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REVIEW ARTICLE

Review on possibilities of domestication with special focus on medicinal properties and variability in Indian Pennywort (*Centella asiatica* (L.) Urban) for its potential commercial cultivation

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Abstract

Indian Pennywort (*Centella asiatica* (L.) Urban) is a traditional medicinal herb, used in various traditional medicine systems. It is a herbaceous perennial preferring a moist microclimate. *C. asiatica* has proven medicinal utility in wound healing, nerve-related ailments and has significant antibacterial and antioxidant activities. Its demand in the global market is on an increasing trend. Phytochemical analysis shows that it is rich in medicinally important asiatic acid, madecassic acid, asiaticoside, brahmoside centellin, centellicin and asiaticin, etc. *C. asiatica* is being collected from wild habitat and it endangers its existence, which emphasize its domestication. The crucial process in domestication is to identify genotypes that exhibit high herbage yield and enhanced biomolecule content. Production of bioactive compounds in medicinal herbs is significantly affected by genotypes and the place of cultivation. It is vital to screen and characterize the germplasm of *C. asiatica* for optimal commercial cultivation in specific environmental conditions. Various niche approaches were being reported for its sustainable cultivation. Various commercial products are on the market, including raw extracts to isolated phytochemicals, gel, powder, capsules, etc. Studies on the production of medicinally important phytochemicals through cell cultures of *C. asiatica,* which may be a key approach for its conservation in wild habitats. Hence, the future work may concentrate on the development of agro techniques for commercial cultivation, selection of suitable genotypes for various medicinal and industrial purposes, more insight into its medicinal properties and improving the efficiency of the medicinal properties through various formulations.

Keywords: *Centella asiatica*; centellosides; chemotypes; Indian pennywort; variability

Introduction

Indian Pennywort (*Centella asiatica* (L.) Urban) is an important medicinal plant in Indian systems of medicine. It belongs to the family Apiaceae and has a pantropical distribution in South East Asian countries such as India, Sri Lanka, China, Indonesia, Malaysia and Madagascar (1) . The plant is found to be vigorous in damp, moist and shady habitats. It grows by producing stolons with long petioles. It is normally used as a vegetable, but its medicinal uses drive the growth in the market. Demand for *C. asiatica* in the global market is on an increasing trend. The herb is widely sourced from wild habitats, which may lead to scarcity and even make it an endangered species. Commercial cultivation efforts for high-quality *Centella* will be obtained using high-quality planting material. Thus, identification of high-yielding planting material requires evaluation of genotypes with higher herbage yield and higher content of medicinal quality. This review presents the medicinal properties, phytoconstituents, variability and scope for commercial cultivation of *C. asiatica*.

Medicinal properties

Centella asiatica is an adaptogen, central nervous system relaxant, sedative, detoxifier, blood purifier, laxative, diuretic and emmenagogue. It is a brain tonic for improving memory and overcoming mental confusion, stress and fatigue. It also has a good effect on obstinate skin diseases and leprosy. In Indian medicine, it is used as a brain tonic and sedative. Many properties of *C. asiatica* as a natural medicine for the digestive system, weight management, immune system booster and cancer treatment propel its market growth. Research indicates that the effect of *C. asiatica* as an antidepressant shows that there are positive effects on behaviour in patients under stress. *C. asiatica* may be a valuable and cost-effective therapeutic option for depression, which needs further intensive research (1, 2). Wound healing properties of *C. asiatica* have been reported by various worke rs (3-5). *C. asiatica* is proven to be used in skin-related treatments such as the removal of stretch marks. The mechanism of the action was found to be the efficacy of *C. asiatica* in the reduction of fibrotic markers and extracellular matrix degradation (6).

C. asiatica is a potential antibacterial agent, especially against *Streptococcus* mutans. The mode of action of the antibacterial activity was also established as the modifications in bacterial cell surface decreasing the cell surface hydrophobicity (7). There was a significant difference in the antioxidant activity of the extracts from cell suspension culture, shoot culture callus extract, with the highest activity in cell suspension culture extracts (8). Extracts of *C. asiatica* with *Moringa* and *Vernonia amygdalina* showed hypoglycemic and antioxidant activities, which can have the antidiabetic effects (9). A bibliographic study on three decades of research in *C. asiatica* has shown that the primary focus of the research has been its efficacy on wound healing and other chronic conditions. The recent studies focus on the cosmetic industry, phytoremediation and the food industry (10). Triterpenoids of *C. asiatica* were reported to have extensive beneficial effects on neurological and skin diseases, in addition to anti-inflammatory, antioxidative stress and anti-apoptotic effects (11, 12).

Phytochemistry

It is reported that there are 139 secondary metabolites isolated from *C. asiatica*, viz., 16 triterpenes, 59 triterpene glycosides, 4 steroids and 2 steroid glycosides. 8 flavonoids, 9 polyacetylenes, 13 phenolic acids and 18 other miscellaneous compounds. Seventy phytochemicals are described for the first time. There is no report on the presence of alkaloids in *C. asiatica* (13). The major constituents of the plant include terpenes and phenols. Glucosides, sterols and polyacetylenes were also reported (Fig. 1). Terpenes include triterpenes and pentacyclic triterpenes of the ursolic acid series, madecassic and their corresponding glycosides. The major centellosides, viz. asiatic acid, madecassic acid, asiaticoside, have well-proven medicinal values. Several minor analogues collectively known as centelloids, belonging to the ursane or oleanane families, were reported. The presence of these minor analogues significantly varies in different chemotypes, depending on geographic origin and environmental conditions (14). The other important phytochemicals are allarine, brahmoside centellin, centellicin and asiaticin.

Variability in Indian Pennywort genotypes

The primary step in the whole process is the identification of genotypes with high herbage yield and higher biomolecule content. Since the biosynthesis of bioactive compounds in medicinal herbs is greatly influenced by genotype (G) × environmental (E) interactions, it is imperative to screen and characterize *C. asiatica* germplasm for commercial cultivation in a particular environmental niche. Hence, it is essential to evaluate Indian germplasm of *C. asiatica* to identify genotype(s) with better agro-morphological characteristics and phytochemical properties for commercial exploitation. The genomic variation among the ecotypes, which resulted in the variation in asiaticoside content, was well established (51). Variation in asioticoside and madecassoside content in various parts of *C. asiatica* was recorded (52). Leaves showed a higher quantity of both saponins. Similar results were recorded in two ecotypes of Madagascar (53). Both season and ecotypes affected the asiaticoside content. Genetic studies are needed to confirm the results.

High genetic diversity is reported in *C. asiatica* genotypes. Significant variability is found in the made cassoside, asiaticoside and their acid forms among the genotypes. According to the same study, chances of potential genetic gain in breeding programs for herbage as well as phytochemical production were substantial (54). Flavonoid and centellosides accumulation are affected by fertilizer application in *C. asiatica* (55). Research indicates that the

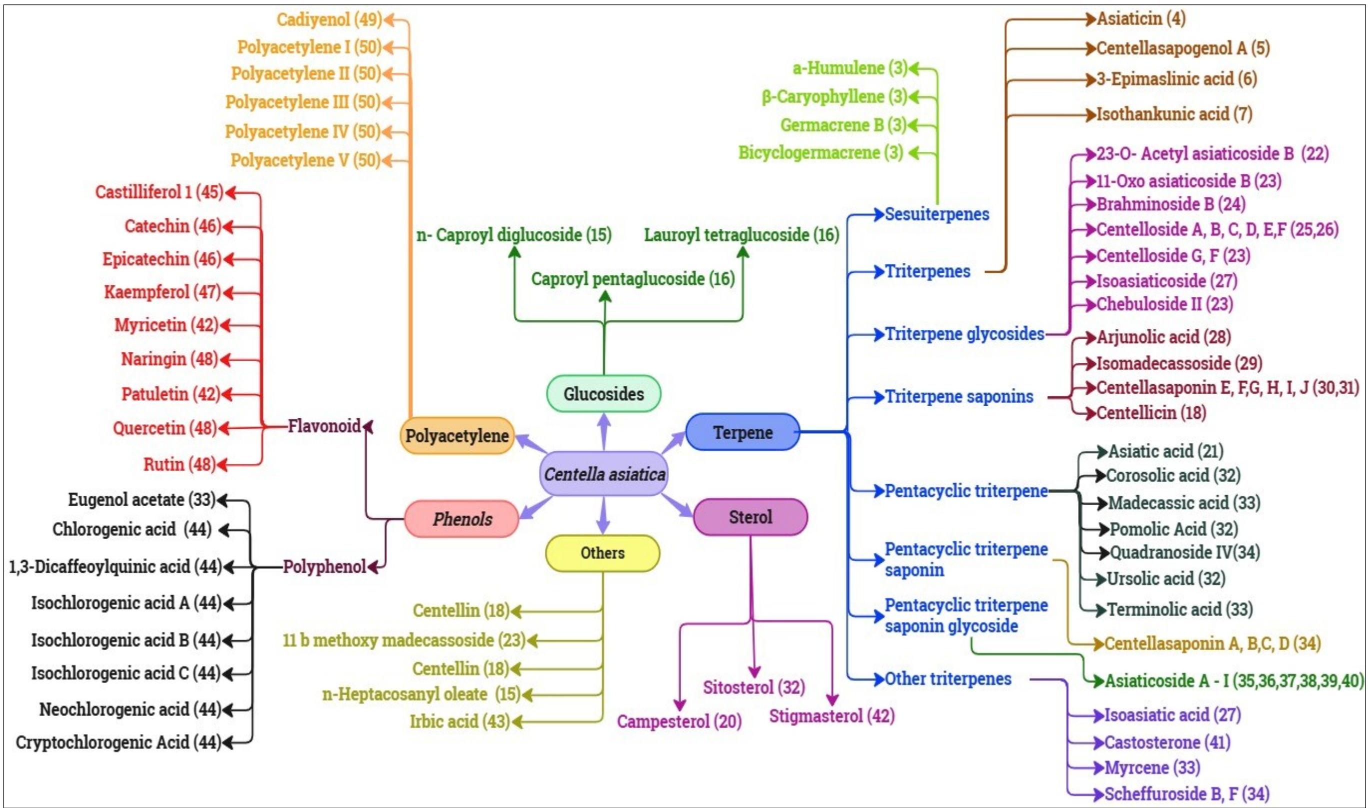

Fig. 1. Chemical constituents of *Centella asiatica* (3, 15-50).

importance of basic and applied research for selecting suitable genotypes for higher plant material medicinally important and with phytochemical yield. Earlier research indicates that saponin and sapogenin content were affected by resource partitioning between primary and secondary metabolism (56). Cultivation of medicinal plants for phytochemicals requires optimized and controlled fertilization.

There are variations in chemotypes/genotypes for the madecassoside and asiaticoside contents due to genetic make-up, expression level and other biosynthetic steps (57). On the contrary, research indicates that asiaticoside content was not accompanied by high yield. Also, the growing conditions significantly affected the herbal yield. There was wide variation in the production of centellosides, viz. asiaticoside, madecassoside, asiatic acid and madecassic acids from *C. asiatica* genotypes. Of these centellosides, asiaticoside and madecassoside are saponins, asiatic acid and madecassic acids are their corresponding sapogenins. *C. asiatica* also reported to possess minor centellosides such as thankuniside, scheffoleside and *Centella* saponins. The quantity of the triterpene compounds changes due to location and environment.

The extraction process and post-harvest handling affected the madecassoside and assiaticoside, which in turn affect the antioxidant activities (58, 59). Variations were found in the asiaticoside and madecassoside contents among the genotypes of Madagascar. Generally, *C. asiatica* genotypes of Madagascar have recorded the highest asiaticoside content (60). There are known pharmaceutical products, viz. Madecassol and Blastostimulina are in the market with *C. asiatica* as the major active ingredients. Research indicates that *C. asiatica* was collected from the wild for increasing demand in the pharmaceutical and cosmetic industries (60). Since commercial cultivation was not undertaken, the overexploitation may endanger the species in its natural habitat.

Triploid and tetraploid of *C. asiatica* were evaluated under field conditions. The tetraploids performed better with larger leaf area, width, petiole length and yield; triterpenoid contents were also high in tetraploids (61). Variation in glucoside content and medicinal properties was reported by (62). The assessment of genetic variability and distribution of genetic variation is very important in the breeding programme. A clear distinguishing leaf characteristic of the genotypes assessed was recorded (63). They also reported that the genetic analyses showed genetic variations found among the genotypes from various locations, which need to be maintained without any loss for further breeding. Habitat-related populations of *C. asiatica* show marked variation in morphological traits, such as leaf area, stolon production, petiole length, leaf colour and other traits (64).

Due to unrestricted exploitation in the pharmaceutical industry and almost nil cultivation, it is listed as a threatened species by the International Union of Nature and Natural Resources and an endangered species (65). Evaluation of *Centella* genotypes is done in various parts where it is being domesticated. Evaluation of different morphotypes from Sri Lanka showed morphologically different characteristics (42). They ensured the possibility of variations among the morphotypes collected from various locations.

Promotion of up-scaled organized agro-commercial cultivation of *C. asiatica* needs to be addressed to fulfil its industrial demand in the country as well as globally. The morphological diversity of the foliar traits and growth pattern can serve as a taxonomic marker for primary *C. asiatica* evaluation (66). Two selected accessions of *C. asiatica* recorded significant variation in growth as well as centelloside content in different months of harvest under two diverse agro-climates. The humid and warm climate in general supported improved biomass and centellosides productivity.

Centella asiatica is reported to be a good herbal source in treating cognitive dysfunction (33). Harvesting during the first month of emergence, the leaves showed the highest quantity of Asiatic acid, showing the best memory-enhancing potential (67). Assessment of two morphologically distinct phenotypes of *C. asiatica* showed that there is distinct variation in the bioactive compounds content among them, which is tissue-specific (24). Research indicates that the genotypes of *C. asiatica* from various parts of Madagascar showed variation in asiaticocide content (68). Evaluation of ten ecotypes of *C. asiatica* in India showed significant variation in the Asiatic acid content, showing the chances of metabolite content-based selection of chemotypes (51). *C. asiatica* morphotypes were assessed for biomass and asiaticosides. Significant variations in biomass yield and asiaticoside content are observed depending on the morphotype and the time of collection. Genotypes/chemotypes of *C. asiatica* were evaluated for high yield and high centellosides content (57). The high herbage yielders with potential centellosides content could be selectively cultivated and utilized for biological and cosmetic applications.

Dry climate reduced the biomass yield and asiaticoside content compared to the sub-humid climate, which was more productive. The results provided more precise information to the economic sector, which confirms the empirical choices made by collectors. They represent the first elements towards sustainable management of the resource and maybe even domestication (53). Polyploids gave more herbage yield and the triterpenoids content than the diploids, expressing the scope for polyploidy breeding (61). The characteristics that have a higher correlation with the total phytochemical quantity were internode length, leaf length, petiole diameter, petiole length, root diameter and root length. The clustering based on phenotype and chemotypic data put the Iranian genotypes in three groups. Leaf length, leaf width, petiole diameter, petiole length, root per node and asiatic acid. These findings will be helpful in the selection of high-yielding genotypes with significant quantities of medicinally important phytochemicals (69). Similar research indicates are there on significant variation in the micronutrients, phenolics, flavonoids, tannins, anthocyanins, carotenoids and ascorbic acid contents, including antioxidant activity of the genotypes of Andaman and Nicobar islands (70).

Asiaticoside content showed a better marker for the selection of genotypes for higher total centelloside content compared to asiatic acid, madecassoside and madecassic acid (71). Though significant morphological variations were found in Vietnam accessions of *Centella asiatica*, the phytochemical contents were quite similar under the same agro-climatic conditions (72). Antioxidant activity of *C. asiatica* was based on the triterpene glycoside content, especially madecassoside and asiaticoside. There was no difference observed in the antioxidant activity of the different plant parts (59).

Global market and the need for commercial cultivation

The major trends in the global market for herbs are witnessed due to the preference of consumers towards naturally derived products. The commercial products from *Centella* are of a wide range, such as liquid extract, smoothing cream, serum, acne gel, tablets, dry leaves, hand soap, *Centella* essence, *Centella* oil, powder, hand sanitizer, vermicelli and hydrating cleanser. At present, most of the *C. asiatica* material collected from the wild for pharmaceutical companies is of very poor quality in terms of its purity and bioactive constituents. In India, *Centella* is harvested from the ditches that are generally contaminated with heavy metals, unacceptable microbial loads (including moulds and yeasts), excess dirt and other harmful chemicals, due to which the raw plant material frequently fails to obtain quality clearance as per the raw herb purity guidelines of WHO (73). The rapid growth of the international market for *C. asiatica* has created a need for establishing more sustainable and economically viable production strategies for this herb and its pure bioactive molecules (74). Hence, it becomes very much essential to promote the commercial cultivation of *C. asiatica*.

There is an immediate need to study the possibility of commercial cultivation of *C. asiatica,* which in turn emphasize a breeding program for the identification of metabolite-specific genotype/chemotype. The first step in the domestication of any species is the identification and selection of genotypes with high yield and high bioactive phytochemical content. Studies regarding the climatic factors on herbage and phytochemical contents have been reported. The phytochemical content was significantly affected by climate, soil and eco-geographical factors, which are site-specific (75-78). The place of cultivation and harvesting period influenced the quantity of the pentacyclic triterpenes in *C. asiatica*. This may affect the quality of the raw materials and hence the herbal medicines from *C. asiatica* (79). Biomass accumulation of tetraploid and diploid *C. asiatica* lines in the field was assessed for the optimal time of harvest. Yield and dry matter content were the highest in the tetraploid line due to its larger leaf size and plant canopy. The tetraploid lines of *C. asiatica* showed higher levels of phytochemicals than diploid lines. Phytochemical accumulation was highest during the four months after planting (61). The effect of the methods of cultivation showed that the biomass from organic cultivation practice showed higher Asiatic acid content than that from the inorganic method. Also, the produce from the first harvest was rich in phytoconstituents (67). Centelloside accumulation was affected by N, P and K fertigation and the plant growth in terms of leaf and herb yield is inversely correlated with the centelloside content. This shows that the nutritional stress may act as a trigger for the secondary metabolite synthesis (56).

A strong negative correlation was reported between saponins and leaf N concentrations and sapogenins were negatively correlated with K concentrations (55). Large-scale cultivation of *C. asiatica* with targeted bioactive compounds can be focused based on documentation of genotypes based on bioactive markers, climatic requirements for better accumulation of the medicinally important phytochemicals and identification of potential niche areas (80). Based on the ecological niche model, annual temperature range and the precipitation pattern significantly affected the centelloside content (80). They proposed that Western Ghats, Northeast India, Eastern Himalaya and Western Himalaya were suitable areas for large-scale cultivation of *C. asiatica* for high centelloside content. Research indicates that suitable cultivation areas for *C. asiatica* were identified through ecological niche modelling with bioclimatic and soil variables and South and Southeast Asia are among the suitable regions for its cultivation (81). They suggest cost-effective alterations like maintenance of optimal pH and modifying the clay content of the soil for open field cultivation rather than controlled atmospheric conditions.

Biotechnological and nanotechnological approaches

The possibilities of production of secondary metabolites by cultured cells with higher levels of desired compounds, *i.e.* concentrations of centelloside metabolites, through biotechnological approaches are being studied. The depletion of the wild stock of *C. asiatica* by unrestricted exploitation and high industrial demand can be avoided by the *in vitro* culture production (34). Steps were taken for the *in vitro* production of centellosides and also conservation of the genotypes. The centellosides content of *in vitro* developed tissues and field-grown leaves was studied (82). It was found that the bioactive principles were higher in the leaves than *in vitro* tissues (60).

In vitro propagated plants had the lowest asiaticoside content. But a significant accumulation of acetoxycentellynol was recorded from the plants as compared to plant material collected *in situ* (68). Phytochemical screening from shoots, callus and cell suspension extracts showed the presence of tannins, flavonoids, terpenoids, saponins and steroids. There were no alkaloids reported. Further density functional theory-based analysis for the structure-activity relationships of phytochemicals from *C. asiatica* showed that ultrasonic-assisted extraction yielded the highest recovery and antioxidant activity (8). Nanoformulations need to be studied for the improvement of the bioavailability of various constituents of *C. asiatica* to enhance its efficacy in treating various disorders (83).

Future Prospects

Many new strategies were being explored for rationalizing the exploitation of *Centalla asiatica* in wild habitat (54). Further, breeding and selection programs are an essential solution for better commercial production, which has still not been up on a wide scale. Sustainability of production depends on the identification of elite genotypes, suitable agrotechniques and the potential genetic exchange between wild and cultivated species. There is good scope for selection as there is high heritability for the fresh herb yield, dry herb yield and centellosides content, except for madecassoside content, which can be given a significant focus (Fig. 2) (84).

Conclusion

Centellosides in *Centella asitica, viz.* asiaticoside, madecassoside, asiatic acid and madecassic acid are pharmaceutically important bioactive compounds. There are many medicinal products in the international market projecting the demand for *C. asiatica*. But commercial cultivation of *C. asiatica* is not commonly practised, which obviously indicates that the raw materials are being collected from wild habitats. This will lead to endangering the species.

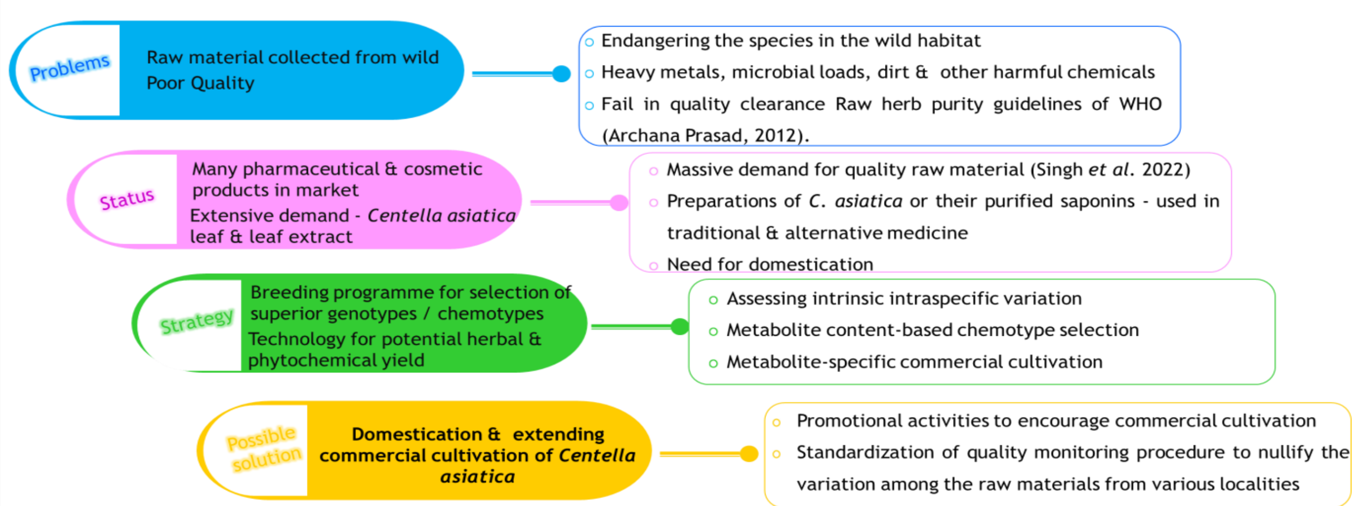

Fig. 2. Scope of sustainable utilization of Indian Pennywort as a commercial medicinal herb.

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Authors' contributions

KI carried out the collection of articles and formulated the concept. MS and AND prepared the draft for the review. PSS and SSJR of the references. MAV and KRS corrected and revised the manuscript. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest: The Authors do not have any conflicts of interest to declare.

Ethical issues: None

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