Review Article
Volume 11:11, 2021

Medicinal Chemistry

ISSN: 2161-0444 Open Access

Recent Advances in Natural Product-Based NF-κB Inhibitors as Anticancer and Anti-Inflammatory Agents

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Abstract

An enormous number of articles hold up that the nuclear factor kappa B (NF-κB) pathway can modulate the pathophysiological conditions of cancer, inflammation, and numerous central nervous system diseases. Surprisingly, for such an important transcription factor, little progress has been made in uncovering the specific effects of the naturally occurring compounds in NF-κB pathway inhibitors. Several natural products and traditional medicines are extensively used by people worldwide in different disease conditions having unknown mechanisms. Among this undiscovered domain, a large number of compounds are isolated and showing their modulatory activity on the NF-κB pathway.

Keywords: Cancer • Inflammation • NF-κB pathway

Introduction

Certain activation of signaling pathways plays a great role in cancer pathogenesis and the growth and progression of the tumor cells. Among the several signaling pathways intensively entangled in cancer progression, NF-κB is one of the important pathways which is actively explored by researchers [1]. This B cell-specific transcription factor NFκB family is first discovered by David Baltimore's group. It contains five different DNA-binding proteins which are actively involved in the formation of homodimers and heterodimers. NF-κB proteins are key regulators of innate and adaptive immune responses that can accelerate cell proliferation, inhibit apoptosis, promote cell migration and invasion, and stimulate angiogenesis and metastasis. The normal activation of the NF-κB is necessary for the survival of the cells and immunity, its deregulation can results development of cancer and multiple inflammatory diseases. Therefore NF-κB is one of the major targets of anticancer and anti-inflammatory molecule development.

Activation of NF-κB: The NFκB and IκB (NFκB-IκBα or NFκB-IκBε) complexes can be formed in the resting status of the cells [2]. And when the extracellular stimuli produce by the Tumor necrosis factor (TNFα), Interleukin-1 (IL1), lipopolysaccharide activates the cells, NF-κB can bind to the targeted genes by entering the nucleus. Upon activation of the NF-κB, the IKK complex is phosphorylated and IκB proteins (IκBα/β) directing to ubiquitination and degradation by proteasomes. After the degradation of the NF-κB complex, it enters the nucleus and binds to the DNA-binding sites for NF-κB.

Literature Review

Natural products as anticancer and anti-inflammatory agents

Several plant derivatives of the different classes of compounds such as phenols, polyphenols, polysaccharides, lignans, sesquiterpenes, diterpenes, triterpenes can inhibit the NF-κB pathway. AP1-b, a polysaccharide is isolated from natural product namely lignified okra (Abelmoschus esculentus (L.) Moench) using hot-water extraction and 40% precipitation of ethyl alcohol. The pure form of the polysaccharide is obtained by DEAE cellulose chromatography. Inhibition of phosphorylation levels of p65 and IκB proteins by AP1-b reveals its anti-inflammatory properties, which in turn, manifests that the anti-inflammatory activity of AP1-b is linked with its NF-κB signaling pathway inhibitory activity. An analytical study is carried out on aaptamine, a constituent of Aaptos suberitoides (sea sponge) to analyze and determine the expression of NF-κB in MDA-MB-231 and Triple-Negative Breast Cancer (TNBC) cell line by performing an immunohistochemistry assay. Results show a reduction in NF-κB expression which reveals the NF-κB inhibitory property of sea sponge. A study on Carica papaya leaf extract (PAL) is carried out using an externally inflammatory conditioned medium-exposed prostatic cell line (RWPE-1 cells) and experimental autoimmune prostatitis (EAP)-effected mice *via* histological analysis to analyze the potential of PAL as a novel therapeutic agent of prostatitis. In both *in-vitro* and *in-vivo* cases, PAL significantly

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Received: 09 November, 2021; **Accepted:** 23 November, 2021; **Published:** 30 November, 2021.

decreases the protein expression related to the NF-κB signaling pathway which is generally over-expressed or up-regulated in externally inflammatory conditioned medium-exposed prostatic cell line (RWPE-1 cells). In these cell lines, PAL particularly suppresses NF-κB p65 nuclear translocation and p65 phosphorylation. Another natural product, caffeic acid phenethyl ester (CAPE) also inhibits the activation of the NF-κB signaling pathway during calcific aortic valve disease (CAVD) conditions by inhibiting Osteogenic Medium (OM)-induced calcification. Several biochemical experiments show that CAPE significantly inhibits the phenotypic transformation of aortic valvular interstitial cells (AVICs) by inhibition of NF-κB phosphorylation. Berberine, an isoquinoline moiety containing the natural product (alkaloid) isolated from Coptis chinensis can be used in the treatment of subarachnoid hemorrhage (SAH)-induced cerebral inflammation and subsequent cerebral injuries such as neurological behavior, cerebral edema, and neural apoptosis as the compound significantly inhibits high mobility group box 1 (HMGB1)/NF-κB signaling pathway. A triterpenoid natural product, deacetyl ganoderic acid F (DeGA F) isolated from Ganoderma lucidum, is used in the treatment of microglia-mediated neuroinflammation. The compound decreases p65 nuclear translocation and, IKK and IκB phosphorylation which reveals the subsequent inhibition of lipopolysaccharide (LPS)-induced NF-κB signaling pathway activation in the brains of mice. Therefore, DeGA F possesses a potential therapeutic potential against diseases related to neuroinflammation. Besides this, the compound is also an edible and medicinal mushroom used against insomnia and dizziness-like diseases. Vitis coignetiae Pulliat, a plant, also known as Meoru in Korea is another natural product that is used for the treatment of cancer and inflammatory diseases. An investigation was carried out to determine the effects of anthocyanins isolated from the fruits of Meoru (AIM) on TNF-α-mediated NF-κB activities using human breast cancer cell lines (MCF-7) by performing a couple of assays such as invasion assay, cell viability assay, western blot analysis, and gelatin zymography. The assay results reveal that TNF-α effects are inhibited by AIM on several NF-κB-regulatory proteins involved in invasion, angiogenesis (ICAM-1, MMP-9, MMP-2, and VEGF), and proliferation of cancer cells (C-myc and COX-2). Hence, we may conclude that AIM can act as an inhibitor of TNF-α-mediated NF-κB activation. Ganoderic acid A (GAA), a natural triterpenoid extracted from Ganoderma lucidum acts as an inhibitor of Rho/ROCK/NF-κB signaling pathway. An investigation was carried out to analyze the effect of the compound on LPS-induced acute lung injury (ALI) using a mice model [3]. The detailed molecular-level mechanism of action of the compound when investigated, it is found that the triterpenoid suppresses the activation of Rho/ROCK/NF-κB signaling pathway to block LPS-induced ALI. Curcumin, a non-toxic naturally occurring phenol obtained from Curcumin longa L., is another inhibitor of NF-κB signaling pathway to ultimately inhibit cervical cancer proliferation. The anticancer effect and molecular mechanism of Curcumin are assessed in monolayer and spheroid models using HeLa cell line. The investigation results reveal that the compound prevents cervical cell growth by the inhibition of the NF-κB signaling pathway. Another naturally occurring compound, 25-methoxy hispidol A (25-MHA), a triterpenoid, obtained from the fruit of Poncirus trifoliata, is known for its antinociceptive properties such as the attenuation of mechanical hyperplasia and complete Freund's adjuvant (CFA)-induced mice paw edema. The molecular mechanism behind these attenuating effects of the compound is the reduction in the production of the p65 subunit of NF-κB. Agallochanin K is one of those eleven undescribed and unknown ent-kauranes which is isolated from Excoecaria agallocha L., a Chinese plant. This compound shows a 79.6% rate of NF-κB inhibition at 100 μM concentration. An investigation suggests that Barbaloin, a naturally occurring anthraquinone, isolated from the leaf extracts of Aloe vera can be used for the treatment of LPS-induced ALI. In this study, the protective effect of the compound was analyzed by histological analysis and LPS-induced macrophages in a mice model. The investigational results reveal that the natural product, Barbaloin suppresses the pro-inflammatory cytokine (IL-6, IL-1β, and TNF-α) expression by reducing the phosphorylation levels of NF-κB p65 and IκBα. Also, Barbaloin decreases the intracellular reactive oxygen species (ROS) levels, which in turn suppresses phosphoinositide-3-kinase (PI3K) and AKT's LPS-induced phosphorylation. Together, Barbaloin can be used for LPS-induced ALI treatment by suppressing the ROS-mediated PI3K/AKT/NF-κB signaling pathway. Crocin isolated from Gardenia jasminoides and Crocus sativus is a water-soluble carotenoid. Crocetin is the converted form of crocin when it is administered through intravenous injection. Crocetin can pass the blood-brain barrier and make affect the central nervous system. Lipopolysaccharide-induced behaviors like anxiety and depression can be inhibited by crocin.

Discussion

According to the study, report crocin can block increased cytokine expression in mice models. Lipopolysaccharide-induced elevated NF-κB can also be inhibited by Crocin. Chlorogenic acid and its ester can inhibit the NF-κB inhibition. The inhibition of the phosphorylation of p65 is behind its activity [4]. Also, the release of inflammatory factors is stimulated by NF-κB. Activated NF-κB can inhibit the apoptosis of some inflammatory cells that may induce inflammation. A Chinese herbal medicine (CHM) formulation, 'Psoriasis 1' is largely used in the parts of China for the treatment of the disease called psoriasis with an unknown mechanism of action. 'psoriasis 1' can down-regulate the expression levels of NF-κB, as well as phosphorylated (p)-NF-κB, IKK. The results revealed that 'psoriasis 1' can suppress the inflammatory response as well as the activation of the NF-κB signaling pathways. Guava leaf extract can suppress insulin secretion and able to control hyperglycaemic conditions. It can also control the oxidative stress related to the NF-kB pathway activation. This cardiac glycoside is isolated from the Adonis amurensis. The lipopolysaccharide-induced mouse model revealed the anti-inflammatory property of the convallatoxin *via* suppression of the NF-kB pathway. Convallatoxin can activate PPARγ that can decrease tshe NF-kB-p65 expression [5]. It can up-regulate the association of the NF-kB-p65 and IκBα that may prevent the translocation of the NF-kB-p65 leading to a decrease in different inflammatory factors. Cheong-Pye-Ko (CPK) and Kyung-Ok-Ko (KOK) are the two oriental medicines used in pulmonary disease. The mixture of these two CPK and KOK (C-KOK) can suppress the NF-κB pathway. In this lipopolysaccharide-induced mouse model they reported that the C-KOK down-regulates the NF-κB pathways *via* modulating heme oxygenase 1 (OH-1) regulation.

Conclusion

In this review, we tried to summarize naturally occurring different classes of compounds that are recently reported for their anti-cancer and anti-inflammatory activity *via* NF-κB pathway inhibition. The importance of the NF-κB pathway inhibition in several pathophysiological conditions by the natural products must be explored. Several biological models may also provide supportive data for investigating the molecular pathway of the isolated compounds with unknown mechanisms.

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How to cite this article: Nandi, Arijit and Das Anwesha. "Recent Advances in Natural Product-Based NF-κB Inhibitors as Anticancer and Anti-Inflammatory Agents ." *Med Chem* 11 (2021) : 597.