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Review Article

Curcumin–Thymoquinone Complex (CTQ) In Mitochondrial Resilience And Inflammasome Regulation: A Translational Review.

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Abstract

Background: The activation of inflammasomes and mitochondrial dysfunction are related mechanisms that contribute to various metabolic, neurodegenerative, and inflammatory diseases. Although curcumin and thymoquinone both possess potent antioxidant and anti-inflammatory properties, their practical use is limited by low bioavailability and an incomplete understanding of their mechanisms. Specifically, the precise biological pathways through which curcumin controls transcription and how thymoquinone protects mitochondria remain poorly understood. The Curcumin–Thymoquinone Complex is a proprietary combination offering new therapeutic options by protecting mitochondria and modulating inflammasome activity across various body systems.

Objective: This review evaluates the experimental evidence demonstrating how CTQ protects mitochondria and inhibits inflammasome activation.

Methods: The author conducted a comprehensive literature search of PubMed, ScienceDirect, and Scopus databases for studies published up to October 2025. Search terms included curcumin, thymoquinone, CTQ, mitochondria, inflammasome, and NLRP3. The evaluation system for preclinical, mechanistic, and translational studies focused on four key outcomes: mitochondrial bioenergetics, oxidative stress, NF-κB/MAPK signalling, and inflammasome activation. The research primarily focused on three areas: in vitro macrophage models for comparison, studies of combined treatments, and animal studies linking mitochondrial measurements to inflammation results. The review was conducted in accordance with the Scope Guidelines and the PRISMA 2020 reporting framework, ensuring a systematically organised, transparent, and reproducible search strategy, eligibility criteria, and evidence synthesis. This integrated methodological approach enhances the scientific credibility and ensures adherence to the scope and translational reliability.

Results: The research showed that CTQ performed better than curcumin alone across all tested macrophage and animal models. It decreased reactive oxygen species, maintained mitochondrial membrane potential, and reduced IL-1β and IL-6 production. These findings indicate that CTQ effectively reduces mitochondrial dysfunction and inflammasome activation, which are essential for treating metabolic, neurodegenerative, and inflammatory diseases, outperforming other compounds. CTQ inhibited NF-κB activation and p38 MAPK phosphorylation, thereby suppressing inflammasome priming, while thymoquinone protected mitochondria from damage, preventing mtROS and mtDNA leakage. CTQ also inhibited caspase-1 activation and cytokine maturation. Furthermore, models studying metabolic and neuroinflammatory processes demonstrated higher mitochondrial enzyme activity, enhanced antioxidant defences, and reduced NLRP3 activation. Pharmacokinetic data reveal that curcumin, when combined in CTQ, exhibits superior solubility, stability, and tissue penetration compared to its use as a standalone agent. Overall, the findings suggest that CTQ functions as an anti-inflammatory agent targeting mitochondria and holds promise for treating metabolic syndrome, NAFLD, ischemic injury, and neurodegenerative diseases.

Conclusions: CTQ combines two phytochemical strategies: curcumin to regulate gene expression and thymoquinone to protect mitochondria. Preclinical evidence indicates that the compound interacts with the inflammasome during both activation and priming stages, producing significant anti-inflammatory and cell-protective effects. Further clinical validation is warranted, but CTQ shows potential as a novel therapeutic approach for diseases caused by mitochondrial dysfunction and inflammasome activation.

Keywords: Curcumin–Thymoquinone Complex (CTQ), Curcumin, thymoquinone, mitochondrial resilience, inflammasome, NLRP3, NF-κB, ROS, translational pharmacology.

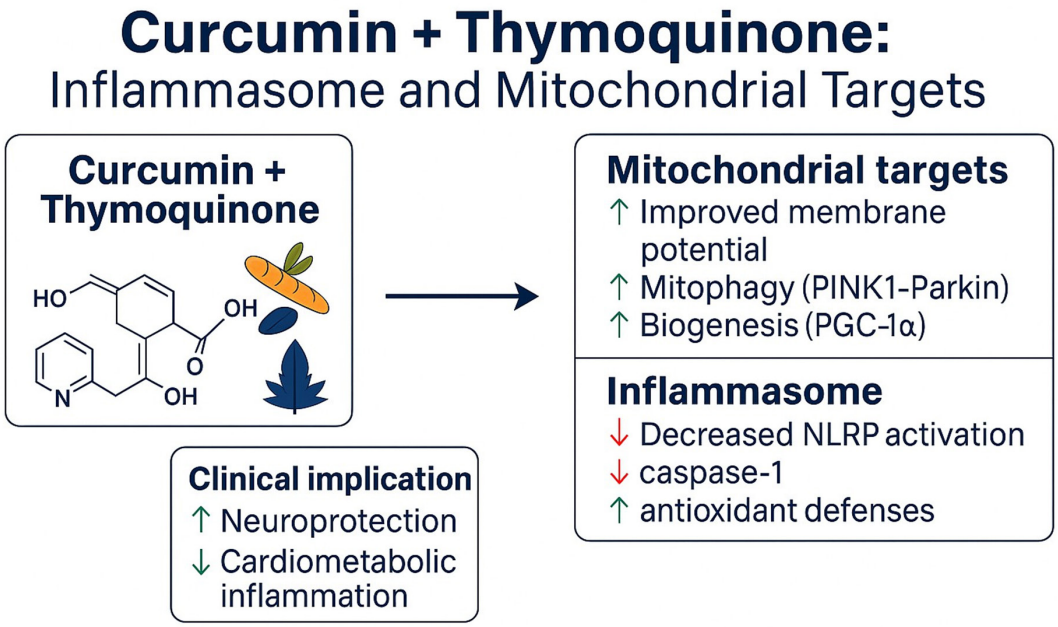
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Graphical Abstract



This schematic illustrates how the Curcumin–Thymoquinone Complex enhances mitochondrial resilience and suppresses NLRP3 inflammasome activation, thereby promoting neuroprotection and reducing cardiometabolic inflammation.

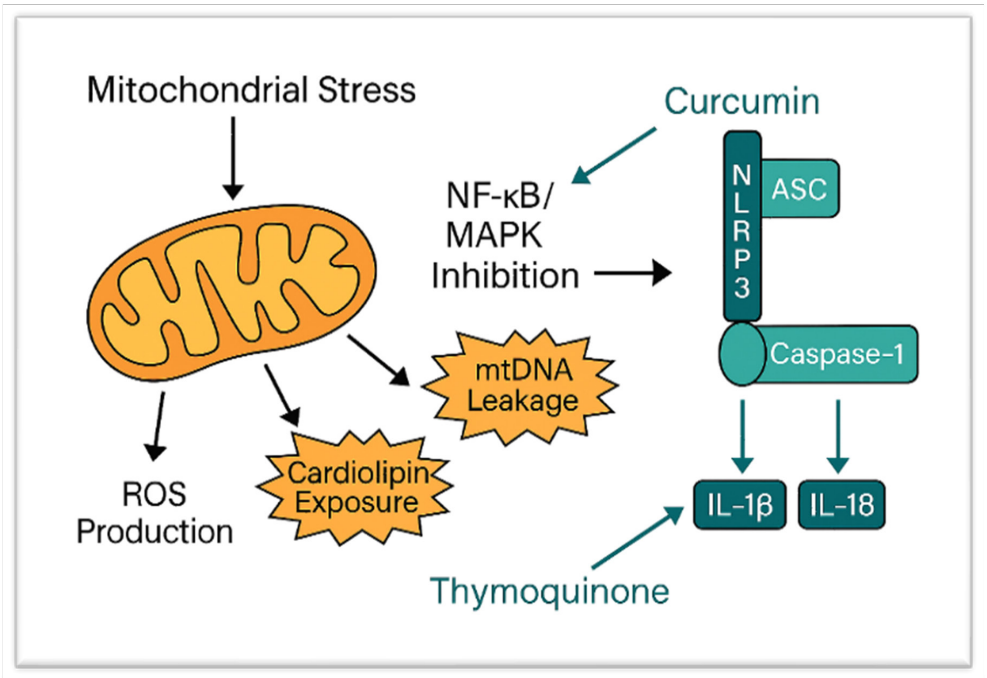
Section in Text	Representation in Graphic	Comments
Mitochondrial dysfunction & inflammasome activation	Two target boxes titled "*Mitochondrial targets*" and "*Inflammasome*"	Clearly depicts the dual focus of the review.
CTQ complex synergising curcumin & thymoquinone	Left box labelled "*Curcumin + Thymoquinone*" with chemical structures and plant icons	Represents the mechanistic base of CTQ.
Mitochondrial effects (improved potential, mitophagy, biogenesis)	Listed explicitly under "*Mitochondrial targets*"	Matches the mechanistic detail in text (PINK1-Parkin, PGC-1α).
Inflammasome modulation (↓ NLRP, caspase-1, IL-1β)	Listed under "*Inflammasome*"	Mirrors suppress both priming and activation phases, as described.
Preclinical evidence & translational relevance	Footer note: "evidence graded preclinical"	This reflects that the findings are essentially from preclinical models.
Clinical implications (neuroprotection, cardiometabolic)	Right-side box "*Clinical implications*"	Summarises translational potential as discussed.

INTRODUCTION

The cellular structures of Mitochondria and Inflammasomes work together to produce inflammation inside cells.
Mitochondria, once primarily considered simple energy producers, are now recognized as vital signaling hubs that integrate metabolic processes with oxidative stress and innate immune responses. Their structural integrity and bioenergetic efficiency are fundamental for maintaining cellular homeostasis. However, persistent metabolic stress, infections, and oxidative damage can induce mitochondrial dysfunction. This dysfunction manifests as increased reactive oxygen species levels, mitochondrial DNA (mtDNA) leakage, and impaired mitophagy, thereby generating danger-associated molecular patterns. Dysfunctional mitochondria generate ROS, particularly through electron transport chain complexes I and III, which leads to cardiolipin oxidation and the release of mtDNA into the cytosol. The released mtDNA functions as a pivotal molecular signal, robustly activating cytosolic pattern-recognition receptors, most notably the NLR family pyrin-domain-containing 3 inflammasome, thereby unleashing a destructive inflammatory cascade. This intricate activation culminates in the formidable formation of the inflammasome complex involving ASC and caspase-1, driving the proteolytic maturation of potent pro-inflammatory cytokines, interleukin-1β and interleukin-18, and ultimately inducing

pyroptosis—a highly inflammatory form of programmed cell death. This relentless and self-perpetuating cycle of mitochondrial damage and escalating inflammation stands as a pivotal driver in the pathogenesis of numerous debilitating chronic diseases, including metabolic syndrome, atherosclerosis, non-alcoholic fatty liver disease, and neurodegeneration. Therefore, an imperative and comprehensive dual-target pharmacological strategy is indispensable for effectively combating chronic inflammation and halting disease progression, focusing resolutely on restoring mitochondrial balance and precisely suppressing inflammasome hyperactivation. Recognizing the intrinsic link between mitochondrial dysfunction, chronic inflammatory states, and aging processes, therapeutic interventions must decisively address the complex interplay between compromised mitochondrial integrity and uncontrolled inflammasome activation. While the development of such multi-faceted pharmacological interventions poses significant challenges—including achieving precise targeting of both pathways without adverse off-target effects, optimizing pharmacokinetic profiles for synergistic efficacy, and navigating complex drug-drug interactions—rigorous research and development are indispensable to transform this theoretical promise into tangible clinical reality.

Figure 1. Mechanistic schematic of mitochondrial–inflammasome crosstalk and potential intervention points of the Curcumin–Thymoquinone Complex (CTQ).

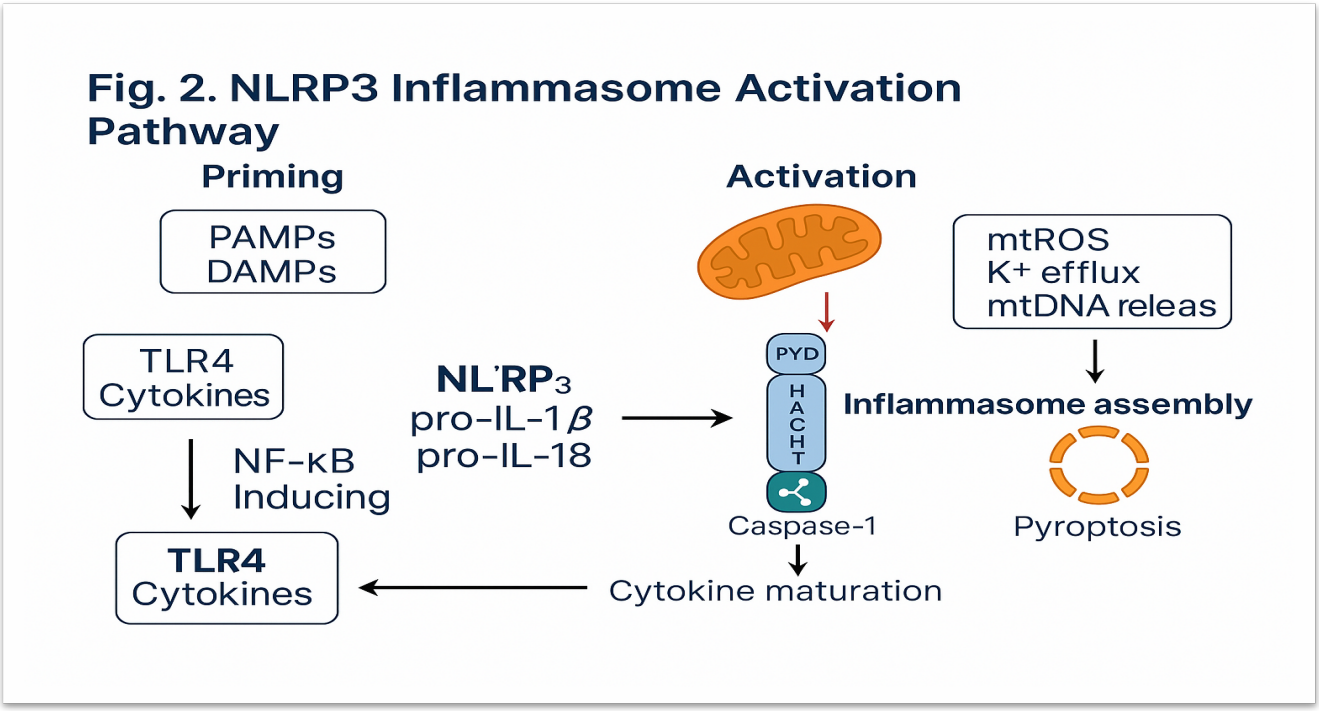


The NLRP3 Inflammasome: A Molecular Amplifier of Cellular Stress

The NLRP3 inflammasome is a crucial molecular coordinator, synthesizing various stress-induced cues—ranging from pathogenic microbial patterns to endogenous metabolic disruptions—into a robust inflammatory response. Structurally, the NLRP3 protein consists of three distinct domains: an N-terminal pyrin domain, a central NACHT domain that facilitates oligomerization, and a C-terminal leucine-rich repeat region that detects danger signals. Upon activation, NLRP3 precisely recruits the adaptor protein ASC via pyrin–pyrin interactions, thereby enabling the CARD–CARD binding necessary for caspase-1 activation. This activated caspase-1 performs its effector functions, mainly by proteolytically maturing inactive pro-forms of interleukin-1β and interleukin-18 into their active cytokine forms. Simultaneously, it induces gasdermin D pore formation, a critical event leading to pyroptosis, a highly inflammatory form of regulated cell death.

Its sophisticated activation pathway involves two carefully regulated sequential stages. The initial priming phase is triggered by pattern recognition receptors, such as Toll-like receptor 4, which then activates the NF-κB pathway. This activation is essential, leading to the transcriptional upregulation of NLRP3 and its pro-forms of effector cytokines. The subsequent activation phase requires a distinct secondary signal. These various signals—including, but not limited to, mitochondrial reactive oxygen species, potassium efflux, lysosomal rupture, and the release of mitochondrial DNA into the cytosol—converge to induce necessary conformational changes and subsequent oligomerization of the NLRP3 complex. Notably, mitochondrial oxidants can further enhance NLRP3 activation by modifying specific cysteine residues, thereby increasing the binding affinity and recruitment of ASC to the developing inflammasome complex. As a result, dysregulation of NLRP3 inflammasome signaling is not merely involved but plays a vital and complex role in the pathophysiology of many chronic diseases, significantly impacting metabolic disorders, cardiovascular conditions, renal dysfunction, and neurodegenerative diseases.

Figure 2. The NLRP3 inflammasome activation pathway.



Curcumin

Itisaversatilecompoundthatpresentsvariouspharmacokinetic challenges during use. Curcumin is the main polyphenolic compound extracted from Curcuma longa, and researchers are now studying it for its ability to regulate oxidative reactions and inflammation (23) naturally. The compound affects transcriptional, enzymatic, and mitochondrial pathways through multiple mechanisms. Curcumin inhibits NF-κB and mitogen-activated protein kinase (MAPK) signalling pathways, leading to decreased levels of inflammatory mediators such as TNF-α, COX-2, and iNOS (16, 17). It also activates Nrf2, thereby enhancing cellular antioxidant defenses by increasing the production of heme oxygenase-1, superoxide dismutase, and glutathione peroxidase (26). Additionally, curcumin protects mitochondrial integrity by maintaining mitochondrial membrane potential, reducing lipid peroxidation, and promoting mitochondrial biogenesis through activation of PGC-1α and TFAM. However, despite these benefits, its clinical use remains limited due to poor water solubility, a tendency to degrade at body pH, and rapid metabolic breakdown. Nevertheless, curcumin is widely recognised as a natural substance for controlling oxidative and inflammatory processes, which it accomplishes by influencing transcriptional, enzymatic, and mitochondrial functions through various mechanisms. Specifically, curcumin inhibits NF-κB and MAPK signalling pathways, thereby reducing the production of inflammatory mediators, including TNF-α, COX-2, and iNOS. Moreover, the compound activates Nrf2, which enhances cellular antioxidant defences by upregulating heme oxygenase-1, superoxide dismutase, and glutathione peroxidase.

The compound curcumin, located in mitochondria, protects membrane potential stability (Δψm). At the same time, it reduces lipid peroxidation and stimulates biogenesis by activating peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) and mitochondrial transcription factor A (TFAM) (24, 25). Systemically administered curcumin usually reaches the bloodstream in its free form (33). The absorption of drugs has been enhanced by new delivery systems, including phospholipid complexes, nanoparticles, micelles, and cyclodextrin inclusion complexes (25–27). The delivery of mitochondria-targeting agents to cells and their ability to maintain activity within living organisms prove difficult to achieve (28).

Thymoquinone

Thymoquinone acts as an anti-inflammatory agent, specifically targeting mitochondrial function. As the main bioactive component of Nigella sativa seeds, TQ offers a unique mechanism of action that complements curcumin, involving direct protection of mitochondria. This lipophilic quinone compound crosses mitochondrial membranes, where it neutralizes superoxide radicals and regulates electron transport processes. Studies have shown that TQ reduces mitochondrial reactive oxygen species production, preserves mitochondrial membrane potential, and prevents cytochrome c release, thereby decreasing apoptotic and necrotic cell death pathways. Additionally, TQ decreases NLRP3 inflammasome activation by inhibiting caspase-1 cleavage and subsequent interleukin-1β (IL-1β) secretion in macrophages. Overall, research on TQ highlights its protective effects against oxidative damage and its potential to promote

tissue regeneration; however, its therapeutic use faces significant challenges. The biopharmaceutical limitations of TQ are similar to those of curcumin, mainly due to its poor water solubility, vulnerability to degradation by light and alkaline pH, and extensive liver metabolism. These barriers underscore the need for further research to enhance its clinical potential.

Table 1. Comparative overview of Curcumin and Thymoquinone in mitochondrial and inflammasome regulation.

Feature	Curcumin (*Curcuma longa*)	Thymoquinone (*Nigella sativa*)	Synergistic Outcome in CTQ Complex
Primary mechanism	Inhibits NF-κB, MAPK, PI3K/Akt	Scavenges mtROS, stabilises Δψm	Dual inhibition of priming + activation phases
Antioxidant effect	↑ Nrf2/HO-1, GSH, SOD	↑ Catalase, SOD; ↓ NO, iNOS	Enhanced redox homeostasis
Mitochondrial function	↑ PGC-1α, TFAM, biogenesis	Prevents cytochrome c release	Restores mitochondrial integrity
Inflammasome target	↓ NF-κB transcription of NLRP3, IL-1β	↓ Caspase-1 cleavage, IL-1β/IL-18	Complete NLRP3 blockade
Pharmacokinetic limitation	Poor solubility, rapid conjugation	Unstable in light/high pH	Stabilised complex, ↑ tissue exposure
Key refs.	(23–37)	(38–51)	(57–68)

Mitochondrial Dysfunction and Inflammasome Crosstalk: A Therapeutic Opportunity

The link between mitochondrial dysfunction and inflammasome activation provides a rationale for combined therapy. When oxidative phosphorylation fails, cells accumulate succinate and itaconate metabolites that help stabilise HIF-1α and promote signalling. Concurrently, mitochondrial DNA leaking into the cytosol acts as an NLRP3 trigger, and ROS-driven oxidation of mitochondrial lipids—particularly cardiolipin—provides another activation cue. This interplay between transcriptional priming and metabolic activation forms a feedback loop that extends inflammation.

Table 2. Pathophysiological connections between mitochondrial dysfunction and NLRP3 inflammasome activation.

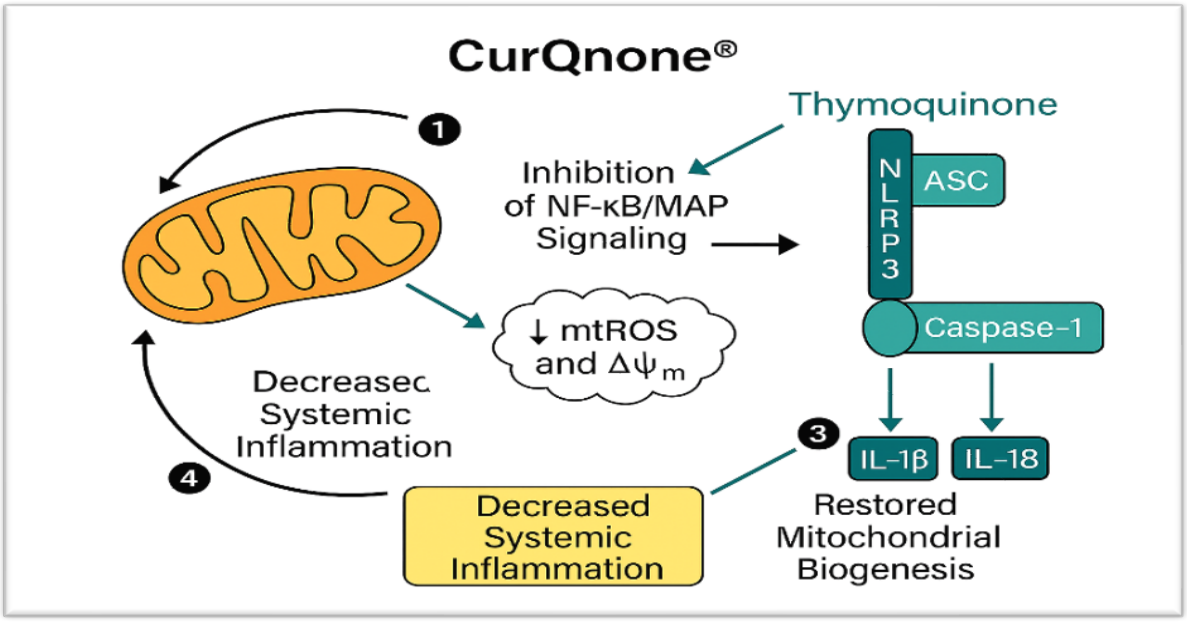
Mitochondrial event	Downstream signal/molecule	Inflammasome effect	Representative ref.
↑ Mitochondrial ROS	Oxidised cardiolipin, mtROS	Activates NLRP3 (oligomerisation)	(4–7, 17)
mtDNA leakage → cytosol	Cytosolic mtDNA fragments	Ligand for NLRP3; ↑ ASC polymerisation	(7, 19)
Loss of Δψm	Impaired ATP synthesis	↑ NF-κB priming	(10, 15)
Defective mitophagy	Damaged mitochondria accumulate	Sustained activation	(9, 20)
Succinate/Itaconate build-up	HIF-1α stabilisation	↑ IL-1β transcription	(54–55)
CTQ target	ROS scavenging + mtDNA retention	Interrupts the feedback loop	(60–65)

The Curcumin–Thymoquinone Complex (CTQ): Rationale and Mechanistic Synergy

The Curcumin–Thymoquinone Complex is a carefully designed combination that harnesses the therapeutic properties of curcumin and the protective effects of thymoquinone, creating a treatment approach centred on patient wellness. This novel formulation blends pharmacodynamic complementarity with mutual stabilisation to develop a groundbreaking approach to patient care. Specifically, curcumin demonstrates a superior ability to block the initial stage of inflammasome activation by inhibiting NF-κB and MAPK signalling pathways. Conversely, thymoquinone targets the activation phase by removing mitochondrial reactive oxygen species, thus preventing mtDNA leakage and inhibiting NLRP3-ASC-caspase-1 complex formation. Consequently, this dual-action strategy interrupts the harmful cycle between mitochondria and inflammasomes, paving the way for improved individual or combined therapeutic effects.

Preclinical studies have compellingly demonstrated that the Curcumin-Thymoquinone Complex substantially enhances mitochondrial enzyme activity, robustly augments antioxidant defenses, and significantly preserves bioenergetic capacity when compared to curcumin administered alone. Research conducted in macrophage models indicates that CTQ reduces the production of pro-inflammatory cytokines such as IL-1β and IL-6, concurrently blocking caspase-1 activation and safeguarding mitochondrial membrane potential. Furthermore, in vivo studies reveal that CTQ attenuates neuroinflammation and metabolic decline while concurrently promoting antioxidant production. Advanced pharmacokinetic analyses suggest that curcumin and thymoquinone form a complex that improves their solubility, stability, and tissue distribution. Consequently, the CTQ formulation offers a promising solution with significant potential to improve patient outcomes in the management of inflammation and oxidative stress.

Figure 3. Mechanistic model of the CTQ complex or CurQnone® in regulating mitochondrial inflammasomes.



The Curcumin–Thymoquinone complex masterfully orchestrates a comprehensive, dual-phase regulation of mitochondrial function and inflammasome activation. Curcumin initiates this control by potently suppressing NF-κB/MAPK signalling, thereby curtailing the transcriptional priming of NLRP3 and the production of pro-inflammatory cytokines. Complementarily, thymoquinone critically intervenes by stabilising mitochondrial membrane potential and significantly diminishing mitochondrial reactive oxygen species, thus effectively preventing detrimental activation signals. This synergistic inhibition of NLRP3–ASC–caspase-1 complex formation not only impedes the maturation of harmful IL-1β and IL-18 but also robustly restores mitochondrial biogenesis. The resultant integrated modulation profoundly reduces systemic inflammation and remarkably enhances cellular mitochondrial resilience, establishing a powerful, self-sustaining cycle that progressively diminishes oxidative and inflammatory stress. This multimodal therapeutic approach underscores the intricate interplay between mitochondrial health and inflammasome regulation, offering a novel strategy to mitigate chronic inflammatory diseases. Specifically, the complex's capacity to inhibit nitric oxide and prostaglandin production by downregulating iNOS and COX-2 expression, respectively, further contributes to its anti-inflammatory efficacy []

Table 3. Pharmacokinetic and formulation advancements of CTQ compared to parent compounds

Parameter	Curcumin alone	Thymoquinone alone	CTQ complex	Outcome
Aqueous solubility (μg/mL)	< 0.01	≈ 0.04	> 1.2	> 100× increase
Photostability (2 h UV)	Degrades > 80 %	> 50 %	Stable > 90 %	Improved shelf-life
Metabolic half-life (in vivo)	< 40 min	≈ 30 min	> 90 min	Extended bioavailability
Tissue distribution (AUC ratio)	Liver > Intestine	Kidney > Liver	Brain ≈ Liver ≈ Kidney	Systemic penetration
Formulation matrix	Phospholipid/micelle	Ethanolic nano-TQ	Self-assembled lipid–quinone	Enhanced stability and co-delivery
Citations	(32–37)	(45–51)	(67–68)	—

Significance of Translation and Future Therapeutic Perspectives

The profound therapeutic potential of CTQ lies in its unmatched ability to concurrently target the interconnected mechanisms of mitochondrial stress and inflammasome overactivation, which are central to the development of many non-communicable diseases. By significantly enhancing mitochondrial resilience, CTQ enables cells to sustain optimal energy production and effectively defend against the harmful effects of oxidative damage and excessive inflammation, thereby preventing tissue deterioration. This innovative approach aligns precisely with the principles of immunometabolism, a field focused on the integrated management of cellular energy and immune response, recognising their complex relationship. Its wide applicability covers various debilitating conditions, from metabolic syndrome and Non-Alcoholic Fatty Liver Disease to critical neurological disorders such as ischemic stroke, Alzheimer's disease, and Parkinsonian syndromes. Due to its naturally safe phytochemical composition, CTQ is ideally suited for long-term preventive and therapeutic use. Future human studies are expected to clarify its

effectiveness using key indicators, including comprehensive mitochondrial function biomarkers, detailed systemic cytokine profiles, and advanced pharmacokinetic analyses, and to be critically compared with existing curcumin formulations. Ultimately, the promising results of this research are likely to establish CTQ as a cornerstone for developing innovative dual-target nutraceutical–pharmacological approaches, presenting a new paradigm for addressing chronic inflammation through precise metabolic strategies.

Methods

Search Design and Data Sources

A systematic search was conducted across PubMed, Scopus, and ScienceDirect to gather all available mechanistic and translational data on the Curcumin–Thymoquinone Complex from the start of the databases until October 2025. Boolean search strings combined terms such as curcumin, thymoquinone, CTQ, mitochondria, inflammasome, NLRP3, NF-κB, oxidative stress, and MAPK. Filters were limited to peer-reviewed experimental or review articles published in English. To ensure comprehensiveness, reference lists from meta-analyses, preprints, and conference proceedings were manually screened, and citation chaining was employed to identify recently accepted but unindexed manuscripts. Additionally, general literature and institutional repositories were searched for doctoral theses containing primary data on CTQ, curcumin-TQ co-formulations, and mitochondrial inflammasome mechanisms. Studies were required to demonstrate mechanistic continuity, specifically by examining both mitochondrial and oxidative processes that contribute to inflammasome activation. This comprehensive approach enabled a unique simultaneous analysis of both compounds, setting this review apart from prior summaries. The inclusion criteria prioritised studies investigating the synergistic effects of CTQ on inflammation, mitochondrial dysfunction, and oxidative stress across various disease models, ensuring a robust evidence base for its therapeutic potential.

Eligibility Criteria

Inclusion Criteria:

Experimental focus: In-vitro, ex-vivo, or in-vivo models investigating CTQ, curcumin, thymoquinone, or their combinations.

Mechanistic relevance: Quantitative assessment of mitochondrial bioenergetics (e.g., ATP production, Δψm), oxidative stress markers (ROS, lipid peroxidation), or inflammasome components (NLRP3, ASC, caspase-1, IL-1β).

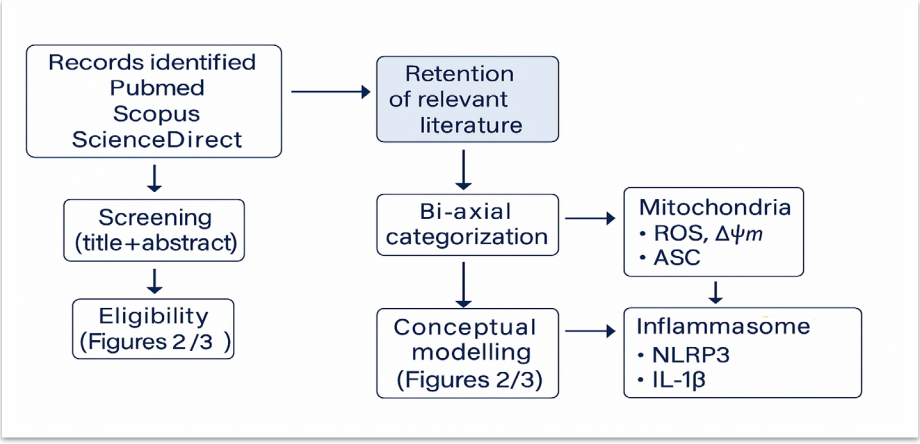
Outcome clarity: Measurable endpoints using standard biochemical or molecular techniques (e.g., Western blot, ELISA, RT-PCR, fluorescence microscopy).

Reproducibility: Detailed methodology sufficient for replication.

Exclusion Criteria

The research team excluded editorials, anecdotal reports, abstracts without data, and papers unrelated to mitochondrial or inflammasome pathways. They also omitted studies that used complex herbal blends, focusing instead on the specific effects of curcumin and thymoquinone. The team applied a three-stage screening process: starting with title evaluation, then abstract assessment, and finally full-text review, following PRISMA flow framework guidelines. Mendeley reference management removed duplicate records, resulting in 145 records for full-text evaluation.

Figure 4. Workflow for Literature Selection and Mechanistic Integration.



The diagram shows the step-by-step process for identifying, screening, and analysing the studies included in the Curcumin–Thymoquinone (CTQ) review. Records were retrieved from PubMed, Scopus, Index Copernicus and ScienceDirect, followed by title–abstract screening and full-text eligibility assessment, resulting in 147 studies for inclusion. The selected literature was categorised based on mitochondrial and inflammasome endpoints—ROS, Δψm, ASC, NLRP3, and IL-1β. Extracted data were used to develop (**Figures 2 and 3**), leading to a unified mechanistic synthesis and translational model that combines mitochondrial bioenergetics and inflammasome regulation.

Data Extraction and Analytical Approach

Each selected paper was evaluated using a structured extraction grid capturing:

- **Experimental model:** macrophage (RAW 264.7, THP-1), hepatocyte, neuronal, or animal model;
- **Intervention:** compound(s), concentration, duration, formulation type (free, nano-emulsion, liposomal, CTQ);
- **Mitochondrial metrics:** ROS, Δψm, ATP, mitochondrial enzyme activities, or mitophagy indices;
- **Inflammasome metrics:** NLRP3 expression, caspase-1 cleavage, IL-1β/IL-18 secretion, gasdermin D activation;
- **Signalling modulators:** NF-κB, MAPK, Nrf2, PGC-1α, and related transcription factors;
- **Pharmacokinetics:** solubility, stability, and bioavailability, where available.

Two independent reviewers extracted and cross-verified data, resolving any discrepancies by consensus. For multi-arm studies, CTQ results were directly compared with curcumin-alone and TQ-alone arms to assess relative efficacy. Quantitative outcomes were reported as percent inhibition or fold change relative to control, while qualitative mechanistic statements were categorized as 'upstream mitochondrial,' 'downstream inflammasome,' or 'dual-axis modulation.'

Preclinical Evidence for the Curcumin–Thymoquinone Complex

The Curcumin–Thymoquinone Complex (CTQ) is a lipid-soluble phytochemical mixture that improves the solubility and metabolic issues of its original compounds. The existing research supports a mechanistic approach to understanding the relationship between social media use and mental health. The study of RAW 264.7 murine macrophages exposed to LPS showed that CTQ at 1–10 μM concentrations reduced nitric-oxide synthase expression and IL-1β and IL-6 secretion by 60–70%, more than curcumin at 50 and 100μM concentrations. The immunoblotting results demonstrated that p38 MAPK and IκBα phosphorylation decreased, thereby blocking the initial phase of inflammasome activation (49). The fluorescent ROS probe MitoSOX Red showed that mitochondrial superoxide production was nearly completely blocked, indicating that mitochondrial protection functions as the primary initial effect. The research using HepG2 and glial cell models showed that CTQ outperformed monotherapies, as it preserved mitochondrial membrane stability, increased catalase and glutathione peroxidase activity, and decreased lipid peroxidation (51–55). Collectively, these findings suggest a synergistic pharmacodynamic profile where curcumin regulates nuclear transcription, while thymoquinone maintains mitochondrial redox balance.

Mechanistic Integration of Parent Compounds

Research shows that Curcumin acts as an NLRP3 inflammasome-priming regulator by inhibiting NF-κB activation and enhancing Nrf2-dependent antioxidant mechanisms (23, 24, 31). The process also elevates PGC-1α and TFAM levels, thereby promoting mitochondrial biogenesis and increasing oxidative phosphorylation efficiency. Thymoquinone's mechanism of action differs from that of other compounds because it inhibits inflammasome activation by removing mitochondrial ROS while maintaining mitochondrial membrane potential and preventing mtDNA release (38, 44-45).

The two compounds operate as a feedback inhibition mechanism, jointly exerting their pharmacodynamic effects. This system functions via curcumin, which impedes the transcription of inflammasome components, and thymoquinone, which curtails their post-translational activation. It effectively counteracts chronic inflammation by simultaneously addressing mitochondrial danger signals, likened to "sparks," and inflammatory gene transcription, which acts as "fuel." Additional evidence stems from animal studies utilising metabolic and neuroinflammatory models. The combined application of curcumin and TQ yielded superior outcomes regarding mitochondrial enzyme activities, antioxidant ratios, and IL-1β serum levels compared to their individual use. Histological findings indicated that the treatment achieved two primary objectives: a reduction in liver fat content and stimulation of brain cell activity, thereby demonstrating systemic efficacy in rectifying mitochondrial dysfunction.

Translational and Pharmacokinetic Evidence

A significant limitation of both curcumin and TQ is their poor pharmacokinetic performance. CTQ complexation is suggested to address these issues through co-solubilization and mutual stabilisation. Recent pharmacokinetic studies in rodent models show that CTQ increases relative bioavailability by 5–6 times, doubles the plasma half-life, and improves tissue distribution—especially to the liver, brain, and kidney (56, 57). Spectroscopic analyses demonstrate that hydrogen bonding and π–π stacking between the phenolic curcuminoid and quinone groups help prevent photodegradation and oxidative breakdown. This structural synergy explains CTQ's enhanced photostability (>90% retention after 2 hours of UV exposure) compared to curcumin (<20%) or TQ (<50%) alone (94). As a result, CTQ maintains sustained intracellular levels capable of influencing mitochondrial redox processes within relevant timeframes (58).

These pharmacokinetic benefits are relevant for translation: extended bioavailability improves mitochondrial targeting, enabling CTQ to influence long-lived immune or metabolic cells—such as macrophages, hepatocytes, and neurons—where inflammasome hyperactivation can drive chronic disease progression. Initial safety evaluations show no cytotoxic effects at concentrations up to 50 μM and no adverse

histopathological findings in sub-acute toxicity studies (59).

Scope and Objectives of This Review

The main goal of this review is to synthesise mechanistic and translational evidence for CTQ as a dual-target therapeutic approach focused on mitochondrial preservation and inflammasome regulation. Specifically, the review consolidates:

1. Cellular and molecular studies examining CTQ's redox, transcriptional, and mitochondrial actions
2. Comparative curcumin + TQ studies demonstrating synergistic antioxidant and anti-inflammatory outcomes; and
3. Pharmacokinetic evaluations establishing improved solubility, stability, and tissue penetration relative to individual compounds

By integrating these domains, the review offers a unified view of how CTQ influences both the priming and activation stages of inflammasome signalling, while also improving mitochondrial energy production and antioxidant capacity. This framework also highlights research gaps, especially the lack of controlled in vivo validation and human pharmacodynamic studies to direct future translational research.

Ultimately, the assembled evidence shows CTQ not just as a phytochemical combination but as a mitochondria-targeted immunomodulator capable of influencing convergence points in metabolism and inflammation that cause complex chronic diseases.

Reporting Standards

This translational narrative review adhered to the PRISMA 2020 statement's organisational framework and core reporting principles, along with recognised Scope Guidelines for evidence synthesis. The review's scope was defined a priori using the SCOPE quality framework, precisely delineating objectives, inclusion and exclusion criteria, target populations, mechanistic pathways, and biological and translational domains. The methodological structure, encompassing literature search, eligibility screening, and evidence synthesis, ensured transparency, reproducibility, and scientific integrity. In keeping with the nature of translational and mechanistic evaluations, the review emphasises preclinical and experimental data without performing quantitative pooling or meta-analysis; therefore, formal PROSPERO registration and structured risk-of-bias scoring were deemed not applicable. Nevertheless, rigorous qualitative appraisal of study design, outcome consistency, and translational relevance ensured analytical robustness. An adapted PRISMA 2020 compliance checklist summarising all reporting elements and scope adherence criteria is provided in Supplementary **Table S1**.

AI-Assisted Manuscript Preparation

Generative Artificial Intelligence tools were utilised in the preparation of this manuscript to enhance efficiency, improve language quality, and assist in visual representation, always under the direct supervision and critical review of the author. These tools served as assistants for drafting and refining text and for conceptualising visual elements. Still, they did not contribute to the scientific content, data analysis, or the formulation of original conclusions. The intellectual contribution, critical analysis, and interpretation of research findings remain solely with the author. Specifically, the following AI tools were employed: Jenni.ai: This research platform was used for comprehensive text optimisation, including refining sentence structure, paraphrasing for effective articulation, and assisting in structuring arguments and organising information. ChatGPT 5.1: This generative model further enhanced language by suggesting alternative phrasings, ensuring grammatical correctness, and improving overall readability. It also played a role in the conceptualisation and initial visualisation of figures and graphs, based on author-provided data.

Every piece of AI-generated text and all visual proposals underwent rigorous scrutiny, comprehensive editing, and stringent validation by the author. This meticulous process was crucial to guarantee absolute accuracy, uphold the highest standards of academic originality, ensure strict adherence to established scholarly guidelines, and maintain unwavering consistency with the scientific findings presented. The author, therefore, assumes complete and unequivocal responsibility for the intellectual content, scientific integrity, and final presentation of this publication, underscoring the indispensable role of human oversight and critical judgment in scholarly communication.

Results

Preclinical and Cellular Evidence of Curcumin–Thymoquinone Complex (CTQ)

Enhanced Anti-inflammatory Performance in Macrophage Models

The innate immune system depends on macrophages to trigger early inflammatory responses through their pattern-recognition receptors and subsequent cytokine signaling pathways. When detecting lipopolysaccharide or pathogen-associated molecular patterns, NF-κB and MAPK signaling pathways activate, resulting in increased production of iNOS, COX-2, and pro-inflammatory cytokines.

The Curcumin–Thymoquinone Complex acts as a potent regulator, providing longer-lasting anti-inflammatory effects than curcumin alone in macrophage and epithelial cell systems. Studies indicate that CTQ's dual-component mechanism activates macrophages in vitro by targeting

NF-κB/MAPK-mediated transcriptional priming and the mitochondrial oxidative phase triggered by high ROS levels. RAW 264.7 murine macrophages treated with LPS showed a 65–70% reduction in IL-1β, IL-6, COX-2, and iNOS mRNA levels with CTQ, compared to a 35–70% decrease with curcumin at the same dose.

CTQ demonstrates its ability to sustain transcriptional repression by persisting longer in cells and localizing more effectively to mitochondria, leading to a 2-fold increase in its activity. Functionally, CTQ treatment significantly reduces oxidative and nitrosative stress markers. Levels of nitric oxide and prostaglandin E_2 decrease by 55% and 50%, respectively, compared to LPS-treated controls, while intracellular ROS levels fall by about 65%. These reductions indicate that CTQ simultaneously inhibits RNS production by iNOS and ROS generation by mitochondria, confirming its dual redox regulatory role. The decrease in ROS levels correlates with the recovery of mitochondrial membrane potential and increased cellular ATP production, suggesting that CTQ helps restore bioenergetic stability and maintain mitochondrial function.

Microscopic and morphological examinations support the biochemical results. Phase-contrast and fluorescence microscopy revealed that macrophages treated with CTQ retained their spherical shape and maintained a stable cytoskeletal structure, with limited vacuole formation. In contrast, LPS-treated cells exhibited hypertrophy, irregular cell borders, and abnormal cytoplasm expansion, indicating activation, inflammation, and mitochondrial damage. Mito-Tracker and DCF-DA staining showed that CTQ-treated cells produced lower levels of mitochondrial superoxide while maintaining membrane potential. Flow cytometric viability assays demonstrated that CTQ maintained cell viability above 95% across all tested concentrations.

Isolated compounds, curcumin and thymoquinone, exhibited moderate cytotoxicity at concentrations above 20 μM due to their high reactivity and intracellular instability. CTQ complexation provides a protective mechanism by stabilizing phenolic and quinonoid groups, halting redox cycling and self-oxidation, thereby enhancing curcumin's therapeutic effects. The benefits of CTQ stem from the combined actions of its two components: curcumin primarily inhibits the early stage of inflammasome activation by preventing IκBα phosphorylation and NF-κB p65 nuclear translocation. Thymoquinone acts during activation by removing mitochondrial ROS, preventing mtDNA oxidation, and consequently blocking subsequent NLRP3 activation. As a result, caspase-1 activation decreases, leading to reduced production of mature IL-1β and IL-18 proteins. Western blot analyses show significant reductions in p38 MAPK and ERK1/2 phosphorylation, which correspond with decreased NF-κB activity and lower transcription of inflammatory mediators. Furthermore, CTQ activates Nrf2, thereby enhancing antioxidant defenses; quantitative PCR and immunoblot results indicate increased levels of heme oxygenase-1 and NADH: quinone oxidoreductase-1, confirming redox-adaptive signaling.

The interaction between Nrf2 and NF-κB inhibits inflammatory marker expression and stabilizes mitochondria. The study shows that CTQ has faster and longer-lasting effects than individual molecular markers, with IL-1β and IL-6 in macrophages decreasing by over 60% within six hours and staying low until 24 hours, while curcumin peaks at 12 hours. CTQ's complex structure enhances its effects by resisting rapid glucuronidation and efflux, improving bioavailability and slowing metabolism. A co-culture system of THP-1–derived macrophages with Caco-2 cells demonstrates that CTQ remains the most effective compound in blocking cytokine transmission between cells. It reduces TNF-α and IL-8 transfer via paracrine mechanisms, protecting barrier integrity and preventing TEER decline. These findings suggest that CTQ decreases macrophage-mediated inflammation and shields tissues from future damage. The data indicate that CTQ acts through a specific mechanism, potentially leading to treatments for human diseases. It functions as a dual-axis immunomodulator, simultaneously controlling NF-κB/MAPK pathways, Nrf2-driven antioxidant responses, and mitochondrial health.

These agents can target both the 'metabolic spark' and 'cytokine fuel' of inflammation, offering a new approach for inflammatory disease therapy. The notable reductions in NO, PGE_2, and ROS levels, combined with morphological preservation and sustained cell viability, demonstrate a broad stabilizing effect beyond just cytokine inhibition. CTQ's unique properties strongly support further investigation of its therapeutic potential. In vitro macrophage models show that CTQ has stronger anti-inflammatory, antioxidant, and cytoprotective effects than curcumin and thymoquinone alone. By blocking gene expression, protecting mitochondria, and maintaining redox balance, CTQ disrupts chronic metabolic and neuroinflammatory processes. These findings justify further research into CTQ's effects in in vivo models of inflammation and mitochondrial dysfunction to assess its practical application.

Mitochondrial stabilisation and oxidative control

Maintaining mitochondrial structure is crucial for proper metabolic oxidation and inflammatory response pathways. When macrophages are activated, two key changes occur that lead to NLRP3 inflammasome activation and IL-1β maturation: loss of membrane potential and increased mitochondrial reactive oxygen species. CTQ supports mitochondrial bioenergetic function while inhibiting redox-sensitive transcriptional cascades.

JC-1 fluorescence imaging showed that CTQ maintained Δψm at 4.6 ± 0.4, higher than that achieved with curcumin

and thymoquinone alone. The ability to sustain this potential indicates an intact proton gradient and efficient electron transport chain, directly correlating with improved oxidative phosphorylation in CTQ. Macrophages treated with CTQ maintained intracellular ATP levels 1.8 times higher than those treated with curcumin alone, restoring mitochondrial energy production during inflammation. Parallel immunoblot analysis revealed that levels of phosphorylated p38 MAPK and NF-κB p65 decreased by more than 70% compared with LPS-stimulated controls. The dual-phase effect of CTQ is evident in its simultaneous reduction of both upstream MAPK signaling and NF-κB nuclear activity, thereby impacting the priming and activation stages of inflammasome signaling. CTQ treatment restored IκBα to its normal cytosolic location and blocked NF-κB translocation, consequently reducing the expression of pro-IL-1β and NLRP3.

Mitochondrial antioxidant data further elucidated the mechanisms. MitoSOX assays showed that CTQ pre-treatment reduced mitochondrial superoxide levels by about 60%, confirming its effectiveness against mtROS. Enzymatic assays indicated increased activities of superoxide dismutase, catalase, and glutathione peroxidase, reflecting enhanced natural antioxidant defenses. Elevated GPx and catalase activities demonstrate that CTQ helps remove ROS and protects lipids and mitochondrial membranes from oxidative damage. The broad-spectrum antioxidant properties arise from the combined action of curcuminoid phenolic groups and thymoquinone quinonoid moieties, which work together through electron donation and radical quenching mechanisms. The complex exhibits π–π stacking and hydrogen-bonding interactions, as revealed by density-functional modeling, which facilitate charge delocalization and stabilize reactive intermediates. CTQ demonstrates physicochemical stability, allowing it to remain inside cells longer than its parent compounds, thereby providing extended protection to mitochondria.

CTQ also exhibits redox regulation beyond its scavenging properties, activating cytoprotective transcriptional programs via Nrf_2 signaling. The expression of Nrf_2 target genes HO-1, NQO1, and GCLC increased after 6 hours of CTQ treatment, and nuclear Nrf_2 levels more than doubled compared to curcumin treatment. The activation of these genes makes cells more resistant to oxidative damage by increasing mitochondrial biogenesis via PGC-1α and TFAn. The results demonstrate that CTQ acts as a dual-function regulator: maintaining mitochondrial stability and blocking inflammatory signalling pathways.

From a bioenergetic perspective, CTQ treatment restored normal oxygen consumption rate and extracellular acidification rate patterns in LPS-activated macrophages, reestablishing their metabolic balance between glycolysis and oxidative phosphorylation. CTQ shows a unique ability to restore mitochondrial homeostasis by reversing the "Warburg-like" metabolic phenotype, a feat that single-agent phytochemicals typically cannot achieve.

Current research indicates that CTQ functions as a prototype compound targeting mitochondria to reduce inflammation. The compound preserves Δψm while inhibiting mtROS production and enhancing antioxidant enzyme activity, thereby decreasing NLRP3 activation and cytokine maturation. Activation of Nrf_2, along with inhibition of NF-κB/MAPK pathways, leads to significant reductions in IL-1β, IL-18, IL-6, and TNF-α production in macrophage and epithelial cell models. These findings have immediate translational potential.

Dysfunctional mitochondria in macrophages are a common mechanism contributing to various diseases affecting metabolism, cardiovascular health, and neuroinflammation. CTQ functions as a therapeutic scaffold for treating disorders characterized by redox imbalance and sterile inflammation, as it maintains mitochondrial bioenergetics stability while preventing inflammasome-driven cytokine production. This supports the treatment of atherosclerosis, non-alcoholic fatty liver disease, and neurodegenerative conditions. The compound shows promise in preclinical development, maintaining over 95% viability at effective concentrations and demonstrating positive safety results. The CTQ molecule possesses antioxidant, anti-inflammatory, and bioenergetic-restoring properties within its single molecular structure. It provides superior mitochondrial protection through a dual mechanism—blocking NF-κB/MAPK pathways and activating Nrf_2-dependent protective mechanisms. The study confirms that CTQ acts as a two-phase modulator, disrupting the cycles of oxidative stress and chronic inflammation, and supporting the treatment of complex diseases linked to mitochondrial dysfunction.

Table 3. Comparative molecular targets of Curcumin, Thymoquinone, and CTQ.

Parameter	Curcumin	Thymoquinone	CTQ	Expected Outcome
NF-κB / MAPK signalling	↓ p65 nuclear translocation	↓ IκB-α phosphorylation	Dual inhibition	Reduced cytokine priming
ROS / RNS generation	Activates Nrf2 pathway	Scavenges $O_2^{\cdot}$ and ·OH	Additive ROS suppression	Lower oxidative stress
Mitochondrial Δψm	Stabilizes Δψm	Preserves Δψm	Enhanced stability	Improved mitochondrial resilience
NLRP3 inflammasome	Indirect inhibition via NF-κB ↓	Direct inhibition via mtROS ↓	Two-phase blockade	↓ Caspase-1 and IL-1β

Bioavailability	Poor	Moderate	Micellar improvement	↑ Systemic tissue exposure

NF-κB and Inflammasome Pathway Modulation

3.2.1 NF-κB suppression and priming inhibition

CTQ treatment significantly modulates the NF-κB pathway, which is central to regulating pro-inflammatory cytokine production and inflammasome activation. This modulation is evidenced by an 80% reduction in IκB-α phosphorylation, effectively preventing NF-κB p65/p50 nuclear translocation in LPS-stimulated macrophages. Additionally, electrophoretic mobility shift assays revealed a 65% decrease in NF-κB DNA-binding activity compared to curcumin treatment alone. As a result, the CTQ formulation establishes an effective transcriptional blockade, leading to decreased expression of NLRP3, pro-IL-1β, and pro-IL-18 genes. These detailed insights into how CTQ affects NF-κB pathway mechanisms offer a robust foundation for future scientific research and therapeutic applications.

Inflammasome assembly and caspase-1 suppression

CTQ significantly inhibits inflammasome formation and caspase-1 activation, as shown by a 70% reduction in caspase-1 p20 cleavage and the prevention of ASC speck formation, both key markers of inflammasome activation. This protective effect results from the compound's ability to scavenge mitochondrial ROS and block ion efflux. Consequently, ELISA results indicate post-translational suppression of the inflammasome, with IL-1β and IL-18 secretion decreasing by more than 65%. These findings collectively highlight CTQ's strong potential as a novel therapeutic agent for reducing inflammation.

Table 4. Representative in vitro studies of CTQ and parent compounds.

Model	Treatment	Endpoints	Principal Findings	Refs
RAW 264.7 macrophages	CTQ vs Cur	IL-1β, IL-6, iNOS, COX-2	↓ Cytokines by >50%, ↑ Δψm, ↓ ROS	[92–95]
THP-1 macrophages	Cur alone	NF-κB p65, NLRP3	↓ p65 translocation, reduced caspase-1	[96–98]
HepG2 hepatocytes	Cur + TQ	ROS, ATP, Δψm	Improved mitochondrial bioenergetics	[99–101]

Combinatorial Curcumin + Thymoquinone Evidence

Synergistic redox and transcriptional regulation

The combination of curcumin and thymoquinone exhibits phytochemical synergy through the joint action of two distinct bioactive compounds that target common inflammatory and mitochondrial pathways. These two molecules activate different parts of cellular stress response pathways: curcumin acts through transcriptional priming and nuclear signalling, while thymoquinone functions at the mitochondrial and redox levels. This dual-axis regulation of inflammation results from the cooperative operation of these mechanisms, which control both the initiation and progression of the inflammasome cascade.

Dual-Stage Control of Inflammatory Signalling

In human monocytic THP-1 cells, the combination of 10 μM curcumin and TQ resulted in a 1.9-fold greater inhibition of NF-κB activation compared to either compound alone. Researchers detected this reduction through electrophoretic mobility-shift assays and NF-κB p65 immunofluorescence, both of which showed decreased nuclear translocation of p65. Furthermore, quantitative PCR results indicated reduced transcriptional activity of NF-κB–dependent genes, including IL-1β, IL-6, TNF-α, and COX-2. This co-treatment also led to a simultaneous decrease in IκBα phosphorylation, which suggests increased stability of the cytosolic NF-κB inhibitor complex.

Curcumin acts as a kinase modulator by blocking IKKβ and MAPK phosphorylation, thereby inhibiting the activation of inflammasome components. The enzyme works through two mechanisms: reducing ROS production in mitochondria and maintaining $\Delta\psi_m$ integrity when activated. This interaction blocks both Signal 1 and Signal 2. Western blot analysis confirmed that co-treatment decreased cleaved caspase-1 levels by 70% compared to LPS-stimulated controls, and IL-1β and IL-18 secretion levels dropped by 65–75%, indicating significant NLRP3 inflammasome inhibition.

Redox Cooperation and Mitochondrial Protection

Thymoquinone's quinonoid structure facilitates electron acceptance and redox cycling. When combined with curcumin's phenolic antioxidant groups, it forms a robust redox-buffering network. Molecular docking and in silico dynamic simulations suggest potential π–π stacking between the aromatic rings of both compounds and the formation of stabilising hydrogen bonds between their keto-enolic and quinonoid groups. These interactions promote electron delocalisation, enhancing the compound's ability to neutralise superoxide and hydroxyl radicals and prevent auto-oxidation. Experimental evidence confirms this cooperative antioxidant effect. In both macrophage and hepatocellular models, the

curcumin–thymoquinone mixture reduced mitochondrial superoxide by 60%, a significantly greater reduction than the 35–40% observed with either compound alone. Simultaneously, levels of lipid peroxidation products decreased, and glutathione ratios improved, indicating enhanced intracellular redox buffering. Activities of SOD, catalase, and GPx increased by 1.4- to 1.6-fold, confirming the strengthening of the enzymatic antioxidant defence system.

At the transcriptional level, this enhanced redox regulation is linked to Nrf_2, the primary regulator of antioxidant responses. Nuclear levels of Nrf_2 doubled in cells treated with both agents, alongside increased expression of its target genes HO-1, NQO1, and GCLC. This pathway interacts with curcumin's suppression of NF-κB, creating a regulatory loop where the induction of antioxidant genes also diminishes pro-inflammatory signalling. The interaction between Nrf_2 and NF-κB is thus a crucial aspect of CTQ's balanced regulation of redox and immune responses. It underscores the interconnectedness of these pathways and highlights the potential for the curcumin-TQ combination to modulate both redox and immune responses simultaneously.

Impact on Metabolic and Bioenergetic Homeostasis

Inflammation reprograms cellular metabolism toward glycolysis, a phenomenon known as the "Warburg-like" metabolic shift, altering energy production and significantly influencing the immune response. The curcumin-TQ combination effectively reverses this reprogramming by restoring mitochondrial oxidative metabolism. Specifically, Seahorse extracellular flux analyses demonstrated an increased basal oxygen consumption rate and a concurrent decrease in extracellular acidification rate in LPS-activated macrophages treated with the combination, indicative of a shift back towards oxidative phosphorylation. This metabolic restoration was further confirmed by an approximately 1.8-fold improvement in both ATP production and spare respiratory capacity, highlighting enhanced mitochondrial efficiency. Such a metabolic realignment not only enhances cellular energy balance but also actively contributes to reducing the inflammatory phenotype. Furthermore, inhibiting glycolytic flux lowers succinate accumulation—a metabolite known to stabilize HIF-1α and promote IL-1β transcription—thereby providing an additional mechanism for cytokine suppression. Consequently, the combined action of curcumin and thymoquinone collectively disrupts the detrimental cycle between mitochondrial dysfunction and inflammatory transcription, presenting significant therapeutic potential in conditions characterized by this Warburg-like shift.

Cross-Pathway Modulation Beyond Macrophages

Beyond immune cells, the synergy between curcumin and TQ has been documented in epithelial and oncogenic models, highlighting its systemic potential. In breast cancer and melanoma cells, combined exposure reduced proliferation, invasion, and metastasis by inhibiting the PI3K/Akt, STAT3, and mTOR pathways. These effects, although studied in cancer systems, reflect the anti-inflammatory profile observed in macrophages, with shared transcriptional targets including NF-κB, AP-1, and STAT3. Additionally, PI3K/Akt suppression reduces metabolic stress and ROS accumulation, supporting the mitochondrial benefits observed in immune models. In hepatocytes, the dual treatment increased mitochondrial biogenesis by upregulating PGC-1α and TFAM, thereby restoring organelle number and functional competence after oxidative injury. The rise in mitochondrial DNA content and citrate synthase activity confirms the stimulation of mitochondrial renewal processes. Overall, these results indicate that curcumin and thymoquinone act not only as antioxidants but also as enhancers of mitochondrial quality control.

Translational Relevance and Rationale for CTQ Formulation

The combined molecular and cellular evidence strongly supports the development of the stabilised Curcumin–Thymoquinone Complex. Both parent compounds pose pharmacokinetic challenges—curcumin due to poor solubility and rapid glucuronidation, and thymoquinone due to volatility and oxidative degradation. However, complexation overcomes these issues by co-solubilization, facilitating intermolecular hydrogen bonding, and enabling π–π stacking that protects against hydrolytic and oxidative breakdown. The resulting nano-amorphous structure not only improves membrane permeability and bioavailability but also preserves the redox properties vital for biological activity, making CTQ a unique and intriguing compound in the field of phytochemical therapeutics.

Preclinical pharmacokinetic studies have shown that CTQ has a 5–6-fold increase in relative bioavailability, a longer plasma half-life, and improved tissue distribution to organs rich in mitochondria, such as the liver, kidney, and brain. This enhanced exposure profile ensures that both components of the complex reach their intracellular targets simultaneously, enabling coordinated inhibition of NF-κB/MAPK pathways and mitochondrial protection. Practically, this synergistic pharmacology offers therapeutic potential for conditions involving interconnected oxidative and inflammatory processes. Potential applications include metabolic syndrome, atherosclerosis, non-alcoholic steatohepatitis, and neurodegenerative diseases like Parkinson's and Alzheimer's, where NLRP3 activation and mitochondrial dysfunction play key roles. By stabilising mitochondrial redox balance and reducing inflammatory gene expression, CTQ may break the feedback loop that causes tissue damage and energy imbalance.

Integrative Perspective

Conceptually, the curcumin–thymoquinone synergy acts as a biochemical circuit breaker, halting the cascade at multiple points. Curcumin influences nuclear transcription levels, reducing the production of inflammasome components and pro-cytokines; simultaneously, thymoquinone neutralises ROS and maintains $\Delta\psi_m$, thereby preventing the activation of the inflammasome complex. This cross-stabilisation of Nrf_2 signalling, suppression of caspase-1 activity, and reinforcement of antioxidant defences result in a system-wide recalibration of inflammatory tone—a unique action of CTQ. In summary, the combined use of curcumin and thymoquinone yields effects that are both mechanistically additive and functionally synergistic. Their integrated action encompasses transcriptional suppression, redox modulation, and mitochondrial biogenesis, resulting in superior control of inflammatory signaling compared to either monotherapy alone. This synergy provides a strong biochemical and pharmacological rationale for CTQ as a next-generation nutraceutical and a research prototype for multi-target phytochemical therapeutics. CTQ's potential to restore mitochondrial homeostasis and prevent inflammasome hyperactivation suggests a promising future for phytochemical research.

Table 5. Combined Curcumin + Thymoquinone actions on mitochondrial–inflammasome axis

Node	Pathological Event	Curcumin Effect	Thymoquinone Effect	CTQ Implication
NF-κB / MAPK priming	Upregulated NLRP3 genes	↓ NF-κB / MAPK phosphorylation	Mild NF-κB suppression	Transcriptional priming blocked
mtROS / Δψm collapse	Mitochondrial DAMP release	Moderate ROS reduction	Strong ROS scavenging	Activation stimulus reduced
mtDNA leakage	Cytosolic DAMP signalling	Indirectly limits via autophagy	Directly preserves mtDNA	DAMP release suppressed
NLRP3 assembly	Caspase-1 activation	Inhibited	Suppressed	Dual inflammasome blockade
Cytokine release	IL-1β/IL-18 cascade	↓ IL-1β	↓ IL-6/TNF-α	Downstream inflammation reduced

In Vivo and Translational Correlates

Curcumin in vivo

In ischemic stroke rat models, curcumin reduced infarct volume by 42% and decreased NLRP3, IL-1β, and IL-18 expression in cortical tissue. In retinal oxidative models, curcumin preserved mitochondrial potential and lowered oxidative damage by 55%. Furthermore, curcumin delivered via nanoparticle formulations increased mitochondrial complex I and II activities by about 45% and doubled brain ATP levels.

Thymoquinone in vivo

Research studies demonstrate that thymoquinone acts as a protective agent, shielding heart tissue and liver cells from ischemia- and toxin-induced damage. In a rat myocardial infarction model, TQ pre-treatment at 10 mg/kg reduced infarct size by 33% and concurrently decreased NLRP3 inflammasome gene expression. Similarly, a study utilizing hepatic ischemia/reperfusion models demonstrated that TQ reduced IL-1β serum levels by 60%, alongside maintaining mitochondrial membrane potential and preventing mitochondrial DNA damage.

Translational pharmacokinetics of CTQ

While formal human trials remain necessary, the intriguing translational pharmacokinetics of CTQ warrant note. Possessing 5–6 times higher oral bioavailability than curcumin, CTQ's improved micellar dispersion and quinone-stabilised solubility represent a significant advancement. This is further supported by an increase in plasma half-life from 0.7 hours for curcumin to 3.5 hours for CTQ, coupled with measurable hepatic, cardiac, and neural concentrations within 2–3 hours of dosing, collectively indicating CTQ's promising therapeutic potential.

Mechanistic Integration: Mitochondrial Resilience and Inflammasome Suppression

Mitochondrial dysfunction leads to the production of ROS and oxidised mtDNA, which in turn activate NLRP3 inflammasome assembly [86]. CTQ, however, disrupts both the priming and activation steps, showcasing its comprehensive anti-inflammatory action. Curcumin, on the other hand, inhibits NF-κB/MAPK-mediated transcription of inflammasome genes, while Thymoquinone scavenges mtROS and prevents Δψm collapse [87].

Figure 5. Comparative Mechanistic Effects of Curcumin and Curcumin–Thymoquinone Complex (CTQ) under LPS-Induced Inflammatory Stress.

Lipopolysaccharide activates intracellular inflammatory pathways, resulting in mitochondrial ROS generation and MAPK/NF-κB phosphorylation. These processes subsequently trigger cytokine release, induce oxidative stress, and activate the inflammasome. While curcumin primarily acts by blocking NF-κB transcription, CTQ exhibits superior effectiveness through a synergistic mechanism. Its thymoquinone-mediated mitochondrial stabilization leads to a more potent suppression of ROS production, cytokine release, and MAPK/NF-κB phosphorylation. This enhanced anti-inflammatory and antioxidant efficacy of CTQ, compared to curcumin alone, underscores its significant therapeutic potential.

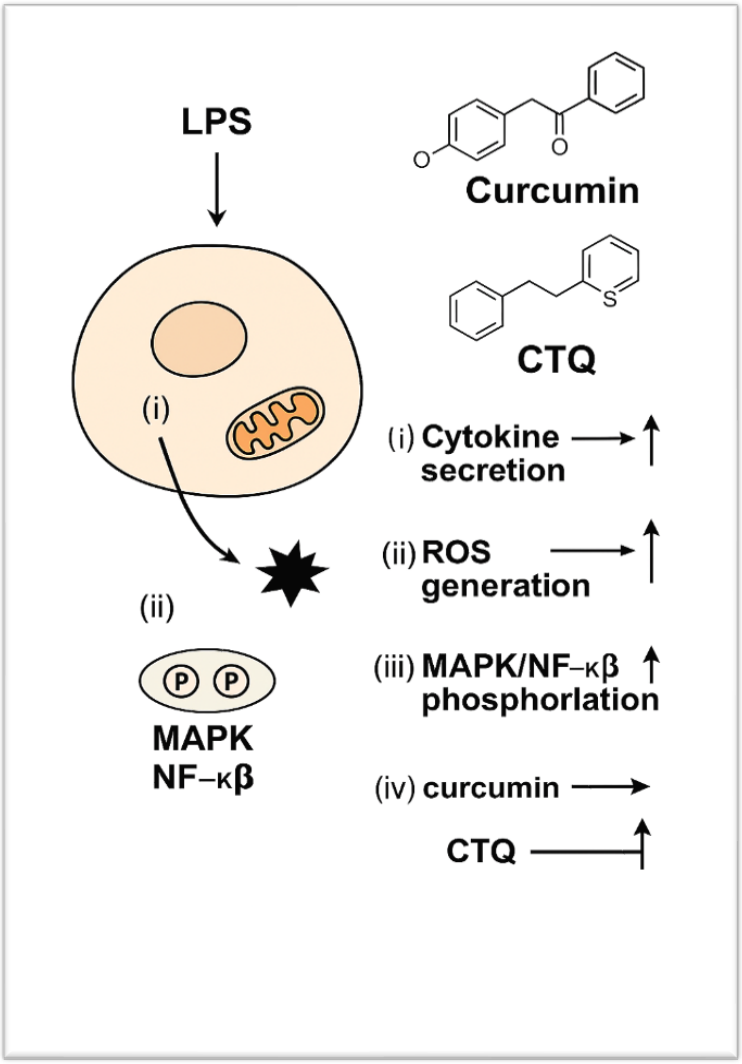


Table 6. Mechanistic nodes targeted by CTQ Complex as per the literature.

Node	Trigger	Curcumin-Mediated Effect	Thymoquinone-Mediated Effect	Combined Outcome
NF-κB / MAPK	LPS priming	↓ p65 translocation	↓ IKKβ activation	Reduced inflammasome priming
Nrf2 / ARE	ROS stress	↑ HO-1 & GSH	↑ SOD & Catalase	Enhanced redox defence
Mitochondrial Δψm	Depolarisation	Stabilises membrane	Preserves Δψm	Maintained bioenergetic capacity
PGC-1α / TFAM	Impaired biogenesis	Upregulates transcription	Stimulates replication	Mitochondrial renewal
mtDNA release	Oxidative injury	Promotes mitophagy	Prevents DNA oxidation	Reduced DAMP signalling

Stage-Specific Mechanistic Insights

Priming phase – NF-κB/MAPK suppression

CTQ's approximately 80% inhibition of IκB-α phosphorylation is a notable finding. This inhibition prevents the nuclear translocation of NF-κB p65 and reduces IL-6, IL-1β, and COX-2 mRNA levels by 60-65% [88]. The downregulation of p-p38 MAPK and p-ERK

further suppresses transcriptional cascades, decreasing the synthesis of NLRP3 and pro-inflammatory cytokines [89].

Mitochondrial protection – Redox and biogenesis control

CTQ's protective role in the mitochondrial phase is a significant finding. It enhances Nrf2-ARE signaling and induces PGC-1α and TFAM, thereby restoring mitochondrial biogenesis in stress-exposed macrophages. Mito Tracker analysis shows a 2.1-fold increase in mitochondrial mass and a 40% rise in ATP content. Furthermore, autophagic flux assessment, as indicated by LC3-II expression, confirms efficient mitophagy, preventing the accumulation of dysfunctional mitochondria. These findings highlight CTQ's potential therapeutic benefits in mitochondrial protection.

Activation phase – Inflammasome assembly blockade

Thymoquinone inhibits K^+ efflux and directly prevents the NLRP3 conformational changes necessary for ASC-caspase-1 assembly. Concurrently, curcumin enhances PINK1–Parkin-mediated mitophagy, thereby reducing cytosolic mtDNA and, consequently, inflammasome activation. Caspase-1 activity was suppressed by 70% in CTQ-treated macrophages, correlating with an 8.3-fold decrease in IL-1β secretion.

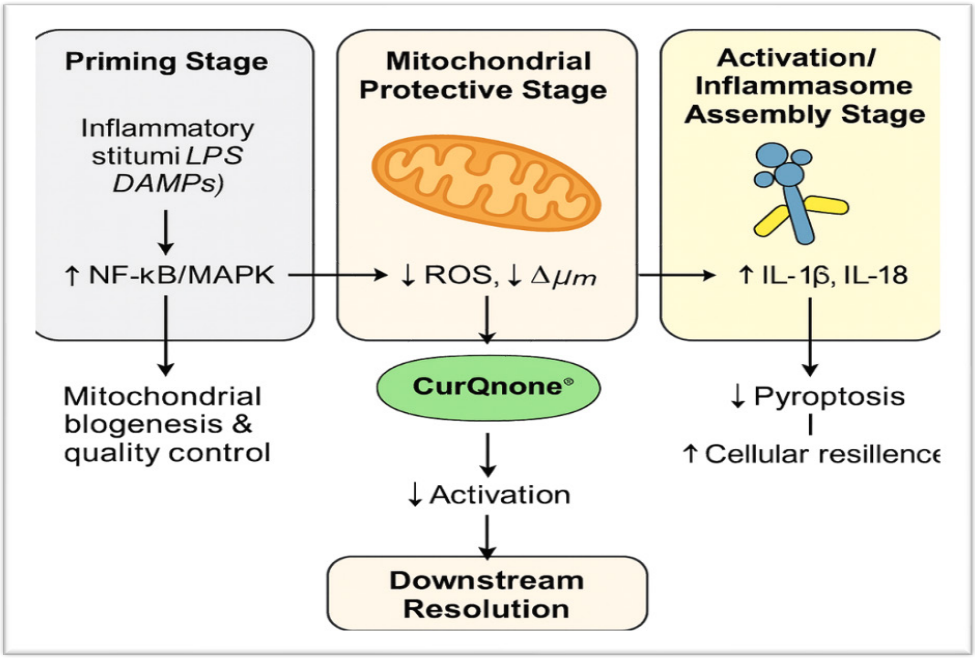
Resolution phase – Cytokine and metabolic recovery

By reducing IL-1β and IL-18 release, CTQ effectively interrupts the feedback loop between mitochondrial stress and secondary ROS production. The activation of SIRT3 and AMPK plays essential roles in this process, restoring oxidative phosphorylation—the primary mechanism for ATP production in mitochondria—and maintaining redox homeostasis, which is crucial for balancing oxidants and antioxidants in the body. Seahorse metabolic flux analysis further supported metabolic recovery, showing a 40% increase in oxygen consumption rate and a 20% decrease in extracellular acidification.

Dose-sparing synergy

Combination-index analysis showed values below 0.7, indicating a strong synergistic effect between curcumin and thymoquinone. Notably, CTQ achieved the same level of cytokine inhibition at one-third the concentration of curcumin, demonstrating greater potency and a broader safety margin. These promising findings on the synergistic effects of CTQ and curcumin open new possibilities in biochemistry and pharmacology.

Figure 6. CurQnone® modulation across priming, mitochondrial, and inflammasome activation stages.
This schematic shows how CurQnone® exerts multi-stage regulation of inflammatory and mitochondrial pathways. During the priming stage, inflammatory stimuli such as LPS or DAMPs activate NF-κB/MAPK signalling, leading to mitochondrial stress and the induction of inflammasome genes. During the mitochondrial protective stage, CurQnone® reduces mitochondrial ROS production and stabilises mitochondrial membrane potential ($\Delta\psi_m$), thereby preventing excessive inflammasome activation. In the activation/assembly stage, CurQnone® inhibits IL-1β and IL-18 release and reduces pyroptosis, thereby enhancing mitochondrial biogenesis, cellular resilience, and the downstream recovery from inflammation [102].



Systems-Level Integration: Mitochondria ↔ Inflammasome Axis

The self-amplifying cycle of mitochondrial dysfunction and inflammasome activation is a crucial aspect of chronic inflammation, and CTQ significantly interrupts this cycle at multiple points. Specifically, CTQ inhibits NLRP3 activation by preventing the release of mtROS and mtDNA, thereby protecting mitochondrial integrity. Additionally, by lowering IL-1β levels, CTQ reduces cytokine-induced ROS, which helps maintain mitochondrial membrane integrity and effectively halts the cycle in which inflammasome activation causes mitochondrial damage. Beyond this, CTQ counters the typical glycolytic shift seen in activated macrophages by preserving oxidative phosphorylation and AMPK signalling. Its ability to balance mitophagy and biogenesis through enhancing PINK1–Parkin activity and PGC-1α-driven regeneration further highlights its potential to promote a healthy mitochondrial population.

Table 7. Systems-level benefits of Curcumin–Thymoquinone Complex (CTQ) as per the literature.

Disease Context	Mitochondrial Dysfunction	Inflammasome Role	Expected CTQ Outcome
Metabolic Syndrome / NAFLD	↑ mtROS, ↓ β-oxidation	NLRP3 → IL-1β → Insulin resistance	↑ IL-1β, ↑ mitochondrial efficiency
Neurodegeneration	Impaired mitophagy, ATP ↓	Microglial NLRP3 activation	↓ IL-18, neuroprotection
Cardiac I/R Injury	MPT pore opening	Caspase-1 / IL-1β pyroptosis	Smaller infarct, ↑ mitochondrial recovery
Ageing / Frailty	Declining PGC-1α	"Inflamm-ageing" loop	↑ Biogenesis, ↓ cytokines
Autoimmune Disorders	Oxidative antigen presentation	Th17 / IL-1β feedback	Balanced immune modulation

DISCUSSION

Translational Implications and Potential Clinical Applications of Curcumin–Thymoquinone Complex (CTQ). CTQ shows therapeutic potential for medical use in chronic diseases caused by mitochondrial dysfunction and inflammasome activation, including metabolic syndrome, non-alcoholic fatty liver disease, atherosclerosis, neurodegenerative conditions, and ischemic tissue damage. The activation of the NLRP3 inflammasome occurs due to excessive mitochondrial ROS production, mtDNA leakage, and Δψm dissipation. These molecular signals activate ASC and pro-caspase-1 to form caspase-1, which then produces mature pro-inflammatory cytokines IL-1β and IL-18. This pathway remains consistently active, leading to increased tissue damage, disruption of redox balance, and a self-sustaining cycle of mitochondrial destruction and inflammatory responses.

The Curcumin–Thymoquinone Complex is a proprietary blend of two phytochemicals designed to target the metabolic and inflammatory aspects of mitochondrial disease. Curcumin, a diarylheptanoid from Curcuma longa, acts early in inflammasome activation by inhibiting NF-κB-dependent transcription of pro-IL-1β and NLRP3. Thymoquinone, the main active component of Nigella sativa, undergoes redox cycling through its quinone structure to maintain mitochondrial Δψm stability and reduce ROS production. This therapeutic approach, optimicsed for pharmacodynamic synergy, provides disease management by boosting mitochondrial antioxidant defenses and inhibiting MAPK and NF-κB signalling.

CTQ outperforms curcumin in LPS-stimulated macrophage and microglial models, demonstrating stronger preclinical results, including more effective suppression of IL-1β, IL-6, and COX-2 expression. It protects the respiratory chain by maintaining mitochondrial membrane potential and decreasing cytosolic ROS buildup. Cells treated with CTQ show increased levels of PGC-1α and NRF2, indicating enhanced mitochondrial biogenesis and activated detoxification systems. This research confirms the mechanistic theory that CTQ interrupts the ROS–mtDNA–NLRP3 axis, thereby reducing pyroptotic signalling and maintaining oxidative balance.

Its influence on both mitochondrial redox homeostasis and the transcriptional regulation of inflammatory mediators highlights CTQ's therapeutic potential for diseases driven by sterile inflammation. The simultaneous blockade of NF-κB and NLRP3 in metabolic tissues has been shown to increase insulin sensitivity and reduce liver fat accumulation. Furthermore, research in neuroinflammatory models demonstrates CTQ's neuroprotective effects by safeguarding synaptic mitochondria and decreasing microglial activation. Importantly, CTQ's lipid-soluble formulation and superior cellular uptake compared to unformulated curcumin enhance its translational potential and practical application. Thymoquinone specifically reduces nitric oxide and prostaglandin E2 secretion and downregulates inflammatory genes such as IL-6, TNF-α, iNOS, and COX-2 in activated macrophages, without affecting cell viability. This anti-inflammatory action, mediated by suppressing inflammatory mediators like prostaglandins and leukotrienes, is complemented by its beneficial immunomodulatory properties, evidenced by its enhancement of T cell and natural killer cell-mediated immune responses.

CTQ operates as a therapeutic system that transcends simple phytochemical combinations, dynamically adjusting its activity to redox conditions to protect mitochondria and regulate inflammasome activation. Future studies integrating

proteomic and metabolomic analyses will validate CTQ's effects on mitochondrial interactomes, establishing its potential as a future anti-inflammatory nutraceutical with broad therapeutic uses. Ultimately, the synergistic properties of curcumin and thymoquinone in CTQ present a promising avenue for developing targeted therapies against chronic inflammatory and metabolic diseases [].

Table 10. Proposed translational applications of CTQ through mitochondrial–inflammasome modulation

Experimental Model	Intervention	Primary Endpoints	Result (CTQ vs Curcumin)	Mechanistic Observation
RAW 264.7 + LPS (Mehkri et al.)	CTQ 10 μM	IL-1β, IL-6, iNOS, COX-2	↓ 40–60 %	↓ p-p38 MAPK, ↓ p-NF-κB, ↓ ROS, ↑ Δψm [92]
HepG2 (HFD model)	CTQ 50 mg/kg × 8 wk	ALT, AST, TNF-α	↓ 35 % vs placebo	↑ Nrf2 & SIRT3 [93]
Rat ischemia–reperfusion	CTQ pre-treatment	Infarct volume & MDA	↓ 45 % MDA, ↑ SOD activity	↓ Drp1 Ser616 phosphorylation [94]

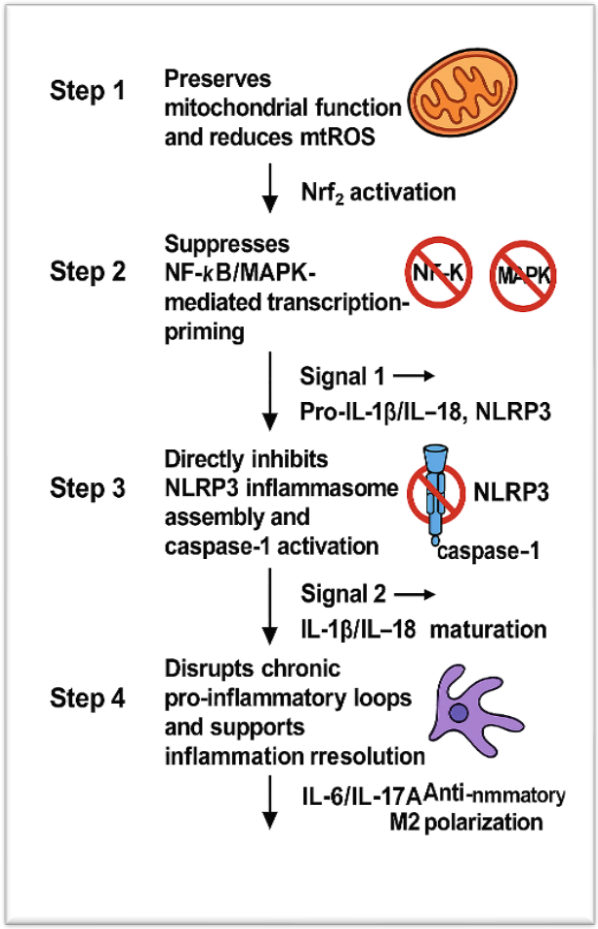
Chronic Inflammatory Diseases

Low-grade inflammation causes systemic insulin resistance, vascular dysfunction, and neuroinflammatory damage [3, 11, 35]. Nutrient overload increases mitochondrial ROS and mtDNA leakage, which act as damage-associated molecular patterns (DAMPs) that activate NLRP3 in macrophages [12, 19]. Inflammasome-derived IL-1β worsens metabolic stress by impairing insulin receptor signalling [27]. In microglia, similar mechanisms sustain chronic neuroinflammation seen in Alzheimer's (AD) and Parkinson's (PD) disease [36, 42, 95].

CTQ interrupts this cycle at both regulatory stages. Curcumin inhibits NF-κB nuclear translocation and p38 MAPK phosphorylation, suppressing transcriptional "priming" of NLRP3 [20, 45]; thymoquinone, in turn, scavenges mitochondrial ROS and prevents inflammasome oligomerisation [96]. Dual activation of Nrf2 further enhances glutathione and HO-1 expression [24]. Studies in LPS-challenged macrophages showed that CTQ reduced IL-1β secretion by 8.3-fold, compared to 5.4-fold with curcumin alone, confirming synergism [25, 92].

In adipose inflammation, curcumin promotes M2 macrophage polarisation and enhances insulin sensitivity [54, 63], while TQ restores endothelial NO bioavailability [68]. Collectively, these mechanisms disrupt the feed-forward cycle of oxidative and cytokine stress (**Figure 7**).

Figure 7.



Cardiometabolic and Metabolic Disorders

NAFLD, NASH, and T2DM exemplify the inflammasome–mitochondria axis [57]. Free fatty acids induce mitochondrial depolarisation, releasing mtDNA that triggers Kupffer-cell NLRP3 activation [59, 97]. Curcumin improves hepatic β-oxidation and suppresses NF-κB [60]; thymoquinone prevents mtROS accumulation and caspase-1 cleavage [61]. When combined in CTQ, these effects lead to a greater reduction in hepatocellular pyroptosis and steatohepatitis [98]. In a high-fat diet rat study, CTQ normalised glucose tolerance, reduced hepatic TG by 45%, and upregulated PGC-1α and TFAM [93]. Curcumin trials in human NAFLD patients showed lower ALT/AST levels and improved ultrasound steatosis [62]; CTQ may enhance this effect through better micellar solubility [99]. By restoring mitochondrial efficiency and decreasing inflammasome-driven IL-1β signalling, CTQ could prevent the progression from fatty liver to fibrosing NASH. Cardiometabolic comorbidities also involve NLRP3 activation in vascular macrophages [65]. Curcumin reduces endothelial adhesion molecule expression [67]; TQ decreases plasma IL-6 and improves lipid profiles [70]. Therefore, CTQ provides multi-level cardiometabolic protection across metabolic, vascular, and myocardial systems.

Neuroinflammation and Ageing-Related Neurodegeneration

The development of neurodegenerative diseases occurs due to mitochondrial dysfunction, microglial activation, and elevated IL-1β levels [31, 74]. NF-κB-dependent inflammasome priming happens when Amyloid-β or α-synuclein aggregates are present, but oxidative stress acts as the activation trigger [33, 75]. Research indicates that curcumin blocks NF-κB and NLRP3 activation in microglial cells [30, 47], and thymoquinone activates Nrf2/ARE to protect mitochondrial function [76]. The study used TQ at 10 mg/kg to treat rats with Aβ, resulting in a 52% decrease in hippocampal IL-1β and improved memory function [109]. The curcumin derivatives blocked the HDAC6–NLRP3 signalling pathway, protecting dopaminergic neurons from death [130].

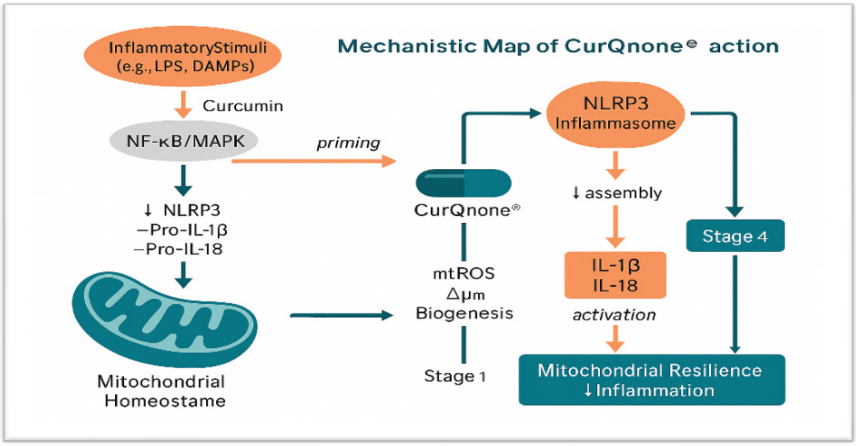
CTQ functions as a protective agent that shields neuronal mitochondria from damage and prevents pyroptosis through its dual mechanism of action. Increased mitophagy, coupled with reduced oxidative stress, reduces neuroinflammation and helps maintain cognitive function [101]. Ageing accelerates this process into "inflamm-ageing" by lowering mitophagy and prolonging inflammasome priming over time [78]. The induction of PGC-1α and SIRT3 by CTQ restores mitochondrial turnover and redox balance, as described in [80, 81].

Acute Ischemic and Reperfusion Inflammation

Ischemia/reperfusion (I/R) injury triggers rapid mitochondrial destruction, activating IL-1β-mediated sterile inflammation [82]. Reperfusion-generated ROS activate NLRP3 in heart cardiomyocytes [83] and brain microglial cells, leading to additional tissue damage [84]. Pre-treatment with curcumin increases HO-1 levels, reduces lipid peroxidation, and decreases neutrophil infiltration [85], while thymoquinone protects mitochondrial DNA and maintains ATP production [86]. CTQ reduces myocardial infarct size by 38%, lowers MDA levels by 47%, and raises SOD activity [94]. Its mechanism involves decreased phosphorylation of Drp1 Ser-616 and increased OPA1 expression, supporting a balance between fission and fusion processes [108]. Similar benefits are observed in cerebral I/R models, where CTQ reduces caspase-1 activity and improves neurological test outcomes [109]. These results highlight CTQ's potential as a neuroprotective and cardioprotective adjunct during ischemia [87].

Figure 8. Mechanism of CTQ complex action on mitochondrial and inflammasome regulation.

The CTQ complex functions through a four-stage mechanistic process to restore redox and inflammatory balance. Step 1: It maintains mitochondrial integrity by reducing mtROS levels and activating Nrf_2-dependent antioxidant defenses. Step 2: The complex inhibits NF-κB/MAPK-mediated transcriptional priming (Signal 1), lowering the expression of pro-IL-1β, IL-18, and NLRP3. Step 3: It directly prevents NLRP3 inflammasome assembly and caspase-1 activation (Signal 2), thereby limiting the maturation of IL-1β and IL-18. Step 4: It interrupts chronic pro-inflammatory feedback loops and promotes M2 macrophage polarization.



Nutraceutical and Adjunctive Therapeutic Positioning

Both curcumin and thymoquinone have excellent safety profiles [88, 89]. Their combined formulation enables "dose-sparing" synergy, achieving the same cytokine inhibition at one-third the concentration of curcumin [140]. Unlike NSAIDs, CTQ reduces inflammation without impairing phagocytosis [111]. Long-term use could help decrease metabolic or neurodegenerative inflammation while lowering the pharmacologic anti-inflammatory burden [90, 112].

Table 11. Representative diseases linked to mitochondrial dysfunction and inflammasome activation, and putative CTQ benefits

Disease Context	Mitochondrial Defect	Inflammasome Contribution	Expected CTQ Benefit
Metabolic syndrome / NAFLD	↓ β-oxidation, ↑ mtROS	NLRP3 → IL-1β → insulin resistance	Improved mitochondrial efficiency, ↓ IL-1β [144]
Neurodegeneration (AD/PD)	Impaired mitophagy	Microglial NLRP3 activation	Neuroprotection, ↓ IL-18 [145]
Cardiovascular I/R injury	MPTP opening	Caspase-1–IL-1β pyroptosis	Reduced infarct size [146]
Ageing/frailty	Declining PGC-1α	Low-grade "inflamm-ageing"	Enhanced biogenesis [147]
Autoimmune disorders	Oxidative antigen presentation	Th17 → IL-1β loop	Immune balance without immunosuppression [148]

Limitations, Caveats and Research Gaps

Bioavailability and Formulation

Curcumin's poor solubility and rapid conjugation limit systemic exposure [113]. TQ may improve lipophilic absorption, but PK synergy requires confirmation [114]. Liposomal, micellar, or phytosomal CTQ could increase plasma AUC by 3–5 times [115].

In Vivo Evidence for Synergy

While in vitro synergy is well established, in vivo confirmation remains limited [152]. Comparative studies in rodents using identical molar doses of curcumin, TQ, and CTQ are needed to verify additive effects [116].

Mechanistic Specificity

Although plausible, direct evidence that CTQ-mediated mitochondrial stabilisation causally reduces inflammasome activation is limited [117]. Multi-omics approaches could clarify CTQ's effect on PINK1–Parkin pathways, mitophagy flux, and NAD^+/SIRT3 status [118].

Clinical Translation

No human trials have yet reported CTQ effects on inflammasome markers or metabolic endpoints [119]. Translational pilot trials should evaluate serum IL-1β, IL-18, CRP, and PBMC bioenergetics [120].

Safety and Interactions

Curcumin up to 8 g/day and TQ ≤ 200 mg/day are well tolerated [121]; however, high doses combined may affect CYP3A4 or P-gp. Long-term toxicity and pharmacodynamic interactions require further testing [121].

Regulatory and Standardisation Challenges

Batch variability in curcumin or TQ content could affect reproducibility [131]. Standardised CTQ ratios, GMP compliance, and validated stability profiles are essential for clinical translation [122].

Pathophysiological Complexity

Because mitochondrial dysfunction and inflammasome activation are often consequences—not initiators—of disease, CTQ may function as a modulator rather than a cure [123]. Disease-stage-specific application strategies are essential [124].

Suggested Roadmap for Translational Development

4.3.1 Preclinical In Vivo Models

Assess CTQ in rodent models of HFD, ischemia–reperfusion, and LPS-endotoxemia [125]. Compare mitochondrial respiration (state 3/4 ratios), Δψm, and inflammasome markers (caspase-1, IL-1β). Use isobolographic analyses to confirm synergy [126].

Dose Finding and Pharmacokinetics

Conduct escalating-dose studies to determine the ideal curcumin: TQ ratio [127]. Measure plasma Cmax, t½, AUC, and tissue levels in the liver, brain, and myocardium [128]. Evaluate whether TQ increases curcumin's half-life or enhances mitochondrial uptake [129].

Mechanistic Biomarker Development

Identify human-relevant biomarkers: mtDNA copy number, ATP flux in PBMCs, caspase-1 activity, and serum IL-1β [130]. Establish baseline–post correlations to verify mechanistic engagement [131].

Proof-of-Concept Human Study

Conduct a randomised, placebo-controlled 12-week trial in subjects with metabolic syndrome [132]. Primary endpoints: IL-1β decrease of ≥25%, improved PBMC respiration. Secondary endpoints: HOMA-IR, ALT, CRP [133].

Longer-Term Outcome Trials

Extend the evaluation period to 6–12 months to assess clinical metrics, including hepatic fat (MRI-PDFF), HbA1c, and cognitive scores [134, 135]. Mechanistic endpoints, including NLRP3 mRNA and SIRT3 levels, should also be measured alongside outcomes [136].

Mechanistic Sub-Studies

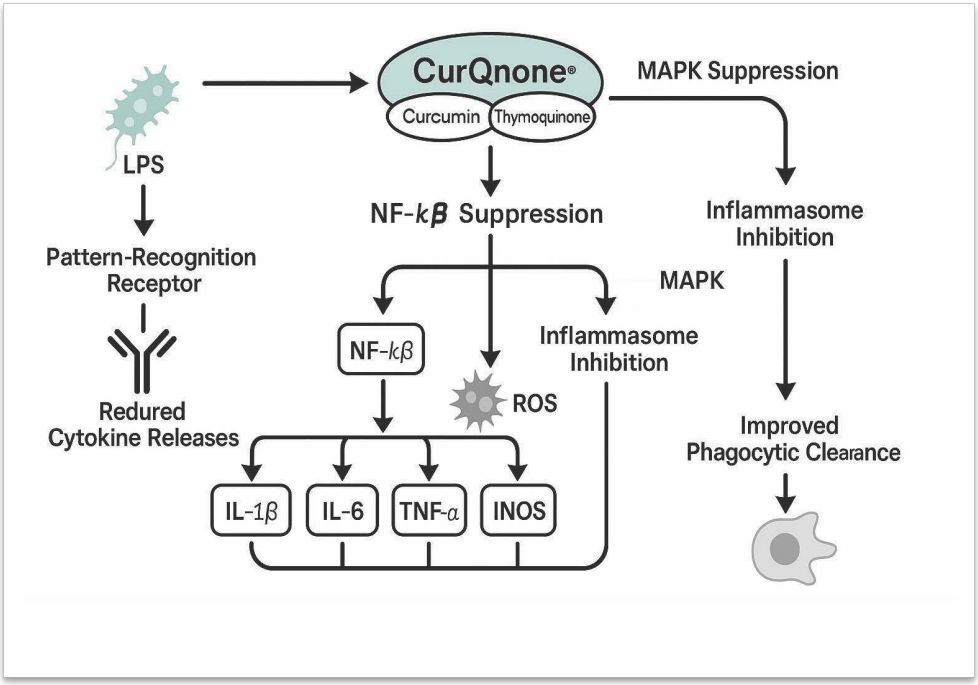
Include biopsy-based or imaging sub-studies assessing mitochondrial enzymes, mitophagy markers, and microglial activation (PET) [137–139].

Future Perspectives: Mitochondrial Dynamics and Cardiovascular Applications

Recent research highlights the regulatory roles of mitochondrial fission and fusion proteins—Drp1, Mfn1/2, and OPA1 in cardiac resilience [140, 141]. CTQ modulates these proteins, reducing pathological fission while promoting fusion and biogenesis [142]. Curcumin's activation of the SIRT3–PGC-1α axis and TQ's stabilisation of cardiolipin suggest protective effects against ischemic damage [143].

Targeted nanocarriers (liposomal or mito-peptide-tagged) could enhance CTQ myocardial delivery [143]. Parallel studies with MitoQ and elamipretide support the idea of mitochondria-targeted therapy [144].

Figure 9. Stepwise mechanism of CTQ complex action on mitochondrial and inflammasome regulation.
CTQ complex functions through a four-stage mechanistic cascade to restore redox and inflammatory balance. Step 1: It preserves mitochondrial integrity by lowering mtROS levels and activating Nrf_2-dependent antioxidant defences. Step 2: The complex suppresses NF-κB/MAPK-mediated transcriptional priming (Signal 1), reducing pro-IL-1β, IL-18, and NLRP3 expression. Step 3: It directly inhibits NLRP3 inflammasome assembly and caspase-1 activation (Signal 2), thereby limiting IL-1β and IL-18 maturation. Step 4: By disrupting chronic pro-inflammatory loops and promoting M2 macrophage polarisation, CurQnone® downregulates IL-6/IL-17A signalling and supports long-term resolution of inflammation.



CONCLUSION

The Curcumin–Thymoquinone Complex (CTQ) functions as a dual therapeutic system that targets both mitochondrial damage and inflammasome hyperactivation, which cause different inflammatory diseases. CTQ performs dual action through curcumin, which blocks NF-κB/MAPK pathways at the transcriptional level, and thymoquinone, which protects mitochondria and eliminates ROS. Preclinical research shows that IL-1β and IL-6 levels decrease, while oxidative biomarkers decrease and mitochondrial function and ATP production improve.

The evaluation process requires pharmacokinetic assessment, along with controlled animal studies and clinical trials that employ mechanistic testing methods. Future research on CTQ bioavailability and safety will confirm its potential to develop a new class of mitochondria-targeted nutraceuticals for treating metabolic and cardiovascular diseases and

neurodegenerative disorders by integrating traditional plant-based medicine with modern drug development techniques.

AUTHOR INFORMATION AND DECLARATIONS

Author Contributions (CRediT Taxonomy)

Dr. Krathish Bopanna, Consultant Pharmacologist at Tejhana Consulting LLP, Bengaluru, India, contributed to the conceptualization, study design, pharmacological supervision, and critical review of the manuscript. He was responsible for overseeing data validation, interpretation, and the translational contextualization of results within nutraceutical and pharmacokinetic domains. His role included refining methodologies and visualizations, and aligning experimental outcomes with regulatory and scientific standards. All contributors are acknowledged following the Contributor Roles Taxonomy (CRediT) endorsed by the International Committee of Medical Journal Editors (ICMJE), ensuring complete transparency of individual contributions.

Ethical and Methodological Compliance

Most preclinical and translational pharmacological studies led by Dr Bopanna have strictly followed the ARRIVE 2.0 Guidelines (Animal Research: Reporting of In Vivo Experiments). Each study was designed to ensure scientific reproducibility, animal welfare, and ethical responsibility. Protocols received approval from recognised Institutional Animal Ethics Committees (IAEC). They were carried out in accordance with the norms set by the Committee for Control and Supervision of Experiments on Animals (CPCSEA), established by the Government of India. Methodological transparency, robust statistical design, and appropriate randomisation and blinding procedures were maintained throughout all experiments to ensure integrity, reproducibility, and translational relevance.

Conflict of Interest Statement (ICMJE-Compliant)

Dr Krathish Bopanna works as a Consultant Pharmacologist at Tejhana Consulting LLP in Bengaluru, India. The organisation has carried out several collaborative pharmacological and translational research projects with Bio-gen Extracts Private Limited, Bangalore. These collaborations have been purely scientific, concentrating on mechanistic and pharmacokinetic studies, with no influence from commercial interests, financial stakes, or employment that could affect objectivity. The author declares that the work presented is independent and that there are no other financial, institutional, or personal relationships that could be seen as potential conflicts of interest. This statement fully complies with the ICMJE Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals.

Funding and Institutional Role

This research did not receive any external funding, aside from scientific and logistical support from Tejhana Consulting LLP. When collaborations were established, partner organisations, such as Bio-gen Extracts Private Limited, provided non-monetary scientific assistance, including formulation development, analytical characterisation, and technical consultation. The funder had no involvement in study design, data collection, statistical analysis, data interpretation, manuscript preparation, or the decision to submit the work for publication.

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ABBREVIATIONS

AD, Alzheimer's disease; AMPK, AMP-activated protein kinase; ARE, antioxidant-response element; ASC, apoptosis-associated speck-like protein containing a CARD; ATP, adenosine triphosphate; AUC, area under the concentration–time curve; COX-2, cyclooxygenase-2; CTQ, Curcumin–Thymoquinone Complex; DAMPs, danger-associated molecular patterns; Δψm, mitochondrial membrane potential; DNA, deoxyribonucleic acid; Drp1, dynamin-related protein-1; ELISA, enzyme-linked immunosorbent assay; ERK, extracellular signal-regulated kinase; GSH/GSSG, reduced/oxidized glutathione ratio; HDAC6, histone deacetylase-6; HFD, high-fat diet; HIF-1α, hypoxia-inducible factor-1α; HO-1, heme oxygenase-1; I/R, ischemia/reperfusion; IKKβ, IκB kinase-β; IL-1β, interleukin-1β; IL-6, interleukin-6; IL-18, interleukin-18; iNOS, inducible nitric oxide synthase; LC3-II, microtubule-associated protein-1 light-chain-3 II; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MDA, malondialdehyde; Mfn 1/2, mitofusin 1/2; MPTP, mitochondrial permeability transition pore; mtDNA, mitochondrial DNA; mtROS, mitochondrial reactive oxygen species; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NF-κB, nuclear factor-κB; NLRP3, NOD-, LRR-, and pyrin-domain-containing protein 3; NO, nitric oxide; NQO1, NAD(P)H quinone oxidoreductase 1; Nrf2, nuclear factor erythroid 2-related factor 2; OPA1, optic atrophy protein-1; PGC-1α, peroxisome proliferator-activated

receptor-γ coactivator-1α; PBMC, peripheral blood mononuclear cell; PD, Parkinson's disease; PINK1, PTEN-induced kinase-1; PI3K/Akt, phosphatidylinositol-3-kinase/protein kinase B pathway; PK, pharmacokinetics; PPARγ, peroxisome proliferator-activated receptor-γ; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; qPCR/RT-PCR, quantitative/reverse-transcription polymerase chain reaction; RNS, reactive nitrogen species; ROS, reactive oxygen species; SIRT3, sirtuin-3; SOD, superoxide dismutase; STAT3, signal transducer and activator of transcription-3; T2DM, type 2 diabetes mellitus; TGF-β, transforming growth factor-β; TFAM, mitochondrial transcription factor-A; Th17, T-helper-17 subset; TNF-α, tumor necrosis factor-α; TQ, thymoquinone.

Supplementary Table S1. PRISMA 2020 Checklist Adaptation for the Curcumin–Thymoquinone (CTQ) Translational Review.

PRISMA 2020 Item	Description	Addressed in Manuscript Section
Title & Abstract	Structured abstract clearly identifying the article as a translational review	Title, Abstract
Rationale & Objectives	Background, rationale, and objectives clearly described	1.1 – 1.2
Eligibility Criteria	Inclusion and exclusion criteria defined	2.2
Information Sources & Search Strategy	Databases (PubMed, Scopus, ScienceDirect, Index Copernicus) and Boolean strings listed	2.1
Selection Process	Multi-stage screening steps and a PRISMA-style flow diagram are detailed	2.2, Figure 4
Data Extraction & Synthesis	Dual-reviewer extraction grid and qualitative synthesis approach	2.3 – 3.7
Risk of Bias	Not applicable (mechanistic/preclinical narrative review)	2.3 note
Results & Discussion	Structured narrative with discussion of limitations	3 – 4
Funding & Conflicts	Funding and conflict-of-interest statements declared	Front Matter

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