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Inhibiting NF-κB Activation by Small Molecules As a Therapeutic Strategy

Subash C Gupta, **Chitra Sundaram**, **Simone Reuter**, and **Bharat B Aggarwal***
Cytokine Research Laboratory, Department of Experimental Therapeutics, The University of Texas M. D. Anderson Cancer Center, Houston, Texas 77030

Abstract

Because nuclear factor-κB (NF-κB) is a ubiquitously expressed proinflammatory transcription factor that regulates the expression of over 500 genes involved in cellular transformation, survival, proliferation, invasion, angiogenesis, metastasis, and inflammation, the NF-κB signaling pathway has become a potential target for pharmacological intervention. A wide variety of agents can activate NF-κB through canonical and noncanonical pathways. Canonical pathway involves various steps including the phosphorylation, ubiquitnation, and degradation of the inhibitor of NF-κB (IκBα), which leads to the nuclear translocation of the p50- p65 subunits of NF-κB followed by p65 phosphorylation, acetylation and methylation, DNA binding, and gene transcription. Thus, agents that can inhibit protein kinases, protein phosphatases, proteasomes, ubiquitnation, acetylation, methylation, and DNA binding steps have been identified as NF-κB inhibitors. Here, we review the small molecules that suppress NF-κB activation and thus may have therapeutic potential.

Keywords

Inflammation; NF-κB; small molecule inhibitors; therapeutics

1. Introduction

The nuclear factor-κB (NF-κB) signaling pathway plays a major role in the development, maintenance, and progression of most chronic diseases. NF-κB controls the expression of genes involved in a number of physiological responses, including immune inflammatory responses, acute-phase inflammatory responses, oxidative stress responses, cell adhesion, differentiation, and apoptosis [1]. Recent studies have suggested that NF-κB dysregulation is associated with many diseases including AIDS, atherosclerosis, asthma, arthritis, diabetes, inflammatory bowel disease, stroke, muscle wasting and viral infections. Mounting evidence indicates that NF-kB acts as a link between inflammation and cancer progression [2–10], making NF-κB essential to and a potential drug target in hematological malignancies and solid tumors [11,12]. NF-κB was first identified in 1986 by Sen and Baltimore [5] in the nucleus bound to an enhancer element of the immunoglobulin kappa light chain gene in B

*To whom correspondence should be addressed: Bharat B Aggarwal, aggarwal@mdanderson.org Phone: 713-794-1817; Fax: 713-745-6339.

cells [5,13]. It is now known to be ubiquitous in nature present in all the cell types and is evolutionary conserved. It belongs to the family of Rel proteins that includes c-Rel, RelA (p65), RelB, NF-κB1 (p50 and its precursor p105), and NF-κB2 (p52 and its precursor p100) all of which can form hetero- or homodimers [14–16].

NF-κB activation is tightly regulated mainly through its localization. In resting cells, NF-κB proteins are kept in the cytoplasm in association with inhibitory IkB proteins including IκBα, IκBβ, and IκBε [15] among which IκBα is the most abundant. NF-κB signaling occurs through the canonical (classical) pathway initiated by NF-κB1 (p50/p105) and a noncanonical (alternative) pathway initiated by NF-κB2 (p52/p100) (Fig 1). Before the active NF-κB is translocated into the nucleus, NF-κB1 and NF-κB2 are cleaved to the active p50 and p52 subunits, respectively. While the classical pathway depends on IKK complex consisting of IKKα, IKKβ, IKKγ and the inhibitory subunit IκBs, the alternative pathway depends on IKKα homodimers and NF-κB inducing kinase (NIK) [17–19]. During classical activation, the IKK complex specifically phosphorylates IκBs on two conserved N-terminal serine residues which target them for E2- and E3-ligase-mediated polyubiquitination and subsequent 26S proteasomal mediated degradation. This process releases and activates NF-κB which now translocates to the nucleus. The activation of alternative pathway, which is commonly associated with RelB results in regulated processing of the p100 precursor protein to p52 and subsequent translocation of p52-RelB heterodimers to the nucleus[18]. Although NF-κB activation occurs mainly through canonical and non-canonical pathways, during the past decade a number of pathways for NF-κB activation has been elucidated (Fig 1).

Once in the nucleus, activated NF-κB undergoes a series of posttranslational modifications, including phosphorylation, acetylation, and methylation. These modifications regulate both the strength and duration of NF-κB activity. RelA/p65 is directly phosphorylated by cAMP-dependent protein kinase (PKA) at Ser^{276}, casein kinase II (CKII) at Ser^{529}, and IKK at Ser^{536} [20,21]. RelA dephosphorylation by protein phosphatase 2A (PP2A) has been reported to decrease NF-κB activity [22]. RelA is subject to inducible acetylation by p300/CBP, and acetylated RelA interacts weakly, if at all, with IκBα [23,24], but maintains its nuclear localization and NF-κB transcriptional response. RelA is also subject to methylation by lysine methyltransferase Set9 (also called Set7 or KMT7) at $Lys^{314/315}$ [25].

Activated NF-κB binds to specific DNA sequences in target genes, which are designated as κB elements, and regulates the transcription of over 500 genes involved in immunoregulation, growth regulation, inflammation, carcinogenesis, and apoptosis (Fig 2). NF-κB is frequently constitutively activated in patients with chronic inflammatory conditions such as cancer and pulmonary, cardiovascular, autoimmune, skin, and neurodegenerative diseases [26]. NF-κB's ability to control multiple genes involved in human diseases makes the NF-κB signaling pathway a novel target for therapy [27,28].

Due to the various levels of regulation, NF-κB signaling pathway can be potentially targeted at various levels including kinases, phosphatases, ubiquitination, nuclear translocation, DNA binding, protein acetyl transferases and methyl transferases (Fig 3).

2. Inhibitors of the NF-κB activation pathway

Given NF-κB's relevance in human diseases and the fact that many drugs interfere with NF-κB signaling, the NF-κB signaling pathway provides a highly attractive target for the therapeutic development. More than 700 inhibitors of the NF-κB activation pathway, including antioxidants, peptides, small RNA/DNA, microbial and viral proteins, small molecules, and engineered dominant-negative or constitutively active polypeptides have been described (Table 1). Several of these molecules act as general inhibitors of NF-κB

activation, while other molecules target specific steps; some molecules possibly target multiple steps in the NF-κB pathway (Fig 3).

2.1. Inhibition of protein kinases

NF-κB activation requires the phosphorylation, polyubiquitination, and subsequent degradation of its inhibitory subunit, IκBα. Hence, inhibiting IκBα phosphorylation ultimately inhibits NF-κB's transcriptional activity [29,30]. IκBα phosphorylation is carried out by IKK, a serine/threonine protein kinase composed of three basic subunits: the kinases IKKα, IKKβ, and the regulatory subunit IKKγ (NEMO). The IKK activation is usually the first common step in the integration of many NF-κB-activating pathways; therefore, one strategy for inhibiting NF-κB activation is to block IKK activation. However, although more than 150 agents have been shown to inhibit NF-κB activation at the IKK step, few studies have investigated the mechanism by which a given agent can inhibit IKK or its activation. The few IKK inhibitors for which a mechanism of action is known can be divided into three general groups: adenosine triphosphate (ATP) analogs, which show some specificity for interacting with IKK; compounds that have allosteric effects on IKK structure; and compounds that interact with a specific cysteine residue (Cys-179) in the activation loop of IKKβ. ATP analogs include natural products such as β-carboline and synthetic compounds such as SC-839, which has an approximately 200-fold preference for IKKβ compared to IKKα [27,31]. Compounds that have allosteric effects on IKK structure include BMS-345541, a synthetic compound that binds to an allosteric site on both IKKα and IKKβ and has an approximately 10-fold greater inhibitory effect on IKKβ than on IKKα [32]. Compounds that interact with Cys-179 IKKβ include thiol-reactive compounds such as parthenolide, arsenite, and certain epoxyquinoids [33–36]; these compounds' interactions with Cys-179 are believed to interfere with phosphorylation- induced IKKβ activation because Cys-179 is located between Ser^{177} and Ser^{181}, which are required for IKKβ activation in response to upstream signals such as tumor necrosis factor (TNF) and lipopolysaccharide (LPS) [37,38]. Gene-based inhibitors can also block IKK activation. Specifically, mutations at the ATP-binding site or in the kinase activation loop can create dominant-negative IKKα and IKKβ, which are capable of blocking NF-κB activation [39–43]. Because of their distinct roles in the canonical and non-canonical NF-κB activation pathways, dominant-negative IKK mutants' can show stimulus-dependent inhibition [44]. Adenoviral-mediated delivery of an IKKβ dominant-negative kinase has been shown to have therapeutic potential for airway inflammatory diseases such as asthma [45,46]. NEMO can also serve as a target for inhibiting the IKK complex. In particular, introducing a cell-permeable 10 amino-acid peptide that corresponds to the NEMO-binding domain of IKKβ can block the binding of NEMO to IKK in response to TNF in the canonical pathway [47].

While activation of NF-κB by many stimuli depends on the phosphorylation of IκBs at N-terminal sites by the IKK complex, the mechanism of NF-κB activation by ultraviolet (UV) radiation involves the IKK-independent phosphorylation of IκBα at a cluster of C-terminal sites that are recognized by casein kinase II (CKII). CKII activity toward IκBα depends on p38 mitogen-activated protein kinase (MAPK) activation. CKII's role as a key survival signal that activates NF-κB and protects tumor cells from apoptosis suggests that CKII may be an attractive target for the treatment of diverse cancers. Apigenin, a plant flavonoid, and emodin, a plant anthraquinone, are competitive inhibitors of CKII that directly interact with the nucleotide-binding sites of CKII [48].

Besides phosphorylating and subsequently degrading the molecules that inhibit NF-κB, protein kinases can also target the functional domains of NF-κB proteins themselves to optimally activate NF-κB. NF-κB proteins can be phosphorylated in the cytoplasm or nucleus by such kinases as glycogen synthase kinase 3β (GSK3β) [49], TRAF-associated NF-κB activator (TANK)-binding kinase 1 (TBK1) [50,51], PKAc [20], mitogen- and

stress-activated protein kinase-1 (MSK-1) [52], MAP3K NIK[53], Tpl2, PKC-θ [54], PI3K, Akt [55–57], p38 MAPK [58], protein tyrosine kinase, PKC-δ [59], RHO-kinase 2 [60], Mitogen activated protein kinase kinase 3 (MEKK3) [61], and receptor tyrosine kinases such as epidermal growth factor receptor, human epidermal growth factor receptor 2 [62]. Antagonistic antibodies or kinase inhibitors that target these molecules may decrease NF-κB activation. Some kinase inhibitors that have the potential to inhibit NF-κB activation include SB203580 and PD0980589 (MAPK inhibitors) [58]; denbinobin (TAK1 inhibitor) [63]; tyrosine kinase inhibitors [62]; rhein, (an MEKK inhibitor) [64,65]; TNAP, betaine (NIK inhibitors) [66–68], epoxyquinol B (a TAK1 crosslinker) [69]; M2L (an extracellular signal-regulated kinase 2 inhibitor) [70,71]; CCK-8 (a p38 kinase kinase inhibitor) [72], KSR2 (an MEKK3 inhibitor) [73], golli BG21 (a PKC inhibitor) [74].

2.2. Inhibition of NF-κB activation by protein phosphatases

Because protein phosphorylation is a dynamic process whereby phosphatases counterbalance kinase action, phosphatases may be used to inhibit NF-κB activation. Protein phosphatase 2A is a serine/threonine phosphatase that has been reported to dephosphorylate and modulate the activity of IKKβ [75]. Cytosine arabinoside, a pyrimidine analogue used to effectively treat acute leukemia, has been reported to induce apoptosis by activating protein phosphatases 2A and 2B-A and dephosphorylating the p65 subunit of NF-κB [22,76]. Recently, OspF, a protein phosphatase from *Shigella flexneri*, was found to dephosphorylate MAPK and prevent histone H3 phosphorylation at Ser^{10} in a gene-specific manner to block the activation of a subset of NF-κB responsive genes [77]. Our previous studies have shown that protein tyrosine phosphatase (PTP) inhibitors can suppress NF-κB activation and that phenylarsine oxide, a specific PTP inhibitor, can promote tyrosine 42 phosphorylation of IκBα [78]. While some PTPs stimulate NF-κB activation, other PTPs negatively regulate NF-κB activation. For instance, PTEN, a tumor suppressor with phosphatase activity is known to inhibit NF-κB activation [79]. Recently, Chew et al., [80] found that WIP1, a Ser/Thr PP2C family of phosphatases act as a negative regulator of NF-κB activation. Overexpression of WIP1 was associated with decreased NF-κB activation, whereas WIP1 knockdown resulted in increased NF-κB activation. The group further showed that WIP1 target Ser^{536} of the p65 subunit of NF-κB.

2.3. Proteasome inhibitors and IκB ubiquitination blockers

The step before NF-κB leaves the cytoplasm involves the ubiquitination of IκB by the SCF-β-TrCP ubiquitin ligase complex followed by the rapid degradation of ubiquitinated IκB by the 26S proteasome [38]. Because IκBα degradation is an important step in the NF-κB activation pathway, inhibiting the proteasomes that degrade IκBα may also serve as a tool for pharmacological intervention. Very specific and potent proteasome inhibitors have been engineered by coupling boronic acid to dipeptides [81]. The dipeptide boronate, bortezomib, the most-studied proteasome inhibitor in clinical development [82], has been shown to inhibit proliferation and induce apoptosis in head and neck [83–85], prostate [86], pancreatic [87], gastric [88], and ovarian [89] cancers. Bortezomib's antitumor properties correlate in part with its ability to inhibit IκBα degradation [83,90]. Other well-known proteasome inhibitors include ALLnL, LLM, Z-LLnV, and Z-LLL, lactacystine, N-cbz-Leu-Leu-leucinal (MG132), MG115, and ubiquitin ligase inhibitors [91]. In addition, we recently identified a novel proteasome inhibitor, salinosporamide A (NPI-0052), which can suppress both constitutive and inducible NF-κB activation in a nanomolar range [92].

Several serine protease inhibitors with chymotrypsin-like specificity, including DCIC, TPCK, TLCK, BTEE, APNE, are also able to block proteasome function. However, unlike other protease inhibitors that block only IκB degradation, serine protease inhibitors can

block IκB phosphorylation as well as degradation. However, not all serine protease inhibitors can inhibit NF-κB activation [93–95].

Among IκB ubiquitination blockers, the YopJ protein of the bacterial pathogen *Yersinia* deubiquitinates and stabilizes IκBα to prevent NF-κB nuclear translocation [96]. The small molecule R0196-9920 has been reported to inhibit IκBα ubiquitination and oral inflammation in mouse models [97,98]. Yaron *et al*., [98] blocked TNFα-induced IκBα degradation by microinjecting phosphopeptides that corresponded to IκBα's signal-dependent phosphorylation site. Presumably these phosphopeptides acted as competitive inhibitors for binding to the ubiquitin ligase complex essential to IκBα degradation. Inhibiting β-TrCP (the recognition subunit of the SCF E3 ligase complex) by specific RNAi treatment or by overexpression of dominant-negative β-TrCP mutants blocked NF-κB activity and sensitized breast cancer cells to chemotherapeutic agents [99]. Recently, A20 (TNFAIP3), a cytoplasmic zinc finger protein, was shown to inhibit NF-κB activation in the TNFR and TLR pathways. The ubiquitin editing property of A20 was shown to be essential for NF-κB inhibition [100].

2.4. Blockage of NF-κB nuclear translocation

One approach for inhibiting NF-κB activation is to use small peptides that cross the cell membrane and block the nuclear translocation of the NF-κB complex [101–103]. For example, SN50, a forty-one-residue synthetic peptide that contains a hydrophobic membrane-translocating region and the nuclear localization sequence of NF-κB p50 [101], can enter cells and compete with NF-κB complexes for the machinery responsible for the nuclear translocation of NF-κB. SN50 effectively inhibits the LPS- and TNF-α-induced nuclear translocation of NF-κB in different cell lines [101,104–107] and mitigates inflammatory responses *in vivo* [108,109]. However, SN50 also blocks the nuclear translocation of a number of other transcription factors [102]. Dehydroxymethylepoxyquinomicin, a fungal epoxyquinoid that has anti-inflammatory and antitumor activity in several mouse models, has been reported to be a specific inhibitor of NF-κB nuclear translocation [110].

2.5. Blocking NF-κB activation by inhibitors of p65 acetylation

The activated p65 subunit of NF-κB undergoes acetylation in the nucleus at multiple lysine residues including K^{122}, K^{123}, K^{218}, K^{221} and K^{310} [23,111]. The opposing activities of histone acetyltransferases and histone deacetylases (HDACs) regulate p65 complex acetylation [24]. Acetylation of p65 also depends on coactivators such as p300 and CREB-binding protein (CBP) [112]. The K^{221} and K^{310} acetylation are associated with increased NF-κB target gene transcription [112] and are required for p65 activation [24], which is supported by the observations that SIRT driven deacetylation at K^{310} inhibits NF-κB target gene transcription [113]. Additionally, K^{122} and K^{123} acetylation reduces p65 DNA binding affinity and increases IκB interaction and nuclear export [111]. Site-specific p300-mediated p65 acetylation thus regulates the specificity of NF-κB- dependent gene expression [111,114].

During the last 5 years, a number of compounds have been reported to inhibit NF-κB by inhibiting acetylation. Gallic acid obtained from natural products such as gallnuts, sumac, oak bark, and green tea was recently reported to possess anti-histone acetyltransferase activity, thus showing potential to downregulate NF-κB activation [115]. Daxx, a protein associated with the death domain of Fas receptor, has been reported to suppress NF-κB transcriptional activity by inhibiting p300/CBP-mediated p65 acetylation [116]. Anacardic acid derived from traditional medicinal plants can also inhibit NF-κB activation by inhibiting p65 acetylation [117].

2.6. Blocking NF-κB activation by methyltransferases

The RelA subunits of NF-κB undergo various posttranslational modifications that create specific marks to recruit different effectors to control NF-κB's temporal and spatial activation [118]. RelA is subject to monomethylation by lysine methyltransferase Set9 (also called Set7 or KMT7) at $Lys^{314/315}$ *in vitro* and *in vivo* in response to stimuli [25]. RelA methylation at these two residues negatively regulates NF-κB function by triggering the ubiquitination and proteasome-mediated degradation of promoter-associated RelA. RelA methylation also serves as a "death" signal for the destruction of DNA-bound, activated NF-κB [25]. Because RelA subunit methylation negatively impacts NF-κB function, designing a molecule that activates Set9 function could potentiate NF-κB inhibition.

2.7. Blockage of NF-κB to DNA binding

The most direct strategy for blocking NF-κB activation is to block NF-κB from binding to specific κB sites on DNA. Some sesquiterpene lactones (SLs) have been reported to inhibit NF-κB [119] by interacting with Cys-38 in the DNA-binding loop of RelA [120,121]. Most SLs can also inhibit DNA binding through an analogous Cys residue in the DNA-binding loops of p50 and c-Rel. Recently, a computer-based structural comparison of 103 SLs predicted that a methylene-carbonyl substructure is important for SL-based inhibition of RelA at Cys-38 [122]. Some SLs, including parthenolide, have been shown to inhibit IKKβ through the reactive Cys-179 in the kinase activation loop [34,121]. Thus, SLs, which target both IKK activity and NF-κB subunit DNA binding [36], have multistep inhibitory activity within the NF-κB signaling pathway.

Blocking specific NF-κB-DNA binding can also be accomplished with decoy oligodeoxynucleotides (ODNs). These ODNs have κB sites and competes for NF-κB dimer binding to specific genomic promoters [123–125]. These oligonucleotides have modifications to increase their stability and their affinity for NF-κB *in vivo* [126–128]. Decoy ODNs have been reported to have therapeutic potential in a number of animal models of inflammation and cancer; for example, directly injecting NF-κB decoy ODNs into implanted adenocarcinoma colon 26 tumors in mice inhibited cachexia without affecting tumor growth [129].

2.8. Other mechanisms of NF-κB inhibition

2.8.1. By gene transfer—One strategy to block NF-κB activation is through the transfer of genes that code for proteins shown to suppress NF-κB activation. The most direct target is IκBα. IκBα mutation at specific phosphorylation sites (Ser^{32} and Ser^{36} replaced to alanine) and ubiquitination sites (Lys^{21} and Lys^{22} mutated to arginine) results in a nondegradable form of IκBα. This results in a stable cytoplasmic pool of IκBα, thereby preventing NF-κB activation [130–132]. Injecting a nonphosphorylatable form of IκBα into bone marrow macrophages has been shown to inhibit osteoclastogenesis and block bone resorption [133]. Additionally, specific C-terminal serine-to-alanine mutations are sometimes included to reduce the constitutive turnover of IκBα [134]. These super-repressor forms of IκBα can still interact with NF-κB dimers to keep the dimers in the cytoplasm permanently [132,134,135]. Such molecules have been used succesfully to inhibit NF-κB activity and to study its role in tumor development [136,137] and to sensitize tumor cells to apoptosis-inducing agents [134,135]. Inhibiting NF-κB through the expression of an IκBα super-repressor (IκBαSR) has also been used to sensitize chemoresistant tumors to TNFα- and CPT-11-induced apoptosis, resulting in tumor regression [138], and to inhibit the proliferation of human head and neck carcinoma cells *in vitro* and *in vivo* [139]. However, IκBαSRs have also been shown to interact with and affect the activity of non-NF-κB pathway proteins including p53 [140], cyclin-dependent kinase 4 [141], and HDACs [142]. Furthermore, IκBαSR

overexpression has been associated with the spontaneous development of squamous cell carcinoma in a murine model [143].

2.8.2. Antioxidants—Antioxidants were suggested as possible NF-κB inhibitors many years ago [144,145]. Treatment with oxidants such as hydrogen peroxide can activate NF-κB in many cell types. In some cell types, antioxidants can inhibit the induction of NF-κB activity in response to a variety of stimuli (e.g., interleukin-1β, LPS, TNFα) [146,147]. However, using antioxidants as NF-κB inhibitors is now regarded with increasing scepticism because the NF-κB-inhibiting properties of pyrrolidine dithiocarbamate, a thiol-containing compound, cannot be attributed to its antioxidant function but rather to its effects as an inhibitor of IκB ubiquitin ligase activity [148]. The ways in which antioxidants block NF-κB activation remain unclear, but it is likely that they act at different steps in the NF-κB pathway in different cell types. Antioxidants have been suggested to inhibit NF-κB activation by scavenging reactive oxygen intermediates that act as signaling molecules to activate the NF-κB pathway and by directly inhibiting IKK kinase activity by modifying critical Cys residues in the IKK kinase activation loop [146,147]. Mitochondrial electron transport inhibitors that suppress reactive oxygen intermediate production (e.g., rotenone) and overexpression of antioxidizing enzymes (e.g., manganese superoxide dismutase and catalase) can block TNFα-induced NF-κB activation [149–151]. Caffeic acid phenethyl ester, a phenolic antioxidant, has been reported to cause direct interference with DNA binding by NF-κB [152] that can be reversed by dithiothreitol [78]. Other antioxidants, *viz*., N-acetylcysteine, calcium chelators (e.g., EGTA, lacidipine), and vitamin C and E derivatives have been reported to inhibit hydrogen peroxide- or stimulus-induced NF-κB activation.

2.8.3. Bacterial, fungal, and viral proteins—Several microorganisms and viruses encode proteins that can inhibit NF-κB activation. Many viruses have developed a number of mechanisms to inhibit NF-κB signaling [153], and three viruses—African swine fever virus (ASFV) [154], rabbit myxoma virus [155], and insect *Microplitis demolitor* bracovirus [156]—encode IκB-like NF-κB inhibitors. The ASFV encodes the A238L IκB-like protein, which can stably interact with RelA to inhibit TNFα-, IFN-γ-, and phorbol ester-induced NF-κB-DNA binding [157]. The poliovirus 3C protease cleaves RelA to reduce NF-κB signaling [158]. In addition, several viruses have adaptor-like or small proteins that inhibit IKK activity [153]. For example, the MC160 protein of *Molluscum contagiosum* [159] and the nonstructural 5B protein of the hepatitis C virus [160] appear to be IKKα-specific and thus may specifically inhibit the noncanonical NF-κB pathway.

The YopJ protein, a Src homology 2 domain protein encoded by *Yersinia pseudotuberculosis*, inhibits NF-κB activation by preventing the phosphorylation and degradation of IκBα [161]. YopJ has also been shown to bind directly to IKKβ *in vitro* and *in vivo* [162]. The *Salmonella typhimurium* AvrA protein also inhibits NF-κB activation, although its mechanism of action may be different than that of the YopJ protein [163].

Gliotoxin produced by the fungus *Aspergillus fumigatus* has been reported to inhibit NF-κB activation by preventing IκB degradation [164]. Several other small molecules synthesized by microorganisms or designed derivatives of such compounds that have NF-κB-inhibiting potential include panepoxydone (from *Lentinus crinitus*) [165], 5,6 epoxycyclohexenone compounds (from *Amycolatopsis*), and cycloepoxydon [166]. Such compounds may affect distinct parts of the NF-κB pathway including DNA binding, nuclear translocation, and IκBα phosphorylation and degradation.

2.8.4. Anti-inflammatory and immunosuppressive agents—Various anti-inflammatory agents including glucocorticoids, non-steroid anti-inflammatory drugs

(NSAIDs), and immunosuppressants have been developed to block NF-κB activation. Glucocorticoids, which are commonly used as anti-inflammatory drugs, strongly inhibit NF-κB activation by mechanisms that are not completely understood but likely include inhibition of DNA binding, IKK activity and transactivation [167]. The glucocorticoids dexamethasone, prednisone and methylprednisolone have been reported to inhibit NF-κB activation. In addition, estrogen and selective estrogen receptor modulators (SERMs) such as raloxifene can act through the estrogen receptor to inhibit NF-κB activation [168,169].

NSAIDs such as sodium salicylate (aspirin) and sulindac have been reported to inhibit NF-κB activation by inhibiting IκBα phosphorylation [170,171]. At higher concentrations, aspirin has been shown to block NF-κB activity by directly binding to and inhibiting the kinase activity of IKKβ by reducing its ability to bind ATP [172]. More recently, aspirin was reported to inhibit proteasome activity [173]. As such, high-dose aspirin therapy may have applications in treating diseases in which NF-κB activity is involved, including cancer [174], diabetes [175], and heart disease [176]. Other NSAIDs such as ibuprofen and indomethacin have also been reported to inhibit NF-κB activation in cell culture [177–180].

Several well known immunosuppressants are known to target NF-κB by distinct mechanisms, some precluding NF-κB nuclear translocation [181], some through inhibiting calcineurin [182], some by binding heat-shock proteins [183] and some by modulating the DNA binding or transactivation potential of NF-κB [184–187]. Examples of immunosuppressants having inhibitory effect on NF-κB activation include cyclosporin A (CsA) [181], FK506 [188,189], PG490 (diterpene triepoxide) [187] and deoxyspergualin [183].

2.8.5. p53 induction—It is known that p53 and NF-κB pathways play opposing roles in human cancer, with p53 acting as a tumor suppressor and NF-κB acting as a tumor activator. The crosstalk between p53 and NF-κB indicates that p53 and NF-κB repress each other's activities owing to their competition for transcriptional coactivator proteins p300 and CBP [190]. A recent study has proposed an additional mechanism of how CBP phosphorylation by IKKα determines whether CBP binds to p53 or NF-κB [191]. Although a number of studies have focused on identifying p53 activators and NF-κB inhibitors individually, few studies have investigated the molecules that target both the pathways simultaneously. Identifying molecules that simultaneously activate p53 and inhibit NF-κB would have great potential in combination therapy for cancer and various other diseases and could provide helpful tools to better understand the crosstalk between the p53 and NF-κB pathways. Quinacrine, an antimalarial drug, and other derivatives of 9 aminoacridine have been shown to simultaneously repress NF-κB and activate p53 in renal cell carcinoma [192]. Other molecules with similar potential include nutlins [193,194], cisplatin [195,196], leptomycin B [197,198], adenosine-2,3-dialdehyde [199], the NSAID JTE-522 [200], and the cyclin-dependent kinase inhibitors R-roscovitine [201,202]; and flavopiridol [203,204].

3. Conclusions and future perspective

NF-κB has been implicated in almost all chronic diseases, and more than 40,000 studies on NF-κB have been published with 9000 on its inhibitors. Although more than 700 different inhibitors (aspirin to IκBα super repressor) of this transcription factor have been reported, yet no NF-κB blocker has been approved for human use. Various steroids and NSAIDs have been found to block NF-κB, but their effects are highly pleiotropic. The molecules that block NF-κB activation lack specificity and thus interfere with NF-κB's physiological roles in immunity, inflammation, and cellular homeostasis. Additionally, whether the concentrations of inhibitors used in tissue culture experiments can be applied *in vivo* is often unclear. Therefore, one of the major challenges facing researchers is to develop NF-κB

inhibitors aimed at treating different diseases based on their ability to target specific pathways or cells, thereby avoiding the risk of undesired side effects. Future studies should also focus on validating *in vitro* data *in vivo*.

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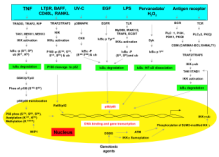

Figure 1.

Schematic representation of major NF-κB activation pathways. In the classical pathway, binding of TNFα to the receptor triggers the sequential recruitment of the adaptors TRADD, TRAF2 and RIP to the membrane. TRAF2 then recruits the IKK complex composed of IKKα, IKKβ and IKKγ (NEMO) through mediation of kinases like TAK1, MEKK1, MEKK3. Activation of the IKK complex leads to the phosphorylation and ubiquitination of IκBα at specific residues followed by its degradation via the proteasome pathway. The p105 subunit of NF-κB then undergoes GSK3β and Tpl2 mediated phosphorylation at S^{903} and S^{907} and subsequent degradation. The heterodimer p50–p65 is then released and migrates to the nucleus where it undergoes a series of posttranslational modifications including phosphorylation, acetylation and methylation and binds to specific κB sites and activates NF-κB target genes [49,205,206]. The alternative pathway is IKKγ independent and is triggered by binding of the CD40, RANK, LTβR, BAFF ligands to their receptor, leading to recruitment of TRAF proteins and the sequential activation of NIK and IKKα. Activation of IKKα then induces the processing of the inhibitory protein p100. p100 proteolysis releases p52 which then translocates to the nucleus and triggers transcription of NF-κB target genes [207]. NF-κB activation in response to UV-C does not depend on IKK activation and relies on sequential recruitment of p38MAPK and CKII. Activated CKII phosphorylates IκBα at C-terminus (S^{283}-T^{299}). The phosphorylated IκBα undergoes ubiquitination and degradation leading to release of active NF-κB in to the nucleus [208,209]. EGF induced NF-κB activation proceeds without serine phosphorylation and ubiquitination of IκBα and is IKK independent. It relies on phosphorylation of IκBα at Tyr^{42} through mediation of tyrosine kinases that triggers its proteasome mediated degradation and subsequent release of active NF-κB to the nucleus [210]. NF-κB activation in response to bacterial endotoxin LPS involves Toll like receptor and is mediated through recruitment of MyD88, TRAF6 and ECSIT. Recruitment of these adaptors leads to sequential activation of IRAK1/2 and IKK and eventual release of active NF-κB [211]. NF-κB activation by pervanadate and H_2O_2 induces phosphorylation of IκBα at Tyr^{42} by protein tyrosine kinase like Syk. The Tyr phosphorylation does not lead to IκBα degradation but makes the binding weak thereby dissociating the IκBα and releasing active NF-κB to the nucleus [212,213]. Antigen receptor viz., T-cell receptor and B-cell receptor mediated signaling to NF-κB activation depends on recruitment of a trimolecular protein complex CARMA1-BCL10-MALT1. In this pathway PKCθ (in T cells) and PKCβ (in B cells) alongwith other kinases act upstream to the trimolecular complex to promote IKKγ polyubiquitination and consequent IKK activation. Activation of IKK through this pathway involves mediation of TRAF2, TRAF6, TAK1 and TAB1 [214,215]. A novel pathway of NF-κB activation originating from the nucleus is associated with DNA damage. Double-stranded DNA breaks in response to genotoxic agents initiate signals that trigger SUMOylation of nuclear-localized IKKγ, preventing its nuclear export. Concomitantly, these breaks activate ATM which phosphorylates SUMO-modified IKKγ, promoting the removal of SUMO and enhancing IKKγ ubiquitination. Ubiquitinated IKKγ then translocates to the cytoplasm, where it activates IKK in cooperation with ATM and the ELKS protein, leading to IκBα phosphorylation and degradation, p65 nuclear translocation and induction of NF-κB dependent target genes [216–219]. NF-κB can also be regulated by phosphatases. WIP1, a Ser/Thr phosphatase was recently shown to negatively regulate NF-κB activation by dephosphorylating p65 at Ser^{536} [80].

Abbreviations: AgR, antigen receptor; ATM, ataxia-telangiectasia mutant; BAFF, B-cell activating factor; BCL, B-cell lymphoma; BCR, B cell receptor; CARMA, CARD-

containing MAGUK protein; CD40L, CD40 ligand; CK, casein kinase; DSBS, Double-stranded DNA breaks; ECSIT, evolutionary conserved signaling intermediates on Toll pathways; EGF, epidermal growth factor; EGFR, EGF receptor; ELKS, glutamate, leucine, lysine, serine-rich protein; GSK, glycogen synthase kinase; Hsp90, heat shock protein 90; IκB, inhibitor of NF-κB; IKK, IκB kinase; IRAK, IL-1R-associated kinase; LTβ, lymphotoxin β; LPS, lipopolysaccharide; MALT, mucosa-associated lymphoid tissue; MAPK, mitogen activated protein kinase; MAPK/Erk kinase kinase; MyD88, myeloid differentiation factor; NF-κB, nuclear factor-κB; NIK, NF-κB-inducing kinase; NEMO, NF-κB essential modulator; PDK, Phosphoinositide-dependent kinase; PI3K, phosphatidylinositol 3-kinase; PKC, protein kinase C; PLC, phospholipase C; RANKL, receptor activator of NF-κB ligand; RIP, receptor-interacting protein; Syk, Spleen tyrosine kinase; TAB, TAK1-binding protein; TAK, transforming growth factor-β-activated kinase; TCR, T cell receptor; TLR, Toll-like receptor; TNF, tumour necrosis factor; TNFR1, TNF receptor 1; Tpl2, tumour progression locus-2; TRADD, TNF-receptor-associated death domain protein; TRAF, TNF-receptor-associated factor.

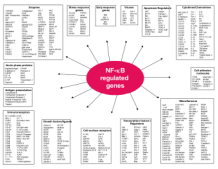

Figure 2.
A list of gene products regulated by NF-κB.

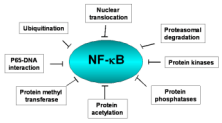

Figure 3.
Potential targets for inhibiting the NF-κB activation pathway.

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Table 1

A list of small molecules as inhibitors of NF-kB pathway

A. Upstream NF-kB	Kahweol	AIDCA derivative	Catalposide	E-73	RelA peptides (P1 & P6)
Natural product	Kava derivatives[2]	TDZD	Cyclolinteinone	Ecabet sodium	***Viral Protein***
15d-PGJ(2)	Licorce extracts	TPCA-1	Dihydroarteanniun	Gabexate mesilate	3C protease (EMC virus)
Calagualine	Manumycin A	Pyridine derivatives	Docosahexaenoic acid	Glimepiride	Canine Distemper Virus
Conophylline	Monochloramine	ACHP	Emodin	Hypochlorite	MNF (myxoma virus)
Evodiamine	N-acetylcysteine	Acrolein	*Ephedrae herba* (Mao) extract	Losartin	***Protein***
Geldanamycin	Nitric oxide	AGRO100*	Equol	LY294002	C5a
Perrilyl alcohol	Nitrosylcobalamin	Amino-pyrimidine	Erbstatin	Pervanadate	DQ 65-79
PSK	Oleandrin	AS602868	Estrogen	Phenylarsine oxide	Fox1j
Rocaglamides	Omega 3 fatty acids	Aspirin	Ethacrynic acid	Phenytoin	GILZ
Viral protein	ox-LDL	Azidothymidine	Fosfomycin	Ro106-9920**	HSCO
Adenovirus E1A	Panduratin A	BAY-11-7082	Fungal gliotoxin	Sabaeksan	HSP-72
NS5A (Hep-C virus)	PEITC	BAY-11-7083	Gamisanghyulyunbueum***	U0126 (MEK inhibitor)	Interleukin-10
Protein	Petrosaspongiolide M	Benzoimidazole derivative	Genipin	***Others***	Interleukin -11
Erbin overexpression	Phytic acid	Benzyl isothiocyanate	Genistein	Vagus nerve stimulation	Interleukin -13
Golli BG21	Piceatannol	BMS-345541	Glabridin	Low level laser therapy	MTS-SR-IκBα
KSR	Pinosylvin	Carboplatin	Glucosamine sulfate	Zinc	Onconase
MAST205	*Plagius flosculosus* extract	CDDO-Me	Glutamine	**D. IκB upregulators/**	RASSF1A gene
NPM-ALK oncoprotein	Plumbagin	CHS 828*	Gumiganghwaltang***	**NF-κB translocation**	ROR-alpha
Hep-C virus protease	Pomegranate extract	Compound 5	Isomallotochromanol	***Natural product***	Surfactant protein A
PEDF	Prostaglandin A1	Compound A	Isomallotochromene	PGG	TAT-SR- IκBα
Rituximab	Quercetin	Cyclopentenones	*Kochia scoparla* fruit extract	15-deoxyspergualin	ZAS3 protein
TNAP	Rengyolone	CYL-19s	L-ascorbic acid	2',8''-biapigenin	ZUD protein
Synthetic	Rosmarinic acid	CYL-26z	Leflunomide metabolite	5F (from *Pteri syeminpinnata*)	β-amyloid protein
Betaine	Rottlerin	Diaylpyridine derivative	Melatonin	*Agastache rugosa* leaf extract	***Synthetic***
Desloratadine	Saikosaponin-d	DPE	Midazolam	Alginic acid	BMD
LY29 and LY30	*Salvia miltiorrhoza* extract	Epoxyquinone	Momordin I	*Antrodia camphorata* extract	Carbaryl
MOL 294 **	Sanguinarine	Gabexate mesilate	*Morinda officinalis* extract	Apigenin	CGS 25462
Pefabloc	*SAm* extract	Gleevec	*Mosla diantherra* extract	Astragaloside IV	DHMEQ

Rhein
SMI and FP
B. IKK activity and IkB phosphorylation
Natural product
[6]-gingerol
1'-Acetoxychavicol acetate
20(S)-Protopanaxatriol
4-Hydroxynonenal
Acetyl-boswellic acids
Anandamide
Anethole
Apigenin
Artemisia vestita[1]
Baoganning
Betulinic acid
Black raspberry extracts
Buddlejasaponin IV
Cacospongionolide B
Calagualine
Cardamomin
Cardamonin
Casparol
Cobrotoxin
Cycloepoxydon
Decursin
Dehydroascorbic acid
Dexanabinol
Digitoxin
Diosgenin
Diterpenes
Docosahexaenoic acid
Staurosporine
Sesquiterpene lactones
Scoparone
Silibinin
Silymarin
Sulforaphane
Sulindac
Tetrandine
Theaflavin
Thienopyridine
Tilianin
Ursolic acid
Vesnarinone
Wedelolactone
Withanolides
Xanthoangelol D
Zerumbone
β-carboline
γ-mangostin
γ-Tocotrienol
Peptide
IKKβ peptide
NEMO CC2-LZ peptide
Protein
Anti-thrombin III
Chorionic gonadotropin
FHIT
HB-EGF
Hepatocyte growth factor
Interferon-α
Interleukin-10
PAN1
Hydroquinone
Ibuprofen
IQCAD
Indolecarboxamide
Isobutyl nitrite
Jesterone dimer
15-deoxyspergualine analog
Methotrexate
MLB120**
Monochloramine
MX781 (Retinoid antagonist)
4-HPR
Nafamostat mesilate
NSAIDs
PS-1145 (MLN1145)
PQD
Pyridooxazinone derivative
SC-514**
Scytonemin
Sodium salicylate
Statins (several)
Sulfasalazine
Sulfasalazine analogs
Survanta
Thalidomide
THI 52
YC-1**
Others
Lead
Mild hypothermia
Saline (low Na+)
C. IkB degradation
Opuntia ficus indica extract
Platycodin saponins
Polymyxin B
Poncirus trifoliata fruit extract
Probiotics
Prostaglandin
Resiniferatoxin
Stinging nettle extracts
Thiopental
Tipifarnib
Titanium
TNP-470
Trichomomas vaginalis
TG-rich lipoproteins
Ursodeoxycholic acid
Xanthium strumarium extract
β- PEITC
8-MSO
β-lapachone
Peptide
Penetratin
VIP
Protein
Activated protein C
HSP-70
Interleukin-13
Intravenous Ig
Murr1 gene product
Neurofibromatosis-2 protein
PACAP
SAIF
ST2 (IL-1-like receptor)
AT514 (serratamolide)
Atorvastatin
Blue honey suckle extract
Buthus martensi extract
Cantharidin
Chiisanoside
Clarithromycin
Cornus officinalis extract
Eriocalyxin B
Gangliosides
Glucocorticoids
HP extracts
Hirsutenone
Human breast milk
JM34
KIOM-79
Leptomycin B
Neomycin
Nucling
Oregonin
OXPAPC
Paeoniflorin
Phallacidin
Piperine
Pitavastatin
Platycodi radix extract
Probiotics
Rapamycin
Rhubarb aqueous extract
Salvia miltiorrhoza extract
SH extract
Selenomethionine
Diltiazem
Dioxin
Dipyridamole
Disulfiram
Enalapril
mEET
Fluvastatin
Indole-3-carbinol
JSH-23
KL-1156
Leflunomide
Levamisole
MEB
Moxifloxacin
Omapatrilat
R-etodolac
Rolipram
SC236 (COX-2 inhibitor)
Triflusal
Volatile anesthetics
E. NF-kB DNA-binding
Inorganic Complex
Metals (chromium, cadmium, gold, lead, mercury, zinc, arsenic)
Natural product
Actinodaphine
Anthocyanins
Arnica montana extract
Artemisinin
Baicalein
Bambara groundnut
β-lapachone

Falcarindol
Flavopiridol
Furonaphthoquinone
Garcinone B
Glossogyne tenuifolia extract
Glycine chloramine
Guggulsterone
Herbimycin A
Honokiol
Hypoestoxide
Indirubin-3'-oxime
Isorhapontigenin
Clarithromycin
Cloricromene
C-K and Rh(2)
Cortex cinnamomi extract
Cryptotanshinone
Cytochalasin D
Black rice extract
Danshenshu
Diterpenoids
Ent-kaurane diterpenoids
Epinastine hydrochloride
Epoxyquinol A
Erythromycin
Evodiamine
Fish oil
Fomes fomentarius extracts
Fucoidan
Gallic acid

PTEN
SOCS1
Viral Protein
Adenovirus
Core protein (Hep-C virus)
Cytomegalovirus
E7 (Papillomavirus)
MC159
MC160
NS5B (Hep-C virus)
vIRF3 (KSHV)
Synthetic
AIM2 overexpression
Angiopoietin-1
Antithrombin
AvrA protein (Salmonella)
β-catenin
Bromelain
CaMKK
CD43 overexpression
FLN29 overexpression
FLIP
G-120
Gax (homeobox protein)
HIV-1 Resistance Factor
Interleukin 4
SspH1 and IpaH9.8
NDPP1 (CARD protein)
Overexpressed ZIP1
p8
p202a

Natural product
5'-methylthioadenosine
Artemisia iwayomogi extract
Alachlor
Amentoflavone
Antrodia camphorata[#]
Artemisia capillaries extract
Aucubin
Baicalein
Blackberry extract
Buchang-tang[***]
Capsaicin
Raxofelast
Ribavirin
Rifamides
Ritonavir
Rosiglitazone
Roxithromycin
DAAS
Serotonin derivative
Simvastatin
SM-7368[**]
T-614
Sulfasalazine
SUN C8079
Triclosan plus CPC
Tobacoo smoke
Verapamil
Others
Heat (fever-like)
Hypercapnic acidosis
Hyperosmolarity

α-MSH
γ-glutamylcysteine synthetase
Bacterial/Viral Protein
K1L (Vaccinia virus protein)
Nef (HIV-1)
Vpu protein (HIV-1)
YopJ
Synthetic
1-Bromopropane
Acetaminophen
Diamide
Dobutamine
F. Proteasome/protease
Natural product
Cyclosporin A
Lactacystine
β-lactone
Peptide
ALLnL
LLM
Ubiquitin ligase
Z-LLL
Z-LLnV
Synthetic
APNE
Boronic acid peptide
BTEE
3,4-dichloroisocoumarin
Deoxyspergualin
DFP
Disulfiram
FK506 (Tacrolimus)

Shenfu
Sophorae radix extract
Sopoongsan
Sorbus commixta extract
Sphondin
T. polyglycosides
Younggaechulgam-tang[***]
α-pinene
Peptide
NCPP
PN50

Mangifera indica bark extract
Mangiferin
Melatonin
Mn-SOD
Mulberry anthocyanins
Myricetin
N-acetyl-L-cysteine
Nacyselyn
Naringin
N-ethyl-maleimide
Nitrosoglutathione
NDGA
Ochnaflavone
Orthophenanthroline
Phenylarsine oxide
PhIP
Phyllanthus urinaria
PMC
PTX

Biliverdin
Brazilian
Calcitriol
Campthothecin
Sutherlandia frutescens
Capsiate
Catalposide
Cat's claw bark
Cheongyeolsaseuptang[***]
Chitosan
Chicory root
CSPDP

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Ganoderma lucidum
Garcinol
Geranylgeraniol
Ginkgolide B
Glycyrrhizin
Halofuginone
Hematein
Herbal compound 861
Hydroxyethyl starch
Hydroxyethylpuerarin
Hypericin
Kamebakaurin
Linoleic acid
Lithospermi radix
Macrolide antibiotics
Mediterranean plant extracts
2-methoxyestradiol
6-MITC
Nicotine
Ochna macrocalyx bark ext.
Oridonin
PC-SPES (8 herb mixture)
PGG
Pepluanone
Phyllanthus amarus extracts
Plant compound A
Polyozellin
Prenylbisabolane 3
Prostaglandin E2
p21 (Rec)
PIAS1
Pro-opiomelanocortin
PYPAF1 protein
Raf Kinase inhibitor
protein *Rhus verniciflua* fruits
SLPI
Siah2
SIRT1 Deacetylase overexpression
Siva-1
Solana nigrum L.
Surfactant protein A
Tom1 overexpression
Transdominant p50
Uteroglobin
VEGF

Synthetic

ADP ribosylation inhibitor
7-amino-4-methylcoumarin
Amrinone
Atrovastat
Benfotiamine
Benzamide
Bisphenol A
Caprofen
Carbocisteine
Celecoxib
Germcitabine
Cinnamaldehyde
2-methoxy CNA
Hypothermia
Alcohol

E. NF-kB transactivation

Natural products

4'-DM-6-Mptox
4-phenylcoumarins
AHUP
Adenosine
c-AMP
Artemisia sylvatica extract
Bifodobacteria
Blueberry & berry mix
BSASM
BF phenylpropanoids
cPrG.HC
Seaweed extract
Fructus benincasae extract
Glucocorticoids
Gypenoside XLIX
Kwei Ling Ko^{3}
LC root
Luteolin
Manassantins A,B
MI bark extract
Mesuol
Nobiletin
Phomol
Psychosine
Qingkailing$^{\#}$
Saucerneol D & E
Shuanghuanglian$^{\#}$
Smilax bockii extract
Bortezomib
Salinosporamide A
TLCK
TPCK

G. Antioxidants

23-hydroxyursolic acid
Aged garlic extract
Anetholdithiolthione
Apocynin
Apple juice/extracts
Arctigenin
Aretemisa p7F
Astaxanthin
Benidipine
bis-eugenol
BG compounds
BHA
CAPE
Carnosol
Carvedilol
Catechol derivatives
Celasterol
Cepharanthine
Chlorogenic acid
Chlorophyllin
Cocoa polyphenols
Curcumin
DHEA
DHEA sulfate
Dehydroevodiamine
Demethyltraxillagenin
Diethyldithiocarbamate
Pyrithione
Pyrrolinedithiocarbamate
Quercetin
Quinozolines
Rebamipide
Red wine
Redox factor 1
Resveratrol
Ginseng derivative
Rotenone
Roxithromycin
S-allyl-cysteine
Sauchinone
Spironolactone
Strawberry extracts
Taxifolin
Tempol
Tepoxaline
tert-butyl hydroquinone
Tetracylic A
Vitamin B6
Vitamin C
Vitamin D
Vitamin E derivatives
Wogonin
xanthohumol
Yakuchinone A, B
α-lipoic acid
α-tocopherol
α-torphryl acetate
α-torphryl succinate
β-Carotene

PSK
Quinic acid
Sanggenon C
Sesamin
Shen-Fu#
Silibinin
Sinomenine
Sword brake fern extract
Tanacetum larvatum extract
Tansinones
Taurine + niacine
TZD MCC-555
Trichostatin A
Triptolide
Tyrphostin AG-126
Ursolic acid
Withaferin A
Xanthohumol
Xylitol
Yan-gan-wan#
Yin-Chen-Hao#
Yucca schidigera extract

Peptide

Ghrelin
Peptide YY
Rapamycin

Viral Protein

African Swine Fever virus
Sendai Virus-C,V proteins
E1B (Adenovirus)
ICP27 (HSV-1)

2-hydroxy CNA
CDS
CP Compound
Cyanoguanidine
HMP
α-difluoromethylornithine
DTD
Evans Blue
Evodiamine
Fenoldopam
FEX
Fibrates
FK778
Flunixin meglumine
Flurbiprofen
Hydroquinone
IMD-0354
JSH-21
KT-90
Lovastatin
Mercaptopyrazine
Mevinolin,
Monoethylfumarate
Moxifloxacin
Nicorandil
Nilvadipine
NO-ASA
Panepoxydone
Peptide nucleic acids
Perindopril
PAD
α-PBN

Trilinolein
Uncaria tomentosum extract
WS extracts
Wortmannin
α-zearalenol

Viral Protein

BZLF1 (EBV protein)
SH gene products (PMV)

Protein

Antithrombin
NF-kappaB-repression factor
PIAS3
PTX-B

Synthetic

17-AAG
TMFC
AQC derivatives
9-aminoacridine
derivatives
Chromene derivatives
D609
Dimethylfumarate
EMDPC
Histidine
HIV-1 PI
Mesalamine
PEITC
Pranlukast
RO31-8220 (PKC inhibitor)
SB203580 (MAPK inhibitor)
Tetrathiomolybdate

Diferoxamine
Dihydroisoeugenol
Dihydrolipoic acid
Dilazep
Fenofibric acid
DMDTC
Dimethylsulfoxide
Disulfiram
Ebselen
Edaravone
EGTA
EPC-K1
Epigallocatechin-3-gallate
Ergothioneine
Ethyl pyruvate

Ganoderma lucidum

polysaccharides
Garcinol
γ-glutamylcysteine synthetase
Ginkgo biloba extract
Glutathione
Hematein
Hydroquinone
Hydroquinone
IRFI 042
Iron tetrakis
Isovitexin
Kangen-karyu extract
Ketamine
Lacidipine
Lazaroids
L-cysteine

H4/N5 (bracovirus)	Pioglitazone	Tranilast	Ligonberries
NS3/4A (Hep-C)	Pirfenidone	Troglitazone	Lupeol
Protein	PNO derivatives	***Others***	Magnolol
Adiponectin	Quinadril	Low gravity	Maltol

[1]Tibetan medicine;

[2]Piper methysticum;

[3]Tortoise shell-Rhizome jelly;

[*]Anticancer drugs;

[**]small molecules;

[***]Oriental medicines;

[#]Traditional Chinese Medicine; 15d-PGJ(2), 15-deoxy-prostaglandin J(2); 17-AAG, 17-allylamino-17-demethoxygeldanamycin; 20(S)-PPT, 20(S)-Protopanaxatriol; 4'-DM-6-Mptox, 4'-demethyl-6-methoxypodophyllotoxin; 6-MITC, 6-Methylsulfinyl) hexyl isothiocyanate; α-MSH, α-melanocyte-stimulating hormone; α-PBN, alpha-phenyl-N-tert-butylnitrone; ACHP, 2-amino-6-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-4-piperidin-4-yl nicotinonitrile; AGRO100, G-quadruplex oligodeoxynucleotide; AHUP, 8-acetoxy-5-hydroxyumbelliprenin; AIDCA, (Amino)imidazolyl carboxaldehyde derivative; ALLnL, N-acetyl-leucinyl-leucynil-norleucynal; APNE, N-acetyl-DL-phenylalanine-b-naphthylester; AQC, 6-aminoquinazoline; BAY-11-7082, E3((4-methylphenyl)-sulfonyl)-2-propenenitrile; BAY-11-7083, E3((4-t-butylphenyl)-sulfonyl)-2-propenenitrile; *BF, Bupleurum fruticosum; BG, Bruguiera gymnorrhiza;* BHA, Butylated hydroxyanisole; BMD, N(1)-Benzyl-4-methylbenzene-1,2-diamine; BMT, o,o'-bismyristoyl thiamine disulfide; BSASM, plant extract mixture; BTEE, N-benzoyl L-tyrosine-ethylester; CaMKK, Calcium/calmodulin-dependent kinase kinase; CAPE, Caffeic Acid Phenethyl Ester; CDDO-Me, C-28 methyl ester of 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid; CDS, Commerical peritoneal dialysis solution; CMP, Chinese medicinal preparations; CNA, Cinnamaldehyde; Compound 5, Uredio-thiophenecarboxamide derivative; CP Compound, 6-Hydroxy-7-methoxychroman-2-carboxylic acid phenylamide); CPC, cetylpyridinium chloride; cPrG.HC, Cycloprodigiosin hycrochloride; CSPDP, Chondrotin sulfate proteoglycan degradation product; CYL-19 s and CYL-26z, two synthetic alpha-methylene-gamma-butyrolactone derivatives; D609, phosphatidylcholine-specific phospholipase C inhibitor; DAAS, diacetoxy acetal derivative of santonin; DFP, diisopropyl fluorophosphates; DHEA, Dehydroepiandrosterone; DHMEQ, Dehydroxymethylepoxyquinomicin; DMDTC, Dimethyldithiocarbamates; DPE, 2-(3,4-dihydroxyphenyl)ethanol; DTD, 4,10-dichloropyrido[5,6:4,5]thieno[3,2-d':3,2- d]-1, 2, 3-ditriazine; EGTA, Ethylene glycol tetraacetic acid; EMC virus, encephalomyocarditis virus; EMDPC, Ethyl 2-[(3-methyl-2,5-dioxo(3-pyrrolinyl)) pyrimidine-5-carboxylate; EPC-K1, phosphodiester compound of vitamin E; FEX, Fexofenadine hydrochloride; FHIT, Fragile histidine triad protein; FLIP, FLICE-Like Inhibitory Protein; G-120, Ulmus davidiana Nakai glycoprotein; GILZ, Glucorticoid-induced leucine zipper protein; HB-EGF, Heparin-binding epidermal growth factor-like growth factor; HMP, 7-(4'-hydroxy-3'-methoxyphenyl)-1-phenylhept-4-en-3-one; *HP, Harpagophytum procumbens;* HSCO, Hepatoma Subtracted-cDNA library Clone One; IQCAD, Imidazolylquinoline-carboxaldehyde derivative; JSH-23, 4-Methyl- -(3-phenyl-propyl)-benzene-1,2-diamine; KL-1156, 6-Hydroxy-7-methoxychroman-2-carboxylic acid phenylamide; KSHV, Kaposi's sarcoma-associated herpesvirus; KSR, Kinase suppressor of ras; *LC, Ligusticum chuanxiong;* LLM, N-acetyl-leucinyl-leucynil-methional; LY294002, [2-(4-morpholinyl)-8-phenylchromone]; MAST205, a serine/threonine kinase; MC160, Mollusum contagiosum virus; MEB, 2-(4-morpholynl) ethyl butyrate hydrochloride; mEET, Mouse estrogen enhanced transcript; Mn-SOD,Manganese superoxide dismutase; MSO, 8-methylsulphinyloctyl; N-(4-hydroxyphenyl) retinamide [4-HPR; NDGA, Nordihydroguaiaritic acid; NCPP, NLS Cell permeable peptides; NFD-37, 2-Methyl-2-(2-methylpropenyl)-2,3-dihydronaphthoquinone [2,3-b]furan-4,9-dione; NH(2)Cl, monochloramine; NO-ASA, Nitric-oxide-donating aspirin; ox-LDL, Oxidized low density lipoprotein; OXPAPC, oxidized 1-palmitoyl-2-arachidonoyl-sn-glycero-3-phosphorylcholine; PACAP, Pituitary adenylate cyclase-activating polypeptide; PAD, 6(5H)-phenanthridinone; PEDF, pigment epithelium derived factor; PEITC, Phenethyl isothiocyanate; PGG, 1,2,3,4,6-penta-O-galloyl-β-D-glucose; PhIP, 2-Amino-1-methyl-6-phenylimidazo[4,5-b]pyridine; PI, protease inhibitor; PIAS1, protein inhibitor of activatated STAT1; Plant compound A, plant-derived phenyl aziridine precursor; PMC, (2,2,5,7,8-pentamethyl-6-hydroxychromane); PMV, Paromyxovirus; PNO, Pyridine N-oxide; PQD, Pyrazolo[4,3-c]quinoline derivative; PSK, Protein-bound polysaccharide; PTEN, phosphatase and tensin homolog; PTX, Pentoxyifylline (1-(5'-oxohexyl) 3,7-dimehylxanthine; PTX-B, pertussis toxin binding protein; Pyridine derivatives, 2-amino-3-cyano-4-aryl-6-(2- hydroxy-phenyl)pyridine derivatives; RH(2) & C-K, intestinal bacterial metabolites Rh(2) and compound K (C-K); RORalpha, Retinoic acid receptor-related orphan receptor-alpha; *SH, Sargassum hemiphyllum;* SAIF, Saccharomyces boulardii anti-inflammatory factor; SLPI, Secretory leucoprotease inhibitor; SMI and FP, Salmeterol and Fluticasone propionate; SOCS, suppressor of cytokine signaling proteins; SspH1 and IpaH9.8, Leucine-rich effector proteins of Salmonella & Shigella; TDZD, 1,2,4-thiadiazolidine derivative; TG, triglyceride; THI 52, 1-naphthylethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline; TLCK, N-α-tosyl-L-lysine chloromethyl ketone; TMFC, 3,4,5-trimethoxy-4'-fluorochalcone; TNAP, TRAFs and NIK-associated protein; *; TP, Tripterygium polyglycosides;* TPCA-1, 2-[(aminocarbonyl)amino]-5-acetylenyl-3-thionphenecarboxamides; TPCK, N-α-tosyl-L-phenylalanine chloromethyl ketone; TZD, Thiazolidinedione; VEGF,

Vascular endothelial growth factor; VIP, Vasoactive intestinal peptide; VVP, Vaccinia virus protein; *WS, Witheringia solanacea;* Z-LLL, N-carbobenzoxyl-L-leucinyl-L-leucinyl-L-norleucinal; Z-LLnV (carbobenzoxyl-leucinyl-leucynil-norvalinal;