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# Corosolic acid and its structural analogs: A systematic review of their biological activities and underlying mechanism of action

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# ABSTRACT

Background: The corosolic acid (CA), also known as plant insulin, is a pentacyclic triterpenoid extracted from plants such as Lagerstroemia speciosa. It has been shown to have anti-diabetic, anti-inflammatory and anti-tumor effects. Its structural analogs ursolic acid (UA), oleanolic acid (OA), maslinic acid (MA), asiatic acid (AA) and betulinic acid (BA) display similar individual pharmacological activities to those of CA. However, there is no systematic review documenting pharmacological activities of CA and its structural analogues. This study aims to fill this gap in literature.

Purpose: This systematic review aims to summarize the medical applications of CA and its analogues.

Methods: A systematic review summarizes and compares the extraction techniques, pharmacokinetic parameters, and pharmacological effects of CA and its structural analogs. Hypoglycemic effect is one of the key inclusion criteria for searching Web of Science, PubMed, Embase and Cochrane databases up to October 2020 without language restrictions. 'corosolic acid', 'ursolic acid', 'oleanolic acid', 'maslinic acid', 'asiatic acid', 'betulinic acid', 'extraction', 'pharmacokinetic', 'pharmacological' were used to extract relevant literature. The PRISMA guidelines were followed.

Results: At the end of the searching process, 140 articles were selected for the systematic review. Information of CA and five of its structural analogs including UA, OA, MA, AA and BA were included in this review. CA and its structural analogs are pentacyclic triterpenes extracted from plants and they have low solubilities in water due to their rigid scaffold and hydrophobic properties. The introduction of water-soluble groups such as sugar or amino groups could increase the solubility of CA and its structural analogs. Their biological activities and underlying mechanism of action are reviewed and compared.

Conclusion: CA and its structural analogs UA, OA, MA, AA and BA are demonstrated to show activities in lowering blood sugar, anti-inflammation and anti-tumor. Their oral absorption and bioavailability can be improved through structural modification and formulation design. CA and its structural analogs are promising natural product-based lead compounds for further development and mechanistic studies.

		AUC	area under the concentrations
Abbrevia	tions	BA	betulinic acid
AA	asiatic acid	Bax	Bcl-2-associated X protein
Akt	protein kinase B	BBB	blood-brain barrier
AMPK	adenosine monophosphate-activated protein kinase	Bcl2	B-cell lymphoma 2

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CA	corosolic acid
CHOP	C/EBP homologous protein
C <sub>max</sub>	maximum plasma concentration
CL	clearance rate
COX-2	cyclooxygenase-2
CYP450	cytochromeP 450
DMSO	dimethyl sulfoxide
Drp1	dynami iatic acid
ERK	extracellular signal-regulated kinase
F	oral bioavailability
GLUT2	glucose transporter 2
GLUT4	glucose transporter 4
GSK3β	glycogen synthase kinase-3β
HCC	hepatocellular carcinoma
HPLC	high performance liquid chromatography
HSCCC	high-speed counter-current chromatography
ΙκΒα	inhibitor of kappa B
IL-1	receptor-associated kinase
iNOS	inducible nitric oxide synthase
JNK IRS-1	c-Jun N-terminal kinase
MA	insulin receptor substrates 1 maslinic acid
MAPK	
mPEG	mitogen-activated protein kinase
MRT	monomethoxy polyethylene glycol mean retention time
MS	mass spectrometry
NF-κB	· ·
NO NO	nuclear factor kappa B nitric oxide
Nrf2	nuclear factor-erythroid 2-related factor 2
OA	oleanolic acid
PDK-1	Phosphoinositide-dependent protein kinase 1, PEPCK,
IDNI	phosphoenolpyruvate carboxykinase
PERK	protein kinase R (PKR)-like endoplasmic reticulum kinase
PI3K	phosphatidylinositol-4,5-bisphosphate 3-kinase
PPARy	peroxisome proliferator activated receptor $\gamma$
PTP1B	Protein tyrosine phosphatase 1B
RLMs	rat liver microsomes
ROS	reactive oxygen species
SGLT1	sodium glucose co-transporter 1
SMEDDS	self-microemulsifying drug delivery system
SOD	superoxide dismutase
SREBP1	sterol regulatory element-binding protein 1
STAT3	signal transducer and activator of transcription 3
T1/2	elimination half-life
TGF-β	transforming growth factor-beta
T <sub>max</sub>	maximum time
TNF-α	tumor necrosis factor alpha
UA	ursolic acid
UA-DLLM	IE ultrasound-assisted dispersive liquid–liquid
	microextraction
UPLC-MS	/MS Ultra-high performance liquid chromatography-mass
	spectrometry/mass spectrometry
V <sub>d</sub>	volume of distribution
VEGF	vascular endothelial growth factor
1-DNJ	1-deoxynojirimycin;

Corosolic acid (CA), an ursane-type pentacyclic triterpenoid, is extracted from a variety of plants such as banaba (Kakuda et al., 2014; Miura et al., 2012; Singh and Ezhilarasan, 2020; Yoon et al., 2006), Japanese loquat leaves (Masatu and Chihiro, 2007; Uto et al., 2013), and so on. CA could exist in plants freely or in the form of saponins. It is often co-existed with the isomer of MA, which had similar structure and chemical properties. CA and MA are derivatives of UA and OA, respectively (Sommerwerk et al., 2015; Wen et al., 2006). CA has many structural analogs including UA, OA, MA, AA and BA, all of which are extracted from plants and have similar pharmacological effects to CA.

CA was first extracted from Lagerstroemia speciosa. Lagerstroemia speciosa, commonly known as banaba. Its leaves were consumed by Philippinos in a variety of forms to treat diabetes mellitus and obesity (Klein et al., 2007). In 1940, Garcia first studied the hypoglycemic effect of banaba (Garcia, 1940). This folk medicinal herb became popular in the 1990s and attracted more attention from scientists all over the world. It was reported that the main active chemical ingredient of plant's leaves was polyphenol, which had the effect of lowering blood sugar (Fukushima et al., 2006). Kakuda et al. (Kakuda et al., 2014) studied the hypoglycemic effect of Lagerstroemia speciosa L. in mice in 1995 and believed that the extract of banaba leaves had beneficial effects on controlling the level of blood sugar. Miura et al., (Miura et al., 2006) studied the antidiabetic effect of CA in KK-Ay mice, and found that it could improve glucose metabolism by reducing insulin resistance. Researchers have conducted a large number of in vitro and in vivo studies to confirm the antidiabetic activity of CA (Klein et al., 2007; Miura et al., 2006)

CA acts as insulin on glucose metabolism, hence it also called plant insulin in treating diabetes mellitus, a group of metabolic disorders caused by absolute or relative insufficient secretion of insulin/or insulin utilization. Diabetes is mainly marked by high blood sugar, which can lead to insomnia, blindness, amputation of limbs, stroke, cardiovascular diseases and cancer (Rees and Alcolado, 2005). The oral hypoglycemic agents include synthetic small molecule drugs such as metformin, pioglitazone, glimepiride and acarbose etc, which act through different mechanisms while injectable agents are represented by insulin, an antidiabetic protein drug. However, all of them provide only temporary treatments, not a complete cure. Furthermore, it was reported that frequent insulin treatments may increase the production of anti-insulin antibodies, leading to resistance and side effects including fat deposition and weight gain (Lester and O'Kell, 2020). Therefore, plant based medications for treating diabetes have attracted significant attention (Sivakumar et al., 2009). CA has been proven to inhibit α-glucosidase and increase cellular uptake of glucose to reduce blood sugar and help to overcome insulin resistance (Hou et al., 2009; Lee and Thuong, 2010; Ni et al., 2019). At the beginning of the 21 st century, it was discovered that CA could also prevent oxidative stress and inflammation (Yamaguchi et al., 2006). More recently, CA was shown to exhibit anti-tumor activity, and has been investigated in various tumor therapies, such as prostate cancer (Ma et al., 2018; Yang et al., 2018), gastric cancer (Cheng et al., 2017; Park et al., 2018; Zhang et al., 2021), hepatocellular carcinoma (Jia et al., 2020; Ku et al., 2015), glioblastoma (Fujiwara et al., 2011). The research on the application of CA and investigation into related mechanism of action has attracted much attention from the scientific community.

The structural analogs of CA also have the effect of lowering blood sugar. The common beneficial effect in glucose metabolism seems to involve the mechanism of inhibiting the  $\alpha$ -glucosidase (Ding et al., 2018; Hou et al., 2009; Khathi et al., 2013; Lee and Thuong, 2010; Ni et al., 2019; Zhang et al., 2017a). Besides the general hypoglycemic effect, the structural analogs of CA also have anti-inflammatory and anticancer effects. For example, UA was used for encephalitis (Lu et al., 2010) and breast cancer (Zhao et al., 2013), and MA was used for arthritis (Shimazu et al., 2019) and colon cancer (Rufino-Palomares et al., 2013; Wei et al., 2019), and so on. A considerable amount of literature reported the related mechanisms.

Pentacyclic triterpenoids do not dissolve well in water due to their rigid scaffold and hydrophobic properties, which is a key factor limiting their application as therapeutic drugs. Many studies were reported to have modified the structure of CA and its structural analogs, such as the introduction of water-soluble sugar group, amino group and other structures (Liu et al., 2020b), and designed formulations to improve its solubility and bioavailability.

This review consists of three parts. The first part focuses on the

extraction and purification methods of CA and its structural analogs. The second part summarizes the pharmacokinetic parameters and pharmacodynamic studies of CA and its structural analogs. The description of structural modification and formulation design of CA and its structural analogs are presented in the third section.

# Search strategy

This systematic review summarizes and compares the extraction techniques, pharmacokinetic parameters, and pharmacological effects of CA and its structural analogs. Web of Science, PubMed, Embase and Cochrane databases were searched for literature published up to October 2020 without language restrictions. The first search keyword is 'corosolic acid'. After preliminary reading, articles describing the structure of corosolic acid were screened out. After screening for abstracts, the final structural analogs are determined as: UA, OA, MA, AA, BA. The hypoglycemic effect is one of the inclusion criteria. Next, the search terms are 'ursolic acid', 'oleanolic acid', 'maslinic acid', 'asiatic acid', 'betulinic acid', 'extraction', 'pharmacokinetic', 'pharmacological'. Through title and abstract screening, irrelevant articles were eliminated and full text of relevant articles were received. A total of 140 relevant articles were selected for the systematic review (Fig. 1).

## Chemistry of corosolic acid and its structural analogs

## Corosolic acid and its structural analogs

CA (2 $\alpha$ , 3 $\beta$ -dihydroxy-urs-12-en-28-oid acid) and its structural analogs (Fig. 2) including UA (3-hydroxy-12-ursen-28-oic acid), OA (3 $\beta$ -hydroxy-olean-12-en-28-oic acid), MA (2 $\alpha$ , 3 $\beta$ -dihydroxyolea-12-en-28-oic acid), AA (2 $\alpha$ , 3 $\beta$ -24-trihydroxyurs-12-en-28-oic acid) and BA (3 $\beta$ -hydroxy-lup-20(29)-en-28-oic acid), were natural pentacyclic triterpenes extracted from plants.

# Extraction and separation

CA and its structural analogs were extracted from plants with water, organic solvents such as methanol or ethanol. Extraction rate was different in different plants. CA can be extracted from either banaba and Japanese loquat leaves, but the extraction yield was unclear (Hou et al., 2009; Masatu and Chihiro, 2007; Miura et al., 2012). The content of UA and OA was higher in Ligustrum lucidum Ait than other plants, and the extraction yield were 0.78% and 0.54%, respectively (Xia et al., 2012). However, the extraction rate of UA and OA in other plants such as



Fig.1. The framework of the literature search.

Comastoma pulmonarium was less than 0.1%. Many literatures reported that MA was extracted from olive (Xie et al., 2019), but its extraction yield was not detailed (Li et al., 2017; Shimazu et al., 2019). AA was only extracted from Centella asiatica (He, 2008). The main component was asiaticoside, which was then hydrolyzed to yield AA. The extraction rate of BA in Dracocephalum tanguticum Maxim was only 0.017% (Wu et al., 2015). A summary of extraction methods and extraction yields are shown in Table 1. Amongst them, an ultrasound-assisted dispersive liquid-liquid microextraction (UA-DLLME) method, using chloroform as extraction solvent and acetone as disperser solvent was reported to have a good extraction efficiency (Wu et al., 2015). High performance liquid chromatography (HPLC) (Xu et al., 2019), a combination of macroporous absorption resin (MAR) column and high-speed counter-current chromatography (HSCCC) (Zhu et al., 2014) are new separation techniques reported to provide final CA and analogues with > 95% in purity (Masatu and Chihiro, 2007).

#### Biochemical synthesis of corosolic acid and its structural analogs

Although CA can be isolated from plants and semi-synthetically prepared by oxidizing hydroxy group at the 3-position from UA followed by introducing a hydroxy group at the adjacent  $2\alpha$  position (Jin-an et al., 2006), it can also be produced by culturing plant cells. A callus from the CA producing plant tissue can be cultivated in a suspension medium. CA can then be isolated from the culture media in higher yields than ones extracted from the plants (Hiromitsu et al., 2004). Furthermore, Zhao Yujia *et al.* constructed a new pathway for the biosynthesis of OA in *Saccharomyces cerevisiae* to improve the yield of OA (Zhao et al., 2018). Li Jing *et al.* (Li and Zhang, 2014) used synthetic biology technology to construct the biosynthetic pathway of BA in *Saccharomyces cerevisiae* to improve the yield of BA.

# Pharmacokinetic and pharmacodynamic studies of corosolic acid and its structural analogs

# Pharmacokinetic studies of corosolic acid and its structural analogs

CA concentrations in rat plasma after oral administration of 20 mg/ kg of CA suspension was determined and the results showed that the oral bioavailability of CA was 0.93% (Liu et al., 2011). The apparent volume of distribution (V<sub>d</sub>) of CA was 114.29 l/kg, which showed that the drug was concentrated in tissues, organs or distributed in large areas of tissues. The larger the volume of the drug distribution, the slower the excretion rate and the longer the retention time in the body. The main pharmacokinetic parameters are shown in Table 2. Rats were given 100 mg/kg UA to study the pharmacokinetic parameters, and the oral bioavailability was 8.72% (Zhang et al., 2017b). The pharmacokinetics of OA in rats was determined by oral administration of 25 mg/kg, and the bioavailability of OA was only 0.7% (Jeong et al., 2007). The oral bioavailability of OA was low, it required intravenous administration. Further pharmacokinetic studies on OA in rats were required to be carried out, because many pharmacokinetic parameters were still lacking. Ultra-high performance liquid chromatography-mass spectrometry/mass spectrometry (UPLC-MS/MS) method was established for the determination of MA and BA mass concentration in normal rat, which was oral administrated of these triterpenic acid extracts at 4.0 g/kg (Li et al., 2018). Both compounds were soluble in 10% Tween-80 water. The half-time of MA and BA was more than 2 h, which indicated that the elimination in the body was slower than CA, OA and AA (UA data is not available), and the dosing interval can be extended. The rats were orally administered with 20 mg/kg of AA suspension and the bioavailability was 16.25% (Yuan et al., 2015). Bioavailability of AA was much higher than those of CA, UA and OA. Compared with structural analogs such as UA, OA, MA, AA and BA, the blood concentration of CA has the shortest time to reach the peak and the clearance rate is the highest.

CA concentrations in plasma was determined after caudal vein



Betulinic acid (BA)

Fig. 2. The structures of corosolic acid and its analogs.

Pharmacodynamic studies of corosolic acid and its structural analogs

that the  $T_{\frac{1}{2}}$  of CA was 1.11 h (Liu et al., 2011). Intravenous injection of UA 20 mg/kg in rats to study the pharmacokinetic parameters (Zhang et al., 2017b). The pharmacokinetics of UA injection in rats need to be further studied, and many pharmacokinetic parameters remain unclear. The pharmacokinetics of OA in rats was determined by intravenous injection of 1 mg/kg and the  $T_{\frac{1}{2}}$  was 0.88 h (Jeong et al., 2007). The rats were injected 2 mg/kg of AA into the lateral tail vein, and the  $T_{\frac{1}{2}}$  of AA was 0.35 h (Yuan et al., 2015). The half-time of AA was less than 0.5h, which indicated that the elimination in the body was faster than CA, OA and AA (UA data is not available), and the dosing interval need to be shortened. The injection pharmacokinetic parameters of CA and its structural analogs are shown in Table 3. The pharmacokinetic process of intravenous injection of MA and BA in rats has not been studied yet, and it is required to be explored in the future.

injection of 2 mg/kg CA aqueous solution in rats and the results showed

Song *et al.* (Song et al., 2006) determined the pharmacokinetic parameters of OA in healthy human plasma. After oral administration of 40 mg once, the mean values of C<sub>max</sub>, T<sub>max</sub>, T<sub>1/2</sub>, AUC<sub>0-24</sub>, AUC<sub>0-∞</sub>, V<sub>d</sub>, CL were 0.012  $\pm$  0.007 µg·ml<sup>-1</sup>, 5.2  $\pm$  2.9 h, 8.73  $\pm$  6.11 h, 0.114  $\pm$  0.075 µg·h·ml<sup>-1</sup>, 0.124  $\pm$  0.107 µg·h·ml<sup>-1</sup>, 3371.1  $\pm$  1990.1 L, 3371.1  $\pm$  1990.1 L·h<sup>-1</sup>, respectively.

The absorption experiment of CA in stomach and intestine contents showed that CA could be absorbed in both stomach and small intestine (Zhang et al., 2019). However, Liu Qingwang et al. (Liu et al., 2011) found that the  $C_{max}$  of CA in rats administrated by intragastric administration of 20 mg/kg was only  $0.30 \pm 0.19 \ \mu$ g/ml, indicating that the oral absorption of CA was slightly poor. The metabolic studies in rat liver microsomes (RLMs) showed that CA in the body could be metabolized partly by CYP1A2 and CYP3A4 (Zhang et al., 2019).

CA and its structural analogs display a broad spectrum of biological activities. Key pathways involved in their individual activity are illustrated in Fig.3.

#### Hypoglycemic

Molecular simulation results showed that CA binds to α-glucosidase through hydrogen bonds to inhibit the  $\alpha$ -glucosidase activity (Ni et al., 2019). Inhibition of its activity could effectively regulate blood sugar, which provided a possibility for CA to treat diabetes. The lowering blood sugar of CA has always been studied in type 2 diabetes KK-Ay mice. Miura et al. (Miura et al., 2006) found out that CA improved glucose metabolism by reducing insulin resistance. Xu Shuwen et al. (Xu et al., 2019) pointed out that CA stimulated glucose consumption by inhibiting phosphoenolpyruvate carboxykinase (PEPCK) mRNA expression. PEPCK is an enzyme which limits the gluconeogenesis of liver and kidney, and its overexpression has been found in almost all diabetes models (Tang et al., 2018). CA downregulated blood lipid and glucose, and upregulated superoxide dismutase (SOD) activity in diabetic rats (Xu et al., 2019). Inhibition of  $\alpha$ -glucosidase and increased cellular uptake of glucose have been proven to be valid strategies for type 2 diabetes mellitus treatment. Yang Jie et al. demonstrated that CA regulated adenosine monophosphate-activated protein kinase (AMPK) activation in an LKB1-dependent manner, and improved insulin sensitivity in mice by modifying the phosphorylation of IRS-1 and its downstream Akt (Yang et al., 2016). Li et al. (Li et al., 2016a) revealed that CA inhibited the proliferation by inhibiting MAPK-and NADPH-mediated extracellular signal-regulated kinase 1/2 (ERK1/2) inactivation, thereby exerting a protective effect on diabetic nephropathy.

UA and OA inhibited α-glucosidase activity by causing

#### Table 1

The extraction method of corosolic acid and its structural analogs from plants.

Drug Source E		Extraction method	Solvents	Extraction yield (% dry leave weight)	Reference	
Corosolic acid (CA)	Banaba	Extracted with water and lower alcohol solvents	Lower alcohol solvents	-	(Yoon et al., 2006)	
	Eriobotrya japonica leaves	Extracted with high concentration lower alcohol	Lower alcohol	-	(Masatu and Chihiro, 2007)	
	Punica granayum peel	UA-DLLME	Chloroform	0.002	(Wu et al., 2015)	
	Weigela subsessilis leaves	Extracted with hydrophilic organic solvent	Methanol	-	(Lee and Thuong, 2010)	
Ursolic acid (UA)	Eriobotrya japonica leaves	Extracted with high concentration lower alcohol	Lower alcohol	-	(Masatu and Chihiro, 2007)	
	Comastoma pulmonarium	UA-DLLME	Chloroform	0.063	(Wu et al., 2015)	
	Punica granayum peel	UA-DLLME	Chloroform	0.004	(Wu et al., 2015)	
	Weigela subsessilis leaves	Extracted with hydrophilic organic solvent	Methanol	-	(Lee and Thuong, 2010)	
	Meconopsis henrici	UA-DLLME	Chloroform	0.015	(Wu et al., 2015)	
	Swertia racemosa	UA-DLLME	Chloroform	0.007	(Wu et al., 2015)	
	Corydalis impatiens	UA-DLLME	Chloroform	0.013	(Wu et al., 2015)	
	Dracocephalum tanguticum Maxim	UA-DLLME	Chloroform	0.064	(Wu et al., 2015)	
	Ligustrum lucidum Ait	Ultrasound and microwave assisted extraction	Ethanol	0.78	(Xia et al., 2011; Xia et al., 2012)	
Oleanolic acid (OA)	Eriobotrya japonica leaves	Extracted with hydrophilic organic solvent	Methanol	-	(Uto et al., 2013)	
	Comastoma pulmonarium	UA-DLLME	Chloroform	0.072	(Wu et al., 2015)	
	Punica granayum peel	UA-DLLME	Chloroform	0.003	(Wu et al., 2015)	
	Meconopsis henrici	UA-DLLME	Chloroform	0.023	(Wu et al., 2015)	
	Swertia racemosa	UA-DLLME	Chloroform	0.096	(Wu et al., 2015)	
	Corydalis impatiens	UA-DLLME	Chloroform	0.078	(Wu et al., 2015)	
	Dracocephalum tanguticum Maxim	UA-DLLME	Chloroform	0.025	(Wu et al., 2015)	
	Ligustrum lucidum Ait	Ultrasound and microwave assisted extraction	Ethanol	0.54	(Xia et al., 2011; Xia et al., 2012)	
Maslinic acid (MA)	Eriobotrya japonica leaves	Extracted with hydrophilic organic solvent	Methanol	-	(Uto et al., 2013)	
	Corydalis impatiens	UA-DLLME	Chloroform	0.001	(Wu et al., 2015)	
	Olive	Ultrasound assisted extraction	Ethanol	-	(Xie et al., 2019)	
Asiatic acid (AA)	Centella asiatica	Subcritical water extracting technology	Methanol	-	(He, 2008)	
Betulinic acid (BA)	Dracocephalum tanguticum Maxim	UA-DLLME	Chloroform	0.017	(Wu et al., 2015)	
	Bark of white birch	Extracted with hydrophilic organic solvent	Ethanol	-	(Zhao et al., 2007)	
	Cornus walteri	Extracted with hydrophilic organic solvent	Methanol	-	(Lee et al., 2019)	
	Zizyphus joazeiro barks	Focused microwave assisted extraction	Ethyl acetate	-	(Fonseca et al., 2017)	

# Table 2

The pharmacokinetic parameters of oral administration of corosolic acid and its structural analogs in rats.

Compounds	$C_{max}$ (µg·ml <sup>-1</sup> )	T <sub>max</sub> (h)	T <sub>1/2</sub> (h)	AUC <sub>0∙t</sub> (µg·h·ml <sup>−1</sup> )	$AUC_{0-\infty}$ (µg·h·ml <sup>-1</sup> )	MRT (h)	CL (L·h <sup>-1</sup> ·kg <sup>-1</sup> )	V <sub>d</sub> (L·kg <sup>-1</sup> )	F (%)	Reference
CA (20 mg·kg <sup>-1</sup> )	0.30±0.19	0.15±0.03	$1.20{\pm}0.27$	0.34±0.17	0.43±0.16	$1.15{\pm}0.17$	52.81±22.54	114.29±80.13	0.93±0.45	(Liu et al., 2011)
UA (100 mg·kg <sup>-1</sup> )	$2.02{\pm}0.02$	0.83±14.1	-	3.84±0.01	3.89±0.01	2.33±7.70	26.62±13.50	-	8.72	(Zhang et al., 2017b)
OA (25 mg⋅kg <sup>-1</sup> )	$0.07{\pm}0.06$	$0.42{\pm}0.30$	$0.78{\pm}0.81$	$0.10{\pm}0.09$	-	-	-		0.7	(Jeong et al., 2007)
MA (4 g·kg <sup>-1</sup> )	$egin{array}{c} 8.56  imes \ 10^5 {\pm} 3.02  imes \ 10^5 \end{array}$	6.50±1.00	2.34±0.81	$6.23  imes 10^{6} \pm 2.45  imes 10^{6}$	${}^{6.25\  imes}_{10^6\pm 2.46\  imes}_{10^6}$	-	11.83±3.59	-	-	(Li et al., 2018)
AA (20 mg·kg <sup>-1</sup> )	$0.39\times10^{-3}$	0.50	0.64	0.70	0.77	0.67	6.68	-	16.25	(Yuan et al., 2015)
$BA (4 g kg^{-1})$	$\begin{array}{l} 1.75 \; \times \\ 10^5 {\pm} 0.35 \; \times \\ 10^5 \end{array}$	7.50±3.00	4.24±1.69	$1.70 \times 10^{6} \pm 0.60 \times 10^{6}$	$1.76 \times 10^{6} \pm 0.60 \times 10^{6}$	-	40.74±14.52	-	-	(Li et al., 2018)

conformational changes of it, and the combination of which displayed a significant synergistic inhibition effect (Ding et al., 2018; Yin et al., 2014). Protein tyrosine phosphatase 1B (PTP1B), is a negative regulator of the insulin signaling pathway. UA and its derivatives, as an inhibitor of PTP1B, enhanced the phosphorylation of insulin receptors (Zhang

et al., 2006). UA lowered blood sugar by regulating insulin secretion and glucose uptake in hyperglycemic rats (Castro et al., 2015; Saadeldeen et al., 2020). Kwon et al. (Kwon et al., 2018) revealed that UA improved islet function, inhibited liver gluconeogenesis, and reduced insulin resistance. Under basal and glucose stimulation conditions, OA could

#### Table 3

The injection pharmacokinetic parameters of corosolic acid and its structural analogs in rats

Compounds	$C_{max}$ (µg·ml <sup>-1</sup> )	T <sub>max</sub> (h)	T <sub>1/2</sub> (h)	$AUC_{0-t}$ (µg·h·ml <sup>-1</sup> )	AUC <sub>0-∞</sub> (µg·h·ml <sup>−1</sup> )	MRT (h)	$\begin{array}{c} \text{CL} \\ (l \cdot h^{-1} \cdot kg^{-1}) \end{array}$	$V_d$ (l·kg <sup>-1</sup> )	Reference
CA (2 mg·kg <sup>-1</sup> ) UA (20 mg·kg <sup>-1</sup> )	8.63±0.52 -	-	1.11±0.19 -	$3.66 {\pm} 0.54$ $8.64 {\pm} 0.02$	$3.75 \pm 0.53$ $9.02 \pm 0.02$	$0.38{\pm}0.06$ $2.13{\pm}23.9$	$0.54{\pm}0.07$ $2.32{\pm}20.5$	0.71±0.38 -	(Liu et al., 2011) (Zhang et al., 2017b)
OA (1 mg·kg <sup>-1</sup> ) AA (2 mg·kg <sup>-1</sup> )	$-$ 1.18 $ imes$ 10 $^{-3}$	- 0.08	0.88±0.40 0.35	0.54±0.17 0.43	- 0.48	0.23±0.11 0.26	1.98±0.55 4.19	0.45±0.21 -	(Jeong et al., 2007) (Yuan et al., 2015)



Fig. 3. Representative pathways involved in mechanisms of action of corosolic acid and its structural analogs

significantly increase the insulin secretion in cultured INS-1823/13 pancreatic  $\beta$ -cells. And under acute glucose stimulation, OA increased insulin secretion in isolated rat islets (Teodoro et al., 2008). Khath et al. (Khathi et al., 2013) found that OA and MA not only down-regulated the expression of glucose transporter SGLT1 and GLUT2, but also inhibited the activity of α-glucosidase. OA and MA can be used as supplementary agents to reduce postprandial blood glucose. AA reduced the blood sugar level in diabetic rats, promoted insulin secretion through β-cells regeneration, and regulated liver glucose-metabolizing enzymes (Ramachandran and Saravanan, 2013). Liu Jun et al. (Liu et al., 2010) revealed that AA significantly conserved pancreatic β-cells to increase serum insulin levels. AA could also induce the Akt kinase activation and the expression of Bcl-xL in vivo. Ramachandran et al. (Ramachandran and Saravanan, 2015) proposed that GLUT4 in skeletal muscle was increased by AA, possibly through protein kinase B (Akt) and antioxidant defense in plasma, thereby improving glucose response. Cell differentiation assay showed that adipogenesis was inhibited and glucose uptake was increased by BA in 3T3-L1 cells (Brusotti et al., 2017). Xie Rui *et al.* (Xie et al., 2017) pointed out that the protective effect of BA on diabetic nephropathy may be realized through AMPK/NF- $\kappa$ B/Nrf2 pathway. The pathways involved is summarized under Diabetes panel of Fig.3.

## Anti-inflammatory

Li *et al.* (Li *et al.*, 2016b) found that mitochondrial fission was prevented by CA through regulating phosphorylation of dynamin-related protein 1 (Drp1) at Ser637 in endothelial cells, which helped block NOX2 oxidase signal transduction and inhibit NLRP3 inflammasome activation. The oxidative stress of endothelial cells and NLRP3 inflammasomes activation were related to the defect of mitochondrial morphology. Drp1, a mitochondrial fission protein, interacted with NOX2 oxidase, leading to NLRP3 inflammasome activation and endothelial dysfunction (Bhatt et al., 2013). Studies have found that acute inflammation was improved by CA through suppressing the

phosphorylation and transcription of IL-1 receptor-associated kinase (IRAK-1) in mouse macrophages (Kim et al., 2016; Zhou et al., 2020). Ma et al. (Ma et al., 2017) showed that UA acted on the target of extracellular signal-regulated kinase 1 (ERK1) and c-Jun N-terminal kinase 2 (JNK2), alleviated inflammation-related signal transduction factors such as ERK1, NF-KB and STAT3, thereby reducing the inflammatory response. Lu Jun et al.(Lu et al., 2010) pointed out that inflammation in prefrontal cortex induced by D-galactose was reduced by UA through inhibiting NF-kB pathway activation. Studies have shown that UA can be used to treat multiple sclerosis. The mechanism was that UA upregulated myelin-related gene expression in oligodendrocytes by peroxisome proliferator activated receptor  $\gamma$  (PPAR $\gamma$ ) activation (Zhang et al., 2020a). Rodriguez et al. (Rodriguez-Rodriguez et al., 2008) found that OA activated endothelium-dependent NO release and reduced calcium ions in smooth muscle cells to relax endothelium in isolated rat mesenteric arteries. MA inhibited inflammatory response and antioxidant effects. Lee et al. (Lee et al., 2020) demonstrated that MA played a key anti-inflammatory effect by modulating inducible nitric oxide synthase (iNOS) in the mice lung tissues. Moreover, MA exerted a powerful anti-inflammatory effect by inhibiting NF-KB signal pathway and tumor necrosis factor alpha (TNF- $\alpha$ ) in cortical astrocytes(Fukumitsu et al., 2016; Huang et al., 2011a). Liou et al. (Liou et al., 2019) found that MA had a protective effect on nonalcoholic fatty liver by regulating the Sirt1/AMPK signaling pathway in mice. Quan et al. (Quan et al., 2013) revealed that lipid accumulation was ameliorated by BA in liver cells through inhibiting sterol regulatory element-binding protein 1 (SREBP1) activity, which was regulated by AMPK-mTOR-SREBP pathway. Huang et al. (Huang et al., 2011b) showed that AA decreased the level of iNOS, COX-2 and NF-KB in the liver to exhibit anti-inflammatory effect. Other scientists revealed that AA suppressed neuroinflammation by inhibiting the production of mitochondrial ROS and blocking NF-KB/STAT3/ERK pathway (Chen et al., 2019; Park et al., 2017; Qian et al., 2018). Li et al. (Li et al., 2019) reported that rheumatoid arthritis was also inhibited by BA through blocking the NF-kB pathway activation. The pathways involved is summarized under Imflammation panel of Fig.3.

## Tumor inhibition

Ma et al. (Ma et al., 2018) demonstrated that CA induced endoplasmic reticulum stress-dependent apoptosis of prostate cancer cells via activations of IRE-1/JNK, PERK/CHOP and Tribbles 3. Yang Jie et al. (Yang et al., 2018) showed that CA possesses anticancer effects by blocking transformation and epigenetic restoration of Nrf2 expression. Cheng Qilai et al. (Cheng et al., 2017) demonstrated that CA induced apoptosis of BGC823 cells by inhibiting nuclear translocation of NF-KB subunit p65 and activation of IkBa. The results showed that the expression of pro-apoptotic proteins like Bcl-2-associated X protein (Bax) increased and anti-apoptotic proteins such as B-cell lymphoma 2 (Bcl-2) decreased. Woo et al. (Woo et al., 2018) revealed that CA induced non-apoptotic cell death by increasing lipid peroxidation of human renal carcinoma Caki cells. The VEGF receptor signaling has been implicated in hepatocellular carcinoma migration, and inhibition of it is an important target for hepatocellular carcinoma (HCC) therapy (Zhang et al., 2012). Ku et al. (Ku et al., 2015) showed that CA had a good anti-cancer effect in HCC cells by inhibiting VEGFR2 kinase activity and down-regulating the downstream Src/FAK/cdc42 signaling axis. Jia et al. (Jia et al., 2020) found that CA also inhibited cancer progression by translocating YAP from nucleus in HCC. Nho et al. (Nho et al., 2013) reported that CA induced apoptosis of human lung adenocarcinoma A549 cells by altering ROS-dependent anti-apoptotic proteins.

UA promoted autophagy-induced apoptosis of MCF-7 cells by activating the MAPK1/3 pathway, which was a novel cellular mechanism to treat cancer (Zhao et al., 2013). The cancer/testis antigen family 45 member A2 is a new non-small-cell lung carcinoma oncogene. UA could also reverse paclitaxel resistance in breast cancer cells (Xiang et al., 2019). Yang *et al.* (Yang et al., 2019) revealed that UA promoted EGFR

T790M NSCLC cell apoptosis through negative regulation of the β-catenin/TCF4/CT45A2 signaling pathway. MA is an anti-tumor drug, which has a strong anti-proliferation effect on HT29 cells. Reyes-Zurita et al. (Reves-Zurita et al., 2009) showed that MA induced apoptosis of HT29 cells by increasing the mitochondrial apoptosis and the expression of Bcl-2, and stimulating the release of mitochondrial cytochrome-C. Wei et al. (Wei et al., 2019) found that MA inhibited the occurrence of colon cancer through AMPK-mTOR pathway. And MA induced autophagy by down-regulating the expression of heat shock protein in Panc-28 cells (Tian et al., 2018). Li et al. (Li et al., 2010) pointed out that MA activated caspase-dependent apoptotic pathway, inhibited the activation of NF-KB and the expression of downstream gene in vitro, thus inhibiting the growth of pancreatic tumors. Wu et al. (Wu et al., 2017) showed that the proliferation of lung cancer cells were inhibited by AA in vitro and in vivo through destroying mitochondria. Hsu et al. (Hsu et al., 2005) found that AA induced cell apoptosis and inhibited breast cancer progression by activating extracellular signal-regulated kinase and P38 MAPK pathway. AA is also a promising tumor treatment sensitizer. It increased the antitumor effect of doxorubicin (Fang et al., 2019). Siddique et al. (Siddique et al., 2017) suggested that AA reduced the preneoplastic lesions by anti-inflammatory and anti-proliferative effects, and could be used as a chemical defence agent to prevent colon cancer. Chintharlapalli et al. (Chintharlapalli et al., 2007) demonstrated that BA inhibited prostate cancer growth by decreasing the expression of VEGF and survivin, and the possible mechanism was that BA activated the degradation of the specific protein 1, 3, and 4. BA exerted antitumor effect by inhibiting cell proliferation and NF-KB pathway, and suppressing signal transducer and activator of transcription 3 (STAT3) activation pathway (Pandey et al., 2010; Shen et al., 2019). The pathways involved is summarized under Cancers panel of Fig.3.

# Anti-oxidant and cellular protection

Studies have shown that the liver may be protected by CA from alcohol-induced damage through regulating MAPK signaling and autophagy activation (Guo et al., 2016). The mechanistic studies showed that CA inhibited the alcohol-activated p38 MAPK signaling and restored the expression of autophagy-related genes inhibited by ethanol. Sarkar et al. (Sarkar et al., 2014) revealed that OA had an antagonistic effect on the changes in fluoride-induced nucleic acid content and proteolytic enzyme activity. Therefore, OA has a potential antioxidant effect on oxidative brain damage induced by fluoride. Li Feng et al. (Li et al., 2017) showed that the level of ROS and the expression of inflammatory cytokines could be decreased by MA. MA also inhibited high glucose-induced endothelial function damage by regulating IRS-1/PI3K/Akt signaling pathway. Jeong et al. (Jeong et al., 2020) found that PM2.5-induced lung injury was protected by MA in mice through regulating the mTOR autophagy pathways. Lv Hongming et al. (Lv et al., 2017) pointed out that the hepatic failure induced by lipopolysaccharide in mice could be treated by AA, and the possible mechanism was related to inhibite the activation of MAPK and NF-KB, which depended on the activation of the AMPK/GSK3 $\beta$  pathway. Jiang Wu et al. (Jiang et al., 2016) reported that AA reduced inflammation by inhibiting NLRP3 inflammasome activation and upregulating Nrf2 protein levels, which had a protective effect on acute lung injury in rats. Li et al. (Li et al., 2016c) found that AA also inhibited it by blocking the TLR4/NF-KB pathway. AA prevent myocardial ischemia injury in rat H9c2 cardiomyocyte model through Akt/GSK-3 $\beta$ /HIF-1 $\alpha$  pathway and glucose metabolism regulation (Dai et al., 2018; Huang et al., 2016). Wu et al. (Wu et al., 2019) revealed that BA reduced the oxidative damage of mouse testes induced by T-2 toxin, a reproductive toxin, by regulating the JAK2/STAT3 pathway. The pathways involved is summarized under Injury panel of Fig.3.

# Reduction in fibrosis

Wang et al. (Wang et al., 2011) reported that UA improved

experimental liver fibrosis by specifically inducing apoptosis of activated hepatocytes. Tang *et al.* (Tang et al., 2012) revealed that AA inhibited liver fibrosis by blocking the TGF- $\beta$ /Smad signaling pathway. Wei *et al.* (Wei et al., 2018) discovered that CCl4-induced liver fibrosis could be reduced by AA in rats through regulating PI3K/AKT/mTOR and Bcl-2/Bax pathways. Zhang *et al.* (Zhang et al., 2020b) found that AA prevented renal fibrosis in rats with unilateral ureteral occlusion by promoting the production of PPAR-γ endogenous ligands. Liu *et al.* (Liu et al., 2020a) revealed that AA reduced hypertrophy and fibrosis differentiation of articular chondrocytes by targeting the AMPK/PI3K/AKT pathway. The pathways involved is summarized under Fibrosis panel of Fig.3.

#### Antiviral

UA, OA and BA are representative antiviral drugs widely existing in nature. Tohme *et al.* (Tohme et al., 2019) pointed out that UA inhibited rotavirus replication and affected the maturation of virus particles *in vitro*. Moreover, UA and OA became new antiviral drugs for hepatitis C virus by inhibiting NS5B activity (Kong et al., 2013). Lin *et al.* (Lin et al., 2015) pointed out that BA applied anti-hepatitis C virus activity by inhibiting COX-2 expression *in vitro*. The pathways involved is summarized under Viral panel of Fig.3.

Studies have shown that CA, known as plant insulin, has a good therapeutic effect on diabetes, and a powerful effect on inflammatory and tumors. Yang Jie et al. demonstrated that CA improved insulin sensitivity in HFD mice by regulating AMPK activation and modifying the phosphorylation of IRS-1and Akt (Yang et al., 2016). Compared with CA, UA also has hypoglycemic and anti-tumor effects, but it has a unique role in inflammation. Ma et al. (Ma et al., 2017) showed that UA acted on the target of ERK1 and JNK2, alleviated inflammation-related signal transduction factors such as ERK1, NF-KB and STAT3, thereby reducing the inflammatory response. UA and OA synergistically inhibited  $\alpha$ -glucosidase. Studies have shown that OA increased insulin secretion in isolated rat islets under acute glucose stimulation (Teodoro et al., 2008). But the mechanisms involved in inflammation and tumors were less well studied. MA inhibited inflammatory response and antioxidant effects. MA is an anti-tumor drug, which has a strong anti-proliferation effect on HT29 cells. The hypoglycemic mechanism of AA is different from that of CA. Liu Jun et al. (Liu et al., 2010) revealed that AA significantly conserved pancreatic  $\beta$ -cells to increase serum insulin levels. AA inhibited oxidative stress and inflammation, and also had neuroprotective effects. AA is also a promising sensitizer for tumor therapy. Studies have shown that BA has a unique role in the treatment of tumors. BA exerted antitumor effect by inhibiting cell proliferation and NF-KB pathway, and suppressing STAT3 activation pathway (Pandey et al., 2010; Shen et al., 2019).

# Structural modification and formulation design of corosolic acid and its structural analogs

## Structural modification of corosolic acid and its structural analogs

Pentacyclic triterpenoids do not dissolve well in water due to their rigid scaffold and hydrophobic properties, which is an important factor limiting their application as therapeutic drugs. Liu *et al.* (Liu *et al.*, 2020b) synthesized C28 modified derivatives of CA and MA based on the principle of splicing. A number of esters were produced by C28 carboxylic acid groups in CA and MA with alcohols derived from 1-deoxynojirimycin (1-DNJ); Some amide derivatives were made from CA and corresponding piperazine derivatives. Xu *et al.* (Xu *et al.*, 2016) found that the water solubilities of CA derivatives of glycosylation at either C (2)-OH or C(3)-OH or both were significantly increased, and the water solubilities were related to the amount and type of glycosides in the ethanol-water system. However, in the dimethyl sulfoxide (DMSO) system, as the water solubilities of CA decreased. Zeng *et al.* (Zeng *et al.*, 2016) fourd the complexities in the dimethyl sulfoxide in the complexities of the derivative increased, but the  $\alpha$ -glucosidase inhibitory activity of CA decreased. Zeng *et al.* (Zeng *et al.*, 2016) fourd the complexities is the complexities of the derivative increased.

2019) revealed that under the both conditions of ethanol-water and DMSO as solvents, partial derivatives coupled with L-amino acid at C-28 of CA and MA had better  $\alpha$ -glucosidase inhibitory activity than acarbose. The results indicated that some derivatives of CA and MA had better  $\alpha$ -glucosidase inhibitory activity than the precursors CA and MA. The IC<sub>50</sub> of the 1-DNJ derivatives of CA and MA with shorter linkers, not overlong linkers was lower than the leading compounds CA and MA, but the  $\alpha$ -glucosidase inhibitory activity of the CA and MA-1-DNJ derivatives was not significantly enhanced compared with CA and MA. Moreover, a free hydroxyl or an amino group of piperazine was likely to enhance the  $\alpha$ -glucosidase inhibitory activity.

Rali et al. (Rali et al., 2016) showed that the modification of OA at C3 and C28 with acetate and ester had a better analgesic effect and enhanced the biological characteristics. Studies have shown that the introduction of H-bond donors at the C-3 position of OA was beneficial to cytotoxicity (Hao et al., 2013). Li Jianfei et al. (Li et al., 2014) showed that the introduction of amide bond in C-28 and carbonyl group in C-11 of AA significantly improved its antitumor activity. BA has poor water solubility and short half-time. Saneja et al., (Saneja et al., 2017b) pointed out that a derivative synthesized by coupling the C-28 carboxylic acid group of BA with the amine group of mPEG improved its solubility and anticancer effect. Saha et al. (Saha et al., 2015) found that the addition of dichloroacetate molecules to the C-3 hydroxyl group of BA formed an ester derivative, which improved solubility and had significant synergistic cytotoxicity to a variety of cancer cells in vitro. Dichloroacetate directed cell metabolism into glucose oxidation by inhibiting PDK16, which put cancer cells at a disadvantage for proliferation (Sun et al., 2010). Xu Jun et al. (Xu et al., 2012) pointed out that some BA derivatives were easily synthesize by introducing fused heterocyclic rings at C-2 and C-3 positions. They showed that derivatives inhibited the expression of the cathepsin K and increased TRAP cytotoxicity in RAW264.7 test, thereby inhibited osteoclast differentiation and bone resorption.

#### Corosolic acid and its structural analogs in drug formulation and delivery

CA had a function similar to cholesterol and could form cholesterolfree CA liposomes by replacing cholesterol. Compared with it, the liposomes of CA could improve the anti-tumor effect of doxorubicin, due to CA enhanced cellular uptake and had anti-inflammatory function (Li et al., 2020). Due to the poor water solubility of UA, the bioavailability of oral administration is low. In recent years, there have been more and more researches on nano drug delivery systems, which could improve the therapeutic activity and safety of drugs. Wang et al., (Wang et al., 2017) loaded UA into poly nanoparticles and applied them to cervical cancer cells and found that it increased UA biocompatibility and water solubility and inhibited cervical cancer cells proliferation. Wang et al. (Wang et al., 2020) found that UA formed a stable high drug loading nanocomposite with paclitaxel by hydrogen bonding and hydrophobic interaction. Raval et al. (Raval et al., 2018) showed that glutathione-conjugated AA loaded albumin nanoparticles enhanced the entry of AA into brain tissue and improved neuroprotective activity. Yang et al. (Yang et al., 2013) pointed out that the oral bioavailability of OA in self-microemulsifying drug delivery system (SMEDDS) was 5.07 times higher than that in tablet form in rat plasma by HPLC. OA liposomes contained a hydrophobic OA core, which improved the drug activity of OA. Gao et al. (Gao et al., 2012) revealed that PEGylated liposomes showed better stability in vitro and would become an effective carrier for anticancer drug. In vitro drug release studies have shown that the sustained release effect of PEGylated liposomes is better than liposomes, and antitumor effect is better (Liu et al., 2016). Stroke is a fatal disease without effective drugs for treatment, because most treatment drugs are unable to penetrate the blood-brain barrier (BBB). Deng Gang et al. (Deng et al., 2019) demonstrated that BA, as an antioxidant agent, formed nanoparticles, and effectively penetrated the BBB and delivered glyburide to the brain to reduce ischemia-induced infarction after

intravenous administration. BA loaded polyethylene glycol nanoparticles had enhanced cytotoxic effect on MCF7 and PANC-1 cells *in vitro*, and prolonged half-life of BA (Saneja et al., 2019; Saneja et al., 2017a).

# Conclusion

CA is the main active ingredient extracted from *Lagerstroemia speciose* leaves. Because of its powerful hypoglycemic effect, it has received widespread attention and is called plant insulin. CA has many structural analogs, including UA, OA, MA, AA and BA, which are pentacyclic triterpenoids extracted from plants and have similar pharmacological effects to CA. Since CA and its structural analogs are largely soluble in organic solvents such as chloroform, methanol, ethanol, extraction methods including UA-DLLME, ultrasonic and microwave assisted extraction and subcritical water extraction are routinely used to extract these active compounds from their source-plants.

The pharmacokinetic process of CA and its structural analogs were studies in rats. The results showed that the bioavailability of AA was 16.25%, and oral absorption was better than CA (0.93%), UA (8.72%) and OA (0.7%), respectively (Jeong et al., 2007; Liu et al., 2011; Yuan et al., 2015; Zhang et al., 2017b), possibly because the C<sub>23</sub> position of AA was substituted by hydroxyl group, which led to an increase in solubility. CA and its structural analogs are pentacyclic triterpenoids. Their rigid skeleton and hydrophobic backbone make it poorly water-soluble and low in bioavailability. Structural modification and formulation design to increase drug solubility played an important role in improving the bioavailability. It has been demonstrated that the introduction of polar groups such as glycosides was a good way to improve the water solubility of triterpenoids (Xu et al., 2016). The SMEDDS, liposomes and nanoparticles and so on were indispensable methods to increase the dissolution of drugs, by which could improve the oral absorption and bioavailability.

CA and its structural analogs have similar effects, such as hypoglycemic, anti-inflammatory and anti-tumor effects. CA and its structural analogs all exhibited the hypoglycemic effect by inhibiting  $\alpha$ -glucosidase and increasing cellular uptake of glucose (Ding et al., 2018; Hou et al., 2009; Khathi et al., 2013; Lee and Thuong, 2010; Ni et al., 2019; Zhang et al., 2017a). Moreover, UA and AA transported glucose through GLUT4, promoted insulin secretion and improved insulin resistance. They also possessed anti-inflammatory, anti-tumor, anti-injury and so on properties. The mechanism of action is the same in reducing blood sugar, but different in anti-inflammatory. Studies have found that CA ameliorated inflammation by suppressing phosphorylation and transcription of IRAK-1 or suppressing NLRP3 inflammasome activation (Kim et al., 2016; Li et al., 2016b). MA exerted anti-inflammatory effects by inhibiting NF- $\kappa$ B pathway and TNF- $\alpha$  (Fukumitsu et al., 2016; Huang et al., 2011a). AA suppressed neuroinflammation by inhibiting the production of mitochondrial ROS, blocking NF-KB/STAT3/ERK and apoptosis pathways (Chen et al., 2019; Park et al., 2017; Qian et al., 2018). Furthermore, many experimental studies have shown that CA and its structural analogs exhibited antitumor effects and could be used as supportive therapy for cancers. The possible mechanisms for inducing tumor cell apoptosis mainly include activating caspase protease, promoting the mitochondrial apoptotic pathway, and regulating NF-kB signaling pathway, and so on (Li et al., 2010; Nho et al., 2013; Reyes--Zurita et al., 2009). NF-kB-independent pathway is a common pathway. CA and its structural analogs could not only inhibit tumor growth through the NF-kB pathway, but also ameliorate inflammation and oxidative damage. For example, CA induced apoptosis of BGC823 cells by inhibiting NF-kB p65 and ameliorated inflammation (Cheng et al., 2017; Kim et al., 2016). AA inhibited acute lung injury in mice by blocking the TLR4/ NF-κB pathway (Li et al., 2016c).

In conclusion, CA and its structural analogs UA, OA, MA, AA and BA were extracted from various plants, all of which were pentacyclic triterpenoids. They have certain effects in lowering blood sugar, antiinflammation and anti-tumor. Their oral absorption and bioavailability were poor which can be improved through structural modification and formulation design. CA and its structural analogs are interesting natural product-based lead compounds for further development and mechanistic studies.

#### Authors' contribution

XPQ: Conceptualization, Methodology, Formal analysis the quality of evidence, Validation, Visualization, Writing-Original draft preparation, Review and Editing; XHZ: Conceptualization, Methodology, Formal analysis the quality of evidence, Validation, Visualization, Writing-Original draft preparation, Review and Editing; LNS: Investigation, Formal analysis, Writing-Review and Editing; WFX: Formal analysis the quality of evidence, Visualization, Writing-Review and Editing; YW: Investigation, Formal analysis, Writing-Review and Editing; SYS: Investigation, Formal analysis, Writing-Review and Editing; MYM: Formal analysis the quality of evidence, Visualization, Writing-Review and Editing; ZPC: Formal analysis the quality of evidence, Visualization, Writing-Review and Editing; ZDW: Supervision, Writing-Review and Editing; CX: Supervision, Writing-Review and Editing; BNC: Conceptualization, Methodology, Supervision, Writing-Review and Editing; YOW: Conceptualization, Methodology, Validation, Writing-Original draft preparation, Review and Editing. All data were generated in-house, and no paper mill was used. All authors agree to be accountable for all aspects of work ensuring integrity and accuracy.

# CRediT authorship contribution statement

Xu-Ping Qian: Conceptualization, Methodology, Formal analysis, Validation, Visualization, Writing – original draft, Writing – review & editing. Xue-Hui Zhang: Conceptualization, Methodology, Formal analysis, Validation, Visualization, Writing – original draft, Writing – review & editing. Lu-Ning Sun: Investigation, Formal analysis, Writing – review & editing. Wei-Fan Xing: Formal analysis, Visualization, Writing – review & editing. Yu Wang: Formal analysis, Writing – review & editing. Shi-Yu Sun: Investigation, Formal analysis, Writing – review & editing. Shi-Yu Sun: Investigation, Formal analysis, Writing – review & editing. Meng-Yuan Ma: Formal analysis, Visualization, Writing – review & editing. Zi-Ping Cheng: Formal analysis, Visualization, Writing – review & editing. Zu-Dong Wu: Supervision, Writing – review & editing. Chen Xing: Supervision, Writing – review & editing. Bei-Ning Chen: Conceptualization, Methodology, Supervision, Writing – review & editing. Yong-Qing Wang: Conceptualization, Methodology, Validation, Writing – original draft, Writing – review & editing.

#### **Declaration of Competing Interest**

We declare that we have no commercial or associative interest that represents a conflict of interest in connection with the work submitted.

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