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Review Article

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

Arijit Nandi[1*], Anwesha Das[2]

[1]*Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research (NIPER), Telangana, India;* [2]*Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research, Gujarat, India*

ABSTRACT

A large number of papers support the idea that the Nuclear Factor Kappa B (NF-κB) pathway can regulate the pathophysiological conditions of cancer, inflammation, and many diseases of the central nervous system. Surprisingly, for such an important transcription factor, little progress has been made in discovering the specific effects of natural compounds as inhibitors of the NF-κB pathway. A number of natural products and traditional medicines are widely used by people all over the world for various diseases for which the mechanism is unknown. Among this undiscovered domain, a large number of compounds were isolated and exhibited their regulatory activity on the NF-κB pathway.

Keywords: Cancer; Inflammation; NF-κB pathway

INTRODUCTION

Certain activations of signalling pathways play an important role in the pathogenesis of cancer as well as in the growth and progression of tumour cells. Among the many signalling pathways that are intimately involved in cancer progression, NF-κB is one of the important pathways actively explored by researchers [1]. The family of NF-κB B cell-specific transcription factors was first discovered by David Baltimore's group. It contains five different DNA-binding proteins, which are actively involved in the formation of modules and heterozygosity. NF-κB proteins are key regulators of innate and adaptive immune responses, which can accelerate cell proliferation, inhibit apoptosis, promote cell migration and invasion, and stimulate angiogenesis and metastasis [2]. Normal activation of NF-κB is required for cell survival and immunity, and its deregulation can lead to cancer development and many inflammatory diseases. Therefore, NF-κB is one of the main targets for the development of anti-cancer and anti-inflammatory molecules [3].

Activation of NF-κB:

- NF-κB and I-κB complexes (NF-κB–I-κB α or NF-κB–I-κB ε) can form when the cell is at rest and when extracellular stimuli are induced by Tumor Necrosis Factor α (TNF α), Inter-Leukin 1(IL1), and lipopolysaccharide.
- NF-κB can bind to target genes upon entry into the nucleus. During NF-κB activation, the IKK complex is phosphorylated, and I-κB proteins (I-κB α/β) are ubiquitinated and degraded by proteasomes.
- After 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 different classes of compounds such as phenols, polyphenols, polysaccharides, lignans, sesquiterpenes, diterpenes, and triterpenes can inhibit the NF-κB pathway. AP1-b, a polysaccharide, is isolated from a natural product, namely lignified okra (*Abelmoschus esculentus Moench*) using it by 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 I-κB proteins by AP1-b reveals its anti-inflammatory properties, which in turn, manifests that

Correspondence to: Arijit Nandi, Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research (NIPER), Hyderabad, India, E-mail: arijitnandi57@gmail.com

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the anti-inflammatory activity of AP1-B is linked with its NF-κB signalling pathway inhibitory activity [4]. An analytical study was carried out on aaptamine, a constituent of *Aaptos suberitoides* (sea sponge), to analyse and determine the expression of NF-κB in MDA-MB-231 and Triple Negative Breast Cancer (TNBC) cell lines by performing an immunohistochemistry assay. Results show a reduction in NF-κB expression which reveals the NF-κB inhibitory property of sea sponge [5].

A study on *Carica papaya* leaf extract (PAL) was 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 analyse the potential of PAL as a novel therapeutic agent for prostatitis. In both *in-vitro* and *in-vivo* cases, PAL significantly decreases the protein expression related to the NF-κB signalling 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 [6]. Another natural product, Caffeic Acid Phenethyl Ester (CAPE) also inhibits the activation of the NF-κB signalling 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 [7]. Berberine, an isoquinoline moiety containing the natural product (alkaloid) isolated from Coptis chinensis can be used in the treatment of Sub Arachnoid Hemorrhage (SAH) induced cerebral inflammation and subsequent cerebral injuries such as neurological behavior, cerebral edema, and neural apoptosism, as the compound significantly inhibits High Mobility Group Box 1 (HMGB1)/NF-κB signaling pathway [8]. The compound decreases p65 nuclear translocation and, IKK and I-κB phosphorylation which reveals the subsequent inhibition of Lipopolysaccharide (LPS)-induced NF-κB signaling pathway activation in the brains of mice. Therefore, DeGAF possesses a potential therapeutic potential against diseases related to neuroinflammation [9].

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. The 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 [10]. 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 [11]. 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 lines. The investigation results reveal that the compound prevents cervical cell growth by the inhibition of the NF-κB signalling pathway [12, 13]. This compound shows a 79.6% rate of NF-κB inhibition at 100 μM concentration [14].

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-1 β, and TNF-α) expression by reducing the phosphorylation levels of p65 and I-κB α. 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 [15]. 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 [16]. Zhang reported chlorogenic acid and its ester can inhibit the NF-κB inhibition. Also, the release of inflammatory factors is stimulated by NF-Kb [17].

DISCUSSION

"Psoriasis 1," a Chinese Herbal Medicine (CHM) formulation, is widely used in parts of China for the treatment of psoriasis, a disease with an unknown mechanism of action. Sun reported that "psoriasis 1' can down-regulate the expression levels of NFκB, as well as Phosphorylated (P) NFκB, IKK. The results revealed that 'psoriasis 1' can suppress the inflammatory response as well as the activation of the number of cells in the NFκB signalling pathways [18]. Jayachandran reported guava leaf extract can suppress insulin secretion and be able to control hyperglycemic conditions. It can also control the oxidative stress related to NF-κB pathway activation. Different phenolic compounds present in the guava leaf extract are behind this activity [19]. Li reported the anti-inflammatory property of convallatoxin, a cardiac glycoside. This cardiac glycoside is isolated from the adonis. The lipopolysaccharide-induced mouse model revealed the anti-inflammatory property of convallatoxin *via* suppression of the NF-κB pathway. Convallatoxin can activate PPAR γ that can decrease the NF-κB-p65 expression. It can up-regulate the association of the NF-κB-p65 and I-κB α and may prevent the translocation of the NF-κB-p65 leading to a decrease in different inflammatory factors [20]. Cheong-Pye-Ko (CPK) and Kyung-Ok-Ko (KOK) are the two oriental medicines used in pulmonary disease. Lee reported that a 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 have attempted to summarize the different classes of natural compounds that have been reported recently

for anticancer and anti-inflammatory activity through inhibition of the NF-κB pathway. The importance of inhibiting the NF-κB pathway under several pathophysiological conditions by natural products needs to be explored. Some biological models can also provide supporting data to study the molecular pathways of compounds isolated with unknown mechanisms.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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