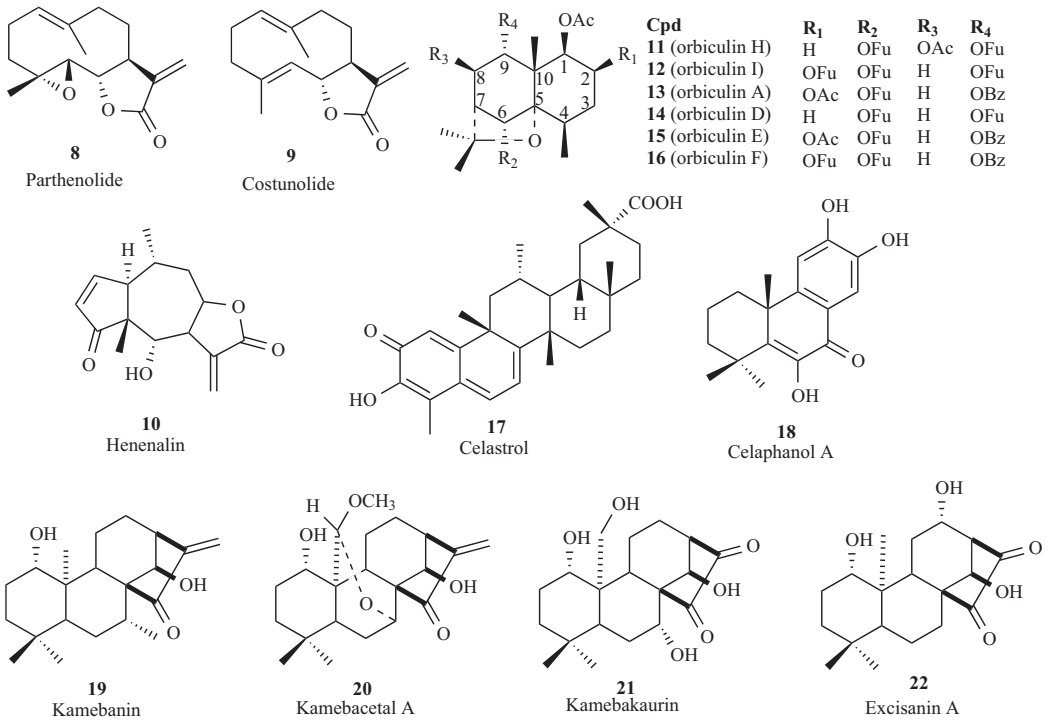

Fig. (2). Some terpenoids with inhibitory activity on NF-κB system.

κB inhibition. However, the epoxide group in parthenolide is not likely important because parthenolide is at least less effective to inhibit both NF-κB activation and NO production.

Sesquiterpene lactones have been proven to be efficacious also in murine models of endotoxemia. Treatment with parthenolide or isohelenin improved the cardiovascular derangement in rats and increased the survival rate in mice subjected to endotoxic shock [39,40]. An important finding of clinical relevance in these studies was that the sesquiterpene lactones exerted a beneficial effect even when given to the animals as posttreatment of endotoxin challenge, i.e., when most of the adverse effects of endotoxin occurred. Therefore, these data clearly indicate that interruption of the NF-κB pathway, even after inflammatory challenge, might be of clinical benefit in sepsis.

Besides sesquiterpene lactones, a number of other sesquiterpenes have been described to have inhibitory effects on NF-κB activation. Jin *et al.* (2002) isolated a series of sesquiterpene esters, including orbiculin H (**11**), orbiculin H (**12**), orbiculin A (**13**), orbiculin D (**14**), orbiculin E (**15**), orbiculin F (**16**) [Fig. (**2**)] from *Celastrus orbiculatus* [41]. Two other compounds including celastrol (**17**) and celaphanol A (**18**) (Fig. (**2**)) were also reported from this plant [41]. Compounds **11**-**18** were examined for their dose-response effect on the LPS-induced NF-κB activation using the NF-κB mediated reporter gene assay system. RAW264.7 cells, which were stably transfected with a NF-κB-mediated reporter gene construct, were stimulated with LPS in the presence of various concentrations of compounds **11**-**18**, and then the expression of reporter gene (secreted alkaline phosphatase gene) in the culture medium was measured. Celastrol (**17**) showed the most potent inhibitory activity in the reporter gene expression, with an IC_{50} value of 0.27 μM, and celaphanol (**18**) was also active with an IC_{50} value of 18.2 μM. Among six dihydro-*β*-agarofuran sesquiterpenes, compounds **11**, **12**, and **14** (having two furoyloxy groups at C-6 and C-9) exhibited moderate inhibitory activities, with IC_{50} values of 33.5, 61.5, and 36.7 μM, respectively; however, compounds **13**, **15**, and **16** (having a benzoyloxy group at C-9) showed very weak activity with IC_{50} values of >300 μM. These results suggest that the furoyloxy groups at C-6 and C-9 are important structural factors of dihydro-β-agarofuran sesquiterpenes in the modulation of NF-κB activity.

Since NF-κB regulates the expression of numerous target genes encoding inflammatory factors, notably the iNOS gene [1,2]. The excessive production of NO, which is produced by iNOS in macrophages and endothelial cells, is responsible for the inflammatory response and implicated in the pathogenesis of several inflammatory diseases such as septic shock, rheumatoid arthritis, graft rejection, and diabetes [42]. The effect of compounds **11**-**18** on the NO production was tested in LPS-stimulated RAW264.7 cells with respect to aminoguanidine, an iNOS inhibitor. Compounds **11**, **12**, **14**, **17**, and **18** inhibited LPS-induced NO production in the RAW264.7 cells dose-dependently with IC_{50} values of 50.4, 51.2, 43.6, 0.23, and 32.6 μM, respectively. These data are comparable to that of aminoguanidine (IC_{50} 16.3 μM) (a positive control) and to those for the NF-κB activation. The cell viability measured by MTT assay showed that all the compounds had no significant cytotoxicity to the RAW264.7

cells at their effective concentration for the inhibition of NF-κB activation and NO production.

Isodon japonicus is a medicinal plant that has been used in folk medicine in China, Japan, and Korea for a remedy for gastrointestinal disorder, tumor, and inflammatory diseases. In an effort to identify the compound(s) that account for the antiinflammatory property of *Isodon japonicus*, Hwang *et al*. (2001) have reported several kaurane diterpenes from this plant with significant inhibitory effects on the NF-κB activation [43,44]. These kaurane diterpenes include kamebanin (**19**), kamebacetal A (**20**), kamebakaurin (**21**), and excisanin A (**22**) [Fig. (**2**)]. It was found that all diterpene compounds inhibited LPS-induced DNA-binding activity of NF-κB dose-dependently and NF-κB activation was completely inhibited in the presence of 10 μg/ml (26.6 μM) of kamebakaurin (**21**) or excisanin A (**22**). Further studies on kamebakaurin also confirmed that kamabakaurin (**21**) prevents the activation of NF-κB by different stimuli in various cell types by directly targeting the DNA-binding activity of p50 [43-45]. Also, treatment of cells with kamebakaurin prevented TNF-α-induced expression of antiapoptotic NF-κB target genes encoding c-IAP1 (hiap-2) and c-IAP2 (hiap-1) members of the inhibitor of apoptosis family, and Bfl-1/A1, a prosurvival Bcl-2 homologue, and augmented the TNF-α-induced caspase 8 activity, thereby resulting in sensitizing MCF-7 cells to TNF-α-induced apoptosis.

Furthermore, the kaurane diterpenes **19-21** also significantly inhibited LPS-induced NO and PGE2 production while they did not influence the DNA binding of AP-1. Therefore, it is likely that the suppression of NF-κB activation could be an inhibitory mechanism of LPS-induced NO and PGE2 production of these kaurane diterpenes [44].

Structurally, as the case of sesquiterpene lactones, the exocyclic methylene moiety of the kaurane diterpenes **19-22** could be the possible functional group responsible for the inhibition of NF-κB activation. However, other factors such as lipophilicity and molecular geometry of naturally occurring diterpenes would be important factors in the inhibition of NF-κB activation [46]. Further studies remained to be elucidated how do kaurane diterpenes participate in the steps of NF-κB activation. However, from the available evidences, these kaurane diterpenes, especially kamabakaurin, are valuable candidates for the intervention of NF-κB-dependent pathological conditions such as inflammation and cancer.

A novel triterpenoid, 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid inhibits NF-κB-mediated gene expression at some stage after translocation of activated NF-κB to the nucleus in ML-1 leukaemia cells [47].

LIGNANS AS NF-KB INHIBITORS

Hwang *et al*. (2003) reported a series of lignans and sesquineolignans including saucerneol D (**23**), saucerneol E (**24**), (−)-saucerneol methyl ether (**25**), (+)-saucernetin (**26**), manassantin A (**27**), and manassantin B (**28**), (Fig. (**3**)) from *Saururus chinensis* [48]. The lignans were evaluated for inhibitory effects on the NF-κB activation in Hela cells, which were transiently transfected with the plasmid of NF-κB directed luciferase expression system. Manassantin A (**27**) and B (**28**) showed the most potent inhibitory activity with IC_{50} values of 2.5 and 2.7 μM, respectively. Saucerneol D (**23**), saucerneol E (**24**), and (−)-saucerneol methyl ether (**25**) also exhibited comparable inhibitory activities with IC_{50} values of 6.1 and 12.7, and 16.9 μM, respectively. Only (+)-saucernetin (**26**) had a weak activity (IC_{50} > 30 μM). The relative potency of these lignans was found to be in the order dilignan > sesquineolignan > lignan, suggesting that the phenylpropanoid moiety attached to C-4 and/or C-4' was important for the inhibition of the stimuli induced NF-κB activation process.

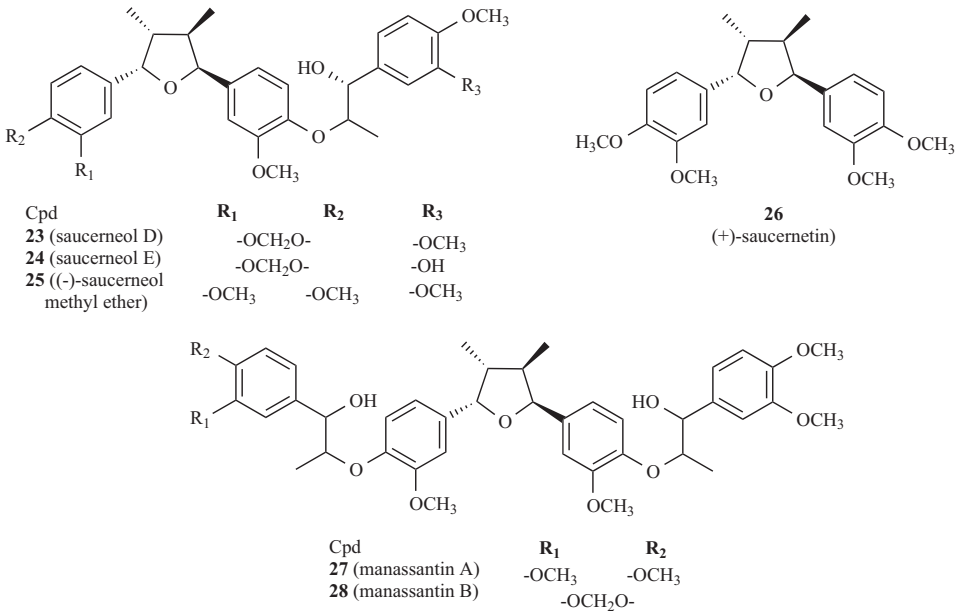

Fig. (3). Some lignans with inhibitory activity on NF-κB system.

More detailed studies on the effects of manassantins on the induced NF-κB activation by various stimuli revealed that both manassantins A and B dose-dependently inhibited the TNF-α induced expression of NF-κB reported gene construct with IC_{50} values of 4.7 and 5.9 μM, respectively. The two manassantins also inhibited LPS-induced expression of NF-κB reported gene construct with similar extent. However, both manassantins A and B only weakly inhibited the PMA-induced expression of AP-1 reported gene construct with IC_{50} values of 38 and 40 μM, respectively [49].

Regarding the mechanisms by which manassantins inhibit NF-κB activation, Lee and colleagues found that manassantins A and B did not prevent induced degradation of IκB-α and DNA-binding activity of NF-κB following stimulation, but inhibited NF-κB activation by various stimuli, as described above, and RelA/p65-overexpression. Lee and coworkers have subsequently demonstrated that manassantins significantly supressed the transcriptional activity of RelA/p65, a critical transactivation subunit of NF-κB [49].

OTHER PLANT-DERIVED NF-KB INHIBITORS

Recent results suggest that silymarin inhibits nitric oxide production and iNOS gene expression by inhibiting NF-κB/Rel activation in RAW 264.7 macrophages. Furthermore, the radical-scavenging activity of silymarin may explain its inhibitory effect on NF-κB/Rel activation [50]. In a recent study, Dhanalakshmi *et al*. [51] revealed that silibinin (a component of silymarin) effectively inhibits constitutive activation of NF-κB in DU145 human prostate adenocarcinoma cells.

Other natural microbial products derived from fungi, such as panepoxydone, cycloepoxydon, and gliotoxin, are also known to inhibit NF-κB activation [52]. Because NF-κB is known to be antiapoptotic and to promote survival in cancer cells, these compounds have been tested *in vitro* for their potential to promote apoptosis. The results showed that these compounds may be advantageous for cancer chemotherapy [52].

CONCLUSION REMARKS

We have herein briefly reviewed the medicinal chemistry of selected naturally occurring NF-κB inhibitors. These compounds include a wide range of classes, e.g. phenols and polyphenols, sesquiterpenes, diterpenes, triterpenes, lignans, among others. Their down-regulation of the activation of NF-κB is mediated through different mechanisms. Those compounds have great potentials for development of antiinflammatory agents and chemopreventive agents for several diseases such as cancer and cardiovascular diseases. However, at the present time, limited information about pharmacokinetics and toxicity of these compounds is available. Therefore, further investigation is needed to assess the efficacy and safety of these natural inhibitors of NF-κB.

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