

# Cardiovascular Protective Effects of *Centella asiatica* and Its Triterpenes: A Review

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## ABSTRACT

*Centella asiatica*, a triterpene-rich medicinal herb, is traditionally used to treat various types of diseases including neurological, dermatological, and metabolic diseases. A few articles have previously reviewed a broad range of pharmacological activities of *C. asiatica*, but none of these reviews focuses on the use of *C. asiatica* in cardiovascular diseases. This review aims to summarize recent findings on protective effects of *C. asiatica* and its active constituents (asiatic acid, asiaticoside, madecassic acid, and madecassoside) in cardiovascular diseases. In addition, their beneficial effects on conditions associated with cardiovascular diseases were also reviewed. Articles were retrieved from electronic databases such as PubMed and Google Scholar using keywords “*Centella asiatica*,” “asiatic acid,” “asiaticoside,” “madecassic acid,” and “madecassoside.” The articles published between 2004 and 2018 that are related to the aforementioned topics were selected. A few clinical studies published beyond this period were also included. The results showed that *C. asiatica* and its active compounds possess potential therapeutic effects in cardiovascular diseases and cardiovascular disease-related conditions, as evidenced by numerous *in silico*, *in vitro*, *in vivo*, and clinical studies. *C. asiatica* and its triterpenes have been reported to exhibit cardioprotective, anti-atherosclerotic, anti-hypertensive, antihyperlipidemic, antidiabetic, antioxidant, and anti-inflammatory activities. In conclusion, more clinical and pharmacokinetic studies are needed to support the use of *C. asiatica* and its triterpenes as therapeutic agents for cardiovascular diseases. Besides, elucidation of the molecular pathways modulated by *C. asiatica* and its active constituents will help to understand the mechanisms underlying the cardioprotective action of *C. asiatica*.

## Introduction

Natural products have served as important sources of medication for thousands of years. As about 34% of modern medicines are derived from natural products between 2000 to 2014, more attention has been focused in drug discovery from medicinal plants [1]. *Centella asiatica* (L.) Urban, a tropical medicinal plant belonging to the family Apiaceae, is widely distributed in many parts of the world especially in Asian countries such as India, China, Nepal, and other Southeast Asia countries including Malaysia and Indo-

nesia [2]. The plant can also be found in Australia, South Africa, the United States, and Europe [2]. *C. asiatica* is known as *pegaga* in Malaysia, *cairuçu-asiático* in Brazil, or *mandukparni* in India, but is most popularly called as Gotu Kola or Indian pennywort in many countries [3, 4]. *C. asiatica* is a creeper plant with long stalk that attains height up to 15 cm. It has clustered and dented-blade leaves with sizes of 2–5 cm. The plant can tolerate a wide range of conditions but is abundantly found in damp and swampy areas, as well as in sandy and clay soil [3, 5].

## ABBREVIATIONS

2K-1C	2-kidney one-clip
ABTS	2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)
AMPK $\alpha$	adenosine monophosphate-activated protein kinase $\alpha$
ANP	atrial natriuretic peptide
CAT	catalase
cGMP	cyclic guanine monophosphate
COX	cyclooxygenase
DPPH	2,2-diphenyl-2-picrylhydrazyl hydrate
NO	nitric oxide
NOS	nitric oxide synthase
ERK	extracellular signal-regulated kinase
GPX	glutathione peroxidase
GSH	glutathione
GSK	glycogen synthase kinase
HAEC	human aortic endothelial cells
HDL	high-density lipoprotein
HMG-CoA	3-hydroxy-3-methyl-glutaryl coenzyme A
HUVEC	human umbilical vein endothelial cells
ICAM-1	intracellular cell adhesion molecule-1
IL	interleukins
JNK	c-Jun N-terminal kinase
LDL	low-density lipoprotein
L-NAME	N $\omega$ -Nitro-L-arginine methyl ester hydrochloride
LPS	lipopolysaccharides
MAPK	mitogen-activated protein kinases
MDA	malondialdehyde
mTOR	mammalian target of rapamycin
NF- $\kappa$ B	nuclear factor- $\kappa$ B
ox-LDL	oxidized low-density lipoprotein
PECAM-1	platelet endothelial cell adhesion molecule-1
ROS	reactive oxygen species
SOD	superoxide dismutase
TAC	transverse aortic constriction
TGF	transforming growth factor
TTFCA	total triterpenic fraction of <i>C. asiatica</i>
VCAM-1	vascular cell adhesion molecule-1
VLDL	very low-density lipoprotein

*C. asiatica* is known for its high nutritional contents and is a good source of dietary fibers [6]. In Malaysia, the plant is eaten raw, boiled, or cooked with coconut milk and usually served as a side dish with rice or as an appetizer. In countries such as India and Thailand, *C. asiatica* is consumed as juice, herbal tea, and tonic drink for health benefits. In Sri Lanka, it is a popular choice of nutritional breakfast, usually cooked as porridge [7]. As a medicinal plant, *C. asiatica* has also been traditionally used in Ayurvedic medicine and traditional Chinese medicine for treatment of various diseases. In traditional Ayurvedic medicine, *C. asiatica* has been used to enhance memory and to treat neurological diseases such as cognitive impairment and neurotoxicity [8]. The plant is also used to treat wounds, skin diseases such as leprosy, psoriasis

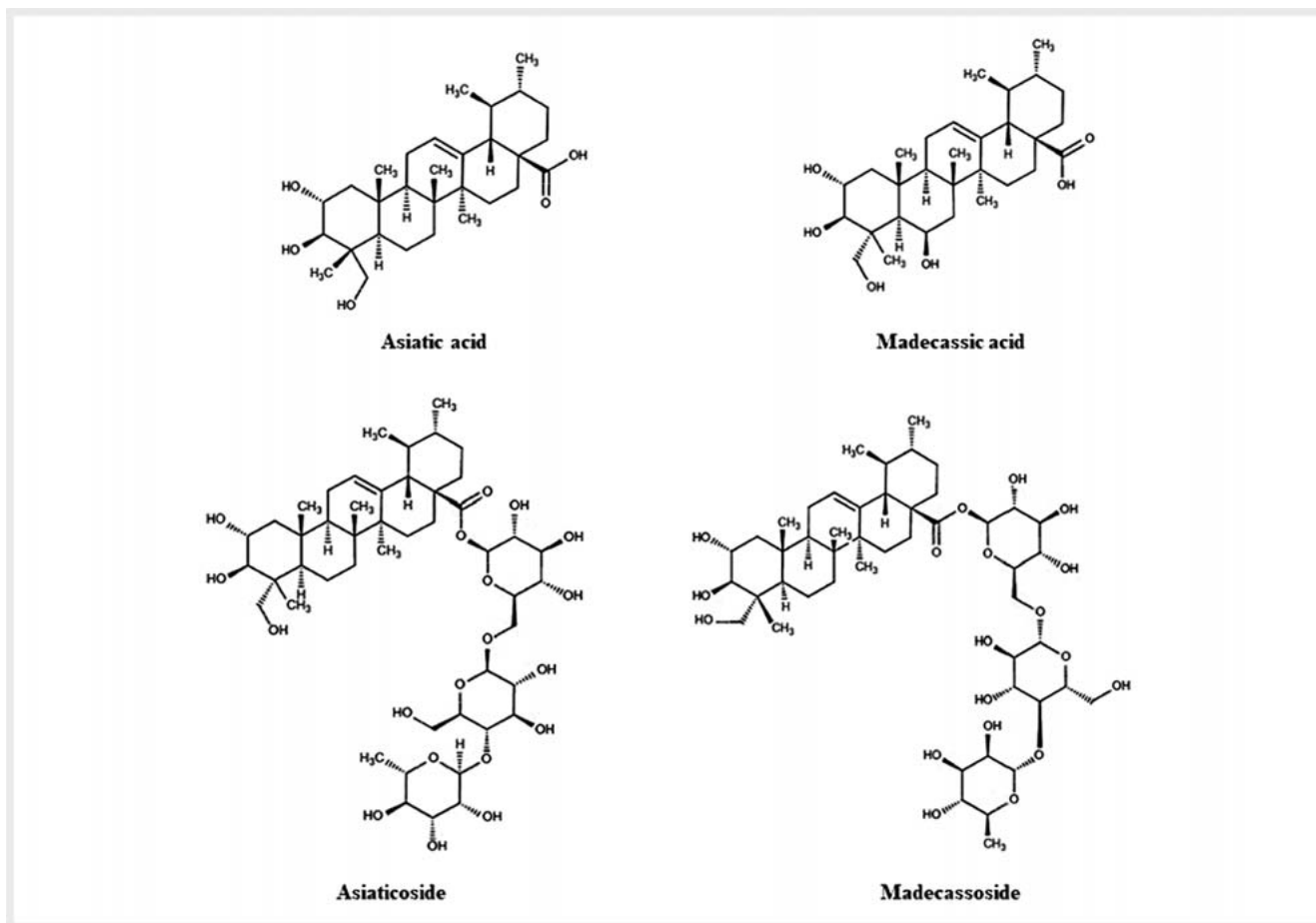
and lupus, and some ailments including vomiting, diarrhea and fever [9, 10].

The major active constituents present in *C. asiatica* are triterpenes, namely asiatic acid, asiaticoside, madecassic acid, and madecassoside (► Fig. 1) [11]. Standardized extracts of *C. asiatica* such as titrated extract of *C. asiatica*, TTFCA, and total triterpenic fraction are marketed under different trade names such as Madecassol, Centellase, and Blastostimulina. The compositions of these highly purified extracts are the same in which 40% of the extracts are asiaticoside and the remaining 60% are a mixture of asiatic acid and madecassic acid [12, 13]. Other standardized extracts of *C. asiatica* include ECa 233, which contains at least 80% asiaticoside and madecassoside [14] and Centellicum, which contains 35% of triterpenes [15]. Besides triterpenes, *C. asiatica* was found to have other phenolic compounds such as flavonoids (quercetin and kaempferol), phytosterol (campesterol, sitosterol, and stigmasterol), gulonic acid, ferulic acid, and chlorogenic acid [16]. Nevertheless, the nutritional and medicinal values of this plant are mainly attributed to the presence of triterpenes [17].

For the past decades, a large number of studies have been conducted to reveal the therapeutic potential and mechanism of action of *C. asiatica*. Accumulating evidence suggested that *C. asiatica* exhibits wound healing [18], neuroprotective [19], antioxidant [20], and anti-inflammatory effects [21] in both *in vitro* and *in vivo* models. Over the past few years, researchers have shown increased interest in exploring the potential use of *C. asiatica* for the treatment of cardiovascular diseases. Several preclinical and clinical studies have investigated cardioprotective effects of *C. asiatica* using various types of *C. asiatica* extracts and its triterpenoids.

Cardiovascular disease continues to be the leading cause of death worldwide. The major types of cardiovascular diseases include ischemic heart disease, stroke, cardiomyopathy, cerebrovascular disease, and rheumatic heart disease. The World Health Organization statistics updated on May 2017 reported that an estimated 17.9 million people died from cardiovascular diseases in 2016, representing 31% of all global deaths [22]. On top of that, Department of Statistics Malaysia reported that ischemic heart disease had remained as the main cause of death in Malaysia from 2005 to 2017. In 2017, 13.9% of all causes of death is ischemic heart disease followed by pneumonia, 12.7%, and cerebrovascular disease, 7.1% [23]. The risk factors for cardiovascular diseases include smoking, obesity, hypertension, diabetes, hyperlipidemia, oxidative stress, and inflammation. These risk factors, present as a single factor or combination of different factors, are associated with the formation and development of fatty streaks and plaques in arteries, which subsequently increases the risk of cardiovascular diseases [24].

A number of reviews on the bioactivities of *C. asiatica* and its chemical constituents have been published previously [4, 12, 25–27]. These reviews focused either on neuroprotective and dermatological effects of *C. asiatica* or reviewed generally on its bioactivities. To date, there is no review article focuses on the cardiovascular protective effects of *C. asiatica* and its active constituents. Therefore, this review aims to provide an overview on pharmacological activities of *C. asiatica* and its active constituents evaluated using *in vitro*, *in vivo*, and clinical studies, with an emphasis on the



► **Fig. 1** Chemical structure of *C. asiatica* triterpenes.

protective effects of *C. asiatica* against cardiovascular diseases and cardiovascular related conditions such as atherosclerosis, hypertension, hyperlipidemia, hyperglycemia, oxidative stress, and inflammation.

## Cardioprotective Effects of *C. asiatica* and Its Triterpenes

Cardiac failure occurs when the heart is incapable to pump sufficient blood to meet the body's demand. Myocardial ischemia and cardiomyopathy are the disease conditions that often lead to cardiac hypertrophy, a compensatory mechanism that eventually develops into cardiac failure and causing sudden death. Various mediators and multitude signaling pathways have been identified to play critical roles in the initiation and development of cardiac hypertrophy. Among the mediators involved are TNF- $\alpha$ , IL, and TGF- $\beta$ 1, which bind to their respective membrane receptors and initiate a cascade of signal transduction pathways [28]. Subsequently, various kinases such as JNK, ERK, p38, mTOR, and GSK are activated by multiple upstream effectors [28,29]. These signaling events ultimately activate NF- $\kappa$ B, which in turn alters the expression of nuclear transcription factors, leading to pathological cardiac hypertrophy [28,30].

The protective effect of *C. asiatica* extracts and its triterpenes against cardiac hypertrophy and myocardial ischemia have been demonstrated in several *in vitro* studies (► **Table 1**) [31–34]. These studies suggested that asiatic acid, one of the triterpenes of *C. asiatica*, exerts protective effects in cardiomyocytes by activating or deactivating key signaling pathways involved in the pathogenesis of cardiac hypertrophy and myocardial ischemia. An *in vitro* study on primary neonatal cardiomyocytes showed that asiatic acid attenuates cardiac hypertrophy and blocks TGF- $\beta$ 1-mediated MAPK signaling events. The authors reported that 2.5–30  $\mu$ M of asiatic acid significantly reduced TGF- $\beta$ 1-induced increased cardiomyocyte surface area and ANP mRNA expression, concomitant with the inhibition of p38 and ERK phosphorylation, as well as NF- $\kappa$ B binding activity [34]. Other researchers have also demonstrated that asiatic acid attenuates myocardial hypertrophy stimulated by IL-1 $\beta$  [33]. Besides, 20  $\mu$ M of asiatic acid was found to inhibit hypertrophic responses induced by angiotensin II in cardiomyocytes by activating AMPK $\alpha$  and blocking mTOR and ERK pathways [32]. Using an *in vitro* model of ischemia-reperfusion injury, Huang et al. reported that asiatic acid protects H9c2 rat cardiomyocytes from oxygen-glucose deprivation/reoxygenation injury through an activation of the Akt/GSK-3 $\beta$ /HIF-1 $\alpha$  pathway [31]. Furthermore, the authors showed that 10  $\mu$ M of asiatic acid prevented cell apoptosis and reduced activities of caspase-3

► **Table 1** Cardioprotective effects of *C. asiatica* and its triterpenoids.

Model	Extract/compound	Effect/mechanism	Reference
<i>In vitro</i>	Asiatic acid	Prevents cardiomyocyte hypertrophic response induced by TGF- $\beta$ 1	[34]
	Asiatic acid	Inhibits cardiomyocyte hypertrophic response stimulated by IL-1 $\beta$	[33]
	Asiatic acid	Attenuates angiotensin II-induced hypertrophy of cardiac myocytes and accumulation of collagen in cardiac fibroblasts	[32]
	Asiatic acid	Protects H9c2 rat cardiomyocytes from oxygen-glucose deprivation/reoxygenation injury	[31]
<i>In vivo</i>	Aqueous extract	Attenuates increased serum myocardial marker enzymes in cardiomyopathy rats	[35]
	Asiatic acid	Prevents cardiac hypertrophy and fibrosis in pressure overload-induced mice	[32]
	Asiatic acid	Prevents cardiac hypertrophy and dysfunction in pressure overload-induced mice	[34]
	Asiatic acid	Improves cardiac function and inhibits cardiac hypertrophy and left ventricular remodeling following coronary artery ligation-induced myocardial infarction	[36]
	Madecassoside	Decreases ischemia-reperfusion injury-induced myocardial infarction	[37]
	Madecassoside	Reduces plasma TNF- $\alpha$ levels, prevents hypotension and tachycardia in LPS-induced rats	[38]

and caspase-9 as well as Bax/Bcl-2 ratio in oxygen-glucose deprivation/reoxygenation-induced H9c2 cardiomyocytes. In addition, asiatic acid also attenuates mitochondrial dysfunction by suppressing ROS overproduction and intracellular Ca<sup>2+</sup> levels as well as enhancing mitochondria membrane potential [31].

Cardioprotective effects of *C. asiatica* have also been demonstrated using *in vivo* models. A previous study showed that oral administration with 200 mg/kg of *C. asiatica* aqueous extract attenuated increased activities of cardiac marker enzymes such as lactate dehydrogenase, creatine phosphokinase, glutamate oxaloacetate transaminase, and glutamate pyruvate transaminase in adriamycin-induced rats [35]. Furthermore, the authors also reported that *C. asiatica* extract enhanced activities of antioxidant enzymes, including total reduced GSH, glutathione-S-transferase, GPX, and SOD, in the heart tissue of adriamycin-induced rats. These data imply that asiatic acid improves cardiac function and enhances antioxidant defense mechanisms of the cardiotoxic agents-treated rat myocardium.

In addition to the cardioprotective effects of *C. asiatica* extracts, triterpenes of *C. asiatica* have also been shown to possess beneficial effects in cardiac injury. Ma et al. reported that 10 and 30 mg/kg asiatic acid administered orally for 7 wk prevented pressure overload-induced cardiac hypertrophy and fibrosis in mice through activation of AMPK $\alpha$  and inhibition of ERK and mTOR [32]. By using a pharmacological inhibitor of AMPK $\alpha$  and AMPK $\alpha$ -knockout mice models, they also demonstrated that AMPK $\alpha$  inhibition ablates the cardioprotective effects of asiatic acid. A previous study demonstrated that oral administration of asiatic acid at daily doses of 100 mg/kg for 2 wk attenuated cardiac hypertrophy and cardiac dysfunction in TAC-induced mice. Asiatic acid was also found to decrease expressions of ANP and TGF- $\beta$ 1 in hypertrophic myocardium of the mice. In terms of molecular pathways, asiatic acid blocks p38 and ERK1/2 phosphorylation, as well as NF- $\kappa$ B activation *in vivo* [34]. Researchers also showed that oral administration of 25 mg/kg of asiatic acid improved cardiac dysfunction and alleviated left ventricular remodeling in rat myocardial infarction model, as evidenced by a marked reduction in cardiac hypertrophy and interstitial fibrosis in the infarct border zone

[36]. Furthermore, the authors also demonstrated that asiatic acid reduces inflammatory cytokine levels such as TGF- $\beta$ 1 and TNF- $\alpha$  and downregulates NF- $\kappa$ B levels as well as attenuates p38 MAPK and ERK1/2 phosphorylation [36]. *In vivo* experimental approaches also showed that 2-h reperfusion with 50 mg/kg of madecassoside protected against ischemia-reperfusion-injury-induced myocardial infarction in Wistar rats through reduction of lipid peroxidation, inflammatory and apoptotic markers [37]. Intragastric administration of 20 mg/kg of madecassoside for 5 d has also been reported to reduce elevated plasma TNF- $\alpha$  levels, delay the fall of mean arterial pressure and diminish tachycardia in LPS-stimulated rats [38]. On top of that, the authors also showed that madecassoside inhibits LPS-induced increased TNF- $\alpha$  levels and NF- $\kappa$ B, ERK, and p38 MAPK activation in neonatal rat cardiomyocytes [38].

### Anti-Atherosclerotic Effects of *C. asiatica* and Its Triterpenes

Atherosclerosis, an underlying pathology of coronary heart diseases, is a chronic inflammatory disease [39]. In the early stage of atherosclerosis, various types of pro-inflammatory mediators, including ox-LDL and cytokines, impair endothelial function, which in turn causes an increase in endothelial permeability and overexpression of cell adhesion molecules on the apical surface of endothelial cells. These subsequently cause a remarkable increase in adhesion and migration of leukocytes across the endothelium. Among all types of leukocytes, mononuclear monocytes play crucial roles in initiating the formation of atherosclerotic lesions. The adhered monocytes migrate into the intima and differentiate into macrophages that are capable to engulf and oxidize lipids. Accumulation of cytoplasmic lipids in these macrophages results in the formation of foam cells, which serve as a hallmark of early atherosclerotic lesion formation [40].

Antithrombotic effect of 10 active compounds isolated from *C. asiatica* was evaluated by subjecting blood collected from rat abdominal aorta to haemostatology, in which platelet reactivity

► **Table 2** Anti-atherosclerotic effects of *C. asiatica* and its triterpenoids.

Model	Extract/compound	Effect/mechanism	Reference
<i>Ex vivo</i>	3,5-di-O-caffeoylquinic acid	Shows antithrombotic and inhibitory effects on platelet reactivity	[41]
Clinical study	Standardized leaf extract in combination with pine bark extract	Stabilizes plaque density in carotid and femoral arteries	[42]
	Total triterpenic fraction	Prevents the progression of atherosclerotic plaques	[43, 44]

► **Table 3** Antihypertensive effects of *C. asiatica* and its triterpenoids.

Model	Extract/compound	Effect/mechanism	Reference
<i>In vivo</i>	Asiatic acid	Improves alteration of the hemodynamics in 2K-1C hypertensive rats	[50]
	Asiatic acid	Reduces blood pressure by improving NO bioavailability in L-NAME-induced hypertensive rats	[51]
	Asiatic acid	Improves hemodynamic abnormalities such as increased blood pressure, heart rate, and hind-limb vascular resistance in high carbohydrate, high-fat-diet-induced metabolic syndrome rats	[52]
	Asiatic acid	Reduces blood pressure by decreasing renin angiotensin overactivity, sympathetic nerve overactivity and improving vascular function in high-carbohydrate and high-fat-diet-induced metabolic syndrome rats	[53]
	Asiaticoside	Reduces systemic blood pressure in hypoxia-induced pulmonary hypertensive rat	[54]
	Asiaticoside	Inhibits raised blood pressure and improves impaired production of NO and cGMP in hypoxia-induced pulmonary hypertensive rat	[55]
Clinical study	TTFCA	Decreases ankle edema by reducing capillary filtration rate	[56]
	TTFCA	Improves microcirculation and capillary permeability in patients with venous hypertension	[57]

and dynamic blood coagulation were measured *ex vivo* (► **Table 2**) [41]. Based on the findings from haemostatometry, Satake et al. reported that only 3,5-di-O-caffeoylquinic acid showed a potential antithrombotic effect. A previous clinical study has reported that *C. asiatica* supplemented with Pycnogenol (pine bark extract) stabilizes the plaque density in the carotid and femoral arteries of asymptomatic subjects by improving plaque echogenicity. The subjects were supplemented with Pycnogenol, at daily doses of 150 mg, and Centellicum (standardized *C. asiatica* leaf extract) at daily doses of 450 mg, for a duration of 6 mo [42]. Other clinical studies have also shown that administration of TTFCA supplemented with Pycnogenol reduces the progression of arterial plaque formation in asymptomatic patients, which is associated with a decrease in oxidative stress [43, 44].

## Antihypertensive Effects of *C. asiatica* and Its Triterpenes

Hypertension is a condition of persistent elevation of systolic or diastolic blood pressure over a baseline level. According to hypertension clinical guidelines published by the American Heart Association in 2018, normal blood pressure level is defined as 119/79 mmHg or below while stage 1 hypertension is now defined as a blood pressure level equivalent to or above 130/80 mmHg [45]. The role of hypertension as one of the risk factors of cardiovascular diseases has been thoroughly investigated in the past decade and its association with cardiovascular diseases is now well established. A Framingham heart study conducted in 1961 suggested

that elevated blood pressure increases the prevalence of coronary heart disease in men and women by 2.6 and 6 folds, respectively [46]. A meta-analysis showed that lowering blood pressure causes a significant reduction in the risk of cardiovascular diseases and mortality [47]. It is well accepted that mechanisms such as sympathetic nervous system hyperactivity, renin-angiotensin-aldosterone system activation, and endothelial dysfunction may result in impairment of NO production, which are involved in the pathogenesis of hypertension [48]. Increased oxidative stress has also been proposed as a mechanism that triggers endothelial dysfunction in hypertension [49].

Asiatic acid has been demonstrated to exhibit antihypertensive effects in 2K-1C renovascular hypertensive rats, where intragastric administration of 30 mg/kg/d of asiatic acid for 4 wk normalized the increased mean arterial blood pressure and heart rate of the rats (► **Table 3**) [50]. They also reported that asiatic acid attenuates renin-angiotensin system activation, overproduction of oxidative stress markers including superoxide anion ( $O_2^-$ ) and MDA, elevated gp91<sup>phox</sup> and TNF- $\alpha$  levels, and NF- $\kappa$ B protein overexpression [50]. Another study showed that oral administration of asiatic acid at daily doses of 10–20 mg/kg for 2 wk enhanced hemodynamic status and re-established vascular function in L-NAME-induced hypertensive rats by increasing NO bioavailability [51]. Pakdeechote et al. reported that intragastric administration of asiatic acid for 3 wk restores metabolic and hemodynamic abnormalities in rats by ameliorating insulin resistance, dyslipidemia, and hypertension and also suppresses excessive release of oxidative stress markers and upregulated NOS expression [52]. In agreement with these findings, asiatic acid administered orally at



► **Table 4** Antihyperlipidemic effects of *C. asiatica* and its triterpenoids.

Model	Extract/compound	Effect/mechanism	Reference
<i>In vivo</i>	Water extract	Enhances hepatic structure, reduces lipid accumulation in hepatocytes and lowers serum lipid levels in high cholesterol-fed rats	[63]
	Fraction of ethanol extract	Reduces total cholesterol, triglyceride and LDL levels in hyperlipidemic mice and golden hamsters	[64]
	Methanol extract	Reduces serum triglyceride levels in streptozotocin-induced diabetic rats	[65]
	Ethanol extract of <i>C. asiatica</i> in combination with <i>F. nilgerrensis</i> ethanol extract	Reduces lipid profile in serum and fatty acid deposition in hyperlipidemic rats	[66]
	Asiatic acid	Improves plasma lipid profile, increases activities of lecithin cholesterol acyltransferase and lipoprotein lipase and decreases HMG-CoA reductase activity in streptozotocin-induced diabetic rats	[67]
	Asiatic acid	Improves plasma lipid profile and altered gene and protein expression of lipid metabolism enzymes in high fat diet-fed rats	[68]
<i>In silico</i>	Asiatic acid	Shows good interaction and affinity towards the HMG-CoA active site	[67]

daily doses of 20 mg/kg for 3 wk has also been shown to improve hypertension and tachycardia, renin-angiotensin system activation, sympathetic nerve hyperactivity, and other metabolic parameters, including total cholesterol, blood glucose and insulin levels. In addition, asiatic acid also improves vascular function in rats [53].

Prophylactic effects of asiaticoside was demonstrated by Wang et al. where intragastric administration of asiaticoside at daily doses of 50 mg/kg for 4 wk diminished elevated mean pulmonary artery pressure, cardiac hypertrophy and pulmonary vascular remodeling in hypoxia-induced pulmonary hypertension [54]. Using real-time quantitative polymerase chain reaction and western blotting, asiaticoside was found to decrease the expression of TGF- $\beta$ 1, TGF- $\beta$  receptor, Smad2/3, and phosphorylated Smad2/3 in the lungs of hypoxic rats. In addition, these authors also demonstrated therapeutic effects of asiaticoside on hypoxia-induced pulmonary hypertension in rats. A recent study also reported that asiaticoside restores blood pressure, improves impaired NO production and cGMP secretion and suppresses increased plasma endothelin-1 levels in established pulmonary hypertension [55].

Venous hypertension causes an increase in blood flow and a reduction in veno-arteriolar reflex, leading to foot and ankle edema. Daily treatment with 90 mg or 180 mg of TTFCA for 4 wk was shown to decrease ankle edema by reducing capillary filtration rate in patients with venous hypertension compared to placebo [56]. Another study has shown that treatment with TTFCA at 180 mg once daily for 2 wk improved microcirculation and capillary permeability in patients with moderate and serious venous hypertension [57].

## Antihyperlipidemic Effects of *C. asiatica* and Its Triterpenes

Hyperlipidemia is one of the major risk factors for cardiovascular diseases [58]. Apart from total plasma cholesterol and triglyceride levels, the level of lipoproteins such as chylomicrons, VLDL, LDL, and HDL is also a reflection of the amount of plasma lipids due to

the fact that lipids are transported by lipoproteins in the blood. An elevated plasma cholesterol level, particularly due to increased LDL levels, has been linked to most of the pathological effects caused by hyperlipidemia. Effects of LDL on endothelial function has been reviewed in depth previously [59]. ox-LDL has also been shown to increase endothelin production, which causes abnormal coronary vasomotion [60]. On the other hand, HDL mediate reverse cholesterol transport, a mechanism by which excess cholesterol is removed from body cells and transported to the liver for elimination from the body. Hence, novel therapeutic approaches focusing on raising HDL-cholesterol levels are being intensively investigated in the past decade [61]. Currently, the primary target and first-line therapy for hyperlipidemia is lowering of plasma LDL cholesterol levels [62] using statins or inhibitors of HMG-CoA reductase, which is a rate-limiting enzyme in the cholesterol synthesis pathway.

There is evidence from several *in vivo* studies that demonstrates antihyperlipidemic properties of *C. asiatica* (► **Table 4**). Oral administration of *C. asiatica* leaf extract prevents lipid droplet accumulation in rat hepatocytes and reduces serum lipid levels in high cholesterol-fed rats [63]. Intragastric administration of a fraction of *C. asiatica* ethanol extract has also been found to improve serum lipid profiles of hyperlipidemic mice and golden hamsters, in addition to its capability of enhancing reverse cholesterol transport [64]. These findings are consistent with other study reporting that streptozotocin-induced diabetic rats treated with *C. asiatica* methanol extract showed a reduction of plasma triglyceride concentrations compared to diabetic rats that did not receive any treatment [65]. Moreover, combination of *C. asiatica* and *Fragaria nilgerrensis* (Rosaceae) ethanol extracts significantly decreased serum lipid profile, prevented hepatic fat deposition and reduced lipid peroxidation in high-fat diet-induced rats [66]. Ramachandran et al. provided convincing evidence that an oral administration of 20 mg/kg of asiatic acid had a beneficial effect in normalizing total cholesterol, triglyceride, LDL, VLDL, free fatty acid, and phospholipid levels in experimental animal models of diabetes [67]. The authors also reported that activities of lipid metabolizing enzymes such as lecithin cholesterol acyltransferase

► **Table 5** Antihyperglycemic effects of *C. asiatica* and its triterpenoids.

Model	Extract/compound	Effect/mechanism	Reference
<i>In vivo</i>	Ethanol extract	Lowers fasting blood glucose levels, improves glucose tolerance, decreases intestinal glucose absorption, and suppresses activities of carbohydrate-digesting enzymes in streptozotocin-induced diabetic rats	[72]
	Asiatic acid	Reduces blood glucose and insulin levels as well as islet fibrosis in Goto-Kakizaki rats	[73]
	Asiatic acid	Protects against diabetic nephropathy in rats via inhibition of oxidative stress and the JNK signaling pathway	[74]
	Asiatic acid	Normalizes plasma glucose and insulin levels in streptozotocin-induced diabetic rats	[67]
	Asiatic acid	Prevents increased activities of glucose-6-phosphatase and fructose-1,6-bisphosphatase of carbohydrate metabolism in streptozotocin-induced diabetic rats	[75]

and lipoprotein lipase were increased by asiatic acid, whereas activity of HMG-CoA reductase was decreased upon asiatic acid treatment. In rats fed with high fat diet, asiatic acid has been demonstrated to exert anti-obesity activity by lowering body weight gain, plasma lipid levels, and expression of lipid-metabolizing enzymes [68]. By using an *in silico* molecular docking study, asiatic acid was found to have a high affinity for the binding site of HMG-CoA reductase, suggesting that asiatic acid is a specific inhibitor of HMG-CoA reductase [67]. To date, among the 4 major triterpenoids derived from *C. asiatica*, only asiatic acid has been shown to possess lipid-lowering effects in several high fat diet-induced animal models. Therefore, future investigations should focus on assessing hypolipidemic activities of asiaticoside, madecassoside, and madecassic acid.

## Antidiabetic Effects of *C. asiatica* and Its Triterpenes

Diabetes mellitus is a group of metabolic disorders characterized by chronic hyperglycemia resulting from abnormal blood glucose regulation. Patients with type 1 diabetes, as a result of insufficient insulin production due to destruction of the pancreatic islet cells, are at higher risks of developing cardiovascular diseases compared to nondiabetic patients [69]. In type 2 diabetes, insulin resistance occurs where the body cells respond poorly to insulin and this causes a persistent increase in blood glucose and insulin levels. Diabetes has been shown to associate with rapid progression of atherosclerosis, as evidenced in diabetic patients exhibiting a greater percent of atheroma volume and a smaller size of coronary artery lumen, compared to nondiabetic individuals [70]. In terms of pathogenesis of diabetes, numerous mechanisms have been proposed, of which vascular changes resulting from hyperglycemia play predominant roles. The roles of endothelial dysfunction, vascular inflammation, increased oxidative stress, arterial calcification, and hypercoagulability in pathophysiology of diabetes have been thoroughly discussed elsewhere [71].

A number of *in vivo* studies have demonstrated the antihyperglycemic activity of *C. asiatica* (► **Table 5**). Kabir et al. has reported that *C. asiatica* ethanol extract decreases intestinal glucose absorption in type 2 diabetic rats and reduces breakdown of carbohydrates through inhibition of  $\alpha$ -amylase and intestinal disaccha-

ridase activities [72]. The authors also demonstrated that oral administration of 1000 mg/kg of *C. asiatica* ethanol extract for 28 d lowers fasting blood glucose levels and improves glucose tolerance in streptozotocin-induced type 2 diabetic rats, but the extract does not alter plasma insulin levels [72]. Furthermore, effects of *C. asiatica* on organ weights and food habits of the rats following chronic administration of *C. asiatica* extract have also been examined, where food intake, water intake and body weight of the rats were significantly decreased. This might be attributed to the high doses used in the study. In contrast to the findings reported by Kabir et al., a previous study found that asiatic acid lowers blood glucose and insulin levels as well as fibrosis of pancreatic islets in Goto-Kakizaki rats, which is a spontaneous type 2 diabetes animal model [73]. Wang's findings are also controversial to the study reported by Ramachandran et al., in which asiatic acid decreases glucose levels but increases insulin levels in diabetic rats [67]. Taken together, it is clear that *C. asiatica* and its active constituents differently alter plasma insulin levels. Hence, antihyperglycemic activity of *C. asiatica* may not correlate with regulation of plasma insulin concentration.

Moreover, a recent study showed that 10, 20, and 40 mg/kg of asiatic acid, administered via oral gavage for 8 wk, protected against diabetic nephropathy in rats via inhibition of oxidative stress and the JNK signaling pathway [74]. A previous study also reported that intragastric administration of asiatic acid suppresses not only elevated plasma glucose and glycosylated hemoglobin levels but also suppresses increased activities of carbohydrate-metabolizing enzymes such as glucose-6-phosphatase and fructose-1,6-bisphosphatase in diabetic rats [75].

## Antioxidant Effects of *C. asiatica* and Its Triterpenes

Oxidative stress is one of the contributors for pathological diseases such as cancer, pulmonary diseases and cardiovascular diseases [76]. It occurs when there is an imbalance between ROS production and antioxidant systems [76]. ROS are by-products of cellular metabolism which are derived from oxygen molecules ( $O_2$ ). The major types of ROS include NO, hydrogen peroxide ( $H_2O_2$ ), hydroxyl radicals ( $\cdot OH$ ), and  $O_2^-$  [77]. In physiological conditions, antioxidant systems, which include enzymatic and nonen-

► **Table 6** Antioxidant effects of *C. asiatica* and its triterpenoids.

Model	Extract/compound	Effect/mechanism	Reference
<i>In vitro</i>	Aqueous extract	Scavenges DPPH free radicals	[80]
	Water extract	Scavenges free radicals such as DPPH, ABTS <sup>+</sup> , H <sub>2</sub> O <sub>2</sub> , and NO, elevates SOD and GSH levels, and inhibits lipid peroxidation	[63]
	Water infusion	Possesses DPPH scavenging activity and ability to reduce Fe <sup>3+</sup>	[20]
	Methanol extract	Possesses total antioxidant and DPPH scavenging activities	[79]
	Methanol extract and triterpene fractions	Shows radical scavenging activities in ABTS, DPPH, NO, peroxy nitrite radical absorbance capacity and oxygen radical absorbance capacity assays	[83]
	50% methanol:water extract	Inhibits auto-oxidation of $\beta$ -carotene and linoleic acid	[81]
	Madecassoside	Reduces H <sub>2</sub> O <sub>2</sub> -induced injury and apoptosis in human umbilical vein endothelial cells	[82]
<i>In vivo</i>	Methanol extract and triterpene fractions	Decreases elevated MDA levels, increases reduced GSH levels and SOD activity in cerebral cortex and hippocampus of scopolamine-induced Wistar rats	[83]
	Asiatic acid	Reduces increased plasma O <sub>2</sub> <sup>-</sup> , MDA, nitrate and nitrite levels as well as restores altered eNOS expression in high carbohydrate, high fat diet-induced metabolic syndrome rats	[52]

zymatic antioxidants, can counterbalance oxidative stress by scavenging free radicals including ROS [78]. The major enzymatic antioxidants include SOD, CAT, and GPX while nonenzymatic antioxidants are vitamins C and E, GSH, and  $\beta$ -carotene [76]. In the vascular wall, several enzymes such as NADPH oxidase, xanthine oxidase, uncoupled endothelial NOS (eNOS), and mitochondria respiratory chain catalyze the reduction of O<sub>2</sub> to O<sub>2</sub><sup>-</sup>. O<sub>2</sub><sup>-</sup> can react with NO to form peroxy nitrite that in turn affects vascular cells directly or it can be converted to H<sub>2</sub>O<sub>2</sub> by SOD. CAT and GPx further convert H<sub>2</sub>O<sub>2</sub> to H<sub>2</sub>O and O<sub>2</sub>. In the presence of iron, the extremely reactive  $\cdot$ OH can be spontaneously produced from H<sub>2</sub>O<sub>2</sub>.

A number of studies have shown that aqueous extract, methanol extract and water infusion of *C. asiatica* possess antioxidant effects (► **Table 6**) [20, 63, 79, 80]. The aqueous extract of *C. asiatica* showed a potent DPPH scavenging activity with IC<sub>50</sub> values of 31.25  $\mu$ g/mL [80] and 9.62  $\mu$ g/mL [63]. Moreover, it has been reported that *C. asiatica* tea infused at 100 °C for 10 min possessed highest antioxidant capacity [20]. On top of that, the total antioxidant activity of *C. asiatica* methanolic extract was found to be 623.78  $\mu$ mol of ascorbic acid/g of sample and the IC<sub>50</sub> values assessed using DPPH assay was 19.89 mg/mL [79]. A previous study showed that 50% methanol:water extract of *C. asiatica* exhibits antioxidant activity with a total phenolic content of 23.1 mg/g [81]. *C. asiatica* aqueous extract also inhibits lipid peroxidation and the increased SOD and GSH levels [63]. Bian et al. also showed that madecassoside reduces lipid peroxidation and apoptosis via inhibition of caspase-3 and p38 MAPK activation [82].

A recent study showed that the highest antioxidant activity was exhibited by methanol extract of *C. asiatica*, followed by triterpene-free fraction of *C. asiatica* and then triterpene-enriched fraction of *C. asiatica* [83]. The authors used several biochemical antioxidant assays include ABTS, DPPH, NO radical scavenging assays, peroxy nitrite radical absorbance capacity, and oxygen radical absorbance capacity assays. In addition, they also investigated *in vivo* antioxidant capability of *C. asiatica* methanol extract using male Wistar rats. Oxidative stress parameters such as lipid peroxidation estimation, GSH levels, and SOD activity in the brain homogenate

were measured. The *in vivo* antioxidant activities of *C. asiatica* were corresponded to the *in vitro* data obtained from the biochemical antioxidant assays [83]. Furthermore, a previous study also showed that asiatic acid reduces oxidative stress markers including O<sub>2</sub><sup>-</sup> production, plasma NO metabolites, and upregulated iNOS/eNOS protein expression in high-carbohydrate, high-fat diet-induced metabolic syndrome rats [52].

## Anti-Inflammatory Effects of *C. asiatica* and Its Triterpenes

Inflammation plays an important role in the pathogenesis of cardiovascular diseases. Hence, treatments targeting inflammatory events may be a promising intervention to attenuate the development of cardiovascular diseases [84]. Pro-inflammatory stimuli including cytokines (IL and TNF- $\alpha$ ) and endotoxin (LPS) bind to their respective membrane receptors and stimulate the release or synthesis of many pro-inflammatory mediators such as prostaglandins, COX, nitric oxide and inducible NOS (iNOS). COX are key enzymes that catalyze the synthesis of prostaglandins from arachidonic acid. COX-1 is constitutively expressed in many cell types while COX-2 expression is highly inducible in response to pro-inflammatory stimuli. It has been reported that LPS modulates the inflammatory responses by recruiting myeloid differentiation primary response protein 88 at the plasma membrane and causing a subsequent activation of several signaling cascades such as the p38, ERK, and JNK pathways [85]. Besides, NF- $\kappa$ B is a key player in the inflammatory response, and upon activation, NF- $\kappa$ B upregulates transcription of a broad range of pro-inflammatory genes, which in turn results in excessive production of various pro-inflammatory mediators.

Anti-inflammatory activities of *C. asiatica* and its bioactive constituents, as well as the underlying mechanisms involved, have been elucidated in numerous preclinical studies (► **Table 7**). *In vivo* studies have shown that methanol and ethanol extracts of *C. asiatica* reduce paw edema volume of rats induced by carra-



► **Table 7** Anti-inflammatory effects of *C. asiatica* and its triterpenoids.

Model	Extract/compound	Effect/mechanism	Reference
<i>In vivo</i>	Aqueous and ethanol extracts	Reduces edema volume in carrageenan-induced paw edema model in rats	[86]
	Methanol extract	Attenuates carrageenan-induced paw edema in rats	[87]
	Asiatic acid	Decreases levels of inflammatory markers such as NO, TNF- $\alpha$ , IL-1 $\beta$ , iNOS, COX-2, and NF- $\kappa$ B in carrageenan-induced paw edema model in mice	[88]
	Asiatic acid	Decreases TNF- $\alpha$ production and iNOS expression in high carbohydrate, high fat diet-induced metabolic syndrome rats	[52]
	Asiatic acid	Prevents cisplatin-induced acute kidney injury by suppressing production of pro-inflammatory cytokines and deactivating NF- $\kappa$ B	[89]

► **Table 8** Effects of *C. asiatica* and its triterpenoids on pro-inflammatory mediators.

Model	Extract/compound	Effect/mechanism	Reference
<i>In vitro</i>	Freeze-dried extract	Reduces monocyte adhesion to HUVEC and protein expression of VCAM-1 and ICAM-1	[97]
	Asiatic acid	Suppresses increased expression of soluble VCAM-1, ICAM-1, PECAM-1, and E-selectin in TNF- $\alpha$ -induced HAEC	[99]
	Asiatic acid	Protects endothelial barrier function by preserving adherens junctions and preventing tight junction redistribution in TNF- $\alpha$ -induced HAEC	[100]
	Asiatic acid	Inhibits production of NO, PGE <sub>2</sub> , IL-6, IL-1 $\beta$ , TNF- $\alpha$ and suppresses iNOS and COX-2 expressions as well as NF- $\kappa$ B activation in LPS-induced RAW264.7 cells	[103]
	Asiaticoside	Attenuates endothelial hyperpermeability and F-actin rearrangement in TNF- $\alpha$ -induced HAEC	[98]
	Asiaticoside	Inhibits endothelial hyperpermeability and increased adhesion molecule expressions in ox-LDL-induced HUVEC	[101]
	Asiaticoside G	Decreases NO and TNF- $\alpha$ secretion in LPS-induced RAW264.7 cells	[102]
	Madecassic acid	Attenuates elevated NO, PGE <sub>2</sub> , TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 levels, suppresses increased iNOS and COX-2 expressions and downregulates NF- $\kappa$ B activation in LPS-induced RAW264.7 cells	[104]
	Madecassoside	Inhibits elevated NO, PGE <sub>2</sub> , TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 levels in LPS-induced RAW264.7 cells	[104]
	Madecassoside	Inhibits TNF- $\alpha$ production, NF- $\kappa$ B activation and phosphorylation of ERK1/2 and p38 in LPS-stimulated neonatal rat cardiomyocytes	[38]

geenan [86, 87]. Huang et al. also showed that intraperitoneal injection of asiatic acid in the hind paw of mice decreases serum NO, TNF- $\alpha$  and IL-1 $\beta$  levels, MDA level, and iNOS, COX-2, and NF- $\kappa$ B expression in a mouse paw edema model [88]. A recent study reported that the protective effects of asiatic acid against cisplatin-induced kidney injury is attributed to its anti-inflammatory and anti-apoptotic actions, where intraperitoneal administration of 50 mg/kg and 100 mg/kg of asiatic acid improved renal functions, reduced number of apoptotic cells, inhibited mRNA expressions of proinflammatory cytokines including TNF- $\alpha$  and IL-1 $\beta$ , and suppressed NF- $\kappa$ B activation in C57BL/6 mice. The authors proposed that the anti-inflammatory effects exerted by asiatic acid may be partially associated with Smad-7 upregulation [89].

### Inhibitory Effects of *C. asiatica* and Its Triterpenoids on Pro-Inflammatory Mediators

Several studies have been performed on cultured cell lines to evaluate effects of *C. asiatica* and its triterpenoids on cellular events of inflammation induced by TNF- $\alpha$ , ox-LDL, and LPS (► **Table 8**). TNF- $\alpha$ , a pro-inflammatory cytokine with pleiotropic roles, is released by many cell types such as macrophages, endothelial cells, fibroblasts, and cardiomyocytes during inflammation. Given its major role in the regulation of inflammatory responses, TNF- $\alpha$  is implicated in many chronic inflammatory diseases such as rheumatoid arthritis, inflammatory bowel disease, and atherosclerosis. In ApoE-knockout mice, abrogation of TNF- $\alpha$  production attenuates the development of atherosclerotic lesions [90, 91]. TNF- $\alpha$  has been shown to increase expression of ICAM-1, VCAM-1, and monocyte chemoattractant protein-1 (MCP-1) in the aorta of ApoE-knockout mice as well as macrophage uptake of ox-LDL [92]. Other than these early atherogenic events, TNF- $\alpha$  has also

been demonstrated to trigger the formation of advanced atherosclerotic plaques [93], which implies the crucial role of this cytokine in the late stage of atherogenesis.

One of the early atherogenic events is oxidization of LDL in the subendothelial space, which subsequently activates endothelial cells by upregulating expression of cell adhesion molecules and increasing monocyte adhesion and migration [94]. Monocytes migrate into the intima layer of the endothelium and differentiate into macrophages, which in turn engulf ox-LDL and cell debris, and ultimately transform into lipid-laden foam cells. ox-LDL acts by binding to its major receptor, lectin-like ox-LDL receptor-1 (LOX-1), which is highly expressed in atherosclerosis, hypertension, diabetes, and heart failure [95].

LPS is a crucial membrane component of Gram-negative bacteria, which provides structural integrity and contributes to the activity of bacterial endotoxin. Mammalian monocytes or macrophages are able to detect Gram-negative infection rapidly by recognizing LPS via Toll-like receptors. Upon binding with the receptors, LPS elicits a strong host inflammatory response that involves the secretion of a wide variety of pro-inflammatory mediators such as TNF- $\alpha$ , IL-1 $\beta$ , and IL-6, and upregulation of expression of enzymes including iNOS and COX-2. LPS also increases ICAM-1 expression via enhancement of RhoA activity and activation of p38 and NF- $\kappa$ B [96].

The beneficial effects of *C. asiatica* and its bioactive constituents in TNF- $\alpha$ - and ox-LDL-induced endothelial activation have been reported (► **Table 8**). In a previous study, *C. asiatica* freeze-dried extract at a dosage of 25  $\mu$ g/mL significantly reduced the protein expression of total and membrane VCAM-1 and ICAM-1, in both normal and gestational diabetic HUVEC stimulated with TNF- $\alpha$ , and this was associated with inhibition of p44/42 MAPK and NF- $\kappa$ B pathways. In addition, 25  $\mu$ g/mL of *C. asiatica* freeze-dried extract also suppressed increased U937 monocyte adhesion elicited by TNF- $\alpha$ . Interestingly, a combination of 10  $\mu$ g/mL of *C. asiatica* extract and 0.1 mM of lipoic acid showed enhanced inhibitory effects, compared to *C. asiatica* extract alone [97]. Fong et al. demonstrated that 25  $\mu$ M and 50  $\mu$ M of asiaticoside significantly attenuated both TNF- $\alpha$ -induced F-actin redistribution and increased permeability of HAEC, as evidenced by the data obtained from immunofluorescent staining and fluorescein isothiocyanate-dextran *in vitro* vascular permeability assay [98]. Following the use of an actin-depolymerizing agent, the authors proposed that the barrier protective effect of asiaticoside does not act through stabilization of F-actin filaments.

Moreover, asiatic acid also attenuates TNF- $\alpha$ -stimulated HAEC activation by suppressing endothelial hyperpermeability and increased expression of soluble VCAM-1, ICAM-1, PECAM-1, and E-selectin [99]. A further mechanistic study on asiatic acid revealed that its barrier protective effect is associated with stabilization of F-actin and diphospho-myosin light chain, preservation of VE-cadherin and  $\beta$ -catenin organization, and prevention of tight junction disassembly [100]. Consistent with these findings, a similar study reported by Jing et al. also showed that asiaticoside protects against endothelial hyperpermeability and inhibits increased expression of adhesion molecules in HUVEC [101].

Previous *in vitro* studies have also shown that triterpenes of *C. asiatica* attenuate release of inflammatory markers elicited by

LPS in several cell lines [38, 102–104]. Inhibition of iNOS, COX-2, IL-6, IL-1 $\beta$ , and TNF- $\alpha$  expressions by asiatic acid in LPS-induced RAW 264.7 cells might be associated with a downregulation of NF- $\kappa$ B activation, and the latter is associated with an abrogation of I $\kappa$ B- $\alpha$  degradation and suppression of nuclear p65 and p50 protein levels [103]. Besides, asiaticoside G has been reported to decrease NO and TNF- $\alpha$  production in LPS-stimulated RAW 264.7 cells [102]. Furthermore, madecassic acid was found to inhibit iNOS, COX-2, TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 via the suppression of NF- $\kappa$ B activation [104] and madecassoside has been reported to attenuate TNF- $\alpha$  production through inhibition of ERK1/2, p38 MAPK and NF- $\kappa$ B pathways in LPS-stimulated neonatal rat cardiomyocytes [38].

## Conclusion

*C. asiatica* is a useful medicinal plant with many potential pharmacological activities. Accumulating evidence from *in vivo* and clinical studies suggested that *C. asiatica* protects against cardiovascular diseases and their related conditions. The mechanisms underlying the cardiovascular protective effects of *C. asiatica* and its triterpenoids have also been revealed using *in vitro* and *in silico* models. Various extracts and compounds isolated from *C. asiatica* have been demonstrated to reduce the occurrence of cardiac hypertrophy, myocardial ischemia, atherosclerosis, hypertension, hyperlipidemia, hyperglycemia, diabetes, oxidative stress, and inflammation. The most widely studied extracts of *C. asiatica* for cardiovascular diseases are aqueous and alcoholic extracts. Among the triterpenes of *C. asiatica*, asiatic acid is the most extensively studied compound followed by asiaticoside and madecassoside. Madecassic acid, however, is the least reported triterpenoid, despite the fact that its therapeutic effects have been reported in a few studies. Therefore, pharmacological activity of madecassic acid should be investigated in detail in the future. While some studies have elucidated the molecular mechanisms underlying the cardiovascular protective effects of *C. asiatica*, more clinical and pharmacokinetic studies are still needed to justify the use of *C. asiatica* and its triterpenes as a therapeutic agent.

## Methodology

A comprehensive literature search was performed for articles published between 1986 and August 2018. The information was retrieved from electronic databases such as PubMed, Google Scholar, ClinicalKey, Science Direct, Springer, and EBSCOhost. Search keywords used were “*Centella asiatica*”, “asiatic acid”, “madecassic acid”, “asiaticoside”, or “madecassoside”. The articles published from 2004 to 2018 were screened, of which articles that reported protective effects of both *C. asiatica* and its active constituents against cardiovascular diseases and conditions leading to these diseases were selected and reviewed thoroughly. A few clinical studies published beyond this period were also included. Original articles and review articles published as full paper, but not abstract, were included in the selection. Review articles on other areas, such as neurology and dermatology, and not written in English were excluded.

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## Conflict of Interest

The authors declare that they have no conflict of interest.

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