AI-Driven Scientific Prompting and Sequential Discovery Pipeline for NF-κB–Targeted Predictive Modeling and Therapeutic Insights in Breast Cancer Using Quercetin from Moringa oleifera

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Abstract

With around 2.3 million new cases in 2020, breast cancer is the most prevalent cancer globally, and current treatments frequently fail because of inherent heterogeneity and adaptive resistance. In breast cancers, inflammation-driven NF-κB signaling is substantially active, promoting cell survival, metastasis, and resistance to treatment. A naturally occurring flavonol, quercetin possesses a wide range of anti-inflammatory, antioxidant, and anti-cancer properties, including the ability to suppress NF-κB. However, quercetin's quick metabolism and low bioavailability limit its therapeutic application. A natural source of quercetin and associated compounds, Moringa oleifera requires strict standardization (HPLC/TLC fingerprinting) for reproducible research due to its high batch-to-batch variability. An AI-driven sequential discovery pipeline to speed up drug development is presented in this paper, which also summarizes preclinical data on quercetin's modulatory effects and NF-κB in breast cancer.We describe: (A) advanced literature mining and prompt engineering strategies; (B) building a knowledge graph that links nodes of the NF-κB pathway, breast cancer hallmarks, quercetin chemistry, and assay endpoints; (C) network pharmacology and causal inference for mechanism prioritization; (D) predictive modeling (QSAR/docking/transcriptomic matching); (E) virtual screening against NF-κB targets (e.g., IKKβ, p65 DNA-binding); (F) lead optimization (balancing potency, ADME, and safety); and (G) an experimental validation roadmap from biochemical assays to in vivo models with defined decision-gates. We use trust-layer knowledge graphs to address bias sources, reproducibility issues, and auditing of AI results. Lastly, we identify important gaps and future approaches, such as clinical PK/PD of quercetin, validated NF-κB biomarkers, and standardization of Moringa extracts.

Keywords: NF-κB; breast cancer; Quercetin; Moringa oleifera; knowledge graph; AI drug discovery; predictive modeling; natural products; inflammation.

1. Introduction

1.1 Breast cancer burden and unmet therapeutic needs

Breast cancer now ranks as the most common malignancy in women worldwide, with an estimated 2.3 million new cases in 2020 [1]. Incidence continues to rise globally [2], driven by aging populations and lifestyle factors. Despite advances in early detection and targeted therapies (endocrine agents for ER^+ tumors, anti-HER2 drugs, PARP inhibitors for BRCA mutant cancers, etc.), unmet needs remain profound. Triple-negative breast cancer (TNBC;

lacking ER/PR/HER2) is particularly aggressive, with high rates of metastasis and poor prognosis [3]. Treatment resistance (to endocrine therapy in luminal subtypes, to chemo/radiation in TNBC) is a major clinical challenge. Tumor heterogeneity and a supportive inflammatory microenvironment contribute to recurrence and metastasis. Thus, identifying new druggable pathways that drive survival and resistance is critical for improved outcomes.

1.2 Inflammation and NF-κB as a druggable axis

Chronic inflammation and cytokine signaling are well-established drivers of breast cancer progression. The NF-κB family of transcription factors (RelA/p65, c-Rel, RelB, p50/p52) is a central mediator of inflammatory survival signaling. In breast tumors, constitutive NF-κB activation is frequently observed and promotes a malignant phenotype [4],[5]. NF-κB drives expression of genes for cell proliferation (Cyclin D1, c-Myc), survival (Bcl-2, IAPs), angiogenesis (VEGF), invasion (MMPs) and pro-inflammatory cytokines (IL-6, TNF-α) [6]. For example, Xu et al. reported that NF-κB dimers activate Cyclin D1, Bcl-2/Bcl-xL and IL-6/IL-8 in breast cancer cells.Conversely, blocking NF-κB abrogates EMT and metastasis in preclinical models[7]. NF-κB also intersects with oncogenic pathways: it cooperates with STAT3 via an IL-6/NF-κB positive feedback loop[8], engages PI3K/Akt and MAPK signals, and can co-regulate genes with ER or HER2 signaling [9],[10]. Clinically, elevated NF-κB activity (e.g. nuclear p65, IKK phosphorylation) correlates with more aggressive, therapy-resistant tumors. Thus NF-κB activation is a central driver of inflammatory survival signaling and therapy resistance in breast cancer, making it an attractive drug target. Inhibiting NF-κB has been shown to resensitize tumors to chemotherapy, radiation, and endocrine therapy in models, highlighting its translational potential.

1.3 Why quercetin and why Moringa oleifera

Quercetin (3,3′,4′,5,7-pentahydroxyflavone) is a prototypical dietary flavonol found in many fruits and vegetables. It exhibits broad anticancer, anti-inflammatory and antioxidant activities [11]. Numerous studies show quercetin can induce apoptosis, cell-cycle arrest (via upregulating p21, GADD45) and inhibit invasion/metastasis in breast cancer cells[12]. Mechanistically, quercetin suppresses NF-κB signaling: it blocks IκBα phosphorylation and RelA(p65) nuclear translocation, preventing pro-survival gene transcription[13]. For example, quercetin prevented TNF-induced RelA recruitment to pro-inflammatory promoters in vitro[14], and in model systems it lowered NF-κB–dependent IL-6 and TNF-α output[15]. Quercetin also affects other oncogenic pathways (inhibiting PI3K/Akt, STAT3, EGFR/IGF1R signaling) and has been reported to synergize with standard therapies (e.g. sensitizing cells to doxorubicin and tamoxifen[16]). These properties make quercetin an appealing multi-target agent in breast cancer.

Moringa oleifera, a traditional medicinal plant, is an abundant natural source of quercetin and related flavonoids. Moringa leaves contain diverse bioactives (phenolic acids, isothiocyanates, vitamins) with rutin (~0.56 mg/g), kaempferol (~0.20 mg/g) and quercetin (reported up to 20.3 μmol/100g or ~610 mg/100g dry weight) as major constituents. Thus, M. oleifera can serve as a phytochemical platform for delivering quercetin. However, as we discuss below, natural extracts are highly variable, and rigorous standardization (HPLC/TLC fingerprinting and potency assays) is needed to make reproducible mechanistic claims about Moringa-derived quercetin.

1.4 Why AI-driven sequential discovery for natural products

Recent advances in AI, literature mining, and systems biology enable new workflows for natural-product drug discovery. Manual literature reviews are time-consuming and prone to bias; in contrast, AI-driven prompting and knowledge graph approaches can systematically extract and connect dispersed data. For example, automated knowledge graph construction has been applied to drug repurposing and rare disease research [17], integrating targets, diseases, pathways and compounds. In oncology, such tools can link tumor signaling nodes (NF-κB), cancer hallmarks, and chemical entities (like quercetin) across studies. Predictive modeling (MLbased QSAR, docking, and transcriptomic signature matching) can then rank candidate mechanisms and compounds in silico. However, uncurated AI outputs risk overfitting and garbage-in/garbage-out bias.

Therefore, we propose a *transparent, stepwise "AI-driven sequential discovery pipeline"* specifically tailored for natural products in breast cancer. This pipeline will convert literature into structured prompts (with reproducibility controls), perform automated mining/PRISMA-style filtering, build a causal knowledge graph linking NF-κB, cancer phenotypes and quercetin/Moringa chemistry, and then apply integrated modeling and virtual screening to prioritize targets and quercetin derivatives. Crucially, we will incorporate audit controls (prompt templates, provenance tracking, bias checks) at each step. In this review, we synthesize the current evidence on NF-κB in breast cancer and quercetin's pharmacology, and use it to illustrate the proposed pipeline. Our goal is to provide a comprehensive, critical analysis that guides future translational efforts.

2. Methods for This Review (Transparent Literature Approach) 2.1 Databases searched, keywords, inclusion/exclusion

We performed a structured search of PubMed/Medline, Scopus, Web of Science and relevant specialized databases up to 2025. Search terms included combinations of "NF-kappaB", "breast cancer", "quercetin", "Moringa oleifera", "phytochemicals", "drug resistance", "nanoformulation", "QSAR", "docking", "knowledge graph", and "AI literature mining". Results were de-duplicated, and a PRISMA-style process was used to select articles for detailed review. Only peer-reviewed publications (original research articles and highquality reviews) were included; conference abstracts, editorials, and blogs were excluded. We prioritized primary studies (in vitro, in vivo, clinical) and mechanistic reviews in cancer biology, phytochemistry, pharmacology, and AI-driven drug discovery.

2.2 Study types prioritized and quality screening

We included preclinical studies on NF-κB signaling in breast cancer cell lines, animal models, and patient samples, as well as studies on quercetin/Moringa in oncology contexts (clearly distinguishing breast cancer from other cancers). In vitro work included immortalized and primary cells; in vivo evidence spanned xenografts and genetic mouse models. We also noted any early-phase clinical or translational data on quercetin or Moringa supplementation in cancer (though breast-specific data are scarce). Study quality was assessed by standard criteria (e.g. replicates, controls, dose relevance) and compared across studies. Conflicting results were analyzed for differences in model systems, doses, or readouts.

2.3 How AI/prompting was used for evidence synthesis (workflow)

This review leverages our AI-driven evidence synthesis pipeline as an organizational framework. Initially, structured prompts were designed to query large language models (LLMs) for specific data extraction (e.g. "List pathways downstream of NF-κB activation in TNBC cells"). Prompt templates were iteratively refined and tested to ensure reproducibility (e.g. using fixed random seeds, temperature settings). Automated text mining and named-entity recognition tools were then applied to identify entities (genes, compounds, pathways) and eliminate duplicates. The extracted information formed the nodes and edges of a knowledge graph (Step C) spanning NF-κB signaling components, breast cancer hallmarks, quercetin derivatives, assay methods, and outcomes. Throughout, we logged prompt versions and AI outputs to maintain an audit trail. Critical appraisal steps (manual filtering of AI hypotheses, checking against known biology) were used to reduce bias and error.

3. NF-κB Signaling in Breast Cancer: Mechanistic Foundation 3.1 Canonical NF-κB pathway (IKKβ–IκBα–p65/p50)

In the canonical pathway, pro-inflammatory stimuli (e.g. TNF-α, IL-1β, LPS) trigger cell-surface receptors (TNFR, IL-1R, TLRs) that activate the IKK complex (IKKα/β/NEMO) [18],[19]. Activated IKKβ phosphorylates IκBα, marking it for ubiquitination and proteasomal degradation. This releases the p65/p50 (RelA/p50) dimer to translocate into the nucleus and bind NF-κB consensus sequences on DNA, turning on transcription of target genes. The genes activated include those for inflammation (IL-6, TNF-α, COX-2), survival (Bcl-2 family, cIAPs), proliferation (Cyclin D1) and adhesion/invasion (MMPs). For example, Xu et al. showed that nuclear RelA/p50 drives Cyclin D1 and Bcl-2 expression in breast tumor cells. Canonical NF-κB signaling thus functions as a rapid-response system linking

cytokines to gene expression. Notably, NF-κB can self-amplify through positive feedback loops (e.g. NF-κB–induced IL-6 maintains pathway activation). Phospho-specific antibodies for IKKβ, IκBα or RelA (Ser536) and reporter assays (κB-driven luciferase) are commonly used to monitor this cascade.

3.2 Non-canonical NF-κB pathway (NIK–IKKα–RelB/p52)

The non-canonical (alternative) NF-κB pathway is engaged by a distinct set of receptors, such as lymphotoxinβ receptor (LTβR), BAFF-R, CD40 and RANK. These activate NF-κB inducing kinase (NIK), which in turn activates IKKα homodimers. IKKα phosphorylates the p100 precursor bound to RelB, leading to partial processing of p100 into p52. The resulting RelB/p52 heterodimer then migrates to the nucleus to regulate genes largely involved in lymphoid organ development and adaptive immunity**[15][30]**. In breast cancer, noncanonical signaling has been less studied than the canonical arm, but it can contribute to cell survival and metastasis. For instance, RelB/p52 has been implicated in anti-apoptotic gene expression (e.g. Bcl-2) and cytokine production (IL-6) in tumor cells**[15]**. Some evidence suggests that basal breast cancers may exploit both NF-κB pathways. Importantly, molecules like NIK are druggable: small-molecule NIK inhibitors or peptides that block p100 processing could selectively blunt non-canonical NF-κB. However, the predominant focus remains on IKKβ and RelA as primary targets (see Section 4).

3.3 Upstream activators (TNF-α, IL-1β, TLRs, RTKs)

As noted, TNF-α and IL-1β are prototypical activators of canonical NF-κB**[30]**. In the breast tumor microenvironment, these cytokines can be produced by tumor-associated macrophages (TAMs) or cancer cells themselves. Toll-like receptor (TLR) ligands (e.g. LPS from microbial dysbiosis) can similarly provoke NF-κB activation. Growth factor receptors also intersect: for example, EGFR/HER2 signaling activates PI3K/Akt, which can engage IKKα/β and p65 phosphorylation. Overexpression of HER2 in breast cancer cell lines is known to constitutively stimulate NF-κB activity, contributing to radiotherapy resistance [20]. Conversely, estrogen receptor (ER) signaling has complex interplay with NF-κB. Classical ERα activity can suppress NFκB in some contexts, but NF-κB can inhibit ER target genes. Intriguingly, studies have identified a positive crosstalk: NF-κB and ER co-regulate survival genes in luminal breast cancers. Thus, both cytokine receptors and oncogenic RTKs funnel signals into the NF-κB network in breast cancer.

3.4 Crosstalk with PI3K/Akt, MAPK, STAT3, p53, ER/HER2

NF-κB signaling interconnects with numerous pathways. The PI3K/Akt axis can phosphorylate and activate IKK, thereby augmenting NF-κB (e.g. via Akt-mediated IKKα activation). In turn, NF-κB-induced cytokines (IL-6) can trigger JAK/STAT3 signaling, creating a pro-survival loop**[18]**. MAPK pathways (ERK, JNK, p38) often act in parallel or tandem with NF-κB in stress responses; for instance, reactive oxygen species (ROS) activate both pathways in cancer cells. Mutant p53 can enhance NF-κB transcriptional activity, promoting invasion and chemoresistance. Conversely, NF-κB can repress p53-mediated apoptosis. Estrogen and HER2 signaling also modulate NF-κB: as noted, NF-κB activation is associated with endocrine resistance and luminal B tumors, while HER2 amplifies NF-κB to promote growth. In a broader sense, NF-κB functions as a master integrator of oncogenic networks**[16]**. For example, activation of NF-κB in breast cancer is often accompanied by upregulation of PI3K/Akt and MAPK pathways, and these pathways jointly regulate cell cycle and survival genes. This extensive crosstalk means inhibiting NF-κB can have multi-faceted effects on tumor biology.

3.5 NF-κB-driven hallmarks: proliferation, survival, EMT, metastasis, angiogenesis

NF-κB drives multiple cancer hallmarks. By upregulating Cyclin D1 and c-Myc, NF-κB promotes G1/S progression and proliferation. It also induces survival genes such as Bcl-xL, Bcl-2 and IAP family members, blocking apoptosis. NF-κB signaling is essential for the epithelial–mesenchymal transition (EMT) program: Huber *et al.* showed that TGF-β induces EMT in mammary carcinoma via NF-κB, and that inhibiting NF-κB abrogates EMT and subsequent lung metastasis. Invasion and metastasis are further fueled by NF-κB-driven matrix remodeling: NF-κB activates MMP-2 and MMP-9 expression (via AP-1 co-activation) to degrade extracellular matrix. NF-κB also stimulates angiogenesis

by upregulating VEGF and IL-8. For instance, quercetin (as discussed later) was shown to reduce tumor VEGF and microvascular density in vivo [20], consistent with blocking NF-κB-induced angiogenic signals. Finally, NF-κB activates pro-inflammatory genes (IL-6, TNF-α, COX-2) that shape the tumor microenvironment, attracting immune cells that often support tumor growth. Collectively, NF-κB activation underpins proliferation, survival, motility, and angiogenesis in breast cancer.

3.6 NF-κB and tumor microenvironment (macrophages, cytokines, stromal signaling)

The tumor microenvironment (TME) is both a source and target of NF-κB signaling. Inflammatory cells (TAMs, neutrophils) produce TNF-α and IL-1β, which activate NF-κB in cancer and stromal cells. NF-κB in cancer cells then drives chemokines (e.g. IL-8, CCL2) that recruit additional immune cells, perpetuating a protumor loop. Recent studies highlight fibroblast interactions: Hendrayani *et al.* showed that breast cancer cells secrete IL-6 to activate STAT3/NF-κB in stromal fibroblasts, which in turn produce IL-6/TNF-α to further activate NF-κB in tumor cells. Thus, NF-κB links cancer and stromal compartments via a feed-forward inflammatory circuit. Other TME factors like hypoxia can also trigger NF-κB (through HIF-1α cross-talk). Importantly, in vivo models demonstrate that NF-κB in myeloid cells can promote tumorigenesis by producing IL-6 and TNF-α. In summary, NF-κB serves as a nodal point integrating signals from the TME (cytokines, stromal interactions) and reciprocally shaping the microenvironment to favor tumor survival and metastasis.

4. NF-κB as a Therapeutic Target in Breast Cancer

4.1 Target nodes and druggability: IKKβ, NEMO, p65 nuclear translocation, DNA binding

Given its central role, multiple components of the NF-κB pathway have been explored as drug targets. IKKβ is perhaps the most validated node: small molecules (e.g. BMS-345541) inhibit IKKβ kinase activity, preventing IκBα phosphorylation. NEMO (IKKγ) is theoretically druggable (peptides that block NEMO–IKKα/β interaction have been designed), though no NEMO inhibitors are clinically used yet. Direct targeting of RelA/p65 has been attempted through decoy oligonucleotides that bind NF-κB response elements, preventing DNA binding. Nuclear translocation of NF-κB can be blocked by inhibitors of the nuclear import machinery (e.g. cell-permeable peptides against nuclear localization signals). Each target has pros and cons: for example, IKKβ inhibitors may cause immune suppression (since IKKβ is essential for inflammatory responses in normal cells). Proteasome inhibitors (bortezomib) indirectly block NF-κB by preventing IκB degradation, and have shown efficacy in hematologic cancers [33], but are toxic. For breast cancer, no NF-κB inhibitor is yet approved. Ongoing strategies include designing p65-binding phytochemicals or synthetic analogs. Of note, due to pathway redundancy, inhibition of a single node may lead to compensatory activation of parallel pathways. This complexity motivates multi-target approaches like those enabled by natural polyphenols (see Section 5).

4.2 NF-κB in therapy resistance (endocrine, chemo, radio)

NF-κB activity is a known mediator of therapy resistance. For endocrine therapy, several lines of evidence indicate NF-κB promotes estrogen-independence. Constitutive NF-κB activation is enriched in the ER+ luminal-B subtype and correlates with tamoxifen resistance. Mechanistically, NF-κB induces alternative survival pathways when estrogen signaling is blocked. For chemotherapy and radiation, many agents paradoxically activate NF-κB as a stress response, which then drives expression of anti-apoptotic genes. Wang and Zhang noted that conventional chemoradiation triggers NF-κB, leading to treatment-resistant breast cancer cells; conversely, inhibiting NF-κB restored chemosensitivity and correlated with longer survival in some studies. In TNBC, where chemotherapy is the mainstay, NF-κB-mediated expression of drug transporters (e.g. MDR1) and survival factors is implicated in resistance. Clinically, high NF-κB activity predicts poor response to adjuvant therapy. Thus, targeting NF-κB could help overcome resistance across modalities.

4.3 Biomarkers of NF-κB activation and patient stratification

Assessing NF-κB activity in patient tumors or blood is challenging but important for stratification. Common biomarkers include immunohistochemical detection of nuclear p65 in tumor biopsy specimens, or elevated transcripts of NF-κB target genes (e.g. IL-6, COX-2) in tumor or serum. Elevated circulating IL-6 and TNF-α can suggest systemic NF-κB activation. Phosphorylated IKKβ (p-IKKβ) or IκBα levels in tumor lysates (by Western blot or ELISA) are alternative markers. Some studies have used NF-κB DNA-binding assays (EMSA or reporter cells) on patient samples. To our knowledge, no validated NF-κB gene signature is clinically used in breast cancer yet. Predictive stratification might consider NF-κB status: for instance, patients with high NFκB expression could be candidates for anti-inflammatory or NF-κB-targeted adjuvants. Prospective validation of such biomarkers remains a gap (see Section 10).

5. Quercetin Pharmacology Relevant to NF-κB Modulation

5.1 Chemical properties, structure-activity considerations

Quercetin is a flavonol with a diphenylpropane (C6–C3–C6) skeleton. It has a catechol (ortho-dihydroxy) ringB (3′,4′-OH) and multiple hydroxyls on rings A and C (3,5,7-OH). This structure confers high antioxidant capacity: the 3′,4′-dihydroxy B-ring and the 2,3-double bond plus 4-keto in the C-ring are key features for radical scavenging activity**[21]**. Indeed, quercetin is often ranked as one of the most potent natural antioxidants tested[21]. Its planar structure also allows stacking interactions with proteins and DNA, which may underlie some of its biological effects. However, the multiple OH groups make it hydrophobic and poorly water-soluble (ca. 2.15 μg/mL in water). Quercetin's physical-chemical drawbacks (low solubility, permeability) must be considered in formulation. In terms of structure–activity, methylation or glycosylation of the 3-OH (as in isoquercetin or rutin) alters solubility and metabolism but may affect target affinity.

5.2 Molecular mechanisms: NF-κB inhibition, antioxidant and antiinflammatory actions

Quercetin modulates multiple molecular pathways relevant to NF-κB. It directly interferes with the NF-κB signaling cascade: studies show quercetin prevents IκBα phosphorylation and degradation, thereby retaining NF-κB in the cytosol. For example, Zhai *et al.* reported that quercetin blocked degradation of IκBα and nuclear translocation of p65 in human cells, leading to lowered IL-1β, IL-6, IL-8 and TNF-α levels. Shi *et al*. demonstrated that quercetin suppresses NF-κB recruitment to pro-inflammatory gene promoters (e.g. COX-2) by inhibiting p300 histone acetyltransferase activity. In short, quercetin acts as an inhibitor of NF-κB activation at multiple points (inhibiting upstream kinase activity, preventing p65 binding) and thus reduces downstream cytokine and survival gene expression. In addition, quercetin's strong antioxidant action can indirectly down-modulate NF-κB, since oxidative stress is a known activator of NF-κB. Quercetin also activates other anti-inflammatory pathways: it has been shown to induce the Nrf2/HO-1 axis (in endothelial cells) while simultaneously suppressing NF-κB, leading to reduced cell adhesion molecules and ROS [22],[23]. Thus, quercetin exerts both direct (kinase inhibition, transcriptional interference) and indirect (antioxidant) NF-κB inhibitory effects.

5.3 Apoptosis, cell cycle, and autophagy links

Consistent with NF-κB inhibition, quercetin promotes apoptosis and cell-cycle arrest in breast cancer cells. It upregulates pro-apoptotic factors (e.g. Bax, FasL) and downregulates Bcl-2, often via p53 or FoxO3a pathways. For instance, Park *et al.* showed that quercetin induced nuclear translocation of FoxO3a, leading to increased p21, GADD45 and FasL transcription in TNBC cells**[22]**. Quercetin also arrests the cell cycle at G1/S phase, partly by suppressing Cyclin D1 (a NF-κB target) and enhancing p21/p27 levels. Additionally, quercetin has been reported to trigger autophagy in breast cancer models via inhibition of Akt/mTOR [24]. While autophagy can be cytoprotective or cytotoxic, in the context of quercetin it appears to contribute to cell death in some studies. Overall, quercetin induces programmed cell death through multiple routes, overlapping with NF-κB's role in survival.

5.4 Anti-metastatic and anti-angiogenic effects

By downregulating NF-κB targets involved in motility, quercetin inhibits metastasis-related phenotypes. It reduces expression of matrix metalloproteinases (MMP-2, MMP-9) and adhesion molecules, impairing invasion. For example, Wu *et al.* found that quercetin treatment reduced MMP-9 and VEGF expression in breast cancer cell lines[25]. In vivo, quercetin inhibited tumor angiogenesis: in MCF-7 xenografts, quercetin significantly lowered circulating VEGF and tumor microvessel density. Mechanistically, quercetin interferes with HIF-1α and AP-1 pathways that drive VEGF transcription[26]. It also suppresses COX-2, which produces pro-angiogenic prostaglandins, by blocking NF-κB/p300 coactivation. Altogether, quercetin's inhibition of NF-κB-regulated MMPs and cytokines underlies its anti-metastatic and anti-angiogenic effects, which have been observed across multiple breast cancer models.

5.5 Synergy with standard therapies (strongest evidence and limits)

Quercetin can potentiate the efficacy of existing treatments. One well-supported example is endocrine therapy: a recent systematic review reported that quercetin combined with tamoxifen acted synergistically in ER^+ breast cancer models, enhancing apoptosis and growth inhibition compared to either agent alone. Mechanistically, quercetin may restore ER signaling balance or suppress compensatory pathways (like NF-κB) that drive endocrine resistance. Similarly, quercetin has been combined with chemotherapeutics: Staedler *et al.* showed that quercetin amplified doxorubicin's tumor-killing effect in highly invasive breast cancer cells, while reducing doxorubicin toxicity in normal cells. Quercetin also synergized with 5-fluorouracil in MDA-MB-231 cells to inhibit proliferation and decrease MMP expression[27]. These examples reflect quercetin's ability to sensitize tumors to therapy, often by blocking survival signals (NF-κB, Akt) that underlie resistance. However, synergy evidence is mostly preclinical. Moreover, quercetin can interact pharmacokinetically with drugs (affecting metabolism)[28], which may lead to unpredictable effects in patients. Thus, while synergy is a promising concept, rigorous in vivo validation and attention to formulation are needed before clinical translation.

6. Moringa oleifera as a Phytochemical Platform for Quercetin Delivery

6.1 Key phytochemicals and how quercetin fits within Moringa chemistry

Moringa oleifera leaf extracts contain a rich mixture of phytochemicals. Notably, they are high in phenolic acids (e.g. gallic, chlorogenic), carotenoids (β-carotene, lutein), vitamins (A, C, E), and glucosinolates/isothiocyanates (e.g. moringin). Among flavonoids, Moringa leaves are particularly rich in rutin, quercetin, and kaempferol. For example, one analysis found rutin at ~555.6 μg/g and kaempferol ~197.6 μg/g in dried leaves; quercetin was quantified as 2030.9 μmol per 100 g (equivalent to ~610 mg per 100 g). Another review notes that Moringa leaves consistently yield significant amounts of quercetin and kaempferol. Quercetin may also be present in glycosylated form (e.g. isoquercetin) or complexed with other molecules. Thus, quercetin is one of the major active flavonols in Moringa, and its abundance makes Moringa an attractive "phytochemical platform" for quercetin delivery. However, it is accompanied by many other bioactives that may modulate its effects.

6.2 Extraction, standardization, and quality control (HPLC/LC-MS fingerprints)

Extracting consistent quercetin content from Moringa requires careful methodology. Solvent type, temperature, time and technique (maceration, Soxhlet, ultrasound-assisted extraction (UAE), supercritical CO_2) dramatically affect yields**[10]**. For instance, ultrasound-assisted extraction (UAE) has been shown to maximize quercetin yield (~65 μg/g) while preserving extract quality[29], whereas simple maceration yields can be more modest (~20–50 μg/g)[30]. Post-extraction, quantification of quercetin is typically performed by HPLC with standards, or LC-MS profiling of the flavonoid fraction. Given this variability, robust quality control is crucial. Multi-component chromatographic fingerprinting (e.g. HPLC with diode-array or LC-MS detection) is recommended to ensure batch reproducibility. Indeed, thin-layer chromatography combined with multivariate analysis has been applied as a routine quality control tool for Moringa extracts**[11]**. In practice, a standardized Moringa quercetin formulation would require a reference profile (retention times, UV spectra or MS pattern) to verify its phytochemical composition.

6.3 Batch variability and reproducibility challenges

A major challenge is the inherent variability of herbal sources. Geographic origin, seasonal factors, plant part, and cultivar differences can significantly alter Moringa's phytochemical profile**[10]**. For example, the same extraction method applied to leaves from different regions can yield differing quercetin concentrations. Similarly, differences in plant growth (soil nutrients, climate) can change flavonoid content. As noted by Fitri *et al.*, such variability makes it difficult to derive universally applicable conclusions from disparate Moringa studies. For translational research, this means mechanistic claims about "Moringa quercetin" need to be tied to authenticated extracts. Ideally, each experimental batch should be fingerprinted, and active component (quercetin) quantified. Otherwise, positive results may not be reproducible by other labs or in clinical settings. Thus, standardization (including use of Good Agricultural Practices for Moringa sourcing) is essential for credible science and potential product development.

6.4 Safety considerations and herb–drug interaction risks

Moringa oleifera leaf is generally regarded as safe at culinary doses, but high-dose extracts have not been extensively tested in humans. Some animal studies suggest liver or renal toxicity at very high doses, but typical nutraceutical doses appear well-tolerated. A more relevant concern is pharmacokinetic interactions. Moringa extracts have been shown in vitro to inhibit CYP450 enzymes (notably CYP3A4, 1A2, 2D6), likely due to flavonoids like quercetin. This implies potential interactions with co-administered drugs that are CYP substrates. For example, quercetin can inhibit CYP3A4, which may raise levels of certain chemotherapeutics or endocrine agents. Therefore, any clinical translation of Moringa or quercetin should include careful evaluation of drug interactions, especially in polypharmacy scenarios common in cancer patients.

7. AI-Driven Scientific Prompting and Sequential Discovery Pipeline (Core Section)

7.1 Prompt engineering framework for literature-to-evidence extraction

Our sequential pipeline begins with Prompt Engineering (Step A) to transform open-ended knowledge into structured data. We design context-specific prompts for LLMs to extract information such as "list NF-κB pathway components involved in apoptosis" or "summarize studies of quercetin in breast cancer models". The prompts follow templates to ensure consistency and reproducibility (e.g., fixed phrasing, delimiters, and zeroshot vs. few-shot formats). Controls like prompt concurrency, temperature settings, and seed setting are used to reduce variability. This approach enables automated extraction of entities and relations (genes, chemicals, pathways, effects) from vast literature, which are then validated by manual curation. Embedding citation retrieval in the prompts also aids traceability. By defining synthetic "prompt logs" and output schemas, we maintain a record of exactly how each piece of evidence was obtained. In essence, we apply the principles of systematic review to AI prompting, thereby minimizing bias and enhancing reproducibility.

7.2 Building an NF-κB–Breast Cancer–Quercetin Knowledge Graph

Next (Step B/C), we perform automated literature mining using the prompts, followed by entity recognition (genes/proteins, diseases, chemicals, phenotypes) and deduplication (via PubMed IDs or DOIs) to curate a corpus of relevant data. From this corpus, we assemble a Knowledge Graph (KG) linking: NF-κB signaling nodes (e.g. IKKβ, RelA, p100), breast cancer hallmarks (proliferation, EMT, metastasis), and phytochemical entities (quercetin, Moringa quercetin glycosides). Edges in the KG represent relationships such as "activates", "inhibits", "is subtype of" or "measured by". For example, an edge could connect "p65 (RelA)" to "Cyclin D1" (relation: activates) with supporting citations**[15]**, and link "Quercetin" to "IKKβ" (relation: inhibits) with relevant references. We also include assay nodes (e.g. "NF-κB reporter assay", "IL-6 ELISA") and outcomes (e.g. "↓ proliferation"). This KG thus encodes causal and correlative data: e.g. "TNF-α → IKKβ → NF-κB → Bcl-2 → survival". We annotate edge weights based on evidence strength (number of studies, experimental model relevance). Such a KG makes it possible to traverse paths (e.g. Quercetin → IKKβ → NF-κB → IL-6 → proliferation) and score mechanistic hypotheses. Notably, we apply algorithms (like those described by Ozer *et al.*) to identify the most biologically relevant subgraphs and reduce irrelevant connections.

7.3 Network pharmacology and causal inference for mechanism ranking

Using the knowledge graph, we perform network pharmacology analysis (Step C) to rank key nodes and mechanisms. We integrate protein–protein interaction databases and pathway knowledge to evaluate "centrality" of NF-κB components within the breast cancer context. Causal inference techniques (Bayesian networks, causal path analysis) are used to identify upstream regulators or downstream effectors most likely to be perturbed by quercetin. For instance, if the KG shows many independent paths from quercetin to metastasis all converging on IKKβ, that suggests IKKβ as a primary mechanism. Additionally, we can incorporate expression/network data (e.g. TCGA breast cancer NF-κB target gene expression) to further prioritize targets. The goal is to shortlist a few high-value hypotheses: e.g. "Quercetin preferentially inhibits NF-κB–mediated cytokine production (IL-6, TNF) and EMT (MMP-9) rather than classical anti-apoptotic pathways." Each hypothesis is accompanied by supporting literature edges from the KG. This semi-automated evidence ranking ensures that the most well-supported mechanisms are carried forward to modeling.

7.4 Predictive modeling: QSAR, docking, transcriptomics signature matching

Next (Step D), we build predictive models to evaluate quercetin and its analogs. QSAR/ML models are trained (or applied) to predict NF-κB inhibition potency based on chemical structure. Existing compound libraries of flavonoids and synthetic analogs are screened virtually. Concurrently, molecular docking is performed for quercetin (and derivatives) against key targets: e.g. the ATP-binding site of IKKβ, the p65 DNA-binding interface, or upstream kinases. Docking scores (with IKKβ crystal structures) provide binding affinity estimates; critical interactions (H-bonds, hydrophobic contacts) can suggest analog design. For example, prior studies have successfully used ligand-based and structure-based QSAR to propose flavonoid inhibitors of IKKβ. In parallel, we use transcriptomic signature matching: if NF-κB-driven gene signatures are known, we search Connectivity Map-like databases for compounds that reverse that signature. Quercetin's published gene expression profiles (or those induced by quercetin in cell assays) can be matched to identify synergistic drugs. These predictive tools help rank which quercetin analog or derivative (glycoside, methylated form) has the best predicted NF-κB modulating profile, along with estimates of off-target or toxicity concerns.

7.5 Multi-objective optimization: potency vs ADME vs safety

In Step E, we perform multi-objective optimization to balance NF-κB inhibitory potency with drug-like properties. Each candidate compound is evaluated for key developability metrics: aqueous solubility, cell permeability, metabolic stability (e.g. predicted CYP clearance), and toxicity risk (e.g. hERG, genotoxicity predictors). For example, QSAR models or in silico ADME calculators can flag poor solubility or high clearance. We then apply optimization algorithms (Pareto ranking, desirability functions) to find an optimal set: e.g. a quercetin analog with slightly lower in vitro potency but dramatically improved solubility might be favored. Specifically for quercetin, known liabilities include low solubility and rapid glucuronidation, so derivatives (glycosides, prodrugs) that improve these traits are prioritized. The optimization is multi-objective: target activity (predicted IKKβ IC_50) vs BBB penetration (for brain metastases?) vs safety (lack of predicted cytotoxic moieties). The output is a ranked list of candidate molecules or formulations (Step F) that best trade off these factors.

7.6 Formulation-aware optimization (nano, complexes, prodrugs)

An important sub-objective is formulation feasibility. We incorporate into the pipeline advanced formulation strategies as design variables (Step F). For instance, a nanotechnology platform (e.g. liposome, polymer nanoparticle) can alter the desirability of certain properties. If formulating as a nanoparticle, solubility and stability issues may be partially mitigated, allowing a more potent but otherwise "unstable" analog to be considered. Examples: phospholipid complexes (phytosomes) of quercetin have achieved ~20-fold increases in bioavailability[31]. We thus include predicted gains from known delivery systems in the optimization. For instance, candidates that dock well but are poor in silico ADME might still be viable if a nano-formulation can be applied. The pipeline flags whether a liposomal, cyclodextrin, or solid dispersion formulation might rescue a lead, and adjusts the objective function accordingly. This ensures our lead candidates are not only potent but also realistically druggable via modern delivery technologies.

7.7 Validation roadmap: assay cascade and decision gates

Step G outlines a tiered experimental validation strategy. We propose a cascade: first, biochemical assays (e.g. IKKβ kinase assay, NF-κB DNA-binding ELISA) to confirm direct target inhibition by top compounds. Next, cell-based assays: NF-κB luciferase reporter cells, and breast cancer cell lines (MCF-7, MDA-MB-231, HER2^+ lines) to assess pathway activity (p65 nuclear translocation by immunofluorescence, IκBα phosphorylation by Western blot) and functional outcomes (cell viability, apoptosis assays). We would include 3D culture or spheroid models co-cultured with macrophages or fibroblasts to capture microenvironment effects. Endpoints here include NF-κB readouts (IL-6 secretion, TNF-α levels, MMP activity) and phenotypes (migration/invasion assays). Promising candidates would then move to in vivo: xenograft or syngeneic breast cancer models, with pharmacokinetic (PK) studies to correlate drug levels with target engagement (e.g. measuring p-IKKβ or nuclear p65 in tumor tissue). Dose finding would be guided by predicted ADME, with starting doses extrapolated from prior PK reports**[7]**. Control groups include standard therapies (tamoxifen or paclitaxel) and known NF-κB inhibitors. At each stage, decision gates are defined: e.g. "compound must show >50% reduction in NF-κB activity and no major toxicity" to advance. This roadmap ensures rigorous progression from in silico prediction to biological proof-of-concept.

7.8 Reproducibility, bias, and auditing AI outputs

Throughout the pipeline, we incorporate safeguards for reproducibility and bias mitigation. As Ozer *et al.* emphasize, automated evidence generation can introduce irrelevant or spurious associations if not carefully filtered. We use multi-pronged checks: manual curation of AI-extracted facts, cross-validation of predictive models on unseen data, and redundancy analysis in the knowledge graph. Knowledge graphs themselves serve as a "trust layer" that makes AI decisions auditable: researchers can trace each inferred mechanism back to original references. To address data bias, we ensure diversity of sources (not only high-impact journals, but also credible open-access literature) and explicitly search for negative data. Any ML models are tested for overfitting (e.g. with holdout sets) and predictions prioritized only if statistically robust. In sum, our pipeline is designed not as a black box but as a transparent, looped workflow where each step's results are validated against human expertise and additional experiments.

8. Lead Optimization Strategy for Quercetin (Natural Product → Developable Lead)

8.1 Developability barriers (solubility, stability, metabolism)

Free quercetin is notorious for poor "developability": it has extremely low aqueous solubility (<1–10 μg/mL) and is chemically unstable (prone to oxidation and conjugation)[6]. Oral bioavailability in humans is correspondingly low; quercetin undergoes extensive first-pass metabolism to glucuronide/sulfate conjugates. Even glycosylated derivatives (e.g. rutin) exhibit limited absorption – for instance, oral rutin yields only ∼20% of quercetin's plasma levels at peak. These PK barriers mean that the nominal doses used in mice (often >50 mg/kg) do not translate directly to feasible human dosing. Additionally, quercetin's rapid clearance results in short half-life. Therefore, any lead optimization must overcome: (a) low solubility, (b) chemical instability (pH, light), (c) rapid metabolism and efflux, and (d) potential off-target effects at high doses.

8.2 Optimization options: analogs, glycosides, derivatives, combinations

To address these barriers, we consider multiple strategies as "analog design" (Step H). One approach is to synthesize quercetin analogs with favorable properties. For example, methylating phenolic OH groups can increase lipophilicity and metabolic stability (as done with tamoxifen derivatives), though it may reduce activity. Converting quercetin to quercetin-3-O-glucoside (isoquercetin) is another strategy: isoquercetin is more water-soluble and has been used as a supplement. Indeed, human studies show that quercetin-4′-Oglucoside reaches higher plasma levels than rutin. Multi-glycosylated versions (e.g. quercetin di- or triglycosides) might further improve solubility and allow transporter-mediated uptake; [166†L208-L215] notes quercetin-3′-O-oligoglucosides had 2–10× higher bioavailability than aglycone. Another avenue is hybridization: linking quercetin to other scaffolds or metal ions (e.g. Ru(II)-quercetin complexes) can create potent hybrids. Co-crystallization with bioenhancers (like piperine) or inclusion in cyclodextrins can also be explored.

8.3 Formulation strategies as “lead optimization”

Formulation science itself can be viewed as lead optimization (Step I). Nanoparticle carriers (liposomes, polymeric NPs, solid lipid NPs) dramatically improve quercetin’s solubility, stability and cell delivery. For instance, chitosan-encapsulated quercetin nanoparticles have shown enhanced uptake and prolonged retention[32]. Quercetin-phospholipid complexes (“phytosomes”) have achieved multi-fold increases in C_max and AUC in vivo. We list these strategies in Table 3: e.g. “Quercetin lecithin phytosome – 20× bioavailability in rats – limitation: cost, scale”. Nanoemulsions and microemulsions can also deliver quercetin across membranes. These formulation optimizations are part of the pipeline: predicted ADME is re-calculated for each hypothetical formulation, and promising formulations are proposed to maximize the effective free drug reaching NF-κB targets.

8.4 Recommended preclinical package for translation

Based on the above, we propose a minimum preclinical package for any candidate quercetin derivative/formulation. This includes physicochemical profiling (solubility, stability, logP), in vitro ADME (microsomal stability, CYP inhibition), and toxicity panels (hERG assay, hepatotoxicity). Functionally, the candidate should be tested for NF-κB pathway activity (via reporter and target gene assays) and for anti-tumor efficacy in at least two breast cancer models (ideally one ER^+ and one TNBC). Pharmacokinetics in rodents should be measured (oral and IV) to confirm that blood levels can reach the in vitro active range. Biomarker development is key: we recommend measuring NF-κB targets (e.g. p65 nuclear localization, IL-6 levels) in treated tumors to establish target engagement. Finally, a pilot efficacy study in a relevant mouse model (e.g. MDA-MB-231 xenograft or genetically engineered model) with PD endpoints (apoptosis markers, proliferation indices) and safety assessment (clinical chemistry, histopathology) would provide proof-ofconcept. If successful, this would justify moving to GLP toxicology and phase I trials.

Table 1. Breast cancer models used to study NF-κB and quercetin

Model/System	Subtype	Stimulus	Assay/Readout	Key Findings
MCF-7 cells	ER+	TNF-α	IκBα phosphorylation, Cyclin D1	Quercetin inhibited p65 translocation and reduced Cyclin D1
MDA-MB-231 cells	TNBC	Inflammatory microenvironment	IL-6, NF-κB activity	Reduced cytokine production and proliferation
Xenograft model	TNBC	Tumor environment	Tumor volume, IL-6	Quercetin reduced tumor growth and inflammation
4T1 cells	TNBC	—	MMP-9 expression	Decreased invasion and metastasis markers

Table 2. Mechanistic endpoints for NF-κB inhibition

Endpoint	Assay Method	Key Observation
IκBα degradation	Western blot	Quercetin prevents degradation
p65 nuclear translocation	Immunofluorescence	Reduced nuclear localization
NF-κB activity	Luciferase reporter assay	Dose-dependent inhibition
Cytokine secretion (IL-6, TNF-α)	ELISA	Decreased cytokine levels
MMP-9 expression	qPCR / Zymography	Reduced metastatic potential

Table 3. Formulation and optimization strategies for quercetin

Approach	Improvement	Limitations	Model
Liposomes / SLN	Increased solubility & bioavailability	Stability issues	Animal studies
Phytosome complex	↑ Cmax and AUC	Cost	Rat PK studies
Nanocrystals	Better dissolution	Physical instability	In vitro
Quercetin glycosides	Improved absorption	Rapid metabolism	Human PK
Cyclodextrin inclusion	Enhanced solubility	Complex formulation	Experimental cyclodextrinnews+1

10. Critical Gaps, Limitations, and Future Directions

10.1 What is strong vs weak evidence today?

Strong evidence: The role of NF-κB in promoting breast cancer cell survival and resistance is well-supported Figby cell and animal studies. Multiple lines of preclinical work show quercetin inhibits NF-κB signaling and downstream effectors (cytokines, IAPs) across diverse models. Synergistic effects of quercetin with therapies (tamoxifen, doxorubicin) have been reported consistently in vitro. Nanoformulations of quercetin have repeatedly demonstrated improved bioavailability in rodents.

Weak evidence: Translational data are scant. No clinical trials have proven efficacy of quercetin or Moringa in breast cancer. Pharmacodynamic biomarkers of quercetin action (e.g. target engagement of NF-κB in patient tumors) are unvalidated. Many in vitro studies use supra-physiological quercetin concentrations, and conflicting results sometimes arise due to different assay conditions. The impact of Moringa extract as a whole (vs. pure quercetin) is poorly studied in cancer models. Overall, while mechanistic rationale is strong, the evidence falls short of clinical validation.

10.2 Standardization gaps for Moringa-derived quercetin

A major gap is the lack of standardized preparation of Moringa extracts. As noted, phytochemical content varies widely (geography, extraction). No pharmacopoeial standards exist for Moringa, and many studies do not fully characterize their material. This undermines reproducibility: one lab's "Moringa leaf extract" could differ drastically from another's. Thus, reported effects (e.g. "Moringa extract inhibits NF-κB") must be interpreted cautiously. The field needs consensus methods: botanical authentication, quantitative HPLC/LCMS profiling, and standardized potency assays. Only with such quality controls can mechanistic findings on "Moringa quercetin" be compared across studies. Analytical fingerprinting (as mentioned) should become routine before any bioassays. Without this, claims about Moringa's effects remain anecdotal.

10.3 Translational gaps (PK/PD, biomarkers, clinical endpoints)

Translational gaps are substantial. Quercetin's human pharmacokinetics are not well-established in the oncology context: studies in healthy volunteers show rapid metabolism to conjugates, but we lack data on how cancer or co-administered therapies alter this. Pharmacodynamic readouts are lacking; for instance, does oral quercetin suppress NF-κB target gene expression in patient tumors? The closest clinical endpoints come from epidemiology (diets high in quercetin-rich foods correlate with slightly lower cancer risk), which is not specific enough. Importantly, valid biomarker endpoints (e.g. serum IL-6 reduction, imaging of tumor inflammation) have not been incorporated into any trials of quercetin or Moringa. To bridge this gap, future studies should include measurement of relevant biomarkers (p65 nuclear IHC, circulating cytokines) in preclinical and clinical models. PK/PD modeling (linking dose, plasma levels, target inhibition) needs to be performed. Finally, combination schedules (quercetin + chemo/hormone) must be optimized: e.g. should quercetin be given pre-emptively to prevent NF-κB activation by chemotherapy? These translational issues remain unresolved.

10.4 AI gaps: missing data, bias, reproducibility; proposed solutions

Our AI pipeline faces its own limitations. One is data sparsity: many biomedical facts are unreported or hidden in negative data, which AI cannot easily access. For example, negative trials of quercetin in cancer are not published, biasing the KG. Model bias is another concern: ML predictors inherit biases in training data (e.g. overrepresentation of certain targets). The danger of overfitting is real if the dataset is small. To mitigate these, we incorporate rigorous audit: all KG-derived associations must be traced to references, and any AI-proposed hypothesis should be cross-checked manually. Techniques like cross-validation, bootstrapping, and hold-out sets are used in modeling to check for overfitting. We also emphasize transparency: the AI "trust layer" (knowledge graph) lets users inspect how conclusions were reached. Finally, external validation (applying the pipeline to a different natural product case, or prospective prediction of a new quercetin analog) will test generalizability. In summary, while AI offers systematic ranking and hypothesis generation, it must be paired with classical scientific rigor and open data to ensure reliability.

11. Conclusion

NF-κB is unequivocally implicated in driving inflammation-linked survival, proliferation and therapy resistance in breast cancer. Quercetin from Moringa shows promise as a multi-target modulator of NF-κB and related pathways, with robust preclinical evidence for apoptosis induction, metastasis inhibition and chemosensitization. However, translating these findings requires overcoming bioavailability and standardization hurdles. Our proposed AI-driven sequential discovery pipeline provides a structured framework to tackle this complexity by integrating literature mining, network modeling, and predictive analytics. The knowledge graph approach can highlight the most relevant

NF-κB nodes for quercetin intervention and suggest optimized analogs and formulations. Yet, all AI suggestions must be validated experimentally. Future work should focus on generating reliable PK/PD and biomarker data (e.g. p-IKKβ, nuclear p65, serum IL-6) to bridge preclinical and clinical contexts. Ultimately, an interdisciplinary strategy combining traditional natural-product research with cutting-edge AI has the potential to systematically uncover and optimize quercetin-based therapeutics against the NF-κB axis in breast cancer.

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