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Review

Phytochemical Modulation of NF-κB Signaling in Pancreatic Ductal Adenocarcinoma: Preclinical Progress and Pharmacological Perspectives

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) remains characterized by aggressive progression, extensive stromal remodeling, early metastatic dissemination, and resistance to systemic therapy. Nuclear factor kappa B (NF-κB) integrates oncogenic, inflammatory, survival, angiogenic, and treatment-induced signals and therefore represents a pharmacologically relevant regulatory node in pancreatic cancer. Phytochemicals including curcumin, xanthohumol, parthenolide, dimethylaminoparthenolide, triptolide, resveratrol, emodin, and related compounds have been investigated as modulators of NF-κB activity, although the strength of mechanistic evidence differs substantially among agents. This review evaluates canonical and noncanonical NF-κB biology in pancreatic cancer, interactions with KRAS, PI3K-AKT, STAT3, MAPK, and Nrf2 signaling, and the consequences of NF-κB modulation for apoptosis, epithelial–mesenchymal transition, angiogenesis, tumor microenvironmental communication, and chemotherapy resistance. Particular emphasis is placed on separating direct pharmacodynamic evidence from downstream pathway association and computational prediction. Curcumin and xanthohumol have been evaluated using direct NF-κB measurements linked to defined antitumor phenotypes and in vivo validation, whereas parthenolide and dimethylaminoparthenolide support a mechanistic relationship between NF-κB activity and gemcitabine resistance. Clinical evidence remains limited and is dominated by early phase curcumin studies, which also illustrate major barriers involving bioavailability, tumor exposure, and target engagement. Future development requires exposure–response analysis, cell-type-specific pharmacodynamics, rational combination therapy, validated biomarkers, and formulations or derivatives with improved pharmacokinetic properties. An evidence-based pharmacological framework may clarify which phytochemical NF-κB modulators warrant further translational development and biomarker-guided evaluation in PDAC.

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1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) represents the predominant histological subtype of pancreatic cancer and is characterized by late clinical presentation, early metastatic dissemination, extensive stromal remodeling, and substantial resistance to systemic therapy. Molecular alterations involving KRAS, TP53, CDKN2A, and SMAD4 cooperate with inflammatory, metabolic, and survival programs to drive disease initiation and progression [1,2]. The extensive desmoplastic and immunosuppressive tumor microenvironment (TME) further contributes to disease progression and therapeutic resistance through reciprocal interactions among malignant epithelial cells, cancer-associated fibroblasts, myeloid populations, extracellular matrix (ECM) components, vascular cells, and inflammatory mediators [3–5].

Nuclear factor-kappa B (NF-κB) signaling constitutes an important molecular interface between oncogenic signaling, inflammation, cell survival, and therapeutic resistance in PDAC. Constitutive NF-κB activity has been demonstrated in pancreatic cancer cells and is associated with transcriptional programs regulating proliferation, resistance to apoptosis, inflammatory signaling, angiogenesis, invasion, and tumor progression [6,7]. Functional interactions between oncogenic KRAS and NF-κB further connect a major genetic driver of PDAC with inflammatory and survival signaling. KRAS-dependent signaling can converge on NF-κB through several regulatory routes, including PI3K/AKT, RALB/TBK1, TAK1, IKK, and cytokine-dependent pathways, thereby reinforcing oncogenic transcriptional programs [8–10].

The NF-κB transcription factor family comprises RELA (p65), RELB, c-REL, NF-κB1 (p50 and its precursor p105), and NF-κB2 (p52 and its precursor p100). Canonical NF-κB signaling predominantly involves activation of the IKK complex, phosphorylation and degradation of inhibitory IκB proteins, and subsequent nuclear translocation of RELA-containing dimers. Noncanonical signaling is primarily regulated through NF-κB-inducing kinase (NIK) and IKKα, which promote processing of p100 to p52 and formation of transcriptionally active RELB-p52 complexes [7,11]. Dysregulation of these pathways can sustain transcriptional programs linking oncogenic and inflammatory stimuli with malignant phenotypes, while extensive crosstalk with KRAS, PI3K/AKT, STAT3, MAPK, redox, metabolic, and cytokine signaling further increases the complexity of NF-κB regulation in PDAC [7].

NF-κB consequently represents an attractive pharmacological node for disrupting multiple processes that support pancreatic tumor progression. Direct and indiscriminate pathway inhibition, however, presents important challenges because physiological NF-κB activity contributes to immune homeostasis, inflammatory responses, cellular survival, and adaptation to stress. Pharmacological strategies that modulate pathological pathway activation, upstream regulatory mechanisms, nuclear translocation, transcriptional activity, or disease-specific signaling crosstalk may therefore provide greater therapeutic precision than generalized systemic NF-κB suppression [7,12].

Phytochemicals provide chemically diverse pharmacological scaffolds capable of modulating NF-κB and its interconnected signaling networks. Curcumin, xanthohumol, parthenolide and its derivatives, resveratrol, triptolide, emodin, cordycepin, and other natural compounds have demonstrated varying degrees of activity against inflammatory, survival, angiogenic, and treatment-resistance pathways in pancreatic cancer [6,13–18]. Importantly,

the strength of evidence for NF-κB involvement differs substantially among these compounds. For some phytochemicals, direct measurements of NF-κB activity have been linked to defined functional phenotypes and validated in vivo, whereas evidence for others is predominantly indirect or reflects modulation of interacting pathways. This distinction is essential because antiproliferative or pro-apoptotic activity alone does not establish NF-κB as the pharmacological mechanism.

Clinical investigation further illustrates both the potential and limitations of phytochemical-based NF-κB modulation. In a phase II study of patients with advanced pancreatic cancer, oral curcumin demonstrated biological activity in a small subset of patients and was accompanied by pharmacodynamic assessment of NF-κB-associated markers. However, systemic exposure remained low despite administration of 8 g/day, highlighting the substantial discrepancy that can arise between concentrations associated with experimental activity and those achievable clinically [19]. These findings emphasize the importance of integrating pathway-specific pharmacodynamics with pharmacokinetics, tumor exposure, formulation, and clinically relevant therapeutic endpoints.

The phytochemicals discussed in this review were selected according to three principal considerations: the availability of experimental evidence supporting NF-κB modulation in pancreatic cancer models, the extent of mechanistic characterization, and their relevance to PDAC associated processes, including survival, inflammation, angiogenesis, invasion, and therapeutic resistance. Priority was given to compounds with experimentally measured NF-κB pharmacodynamic activity and relevant functional outcomes, while selected agents with broader multitarget or indirect evidence were included to illustrate differences in mechanistic support. The compounds discussed are therefore representative rather than exhaustive. Thymoquinone, a bioactive constituent of *Nigella sativa*, represents another relevant phytochemical with reported inhibitory effects on NF-κB associated signaling and antitumor activity in experimental pancreatic cancer models. Its inclusion further illustrates the diversity of natural compounds investigated for their potential to modulate inflammatory and oncogenic signaling in PDAC.

This review examines phytochemicals as pharmacological modulators of NF-κB signaling in pancreatic cancer, with emphasis on the molecular architecture of canonical and noncanonical NF-κB signaling, interactions with oncogenic and inflammatory pathways, and consequences for apoptosis, epithelial–mesenchymal plasticity, angiogenesis, invasion, TME communication, and therapeutic resistance. Evidence from cellular and animal models, computational and network pharmacology, and clinical studies is evaluated according to the extent of direct pathway modulation and functional validation. Particular attention is given to pharmacodynamic evidence, cell-type-specific effects, combination therapy, bioavailability, tumor exposure, formulation strategies, and the experimental requirements necessary to distinguish computational prediction or pathway association from direct pharmacological modulation of NF-κB. Throughout the review, particular attention was given to distinguishing direct mechanistic evidence from indirect pathway associations and computational predictions, thereby providing an evidence-based framework for evaluating the translational potential of phytochemical NF-κB modulators in PDAC.

2. NF-κB Signaling in Pancreatic Cancer Biology

2.1. Molecular Organization of NF-κB Signaling

NF-κB signaling is mediated by five structurally related transcription factors: RELA (p65), RELB, c-REL, NF-κB1 (p50 and its precursor p105), and NF-κB2 (p52 and its precursor p100). These proteins share a conserved Rel homology domain that mediates DNA binding, dimerization, nuclear localization, and interactions with inhibitory IκB proteins [7,20]. Transcriptionally active NF-κB complexes regulate genes involved in inflammation, immune

responses, proliferation, cell survival, angiogenesis, migration, invasion, and adaptation to cellular stress.

Canonical NF-κB signaling is activated by inflammatory cytokines, Toll-like receptor (TLR) ligands, and cellular stress. Activation of the IKK complex promotes phosphorylation and subsequent proteasomal degradation of IκBα, thereby releasing predominantly RELA-p50 dimers for nuclear translocation. Nuclear NF-κB subsequently binds κB regulatory elements and coordinates transcriptional programs involved in inflammation, survival, proliferation, and stress adaptation [7,20].

Noncanonical NF-κB signaling is regulated primarily through NF-κB-inducing kinase (NIK) and IKKα. Stabilization of NIK promotes IKKα-dependent phosphorylation and proteolytic processing of p100 to p52, permitting formation and nuclear accumulation of transcriptionally active RELB-p52 complexes. Both canonical and noncanonical NF-κB pathways are active in pancreatic cancer, although their upstream regulators, kinetics, transcriptional outputs, and biological functions are distinct [7,11].

2.2. Constitutive NF-κB Activation in Pancreatic Cancer

Constitutive NF-κB activity represents a recurrent molecular feature of pancreatic cancer. Li et al. demonstrated constitutive NF-κB DNA-binding and IKK activity in human pancreatic carcinoma cell lines and showed that pharmacological suppression by curcumin inhibited IKK activity, reduced NF-κB DNA binding, suppressed proliferation, and induced apoptosis [6]. These findings established a direct relationship between persistent NF-κB signaling and pancreatic cancer cell survival.

Persistent NF-κB activation generates transcriptional conditions favorable to malignant progression through regulation of anti-apoptotic proteins, inflammatory mediators, angiogenic factors, chemokines, and matrix-remodeling enzymes [7,20]. NF-κB therefore functions less as an isolated oncogenic pathway than as a transcriptional convergence point through which oncogenic mutations, inflammatory signals, microenvironmental interactions, metabolic stress, hypoxia, and treatment-induced cellular stress can influence tumor behavior [7].

The contribution of NF-κB signaling is not restricted to the canonical pathway. Pancreatic cancer cells can exhibit activation of both canonical and noncanonical NF-κB signaling, and the relative contribution of RELA- and RELB-containing complexes may differ according to upstream stimuli and cellular context [11]. This distinction is pharmacologically relevant because suppression of a single NF-κB regulatory component may not uniformly inhibit the transcriptional outputs generated by both signaling branches.

2.3. Functional Interaction Between KRAS and NF-κB

Oncogenic KRAS establishes multiple routes to NF-κB activation in pancreatic cancer. Rather than operating through a single linear pathway, KRAS-dependent signaling converges on NF-κB through several effector and inflammatory networks. These include PI3K/AKT-associated signaling, RALB/TBK1, TAK1-containing signaling complexes, and additional kinase and cytokine-dependent mechanisms that reinforce NF-κB transcriptional activity [8–10].

Glycogen synthase kinase 3α (GSK3α) contributes to oncogenic KRAS associated NF-κB signaling through distinct regulatory mechanisms. GSK3α promotes stabilization of the TAK1/TAB complex, supporting canonical NF-κB activation, while also contributing to noncanonical NF-κB regulation. These mechanisms should therefore be distinguished rather than interpreted as a single linear signaling cascade [10]. RALB-dependent activation of TBK1 represents an additional KRAS-associated survival pathway capable of sustaining NF-κB-related transcriptional programs [9]. These interconnected routes illustrate how

NF-κB can integrate signals generated by oncogenic KRAS without functioning as a simple downstream extension of a single KRAS effector pathway.

Inflammatory signaling further reinforces this relationship. Cytokines produced by malignant and stromal cells can activate receptor-proximal signaling cascades that converge on IKK and NF-κB, generating feedback between oncogenic and inflammatory programs. Persistent KRAS-NF-κB signaling can consequently influence cell survival, cytokine production, invasive behavior, stromal communication, and therapeutic response. NF-κB therefore represents a pharmacologically relevant convergence point within KRAS-driven PDAC, although inhibition of NF-κB cannot be assumed to suppress all KRAS-dependent biological functions [7,20].

2.4. Emerging Regulatory Mechanisms of NF-κB in PDAC

Recent mechanistic studies have expanded the molecular framework of NF-κB regulation in PDAC beyond conventional receptor-IKK-IκB signaling. Epigenetic regulation, protein stability, and noncanonical functions of metabolic enzymes can independently modify NF-κB activity, revealing additional points at which oncogenic and stress-responsive signals converge on the pathway.

Nuclear receptor-binding SET domain protein 2 (NSD2) acts as a negative regulator of NF-κB during KRAS-driven pancreatic tumorigenesis. NSD2-mediated H3K36 dimethylation promotes NFKBIA expression and increases IκBα-mediated restraint of p65 phosphorylation and nuclear translocation. NSD2 also interacts with the DNA-binding domain of p65 and attenuates its transcriptional activity. Loss of NSD2 enhances pancreatic tumorigenesis, whereas NF-κB inhibition attenuates phenotypes associated with NSD2 deficiency and sensitizes NSD2-null PDAC to gemcitabine [21].

Metabolic enzymes can also acquire nonmetabolic functions that directly regulate NF-κB. Under hypoxic conditions, hexokinase 2 (HK2) functions as a protein kinase and phosphorylates IκBα at T291 in PDAC cells, promoting NF-κB activation and downstream transcription. This nonmetabolic HK2 activity increases proliferation, migration, and invasion, establishing a direct mechanistic connection between metabolic adaptation, hypoxic stress, and inflammatory transcription [22].

Regulation of p65 protein stability represents another recently defined mechanism. Digestive organ expansion factor (DEF) interacts with p65 and protects it from ubiquitin-proteasome-mediated degradation, thereby stabilizing p65 and supporting pancreatic tumor growth. Disruption of the DEF-p65 interaction using a rationally designed peptide reduced p65 abundance and inhibited pancreatic cancer growth in vitro and in vivo [23].

Together, these findings identify IκBα expression and phosphorylation, p65 stability, epigenetic regulation, and metabolic-enzyme signaling as experimentally defined control points for NF-κB in pancreatic cancer. They also demonstrate that similar NF-κB transcriptional outputs can arise through distinct upstream mechanisms, an important consideration when evaluating the molecular specificity of pharmacological NF-κB modulators.

2.5. NF-κB Within the Pancreatic TME

PDAC develops within a dense and heterogeneous TME containing cancer-associated fibroblasts (CAFs), pancreatic stellate cells (PSCs), tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), endothelial cells, lymphoid populations, and abundant ECM. NF-κB signaling operates across malignant and nonmalignant cellular compartments, thereby connecting tumor-intrinsic oncogenic signaling with inflammatory, stromal, vascular, and immune-regulatory processes [3–5].

NF-κB-associated transcription can promote production of IL-6, IL-8, chemokines, VEGF, matrix metalloproteinases, and other inflammatory and matrix-remodeling media-

tors. These factors can influence fibroblast activation, myeloid-cell behavior, angiogenesis, ECM remodeling, epithelial plasticity, and therapeutic response [3,5,7]. Reciprocal signaling from stromal and immune populations can in turn activate NF-κB within malignant cells, establishing feedback between tumor-cell-intrinsic and microenvironmental signaling [3,5].

The biological consequences of NF-κB activity are therefore strongly cell-context-dependent [20]. NF-κB activation within malignant epithelial cells can support survival, invasion, and treatment resistance, whereas pathway activity within macrophages, fibroblasts, and other immune populations can produce distinct inflammatory or immunoregulatory responses. Systemic NF-κB inhibition cannot consequently be assumed to reproduce the effects of selective pathway suppression within malignant cells.

This cellular complexity has important implications for phytochemical pharmacology. NF-κB modulation should not be evaluated exclusively through tumor-cell viability or apoptosis assays. Mechanistic assessment should determine whether candidate compounds alter pathway activity within specific cellular compartments and whether these changes affect tumor–stromal communication, inflammatory mediator production, angiogenesis, ECM remodeling, immune regulation, and treatment-induced adaptive responses. These considerations provide the biological framework for evaluating phytochemical NF-κB modulators in subsequent sections. Collectively, the oncogenic, inflammatory, growth-factor, and PDAC-specific regulatory mechanisms that converge on canonical and noncanonical NF-κB signaling, together with reciprocal tumor-microenvironment interactions and major downstream biological consequences, are summarized in Figure 1.

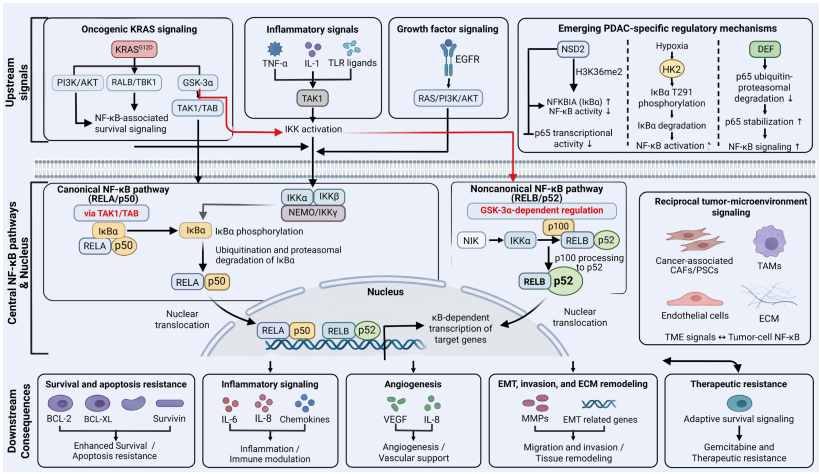


Figure 1. NF-κB signaling architecture and regulatory convergence in pancreatic ductal adenocarcinoma (PDAC). Oncogenic KRAS signaling converges on NF-κB through PI3K/AKT, RALB/TBK1, and GSK-3α associated mechanisms. GSK-3α promotes TAK1/TAB complex stabilization and contributes to canonical NF-κB activation, while also regulating noncanonical NF-κB signaling. These regulatory connections are represented separately to distinguish their respective contributions to NF-κB pathway activity. Inflammatory inputs (TNF-α, IL-1, TLR ligands), and growth-factor signaling (EGFR/RAS/PI3K/AKT) converge on canonical and noncanonical NF-κB pathways. Canonical signaling proceeds through IKK-mediated IκBα phosphorylation and degradation and RELA/p50 nuclear translocation, whereas noncanonical signaling proceeds through NIK-IKKα-dependent p100 processing to RELB/p52. PDAC-specific regulators further tune pathway activity, including NSD2 (NFKBIA induction, p65 restraint), hypoxia-driven HK2 phosphorylation of IκBα, and DEF-mediated p65 stabilization. Reciprocal crosstalk with CAFs/PSCs, TAMs, endothelial cells, and the ECM shapes NF-κB output, which drives survival and apoptosis resistance, inflammation, angiogenesis, EMT, invasion and ECM remodeling, and therapeutic resistance. Created in BioRender. Syed, M. F. (2026) https://BioRender.com/qtqyp9z.

3. Pharmacological Rationale for Targeting NF-κB

Persistent NF-κB activation provides a pharmacological opportunity in PDAC because multiple malignant phenotypes converge on the same transcriptional regulatory network. NF-κB coordinates genes involved in cell survival, inflammatory signaling, angiogenesis, invasion, and adaptation to cellular stress, enabling pathway activation to influence several tumor-promoting processes simultaneously [7,12,24]. Pharmacological inhibition of NF-κB can therefore reduce pro-survival transcription, lower the apoptotic threshold, attenuate inflammatory and angiogenic signaling, and modify adaptive responses to anticancer treatment [6,12,24]. The therapeutic relevance of these effects, however, depends on demonstrating pathway modulation at concentrations compatible with the observed biological phenotype.

3.1. NF-κB Modulation and Apoptosis Sensitization

NF-κB contributes to pancreatic cancer cell survival through transcriptional regulation of anti-apoptotic and pro-survival proteins. Constitutive pathway activity can increase the threshold required for apoptosis and thereby promote persistence of malignant cells under oncogenic, metabolic, and therapeutic stress. Suppression of NF-κB provides a mechanism for reducing these survival signals and increasing susceptibility to apoptotic stimuli [6,7,12].

Curcumin provides direct experimental evidence for this relationship. In pancreatic carcinoma cells, inhibition of constitutive IKK activity and NF-κB DNA binding by curcumin was accompanied by suppression of proliferation and induction of apoptosis [6]. These findings demonstrate that pathway inhibition can occur together with a defined functional response and establish an experimental basis for evaluating phytochemicals as modulators of NF-κB-dependent survival.

NF-κB modulators may consequently function as therapeutic sensitizers rather than exclusively as directly cytotoxic agents. This distinction is pharmacologically important because inhibition of adaptive survival signaling may enhance responsiveness to another therapeutic agent at concentrations below those required for extensive phytochemical-induced cytotoxicity [13,24]. Concentration–response and temporal analyses are therefore necessary to distinguish pathway-specific sensitization from nonspecific toxicity.

3.2. NF-κB Modulation and Therapeutic Resistance

Therapeutic resistance provides an additional rationale for targeting NF-κB in PDAC. Cytotoxic treatment can activate stress-responsive and inflammatory signaling pathways that promote cell survival and modify tumor-cell interactions with the surrounding microenvironment. NF-κB can participate in this adaptive response by increasing transcription of anti-apoptotic proteins, inflammatory mediators, angiogenic factors, and other genes that diminish treatment efficacy [7,12,24].

Experimental studies combining phytochemical NF-κB modulators with chemotherapy provide a pharmacological rationale for targeting adaptive survival signaling in PDAC. Curcumin, for example, enhanced gemcitabine associated antitumor activity in pancreatic cancer models, accompanied by suppression of NF-κB activity and downstream survival pathways [13]. The compound specific evidence and combination strategies are discussed in Sections 5 and 9.

These observations establish an important pharmacological distinction between direct cytotoxicity and chemosensitization. Suppression of an adaptive NF-κB response may increase treatment sensitivity without requiring the NF-κB modulator itself to serve as the principal cytotoxic agent. This concept provides a mechanistic basis for combination strategies involving phytochemicals and conventional anticancer therapy [13,24].

3.3. NF-κB as a Target of Natural Phytochemical Pharmacology

Phytochemicals are particularly relevant to NF-κB pharmacology because structurally diverse compounds can influence different levels of the signaling pathway. Reported mechanisms include modulation of upstream kinases, IKK activity, IκBα phosphorylation and stability, RELA/p65 phosphorylation and nuclear localization, NF-κB DNA binding, transcriptional activity, and signaling networks that converge on NF-κB [6,13,16,25]. Such multitarget pharmacology may be advantageous when compensatory pathways sustain malignant phenotypes, but it also complicates attribution of biological activity to a specific molecular mechanism.

Evidence for NF-κB modulation should therefore be interpreted according to the level at which pathway activity has been demonstrated. Direct pharmacodynamic evidence includes changes in IKK activity, IκBα phosphorylation or degradation, RELA/p65 phosphorylation or nuclear localization, NF-κB DNA-binding activity, transcriptional reporter activity, or appropriately validated NF-κB transcriptional signatures. Changes in downstream proteins such as VEGF, IL-8, cyclooxygenase-2, BCL-2 family members, or matrix metalloproteinases provide stronger mechanistic support when accompanied by direct pathway measurements but are insufficient independently to establish NF-κB inhibition [6,13,16,25].

Computational docking, network pharmacology, pathway enrichment, and transcriptional association can identify plausible compound–target relationships and prioritize candidates for experimental investigation. These approaches remain hypothesis-generating unless supported by biochemical or cellular target-engagement evidence. Similarly, induction of apoptosis, reduced proliferation, or inhibition of migration and invasion does not independently demonstrate NF-κB dependence.

3.4. Therapeutic Window and Pharmacological Selectivity

Direct systemic suppression of NF-κB presents substantial challenges because physiological NF-κB activity contributes to immune regulation, inflammatory responses, cellular survival, and tissue homeostasis [26]. The biological consequences of pathway inhibition are also cell-context-dependent [20]. Suppression of persistent NF-κB activity within malignant epithelial cells may reduce survival and therapeutic resistance, whereas modulation of the pathway within macrophages, fibroblasts, or lymphoid populations can produce different immunological and inflammatory consequences.

Pharmacological selectivity therefore represents an important determinant of therapeutic feasibility. Tumor-directed delivery, modulation of pathological upstream regulators, transient pathway inhibition, cell-type-selective targeting, and rational combination therapy may provide a more favorable therapeutic index than sustained systemic blockade of NF-κB transcriptional activity [12].

Phytochemicals introduce additional challenges related to solubility, chemical stability, absorption, metabolism, systemic exposure, tumor penetration, formulation, and molecular specificity. Curcumin illustrates this translational problem because biological activity has been observed clinically despite low circulating concentrations following high-dose oral administration [19]. Increased systemic exposure through formulation or chemical modification must therefore be connected to intratumoral target engagement and pharmacodynamic response rather than considered sufficient evidence of improved therapeutic activity.

Pharmacological evaluation of phytochemical NF-κB modulators consequently requires integration of concentration–response relationships, molecular target engagement, pathway-specific pharmacodynamics, pharmacokinetics, tumor exposure, cellular specificity, functional outcomes, and toxicity. This evidence-based framework distinguishes experimentally validated NF-κB modulation from indirect pathway association, compu-

tational prediction, or broad anticancer activity and provides the basis for evaluating individual phytochemicals in subsequent sections.

4. Phytochemicals as Pharmacological Modulators of NF-κB Signaling

Phytochemicals constitute a chemically diverse source of bioactive molecules capable of modulating inflammatory, oncogenic, metabolic, and stress-response signaling in pancreatic cancer. Reported effects on NF-κB signaling occur at multiple regulatory levels, including upstream kinase activity, IκBα phosphorylation and degradation, RELA/p65 phosphorylation and nuclear localization, NF-κB DNA binding, transcriptional activity, and expression of downstream inflammatory, survival, angiogenic, and invasion-associated genes [6,13,16,25]. The pleiotropic pharmacology of these compounds may be advantageous when compensatory signaling networks sustain tumor survival, but it also complicates attribution of biological effects to NF-κB itself.

Throughout this review, a distinction is made between pathway association, pharmacodynamic modulation, and experimentally validated causal mechanisms. Importantly, direct measurement of NF-κB inhibition establishes pharmacodynamic pathway modulation but does not independently demonstrate that NF-κB is the primary molecular target or that its inhibition is necessary for the observed antitumor phenotype. Evidence that a phytochemical suppresses NF-κB activity concurrently with antitumor effects should not be interpreted as definitive proof that NF-κB inhibition is the sole or primary mediator of the observed biological response. In many studies, NF-κB modulation is demonstrated alongside changes in proliferation, apoptosis, invasion, angiogenesis, or chemotherapy sensitivity; however, such findings generally establish pharmacodynamic association rather than direct mechanistic causality. Stronger evidence is provided when NF-κB activity is measured directly and linked to specific biological outcomes through concentration–response relationships, genetic or pharmacological pathway interrogation, rescue experiments, or complementary in vivo validation. Accordingly, the compounds discussed in this review are categorized based on the strength of available mechanistic evidence, ranging from direct pharmacodynamic modulation of NF-κB signaling to broader pathway associations in which NF-κB represents one component of a multifaceted biological response. This framework is intended to provide a balanced interpretation of the current evidence and to avoid overstating target engagement or mechanism-specific conclusions where definitive causal validation remains unavailable.

Figure 2 summarizes the experimental evidence supporting phytochemical modulation of NF-κB in PDAC, distinguishing direct pathway measurements from broader multitarget pharmacology and findings derived from other disease contexts.

As defined in Section 3, phytochemical evidence is interpreted according to disease context, direct NF-κB pharmacodynamics, functional validation, and in vivo confirmation. This framework distinguishes direct pathway modulation from downstream association, broad cytotoxicity, and computational prediction.

Several phytochemicals have been examined using direct NF-κB measurements in pancreatic cancer models. Curcumin suppresses constitutive IKK activity and NF-κB DNA binding in pancreatic carcinoma cells and modulates NF-κB-regulated gene products in experimental models [6,13]. Xanthohumol inhibits basal and TNF-α-induced NF-κB activity in pancreatic cancer cells at concentrations below those required for substantial antiproliferative effects and reduces VEGF, IL-8, endothelial tube formation, and tumor-associated angiogenesis in vivo [16]. Emodin suppresses constitutive and gemcitabine-induced NF-κB activity and has been linked to IKKβ/IκBα/p65 regulation, apoptosis, angiogenic signaling, and reversal of gemcitabine resistance [15,25,27]. Parthenolide and its derivative dimethylaminoparthenolide (DMAPT) have similarly been investigated in pancreatic cancer models in which NF-κB modulation is associated with antitumor or

therapeutic-sensitizing activity [28,29]. These compounds therefore provide pancreatic cancer-specific experimental frameworks in which pathway modulation can be evaluated together with functional phenotypes.

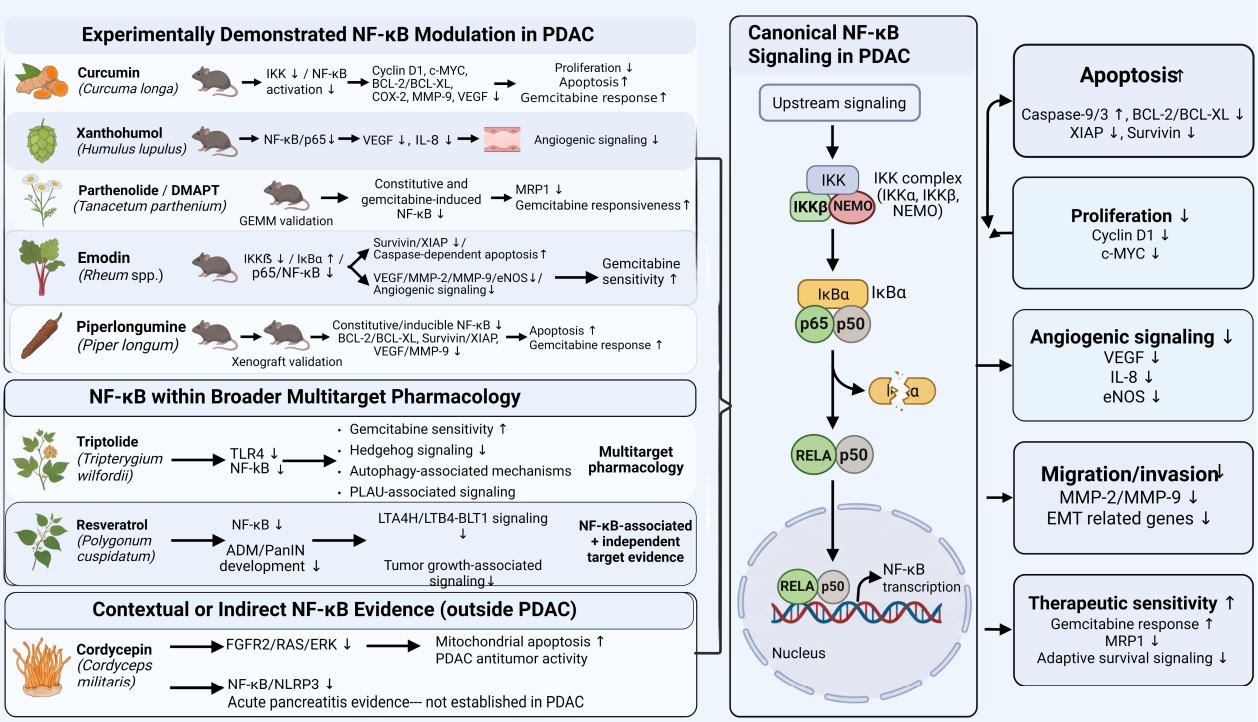


Figure 2. Evidence-stratification of phytochemical modulation of NF-κB signaling in PDAC. Phytochemicals are grouped according to the experimental evidence supporting NF-κB modulation and the disease context in which their activity has been investigated. Curcumin, xanthohumol, parthenolide/dimethylaminoparthenolide (DMAPT), emodin, and piperlongumine demonstrate NF-κB pharmacodynamic modulation in PDAC, accompanied by functional antitumor effects and varying degrees of in vivo validation. Triptolide and resveratrol affect NF-κB within broader pharmacological responses involving additional molecular pathways. Cordycepin shows PDAC antitumor activity through FGFR2/RAS/ERK signaling and mitochondrial apoptosis, whereas its NF-κB/NLRP3 regulation derives from acute pancreatitis models rather than PDAC. The central schematic depicts canonical IKK-IκBα-RELA/p50 signaling and the main downstream phenotypes affected, namely increased apoptosis, reduced proliferation, attenuated angiogenesis, decreased migration and invasion, and enhanced therapeutic sensitivity. This evidence stratification distinguishes experimentally measured NF-κB pathway modulation in PDAC from broader pharmacological associations and findings obtained in other disease contexts. Concurrent NF-κB modulation and antitumor activity do not independently establish direct molecular target engagement or demonstrate that NF-κB inhibition is necessary for the observed biological response. Created in BioRender. Syed, M. F. (2026) https://BioRender.com/qtqyp9z.

Other phytochemicals influence NF-κB within broader pharmacological responses involving interconnected signaling pathways. Triptolide and resveratrol, for example, have been associated with NF-κB modulation together with effects on TLR4, AKT, apoptosis, autophagy, and stress-response pathways, whereas resveratrol affects several survival and inflammatory networks in addition to NF-κB [14,15,18,25,30]. These compounds should therefore be interpreted as multitarget agents for which NF-κB represents one component of a broader pharmacological response rather than an isolated molecular target.

Xanthohumol further illustrates the importance of signaling-network context. In PANC-1 pancreatic cancer cells, xanthohumol combined with phenethyl isothiocyanate reduced NF-κB p65 DNA binding and expression while increasing Nrf2 activity and downstream

antioxidant responses [31]. Subsequent experimental work incorporating pancreatic cancer cells and xenograft models demonstrated modulation of NF-κB together with Nrf2, COX-2, and STAT3-associated responses, further illustrating that phytochemical activity can involve coordinated regulation of inflammatory, redox, and survival networks rather than an isolated signaling node [32].

Disease specificity is equally important when classifying evidence. Cordycepin has demonstrated pancreatic cancer-specific antitumor activity through mechanisms including mitochondrial apoptosis and FGFR2/Ras/ERK signaling [17,33], whereas evidence directly connecting cordycepin with NF-κB and NLRP3 inflammasome regulation derives from experimental acute pancreatitis rather than pancreatic cancer. In the latter setting, cordycepin suppressed NF-κB and NLRP3 activation through an AMPK-associated mechanism [34]. These findings support the biological plausibility of NF-κB modulation by cordycepin but should not be interpreted as direct evidence of this mechanism in PDAC.

Computational docking, network pharmacology, molecular dynamics simulations, pathway enrichment, and transcriptomic association can further identify plausible interactions between phytochemicals and NF-κB-associated signaling networks. These approaches are valuable for candidate prioritization but remain hypothesis-generating until supported by biochemical or cellular target-engagement studies [35–38]. Mechanistic interpretation should therefore distinguish direct NF-κB modulation from downstream association, broader network effects, and computational prediction.

An evidence-based classification integrating disease context, direct pathway measurements, functional phenotypes, in vivo validation, and pharmacological exposure provides a more rigorous framework for evaluating phytochemical NF-κB modulators. The evidence supporting phytochemical modulation of NF-κB in PDAC can therefore be stratified according to direct pathway pharmacodynamics, disease-specific functional validation, in vivo confirmation, and whether NF-κB modulation occurs within a broader multitarget or non-PDAC pharmacological context (Figure 2). Table 1 summarizes the principal phytochemicals according to disease context, direct NF-κB pharmacodynamic evidence, functional outcomes, and in vivo validation, thereby distinguishing experimentally supported pathway modulation from indirect or context-dependent associations.

Table 1. Pharmacological evidence for major phytochemical modulators of NF-κB signaling in pancreatic ductal adenocarcinoma.

Phytochemical	Experimental Model/Context	NF-κB-Related Pharmacodynamic Evidence	Principal Functional Outcome	In Vivo Validation	Evidence Interpretation	Key References
Curcumin	Human pancreatic carcinoma cells; pancreatic cancer cells ± gemcitabine; orthotopic pancreatic tumor model	Inhibition of constitutive IKK activity and NF-κB activation; suppression of NF-κB-regulated proteins including cyclin D1, c-MYC, BCL-2, BCL-XL, cIAP-1, COX-2, MMP-9, and VEGF	Reduced proliferation; increased apoptosis; enhanced gemcitabine response; reduced invasion- and angiogenesis-associated signaling	Orthotopic model; enhanced gemcitabine-mediated tumor inhibition	Direct PDAC NF-κB pharmacodynamic evidence with in vivo validation	[6,13]

Table 1. *Cont.*

Phytochemical	Experimental Model/Context	NF-κB-Related Pharmacodynamic Evidence	Principal Functional Outcome	In Vivo Validation	Evidence Interpretation	Key References
Xanthohumol	BxPC-3, AsPC-1, MIA PaCa-2; basal and TNF-α-stimulated conditions; pancreatic xenograft models	Concentration-dependent inhibition of NF-κB activity/p65 activation; reduced VEGF and IL-8; xanthohumol + PEITC also modulated NF-κB together with Nrf2, COX-2, and STAT3	Reduced tumor-cell-induced endothelial tube formation; inhibition of proliferation and tumor-associated angiogenesis	Xenograft model; reduced tumor growth and microvascular density	Direct PDAC NF-κB pharmacodynamic evidence linked to angiogenesis with in vivo validation	[16,31,32]
Partheno-lide/DMAPT	Pancreatic cancer cells; gemcitabine-resistant cells; genetically engineered pancreatic cancer mouse model	Suppression of constitutive and gemcitabine-induced NF-κB activity; parthenolide also associated with decreased MRP1	Enhanced gemcitabine-mediated growth inhibition; reduced drug resistance, invasion and angiogenic activity	Genetically engineered mouse model; DMAPT + gemcitabine prolonged survival relative to placebo and reduced pancreatic tumor burden	Direct NF-κB-associated evidence for therapeutic sensitization; in vivo validation strongest for DMAPT combination therapy	[28,29,39]
Resveratrol	Pancreatic cancer cells; xenografts; KRAS-driven pancreatic precancerous models; 3D acinar cultures	Suppression of NF-κB signaling during early pancreatic tumorigenesis; additional activity through LTA4H/LTB4-BLT1 and other signaling networks	Reduced proliferation and anchorage-independent growth; attenuation of acinar-to-ductal metaplasia and PanIN formation	Xenograft and pancreatic tumorigenesis models; reduced tumor development	Pancreatic-specific NF-κB evidence within broader multitarget pharmacology	[14,30]
Triptolide	PANC-1; pancreatic cancer cells treated with hydroxycamp-tothecin; additional pancreatic models	Inhibition of TLR4-mediated NF-κB signaling; combination treatment associated with NF-κB inhibition and caspase-9/-3 activation	Increased apoptosis and gemcitabine sensitivity; enhanced cytotoxicity with hydroxy-camptothecin	Preclinical pancreatic tumor models; antitumor activity demonstrated	PDAC-specific NF-κB-associated evidence within a broader multitarget mechanism	[18,40]

Table 1. *Cont.*

Phytochemical	Experimental Model/Context	NF-κB-Related Pharmacodynamic Evidence	Principal Functional Outcome	In Vivo Validation	Evidence Interpretation	Key References
Emodin	Parental and gemcitabine-resistant SW1990; gemcitabine-resistant PANC-1 and MIA PaCa-2; implanted pancreatic tumors	Suppression of constitutive/gemcitabine-induced NF-κB activity; decreased IKKβ and NF-κB p65, increased IκBα; reduced NF-κB DNA-binding/activity; modulation of survivin and XIAP	Increased apoptosis; restoration of gemcitabine sensitivity; reduced VEGF, MMP-2, MMP-9 and eNOS; reduced angiogenic activity	Implanted tumor models; reduced tumor growth and angiogenesis	Direct PDAC NF-κB evidence linked to chemoresistance, apoptosis and angiogenic regulation	[15,25,27]
Piperlongumine	Pancreatic cancer cells ± gemcitabine; pancreatic xenograft model	Inhibition of constitutive and inducible NF-κB activation; decreased NF-κB-regulated c-MYC, cyclin D1, BCL-2, BCL-XL, survivin, XIAP, VEGF and MMP-9	Enhanced gemcitabine-induced apoptosis and tumor suppression; reduced proliferative and angiogenic markers	Xenograft model; enhanced gemcitabine-mediated tumor suppression	Direct NF-κB-associated chemosensitization with in vivo validation	[41]
Cordycepin	MIA PaCa-2, Capan-1; MIA PaCa-2 xenografts; experimental acute pancreatitis for NF-κB/NLRP3 evidence	PDAC studies demonstrate mitochondrial apoptosis and FGFR2/Ras/ERK modulation; direct NF-κB/NLRP3 suppression derives from experimental acute pancreatitis rather than PDAC	Reduced proliferation and colony formation; S-phase arrest; mitochondrial apoptosis; reduced pancreatic tumor growth	Xenograft model; antitumor activity demonstrated; NF-κB mechanism not established in PDAC	Biological plausibility for NF-κB modulation, but direct NF-κB evidence is outside the PDAC disease context	[17,33,34]

Abbreviations: BCL-2, B-cell lymphoma 2; BCL-XL, B-cell lymphoma-extra-large; cIAP-1, cellular inhibitor of apoptosis protein-1; COX-2, cyclooxygenase-2; DMAPT, dimethylaminoparthenolide; IKK, IκB kinase; IL-8, interleukin-8; LTA4H, leukotriene A4 hydrolase; MMP, matrix metalloproteinase; MRP1, multidrug resistance-associated protein 1; NF-κB, nuclear factor kappa B; Nrf2, nuclear factor erythroid 2-related factor 2; PDAC, pancreatic ductal adenocarcinoma; PEITC, phenethyl isothiocyanate; TLR4, Toll-like receptor 4; VEGF, vascular endothelial growth factor; XIAP, X-linked inhibitor of apoptosis protein.

5. Major Phytochemical NF-κB Modulators

To minimize redundancy and improve conceptual clarity, the biological role of NF-κB in PDAC pathogenesis, including its interaction with KRAS-driven oncogenic signaling, is discussed in dedicated earlier sections. Subsequent sections therefore focus specifically on

the pharmacological modulation of NF-κB by selected phytochemicals and the associated experimental evidence, rather than repeating the underlying mechanistic framework. Where relevant, readers are referred to the preceding sections for detailed discussion of NF-κB signaling, KRAS-NF-κB crosstalk, and their contributions to pancreatic tumor initiation, progression, metastasis, and therapeutic resistance. This structure allows emphasis on compound-specific pharmacodynamic evidence, target engagement, and translational relevance while avoiding duplication of biological concepts discussed elsewhere in the review.

5.1. Curcumin

Curcumin is a polyphenolic constituent of Curcuma longa and one of the most extensively investigated phytochemicals in pancreatic cancer. Its pharmacological activity encompasses inflammatory, survival, apoptotic, and stress-response pathways, with NF-κB representing one of the most consistently examined molecular nodes. In human pancreatic carcinoma cells, constitutive NF-κB DNA-binding and IKK activities were directly demonstrated, and curcumin suppressed IKK activity and NF-κB activation in association with reduced proliferation and induction of apoptosis [6,42].

Subsequent studies extended these findings to therapeutic sensitization. In pancreatic cancer cells and an orthotopic pancreatic tumor model, curcumin potentiated the antitumor activity of gemcitabine and suppressed NF-κB activation together with NF-κB-regulated proteins involved in proliferation, survival, invasion, and angiogenesis, including cyclin D1, c-MYC, BCL-2, BCL-XL, cellular inhibitor of apoptosis protein-1, cyclooxygenase-2, MMP-9, and VEGF [13]. These findings link pathway modulation with apoptosis, reduced proliferation, and inhibition of tumor-associated angiogenic signaling.

The molecular activity of curcumin extends beyond NF-κB. Experimental and recent integrative evidence implicates PI3K/AKT, STAT3, MAPK, IL-6/ERK, epithelial–mesenchymal plasticity, and stromal signaling in its activity against pancreatic cancer. A recent synthesis of PDAC studies identifies PI3K/AKT/NF-κB and IL-6/ERK/NF-κB among the signaling networks affected by curcumin and its analogues, emphasizing the multitarget nature of its pharmacology [42].

Clinical investigation provides an important translational dimension. In a phase II study involving 25 patients with advanced pancreatic cancer, oral curcumin at 8 g/day was associated with biological activity in a small subset of patients and pharmacodynamic changes in NF-κB-associated markers in peripheral blood mononuclear cells. Systemic exposure to parent curcumin remained low, however, illustrating the discrepancy between experimentally active concentrations and clinically achievable exposure [19]. Curcumin therefore provides substantial experimental evidence for NF-κB modulation while simultaneously illustrating the pharmacokinetic challenges associated with clinical translation of phytochemicals.

5.2. Xanthohumol

Xanthohumol is a prenylated chalcone derived predominantly from Humulus lupulus and provides direct experimental evidence for NF-κB modulation in pancreatic cancer. Saito et al. demonstrated concentration-dependent inhibition of NF-κB activity by xanthohumol in BxPC-3, AsPC-1, and MIA PaCa-2 pancreatic cancer cells under basal conditions and following TNF-α stimulation [16]. Importantly, NF-κB suppression was observed at concentrations below those required to produce substantial antiproliferative effects, supporting a pharmacodynamic effect on the pathway rather than a secondary consequence of nonspecific cytotoxicity.

NF-κB inhibition was accompanied by decreased VEGF and IL-8 expression and reduced pancreatic cancer cell-induced endothelial tube formation. Consistent with these findings, xenograft studies demonstrated reduced tumor growth, Ki-67 expression, CD31+

microvascular density, NF-κB p65 activation, VEGF, and IL-8. Together, these observations establish a mechanistic sequence linking xanthohumol exposure to NF-κB suppression, attenuation of proangiogenic signaling, and inhibition of tumor-associated angiogenesis [16].

Additional experimental evidence indicates that xanthohumol can influence interconnected inflammatory and redox regulatory networks. In pancreatic cancer cells, combined xanthohumol and phenethyl isothiocyanate treatment inhibited NF-κB while increasing Nrf2-associated responses, demonstrating reciprocal modulation of inflammatory and antioxidant signaling [31]. Subsequent experimental work incorporating pancreatic cancer cells and xenograft models further implicated NF-κB, Nrf2, COX-2, and STAT3-associated responses in the antitumor effects of this combination [32].

Collectively, direct measurement of NF-κB activity, modulation of downstream VEGF and IL-8 signaling, functional angiogenesis assays, and in vivo validation establish a well-defined pharmacodynamic relationship between xanthohumol-mediated NF-κB inhibition and suppression of pancreatic tumor-associated angiogenesis.

5.3. Resveratrol

Resveratrol is a naturally occurring stilbene polyphenol found predominantly in grapes, berries, peanuts, and related plant sources. Its antitumor activity in pancreatic cancer has been associated with modulation of multiple signaling networks involved in proliferation, survival, inflammation, invasion, and therapeutic resistance [14,30].

A well-defined pancreatic cancer-specific molecular target of resveratrol is leukotriene A4 hydrolase (LTA4H). Resveratrol directly bound to LTA4H in vitro and in pancreatic cancer cells, reduced leukotriene B4 production and BLT1 expression, inhibited proliferation and anchorage-independent growth, and suppressed tumor formation in a xenograft model. Genetic suppression of LTA4H reduced the inhibitory effects of resveratrol, providing functional evidence for target dependence [14].

Resveratrol has also been associated with modulation of AKT, NF-κB, inflammatory signaling, apoptosis, invasion, and therapeutic-response pathways in pancreatic cancer. Pancreatic cancer-specific evidence also directly implicates NF-κB in the effects of resveratrol during early tumorigenesis. In KRAS-driven pancreatic precancerous models and three-dimensional acinar cultures, resveratrol attenuated acinar-to-ductal metaplasia and PanIN formation together with suppression of NF-κB signaling [30]. Nevertheless, resveratrol remains a multitarget phytochemical, and its pharmacological activity should not be attributed exclusively to NF-κB.

Additional direct measurements of NF-κB target engagement, concentration-dependent pathway modulation, and causal perturbation will be necessary to determine the relative contribution of NF-κB suppression to the antitumor and therapeutic-sensitizing effects of resveratrol in PDAC.

5.4. Triptolide

Triptolide is a diterpenoid triepoxide derived from Tripterygium wilfordii with antitumor activity across experimental pancreatic cancer models. Its pharmacological effects include inhibition of proliferation, induction of apoptosis, disruption of transcriptional programs, and modulation of cellular stress and survival pathways.

In PANC-1 cells, triptolide enhanced sensitivity to gemcitabine through inhibition of TLR4-mediated NF-κB signaling, accompanied by increased apoptosis and attenuation of survival signaling [18]. Additional evidence indicates that combination treatment with triptolide and hydroxycamptothecin increases pancreatic cancer cell cytotoxicity, with activation of caspase-9 and caspase-3 and inhibition of NF-κB signaling [40]. These findings associate

NF-κB suppression with the enhanced cytotoxic and pro-apoptotic effects of combined triptolide and hydroxycamptothecin treatment.

The pharmacological activity of triptolide nevertheless extends considerably beyond NF-κB. Triptolide suppresses Hedgehog signaling in pancreatic cancer cells and has also been linked to autophagic regulation and inhibition of PLAU-associated proliferative and migratory programs [43,44]. The latter study combined network pharmacology with experimental validation, illustrating the broader multitarget profile of triptolide [44].

NF-κB modulation should therefore be interpreted as an important component of triptolide pharmacology rather than an isolated mechanism of action. Its ability to affect transcriptional regulation, apoptosis, autophagy, and stress-response pathways may contribute collectively to its antitumor and therapeutic-sensitizing activity.

5.5. Emodin

Emodin is a naturally occurring anthraquinone found in several medicinal plants and has demonstrated antitumor and therapeutic-sensitizing activity in experimental pancreatic cancer models. Multiple studies provide pancreatic cancer-specific evidence linking emodin with NF-κB modulation.

Emodin suppressed constitutive and gemcitabine-induced NF-κB activity in pancreatic cancer cells and enhanced gemcitabine-associated growth inhibition and apoptosis. These effects were observed in both parental and gemcitabine-resistant SW1990 cells, linking NF-κB suppression with reversal of a treatment-resistant phenotype [15,45].

Additional in vivo evidence connects emodin-mediated NF-κB modulation with apoptosis and angiogenesis. Emodin enhanced gemcitabine-associated antitumor activity and altered AKT/NF-κB-associated survival and mitochondrial apoptotic signaling. In pancreatic cancer cells and implanted tumors, emodin also decreased NF-κB activity together with VEGF, MMP-2, MMP-9, and eNOS and suppressed tumor-associated angiogenesis [27].

More recent evidence further implicates the IKKβ/NF-κB axis in emodin-mediated reversal of gemcitabine resistance. In gemcitabine-resistant PANC-1 and MIA PaCa-2 cells, emodin decreased IKKβ and NF-κB p65 expression and NF-κB activity, increased IκBα, and altered downstream apoptotic regulators including survivin, XIAP, caspase-9, and caspase-3 [25]. Together, these studies support a relationship between emodin-mediated suppression of IKKβ/NF-κB signaling, mitochondrial apoptosis, angiogenic regulation, and therapeutic sensitization.

5.6. Cordycepin

Cordycepin (3′-deoxyadenosine) is a naturally occurring nucleoside analogue derived predominantly from Cordyceps militaris and related Cordyceps species. Experimental studies demonstrate pancreatic cancer-specific antitumor activity through inhibition of proliferation, induction of cell-cycle arrest, and activation of apoptosis.

In MIA PaCa-2 and Capan-1 cells, cordycepin reduced cell viability and colony formation and induced apoptosis in a concentration- and time-dependent manner. These effects were associated with loss of mitochondrial membrane potential, increased Bax, cleaved caspase-9, cleaved caspase-3, and cleaved PARP, and decreased BCL-2 expression. Antitumor activity was also demonstrated in MIA PaCa-2 xenografts, supporting involvement of the mitochondrial intrinsic apoptotic pathway in vivo [17].

Additional pancreatic cancer-specific evidence identified FGFR2/Ras/ERK signaling as a molecular target of cordycepin. Cordycepin inhibited pancreatic cancer growth in vitro and in vivo, induced caspase-dependent apoptosis and S-phase arrest, and reduced Ras expression and ERK phosphorylation. Direct interaction with FGFR2 was demon-

strated, linking molecular target engagement with inhibition of downstream Ras/ERK signaling [33].

Cordycepin also possesses anti-inflammatory activity involving NF-κB and NLRP3 signaling; however, this evidence derives from experimental acute pancreatitis rather than pancreatic cancer. In caerulein-induced acute pancreatitis, cordycepin reduced IL-6, IL-1β, and TNF-α production and suppressed NF-κB and NLRP3 inflammasome activation through an AMPK-associated mechanism [34]. Thus, pancreatic cancer-specific antitumor activity of cordycepin is currently supported more directly by mitochondrial apoptosis and FGFR2/Ras/ERK modulation, whereas its ability to regulate NF-κB/NLRP3 signaling within the pancreatic TME remains to be established.

5.7. Emerging and Indirect NF-κB Modulators

Several additional phytochemicals demonstrate antitumor activity in pancreatic cancer through signaling pathways that intersect functionally with NF-κB but currently lack sufficient pancreatic cancer-specific evidence to classify NF-κB as a principal pharmacological mechanism.

Cucurbitacin E inhibits pancreatic cancer cell growth predominantly through modulation of STAT3-associated signaling. In PANC-1 cells, cucurbitacin E produced concentration- and time-dependent growth inhibition, induced G2/M cell-cycle arrest and apoptosis, suppressed STAT3 phosphorylation, and increased p53 expression [46]. Although STAT3 and NF-κB participate in interconnected inflammatory and survival networks, these findings do not establish direct NF-κB modulation by cucurbitacin E in pancreatic cancer.

Fisetin has demonstrated therapeutic-sensitizing activity in pancreatic cancer through a distinct signaling mechanism. In MIA PaCa-2 cells, fisetin enhanced gemcitabine-induced cytotoxicity and apoptosis and altered ERK-MYC signaling [47]. These findings support fisetin as a candidate phytochemical for combination therapy but do not independently establish NF-κB as the molecular mechanism responsible for its activity.

Oridonin similarly exhibits pancreatic cancer-specific pro-apoptotic activity through pathways distinct from directly demonstrated NF-κB modulation. In SW1990 cells, oridonin induced concentration-dependent apoptosis through activation of p38 MAPK, followed by p53 and p21 activation and caspase-9 and caspase-3 signaling. Pharmacological inhibition of p38 attenuated these responses, providing functional evidence for involvement of the p38-p53-caspase axis [48]. Oridonin has also demonstrated therapeutic interaction with gemcitabine in pancreatic cancer models, further supporting its relevance as a multitarget phytochemical [49].

These compounds remain relevant to the broader pharmacological framework because STAT3, ERK/MYC, p38 MAPK, p53, apoptotic signaling, and NF-κB form interconnected regulatory networks capable of influencing pancreatic cancer survival and treatment response [7]. Their inclusion should nevertheless distinguish pathway crosstalk from direct NF-κB modulation. Classification as pancreatic cancer-specific NF-κB modulators will require direct assessment of IKK/IκB signaling, RELA activation or nuclear localization, NF-κB DNA binding or reporter activity, together with causal validation linking pathway modulation to the observed phenotype.

6. Molecular Crosstalk Between NF-κB and Oncogenic Signaling in Pancreatic Cancer

NF-κB signaling operates within an interconnected oncogenic and inflammatory network rather than as an isolated transcriptional pathway. In PDAC, constitutive NF-κB activity is integrated with KRAS, EGFR, PI3K/AKT, MAPK, STAT3, redox signaling, and inflammatory cytokine networks that collectively regulate tumor-cell survival, proliferation,

invasion, angiogenesis, and therapeutic resistance [7]. Both canonical and noncanonical NF-κB signaling are active in pancreatic cancer, further increasing the complexity of pathway regulation and its pharmacological modulation [11].

6.1. KRAS and NF-κB Signaling

As outlined in Section 2.3, oncogenic KRAS promotes NF-κB signaling through multiple regulatory routes. The pharmacological significance of this interaction lies in the convergence of oncogenic survival pathways, inflammatory transcription, and adaptive therapeutic responses. Oncogenic KRAS is a principal molecular driver of PDAC and establishes several mechanistic connections with NF-κB signaling. Constitutive NF-κB activity in pancreatic cancer cells can be maintained through an EGFR/RAS/PI3K/AKT/IKK signaling axis, linking growth-factor and oncogenic signaling directly to NF-κB-dependent transcription [8]. KRAS-dependent NF-κB regulation also involves TAK1 and its associated signaling complex. Mutant KRAS increases GSK-3α activity, which stabilizes the TAK1/TAB complex and promotes IKK-dependent canonical NF-κB signaling while also supporting noncanonical NF-κB activity [10].

TBK1 provides an additional connection between oncogenic KRAS and NF-κB-dependent survival. Functional genomic screening identified TBK1 as a synthetic-lethal dependency in KRAS-driven cancer cells, where TBK1 supports NF-κB-mediated anti-apoptotic signaling involving c-REL and BCL-XL [9]. In PDAC models, direct interference with the IKK/NEMO complex suppresses KRAS-associated NF-κB activation, enhances gemcitabine-induced apoptosis, and reduces orthotopic tumor growth, further demonstrating the functional importance of this signaling convergence [50].

These interconnected pathways provide a mechanistic basis for the activity of phytochemicals that suppress NF-κB downstream of oncogenic signaling. Such effects may attenuate KRAS-associated survival and stress-adaptation programs even in the absence of direct KRAS inhibition [6,10].

6.2. PI3K/AKT and NF-κB Signaling

PI3K/AKT signaling contributes to proliferation, metabolic adaptation, apoptosis resistance, and therapeutic response in pancreatic cancer. Mechanistically, AKT can promote IKK activity and NF-κB-dependent transcription, establishing a direct connection between kinase-mediated survival signaling and inflammatory transcription. In pancreatic cancer cells, inhibition of PI3K or AKT decreases constitutive IKK and NF-κB activity, demonstrating functional integration of the PI3K/AKT and NF-κB pathways [8].

Several phytochemicals act at this signaling interface. Emodin enhances the antitumor activity of gemcitabine in pancreatic cancer models while reducing phosphorylated AKT and NF-κB activation, accompanied by a decreased BCL-2/BAX ratio, cytochrome c release, and activation of caspase-9 and caspase-3 [51]. Curcumin similarly suppresses constitutive IKK/NF-κB activity and NF-κB-regulated gene expression in pancreatic cancer cells [6]. In BxPC-3 and PANC-1 cells, curcumin also inhibited oxidative stress-induced migration, invasion, and epithelial–mesenchymal transition through suppression of the PI3K/AKT/NF-κB axis [52].

These findings demonstrate that concurrent modulation of PI3K/AKT and NF-κB can influence both survival and invasive phenotypes in pancreatic cancer and represents an important component of the multitarget pharmacology of several natural compounds.

6.3. STAT3 and NF-κB Signaling

STAT3 and NF-κB are major transcriptional regulators of inflammatory and pro-survival programs in PDAC. Their transcriptional outputs converge on cytokine production,

proliferation, apoptosis resistance, angiogenesis, and TME communication. Cytokines such as IL-6 can sustain STAT3 activity within malignant and stromal compartments, whereas NF-κB-dependent inflammatory signaling can reinforce cytokine production, creating interconnected transcriptional circuits that favor tumor persistence [53,54].

Natural compounds can modulate multiple components of these networks simultaneously. In pancreatic cancer models, xanthohumol combined with phenethyl isothiocyanate reduced NF-κB activity while altering Nrf2-associated responses [31]. Subsequent studies in PSN-1 pancreatic cancer cells demonstrated decreased NF-κB activation together with reduced COX-2 and nuclear STAT3, accompanied by antiproliferative and proapoptotic effects and antitumor activity in xenograft models [32]. These findings demonstrate coordinated modulation of inflammatory, survival, and redox-responsive pathways rather than restriction of phytochemical activity to a single transcriptional regulator.

6.4. Nrf2 and NF-κB Signaling

Nrf2 coordinates antioxidant and cellular stress responses, whereas NF-κB regulates inflammatory, survival, and immune-associated transcription. Functional interactions between these pathways influence redox homeostasis, inflammatory signaling, apoptosis, and adaptation to therapeutic stress. Their relationship is context-dependent because Nrf2 activation can protect cells against oxidative injury but may also support the survival and metabolic adaptation of established tumor cells [55].

This signaling interface is directly relevant to phytochemical activity in pancreatic cancer. In PANC-1 cells, combined xanthohumol and phenethyl isothiocyanate treatment decreased NF-κB p65 DNA-binding activity and p65 expression while increasing Nrf2 activity and expression of downstream antioxidant genes, including GSTP, NQO1, and SOD [31]. Studies in additional pancreatic cancer models have similarly demonstrated coordinated modulation of Nrf2 and NF-κB together with changes in COX-2, STAT3, proliferation, apoptosis, and tumor growth [32]. These observations indicate that the biological consequences of phytochemical-mediated NF-κB inhibition can depend on simultaneous changes in cellular redox-regulatory pathways.

Recent evidence further demonstrates that NF-κB output in PDAC is determined not only by upstream signaling but also by transcription-factor usage and chromatin context. Aggrey-Fynn et al. used transcriptomic, genome-wide occupancy, chromatin-accessibility, single-cell, and tissue-based analyses to distinguish canonical TNF-α/RELA signaling from noncanonical TWEAK/RELB signaling in PDAC. TNF-α preferentially activated RELA, whereas TWEAK selectively engaged RELB. RELA displayed greater capacity to engage different chromatin states and remodel regulatory regions, whereas RELB activity was more dependent on pre-existing chromatin accessibility and cooperating transcription factors [56]. These findings establish an additional layer of NF-κB regulation in PDAC and indicate that suppression of canonical RELA activity does not necessarily predict equivalent inhibition of noncanonical RELB-dependent transcription.

7. NF-κB Control of Apoptosis, EMT, Angiogenesis, and Invasion

NF-κB regulates several interconnected phenotypes that contribute to PDAC progression and therapeutic resistance, including apoptotic resistance, epithelial–mesenchymal plasticity, angiogenesis, invasion, and adaptation to treatment-induced stress. These effects are mediated through transcriptional programs controlling cell-survival proteins, inflammatory mediators, angiogenic factors, chemokine receptors, and matrix-remodeling enzymes. Consequently, phytochemical modulation of NF-κB can influence multiple tumor-promoting processes, although the relative contribution of NF-κB depends on cellular context and interactions with parallel oncogenic and stress-response pathways [7,20].

7.1. Apoptotic Resistance

Resistance to apoptosis enables pancreatic cancer cells to survive oncogenic, metabolic, and therapeutic stress. Constitutive NF-κB activity contributes to this phenotype by maintaining transcriptional programs involving anti-apoptotic and pro-survival proteins, including BCL-2 family members, XIAP, survivin, and other regulators of caspase-dependent cell death [6,7,13]. Persistent pathway activation can therefore increase the apoptotic threshold and reduce responsiveness to cytotoxic therapy.

Direct experimental evidence connects phytochemical-mediated NF-κB inhibition with restoration of apoptotic signaling. Curcumin suppresses constitutive IKK and NF-κB activity in pancreatic cancer cells, accompanied by inhibition of proliferation and induction of apoptosis [6]. In an orthotopic model, curcumin enhanced gemcitabine activity while suppressing NF-κB and NF-κB-regulated proteins associated with proliferation, survival, and angiogenesis [13]. Curcumin-mediated inhibition of NF-κB and pancreatic tumor growth has also been linked to down-regulation of specificity proteins, indicating coordination between NF-κB and broader transcriptional networks [57].

A similar relationship is observed with emodin in gemcitabine-resistant pancreatic cancer cells. Emodin reduced IKKβ and NF-κB p65 expression and NF-κB DNA-binding activity, increased IκBα, and altered downstream apoptotic regulators, including survivin, XIAP, caspase-9, and caspase-3. These molecular changes were accompanied by increased apoptosis and restoration of gemcitabine sensitivity [25]. Thus, inhibition of NF-κB-associated survival signaling can lower the apoptotic threshold and enhance the response to chemotherapy.

Other phytochemicals, including triptolide, fisetin, and oridonin, also induce apoptosis through mitochondrial oxidative stress, as well as MAPK, PI3K/AKT, STAT3, and related pathways [18,47,48]. Apoptosis alone, however, does not establish NF-κB dependence. Mechanistic evidence is strengthened when functional responses coincide with changes in IKK activity, IκBα phosphorylation or degradation, RELA/p65 nuclear localization, NF-κB DNA-binding or transcriptional activity, and downstream NF-κB-regulated survival proteins.

7.2. EMT and Epithelial Plasticity

EMT and related states of epithelial–mesenchymal plasticity contribute to PDAC cell adaptation, invasion, dissemination, and therapeutic resistance. NF-κB participates in these processes through interactions with PI3K/AKT, STAT3, TGF-β, MAPK, and hypoxia-responsive signaling. These interconnected pathways regulate EMT-associated transcriptional programs and changes in epithelial adhesion, cytoskeletal organization, and matrix-remodeling activity [7,58].

Experimental studies demonstrate that phytochemical-mediated NF-κB modulation can interfere with these processes. Curcumin inhibited migration, invasion, and EMT in pancreatic cancer cells through suppression of PI3K/AKT/NF-κB signaling, accompanied by attenuation of mesenchymal characteristics and restoration of epithelial features [52]. NF-κB-dependent epithelial plasticity is also influenced by stromal signaling. Under hypoxic conditions, pancreatic stellate cell-derived IL-6 promoted ERK/NF-κB activation, EMT, and invasion in pancreatic cancer cells, whereas curcumin attenuated these responses and reduced MMP-9 expression [58].

These findings connect NF-κB with both tumor-cell-intrinsic and stromal regulation of epithelial plasticity. The involvement of multiple convergent pathways further indicates that phytochemical suppression of EMT generally reflects coordinated modulation of inflammatory, oncogenic, and microenvironmental signaling rather than inhibition of NF-κB in isolation.

7.3. Angiogenesis

NF-κB connects inflammatory signaling with angiogenesis through transcriptional regulation of pro-angiogenic mediators, particularly VEGF and IL-8. Production of these factors by pancreatic cancer cells can promote endothelial activation and vascular remodeling, thereby coupling tumor-cell inflammatory signaling to changes in the surrounding vascular compartment [13,16].

Xanthohumol provides direct experimental evidence for this relationship. Suppression of basal and TNF-α-induced NF-κB activity by xanthohumol in pancreatic cancer cells was accompanied by decreased VEGF and IL-8 expression and reduced cancer cell-induced endothelial tube formation. In vivo, xanthohumol decreased tumor growth, Ki-67 expression, CD31+ microvascular density, NF-κB p65 activity, VEGF, and IL-8 [16].

The concordance between NF-κB inhibition, reduced pro-angiogenic mediators, impaired endothelial responses, and decreased tumor microvascular density establishes a mechanistic connection between phytochemical-mediated NF-κB suppression and inhibition of tumor-associated angiogenesis. This relationship also illustrates how pathway modulation within malignant cells can produce functional consequences in a distinct cellular compartment of the TME.

7.4. Invasion and Metastatic Progression

NF-κB contributes to pancreatic cancer invasion through regulation of inflammatory mediators, chemokine signaling, matrix-remodeling enzymes, and cellular adaptation to hypoxic and therapeutic stress. These processes facilitate interactions between tumor cells and the surrounding ECM and can promote local tissue infiltration and subsequent dissemination [7,59].

Therapeutic stress can further activate this invasive program. Gemcitabine exposure increases ROS production in pancreatic cancer cells, leading to activation of NF-κB and HIF-1α, up-regulation of CXCR4, and increased invasive behavior [59]. This mechanism demonstrates that NF-κB can function both as a constitutively active survival pathway and as an adaptive response induced by chemotherapy. Treatment-induced NF-κB activation may therefore contribute simultaneously to cell survival and acquisition of a more invasive phenotype.

Phytochemical modulation of NF-κB and its interacting pathways can attenuate these responses. Curcumin suppresses NF-κB-associated EMT and invasion, resveratrol inhibits NF-κB activation and pancreatic tumorigenesis, and emodin suppresses the IKKβ/NF-κB axis in gemcitabine-resistant pancreatic cancer cells [25,30,52]. These observations connect NF-κB modulation with reduced invasive behavior and therapeutic adaptation, although the multitarget pharmacology of these compounds precludes attribution of all anti-invasive effects exclusively to NF-κB.

Migration, invasion, dissemination, and metastatic colonization represent biologically distinct stages of tumor progression. Two-dimensional migration assays and ECM-based invasion assays demonstrate altered cellular motility or invasive capacity but do not independently establish suppression of metastasis. Evidence for anti-metastatic activity requires appropriate in vivo assessment of dissemination, metastatic burden, or colonization. This distinction is particularly relevant for phytochemical studies, in which evidence for altered migration and invasion is substantially more extensive than direct demonstration of reduced metastatic progression.

8. NF-κB Signaling Within the Pancreatic TME

PDAC develops within a highly desmoplastic and immunoregulatory TME composed of cancer-associated fibroblasts (CAFs), pancreatic stellate cells (PSCs), TAMs, other

myeloid populations, endothelial and lymphoid cells, and an abundant ECM. Reciprocal interactions among these cellular and structural components influence tumor growth, immune evasion, invasion, vascular function, and therapeutic response [3,60]. NF-κB functions at the interface of tumor-intrinsic and microenvironmental signaling by integrating inflammatory cytokines, cellular stress, and innate immune signals with transcriptional programs controlling survival, inflammation, angiogenesis, and tissue remodeling [3,7,20].

8.1. Tumor–Stromal Communication

Tumor cells and stromal populations in PDAC communicate through cytokines, chemokines, growth factors, metabolites, and ECM-associated signals. These reciprocal interactions generate inflammatory and fibrotic circuits that can sustain malignant phenotypes and contribute to treatment resistance. CAFs and TAMs are particularly important components of this communication network, and their phenotypic heterogeneity influences immune-cell recruitment, ECM remodeling, and therapeutic response [3,60]. Recent spatial multi-omics analysis further resolved spatially organized CAF subtype gradients associated with metabolic support and immune remodeling in PDAC, reinforcing the importance of evaluating stromal signaling in a spatial and cell-state-specific context [61].

NF-κB contributes to this intercellular communication through cytokine and stress-responsive transcription. Activation of NF-κB in malignant or stromal compartments can alter expression of cytokines, chemokines, angiogenic mediators, and matrix-remodeling enzymes, thereby influencing neighboring cell populations. Conversely, soluble factors produced by stromal and immune cells can activate NF-κB within pancreatic cancer cells. This bidirectional signaling establishes a mechanistic connection between tumor-cell NF-κB activity and the inflammatory microenvironment [3,7].

8.2. CAFs and Pancreatic Stellate Cells

CAFs and activated PSCs are major contributors to the desmoplastic stroma of PDAC. These populations regulate collagen and ECM deposition, tissue mechanics, vascular function, inflammatory signaling, and communication with malignant and immune cells. Importantly, CAFs are functionally heterogeneous, and distinct fibroblast states can exert different effects on tumor progression and immunity.

Direct experimental evidence links phytochemical activity with tumor–stromal signaling in pancreatic cancer. Under hypoxic conditions, curcumin inhibited PSC activation and migration and reduced IL-6 production. Conditioned medium from PSCs promoted invasion and EMT in BxPC-3 and PANC-1 cells, accompanied by increased ERK and NF-κB phosphorylation. Curcumin attenuated these responses and reduced changes in E-cadherin, vimentin, and MMP-9, identifying an IL-6/ERK/NF-κB signaling axis connecting PSC activity with pancreatic cancer-cell invasion and EMT [58].

Recent single-cell multi-omic analysis has further demonstrated that inflammatory fibroblast signaling in PDAC extends beyond NF-κB. IL-1-responsive CAFs exhibit increased NFAT transcriptional activity, and pharmacological NFAT inhibition reduced tumor weight and fibrosis in a mouse model of PDAC [62]. These findings reveal that fibroblast-mediated inflammation is regulated by interacting transcriptional networks and support a cell-compartment-specific interpretation of phytochemical activity within the PDAC microenvironment.

8.3. TAMs and Immune-Suppressive Myeloid Populations

TAMs and other myeloid populations contribute substantially to the immunosuppressive phenotype of PDAC. These cells produce cytokines, chemokines, growth factors, proteases, and angiogenic mediators that can influence tumor-cell survival, ECM remodeling, vascular function, immune-cell recruitment, and therapeutic response. CAFs and TAMs also engage in reciprocal communication that reinforces desmoplasia and immune suppression [3,60].

NF-κB signaling within the myeloid compartment is highly context-dependent. Its biological consequences vary according to macrophage state, upstream stimulus, signaling duration, and interactions with neighboring tumor and stromal cells [3]. Recent PDAC evidence illustrates this complexity: bacterial components and tumor debris were shown to influence TAM phenotypes and promote pancreatic cancer progression through NF-κB-associated inflammatory signaling, EMT, and increased PD-L1 expression [63].

Consequently, inhibition of NF-κB in malignant epithelial cells cannot be assumed to produce equivalent effects when the pathway is modulated in macrophages or other immune populations. The antitumor consequences of phytochemical NF-κB modulation therefore depend not only on the magnitude of pathway inhibition but also on the cellular compartment in which modulation occurs.

8.4. ECM and Inflammatory Signaling

Extensive ECM deposition is a defining feature of PDAC. Collagens, fibronectin, hyaluronan, proteoglycans, and matrix-remodeling enzymes contribute to altered tissue mechanics, vascular compression, invasive behavior, immune-cell trafficking, and restricted therapeutic delivery. CAFs represent a major source of ECM components, although malignant and immune cells also participate in matrix remodeling [3,5].

NF-κB can influence ECM remodeling indirectly through transcriptional regulation of inflammatory cytokines, chemokines, and matrix metalloproteinases. In the PSC-pancreatic cancer interaction described above, curcumin-mediated suppression of the IL-6/ERK/NF-κB axis was accompanied by reduced MMP-9 expression and decreased invasion and EMT [58]. Network pharmacology studies identifying MMP-2, MMP-9, or related ECM proteins as highly connected nodes provide complementary hypotheses regarding pathway interactions, but network connectivity alone does not establish NF-κB-dependent regulation or direct phytochemical target engagement.

Collectively, NF-κB signaling in PDAC is shaped by reciprocal interactions among malignant epithelial cells, fibroblasts, myeloid populations, inflammatory mediators, and the ECM. The coexistence of NF-κB-dependent and NF-κB-independent inflammatory programs, including the recently identified IL-1/NFAT axis in CAFs, underscores the cellular heterogeneity of tumor-associated inflammation [62]. The pharmacological consequences of phytochemical-mediated NF-κB modulation are therefore determined by cellular context, pathway selectivity, and interactions with parallel stromal and immune signaling networks. The compartment-specific functions of NF-κB across malignant epithelial cells, CAFs/PSCs, tumor-associated myeloid populations, endothelial cells, and the ECM, together with their reciprocal interactions and potential modulation by phytochemicals, are summarized in Figure 3.

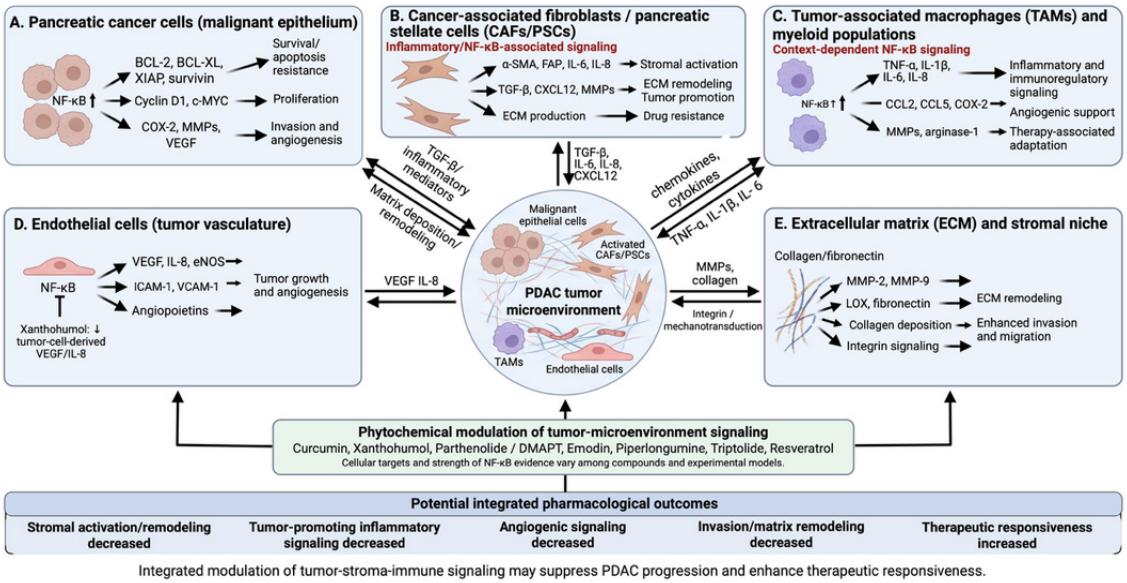


Figure 3. Cell-compartment-specific NF-κB signaling and phytochemical modulation within the PDAC tumor microenvironment (TME). NF-κB operates across the malignant epithelial, stromal, myeloid, endothelial, and extracellular-matrix (ECM) compartments of the PDAC TME. In malignant epithelial cells, NF-κB transcription drives survival, proliferation, invasion, matrix remodeling, and therapeutic resistance via anti-apoptotic proteins, cell-cycle regulators, COX-2, MMPs, and VEGF. In CAFs/PSCs, inflammatory and profibrotic signaling promotes stromal activation, ECM production, and tumor-supportive paracrine crosstalk. TAMs and other myeloid cells supply cytokines, chemokines, and matrix-remodeling factors, though the effect of NF-κB modulation here is context-dependent. Endothelial signaling supports angiogenesis through VEGF, IL-8, and adhesion molecules, while reciprocal tumor–stroma–ECM interactions promote matrix deposition, mechanotransduction, invasion, and treatment resistance. Phytochemicals (curcumin, xanthohumol, parthenolide/DMAPT, emodin, piperlongumine, triptolide, resveratrol) can influence these networks, but the cellular targets and strength of direct NF-κB evidence vary across compounds and models. Collectively, modulation of tumor–stroma–immune–vascular signaling may alter stromal activation, inflammation, angiogenesis, matrix remodeling, invasion, and therapeutic responsiveness. Created in BioRender. Syed, M. F. (2026) https://BioRender.com/qtqyp9z.

9. NF-κB Modulation in Therapeutic Resistance and Combination Therapy

Therapeutic resistance in PDAC arises through interconnected mechanisms involving persistent survival signaling, impaired apoptosis, metabolic adaptation, altered drug transport, tumor–stromal interactions, and stress-responsive transcriptional programs [3,5]. NF-κB contributes to these processes by regulating genes involved in cell survival, inflammation, invasion, angiogenesis, and adaptation to cytotoxic stress [7,12]. Importantly, anticancer treatment can itself activate NF-κB, establishing an adaptive response that reduces treatment-induced apoptosis and may promote more aggressive cellular phenotypes [24,59]. Modulation of this response provides a mechanistic basis for combining conventional therapy with phytochemicals capable of suppressing NF-κB-associated survival programs.

9.1. NF-κB as a Mediator of Adaptive Therapeutic Resistance

Gemcitabine provides one of the most extensively investigated experimental settings for understanding NF-κB-mediated therapeutic adaptation in pancreatic cancer. Treatment can activate NF-κB and increase expression of pro-survival proteins, thereby increasing resistance to chemotherapy-induced apoptosis [12,13]. Gemcitabine can also induce reactive oxygen species (ROS)-dependent activation of NF-κB and hypoxia-inducible factor-1α (HIF-

1α), resulting in increased C-X-C chemokine receptor type 4 (CXCR4) expression and enhanced invasive behavior. These findings demonstrate that treatment-induced NF-κB activity can simultaneously influence tumor-cell survival and invasive adaptation [59].

Acquisition of drug resistance can further reinforce NF-κB signaling. Gemcitabine-resistant pancreatic cancer cells exhibit increased NF-κB activity, and pharmacological inhibition of the pathway can restore treatment sensitivity. Parthenolide suppressed NF-κB activity in resistant cells at concentrations below those required for substantial growth inhibition and reduced multidrug resistance-associated protein 1 (MRP1) expression, invasive activity, angiogenic potential, and gemcitabine resistance [39]. The separation between pathway inhibition and overt cytotoxicity provides pharmacodynamic evidence that NF-κB suppression is not merely secondary to loss of cell viability.

Additional experimental evidence supports a functional relationship between NF-κB signaling and chemotherapy response. In PANC-1 cells, activation of Toll-like receptor 4 (TLR4)/NF-κB signaling decreased gemcitabine sensitivity, whereas inhibition of this pathway increased apoptosis and treatment response [18]. Together, these findings position NF-κB as both a constitutive survival pathway and an inducible adaptive mechanism capable of modifying cellular responses to therapeutic stress.

9.2. Phytochemical Modulation of NF-κB for Therapeutic Sensitization

Structurally diverse phytochemicals have demonstrated the ability to enhance chemotherapy response through modulation of NF-κB and interconnected survival pathways. Curcumin represents one of the most extensively investigated examples. In an orthotopic pancreatic cancer model, curcumin potentiated gemcitabine-mediated tumor inhibition and suppressed NF-κB activation together with NF-κB-regulated proteins involved in proliferation, survival, invasion, and angiogenesis, including c-MYC, BCL-2, BCL-XL, cyclooxygenase-2 (COX-2), matrix metalloproteinases (MMPs), and vascular endothelial growth factor (VEGF) [13]. Clinical investigation of curcumin with gemcitabine-based chemotherapy demonstrated feasibility and acceptable tolerability in patients with gemcitabine-resistant pancreatic cancer, although definitive therapeutic benefit was not established [64].

Parthenolide and its more water-soluble derivative dimethylaminoparthenolide (DMAPT) provide additional evidence linking natural product pharmacology with NF-κB-directed chemosensitization. Both compounds inhibit constitutive and gemcitabine-induced NF-κB activity and enhance gemcitabine-mediated growth inhibition in pancreatic cancer cells [28]. DMAPT was subsequently evaluated with gemcitabine in a genetically engineered mouse model of pancreatic cancer, where combination treatment prolonged survival relative to placebo and altered circulating inflammatory mediators, extending the NF-κB-directed combination strategy into an immunocompetent in vivo model [29]. Parthenolide-mediated suppression of NF-κB in gemcitabine-resistant cells has additionally been associated with decreased MRP1 expression and reduced invasive and angiogenic phenotypes [39].

Piperlongumine also provides direct evidence for NF-κB-associated chemosensitization. Piperlongumine inhibited constitutive and inducible NF-κB activation and potentiated gemcitabine-induced apoptosis in pancreatic cancer cells. These effects were accompanied by decreased expression of NF-κB-regulated proteins involved in proliferation, survival, invasion, and angiogenesis, including c-MYC, cyclin D1, BCL-2, BCL-XL, survivin, XIAP, VEGF, and MMP-9. In vivo, piperlongumine enhanced gemcitabine-mediated tumor suppression, decreased proliferative and angiogenic markers, and increased tumor-cell apoptosis [41].

Other phytochemicals demonstrate convergence on related resistance mechanisms. Triptolide enhanced gemcitabine sensitivity through inhibition of TLR4/NF-κB signaling, accompanied by decreased phospho-p65, survivin, cyclin D1, and BCL-2 and increased Bax and apoptosis [18]. Emodin reversed gemcitabine resistance through inhibition of the

IKKβ/NF-κB pathway, with corresponding changes in IκBα, survivin, XIAP, caspase-9, and caspase-3 [25]. Apigenin similarly enhanced gemcitabine-induced growth inhibition and apoptosis through suppression of AKT and NF-κB activity, with combination activity also demonstrated in vivo [65].

Collectively, these studies demonstrate that phytochemical-mediated therapeutic sensitization can involve suppression of both constitutive and treatment-induced NF-κB signaling. The downstream consequences extend beyond apoptosis to include modulation of drug-resistance proteins, inflammatory signaling, invasion, and angiogenesis. NF-κB therefore represents a convergence point through which chemically distinct natural products can modify several components of the adaptive response to anticancer therapy. Representative preclinical combination strategies, their NF-κB-related pharmacodynamic findings, in vivo validation, and the distinction between direct pathway modulation and broader chemosensitizing mechanisms are summarized in Table 2.

Table 2. Preclinical combination-therapy and pharmacological optimization of phytochemicals and natural product-derived agents in pancreatic ductal adenocarcinoma.

Agent	Experimental Model	Treatment/ Combination	NF-κB-Related Pharmacodynamic Findings	Therapeutic Outcome	In Vivo Validation	Evidence-Based Interpretation	Key References
Curcumin	Pancreatic cancer cells; orthotopic pancreatic tumor model	Curcumin + gemcitabine	Suppressed NF-κB activation and NF-κB-regulated proteins involved in proliferation, survival, invasion, and angiogenesis, including c-MYC, cyclin D1, BCL-2, BCL-XL, COX-2, MMP-9, and VEGF	Enhanced gemcitabine-mediated growth inhibition and apoptosis; reduced proliferative, invasive, and angiogenic signaling	Orthotopic model; enhanced gemcitabine-mediated tumor inhibition	Provides a preclinical rationale for suppressing constitutive and treatment-associated survival signaling to enhance gemcitabine response; translation is constrained by limited systemic exposure to conventional oral curcumin	[13]
Partheno-lide/DMAPT	Pancreatic cancer cells; gemcitabine-resistant cells; genetically engineered pancreatic cancer mouse model	Parthenolide or DMAPT + gemcitabine	Inhibited constitutive and gemcitabine-induced NF-κB activity; parthenolide decreased MRP1 and NF-κB-associated resistance phenotypes	Enhanced gemcitabine-mediated growth inhibition; reduced resistance, invasion, and angiogenic activity; DMAPT combination prolonged survival relative to untreated controls	Genetically engineered mouse model; DMAPT + gemcitabine prolonged survival relative to placebo	Suppression of constitutive and gemcitabine-induced NF-κB activity supports a pharmacological relationship between pathway inhibition and enhanced gemcitabine responsiveness; DMAPT extends this strategy to an immunocompetent genetically engineered model	[28,29,39]

Table 2. *Cont.*

Agent	Experimental Model	Treatment/ Combination	NF-κB-Related Pharmacodynamic Findings	Therapeutic Outcome	In Vivo Validation	Evidence-Based Interpretation	Key References
Piperlongumine	Pancreatic cancer cells; pancreatic tumor xenografts	Piperlongumine + gemcitabine	Inhibited constitutive and inducible NF-κB activation; decreased c-MYC, cyclin D1, BCL-2, BCL-XL, survivin, XIAP, VEGF, and MMP-9	Potentiated gemcitabine-induced apoptosis and tumor suppression; reduced proliferation and angiogenesis	Xenograft model; enhanced tumor suppression and apoptosis	NF-κB suppression was associated with enhanced gemcitabine-induced apoptosis and increased antitumor activity in vivo	[41]
Triptolide	PANC-1 cells, PANC-1 xenograft model	Triptolide + gemcitabine	Inhibited TLR4-mediated NF-κB signaling; decreased phospho-p65 and NF-κB-associated survival proteins including survivin, cyclin D1, and BCL-2	Increased gemcitabine sensitivity and apoptosis; increased Bax	Pancreatic tumor model; enhanced gemcitabine-mediated antitumor activity	Supports therapeutic sensitization through TLR4/NF-κB suppression, but triptolide remains a multitarget agent	[18]
Triptolide	Pancreatic cancer cells	Triptolide + hydroxycamptothecin	Combination associated with inhibition of NF-κB signaling and activation of caspase-9 and caspase-3	Increased cytotoxicity and apoptosis	No in vivo validation reported in the cited study	NF-κB inhibition accompanied enhanced cytotoxicity and caspase-dependent apoptosis following combination treatment; evidence is currently limited to cell-based models	[40]
Emodin	Parental and gemcitabine-resistant SW1990; gemcitabine-resistant PANC-1 and MIA PaCa-2 cells; implanted pancreatic tumor models	Emodin + gemcitabine	Suppressed constitutive/gemcitabine-induced NF-κB; decreased IKKβ and p65; increased IκBα; altered survivin, XIAP, caspase-9 and caspase-3	Restored gemcitabine sensitivity; increased apoptosis; reduced angiogenic signaling	Implanted tumor models; enhanced antitumor and antiangiogenic activity	Provides evidence that inhibition of IKKβ/NF-κB-associated survival signaling can reverse a drug-resistant phenotype	[15,25,27]

Table 2. *Cont.*

Agent	Experimental Model	Treatment/ Combination	NF-κB-Related Pharmacodynamic Findings	Therapeutic Outcome	In Vivo Validation	Evidence-Based Interpretation	Key References
Apigenin	Pancreatic cancer cells and in vivo pancreatic cancer model	Apigenin + gemcitabine	Suppressed AKT and NF-κB activity	Enhanced gemcitabine-induced growth inhibition and apoptosis	Xenograft model; enhanced tumor growth inhibition	Supports combined inhibition of interconnected AKT/NF-κB survival signaling; mechanistic specificity for NF-κB is less developed than for curcumin, piperlongumine, or parthenolide/DMAPT	[65]
Oridonin	Pancreatic cancer models; SW1990 used for mechanistic monotherapy studies	Oridonin + gemcitabine	Combination antitumor activity has been reported, whereas mechanistic studies primarily implicate p38 MAPK–p53/p21–caspase signaling	Enhanced antitumor activity with gemcitabine; oridonin alone induces apoptosis	Xenograft model; enhanced antitumor activity	Combination activity is supported in pancreatic cancer models, whereas available mechanistic evidence primarily implicates p38 MAPK–p53/p21–caspase signaling rather than direct NF-κB modulation	[48,49]
Fisetin	MIA PaCa-2 cells	Fisetin + gemcitabine	ERK-MYC modulation was associated with the combination response; direct NF-κB dependence was not demonstrated	Enhanced gemcitabine-induced cytotoxicity and apoptosis	Not reported for this combination	Supports phytochemical-mediated chemosensitization through an NF-κB-independent or incompletely defined mechanism	[47]
CK21 (triptolide prodrug analogue)	Pancreatic cancer cell lines; patient-derived organoids; heterotopic and orthotopic xenografts	Optimized triptolide-derived prodrug strategy	Transcriptomic and functional analyses demonstrated suppression of NF-κB signaling, mitochondrial dysfunction, increased ROS, decreased BCL-2, and mitochondrial apoptosis	Antitumor activity against established pancreatic tumors with improved preclinical pharmacological characteristics relative to limitations of parent triptolide	Heterotopic and orthotopic xenografts; reduced established tumor growth	Illustrates chemical optimization of a natural-product scaffold as an alternative to relying on the pharmacological properties of the parent phytochemical	[66]

Abbreviations: AKT, protein kinase B; CK21, triptolide prodrug analogue; ERK, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinase; MYC, MYC proto-oncogene; p38 MAPK, p38 mitogen-activated protein kinase.

9.3. Pharmacological Considerations for Combination Therapy

Combination therapy may offer a more pharmacologically realistic strategy for many phytochemical NF-κB modulators than their use as independent cytotoxic agents. Suppression of adaptive NF-κB signaling could lower the threshold for treatment-induced apoptosis and attenuate compensatory survival responses without requiring the phytochemical itself to achieve concentrations sufficient for direct tumor eradication. This distinction is particularly relevant for compounds such as curcumin, for which extensive preclinical activity contrasts with limited systemic exposure following conventional oral administration [19,64].

The therapeutic relevance of phytochemical-mediated chemosensitization depends on demonstrating NF-κB modulation at pharmacologically achievable concentrations. Concentration–response relationships should therefore be integrated with pathway-specific pharmacodynamic measurements, tumor exposure, treatment sequencing, and pharmacokinetic compatibility. Temporal relationships are particularly important because inhibition of an adaptive NF-κB response before or during chemotherapy may produce different biological effects from pathway suppression after the cytotoxic response has already been established. Evaluation across malignant epithelial, stromal, and immune compartments is also required because the biological consequences of NF-κB modulation are cell-context-dependent.

Quantitative assessment of drug interactions is equally important. Greater inhibition of proliferation, tumor growth, or increased apoptosis following combination treatment demonstrates an enhanced combination effect but does not independently establish pharmacological synergy. Dose–response matrices and validated interaction models are required to distinguish additive, synergistic, and antagonistic interactions. Integration of these analyses with pathway-specific target engagement, pharmacokinetic/pharmacodynamic relationships, tumor exposure, and toxicity will be essential for identifying phytochemical-based combination strategies with realistic translational potential.

10. Computational and Network Pharmacology Approaches for Identifying Phytochemical Modulators of NF-κB

Computational pharmacology provides a complementary framework for identifying and prioritizing phytochemicals capable of modulating NF-κB-associated signaling in PDAC. Transcriptomic analysis, network pharmacology, molecular docking, molecular dynamics (MD) simulation, and pathway-enrichment approaches can identify candidate compounds, predict potential molecular targets, and define signaling networks that warrant experimental investigation. These approaches are particularly relevant to phytochemicals because many natural products exhibit multitarget pharmacology and influence interconnected inflammatory, oncogenic, metabolic, and stress-response pathways.

10.1. Transcriptomic and Pathway-Based Identification of NF-κB Activity

Transcriptomic profiling can define NF-κB-associated transcriptional states and determine whether phytochemical exposure alters inflammatory or oncogenic gene-expression programs. Expression of pathway components such as RELA, NFKB1, NFKB2, IKBKB, and CHUK can be integrated with validated NF-κB-regulated genes to construct pathway-level signatures. Assessment of downstream transcriptional activity is particularly important because expression of an individual NF-κB pathway component does not necessarily reflect pathway activation.

Integration of NF-κB signatures with KRAS, STAT3, PI3K/AKT, MAPK, inflammatory cytokine, apoptosis, oxidative stress, hypoxia, and EMT-associated programs can provide a broader representation of phytochemical activity. Such analyses can also distinguish whether NF-κB modulation represents a predominant transcriptional response or one component of a wider signaling alteration. Single-cell and spatial transcriptomic

approaches can further resolve pathway activity across malignant epithelial, fibroblast, myeloid, endothelial, and lymphoid compartments, which is particularly relevant given the cell-context-dependent functions of NF-κB within the PDAC TME.

A recent multidimensional analysis of curcumin illustrates the potential of this approach. Integration of network pharmacology with pancreatic cancer transcriptomic datasets identified multiple candidate curcumin-associated targets and differentially expressed hub genes. The analysis incorporated independent Gene Expression Omnibus (GEO) datasets, protein–protein interaction (PPI) networks, immune-cell associations, machine learning, and molecular docking and identified VIM, CTNNB1, CASP9, AREG, and HIF1A as feature genes associated with the predicted activity of curcumin in pancreatic cancer [38]. These findings provide testable molecular hypotheses but do not independently demonstrate that these proteins are direct pharmacological targets of curcumin.

10.2. Network Pharmacology and Multitarget Prediction

Network pharmacology is well suited to phytochemical research because it evaluates relationships among compounds, predicted molecular targets, signaling pathways, and disease-associated genes rather than assuming a single compound–single target mechanism. Protein–protein interaction networks and pathway-enrichment analyses can identify highly connected proteins and biological processes potentially affected by phytochemical exposure.

Candidate proteins including PTGS2, MMP2, MMP9, CASP3, CASP8, CASP9, and HSP90AA1 connect inflammatory signaling with apoptosis, invasion, matrix remodeling, and cellular stress responses. Identification of such proteins as network hubs can guide experimental prioritization and reveal potential connections between NF-κB and downstream phenotypes. However, network centrality reflects computational connectivity and does not establish direct compound–protein binding, pathway dependence, or pharmacological inhibition.

Pancreatic cancer studies increasingly illustrate the utility of integrating network analysis with experimental or structural approaches. Network pharmacology and molecular docking have identified potential interactions between phytochemical components and signaling proteins such as AKT1, EGFR, STAT3, MAPKs, TP53, and inflammatory mediators [35,36]. More recently, network pharmacology combined with experimental validation identified p53-associated signaling as a potential component of the response to sulforaphane in pancreatic cancer cells [37]. These studies reinforce the multitarget nature of phytochemical pharmacology but also demonstrate that predicted networks require biological validation before causal mechanisms can be assigned.

10.3. Molecular Docking and Molecular Dynamics Simulation

Molecular docking can predict the structural compatibility of a phytochemical with a candidate protein-binding site and can assist in prioritizing compound–target pairs for further investigation. MD simulations can extend docking analyses by examining the temporal stability, conformational behavior, and intermolecular interactions of predicted complexes. These approaches are useful for hypothesis generation, particularly when combined with experimentally established protein structures and appropriately validated computational protocols.

Docking scores or predicted binding energies, however, do not establish biochemical inhibition or activation. A favorable docking pose cannot independently demonstrate intracellular target engagement, pathway modulation, selectivity, or therapeutic activity. Interpretation requires additional caution when compounds are docked against transcription factors or proteins lacking clearly validated ligand-binding pockets. Numerical docking values are also highly dependent on protein structure selection, protonation state, ligand preparation, docking software, scoring functions, and search parameters, limiting direct comparison across independent studies.

Recent pancreatic cancer studies demonstrate increasingly sophisticated computational workflows incorporating network pharmacology, docking, MD simulations, and binding free-energy calculations [36–38]. Such approaches can strengthen structural hypotheses and prioritize targets for experimental testing, but even stable computational complexes remain predictions until supported by biochemical or cellular target-engagement evidence.

10.4. Experimental Validation and Translational Integration

Computational predictions gain pharmacological relevance when followed by sequential experimental validation. Candidate compound–target interactions can initially be examined using biochemical binding or activity assays where appropriate. NF-κB pathway modulation can subsequently be assessed through IKK activity, IκBα phosphorylation and degradation, RELA/p65 phosphorylation and nuclear translocation, NF-κB DNA-binding assays, transcriptional reporter systems, and changes in validated downstream transcriptional targets.

Functional consequences can then be evaluated using proliferation, apoptosis, EMT, migration, invasion, angiogenesis, and treatment-response assays. Genetic perturbation, pathway inhibition, rescue experiments, and orthogonal target-engagement approaches provide additional evidence for causality and help distinguish direct NF-κB-dependent effects from secondary consequences of cytotoxicity or modulation of parallel signaling pathways.

In vivo validation further requires demonstration that pharmacologically achievable exposure produces pathway modulation within the tumor. Integration of pharmacokinetic and pharmacodynamic measurements can establish relationships among administered dose, systemic exposure, intratumoral compound concentration, NF-κB target engagement, biological response, and toxicity. Cell-type-resolved analyses are particularly informative because suppression of NF-κB in malignant epithelial cells may have different consequences from pathway modulation in fibroblasts, macrophages, or other immune populations.

An integrated sequence of computational prioritization, biochemical validation, cellular target engagement, functional characterization, in vivo pharmacology, and pharmacokinetic/pharmacodynamic assessment provides a rigorous framework for developing phytochemical NF-κB modulators. Computational methods can substantially narrow the experimental search space and identify mechanistically plausible compound–target relationships, but direct experimental evidence remains necessary to establish NF-κB pathway dependence and translational pharmacological relevance. Representative computational studies and the extent of their experimental validation are summarized in Table 3, highlighting the distinction between predicted compound–target networks, experimentally supported mechanisms, and direct evidence of NF-κB modulation.

Table 3. Computational approaches and experimental validation of phytochemical-associated molecular targets in pancreatic cancer.

Agent/Study Context	Computational Approach	Predicted Targets/Molecular Features	Principal Computational Finding	Experimental Validation	Relevance to NF-κB	Evidence Interpretation	Key Reference
Curcumin	Transcriptomics, network pharmacology, PPI analysis, immune-cell association, machine learning, molecular docking	VIM, CTNNB1, CASP9, AREG, HIF1A	Identified feature genes and candidate molecular networks associated with curcumin activity in pancreatic cancer	No direct target-engagement validation reported for the predicted feature genes	Potential pathway/network association; direct NF-κB modulation was not established by the computational analysis	Hypothesis-generating evidence; the identified feature genes represent computational associations rather than experimentally validated direct curcumin targets	[38]

Table 3. *Cont.*

Agent/Study Context	Computational Approach	Predicted Targets/Molecular Features	Principal Computational Finding	Experimental Validation	Relevance to NF-κB	Evidence Interpretation	Key Reference
Phytochemical components	Network pharmacology and molecular docking	AKT1, EGFR, STAT3, MAPKs, TP53 and inflammatory mediators	Identified multitarget signaling networks potentially affected by phytochemical constituents	Limited experimental validation of predicted compound–target interactions	Predicted networks intersect with signaling pathways that regulate or interact with NF-κB	Network-level association without experimental confirmation of direct compound–target binding or NF-κB dependence	[35]
Natural-product constituents	Network pharmacology, pathway enrichment and molecular docking	Signaling proteins associated with proliferation, apoptosis and inflammatory pathways	Predicted multiple compound–target-pathway relationships relevant to pancreatic cancer	Predominantly computational evidence	Potential connection with NF-κB-associated inflammatory and survival networks	Candidate prioritization rather than evidence of direct pathway inhibition	[36]
Sulforaphane	Network pharmacology integrated with experimental analysis	p53-associated signaling network	Identified p53-associated signaling as a candidate component of sulforaphane activity	Experimental validation in pancreatic cancer cells	NF-κB was not established as the principal experimentally validated mechanism	Computational predictions supported by cellular validation, but NF-κB dependence remains unestablished	[37]

Abbreviations: AREG, amphiregulin; CTNNB1, catenin beta 1; EGFR, epidermal growth factor receptor; HIF1A, hypoxia-inducible factor 1 subunit alpha; PPI, protein–protein interaction; TP53, tumor protein p53; VIM, vimentin.

11. Preclinical and Clinical Evidence for Phytochemical NF-κB Modulation

The evidence supporting phytochemical modulation of NF-κB in pancreatic cancer spans cell-based experiments, xenograft and genetically engineered mouse models, patient-derived organoids, and a limited number of clinical studies. The strength of this evidence varies considerably among compounds and depends on whether NF-κB modulation has been directly demonstrated, linked to a defined functional phenotype, reproduced in vivo, and achieved at pharmacologically relevant exposures. Computational predictions or changes in downstream proteins alone provide a lower level of mechanistic support than direct pathway measurements combined with functional and in vivo validation.

11.1. Preclinical Evidence

Curcumin has one of the most extensively characterized preclinical profiles among phytochemical NF-κB modulators in pancreatic cancer. Initial studies demonstrated constitutive IKK and NF-κB activity in pancreatic cancer cells and showed that curcumin suppressed pathway activation together with cellular proliferation and survival [6]. In an orthotopic pancreatic cancer model, curcumin enhanced the antitumor activity of gemcitabine and reduced NF-κB activation and NF-κB-regulated proteins associated with proliferation, survival, invasion, and angiogenesis [13]. These studies establish a progression from cellular pathway modulation to functional and in vivo antitumor effects.

Xanthohumol provides particularly direct evidence connecting NF-κB modulation with a defined biological phenotype. In BxPC-3, AsPC-1, and MIA PaCa-2 cells, xanthohumol inhibited basal and TNF-α-induced NF-κB activity at concentrations below those required for substantial antiproliferative activity. Pathway inhibition was accompanied by reduced VEGF and IL-8 production and impaired pancreatic cancer cell-induced endothelial tube formation. Xenograft studies subsequently demonstrated decreased NF-κB p65 activation,

VEGF, IL-8, Ki-67, CD31+ microvascular density, and tumor growth [16]. The concordance among pathway modulation, downstream molecular changes, functional angiogenesis assays, and in vivo validation provides a well-defined pharmacodynamic relationship.

Parthenolide and DMAPT extend this evidence to therapeutic resistance. Parthenolide suppresses NF-κB activity in gemcitabine-resistant pancreatic cancer cells at concentrations below those required for substantial growth inhibition and reduces MRP1 expression, invasion, angiogenic activity, and gemcitabine resistance [39]. DMAPT inhibits constitutive and gemcitabine-induced NF-κB activity and enhances gemcitabine-mediated growth inhibition in pancreatic cancer cells. Subsequent evaluation in a genetically engineered mouse model demonstrated in vivo activity of DMAPT combined with gemcitabine, including prolonged survival relative to placebo and alterations in circulating inflammatory mediators [28,29].

Additional compounds provide mechanistically informative preclinical evidence. Piperlongumine suppresses constitutive and inducible NF-κB activation, alters NF-κB-regulated survival and angiogenic proteins, and enhances gemcitabine activity in pancreatic cancer cells and xenograft models [41]. Triptolide enhances gemcitabine sensitivity through inhibition of TLR4/NF-κB signaling in PANC-1 cells, with corresponding changes in apoptosis and tumor growth in vivo [18]. Emodin suppresses IKKβ/NF-κB signaling and restores gemcitabine sensitivity in resistant pancreatic cancer cells, further linking pathway inhibition with therapeutic response [25].

Chemical optimization of natural-product scaffolds provides another route toward improving translational pharmacology. CK21, a prodrug analogue of triptolide, was evaluated across pancreatic cancer cell lines, patient-derived organoids, and heterotopic and orthotopic xenograft models. Transcriptomic and functional analyses demonstrated suppression of NF-κB signaling, mitochondrial dysfunction, increased ROS, decreased BCL-2, and induction of mitochondrial apoptosis. CK21 also demonstrated antitumor activity against established pancreatic tumors with an improved preclinical pharmacological profile relative to limitations associated with parent triptolide [66].

Collectively, these studies demonstrate that the most informative preclinical evidence combines direct NF-κB measurements with concentration–response relationships, downstream molecular changes, functional phenotypes, and in vivo confirmation. The broader phytochemical literature contains substantially more evidence for antiproliferative or pro-apoptotic activity than for direct NF-κB target engagement. This distinction is important because antitumor activity alone does not establish NF-κB as the causal pharmacological mechanism.

11.2. Clinical Evidence

Clinical evidence remains considerably less developed than the preclinical literature and is dominated by studies of curcumin. In a phase II study, Dhillon et al. administered oral curcumin at 8 g/day to 25 patients with advanced pancreatic cancer, of whom 21 were evaluable for response. Two patients demonstrated clinical biological activity, including one patient with stable disease for more than 18 months and another with a brief but substantial tumor regression. Pharmacodynamic analyses included NF-κB and COX-2 expression in peripheral blood mononuclear cells, together with circulating cytokines. Despite the high oral dose, circulating curcumin concentrations remained low and were detected predominantly as glucuronide and sulfate conjugates, demonstrating poor systemic bioavailability [19].

Combination studies have subsequently examined curcumin with gemcitabine-based chemotherapy. A phase I/II study in patients with gemcitabine-resistant pancreatic cancer demonstrated that oral curcumin could be administered with gemcitabine-based treatment, although the study did not establish definitive therapeutic efficacy attributable to

curcumin [64]. Development of more bioavailable curcumin formulations has further demonstrated that pharmaceutical optimization can substantially increase systemic exposure. In a phase I study of Theracurmin in patients with pancreatic or biliary tract cancer, daily administration of 200 or 400 mg curcumin produced measurable plasma exposure during gemcitabine-based chemotherapy, although increased systemic exposure did not establish intratumoral NF-κB target engagement or therapeutic efficacy attributable to curcumin [67]. Epelbaum et al. (2010) reported gastrointestinal tolerability concerns in a study involving 17 patients with advanced pancreatic cancer receiving oral curcumin at 8 g/day alongside gemcitabine [68]. Five patients (29%) discontinued curcumin because of persistent abdominal fullness or pain, while two additional patients required dose reduction to 4 g/day [68]. These findings highlight the tolerability challenges associated with high oral doses of curcumin during combination chemotherapy and underscore the importance of formulation optimization, treatment feasibility, and clinically achievable exposure.

The clinical findings also illustrate an important distinction between pharmacodynamic activity and therapeutic efficacy. Changes in NF-κB-associated markers in peripheral blood cannot be assumed to demonstrate equivalent pathway inhibition within pancreatic tumors. Establishing intratumoral target engagement requires tumor-specific pharmacodynamic measurements or validated surrogate biomarkers with demonstrated relationships to tumor pathway activity. Similarly, improved systemic exposure does not establish clinical efficacy unless increased drug exposure is accompanied by tumor target engagement and clinically meaningful therapeutic outcomes.

Despite promising preclinical activity, several important limitations constrain the clinical translation of phytochemical NF-κB modulators in PDAC. Curcumin remains the most extensively investigated compound clinically; however, its development is hindered by poor aqueous solubility, limited oral bioavailability, rapid metabolism, and uncertain intratumoral target engagement, which may restrict the achievement of pharmacologically effective concentrations in pancreatic tumors. Xanthohumol, parthenolide, and related compounds demonstrate potent NF-κB inhibitory activity in experimental models, but their clinical development is limited by insufficient pharmacokinetic characterization and uncertainty regarding clinically achievable exposure levels. Although dimethylaminoparthenolide (DMAPT) was designed to improve the bioavailability of parthenolide, further studies are required to establish long-term safety, pharmacodynamic biomarkers, and therapeutic windows in humans. Triptolide exhibits strong antitumor efficacy but is associated with concerns regarding systemic toxicity and a relatively narrow therapeutic index, prompting the development of optimized derivatives and prodrugs such as CK21. Similarly, emodin, resveratrol, and piperlongumine influence multiple cellular pathways in addition to NF-κB, which may contribute to therapeutic activity but also complicates assessment of pharmacological selectivity and mechanism-based target engagement. Collectively, these considerations highlight that preclinical efficacy alone is insufficient for clinical advancement. Future translational development should prioritize rigorous pharmacokinetic–pharmacodynamic evaluation, assessment of clinically relevant exposure–response relationships, validation of NF-κB-specific biomarkers, and formulation strategies that improve bioavailability while minimizing systemic toxicity.

At present, clinical evidence is insufficient to establish phytochemical-mediated NF-κB inhibition as an effective therapeutic strategy for PDAC. The substantial difference between preclinical activity and clinical evidence reflects several pharmacological barriers, including limited bioavailability, rapid metabolism, uncertain intratumoral exposure, multitarget activity, and incomplete demonstration of pathway-specific pharmacodynamics. Clinical development therefore requires integration of pharmacokinetic measurements with tumor

exposure, NF-κB-specific pharmacodynamic biomarkers, safety, and clinically relevant efficacy endpoints.

The broader pancreatic cancer literature continues to identify NF-κB, inflammatory cytokines, PI3K/AKT, STAT3, oxidative stress, apoptosis, angiogenesis, and invasion as recurrent pathways affected by phytochemicals, but the majority of evidence remains preclinical [69]. The translational gap between extensive experimental activity and limited clinical validation remains a defining challenge for phytochemical pharmacology in pancreatic cancer. The available human evidence, including conventional curcumin, curcumin combined with gemcitabine, and the Theracurmin formulation, is summarized in Table 4, with emphasis on pharmacokinetics, tolerability, pharmacodynamic assessment, clinical findings, and remaining translational limitations.

Table 4. Clinical and translational evidence for phytochemical NF-κB modulation in pancreatic cancer.

Agent/Formulation	Study and Population	Treatment	Pharmacokinetic Evidence	NF-κB/Pharmacodynamic Assessment	Clinical Findings	Translational Limitation	Key References
Curcumin	Phase II; 25 patients with advanced pancreatic cancer; 21 evaluable for response	Oral curcumin, 8 g/day	Low circulating parent curcumin; systemic exposure predominantly reflected glucuronide and sulfate conjugates	NF-κB and COX-2 expression assessed in peripheral blood mononuclear cells; circulating cytokines also evaluated	Biological activity observed in a small subset; one patient had stable disease >18 months and one had a brief substantial tumor regression	Poor systemic bioavailability; peripheral-blood pharmacodynamics do not establish intratumoral NF-κB target engagement	[19]
Curcumin + gemcitabine-based chemotherapy	Phase I/II; patients with gemcitabine-resistant pancreatic cancer	Oral curcumin + gemcitabine-based chemotherapy	Conventional oral curcumin remained subject to limited bioavailability	Tumor-specific NF-κB target engagement was not established	Combination treatment was feasible; definitive therapeutic efficacy attributable to curcumin was not established	Limited exposure and absence of demonstrated intratumoral NF-κB pharmacodynamics restrict mechanistic interpretation	[64]
Curcumin with gemcitabine	Epelbaum et al., 2010; 17 patients with advanced pancreatic cancer	Oral curcumin, 8 g/day with gemcitabine	Systemic curcumin exposure not quantified in the study	Intratumoral NF-κB target engagement not demonstrated	Five patients discontinued curcumin because of abdominal fullness or pain; two required dose reduction	Gastrointestinal tolerability limits feasibility of high oral doses; clinical efficacy attributable to curcumin remains unestablished	[68]
Theracurmin® (highly bioavailable curcumin formulation)	Phase I study; 16 patients with pancreatic or biliary tract cancer after failure of standard chemotherapy	Oral Theracurmin (200 or 400 mg curcumin/day) with gemcitabine-based chemotherapy	Median peak plasma curcumin concentrations were 324 ng/mL at 200 mg/day and 440 ng/mL at 400 mg/day.	NF-κB activity and circulating cytokines were evaluated; intratumoral NF-κB target engagement was not demonstrated.	Demonstrated feasibility of improving systemic curcumin exposure through formulation	Improved plasma exposure alone does not establish tumor delivery, NF-κB target engagement, or therapeutic efficacy	[67]

Abbreviations: COX-2, cyclooxygenase-2; NF-κB, nuclear factor kappa B.

12. Pharmacological Limitations and Translational Opportunities

The extensive preclinical activity of phytochemical NF-κB modulators contrasts with their limited clinical development in PDAC. Translation is constrained by unfavorable phar-

macokinetics, insufficient tumor exposure, pleiotropic pharmacology, uncertainty regarding direct target engagement, and the context-dependent functions of NF-κB across malignant and nonmalignant cellular compartments [12,19,69]. Addressing these limitations requires integration of drug-delivery strategies with pathway-specific pharmacodynamics and mechanistically informed patient and tumor characterization.

12.1. Bioavailability, Tumor Exposure, and Drug Delivery

Poor bioavailability represents a major limitation for several phytochemicals. Low aqueous solubility, incomplete intestinal absorption, extensive first-pass metabolism, rapid conjugation, and systemic clearance can prevent concentrations associated with experimental activity from being achieved within pancreatic tumors. Curcumin provides the clearest example. Oral administration at 8 g/day produced relatively low circulating concentrations in patients with advanced pancreatic cancer, despite evidence of biological activity in a small subset of patients [19]. The disparity between concentrations commonly used in experimental systems and clinically achievable exposure represents an important barrier to translation.

Nanoparticles, lipid-based delivery systems, liposomes, micelles, phospholipid complexes, and other formulation strategies can improve solubility, stability, absorption, and biodistribution of poorly bioavailable phytochemicals. Nanostructured curcumin formulations generally increase systemic and tumor exposure compared with free curcumin in preclinical pharmacokinetic studies, although the magnitude of improvement varies substantially among delivery platforms [70]. Structural optimization and prodrug development provide complementary approaches, particularly when limitations arise from rapid metabolism, chemical instability, or unfavorable physicochemical properties.

Increased systemic exposure alone, however, does not establish improved pharmacological activity. Drug-delivery studies require integration of plasma pharmacokinetics with intratumoral drug concentration, NF-κB target engagement, downstream pharmacodynamic responses, and toxicity. The relevant translational endpoint is therefore not simply increased circulating drug concentration but sufficient tumor exposure to modulate the intended pathway at a tolerable dose.

12.2. Pleiotropic Pharmacology and Mechanistic Specificity

Pleiotropic activity represents both a potential advantage and a major challenge for phytochemical pharmacology. Curcumin, resveratrol, triptolide, emodin, xanthohumol, and related compounds influence multiple signaling networks, including NF-κB, STAT3, PI3K/AKT, MAPK, Nrf2, oxidative stress responses, apoptosis, and inflammatory signaling. Simultaneous modulation of interconnected pathways may restrict compensatory signaling; however, extensive molecular promiscuity complicates identification of the pharmacologically dominant mechanism [6,14,16,69].

Suppression of NF-κB following phytochemical exposure does not necessarily indicate direct interaction with an NF-κB pathway component. Reduced pathway activity may result from inhibition of upstream kinases, altered cytokine signaling, changes in cellular redox state or metabolism, induction of proteotoxic or mitochondrial stress, or generalized cytotoxicity. Mechanistic studies therefore require temporal and concentration-dependent pathway measurements together with direct target-engagement approaches where feasible.

Recent studies have expanded the molecular architecture controlling NF-κB in PDAC and provide experimentally defined nodes for mechanistic interrogation. Digestive organ expansion factor (DEF) directly interacts with p65 and protects it from ubiquitin-mediated degradation [23]. Disruption of the DEF-p65 interaction decreases p65 abundance and sup-

presses pancreatic tumor growth, identifying p65 stability as a potential pharmacologically tractable regulatory mechanism [23].

NF-κB activity is also regulated through epigenetic and metabolic mechanisms. Nuclear receptor-binding SET domain protein 2 (NSD2)-mediated H3K36 dimethylation promotes NFKBIA expression and consequently increases IκBα-mediated restraint of p65 phosphorylation and nuclear translocation. NSD2 additionally interacts with p65 and attenuates its transcriptional activity, whereas NSD2 loss enhances NF-κB signaling and sensitizes experimental PDAC models to combined NF-κB inhibition and gemcitabine [21].

Metabolic enzymes can similarly acquire noncanonical functions that converge on NF-κB. Hexokinase 2 (HK2) acts as a protein kinase in PDAC cells and phosphorylates IκBα at T291 under hypoxic conditions, promoting NF-κB activation, proliferation, migration, and invasion [22]. More recently, nuclear translocation of aldolase A (ALDOA) was shown to promote pancreatic cancer progression through NF-κB activation, linking metabolic-enzyme regulation with inflammatory transcription [71].

These mechanisms provide a broader framework for determining where phytochemicals act within the NF-κB signaling architecture. Pharmacodynamic analyses incorporating IκBα abundance and phosphorylation, p65 stability, phosphorylation and nuclear localization, RELA- and RELB-associated transcriptional outputs, and downstream mediators can distinguish direct pathway modulation from upstream or secondary effects.

12.3. Cellular Context and Tumor-Selective NF-κB Modulation

NF-κB performs essential physiological functions in immune regulation, inflammation, stress responses, and cellular homeostasis. Indiscriminate systemic inhibition may therefore produce biological effects that differ substantially from selective suppression of pathological NF-κB activity within malignant cells [12,26].

This distinction is particularly important in PDAC because NF-κB operates across malignant epithelial cells, CAFs, macrophages, other myeloid populations, endothelial cells, and lymphoid populations. Within tumor cells, persistent NF-κB activation can promote survival, invasion, angiogenesis, and therapeutic resistance. In immune and stromal compartments, however, the consequences of pathway modulation depend on cellular state, upstream stimulus, signaling duration, and interactions with neighboring cells [3,20].

Cell-type-resolved pharmacodynamic assessment can therefore provide substantially greater mechanistic information than analysis of whole-tumor lysates. Single-cell transcriptomics, spatial profiling, multiplex imaging, and cell-specific pathway assays can determine whether treatment suppresses NF-κB predominantly within malignant cells or simultaneously alters inflammatory and immune programs in stromal compartments. Tumor-directed delivery systems may further increase the therapeutic window by concentrating pathway-modulating compounds within the tumor while limiting systemic exposure.

12.4. Translational Development of Phytochemical NF-κB Modulators

Translation of phytochemical NF-κB modulators requires alignment among compound exposure, molecular target engagement, pathway modulation, functional response, and therapeutic outcome. Concentration–response experiments should establish whether NF-κB inhibition occurs below concentrations producing generalized cytotoxicity. Orthogonal pathway measurements can determine whether changes in p65 activity are accompanied by altered IκBα regulation, DNA binding, transcriptional output, and downstream biological responses.

Chemically optimized analogues and derivatives provide an additional opportunity to overcome limitations of parent natural products. Modification of natural-product scaffolds can improve solubility, metabolic stability, potency, selectivity, or tissue exposure while retaining

desirable pathway activity. The development of triptolide derivatives and parthenolide-derived DMAPT illustrates how natural products can function as pharmacological starting points rather than necessarily serving as the final therapeutic molecules [28,29,66].

Combination therapy provides another translational route, particularly when phytochemical concentrations sufficient for direct tumor eradication cannot be achieved safely. At lower exposures, suppression of adaptive NF-κB signaling may enhance sensitivity to conventional therapy. Such combinations require formal dose–response analysis, temporal sequencing, pharmacokinetic compatibility, tumor-specific pharmacodynamic assessment, and evaluation of toxicity. Enhanced activity of a combination should not be classified as synergy without quantitative interaction analysis.

The expanding molecular understanding of NF-κB regulation in PDAC also creates opportunities for biomarker-guided development. Regulatory mechanisms involving NSD2/NFKBIA [21], DEF/p65 [23], HK2/IκBα [22], and ALDOA-associated NF-κB activation [71] demonstrate that similar NF-κB transcriptional outputs can arise through distinct upstream mechanisms. Defining these regulatory states may help identify tumors in which NF-κB dependence is greatest and determine whether a candidate phytochemical acts at an upstream regulator, the core NF-κB machinery, or a downstream transcriptional program. Integration of these molecular features with pharmacokinetic/pharmacodynamic measurements and cell-type-resolved pathway analysis provides a rational framework for advancing phytochemical NF-κB modulators toward translational development. A stepwise framework integrating computational prioritization, mechanistic validation, in vivo pharmacology, PK/PD assessment, rational combination strategies, biomarker development, and clinical translation of phytochemical NF-κB modulators in PDAC is summarized in Figure 4.

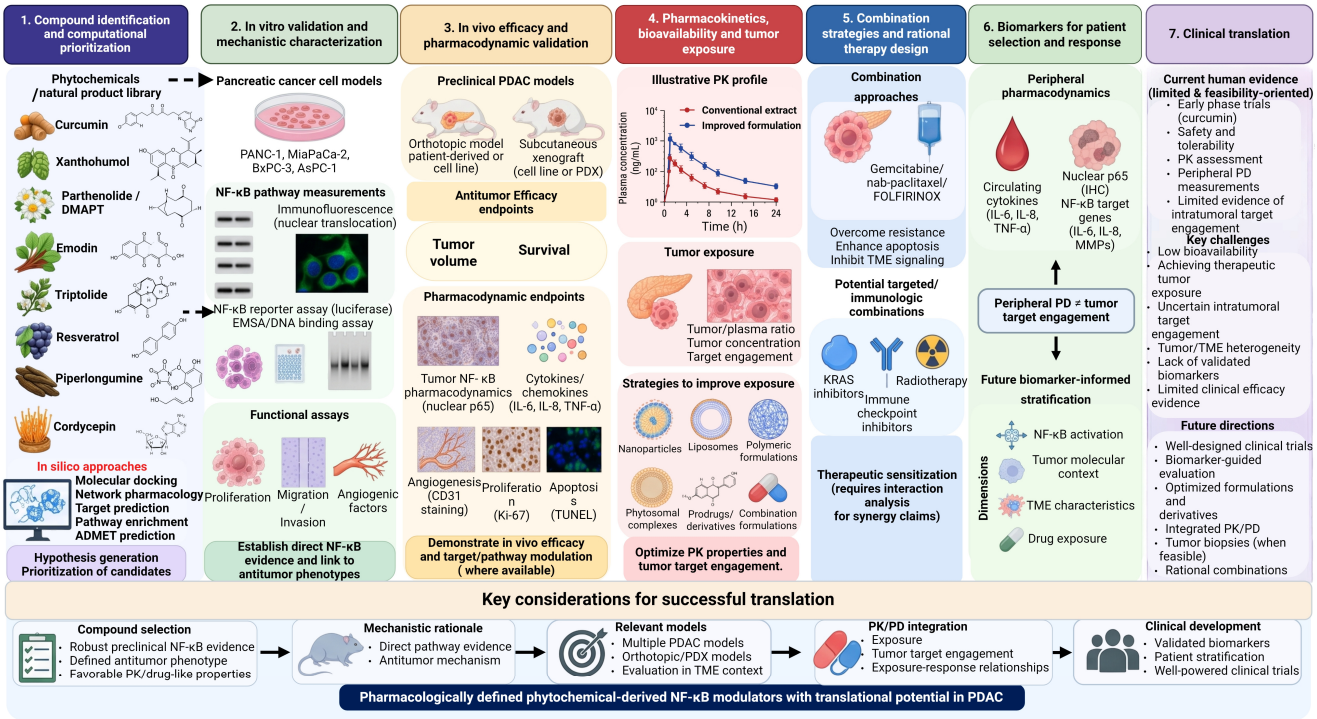


Figure 4. Translational framework for developing phytochemical NF-κB modulators in PDAC. A stepwise framework is proposed for advancing phytochemical and natural-product-derived NF-κB modulators from computational prioritization to clinical investigation in pancreatic ductal adenocarcinoma (PDAC). Candidates identified through natural-product libraries, molecular docking, network pharmacology, target prediction, pathway enrichment, and ADMET assessment require experimental validation in pancreatic cancer models. Mechanistic studies should establish concentration-dependent

NF-κB modulation using pathway-specific pharmacodynamic readouts and link pathway activity to functional phenotypes. In vivo work should pair antitumor efficacy with intratumoral NF-κB pharmacodynamics and pharmacokinetic/pharmacodynamic (PK/PD) assessment of systemic exposure, tumor drug concentration, and target engagement. Formulation and chemical optimization may improve bioavailability and tumor exposure, while rational combinations with chemotherapy, targeted agents, immunotherapy, or radiotherapy require mechanistic justification and quantitative interaction analysis. Biomarker development should separate peripheral pharmacodynamic changes from intratumoral target engagement and incorporate NF-κB activity, tumor molecular context, TME features, and drug exposure. Clinical translation ultimately requires pharmacologically achievable tumor exposure, validated biomarkers, biomarker-informed patient stratification, and well-designed trials. Created in BioRender. Syed, M. F. (2026) https://BioRender.com/qtqyp9z.

13. Future Perspectives and Conclusions

13.1. Future Perspectives

Phytochemical modulation of NF-κB represents a mechanistically compelling but incompletely translated pharmacological strategy in PDAC. Current evidence demonstrates that selected natural compounds can suppress constitutive or treatment-induced NF-κB activity and influence apoptosis, angiogenesis, invasion, inflammatory signaling, and therapeutic resistance. The strength of this evidence, however, varies substantially among compounds, emphasizing the need to prioritize candidates supported by direct pathway measurements rather than general antiproliferative or cytotoxic activity.

Future development should prioritize compounds supported by concentration–response relationships and direct NF-κB pharmacodynamics, followed by causal validation across patient-derived organoids, tumor–stromal cocultures, immune-competent models, and genetically engineered mouse models. Single-cell and spatial profiling, proteomics, phosphoproteomics, and multiplex imaging can define cell-compartment-specific pathway responses and identify biomarkers of NF-κB dependence.

Computational prioritization should be followed by biochemical and cellular target-engagement studies, whereas chemical optimization and tumor-directed delivery should be evaluated through integrated pharmacokinetic/pharmacodynamic analyses. Rational combination strategies require temporal sequencing, pharmacokinetic compatibility, quantitative interaction analysis, intratumoral target engagement, and clinically relevant efficacy endpoints.

13.2. Conclusions

NF-κB represents an important pharmacological convergence node linking oncogenic signaling, inflammation, cell survival, epithelial plasticity, angiogenesis, invasion, TME communication, and therapeutic resistance in PDAC. Its integration with KRAS, PI3K/AKT, STAT3, MAPK, redox, metabolic, and inflammatory signaling provides multiple opportunities for pharmacological intervention while simultaneously increasing the complexity of attributing therapeutic effects to a single molecular mechanism.

Phytochemicals provide chemically diverse scaffolds capable of influencing different components of this signaling network. Direct NF-κB modulation has been demonstrated most clearly for selected compounds, including curcumin, xanthohumol, and parthenolide and its derivative DMAPT, with additional pathway-specific evidence for piperlongumine, triptolide, and emodin. Other natural compounds demonstrate relevant antitumor activity through interconnected signaling pathways but require further evidence before their effects can be attributed specifically to NF-κB modulation.

Preclinical studies demonstrate that suppression of NF-κB can influence apoptosis, angiogenic signaling, invasion, and chemotherapy response. Clinical evidence remains substantially more limited, with curcumin as the principal example of human investigation

and a case that also illustrates the pharmacokinetic barriers to translating phytochemical activity from experimental models to patients. Poor bioavailability, insufficient tumor exposure, pleiotropic pharmacology, cellular heterogeneity, and incomplete demonstration of target engagement remain major challenges.

Progress will therefore depend on moving beyond descriptive phytochemical anticancer activity toward mechanism-based pharmacology integrating compound exposure, molecular target engagement, NF-κB-specific pharmacodynamics, cellular specificity, functional response, and therapeutic outcome. Improved formulations and chemically optimized derivatives, rational combination strategies, patient-derived experimental systems, cell-type-resolved analyses, and validated pharmacodynamic biomarkers may help identify which phytochemical scaffolds have realistic translational potential. Ultimately, successful development will require demonstration that pharmacologically achievable tumor exposure produces defined NF-κB modulation and therapeutic benefit at tolerable doses. This framework may enable selected phytochemical-derived agents to progress from experimental observations toward pharmacologically defined adjunctive strategies for PDAC.

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