

Pharmacological Mechanisms of Cryptotanshinone: Recent Advances in Cardiovascular, Cancer, and Neurological Disease Applications

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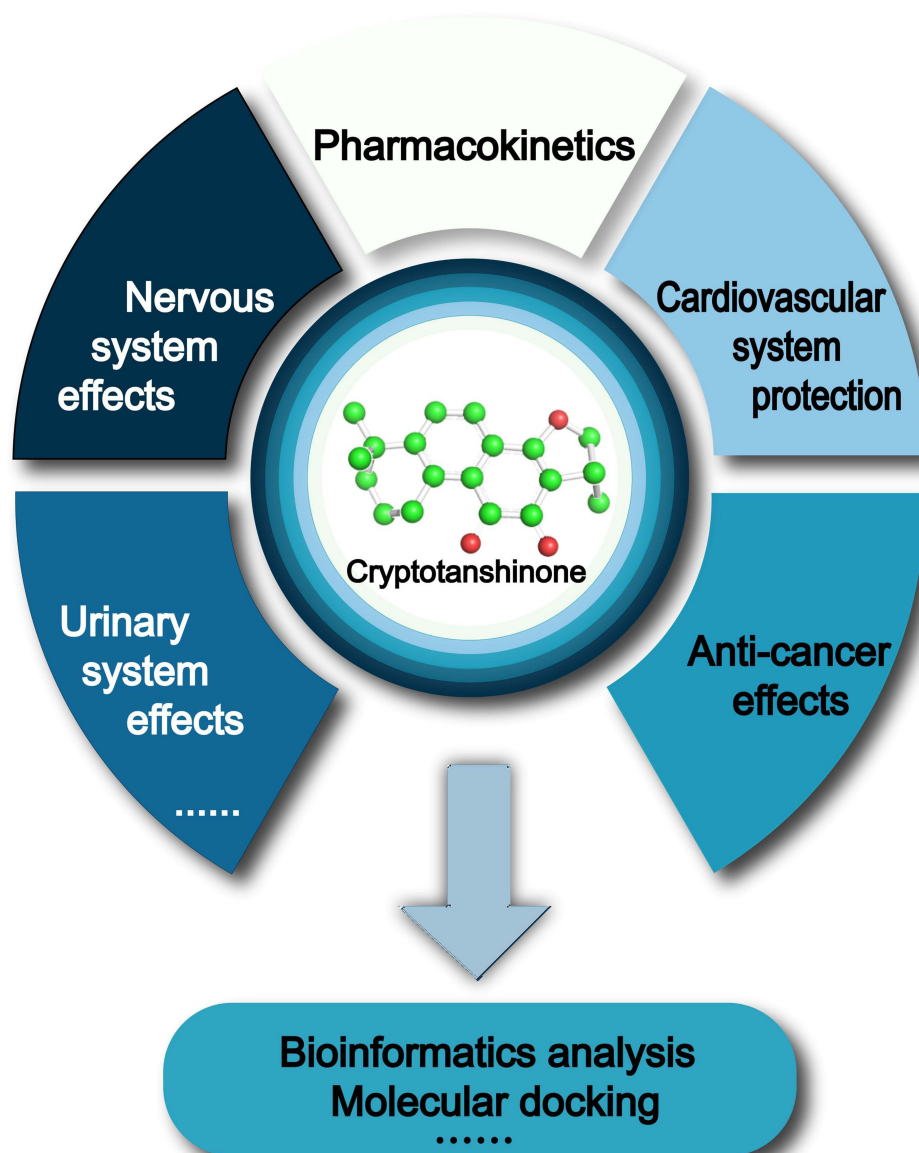
Abstract: Cryptotanshinone (CTS) is an important active ingredient of *Salvia miltiorrhiza* Bge. In recent years, its remarkable pharmacological effects have triggered extensive and in-depth studies. The aim of this study is to retrieve the latest research progress on CTS and provide prospects for future research. The selection of literature for inclusion, data extraction and methodological quality assessment were discussed. Studies included (1) physicochemical and ADME/Tox properties, (2) pharmacological effects and mechanism, (3) conclusion and bioinformatics analysis. A total of 915 titles and abstracts were screened, resulting in 184 papers used in this review; CTS has shown therapeutic effects on a variety of diseases by modulating multiple molecular pathways. For example, CTS primarily targets NF- κ B pathway and MAPK pathway to have a therapeutic role in cardiovascular diseases; in cancer, CTS shows superior efficacy through the PI3K/Akt/mTOR pathway and the JAK/STAT pathway; CTS act on the Nrf2/HO-1 pathway to combat neurological diseases. In addition, key targets of CTS were predicted by bioinformatics analysis, referring to disease ontology (DO), Kyoto Encyclopedia of Genes and Genomes (KEGG) and gene ontology (GO) enrichment analysis, with R Studio; AKT1, MAPK1, STAT3, P53 and EGFR are predicted to be the key targets of CTS against diseases. The key proteins were then docked by Autodock software to preliminarily assess their binding activities. This review provided new insights into research of CTS and its potential applications in the future, and especially the targets and directly binding modes for CTS are waiting to be investigated.

Keywords: cryptotanshinone, pharmacological effects, molecular mechanism, bioinformatics analysis

Introduction

Salvia miltiorrhiza Bge. is a widely used herb throughout the world, particularly in China, where it has been used for millennia.¹ It is predominantly found in China, particularly in humid regions with a temperate climate and an abundance of light. Additionally, it is found in Mongolia, Korea, Japan, the United States, and New Zealand.² In traditional medicine, *Salvia miltiorrhiza* is regarded as a substance that promotes blood circulation and eliminates blood stasis, nourishes the blood, tranquilizes the mind, and regulates menstrual bleeding. Given its superior efficacy, modern medicine utilizes it to treat a range of diseases, including liver diseases and tumors.³ To date, numerous chemical compounds have been extracted from the *Salvia miltiorrhiza*. These include hydrophilic phenolics, such as salvianolic acid, rosmarinic acid, and caffeic acid, as well as lipophilic diterpene quinones, including tanshinone IIA and cryptotanshinone, etc. Additionally, the plant has been found to contain other beneficial secondary metabolites, including polysaccharides and alkaloids, which exhibit promising pharmacological activities.⁴ Being one of active ingredients in

Graphical Abstract



this herb medicine,^{1,2} cryptotanshinone (CTS) (Figure 1) has subsequently received a large number of modern pharmacological studies, suggesting its great medicinal potential.^{5–9}

Currently, there have been several reviews retrieving the anti-cancer activities and molecular mechanism of CTS, however, the reviews about CTS's multifunction are limited up to the end of 2020.^{5–7} Therefore, an update systematic review on the ingredient, especially focusing on its multiple pharmacological effects and mechanism, is helpful to supporting future investigation for the active ingredient's potential applications.

In this paper, the last progress of research is updated on pharmacological effects and molecular mechanisms of CTS against various diseases, such as cancerous, cardiovascular, neurological, respiratory and motor system diseases. Especially, much new knowledge, such as about urinary system protection, motor system protection, and respiratory system protection, endocrine system protection, and mechanisms of the CTS, is retrieved in the review. Meanwhile, this paper further provides an updated systematic prediction of the possible mechanisms and targets of CTS against diseases

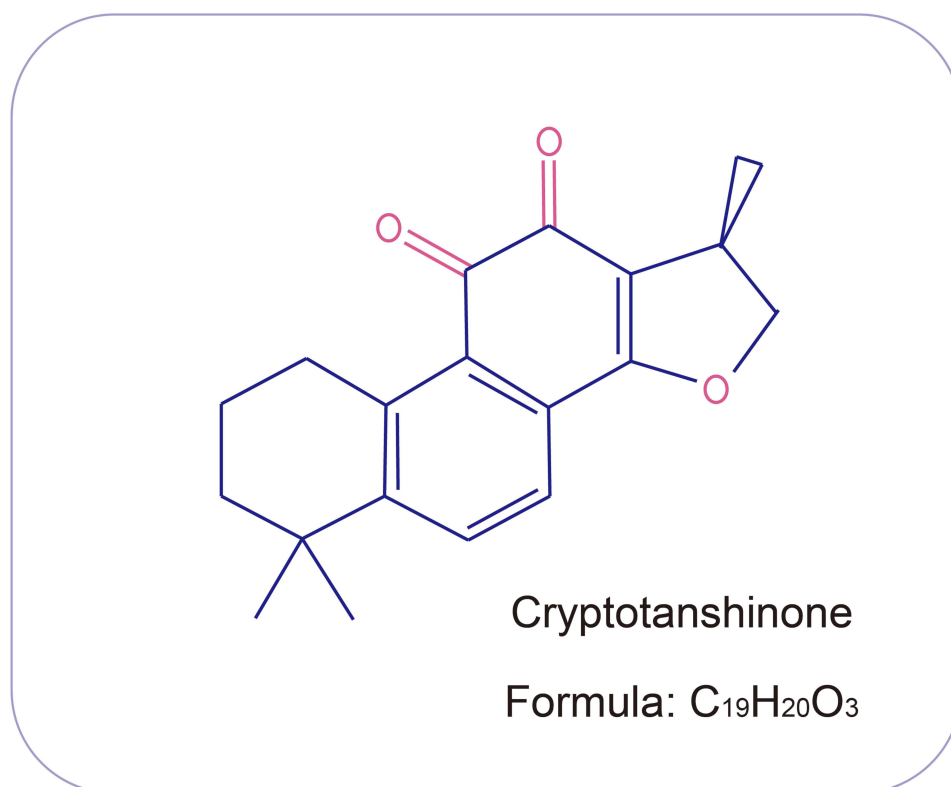


Figure 1 Meta-Analyses (PRISMA) flowchart for inclusion and exclusion of literature in this review.

through bioinformatics analysis, including Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway and Disease Ontology Semantics and Enrichment (DOSE) analysis, with the reported genes or proteins related to CTS's pharmacological effect.

Methods

The following terms were searched in the PubMed, and Web of Science databases “(cryptotanshinone) AND (“2017/01/01”[Date - Publication]: “2024/08/01”[Date - Publication])” and “(ALL=(cryptotanshinone)) and DOP=(“2017–01-01 / 2024-08-01”). 08–01)”. As a result, 417 and 498 records were collected from the two databases, individually. Documents related to tanshinone IIA, tanshinone I, and dihydrotanshinone I studies were manually excluded. Subsequently, studies related to the preparation, synthesis, optimization of processes, derivatives, biotransformation transformation, analytical methods of cryptotanshinones were excluded based on the title, abstract, and content of the article (113 of the excluded papers were accompanied by reasons for exclusion). Finally, 184 eligible articles were included. According to prisma statement,^{10,11} the prisma flowchart for this review is shown in [Figure 2](#).

Physicochemical and ADME/Tox Properties

Physicochemical Properties

Cryptotanshinone (Molecular Formula: C₁₉H₂₀O₃, WM: 296.39, pKa: 4.9) ([Figure 1](#)), a heterocyclic diterpenoid quinone, orange needle-like crystals, soluble in dimethyl sulfoxide, methanol, chloroform and ether.^{12,13} Oil-water partition coefficient LogP: 3.44, slightly soluble in water (0.00976 mg/mL).¹⁴

Pharmacokinetics

In an in vitro assay, the gastrointestinal absorption transport properties of CTS (bidirectional transport assay in Caco-2 cells) Papp (a→b): 0.98×10⁻⁶ cm/s; Papp (b→a): 8.36×10⁻⁶ cm/s.¹⁵ In human trials, cryptotanshinone blood levels were

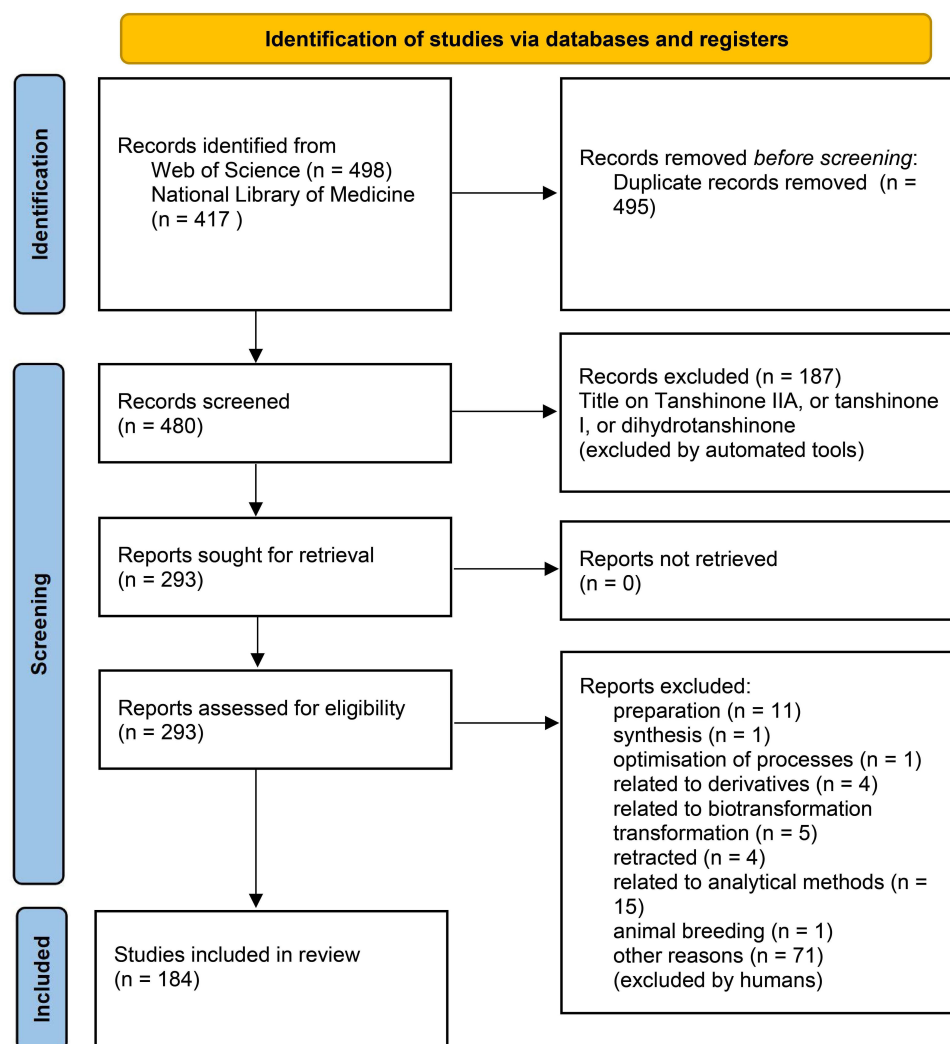


Figure 2 The structure of cryptotanshinone.

below 88 ng/mL after 24h of oral administration of tanshinone capsules containing 88 mg CTS in healthy Chinese volunteers.¹⁶ All the above studies showed that CTS was poorly absorbed orally. Studies have shown that the distribution of CTS in the body 48h after oral administration: liver > lung > prostate > kidney > heart > plasma > spleen > brain.¹⁷ UDP-glucuronosyltransferase (UGT) and CYP enzymes are able to breakdown CTS to create hydroxylation products, S-cysteine binding reaction products, and other complicated reaction products. Currently, 45 CTS metabolites have been discovered.¹⁸ Among them, Tanshinone IIA, the dehydrogenation product of CTS, has now been shown to possess numerous pharmacological activities such as anticancer, anti-Alzheimer's disease and cardiovascular protection,¹⁹ which responds to the great drug-forming potential of CTS. CYP enzymes and UGT enzymes are major metabolic enzyme systems in humans, and CTS has the ability to inhibit CYP enzyme activity, activate PXR and induce UGT gene expression.^{20,21} Therefore, attention should be paid to drug-drug interactions when using CTS containing preparations in combination with other drugs.

Bioavailability

Low bioavailability of CTS has been reported, which may be closely related to the in vivo metabolism of CTS and P-glycoprotein (P-gp) mediated efflux.²² This significantly affects the potential for the prescription drug development of CTS, for which researchers have used a variety of approaches to improve the bioavailability of CTS. Initially, the

bioavailability of CTS can be improved through drug interactions. Studies have shown that CTS improves the efficacy of anticoagulants. For example, CTS is able to significantly inhibit the hydroxylation of warfarin by interfering with CYPase-mediated warfarin metabolism, and increasing the steady-state concentration of warfarin in the body and prolonging the duration of action of the drug.²³ In addition, the active ingredients of *S. miltiorrhiza* act synergistically to enhance the oral absorption of CTS. Researchers used UPLC-MS/MS to determine the plasma concentrations of tanshinone and polyphenols in rats to study their pharmacokinetic interactions, and found that the polyphenolic components affected the pharmacokinetics of CTS and significantly improved the oral bioavailability of CTS.²⁴ Firstly, studies have shown that synergistic effects between CTS and drugs are associated with P-gp mediated glycoprotein efflux,^{25,26} inhibition of transporter proteins²⁷ and liver microsomal CYP enzyme system.²⁸ Secondly, the synthesis of CTS derivatives may elevate bioavailability of CTS. Some researchers designed and synthesized 45 aromatic ring hybrid derivatives of CTS and investigated the cardioprotective effects of the derivatives by in vitro hypoxia/reoxygenation model.²⁹ The results showed that the synthesized CTS derivatives had higher polarity and better biological activities. Moreover, with the advancement of modern science and technology, CTS is able to be made into solid dispersions,³⁰ liposome preparations,³¹ nano-loaded particles²⁹ and other novel drug delivery systems to enhance the bioavailability of CTS.

Potential Toxicity

Results from in vitro cell experiments indicate that pretreatment with 10 μ M CTS for 24 hours did not cause observable damage to H9c2 cardiomyocytes, however, when treated with 3 μ M CTS for the same duration, there was a significant decrease in proliferation observed in human fibroblast-like synovial cells (FLS).³² This evidence suggests a potential adverse impact of CTS and varying degrees of toxicity in different types of tissue cells. However, current research papers lack a comprehensive dual interpretation of CTS potency and toxicity. As the administered dose increases, the drug toxicity would potentially become evident. Future studies should consider the dual role of potency and toxicity to fully harness the potential of CTS from a clinical perspective. Studies demonstrate that LD50 of a *S. miltiorrhiza* injection containing the main ingredient CTS,³¹ is 68.72 g/kg, and both chromosomal aberration and mouse bone marrow micronucleus tests indicate no genotoxicity of the injection.³³ In an acute toxicity study, intravenous administration of CTS at a dose of 32 g/kg did not cause death or other toxicity in rats. In the subchronic toxicity study, triglyceride and body weight reductions were detected without lethal effects.³³ In the zebrafish model, zebrafish embryos were retarded at a teratogenicity index (TI) of 2 for CTS, and this teratogenic effect was mitigated with time. Additionally, other teratogenic effects of CTS included scoliosis, abnormal yolk sac/tail development and pericardial edema.³⁴ Despite the absence of evidence indicating that CTS exhibits pronounced acute toxicity, the possibility of its toxicity cannot be disregarded. The efficacy of drugs should base on safety, and future research should focus on elucidating whether prolonged CTS administration may result in adverse effects on normal tissues and organs or exacerbate the risk of organ damage.

Clinical Studies

Salvia miltiorrhiza Bge. has a long history of use in the treatment of cardiovascular disease. In recent years, several clinical trials have been developed with the aim of comprehensively examining its safety and efficacy. In addition to their efficacy in the treatment of cardiovascular disease, danshen preparations have been demonstrated to improve the prognosis of patients undergoing percutaneous coronary intervention.^{35,36} Furthermore, danshen preparations are utilized in conjunction with other proprietary Chinese medicines for the management of cardiovascular disease, stroke, and alcoholic fatty liver disease.^{37–39} Furthermore, a review of the existing literature revealed that, while there are currently no clinical trials investigating CTS, tanshinone IIA, which shares a similar structural composition with CTS, has been approved for use as a proprietary drug (tanshinone IIA sodium sulfonate) and has already been the subject of several clinical trials.⁴⁰ A comparison of cryptotanshinone with tanshinone IIA indicates that both belong to the group of chemical compounds known as diterpene quinones, and that they are similarly characterized by low bioavailability. This undoubtedly presents a significant challenge for the clinical translation of the drug. Despite the numerous studies on CTS's pharmacological activity, the issue of bioavailability remains a significant challenge at clinical levels. The use of

tanshinone IIA as a reference for improving solubility through salt formation has the potential to significantly enhance the pharmaceutical potential of CTS and facilitate its clinical application.

Pharmacological Effects and Mechanism of CTS

Cardiovascular System Protection

Protection of Cardiac Ischemia/Reperfusion Injury

Ischemia/Reperfusion Injury (IR) is a pathological process that causes further damage to the myocardium after blood flow is restored to the myocardium under ischemic conditions. Reperfusion results in more severe pathological outcomes in ischemic tissues of the heart.⁴¹ Mechanisms of IR include oxidative stress, impaired mitochondrial energy metabolism,⁴² inflammatory responses⁴³ and intracellular Ca^{2+} overload.⁴⁴ Firstly, CTS enhances cell viability through downregulation of ERK and NF- κ B pathways, promotes Bcl-2 anti-apoptotic gene expression and inhibits ROS and MDA production, which ameliorates myocardial oxidative stress and inhibits apoptosis.⁴³ Second, CTS suppresses cysteine 3 cleavage and cardiomyocyte apoptosis through upregulation of the MAPK3 pathway, thus exerting a protective effect against IR.⁴⁰ Third, under normal physiological conditions, intracellular and extracellular Ca^{2+} are maintained in balance. During myocardial hypoxia/reoxygenation injury, Ca^{2+} plays a signaling role by activating CaM kinase (CaMK), which promotes cardiomyocyte death in IR injury.⁴⁴ CTS reduces intracellular CaM and CaMKII δ expression and protects damaged cardiomyocytes.⁴⁵ In addition, intracellular PDK4 upregulation leads to cardiomyocyte hypoxia and induces I/R injury.⁴⁶ Studies have shown that CTS effectively inhibit PDK4 expression and improve cellular metabolism.⁴⁷

Protection of Atherosclerosis

The generation of atherosclerosis typically follows a specific pattern. Firstly, damaged endothelial cells secrete oxidized low-density lipoprotein (LDL) into the bloodstream where it accumulates. In response to stimuli such as oxidized LDL and proinflammatory mediators, endothelial cells produce monocyte chemoattractant protein-1(MCP-1).⁴⁸ Secondly, MCP-1 attracts monocytes across the gaps between endothelial cells, and enters the damaged site selectively. Finally, these monocytes bind to endothelial adhesion molecules and penetrate the intima layer, where they further differentiate into macrophages. Macrophages recognize oxidized and aggregated modified LDL through scavenger receptors before engulfing the large amounts of LDL present in the affected area and forming foam cells.⁴⁹ On the one hand, oxidatively modified low-density lipoprotein (Ox-LDL) in mRNA significantly induces intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), E-selectin (an important factor associated with atherosclerosis) and promotes the progression of atherosclerosis. A study has shown that CTS is able to reduce the concentration of body fat as well as serum cholesterol and triglyceride levels,⁴⁹ and CTS inhibits IKK β -I κ B via NF- κ B pathway interactions and phosphorylation-mediated p65 nuclear translocation reduces the expression of ICAM-1, VCAM-1 and E-selectin,⁵⁰ and exerting anti-atherosclerotic effects. On the other hand, CTS weakens the progression of atherosclerosis induced by oxLDL through the pathway involving Lectin-like oxidized LDL receptor-1 (LOX-1).⁵¹ It also has a protective effect on injured endothelial cells by hindering TNF- α induced monocyte adhesion and restraining the production of ICAM-1 and VCAM-1 molecules.⁵² Additionally, it inhibits angiogenesis and migration through VEGFR2 and PKM2 signaling pathways,^{53,54} and offers protective effects against atherosclerosis. Furthermore, studies on zebrafish and mice models suggest that CTS has a potent anti-angiogenic effect, which is possibly due to its mechanisms of transcription of TNF- α through NF- κ B and STAT3 pathways and mRNA stability associated with TNF- α transcription achieved by CTS.⁵⁵

As the atherosclerotic disease progress, the generated lipids and foam cell death debris accumulate and continue to generate fibrous plaques. Additionally, some smooth muscle cells (SMC) enter a proliferative state, migrate beyond the intima, and secrete extracellular matrix to create fibrous caps, which in turn cause pathological events such thrombosis, acute coronary syndrome, and myocardial infarction.⁴¹ The partial re-differentiation of SMCs into dividing and macrophage-like cells results in subsequent inflammatory reactions, cell necrosis, and cyto-calcification.⁵⁶ The results of an in vitro experiment suggest that CTS may exert its anticoagulant effects through the cyclooxygenase-2/mPGES-1/ endothelial prostaglandin EP3 pathway, and subsequent animal experiments demonstrate that CTS selectively reduces EP3 isoform expression, which provides a theoretical basis for subsequent in-depth studies on the anti-atherosclerotic

effects of CTS via this pathway.⁵⁷ Studies conducted in animal models have shown that CTS possesses protective effects against atherosclerosis. In zebrafish model studies, CTS reduces oxidative stress injury and inhibits thrombosis through the coagulation cascade.⁵⁸ Further studies have demonstrated that CTS has antithrombotic actions by blocking COX-1 and TNF- α to drastically diminish phenylhydrazine induced endogenous thrombosis and decrease TXA2-mediated platelet aggregation to control the coagulation cascade.⁵⁹ Studies in rats showed that CTS pre-protection significantly reduced ischemia induced apoptosis and endothelial activating cytokines (ET-1, vWF, P-selectin), and exerting a protective effect against myocardial infarction.⁴³

Protection of Cardiac Hypertrophy

Under normal physiological conditions, cardiac myocytes can exhibit an increase in cell size without change in number, a physiological effect that facilitates the function and efficiency of cells to enhance their work,⁶⁰ and a compensatory response to maintain cardiac function. However, when external stimuli (such as hypertension, diabetes mellitus, and myocardial infarction) continue to act on the heart muscle cells, this process becomes pathological and eventually leads to heart failure (HF).⁶¹ Cardiac hypertrophy in the pathological state leads to decreased cardiac contractility and adaptability, and ventricular remodeling, which in turn leads to cardiac fibrosis and cardiomyocyte death.⁶² Angiotensin II (Ang II) binds to endothelin receptor-1 and induces myocardial hypertrophy by generating activated nuclear protein kinase D (PKD),⁶³ and CTS reduces Ang II-stimulated NOX-2 and NOX-4 expression and reactive oxygen species production, ameliorating cardiac fibrosis through ERK1/2 pathway.⁶⁴ In addition, the p38/MAPK pathway in pathological cardiac hypertrophic cells controls cell growth and poor gene expression,⁶⁵ and studies have shown that CTS regulates the STAT3 pathway during early adipogenesis to inhibit preadipocyte differentiation.⁶⁶ In an in vitro study, CTS was experimentally found to downregulate the expression of p38/MAPK and Smad signaling in mesenchymal stem cells,⁶⁷ and the finding contributes to further research on the protective effect of CTS on cardiac hypertrophy. In addition, the latest experimental results showed that CTS not only effectively alleviated cardiac hypertrophy, but also alleviated fibrosis, and effectively inhibited the mRNA expression of fibrosis-related biomarkers Tgfb, Ccn2, Col1a1 and Col3a1 in mice.²⁷

Protection of Myocarditis

Cardiac inflammation (CI) is an inflammatory disease that occurs due to the mediation of inflammatory cytokines, typically caused by either an overactive immune system or external infections. The progression of myocarditis can lead to various heart diseases and even heart failure (HF).⁶⁸ Inflammatory triggers, such as endogenous signals (such as HMGB-1), are recognized by cardiac pattern recognition receptors (PRRs) and bind to these receptors primarily located on the plasma membrane or inclusions, including Toll-like receptors (TLRs).^{69,70} CTS ameliorates Ang II induced TLR 4 inflammatory vesicle activation-mediated myocardial injury via the EPK pathway,⁷¹ or exerts anti-inflammatory effects via TLR 4 mediated downregulation of IL-1 β , IL-6, TNF- α , COX-2 and iNOS in microglia.²⁵

Subsequently, the receptor emits inflammatory signals that act on effector cells or the complement system. Research demonstrates that CTS targets Ca²⁺ to inhibit the activation of NLRP3 inflammasome and reduces reactive oxygen species (mtROS) production during the activation process to prevent inflammasome-mediated diseases. Results from subsequent cell transfection experiments showed that CTS specifically inhibits the activation of NLRP3.⁷² Additionally, in vitro cell experiments show that CTS inhibits biofilm formation of *Staphylococcus aureus* by reducing the production of PIA, ATLE, and AAP, indicating therapeutic effects against endocarditis caused by *Staphylococcus epidermidis*. In vivo animal model studies show that CTS is able to reduce DOX induced cardiac toxicity in rats with heart failure through p38 pathway, and indicating protective effects on the heart.³¹

In brief, CTS showed huge potential in the treatment of cardiovascular diseases and the summary of the effect mechanism on the reported is shown in [Figure 3](#) and [Table 1](#).

Anti-Cancer Effect

Anti-Proliferation

Abnormal cell growth is a key factor in cancer development and is closely linked to the signaling pathways and protein expression associated with cell cycle-related growth. The PI3K/Akt/mTOR, JAK/STAT3, and AMPK pathways play

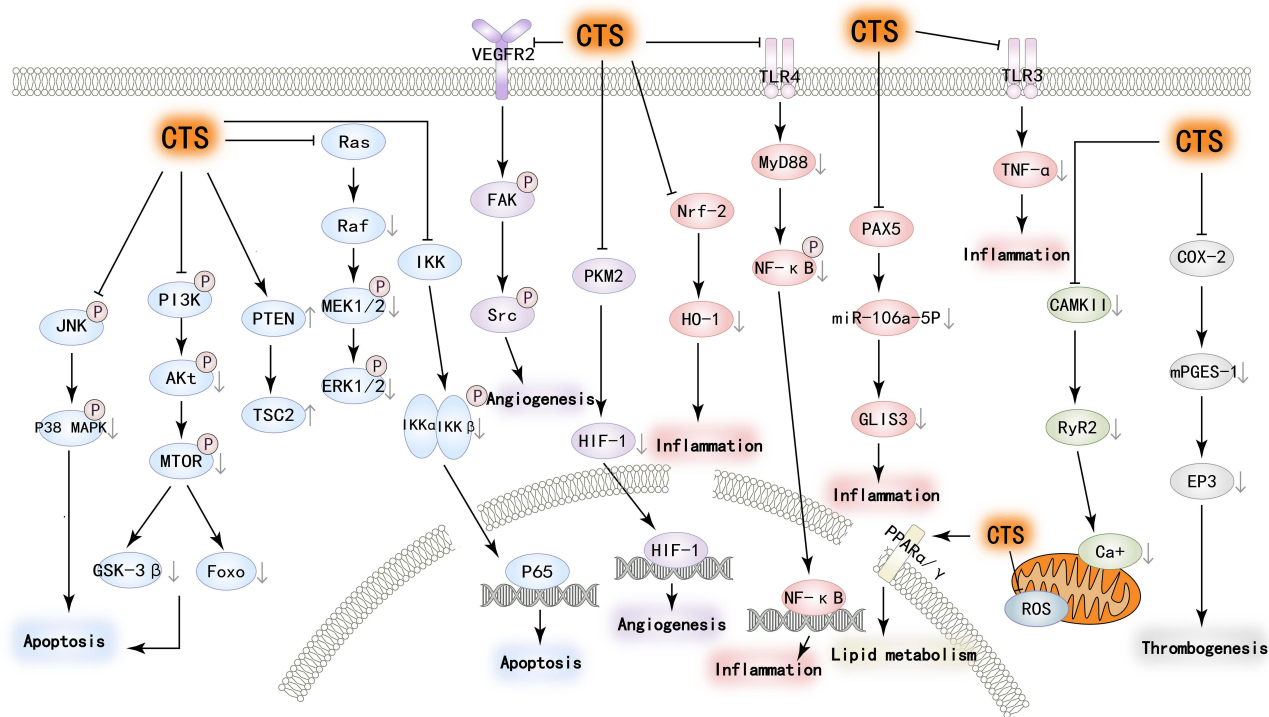


Figure 3 The main targets and pathways affected by CTS against cardiovascular system, nervous system, and urinary system diseases.
Notes: The symbols “↓”, “↑”, “p” and “-” indicate downregulation, upregulation, inhibition and phosphorylation of proteins, respectively, and the line with arrows “→” indicates single transduction.

crucial roles on promoting abnormal cell growth in cancers.⁷³ Studies have indicated that CTS has the ability to target the PI3K/Akt/mTOR pathway, thereby inhibiting the growth of multiple types of cancer cells including liver cancer,⁷⁴ breast cancer,⁷⁵ colorectal cancer,⁷⁶ and lung cancer.⁷⁷ Additionally, upstream proteins such as IGF and GPFR, as well as regulatory factors like PTEN, are involved in this pathway.⁷⁸ For example, by inhibiting the IGF-1R-mediated PI3K/Akt pathway, CTS suppresses the proliferation of lung cancer cells,⁷⁷ GPFR, a seven-transmembrane protein important for

Table 1 Studies on Anti-Cardiovascular Disease Effect of CTS

Author and Year	Disease/Model	Animal/Cell	Dose	Effect
Wang et al 2021 ³⁴	Disease: Cardiac ischemia/perfusion re-injury Model: In vivo: Ligation of left anterior descending coronary artery In vitro: Hypoxic chamber with 95% N ₂ and 5% CO ₂	Animal: Neonatal C57/B6J mouse Cell: Cardiomyocytes	In vivo: 0, 1, 2 mg/kg, In vitro: 0, 10, 20 μM	Reduce apoptosis
Liu et al 2017 ⁴⁵	Disease: Myocardial ischemia Model: In vitro: Hypoxic chamber with 95% N ₂ and 5% CO ₂	Cell: Cardiomyocytes	In vitro: 0.054, 0.108 μg/mL	Inhibition of calcium overload, antioxidant, anti-apoptosis
Zhao et al 2016 ⁵⁰	Disease: Atherosclerosis Model: In vitro: ox-LDL (10 μg/mL) cell model	Cell: Primary HUVEC cells	In vitro: 50 nM	Inhibition of adhesion molecule expression

(Continued)

Table I (Continued).

Author and Year	Disease/Model	Animal/Cell	Dose	Effect
Liu et al, 2015 ⁵¹	Disease: Atherosclerosis Model: In vivo: Feeding induced atherosclerosis In vitro: carried out in oxidized LDL (oxLDL)-stimulated HUVECs	Animal: (ApoE-/-) mice, Cell: HUVEC cells	In vivo: 15, 45 mg/kg In vitro: 2.5, 5, 10 μ M	Inhibition of adhesion molecule expression
Saviano et al 2022 ⁵⁷	Disease: Thrombosis Model: In vivo: The mouse tail was cut 5 mm from the tip of the tail to induce bleeding	Animal: CD-1 mice	In vivo: 3 mg/kg	Anticoagulant
Sheng et al 2020 ⁵⁸	Disease: Thrombosis Model: In vivo: PHZ (0.75 μ M) embryo damage model	Animal: Genetically modified zebrafish	In vivo: 2 μ g/mL	Inhibition of oxidative stress, coagulation cascade response
Li et al 2021 ⁵⁹	Disease: Thrombosis Model: In vivo: 1-phenyl 2-thiourea (0.2 mm) embryo damage model	Animal: Zebrafish embryo	In vivo: 1 μ g/mL	Inhibits oxidative stress, anti-inflammatory, inhibits thrombosis
Zhang et al 2021 ⁴³	Disease: Coronary embolism Model: In vivo: Coronary microembolization surgery	Animal: SD rats	In vivo: 5, 15, 45 mg/kg	Inhibition of endothelial activation, cardiomyocyte oxidative stress and apoptosis
Ma et al 2014 ⁶⁴	Disease: Cardiac fibrosis Model: In vivo: Ligation of left anterior descending coronary artery, In vitro: Ang II (100 nM) cell model	Animal: SD rats Cell: CF cells	In vivo: 30, 60 mg/kg, In vitro: 10, 20 μ M	Inhibits oxidative stress, fibrosis

Abbreviations: CTS, Cryptotanshinone; H₂O₂, Hydrogen peroxide; Ox-LDL, Oxidized low-density lipoprotein; HUVEC, Human umbilical vein endothelial cells; ApoE, Apolipoprotein E; AngII, Angiotensin II; PHZ, phenyl hydrazine; SD, Sprague Dawley.

the growth and proliferation of its target cells,⁷⁹ also mediates the regulatory effect of CTS on the PI3K/Akt/mTOR signaling pathway to inhibit the growth of ER-negative breast cancer cells.⁷² Moreover, CTS alters the stability of PTEN in cell experiments and gene silencing experiments, thus regulating the phosphorylation of downstream pathways and resulting in an anticancer effect on cell proliferation.⁸⁰ Downstream targets of CTS through the PI3K/Akt/mTOR pathway include NF- κ B and GSK-3 β . For instance, CTS causes apoptosis by regulating the PI3K/Akt/NF- κ B signaling pathway and amending the expression of Bax and Bcl-2.⁸¹ It can also restrict the G0/G1 cell cycle and induce apoptosis in non-small cell lung cancer cells by means of the PI3K/Akt/GSK3 β pathway.⁸² Furthermore, research indicates that CTS may act as a potential inhibitor of SIRT3, which has been demonstrated to impede colorectal cancer proliferation by targeting SIRT3 proteins and arresting the cell cycle in the S phase.⁸³

The STAT family of transcription activators play a significant role in the proliferation, apoptosis, and regulation of the tumor microenvironment. Hence, they are considered an effective anti-cancer target.⁸⁴ CTS functions as an efficient STAT3 inhibitor, and combination of CTS with paclitaxel is able to suppress tumor cell growth through JAK/STAT3 signaling pathway suppression and promote apoptosis.⁸⁵ What's more, research has shown that CTS induce renal carcinoma cell and gastric cancer cell apoptosis by inhibiting the JAK/STAT3 pathway and suppressing proliferation.^{86,87} In addition to effectively inhibiting STAT3 expression, CTS may also exert an anticancer effect by inhibiting other members of the STAT family, such as STAT1 and STAT5.⁸⁸

In addition to its known mechanisms of action, CTS has been found to also impede cancer cell proliferation through alternative molecular targets or pathways. First, CTS activates the AMPK/TSC2 axis to suppress downstream protein mTORC1 signal transduction, thus hindering cancer cell growth.⁷⁸ Second, cyclin-dependent kinase (CDK) is capable of stimulating continuous cell proliferation,⁸⁹ and CTS acts as a novel CDK4 inhibitor by down-regulating the expression of mutant oncogene Kras to block the transition of cells from G0/G1 phase to S phase, thereby inhibiting cancer cell growth.⁴⁷ What's more, studies have demonstrated that CTS may target TAZ downstream of Hippo, attenuating the stemness of NSCLC by translocating from the nucleus to the cytoplasm.⁹⁰

Suppression of Invasion and Metastasis

Angiogenesis during cancer metastasis is closely related to the recruitment of metalloproteinases (MMP family),⁹¹ and CTS decreases MMP expression and increases metalloproteinase (TIMP) expression to inhibit invasion and metastasis in colon and non-small cell lung cancers.^{92–94} During angiogenesis, EMT activation converts epithelial cells into mesenchymal cells, which is produced by N-cadherin or E-cadherin-mediated cell-cell interactions,⁹¹ and CTS downregulates the mTOR/ β -catenin/N-cadherin signaling pathway and reduces N-cadherin expression thereby inhibiting bladder cancer cell invasion and metastasis.⁹⁵ In addition, focal adhesion kinases (FAK) are a class of non-receptor protein tyrosine kinases (PTKs) in the cytoplasm that promote invasion and metastasis of cancer cells,⁹⁶ and CTS downregulates FAK and C-myc transcription to inhibit ovarian cancer cell metastasis.⁹⁷

Inducing Autophagy

Autophagy is a biological process in which lysosomes degrade their own proteins and organelles under the regulation of ATG genes,⁹⁸ and autophagy is able to inhibit tumor growth to promote tumor apoptosis and has an inhibitory effect on tumor development to some extent.⁹⁹ On the one hand, CTS has the ability to regulate the Atg5 gene in cancer cells, enhance the expression of Beclin-1 and LC3-II, and trigger autophagy in cancer cells via the traditional Beclin-1 signaling route.^{75,100} On the other hand, CTS promotes autophagy in HCT116 colon cancer cells by enhancing endoplasmic reticulum stress, which later affects downstream Bad/Bcl-2 expression to promote apoptosis.¹⁰¹ Given that CTS inhibits P-gp mediated efflux⁹³ and its antitumor activity, CTS induces ROS production, promotes cellular autophagy and leads to cancer cell death in multi-drug resistant colon cancer.¹⁰²

Promoting Apoptosis

Apoptosis is the process of programmed cell death that occurs in organisms under physiological or pathological conditions.¹⁰³ Imbalances in the regulation of cell proliferation and death are central to cancer development, where DNA damage and external signaling can trigger apoptosis.¹⁰⁴ CTS is an active herbal substance with great potential for fighting cancer, as it upregulates the Bax/Bcl-2 ratio through multiple signaling pathways such as JNK/p38, PI3K/Akt, JAK/STAT3, and NF- κ B, overexpresses Caspase family proteins, and induces apoptosis in various types of cancer cells, including gastric cancer,¹⁰⁵ liver cancer,⁷⁴ colon cancer,⁹³ and cholangiocarcinoma.⁸¹ The transcription factor p53 is upstream of the apoptotic signaling pathway, and it targets the PUMA promoter region to promote apoptosis.⁷⁴ CTS not only upregulates p53 gene expression for apoptosis induction,¹⁰⁶ but also increases PUMA protein expression to further exert a potent anticancer effect.¹⁰⁷ Additionally, CTS induces necroptosis by increasing Caspase-3 protein levels via the JNK/p38 pathway in gastric cancer cell lines, and activates the RIP1/RIP3/MLKL pathway for Ca²⁺ and ROS-overexpression induced necroptosis in NSCLC cells.¹⁰⁸

Immunomodulation

Tumor immunotherapy is an emerging therapy that activates the specific response of the body's immune system to fight tumors.¹⁰⁹ Based on the therapeutic principles of tumor immunotherapy, numerous bioactive compounds derived from plant sources have shown remarkable anti-tumor efficacy.¹¹⁰ CTS has significant anti-cancer potential and acts on multiple pathways in the human immune system to achieve therapeutic effects.

CTS not only targets and inhibits THEMIS2/MET signal transduction, which reduces stemness and chemical resistance in cancer cells,¹¹¹ but also collaborates with hesperetin to inhibit JAK2/STAT3 phosphorylation, resulting in tumor antigen-specific Th1 immunity.¹¹² Moreover, some studies have shown that CTS down-regulates the TRAF6/

ASK1 signaling pathway, and stimulates macrophages TAM to differentiate into the M1 phenotype, inhibits breast cancer cell proliferation, and induces autophagy.¹¹³ In addition, cryptotanshinone also has activity against bladder cancer through inhibition of NLRP 3 expression.¹¹⁴ In one study on liver cancer, CTS combined with arsenic trioxide enhanced AMPK phosphorylation which promoted TAM differentiation into the M1 phenotype, and accelerated glycolysis in tumor tissue.¹¹⁵ Besides, CTS also is combined with other treatment methods to regulate the immune system's anti-cancer effects. For instance, when CTS is used in conjunction with the immune checkpoint inhibitor PD-L1, it enhances specific immune responses and memory responses.¹¹⁶

Reducing Drug Resistance

Drug resistance in tumor cells is a significant cause of tumor treatment failure. The mechanisms behind this include the efflux of drugs by transporter pumps, expression of proto-oncogenes or oncogenes, DNA repair, and tumor stem cells.¹¹⁷

The etiology of Chronic Myelogenous Leukemia (CML) is associated with the generation of BCR-ABL fusion genes, which could be a target for the treatment of chronic granulocytic leukemia.¹¹⁸ CTS could act as an inhibitor of STAT5 or STAT3 (BCR-ABL downstream protein) to downregulate C-myc in CML and reverse BCR-ABL kinase non-dependent drug resistance.⁸⁸

To enhance the sensitivity of anticancer drugs, several therapeutic approaches are used with CTS. CTS enhances DNA damage induced by the chemotherapeutic drug cisplatin to improve drug efficacy.¹¹⁹ Additionally, CTS reverses drug resistance in breast cancer by inhibiting the formation of membrane protein BCRP oligomers, independent of ER α receptors.¹²⁰ Moreover, CTS improves the effectiveness of gefitinib in human lung cancer H1975 cells.¹²¹ It is worth noting that the synergistic administration of CTS and temozolomide reverses the repair effect of MGMT on DNA damage in cancer cells, thereby enhancing the apoptosis induced by temozolomide alkylation.¹²²

Adjusting Glycolysis

Cancer cells undergo metabolic reprogramming to switch to a “glycolytic-led” metabolic mode, ensuring their survival and meeting their energy needs. This metabolic switch affects various functions of cancer cells, such as proliferation, apoptosis, and metastasis.^{123–125} Studies have shown that CTS inhibits the expression of tumor tissue-associated glycoproteins, including GLUT1/2, LDHA, HK2, and PKM2.^{111,126} It suggests that CTS may impact glycolysis in tumor cells through certain key signaling pathways, which ultimately affects their growth and proliferation.

For example, CTS inhibits ATP production in ovarian cancer cells, induces activation of AMPK, which controls the energy reduction process, and inhibits glycolysis and oxidative phosphorylation (OXPHOS),¹²³ Further studies showed that both AMPK inhibitors and silencing AMPK could partially reverse the therapeutic effects of CTS.¹²⁴ In addition, in hepatocellular carcinoma, STAT3 may regulate glycolysis through the HK2 pathway.¹²⁷ Further studies have revealed that STAT3 inhibits the transcriptional activity of downstream SIRT3 to regulate glycolysis and proliferation in breast cancer cells.¹²⁸ In addition, PKM2, which is a rate-limiting enzyme in glycolysis, is downregulated by CTS to inhibit the proliferation, migration, and invasion of breast cancer cells through the PKM2/ β -Catenin pathway.¹²⁹

Summarily, CTS also showed promising potential in the treatment of cancers with the effect mechanism via multiple targets and pathways (Figure 4 and Table 2).

Nervous System Effects

Alzheimer's Disease

According to reports, CTS has a Papp (a $\rightarrow$ b) in the blood-brain barrier (BBB) cell model of 1×10^{-7} cm/s to 1×10^{-6} cm/s,¹³¹ indicating that CTS can be transported through the BBB and absorbed into the brain, and providing a solid scientific premise for its use in the treatment of Alzheimer's Disease (AD). AD is a complex degenerative nerve disease that is currently believed by the mainstream view of scientific research to have its primary cause in the deposition of extracellular β -amyloid protein (A β), and leading to the development of neuroinflammatory plaques, or the intracellular hyperphosphorylation and accumulation of Tau microtubule-associated protein as neurofibrillary tangles.¹³² Scientific research has shown that CTS has good pharmacological activity in improving A β deposition and Tau hyperphosphorylation.¹³³

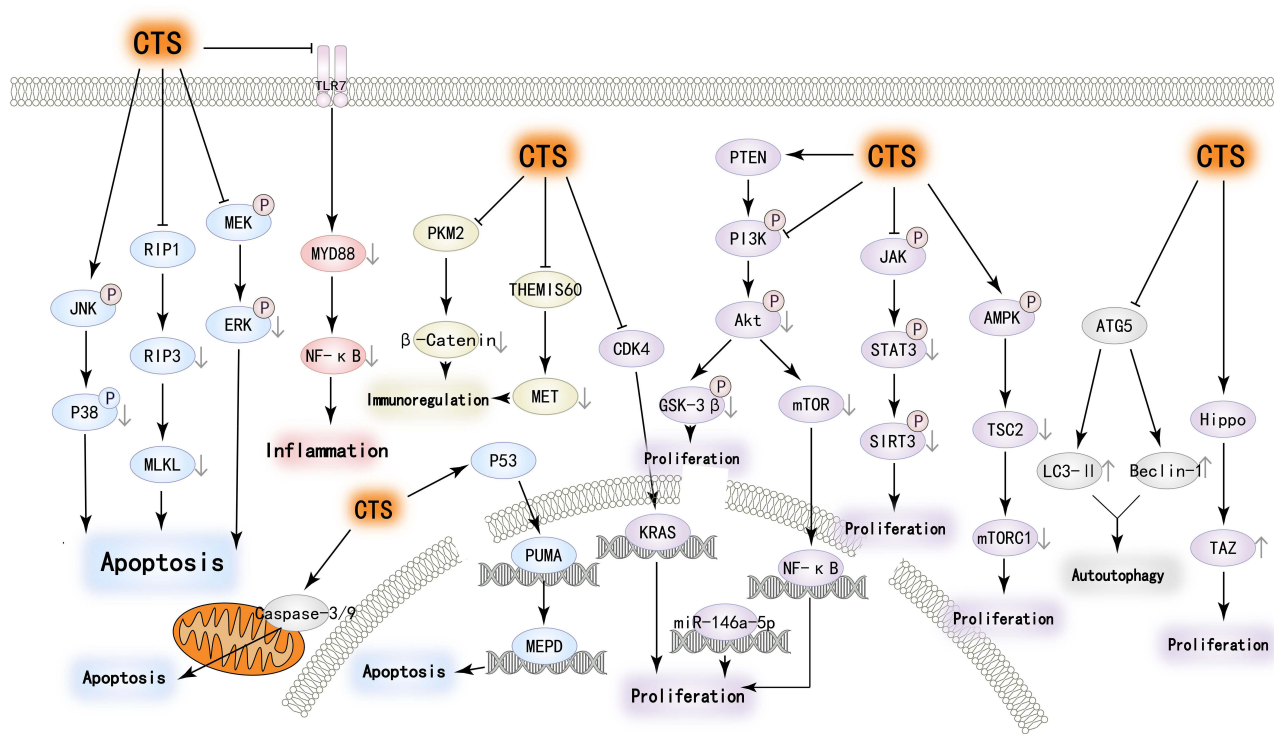


Figure 4 The main targets and pathways of CTS against cancer.
Notes: The symbols “↓”, “↑”, “⊥” and p indicate downregulation, upregulation inhibition and phosphorylation of proteins, respectively, and the line with arrow “→” indicates single transduction.

A study to examine the effect of CTS on short-term working memory in male CD mice with AD.¹³⁴ They used a Y-maze task and analyzed hippocampal tissues to measure the amount of change in Aβ1-42 protein expression. The results showed that CTS attenuated Aβ1-42 induced learning deficits, demonstrating its anti-Alzheimer’s disease

Table 2 Studies on the Anti-Cancer Action of CTS

Author and Year	Disease/Model	Animal/Cell	Dose	Effects
Luo et al 2020 ⁷⁴	Disease: Liver cancer Model: In vivo: Cell derived xenograft	Animal: BALB/c naked mouse Cell: Huh7, MHCC97-H cells	In vivo: 50 mg/kg In vitro: 0, 3, 6, 12 μM	Inhibit proliferation, increases autophagy, apoptosis
Vundavilli et al 2021 ¹³⁰	Disease: Colon cancer	Cell: HT29 cells, HCT116 cells	In vitro: 20 μM	Induction of apoptosis
Liang et al 2018 ¹²⁶	Disease: Colon cancer Model: In vivo: Cell derived xenograft model	Animal: naked mouse Cell: HT1116, SW3 cells	In vivo: 10 mg/kg In vitro: 50 μM	Inhibit proliferation
Huang et al 2022 ¹¹²	Disease: Triple-negative breast cancer	Cell: MDA-MB, Hs5T cells	In vitro: 20 μM	Inhibition of proliferation, invasion, cancer stemness
Noori et al 2022 ¹¹¹	Disease: Lymphoma Model: In vivo: Delayed type hypersensitivity model	Animal: BALB/c mice	In vivo: 20 mg/kg	Inhibit proliferation
Yen et al 2022 ¹¹³	Disease: Triple-negative breast cancer	Cell: RAW 264.7, MDA-MB-231 cells	In vitro: 20 μM	Inhibition of proliferation, migration

(Continued)

Table 2 (Continued).

Author and Year	Disease/Model	Animal/Cell	Dose	Effects
Shi et al 2020 ⁷⁵ Terado et al 2022 ⁴⁷	Disease: Lymphoma Disease: Pancreatic, colon cancer	Cell: SKBR-3 cells Cell: MIAPaCa-2, BxPC3, DLD1 cells	In vitro: 5 μ M In vitro: 0, 10, 20 μ M	Inhibits proliferation, growth Inhibits proliferation, growth
Dong et al 2018 ⁸⁸	Disease: Leukaemia	Cell: K562, K562/ADR cells	In vitro: 0, 1, 2.5, 5, 7.5, 10, 20, 30 μ M	Inhibits proliferation and reduces drug resistance
Yang et al 2018 ¹²⁸	Disease: Ovarian cancer Model: In vivo: cell derived xenograft model	Cell: A2780 cells	In vivo: 10 mg/kg In vitro: 0, 5, 10 μ M	Inhibits proliferation and increases apoptosis
Wang et al 2017 ⁸⁵	Disease: Squamous carcinoma of the tongue	Cell: CAL27, SCC9 cells	In vitro: 0, 5, 8, 10, 16 μ M	Inhibits proliferation, migration, and increases apoptosis
Fu et al 2021 ¹³	Disease: Colon cancer	Cell: HCT116, SW620 cells	In vitro: 0, 1, 10 μ M	Inhibits growth, proliferation, and promotes apoptosis.
Zhang et al 2018 ⁷⁷	Disease: Colon cancer Model: In vivo: Syngeneic model	Animal: BALB/c mice Cell: CT26, HUVEC cells	In vivo: 20, 80 mg/kg In vitro: 0, 1, 5, 10, 20 μ M	Inhibition of growth, proliferation, and invasion
Chen et al 2017 ⁸⁷	Disease: Kidney cancer Model: In vivo: Cell derived xenograft model	Animal: Naked mouse Cell: A498, ACHN cells	In vivo: 5 mg/kg In vitro: 0, 2.5, 5 μ M	Inhibits proliferation and promotes apoptosis
Guo et al 2022 ⁹⁷	Disease: Ovarian cancer Model: In vivo: Orthotopic ovarian cancer mouse model	Animal: NSG mice Cell: OVCAR3, HEYA8 cells	In vivo: 5 mg/kg In vitro: 0, 5, 10, 20 μ M	Inhibition of proliferation, growth, migration
Wang et al 2019 ⁹⁴	Disease: Non-small cell lung cancer	Cell: A549 cells	In vitro: 20 μ M	Inhibition of proliferation, invasion
Liu et al 2020 ⁹⁰	Disease: Glioma Model: In vivo: Cell derived xenograft model	Animal: BALB/c mouse Cell: U3 cells	In vivo: 25 mg/kg In vitro: 0, 1.25, 2.5, 5, 10, 20 μ M	Inhibition of proliferation, invasion, migration
Ni et al 2021 ¹²⁰	Disease: Lymphoma	Cell: MCF-7, MDA-MB-231 cells	In vitro: 5, 10, 20 μ M	Reducing drug resistance
Liu et al 2017 ¹⁰⁵	Disease: Gastric cancer Model: In vivo: Cell derived xenograft model	Animal: BALB/c mouse Cell: AGS, MKN-28, MKN-45 cells	In vivo: 1, 10 mg/kg In vitro: 10 μ M	Inhibits growth and proliferation and promotes apoptosis
Xu et al 2017 ¹⁰²	Disease: Colon cancer	Cell: SW620, Ad300 cells	In vitro: 10 μ M	Promotes autophagy, apoptosis
Zhao et al 2022 ¹⁰⁸	Disease: Non-small cell lung cancer Model: In vivo: Cell derived xenograft model	Animal: C57BL/c mice	In vivo: 15, 30 mg/kg	Promotes necrotic apoptosis
Kim et al 2018 ⁸²	Disease: Non-small cell lung cancer	Cell: A549, H460 cells	In vitro: 0, 10, 20, 40 μ M	Inhibits growth and proliferation and promotes apoptosis

(Continued)

Table 2 (Continued).

Author and Year	Disease/Model	Animal/Cell	Dose	Effects
Liu et al 2019 ¹⁰⁸	Disease: Lewis lung cancer Model: In vivo: Cell derived xenograft model	Animal: C57BL/c mice Cell: A549 cells	In vivo: 10 µg/mouse In vitro: 0, 1.25, 2.5, 5, 10 µM	Inhibits proliferation and promotes immune response
Jin et al 2020 ⁹⁰	Disease: Non-small cell lung cancer	Cell: A549, H1299 cells	In vitro: 0, 1, 5, 10, 20 µM	Proliferation inhibition, cancer stem cell differentiation
Chen et al 2017 ⁷⁸	Disease: Rhabdomyosarcoma, prostate cancer, breast cancer	Cell: Rh30, MCF-7, MEF cells	In vitro: 0, 2.5, 5, 10, 20 µM	Inhibit proliferation
Zhou et al, 2020 ¹²⁹	Disease: Lymphoma	Cell: MCF-7, MDA-MB-231 cells	In vitro: 0, 5, 10, 20 µM	Inhibition of proliferation, migration, invasion
Cai et al 2022 ¹²¹	Disease: Lung cancer Model: In vivo: Cell derived xenograft model	Animal: BALB/c mice Cell: H1975 cells	In vivo: 20 mg/kg In vitro: 5 µM	Inhibits proliferation and reduces drug resistance
Jiang et al 2022 ¹¹⁵	Disease: Liver cancer Model: In vivo: Cell derived xenograft model	Animal: BALB/c mice Cell: Hepa I-6, macrophage cells	In vivo: 40 mg/kg In vitro: 0, 0.5, 2.5, 5 µM	Inhibit proliferation
Yu et al 2018 ¹⁰⁷	Disease: Salivary gland tumors	Cell: MEC-I cells	In vitro: 10, 14 µM	Promote apoptosis
Jiang et al 2023 ¹⁰⁰	Disease: Oral squamous cell carcinoma Model: In vivo: Cell derived xenograft model	Animal: Naked mouse Cell: HSC-3, HN-6 cells	In vivo: 30 mg/kg In vitro: 0, 10, 20 µM	Promoting autophagy
Ma et al 2023 ⁹²	Disease: Breast cancer	Cell: MCF-7 cells	In vitro: 2.5, 5, 7.5, 10, 12.5, 15, 17.5, 20 µM	Inhibition of invasion and metastasis
Tang et al 2024 ¹¹⁴	Disease: Bladder Cancer	Cell: SV-40 cells	In vitro: 2, 4 µM	Improvement of the immune microenvironment
Zhu et al 2023 ¹²²	Disease: Glioblastoma	Cell: LN229, U87-MG cells	In vitro: 4 µM	Reduce drug resistance
Wang et al 2024 ¹²³	Disease: Ovarian cancer	Animal: Naked mouse Cell: A2780, Caov3, IOSE80 cells	In vivo: 10 mg/kg In vitro: 0, 2, 4, 6 µM	Inhibition of glycolysis and oxidative phosphorylation
Cheng et al 2024 ¹²⁴	Disease: Cutaneous melanoma Model: In vivo: The allograft tumor model	Animal: Naked mouse Cell: B16F10, A375 cells	In vivo: 10 mg/kg In vitro: 0, 5, 10, 20 µM	Adjust glycolysis

Abbreviations: HUVEC, Human umbilical vein endothelial cells; Huh7, Hemochromatotic; MHCC97-H, Human high metastatic liver cancer cells; HT29, Human colorectal adenocarcinoma cells; HCT116, Human colorectal carcinoma cells; Hs5T, 5-Hydroxytryptamine; ADR, Human breast cancer adriamycin-resistant cell line; RAW 264.7, Mouse mononuclear macrophages cells; MDA-MB-231, Human breast cancer cells; SKBR-3, Human breast adenocarcinoma cells; MIAPaCa-2, Human pancreatic cancer cells; BxPC3, Human in situ pancreatic adenocarcinoma cells; DLD1, Human colorectal adenocarcinoma epithelial cells; K562, Human chronic myeloid leukaemia cells; A2780, Human ovarian cancer cells; CAL27, Human tongue squamous carcinoma cells; SCC9, Human tongue squamous cell carcinoma; SW620, Human colorectal adenocarcinoma cells; CT26, Mouse colon cancer cells; A498, Human kidney cancer cells; ACHN, Human renal cell adenocarcinoma cells; NSG, Non-obese diabetes-protein kinase DNA-activated catalytic combined immune deficiency; OVCAR3, Human ovarian cancer cells; HEYA8, Human ovarian cancer cells; A549, Human pulmonary carcinoma cells; U3, Human bladder cancer cells; MCF-7, Human breast cancer cells; AGS, Human gastric adenocarcinoma cells; MKN-28, Human gastric cancer high metastatic cells; MKN-45, Human gastric cancer cells; SW620, Human colorectal adenocarcinoma cells; Ad300, Human colorectal adenocarcinoma cells; H460, Human macrophage lung cancer cells; H1299, Human non-small cell lung cancer cells; Rh30, Human rhabdomyosarcoma cells; MEF, Mouse embryonic fibroblasts; H1975, Human lung adenocarcinoma cells; Hepa I-6, Mouse liver cancer cells; MEC-I, Human chronic B-cell leukaemia cells.

pharmacological effects by improving Aβ deposition. In a more detailed mechanistic study, researchers established a transgenic *Caenorhabditis elegans* model of AD. They found that CTS inhibited ROS and downregulated the expression of the ACHE gene ACE-2, suggesting that CTS could regulate ACHE gene expression to attenuate Aβ aggregation

levels.¹³⁵ Furthermore, network pharmacology combined with studies on cellular models demonstrated that CTS also activated the PI3K/Akt/GSK3 β pathway to inhibit Tau hyperphosphorylation.¹³⁶

Researchers also created CTS derivatives from the oxygen-containing products of *Cryptobacterium hidradii* biotransformation in order to more effectively use CTS for the treatment of neuroinflammation brought on by AD. These derivatives had anti-neuroinflammatory effects by inhibiting the TLR 4 mediated MAPK signaling pathway and had higher bioavailability and stronger bioactivity in comparison to CTS.⁶⁹ It is worth mentioning that in recent years a combination of computerized virtual screening and scientific experiments have been favored, such as simulating the binding of CTS and AD disease proteins and finding potential molecular targets on the basis of which the scientific hypothesis was validated by cellular and animal experiments.^{132,134} This provides viable ideas for finding potential targets for small molecule drugs against the disease.

Parkinson's Disease

Parkinson's disease (PD) is a progressive movement disorder caused by changes in various molecular processes such as mitochondrial function and calcium homeostasis.¹³⁷ One potential treatment for PD is CTS, which has been shown to reduce oxidative stress damage to neuronal cells.

A study demonstrated the effectiveness of CTS in treating PD.¹³⁸ They found that CTS significantly improved the expression of tyrosine hydroxylase, which is the rate-limiting enzyme in catecholamine neurotransmitter synthesis. CTS also inhibited MPTP induced dopaminergic cell loss and delayed the progression of PD. Further studies revealed that CTS increased the expression activities of antioxidant enzymes such as SOD, GSH-Px, and CAT, which reduced oxidative stress in neuronal cells and thus exerted anti-PD effects.

In a hiNPC-induced in vitro model, CTS was shown to significantly reduce mitochondrial reactive oxygen species and increase mitochondrial membrane potential through mitochondrial repair.¹³⁹ This effect was mediated by the Nrf-2 pathway. Additionally, CTS reduced MPP induced cellular oxidative stress and apoptosis, indicating that STAT3 may be a potent target of CTS against PD.¹⁴⁰

Protection of Ischemic Stroke

Ischemic stroke (ISD) is a cerebral blood clot or interruption of cerebral blood flow caused by an etiology such as cardiac and arterial embolism,¹⁴¹ whose molecular mechanisms involve cellular excitotoxicity, mitochondrial dysfunction, platelet activation, and cell death processes.¹⁴² Researchers used an animal model to investigate the protective effects of tanshinones on cerebral ischemic injury in rats, and found that tanshinone components inhibited platelet aggregation and attenuated permanent brain injury in rats.¹⁴³ Further studies showed that CTS restored the protein level of FOXP4 and phosphorylation of STAT5 at a median effective concentration (EC50) of 485.1 $\mu\text{g/mL}$, suggesting that CTS could exert therapeutic effects on ischemic stroke in MCAO rats through the STAT pathway.¹⁴⁴

Cerebral Ischemia/Reperfusion Injury (I/R)

Brain Ischemia Reperfusion Injury (BIRI) is a pathological phenomenon in which brain tissue damage is exacerbated when blood flow recanalization is restored after ischemic stroke.¹³⁸ CTS not only regulates microglia polarization to protect against BIRI,¹⁴⁵ but also activates the Nrf2/HO-1 signaling pathway to inhibit OGD/R induced oxidative stress and neuronal apoptosis in hippocampal neurons.¹⁴⁶

Neuroprotection

Neuroinflammation is linked to the development of degenerative neurological diseases.¹⁴⁷ CTS has anti-inflammatory properties that regulate the Nrf2/HO-1 pathway through the PI3K/Akt signaling pathway, mitigating microglial inflammatory response, and decreasing the release of pro-inflammatory mediators such as IL-1 β , IL-6 and TNF- α , and protecting neurons from inflammatory damage.¹⁴⁸

Moreover, CTS significantly inhibits inflammation induced neuropathic pain. It relieves oxaliplatin induced nerve pain¹⁴⁹ and alleviates monosodium urate induced neuropathic pain¹⁵⁰ while inhibiting the chronic constrictive injury induced postoperative neuropathic pain and its inflammatory progression in rats by suppressing the PI3K/Akt signaling pathway.¹⁴⁵ Furthermore, CTS exhibits neuroprotective effects, including inhibition of A β aggregation and

cerebrovascular endothelial cell inflammatory responses to counteract vascular dementia (VD),¹⁵¹ and promotion of neuronal growth and memory improvement via the extracellular ERK1/2 signaling pathway.^{152,153}

Digestive System Protection

Inflammatory Bowel Disease (IBD) is a chronic and recurrent inflammatory disease of the gastrointestinal tract.¹⁵⁴ One potential treatment for IBD is CTS, which has shown promising results in animal models of the disease.

In a mouse model of ulcerative colitis (UC) induced by sodium dextran sulfate, CTS significantly improved the pathological changes of colonic tissues and reduced inflammation. CTS inhibited the expression of COX-1, COX-2, RIP3, NF- κ B, and p65, as well as the secretion of TNF- α and IL-6. These findings suggest that the efficacy of CTS in treating ulcerative colitis is correlated with its anti-inflammatory effect.

In depth studies have shown that CTS regulates STAT3 phosphorylation to restore the balance of Th17/Treg cells in UC, which is an important mechanism in the pathogenesis of IBD.¹⁵⁵ Furthermore, CTS has also shown potential medicinal value in chemotherapy induced colitis disease models. It has been reported to significantly increase serum TG/TC levels and effectively alleviate 5-fluorouracil (5-FU) and irinotecan (CPT-11) induced colitis by modulating fecal bacteria-mediated lipid metabolism in colon cancer mice.¹⁵⁶

Urinary System Protection

Ischemia/reperfusion injury (I/R) is a major cause of kidney damage and organ function loss.¹⁵⁷ Increased production of ROS and activation of apoptotic pathways are key contributors to kidney I/R injury.

In vitro experiments have shown that CTS downregulates PI3K/Akt pathway phosphorylation, inhibits Bax and Caspase-3 activity, and decreases Bcl-2 expression in HK2 cells.¹⁵⁸ CTS exerts protective effects on renal tubular epithelial cells by inhibiting hypoxia/reoxygenation induced oxidative stress and apoptosis. Further animal experiments have shown that the anti-apoptotic effect is associated with inhibition of the p38/MAPK pathway.¹⁵⁹

As inflammatory injury persists, renal fibrosis may occur.¹⁶⁰ However, CTS pretreatment has been shown to significantly attenuate the pathological process induced by renal IR and inhibit apoptosis and inflammatory responses. NF- κ B signaling may be involved in these effects.¹⁵⁹ The Nrf2/HO-1 pathway may be a compensatory mechanism for the NF- κ B induced inflammatory response as inflammation progresses and leads to renal interstitial fibrosis. CTS has been found to have a direct antifibrotic effect by blocking NF- κ B and Nrf2/HO-1 signaling in a Unilateral Ureteral Obstruction (UUO) model.¹⁶¹

Motor System Protection

Due to the potent anti-inflammatory properties of CTS, it has demonstrated efficacy in treating various types of joint diseases. First, Osteoarthritis (OA) is an irreversible damage to articular cartilage induced by cartilage extracellular matrix (ECM) deposition.¹⁶² Studies have shown that CTS has efficacy in preventing IL-1 β induced inflammation and improving OA progression.¹⁵⁰ miRNAs, as a class of important regulators of biological functions, are closely related to the pathogenesis of OA, where miR-106a-5p prevents OA cartilage degradation and ameliorates cartilage damage by directly targeting GLIS3, and CTS regulates the PAX5/miR-106a-5p/GLIS3 axis to protect chondrocytes from damage.¹⁶³ CTS additionally has the ability to regulate the methylation of miR-574-5p and modify the production of YAF2 to decrease apoptosis in cytosolic chondrocytes, according to RT-PCR and other experiments.¹⁶⁴ Second, rheumatoid arthritis (RA), as a class of autoimmune diseases, has a pathological process associated with synovial tissue proliferation and inflammatory development.¹⁶⁵ Th cells play a significant role in immunological disease regulation, and Th17 and Treg homeostasis are crucial in the development of rheumatoid arthritis (RA). Since IL-6/STAT3 is required for the development of Th17 and Treg cells, CTS is able to promote the restoration of homeostasis in these cells.¹⁶⁶ In addition, CTS treatment is also efficacious in osteoporosis (OS), and its molecular mechanism is associated with CTS inhibition of ERK phosphorylation and NF- κ B activation in Bone Marrow-derived Macrophages (BMM).¹⁶⁷

Respiratory System Protection

CTS has therapeutic effects mainly on pulmonary fibrosis and lung inflammation in the respiratory system. On the one hand, a work showed that CTS reduced pulmonary inflammatory infiltration in radiation induced lung injury (RILI) rats, with a significant decrease in α -SMA levels and a significant elevation in MMP-1 expression.¹⁶⁸ This study suggests that CTS has good therapeutic effects on pulmonary fibrosis, but the exact molecular mechanism remains to be explored. In a more in-depth study, it was shown that CTS firstly alleviated pulmonary fibrosis via inhibition of the TGF- β /Smad pathway. Luciferase reporter gene assay showed that CTS inhibited the transcriptional activity of STAT3; overexpression of STAT3 attenuated the CTS inhibition of TGF- β 1 induced COL-I and α -SMA. This information suggests that CTS may block the TGF- β /Smad signaling pathway and STAT3 to prevent lung fibrosis.¹⁶⁹ This series of studies demonstrates the unparalleled medicinal value of CTS, the active ingredient of herbal medicine, in the treatment of pulmonary fibrosis. On the other hand, considering the anti-inflammatory activity of CTS, it not only plays a role in attenuating the allergic airway inflammatory response by inhibiting p38 phosphorylation and downregulating NF- κ B pathway,¹⁷⁰ also exerts anti-inflammatory effects by inhibiting STAT3 phosphorylation and further inhibiting TWEAK and TGF- β 1 signaling in airway smooth muscle cell.¹⁷¹

Endocrine System Protection

The therapeutic effects of CTS on the endocrine system are mainly in the treatment of polycystic ovary syndrome and improvement of benign prostatic hyperplasia. Polycystic ovarian syndrome (PCOS) is one of the most common endocrinological disorders, mainly manifested by menstrual disorders caused by excessive androgens, infertility and other.¹⁷²

First, high expression of CTBP1-AS is one of the important causative factors of PCOS, and a clinical trial showed that CTBP1-AS expression levels were significantly upregulated in PCOS patients compared with controls, and CTS treatment significantly inhibited CTBP1-AS levels.¹⁷³ Second, the expression of inflammatory factors is induced by HMGB1, which is known to be able to activate the TLR4 signaling pathway and NF- κ B. This enhances the pathological process of PCOS.¹⁷⁴ Researchers found that CTS downregulates the HMGB1/TLR4/NF- κ B pathway to alleviate PCOS.¹⁷⁵ Furthermore, it has been shown that CTS inhibits iron death, reduces ROS production and inhibits HMGB1/MAPK/ERK signaling pathway transduction for medicinal efficacy in an in vivo rat model of PCOS.¹⁷⁶

In addition, it shown that CTS inhibits Androgen/Androgen receptor (AR) signaling pathway and EGFR/STAT3 axis to regulate the balance of proliferation and apoptosis and reduce fibrosis to improve the development of Benign Prostatic Hyperplasia (BPH).¹⁷⁷

Others

CTS has certain antibacterial and antiviral abilities, such as CTS inhibits the formation of staphylococcal surface biofilm,⁶² and exerts antibacterial effects through synergistic use with aminoglycosides and phosphomycin drugs to disrupt the cell wall and inhibit protein and nucleic acid synthesis.^{178,179} CTS plays a therapeutic and protective role against also inhibiting COVID-19 virus DNA replication.¹⁸⁰

CTS has some therapeutic effects on skin-related diseases, such as CTS is able to regulate skin microbiome and lipid metabolism to alleviate acne and acne induced inflammation,¹⁸¹ attenuate psoriatic hyperplasia by inhibiting STAT3 activation,¹⁸² and inhibit STAT3 phosphorylation and T cell proliferation to alleviate the progression of systemic lupus erythematosus.¹⁸³

An in vitro experiment showed that 0.02–0.1 μ M of CTS could effectively reduce UV radiation induced ROS production in HaCaT cells and HFF-1 cells, and this effect was associated with CTS activation of Nrf2-mediated antioxidant signaling pathway and activation of AMPK/SIRT1/PGC-1 α signaling pathway to improve mitochondrial dysfunction.¹⁸⁴ In addition, CTS alleviates CoCl₂ induced hypoxic retinal disease by reducing transcript levels and protein expression of HIF-1 α and mRNA to protect retinal pigment epithelial cells.^{185,186}

What's more, CTS significantly reduced placental and blood serum insulin levels in gestational diabetic mice and ameliorated their oxidative stress and inflammatory responses by modulating NF- κ B signaling.^{187,188}

The main effects of cryptotanshinone against disease and related molecular mechanisms in [Table 3](#).

Table 3 Disease and Mechanisms of the Major Action of CTS

Author and Year	Diseases	Mechanism	Effects
Zhao et al 2022 ¹⁰⁸	Non-small cell lung cancer	Upregulated the RIP1/RIP 3/MLKL pathway	Promoting the necrotizing apoptosis
Kim et al 2018 ⁸²	Non-small cell lung cancer	Downregulation of the PI3K/Akt/GSK-3 β pathway	Inhibit growth, proliferation, and promote apoptosis
Jin et al 2020 ⁹⁰	Non-small cell lung cancer	Up-regulating the Hippo pathway	Inhibition of proliferation
Zhang et al 2018 ⁷⁷	Lung cancer	Downregulation of the IGF-1R/PI3K/Akt pathway	Inhibition of proliferation and migration
Luo et al 2020 ⁷⁴	Liver cancer	Downregulation of the PI3K/AKT/mTOR pathway	Inhibit proliferation and increased autophagy and apoptosis
Han et al 2019 ⁸⁴	Liver cancer	Down-regulation of the JAK2/STAT3 and TLR7/MyD88/NF- κ B pathway	Inhibit proliferation, growth, and promote apoptosis
Jiang et al 2022 ¹¹⁵	Liver cancer	Up-regulation the AMPK signaling pathway	Inhibition of proliferation
Chen et al 2024 ¹²⁴	Melanoma	Activation of AMPK and down-regulation of the HIF-1 α / PFK pathway	Inhibition of proliferation
Liang et al 2018 ¹²⁶	Colorectal cancer	Inhibition of the STAT3 and p-STAT3 proteins	Inhibition of proliferation
Terado et al 2022 ⁴⁷	Colorectal cancer	Inhibition of RKAS protein activation	Inhibition of proliferation and growth
Zhang et al 2018 ⁷⁶	Colorectal cancer	Reduced the MMP / TIMP ratio and inhibited the PI3K / Akt / mTOR pathway	Inhibit the growth, proliferation, and invasion
Song et al 2023 ⁸³	Colorectal cancer	Inhibition of the SIRT3 protein	Inhibition of proliferation
Yang et al 2018 ¹²⁸	Oophoroma	Inhibition of the STAT3/SIRT3 pathway	Inhibited proliferation and increased apoptosis
Wang et al 2024 ¹²³	Oophoroma	Downregulation of the GLUT1/HK2/PKM2/LDHA pathway	Inhibit proliferation and promote apoptosis
Dong et al 2018 ⁸⁸	Chronic myelocytic leukemia	Inhibition of STAT5 phosphorylation	Inhibit proliferation and reduce drug resistance
Ni et al 2021 ¹²⁰	Breast cancer	Inhibition of the BCRP protein activity	Reduce drug resistance
Noori et al 2022 ¹¹¹	Breast cancer	Reduce the JAK2/STAT3 phosphorylation	Inhibition of proliferation
Shi et al 2020 ⁷⁵	Breast cancer	Downregulation of the PI3K/AKT pathway	Inhibition of proliferation and growth
Chen et al 2017 ⁷⁸	Breast cancer	Upregulating the AMPK/TSC2 pathway	Inhibition of proliferation
Zhou et al 2020 ¹⁰⁸	Breast cancer	Downregulation of the PKM2/ β -catenin pathway	Inhibit the proliferation, migration, and invasion
Ma et al 2023 ⁹²	Breast cancer	Overexpression of Bax/Bcl-2 ratio; inhibition of MMP2 and MMP9 proteins	Inhibition of migration, and invasion
Huang et al 2022 ¹¹²	Sanyin breast cancer	Downregulation of the THEMIS2 protein	Inhibit proliferation, invasion, and cancer stemness
Ye et al 2022 ¹¹³	Sanyin breast cancer	Downregulation of the TRAF6/ASK1 pathway	Inhibition of proliferation and migration
Yu et al 2018 ¹⁰⁷	Saliva gland tumor	Inhibition of the STAT3/PUMA pathway	Promote apoptosis
Cao et al 2024 ⁸⁷	Gastric cancer	Downregulation of the JAK2/STAT3 pathway	Inhibition of proliferation
Wang et al 2021 ³⁴	Cardiac ischemia / perfusion reinjury	Up-regulation of the MAPK pathway	Reduced in normal cell apoptosis
Liu et al 2017 ⁴⁵	Ischemia myocardial	Suppressed CaM and CaMKII δ expression and promoted RyR 2 and PLB expression	Inhibition of calcium overload
Zhao et al 2018 ⁶⁵	Atherosclerosis	Inhibition of the NF- κ B pathway	Inhibition of the focal adhesion molecule expression
Saviano et al 2022 ⁵⁷	Thrombus	Downregulation of the Cyclooxygenase-2/mPGES-1/EP3 pathway	Anticoagulation
Zhang et al 2021 ⁴³	Coronary embolism	Inhibition of the NF- κ B pathway	Inhibition of oxidative stress
Rahman et al 2016 ⁶⁶	Obesity	Up-regulation of the p38 / MAPK pathway	Inhibition of brown adipose tissue differentiation
Wu et al 2020 ²⁵	Neuroinflammation	Downregulation of the MAPK pathway	Inhibition of neuroinflammation

(Continued)

Table 3 (Continued).

Author and Year	Diseases	Mechanism	Effects
Maione et al 2018 ¹³⁴	Alzheimer's disease	Downregulation of the NF- κ B/I κ B- α pathway	Anti-inflammatory, neuroprotective conditions
Lyu et al 2022 ¹³⁶	Alzheimer's disease	Downregulation of the PI3K/Akt/GSK22 β pathway	Reduces tau hyperphosphorylation and restores synaptic function
Fei et al 2017 ¹⁴³	Parkinson's disease	Promoting the NRF2 protein expression	To restore the mitochondrial function
Xu et al 2022 ¹⁴⁶	Parkinson's disease	Downregulation of the Nrf2/HO-I pathway	Inhibition of oxidative stress and apoptosis
Zhang et al 2019 ¹⁴⁸	Inflammation and neuropathic pain	Downregulation of the PI3K/Akt pathway and inhibiting the NLRP3 protein	Inhibition of inflammation and neuropathic pain

Outlook

Bioinformatics serves as a powerful analytical approach, and the integration of bioinformatic analysis with a diverse array of analytical tools enables us to identify potential molecular targets for natural small molecules.^{189,190} On the basis of continuously updated literature, we explored the potential pathways and targets of CTS by bioinformatics analysis,¹⁹¹ and based on the results of the analysis, we put forward a novel speculation on the potential targets of CTS.

Firstly, DO enrichment analysis (Figure 5) showed that CTS possessed significant anti-tumour activity against several types of tumours, especially peripheral nervous system tumours, motor nervous system tumours, ovarian cancers and benign tumours. Although the effect of CTS on ovarian cancer has been reported in the literature, little literature has focused on its efficacy and related molecular mechanisms in peripheral nervous system and motor nervous system tumours. In addition, the enrichment results suggest that CTS has good pharmacological activity against ischaemic diseases, so the pharmacological activity and molecular mechanisms associated with it deserve more in-depth exploration.

Secondly, KEGG enrichment analysis (Figure 5) showed that CTS involves molecular pathways including tumor metabolism, tumor drug resistance, lipids and atherosclerosis, AGE signalling pathway, endocrine resistance and so on. It is worth mentioning that among the results obtained from this bioinformatic analysis, Lipid and atherosclerosis, Shigellosis, AGE-RAGE signalling pathway in diabetic complications, Endocrine resistance, and Proteoglycans in cancer (the top 20 in KEGG enrichment results) were first enriched. These four new pathways accounted for 1/5 of the top 20

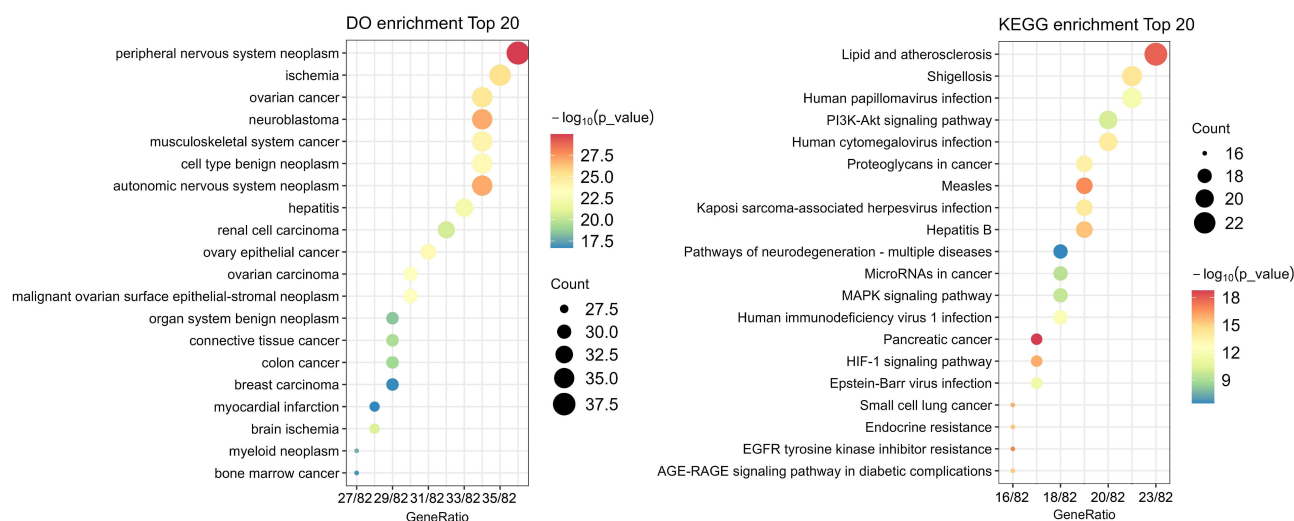


Figure 5 The dotplots of DO and KEGG analysis using the reported proteins or genes for CTS against diseases (2017–2024).

Abbreviations: DO, Disease ontology; KEGG, Kyoto encyclopedia of genes and genomes pathway; CTS, Cryptotanshinone.

pathways in the KEGG enrichment results, however, the mechanisms related to these pathways have been rarely studied, and the targets behind these pathways are still unclear. Therefore, it is still promising to use advanced techniques to clarify the key pathways involved, elucidate the drug-protein/gene binding forms, and explore the potential pharmacological activities of CTS.

Subsequently, GO enrichment analysis (Figure 6) showed that CTS mainly affects cellular components distributed in cell membrane or organelle membrane, cytoplasmic vesicle lumen or cytoplasm, and influences oxidative stress, apoptosis, and cell proliferation through binding to enzymes. Based on the results of the above analyses, we have made a speculation that the potential molecular targets of CTS may be located in organelle membranes and affect the biological functions of cells by binding to enzymes in the membranes. The above results deserve to be further verified by high-throughput experimental techniques such as *in vivo* and *ex vivo* experiments and histological analyses.

To further explore the potential connections of the CTS target proteins, we input the targets reported in the literature into the STRING web server to obtain the potential Protein Protein Interaction Networks (PPIs).¹⁹² As shown in Figure 7, 92 nodes and 232 edges were generated in the PPI network after setting the minimum interaction score to 0.9 and hiding the isolated nodes. As shown in Figure 7, we have ranked the proteins in the network by the degree of the nodes. The most highly correlated eight proteins in the PPI network are TP53 (degree: 25), STAT3 (degree: 23), MAPK1 (degree: 20), AKT1 (degree: 18), PTPN11 (degree: 17), PIK3CA (degree: 17), BCL2L1 (degree: 16) and EGFR (degree: 15). We

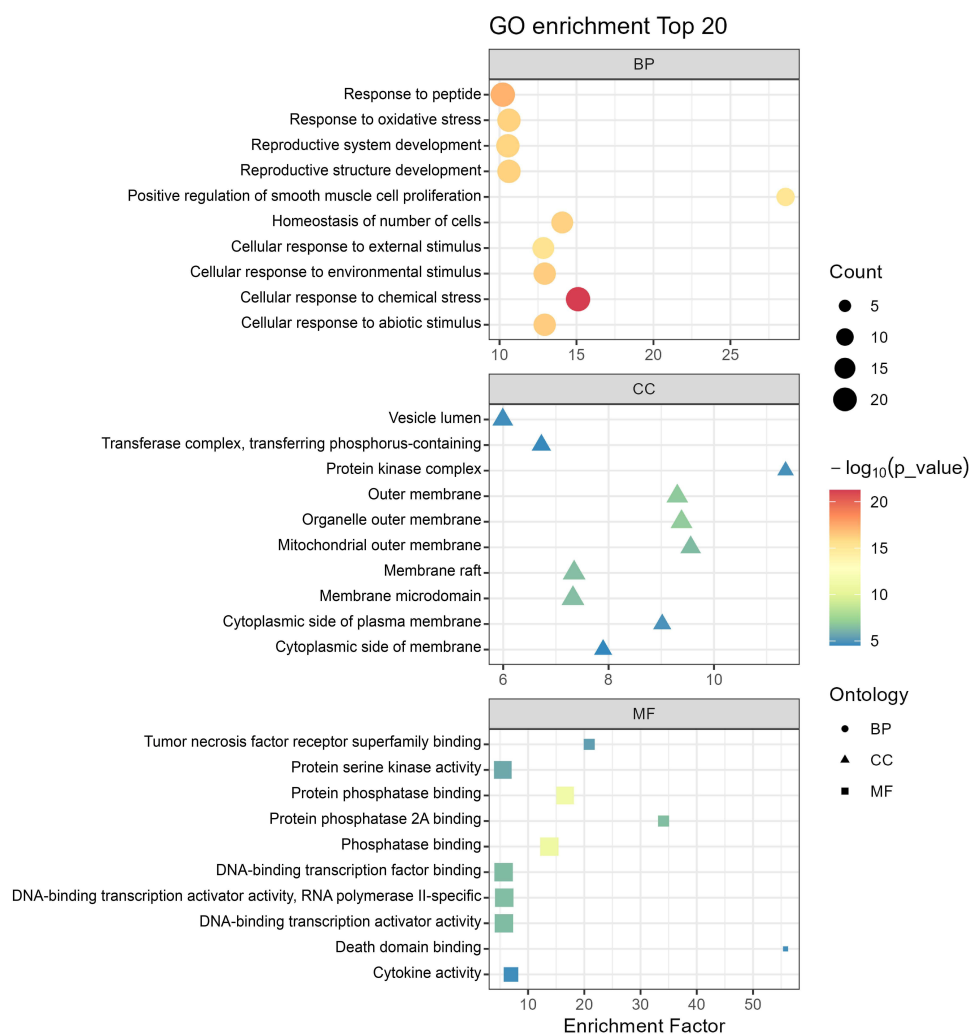


Figure 6 The dotplots of GO analysis using the reported proteins or genes for CTS against diseases (2017–2024).

Abbreviation: GO, gene ontology.

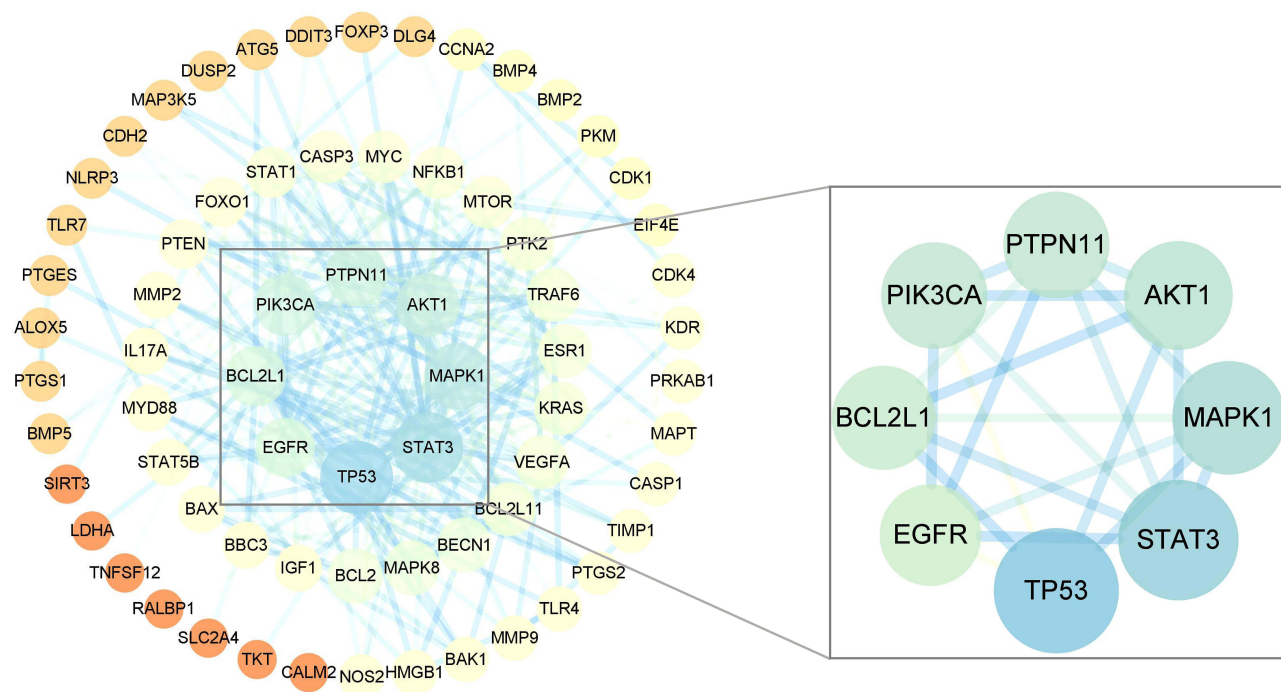


Figure 7 PPI network using the reported proteins or genes for CTS against diseases (2017–2024).

Abbreviations: PPI, Protein-protein interactions; CTS, Cryptotanshinone.

speculate that there are still potential targets of CTS that have not yet been demonstrated by research. In addition, although there is a large body of literature suggesting that CTS can affect the expression of these proteins, the exact molecular mechanisms, and the effects of CTS on biological functions through these target proteins need to be explored in depth by researchers.

Subsequently, we used Autodock Tools 1.5.7 for molecular docking of target proteins with CTS. Following pretreatment of the docking molecules, the CTS (ZINC: 000002109876) binding scores to TP53 (PDB no. 6my0), STAT3 (PDB no. 6gfa), MAPK1 (PDB no. 2ojj), AKT1 (PDB no. 6hhg), PTPN11 (PDB no. 6bmu), PIK3CA (PDB no. 6r9v), BCL2L1 (PDB no. 1lx1) and EGFR (PDB no. 2ity) and the binding active sites were as shown in Figure 8.

As shown in the Figure 8, CTS binds to TP53 and forms a hydrogen bond with the amino acid residue MET-1584, measuring 3.6 Å in length. It also binds to STAT3 protein, forming two hydrogen bonds with the amino acid residue KYS-271, with lengths of 2.8 Å and 3.2 Å respectively. Additionally, it binds to MAPK1, establishing a hydrogen bond with the amino acid residue VAL-304, which measures 1.9 Å. Moreover, CTS binds to AKT1 protein, forming two hydrogen bonds with the amino acid residues ALA-329 and ARG-328, with bond lengths of 1.9 Å and 2.2 Å respectively. Furthermore, when bound to PTPN11, CTS forms a hydrogen bond with the amino acid residue GLN-446, measuring 2.0 Å. Bound to PIK3CA, it forms two hydrogen bonds with the amino acid residues VLEU-54 and VLEU-55, measuring 2.8 Å and 3.2 Å respectively. In total, it forms four hydrogen bonds with the amino acid residues LEU-570, LYS-548, and VAL-572, measuring 2.5 Å, 3.0 Å, 2.3 Å, and 3.5 Å respectively. Moreover, CTS binds to BCL2, forming a hydrogen bond with the amino acid residue GLN-3, with a length of 1.9 Å. Lastly, it binds to EGFR, forming hydrogen bonds with the amino acid residues ARG-889 and GLY-863, with lengths of 3.4 Å and 2.0 Å respectively. Despite the extensive literature demonstrating the impact of CTS on the expression of these proteins and their regulation of associated signalling pathways, there is limited direct evidence regarding their specific targets and binding sites. Our docking results, however, clearly illustrate the binding of CTS to these proteins. Based on these findings, we predict the binding scores and hydrogen bond lengths, indicating potential interactions between CTS and its

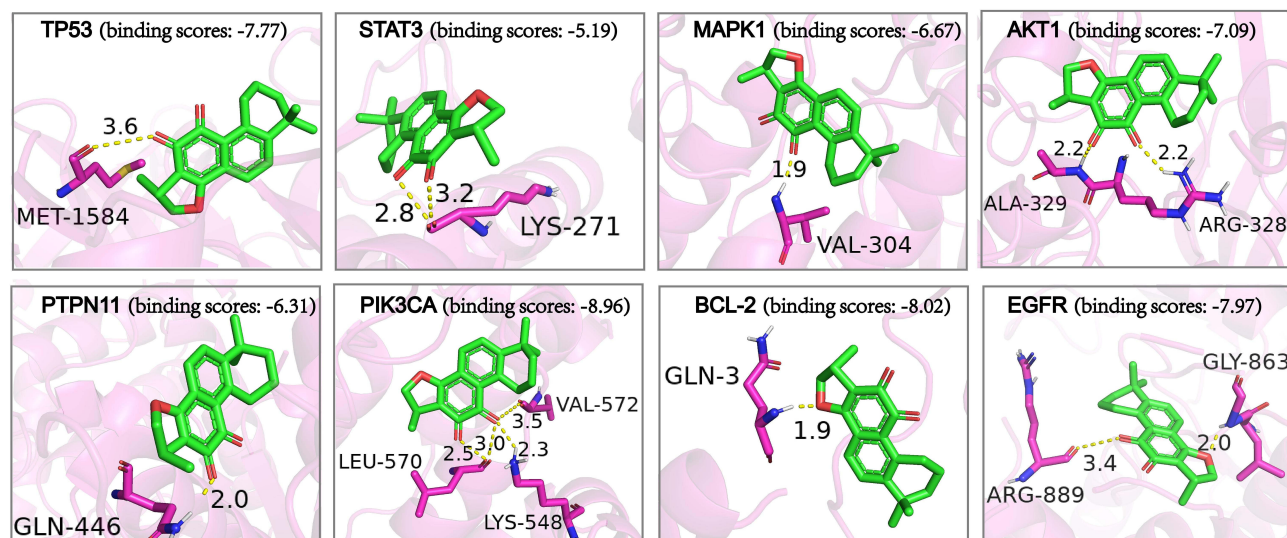


Figure 8 Molecular docking results of eight proteins with CTS.

target proteins. It is important to note that further mechanistic studies are required, particularly focusing on the active sites and binding modes of CTS in direct association with these target proteins. The results of our target prediction offer new insights for future researchers to explore the untapped research potential of CTS through comprehensive pharmacological investigations.

Conclusion

Since 1990, over 300 research papers on CTS have been published on the PubMed database. Among these, approximately 40% (118 papers) are related to the anticancer activity of CTS. CTS has been shown to promote autophagy and apoptosis in cancer cells, inhibit cancer cell proliferation and differentiation, suppress cancer cell migration and invasion, improve the tumor microenvironment, and reduce extracellular matrix formation. CTS shows promising pharmacological activity against more than 10 cancers, including breast, liver, non-small cell lung and tongue squamous cell carcinomas. This suggests that CTS is a natural small molecule with significant anticancer potential. However, there is still no new CTS-based drugs on the market. Therefore, future research is able to focus on further exploring potential molecular targets of CTS, comprehensively elucidating the pharmacology and toxicology of CTS, and promoting the development of new CTS-based drugs.

It is worth noting that among the 19 research papers published on PubMed in 2023, only 3 are related to the anticancer effects of CTS. The other 16 papers cover various pharmacological research directions, including anti-inflammatory, anti-fibrotic, and other pharmacological activities, exploration of drug targets, the role and mechanism of CTS in combination therapy with clinical drugs, and the preparation of novel nanoscale formulations. This indicates that researchers are increasingly interested in the multi-target and multi-pathway pharmacological effects of CTS and its potential clinical applications. This shift also provides insights into future research directions for CTS.

While CTS possesses excellent pharmacological activity, its low bioavailability and potential toxicity have been significant challenges for its development into drugs. To address this issue, researchers have been working on developing CTS derivatives, studying the synergistic effects of CTS with clinical drugs, and developing novel nanoscale formulations to enhance efficacy and reduce toxicity. While CTS exhibits promising pharmacological activity, its low bioavailability and potential toxicity present significant hurdles in the development of a viable pharmaceutical product. To address this issue, researchers have been developing CTS derivatives, investigating the potential for CTS to act synergistically with clinical drugs, and developing novel nanoscale formulations to improve efficacy and reduce toxicity. At this stage of research, there is a paucity of reports on the enhancement of drug bioavailability by the modification of delivery systems, and the scientific research on this topic remains promising. Furthermore, despite the extensive research literature on the pharmacological activity and molecular mechanism of CTS, there is a paucity of clinical studies on CTS.

The safety and efficacy of CTS in humans remain unknown, which presents a significant challenge for the clinical translation of CTS. As a promising natural small molecule compound, CTS still requires further investigation of its key drug targets in future studies. In light of these considerations, it is imperative to enhance the bioavailability of CTS by optimizing the delivery system and to initiate clinical trials on CTS.

Abbreviations

CTS, Cryptotanshinone; NF- κ B, nuclear factor kappa-B; Src, proto-oncogene tyrosine-protein kinase; FAK, focal adhesion kinase; MAPK, mitogen-activated protein kinase; PI3K, phosphatidylinositol 3-kinase; protein kinase B; GSK3 β , glycogen synthase kinase3 β ; Nr2f2, nuclear factor erythroid 2-related factor 2; HO-1, heme oxygenase 1; Smad, drosophila mothers against decapentaplegic protein; AMPK, AMP-activated protein kinase; SIRT1, silent information regulator factor 2-related enzyme 1; PGC-1 α , peroxisome proliferator-activated receptor-gamma coactivator; KEGG, kyoto encyclopedia of genes and genomes pathway; GO, gene ontology; DOSE, disease ontology semantic and similarity enrichment analysis; PPI, protein-protein interactions; MTOR, mammalian target of rapamycin; EGFR, epidermal growth factor receptor; Papp, apparent permeability coefficient; UGT, UDP-glucuronosyltransferase; CYP, cytochrome; PXR, pregnane X receptor; UPLC-MS/MS, ultra-performance liquid chromatography-tandem mass spectrometric; P-gp, P-glycoprotein; LD50, lethal dose 50; IR, Ischemia/Reperfusion Injury; ROS, reactive oxygen species; MDA, malondialdehyde; CaMK, Ca²⁺/calmodulin-dependent protein kinase; Bcl-2, B-cell lymphoma-2; mtROS, reactive oxygen species; LDL, low-density lipoprotein; MCP-1, monocyte chemoattractant protein-1; Ox-LDL, low-density lipoprotein; ICAM-1, intercellular adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1; VEGFR2, vascular endothelial growth factor receptor 2; PKM2, Pyruvate kinase M2; TNF- α , tumor necrosis factor- α ; STAT3, signal transducer and activator of transcription 3; SMC, smooth muscle cells; EP3, prostaglandin E receptor 3; ET-1, endothelin-1; vWF, von Willebrand Factor; COX-1, TI, teratogenicity index; cyclooxygenase-1; HF, heart failure; PRRs, pattern recognition receptors; Ang II, Angiotensin II; NOX, NADPH Oxidases; CI, Cardiac inflammation; iNOS, inducible nitric oxide synthase; TLR, Toll-like receptor; AAP, amino alkyl phosphoramidite; IGF, Insulin-like growth factor; PTEN, protein tyrosine phosphatase; Bax, BCL2-Associated X; Bcl-2, B-cell lymphoma-2; JAK, tyrosine-protein kinase; CDK, cyclin-dependent kinase; NO, nitric oxide; Hippo, Serine/threonine-protein kinase hippo; NSCLC, non-small cell lung cancer; MMP, mitochondrial membrane potential; PARP, poly ADP-ribose polymerase; Bid, BH3 interacting domain death agonist; TIMP, tissue Inhibitor of metalloproteinases; PTKs, protein tyrosine kinases; C-myc, cellular-myelocytomatosis viral oncogene; ATG, anti-thymocyte globulin; Bad, BCL2 associated agonist of cell death; P53, Cellular tumor antigen p53; PUMA, p53 up-regulated modulator of apoptosis; MET, mesenchymal-epithelial transition factor; MLKL, mixed lineage kinase domain-like protein; TAM, tumor-associated macrophage; Th, helper T cell; TRAF6, TNF receptor-associated factor 6; ASK1, apoptosis Signal-Regulating Kinase 1; IL-6, interleukin-6; CML, Chronic Myelogenous Leukemia; Era, Estrogen receptor α ; GLUT1/2, glucose transporter protein; LDHA, L-lactate dehydrogenase A chain; HK2, Interleukin-2; PPAR γ , peroxisome proliferator-activated receptor γ ; AD, alzheimer's disease; A β , amyloid protein; PD, parkinson's disease; an IIA, tanshinone IIA; SOD, superoxide dismutase; GSH-Px, glutathione peroxidase; CAT, catalase; ISD, ischemic stroke; BIRI, brain ischemia reperfusion injury; EC₅₀, median effect concentration; MPTP, mitochondrial permeability transition pore; OGD/R, oxygen glucose deprivation/reoxygenation; IBD, inflammatory bowel disease; UC, ulcerative colitis; 5-FU, 5-fluorouracil; CPT-11, irinotecan; VD, vascular dementia; OA, osteoarthritis; UUO, unilateral ureteral obstruction; ECM, extracellular matrix; YAF2, YY1-associated factor 2; MPP, membrane permeable peptide; hiNPCs, human-induced neural progenitor cells; RT-PCR, reverse transcription polymerase chain reaction; RA, rheumatoid arthritis; BPH, benign prostatic hyperplasia; BMM, bone marrow-derived macrophages; RILI, radiation induced lung injury; AR, androgen/androgen receptor; TWEAK, tumor necrosis factor ligand superfamily member; PCOS, Polycystic ovarian syndrome; BBB, blood brain barrier; MF, molecular function.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests.

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