Review Article

Review on Pharmacological and Potential Cosmeceutical Values of *Centella asiatica* (Pegaga)

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Abstract

Centella asiatica or also known as pegaga in Malaysia is a herbaceous perennial plant that belongs to the family of Apiaceae. This plant had been used for decades for its medicinal properties and immense potential. The present study aimed to review the pharmacological and potential cosmeceutical values of *Centella asiatica*. This review was based on research articles, reports, clinical trials, *in vitro* and *in vivo* trials retrieved from electronic databases and limited to the publication from the year 2015 onward. It excluded any articles related to food processing and trials that combined with other types of plants. Among the database used were the US National Library of Medicine (PubMed), ScienceDirect, EMBASE, Frontiers, Elsevier and Google Scholar. The pharmacological actions of *Centella asiatica* were determined through the disease model and its pathological mechanisms or any major findings based on the trials conducted. These findings were then classified according to the cardiovascular system, neurological system, endocrine system and digestive system. In terms of cosmeceutical values, *Centella asiatica* has immense potential in demonstrating anti-aging, skin hydration, anti-acne, enhancement of skin regeneration and skin barrier properties. These properties are highly regarded in the skincare industry, and therefore, this review can be used as a reference in further development of naturally based products. The phytochemical constituents responsible for most therapeutic actions were madecassoside, madecassic acid, asiaticoside and asiatic acid. Anti-inflammatory and antioxidants properties were found to be the core mechanisms of *Centella asiatica* and covered most of the pathologies.

Keywords: *Centella asiatica*, cardiovascular disease, neurological disease, endocrine disease, oxidative stress, cosmeceutical

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1.0 Introduction

Centella asiatica is a low-growing perennial herbaceous plant that belongs to the family of Apiaceae or Umbelliferae (1). Previously, *Centella asiatica* was classified in the subfamily of Mackinlayoideae (2), however, this plant was displaced to the subfamily of Hydrocotyloideae due to the molecular phylogeny research (3). Table 1 shows the taxonomy classification of *Centella asiatica* (4). This plant had multiple nomenclatures apart from *Centella asiatica* which usually employed in the scientific term. Other synonym names are *Hydrocotyle asiatica, Hydrocotyle lunata, Hydrocotyle brasiliensis, Trisanthus cochinchinensis, Centella erecta, Centella coriacea* and *Glyceria asiatica*. There were also several local names such as Indian pennywort or asiatic pennyworth in English, sombrerito and hierba de clavo in Spanish, hydroctyle asiatique or écuelle d'eau in France, ji xue cao in China, Brahmi in India, tsubokusa in Japan, pegaga in Malaysia, asiatische sumpfpfennigkraut in Germany and gotu kola in several Asian countries (1,2).

Figure 1 shows the morphology of *Centella asiatica.* It is described as a perennial creeping herb with internodes rooting and shovel shaped leaves. The stem of the plant is slender, creeping stolons with shallow grooves which sometimes looks reddish-green or brownish (5). The flowers are green or pinkish-white in colour bloom in small, dense and rounded umbels. The seeds are oval in shape and 3-5mm in length. (5). This plant is tasteless but it has an aromatic scent due to the essential oil or resin presence in its organs (1). For medicinal purposes, the whole plant including the leaves and stem were dried up and used to make the medicine (6).

Table 1: The taxonomy classification of *Centella asiatica* adapted from Brinkhaus *et al.* (4)

Classification	**Nomenclatures**
Kingdom	Eukaryota
Subkingdom	Embryophyta
Division	Spermatophyta
Subdivision	Angiospermae
Class	Dicotyledoneae
Subclass	Rosidae
Superorder	Aralianae
Order	Araliales (Umbelliflorae)
Family	Apiaceae or Umbelliferae
Subfamily	Hydrocotyle
Genus	*Centella*
Species	*Centella asiatica*

Figure 1: Morphology of *Centella asiatica*.

There are several identified phytochemical constituents isolated from *Centella asiatica.* The constituents are classified into triterpenes, phenolic compounds, alkaloids, carbohydrates, vitamins, essential oil, mineral, amino acid and glycosides as summarized in Table 2 (7–9). With those constituents, *Centella asiatica* can produce a wide range of functions and has a great market value attributed to its rich therapeutic properties. However, the research required more scientific approaches and evidence to justify its potential values. Moreover, there were lack of reviews highlighting on the cosmeceutical values *of Centella asiatica* regardless of rising demand in skin care or cosmetic industry. Centella asiatica had gaining popularity as a natural based skin care ingredient with ample of benefits to the skin. Therefore, this study incorporated a detailed review and summarized the pharmacological effects and potential cosmeceutical values of *Centella asiatica*.

Table 2: Phytochemical constituents of *Centella asiatica.*

Main classes	**Phytochemical constituents**
Triterpenes	Asiaticoside, asiatic acid, centelloside, madecassoside, brahmoside, brahminoside (saponin glycosides), asiaticentoic acid, centellic acid, centoic acid, madecassic acid, indocentoic acid, terminolic acid and betulic acid
Phenolic compounds	*Flavonoids*: Kaempferol, kaempferol-3-o-β-d-glucuronide, castilliferol, quercetin, quercetin-3-o-β-d-glucuronide, castillicetin, apigenin, rutin, luteolin, naringin
	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 Terpenoids

Alkaloids	Hydrocotylin
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
Volatile oils and fatty oils	*Terpenoids variation:* β-caryophyllene, trans β-farnesene and germacrene D (sesquiterpenes), α-pinene and β-pinene.
	Fatty acids: Linoleic acid, linolenic acid, lignocene, oleic acid, palmitic acid, stearic acid
Amino acids	Alanine and serine (major components), aminobutyrate, aspartate, glutamate, histidine, lysine, threonine, arginine, leucine, iso-leucine, valine, methionine, tyrosine, phenylalanine, proline, cystine, glycine
Glycoside	Asiaticoside A, asiaticoside B, madecassoside, centelloside, brahmoside, brahminoside, thankuniside, glycoside D, and glycoside E

2.0 Method

2.1. Identification of studies

A comprehensive search was conducted on literature published from the year 2015 to 2021 with restriction to English language publications. The search was performed via an electronic database and cross-referencing of the articles. Among the database used were the US National Library of Medicine (PubMed), ScienceDirect, EMBASE, Frontiers, Elsevier and Google Scholar. The literature was obtained through keyword searches such as *Centella asiatica*, cardiovascular disease, neurological disease, endocrine disease and oxidative stress.

2.2. Selection of studies

This review paper was based on previous research articles, experimental studies, reports and clinical trials in which described the effectiveness of *Centella asiatica* in pharmacological and cosmeceutical applications. The preferential literature was primarily assessed through titles and abstracts and followed by a full report analysis of the publication against the predetermined inclusion criteria.

2.3. Inclusion and exclusion criteria

The inclusion criteria were comprised of *Centella asiatica* plants or extracts, medicinal therapy, topical application, in vitro trials, in vivo trials, in silico trials, assessment reports, previous reviews, monograph and experimental outcomes. The articles related to food processes and experimental herbal treatment which combines with other types of plants besides *Centella asiatica* were excluded in this narrative review.

3.0 Results and Discussion

In this review, there were proximately 115 studies retrieved from electronic databases and obtained through the keywords search. After screening each of the articles, 71 articles were excluded from this review with 46 of the articles were published before 2015 and 25 of the articles were in the exclusion criteria

which involving the combination with other type of plants and food processes. 40 of the articles were identified within the inclusion criteria and were used in this review. Among the 40 articles, there were 12 articles from *in vitro* experiments, 14 were *in vivo* experiments, 10 *in vitro* and *in vivo* experiments, 2 clinical trials and 2 assessment reports.

3.1. Pharmacological effects of Centella asiatica on the cardiovascular system

Several types of research had shown promising results in the effects of *Centella asiatica* on cardiovascular disease. Asiatic acid and asiaticoside were the most used compounds to test the effect of this plant. This section mainly focuses on the cardioprotective, anti-atherosclerotic and anti-hypertensive effects of *Centella asiatica* on cardiovascular diseases such as myocardial ischemic or reperfusion injury, myocardial infarction, cardiac hypertrophy, atherosclerotic and pulmonary hypertension. The summary of pharmacological effects of *Centella asiatica* on cardiovascular system can be viewed in Table 3.

Centella asiatica constituent particularly asiatic acid had demonstrated its cardioprotective effects via the activation and deactivation of signalling pathways involved in the pathophysiology of myocardial ischemia, myocardial infarction and cardiac hypertrophy. In vitro study by Huang *et al* have shown that asiatic acid exerted its cardioprotective effects by the stimulating the Akt/GSK-3β pathways and increases HIF-1α level in hypoxic cardiomyocytes. The signalling pathways of Akt/GSK-3β had been associated with the cardiomyocyte survival by acting as a negative feedback regulator that limits the cell apoptotic event upon activation. HIF-1α also exhibit protecting factor by enhancing gene transcription for cell survival, prevent accumulation of reactive oxygen species and block the permeability of mitochondrial transition pore. Besides, asiatic acid at 10 μM for 4 hours significantly enhances the cell viability through the decrease of lactate dehydrogenase (LDH) and produces anti-apoptotic effect through reduction of caspases activity and Bax/ Bcl-2 ratio. Furthermore, it can also reverse mitochondrial dysfunction by promoting membrane potential activity, reduces intracellular calcium ion concentration (10,11).

Asiatic acid can also prevent cardiac hypertrophy and fibrosis by activating the AMP-activated protein kinase α (AMPKα) and decreases pressure overload, angiotensin II and collagen accumulation (12). According to Huo *et al*., asiatic acid of 25 mg/kg enhanced cardiac functioning in myocardial infarction by decreasing the mRNA expression of inflammatory cytokines and decreases the interstitial myocytes fibrosis in the infarct border zone. Furthermore, asiatic acid also inhibited the p38 MAPK and ERK1/2 phosphorylation located in the myocardium to prevent the left ventricular remodelling which is one of the factor of myocardium infarction (13). Another study reveals that asiatic acid can be used to prevent and treat cardiac diseases by inhibiting the excessive interleukin-1β (IL-1β) expression and ANP, inactivated the NF-κB binding action and preventing TAC-induced cardiac hypertrophy (14).

Hypertension or high blood pressure can cause serious complications on the heart if left untreated. With constant excessive pressure, the wall of the arteries becomes harden and the flow of oxygenated blood to the heart reduces. Hence, it may result in a series of cardiovascular events such as heart attack, angina, heart failure and stroke (15). The roles of the autonomic nervous system, renin-angiotensin system and endothelial functioning are important as it is related to

the mechanism of blood pressure control (16). Asiatic acid and asiaticoside exhibited anti-hypertensive effects through a combination of anti-inflammatory and antioxidant action. A study on renovascular hypertensive rats demonstrated the effect of asiatic acid on alleviation of hemodynamic disturbance through suppression of renin-angiotensin system (RAS) activation, overexpression of oxidative stress markers and inflammatory mediator (17). The study from Wang *et al*. indicated that administration of asiaticoside in hypoxic rats decreases pulmonary hypertension via suppression of TGF-βRI and TGF-βRII overexpression and inhibition of Smad2/3 phosphorylation signalling. On top of that, asiaticoside can also prevent vascular remodelling through restriction on pulmonary arterial smooth muscle cells (PASMCs) proliferation in a controlled dose by enhancing PASMCs apoptosis in hypoxic conditions (18). Another study from the same author further investigated the role of asiaticoside on pulmonary hypertension. They found that the asiaticoside can activate the nitric oxide (NO) signalling pathways by promoting the serine/threonine-specific protein kinase/eNOS phosphorylation and therefore enhancing the NO proliferation and block the endothelial cells from apoptosis caused by hypoxic conditions (19).

Table 3: Pharmacological effects of *Centella asiatica* on cardiovascular system.

Effects	Diseases model	Model	Extract/ compound	Compound concentration	Duration of intervention	Animal/ cells	Mechanism/ finding	Reference
Cardioprotective	Myocardial ischemic/ reperfusion injury	*In vitro*	Asiatic acid	10 µM	4 hours	Rat H9c2 cardiomyocytes	↓ Apoptotic cardiomyocyte death by ↓ caspase-3, ↓ caspase-9, ↓ Bax/Bcl-2 ratio, ↑Akt/GSK-3β/HIF-1α pathway, ↑mitochondrial function, ↓ ROS, ↑ MMP and ↓ Ca^{2+}	(11)
	Cardiac hypertrophy	*In vivo & in vitro*	Asiatic acid	10-30 mg/kg	7 weeks	Aortic banding and AMPKa2 knockout mice	↓ Cardiac hypertrophy, ↓ pressure overload, ↓ Ang II in myocytes, ↓ cardiac fibrosis, ↓ collagen accumulation, ↑ AMPKα, ↓ mTOR/ P70S6K/ S6 pathways, ↓ ERK	(12)
	Myocardial infarction	*In vivo*	Asiatic acid	25 mg/kg	4 weeks	Rat subjected to coronary artery ligation	↓TGF-β1, ↓ p38 MAPK, ↓ ERK1/2, ↓ cardiac remodelling, ↓ cardiac fibrosis, ↓ cardiac hypertrophy	(13)
	Cardiac hypertrophy	*In vivo & in vitro*	Asiatic acid	2.5-30 µM	24 hours	C57BL/6 mice and cultured neonatal mice cardiac myocytes	↓ IL-1β-induce hypertrophic respond, ↓ NF-κB binding activity, ↓ cardiomyocyte surface area, ↓ ANP expression, ↓ cardiac pressure overload, ↓ left ventricular chamber dimensions	(14)

Anti-hypertensive	Renovascular hypertension	*In vivo*	Asiatic acid	30 mg/kg	4 weeks	Male Sprague-Dawley rats	↓ RAS, ↓ ACE, ↓ Ang II, ↓ AT_1R, ↑ AT_2R, ↓ NADPH oxidase ($gp91^{phox}$, $p47^{phox}$), ↓ MDA, ↓ ROS, ↑ NOx ↓ NF-κB, ↓ TNF-α,	(17)
	Pulmonary hypertension	*In vitro & in vivo*	Asiaticoside	50-100 mg/kg	4 weeks	Adult male Sprague-Dawley rats	↓ HPH, ↓ TGF-βRI, ↓ TGF-βRII, ↓ Smad2/3 signalling, ↓ PASMCs, ↑ PASMCs apoptosis	(18)
	Pulmonary hypertension	*In vitro & in vivo*	Asiaticoside	50 mg/kg	4 weeks	Adult male Sprague-Dawley rats	↓ HPH, ↓ Endothelial damage, ↑ NO production, ↓ cGMP, ↑ p-Akt	(19)

GSK-3β- glucose synthase kinase-3β, Akt- serine/threonine-specific protein kinase, HIF-1α- hypoxia-inducible factor 1α, ROS- reactive oxygen species, MMP- mitochondrial membrane potential, Ca^{2+}- calcium ion, Ang II- angiotensin II, AMPKα- adenosine monophosphate-activated protein kinase α, mTOR- mammalian target of rapamycin, ERK- extracellular signal-regulated kinase, TGF-β1- transforming growth factor beta, MAPK- mitogen-activated protein kinase, IL-1β- interleukins-1β, NF-κB- nuclear factor- κB, ANP- arterial natriuretic peptide, TNF-α- tumour necrosis factor-alpha, MLC- myosin light chain, VE- vascular endothelial, ZO- zona occludens, RAS- renin-angiotensin system, ACE- angiotensin converting enzyme, NADPH- nicotinamide adenine dinucleotide phosphate, MDA- malondialdehyde, NOx- nitric oxide metabolism, HPH- hypoxia-induced pulmonary hypertension, TGF-βR- transforming growth factor beta receptor, PASMCs- pulmonary arterial smooth muscle cells, NO- nitric oxide, cGMP- cyclic guanosine monophosphate

3.2. Pharmacological effects of Centella asiatica on neurological systems

The neurological system is composed of a very complex and specialized structures which made it susceptible to multiple disorders and injuries that may impede cognitive and sensory-motor functioning. *Centella asiatica* had been identified to exhibit a neuroprotective effect against neural-related disease and enhanced the regeneration of injured nerves (20). Summary of pharmacological effects of *Centella asiatica* on neurological system can be viewed in Table 4.

Oxidative stress has been linked to the etiopathology of Alzheimer's disease (AD) and Parkinson's disease (PD). It occurs when there are imbalanced states between the reactive oxygen species (ROS) and antioxidants. ROS in normal conditions plays role in protection against foreign particles like xenobiotics and regulation of intracellular signalling cascade (20,21). However, an elevated level of ROS negatively affects neuronal activity resulting in cognitive impairment (20). Enzymes like superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX) are the first line defence involved in the mechanism of antioxidants against the generation of ROS (22). Activation of nuclear factor erythroid-2-related factor 2 (Nrf2) antioxidant signalling pathways also helps in the cellular defence against ROS mediated oxidative damage (23). Several previous studies have supported the aforementioned indicator of antioxidants found in *Centella asiatica*. Chiroma *et al*. reported that administration of *Centella asiatica* can attenuates the cognitive dysfunction effect of D-galactose (D-gal) and aluminium chloride ($AlCl_3$). This study depicted *Centella asiatica* ability in compensating the cholinergic impairment by reducing the AChE level and altered the oxidative balance by stimulating SOD and GPX activity while reducing the malondialdehyde (MDA) level which responsible in ROS generation (24). Studies from Matthews *et al*. demonstrated the uses of *Centella asiatica* water extract in reducing oxidative stress via enhancing the transcription of antioxidant response element (ARE) genes expression including the Nrf2 pathways resulting in the decrease of plaque-associated SOD1 (25). Other studies also portrayed similar findings of *Centella asiatica* antioxidant effect involving enhancement of SOD, GPX, catalase, and glutathione reductase (26,27).

Furthermore, there is a positive correlation between neuroinflammation and the mechanisms of neurodegenerative diseases like AD and PD (28). Excessive activation of microglia triggers the release of various pro-inflammatory mediators and neurotoxins including nitric oxide (NO), pro-inflammatory cytokines (TNF-α, IL-1β,) and formation of ROS (29). Substantial release of immune responses will result in chronic neuroinflammation that induces Aβ burden with tau hyperphosphorylation in AD and dopaminergic degeneration in PD (30,31). Studies had shown tha*t Centella asiatica* significantly decreases the release of pro-inflammatory factors such as NO, TNF-α and ROS via inhibition of NF-kB transcription factor in PI3K/AKT and ERK1/2 signalling pathways (32,33). The anti-inflammatory properties of *Centella asiatica* were attributed from the madecassic acid compound according to Zetty *et al.* (33). Besides, madecassoside at maximum non-toxic dose was justified to possess antioxidative properties as it can attenuate the ROS proliferation by suppressing the gene expression of pro-neuroinflammatory mediators (34).

Brain-derived neurotrophic factor (BDNF) is fundamental in cognitive function as it is closely associate with roles of neurons maintenance, plasticity, survival and regulation (35). In neurodegenerative disorder, downregulation of BDNF concentration was observed in the brain and blood. This may be the result of excess production of pro-inflammatory mediators and ROS causing the development of neuroinflammation which modulate neuronal function and increase neurotoxicity (36). According to Nataraj *et al*., pre-treatment with asiatic acid significantly improve the diminished expression of neurotrophic factors (NTFs) such as BDNF, glial cell line-derived neurotrophic factor (GDNF) and Vascular endothelial growth factor (VEGF) which was caused by neurotoxicity (37). Therefore, *Centella asiatica* and its derivatives have proven to be effective in elevating the BDNF protein expression as well as attenuating the core of neuroinflammation which affect the BDNF level including inflammatory cytokines and oxidative (26, 37–40).

In addition, Centella asiatica can also exhibit neuroprotective effect through metabolic pathway. Study by Speers A.B *et. al.* depicted the effect of *Centella asiatica* on altering the metabolomic profile which can induce cognitive progression by restoring mitochondria functioning as well as oxidant imbalance and improving synaptic density. In this case, the dose 500 mg/kg/day of *Centella asiatica* had significantly altered purine, nicotinate, nicotinamide and glycerophospholipid metabolism in the brain. Through purine metabolism pathways, *Centella asiatica* normalized the level of inosine and hypoxanthine whereas in nicotinate and nicotinamide pathways, there were upregulation in the cortisol level of nicotinamide adenine dinucleotide (NAD+) and its precursors. For glycerophospholipid metabolism pathways, Centella asiatica significantly enhances choline-containing compound at cortical level which responsible in increasing the concentration of acetylcholine (ACh) neurotransmitter (41). Centella asiatica had also proven in modifying the metabolic pattern of amino acid and energy metabolism through apparent increase in several metabolites such as isoleucine, lactate, proline, methionine, valine, leucine and glutamine. These metabolites plays a significant roles in the brain biochemical functioning including protein synthesis, energy metabolism, neurotransmitter production, protection from ROS and glutamate compartmentalisation (42).

In summary, *Centella asiatica* and its derivatives showed tremendous benefits in the neurological system. It can alleviate oxidative stress, repairs mitochondrial

abnormalities, suppress the exacerbated inflammatory response, improve the BDNF concentration and altered the metabolomic profile in the brain. Furthermore, *Centella asiatica* can also reduce neuron cell death by decreasing cell apoptosis which then increases the chances of neuronal survival.

Table 4: Pharmacological effects of *Centella asiatica* on neurological system

Effects	Diseases	Model	Extract/ compound	Compound concentration	Duration of intervention	Animal/ cells	Mechanism/ finding	Reference
Neuroprotective and antioxidant	Alzheimer's disease	*In vitro*	*Centella asiatica* extract	200, 400 & 800 mg/kg	70 days	Male albino Wistar rats	↓ D-gal/$AlCl_3$, ↑ cognitive impairment, ↓ AChE levels, ↓ oxidative stress, ↓ ultrastructural alteration of neurons	(24)
Neuroprotective and antioxidant	Alzheimer's disease	*In vivo & in vitro*	*Centella asiatica* extract	200, 500 & 1000 mg/kg/day	5 weeks	Male, female 5XFAD & wild-type mice	↑ ARE expression, ↑ Nrf2, ↑ other Nrf2 targets, ↓ oxidative stress ↓ Aβ plaque-associated SOD1, ↑ antioxidant responds	(25)
Neuroprotective and antioxidant	Lead exposures induce behavioural deficit & neurotoxicity	*In vivo*	*Centella asiatica leaf extract*	200 mg/kg/day	6 weeks	Adult Wistar rats	↑ protection from neurotoxic effects, ↑ motor activity, ↑ cognitive function, ↑ AChE activity, ↓ ROS, ↑ SOD, ↑ catalase, ↑ GPX, ↑ glutathione reductase, ↑ GSH, ↓ MDA	(43)
Antioxidant	Alzheimer's disease	*In vivo & in vitro*	Methanolic extract of *Centella asiatica*	100 mg/kg	14 days	Male Wistar rats	↓ MDA, ↑ GSH, ↑ SOD, ↓ AChE	(27)
Neuroprotective, antioxidant and increase mitochondrial expression	Alzheimer's disease	*In vivo & in vitro*	*Centella asiatica* aqueous extract	100 µg/mL	2 days	MC65 and SH-SY5Y neuroblastoma cells	↓ Aβ-induce ROS, ↑ ATP, ↑ OCR, ↓ bioenergetic deficit, ↑ mitochondrial gene and protein expression, ↑ Ca^{2+}, ↑ antioxidant response gene, ↑ mitochondrial genes	(44)
Neuroprotective, antioxidant and anti-inflammation	Parkinson's disease	*In vivo & in vitro*	Asiatic acid	25, 50 & 100 mg/kg	5 weeks	Human neuroblastoma (SH-SY5Y) cells	↓ ROS, ↑ MMP, ↓ glutamate toxicity, ↓ DNA damage, ↓ apoptosis, ↑ cytochrome c, ↓ activation of caspase-9, -8, -6, -3, ↑ Bcl-2, ↓ Bax expressions, ↑ Akt kinase activation	(45)
Anti-inflammation and antioxidant	Alzheimer's disease & Parkinson's disease	*In vitro*	*Centella asiatica* leaf extract in ethanol	50-300 µg/mL	24 hours	Lipopolysaccharide (LPS)-stimulated BV2 microglial cells	↓ ROS, ↓ NO, ↓ TNF-α, ↓ Akt, ↓ ERK1/2, ↓ NF-κB,	(32)
Neuroprotective, antioxidant and anti-inflammation	Alzheimer's disease	*In vivo & in vitro*	Raw-extract *Centella asiatica (RECA)*	*In vitro* (3.91–1000 µg/mL) *In vivo* (250, 300 & 350 mg/kg)	22 days	SH-SY5Y, RAW 264.7 cell and adult male Sprague Dawley rats	↓ AChE, ↓ NO, ↓ PGE_2, ↓ TNF-α, ↓ ROS, ↑ GSH,	(33)

Anti-inflammation	Neuro-degeneration	*In vitro*	Madecassoside	4.75 & 9.5 µg/mL	24 hours	BV2 microglia cells	↓ ROS, ↓ iNOS, ↓ COX-2, ↓ HO-1, ↓ STAT1, ↓ NF- κB	(34)
Neuroprotective	Parkinson's disease	*In vivo & in vitro*	Asiatic acid	100 mg/kg	5 weeks	Adult male C57BL/6 mice	↑ DAT, ↑ VMAT-2, ↓ p-JNK, ↓ p-P38, ↑ BDNF, ↑ GDNF, ↑ VEGF, ↑ TrkB, ↑ p-P13K, ↑ p-Akt, ↑ p-GSK3β, ↑ p-mTOR, ↑ p-p70S6K	(37)
Neuroprotective	Hemi-parkinsonism	*In vivo*	Asiaticoside	50 mg/kg/day	3 weeks	Adult male Sprague-Dawley rats	↑ SOD, ↑ LPO, ↑ CAT, ↑ dopamine, ↑ glutamate, ↑ Syn1, ↑ Stx1A, ↑ P13K, ↑ PDK1, ↓ PEBP, ↑ VMAT-2, ↑ TH, ↑ MAPK, ↑ BDNF, ↑ NGF	(38)
Neuroprotective, memory and intelligent improvement	Stress-induce hippocampus impairment	*In vivo*	*Centella asiatica* ethanol extract	150, 300 & 600 mg/kg	4 weeks	Male Sprague Dawley rats	↑ memory improvement, ↑ BDNF, ↑ TrkB, ↑ ERK1/2	(39)
Neuroprotective and memory improvement	Chronic stress	*In vivo*	Ethanolic extracts of *Centella asiatica* leaf	150, 300 & 600 mg/kg/day	28 days	Male Sprague Dawley rats	↑ hippocampal BDNF	(40)
Neuroprotective and cognitive improvement	Alzheimer's disease	*In vivo*	*Centella asiatica* water extract	200, 500 & 1000 mg/kg/day	5 weeks	Male and female 5xFAD mice	Altered purine metabolism (↑ inosine, ↑ hypoxanthine), nicotinate & nicotinamide metabolism (↑NAD+), glycerophospholipid metabolism (↑GPC, ↑citicoline, ↑ACh)	(41)
Neuroprotective and reducing effect of chronic stress	Chronic stress	*In vivo*	Aqueous *Centella asiatica* extract	200, 400 & 800 mg/kg/day	21 days	Wistar rats	↑ lactate, ↑ isoleucine, ↑ proline, ↑ methionine, ↑ valine, ↑ leucine and ↑ glutamine	(42)

D-gal/$AlCl_3$- D-galactose/ aluminium chloride, AChE- acetylcholinesterase, ARE- antioxidant response element, Nrf2- nuclear factor erythroid-2-related factor 2, other Nrf2 targets- heme oxygenase-1, NAD(P)H quinone dehydrogenase 1, glutamate-cysteine ligase catalytic subunit, Aβ- amyloid-β, SOD- superoxide dismutase, GPX- glutathione peroxidase, GSH- glutathione, MDA- malondialdehyde, ROS- reactive oxygen species, OCR- oxygen consumption rate, Ca^{2+}- calcium, MMP- metalloproteinase, Bcl-2- B cell lymphoma 2, Akt- serine/threonine-specific protein kinase, NO- nitric oxide, TNF-α- tumour necrosis factor-alpha, ERK- extracellular signal-regulated kinase, NF-κB- nuclear factor- κB, PGE_2- prostaglandin E2, iNOS- nitric oxide synthase, COX-2- cyclooxygenase 2, HO-1- heme oxygenase 1, STAT1- signal transducer and activator of transcription 1, DAT- dopamine transporter, VMAT-2- vesicular monoamine transporter-2, JNK- c-Jun N-terminal kinase-p53-Bax, BDNF- brain-derived neurotrophic factor, GDNF- glial cell line derived neurotrophic factor, VEGF- vascular endothelial growth factor, TrkB- tyrosine kinase B receptor, PI3K- phosphatidylinositol 3 Kinase, GSK3β- glycogen synthase kinase 3β, mTOR- mammalian target of rapamycin, LPO- lipid peroxidase, CAT- catalase, Syn1- synaptojanin 1, Stx1A- syntaxin-1A, PDK1- phosphoinositide-dependent kinase-1, PEBP- phosphatidylethanolamine binding protein, TH- tyrosine hydroxylase, MAPK- mitogen-activated protein kinase, NGF- nerve growth factor, NAD+-nicotinamide adenine dinucleotide, GPC-glycerophosphocholine, ACh-acetylcholine.

3.3. Pharmacological effects of Centella asiatica on endocrine systems

Centella asiatica and its derivatives show promising results in the treatment of endocrine disorders such as diabetes mellitus, obesity and osteoporosis. Asiatic acid and madecassoside were the most studied compounds in treating endocrine-related diseases. Summary of pharmacological effects of *Centella asiatica* on endocrine system can be viewed in Table 5.

Type 2 diabetes mellitus (T2DM) is a metabolic disorder characterized by elevated blood glucose levels due to insulin resistance, insufficient insulin secretion and exacerbation of glucagon secretion (46). Oxidative stress resulted from the lipid peroxidation process have been linked to the development of T2DM and the occurrence of diabetes complications (47). Moreover, inflammation also contributed to the mechanisms of T2DM as there was an elevated level of

pro-inflammatory cytokines such as TNF-α, interferon (IFN)-γ and interleukins (IL) induced by beta-cell dysfunction and insulin resistance (48). Recent studies have provided clear evidence on the potential benefit of *Centella asiatica* in manifesting antidiabetic properties against oxidative stress and inflammation.

Based on studies conducted on induced diabetes mellitus rats, the results showed *Centella asiatica* significantly reduced blood glucose level, decreases the formation of free radicals or ROS induced by lipid peroxidation, improves antioxidants activity, decreases lipid profile and reduced the pro-inflammatory cytokines (49–52). According to Maulidiani *et al*., the *Centella asiatica* extract was able to decrease glucose levels by restoring the function of the tricarboxylic acid (TCA) cycle's which responsible for glycolysis and gluconeogenesis. This claim was supported by the elevation of pyruvate, lactate, alanine and other TCA intermediates that indicates the enhancement of the glycolysis process and suppression of gluconeogenesis (49). Besides, *Centella asiatica* effect on ROS and free radical generation could be observed in the reduction of malondialdehyde (MDA), the main end-product of the lipid peroxidation mechanism. The *Centella asiatica* can also be classified as a potent antioxidant as it activated the glutathione (GSH) synthesis to the point of overcompensating the antioxidant depletion caused by oxidative stress (52). Moreover, a study from Bubuya *et al*., elucidated that treatment with *Centella asiatica* effectively reduced the level of pro-inflammatory cytokines like TNF-α and IFN-γ by 78% and 42% respectively while the anti-inflammatory cytokines like IL-4 and IL-10 level elevates. This suggested that the *Centella asiatica* enhances the production of the anti-inflammatory cytokines to counteract the pro-inflammatory mediators (50).

Table 5: Pharmacological effects of *Centella asiatica* on endocrine system.

Effects	Diseases	Model	Extract/ compound	Compound concentration	Duration of intervention	Animal/ cells	Mechanism/ finding	Reference
Antidiabetic, anti-hyperglycaemic & anti-hyperlipidaemic	Type 2 diabetes mellitus	*In vivo*	*Centella asiatica* extract / asiatic acid	300mg/kg	4 weeks	Obese diabetic Sprague–Dawley rats	↓ glucose level, ↑ insulin, ↓ cholesterol, ↓ HDL, ↓ LDL, ↑ choline, ↑ succinate, ↑ lactate, ↓ glycerol, ↓ GPC, ↓ leucine, ↓ isoleucine	(49)
Antioxidant & anti-inflammatory	Diabetes mellitus	*In vivo*	*Centella asiatica* methanolic extract	500 & 1000 mg/kg	2 weeks	Male Sprague-Dawley rats	↓ glucose level, ↑ weight gain, ↓ kidney and brain weight/body weight ratio, ↓ MDA, ↓ ROS induce lipid peroxide, ↑ FRAP, ↑ ORAC, ↑ GSH, ↑ GST, ↑ GPX, ↓ TNF-α, ↓ IFN-γ, ↑ IL-10, ↑ IL-4	(50)
Antidiabetic	Type 2 diabetes mellitus	*In vivo*	*Centella asiatica* extract	300, 600, 1200 mg/kg/day	1 week	Male albino Wistar rats	↓ glucose level, ↓ feed intake, ↑ weight,	(51)
Antioxidant & anti-inflammatory	Type 2 diabetes mellitus	*In vivo*	*Centella asiatica* extract	500 mg/kg	2 weeks	Male Sprague-Dawley rats	↑ body and liver weight, ↓ MDA, ↑ FRAP, ↑ GSH, ↑ GST, ↑ GPX, ↓ IL-1β, ↓ MCP-1, ↓ TNF-α, ↓ IL-4, ↓ TG,	(52)

HDL- high-density lipoprotein, LDL- low-density lipoprotein, GPC- glycerophosphorylcholine, MDA- malondialdehyde, ROS- reactive oxygen species, FRAP- ferric reducing antioxidant power, ORAC- oxygen radical absorbance capacity, GSH- glutathione, GST- glutathione S-transferase, GPX- glutathione peroxidase, TNF-α- tumour necrosis factor-alpha, IFN-γ- interferon-γ, IL- interleukins, MCP-1- monocyte chemoattractant protein-1, TG- triglycerides.

3.4. Potential cosmeceutical benefits of Centella asiatica to the skin

Centella asiatica and its triterpenoid constituents were known for anti-inflammatory and antioxidant effects. Many researchers have tried to incorporate *Centella asiatica* in the treatment of skin conditions such as eczema, burns, leprosy psoriasis, and scleroderma (53). However, there were very few researches explored its benefits in the cosmeceutical area even though the mechanisms seem to be similar. These cosmeceutical benefits include skin hydration, anti-acne, anti-aging, repigmentation and collagen proliferation. Summary of potential cosmeceutical benefits of *Centella asiatica* to the skin is exhibited in Table 6.

3.4.1. Anti-aging properties

The development of oxidative stress especially in the skin has mainly contributed to the progression of skin aging and wrinkles (54). Oxidative stress categorized by reactive oxygen species (ROS) and free radicals has significantly affected the extracellular matrix enzymes that modulate the collagens, elastic fibres and proteoglycans which is important in maintaining skin integrity (55). Previous studies have confirmed that *Centella asiatica* has the ability to reduce oxidative stress by suppressing the production of ROS and elevated the production of antioxidant (55–57). A scientific report on skin aging further explained that *Centella asiatica* callus extract was able to reduce the cytotoxicity damage and production of ROS as well as increase the formation of antioxidants like CAT, GPX and SOD (55). Furthermore, oxidative stress also influences the production and degradation of collagen (54). *Centella asiatica* can enhance the production of collagen especially type I and III via SMAD signalling pathways and also inhibit the synthesis of collagenases such as MMP-1 or MMP-9 (55,58,59). Thus, preventing the skin from losing its elasticity which leads to wrinkles formation (55).

3.4.2. Skin hydration properties

Skin hydration is the principal factor for maintaining proper skin function, barrier and homeostasis. It is important for both cosmetic and biological purposes as it links to the pathological of skin disease and also influences the appearance of skin. Improper skin hydration can also influence skin aging as it accelerated the fragmentation of the collagen network (60). Past study had shown that *Centella asiatica* can improve skin hydration up to 24 hours period and prevent transepidermal water loss (61). Madecassoside also helped in increasing the moisturising content with increased expression of aquaporin-3 (AQP3) as it facilitated the transportation of water and glycerol to the skin. The expression of loricrin (LOR) and involucrin (IVL) which were responsible for skin barrier enhancement were also increased and thus preventing the loss of skin moisture content (56).

3.4.3. Anti-acne properties

The formation of acne is characterized by excessive sebum production, bacterial colonization and blocked pores (62). Anti-microbial and anti-inflammatory properties of *Centella asiatica* make a great combination in dealing against acne (63). In a study by Shen *et al*., *Centella asiatica* particularly madecassoside suppressed the inflammation responses resulted from *Propionibacterium acnes* by inhibited pro-inflammatory cytokines such as IL-1β, Toll-like receptor-2 (TLR2) and NF-κB. It also enhanced the skin barrier through the inducement of skin hydration by increasing the AQP3, LOR, IVL and hyaluronan expression and thus prevented against acne formation (56). In terms of

antimicrobial activity, Centella asiatica shows mild antibacterial activity against *P. acne, S. aureus, P. aeruginosa and E. coli* with less than 15 mm inhibition zones (63) except for *Streptococcus pyogenes* which according to Young-Min Goo *et. al.* exhibit larger inhibition zone comparing to *P. acne* (64).

3.4.4. Skin lightening properties

Melanin is created in skin cells by the enzyme tyrosinase, and it enhances skin resistance to UV radiation, dryness, and severe temperatures. However, too much melanin production causes pigmentation, such as freckles and liver spots, as well as skin damage (65). In a report by Goo *et al*. it was claimed that *Centella asiatica* may possess a skin whitening effect as the result of the experiment showed a reduction of melanin content up to 20 per cent comparing with the control group (64). A study from Y. Ling *et al.* also supported the statement with madecassoside inhibition on melanocyte dendrite retraction resulting in depigmentation in vitiligo (66). This statement needed further studies as there was insufficient information on the pathways or mechanism that causes whitening effects. However, this can also be a potential indicator for further investigation on *Centella asiatica* effects. Other than that, tyrosinase-mediated inhibition in melanin biosynthesis has been exploited as a whitening indication in natural products. Seo *et al.* had reported that water extract, ultrasound-assisted water extract and focused high ultrasound-assisted water extract had exhibited *in vitro* tyrosinase inhibition activity with inhibition effects of 53.22%, 51.11% and 61.52% respectively with concentration dependent behaviour (65).

3.4.5. Hair care properties

Hair is one of the most complicated integrated systems, with multiple morphological components that work together as a unit (67). Hair serves as a biological barrier between the body and its surroundings, as well as influencing social interactions. As a result, hair loss or baldness, also known as alopecia, has a direct impact on one's self-confidence, influencing his or her daily lives (68). The specialised mini-organ, hair follicle (HF), anchoring each hair into the epidermis, controls and generates the growth and morphology of hair fibre (69). Choi *et al.* had published a first report that investigated the hair growth-promoting effect and cellular mechanisms of titrated extract of *C. asiatica* (TECA) in hair inductive potential in 3D spheroid cultured human dermal papilla (HDP) cells. In the study, TECA improved HDP cell viability and spheroid formation in 3D culture. These findings also showed that inhibiting signal transducer and activator of transcription (STAT) signalling and upregulating the expression of HDP hallmark genes improved HDP cells' hair induction properties. It was discovered that TECA inhibited ROS-induced cellular senescence, which was also shown in DP cells from alopecia sufferers. As a result of these findings, TECA may be a contender for scalp alopecia (70).

In another study by Saansoomchai *et al.*, the stimulating impact of treating cells with ethanol crude extract of *C. asiatica*, as measured by the expression of mRNA of vascular endothelial cell growth factor (VEGF), was investigated using reverse transcriptase-polymerase chain reaction (RT-PCR). It was found that, ethanol crude extract of *C. asiatica* stimulated VEGF expression, presumably leading to cell proliferation in human follicular dermal papilla cells. VEGF gene expression was significantly stimulated by ethanol crude extracts of 500-g/mL *C. asiatica* (37.30 ± 9.47). This was significantly higher than minoxidil's marginally enhanced VEGF gene expression (1.99 ± 0.07) (71). According

to this study, the ethanol crude extract of C. asiatica will be beneficial in the creation of hair care products and hair loss therapy.

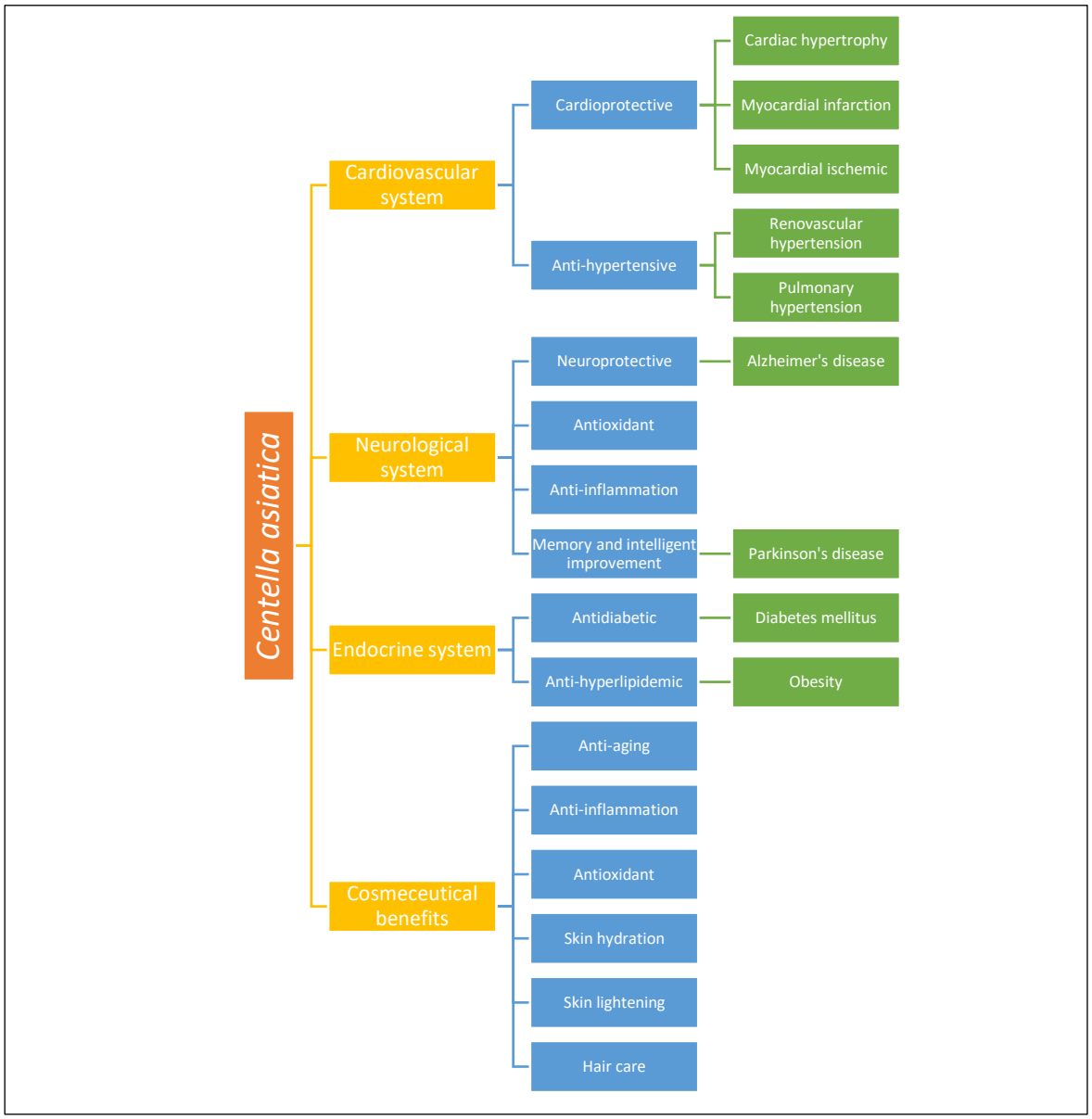
Table 6: Potential cosmeceutical benefits of *Centella asiatica* to the skin.

Effects	Model	Extract/ compound	Compound concentration	Duration of intervention	Animal/ cells	Major finding	Reference
Anti- inflammation & skin hydration activity against *P. acnes*	*In vitro*	Madecassoside	12.5, 25,50 & 100 µM	4 hours	Human dermal fibroblast, HaCaT & human monocytic cell line THP-1	↓ IL-1β, ↓ TLR2, ↓ NF-κB, ↑ AQP3, ↑ LOR, ↑ IVL, ↑ HA, ↑ HAS1, ↑ HAS2, ↑ HAS3, ↓ ROS	(56)
Antibacterial, anti-inflammatory, and skin-whitening	*In vitro*	*Centella asiatica* methanol & water extract	62.5, 125,250,500 & 1000 ppm	48 hours	B16F10 cell line, 7 bacteria strains, HDF	↑ anti-microbial activity against *Streptococcus pyogenes,* ↓ NO, ↓ melanin content, ↑ skin wrinkle improvement	(64)
Skin flap survival	*In vivo*	Asiaticoside	40 mg/kg/day	7 days	Dorsal McFarlane flaps from rats	↑ skin flap survival, ↓ tissue water content, ↑ SOD, ↓ MDA, ↓ TNF-α, ↓ IL-6, ↑ neovascularization, ↓ neutrophil density, ↑ VEGF, ↓ IL-1β, ↑ number and quality of regenerated blood vessels, ↑ blood supply to the tissue	(57)
Anti-skin-aging	Scientific reports	*Centella asiatica* callus extract	15–60 µg/mL	24 hours	Human foreskin fibroblasts	↓ cytotoxicity of H_2O_2 ↓ ROS, ↑ CAT, ↑ GPX1, ↑ SOD1, ↓ oxidative damage, ↓ cell death, ↓ MMP-9, ↓ skin aging	(55)
Wound healing	*In vivo*	Asiaticoside	100 g	12 days	Male white albino rabbits	No irritation, ↓ wound size, ↑ epithelialisation, ↓ epithelization period	(58)
Skin hydration and barrier function effects	Clinical trial	*Centella asiatica* stem cell extract	-	24 hours	Women with mean aged 40 and normal skin	↑ skin hydration after 24 hours, ↑ skin hydration at each evaluation time point, ↓ post-stripping transepidermal water loss	(61)
Collagen III Synthesis and Proliferation	*In vitro*	*Centella asiatica* ethanolic extract	3.125, 6.25 & 12.5 mg/ml	72 hours	Human dermal fibroblast (HDF)	↑ HDF proliferation, ↑ collagen III synthesis	(59)
Skin lightening (Repigmentation of vitiligo and post-inflammatory hypopigmentation)	*In vitro*	Madecassoside	10,50 &100 µg/mL	300 minutes	Human melanocytes	↓ retraction of melanocyte dendrites, ↓ MMP in melanocytes under oxidative stress, ↓ accumulation of Ca^{2+}, ↓ mitochondria injury, ↑ recovers Ca^{2+} homeostasis, ↑ LC3-I to LC3-II conversion	(66)
Skin lightening properties (tyrosinase inhibition)	*In vitro*	*Water extract, ultrasound-assisted water extract and focused high ultrasound-assisted water extract*	1 mg/mL	15 minutes	Tyrosinase enzyme (dopachrome method)	↓ tyrosinase activity, ↓ melanogenesis, ↓ melanin content	(65)

Human dermal papilla cell viability	*In vitro*	*Titrated extract of C. asiatica*	25µg/mL	48 hours	Human dermal papilla cells	↓ SOCS1 SOCS3, ↓ STAT5 & STAT3 signaling, ↑ spheroid cultured HDP cells. ↑ ALP, BMP2 & NOG, ↑ hair inductivity of HDP cells	(70)
Proliferation of human follicular dermal papilla	*In vitro*	*Ethanol extracts and fractions*	500 & 1000g/mL	24 hours	Hair follicle dermal papilla cells	↑ VEGF mRNA expression, ↑ cell proliferation	(71)

P. acnes- Propionibacterium acnes, HaCaT- human epidermal keratinocyte, IL- interleukin, TLR2- Toll-like receptor-2, NF- κB- nuclear factor-κB, AQP3- aquaporin-3, LOR- loricrin, IVL- involucrin, HA- hyaluronan, HAS- hyaluronan synthesis, ROS- reactive oxygen species, HDF- human dermal fibroblast, SOD- superoxide dismutase, MDA- malondialdehyde, TNF-α- tumour necrosis factor-alpha, VEGF- vascular endothelial growth factor, H_2O_2- hydrogen peroxide, GPX- glutathione peroxidase, CAT- catalase, MMP-9- matrix metallopeptidase-9, MMP- mitochondrial membrane potential, LC3- microtubule-associated protein light chain 3, SOCS- suppressor of cytokine signalling, STAT- signal transducer and activator of transcription, HDP- human dermal papilla, ALP- alkaline phosphate, BMP- bone morphogenetic protein, NOG- nogging, VEGF- vascular endothelial growth factor,

Figure 2: Pharmacological and cosmeceutical effects of *Centella asiatica*



4.0 Conclusion

Centella asiatica was one of the potential herbaceous plants that can be exploited for application in pharmaceuticals and cosmeceuticals. The main constituents of this plant consist of madecassoside, madecassic acid, asiaticoside and asiatic acid. However, the concentration of *Centella asiatica* constituents may be varied depending on the origin of the plant. Thus, there were no conclusive evidence on the exact concentration of the plant component, and it was difficult to determine which constituents exhibited the most effect or action. Most studies used the whole plant or leaf extract in their investigation. However, there were also standardized extracts that focussed on particular constituent. Figure 2 portrayed the overall pharmacological and cosmeceutical effects of *Centella asiatica.* Despite all evidence on the effect of *Centella asiatica*, it needs more refining and should be explored meticulously to provide more accurate data to support future clinical application. There were a lot of studies that exhibited promising outcomes for both pharmacological and cosmetic benefits both *in vitro* and *in vivo*, however, there were lack of clinical or human study evidence on the utilization of *C. asiatica* extracts for specific diseases and cosmetic issues. Therefore, further study should focus more on the clinical studies to strengthen, support and broaden the usage of *C. asiatica* in health promoting applications.

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