Indian Journal of Pharmaceutical Chemistry and Analytical Techniques (IJPCAT)
ISSN: 3049-3765 | Vol. 01 Issue 01, February 2025 | pp. 37-49

New Developments in Nf-Kb Inhibitors Derived from Natural Products For The Treatment Of Cancer And Inflammation

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Abstract:

NF-κB, a transcription factor, regulates immunity, inflammation, and oncogenesis. Although temporary activation is necessary for cellular homeostasis, chronic dysregulation of the NF-κB pathway can lead to cancer progression and inflammatory disorders. Synthetic inhibitors targeting NF-κB are effective but tied with toxicity, drug resistance, and suppression of the immune system, which led researchers to pursue natural inhibitors from medicinal plants, dietary compounds, and marine sources. This paper discusses the most important advances of the last few years in natural compounds in NF-κB inhibitors, specifically polyphenols (curcumin, resveratrol, EGCG), flavonoids (quercetin, luteolin), alkaloids (berberine and evodiamine), and terpenoids (andrographolide and celastrol), by IKK inhibition and reduction of oxidative stress and inflammatory mediators. These agents show promise for anti-tumor effects through induction of apoptosis and overcoming drug resistance in cancer therapy as well as in inflammatory diseases by the relief of chronic activation of immunity. Despite their advantages, challenges related to bioavailability, standardization, and clinical validation remain, necessitating further research into advanced drug delivery systems and combination therapies. By integrating natural NF-κB inhibitors into modern pharmacology, they hold promise as safer and more effective alternatives or adjuncts to conventional treatments for cancer and chronic inflammatory disorders.

Keywords: NF-Kb (Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells), Cellular Homeostasis, Chronic NF-Kb Dysregulation, Toxicity, Drug Resistance, Medicinal Plants, Dietary Compounds, Marine Sources, Polyphenols (Curcumin, Resveratrol, EGCG), Flavonoids (Quercetin, Luteolin), Alkaloids (Berberine, Evodiamine), Terpenoids (Andrographolide, Celastrol).

INTRODUCTION

The transcription factor NF-κB affects various cellular processes, such as immunological responses, inflammation, apoptosis, and oncogenesis. Five protein subunits—RelA (p65), RelB, c-Rel, p50, and p52—form homo- or heterodimers to regulate gene expression. Normal physiological conditions cause NF-κB to stay inactive in the cytoplasm, coupled to its inhibitory protein, IκB. In response to stimuli such pro-inflammatory cytokines, microbial infections, oxidative stress, and carcinogens, IκB phosphorylates and degrades, allowing NF-κB to translocate into the nucleus and activate target genes. Transient NF-κB activation is necessary for host defense and cellular homeostasis, but uncontrolled activation can lead to pathological conditions such autoimmune disorders, cardiovascular illnesses, neurodegeneration, and cancer. NF-κB is a crucial therapeutic target due to its widespread role in disease development [1].

To mitigate NF-κB-mediated pathologies, several synthetic inhibitors have been developed to suppress its activation at different levels. These include small-molecule inhibitors targeting IκB kinase (IKK), proteasome inhibitors preventing IκB degradation, and decoy oligonucleotides blocking NF-κB DNA binding. While these pharmacological agents have shown promise in preclinical and clinical studies, their long-term use is often associated with significant drawbacks, including systemic toxicity, immunosuppression, and drug resistance. Moreover, the non-specific inhibition of NF-κB may disrupt essential immune functions, leading to adverse side effects. These challenges have led researchers to explore natural NF-κB inhibitors derived from medicinal plants, dietary compounds, and marine sources, which offer a more holistic and potentially safer approach to modulating NF-κB activity.

Polyphenols, flavonoids, alkaloids, and terpenoids can regulate NF-κB activation by suppressing IKK activity, reducing ROS-mediated activation, and modulating upstream signaling pathways. Anti-inflammatory and anticancer compounds including curcumin, resveratrol, berberine, and celastrol have been extensively investigated and show efficacy in preclinical animals with less side effects than synthetic medications.

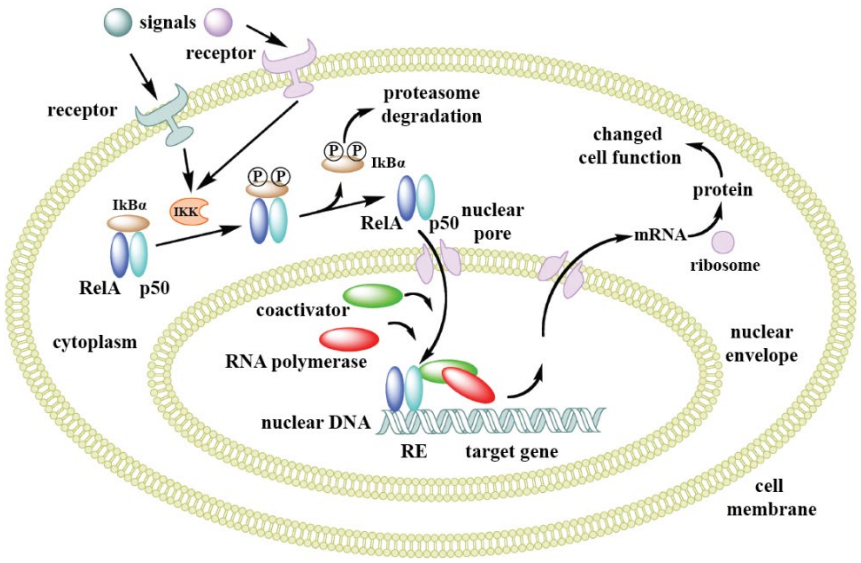

Figure 1: NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) **[2]**

Additionally, natural NF-κB inhibitors often exhibit multitargeted effects, influencing parallel pathways such as apoptosis, autophagy, and angiogenesis, thereby enhancing their therapeutic potential. As research advances, optimizing the bioavailability, selectivity, and clinical applicability of these compounds through advanced formulations and combination therapies may pave the way for their integration into modern pharmacological treatments.

1.1. Background Information

NF-κB activation is principally mediated by two pathways: canonical and non-canonical, which govern immunological and inflammatory responses. The canonical route is activated by pro-inflammatory cytokines (e.g., TNF-α, IL-1β), pathogens, and oxidative stress, causing IκB protein phosphorylation and degradation. This causes NF-κB dimers, primarily the p50/RelA complex, to translocate into the nucleus and activate genes involved in inflammation, immunological regulation, cell proliferation, and survival. On the other hand, CD40L and BAFF activate the non-canonical pathway, which processes p100 into p52, which binds to RelB to regulate lymphoid organ development and adaptive immunity genes. Dysregulated NF-κB signaling contributes to chronic inflammation, autoimmune disorders, and tumor progression, making it an attractive therapeutic target. Natural NF-κB inhibitors, including polyphenols, flavonoids, and alkaloids derived from medicinal plants, have shown significant potential in suppressing NF-κB activity by targeting key molecules

within these pathways. Compounds such as curcumin, resveratrol, and celastrol inhibit IκB kinase (IKK), reduce oxidative stress, and modulate upstream signaling cascades, thereby exhibiting potent anti-inflammatory and anticancer effects [3]. Their ability to interfere with multiple nodes of NF-κB activation highlights their potential as safer alternatives to synthetic inhibitors, warranting further investigation for clinical applications.

1.2. Objectives of the study

- To summarize recent advancements in NF-κB inhibitors derived from natural products.
- To elucidate the molecular mechanisms of these bioactive compounds.
- To discuss their potential in cancer and inflammatory disease therapy.

1.3. Importance of the Topic

The importance of studying natural NF-κB inhibitors is to overcome synthetic medication limitations such toxicity, drug resistance, and non-specific immune suppression. The importance of NF-κB in inflammation-driven illnesses and cancer progression makes it a crucial therapeutic target. Synthetic medicines that suppress NF-κB over time may cause unexpected effects such as reduced immune function and treatment resistance. Due to their multitargeted processes, ability to control oxidative stress, and decreased toxicity, polyphenols, flavonoids, and alkaloids are safer and more sustainable. These bioactive chemicals can also sensitize cancer cells to chemotherapy and reduce inflammation-induced tumor development, improving traditional treatments. Through evidence-based research, optimizing bioavailability, standardizing extraction methods, and integrating them into clinical practice can revolutionize cancer and chronic inflammatory disorder treatment, making it more effective and patient-friendly.

2. CLASSES OF NATURAL NF-KB INHIBITORS AND THEIR MECHANISMS

Nuclear factor-kappa B (NF-κB) is a crucial transcription factor involved in inflammation, immunity, and cancer progression. The overactivation of NF-κB has been linked to chronic inflammatory diseases and tumorigenesis. Various natural compounds, including polyphenols, flavonoids, alkaloids, and terpenoids, have shown potent NF-κB inhibitory activity, offering therapeutic potential in inflammatory and cancerous conditions. These bioactive molecules exert their effects by targeting key proteins in the NF-κB signaling pathway, ultimately reducing inflammation and suppressing tumor progression.

1. Polyphenols: Powerful NF-κB Inhibitors

Polyphenols, a diverse group of plant-derived compounds, include curcumin, resveratrol, and epigallocatechin gallate (EGCG), all of which effectively modulate NF-κB signaling by preventing its nuclear translocation through inhibition of IκB kinase (IKK) [9].

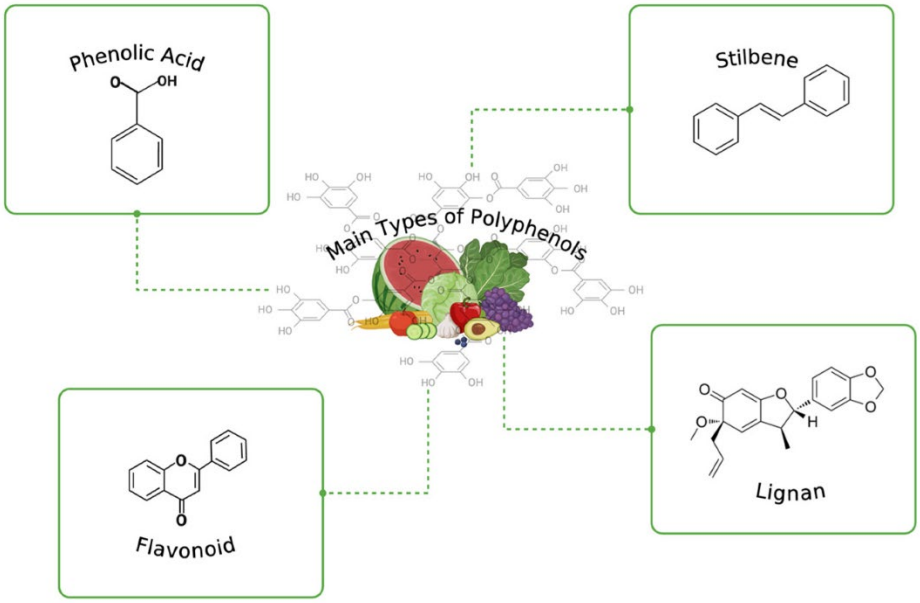

Figure 2: Polyphenols [4]

- **Curcumin:** Curcumin is a well-studied polyphenol from turmeric (Curcuma longa) with anti-inflammatory and anticancer effects. It prevents IκB phosphorylation and degradation by directly blocking IKKβ, suppressing NF-κB activation. Curcumin inhibits pro-inflammatory cytokines like TNF-α, IL-6, and IL-1β, making it a possible treatment for inflammatory illnesses and malignancies.
- **Resveratrol:** A natural stilbenoid found in grapes, berries, and peanuts, resveratrol inhibits NF-κB through the activation of sirtuin 1 (SIRT1), a deacetylase enzyme that negatively regulates NF-κB signaling. By enhancing apoptosis and reducing inflammation, resveratrol exhibits potential in cancer prevention and treatment.
- **EGCG:** The major catechin in green tea (Camellia sinensis), EGCG effectively blocks NF-κB activation by preventing IκB degradation. This inhibition suppresses inflammatory responses and tumor progression, highlighting its therapeutic relevance in diseases such as cancer and cardiovascular disorders.

2. Flavonoids: Potent Anti-Inflammatory Agents

Flavonoids, another major class of plant polyphenol, include quercetin, luteolin, and apigenin. These compounds exhibit strong NF-κB inhibitory effects, contributing to their anti-inflammatory and anticancer properties.

- **Quercetin:** Quercetin, found in apples, onions, and citrus fruits, is a flavonoid that prevents TNF-α-induced NF-κB

activation. Quercetin reduces inflammation in chronic disorders like arthritis and cardiovascular disease by decreasing inflammatory mediators.

- **Luteolin & Apigenin:** Flavones in celery, parsley, and chamomile inhibit NF-κB-mediated gene transcription. Inhibiting pro-inflammatory enzymes like COX-2 and iNOS reduces inflammation-driven carcinogenesis.

3. Alkaloids: Modulating NF-κB in Cancer and Inflammatory Disorders

Alkaloids, a diverse class of naturally occurring nitrogen-containing compounds, have shown remarkable ability to modulate NF-κB signaling. Some prominent alkaloids with NF-κB inhibitory activity include berberine, evodiamine, and sanguinarine.

- **Berberine:** A bioactive isoquinoline alkaloid from Berberi's species, berberine effectively inhibits NF-κB activation in colorectal cancer by blocking IKK phosphorylation. This inhibition downregulates pro-inflammatory cytokines and apoptotic regulators, making berberine a potential chemopreventive agent.
- **Evodiamine:** Evodiamine, derived from Evodia rutaecarpa, inhibits NF-κB nuclear translocation, decreasing inflammatory cytokines. Its anti-inflammatory and anticancer properties make it an attractive therapeutic candidate.
- **Sanguinarine:** A benzophenanthridine alkaloid from Sanguinaria canadensis, sanguinarine downregulates NF-κB and STAT3 signaling, leading to the suppression of cancer cell proliferation. Additionally, it exhibits strong anti-inflammatory effects by inhibiting key inflammatory enzymes and cytokines.

4. Terpenoids: Multifunctional NF-κB Inhibitors

Terpenoids, a large and diverse group of naturally occurring compounds, have been widely studied for their NF-κB inhibitory effects. Notable terpenoids include andrographolide, celastrol, and ginsenosides.

- **Andrographolide:** A diterpene lactone from Andrographis paniculata, andrographolide prevents IκB degradation, thereby inhibiting NF-κB activation. Its potent anti-inflammatory properties have been demonstrated in conditions such as rheumatoid arthritis, sepsis, and neuroinflammation.
- **Celastrol:** A triterpenoid from Tripterygium wilfordii, celastrol disrupts NF-κB-DNA binding, effectively suppressing inflammation and cancer progression. Due to its strong inhibitory effects, celastrol is being explored as a potential therapeutic agent in cancer treatment.
- **Ginsenosides:** Saponins found in Panax ginseng, ginsenosides modulate NF-κB and mitogen-activated protein kinase (MAPK) signaling pathways. These bioactive compounds reduce chronic inflammation and enhance immune function, making them valuable in

treating inflammatory and metabolic disorders.

Table 2: Key References on NF-κB Inhibitors in Cancer and Inflammatory Diseases

Authors	Study	Focus Area	Methodology	Key Findings
Kunnumakkara et al. (2018) [5]	Investigation of natural compounds in chronic diseases	Role of curcumin, resveratrol, and EGCG in NF-κB inhibition	Literature review and experimental data analysis	Demonstrated that these natural compounds suppress NF-κB activation, reducing inflammation in chronic diseases and cancer
Lu & Zhao (2020) [6]	Study on NF-κB targeting in inflammatory diseases	Role of Chinese herbal medicines in modulating NF-κB for ulcerative colitis treatment	Systematic review of traditional Chinese medicine studies	Identified specific herbal compounds that inhibit NF-κB, reducing inflammation and improving gut health
Markopoulos et al. (2018) [7]	Analysis of NF-κB-regulated miRNAs in cancer	Impact of NF-κB on miRNA expression and tumor progression	Molecular and bioinformatics analysis of NF-κB-regulated miRNAs	Highlighted the role of NF-κB in regulating inflammation-related miRNAs and proposed NF-κB inhibitors as potential cancer therapeutics
Paul et al. (2018) [8]	Experimental evaluation of NF-κB inhibition in cancer therapy	Therapeutic potential of IKKα and NIK inhibitors in cancer treatment	Laboratory experiments on cancer cell lines treated with IKKα and NIK inhibitors	Showed that inhibiting IKKα and NIK reduces tumor growth, enhances chemotherapy efficacy, and improves treatment outcomes

3. PHARMACOLOGICAL APPLICATIONS IN CANCER AND INFLAMMATORY DISEASES

The transcription factor NF-κB plays a pivotal role in regulating immune responses, inflammation, and cellular survival. Its persistent activation is associated with chronic inflammatory diseases and cancer progression. Natural compounds, including polyphenols, flavonoids, alkaloids, and terpenoids, have emerged as promising NF-κB inhibitors with significant pharmacological applications. These bioactive molecules not only modulate NF-κB activity but also enhance the effectiveness of conventional therapies, making them valuable in cancer treatment and inflammatory disease management [9].

3.1. Cancer Therapy: Enhancing Apoptosis and Tumor Suppression

Cancer cells exploit NF-κB signaling to evade apoptosis, sustain proliferation, and resist chemotherapy. Targeting NF-κB can restore apoptotic pathways, inhibit tumor progression, and enhance the efficacy of anticancer treatments. Natural inhibitors such as curcumin, resveratrol, and EGCG have demonstrated remarkable anticancer properties by modulating NF-κB-mediated survival signaling. Curcumin, a polyphenolic compound from turmeric (Curcuma longa), suppresses NF-κB activation by inhibiting IκB kinase (IKK), leading to decreased expression of anti-apoptotic proteins such as Bcl-2 and survivin. It has been shown to reduce cancer cell proliferation in breast, colon, and lung cancers and enhance tumor sensitivity to chemotherapy agents like cisplatin and doxorubicin. Resveratrol, a natural stilbenoid found in grapes and berries, downregulates NF-κB signaling via sirtuin 1 (SIRT1) activation, promoting apoptosis and inhibiting angiogenesis in tumors, thereby reducing cancer progression. It also enhances the efficacy of chemotherapy drugs by sensitizing resistant cancer cells to treatment. EGCG (Epigallocatechin Gallate), a catechin from green tea (Camellia sinensis), blocks NF-κB activation and inhibits tumor-promoting cytokines such as IL-6 and TNF-α. It has demonstrated anticancer effects in prostate, breast, and liver cancers by suppressing cell proliferation and inducing apoptosis. By targeting NF-κB, these natural compounds contribute to cancer progression inhibition, apoptosis induction, and tumor resistance reduction to chemotherapy.

3.2. Inflammatory Diseases: Modulating NF-κB to Reduce Chronic Inflammation

Hyperactivation of NF-κB is a major cause of inflammatory disorders such as RA, IBD, asthma, and neuroinflammatory syndromes. Natural inhibitors reduce inflammation and tissue damage by inhibiting NF-κB-mediated cytokine release. In rheumatoid arthritis (RA), NF-κB induces pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, and MMPs), causing joint inflammation and cartilage deterioration. In RA models, natural substances including berberine, quercetin, and luteolin reduce synovial inflammation and cartilage damage by blocking NF-κB activation. IBD, including Crohn's and ulcerative colitis, is caused by NF-κB-

mediated inflammation that disrupts the intestinal barrier. Curcumin and andrographolide lower gastrointestinal inflammation by inhibiting NF-κB activation, reducing inflammatory mediator synthesis. Overproduction of cytokines like IL-5 and IL-13 by NF-κB causes excessive mucus secretion and airway remodeling in asthma and respiratory inflammation. EGCG and celastrol have shown anti-asthmatic benefits via lowering airway inflammation and suppressing NF-κB activity in preclinical investigations. NF-κB inhibitors may be useful in controlling chronic inflammatory disorders as supplemental or alternative therapy [10].

3.3. Synergistic Effects with Conventional Therapies: Enhancing Efficacy and Reducing Side Effects

One of the most promising aspects of natural NF-κB inhibitors is their ability to enhance the effectiveness of conventional cancer therapies while mitigating drug resistance and side effects. Many tumors develop resistance to chemotherapy by activating NF-κB signaling, which promotes cell survival and drug efflux. Several studies have explored the role of NF-κB inhibitors in overcoming this resistance and improving treatment efficacy. Research has demonstrated that natural compounds such as curcumin, resveratrol, and berberine can sensitize resistant cancer cells to chemotherapeutic agents by suppressing NF-κB-mediated survival pathways. Additionally, chronic inflammation is a key driver of tumor initiation and metastasis, and NF-κB inhibitors have been shown to suppress inflammation-induced tumorigenesis while enhancing immunotherapy responses.

Experimental studies have further demonstrated the potential of compounds like celastrol and andrographolide in enhancing immune checkpoint inhibitors by reducing tumor-associated inflammation and improving immune response. Moreover, chemotherapy and immunotherapy often cause severe side effects, including systemic inflammation and organ toxicity. Natural compounds such as ginsenosides and quercetin have been found to reduce chemotherapy-induced inflammation and oxidative stress, thereby improving patient tolerance to treatment.

4. DISCUSSION

The therapeutic potential of natural NF-κB inhibitors lies in their ability to regulate inflammation and cancer pathways through mechanisms like IKK suppression, ROS modulation, and apoptosis induction. However, challenges such as standardization, bioavailability, and clinical validation must be addressed for their integration into modern medicine. Future research should focus on personalized medicine, combination therapies, and long-term safety to optimize their clinical application [11].

4.1. Interpretation of Findings

The therapeutic potential of natural NF-κB inhibitors stems from their ability to regulate key molecular pathways involved in inflammation and carcinogenesis. These inhibitors primarily exert their effects

through three main mechanisms: IKK suppression, reactive oxygen species (ROS) modulation, and apoptosis induction. Inhibiting IκB kinase (IKK) prevents the degradation of IκB, blocking NF-κB translocation to the nucleus and reducing the expression of pro-inflammatory cytokines and survival proteins. Compounds like curcumin, berberine, and celastrol have shown efficacy in suppressing IKK activity in various disease models. NF-κB activation is often driven by oxidative stress, which contributes to chronic inflammation and tumorigenesis, and natural inhibitors like EGCG and resveratrol exert antioxidant effects by neutralizing ROS, thus preventing NF-κB activation. Additionally, by inhibiting NF-κB, natural compounds restore apoptotic pathways in cancer cells, making them more susceptible to programmed cell death. Curcumin, resveratrol, and ginsenosides have demonstrated the ability to downregulate anti-apoptotic proteins (Bcl-2, Bcl-xL) and upregulate pro-apoptotic factors (Bax, caspases), thereby promoting cell death in tumor cells. While these findings highlight the broad-spectrum activity of natural NF-κB inhibitors, their non-specific action necessitates further refinement to enhance selectivity. Excessive NF-κB inhibition may compromise immune function, underscoring the need for controlled and targeted therapeutic strategies [12].

4.2. Implications and Significance

The increasing interest in phytochemicals for drug development underscores the need for rigorous scientific validation to ensure their safety, efficacy, and consistency. Several critical aspects must be addressed to facilitate their integration into clinical practice. Standardization of extraction and purification is essential, as natural NF-κB inhibitors are often derived from plant sources, and variations in plant species, cultivation conditions, and extraction methods can influence their bioactivity. Establishing standardized protocols ensures batch-to-batch consistency in pharmaceutical formulations. Due to quick metabolism and low systemic absorption, several phytochemicals, including curcumin and resveratrol, have poor bioavailability, making dosage optimization and bioavailability increase difficult. Nanoparticle encapsulation, liposomal formulations, and prodrug methods are being investigated to improve drug delivery. Furthermore, while numerous preclinical studies support the efficacy of natural NF-κB inhibitors, large-scale clinical trials are necessary to establish their safety and effectiveness in human populations. Regulatory approval from agencies like the FDA and EMA requires comprehensive toxicological and pharmacokinetic studies, which remain a key challenge in phytochemical-based drug development. By addressing these challenges, natural NF-κB inhibitors can transition from experimental compounds to standardized therapeutic agents, bridging the gap between traditional medicine and modern pharmacology [13].

4.3. Future Research Priorities

To maximize the therapeutic potential of natural NF-κB inhibitors, future research should focus on personalized medicine

approaches, multi-targeted therapies, and long-term safety studies. The response to NF-κB inhibitors varies among individuals based on genetic predisposition, metabolic differences, and disease progression. Future studies should explore biomarker-driven approaches to tailor NF-κB inhibitor therapy to specific patient subgroups, including genetic screening for NF-κB pathway mutations to identify patients most likely to benefit and pharmacogenomics studies to optimize dosing strategies based on individual metabolism and drug clearance rates. Given the complexity of cancer and inflammatory diseases, combining natural NF-κB inhibitors with other therapeutic modalities may provide superior clinical outcomes. For instance, in immunotherapy synergy, many tumors evade immune detection by exploiting NF-κB signaling, and combining natural inhibitors like celastrol or berberine with checkpoint inhibitors (e.g., PD-1/PD-L1 antibodies) may enhance immune responses against tumors. Additionally, NF-κB inhibitors may sensitize cancer cells to conventional treatments, reducing drug resistance. Curcumin and resveratrol, for example, have been shown to enhance the cytotoxic effects of chemotherapy agents like cisplatin and paclitaxel. While natural compounds are often perceived as safe due to their plant origins, long-term usage may present unforeseen risks [14]. Chronic toxicity studies should be conducted to evaluate the potential side effects of prolonged NF-κB inhibition, particularly in relation to immune suppression, and organ-specific toxicity assessments are necessary to determine whether prolonged NF-κB inhibition affects liver, kidney, or cardiovascular function.

5. CONCLUSION

NF-κB is a crucial transcription factor involved in immune regulation, inflammation, and oncogenesis, making it a key target for therapeutic intervention in cancer and chronic inflammatory diseases. While synthetic inhibitors have been developed to suppress NF-κB activation, their long-term use is often associated with toxicity, drug resistance, and immune suppression. Natural products, including polyphenols, flavonoids, alkaloids, and terpenoids, have demonstrated significant potential in modulating NF-κB signaling through various mechanisms, such as inhibiting IKK activation, preventing IκB degradation, and reducing oxidative stress. Compounds like curcumin, resveratrol, berberine, and celastrol exhibit strong anti-inflammatory and anticancer effects, with relatively lower toxicity compared to synthetic drugs. Moreover, their multitargeted mechanisms allow them to regulate multiple signaling pathways, enhancing their therapeutic efficacy. Despite these promising findings, challenges such as bioavailability, standardization, and clinical validation remain, necessitating further research and development. Optimizing natural NF-κB inhibitors through advanced formulations, combination therapies, and clinical trials could lead to more effective and safer treatment strategies, paving the way for their integration into modern pharmacology for managing cancer and inflammatory disorders [15]

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