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CINNAMALDEHYDE NANOPARTICLES AND THEIR ANTI-CANCER MECHANISM: A COMPREHENSIVE REVIEW

Parwan Ali Ujjan[*1], Abdul Majid[2], Dr: Ghulam Mujadid Qureshi[3], Shagufta Andleeb[4], Murk Saleem[5], Dur e Shahwar[6]

[*1,2]*Department of Biochemistry, Shah Abdul Latif University, Khairpur,*
[3]*Department of MLT, University of Modern Science, Tando Muhmmad Khn,*
[4]*Department of Physiology, University of Sindh Jamshoro*
[5]*Institute of Biomedical Engineering LUMHS*
[6]*Faculty of Pharmacy, University of Sindh Jamshoro*

[*1]parwanaliujjan@gmail.com

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Corresponding Author: *
Parwan Ali Ujjan

Abstract

Cinnamaldehyde (CA), the principal phenylpropanoid of Cinnamomum species, exhibits multifaceted anticancer activity but is constrained by volatility, poor aqueous solubility, and rapid biotransformation. Nanoparticle formulations (CNNPs) including solid lipid nanoparticles, chitosan-based hybrids, and mesoporous composites address these liabilities by improving encapsulation efficiency, physicochemical stability, controlled release, and tumor-selective delivery via ligand mediation (e.g., folate or transferrin receptors). Mechanistically, CNNPs elevate reactive oxygen species (ROS), precipitating mitochondrial membrane potential loss ($\Delta\Psi m$), cytochrome-c efflux, and caspase-3/9 activation, while concurrently attenuating pro-survival signaling through PI3K/Akt–mTOR and NF-κB pathways and enforcing G0/G1 or G2/M cell-cycle arrest with p53/p21 engagement. Mounting evidence positions autophagy as a central determinant of therapeutic outcome: CA triggers ER-stress (PERK–CHOP) and epigenetic remodeling that up-regulates Beclin-1 and ATG family members, drives LC3-II accumulation, and under defined conditions promotes autophagic cell death. Because autophagy is intrinsically context dependent and can be cytoprotective or cytotoxic, nanoparticle design (size, surface charge, ligand density, endosomal escape features), exposure kinetics, and tumor genotype collectively bias directionality. This review synthesizes 2020–2025 advances in CIN-NP engineering and cancer biology with an autophagy-first lens, integrates crosstalk among ROS, mitochondrial dysfunction, and mTOR signaling, and delineates best practices for verifying autophagic flux. Key translational challenges including nanotoxicity, off-target biodistribution (e.g., hepatic uptake with folate targeting), endosomal trapping, manufacturing scalability, and assay interference risks are critically appraised. Finally, a forward agenda is proposed that links rational CIN-NP design to rigorous mechanistic validation and in-vivo pharmacology to accelerate clinically meaningful, autophagy-informed nanotherapeutics.

1. Introduction

Plant-derived small molecules remain fertile ground for oncology, yet biopharmaceutic liabilities notably poor aqueous solubility, chemical instability, and rapid metabolism often

compromise clinical translation. Cinnamaldehyde (CA), the principal aromatic aldehyde of Cinnamomum spp., exemplifies this opportunity–liability paradox. Extensive preclinical evidence attributes to CA anti-inflammatory, antioxidant, metabolic, and anticancer activities across diverse tumor models, but free-drug volatility and metabolic instability constrain systemic exposure and produce variable efficacy (Han et al., 2024; Guo et al., 2024). Nanoparticle (NP) formulations have emerged to mitigate these limitations by encapsulating CA, shielding it from degradation, enabling sustained/triggered release, and supporting active targeting via surface ligands such as folate and transferrin (Chen et al., 2022; Shetty et al., 2021).

Beyond delivery advantages, CA engages multiple cell-death and pro-survival pathways that together shape therapeutic outcomes. At the mitochondrial interface, CA and CNNPs frequently increase reactive oxygen species (ROS), precipitating loss of mitochondrial membrane potential, cytochrome-c release, and caspase-9/3 activation, consistent with intrinsic-pathway apoptosis (Zhou et al., 2022). On canonical survival axes, reports document PI3K/Akt down-modulation and NF-κB inhibition, aligning with suppressed epithelial-mesenchymal transition (EMT) and reduced expression of pro-survival genes (Wang et al., 2022; Guo et al., 2024). These changes can sensitize tumor cells to death signals or augment the activity of co-delivered chemotherapeutics; indeed, CA-modified chitosan–lactobionic acid hybrid NPs co-loaded with doxorubicin have shown mechanistic synergy in vitro and in vivo (Zhou et al., 2022).

Autophagy has recently emerged as a central, potentially decisive node in the response to CA and CNNPs. Mechanistic studies in gastric cancer demonstrate that CA triggers endoplasmic-reticulum stress (PERK-CHOP) and epigenetic remodeling via G9a inhibition, leading to Beclin-1 and ATG5 up-regulation, LC3B conversion (LC3-II accumulation), and p62 degradation; pharmacologic or genetic autophagy blockade attenuates CA-induced cell death, supporting a model of autophagy-mediated cytotoxicity in specific contexts (Kim et al., 2022). Nevertheless, autophagy's context dependence is well recognized: depending on tumor genotype, metabolic state, microenvironmental stressors, and NP exposure kinetics (dose, release rate, intracellular trafficking), autophagy may be cytoprotective (facilitating stress adaptation) or cytotoxic (culminating in autophagic cell death) (Cao et al., 2024). Accordingly, rigorous flux verification (e.g., bafilomycin/chloroquine blockade, tandem mCherry–GFP-LC3 reporters) is essential to discriminate between increased autophagosome formation and impaired degradation an interpretive pitfall in much of the small-molecule autophagy literature.

From a drug-delivery perspective, physicochemical tuning of CNNPs (size, polydispersity index, ζ-potential, encapsulation efficiency) and incorporation of targeting ligands can elevate local tumor exposure while reducing off-target toxicity. For example, solid lipid nanoparticles have achieved sub-100-nm sizes with stable, negative ζ-potentials and sustained release of CA (Chen et al., 2022). Folate-decorated magnetic CNNPs increased cellular uptake, activated caspases, reduced tumor burden, and prolonged systemic exposure relative to free CA (Shetty et al., 2021). At the same time, biodistribution caveats must be acknowledged: folate receptor-β expression on activated hepatic macrophages can sequester folate-targeted carriers, and transferrin-based systems face endosomal trapping design challenges that motivate PEGylation, ligand-density optimization, and endosomal escape motifs.

Finally, translation demands attention to assay artifacts and preclinical robustness. CA's α,β-unsaturated aldehyde renders it chemically reactive and classifiable as a PAINS-like scaffold in certain screening contexts; thus, orthogonal controls and in vivo corroboration are critical. A 2025 systematic review of animal cancer models reported reduced tumor volume and weight with CA but emphasized cautious interpretation and the need for rigorous experimental design (Luo et al., 2025).

A mechanistic overview of how CNNPs converge on mitochondrial apoptosis and ER-stress-regulated autophagy together with the context-dependent bifurcation between

apoptosis and autophagic cell death is summarized in **Figure 1** (Kim et al., 2022; Zhou et al., 2022; Cao et al., 2024).

2. Cinnamaldehyde: structure, source, and physicochemical traits

Cinnamaldehyde (CA) is a phenylpropanoid (C6-C3) bearing an α,β-unsaturated aldehyde that underlies both its biological activity and chemical reactivity. In nature, CA occurs predominantly in the bark of Cinnamomum cassia and related Cinnamomum species, typically alongside cinnamic acid and cognate phenylpropanoid congeners (Guo et al., 2024; Han et al., 2024). The conjugated π-system confers lipophilicity and volatility, which together contribute to poor aqueous solubility and a tendency toward rapid loss from aqueous systems features that motivate nano-encapsulation to sustain effective concentrations in biological milieus (Han et al., 2024; Chen et al., 2022). In formulation terms, these traits are directly reflected by the improved encapsulation efficiency, ζ-potential control, and sustained-release profiles reported for various CIN-NP platforms (Chen et al., 2022).

At the same time, CA's electrophilic aldehyde (Michael acceptor) character raises assay-design concerns: reactive scaffolds may cause PAINS-like (pan-assay interference) artifacts in certain in-vitro screens, necessitating orthogonal validation (e.g., chemical rescue controls, alternative assay modalities) and in-vivo corroboration when attributing mechanistic effects to CA or CNNPs (Luo et al., 2025). Together, the natural source and physicochemical profile of CA rationalize a nanomedicine strategy: encapsulation stabilizes the payload, moderates release kinetics, and enables ligand-guided delivery, while rigorous experimental design mitigates interpretive risks (Chen et al., 2022; Luo et al., 2025).

3. Phytochemical significance: extraction, biosynthesis, classification .

Traditional extraction of CA employs steam distillation or organic-solvent extraction to yield CA-rich essential oil; modern processes such as supercritical fluid extraction can enhance recovery, purity, and storage stability (Guo et al., 2024). Biosynthetically, CA is produced through the phenylpropanoid pathway, downstream of L-phenylalanine, in parallel with cinnamic acid and related derivatives a route that explains its frequent co-occurrence with congeners in cinnamon bark (Guo et al., 2024).

Functionally, CA is classified among bioactive phenylpropanoids with redox-modulating and anti-inflammatory properties relevant to tumor biology and microenvironmental signaling (Han et al., 2024). For therapeutic development, encapsulation provides a practical way to decouple flavor/aroma volatility from pharmacologic dosing: by embedding CA within solid lipid nanoparticles, biopolymer carriers (e.g., chitosan), or mesoporous composites, developers can stabilize the payload and control its spatiotemporal release without compromising the molecule's core bioactivity (Chen et al., 2022; Han et al., 2024)

4. Pharmacological potentials brief overview .

Beyond oncology, CA exhibits anti-inflammatory (e.g., NF-κB suppression), antioxidant, antimicrobial, metabolic, cardiovascular, and neuroprotective effects, establishing a broad safety-pharmacology context for its use as a therapeutic payload (Guo et al., 2024; Han et al., 2024). These pleiotropic actions intersect tumor biology for example, lower pro-inflammatory cytokines and repression of EMT drivers can reduce survival signaling and invasiveness making CA an attractive multi-target payload for nanoparticle design, especially when paired with active targeting and controlled-release approaches (Guo et al., 2024; Wang et al., 2022).

4.1 Antimicrobial activity .

CA exerts membrane-active and redox-modulating actions across bacterial and fungal species. Nano-encapsulation often enhances apparent antimicrobial performance by maintaining local concentrations and providing controlled release against biofilms or structured microenvironments (Chen et al., 2022; Muhoza et al., 2021). While antimicrobial endpoints are not directly oncologic, they inform formulation science: stability, release kinetics, and payload integrity under physiologic conditions parameters essential for CNNPs in cancer are probed in

these studies and translate to tumor settings, where dysbiosis and biofilm-like structures may influence drug distribution (Muhoza et al., 2021; Han et al., 2024). Accordingly, antimicrobial investigations provide valuable benchmarks for encapsulation efficiency, particle stability, and payload retention, which we leverage when selecting CIN-NP platforms for mechanistic oncology experiments (Chen et al., 2022; Muhoza et al., 2021).

4.2 Antioxidant activity .

CA's impact on oxidative homeostasis is context dependent. Under basal conditions, CA can scavenge ROS and support redox balance; in tumor contexts, CA (and CNNPs) often increase ROS by perturbing mitochondrial function, thereby collapsing ΔΨm, enhancing cytochrome-c efflux, and activating caspases events that bias toward apoptosis or autophagy-mediated cell death depending on flux status (Guo et al., 2024; Zhou et al., 2022). Nanocarriers are critical in tuning this balance: by modulating exposure kinetics (release rate, intracellular trafficking) and subcellular localization, CNNPs can amplify mitochondrial stress within cancer cells while reducing off-target oxidative injury to normal tissues (Zhou et al., 2022; Yan & Li, 2022). This adjustable redox lever combined with autophagy pathway engagement positions CNNPs as precision stressors with potential to overcome survival signaling and drug resistance.

4.3 Neuroprotective properties

In neuronal systems, CA modulates oxidative and inflammatory cascades, often protecting cells from stress-induced injury, and highlighting the mitochondria-centric nature of its actions (Guo et al., 2024). These observations, although outside oncology, underscore the relevance of quality-control pathways notably autophagy and mitophagy for cellular survival. Mechanistic work in non-tumor models shows CA can influence PINK1/Parkin signaling and LC3 dynamics under oxidative challenge (Ke et al., 2022). Such cross-domain evidence supports our later cancer-focused analyses: CNNPs that elevate ROS and perturb ΔΨm may also interface with mitophagy and autophagy flux, shaping whether the net outcome is cytoprotective recycling or cytotoxic self-digestion in tumor cells (Guo et al., 2024; Ke et al., 2022).

4.4 Anti-inflammatory activity .

CA attenuates NF-κB activation and downstream pro-inflammatory cytokines (e.g., IL-6, TNF-α), and cross-talks with PI3K/Akt–mTOR signaling axes that also set autophagy tone (Guo et al., 2024). In tumors, dampening NF-κB and PI3K/Akt can reduce survival signals and EMT programs, potentially sensitizing cells to apoptosis or autophagic death (Wang et al., 2022). CNNPs add further control by targeted uptake and endosomal-escape design, elevating intracellular CA while limiting systemic inflammation. Because mTOR integrates nutrient and stress signals to modulate autophagy, the combined effects of NF-κB suppression and PI3K/Akt-mTOR down-shift may pivot autophagic flux toward cytotoxic outcomes under defined exposure and genetic contexts (Guo et al., 2024; Cao et al., 2024). These mechanistic intersections justify our autophagy-first lens in Section 6.5.

4.5 Other activities .

Outside oncology, CA shows antidiabetic (glycemic control, insulin sensitivity) and cardioprotective tendencies properties that may influence tolerability and systemic physiology during cancer therapy (Han et al., 2024). From a translational viewpoint, such effects could affect host metabolism, drug distribution, and organ stress responses, shaping the therapeutic window of CNNPs. Integrating these non-oncologic data into dosing and safety assessments can support rational clinical development while maintaining mechanistic focus on tumor-selective stress and autophagy modulation (Han et al., 2024).

5. Cinnamaldehyde nanoparticles: platforms, encapsulation & characterization

Across diverse platforms, cinnamaldehyde-loaded nanoparticles (CINNPs) exhibit tunable physicochemical properties—size, polydispersity index (PDI), ζ potential, and encapsulation efficiency—that directly influence stability, release kinetics, and biological performance. These formulation variables, combined with

targeting ligands and endosomal escape strategies, determine intracellular exposure profiles and mechanistic outcomes such as ROS elevation, mitochondrial dysfunction, and autophagy flux. Platform diversity. CINNPs have been engineered on multiple chassis—including solid lipid nanoparticles (SLNs), chitosan-based hybrids, and mesoporous bioactive glass–polymer (MBGN/PHBV) microspheres—to overcome CA's volatility, poor aqueous solubility, and chemical lability while enabling tunable loading and release (Chen et al., 2022; Chotchindakun et al., 2021; Muhoza et al., 2021). Process intensification tools such as high-energy ultrasonication and selection of biopolymer wall materials (e.g., chitosan, hydroxypropyl methylcellulose, HPMC) further optimize particle size, PDI, ζ potential, and encapsulation efficiency, thereby improving colloidal stability and dose precision (Phyo et al., 2025). Collectively, these platforms provide the formulation latitude to align exposure kinetics with the mechanistic intent (e.g., driving ROS-mediated mitochondrial stress and autophagy in tumor cells). Representative metrics. SLN CIN systems prepared by ultra-high-pressure homogenization have reported size ~74 ± 5 nm, PDI 0.153 ± 0.032, and ζ potential −44.36 ± 2.2 mV, with clear evidence of sustained release and favorable physical stability—useful benchmarks for oncologic applications that require tumor interstitial penetration and reproducible release (Chen et al., 2022). In a complementary approach, MBGN/PHBV microspheres preserved CA activity, maintained biocompatibility with MG63 cells, and provided multi-day release, illustrating a slow-delivery option that could be mapped to solid-tumor dosing regimens or local depot strategies (Chotchindakun et al., 2021). Chitosan-based hybrids functionalized with CA (and often co-loaded with a chemotherapeutic such as doxorubicin) add the possibility of active targeting (e.g., via lactobionic acid) and combination therapy, achieving in vitro/in vivo synergy by coordinating redox stress, mitochondrial depolarization, and apoptotic signaling (Zhou et al., 2022). Release & stability. Across platforms, encapsulation shields CA from light/oxidation and reduces volatilization, enabling zero- or near-zero-order release windows or stimuli-responsive profiles (e.g., pH-mediated) that enhance intracellular exposure while limiting burst-related toxicity (Chen et al., 2022; Muhoza et al., 2021). In turn, size/PDI control improves dispersion reproducibility and ζ potential tuning reduces aggregation and opsonization, both of which are essential for credible mechanistic interpretation in cell studies and for pharmacokinetic consistency in vivo (Chen et al., 2022; Phyo et al., 2025). Assay caveats. Because CA bears an α,β-unsaturated aldehyde (a Michael acceptor), it can display PAINS-like interference in certain in vitro assays. Consequently, formulation characterization should be coupled to orthogonal confirmatory analytics—for example, HPLC stability under relevant buffers/serum, dialysis-based or USP apparatus release kinetics, and light/oxidation stress tests—to reduce artifactual readouts before drawing biological conclusions (Luo et al., 2025). When paired with robust mechanistic assays (e.g., autophagy flux rather than static LC3-II), such rigor ensures that the observed anticancer effects indeed arise from CINNP pharmacology rather than nonspecific reactivity. Table 1. Representative cinnamaldehyde nanoparticle (CINNP) platforms, physicochemical characteristics, targeting strategies, and key mechanistic readouts.

Table 1Representative cinnamaldehyde nanoparticle (CINNP) platforms, physicochemical characteristics, targeting strategies, and key mechanistic readouts. Metrics include size, polydispersity index (PDI), ζ potential, encapsulation efficiency (EE), and release profiles, alongside biological endpoints such as ROS elevation, ΔΨm collapse, caspase activation, and autophagy markers (LC3-II, p62). References indicate primary sources for formulation and mechanistic data.

Platform / Formulation	Size / PDI	ζ Potential	Targeting	Model / System	Encapsulation efficiency / Release metric	Key Readouts	Ref.
SLN CIN	74 ± 5 nm / 0.153 ± 0.032	−44.36 ± 2.2 mV		Physical characterization; antimicrobial test bed (transferable to oncology)	Retention: ~52.36% CA after 15 d (slow release); stability confirmed (DSC/UV)	Sustained release; good colloidal stability	(Chen et al., 2022)
Chitosan LA/CA-DOX hybrid NPs	~200–300 nm (reported)		Lactobionic acid	HeLa (in vitro); murine (in vivo)	Release: DOX/CA profiles reported; controlled intracellular exposure (qualitative)	ROS↑, ΔΨm↓, caspase 3/9↑; in vivo antitumor synergy	(Zhou et al., 2022)
Fe_3O_4-Folate-CIN (FiCF)	~10 nm core (TEM)		Folate (FR α)	Breast cancer cells (in vitro); murine model (in vivo); PK in rats	EE/Release: Not explicitly reported; folate mediated uptake improved exposure	Uptake↑; caspases↑; tumor burden↓; circulation↑ vs free CA	(Shetty et al., 2021)
MBGN/PHBV/CIN microspheres	μm scale microspheres; nanoscale MBGN			MG 63 compatibility; antibacterial assays	Release: Multi day CA release; payload retention under assay conditions (qualitative)	Biocompatibility; multi day controlled release	(Chotchindakun et al., 2021)
Wax based SLNs (beeswax / propolis wax) + CA	Optimized nanoscale (RSM guided)			Physicochemical + release tests	EE: Highest at wax:CA = 1:0.25 (qualitative peak EE); Release: sustained (multi day)	Spherical morphology (β′ polymorph); controlled CA	(Shirvani et al., 2023)

						release; improved protection	
pH responsive chitosan NPs (Schiff base CA)	Sub micron to nano (varies)	Positive (chitosan)		Packaging/biomaterials contexts (translatable formulation science)	Release: Acid triggered; faster at lower pH; retention > 85% after 48 d (powder) in one system (qualitative)	pH responsive CA release; antibacterial activity (model systems)	(Hou et al., 2024; Yu et al., 2024)
pH responsive chitosan NPs (TCIN ± PTX/CUR co load)	114-170 nm; PDI < 0.4	zeta > +40 mV		HeLa, MDCK (in vitro)	Release: higher at pH 6.5 than pH 7.4 (tumor like microenvironment); EE not explicitly stated	Monodisperse, stable; co therapeutic potential with CA (TCIN)	(Barrera Martínez et al., 2024)
Magnetic glucose coated "Cinnamon" NPs (Fe_3O_4@Glu Cinnamon)	26.8-60.2 nm (DLS)	−15.4 mV	Magnetic guidance (concept)	SW480 (CRC cells, in vitro)	Release: Not reported; DL noted; magnetic properties for targeting (qualitative)	Apoptosis↑; cell cycle arrest (S/G2 M); down regulation of CRC oncogenes (SNAI1, THBS2, INHBA)	(Ahmadzadeh Chaleshtori et al., 2025)
Tf conjugated lipid carriers (design blueprint for CIN payloads)	140-167 nm (NLC Tf example)	Variable	Transferrin (TfR1)	Melanoma (example); concept readily portable to CIN payloads	EE/Release: platform supports drug loading with Tf conjugation; proof of concept for Tf targeting	Tf conjugation ↑ uptake/cytotoxicity vs non targeted; TfR targeting widely validated across cancers (review)	(Altuwaijri & Atef, 2024; Li et al., 2024; Jianru Li et al., 2023)

5.2 Targeted delivery: folate and transferrin .

Folate receptor (FR) targeting. Folate-decorated CINNPs leverage overexpression of FRα on many epithelial tumors to improve uptake. In a representative study, folate-conjugated Fe_3O_4-CIN nanoparticles (FiCF) increased cellular accumulation, activated caspases, reduced tumor burden in mice, and prolonged circulation when compared with free CA, validating FR-mediated active targeting for CINNPs (Shetty et al., 2021). However, in vivo biodistribution is not trivial: FRβ on activated macrophages—notably in the liver—can sequester folate-tagged carriers, reducing tumor delivery. This risk can be modulated by surface chemistry, ligand density, PEGylation, and administration route, all of which influence recognition and clearance (Ibrahim et al., 2023).

Transferrin receptor (TfR) targeting. Transferrin (Tf) and Tf-mimetic strategies exploit widespread TfR overexpression in tumors to promote receptor-mediated endocytosis and endosomal trafficking. Recent overviews summarize design space (ligand format, multivalency), safety, and translation status of Tf-targeted nanocarriers; these principles are directly portable to CINNPs for enhancing intracellular delivery (Li et al., 2024). A common hurdle across FR and Tf systems is endosomal trapping; design additions such as proton-sponge polymers, pH-responsive lipids, or membrane-active peptides can facilitate endosomal escape, increasing cytosolic bioavailability where CA can interact with mitochondrial and signaling targets. Design principles and liabilities for folate/TfR-targeted CINNPs, including receptor-mediated endocytosis, endosomal escape strategies, ligand-density trade-offs, and the liver FRβ sequestration caveat, are visualized in Figure 2 (Shetty et al., 2021; Ibrahim et al., 2023; Li et al., 20

6. CIN NPs and Cancer Overview of Anti-Cancer Potential

As mapped in **Figure 1**, CA-loaded carriers elevate ROS to trigger ΔΨm collapse and caspase-9/3 activation, while PERK-CHOP-driven mTOR downshift promotes an autophagy program that depending on exposure and genotype can tip toward cytotoxic autophagy (Kim et al., 2022; Zhou et al., 2022; Cao et al., 2024). The schematic contextualizes how cinnamaldehyde-loaded nanoparticles (CIN NPs) integrate multiple mechanistic axes, coupling drug delivery gains (encapsulation, controlled release, targeted uptake) with oxidative and mitochondrial stress pathways. Hybrid chitosan-lactobionic acid carriers functionalized with CA and co-loaded with doxorubicin (DOX) exemplify this approach: they elevate intracellular ROS, collapse ΔΨm, activate caspase-9/3, and suppress tumor growth in vivo, while leveraging lactobionic acid-mediated targeting to enrich within tumor tissue (Zhou et al., 2022). Complementary designs include folate-decorated magnetic CIN NPs (FiCF), which increase cellular uptake, trigger caspase activation, reduce tumor burden, and extend systemic exposure relative to free CA (Shetty et al., 2021). Delivery-centric work with solid lipid nanoparticles (SLNs) further reports sub-100 nm size, low PDI, negative ζ potential, and sustained release quantitative formulation benchmarks that align exposure kinetics with mechanistic intent (Chen et al., 2022). Mechanistically, CIN NPs push oxidative stress toward the intrinsic apoptosis axis, typified by ΔΨm loss, cytochrome c release, and caspase-9/3 activation (Zhou et al., 2022; Yan & Li, 2022). In parallel, they downshift PI3K/Akt-mTOR survival signaling and dampen NF-κB activity, thereby attenuating EMT and pro-survival gene programs (Wang et al., 2022; Guo et al., 2024). Autophagy has emerged as a central determinant: CA can trigger ER stress via PERK–CHOP and inhibit G9a, upregulating Beclin-1/ATG5/LC3B while reducing p62, with autophagy-mediated cytotoxicity documented in gastric cancer (Kim et al., 2022). Because autophagy is context-dependent, its net outcome cytoprotective or cytotoxic turns on tumor genotype, microenvironmental stressors, and nanoparticle exposure kinetics (Cao et al., 2024). Translationally, CIN NPs face delivery caveats notably FR-β–mediated sequestration of folate-tagged carriers in the liver and endosomal trapping addressable via ligand density tuning, PEGylation, and endosomal escape motifs (Ibrahim et al., 2023; Li et al., 2024). Finally, because CA is an α,β-unsaturated aldehyde and can behave as a

PAINS-like scaffold in certain assays, rigorous orthogonal controls and in vivo corroboration are essential to avoid over-attribution (Luo et al., 2025).

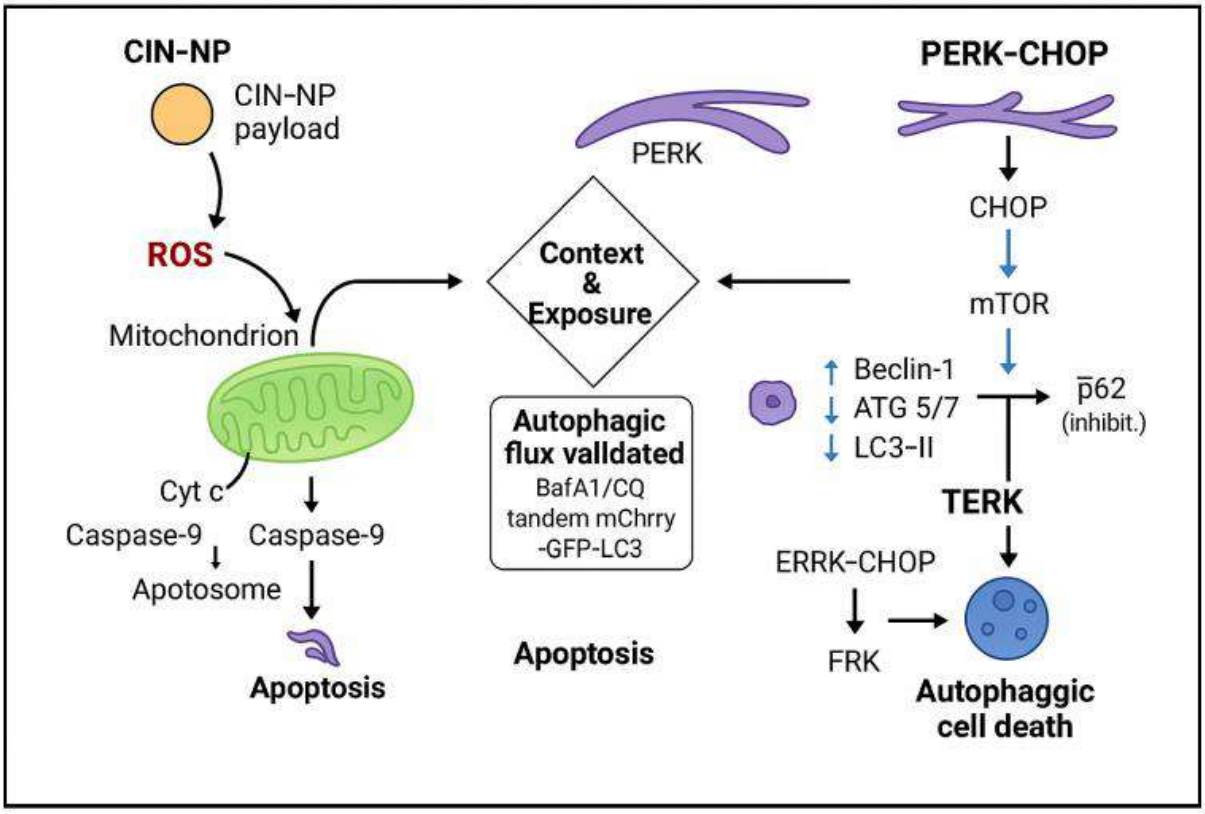

Figure 1 Mechanistic overview of CIN NP-mediated anti-cancer pathways. The schematic illustrates targeted uptake via folate and transferrin receptors, endocytosis, and endosomal escape, followed by ROS elevation, mitochondrial membrane potential (ΔΨm) collapse, and caspase-9/3 activation. It also highlights PERK–CHOP-driven mTOR downshift and autophagy modulation, along with design considerations such as PEGylation and ligand density tuning to overcome biodistribution caveats.

6.1 ROS-Mediated Apoptosis

The ROS→ΔΨm↓→cyt c→caspase-9/3 axis depicted in Figure 1 underlies the intrinsic apoptosis observed with CIN NPs in multiple models (Zhou et al., 2022). Across diverse cinnamaldehyde-loaded nanoparticle (CIN NP) platforms, ROS accumulation emerges as the primary upstream trigger for mitochondrial pathway apoptosis. Hybrid CA–chitosan/lactobionic acid (LA) carriers and CA–indocyanine green (ICG) lipid nanoparticles consistently produce ROS↑, loss of ΔΨm, cytochrome-c efflux, and caspase-9/3 activation, accompanied by Bax↑/Bcl-2↓ patterns indicative of outer mitochondrial membrane permeabilization (MOMP) (Zhou et al., 2022; Yan & Li, 2022). In the CA–DOX hybrid system, controlled ROS elevation synergizes with doxorubicin to intensify mitochondrial stress and amplify downstream caspase cascades, yielding superior in-vitro apoptosis and in-vivo tumor suppression relative to single-agent controls (Zhou et al., 2022). Notably, the carrier matrix (lipid vs polymer) modulates both the time course and magnitude of ROS exposure: sustained-release solid lipid nanoparticles (SLNs) prolong intracellular CA residence, enabling cumulative oxidative pressure without excessive burst toxicity (Chen et al., 2022), whereas active-targeting ligands (e.g., LA, folate) raise local payload concentration at the tumor interface, sharpening the apoptotic threshold and improving uptake (Shetty et al., 2021; Zhou et al., 2022). Mechanistic verification typically integrates ΔΨm probes (e.g., JC-1), caspase-activity assays, and antioxidant rescue

(e.g., N-acetylcysteine, NAC) to confirm ROS-dependence of cell death. In photo/thermal-assisted constructs (CA + ICG), dual modalities intensify oxidative injury, accelerating ΔΨm collapse and caspase activation under controlled light/heat exposure (Yan & Li, 2022). Importantly, ROS-mediated apoptosis in CIN NP studies intersects with autophagy programs: elevated ROS can trigger PERK–CHOP ER stress and depress mTOR activity, initiating an autophagic response characterized by LC3-II accumulation, Beclin-1 and ATG5/7 upregulation, and p62 downshift (Kim et al., 2022). Whether autophagy subsequently facilitates apoptosis (by degrading pro-survival components and sustaining mitochondrial disruption) or competes with it (cytoprotection via recycling and redox buffering) depends on autophagy-flux status and exposure kinetics (Cao et al., 2024). Consequently, robust interpretation requires reading ROS/apoptosis endpoints alongside autophagy-flux assays such as bafilomycin A1/chloroquine (BafA1/CQ) blockade tests, tandem LC3 reporters (e.g., mRFP-GFP-LC3), and time-resolved ΔΨm/ROS profiling to attribute cytotoxic outcomes accurately (Kim et al., 2022; Cao et al., 2024). Collectively, these data position ROS-driven intrinsic apoptosis as a reproducible, mechanism-anchored hallmark of CIN NP therapy, with formulation-controlled exposure and ligand-guided targeting serving as levers to tune mitochondrial injury and maximize therapeutic index (Zhou et al., 2022; Chen et al., 2022; Shetty et al., 2021; Yan & Li, 2022).

6.2 Mitochondrial Dysfunction & Membrane Potential Disruption

CNNPs consistently compromise mitochondrial integrity, reflected by ΔΨm loss, matrix swelling, ATP depletion, and permeability transition pore (PTP) opening, culminating in cytochrome-c release and intrinsic apoptosis (Zhou et al., 2022; Yan & Li, 2022). In CA–DOX hybrid carriers, mitochondrial stress is central: ROS-linked ΔΨm collapse precipitates caspase-9/3 activation and tumor regression (Zhou et al., 2022). Outside oncology, CA's regulation of mitochondrial quality control including PINK1/Parkin-linked mitophagy has been observed under oxidative challenge (Ke et al., 2022), providing mechanistic plausibility that CA payloads can also engage mitophagy/autophagy programs in tumor cells (Kim et al., 2022).

Formulation levers influence the degree of mitochondrial insult. Sustained-release SLNs extend exposure to CA, while targeted carriers (e.g., folate, LA) concentrate payload intracellularly; both effects amplify ΔΨm loss and downstream apoptosis markers (Chen et al., 2022; Shetty et al., 2021; Zhou et al., 2022). Because ΔΨm dynamics can be confounded by dye-loading artifacts, robust designs pair JC-1/TMRM with orthogonal endpoints ATP assays, caspase-9 activation, and cyt c immunoblotting to confirm mitochondria-driven death (Zhou et al., 2022). Finally, mitochondria-centric stress crosstalks with autophagy: mTOR down-shift and Beclin-1/ATG activation are common in CA contexts, and flux validation is essential to distinguish adaptive mitophagy from cytotoxic autophagy (Kim et al., 2022; Cao et al., 2024).

6.3 Inhibition of Pro-Survival Pathways (PI3K/Akt & NF-κB) .

CNNPs and free CA interfere with canonical pro-survival signaling, notably PI3K/Akt–mTOR and NF-κB, thereby sensitizing tumor cells to stress and limiting EMT. In ovarian cancer models, CA suppressed EGF-induced EMT, reduced Akt signaling, and reversed mesenchymal markers an effect confirmed by a 2024 corrigendum adjusting figure labels without altering mechanistic conclusions (Wang et al., 2022). Broad pharmacology reviews also document CA's NF-κB inhibition, aligning with decreased inflammatory tone and survival gene expression (Guo et al., 2024). In silico work supports direct binding interactions of CA with PI3K/Akt/PDK1, reinforcing plausibility for pathway engagement, though cell-based and in vivo validation remain determinative (Olayiwola & Gollahon, 2025).

At the NP level, delivery gains magnify pathway modulation. By raising intracellular CA, targeted CNNPs can down-regulate Akt/mTOR, impede NF-κB nuclear translocation, and lower EMT drivers, thereby supporting apoptosis or autophagy-mediated cytotoxicity depending on

flux status (Shetty et al., 2021; Zhou et al., 2022; Kim et al., 2022). Mechanistically, mTOR down-shift is the hinge between survival blockade and autophagy induction; in CA studies, PERK–CHOP ER-stress frequently precedes mTOR suppression, with subsequent increases in Beclin-1/ATG5/LC3 and p62 reduction (Kim et al., 2022). Because NF-κB and PI3K/Akt are intertwined with drug resistance, integrating pathway assays (p-Akt/p-mTOR immunoblots; NF-κB luciferase reporters) alongside death pathway readouts is essential to capture the combined impact of CNNPs (Wang et al., 2022; Guo et al., 2024).

6.4 Cell Cycle Arrest & DNA Fragmentation

CIN NPs can arrest the cell cycle at G0/G1 or G2/M, often through p53/p21 activation, and promote DNA fragmentation detectable by TUNEL or laddering assays. In CA–DOX hybrids, apoptosis induction co-occurs with cycle blockade, reflecting convergent stress and survival pathway inhibition (Zhou et al., 2022). Reviews summarizing CA's multi-system pharmacology and anti-cancer potential also report p53/p21-linked cycle arrest and genotoxic endpoints across tumor types (Han et al., 2024; Guo et al., 2024). Mechanistically, ROS-dependent damage, mitochondrial signaling, and PI3K/Akt–mTOR downshift converge to halt cycle progression, and targeted CIN NP uptake can further intensify checkpoint enforcement (Shetty et al., 2021; Zhou et al., 2022). The schematic representation of CIN NP-mediated uptake and intracellular trafficking (**Figure 2**) contextualizes these mechanisms, illustrating how targeted delivery and endosomal escape precede cell cycle arrest and apoptosis.

Because cycle arrest may precede or accompany autophagy/apoptosis, integrated designs quantify BrdU/EdU incorporation, cyclin/CDK levels, p53/p21 induction, and TUNEL positivity alongside caspase and autophagy flux markers to determine sequence and contribution (Zhou et al., 2022; Kim et al., 2022). This multimodal approach limits over-interpretation from single endpoints and aligns with best practices for small molecule payloads that may exhibit PAINS-like reactivity in some assay contexts (Luo et al., 2025).

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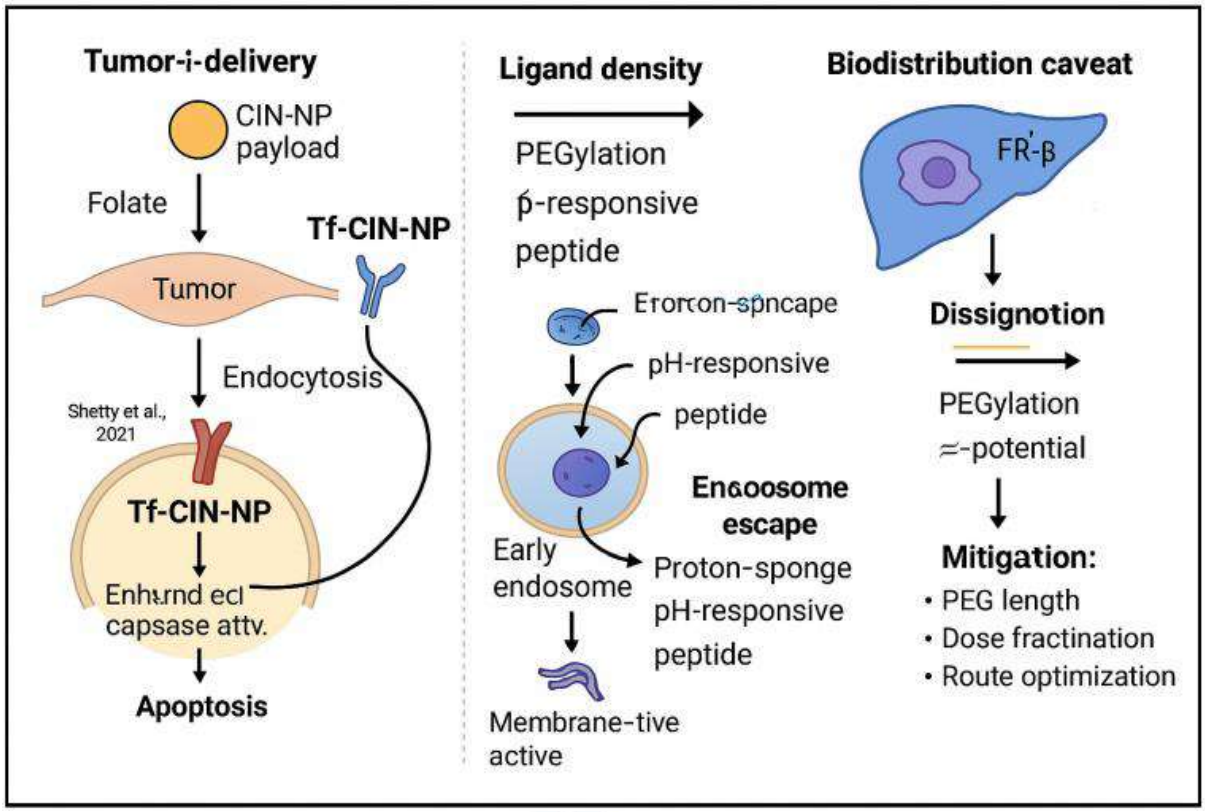

Figure 2. Schematic representation of CIN NP-based targeted delivery and intracellular trafficking. The illustration depicts tumor-targeted uptake via folate and transferrin receptors, endocytosis of CIN-NP payloads, and subsequent endosomal escape facilitated by proton-sponge and pH-responsive peptides. The diagram also highlights ligand density modulation through PEGylation and biodistribution caveats linked to FRβ expression, along with mitigation strategies such as PEG length optimization, dose fractionation, and route adjustment.

6.5 Autophagy Core Discussion

In gastric cancer cells, cinnamaldehyde (CA) treatment at 40 μM for 24 h increased LC3-II accumulation and reduced p62/SQSTM1 levels, while co-treatment with bafilomycin A1 (100 nM, 4 h) blocked lysosomal degradation, confirming active autophagic flux (Kim et al., 2022). Similarly, CA-induced autophagy was validated using tandem mCherry–GFP–LC3 reporters, where a shift from yellow puncta (autophagosomes) to red puncta (autolysosomes) indicated progression beyond formation to degradation. These flux-level assays combined with pharmacologic inhibition (chloroquine, 20 μM) are essential to distinguish cytotoxic autophagy from cytoprotective recycling and avoid misinterpretation based on static LC3-II elevation alone. Consistent with Figure 1, CA can engage ER stress (PERK→CHOP) and epigenetic G9a inhibition to induce Beclin-1/ATG5/LC3 activation; we therefore apply flux-level criteria (BafA1/CQ, tandem LC3 reporters) to distinguish cytotoxic from cytoprotective autophagy (Kim et al., 2022; Cao et al., 2024). Autophagy is the central mechanistic axis in CA/CIN NP oncology and demands scrutiny at the level of flux rather than static markers. In gastric cancer, CA drove PERK→CHOP signaling, suppressed G9a (EHMT2), increased Beclin-1/ATG5/LC3B, and reduced p62/SQSTM1; importantly, pharmacologic or genetic blockade of autophagy rescued viability, supporting autophagy-mediated cytotoxicity under defined conditions (Kim et al., 2022). CIN NPs magnify these effects by controlling intracellular exposure profiles and, when actively targeted (e.g., lactobionic acid, folate), by enriching payload within tumor cells to raise local effective concentrations (Zhou et al., 2022; Shetty

et al., 2021). Mechanistically, ROS acts upstream and converges on PERK–CHOP and AMPK/mTOR nodes to tilt the autophagy rheostat: as mTOR activity declines, ULK1 and Beclin-1 complexes engage, LC3-I lipidates to LC3-II, and p62 decreases with ongoing flux, aligning stress signaling with degradative capacity. Because elevated autophagosome markers can reflect either increased formation or blocked degradation, flux validation is non-negotiable. Recommended assays include bafilomycin A1 or chloroquine blockade to reveal autophagosome accumulation when lysosomal degradation is inhibited, tandem mCherry–GFP–LC3 reporters to discriminate autophagosomes (acid-labile GFP) from autolysosomes (mCherry-only), and time-resolved LC3/p62 immunoblotting to map the kinetics of induction versus clearance (Kim et al., 2022; Cao et al., 2024). CIN NP studies should integrate these flux measures with orthogonal endpoints cell survival, apoptosis markers (caspase-9/3, Bax/Bcl-2), mitochondrial stress (ΔΨm, cyt-c) to determine whether autophagy functions as a cell-death driver (cytotoxic autophagy) or as a stress-adaptation pathway (cytoprotective autophagy). Design levers embedded in CIN NPs directly influence autophagy outcomes. Sustained-release solid lipid nanoparticles (SLNs) prolong intracellular CA residence, sustaining mTOR down-shift and autophagosome formation while avoiding burst toxicity (Chen et al., 2022). Targeting ligands (LA, folate) heighten intracellular CA to reinforce PERK–CHOP engagement and deepen autophagy program activation (Shetty et al., 2021; Zhou et al., 2022). Conversely, biodistribution caveats such as folate-receptor-β uptake by liver macrophages can sequester folate-tagged NPs away from tumors, diluting autophagy effects in the intended tissue (Ibrahim et al., 2023). Endosomal entrapment similarly limits access of CA to cytosolic targets; incorporating proton-sponge polymers, pH-responsive lipids, or membrane-active peptides enhances endosomal escape and aligns intracellular exposure with autophagy induction windows (Li et al., 2024). Finally, PAINS-aware experimental discipline is crucial. As an α,β-unsaturated aldehyde, CA is electrophilic and can confound certain screens; thus, CIN NP autophagy claims should include chemical rescue controls (e.g., antioxidant or nucleophile competitors), time-course flux datasets, and ideally in vivo corroboration to substantiate cytotoxic autophagy rather than assay artifact (Luo et al., 2025; Kim et al., 2022). When these controls are in place, convergent evidence from 2020–2025 supports an autophagy-first therapeutic logic for CIN NPs, particularly in tumors dominated by PI3K/Akt–mTOR survival signaling where mitochondrial vulnerabilities are exploitable and ROS–ER-stress crosstalk can be leveraged to push the autophagy program beyond adaptation into lethality (Cao et al., 2024; Zhou et al., 2022). Practically, this means designing CIN NP regimens that

(i) tune exposure kinetics to sustain mTOR suppression and flux

(ii) (ii) co-monitor apoptosis and autophagy to avoid misattribution and

(iii) (iii) engineer targeting/escape features that overcome sequestration and endosomal barriers thus translating autophagy-centric mechanism into consistent anti-tumor efficacy.

6.5.1 The Dual Role of Autophagy in Cancer .

Autophagy's biphasic nature cytoprotective vs cytotoxic demands context-specific interpretation. In early stress, autophagy can recycle damaged organelles and buffer oxidative load, thereby protecting tumor cells; under sustained ROS/ER-stress with mTOR down-shift, autophagy may over-activate and become cytotoxic (Kim et al., 2022; Cao et al., 2024). CNNPs modulate this balance via exposure kinetics: sustained release and targeted uptake move cells from reversible stress adaptation to commitment toward autophagy-mediated death (Chen et al., 2022; Shetty et al., 2021). Conversely, sub-therapeutic exposure can enhance cytoprotection, diminishing net anti-tumor effects.

Operationally, distinguishing the two roles requires flux-level assays paired with functional tests (e.g., autophagy inhibition via BafA1/CQ or ATG knockdown) to observe rescue or exacerbation of death. Where inhibition rescues viability, autophagy contributes cytotoxicity; where inhibition sensitizes cells, basal autophagy was protective (Kim et al., 2022; Cao

et al., 2024). Tumor genotype (e.g., p53 status), metabolic state, and microenvironmental stress (hypoxia, nutrient limitation) further bias autophagy directionality, and CIN-NP studies should report these variables alongside flux data (Guo et al., 2024; Wang et al., 2022). This framework grounds the mechanistic claims in Section 6.5.2.

6.5.2 CNNPs and Autophagic Cell Death .

Evidence from 2020–2025 implicates autophagy-mediated cytotoxicity as a bona fide outcome of CA/CIN-NP exposure under specific contexts. In gastric cancer, CA induced PERK–CHOP ER-stress, G9a inhibition, Beclin-1/ATG5/LC3B activation, and p62 reduction; autophagy blockade attenuated death, indicating autophagic cell death rather than apoptosis alone (Kim et al., 2022). CIN-NP designs that raise intracellular CA via LA or folate targeting enhance these signals and can synergize with chemotherapeutics (e.g., DOX) to consolidate autophagy-linked cytotoxicity in vivo (Zhou et al., 2022; Shetty et al., 2021).

Upstream, ROS–mTOR crosstalk is the key integration point. CIN-NP-induced ROS↑ funnels to PERK–CHOP and AMPK, lowering mTOR and initiating autophagosome biogenesis (Kim et al., 2022). When exposure kinetics are sufficient (sustained release; endosomal escape), autophagic throughput exceeds cytoprotective capacity and becomes cell-killing observable as flux-dependent LC3-II accumulation, p62 degradation, and rescue by autophagy inhibitors (Cao et al., 2024; Kim et al., 2022). CIN-NP systems should therefore report time-resolved flux and inhibitor rescue to claim autophagic death credibly.

Translation requires attention to delivery caveats. FR-β–mediated liver uptake of folate-tagged NPs lowers tumor payload (Ibrahim et al., 2023); endosomal trapping limits cytosolic access to autophagy machinery; and PAINS-like reactivity can mislead static assay 2025). Mitigation strategies include PEG length optimization, ligand-density tuning, dose fractionation, and integration of endosomal-escape chemistries (Li et al., 2024). With these controls, the cumulative data point to CNNPs as autophagy-forward therapeutics capable of driving cytotoxic autophagy particularly in tumors dependent on PI3K/Akt–mTOR and buffered by NF-κB, where survival blockade and mitochondria-centric stress co-operate (Wang et al., 2022; Guo et al., 2024).

8. Conclusion and Research Outlook .

Cinnamaldehyde-loaded nanoparticles (CIN NPs) consistently couple delivery advantages (encapsulation, controlled release, targeting) with multi-pathway stress ROS elevation, ΔΨm collapse, caspase-9/3 activation, PI3K/Akt–mTOR downshift, and autophagy engagement yielding reproducible anti-tumor activity across models. The emerging autophagy-first logic frames CA-driven PERK→CHOP signaling, G9a inhibition, LC3-II/Beclin-1/ATG5 upregulation, and p62 decline as a programmable cytotoxic mechanism provided flux is verified and exposure kinetics are tuned. Translationally, performance hinges on overcoming folate-receptor-β sequestration, endosomal trapping, and off-target reactivity typical of α,β-unsaturated aldehydes; ligand-density optimization, PEGylation, and endosomal-escape motifs, alongside PAINS-aware controls and in vivo corroboration, are essential to de-risk attribution and sustain efficacy. This review advances an autophagy-first design framework linking CINNP exposure kinetics to verified flux and mitochondrial apoptosis, offering practical levers for translation beyond prior delivery-focused surveys.

Research outlook:

(i) Flux-resolved autophagy mapping across diverse genotypes and microenvironmental states to delineate conditions under which autophagy is cytotoxic versus cytoprotective.
(ii) Exposure response engineering using sustained-release solid lipid nanoparticles (SLNs) and stimuli-responsive carriers to stabilize mTOR suppression and synchronize ROS–ER stress crosstalk.
(iii) Rational combination strategies including doxorubicin (DOX), mTOR/ULK1 modulators, or G9a inhibitors to drive autophagy beyond adaptive thresholds.
(iv) Development of PK/PD models linking nanoparticle biodistribution to mechanistic

biomarkers such as LC3-II/p62 dynamics and PERK–CHOP signatures. (v) Macrophage-evasion and organ-sparing designs to optimize tumor-selective delivery and minimize off-target sequestration.

Executed with rigorous orthogonal assays and stratification by tumor biology, these steps can translate the autophagy-centric mechanism of CINNPs into durable clinical benefit.

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