Review Article

A narrative review of the pharmacology of ginsenoside compound K

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Background and Objective: The ginsenoside compound K [20-o-beta-dglucopyranosyl-20 (S)-protopanaxadiol; CK] is the main deglycosylated metabolite of ginsenoside. As a rare ginsenoside converted from the active substance of ginseng by intestinal bacteria, CK has higher biological activity than other ginsenosides. It has demonstrated diverse and intriguing biological activities, including anti-carcinogenic, anti-diabetic, anti-inflammation, anti-allergy, anti-angiogenesis, anti-aging, neuroprotective, and hepatoprotective effects. The purpose of this review was to elucidate the rich pharmacological activities and related mechanisms of ginsenoside CK *in vivo* and *in vitro*, as well as the potential therapeutic value of CK as a drug in a variety of systemically related diseases.

Methods: The PubMed database was searched for articles published in English from February 2008 to December 2021 using related keywords such as "Ginsenoside compound K", "compound K", and "CK". About 140 research papers and reports written in English were identified. These papers mainly concentrated on the pharmacological activities of CK in cancer prevention, immune regulation, diabetic improvement, central nervous system (CNS) protection, cardiovascular protection, skin improvement, and hepatoprotection.

Key Content and Findings: This paper describes the synthesis, pharmacokinetics, and adverse reactions of CK, as well as great detailed summarized of the relevant pharmacological activities. Such diverse intriguing biological properties of CK have been found.

Conclusions: On account of CK's numerous pharmacological activities and anti-carcinogenic, anti-inflammation, antiallergic, anti-diabetic, anti-angiogenesis, anti-aging, neuroprotective, and hepatoprotective effects, strong evidence is available for CK as a preventive or therapeutic agent for various diseases. However, further studies are needed to evaluate the safety and effectiveness of CK as a drug and its application in the medical field.

Keywords: Ginsenoside compound K; pharmacology; cancer; diabetes

Submitted Dec 03, 2021. Accepted for publication Feb 18, 2022.

doi: 10.21037/atm-22-501

View this article at: https://dx.doi.org/10.21037/atm-22-501

Introduction

Ginseng is a traditional Chinese herb with a long history of use in traditional Chinese medicine (TCM). It has powerful tonic effects and is widely used in various medicines (1). With the development of extraction technology, the most pharmacologically active constituents of ginseng have been reported to be ginsenosides, a group of triterpene saponins (2). To date, more than 150 active constituents have been extracted from the roots, stems, leaves, fruits, and flowers of ginseng (3). Studies have reported that ginsenosides are not absorbed intact in vivo, but need to be metabolized by intestinal microflora before being absorbed through the intestinal tract (4-6). Other studies have shown that deglycosylation is the major metabolic pathway involved in the transformation of ginsenosides to deglycosylated ginsenoside, which have higher biological activity than ginsenosides (7,8). Compound K (CK, 20-o-beta-d-glucopyranosyl-20 (S)-protopanaxadiol, $C_{36}H_{62}O_8$) is the major deglycosylated metabolite of ginsenoside (8). Recent *in vivo* and *in vitro* studies have reported that CK is involved in multiple pharmacological processes and possesses anti-carcinogenic (9), anti-diabetic (10), anti-inflammatory (11), anti-allergic (12), anti-angiogenic (13), anti-aging (14), and hepatoprotective effects (15), as well as effects on the central nervous system (CNS) (16). In particular, many studies have investigated its pharmacological effects. However, no study has investigated the complete integration of the pharmacological activity of CK. Therefore, we reviewed the pharmacological activity and associated mechanisms of CK in detail and updated the literature in recent years. It is expected to be helpful in developing potential agents to treat related diseases.

We present the following article in accordance with the Narrative Review reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-501/rc).

Methods

The PubMed database was searched for articles published in English from February 2008 to May 2021 using related keywords such as “Ginsenoside compound K”, “compound K”, and “CK”. The information used to write this paper was collected from the sources listed in *Table 1*.

Biotransformation, pharmacokinetics, and safety of CK

The ginsenoside CK belongs to the family of tetracyclic dammarane-type triterpenoid saponins. Based on their chemical structure, dammarane group ginsenosides are classified into two types: protopanaxadiol (PPD), which includes Ra1, Ra2, Ra3, Rb1,Rb2, Rb3, Rc, Rd, Rg3, Rh2, F2, and CK, and protopanaxatriol (PPT), which includes Re, Rf, Rg1, Rg2, Rh1, and F1 (*Figure 1*) (17,18).

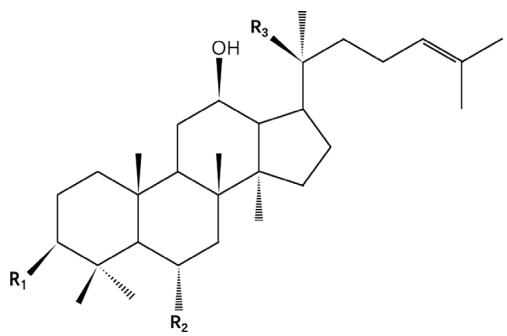
Japanese researchers originally isolated CK from a mixture of Rb1, Rb2, and Rc, which were hydrolyzed from ginseng by a soil bacterium (19). Although its structure was identified in 1972, the finding that Rb1 and Rb2 were metabolized into CK by intestinal bacteria in rats via a specific pathway was reported 20 years later (20,21). Hasegawa *et al.* (22,23) investigated the specific transformation pathway of CK by intestinal microflora and speculated that CK was the most likely form of protopanaxadiol saponins that underwent intestinal absorption. The specific metabolic pathways of Rb1 and Rb2 metabolism to CK by intestinal bacteria are shown in *Figure 2* (23,24). After the oral administration of Rb1 to rats, a high concentration of CK, but no Rb1, was found to be present in their intestinal contents, plasma, and urine (25-27). Researchers have focused on the biological functions of CK and methodology for the effective production of CK from major ginsenosides.

The bioavailability of ginsenosides without transformation and modification suggests low absorption in the intestinal tract (28,29). After the oral administration of ginsenosides, a series of biological transformations occur in the intestinal tract, and they are converted into deglycosylated metabolites with higher biological activities than their precursor compounds (7). Other studies have reported that intestinal bacteria or soil fungi around ginseng roots as well as some microorganisms hydrolyze ginsenosides to form CK (30,31). The various methods for microbial conversion are summarized in *Table 2* (7).

The enzyme β-glucosidase, with a molecular weight of 320 kDa and 4 identical subunits (80 kDa), is a key enzyme in the hydrolysis of Rb1 into CK (45) and was initially purified from metabolizing bacteria isolated from human intestinal feces (46). Subsequently, β-glucosidase that promoted more specific and effective transformation

Table 1 The search strategy summary

Items	Specification
Date of search	30, July 2021
Database and other sources searched	PubMed
Search terms used	Ginsenoside compound K [all fields] OR compound K [all fields] OR CK [all fields] OR G-CK [all fields]
Timeframe	1990-December 2021
Inclusion and exclusion criteria	All study type will be included
Selection process	Study selection will be performed by Tao Liu and Lu Zhu independently. Any disagreement about the inclusion of studies will be resolved through discussion



Ginsenoside		R1	R2	R3
PPD-type	Compound K	OH	H	O-Glc
	Rb1	O-Glc-Glc	H	O-Glc-Glc
	Rb2	O-Glc-Glc	H	O-Glc-Arap
	Rc	O-Glc-Glc	H	O-Glc-Araf
	Rd	O-Glc-Glc	H	O-Glc
	Rg3	O-Glc-Glc	H	OH
	F2	O-Glc	H	O-Glc
	Rh2	O-Glc	H	OH
	PPD	OH	H	OH
PPT-type	Re	OH	O-Glc-Rha	OH
	Rf	OH	O-Glc-Glc	O-Glc
	Rg1	OH	O-Glc	OH
	Rg2	OH	O-Glc-Rha	O-Glc
	Rh1	OH	O-Glc	OH
	F1	OH	OH	O-Glc
	PPT	OH	OH	OH

Glc, glucose
Arap, arabinose in pyranose form
Araf, arabinose in furanose form
Rha, rhamnose

Figure 1 Chemical structures of ginsenosides.

was found and purified in the soil of ginseng fields (47,48). Later, researchers extracted β-glycosidase from *Sulfolobus solfataricus* and other acid-resistant hot microbiota, and its degree of transformation and efficiency were higher than those previously reported (49-51). Subsequent studies focused on the activity and conversion efficiency associated with the design and modification of enzymes (45,52,53). Shin *et al.* (45) designed W361f, a variant of β-glycosidase, which had 4.2 times the activity of Rd, and 3.7 times higher catalytic efficiency and 3.1 times lower binding energy than the wild-type enzyme. They also found that semi-rational design was a useful tool to enhance the hydrolytic activity of β-glycosidase. Therefore, it is important to discover and modify catalytic enzymes to improve the utilization and production efficiency of CK (54).

As intestinal microflora is important for the biotransformation and pharmacological activity of CK, it is necessary to study the metabolic pathways that regulate intestinal microflora. Recent studies have indicated that western dietary habits and NUTRIOSE (ROQUETTE Frères, Lestrem, France) were more likely to improve the concentration level of CK (55,56). Furthermore, a study of human metabolism found that a high-fat diet significantly accelerated and increased the absorption of CK, and that the concentration level of CK in women was higher than that in men (57). A randomized double-blind study

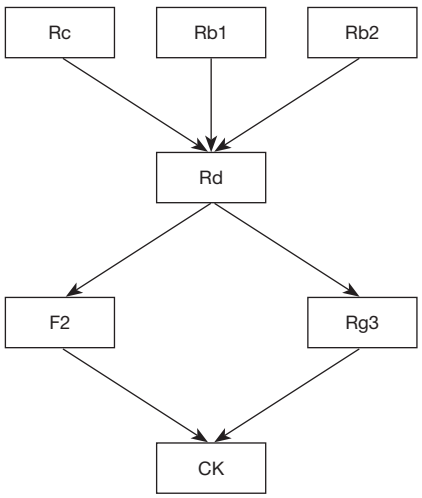


Figure 2 Biotransformation of major PPD-type ginsenosides to CK. PPD, protopanaxadiol; CK, 20-o-beta-d-glucopyranosyl-20 (S)-protopanaxadiol.

reported the gender- and food-related impacts on CK pharmacokinetics (58).

Another pharmacokinetic study of CK reported the drug levels in blood samples of 10 healthy men 36 hours after the administration of Korean ginseng extract (59). The mean maximum plasma concentration (C_{max}) of CK was significantly higher than the level of Rb1 (8.35±3.19 *vs.* 3.94±1.97 ng/mL) and the mean time to reach the C_{max} (T_{max}) of CK was longer than that of Rb1 (12.20±1.81 *vs.* 8.70±2.63 h). The delay in the absorption of CK supports the idea that intestinal microflora transforms Rb1 to CK. The plasma half-life ($t_{1/2}$) of CK was 7 times shorter than that of Rb1. These results indicate that the pharmacokinetics of CK are significantly different from those of Rb1. In another study (58), 76 participants received CK or placebo in 7 single oral doses (25, 50, 100, 200, 400, 600, 800 mg) while fasting; the time range to reach T_{max} was 1.5–6.0 h, and the exposure to CK increased linearly in the range of 100 to 400 mg. The steady-state was reached after the seventh administration and no severe adverse events (AEs) were observed. The most reported AEs were watery stool (diarrhea) and bellyache, and all AEs were mild or moderate, most of them were disappeared or reversible without any treatment (57,58). These results indicated that CK was safe and well-tolerated over the treatment period.

In a toxicity study, the oral administration of CK to rats and mice did not cause death or toxicity at the maximum doses of 8 and 10 g/kg, respectively (60). In a 26-week toxicity study, rats were administered CK at doses of 13, 40, or 120 mg/kg and observed at 26 weeks and at 4-week recovery periods. Compared with the control group, asthenia, fur-loss, hypoactivity and body weight reduction were observed in 120 mg/kg male rat group, the hepatotoxicity and nephrotoxicity including elevated serum ALT and ALP, higher liver relative weight with similar histological changes to the 90-day sub-chronic intravenous CK in rat, and higher kidney relative weight with no histological changes were also showed in 120 mg/kg male rat group, but the toxicity were reversible after 4-week recovery. No abnormalities in routine activity, laboratory markers, and histopathological examination were found in the 13 and 40 mg/kg CK groups (60). In addition, the no observed harmful effect level was 40 mg/kg in males and 120 mg/kg in female rats. In a beagle toxicity study, animals in the 36 mg/kg group showed reversible hepatotoxicity and significant weight loss during the study period. Animals in the 4 and 12 mg/kg groups did not show any significant toxicity (61).

CK has been shown to be safe and well tolerated in animal and human subjects. These preclinical results suggest that the liver may be a toxic organ for CK. Although the relative weight of the kidney was high, there was no histological change, but nephrotoxicity should be noted. CK-related AEs in clinical trials were diarrhea and abdominal pain. Drug-related AEs is common for drug-induced diarrhea. There are few clinical trials on CK and few reports on CK-related AEs. Therefore, further studies are needed to investigate the mechanisms of CK-induced toxicity, especially hepatotoxicity, and GCK-induced gastrointestinal tract.

Pharmacological properties of CK

The numerous pharmacological effects of CK, including cancer prevention (62), immune regulation (63), diabetic improvement (64), CNS protection (65), cardiovascular protection (66), skin improvement (67), and hepatoprotection (68) have been demonstrated *in vitro* and *in vivo* using animal models. The detailed pharmacological effects of CK are discussed below. The major functions and action targets of CK are summarized in *Tables 3*,*4*.

Anticarcinogenic effects of CK

The number of cancer patients is increasing annually;

Table 2 Production of CK by microbial conversion

Microorganism classification	Transformation pathways	Source	Processing condition	Reference
Bifidobacterium K-103 and *Eubacterium A-44*	Rc → Rd → CK	Human feces	37 ℃, pH 7.0	Bae *et al.* (32)
Bifidobacterium K-506 and *Bacteroides HJ-15*	Rc →M_b → CK	Human feces	37 ℃, pH 7.0	Bae *et al.* (32)
Bifidobacterium sp. Int57, Bif. sp. SJ32, Aspergillus niger, and *A. usamii*	Rb1 → Rd and F2 → CK	Human feces	37 ℃, pH 5.0	Chi *et al.* (31)
*Bifidobacterium sp. Int57*and *SJ32*	Rb2 and Rc → Rd and F2 → CK	Human feces	37 ℃, pH 5.0	Chi *et al.* (30)
Aspergillus niger	Rb2→ Compound O and Compound Y→ CK; Rc → Mc → CK	–	37 ℃, pH 5.0	Chi *et al.* (30)
Esteya vermicola CNU120806	Rd → F2 → CK	Nematodes in forest soil	50 ℃, pH 5.0	Hou *et al.* (33)
Paecilomyces bainier sp. 229	*P. notoginseng saponins* → CK	Soil around ginseng roots	28 ℃, pH 6.0	Zhou *et al.* (34)
Fusarium sacchari	*P. notoginseng saponins* → CK	Soil around ginseng roots	30 ℃, pH 5.5	Han *et al.* (35,36)
Fusarium moniliforme	*P. notoginseng saponins* → CK	–	–	Yang *et al.* (37)
Cladosporium cladosporioides	Rb1→Rd or gypenoside XVII → F2 → CK	–	30 ℃, pH 7.0	Wu *et al.* (38)
Acremonium strictum	Rb1→CK	Soil around ginseng roots	–	Chen *et al.* (39)
Aspergillus niger g.848	Rb1→Rd→ F2 → CK	Chinese koji	30 ℃, pH 5.0	Liu *et al.* (40)
Aspergillus niger	P. notoginseng saponins → CK	–	–	Zhou *et al.* (41)
Leuconostoc citreum LH1	Rb1→CK	Kimchi	30 ℃, pH 6.0	Quan *et al.* (42)
Leuconostoc mesenteroides DC102	Rb1→Rd or gypenoside XVII→ F2 → CK	Kimchi	30 ℃, pH 7.0	Quan *et al.* (43)
Lactobacillus paralimentarius LH4	Rb1→Rd or gypenoside XVII→ F2 → CK	Kimchi	30 ℃, pH 6.0	Quan *et al.* (44)

"–" indicates not mentioned. CK, 20-o-beta-d-glucopyranosyl-20 (S)-protopanaxadiol.

however, an effective cancer treatment is still lacking and no specific drug can cure cancer (138). Thus, the identification of new therapeutic drugs for cancer is urgent. The anti-tumor effects of CK are different *in vivo* and in vitro. Several studies have reported the cytotoxic and growth-inhibiting effects of CK on tumor cells, whereas other studies have reported that CK inhibits tumor cell metastasis and tumor growth (70,79,87,88,90,139). Therefore, CK may be a potentially important anticancer drug.

Inhibition of tumor growth by CK

In an *in vivo* study, CK significantly inhibited the growth of nasopharyngeal carcinoma (HK-1) tumors (91). On the 5th day after treatment, the tumor size in the CK treated group was 25.6% smaller than that in the control group (91). Also, CK dose-dependently reduced the tumor growth of colorectal cancer (HCT-116) (79) and significantly inhibited tumor growth in an athymic nude mouse xenograft model of colorectal cancer cells (HCT-116, SW-480, HT-29). At 3 weeks after CK treatment; the high-dose group (30 mg/kg) had a stronger antitumor effect compared with low-dose group (15 mg/kg), which was dose- and time-dependent (77). These studies suggested that CK might prevent or treat colorectal cancer (77). Furthermore, CK inhibited the growth and colony formation of cancer cells in mice transplanted with human liver cancer cells and boosted the anti-tumor effect of gamma rays in a nude mouse xenograft human lung cancer cell (NCI-H460) model, indicating that it might be an adjuvant of radiotherapy for tumor treatment (71,74).

Table 3 Anticarcinogenic effects of CK

Cancer type	Cell lines	Mode of action	Ref.
Lung cancer	A549, H1975	CK induced apoptosis and autophagy via AMPK-mTOR and JNK pathways	(69)
		CK inhibited growth via HIF-1α-mediated glucose metabolism	(70)
	HCI-H460	CK induced apoptosis via ROS	(71)
Liver cancer	MHCC97-H	CK induced apoptosis via Fas and mitochondria mediated caspase-dependent pathway	(72)
	HIT	CK attenuated metastatic growth via translocation of NF-κB p65 and reduction of MMP-2/9	(73)
	HepG2, SMMC-7721	CK induced ER stress and apoptosis by regulating STAT3	(74)
Colon cancer	HCT-116, HT-29	CK blocked cell cycle at the G1 phase and had antiproliferative effects	(75)
		CK enhanced sensitivity to TRAIL-induced apoptosis via autophagy-dependent and -independent DR5 upregulation	(76)
	HCT-116	CK induced apoptosis and cycle arrest via down-regulation of CDC25A, CDK4/6, cyclin D1/3, and up-regulation of p53/p21, FoxO3a-p27/p15, and Smad3	(77)
		CK induced autophagy and apoptosis via generation of reactive oxygen species and activation of JNK	(78)
		CK enhanced the effects of fluorouracil	(79)
	HT-29	CK induced mitochondria-dependent and caspase-dependent apoptosis via the generation of ROS	(80)
		CK inhibited growth and inducing apoptosis via inhibition of histone deacetylase activity	(81)
		CK induced apoptosis via CAMK-IV/AMPK pathways	(82)
	SW-480	CK induced apoptosis and cycle arrest	(83)
Brain tumors	U87MG, U373MG	CK inhibited growth, migration, and stemness via PI3K/ Akt/mTOR pathway	(84)
		CK suppressed phorbol ester-induced MMP-9 expression by inhibiting AP-1 and MAPK signaling pathways	(85)
	U251MG, U87MG	CK suppressed viability via down-regulation of cell adhesion proteins and cell-cycle arrest	(86)
	SK-N-BE(2), SH-SY5Y	CK induced ROS-mediated apoptosis and autophagic inhibition	(87)
	C6	CK attenuated SDF-1-induced migration	(88)
Gastric carcinoma	BGC823, SGC7901	CK inhibited growth via the Bid-mediated mitochondrial pathway	(89)
Osteosarcoma	MG-63	CK inhibited migration and invasion via the PI3K/mTOR/p70S6K1 signaling pathway	(90)
Nasopharyngeal carcinoma	HK-1	CK induced apoptosis via activation of apoptosis-inducing factor	(91)
Bladder cancer	T24	CK induced apoptosis via the ROS-mediated p38 MAPK pathway	(92)
Leukemia	HL-60	CK induced apoptosis via the caspase-8-dependent pathway	(9)
	U937	CK induced G1 phase arrest of the cell cycle via up-regulation of p12 and activation of JNK	(58)
	Kasumi-1, MV4-11	CK inhibited growth via inhibition of synthesis	(93)
Breast cancer	MCF-7	CK induced programmed necrosis via GSK3β	(94)
Myeloma	U266	CK induced apoptosis via inhibition of JAK1/STAT3 signaling	(95)

CK, Ginsenoside compound K; AMPK, adenosine monophosphate protein kinase; mTOR, mammalian target of rapamycin; JNK, c-Jun N-terminal kinase; ROS, reactive oxygen species; MMP, metalloproteinase; HIF, hypoxia inducible factor; STAT, signal transducer and activator of transcription; TRAIL, related apoptosis-inducing ligand; DR5, death receptor; CDC, recombinant cell division cycle protein; CDK, cyclin-dependent kinases; FoxO3a, Forkhead box O3; Smad3, drosophila mothers against decapentaplegic; CAMK-IV, calmodulin-activated protein kinase; PI3K, phosphatidylinositol 3-kinase; Akt, protein kinase B; AP-1, activated protein-1; MAPK, mitogen-activated protein kinase; SDF-1, stromal cell derived factors-1; GSK3β, glycogen synthase kinase; JAK, janus kinase.

Table 4 Pharmacology of CK

Biological activities	Models	Targets	Description	Ref.
Anti-inflammatory and anti-allergic effects	LPS-induced RAW264.7 and HEK293	iNOS, COX-2	CK inhibited the production of NO and PGE2	(11)
		Dectin-1,ROS	CK inhibited the production of systemic inflammatory cytokines	(96)
		IRAK-1, IKK-β, NF-κB	CK inhibited the production of proinflammatory cytokines	(97)
		AKT1	CK inhibited the production of IL-1β, IFN-β, and TNF-α	(98)
	Oxazolone-induced mouse dermatitis	COX-2, Th cells	CK inhibited the production of IFN-γ, and IL-4	(12)
	LPS-induced lethal shock	TLR4/LPS, NF-κB, MAPK	CK reduced the levels of systemic inflammatory cytokines in mice and reversed the fatal sequelae of sepsis	(99)
	Collagen-induced arthritis	CCL21/CCR7	CK suppressed T-cell priming	(100)
		β-arrestin1, AP2	CK inhibited the activity of B cells	(101)
		β-arrestin2, $G\alpha_i$, TLR4, NF-κB	CK regulated macrophage function	(102)
		TCR, CD28, CTLA-4, PD-1	CK suppressed the abnormal activation of T lymphocytes	(103)
	Adjuvant-induced arthritis	memory B cells, T cells	CK downregulated memory B cells	(104)
		TNF-α, TNFR 2, GR	CK inhibited proliferation, migration, and secretion of FLS	(105)
		T cells	CK suppressed T cell activation (T cell proliferation, CD25 and IL-2)	(106)
		B cells, macrophages	CK affected the function of immune cells and effector cells (FLS) to attenuate inflammatory responses	(107)
	DSS-induced colitis rats	PXR/NF-κB	CK targeted PXR/NF-κB interactions to cause anti-inflammatory effects without damaging PXR function in healthy rats	(108)
		NF-κB	CK promoted the recovery of the progression of colitis and inhibited pro-inflammatory cytokine production	(109)
	IMQ-induced psoriasis mice	REG3A/RegIIIγ	CK inhibited keratinocyte proliferation and ameliorated psoriasis-like hyperkeratosis	(110)
	TNF-α-induced astroglial cells	NF-κB, JNK	CK inhibited the production of VCAM-1 induced by TNF-α	(111)
	U937, RAW264.7 cells	NF-κB, AP-1	CK had an immunomodulatory role in innate immune responses	(63)

Table 4 (*continued*)

Table 4 (*continued*)

Biological activities	Models	Targets	Description	Ref.
Anti-diabetic effects	db/db mice	plasma adiponectin	CK enhanced insulin secretion	(10,112)
	MIN6 pancreatic β-cells	GLUT2	CK enhanced insulin secretion	(113)
	HFD/STZ-induced T2DM, HepG2	PEPCK, G6Pase	CK suppressed gluconeogenesis	(114)
		PI3K/Akt	CK suppressed insulin resistance	(115)
		AMPK	CK suppressed gluconeogenesis	(116)
	High glucose-induced 3T3 adipocytes	ER stress, NLRP3 inflammasome	CK improved insulin signaling	(117)
	3T3-L1 adipocytes	GLUT4, AMPK, PI3K	CK stimulated glucose uptake	(118)
	Palmitate-induced damage of MIN6 cells	AMPK/JNK	CK protected pancreatic islet cells against apoptosis	(119)
	NCI-H716	bile acid receptor, GLP-1, TGR5	CK stimulated GLP-1 secretion	(120)
	High-fat diet/ streptozotocin-induced diabetic mice	NLRP3 inflammasome, NF-κB/p38	CK had a protective effect on diabetic nephropathy	(121)
Neuroprotective effects	LPS-induced microglia, Sepsis and cerebral ischemia mouse models	NF-κB /AP1	CK reduced the volume of ischemic cerebral infarction and inhibited microglial cell activation	(16)
	CCH rats	pser9-gsk-3, IDE PKB/Akt	CK attenuated cognitive deficits	(122)
	Primary astrocytes	mTOR	CK enhanced autophagy to promote Aβ-clearance	(123)
	Scopolamine hydrobromide-induced memory impaired mouse	Nrf2/Keap1, Aβ	CK reduced oxidative damage to neurons, inhibited neuronal apoptosis, and improved memory function	(65)
	HT22 cells	GLUT, ATP	CK adjusted energy metabolism to inhibit neuronal damage	(124)
	Behavioral despair model and CUMS model in mice or rats	5-HT, DA, BDNF, NGF	CK enhanced antioxidant capacity and increased neurotrophic protein expression	(125)
	CA3 pyramidal neurons	GABA	CK inhibited the transmission of CA3 pyramidal neurons, affected hippocampal mediated physiological functions	(27)
	African xenopus oocytes	$GABA_C$ Receptor	CK inhibited GABA-induced introverted peak current (I_{GABA})	(126)
	Pentylenetetrazole or lithium chloride-rutin-induced epilepsy rats	GABA, GABAAR	CK promoted the release of GABA and enhanced GABAA-mediated inhibitory synaptic transmission	(127)
	Menopausal depressive-like state in female mice	5-HT2A	CK improved depressive-like state	(128)

Table 4 (*continued*)

Table 4 (*continued*)

Biological activities	Models	Targets	Description	Ref.
Anti-angiogenesis effects	bFGF-induced HUVECs	p38, AKT	CK inhibited bFGF-induced angiogenesis	(13)
	S1P-induced HUVECs	SPHK1, MMP	CK inhibited HUVECs migration	(129)
	TNF-α-induced monocyte-endothelial cells	VCAM-1, NF-κB	CK blocked leukocyte endothelial interactions and transport.	(130)
	ox-LDL-induced injury in HUVECs	NF-κB, p38MAPK, JNK	CK prevented inflammation and apoptosis	(131)
	PDGF-BB-induced VSMC	CDK2, CDK4, cyclinE, cyclinD1, MMP-2, MMP-9	CK inhibited abnormal VSMC proliferation and migration	(132)
	I/R-induced mice	Akt/PI3K, eNOS	CK induced cardiac protection	(133)
	I/R-induced H9C2 cells	PI3K/Akt	CK inhibited autophagy-mediated apoptosis	(134)
Anti-aging effects	HaCaT cells, hairless mice	HAS2	CK increased the production of HA	(14)
	TNF-α-stimulated dermal fibroblasts	MMP-1, c-Src, ERK, AP-1	CK inhibited collagen degradation	(135)
	UV- irradiated HaCaT cells	XPC, ERCC1	CK suppressed apoptosis by inducing DNA repair	(136)
	UVB- irradiated NIH3T3 cell	MMP-1, COX-2, HAS-1 and -2	CK increased the production of HA and type I procollagen	(67)
	UVA-irradiated fibroblasts	MMP-1	CK up-regulated the production of type I procollagen	(137)
Hepatoprotective effects	APAP-induced liver injury in rats	JNK	CK alleviated hepatotoxicity	(15)
	SVP-induced hepatotoxicity in rats	sHE, iron homeostasis	CK alleviated hepatotoxicity	(68)

CK, Ginsenoside compound K; TNF, tumor necrosis factor; iNOS, inducible nitric-oxide synthase; COX-2, cyclooxygenase; AKT, Serine/threonine protein kinase; IRAK, interleukin-1 receptor-related kinase; IKK-β, inhibitor of nuclear factor kappa-B kinase; TLR, toll like receptor; CCL, CC chemokine ligand; CCR7, chemokine receptor; AP2, adaptor protein 2; LPS, lipopolysaccharide; IL, interleukin; IFN, interferon; $G\alpha_i$, guanine nucleotide-binding protein subunit alpha; TCR, T cell receptor; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; CD28, cluster of differentiation 28; PD-1, programmed cell death protein 1; TNFR 2, tumor necrosis factor receptor; GR, glucocorticoid receptor; FLS, fibroblast-like synovial; PXR, progesterone X receptor; GLUT2, glucose transporter protein 2; PEPCK, phosphoenolpyruvate carboxy kinase; G6Pase, glucose 6-phosphatase; ER stress, endoplasmic reticulum stress; NLRP3, NOD-like receptors; GLP-1, glucagon-like peptide-1; TGR5, G protein-coupled receptor 5; Nrf2, nuclear factor E2-related factor 2; Keap1, Keleh-like ECH-associated protein l; GABA, gamma-aminobutyric acid; 5-HT, serotonin; GABAAR, gamma-aminobutyric acid-A receptor; S1P, sphingosine-1-phosphate; Ox-LDL, oxidized low density lipoprotein; PDGF-BB, platelet-derived growth factor; SPHK1, sphingosine kinase 1; VCAM-1, vascular cell adhesion molecule 1; HA, hyaluronic acid; HAS, hyaluronic acid synthase; XPC, Xeroderma pigmentosum-C; ERCC1, excision repair cross-complementation group 1; APAP, acetaminophen; SVP, sodium valproate.

Cytotoxicity of CK

Studies have been conducted to investigate the cytotoxicity of CK against mouse high-metastatic melanoma (B16-BL6), human hepatoma (HepG2), human myeloid leukemia (K562), human high-metastasis lung carcinoma (95-D), human leukemia (HL-60), and human colon cancer cell lines (9,41,80). The mean concentrations of CK that inhibited cell proliferation by 50% (IC_{50}) were 12.7, 11.4, 8.5, 9.7, 14, and 32 μmol/L, respectively, and the effect was time-dependent (9,41,80).

The anti-proliferative effects of CK

In another experiment, CK exhibited significant anti-proliferative effects against human colorectal cancer cell lines (HCT-116 and SW-480) at concentrations of 30–50 μM, indicating that it might be an effective anti-carcinogenic medicine (83). Similarly, the anti-proliferative effects of CK on human and animal tumor cell lines have been demonstrated in many studies (9,41,80). Furthermore, CK significantly induced cell cycle arrest during the G1 phase in non-small cell lung cancer cells (A549, H1975) (69), human colorectal cancer cells (HCT-116, HT-29) (75,77,81), glioblastoma cells (U87MG, U373MG) (84), human glioblastoma cells (U251 MG, U87-MG) (86), human monocytes (U937) (140), and acute myeloid leukemia cells (93), which was dose- and/or time-dependent. The major regulatory targets of CK were found to be cyclin-dependent inhibitors, including p21, p27, p15, and cyclin D (75,77,81). Furthermore, CK blocked the cell cycle at the G2 phase in human gastric cancer cells (BGC823 and SGC7901) to exert an anti-proliferative effect (89).

The apoptotic effects of CK

Apoptosis was shown to be significantly induced by CK in A549 (69), H1975 (69), and HL-60 (9) cell lines, human colorectal cancer cells (HCT-116, HT-29) (75-78,80-82), glioblastoma cells (U87MG, U373MG) (84), human glioblastoma cells (U251 MG, U87-MG) (86), human monocytes (U937) (140), acute myeloid leukemia cells (93), human gastric cancer cells (BGC823 and SGC7901) (89), human hepatocellular carcinoma (HCC) cells (MHCC97-H) (72), and bladder cancer cells (T24) (92).

It was also shown to induce apoptosis in cancer cells via a caspase-dependent pathway at a concentration that had low toxicity to normal cells (72). The induction of apoptosis in HT-29 and HCT-116 cells by CK was mediated by mitochondrial-dependent and caspase-dependent mechanisms via the generation of reactive oxygen species (ROS), and the mitogen-activated protein kinase (MAPK), the calmodulin-activated protein kinase/adenosine monophosphate protein kinase (AMPK) pathway, and the tumor necrosis factor (TNF)-related apoptosis-inducing ligand-mediated death receptor pathways (76,78,80,82). The transcriptional activation of multiple tumor-promoting pathways in CRC was inhibited by CK, indicating that it might prevent or treat CRC (77). Morphological changes were induced in HL-60 cells by CK, leading to cell apoptosis, as indicated by typical characteristics such as DNA fragmentation (9).

Autophagy leads to cell adaptation, cell survival, or cell death (87). The regulation of autophagy is increasingly being regarded as a promising cancer treatment (87). A study showed that CK induced the ROS-mediated inhibition of autophagy flux, which inhibited the proliferation of neuroblastoma cells and promoted cell apoptosis (87). In non-small cell lung cancer cells (A549, H1975), CK promoted autophagy to induce cell apoptosis through the AMPK-mTOR and c-Jun N-terminal kinase (JNK) signaling pathways (69). In addition, CK induced the apoptosis of colon cancer cell lines (HT-29, HCT-116) through autophagy via ROS production and JNK activation (76,78).

Inhibition of tumor cell invasion and metastasis by CK

The invasion and metastasis of tumor cells are important for the prognosis of cancer patients and are therapeutic targets of tumor therapy. CK Significant reductions in the colony formation, adhesion, and invasion of HCC cells were exerted by CK in vitro, and it inhibited metastasis and growth of HCC *in vivo* related to the nuclear export of nuclear factor-kappa B (NF-κB) p65 nuclear export and the reduction of metalloproteinase 2/9 (MMP-2/9) expression (73). It was also shown that CK reduced glioblastoma cell markers (CD133, Nanog, Oct4, and Sox2) to inhibit their growth, metastasis, and invasion potential (84). The migration and invasiveness of C6 glioma and astroglioma cells was inhibited by CK, suggesting it might control the growth and invasiveness of brain tumors (85,88). Osteosarcoma is a malignant bone tumor, and CK was shown to inhibit the migration and invasion of osteosarcoma cells via the PI3K/mTOR/p70S6K1 signaling pathway (90).

Myelosuppression of CK

In a study of the effects of CK on myelosuppression in mice induced by cyclophosphamide (CTX), CK could increase the thymus index, the yields of colony formation units-granulocyte monocyte and colony formation units-megakaryocytic. CK could control apoptosis and promote cells to enter the normal cell cycle by the bcl-2/bax signaling pathway and MEK/ERK signaling pathway. It suggested that CK can improve the hematopoietic function of myelosuppression among mice (141).

Anti-inflammatory and anti-allergic effects of CK

Inflammation, including the sustained production of

nitric oxide (NO) and prostaglandins (PGs), is important in the pathophysiological changes of rheumatic diseases and other inflammatory diseases (142). Recent studies have shown that the anti-inflammatory activities of CK on lipopolysaccharide (LPS)-induced mononuclear macrophages (RAW264.7), and reported that CK down-regulated inducible nitric-oxide synthase (iNOS) levels, ROS, and cyclooxygenase-2 proteins by inhibiting nuclear factor-κB (NF-κB) and MAPK activation, which suppressed NO and prostaglandin E2 (PGE2) production (IC_{50} =0.012 and 0.004 mM, respectively) (11,143). It also could inhibit the migration of RAW264.7 by blocking the activation of NF-κB and up-regulating the expression of PPARγ and, indicating that CK could inhibit the activation of inflammatory macrophages and increase the expression of anti-inflammatory macrophages (144). It had a negative regulatory effect on the production of proinflammatory cytokines, and the activation of inflammatory pathways in LPS- or zymosan-induced mononuclear macrophages at non-cytotoxic concentrations, indicating that CK is involved in the regulation of inflammation (96-99). When administered *in vivo*, CK inhibited the production of systemic inflammatory cytokines and reduced the mortality rate of inflammatory shock in mice (99). Therefore, CK might control excessive lethal inflammation (96-99).

In a collagen-induced arthritis (CIA) model, CK inhibited the abnormal activation and differentiation of T cells and B cells and improved the outcome of CIA by reducing the proportion of M1 and M2 macrophages (100-102). C-K could promote TLR4-Gαs coupling and inhibit TLR4-Gαi coupling through β-arrestin2 regulation in macrophages, leading to the function inhibition of immune cells including macrophage polarization and phagocytosis (102). Several studies using complete Freund's adjuvant-induced adjuvant-arthritis rats models have reported that CK reduced disease severity, foot-pad swelling, and the degree of pathology in the joints by inhibiting the proliferation of B cells, T cells, and fibroblast-like synoviocytes, and the level of autoantibodies, macrophage phagocytosis, and the secretion of proinflammatory cytokines (104-107).

Other studies using dextran sodium sulfate-induced colitis mouse models showed that CK relieved histopathological injury in mild and severe colitis. In these studies, CK targeted the progesterone X receptor (PXR)/NF-κB interactions to improve myeloperoxidase (MPO) activity, reduce the production of proinflammatory cytokines (TNF-α, IL-1β, and IL-6), and increase the anti-inflammatory cytokines (108,109). In addition, CK also could as a drug candidate for IgA nephropathy through inhibiting the activation of NLRP3 inflammasome in renal tissues, macrophages and bone marrow-derived dendritic cells, enhancing the induction of autophagy through increased SIRT1 expression, and eliciting autophagy-mediated NLRP3 inflammasome inhibition (145).

Anti-diabetic effects of CK

Diabetes mellitus, caused by a deficiency in insulin secretion and action, often leads to chronic progressive disease, functional decline, and failure of multiple tissues and organs due to metabolic disorders (146). At present, there are no effective drugs to treat diabetes. Current treatments focus on stimulating insulin production, increasing the sensitivity of peripheral tissues to insulin, and inhibiting liver glucose output using insulin-like preparations (146). Importantly, CK also promotes these functions.

In vitro studies using HIT-T15 cells and primary cultured islet cells have shown that CK enhances insulin secretion in a dose-dependent manner, which may be related to adenosine triphosphate (ATP)-sensitive K^+ channels (10). Similar to sulfonylurea, CK stimulated insulin secretion and enhanced the anti-diabetic effect of metformin in db/db mice. Thus, CK has potential applications for diabetic therapy when used in combination with sulfonylurea (112). A study using MIN6 pancreatic β-cells reported that CK significantly enhanced insulin secretion by up-regulating the expression of glucose transporter protein 2 (113,117).

In a long-term study of db/db mice, CK enhanced plasma adiponectin production, changed glucose metabolism in the liver from glucose production to glucose utilization, which improved insulin sensitivity, induced hypoglycemic effects, and improved glucose tolerance (10). After feeding diabetic model mice with CK 30 mg/kg/day for 4 weeks, hypoglycemic and insulin sensitivity of type 2 diabetes was improved by reducing phosphoenolpyruvate carboxy kinase and glucose 6-phosphatase expression in the liver (114). Hyperglycemia and insulin resistance in diabetic rats was improved by CK via enhancement of insulin sensitivity and insulin signaling and inhibiting inflammation (115,117).

Anti-diabetic effects were induced by CK by reducing the expression of key gluconeogenic enzymes in the liver and hepatic gluconeogenesis was inhibited by enhancement of AMPK activity (116). Furthermore, CK promoted the uptake of glucose by adipocytes, indicating it might have hypoglycemic properties and insulin-like activity, which is important for its potential used in diabetes (118). Treatment

with CK prevented pancreatic islet destruction and retained more insulin in db/db mice (10). These anti-diabetes effects of CK were mediated by inhibiting the AMPK-JNK pathway and preventing apoptosis of pancreatic islet cells *in vitro* and *in vivo* (119).

Glucagon-like peptide-1 inhibits pancreatic β-cell apoptosis and stimulates glucose-stimulated insulin secretion (147). Studies showed that CK induced hypoglycemic effects by stimulating the secretion of glucagon-like peptide-1 in NCI-H716 cells via bile acid receptor activation (120) (125) and protected against diabetic nephropathy by inhibiting NLRP3 inflammasome activation and NF-κB/p38 signaling pathway (121,126).

Effects of CK on the CNS

Many studies have reported that CK improves the cognition of neurological diseases, has a neuroprotective effect (122), and protects neurotransmission (27).

Cognition and neuroprotection effects of CK

Amyloid-β (Aβ) peptide is a biomarker of Alzheimer's disease (AD) (148). It has been shown that CK promotes the clearance of Aβ by enhancing autophagy in primary astrocytes and improves memory in scopolamine hydrobromide-injured mice by inhibiting Aβ accumulation and activating the Nrf2/Keap1 signaling pathway (123). In addition, CK reduced oxidative damage to neurons and inhibited neuron apoptosis (65). In a slow cerebral hypoperfusion (CCH) rat model, CK inhibited CCH-induced neuron injury and Aβ accumulation. Furthermore, CK attenuated cognitive deficits in vascular dementia rats (122). When HT22 cells were incubated with CK and exposed to Aβ, neuronal damage caused by Aβ was inhibited by activating the energy metabolism signaling pathway (124). Therefore, CK might be a useful preventive or therapeutic agent for AD (65,122-124). When treating nervous system disease, chemotherapy often leads to neurocognitive impairment, including learning and memory. Thus, permanently repairing and improving cognitive impairment are important for the patient (149). Treatment with 10 mg/kg CK alleviated the reduction of hippocampal neurogenesis caused by cyclophosphamide indicating CK might improve or repair the side-effects caused by chemotherapy agents (108,112,131,149).

Microglia activation is important in the pathogenesis of various neurological diseases. The anti-inflammatory and neuroprotective effects of CK have been demonstrated in brain disease models of sepsis (systemic inflammation) and brain ischemia in mice. It was shown to reduce the infarct volume of ischemic brains induced by middle cerebral artery occlusion and suppress microglial activation in the ischemic cortex as well as inhibiting the activities of ROS, MAPKs, and NF-κB/activator protein to suppress microglial activation in LPS-induced BV2 cells and primary cultured microglial cells (16). The expressions of brain-derived neurotrophic factor and nerve growth factor were increased in rats treated with CK, indicating that it promotes neurotrophic protection of the CNS (125).

The proliferation and differentiation of Schwann cells are critical for the remyelination of injured peripheral nerve. It was shown that CK induced cell proliferation, migration and differentiation via the activation of MEK/ERK1/2 and PI3K/AKT pathways in cultured primary Schwann cells (133,150).

Neurotransmission modulation by CK

At a dose of 10 μmol/L, CK increased the spontaneous release of gamma-aminobutyric acid (GABA) by promoting the release of Ca^{2+} from presynaptic Ca^{2+} stores and inhibited the transmission of hippocampal CA3 pyramidal neurons in rats and the physiological functions mediated by the hippocampus (27). It also inhibited GABA-induced inward peak current (I_{GABA}) by inhibiting GABA receptor $_C$ ($GABA_C$) (IC_{50} value of 52.1±2.3 μmol/L) (126). This suggests that CK may regulate $GABA_C$ receptor channel activity in the brain. An imbalance between GABA-mediated inhibition and glutamate-mediated excitation is a major pathological mechanism of epilepsy and therefore GABA and glutamate neurotransmission have become important targets for epilepsy control (127). By promoting the release of GABA in the hippocampus and enhancing GABA-mediated inhibitory synaptic transmission, CK exerted an antiepileptic effect.

Yamada *et al*. (128) found that CK had a beneficial effect in a mouse model of depression-like state induced by ovariectomy by preventing postoperative prolonged fixation, which was mediated by the serotonin (5-HT) receptor in a dose-dependent manner. Song *et al*. (125) established a chronic unpredictable mild stress model in rats, and found that CK alleviated depression-like behavior, increased the levels of 5-HT, dopamine, and their metabolites in the prefrontal cortex and hippocampus, and reversed monoamine oxidase B overexpression in the prefrontal cortex and hippocampus. These results suggest CK has an antidepressant effect in rodents, which is related to the

regulation of monoamine neurotransmitter concentrations.

Anti-angiogenesis effects of CK

Few studies have investigated the cardiovascular effects of CK, although it has a protective effect on vascular endothelial cells and smooth muscle cells (13,132).

It has been shown that CK attenuates the expression of cyclin D1 and significantly inhibits the proliferation, migration, and lumen formation of basic fibroblast growth factor (bFGF)-induced human umbilical vein endothelial cells (HUVECs), and prevents bFGF-induced angiogenesis in mice (13,129).

The adhesion of leukocytes to endothelial cells and leukocyte transport are involved in the early stage of atherosclerosis (130). Anti-atherogenic effects were exerted by CK by negatively regulating NF-κB signaling and blocking leukocytes transport by inhibiting interactions between leukocytes and endothelial cells (130). It also reduced HUVEC inflammation and apoptosis induced by oxidized low-density lipoprotein by inhibiting the nuclear translocation of NF-κB and phosphorylation of p38MAPK and JNK (131). Furthermore, CK significantly inhibited the proliferation of vascular smooth muscle cells stimulated by platelet-derived growth factor BB *in vitro* by a dose-dependent mechanism involving the blockade of cells in the G1 phase (132). Formation of the angiogenic intima was significantly inhibited *in vivo* by CK indicating it might be a candidate therapeutic agent for atherosclerosis (132).

In a mouse model of myocardial ischemia-reperfusion (I/R) injury, CK protected the myocardium, reduced the infarct area, and inhibited myocardial cell apoptosis, indicating that it has a protective effect on the heart damaged caused by I/R (133,134).

Anti-aging effects of CK

The local application of CK to the skin of hairless mice increased the hyaluronic acid content in the epidermis and papillary dermis by up-regulating hyaluronic acid synthase 2 (14). Therefore, the local use of CK may prevent or improve xerosis and wrinkles in the skin (14). It suppressed MMP-1 secretion and increased type I procollagen secretion in TNF-α-stimulated human skin fibroblasts (HS68 cells), which inhibited collagen degradation in human fibroblasts (135). It also down-regulated MMP-1 activity, cyclooxygenase-2 production, and restored the production of type I collagen in ultraviolet (UV) A/UVB-irradiated fibroblasts and protected UV-irradiated HaCaT cells from apoptosis by inducing DNA repair (67,136,137). These studies indicate that CK has anti-aging and hydrating effects and could be used in cosmetic products to protect skin from UV and increase skin moisture levels (137).

Hepatoprotective effects of CK

Studies have shown that CK has hepatoprotective activity. It inhibited liver injury induced by acetaminophen *in vivo* and significantly reduced aspartic aminotransferase and alanine aminotransferase concentrations by inhibiting JNK signaling in HepG2 cells (15). It also significantly reversed liver injury induced by sodium valproate (SVP) and had a marked hepatoprotective effect on SVP-induced hepatotoxicity via antioxidant effects including regulation of the peroxisome pathway, downregulating soluble epoxide hydrolase (sHE, UniProt ID P80299) and regulating iron homeostasis dependent on hepcidin upregulation (68).

Conclusions

As rare ginsenoside, CK does not exist in natural ginsenoside but can be produced effectively with the advent of modern enzyme technology. It is generally agreed that compound K is more bioavailable than the parent ginsenosides, including Rb1, Rb2, and Rc, and is the major contributing factor to the health benefits of ginseng. It has a wide range of pharmacological functions, especially anticancer effects. The application of CK provides a new perspective for the development of anticancer agents. Similarly, CK has important roles in many physiological processes and could be used as a preventive or therapeutic agent for various diseases.

Although it is possible that new mechanisms not mentioned in this article in the foreseeable future, many mechanisms of CK remain unknown. Firstly, most of understanding of various systemic diseases pharmacological effects of CK and its precursor are derived from animal and cell models, the results cannot be directly translated to the healthy normal population, further experiment verification about human *in vitro* are necessary. Secondly, more experiments need to be carried out to corroborate the specific role of CK in related systemic diseases and related mechanisms. Thirdly, further clinical trials are requirement for investigating the safety and efficacy of CK. Fourthly, ginseng and ginsenosides have been proved to have a variety of pharmacological effects, further research is required to

establish whether CK is the major component of ginseng responsible for its pharmacological activities.

In conclusion, we need to carry out more studies to improve the relevant mechanisms of CK, so as to better provide help for the clinical application of CK.

Acknowledgments

Funding: This work was supported by the Chengdu Science and Technology Bureau Technology Innovation R&D Project (grant No. 2021-YF05-00595-5N).

Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-501/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-501/coif). All authors report the study was supported by Chengdu Science and Technology Bureau Technology Innovation R&D Project (grant No. 2021-YF05-00595-5N). The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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(English Language Editor: J. Jones)

Cite this article as: Liu T, Zhu L, Wang L. A narrative review of the pharmacology of ginsenoside compound K. Ann Transl Med 2022;10(4):234. doi: 10.21037/atm-22-501