

Asiaticoside: A Wonderful Herbal Component of Versatile Therapeutic benefits with Special Reference to Wound Healing Activity

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ABSTRACT

Wound healing is a natural process. The integrity of the skin and injured tissue restoration include many cellular and biochemical phenomena. There are different kinds of conventional dosage forms that are utilised for the wound healing process. Apart from various conventional dosage forms, herbal therapies are gaining more importance nowadays. The herbal therapies are known for their non-habitual nature and have very less side effects as compared to conventional dosage forms. Recently, asiaticoside, an important chemical constituent of gotu kola that is extracted by different methods, is being utilised in wound healing. Asiaticoside has excellent wound healing capability. There are many studies on asiaticoside which reveal that it is a gold herbal compound that is used in the management of wound. Apart from its wound healing activity it also shows antidepressant, antidiabetic, anti-inflammatory, anti-pyretic action. This review article gives a comprehensive detail of asiaticoside and its various pharmacological actions and pharmacognostic features.

Keywords: Herbal therapy; *Centella asiatica*; Asiaticoside; Wound healing; Gotu kola

INTRODUCTION

Herbal therapies are widely used in the treatment or management of many diseases. The term herbal therapy means utilisation of ingredients that are obtained from natural sources. There are many herbal plants which contain broad range of therapeutic active ingredients. These active ingredients from plants are isolated by different methods. There are different guidelines for the preparation of infusion, decoction, extracts, tinctures, ointments, poultices, powders, decoction, salves, syrups and powder [1]. The active ingredients that show therapeutic effectiveness are present in different parts of plants, for example rhizomes of Zinger (*Zingiber officinalis*) [2], fruit of Cardamom (*Elettaria cardamom*) [3], flowering top Datura (*Datura metal*) [4], leaflets of Senna (*Cassia angustifolia*) [5,6]. Now-a-day, herbal plants are widely utilised to cure many disease e.g. asiaticoside that show excellent therapeutic activity related to wound healing. It is believed that herbal remedies show less side effects, less likely to cause dependency and safer than synthetic compound

[7]. Due to these, herbal therapies gaining interest now-days. Many drug plants as well as their preparation are utilised to treat many health related problems. This review article highlights one such wonderful herbal compound that is asiaticoside. It shows many excellent therapeutic activities, the major being related to wound healing activity [8].

LITERATURE REVIEW

Pharmacognosy parameter of Gotu Kola

Gotu kola is also called brahma-Mandukarni. It is obtained from fresh and dried stem of *Centella asiatica* belonging to Umbelliferae family. The Mandukparni (Gotu kola) is widely distributed in Sri Lanka, India, Madagascar, Africa, Australia, Indonesia, China and Vietnam with an altitude of 650 meter [9]. The taxonomy and the major chemical constituents of Gotu kola plant are shown in Table 1 and Figure 1, respectively.

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Received: June 28, 2021; **Accepted:** July 12, 2021; **Published:** July 19, 2021

Citation: Kumar M, Mandal UK (2021) Asiaticoside: A Wonderful Herbal Component of Versatile Therapeutic benefits with Special Reference to Wound Healing Activity. J Clin Exp Dermatol Res. S9:571.

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Classification	Name
Kingdom	Plantae
Division	Magonoliophyta
Class	Magnolipsida
Order	Apiales
Family	Apiaceae
Genus	Centella
Species	Centella asiatica (L) urban

Table 1: Taxonomy of Gotu kola plant.

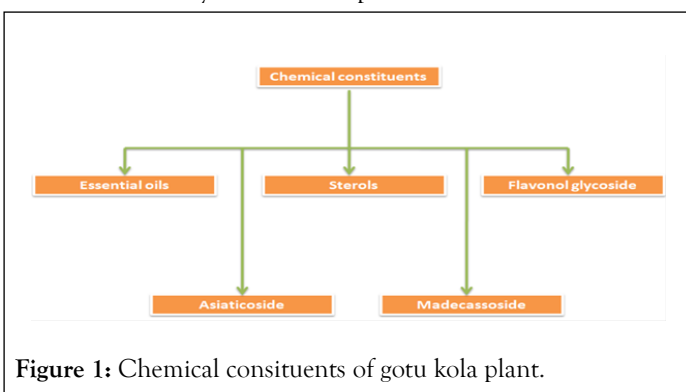


Figure 1: Chemical constituents of gotu kola plant.

Centella asiatica is utilised to treat dermatitis and it accerlates the healing of superfical wound. Asiaticoside and its derivatives also promote fibroblast prolifration and collagen synthesis. It is used as nervine tonic and as anti-anxiety, anti-stress, and sedative agent. It is utilised in the treatment of skin related disease, syphilise, leprosy and also in the wound healing [10,11]. The alcoholic extract of whole plant has anti-cancer activity.

EXTRACTION PROCEDURES OF ASIATICOSIDE FROM *CENTELLA ASIATICA*

The asiaticoside is extracted from the *Centella asiatica* by using different methods. Some of them are explained as follow:

Conventional liquid solvent extraction

According to one study (Figure 2), 3 gram of *Centella asiatica* is dissolved in 100 mL of ethanol/water/ethanol, then the solution is stirred 1200 RPM for 24 hrs and asiaticoside is extracted to that solvent [12].

The Mandukparni (Gotu kola) is widely distributed in Sri Lanka, India, Madagacar, Africa, Australia, Indonesia, China and Vietnam with an attitude of 650 meter

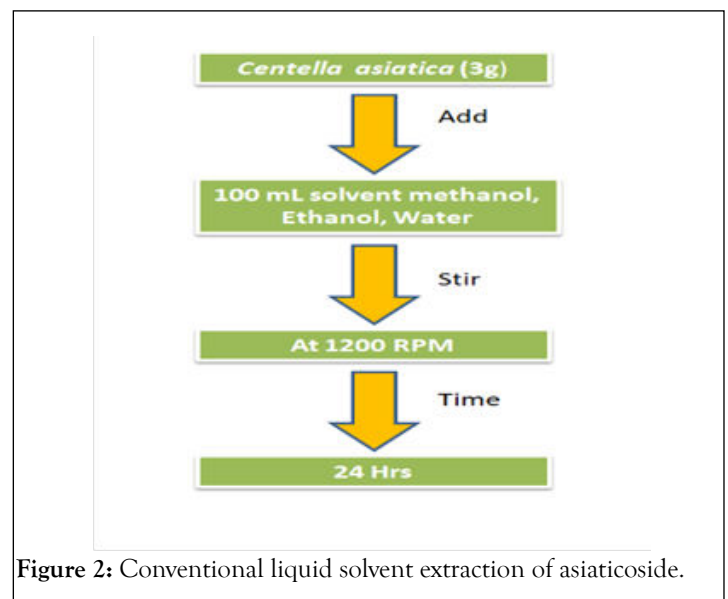


Figure 2: Conventional liquid solvent extraction of asiaticoside.

Heat flux extraction

In this procedure (Figure 3), the *Centella asiatica* (3 gram) is added to methanol (64°C), water (100°C), Ethanol (78°C). The solvent is then the heated for 5 hrs to extract asiaticoside [12].

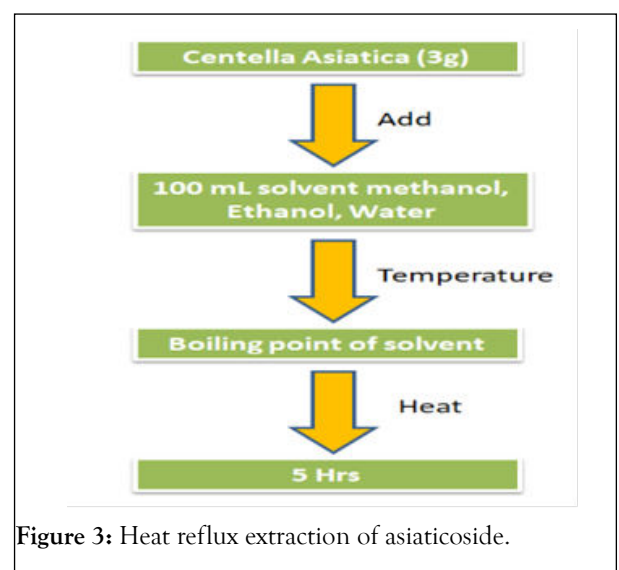


Figure 3: Heat reflux extraction of asiaticoside.

Soxlet extraction

Centella asiatica (3 gram) is added to 100 mL of methanol, ethanol, water and boiled for 5 hrs at the boiling point of each solvent [12] (Figure 4).

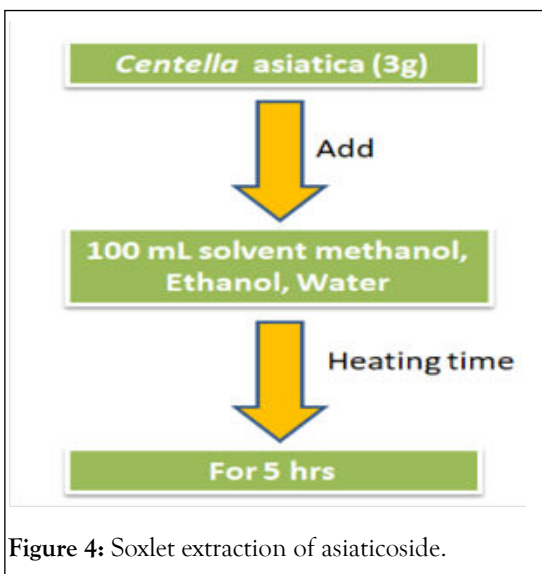


Figure 4: Soxlet extraction of asiaticoside.

Ethanollic extract of asiaticoside

The aerial part of *Centella asiatica* is dried at a temperature of 40°C, then ground to form coarse powder. The herb is macerated with 95% ethanol. After three days, the supernatant is collected. The solvent is then evaporated and extract is stored at -20°C (Figure 5) [13].

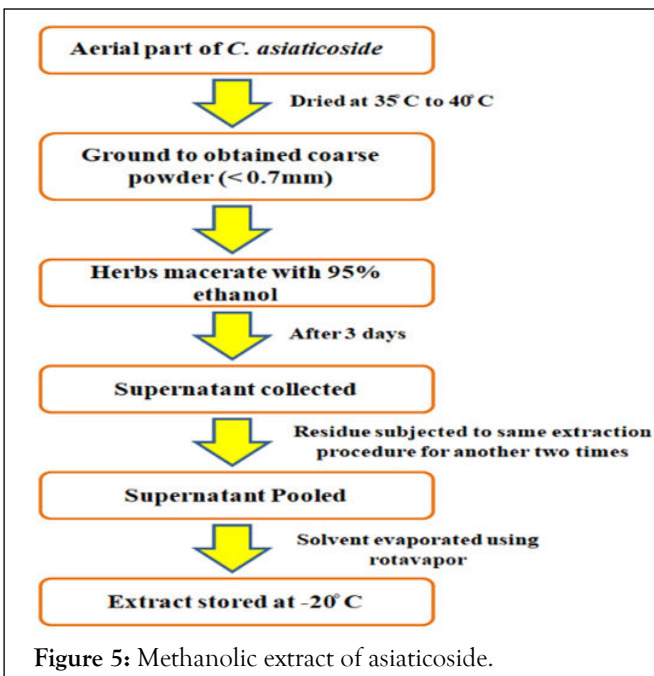


Figure 5: Methanollic extract of asiaticoside.

DISCUSSION

Asiaticoside (Figure 6) is derived from plant *Centella asiatica* (Brahma-Mandukarni), which is a trisaccharides terpenene. The single crystal X-ray has been used in the determination of asiaticoside. The glycoside, C₄₈H₇₈O₁₉, is prismatic with space group monoclinical, C₂ and lattice constant a=41.46, b=17.988, β=99.66, cell volume v=5602.3, Z=4 [14].

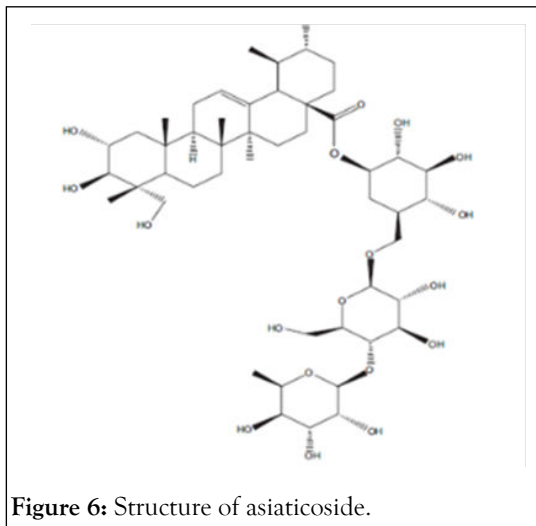


Figure 6: Structure of asiaticoside.

There are different High Pressure Liquid Chromatography (HPLC) methods that are already reported for the determination of asiaticoside. Some of them are described in Table 2. In most of the methods, authors used mobile phase with a composition of acetonitrile as organic phase and orthophosphoric acid of acidic pH as aqueous phase.

UV detection ranged from 205 to 210 nm and run time varied from 4.3 to 11.6 minutes [15-18]. In majority of the methods, C18 column was used for separation of asiaticoside, except in one method reported by Da Rocha et al.[16] where C8 column was used.

When the asiaticoside rich cream applied to the animal, it reduced the area of wound [16]. Azis et al. [13] examined the *In-vitro* and *In-vivo* wound healing studies of methanollic fraction of *Centella asiatica* on New-Zealand white albino rabbit.

The asiaticoside was used in the concentration of 119.89 µg/mL, which was capable to heal wound. Author found that the untreated group showed normal healing while the extract treated group showed faster wound healing activity.

Solvent system	Column	Detector	Wavelength	Flow rate	Injection volume	Retention time	References
Orthophosphoric acid (0.3%): Acetonitrile (80:20)	C-18; size 250 × 460 mm	UV detector	210 nm	1.8 mL/min	20 µL	5.0 min	[15]

Acetonitrile: 0.1% H ₃ PO ₄ (30: 70)	C-8 (250 × 4.6 mm, 5 μm)	UV detector	206 nm	1.0 mL/min	20 μL	7.60 min	[16]
Acetonitrile: Orthophosphoric buffer	RP-18e (5 μm)	Photo diode array detector	210 nm	1.8 mL/min	20 μL	11.60 min	[17]
Acetonitrile: Phosphate buffer pH 3 (50: 50)	C-18, 5 μm (150 mm × 4.6)	PDA plus detector	205 nm	1.0 mL/min	20 μL	4.342 min	[18]

Table 2: Chromatographic condition of HPLC method of asiaticoside.

Various therapeutics benefits of Asiaticoside

Wound healing activity: The process of wound healing is a natural process which requires medical care and appropriate management. There are different kinds of materials or medical treatments currently available that are used for wound healing. The different medical care materials have characteristic features and they act according to their ability. Some of them provide the physical protection to wound, some of them are capable to deliver the drug directly into the affected area and some of them protect the wound from foreign pathogens. Asiaticoside is newly found herbal therapy which is effectively used in the management of wound or burn related wound healing. The topical application of asiaticoside can cause the macrophages migration to epidermis and corneum of tissue surrounding the wounds, but no effect on polymorphonuclear leucocyte migration. Asiaticoside also increases the IL-1β level [19]. Some reported wound healing activities of asiaticoside are given below:

Ruszymah et al. [20] reported the wound healing efficacy of aqueous extract of *Centella asiatica*. The different concentration of *Centella asiatica* used were 7.8, 15.6, 31.2, 62.5, 125, 250, 500, 1000 ppm. The highest concentration of *Centella asiatica* i.e. 1000 ppm showed anti-proliferative effect [20]. Shetty et al. [21] explored the effect of *Centella asiatica* on dexamethasone suppressed and normal wound healing in rat model. Asiaticoside used in the dose of 4 g/kg. He observed that there is significant increase in the wound breaking strength in the extract treated group [21]. sukla et al. [22] studied the *in-vitro* and *in-vivo* wound healing activity of asiaticoside. He studied the effect of asiaticoside in normal and diabetic animal and observed that there is faster wound healing in the group treated with asiaticoside as compared to the control group [22]. Ahmed et al. [23] tested the asiaticoside rich fraction to check the efficacy in wound healing. Authors check wound healing activity of *Centella asiatica* PEG/PVP hydrogel on rabbit. They observed that the asiaticoside treated group reduce the size of wound indicates that contraction epithelialization and subsided [23]. Sung et al. [24] researched the wound healing activity of asiaticoside on Sprague-Dawley rats. The process of wound healing on excision wound model was checked for the period of one month. Author found that, there was decrease in the wound excision with time passage [24]. Aylin et al. [25] studied the wound healing efficacy of *Centella asiatica* on female albino rats.

Author observed that, the asiaticoside treated group showed better wound healing activity as compare to the control group[25]. Sandipan et al. [26] reported the wound healing activity of hydro-alcoholic extract of *Centella asiatica* on Wistar albino rat (either sex). When the asiaticoside rich cream applied to the animal, it reduced the area of wound [26]. Azis et al. [13] examined the *In-vitro* and *In-vivo* wound healing studies of methanolic fraction of *Centella asiatica* on New- Zealand white albino rabbit. The asiaticoside was used in the concentration of 119.89 μg/mL, which was capable to heal wound. Author found that the untreated group showed normal healing while the extract treated group showed faster wound healing activity [13].

Antidepressant activity of asiaticoside: Depression is a mood disorder in which there is feeling of ignorance, lack of concentration, thoughts of suicide, and loss of interest in activities. Currently there are many treatment options that are utilised in the management of depression. The anti-depressant are capable to restore the state of psychological wellness [27]. Nowadays herbal therapies are gaining more interest. There are many reports on anti-depressant activity of asiaticoside. Some reported anti-depressant activities of asiaticoside are given below:

Luo et al. [28] researched the anti-depressant effect of asiaticoside on male mice. Author observed that, there was enlargement in the BDNF, PSD-95 and synaptic expression in hippocampus but not in the frontal cortex, after administration of asiaticoside [28]. Tianheng et al. [29] investigated the anti-depressant like properties of asiaticoside on male-sprague-dawley rat. Author observed that borneal can open the BBB and enhance the distribution in brain. The asiaticoside and borneal have synergistic effect in order to treat depression [29]. Luoqing et al. [30] examined the asiaticoside anti-depressant action on male mice model. Authors found that the asiaticoside elevated the level of 5-HT and NE (Nor- epinephrine). Asiaticoside produces the anti-depressant activity by activation of BDNF signalling [30]. Liang et al. [31] reported the anti-depressant action asiaticoside on male mice model. The authors investigated that, asiaticoside showed anti-depressant action evaluated by FST (Force Swimming Test) [31].

Anti-inflammatory activity of asiaticoside: Asiaticoside is triterpenoid that shows anti-inflammatory and anti-oxidant action. The lipopolysaccharides are inhibited by the dose of asiaticoside. Furthermore, as it inhibits pro-inflammatory mediators, including IL-6 and TNF-α level, PGE2 and COX-2 expression. Jingyuan et al. [32] studied the anti-inflammatory and anti-oxidant activity asiaticoside. Asiaticoside inhibited the

up-regulation of COX-2 in dose dependent level [32]. Hence we can use asiaticoside in future for producing anti-inflammatory activity. Yang et al. [33] reported the anti-inflammatory effect of asiaticoside on mice model. Author observed that the given dose of asiaticoside inhibits the pathway of p38-MAPK. This inhibition of this pathway reveals that asiaticoside is capable to produce anti-inflammatory activity [33]. Haung et al. [34] investigated the potential effect of asiaticoside loaded PLGA electrospun nanofibre. It enhances the gene expression of inflammatory cytokines as revealed *via in-vitro* studies [34].

Anti-diabetic activity of asiaticoside: Diabetes is chronic metabolic disorder, in which there is increase in the glucose level in blood for prolong period of time. Diabetes if left untreated, it produces many serious side effects such as eye disease, kidney failures, etc. There are many synthetic drugs currently used in the management of diabetes mellitus. There are many reports which reveal the anti-diabetic activity of asiaticoside. The

ethanolic and methanolic extract of asiaticoside significantly lower the bold glucose level in mice model [35]. Fitrianda et al. [36] investigated the anti-diabetic activity of ethanolic extract of *Centella asiatica*. Author administered the asiaticoside in dose of 1.4, 2.8, 5.6 mg for 21 days, which showed glucose lowering action in alloxan-induced mice model [36]. Sasikala et al. (2018) studied glucose lowering activity of ethanolic extract of *Centella asiatica* on streptozotocin induced diabetic rats. The extract was administered to rat in a dose of 300 mg/kg, which shows glucose lowering action on rat [37]. Mehta et al. reported the glucose lowering activity of *Centella asiatica*. By using soxlet apparatus the hydro-alcoholic extraction from leaf of *C. asiaticoside* was carried out. By using Molegro virtual docker the docking screening was performed. The *In-vitro* antidiabetic assay showed glucose lowering activity due to inhibition of α -amylase and β -glucosidase enzymatic activity [38] (Table 3).

Sr. No	Aim of study	Animal model	Outcome of research	References
1.	The wound healing study of methanolic fraction of <i>Centella asiatica</i> : <i>In-vitro</i> , <i>In-vivo</i> study	Rabbit (New-zealand white albino)	Shows better result as compared to the vehicle control group	[13]
2.	To check wound healing effect of <i>Centella asiatica</i> on normal and dexamethasone suppressed Wistar albino rat	Wistar albino rat	The extract treated group shows significant increase in the wound breaking strength	[21]
3.	<i>Centella asiatica</i> loaded hydrocolloids wound dressing in the effective wound healing an <i>In-vivo</i> study	Male D-sprague dawley rats	The hydrocolloids loaded with <i>Centella asiatica</i> enhance the healing effect in infection and abrasion wound in rat	[24]
4.	The wound healing in albino rat: A comparative efficacy of <i>Tajects erecta</i> and <i>Centella asiatica</i>	Albino rat	Shows promising wound healing activity	[26]
5.	<i>Centella asiatica</i> used in wound healing: An <i>In-vitro</i> and <i>In-vivo</i> study	Guinea pigs	As compared to vehicle treated diabetic group, 0.4% of asiaticoside shows 42% reduction in the area of wound in diabetic animal	[22]
6.	Antidepressant effect of asiaticoside on mice model	Male swiss mice	The present study reveals that asiaticoside shows antidepressant like effect	[31]
7.	The anti-inflammatory and anti-pyretic effect of asiaticoside on rat	Adult male sprague dawley rats	Asiaticoside shows anti-inflammatory action and capable to lower the elevated temperature	[32]
8.	The anti-diabetic effect of <i>Centella asiatica</i> and <i>Andrographis paniculata</i>	Wistar rat	The combination of <i>Centella asiatica</i> and <i>Andrographis paniculata</i> shows anti-diabetic effect	[39]

9.	The antidepressant action of asiaticoside by promoting the distribution in to the brain	Male sprague dawley rats	The asiaticoside shows antidepressant action	[29]
10.	The <i>Centella asiatica</i> pharmacological properties in order to accelerate wound Healing	New Zealand white albino rabbit	There is reduction in the wound was observed in the group treated with asiaticoside rich hydrogel	[23]

Table 3: Recent studies on *Centella asiatica* activities.

CONCLUSION AND FUTURE PROSPECTIVE

The herbal therapies are widely used in the treatment or management of many diseases. The herbal therapies have negligible side effects and also effective have pharmacological activities, so that herbal therapies gaining interest now-days. Asiaticoside is a herbal active constituent that is obtained from *Centella asiatica*. The different formulations or asiaticoside rich fraction are utilised in the wound healing. Asiaticoside has wound healing activity apart from that, it is also used in the treatment of other diseases such as diabetes, fever, stress etc. The various formulations such asiaticoside loaded nanoparticles, Liposomes, hydrocolloids, may be used in targeted delivery of asiaticoside. In future, asiaticoside based novel drug delivery may be explored further to establish it as an alternative better option for the treatment of various wounds, diabetes and depression.

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