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Pharmacogenomic Regulation of the NF-κB–Nrf2 Axis by Curcumin: A Precision Molecular Approach to Inflammation and Oxidative Stress

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Abstract

Introduction: Chronic inflammation and oxidative stress are major mechanisms in degenerative diseases, including cancer, diabetes, and cardiovascular disorders. The NF-κB and Nrf2 pathways play a role in maintaining redox balance and inflammatory response. Curcumin, the main bioactive compound of *Curcuma longa L*., can simultaneously modulate both pathways through pharmacogenomic mechanisms influenced by individual genetic variations.
Method: This study used the Systematic Literature Review method in accordance with the PRISMA 2020 guidelines. Searches were conducted in PubMed, Scopus, ScienceDirect, and Google Scholar until October 2025 using the keywords "Curcumin," "NF-κB," "Nrf2," "Oxidative Stress," and "Pharmacogenomics." Studies assessing the molecular modulation of NF-κB/Nrf2 by curcumin and gene-dependent effects were included.
Results and Discussion: A total of 31 studies met the inclusion criteria, including in vitro, in vivo, in silico, and clinical studies. Curcumin suppressed NF-κB activation and activated Nrf2/HO-1, thereby reducing ROS and proinflammatory cytokines. Variations in the ERCC5 rs751402 gene, as well as the expression of SLC7A11 and ATAD3A/B, influenced the cellular response to curcumin. In silico and network pharmacology analyses revealed multigenic targets related to inflammation and oxidative stress. Nanoformulations enhance bioavailability and clinical immune response.
Conclusion: Curcumin acts as a dual-regulator pharmacogenomic agent that balances the NF-κB and Nrf2 pathways, reducing inflammation and oxidative stress in a gene-dependent manner. These findings support its potential as a natural biomolecule for the development of precision therapies for chronic diseases involving inflammation and oxidative stress.

Keywords: Curcumin, NF-κB, Nrf2, Oxidative Stress, Pharmacogenomics

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1. INTRODUCTION

Chronic inflammation and oxidative stress represent interrelated pathophysiological mechanisms that substantially contribute to the progression of multiple degenerative diseases, including cancer, diabetes mellitus, cardiovascular disorders, and neurodegenerative conditions.[1] An imbalance between the production of reactive oxygen species (ROS) and the capacity of endogenous antioxidant defense systems to neutralize them leads to biomolecular injury affecting DNA, proteins, and lipids. This disruption results in cellular dysfunction and may accelerate biological aging.[2]

At the molecular level, two key signaling pathways regulate the balance between oxidative and inflammatory responses: the NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) pathway and the Nrf2 (nuclear factor erythroid 2-related factor 2) pathway. NF-κB activation promotes the transcription of pro-inflammatory mediators, including IL-6, TNF-α, and COX-2. In contrast, Nrf2 activation enhances endogenous antioxidant responses by upregulating targets such as HO-1, NQO1, and SOD2.[4] Therefore, maintaining equilibrium between both pathways is critical. Excessive NF-κB activation suppresses Nrf2-mediated antioxidative transcription and increases ROS production, whereas enhanced Nrf2 activity can downregulate NF-κB signaling through HO-1 induction and reduced expression of pro-inflammatory cytokines. An imbalance between these two pathways causes increased oxidative damage and the progression of chronic diseases, especially systemic inflammation and diseases mediated by oxidative stress. Consequently, compounds capable of selectively suppressing NF-κB while activating Nrf2 are essential in restoring redox homeostasis. Curcumin—the principal bioactive constituent of *Curcuma longa L*. (turmeric)—demonstrates this dual regulatory potential. However, existing literature has not yet comprehensively elucidated its mechanism within the framework of precision molecular pharmacogenomics, a perspective crucial for the development of genetics-guided clinical trials.

Curcumin, the predominant polyphenolic compound found in *Curcuma longa L*., has been widely investigated for its anti-inflammatory, antioxidant, and immunomodulatory properties (Figure 1).[5] At the molecular level, curcumin inhibits NF-κB activation by downregulating pro-inflammatory mediators such as

TNF-α, IKKβ, IL-6, and IL-8. Simultaneously, it promotes Nrf2 activation via dissociation of the Keap1–Nrf2 complex, resulting in increased expression of cytoprotective genes, including HO-1.[6] Emerging pharmacogenomic and bioinformatic evidence indicates that curcumin's modulation of the NF-κB–Nrf2 pathway is highly gene-dependent, with interindividual genetic variability significantly influencing therapeutic responsiveness. Both in vivo and in silico experimental findings increasingly support curcumin as a dual-pathway modulator, highlighting its potential integration within a genetically stratified precision-therapy approach. To our knowledge, no previous systematic review has synthesized molecular, bioinformatic, and pharmacogenomic evidence to establish a precision-based conceptual framework of curcumin action targeting the NF-κB–Nrf2 interaction axis. For example, a study by Maboudian, M et al. (2024) reported that the role of curcumin in chronic obstructive pulmonary disease (COPD) can suppress NF-κB expression and activate Nrf2, thereby reducing tissue oxidative stress and macrophage inflammation.[7] Furthermore, Li et al. (2021) found that in copper-induced nephrotoxicity, curcumin inhibits the mitochondrial apoptosis and NF-κB pathways and activates the Nrf2/HO-1 pathway as a protective mechanism.[8] Clinically, Karimi, A et al. (2022) showed that administration of nanocurcumin to sepsis patients reduced inflammatory biomarkers and enhanced immune response through NF-κB modulation.[9]

In addition to its biological effects, pharmacogenomic evidence shows that genetic variation plays a role in determining the response to curcumin. For example, the ERCC5 rs751402 polymorphism is known to affect catalase enzyme activity and sensitivity to oxidative stress in breast cancer,[2] while the expression of the SLC7A11 and ATAD3A/B genes is associated with cancer cell sensitivity to curcumin in the NCI-60 panel.[10] These findings confirm that curcumin activity is mediated by complex genetic regulation and support its potential as a molecular biotechnology-based precision therapy agent.

Although numerous studies have demonstrated curcumin's therapeutic potential as an antioxidant and anti-inflammatory agent, the existing evidence is limited by substantial methodological and biological heterogeneity. Variations in experimental models, differences in formulation types (such as free curcumin, nanoparticle-based, or

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liposomal preparations), and the absence of genetic stratification contribute to inconsistent outcomes and hinder translational interpretation. Accordingly, an integrative synthesis that bridges bioinformatic, experimental, and clinical findings within a pharmacogenomic framework is warranted to facilitate a more precise understanding of curcumin's molecular effects.

Grounded in this rationale, the present study conducts a systematic literature review to examine the pharmacogenomic regulatory mechanisms of curcumin in modulating the NF-κB–Nrf2 interaction axis, which underlies inflammatory and oxidative stress-related processes. This review seeks to provide an integrated understanding of how genetic variability influences curcumin's molecular activity, thereby informing the development of precision biotechnology-based therapeutic approaches using natural compounds. Ultimately, the findings are expected to contribute to the advancement of individualized treatment strategies within the emerging paradigm of molecular-based precision medicine. This article not only performs a systematic synthesis but also builds a new conceptual model of NF-kB-Nrf2 interactions based on curcumin genetic modulation. To our knowledge, this is the first systematic synthesis to conceptualize curcumin's dual regulation of NF-κB and Nrf2 pathways through a pharmacogenomic lens, providing a biologically grounded framework for future gene-guided clinical applications.

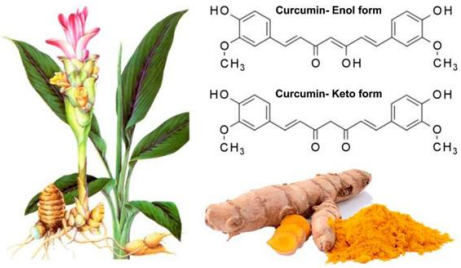

Figure 1. Chemical Structure of Curcumin.[5]

2. METHOD

2.1 RESEARCH DESIGN

This study employed a systematic literature review (SLR) approach following the PRISMA 2020 guidelines. The method was designed to identify, critically evaluate, and synthesize current scientific evidence on the pharmacogenomic regulation of curcumin in modulating the NF-κB–Nrf2 axis associated with inflammation and oxidative stress. The SLR approach was selected due to its ability to integrate findings from diverse research models—including in silico, in vitro, in vivo, and clinical studies—thus enabling a comprehensive assessment of the relationship between genetic variability, molecular pathway modulation, and curcumin's biological activity

within a precision biotechnology context.

2.2 DATA SOURCES AND SEARCH STRATEGIES

A systematic literature search was performed using PubMed, Scopus, ScienceDirect, and Google Scholar databases up to October 2025. The search strategy incorporated Boolean operators (AND, OR) and included keywords such as “curcumin,” “NF-κB,” “Nrf2,” “oxidative stress,” and “pharmacogenomics”. Only peer-reviewed articles written in English and published between 2020 and 2025 were eligible. Title and abstract screening were independently conducted by two reviewers (AQS and KN), followed by full-text assessment of potentially relevant articles. Discrepancies were resolved through discussion until consensus was achieved. Details of the search strategy, last search date, and language filters are shown in Table 1 to ensure transparency and replication. The literature selection flow is illustrated in Figure 2, in accordance with the PRISMA 2020 format. Each study was also assessed using a quality assessment system based on study modality (ROBINS-I/RoB 2/SYRCLE), and these findings were integrated into the discussion.

2.3 INCLUSION AND EXCLUSION CRITERIA

Literature selection followed the PICOS framework (Population, Intervention, Comparison, Outcomes, and Study Design) to ensure alignment with the research objectives. Eligible articles included in vitro, in vivo, in silico, and clinical studies investigating curcumin’s molecular and genetic effects on the NF-κB and/or Nrf2 pathways, with relevance to pharmacogenomic regulation of inflammation and oxidative stress. Studies were required to be written in English and published between 2020 and 2025. Exclusion criteria comprised articles that did not meet PICOS requirements, lacked discussion of the NF-κB–Nrf2 axis or pharmacogenomics, were unavailable in full-text form, or consisted of reviews, editorials, opinion papers, or reports without primary data. Articles that were inaccessible or lacked genetic analysis were also excluded from the analysis. The operational definitions of the inclusion and exclusion criteria are summarized in Table 2.

2.4 DATA EXTRACTION AND ANALYSIS

Extracted data included the author’s name, publication year, journal, study design, biological model, primary molecular targets (e.g., ERCC5, SLC7A11,

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ATAD3A/B, HO-1, NQO1, Keap1), and pharmacogenomic findings related to NF-κB–Nrf2 pathway modulation. The analysis was conducted using a qualitative-descriptive approach combined with thematic synthesis to identify interrelationships between genetic variability and the molecular activity of curcumin.

2.5 ARTICLE QUALITY AND VALIDITY ASSESSMENT

A quality appraisal was carried out to ensure methodological robustness and validity of the included studies. The evaluation focused on four criteria:

1) clarity of study design and methodological accuray,
2) relevance to pharmacogenomic regulation of curcumin on the NF-κB–Nrf2 axis,
3) journal credibility based on Scopus indexing status and peer-review process, and
4) completeness and practical applicability of research data.

Assessment was independently performed by two reviewers, and studies were classified as high, moderate, or low quality following mutual consensus. In addition, the risk of bias was evaluated according to the type of study using tools such as RoB 2 for clinical trials (randomized controlled trials), SYRCLE's RoB for animal studies, and ROBINS-I for observational studies.

2.6 METHODOLOGICAL JUSTIFICATION

The PRISMA 2020-based SLR framework was selected due to its systematic and transparent nature in evaluating evidence across diverse study models. This approach enabled integration of bioinformatic, experimental, and clinical data, facilitating a deeper understanding of genetic variability and its influence on curcumin's molecular mechanisms targeting the NF-κB–Nrf2 axis. Beyond providing a descriptive synthesis, the method supports the development of a conceptual pharmacogenomic model applicable to precision biotechnology and future personalized therapy design.

2.7 ETHICAL CONSIDERATIONS

Ethical approval was not required for this study, as it utilized secondary data obtained from publicly available scientific publications. No direct involvement of human or animal subjects was present; therefore, no ethical risks were associated with the research process.

3. RESULTS

3.1 STUDY SCREENING FINDINGS

A total of 31 studies met the inclusion criteria following the PRISMA 2020 screening process. These comprised in vitro, in vivo, and in silico analyses, along with several randomized controlled

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clinical trials evaluating curcumin's molecular effects on the NF-κB–Nrf2 regulatory axis in inflammation- and oxidative stress–related conditions. All included studies were published between 2020 and 2025, predominantly in reputable journals such as Frontiers in Pharmacology, Molecules, BMC Cancer, and International Journal of Molecular Sciences.

Most of the research focused on gene expression regulation, antioxidant enzyme activation, and molecular signaling pathway interactions. In this study, the authors divided the studies into three models, namely in vivo or in vitro studies (29.03%), in silico and bioinformatics studies (45.16%), and clinical and translational studies (22.58%).

3.2 CHARACTERISTICS OF FINDINGS

Of the 31 included studies, nine were conducted using in vitro or in vivo approaches, fifteen employed in silico or bioinformatic methods, and seven involved clinical or translational investigation. To enhance interpretation of evidence strength, the studies were further categorized according to their level of evidence, as summarized in Table 3.

Table 3. Level of Evidence

Type of Study	Level of Evidence
In silico	Very Low
In vitro	Low
In vivo	Moderate
Clinical Study	High

Most studies are preclinical (in silico and in vitro), with only 22.58% being clinical-based. Of these clinical studies, three are categorized as high-quality studies (randomized controlled trials), while the rest are of moderate quality. This information is important for assessing the strength of the generalization of the findings, as most molecular mechanisms have not been thoroughly validated through genetic stratification-based clinical trials. Therefore, the synthesis results should be read in context as a theoretical basis for the development of precision therapy, not as definitive clinical translational evidence. The predominance of non-clinical studies highlights the need for further translational validation, underscoring the scientific relevance of synthesizing pharmacogenomic evidence to bridge preclinical findings and potential precision-based clinical applications.

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3.2.1 IN VITRO AND IN VIVO STUDIES

A total of nine in vitro and in vivo studies demonstrated consistent molecular effects of curcumin, notably the suppression of NF-κB activation accompanied by Nrf2 induction. These interactions collectively contributed to reduced oxidative stress and attenuation of inflammatory responses. Experimental findings highlighted curcumin's ability to inhibit IKKβ activity, decrease cytokine expression (IL-6, COX-2), and promote downstream antioxidant gene expression such as HO-1 and NQO1. These results reinforce curcumin's role as a dual modulator of inflammatory and redox signaling pathways, supporting its mechanistic plausibility in preclinical models. (See Table 4 for detailed comparison of molecular endpoints).

3.2.2 IN SILICO STUDIES AND BIOINFORMATICS

Fifteen in silico and bioinformatic studies further supported the molecular evidence by identifying multiple genetic and signaling targets modulated by curcumin. Network pharmacology and computational modeling revealed multigenic pharmacogenomic activity, particularly involving ERCC5, SLC7A11, ATAD3A/B, and components of the Keap1-Nrf2 complex. These models demonstrated curcumin's capability to influence gene expression regulation, kinome modulation, and immunometabolic signaling networks. Although in silico evidence provides mechanistic insight, its predictive nature highlights the necessity of translational validation. (Details summarized in Table 5).

3.2.3 CLINICAL AND TRANSLATIONAL STUDIES

Seven clinical and translational studies reported therapeutic benefits of curcumin, including reduced inflammatory biomarkers, enhanced antioxidant capacity, and improved immunological regulation across multiple disease models such as sepsis, cancer, and hepatic injury. Nanoformulated curcumin demonstrated superior bioavailability relative to conventional preparations, contributing to measurable clinical improvement in randomized trials. However, most interventions did not incorporate genetic

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stratification, suggesting that outcomes were not optimally tailored to interindividual variability. This observation underscores the importance of integrating pharmacogenomic parameters in future clinical trials to enhance therapeutic precision. (See Table 6 for summarized clinical outcomes).

3.3 PHARMACOGENOMIC REGULATION OF GENETIC INVOLVEMENT

Of the 31 articles, 9 explicitly highlighted pharmacogenomic aspects, particularly the involvement of genetic variations that affect the response to curcumin.

- ERCC5 rs751402 affects catalase activity and sensitivity to oxidative stress.[2]
- SLC7A11 and ATAD3A/B are associated with the sensitivity of cancer cells to curcumin.[10]
- The Keap1-Nrf2-ARE pathway is central to regulation, where Nrf2 activation downregulates NF-κB expression through target genes such as HO-1, NQO1, and GCLC.[6]
- Variations in TGF-β, IL-6, and TNF-α expression have also been reported to mediate the inflammatory response influenced by curcumin.[5]

These findings reinforce the concept that curcumin's efficacy is gene-dependent, indicating the need for a precision pharmacogenomics approach in its clinical application.

3.4 THEMATIC ANALYSIS AND EVIDENCE INTEGRATION

Thematic analysis grouped 31 studies into three main studies. These three studies form the basis of the integrative pharmacogenomic mechanism, in which curcumin acts as a dual regulator that maintains the balance between inflammatory and antioxidant responses through NF-κB–Nrf2 transcriptional regulation.

3.5 DATA SYNTHESIS AND GRAPHICAL REPRESENTATION

Based on the synthesis results, it was found that curcumin and its derivatives (nano-, liposomal-, and polymeric complexes) affect more than 40 target genes, including Keap1, HO-1, NQO1, TNF-α, IL-6, SOD2, and ERCC5.[2,6]

A conceptual overview is presented in the Molecular Interaction Flowchart (Figure 3), which shows that curcumin suppresses the NF-κB pathway through IKKβ inhibition, activates Nrf2 by breaking the Keap1–Nrf2 complex bond, and increases the expression of HO-1, NQO1, and GCLC, which strengthens antioxidant defenses.[3,6]

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Cross-talk between these two pathways mediates protective, anti-inflammatory, and adaptive redox effects. These findings indicate that although curcumin consistently influences NF-κB regulation and Nrf2 activation at various levels of biological models, the strength of evidence supporting clinical translation still depends on further validation through genetic stratification-based intervention trials. Therefore, the synthesized results in this study were not only analyzed descriptively but also critically examined in the discussion section to evaluate the molecular mechanisms, pharmacogenomic relevance, and potential integration of curcumin as a precision therapy candidate. This analysis also aims to propose a new conceptual framework that links cross-study molecular findings with future therapeutic implementation strategies based on individual genetic profiles. Taken together, these multi-model findings substantiate curcumin's mechanistic potential as a dual-pathway pharmacogenomic agent; however, the variability in methodological approaches and limited incorporation of genetic stratification indicate the necessity for deeper critical analysis, which is elaborated in the Discussion section.

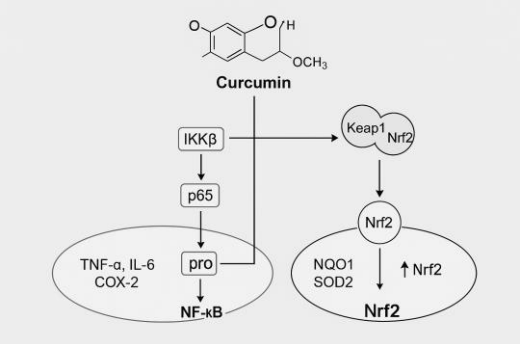

Figure 3. Molecular Interaction Flow Chart

4 DISCUSSION

4.1 REGULATION OF NF-kB PHARMACOGENOMICS BY CURCUMIN (ANTI-INFLAMMATORY PATHWAY)

The NF-κB pathway functions as a central transcriptional regulator of inflammatory mediators such as IL-6, COX-2, and TNF-α. Its activation, typically triggered by stimuli including LPS, TNF-α, and IL-1β via IκBα phosphorylation, facilitates nuclear translocation of the p65/p50 complex, leading to pro-inflammatory gene expression. Excessive activation of NF-κB contributes to persistent inflammation, oxidative stress, and immune dysregulation, which are hallmarks of chronic degenerative diseases.[11]

Curcumin is the main bioactive polyphenol of *Curcuma longa L.*, and has been shown to suppress NF-κB activation through various precise molecular mechanisms.[5] In vitro studies show that curcumin inhibits IκBα phosphorylation, prevents p65 translocation to the nucleus, and reduces IL-6 and

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COX-2 expression.[3,11] Animal studies also show a decrease in TNF-α levels and a hepatoprotective effect against oxidative stress caused by radiation and environmental toxins.[12]

Pharmacogenomically, genetic variation can influence the response to curcumin. ERCC5 polymorphism (rs751402) has been reported to correlate with increased antioxidant activity.[2] In addition, curcumin also reduces the expression of proinflammatory genes.[8] A double-blind clinical trial in sepsis patients reported that nanocurcumin significantly reduced serum NF-κB p65 and IL-6 levels ($p<0.05$) and improved cellular immune function.[9] Thus, curcumin acts as a precision genomic modulator of the NF-κB pathway through epigenetic, transcriptional, and pharmacogenomic mechanisms.

4.2 PHARMACOGENOMIC ACTIVATION OF Nrf2 BY CURCUMIN (ANTIOXIDANT AND REDOX PATHWAY)

The transcription factor Nrf2 (Nuclear factor erythroid 2–related factor 2) is the main guardian of cellular redox homeostasis. Under physiological conditions, Nrf2 binds to Keap1 and undergoes proteasomal degradation. When oxidative stress occurs, the cysteine residue of Keap1 is oxidized, releasing Nrf2 so that it can move to the nucleus and activate the expression of protective genes such as HO-1, NQO1, and GCLC.[1]

Curcumin activates the Nrf2 pathway through covalent modification of the cysteine residue in Keap1, which prevents Nrf2 degradation and increases its nuclear translocation. This activation increases the expression of HO-1 and NQO1 and decreases ROS levels, as demonstrated in models of aflatoxin B1 exposure and systemic oxidative stress.[13] In vitro studies also show that curcumin suppresses pollutant-induced oxidative stress through activation of the Nrf2/HO-1 pathway, along with a decrease in NF-κB expression.[14]

Meanwhile, molecular docking shows curcumin's interaction with Kelch-binding proteins in Keap1, strengthening the stability of the Nrf2 complex in the nucleus and increasing the transcription of antioxidant genes.[15] Therefore, curcumin can be considered a nutrigenomic molecule with specific action on the Nrf2 pathway through a precision genetic mechanism.

4.3 INTERACTION BETWEEN NF-kB AND Nrf2: INTEGRATED PHARMACOGENOMIC INSIGHTS

The relationship between NF-κB and Nrf2 is antagonistic yet interdependent. Activation of NF-κB can inhibit Nrf2 expression through increased HDAC activity, while activation of Nrf2 can suppress NF-κB through increased HO-1 expression and decreased ROS.[15] The balance between these two pathways determines cellular adaptation to oxidative stress and inflammation.

Curcumin has the unique ability to modulate both pathways simultaneously. A study in Frontiers in Cell and Developmental Biology (2022) showed that curcumin simultaneously decreases NF-κB activity and increases Nrf2 expression, resulting in synergistic anti-inflammatory and antioxidant effects. Recent omics analysis shows that genes such as HO-1, IL-6, TNF, and TP53 are located in the crosstalk region directly controlled by curcumin.[6]

A network pharmacology approach shows that connecting proteins such as MAPK1 play an important role in the interaction of these two pathways.[14] The integration of transcriptomic and proteomic data confirms that curcumin does not work alone, but rather through cross-pathway coordination in maintaining redox-inflammatory balance.[6]

Thus, curcumin can be viewed as an integrative pharmacogenomic agent that regulates the NF-κB–Nrf2 axis through cooperative mechanisms, thereby holding potential for use in precision therapy based on natural biomolecules.

4.4 CLINICAL IMPLICATIONS AND FUTURE PROSPECTS

The pharmacogenomic regulation of curcumin on the NF-κB–Nrf2 axis opens up great opportunities in the development of precision molecular therapeutics. This dual modulation is relevant to various chronic diseases based on inflammation and oxidative stress, such as COPD, cancer, diabetes mellitus, and neurodegenerative disorders.[16]

Meanwhile, the low bioavailability of curcumin remains a major challenge. The development of innovative formulations such as nanocurcumin, liposomal curcumin, and polymeric conjugates has been shown to improve its stability, absorption, and biological effects.[5] On the other hand, the integration of omics (genomics, proteomics, metabolomics) with computational biology enables the mapping of patient genetic profiles so that doses and formulations can be tailored individually. Thus,

curcumin functions not only as an anti-inflammatory and antioxidant agent, but also as a prototype molecule in genetic-based precision medicine biotechnology.

5 CONCLUSION

Curcumin is a bioactive compound that shows high potential as a precision biotechnology agent through its ability to regulate the molecular balance between NF-κB and Nrf2. This regulation occurs through a complex pharmacogenomic mechanism, in which curcumin suppresses the expression of proinflammatory genes controlled by NF-κB and simultaneously induces the activation of protective genes mediated by Nrf2, such as HO-1 and NQO1. This dual modulation illustrates a dual regulator pattern capable of maintaining the balance between inflammatory processes and redox defense at the cellular level.

Evidence from bioinformatics analysis, network pharmacology, and in vitro and in vivo studies shows that the response to curcumin is highly influenced by individual genetic variation. These findings reinforce the relevance of curcumin in the fields of pharmacogenomics and precision medicine, as its biological effects can be optimized based on each individual's genetic profile.

Overall, a deeper understanding the regulation of the NF-κB–Nrf2 axis by curcumin contributes significantly to the development of personalized therapy based on natural biomolecules, especially for the management of chronic diseases involving inflammation and oxidative stress. The integration of computational biology approaches, omics analysis, and innovations in curcumin formulation in the future is expected to strengthen the application of biotechnology in realizing a new paradigm of molecular-based precision medicine. These findings highlight the necessity for future gene-stratified clinical trials to validate curcumin's therapeutic potential within precision molecular medicine.

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Appendix

Table 1. Details of Search Strategy, Last Search Date, and Language Filter

Database	Search String (Boolean Operators)	Date of Last Search	Filters Applied	Inclusion Criteria	Exclusion Criteria
PubMed (MEDLINE)	("Curcumin" OR "Curcuma longa" OR "diferuloylmethane") AND ("NF-κB" OR "Nrf2" OR "Keap1" OR "oxidative stress") AND ("pharmacogenomic" OR "gene expression" OR "precision medicine")	29 Okt 2025	English; 2020–2025	Original studies (in vitro, in vivo, in silico, clinical) assessing curcumin's modulation of NF-κB/Nrf2 pathways and genetic variation	Reviews, commentaries, or studies without molecular endpoints
Scopus	TITLE-ABS-KEY ("curcumin" AND ("NF-κB" OR "Nrf2") AND ("pharmacogenomic" OR "genetic variation" OR "personalized therapy"))	29 Okt 2025	English; 2020–2025	Same as above	Duplicates; non-original data
ScienceDirect	("Curcumin" AND "Nrf2" AND "NF-κB" AND ("gene" OR "pharmacogenomic" OR "precision medicine"))	31 Okt 2025	English; 2020–2025	Same as above	Studies with incomplete molecular data
Google Scholar	"Curcumin" + "NF-κB" + "Nrf2" + "pharmacogenomic" + "gene polymorphism"	31 Okt 2025	English; 2020–2025	Cross-verification of	Unindexed or low-quality preprints

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				gray literature (DOI only)	

Table 2. Operational Definitions of Inclusion and Exclusion Criteria

Category	Inclusion Criteria	Exclusion Criteria
Study Type	Original research (in vitro, in vivo, in silico, or clinical).	Reviews, editorials, commentaries.
Intervention	Curcumin or Curcuma longa extract (any formulation).	Multi-herbal mixtures without isolated curcumin.
Mechanistic Focus	Studies assessing NF-κB or Nrf2 signaling, oxidative stress, or gene-related modulation.	Studies with non-molecular endpoints (e.g., only physiological outcomes).
Pharmacogenomic Aspect	Pharmacogenomic-related studies were defined as those assessing the modulation of gene expression, polymorphism, or molecular targets (e.g., Nrf2, NF-κB, HO-1, Keap1) influenced by curcumin exposure, including preclinical and clinical studies that analyze genetic or molecular pathways of drug response.	No genomic data reported.
Language and Publication	English, peer-reviewed, published 2020–2025.	Non-English, unpublished, or predatory journals.

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Table 4. In Vitro and In Vivo Studies

Reference	Title	Author (Year)	Hasil Utama
Ecotoxicology and Environmental Safety	Involvement of the inhibition of mitochondrial apoptotic, p53, NF-κB pathways and the activation of Nrf2/HO-1 pathway in the protective effects of curcumin against copper sulfate-induced nephrotoxicity in mice	Dai, C et al. (2023)	The effect of curcumin on $CuSO_4$-induced nephrotoxicity. Curcumin inhibits mitochondrial apoptosis and NF-κB, activates Nrf2, and protects the kidneys.[8]
Frontiers in Pharmacology	Curcumin Restrains Oxidative Stress of After Intracerebral Hemorrhage in Rat by Activating the Nrf2/HO-1 Pathway	Duan, C et al. (2022)	Curcumin activates Nrf2, suppresses hepatic oxidative stress, inhibits IKKβ, and increases HO-1.[17]
Toxics	Nano-Curcumin Prevents Copper Reproductive Toxicity by Attenuating Oxidative Stress and Inflammation and Improving Nrf2/HO-1 Signaling and Pituitary-Gonadal Axis in Male Rats	Sarawi, WS et al. (2022)	Increases Nrf2 expression, decreases TLR4/NF-κB, improves gonadal dysfunction.[18]
Frontiers in Pharmacology	*Curcumae Rhizoma* - combined with *Sparganii Rhizoma* in the treatment of liver cancer: Chemical analysis using UPLC-LTQ-Orbitrap MS^n, network analysis, and experimental assessment	Wei, J et al. (2022)	Inhibits IKK activation, reduces COX-2 & ROS.[3]

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Reference	Title	Author (Year)	Hasil Utama
ACS Omega	Exploration of the Molecular Mechanism of Curcuma aromatica Salisb's Anticolorectal Cancer Activity via the Integrative Approach of Network Pharmacology and Experimental Validation	Yin, ZH et al. (2024)	The role of curcumin in colorectal cancer is to inhibit tumor cell proliferation, migration, and invasion; and to increase apoptosis.[19]
International Journal of Molecular Science	Curcumin Ameliorates Particulate Matter-Induced Pulmonary Injury through Bimodal Regulation of Macrophage Inflammation via NF-B and Nrf2	Lee, MK et al. (2023)	Suppresses NF-κB & activates Nrf2; protects the lungs from inflammation caused by particulate matter.[14]
BMC Complementary Medicine and Therapies	Curcumin protects radiation-induced liver damage in rats through the NF-κB signaling pathway	Li, W et al. (2021)	Inhibiting NF-κB in radiation-induced liver damage (RILD).[12]
Foods	Dietary Curcumin Alleviated Acute Ileum Damage of Ducks (Anas platyrhynchos) Induced by AFB1 through Regulating Nrf2-ARE and NF-kB Signaling Pathways	Jin, S et al. (2021)	Curcumin effectively protects the ileum structure of ducks from acute damage caused by Aflatoxin B1 (AFB1) by activating the Nrf2 antioxidant pathway and inhibiting the NF-kB inflammatory pathway.[20]
Research Square	Nanocurcumin alleviate inflammation and oxidative stress in LPS-induced mastitis model via activation of Nrf2 and suppressing TLR4 mediated NF-κB and HMGB1 signaling pathways	Lebda, MA et al. (2021)	Nanocurcumin can be an alternative treatment for lipopolysaccharide (LPS)-induced mastitis in rats by increasing Nrf2 activation as an antioxidant defense factor and suppressing the

Reference	Title	Author (Year)	Hasil Utama
			inflammatory response by downregulating Nf-kB gene expression.[11]

Table 5. In Silico and Bioinformatics Studies

Reference	Title	Author (Year)	Hasil Utama
Asian Pacific Journal of Cancer Prevention	Effects of ERCC5 rs751402 polymorphism on oxidative stress and the impact of curcumin on catalase activity in breast carcinogenesis	Pongsavee, M (2022)	The role of curcumin in breast cancer in the ERCC5 rs751402 polymorphism gene is to increase the activity of antioxidant enzymes (catalase), thereby reducing ROS and cell proliferation, resulting in a decrease in oxidative stress.[2]
BMC Cancer	Pharmacogenomics of in vitro response of the NCI-60 cancer cell line panel to Indian natural products	Sankaran, H et al. (2022)	SLC7A11 & ATAD3A/B determine the sensitivity of cancer cells to curcumin.[10]
Egyptian Journal of Medical Human Genetics	Evaluation of the effects of curcumin on chronic obstructive pulmonary disease with a bio-computational approach	Maboudian, M et al. (2024)	The role of curcumin in COPD is to suppress NF-κB, activate Nrf2, and reduce ROS and macrophage inflammation.[7]
Nutrients	Therapeutic Role of Curcumin in Diabetes: An Analysis Based on Bioinformatic Findings	Mahmoudi, A et al. (2022)	The role of curcumin as an antioxidant and anti-inflammatory agent in diabetic patients by regulating various genes and pathways, such

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Reference	Title	Author (Year)	Hasil Utama
			as activating PI3K-Akt, reducing ROS, and inhibiting inflammation.[21]
Frontiers in Pharmacology	Toward Regulatory Effects of Curcumin on Transforming Growth Factor-Beta Across Different Diseases: A Review	Ashrafizadeh, M et al. (2020)	Curcumin can modulate TGF-β in different ways depending on the type of disease, such as controlling inflammation, fibrosis, and cancer, so curcumin is referred to as a multifunctional therapy.[5]
GSC Biological and Pharmaceutical Sciences	In-silico investigation of curcumin drug-likeness, gene-targets and prognostic relevance of the targets in panels of human cancer cohorts	Oshevire, DB et al. (2021)	Confirming the drug-likeness of curcumin and its relationship to tumor expression and cancer patient prognosis.[22]
Antioxidants	Bioactive Compounds in Oxidative Stress-Mediated Diseases: Targeting the NRF2/ARE Signaling Pathway and Epigenetic Regulation	Thiruvengadam, M et al. (2021)	Curcumin as a preventative and therapeutic agent for diseases triggered by oxidative stress, such as diabetes, cancer, heart disease, neurodegenerative diseases, and fibrosis. Curcumin can protect the body from oxidative stress through three mechanisms, namely increasing Nrf2 activation, modulating various kinases such as PI3K/Akt or MAPK, and epigenetic regulation of the Nrf2 promoter.[16]
Molecules	Nrf2 Regulation by Curcumin: Molecular Aspects for Therapeutic Prospects	Shahcheraghi, SH et al. (2022)	Nrf2 activation → protection against oxidation, inflammation, toxicity, DNA damage.[1]

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Reference	Title	Author (Year)	Hasil Utama
Pharmaceuticals	Natural Coumarin Derivatives Activating Nrf2 Signaling Pathway as Lead Compounds for the Design and Synthesis of Intestinal Anti-Inflammatory Drugs	Stasi, LCD (2023)	Nrf2/Keap1 activation suppresses NF-κB & proinflammatory cytokines.[23]
Frontiers in Pharmacology	Research progress on the mechanism of curcumin anti-oxidative stress based on signaling pathway	Cui, J et al. (2025)	Regulates Keap1-Nrf2/ARE, NF-κB, NOX, MAPK; reduces ROS & inflammation.[24]
Frontiers in Pharmacology	Turmeric and Its Major Compound Curcumin on Health: Bioactive Effects and Safety Profiles for Food, Pharmaceutical, Biotechnological and Medicinal Applications	Sharifi-Rad, J et al. (2020)	Curcumin is a multifunctional bioactive agent with broad health benefits, particularly as an antioxidant and anti-inflammatory agent.[25]
Frontiers in Pharmacology	Targeting Cytokine Release Through the Differential Modulation of Nrf2 and NF-kB Pathways by Electrophilic/ Non-Electrophilic Compounds	Fagiani, F et al. (2020)	Both electrophilic and non-electrophilic curcumin derivatives can influence innate immune responses through different mechanisms, namely by involving differential regulation of the Nrf2 and NF-kB pathways. [26]
Frontiers in Cell and Developmental Biology	Dissecting the Crosstalk Between Nrf2 and NF-κB Response Pathways in Drug-Induced Toxicity	Gao et al. (2022)	Curcumin acts as a dual regulator, activating Nrf2 and inhibiting NF-κB. This can prevent chronic diseases.[6]

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Reference	Title	Author (Year)	Hasil Utama
Evidence-Based Complementary and Alternative Medicine	Uncovering the Mechanism of Curcuma in the Treatment of Ulcerative Colitis Based on Network Pharmacology, Molecular Docking Technology, and Experiment Verification	Liu et al. (2021)	Curcumin has potential as an adjuvant therapy for ulcerative colitis. Its therapeutic effects are mediated by anti-inflammatory activity, the ability to regulate immune responses, and protection of intestinal mucosal integrity.[27]
Frontiers in Pharmacology	Immunomodulatory Effects and Mechanisms of Curcuma Species and Their Bioactive Compounds: A Review	Yuandani et al. (2021)	All species of curcumin exhibit strong immunomodulatory potential. This activity is primarily associated with the inhibition of the NF-κB inflammatory pathway, the regulation of cytokine production, and the reduction of oxidative stress. Of these species, *Curcuma longa* has been the most widely studied, with curcumin and polysaccharides as the active components that contribute most to its immunomodulatory activity.[28]

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Table 6. Clinical and Translational Studies

Reference	Title	Author (Year)	Hasil Utama
Cancer Drug Resistance	Oxidative stress and redox signaling in CRPC progression: therapeutic potential of clinically-tested Nrf2-activators	Mondal, D et al. (2021)	Curcumin is the main bioactive compound in turmeric that has broad health benefits, such as anti-inflammatory and antioxidant properties.[15]
Brazilian Journal of Pharmaceutical Sciences	Curcumin supplementation in the treatment of patients with cancer: a systematic review	Anunciacao, TA et al. (2021)	Oral curcumin supplementation can provide benefits as a complementary therapy for cancer patients, reducing inflammatory markers and increasing antioxidant capacity.[29]
Frontiers in Nutrition	Evaluating the effects of curcumin nanomicelles on clinical outcome and cellular immune responses in critically ill sepsis patients: A randomized, double-blind, and placebo-controlled trial	Karimi, A et al. (2022)	Improved immune regulation and reduced inflammation, as well as improved organ failure scores (SOFA and MODS) in ICU sepsis patients given additional nanocurcumin intervention therapy via nasogastric tube.[9]
International Journal of	Natural Products for the Prevention and Treatment of Oral Mucositis: A Review	Ferreira, AS et al. (2022)	Administration of curcumin longa as an adjunct to standard therapy in cases of oral mucositis in immunocompromised patients can suppress the

Reference	Title	Author (Year)	Hasil Utama
Molecular Sciences			NF-Kb inflammatory pathway, increase endogenous antioxidants, and support the regeneration of damaged mucosal tissue.[30]
Elevate Series	Impact of dietary ingredients on radioprotection and radiosensitization: a comprehensive review	Islam MM et al. (2024)	The combination of dietary interventions and natural food components, such as curcumin, has great potential as a radioprotective agent for normal tissues, making cancer cells radiosensitive, increasing antioxidant activity, suppressing ROS, repairing DNA, and inhibiting inflammation.[31]
Int. J. Pharm. Sci. Rev. Res.	How Effective is Curcumin in Prevention of Cancer	Mercy, PM (2021)	Curcumin is one of the natural cancer prevention agents, due to its multi-target effects.[4]
Antioxidants	Aflatoxin B1 Toxicity and Protective Effects of Curcumin: Molecular Mechanisms and Clinical Implications	Dai, C et al. (2022)	Curcumin is safe for preventing organ damage caused by exposure to aflatoxin (AFB1). Curcumin has been proven to counteract the toxic effects of AFB1 through its antioxidant and anti-inflammatory properties, reducing ROS, increasing antioxidant enzyme activity, inhibiting inflammatory pathways, and suppressing the expression of CYP450, which converts AFB1 into toxic metabolites.[4]

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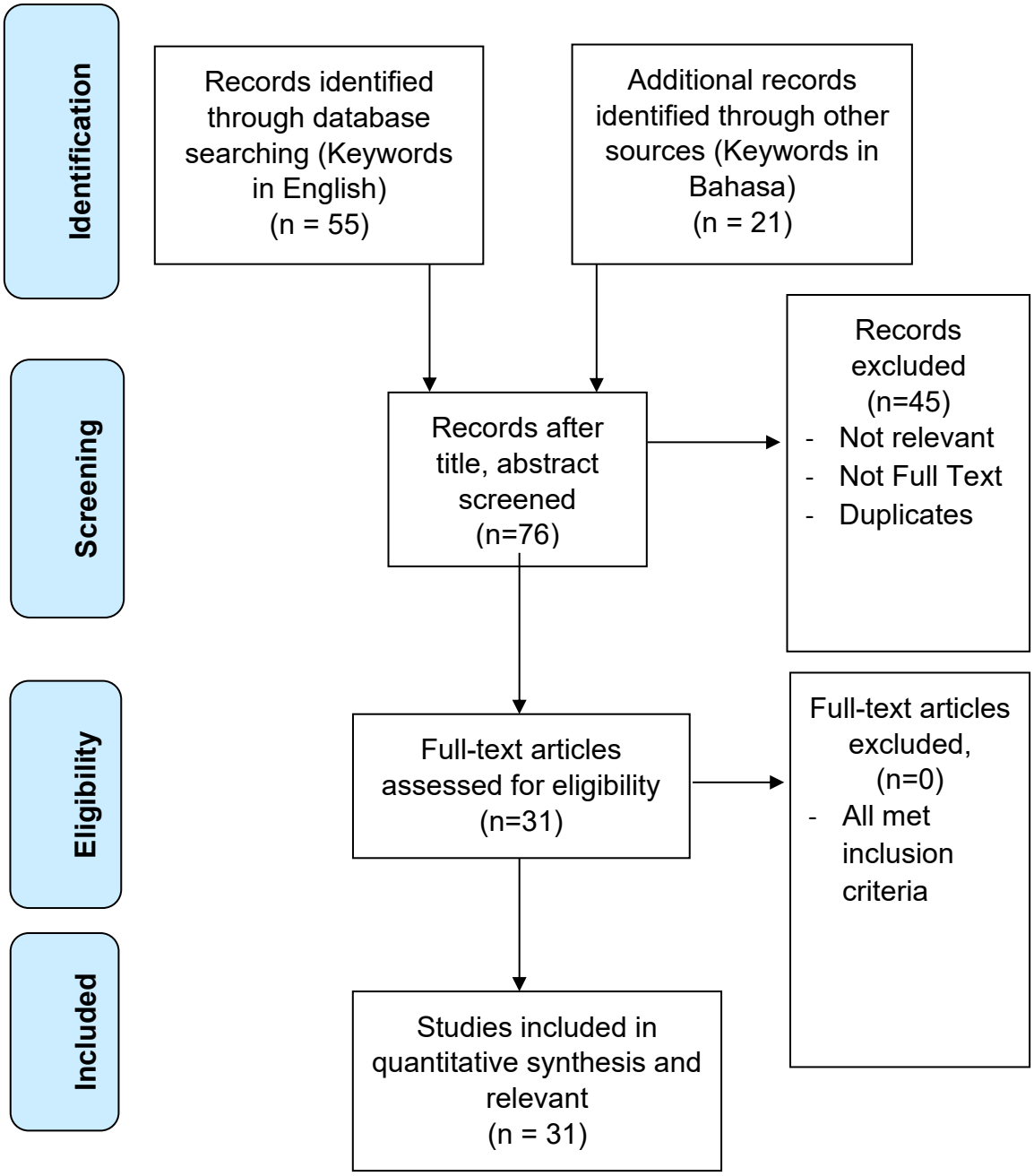

Figure 2. Inclusion Criteria Chart