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A systematic review on the chemical constituents of *Centella asiatica*

CHONG NJ, AZIZ Z*

Department of Pharmacy, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia.

ABSTRACT

Several reviews have examined various aspects of *C. asiatica* including the chemistry, pharmacology, and clinical uses but none of these reviews use the systematic review approach to locate and condense all the findings. The aim of this study was to systematically review the chemical constituents of *C. asiatica*. Electronic databases were searched for studies examining the chemical constituents of *C. asiatica* published from 1949 to 2011. Specialised journals, conference proceedings were also searched. Two review authors independently scrutinised search results and extracted data from eligible studies. From the 183 potentially relevant studies, 49 studies met the inclusion criteria and were included in the review. The review showed that *C. asiatica* has diverse and complex chemical constituents which included terpenes (monoterpenes, sesquiterpenes, diterpenes, triterpenes, tetraterpenes), phenolic compounds (flavonoids, phenylpropanoids, tannins), polyacetylenes group, alkaloids, carbohydrates, vitamin, mineral and amino acid. Most of the pharmacological activities of *C. asiatica* were examined in animal models using the extract or a mixture of chemical constituents. The most tested constituent was asiaticoside and it may be responsible for most of the pharmacological activities of *C. asiatica*. This review highlights that *C. asiatica* has diverse and complex chemical constituents and triterpenes were the major constituents.

Keywords: Terpenes, Triterpenes, Asiaticosides, Neuroprotective, Wound healing, Anti-Gastric ulcers

Corresponding author:

INTRODUCTION

Centella asiatica (L.) Urb (also known as gotu kola) is an herbaceous plant of the Apiaceae family and grows well in warm-climate countries. Its leaves contain triterpenes which have been shown in animal studies to have anti-inflammatory properties [1-2], wound healing activities [3-5] and anti-anxiety effects [6-7]. Many commercial medicinal preparations of *C. asiatica* marketed claim these products to be useful for improving venous insufficiency of the lower limbs, wound healing, skin diseases and anxiety [8-9]. Whilst the many pharmacological effects of *C. asiatica* observed in experimental animals have been attributed to several chemical constituents of the plant particularly triterpenes, there is currently insufficient clinical evidence to support its use in human [5, 10-13].

Extract of *C. asiatica* has been formulated into commercial medicinal preparations and are available over-the-counter across the world. The commercial preparations contain TECA (titrated extract of *Centella asiatica*), TTFCA (total triterpenoid fraction of *Centella asiatica*) and TTF (total triterpenic fraction). The European Medicines Agency confirms that while different acronyms are used to describe the content of these preparations, they do in fact describe the same extract.[14] Some of the commercial brands marketed are Madecassol® (TECA), Centellase® (TTFCA) and Blastoestimulina® (containing 40% of asiaticoside, 60% of asiatic acid and madecassic acid).

Triterpenes comprising of asiatic acid, madecassic acid, madecassoside and asiaticoside are the most frequent constituents isolated from *C. asiatica.* [8, 15-16]. The triterpenes isolated from *C. asiatica* are mainly pentacyclic triterpenic acids and that the asiatic acid, asiaticoside, madecassic acid, madecassoside, brahmoside, brahmic acid, brahminoside and other triterpenic glycosides of *C. asiatica* are of the ursane- or oleanane-type [17]. Of all the constituents of *C. asiatica*, the most investigated constituent is asiaticoside [18]. A small amount of essential oil has also been found in *C. asiatica* [16-17]. Other constituents reported present in *C. asiatica* include flavonoids such as quercetin and kaempferol [16-18] and some phytosterols such as campesterol, sitosterol and stigmasterol [18].

Several reviews have examined various aspects of *C. asiatica* including the chemistry, pharmacology, and clinical uses [8-9, 19-22]. However, none of these reviews adopted the systematic review methodology which locate and condense all available studies and used clear inclusion and exclusion criteria for inclusion of studies into the review. This review aims to update the previous non-systematic reviews and establish the chemical constituents of *C. asiatica*. Researchers would have access to synthesised and consolidated findings and saves them the time-consuming process of retrieving large volume of information from different sources

MATERIAL AND METHODS

Identification of studies

We conducted a comprehensive literature search for published and unpublished articles from 1949 to March 2011. The search included electronic database searches, hand searches and cross-referencing of included studies published in English and other languages. We searched 29 electronic databases and also performed hand searches on specialised journals such as *Journal of Tropical Medicinal Plants* and *Journal of Medicinal and Aromatic Plant Sciences* which are not indexed in any electronic databases. Proceedings from conferences were also searched to identify abstracts presenting research of the chemical constituents of *C. asiatica* that was not identified during other searches.

Experts in the field were also contacted to determine whether there were any unpublished data that could have been included in the review. References of related reviews and full text papers obtained through searches were checked for any studies that might be missed. Two review authors independently scrutinised abstracts and titles of studies from the searches. We retrieved full reports of potentially eligible studies for further assessment and the decision to include or exclude a study against the eligibility criteria was independently made by the two review authors. Studies that met the inclusion criteria were selected for data extraction. We extracted data using a pre-specified extraction form.

Inclusion and exclusion of studies

We included all studies, which examined the chemical constituents of *C. asiatica* grown in natural habitats. Studies that focused on identifying and analyzing specific constituents such as minerals, amino acids and essential oils were also included. We excluded studies which examined plants grown *in vitro;* investigated chemical constituents with modified functional group(s); compared the efficiency of different methods to analyse chemical constituents of *C. asiatica;* developed or improved analytical methods to analyse chemical constituents; validated or optimised methods used to analyse chemical constituents; investigated the effect of heat processing or drying techniques on the chemical constituents; examined the effects of precursors on the accumulation of chemical constituents; inspected the effects of different growth media on the content of chemical constituents; determined the level of chemical constituents in plasma; determined the chemical constituents in *C. asiatica* in pharmaceutical formulations; investigated the relationship of chemical constituents with expression level of genes; published as an abstract but not as a full paper; and review articles.

RESULTS AND DISCUSSIONS

Selection of studies

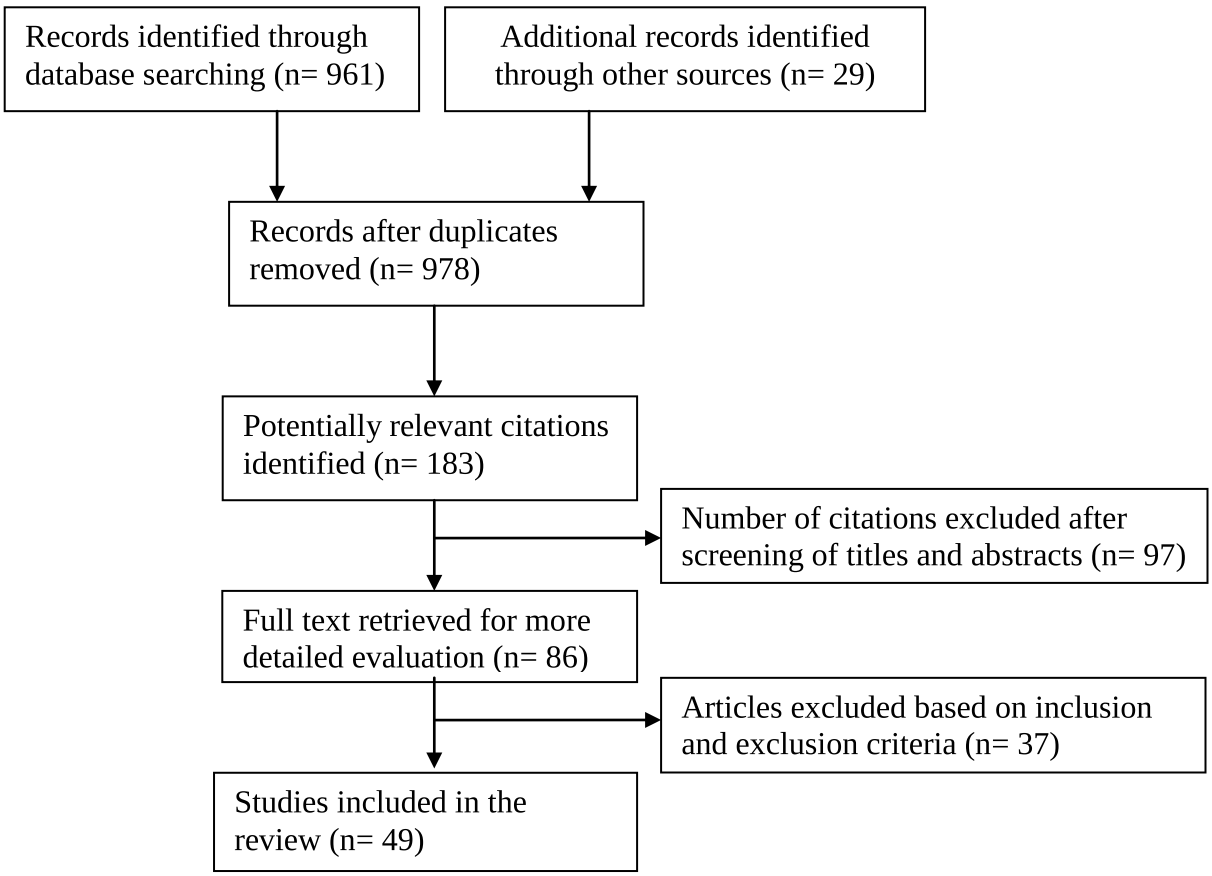

Figure 1 Flow chart of result of searches, studies identified and included in this review

Figure 1 shows from an initial 183 potentially relevant citations identified using the search strategy; forty-nine studies met the inclusion and provided data for this review.

Description of included studies

The chemical constituents of *C. asiatica* were first examined in the 1940s, which then continued throughout the 20th century and become more extensive in the 21st century (Table 1). The considerable volume of work on the identification of the chemical constituents of *C. asiatica* reflected the widespread interest in this plant possibly because it is an herb commonly used in Ayurvedic medicines for its effect on the mind, blood circulation, wound healing and skin diseases [8-9].

The majority of these studies were conducted in Asia with twelve studies from India and eight studies from Malaysia. Other Asian countries involved in examining the chemical constituents of *C. asiatica* include China, Japan, Korea, Sri Lanka and Pakistan (Table 1). Seven other studies were conducted in South Africa, Europe and United States of America.

Table 1 Chemical constituents of *Centella asiatica*

Study	Plant Origin	Part of Plants	Constituents Investigated	
			Main Groups	**Constituents**
[23]	Not Stated	Not Stated	triterpenic saponin	asiaticoside
[24]	Not Stated	Not Stated	triterpenic acid	brahmic acid
[25]	India	Not Stated	saponin	saponin
[26]	India	Not Stated	triterpenic acid triterpenic saponin isomer of glucose oligosaccharide monosaccharide	asiatic acid, brahmic acid asiaticoside, brahmoside, brahminoside mesoinositol centellose glucose
[27]	India	Not Stated	mineral vitamin	calcium, phosphorus, iron ascorbic acid, nicotinic acid
[28]	Not Stated	Underground part	polyacetylene	polyacetylene
[29]	Japan	Whole plant	monoterpene sesquiterpene triterpenic steroid -	α-pinene, β-pinene, myrcene, γ-terpinene bornyl acetate, α-copaene, β-elemene, β-caryophyllene, trans-β-farnesene, germacrene-d, bicycloelemene, campesterol, stigmasterol, sitosterol unidentified terpenic acetate
[30]	Not stated	leaves	triterpenic saponin	asiaticoside
[31]	Not stated	leaves	triterpenic saponin triterpenic acid	asiaticoside-a, asiaticoside-b 6β-hydroxyasiatic acid, terminolic acid
[32]	India	Leaves	triterpenic saponin	asiaticoside
[33]	Pakistan	Not stated	amino acid	aspartic acid, glutamic acid, leucine, iso-leucine, valine, methionine, lysine, histidine, tyrosine, phenylalanine, alanine, threonine, glycine
[34]	India	Not stated	triterpenic acid triterpenic saponin	asiatic acid, madecassic acid asiaticoside, madecassoside
[35]	India	Not stated	polyacetylene	11-oxoheneicosanyl cyclohexane, dotriacont-8-en-1-oic acid
[36]	Malaysia	Leaves	amino acid	aspartic acid, glutamic acid, serine, glycine, histidine, arginine, threonine, alanine, proline, tyrosine, valine, methionine, cystine, isoleucine, leucine, phenylalanine, lysine
[37]	Malaysia	Root	mineral	phosphorus, potassium, calcium, magnesium, manganese, iron, zinc, sodium, copper
		Stem	mineral	phosphorus, potassium, calcium, magnesium, manganese, iron, zinc, sodium, copper
		Leaves	mineral	phosphorus, potassium, calcium, magnesium, manganese, iron, zinc, sodium, copper
[38]	Italy	Not stated	triterpenic acid triterpenic saponin	asiatic acid, madecassic acid asiaticoside, madecassoside

[39]	India	Plant without root	triterpenoid glycoside	3-o-[α-l- arabinopyranosyl] 2α, 3β, 6β, 23-α tetrahydroxyurs-12-ene-28-oic acid
			triterpenic acid	6β-hydroxyasiatic acid, asiatic acid
[40]	Not stated	Aerial parts	triterpenic saponin	madecassoside, asiaticoside
[41]	Sri Lanka	Aerial parts	triterpene oligoglycoside	centellasaponin b, centellasaponin c, centellasaponin d
			triterpenic saponin	madecassoside, asiaticoside, asiaticoside b, sceffoleoside a
[42]	Korea	Aerial parts	triterpenic saponin	asiaticoside, madecassoside
[43]	Malaysia	Leaves	monoterpnene diterpene sesquiterpene	linalool neophytadiene α-copaene, β-elemene, β-caryophyllene, α-humulene, (e)-b-farnesene, δ-cadinene, epi-bicyclosesquiphellandrene, epiglobulol
		Stolon	sesquiterpene	α-copaene, β-elemene, β-caryophyllene, α-humulene, (e)-b-farnesene, δ-cadinene, epi-bicyclosesquiphellandrene
		Root	sesquiterpene	α-copaene, β-elemene, 1-decanol, β-caryophyllene, α-humulene, (e)-b-farnesene, β-acoradiene, δ-cadinene, epi-bicyclosesquiphellandrene, epiglobulol
[44]	Not stated	Not stated	polysaccharide	pectin
[45]	Not stated	Not stated	phenol	total phenolic
[46]	Not stated	Not stated	polysaccharide	arabinogalactan
[47]	India	Aerial parts	flavonoid	quercetin, kaempferol
[48]	China	Whole Plant	triterpenoid glycoside	asiaticoside c, asiaticoside d, asiaticoside e, asiaticoside f
			triterpenic saponin triterpenoid	asiaticoside, madecassoside scheffuroside b
[49]	South Africa	Not stated	monoterpene	α-thjuene, α-pinene, β-pinene, myrcene, α-terpinene, ρ-cymene, limonene, γ-terpinene, terpinolene, terpinen-4-ol, methyl thymol, pulegone, methyl carvacrol, linalool, 3-nonen-2-one, menthone, chrysanthenyl acetate, bornyl acetate
			monoterpene hydrocarbons	camphene, α-phellandrene
			sesquiterpene	bicycloelemene, β-elemene, β-caryophyllene, γ-elemene, aromadendrene, α-humulene, allo-aromadendrene, germacrene d, γ-curcumene, bicyclogermacrene, germacrene a, δ-cadinene, germacrene b,
				caryophyllene oxide, humulene epoxide, isopauthenol, neophytadiene
			sesquiterpene	spathulenol, viridiflorol

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			alcohol sulfide sesquiterpenoid	mintsulfide
[50]	Not stated	Not stated	polysaccharide	pectin
[51]	Not stated	Not stated	polysaccharide	arabinogalactan
[52]	Japan	Aerial parts	triterpenic acid	ursolic acid, pomolic acid, 2α, 3α-dihydroxyurs-12-en-28-oic acid, 3-epi-maslinic acid, asiatic acid
			triterpenes polyphenol	corosolic acid rosmarinic acid
[53]	Spain	Not stated	triterpenic acid triterpenic saponin	asiatic acid, madecassic acid asiaticoside, madecassoside
[54]	China	Aerial parts	triterpenoid glycoside	2α, 3β, 20, 23- tetrahydroxyurs-28-oic acid
[55]	Malaysia	Leaves Root Petioles	triterpenic saponin triterpenic saponin triterpenic saponin	asiaticoside, madecassoside asiaticoside asiaticoside, madecassoside
[56]	Malaysia	Aerial parts	polyacetylene	cadiyenol
[57]	South Africa	Leaves	mineral	calcium, phosphorus, sodium, manganese, copper, zinc, magnesium, iron
[58]	Madagascar Not stated	Leaves Leaves	triterpenic saponin triterpenic acid c15-polyacetylene	asiaticoside, madecassoside madecassic acid, asiatic acid 8-acetoxycentellynol
[59]	Japan	Aerial parts	triterpenic saponin phenol phenolic acid	asiaticoside chlorogenic acid 3,5-di-o-caffeoyl quinic acid, 1,5-di-o-caffeoyl quinic acid, 3,4-di-o-caffeoyl quinic acid, 4,5-di-o-caffeoyl quinic acid
			flavonoid	kaempferol, quercetin, kaempferol-3-o-b-d-glucoside, quercetin-3-o-b-d-glucoside
[60]	Pakistan	Aerial parts	not available	centellin, asiaticin, centellicin
[61]	China	Aerial parts	triterpenic saponin	2α, 3β, 23-trihydroxyurs-20-en-28-oic acid, 2α, 3β, 23-trihydroxyurs-20-en-28-oic acid o-α-l-rhamnopyranosyl- (1→4) - o-β-d-glucopyranosyl-(1→6)-o-β-d- glucopyranosyl ester
[62]	India	Not stated	vitamin tetraterpene	ascorbic acid β-carotene
[63]	India	Roots	triterpenic saponin	asiaticoside
[64]	South Africa	Leaves	triterpenic acid triterpenic saponin	asiatic acid, madecassic acid asiaticoside, madecassoside
[65]	Not stated	Leaves	triterpenic saponin	asiaticoside, madecassoside
[66]	India	Whole plant	flavonoid polyphenol	castilliferol, castillicetin isochlorogenic acid
[67]	Malaysia	Leaves Petioles	triterpenic saponin triterpenic acid triterpenic saponin triterpenic acid	asiaticoside, madecassoside asiatic acid asiaticoside, madecassoside asiatic acid
		Roots	triterpenic saponin	madecassoside

			triterpenic acid	asiatic acid
[68]	Malaysia	Not stated	phenol	total phenolic
[69]	Malaysia	Leaves	tanin	tannin, phlobatannin
			saponin	saponin
			terpenoid	terpenoid
			triterpene	cardiac glycoside
			flavonoid	flavonoid
			alkaloid	alkaloid
[70]	China	Not stated	triterpenic saponin	asiaticoside
[71]	United States of America	Leaves	triterpene glycoside	23-*o*-acetylmadecassoside, 23-*o*-acetylasiaticoside b (oleanane)
			triterpenic acid triterpenic saponin	asiatic acid, madecassic acid asiaticoside, madecassocide, asiaticoside c asiaticoside f
			triterpenic steroid	sitosterol 3-*o*-*β*-glucoside, stigmasterol 3-*o*-*β*-glucoside
			flavonoid glycoside	querectin-3-*o*-*β*-d-glucuronide

Most of the studies used aerial part of the plant or the whole plant and this is consistent with the reports of the World Health Organization (WHO)[15] monographs published in 1999. More than a quarter of these studies used *C. asiatica* leaves. However, other parts of *C. asiatica* were also examined including stems and roots (Table 1).

It is not possible to characterise the main constituents of *C. asiatica* based on its origin as 13 studies did not provide information on the source of the plant material sampled. Additionally, although most of the included studies were conducted with the aim of examining the leaves of *C. asiatica* for various types of terpenes such as monoterpenes, sesquiterpenes, and triterpenes, several other studies focused only on analyzing specific constituents. For example, four studies set out to examine the amino acid or mineral constituents [33, 36-37, 57] constituents and three studies the essential oil constituents of *C. asiatica* [29, 43, 49]. Another five studies examined only the asiaticoside [23, 30, 32, 63, 70]. Generally, we found the chemical constituents of *C. asiatica* to vary considerably between samples collected in each of the different locations. It is well established that the constituents of plants vary depending on the source of the plant material [64, 70, 72].

Constituents of C. asiatica and their pharmacological activities

Table 2 The chemical constituents of *Centella asiatica* were systematically classified.

Classes of chemical constituents	Chemical constituents
monoterpenes	
Acyclic monoterpenes	3-nonen-2-one
Monocyclic monoterpenes	Linalool, myrcene, *γ*-terpinene, terpinolene, limonene, *Α*-terpinene, *α*-phellandrene, *ρ*-cymene, terpinen-4-ol, pulegone, menthone, methyl carvacrol, methyl thymol,

Bicyclic monoterpenes	*Α*-thujene, α-pinene, *β*-pinene, camphene, bornyl acetate, chrysanthenyl acetate
Sesquiterpenes	
Acyclic sesquiterpenes	Trans-β-farnesene, decan-1-ol
Monocyclic sesquiterpenes	Germacrene a, germacrene b, germacrene d, *β*-elemene, *Γ*-elemene, *γ*-curcumene, bicyclogermacrene, bicycloelemene, humulene epoxide, *α*-humulene
Bicyclic sesquiterpenes	Epibicyclosesquiphellandrene, *α*-cadinene, *δ*-cadinene, caryophyllene oxide, *β*-caryophyllene, *β*-acoradiene
Tricyclic sesquiterpenes	Spathulenol, *allo*-aromadendrene, viridiflorol, epiglobulol, mintsulfide, *α*-copaene
Diterpenes	
Acyclic diterpenes	Neophytadiene
Triterpenes	
Ursane-type pentacyclic triterpenes	Asiatic acid, madecassic acid/ brahmic acid/ 6β-hydroxyasiatic acid, 2α, 3α-dihydroxyurs-12-en-28-oic acid, 2α, 3β, 23-trihydroxyurs-20-en-28-oic acid, 2α, 3β, 20, 23-tetrahydroxyurs-28-oic acid, pomolic acid, corosolic acid, ursolic acid
Ursane-type pentacyclic triterpenes saponins	Asiaticoside a/ madecassoside/ brahminoside, asiaticoside c, asiaticoside d, asiaticoside e, asiaticoside f, asiaticoside, 2α, 3β, 23-trihydroxyurs-20-en-28-oic-acid *o*- α-l-rhamnopyranosyl-(1→4) -*o*-β-d-glucopyranosyl-(1→6)-o-β-d-glucopyranosyl ester, centellasaponin b, centellasaponin c, scheffuroside b, 3-o-[α-l-arabinopyranosyl] 2α, 3β, 6β, 23-α tetrahydroxyurs-12-ene-28-oic acid, 23-*o*-acetylmadecassoside
Oleanane-type pentacyclic triterpenes	3-*epi*-maslinic acid, terminolic acid
Oleanane-type pentacyclic triterpenes saponins	Asiaticoside b, centellasaponin d, scheffoleoside a, 23-*o*-acetylasiaticoside b
Steroid type triterpenes	Stigmasterol, sitosterol, campesterol, sitosterol 3-*o*-*β*-glucoside, stigmasterol 3-*o*-*β*-glucoside
Tetraterpenes	*Β*-carotene
Phenols	
Flavonoids	Kaempferol, kaempferol-3-*o*-β-d-glucuronide, castilliferol, quercetin, quercetin-3-o-β -d-glucuronide, castillicetin,
Phenylpropanoids	Rosmarinic acid, chlorogenic acid, 3,4-di-*o*-caffeoyl quinic acid, 1,5-di-*o*-caffeoyl quinic acid, 3,5-di-*o*-caffeoyl quinic acid, 4,5-di-*o*-caffeoyl quinic acid, isochlorogenic acid
Tannin	Tannin, phlobatannin
Alkaloids	Alkaloids
Carbohydrate	
Monosaccharide	Glucose, mesoinositol
Oligosaccharide	Centellose
Polysaccharide	Pectin, arabinogalactan
Vitamin	Ascorbic acid, nicotinic acid, β-carotene
Mineral	Calcium, phosphorus, iron, potassium, calcium, magnesium, manganese, zinc, sodium, copper
Amino acid	Alanine, arginine, aspartic acid, glutamic acid, leucine, iso-leucine, valine, methionine, lysine, histidine, tyrosine, phenylalanine, threonine, glycine, serine, threonine, proline, cystine
polyacetylene	8-acetoxycentellynol, cadiyenol, dotriacont-8-en-1-oic acid, 11-oxoheneicosanyl

	cyclohexane
others	asiaticin, centellicin, centellin

We classified chemical constituent of *C. asiatica* into terpenes (monoterpenes, sesquiterpenes, diterpenes, triterpenes, tetraterpenes), phenolic compounds (flavonoids, phenylpropanoids, tannins), polyacetylenes group, alkaloids, carbohydrates, vitamin, mineral and amino acid (Table 2). Consistent with other reviews [8, 17, 73], our review shows that terpene was the dominant group of chemical constituents in *C. asiatica.*

The monoterpenes identified existed in acyclic, monocyclic and bicyclic frameworks while the sesquiterpenes reported in the studies also existed in tricyclic structures in addition to acyclic, monocyclic and bicyclic structures. The triterpenes in *C. asiatica* are pentacyclic triterpenes and the two types of pentacyclic triterpenes reported are ursane-type and oleanane-type (Table 2). Similarly, two other reviews also reported on these two types pentacyclic triterpenes [17, 73]. Some of these pentacyclic triterpenes carry sugar moieties and are known as pentacyclic triterpenes saponins which included asiaticoside, asiaticoside A, C, D, E and F, madecassoside, centellasaponin B, centellasaponin C and scheffuroside B (Table 2).

The leaves of *C. asiatica* contain various types of terpenes such as monoterpenes, sesquiterpenes and triterpenes (Table 1). The aerial parts of *C. asiatica* contain triterpenes, phenols and cadiyenol while the root also contains monoterpenes, sesquiterpenes and triterpenes in addition to some minerals. It should be noted that it is impossible to characterise with certainty the main chemical constituents of the plant according to the parts of the plant since up to 20 studies out of the 49 included in this review did not report which part of the plant the compounds were extracted from.

Consistent with previous reports, our review confirmed that the most reported chemical compounds were asiaticoside, madecassoside, asiatic acid and madecassic acid [8, 15-16, 73]. We found asiaticoside which was first reported in 1949 by Boiteau and colleagues to be the main compound reported. This is also consistent with reports from two other non-systematic reviews [18-19]. Asiaticoside appears to be responsible for most of the pharmacological activities of *C. asiatica* reported. In animal studies, asiaticoside has been shown to exhibit central nervous system protective effects such as antidepressant-like effect [74], anxiolytic-like effect [6-7], wounds healing [4, 75] and anti-gastric ulcers properties [76-77]. In wound healings, it is known that several local growth factors help in the wound healing process. It is possible that asiaticoside has the ability to stimulate the growth factors or it may have growth factor like activity [75].

The second most frequently isolated compound was madecassoside. A total of 13 studies reported the presence of madecassoside albeit in varying quantities in the different studies. We noted that madecassoside has been isolated from samples of *C. asiatica* from the same geographical regions as *C. asiatica* which contained asiaticoside. In animal models, the pharmacological effects of madecassoside from C. asiatica have been examined in at least four studies [2, 78-80]. Liu et al. [2] demonstrated the anti-inflammatory properties of madecassoside in mice. They suggested that madecassoside may improve type II collagen-induced arthritis (CIA) through regulating the abnormal humoral and cellular immunity, such as the excessive activation of T lymphocytes and the overproduction of auto-antibodies which are essential for the development of CIA. Type II CIA is commonly used as an animal model of inflammatory diseases similar to rheumatoid arthritis [81]. Madecassoside has also been reported to possess anti-oxidant properties [80] and protects against myocardial ischemia reperfusion injury in ischaemia reperfusion model [78-79].

The other two frequently reported chemical compounds are asiatic acid and madecassic acid. Other than the four most frequently reported chemical compounds, all the other chemical constituents such as centellasaponin B, brahmoside, germacrene A, linalool and kaempferol were reported in only one or two studies. Krishnamurthy et al. [82] showed that asiatic acid might posses neuroprotective potential against cerebral ischemia that is mediated partly through decreased blood-brain barrier permeability and reduction in mitochondrial injury in mouse model. However, the pharmacological activities of the individual madecassic acid have not been examined.

Like other Apiaceae, *C. asiatica* is characterised by the presence of essential oil. The essential oil of *C. asiatica* is made up of a wide variety of monoterpenes and sesquiterpenes. According to Sarker and Nahar [83], phenylpropanoids are widespread in plants that produce essential oils. This seems to be true for *C. asiatica* as phenylpropanoids were reported in four studies included in the present review [52, 59-60, 66]. Flavonoids were another group of phenolic compounds found in *C. asiatica* apart from phenylpropanoids (Table 2). Among the flavonoids found were kaempferol, quercetin and two new flavonoids, which are castilliferol and castillicetin [66].

The presence of polyacetylenes in *C. asiatica* was reported by Schulte et al. [28]. This is expected as some of the most bioactive polyacetylenes are found in the Apiaceae family [84]. The presence of polyacetylenes in *C. asiatica* is important as polyacetylenes could have the potential to be used as nutraceuticals even though they have been reported to be toxic to fungi, mammalian cells, and responsible for allergic skin reactions [84].

Although the chemistry of *C. asiatica* has been well studied, there could still be other compounds, which remain to be isolated and identified. This systematic review served as a source of information useful for minimising duplication of effort in chemical compound isolation and identification. Coupled with the rapid development of technology and improvement of analytical techniques, it is hoped that the identification and characterisation efforts could be facilitated in the near future to help the development of *C. asiatica* as a source of potential drug candidate in view of its many reported therapeutic effects. Future researches on chemical studies of *C. asiatica* might consider to target on isolation and identification of novel chemical compounds, report the origin of plant materials used and which part of plant used. Pharmacological activities of individual chemical constituents of *C. asiatica* are the area that future researchers should consider.

Strengths and limitations

Among the strengths of our review is that, we also included studies published in languages other than English to minimise publication and language biases. By having two independent review authors in the process of study selection, data extraction and analysis, we have minimised the selection bias of including studies which favour a specific findings in the review. Systematic reviews on plants, especially on the chemical constituents, typically involve a diverse body of literature that can be voluminous. For this reason, we have strived to screen all potentially relevant articles using eligibility criteria to reduce the risk of bias of this systematic review.

Nevertheless, bias due to incomplete data reporting could not be totally avoided as several studies did not report the source of plant materials used and which part of the plant was used. Also, hand searches were carried out only for articles published in English language. Systematic review is not perfect [85] as it is difficult to locate all potentially relevant studies for inclusion and we may not have identified all relevant studies. Among the other limitations of this review were variations in methodology in original studies, the source and plant material used. However, in general, we found that most of the studies included have used some validated methods for the identification and assessment of compounds, which were based on published literature.

CONCLUSIONS

Chemical investigations on *C. asiatica* have shown that it has diverse and complex chemical constituents. Overall, the chemical constituents of *C. asiatica* are well studied. Even though there were variations in methodology between the studies, the constituents examined and the plant material used; triterpenes were the major constituents consistently identified. The triterpenes identified were mainly pentacyclic triterpenes, belonging to ursane- or oleanane-type, including asiaticoside, madecassoside, asiatic acid and madecassic acid. This review provides information on the chemical constituents of *C. asiatica* using rigorous methodology to locate, identify and synthesise information from all relevant studies published over a fifty-year period. It provides researchers access to synthesized and consolidated findings and saves them the time-consuming process of retrieving large volume of information from different sources.

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