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Research progress on pharmacological effects and mechanisms of cycloastragenol

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Highlights

- Cycloastragenol exhibits anti-aging, anti-cancer, and anti-fibrosis effects.
- Although cycloastragenol shows innovative therapeutic potential, further clinical trials are essential to confirm its clinical applicability.
- Cycloastragenol offers innovative therapeutic avenues for enhancing surgical recovery.

Abstract

Cycloastragenol, a key bioactive compound extracted from Astragalus membranaceus, has attracted increasing attention for its therapeutic potential in anti-aging, cancer treatment, and fibrosis prevention. This review summarizes the pharmacological activities of Cycloastragenol at molecular, cellular, and systemic levels, and discusses its efficacy across various disease models and potential perioperative applications. Current evidence demonstrates that Cycloastragenol exerts dose-dependent therapeutic efficacy through specific molecular targets. However, its clinical translation remains limited, particularly in surgical recovery contexts, underscoring the need for further validation through well-designed clinical trials focused on perioperative outcomes.

Keywords: Cycloastragenol, pharmacological effect, mechanisms of action, research progress

Introduction

Cycloastragenol (CAG), a bioactive triterpenoid derived from Astragalus membranaceus, is primarily obtained through enzymatic hydrolysis of its glycosylated precursor astragaloside IV [1, 2]. This structural modification enhances CAG's pharmacokinetic properties by increasing its lipophilicity, thereby facilitating transmembrane permeability and systemic absorption [3].

CAG's robust organoprotection, anti-inflammatory efficacy, and promotion of cellular stress resistance position it as a candidate for improving perioperative outcomes. Emerging evidence have demonstrated CAG's broad pharmacological activities, including telomerase activation, anti-senescence effects, cardioprotection,

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neuropsychiatric modulation, and immune regulation [4-8]. These findings have positioned CAG as a promising candidate for therapeutic applications in various disease contexts.

This review systematically examines the molecular mechanisms and therapeutic potential of CAG, with a particular emphasis on its multi-target regulatory effects on key signaling pathways. By integrating recent pharmacodynamic insights and preclinical studies, we aim to elucidate CAG's translational relevance in precision medicine, particularly in the context of managing age-related and chronic diseases, as well as its emerging potential for improving perioperative outcomes. We further propose novel strategies leveraging CAG's multi-target actions for managing age-related decline and chronic conditions, with implications for optimizing perioperative care and enhancing recovery.

Pharmacological effects of cycloastragenol

Anti-aging effects and cognitive protection

Aging is an inevitable biological process, and telomere shortening is a recognized contributor to cell senescence. CAG is currently the only known telomerase activator with potent anti-aging effects [5, 9, 10]. It delays cellular senescence by upregulating telomerase reverse transcriptase (TERT) mRNA expression and elongating telomeres [11]. In 2012, Cao et al. investigated the anti-aging mechanism of CAG using a D-galactose-induced aging mouse model, and demonstrated that CAG administration significantly enhanced total superoxide dismutase (SOD) activity and total antioxidant capacity, reduced malondialdehyde (MDA) levels, and increased hydroxyproline content [10]. Neuroprotective studies revealed that CAG activated the phosphatidylinositol 3-kinase/protein kinase B/mechanistic target of rapamycin (PI3K/Akt/mTOR) and cAMP response element binding pathways, promoted the expression of synaptic plasticity-related proteins, and alleviated cognitive impairment in Alzheimer's disease models [5, 12]. Hong et al. reported that both CAG and astragalusoside IV reduced the expression levels of p16, cleaved-caspase 3, and Bcl-2 Associated X Protein (BAX), while increasing the expression level of Bcl-2 and TERT, thereby protecting nucleus pulposus cells from high-glucose-induced senescence and apoptosis [13]. Similarly, Ikram et al. showed that CAG downregulated the expression of phosphorylated c-jun n-terminal kinase, phosphorylated p38 mitogen-activated protein kinase, and phosphorylated extracellular signal-regulated kinase (p-JNK, p-P38, and p-Erk), while upregulating the expression of nuclear factor erythroid 2-related factor 2, heme oxygenase-1, phosphorylated tropomyosin receptor kinase B, brain-derived neurotrophic factor, and neuronal nuclear protein (Nrf2, HO-1, p-TrKB, BDNF and NeuN). These changes significantly reduced microglial activation and inflammatory cytokine production, improving oxidative stress, metabolic disturbances, neuroinflammation, apoptosis, and memory impairment in AD mouse models [7]. In D-galactose-induced aging mice, CAG treatment (10 mg/kg for 8 weeks) reduced β-amyloid deposition in the hippocampus by 50%, and Morris water maze testing demonstrated a 35% improvement in spatial memory [4]. Additionally, CAG has been shown to significantly improve behavioral performance and hippocampal structure in AD rat models, thereby enhancing cognitive function, memory, and learning ability [14]. A clinical study also demonstrated that oral administration of a CAG-containing formulation in 20 healthy individuals over 6 months led to a 12% increase in telomere length and marked improvement in skin elasticity [15].

Anti-cancer effect

With rapid economic development and improved living standards, the prevalence of cancer in China has increased markedly. In 2022, approximately 4.82 million new cancer cases and 2.57 million cancer-related deaths were reported [16, 17]. Recent studies suggest that CAG demonstrates notable anti-cancer effects [18]. Mechanistically, CAG binds to target tissue protease B and inhibits lysosomal degradation of major histocompatibility complex class I (MHC-I), thereby promoting MHC-I accumulation on the cell membrane (**Figure 1**). This enhances tumor antigen presentation and augments the cytotoxic activity of $CD8^+$ T cells [19]. Deng et al. reported that combining CAG with a programmed death-1 antibody significantly improved survival in tumor-bearing mice [19]. In colorectal cancer organoid models, CAG in combination with anti-programmed death-1 upregulated MHC-I expression and enhanced the cytotoxicity of $CD8^+$ T cells against tumor cells. Furthermore, CAG also has been shown to inhibit matrix metalloproteinase (MMP)-2 activity and its associated calcification effects, contributing to the amelioration of abdominal aortic aneurysm [20].

Anti-fibrotic effect

Fibrosis is a progressive pathological condition characterized by excessive deposition of extracellular matrix, resulting in tissue distortion and

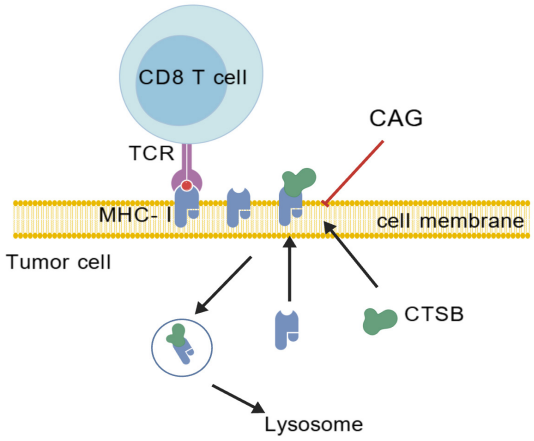

Figure 1. The main anti-cancer pathways of CAG. CD8 T cell, cytotoxic tlymphocyte; TCR, T cell receptor; MHC-I, major histocompatibility complex I; CAG, cycloastragenol; CTSB, Cathepsin B.

gradual loss of organ function [21]. Fibrosis can affect any solid organ, particularly the lungs, liver, heart, and kidneys, and is closely associated with chronic diseases such as diabetes and hypertension. Statistics suggest that about 45% of deaths in Western countries are related to fibrosis-associated diseases [22]. CAG has demonstrated significant anti-fibrotic activity across various organs. In a liver fibrosis mouse model, CAG reduced serum levels of alanine aminotransferase and aspartate aminotransferase, decreased the expression of collagen I and α-smooth muscle actin (α-SMA) in hepatic tissues, and lowered the level of key enzymes and metabolites [1]. In CCl_4-induced hepatic fibrosis in mice, CAG upregulated MMP8, MMP9, MMP12, and interleukin- 6 (IL-6) expression, contributing to fibrosis resolution [23]. In cardiac fibrosis, Dong et al. showed that CAG alleviated isoproterenol-induced myocardial fibrosis and cardiac dysfunction by inhibiting the expression of oxidative stress-related factor NADPH oxidase 4, suppressing phosphorylation of key proteins in the nuclear factor κappa B (NF-κB) signaling pathway (p-IκBα, NF-κB, p-p65), and transforming growth factor-β (TGF-β) expression and inducible nitric oxide synthase transcription [24]. In addition, preliminary studies combining network pharmacology, molecular docking, and animal experiments suggest that CAG may attenuate renal fibrosis in mice by targeting MMP3 and MMP2, reducing collagen fiber deposition, and lowering the expression of TGF-β1, α-SMA, MMP3, and MMP2 in renal tissues [25]. Although clinical data in humans are lacking, preclinical studies in murine models support the therapeutic potential of CAG in hepatic fibrosis [23].

Anti-inflammatory and anti-oxidative stress effects

Oxidative stress arises from an imbalance between oxidative and antioxidant processes, often accompanied by excessive accumulation of reactive oxygen species (ROS). This imbalance can induce tissue inflammation, which in turn exacerbates oxidative stress, forming a vicious cycle that ultimately leads to tissue damage [26].

At the molecular level, CAG exerts bidirectional regulatory effects on key signaling pathways (**Figure 2**). It suppresses nuclear translocation of NF-κB p65 and reduces p-NF-κB p65 expression, leading to significant downregulation of pro-inflammatory cytokines (e.g., TNF-α, IL-1β, and IL-6), while upregulating anti-inflammatory cytokines (e.g., IL-4 and IL-10) [27-33]. Simultaneously, CAG facilitates dissociation of Nrf2 from Kelch-like ECH-associated protein 1 (Keap 1), promotes its nuclear translocation, and enhances the transcription of antioxidant genes such as HO-1 and Aquaporin 9 (AQP9). It also decreases ROS and MDA levels, elevates SOD activity, and modulates apoptosis by reducing the Bax/Bcl-2 ratio, inhibiting caspase-3 activity, and suppressing cytochrome C release [28, 30-36].

At the cellular level, CAG inhibits CD69/CD25 activation marker expression on $CD3^+$ T cells, blocks lymphocyte progression from G0/G1 to S/G2/M phase, and promotes microglial polarization from the M1 to M2 phenotype, demonstrating anti-inflammatory effects [31, 37]. It also mitigates cisplatin-induced inflammation in HK-2 cells by reducing IL-6 and IL-18 levels, suppresses ROS production and mitochondrial cytochrome C release in HT22 cells, and upregulates cleaved caspase-3 and Bcl-2 expression to attenuate oxidative stress damage [29, 35]. Additionally, Liu et al. found that CAG reduced ROS and MDA levels, enhanced SOD activity, and improved viability in C2C12 cells [34]. Network pharmacology studies further revealed its ability to ameliorate primary hepatocyte injury in mice, decrease alanine aminotransferase and aspartate aminotransferase levels in culture supernatants, inhibits p-NF-κB p65 expression, and upregulates adenosine 5'-monophosphate-activated protein kinase, Nrf2, and HO-1 at both gene and protein levels to alleviate alcoholic liver injury [33].

At the tissue and organ level, CAG provides protection against acute myocardial infarction by inhibiting inflammation and cardiomyocyte apoptosis [27]. It also alleviates intestinal inflammation in ulcerative colitis models, im-

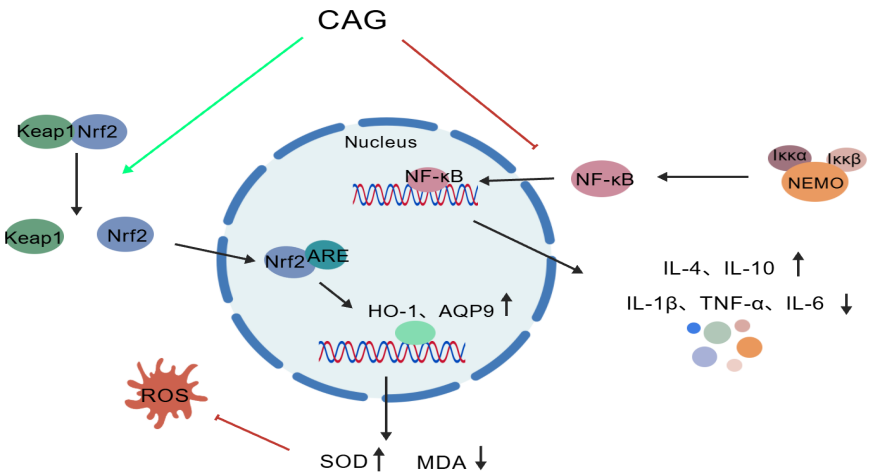

Figure 2. Bidirectional regulatory mechanisms of CAG in anti-inflammatory and antioxidant responses. CAG, cycloastragenol; Nrf2, nuclear factor erythroid 2-related factor 2; Keap1, Kelch-like ECH-associated protein 1; ARE, Antioxidant Response Element; HO-1, heme oxygenase 1; AQP9, Aquaporin 9; SOD, superoxide dismutase; MDA, malondialdehyde; ROS, reactive oxygen species; NF-κB, nuclear factor κappa B; IKKβ, inhibitor of kappa B kinase; IKKα, IκB kinase α; NEMO, nuclear factor-κappa B essential modulator; IL-4, Interleukin 4; IL-10, Interleukin 10; IL-6, Interleukin 6; IL-1β, Interleukin-1 beta; TNF-α, tumor necrosis factor-α.

proves hepatic function in alcoholic liver injury, mitigates cisplatin- and gentamicin-induced renal injury, and prevents airway hyperresponsiveness and mucus hypersecretion in asthmatic mice [28, 29, 32, 33, 38]. Li et al. have demonstrated that CAG reduces neuronal damage in ischemic stroke models by regulating p53 acetylation and the Bax/Bcl-2 ratio [30]. Furthermore, a study confirmed that CAG promoted hepatic regeneration via upregulating AQP9 expression in hepatocytes, which enhances gluconeogenesis and reduces oxidative stress [36].

Notably, clinical studies have shown that CAG modulates the Th1/Th17/Th2 cytokine balance in peripheral blood mononuclear cells (PBMCs) of acute myocardial infarction patients, highlighting its clinical translational potential [27].

Other Effects

Maintenance of skin health

CAG demonstrates multifaceted therapeutic potential in skin diseases through molecular pathway modulation and cellular homeostasis regulation. As the body's primary defense system, skin integrity is crucial. In diabetes-induced ulcerative models, CAG promoted wound healing by increasing SOD activity by 40% and upregulating endothelial eNOS expression by 2.1-fold [39]. In melanocytes, CAG regulates pigmentation via coordinated upregulation of MITF/TYRP1/2 by 1.8-2.3 fold, alongside modulation of p38 MAPK phosphorylation. These effects reduce pro-apoptotic Bax expression by 65%, lower MDA levels by 48%, and elevate catalase (CAT) activity by 35%, thereby attenuating oxidative stress and delaying vitiligo progression [40].

CAG also preserves dermal architecture through extracellular matrix remodeling via fibroblast activation. It upregulates MMP1/9/13 by 2.1-2.7 fold and enhances collagen and hyaluronic acid synthesis by 58% [41]. In keratinocytes, CAG exerts dual regulatory effects by inhibiting proliferation by 45% while inducing autophagy (LC3-II increased by 2.3 fold) and upregulating laminin and palmitoyltransferase (1.6 fold), thereby contributing to the maintenance of the physicochemical skin barrier [42]. These findings collectively position CAG as a promising candidate for managing diverse dermatological disorders through multi-targeted mechanisms.

Regulation of bone metabolism

Bone homeostasis is essential for maintaining skeletal integrity. It not only supports locomotion, but also regulates systemic calcium and mineral metabolism. Disruption of this balance can lead to osteoporosis, fractures, and other bone-related disorders [43]. Current research focuses on two major pathological mechanisms: excessive bone resorption caused by overactive osteoclasts and impaired bone formation due to reduced osteoblast activity [44]. Studies have shown that CAG not only alleviates the inhibition of osteogenic differentiation induced by glucocorticoids by activating telomerase but also inhibits the formation and function of osteoclasts by targeting the intracel-

lular signaling pathway induced by RANKL [45, 46]. In glucocorticoid-induced avascular necrosis of the femoral head, CAG inhibits osteoclast activity and prevents bone loss [47]. In addition, CAG serves as an exogenous enhancer of chondrogenesis from human adipose-derived mesenchymal stem cells, facilitating the formation of cartilage and maintaining the phenotypic stability of active chondrocytes [48]. These findings indicate that CAG holds therapeutic potential in improving bone loss and enhancing cartilage regeneration, contributing to overall skeletal health.

Others

Beyond these established effects, CAG also demonstrates anti-obesity potential. It reduces lipid accumulation by downregulating key adipogenic transcription factors such as PPARγ and C/EBPα, while upregulating Gli1, a pivotal Hedgehog signaling mediator [49]. CAG also protects against doxorubicin-induced podocyte injury through modulation of metabolic pathways including glycerophospholipid, amino acid, glutathione, and purine metabolism. In cerebral ischemia-reperfusion models, CAG significantly improves neurological function scores while reducing cerebral infarct volumes, demonstrating neuroprotective efficacy against focal cerebral ischemia-reperfusion injury [50, 51].

Pharmacokinetics of CAG

CAG, the principal bioactive component of Astragalus membranaceus, predominantly exists in its natural form as saponin derivatives such as astragaloside IV. Pharmacokinetic profiling indicates that CAG exhibits limited oral bioavailability due to its dependence on gut microbiota-mediated hydrolysis for activation [52]. Following both intraperitoneal and oral administration, active metabolites are detectable in systemic circulation, with peak plasma concentrations observed within 0.5-0.75 hours [52].

The compound is eliminated via dual routes, including renal (urinary) and hepatobiliary (fecal) routes [53]. Notably, enterohepatic recirculation contributes to characteristic biphasic or multiphasic plasma concentration-time profiles, owing to reabsorption of biliary-excreted metabolites [54]. Pharmacokinetic analyses in rodent models demonstrate moderate metabolic turnover, evidenced by an elimination half-life of 3-5 hours. At an oral dose of 10 mg/kg in rats, CAG exhibits dose-proportional pharmacokinetics, with a peak plasma concentration of 1,152 ng/mL and increasing AUC values [8].

Mechanistically, biotransformation primarily involves CYP450-mediated phase I oxidation and phase II glucuronidation [54]. However, the specific CYP450 isoforms and detailed metabolic pathways remain to be fully elucidated.

Discussion

Innovativeness

CAG emerges as a novel therapeutic agent, offering distinct advantages over conventional pharmacological interventions due to its multi-modal mechanisms of action. Unlike traditional antioxidants like vitamin C and E, which primarily mitigate oxidative stress with limited efficacy, or targeted therapies like rapamycin, which carry immunosuppressive risks, CAG activates telomerase to elongate telomeres, thereby delaying aging-associated pathologies, including osteoporosis, Alzheimer's disease, and cardiovascular dysfunction. This is complemented by its ability to extend cellular replicative lifespan and slow senescence progression [6].

In oncology, CAG circumvents severe myelosuppression, hepatorenal toxicity, and immunosuppression commonly associated with conventional DNA synthesis inhibitors (e.g., cyclophosphamide). Instead, it exerts synergistic antioxidant, anti-inflammatory, and tissue-regenerative effects, achieving tumor suppression with minimal off-target cytotoxicity.

For fibrotic disorders, where glucocorticoid therapies pose metabolic risks and integrative approaches often lack mechanistic clarity, CAG uniquely modulates fibrotic progression via dual suppression of profibrotic factor secretion and telomerase-mediated senescence delay. This mechanism concurrently addresses metabolic dysregulation, demonstrating enhanced safety profiles in hepatic fibrosis and chronic kidney disease compared to established therapies.

CAG also demonstrates therapeutic innovation in the management of chronic renal failure, offering cost-effective functional preservation and metabolic regulation superior to resource-intensive hemodialysis or transplantation. In respiratory diseases, CAG overcomes the limitations of glucocorticoid resistance and systemic side effects through dual anti-inflammatory and tissue-repair mechanisms, effectively mitigating disease progression in both stable and acute phases of chronic obstructive pulmonary disease and bronchitis.

Distinct from single-target drugs, CAG's poly-

Table 1. Pharmacological effects of cycloastragenol and its direct targets

Pharmacological effect	Direct target
Counteract aging and ameliorate cognitive dysfunction	TERT
Anti-cancer effect	CTSB-MHC-I
Anti-fibrotic effect	MMPs, TGF-β
Anti-inflammatory and anti-oxidative stress effect	Nrf2/ARE, NF-κB

Note: TERT, telomerase reverse tranase; CTSB, Cathepsin B; MHC-I, major histocompatibility complex I; MMPs, Matrix metalloproteinases; TGF-β, Transforming growth factor beta; Nrf2, Nuclear Factor erythroid 2-Related Factor 2; ARE, Antioxidant Response Element; NF-Kb, recombinant nuclear factor kappa B.

pharmacological nature enables synergistic therapeutic outcomes for complex comorbidities, positioning it as a cornerstone for developing low-toxicity combination therapies. Its natural origin and cost-effectiveness further enhance its clinical translation potential across diverse medical disciplines.

Safety profile

CAG demonstrates a favorable safety profile at low therapeutic doses (25-100 μM), with no significant cytotoxicity observed in cellular or animal models. However, cytostatic effects emerge at higher concentrations, necessitating dose optimization for clinical applications [6]. Preclinical studies in abdominal aortic aneurysm models reveal that daily administration of 125 mg/kg effectively attenuates disease progression while maintaining an acceptable safety margin, with no severe adverse events documented during treatment [55]. These findings collectively confirm its controllable toxicity window when administered within established dosage parameters.

Comparative analysis

CAG exerts its anti-fibrotic effects through strategic inhibition of TGF-β/Smad signaling, thereby suppressing fibroblast activation, collagen biosynthesis, and pathological extracellular matrix remodeling. Concurrently, it enhances hepatic sinusoidal endothelial cell functionality to ameliorate microcirculatory dysfunction. In contrast, its anticancer activity is driven by cathepsin B (CTSB)-mediated lysosomal regulation, where CAG preserves MHC-I integrity and amplifies tumor antigen presentation. This mechanism potentiates $CD8^+$ T cell immunity and synergistically enhances the efficacy of programmed death-1 antibodies through coordinated upregulation of antigen-processing machinery and immune transcription factors.

While both therapeutic actions involve modulation of the PI3K/Akt pathway, their downstream cascades exhibit mechanistic divergence: anticancer effects activate immune surveillance and tumor cell cycle arrest, whereas antifibrotic responses counteract NF-κB-driven inflammation and epithelial-mesenchymal transition to facilitate tissue regeneration.

Conclusion

CAG demonstrates polypharmacological efficacy through coordinated modulation of ROS and inflammatory cytokines (e.g., TGF-β1, TNF-α), orchestrating multi-pathway regulation across the Keap1/Nrf2/HO-1, NF-κB, Wnt, MAPK, and apoptotic cascades (**Table 1**). Its therapeutic actions extend to telomerase activation and dynamic control of inflammatory-oxidative-apoptotic axes, collectively enabling multi-organ protective effects in pulmonary, cardiovascular, hepatic, and renal systems through spatially resolved mechanism networks.

While CAG appears to exhibit an enhanced safety profile compared to conventional therapeutics, clinical translation requires rigorous validation via large-scale trials. Current investigations have primarily focused on telomerase activation and antioxidant capacity, leaving other molecular targets insufficiently characterized. Despite evidence suggesting pleiotropic signaling modulation, comprehensive system-level analyses of its cross-pathway regulatory networks are still lacking. Furthermore, fundamental questions remain regarding its gut microbiota crosstalk and tissue-specific mechanism prioritization, necessitating integrated multi-omics approaches to fully elucidate its therapeutic architecture.

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