HEALTH BENEFITS AND TOXICITIES OF THE CONSUMPTION OF *CENTELLA ASIATICA*: A SCOPING REVIEW

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Abstract

Introduction: *Centella Asiatica* is a well-known herb used in alternative medicine. Despite being widely used, few papers investigated the health benefits of *C. asiatica* in depth. Other than concerning its up-to-date benefits, the toxicity of *C. asiatica* needs to be addressed as well. As previous studies did not show any toxicities of this herb in detail, further investigation is necessary. Hence, the main objective of this review is to investigate the benefits and toxicities of the consumption of *Centella Asiatica*. **Methods:** A scoping review was conducted according to the Arksey and O'Malley framework in two different phases: primary phase using electronic databases such as PubMed, Scopus, ResearchGate, and Google Scholar, and a secondary phase known as manual literature search. **Results:** Finally, 21 articles were included in the review. The health benefits of *C. asiatica* included neuroprotective, antihyperglycemic, anti-cancer, antioxidant, gastroprotective, nephroprotective, hepatoprotective, antihypertensive, anti-inflammatory, anxiolytic and antidepressant, and antiepileptic benefits. Unfortunately, all the papers did not discuss the toxicities of *C. asiatica* although two of them mentioned the positive herb-drug interactions of *C. asiatica*. Within the themes extracted from all reviewed studies, a neuroprotective benefit was the most largely mentioned with some of the chemical components of *C. asiatica* such as asiatic acid (AA) being primarily investigated in some papers. **Conclusions:** All the studies mainly investigate the same areas of health benefits of *C. asiatica* while some research discovers new areas, particularly in mental-related conditions. This study evaluates the breadth of information contained in the available literature and identifies the potential for a future systematic evaluation of specific updated health benefits or toxicities that have yet to be examined due to a lack of data.

KEYWORDS: Centella Asiatica, Health benefits, Toxicities

Introduction

Centella asiatica is a tropical medicinal plant belonging to the family *Apiaceae*. This herbal plant can be found in the Nusantara region, the Indian subcontinent and the East Asian area. In some countries, *Centella asiatica* has been cultivated widely since this herb contains a lot of medical properties mentioned in traditional Chinese and ayurvedic medicines for a long period of time. The chemical constituents of *C. asiatica* consist of triterpenes which include asiaticoside and madecassosid (Shahab Uddin et al., 2017) alongside aglycons, asiatic acid and madecassic acid (Alfarra & Omar, 2013; Chong & Aziz, 2011). The most active constituent is asiaticoside, a substance that prevents infectious agents or organisms from spreading (National Centre for Biotechnology Information, 2021). Mukherjee et al. (2007) showed that the extract of *C. asiatica* has a higher inhibition effect compared to physostigmine, a reversible acetylcholinesterase (AChE) inhibitor. However, Orhan et al. (2013) stated that only 200 μg/mL can inhibit approximately half of acetylcholinesterase (AChE). In addition, the polyphenol compounds and flavonoids are readily available in *C. asiatica* to perform a better antioxidant activity, especially in the leaves since they contain the highest phenolic compounds. One paper suggests the antioxidant activity of *C. asiatica* as this herb has a protective role against γ-radiation-induced DNA damage (Joy & Nair, 2009). Meanwhile, Asiaticoside and Asiatic Acid, chemical components of *C. asiatica* demonstrated have been shown in animal studies to have antidepressive, neuroprotective, and anxiolytic effects (Puttarak et al., 2017; Sultan et al., 2011). Furthermore, the chemical properties of *C. asiatica* contain significant amounts of insoluble dietary fibers (Kabir et al, 2014). Because of their high viscosity and the ability to bind to glucose, these dietary fibers usually inhibit diffusion and decrease the transit time of ingested foods in the GI tract.

The consumption of C. asiatica within recommended dosage will not produce any sign of toxicity or side effect. However, studies found that, high dose consumption of *C. asiatica* may lead to stomach upset, nausea, headache, dizziness, and drowsiness. (Jantwal et al., 2007; Tan et al., 2021). For the restriction issue, it is advisable for women during pregnancy and lactation not to consume this herb as it may have emmenagogue effects. Prolonged treatment with high doses of *C. asiatica* exhibits the reduction of active properties' metabolism, which might increase the toxicity risk.

Despite extensive research, the list of health advantages of this plant is out-of-date, particularly with regard to the most recent results on its benefits. Aside from that, the toxicities of this herb's ingestion is still not clear. Hence, the aims of this review are to identify the health advantages of C. Asiatica consumption and its toxicity level.

Methods

In order to search for the articles, this study used the scoping review method, using 6 stages created by Arksey and O'Malley (2005) to discuss the evidence from various articles and journals. Those 6 stages are identifying the research question; identifying relevant studies; study selection; charting the data; collating, summarizing, and reporting the results and consultation. The research question of this review is related to the benefits and toxicities of the

consumption of *C. Asiatica;* what are the benefits of the consumption of C. asiatica? and what are the toxicities of the consumption of C. asiatica? Next, there are two methods used in search for relevant studies. The first method of searching for relevant studies is using online searching. Several search engines were used to identify articles with suitable keywords such as PubMed, Scopus, ResearchGate, and Google Scholar. In this study, other than the term *"health benefits and toxicities of centella asiatica"*, other words such as *"health benefits or toxicities of centella asiatica"*, *"centella asiatica"*, *"pennywort"*, and *"gotu kola"* were also used to find qualified papers. For titles that appear to be relevant to the topic of this scoping review, the abstracts of each reference were reviewed according to the inclusion and exclusion criteria that were defined. Some criteria that include inclusion and exclusion were used to eliminate unrelated papers on the topic. The inclusion criteria include studies which are published in English, using in vivo experimental methods and focusing on the consumption of the *C. asiatica*. All the data is then charted on a 'data charting form' in Excel. After the process of 'charting the data' is completed, the data from the studies included were presented through numerical and thematic analysis. Then, the reviewed papers were sorted according to the themes. The presentation of the results was followed according to the themes and the number of papers associated with each theme. The last stage, which was consultation was not applied in this review since there was no consumer or stakeholder involved.

Results

The initial search for articles related to the study from various databases identified a total of 866 articles. Then, all 866 articles were screened based on their titles and abstracts and 827 articles were then excluded. Next, 39 remaining articles were evaluated for eligibility by reviewing their full-text articles. Finally, after full- text articles were examined via manual literature review, 21 studies were included in the review. Themes were formed and named by analyzing and combining the codes from each article. From the thematic analysis, 11 themes were derived: neuroprotective in six articles, antihyperglycemic in five articles, anti-cancer in four articles, antioxidant in two articles, anti-inflammatory in two articles, gastroprotective in two articles, nephroprotective in two articles, hepatoprotective in one article, antihypertensive in one article, anxiolytic and antidepressant in one article and antiepileptic in one article. The themes or health benefits and subthemes discussed in each study were listed in Table 1.

Table 1: Themes and Subthemes of Included Studies (n=21)

Theme (Health Benefits)	Subtheme (Experimental reasons)	Article
1. Neuroprotective	● Decrease Acetylcholinesterase (AChE) activity in the brain	Doulah, Mahmoodi, & Pourmahdi Borujeni (2020); Firdaus et al. (2020)
	● Improve memory	Mitha, Yadav, & Bolumbu (2021); Yuliani et al. (2021)
	● Improve cognitive disrupt	Doulah, Mahmoodi, & Pourmahdi Borujeni (2020)
	● Normalizes oxidative stress	Mitha, Yadav, & Bolumbu (2021)

	• Upregulate BDNF expression	Doulah, Mahmoodi, & Pourmahdi Borujeni (2020)
	• Prevent hippocampal cell death	Yuliani et al. (2021)
2. Antihyperglycemic	• Regulate blood glucose levels	Ariastuti et al. (2020); Giribabu et al. (2020); Setyaningsih et al. (2021)
	• Improve insulin expression	Ariastuti et al. (2020); Giribabu et al. (2020); Uddandrao et al. (2020)
	• Regenerate pancreatic β cells	Ariastuti et al. (2020); Oyenihi et al. (2019)
	• Mitigate diabetes-induced alterations in testicular fatty acids	Oyenihi et al. (2019)
	• Inhibit adipogenesis	Uddandrao et al. (2020)
3. Anti-cancer	• Reduce heart TNF-α concentration	Hartanto, Purwaningsih & Krisnamurti (2021); Sriepindonnta et al. (2021)
	• Reduce the incidence of polyps	Siddique et al. (2017)
	• Normalise the concentration of LPO	
4. Antioxidant	• Reduce the production of reactive species	Oyenihi et al. (2019)
	• Improve antioxidant capacity	
	• Restore the levels of Vitamin C & E	Siddique et al. (2017)
5. Gastroprotective	• Reduce ulcer	Husori et al. (2021)
	• Strengthen mucosal defensive factors	
	• Inhibit lipid peroxidation	Zheng et al. (2016)
6. Nephroprotective	• Decrease proteinuria	Setyaningsih et al. (2021)
	• Deplete glomerulosclerosis	
	• Inhibit vascular remodelling in the kidney	
	• Lower urine volume, kidney weight and	Wijayaningsih et al. (2020)

	glycosuria	
7. Hepatoprotective	• Decrease the liver weight • Reduce liver tissue damage • Increase the cytokines level	Choi et al. (2016)
8. Antihypertensive	• Attenuate systolic blood pressure • Prevent the rise of Brain Natriuretic Peptide (BNP) level	Bunaim et al. (2021)
9. Anti-inflammatory	• Protect the cerebrum against inflammation-induced damage	Giribabu et al. (2020)
10. Anxiolytic and Antidepressant	• Decrease the anxiety levels • Lower the behavioural despair or depression	Ceremuga et al. (2015)

Other than the health benefits of *C. asiatica*, this paper also aims to identify whether there are any toxicities with regards to the consumption of *C. asiatica* mentioned in those reviewed papers. Unfortunately, most articles do not discuss the toxicities of overdoses of *C. asiatica* in depth. Most papers, however, stated that *C. asiatica* with higher doses give a greater effect on how the herb shows its properties. In terms of herb-drug interactions between *C. asiatica* and other types of drugs, most of the papers also do not discuss this topic. However, two papers briefly mentioned this herb-drug intervention which are Ceremuga et al. (2015) and Kumar et al (2021). Ceremuga et al. (2015) reported a significant result which shows the co- administration of *C. asiatica* and midazolam gives a significant effect compared to treatment with midazolam alone. Meanwhile, Kumar et al. (2021) proved the co-administration of *C. asiatica* with drugs exhibits a greater result in protecting seizures in rats compared to the treatment of the drugs alone.

Discussion

This scoping review was conducted to investigate the benefits and toxicities of the consumption of *C. asiatica* on human health. Hence, this study wants to assess all the information about the health benefits of *C. asiatica* in recent years. Besides, this study also aims to identify if there is any toxicity related to overconsumption of *C. asiatica* reported by the papers that were involved in the thematic analysis.

Findings from the review showed that the neuroprotective benefits of *C. asiatica* was the most widely assessed in the studies involved. One of the primary experimental reasons that the authors come out in the domain of neuroprotection is the decrease of acetylcholinesterase (AChE) activity in the brain, which is one of the subthemes under this

health benefit. Based on Doulah, Mahmoodi & Pourmahdi Borujeni (2022) as well as Firdaus et al (2020), the inhibition of AChE enzyme increases the amount of acetylcholine, a type of neurotransmitter which increase the synaptic transmission in the Alzheimer Disease (AD) brain. In addition, the AChE inhibition was contributed by the high concentration of triterpenes such as asiaticoside and madecassoside found in the *C. asiatica*, as these bioactive components were known for several advantageous pharmacological activities.

The toxicities of *C. asiatica* are more likely to occur in cases of overdose consumption and herb-drug interaction. The majority of the papers reviewed did not report any cases of *C. asiatica* overdoses. However, two of the papers did mention the herb-drug interactions of *C. asiatica* with positive results shown (Ceremuga et al . 2015 and Kumar et al. 2021). This occurs because most papers focus solely on the health benefits of this herb, with no mention of overdoses or drug interactions.

The reviewed papers also come with different physical attributes that can be discussed. Firstly, the majority of the papers reviewed in this study were done by the researcher from Indonesia, one of the Southeast Asian countries, as well as the nation of India. *C. asiatica* or gotu kola is a native plant to both countries which eases the investigation towards this herb. However, there seems to be less literature produced by Malaysians, although this herb is quite well-known in our population. 'Daun pegaga', another name of *C. asiatica* in Malay, is also famous for being consumed raw as 'ulam' in rural areas. Hence, it has become a necessity for researchers in Malaysia to study *C. asiatica* in depth as the data are very beneficial for our society.

Secondly, with regard to experimental rats, over 90% of the reviewed papers utilize either Sprague-Dawley (SD) or Wistar rats as a model. There are some differences between these two laboratory rats. One of the differences is its growth rate. Based on Kühn et al (1983), SD rats have a higher growth rate and food conversion than Wistar rats, when they are kept at room temperature. Other than that, the metabolic effects of Wistar rats were detected earlier compared to SD rats. For instance, Marques et al. (2015) recorded an earlier detection of metabolic effects caused by high fat (HF) diet in Wistar rats than SD rats although both rats can be used in HF diet-induced obesity experiment.

Conclusion(s)

To conclude, *C. asiatica* has a number of benefits including neuroprotective, antihyperglycemic and anti-cancer benefits. In addition, the toxicities of *C. asiatica* did not disclose the dose that they used in the reviewed papers even though some of the literature states a positive herb-drug interaction of *C. asiatica*. It is recommended that future research should include an experimental study design to determine the effectiveness of *C. asiatica* in combating specific diseases.

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