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REVIEW

Cryptotanshinone: an Encouraging Natural Compound for Treating Metabolic Diseases

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Abstract

Purpose of the review Cryptotanshinone (CPT) is a bioactive diterpene quinone isolated from Salvia species and is particularly abundant in *Salvia miltiorrhiza. Danshen,* a traditional Chinese medicinal preparation derived from the dried roots of Salvia miltiorrhiza Bunge, has been used for centuries to treat diverse ailments, including metabolic disorders. However, the specific therapeutic potential of CPT alone in metabolic diseases remains largely underexplored. Metabolic disorders have nearly tripled over recent decades worldwide. Current estimates indicate that type 2 diabetes mellitus (T2DM) affects approximately 529 million individuals globally, while obesity impacts almost 600 million people. In the context of cardiovascular disease, researchers estimate a global burden of 523 million cases. Although these conditions often progress silently, they can lead to severe complications that drastically impair both the quality and life expectancy. Therefore, the search for effective and safe therapeutic strategies for metabolic diseases is imperative. This review aims to evaluate CPT therapeutic potential in metabolic diseases. It also highlights existing knowledge gaps and proposes future research directions. Additionally, we integrate an analysis of CPT's chemical and physicochemical properties, as well as its pharmacokinetic profile.

Recent findings Several studies indicate that CPT may counteract some of the metabolic alterations in metabolic disorders, including insulin resistance, weight gain, and altered blood lipid levels. Its therapeutic potential appears to arise from its ability to modulate antioxidant, anti-inflammatory, and catabolic pathways, as well as the microbiome.

Summary The global prevalence of metabolic disease continues to increase. In this review, we synthesize current evidence on the effects of CPT in metabolic diseases, identify critical knowledge gaps and propose future research directions to more effectively harness its therapeutic potential in this context.

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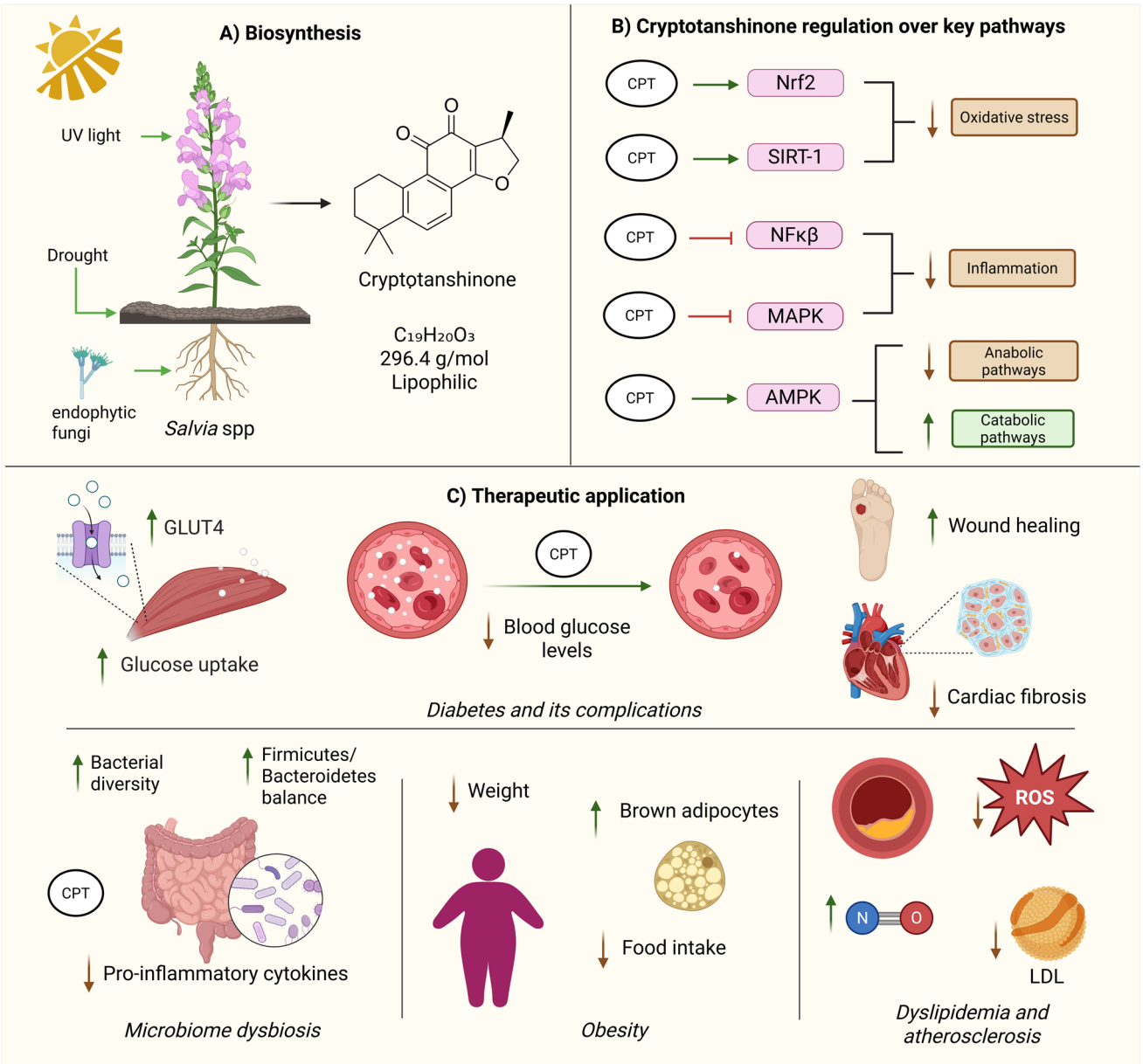
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Graphical Abstract



Keywords Cryptotanshinone · Metabolic disease · Oxidative stress · Inflammation · Dysbiosis

Introduction

Cryptotanshinone (CPT) is a diterpenoid quinone belonging to the tanshinone class of compounds. It is a secondary metabolite of several *Salvia* species within the *Lamiaceae* family, including *Salvia abrotanoides*, *Salvia yangii*, and *Salvia miltiorrhiza* [1].

The best-characterized source of CPT is *Danshen*, the dried roots and rhizomes of *Salvia miltiorrhiza* Bunge. This plant has been used in traditional Chinese medicine for millennia for a wide range of therapeutic purposes, including the management of metabolic diseases [2–4]. Researchers have isolated more than 200 compounds from *Danshen*. Among the lipophilic constituents, the tanshinones—including tanshinone I, tanshinone IIA, tanshinone IIB, CPT- represent a major bioactive group [5]. CPT, in particular, exhibits various pharmacological properties and modulates several cell-signaling pathways [3], some of which are involved in the development and progression of metabolic diseases.

Metabolic diseases—including obesity, dyslipidemia, and type 2 diabetes—have tripled over the past three decades [6]. Their rising prevalence highlights the urgent need for complementary and integrative therapeutic strategies. In this context, natural compounds with pleiotropic bioactivities are gaining considerable attention for their potential roles in prevention and treatment. Among these, CPT has shown promising pharmacological effects; however, its application in metabolic diseases remains insufficiently investigated.

This review addresses CPT biosynthesis and discusses key pharmacokinetic and physicochemical properties relevant to its therapeutic development. Importantly, it integrates current evidence and identifies persistent knowledge gaps to guide future research on the therapeutic potential of CPT for the management of metabolic disorders.

Cryptotanshinone Biosynthesis

The biosynthetic pathway of cryptotanshinone (CPT) in *Salvia* species remains only partially elucidated, yet significant advances, particularly from multi-omics analyses and P450 functional characterization, have substantially clarified its biochemical framework.

Formation of Tanshinone Scaffold

Like all abietane-type diterpenoids, CPT synthesis begins with the formation of isopentenyl pyrophosphate (IPP) and dimethylallyl pyrophosphate (DMAPP), derived from either the cytosolic mevalonate (MVA) pathway or the plastidial methylerythritol phosphate (MEP) pathway [7]. Condensation of one DMAPP and three IPP molecules by geranylgeranyl diphosphate synthase (GGPPS) yields geranylgeranyl diphosphate (GGPP), a major flux-controlling precursor whose regulatory importance has been demonstrated through metabolic engineering [7]. Subsequently, GGPP undergoes cyclization mediated by diterpene synthases specifically copalyl diphosphate synthase (CPS) and kaurene synthase-like (KSL) enzymes to produce miltiradiene, the hydrocarbon scaffold from which all tanshinones, including CPT [8, 9]. Key intermediates and enzymes are represented in Fig. 1.

Structure Modification by the Cytochrome P450 Family

From miltiradiene, the biosynthesis of CPT requires a series of complex enzymatic transformations and depends on a cascade of oxidative, aromatization, and heterocyclization reactions, catalyzed almost exclusively by cytochrome P450 (CYP450) enzymes. Multiple members of the CYP76AH and CYP76AK subfamilies convert miltiradiene into ferruginol and its hydroxylated derivatives, establishing the oxygenation pattern necessary for further skeletal rearrangements [9–11]. Recent studies show that members of the CYP71D subfamily drive two essential steps in CPT biosynthesis. Primarily CYP71D375 and CYP71D373 enzymes perform C-1 hydroxylation and catalyze the crucial ether ring formation, generating the distinctive heterocyclic D-ring of cryptotanshinone [9, 12]. Key intermediates and CYP450 enzymes are represented in Fig. 2. This late-stage oxidative heterocyclization is one of the most complex reactions known within the tanshinone family and defines the branch separating CPT from related compounds such as phenolic abietane-type nor-diterpenoids.

Influence of Abiotic and Biotic Stressors on CPT Biosynthesis

CPT production in *Salvia spp*. varies considerably depending on environmental conditions, and its recovery yield from plant material has been extensively described as low [4]. As a stress-induced secondary metabolite, CPT functions as a phytoalexin, accumulating predominantly in the root periderm, especially at the soil–plant interface. CPT production varies in response to abiotic stressors, such as high UV radiation, drought, and salinity, which elevate reactive oxygen species (ROS) and activate defense pathways that upregulate tanshinone biosynthesis [13]. Quinone-type compounds, such as CPT, can undergo redox cycling, thereby activating antioxidant system and improving stress tolerance [7, 14–16].

Biotic interactions also play a key role. Inoculation with endophytic fungi, such as *Penicillium meloforme, Berkeleyomyces basicola, Acremonium sclerotigenum, Talaromyces sp., and Penicillium canescens*, has been shown to significantly increase CPT accumulation in S. miltiorrhiza and S. *abrotanoides* [17], highlighting the ecological role of CPT as a metabolite responsive to microbial cues. Similarly, inoculation *with Talaromyces sp*. and *Penicillium canescens* increased the CPT recovery yield in *Salvia abrotanoides* [18]. Likewise, exogenous plant hormones and elicitors, including methyl jasmonate, salicylic acid, abscisic acid, indole-3-acetic acid, cytokinins, gibberellin A_3, nitric oxide, ethephon, and strigolactones, have been used experimentally to artificially boost CPT biosynthesis by modulating stress- and defense-related signaling [19].

In summary, CPT production in Salvia spp. is susceptible to environmental factors. Accordingly, the modulation of specific cultivation parameters presents a valuable strategy

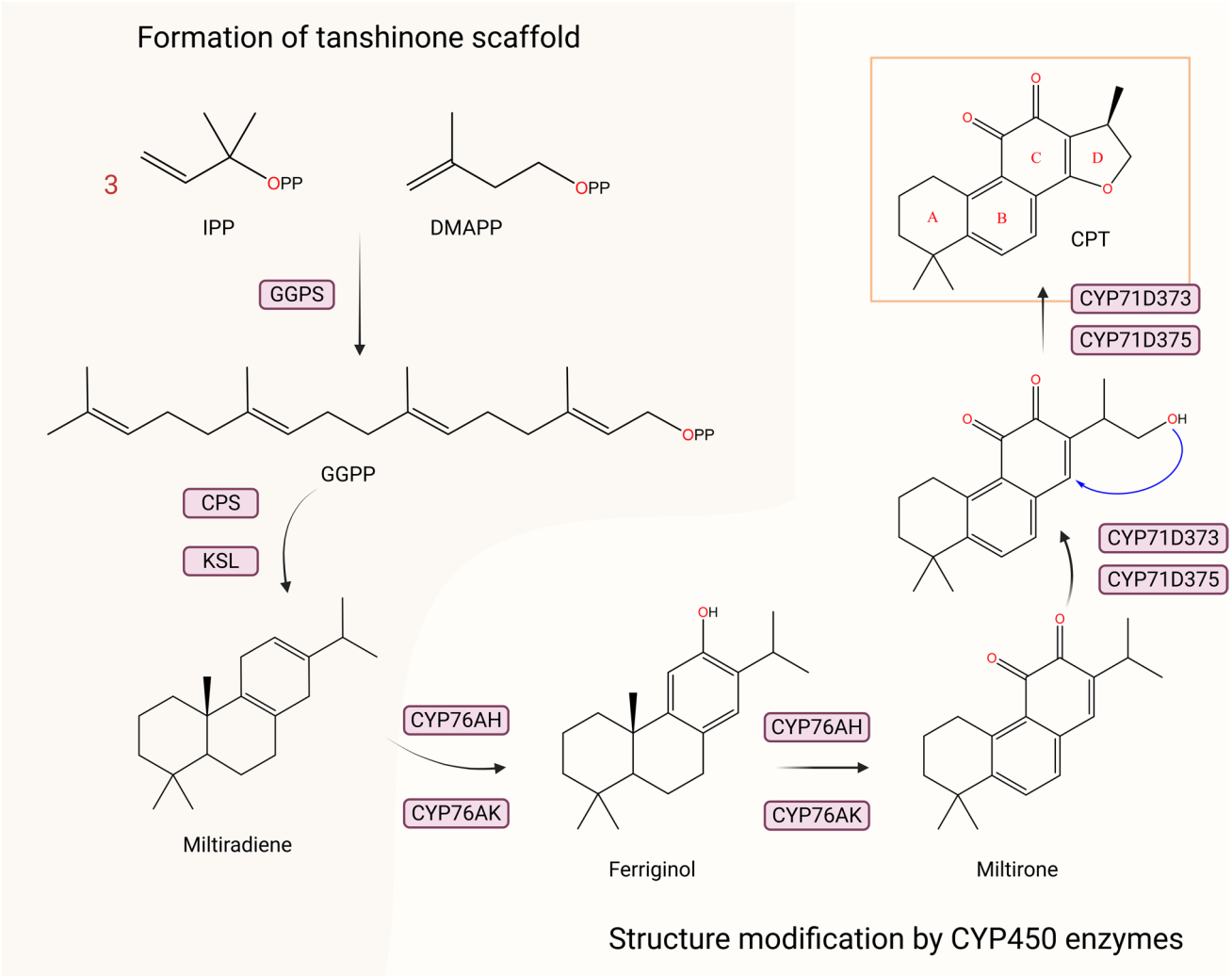


Fig. 1 CPT biosynthesis. The biosynthetic pathway of CPT in *Salvia spp* is schematically simplified. Key metabolic intermediates are shown and enzymes are highlighted in red boxes. Abbreviations: IPP, isopentenyl pyrophosphate; DMPP, dimethylallyl pyrophosphate; GGPS, geranylgeranyl diphosphate synthase; GGPP, geranylgeranyl diphosphate; CPS, copalyl diphosphate synthase; KSL, kaurene synthase-like. Created using ChemDraw and BioRender

for improving CPT yields in *Salvia* spp. The optimization of CPT production remains an active and promising area of research.

Physical and Chemical Properties of Cryptotanshinone

CPT, with the molecular formula $C_{19}H_{20}O_3$, is designated by the IUPAC name *(1R)-1,6,6-trimethyl-2,7,8,9-tetrahydro-1H-naphtho[1,2-g][1]benzofuran-10,11-dione* (PubChem). Its chemical structure exhibits the characteristic abietane-diterpenoid backbone and, as illustrated in Fig. 2, differs only slightly from other *Danshen*-derived tanshinones, such as tanshinones IIA and dihydrotanshinone. CPT has a molecular weight of 296.4 g/mol, has a melting point of 184 °C, and appears as orange crystals in its pure form [3]. Due to its susceptibility to photodegradation and alkaline hydrolysis, CPT requires storage under dry, light-protected conditions at 2–8 °C to preserve stability [2].

CPT exhibits fluorescence that varies with the surrounding conditions; e.g., intensity varies with the pH of the medium. It shows an excitation wavelength of 325 nm and an emission wavelength of 404 nm at room temperature [20]. CPT has a pKa of 4.9 and is poorly soluble in water. Nevertheless, it is highly soluble in organic solvents such as dimethyl sulfoxide (DMSO), methanol, ethanol, chloroform, and ether [2, 21]. Table 1 compares the physical and

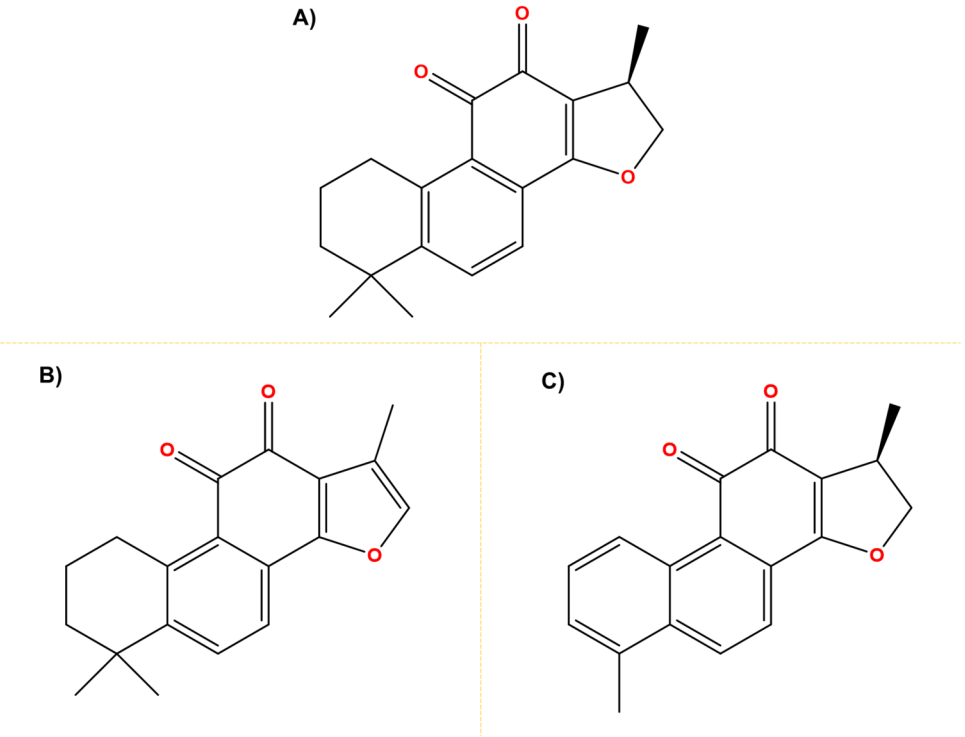


Fig. 2 Chemical structure of Cryptotanshinone and related tanshinones. Chemical structure of: **A** Cryptotanshinone, **B** Tanshinone IIA, **C** Dihydrotanshinone I. Created with ChemDraw

chemical features of cryptotanshinone with those of closely structurally related tanshinones.

CPT and other tanshinones are commonly isolated from plant material using multi-step chromatographic techniques, including silica gel column chromatography and semi-preparative high-performance liquid chromatography (HPLC) [24]. In addition to natural extraction, CPT can now be synthesized chemically and is commercially available through various suppliers.

Pharmacokinetics

For a compound to exert its biological effects, it must be capable of crossing cellular membranes without becoming trapped within them, allowing it to reach its intended pharmacological target. Lipinski's Rule of Five provides a widely accepted set of physicochemical criteria to predict the suitability of a compound for oral administration. CPT complies with all Lipinski's rules, exhibiting fewer than five hydrogen bond (H-bond) donors, fewer than 10 H-bond acceptors, a molecular weight under 500 g/mol, and a log P value below 5 [25] (Table 1). Despite meeting these parameters, CPT has extremely low aqueous solubility, which significantly impairs its dissolution and, consequently, its pharmacokinetic profile. Moreover, additional limitations—such as extensive first-pass metabolism and limited systemic bioavailability—pose further challenges for its in vivo evaluation and potential clinical application, as discussed in the following sections.

Bioaccessibility, Absorption, and Bioavailability

CPT exhibits very low bioaccessibility due to its limited solubility (Fig. 3A). Different formulations or extracts markedly influence its bioavailability. For instance, administration of *S. miltiorrhiza* extract resulted in significantly higher maximum serum concentration (C max) and area under the curve (AUC) in rats than did administration of pure CPT in the same concentration as that in the extract. This evidence suggests synergistic interactions with other extract components that contribute to CPT absorption [26].

Regarding absorption, researchers measured CPT permeability in Caco-2 monolayers and found high apical-to-basolateral permeability ($7.99 \pm 1.26 \times 10^{-6}$ cm/s) [27]. However, animal studies have consistently evidenced CPT's low oral bioavailability. For instance, it was undetectable in pig plasma following a 40 mg/kg oral dose and exhibited only 2.05% oral bioavailability in rats after a 100 mg/kg dose [27]. CPT is a known substrate of P-glycoprotein

Table 1 Physical and chemical features of Cryptotanshinone and related tanshinones

Properties	Cryptotanshinone	Tanshinone IIA	Dihydrotanshinone I
Molecular formula	$C_{19}H_{20}O_3$	$C_{19}H_{18}O_3$	$C_{18}H_{14}O_3$
IUPAC name	(1R)-1,6,6-trimethyl-2,7,8,9-tetrahydro-1H-naphtho[1,2-g][1]benzofuran-10,11-dione	1,6,6-trimethyl-8,9-dihydro-7H-naphtho[1,2-g][1] benzofuran-10,11-dione	(1R)-1,6-dimethyl-1,2-dihydronaphtho[1,2-g][1] benzofuran-10,11-dione
CAS number	35825–57-1	568–72-9	87205–99-0
Molecular weight	296.4 g/mol	294.34 g/mol	278.30 g/mol
Num. H-bond donors	0	0	0
Num. H- bond acceptors	3	3	3
Log P consensus[1]	3.43	3.80	3.03
Melting point	184 °C	209 – 210 °C	214–218 °C
Pure crystal appearance	Orange	Orange-red	Red
pK_a	(Acid) 7.964[2] (Base) 3.514[2]	(Acid)7.619[2] (Base)3.805[2]	(Acid)7.52[2] (Base)3.211[2]
Water solubility	<0.1 mg/mL	2.8×10^{-6} mg/mL	4.80×10^{-4} mg/mL

[1]Data obtained from Swiss-sADME software [22], [2] Data obtained from ADMETLAB 3.0 [23]

(P-gp/MDR1), which likely contributes to its poor bioavailability by promoting efflux back into the intestinal lumen and enhancing the first-pass effect [28] (Fig. 4B).

Moreover, CPT has been shown to upregulate P-gp/MDR1 and CYP3A4 expression in human hepatocytes cells culture (HepG2) by activating the pregnane X receptor (PXR) [29]. In parallel, the AUC of Fexofenadine, a known MDR1 substrate, decreased by 37.2% in healthy volunteers following 10 days of oral administration of an ethanolic *Danshen* extract [30]. These findings suggest that repeated CPT administration may further intensify its first-pass effect, potentially worsening its already limited oral bioavailability.

Researchers are developing formulation strategies to enhance CPT bioavailability. When they incorporated CPT into solid lipid nanoparticles and orally administered them to rats, they observed a twofold increase in Cmax and AUC compared with orally administered CPT dispersion, likely because this formulation reduced first-pass metabolism [31]. In another study, investigators used hydroxypropyl-β-cyclodextrin inclusion complexes and increased CPT oral bioavailability in rats to approximately 6.9% [32]. More recently, Zhao et al. developed CPT nanocrystals that significantly improved oral bioavailability, absorption rates, and Cmax duplication in healthy rats compared to raw CPT. This preparation also augmented compound stability when stored at 4 °C [33].

Therefore, the development of novel formulations to enhance CPT bioavailability represents a promising opportunity to promote the therapeutic use of the compound.

Distribution

Wang et al. used ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) to evaluate tissue distribution of tanshinones following oral administration of either a liposoluble extract of *Salvia miltiorrhiza* or isolated tanshinones [26]. The compounds were primarily distributed in highly perfused organs, including the liver, lungs, and kidneys. Specifically, the distribution hierarchy of CPT was: liver, lung, prostate, kidney, heart, plasma, spleen, and brain [26] (Fig. 4C).

Although studies have not yet reported the plasma protein binding rate of CPT, tanshinone IIA, its major metabolite, exhibits a binding rate of 99.7% [34]. This finding suggests that CPT may exhibit a high affinity for plasma proteins. A high protein-binding rate is associated with increased potential for drug-drug and drug-nutrient interactions.

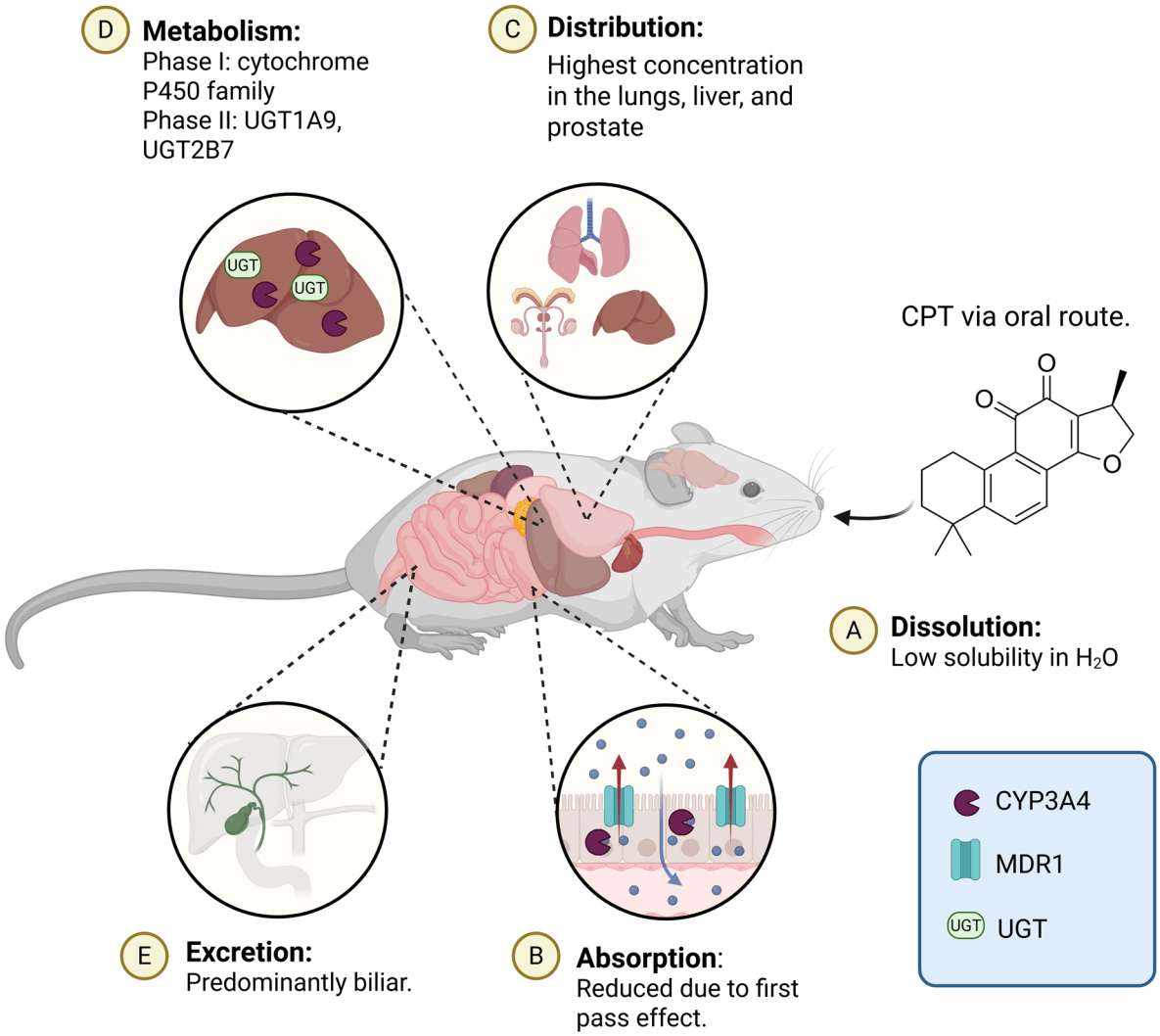


Fig. 3 Pharmacokinetics of Cryptotanshinone (CPT), described primarily in animal models. **A** Dissolution: CPT exhibits poor aqueous solubility, limiting its bioaccessibility. **B** Absorption: Despite high membrane permeability, its oral absorption is compromised due to extensive first-pass effect mediated by cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (MDR1). **C** Distribution: After systemic administration, CPT preferentially accumulates in highly perfused organs like the lungs, liver, and prostate. **D** Metabolism: Undergoes phase I and phase II metabolism mediated by the cytochrome P450 family and Glucuronosyltransferases (UGT), respectively. **E** Excretion: Elimination occurs predominantly via the biliary route, reflecting its high lipophilicity. Created in BioRender

Metabolism

CPT undergoes both phase I and phase II reactions, as demonstrated by the identification of its primary metabolites in rat bile following intravenous administration. Among phase I reactions, dehydrogenation of saturated rings predominates, leading to the formation of tanshinone IIA (Fig. 4B), the most abundant metabolite that retains bioactivity. CPT may also undergo mono- or dihydroxylation, producing various derivatives, including hydroxycryptotanshinone, 3-hydroxycryptotanshinone, and 18-hydroxycryptotanshinone [35, 36]. Using human liver microsomes, Zeng et al. identified 47 phase I metabolites (Zeng et al., 2018). The cytochrome P450 isoenzymes CYP2C19, CYP2A6, CYP3A4, and CYP1A2 were found to be primarily responsible for these reactions [37] (Fig. 4D).

In phase II metabolism, O-glucuronidation is the dominant pathway, mediated by the glucuronosyltransferases UGT1A9, UGT2B7, and UGT2B4 [37] (Fig. 4D).

Moreover, CPT has been identified as a potent inhibitor of the CYP1A2 isoenzyme, suggesting that its co-administration with drugs such as paracetamol or other CYP1A2 substrates may increase the risk of toxicity [38]. *In silico* analysis using SwissADME3.0 also indicates inhibitory activity against other CYP450 isoenzymes, including CYP2C19, CYP2C9, and CYP3A4 [22], thereby increasing the likelihood of drug-drug interactions.

Toxicity

The toxicity profile of CPT by itself has been previously evaluated in several preclinical studies. *In vivo* data indicate that CPT does not induce hepatic or renal toxicity at a 20 mg/kg following 24 h treatment [39] In addition, a patent report describing intragastric administration of CPT at a dose of 1.5 g/kg in healthy mice for 7 consecutive days did not identify any overt toxic effects. Furthermore, continuous intragastric administration of CPT for 30 days at doses of 200 mg/kg/day was not associated with clinical signs of toxicity and did not result in detectable anatomical or histopathological alterations in major organs [40]

Elimination

CPT and its metabolites undergo elimination primarily through the biliary route due to their high liposolubility [35]. *In silico* analyses estimate its half-life at approximately 17.3 h [3] (Fig. 4E).

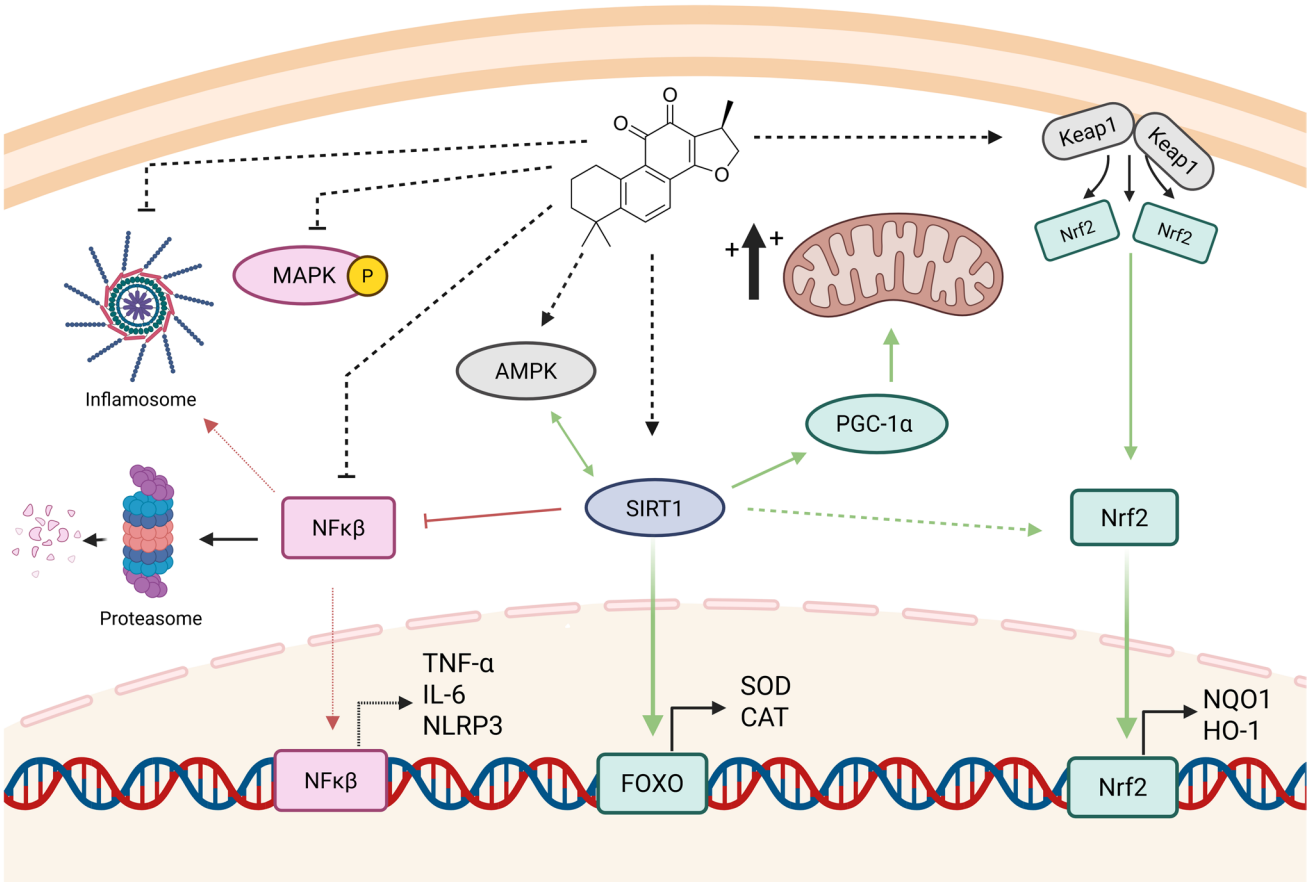


Fig. 4 CPT exerts antioxidant and anti-inflammatory effects by modulating key signaling pathways. Regarding its antioxidant activity, CPT promotes dissociation of Nrf2 from Keap1, facilitates nuclear translocation of Nrf2, and enhances the expression of antioxidant enzymes (e.g., NQO1, HO-1). CPT also activates SIRT1, which in turn increases FOXO-mediated transcription of antioxidant genes (e.g., SOD, catalase), induces PGC-1α expression—thereby supporting mitochondrial function—and activates AMPK. AMPK, in turn, can also activate SIRT1, establishing a positive feedback loop. Concerning its anti-inflammatory activity, CPT inhibits NF-κB nuclear translocation and thus decreases pro-inflammatory mediators, including TNF-α, IL-6, and NLRP3. Additionally, SIRT1 activation by CPT promotes proteasomal degradation of NF-κB. CPT can also attenuate MAPK signaling pathway activation and inflammasome formation. Created with BioRender.com

Despite CPT pharmacokinetic limitations, *in vivo* studies suggests that pharmacological relevant effects can still be achieved following oral administration. This indicates that relatively low plasma concentrations of CPT may be enough to elicit therapeutic effects. Numerous studies have demonstrated CPT strong pharmacological activity, with its anticancer effects receiving the most attention [3]. In contrast, the potential effects of CPT on metabolic diseases remain comparatively underexplored and are therefore addressed in the following section.

Effects of CPT on Mechanisms Implicated in Metabolic Diseases

Metabolic diseases are a group of non-transmissible pathologies associated with metabolic alterations, such as type II diabetes mellitus (T2DM), dyslipidemia, and obesity [41]. Metabolic diseases represent a significant burden on the global health system, and their prevalence has tripled over the past three decades [6]. Environmental, lifestyle, and genetic factors contribute to its development [42]. When not treated properly, they lead to significant complications and diminish patients' quality of life [41]. Metabolic diseases tend to coexist, and the pathophysiological mechanisms associated with their development are generally interconnected [6]. In general, all of them are mediated by increased oxidative stress and low-grade inflammation. In addition, recent research has linked intestinal dysbiosis to the development and progression of metabolic disease [43]. Then, CPT yields a promising therapeutic molecule because it could target multiple mechanisms central to metabolic diseases, as described in the next section.

Oxidative Stress

Oxidative stress has a crucial role in the development and progression of metabolic diseases. The endogenous antioxidant defense system neutralizes reactive oxygen species (ROS) generated during cellular metabolism under physiological conditions [44]. However, when ROS production exceeds the antioxidant capacity, cellular and tissue damage occur due to oxidative stress [45].

The antioxidant potential of a compound refers to its ability to donate electrons to stabilize free radicals or inhibit their generation. It also relates to its capacity to regenerate endogenous antioxidant molecules or to activate intracellular antioxidant pathways. In this way, mitigating oxidative damage at the cellular level [46]. In particular, a study by Wang et al. (2003) demonstrated that a *Danshen* extract can dose-dependently reduce hydroxyl radical formation *in vitro* [47]. However, further studies are needed to elucidate the specific contribution of CPT to free radical neutralization.

The majority of research evaluating the antioxidant mechanisms of CPT has focused on its modulation of key regulators of redox homeostasis, particularly the Nrf2 and AMPK/SIRT1 pathways.

Relevant Antioxidant Pathways

Nrf2 (nuclear factor erythroid–related factor 2) is a transcription factor that, under basal conditions, is sequestered in the cytoplasm by Keap1 (Kelch-like ECH-associated protein 1), which facilitates its ubiquitination and subsequent proteasomal degradation [48]. Upon increased oxidative stress, Nrf2 dissociates from Keap1, translocates to the nucleus, and activates the transcription of genes encoding cytoprotective enzymes, such as heme oxygenase-1 (HO-1) and NAD(P)H quinone dehydrogenase 1 (NQO1), as well as enzymes related to glutathione generation. Therefore, Nrf2 activation enhances antioxidant and detoxification responses, promoting cellular survival [49] (Fig. 4).

The AMPK/SIRT1 axis plays a pivotal role in regulating oxidative stress. Adenosine monophosphate-activated protein kinase (AMPK) is a serine/threonine kinase that functions as a key metabolic regulator. AMP binding and Thr172 phosphorylation by liver kinase B1 (LKB1) can activate this kinase [50]. AMPK activation leads to the phosphorylation of its downstream targets, favoring catabolic pathways and inhibiting anabolic ones, thereby increasing the intracellular NAD^+/NADH ratio. The increased NAD+levels activate silent information regulator 1 (SIRT1), a NAD^+-dependent class III histone/ protein deacetylase. A positive feedback loop exists between SIRT1 and AMPK. When SIRT1 is activated, it can also favor AMPK activity by activating LKB1 [51, 52]. Over the SIRT1 targets related to management of oxidative stress are Forkhead box O (FOXO) family members. FOXO transcription factors bind to the promoter regions of antioxidant genes including superoxide dismutase (SOD) and catalase (CAT), thereby promoting their transcription and synthesis [53] (Fig. 4). Another target of SIRT1 is the peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC1α), which increases mitochondrial function and transcription of antioxidant proteins. Additionally, several models have described how SIRT1 can increase Nrf2 expression and nuclear translocation [54].

CPT Antioxidant Effects in Experimental Models

Likewise, *in vivo* and *in vitro* models have evaluated CPT antioxidant capacity. For example, Song et al. investigated the antioxidant effects of CPT in mice models of chronic obstructive pulmonary disease (COPD) induced by cigarette smoke (CS) and lipopolysaccharide (LPS). Administration of CPT at 60 mg/kg significantly attenuated oxidative stress in the COPD model mice. CPT treatment effectively reduced ROS levels and led to a marked increase in the expression and activity of antioxidant enzymes, such as CAT and SOD, as well as in L-glutathione synthesis. *In vitro*, CPT treatment of BEAS-2B bronchial epithelial cells under CS and LPS stimulation resulted in enhanced Nrf2 dissociation from Keap1, increased Nrf2 expression, and nuclear translocation. These effects were consistent with those observed in lung tissues from the murine model [55].

Meanwhile, a study by Guo et al. examined the effects of CPT on oxidative stress and mitochondrial function in keratinocytes (HaCaT) and fibroblasts (HFF-1) exposed to UV irradiation. The results demonstrated that UV exposure reduced nuclear Nrf2 localization and, subsequently, HO-1 and NQO1 expression. However, treatment with CPT restored the expression of these proteins, mitigating UV-induced oxidative damage [56]. Additionally, the study assessed the AMPK/SIRT1/PGC-1α signaling pathway, which similarly decreased with UV exposure. CPT treatment effectively reversed these effects, promoting mitochondrial biosynthesis and reducing mitochondrial dysfunction [56].

In another study, Nagappan et al. evaluated the effects of CPT on ethanol-induced oxidative stress in HepG2 and AML-12 cell lines and in a C57BL/6 mouse model. The study demonstrated that CPT effectively reduced oxidative stress and inflammation in the liver by activating the AMPK/SIRT1/Nrf2 signaling pathway. The findings indicated that ethanol exposure decreased the expression of AMPK, SIRT1, and Nrf2, as well as antioxidant genes, including catalase, superoxide dismutase, and glutathione peroxidase. Additionally, ethanol treatment decreased hepatic glutathione (GSH) levels, thereby increasing CYP2E1 activity and contributing to heightened ROS generation. Notably, CPT administration was found to reverse the adverse effects induced by ethanol [57]. The effects of CPT on the key pathways involved in oxidative stress regulation, as described above, are summarized in Fig. 4.

Although the antioxidant effects of CPT are well-documented, it is necessary to evaluate its impact in the context of metabolic diseases. Usually, oxidative stress is accompanied with inflammation [44]. Low-grade inflammation strongly contributes to the development and progression of metabolic diseases. Notably, CPT modulates key inflammatory pathways, as discussed in the following section.

Chronic Low-grade Inflammation

It is well known that metabolic diseases are related to chronic low-grade inflammation. Patients with metabolic disease show elevated levels of inflammatory mediators, including tumor necrosis factor-alpha (TNF-α), interleukin-1 and 6 (IL-1, IL-6), as well as changes in immune cells activation [42, 58]. Some key pathways involved in inflammation include NF-κβ and MAPK.

Inflammatory Signaling Pathways

Firstly, the nuclear factor K-light-chain-enhancer of activated B cells (NF-κβ) family of transcription factors plays an important role in regulating inflammatory processes and the immune response. Under resting conditions, NF-κB is sequestered in the cytoplasm by inhibitory IκB proteins. Upon exposure to inflammatory stimuli, IκB is phosphorylated by IκB kinase (IKK), leading to its proteasomal degradation and the subsequent translocation of NF-κB to the nucleus. Once in the nucleus, NF-κB promotes inflammation by inducing the expression of pro-inflammatory cytokines like TNF-α and IL-6; chemokines; adhesion molecules like intracellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1); pro-inflammatory enzymes like cyclooxygenase 2 (COX-2) and inducible nitric oxide synthase (iNOs); and genes involved in immune cell proliferation and differentiation [59–61]. Also, the NF-κB pathway led to inflammasome priming by upregulating NOD-like receptor family pyrin domain-containing 3 (NLRP3). Additional stimulus, including endogenous damage signals such as cholesterol and ATP, are required for NLRP3 activation and inflammasome complex assembly. Studies have shown that oxidized mitochondrial DNA (ox-mtDNA), derived from mitochondrial damage, binds to and activates NLRP3. Upon activation, NLRP3 self-oligomerizes and recruits apoptosis-associated speck-like (ASC), which acts as a platform for the autoactivation of caspase-1, which later cleaves pro-IL-1β and pro-IL-18 into their mature forms [60, 62, 63].

In another hand, Mitogen activated protein kinase (MAPK) pathways are known to participate in inflammatory processes. In typical MAPK pathways, three consecutive phosphorylation events occur: MAPK kinase kinase phosphorylates a MAPK kinase, which later phosphorylates a MAPK. Among the most studied MAPK pathways related to inflammation are the p38, c-Jun NH_2-terminal kinase (JNK), and extracellular signal-regulated kinase (ERK). When phosphorylated, downstream of ROS and other stimuli, they activate transcription factors such as AP-1 and NF-κβ, leading to the transcription of inflammatory mediators such as TNF-α, IL-6, IL-8, iNOS, and COX-2 [64].

CPT Anti-inflammatory Effects in Experimental Models

Multiple studies demonstrate CPT's anti-inflammatory effects across different models. In an *in vitro* lipopolysaccharide (LPS)-induced inflammation model, Tang et al. reported that CPT reduced TNF-α and IL-6 secretion in RAW264.7 macrophages. Mechanistically, CPT suppressed ERK1/2, JNK, and p38 phosphorylation as well as NF-κB p65 nuclear translocation, thereby impairing both NF-κB and MAPK signaling pathways [65]. Similarly, Li et al. confirmed the anti-inflammatory effects of CPT in the same model, showing that CPT treatment inhibited IκB phosphorylation and degradation, as well as IKK-α/β phosphorylation, ultimately reducing NF-κB p65 nuclear translocation. Consistently, CPT also blocked the phosphorylation of MAPK proteins JNK, ERK, and p38. Inhibition of both NF-κB and MAPK pathways translated into decreased expression of pro-inflammatory cytokines and enzymes, including TNF-α, IL-6, iNOS, and COX-2 [66]. More recently, Meyers et al. reported that CPT treatment inhibited NLRP3 inflammasome activation but not inflammasome priming, in LPS-stimulated human and mouse macrophages. CPT diminished caspase-1 activation and IL-1β secretion, without affecting TNF-α production. CPT (10–40 μM) reduced ATP-induced ASC oligomerization by reducing mtROS production. This effect has also been validated in a murine model of LPS-induced sepsis, where CPT administration decreased IL-1β levels, reduced mtROS, and conferred protection against multi-organ injury [63].

In a neuroinflammation model using LPS-stimulated BV-2 microglial cells, CPT (5 and 10 μM) significantly reduced the expression of IL-6, TNF-α, IL-1β, inducible nitric oxide synthase (iNOS), cyclooxygenase 2 (COX2), and NLRP3 via inhibition of the NF-κB pathway [67]. It is remarkable that, in their study, Nrf2 knock-out diminished CPT's effects on certain inflammatory mediators, suggesting that oxidative stress reduction by CPT may play an essential role in its anti-inflammatory effect [67]. CPT activation of the AMPK/SIRT1 pathway could also negatively regulate inflammation. SIRT1 directly deacetylates the p65 subunit of NF-κB, thereby not only suppressing its transcriptional activity but also promoting its proteasomal degradation [68]. The effects of CPT on inflammation regulation, as described above, are summarized in Fig. 4.

Beyond its effect on PAMP-mediated inflammation, CPT's impact on low-grade inflammation in metabolic diseases remains less explored. In our research group, we have evaluated the anti-inflammatory effect of CPT on metabolic inflammation. Our findings showed that CPT treatment decreased COX-2 expression in hepatocytes (C9) and Langerhans β cells (RIN-m5F) exposed to palmitic acid and also diminished lipotoxicity [69].

Taken together, these findings highlight CPT as a promising multi-target anti-inflammatory agent, with potential therapeutic activity in metabolic inflammation common to metabolic diseases.

Gut Microbiota Dysbiosis

It is now well established that the gut microbiota performs key physiological functions in the human body, such as protecting against the invasion of pathogenic microorganisms, strengthening the intestinal barrier, enhancing digestion and metabolism, facilitating the production and absorption of micronutrients, and supporting the maturation of the immune system [70].

However, when gut microbial dysbiosis occurs, these beneficial functions are impaired. Intestinal dysbiosis, often induced by a diet lacking in fiber and essential nutrients, results in increased levels of bacterial endotoxins, such as lipopolysaccharides, heightened oxidative stress, elevated production of pro-inflammatory cytokines, and increased gastrointestinal permeability [43]. These pathological alterations have been strongly implicated in the onset and progression of metabolic diseases, including obesity, type 2 diabetes mellitus (T2DM), metabolic syndrome (MetS), and metabolic dysfunction-associated fatty liver disease (MAFLD)[71].

Dysbiosis commonly involves a disrupted Firmicutes/Bacteroidetes ratio, reduced microbial diversity, and impaired production of short-chain fatty acids (SCFAs). SCFAs are bacterial metabolites essential for energy regulation, gut barrier integrity, and anti-inflammatory signaling [72, 73]. Furthermore, several metabolites produced by the gut microbiota influence host metabolism by interacting with G-protein-coupled receptors (GPCRs), potentially affecting lipid homeostasis, insulin sensitivity, and even gene expression via epigenetic mechanisms [74]. Microbiome research broadly supports these mechanisms, but the relevance of CPT in this context remains uncertain. Only a limited number of exploratory studies have examined whether CPT alters gut microbiota. Current evidence on its role in shaping microbial composition, particularly in metabolic diseases, remains preliminary and poorly characterized.

CPT Effects over Gut Microbiota in *in vivo* Models

A few preclinical studies have begun to explore the potential interaction between CPT and the gut microbiota. For example, Lin and colleagues used a 5-fluorouracil/irinotecan-induced colitis model in mice with colon cancer. In this study, CPT treatment alleviated intestinal mucosa damage and reduced infiltration of inflammatory cells. Importantly, they noted that CPT therapy was associated with a decrease

in the relative abundance of Muribaculaceae, alongside increases in Lactobacillus, Alistipes, and Odoribacter, as identified by 16S rDNA sequencing. [75]. Notably, studies have previously linked an increased abundance of *Lactobacillus* spp. to improved metabolic parameters in models of obesity [76] and diabetes [77]. Likewise, *Alistipes*, a genus from the phylum Bacteroidetes, is often reported to be reduced in individuals with metabolic disorders such as T2DM [78]. The above suggests that changes induced by CPT treatment in the abundance of the previously mentioned bacterial genera may improve metabolic health. Collectively, these initial observations suggest that CPT may improve metabolic outcomes by influencing microbial composition. However, more research has to be made to conclusively demonstrate this effect.

In a separate investigation, Bian and colleagues examined the impact of CPT on the gut-brain axis utilizing a Wistar rat model subjected to chronic unpredictable mild stress (CUMS). After administering CPT at 20 mg/kg via intraperitoneal injection, microbiota analysis revealed a notable alteration in microbial composition, characterized by decreased levels of *P. merdae* and *P. distasonis* and increased levels of *Pseudomonas caeni*. The CPT treatment was also associated with a significant decline in pro-inflammatory cytokines, including TNF-α, IL-6, and IL-1β, an outcome the researchers suggested might be partly influenced by changes in the gut microbiota [70]. Although chronic inflammation is a defining feature of metabolic disorders, the relevance of these findings to metabolic conditions remains unclear. Nonetheless, these results imply a potential, albeit still preliminary, role for microbiota modulation in the broader biological effects of CPT.

Finally, Li and colleagues found that CPT treatment could help alleviate radiation-induced pulmonary fibrosis by modulating the bile acid–gut microbiota axis. CPT partially restored microbiota composition, leading to increased levels of *Akkermansia*, a genus known for its protective effects against radiation-induced intestinal damage [79]. Moreover, studies link reduced levels of *Akkermansia muciniphila* to metabolic issues arising from a high-fat diet (HFD), including obesity and type 2 diabetes mellitus (T2DM) [80, 81]. While these associations suggest that shifts in *Akkermansia* induced by CPT might have broader metabolic effects, such interpretations are not yet confirmed and require further research.

While current evidence primarily comes from models not explicitly related to metabolic diseases, the finding that CPT may affect gut microbiome composition and reduce inflammatory responses suggests a potential, albeit still very preliminary, pathway for addressing metabolic disorders [82]. One possible benefit of taking CPT orally is its ability to exert local effects on the gut microbiota, even if it does not undergo significant systemic absorption. However, future research must determine whether CPT induces reproducible changes in the gut microbiome in models of metabolic diseases and whether these changes produce clinically meaningful outcomes.

Impact of CPT on Metabolic Disease Models

Diabetes and its Complications

The most common form, type 2 diabetes mellitus (T2DM), is characterized by chronic hyperglycemia driven by insulin resistance and β-cell dysfunction, often linked to obesity and low-grade chronic inflammation.

Diabetes is one of the most prevalent chronic diseases globally, exerting a profound impact on morbidity and quality of life. Recent estimates indicate that in 2022, approximately 828 million adults aged 18 years or older were living with diabetes—an alarming increase of over 600 million cases since 1990 [83].

Key Physiopathological Features

At the molecular level, impaired insulin signaling is a hallmark of T2DM. Studies have described that activation of inflammatory pathways, such as NF-κB, JNK, and JAK/STAT, can impair insulin signaling [84]. A decrease in PI3K/AKT and AMPK activation disrupts the translocation of GLUT4 to the plasma membrane, thereby compromising glucose uptake in skeletal muscle and adipose tissue. This condition perpetuates hyperglycemia and stimulates hepatic gluconeogenesis [85]. Persistent glucotoxicity exacerbates metabolic dysfunction by generating advanced glycation end-products (AGEs) and oxidative stress, which activate protein kinase C (PKC) and NF-κB, thereby promoting a pro-inflammatory milieu that damages both the endothelium and microvasculature[86]. Furthermore, the aberrant activation of signal transducer and activator of transcription 3 (STAT3) in target tissues promotes the expression of fibrogenic mediators, including matrix metalloproteinase-9 (MMP-9) and connective tissue growth factor (CTGF), which contribute to long-term complications such as diabetic cardiac fibrosis [87]. These pathological mechanisms point out the need for molecules that can modulate multiple related pathways.

CPT Effects on Diabetes and its Complications in Preclinical Models

Few studies have evaluated the effect of CPT on this pathology and its complications. For instance, Kim et al. used

C2C12 skeletal muscle myoblasts to demonstrate that CPT at 20 μM significantly enhanced glucose uptake by increasing GLUT4 translocation to the plasma membrane. After using an AMPK inhibitor, increased glucose uptake was abolished [85]. The same authors also evaluated the CPT effect *in vivo* over obese *ob/ob* mice (*C57BL/6 J-Lep*^{ob}). CPT treatment at 600 mg/kg/day resulted in significant reductions in 12 h-starved blood glucose after the 3rd day of treatment, and 2.5–threefold higher AMPK activity, compared to the control group [85].

Moreover, CPT could inhibit the activity of protein tyrosine phosphatase 1B (PTP1B), a known negative regulator of insulin signaling. CPT may regulate PTP1B through direct interaction [88] or by modulating the AMPK/SIRT1 axis. SIRT1-mediated deacetylation of PTP1B improves insulin signaling [89]. Indeed, studies report that insulin-resistant cells downregulate SIRT1 [89]. Collectively, these findings support CPT's antidiabetic properties and highlight its potential to restore systemic energy homeostasis.

However, the effects of CPT are not limited to metabolic regulation; researchers have reported that it aids in the treatment of diabetes-related complications, such as diabetic foot ulcers. In this context, evidence suggests that CPT accelerates wound healing. In a murine excisional wound model, daily administration of CPT at 300 mg/kg for 16 days significantly enhanced wound closure. The CPT-treated group exhibited an 83% wound closure rate, compared to 68% in the control group [86].

Additionally, histological studies demonstrate its ability to reduce cardiac fibrosis in a murine model of streptozotocin-induced type 1 diabetes. The findings indicated that CPT decreased the mRNA and protein levels of STAT3, MMP-9, and connective tissue growth factor in cardiomyocytes cultured in high glucose, similarly to the reductions observed in the hearts of STZ-treated rats [87]. These findings emphasize the remarkable therapeutic potential of CPT in diabetic complications beyond glucose regulation.

Dyslipidemia and Atherosclerosis

Dyslipidemias are characterized by alterations in plasma lipid levels, including total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides. Dyslipidemias constitute a significant risk factor for the development of atherosclerosis. Atherosclerosis is a chronic inflammatory condition marked by the formation of plaques within the arterial intima. This process progressively restricts blood flow to organs and tissues, leading to cardiovascular diseases (CVD) [90].

Epidemiological studies estimate global prevalence rates of dyslipidemia in the adult population at 28.77% for hypertriglyceridemia, 24.09% for hypercholesterolemia, 38.4% for low HDL-C, and 18.93% for high LDL-C [91]. In respect of cardiovascular disease (CVD), the global burden has increased substantially over the past decades. In 1990, studies reported an estimated 271 million cases; by 2019, this number had risen to 523 million. Current projections indicate that the prevalence of CVD will continue to increase in the coming years [92].

Key Physiopathological Features

In atherosclerosis, endothelial dysfunction increases endothelial permeability, allowing LDL to migrate to the vascular endothelium and become oxidized [93]. The accumulation of oxidized LDL (oxLDL) triggers the activation and migration of immune cells, especially monocytes, to the lesion zone; smooth muscle cells migration to the intima; ROS generation; the release of proinflammatory mediators such as tumor necrosis factor-alfa (TNF-α); and the activation of proinflammatory pathways like NF-κB [94]. Among the key molecules involved in the initial steps of atherosclerosis development are Lectin-like oxidized LDL receptor-1 (LOX-1), which mediate proatherogenic events (Barreto, Karathanasis, Remaley, & Sposito, 2021). Intracellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1), which are expressed in response to TNF-α, also play key roles in promoting monocyte adherence and migration to the endothelium [93]. On its part, matrix metalloproteinase 2 and 9 (MMP-2, 9) mediate the degradation of the extracellular matrix in the lesion zone and allow smooth muscle cell migration. Studies showed that TNF-α and the MAPK pathway regulate MMP production, particularly MMP-9 [95].

CPT Effects on Dyslipidemias in Preclinical Models

In vivo studies indicate that CPT treatment can reduce blood lipid levels and modulate key lipid-metabolism pathways. For example, Kim et al. observed that 600 mg/kg/day treatment with CPT reduced serum triglyceride and cholesterol levels by 4% and 20%, respectively, compared with the control group in an ob/ob murine model fed a high-fat diet (HFD)[85]. Similarly, Ni et al. reported that in mice fed an HFD, CPT treatment serum lipid levels and adipose tissue accumulation [96].

Regarding the molecular mechanisms underlying these beneficial effects, Mariangela and colleagues reported that CPT can act as both a ligand and an inhibitor of pancreatic lipase (PL), with an IC50 of 6.86 ± 0.43 μM [97]. The authors evaluated CPT's inhibitory activity *in vitro* and corroborated these findings through molecular docking analyses. PL is a triacylglycerol acyl hydrolase essential for the absorption of dietary fats; therefore, its inhibition

could reduce intestinal fat uptake, thereby lowering circulating lipid levels and lipid accumulation in the vascular endothelium.

Another proposed mechanism involves modulation of the eIF4F translation initiation complex. Previous work from our group demonstrated that CPT can influence the activity of eIF4A, a core component of the eIF4F complex, in *in vitro* cancer models [98, 99]. The eIF4F complex plays an essential role in regulating the translation of proteins essential for lipid biosynthesis, transport, and storage. Its dysregulation leads to increased expression of key lipid-related proteins. These include CD36, which promotes fatty acid uptake; phosphatidate phosphatase (LPIN2), involved in triglyceride synthesis; beta-2-glycoprotein 1 (APOH), implicated in lipoprotein transport; and perilipin-2 (PLIN2), a structural component of lipid droplets [100]. Collectively, these findings suggest that CPT may confer metabolic benefits by modulating eIF4F activity, thereby reducing lipid synthesis and accumulation. However, additional research is necessary to validate this proposed mechanism.

CPT Effects on Atherosclerosis in Preclinical Models

The anti-atherogenic properties of *Danshen* extract have been extensively documented [101, 102] and constitute one of the most widely recognized therapeutic applications of this traditional herbal remedy. However, only a few studies have explored the CPT-specific contribution to this effect.

In an *in vivo* study, CPT at 15 and 45 mg/kg significantly reduced atherosclerotic plaque formation and improved plaque stability in ApoE$^{-/-}$ mice fed a high-fat diet, without altering the serum lipid profile. Notably, CPT treatment reduced circulating levels of proinflammatory cytokines and decreased the LOX-1 and NF-κB expression in aortic sinus lesions in a dose-dependent manner. The same authors also demonstrated that CPT inhibited oxLDL-induced monocyte adhesion to human umbilical vein endothelial cells (HUVECs) in vitro. Collectively, these findings suggest that CPT exerts vasculoprotective effects by targeting key modulators of atherogenesis [103].

Consistent evidence from multiple *in vitro* studies confirms CPT's protective effects on endothelial cells. HUVECs treated with CPT reduced OxLDL or TNF-α induced LOX-1 expression [88, 98], reduced ICAM-1 and VCAM-1 adhesion molecules [93, 104], reduced monocyte chemoattractant protein-1 (MCP-1) expression [93], and restored nitric oxide production [93, 104]. CPT treatment also reduced ROS generation and NF-κB activation [97, 98] in these cells.

Related to CPT in vitro effects on vascular smooth muscle cells, treatment reduced TNF-α- induced NF-κB activity and MMP-9 secretion. CPT also inhibited the MAPK pathway [95].

Within this framework, CPT not only helps regulate lipid profile but also downregulates key mediators of atherosclerosis. Therefore, CPT emerges as an ideal candidate for the treatment of dyslipidemia and atherosclerosis.

Obesity

Obesity occurs when energy intake exceeds energy expenditure, often due to a sedentary lifestyle and excessive nutrition, as noted by the World Health Organization [105]. Obesity continues to rise globally, and projections indicate that by 2025 it will affect 18% of men and 21% of women worldwide [106].

Key Physiopathological Features

Obesity's classic characteristics include disturbances in energy metabolism, persistent low-grade inflammation, insulin resistance, and increased adipogenesis [107]. A crucial factor in this pathology is the impairment of the AMPK pathway. Decreased AMPK activity leads to increased fat storage, reduced energy expenditure, and metabolic disorders [96, 108].

CPT Effects on Obesity in Preclinical Models

In the study of Kim et al. mentioned earlier, the authors also evaluated the effects of CPT on obesity in the ob/ob murine model. The authors administered CPT orally (0, 200, 400, and 600 mg/kg/day) for 1 month and monitored body weight daily. During the study, body weights in the control group increased, while CPT led to a dose-dependent reduction, with a maximum decrease of about 40% at 600 mg/kg/day. This dose also reduced food intake; the average food intake of control animals was 4.9 ± 0.6 g, while CPT-treated animals consumed 3.9 ± 0.5 g. By the end of the monitoring period, CPT-treated animals also accumulated less fat in their adipose tissues. Interestingly, AMPK activity was significantly increased in CPT-treated mice [85].

Also, in a more recent study, Jie Ni and colleagues found a similar result in an HFD obesity mouse model. Treatment with 200 or 400 mg/kg/day of CPT for 6 weeks reduced body weight gain, food intake, glucose levels, serum lipids, and adipose tissue volume compared with the HFD control group. Importantly, CPT-treated mice showed increased adipose tissue browning and thermogenesis, possibly correlated with increased AMPK activity. *In vitro*, CPT prevented lipid droplet formation from MSCs, activated brown genes, and enhanced AMPK pathway activity [96].

Table 2 Summary of the CPT's effects across different metabolic disease models

Pathology	Experimental model	Effects observed	Pathways / targets modulated by CPT
Diabetes	**In vitro:** C2C12 skeletal muscle cells with 20 µM CPT **In vivo:** obese mice treated with 600 mg/kg/day ↓ fasting blood glucose in 12 h and mouse excisional wound model treated with 300 mg/kg/day for 16 days	Improved glucose uptake and reduced fasting blood glucose, acceleration of wound healing and reduction of cardiac fibrosis markers	↑ AMPK, ↑ GLUT4 translocation; possible modulation of PTP1B via the AMPK/SIRT1 axis; ↓ STAT3, MMP-9
Atherosclerosis	**In vitro:** HUVEC and U937 cells exposed to oxLDL or TNF-α **In vivo:** ApoE$^{-/-}$ mice administered at 15 and 45 mg/kg of CTP	Reduced oxLDL uptake and monocyte recruitment, decreased endothelial oxidative stress and inflammatory signaling, preservation of endothelial barrier function, and attenuation of plaque development and progression with improved stability	↓ LOX-1; ↓ ICAM-1, VCAM-1, MCP-1; ↓ ROS; ↓ activation of NF-κB (p65) and ERK; ↓ MMP-9 in vascular cells; ↑ eNOS phosphorylation and ↑ NO production
Obesity	**In vitro:** MSCs **In vivo:** Obese mice treated orally with 0, 200, 400 or 600 mg/kg/day for 1 month and another similar study tried with High-fat diet mice treated with 200–400 mg/kg/day for 6 weeks	Reduction of body weight, food intake and fat accumulation, together with a shift toward a more thermogenic and metabolically active adipose phenotype, associated with AMPK activation	↑ AMPK in adipose tissue; ↑ adipose tissue browning; ↑ thermogenesis; ↓ formation of lipid droplets

Although results are promising, clinical trials are required to confirm its effectiveness and safety for the treatment of obesity in humans.

The CPT's effects across the different metabolic disease models presented throughout the text were summarized in Table 2. In Table 3, to reinforce the relevance of the information presented in this manuscript, we compared CPT effects over different tissues relevant to metabolic diseases with the reported effects of commonly used drugs, metformin and statins. It should be noted that the comparison is only illustrative because the effects of CPT have not been evaluated in clinical studies.

Table 3 Effects of CPT over key tissues involved in metabolic disease in comparison to metformin and statins

Tissue	Cryptotanshinone (CPT)	Metformin	Statins	References
Skeletal muscle	Enhanced glucose uptake by increasing GLUT4 translocation to the plasma membrane AMPK activation	Increases glucose uptake in muscle by activating AMPK; improves insulin sensitivity	No direct effect on GLUT4; slight increase in insulin sensitivity in some studies, mainly secondary to decreased systemic inflammation	[85, 109, 110]
Heart (cardiomyocytes)	Decreased the mRNA and protein levels of STAT3, MMP-9, and connective tissue growth factor	Cardioprotective effect via AMPK; reduction in oxidative stress and inflammation; no marked direct antifibrotic effect	Strong cardioprotective effect; decreased inflammation, oxidative stress, and ventricular remodeling	[87, 111, 112]
Adipose tissue	Decrease in body weight, increased browning and thermogenesis	Decrease in body weight, increase in fatty acid oxidation; decrease in adipose inflammation	Slightly increase the levels of adiponectin	[96, 113, 114]
Blood	Decrease serum triglyceride and cholesterol	Decrease in triglycerides and cholesterol levels as a side effect	Decrease in total cholesterol, LDL, triglycerides and HDL	[96, 115, 116]
Vascular smooth muscle	Inhibited MMP-9 secretion induced by TNF-α	Reduces vascular inflammation via AMPK; decreases ROS production; indirect endothelial protection	Potent anti-inflammatory and anti-atherosclerotic effect	[95, 117, 118]

Perspectives

The Chinese population has used Danshen for centuries for treating different ailments, including metabolic diseases. However, the effects of the isolated Danshen components over metabolic diseases have not yet been investigated

thoroughly. Within this herbal preparation components, CPT has gathered attention as a potential therapeutic molecule for modulating important pathways involved in metabolic disease.

In the last decades, metabolic diseases such as obesity, type 2 diabetes, and dyslipidemia have tripled [6]. These pathologies are characterized by chronic low-grade inflammation, increased oxidative stress, and altered metabolic signaling. CPT has demonstrated the ability to modulate key signaling pathways, including AMPK, SIRT1, Nrf2/Keap1, NF-κB, and PI3K/Akt [55–57], positioning it as a multi-target therapeutic candidate with the potential to intervene at critical nodes of metabolic dysregulation.

Preclinical studies have demonstrated that CPT improves insulin sensitivity, reduces adipogenesis, modulates lipid metabolism, and promotes mitochondrial biogenesis [85, 96, 108]. Moreover, CPT attenuates vascular inflammation and stabilizes atherosclerotic plaques independent of lipid levels, suggesting vascular-protective effects [93, 103]. Notably, studies have reported that CPT accelerates wound healing in diabetic models, highlighting its relevance in addressing secondary complications of metabolic diseases [86]. Nevertheless, well-designed clinical trials are required to adequately evaluate the effects of CPT over metabolic diseases in humans.

Importantly, in the context of CPT for treating metabolic disease, an important knowledge gap lies in determining its effects over microbiome dysbiosis. Future research should prioritize studies specifically designed to evaluate the modulatory effects of CPT on gut dysbiosis associated with metabolic disease. Investigations using metabolic disease murine models are required to corroborate CPT treatment impact on microbial profiles and inflammatory markers. Provided that favorable outcomes are obtained, these preclinical findings could support the progression toward translational studies in humans involving oral administration of CPT.

Another important area of opportunity lies in the development of strategies aimed at improving the bioavailability of CPT. As discussed above, CPT exhibits significant pharmacokinetic limitations including low aqueous solubility (<0.1 mg/mL), which severely limits dissolution and absorption in the gastrointestinal tract. In addition, extensive first-pass metabolism and P-glycoprotein (P-gp)-mediated efflux further reduce its systemic availability [26].

One promising approach to overcome these limitations involves generation of structurally modified CPT derivatives that retain pharmacological activity while exhibiting improved physicochemical properties. In this regard, Fangfeng and colleagues reported synthesis of CPT derivatives with a lower Log P value by attaching aromatic acid moieties at the A ring. However, the pharmacological properties of these derivatives were only preliminary evaluated [119]. Comprehensive *in vitro* and *in vivo* studies are therefore required to confirm their safety, bioactivity, and therapeutic potential. Furthermore, the incorporation of alternative, more readily hydrolysable and hydrosoluble substituents into the CPT structure may be a good strategy to enhance oral bioavailability.

The development of novel formulations represents another approach to improving oral bioavailability. Advanced strategies such as solid lipid nanoparticles, hydroxypropyl-β-cyclodextrin inclusion complexes, and nanocrystal formulations have already produced substantial improvements in CPT's solubility, intestinal uptake, and systemic exposure [26, 120]. Following these advances in formulation design, recent trends in nanomedicine have shifted toward designing targeted nanocarrier systems capable of directing CPT to specific tissues, such as muscle and adipose depots, to further enhance its pharmacological efficacy and minimize systemic loss.

Lipid-based nanocarriers, such as liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs), have demonstrated high biocompatibility and the ability to encapsulate hydrophobic compounds like CPT, enhancing their solubility and controlled release [121]. For adipose tissue targeting, lipid and polymeric nanocarriers modified with ligands such as the prohibitin-binding peptide CKGGRAKDC or integrin-binding iRGD have shown selective accumulation in white and brown fat depots, facilitating drug delivery directly to adipocytes and macrophages involved in lipid metabolism [122]. In addition, biomimetic nanocarriers, such as cell membrane-coated systems, offer improved immune evasion and longer circulation times, which could extend CPT's residence in target tissues [123]. For skeletal muscle delivery, ligand-conjugated nanocarriers using transferrin receptor 1 (TfR1) antibodies, muscle-homing peptides, or aptamers have been shown to increase selective uptake and retention in muscle fibers while minimizing off-target accumulation [124].

In conclusion, CPT is a plant-derived compound with significant therapeutic potential in the context of metabolic disease. Its multi-target pharmacological profile and capacity to modulate several hallmarks of metabolic dysfunction make it an attractive candidate for future integrative strategies. Further research is essential to optimize its bioavailability and validate its clinical efficacy in metabolic contexts.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Conflicts of interest The authors declare no competing interests.

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