Horticulture, Environment, and Biotechnology
https://doi.org/10.1007/s13580-023-00561-8

REVIEW ARTICLE

Pharmacological effects of pentacyclic triterpenoids isolated from *Centella asiatica*

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Received: 13 January 2023 / Revised: 11 September 2023 / Accepted: 11 September 2023

Abstract
Centella asiatica (CA) is one of the most popular traditional herbal medicines worldwide. It has been used for centuries in many countries, especially for curing skin damage, and is now applied to treat various human diseases. There are various types of triterpenoids from *Centella asiatica*, with four pentacyclic triterpenoids with the main properties being shown by four pentacyclic triterpenoids: asiaticoside, madecassoside, asiatic acid, and madecassic acid. These terpenoids have similar structures, however each has a slightly different properties. Asiaticoside, madecassoside, asiatic acid, and madecassic acid are synthesized through the isoprenoid pathway known as mevalonate pathway to produce hydrophobic triterpenoid structures (aglycone) which contain hydrophilic sugar chains (glycone). Furthermore, asiaticoside and madecassoside are distinguished by a glycone, and asiatic acid and madecassic acid are distinguished by a aglycone. These pentacyclic triterpenoids have a wide spectrum of beneficial effects and have been used as anti-inflammatories, skin wound treatments, scar treatments, and cosmetics agents. This review aimed to provide a description of the four compounds, of their structure, pharmacological properties, applications in the treatment of various diseases, known mechanisms of action, and commentary on industrial applications.

Keywords Asiatic acid · Asiaticoside · Madecassic acid · Madecassoside · Traditional herbal medicine

1 Introduction

Centella asiatica (CA) is a herbaceous and creeping perennial plant belonging to the family Apiaceae and is native to more than 20 geographic locations regions around the world. Adapted to high temperatures and humid conditions, CA grows mainly in in India, Sri Lanka, Indonesia, Malaysia, Madagascar, and other tropical or subtropical regions (Sabaragamuwa et al. 2018; Shin et al. 2021). It has various native names, such as tiger grass in India, pennywort in Western countries, Gotu kola, babassu, thankuni, and Koroko-Rona (Gohil et al. 2010; Sabaragamuwa et al. 2018). CA grows in over 50 countries with subtropical/tropical climates and high humidity, yet it has not grown well in the wild in South Korea (Yousaf et al. 2020). Due to recent developments, cultivation conditions have been optimized, and CA is now artificially grown in some provinces of South Korea, such as Jeju-do, Gyeongsangnam-do, and Jeollanam-do. The slender and creeping plant CA grows well in humid conditions, such as those found in ponds, wetlands, and lakes. Despite this, CA is often observed found in sunny areas, e.g., stone walls at 2,000 feet above sea level in India and Sri Lanka (Yousaf et al. 2020). The height of an adult CA plant is 10–35 cm, and the leaves have two scale-like degenerative leaves near the root node (Yousaf et al. 2020). The true leaves of CA are axillary in scaly leaves, with petioles 4–20 cm long, leaf blades are circular, 2–6 cm in diameter, and their surface is glabrous and has crenate margins (Yousaf et al. 2020). Flowering occurs from July to August, and 2–5 purple or pink flowers hang humbly at the end of an extremely short (2–8 mm) or absent peduncle. CA's inflorescence and 5 petals are surrounded by two egg-shaped involucral bracts. Its stamen is small, with black or purple anthers. The fruit is a mericarp, a round oblate of about 3 mm in length. An areola is present on the outside of the

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Published online: 29 January 2024

mericarp, a protruding area with hair at first that then gradually disappears. The stem is characterized by a leptocaul that extends sideways and by roots coming down from the nodes and roots come down from the nodes, with two scale-like degeneration leaves adjacent to them. As for the roots, the main one is dark brown and has a diameter of 2–7 mm.

CA has been used as a traditional medicinal herb by tribal communities for about 2,000 years. It was considered sacred in Ayurveda, an ancient Indian medicine, and called "Brami", meaning the best of the best (Shinomol et al. 2011; Yousaf et al. 2020). In Ayurveda, CA was used to treat various skin diseases, leprosy, stomach ulcers, elephantiasis, kidney disease, asthma, bronchitis, and vitiligo (Shinomol and Muralidhara 2008). In Malaysia, it was used to treat anxiety, eczema, and mental fatigue (Harun et al. 2019). In the Western medicine, the alcoholic extract of CA was used in the mid-twentieth century for treating leprosy (Gohil et al. 2010). Fresh CA extracts have long been used to treat skin wounds by people of the Malaysian Peninsula and the island of Java in Indonesia (Samuel et al. 2022). Overall, it has been used as a medicine against degenerative arthritis, eczema, diarrhea, fever, genital diseases, hepatitis, and jaundice in many countries, and has also been used to treat mental and physical fatigue and detoxification (Xia et al. 2015).

Until now, more than 130 secondary metabolites have been identified in CA, including ursane-type triterpenes, oleanane-type triterpenes, ursane-type triterpene glycosides, oleanane-type triterpene glycosides, dammarane-type triterpene glycosides, steroids, steroid glycosides, flavonoids, polyacetylenes, phenolic acids, and so on (Kunjumon et al. 2022a). Since the latest decade, several reviews have been published dealing with various pharmacological effects of CA, focusing on its bioactive compounds (Bylka et al. 2014; Farooqui et al. 2018; Gohil et al. 2010; Kim et al. 2022; Lv et al. 2018; Razali et al. 2019). Among them, the most famous and important pharmacological compounds in CA are ursane-type pentacyclic triterpenoids, including asiatic and madecassic acids, and ursane-type triterpene glycosides, including asiaticoside and madecassoside (Matsuda et al. 2001; Siddiqui et al. 2007; Sun et al. 2020). However, although a number of investigations on pharmacological and therapeutic potentials of CA have been well-documented in recent decades, the review articles on the secondary metabolites present in this medicinal herb are still unsatisfactory. Continuous attention and updates of the current study on the pharmacological potential of CA in terms of biologically active ingredients are important. There are assertions concerning the fundamental processes implicated in the herb's biological effects, however, additional scientific evidence is required to substantiate its escalating usage (Gohil et al. 2010). Therefore, in this review, we aimed to incorporate a detailed account of the major four triterpenoids in terms of their structure, biosynthetic pathway, determination, pharmacological activity, and industrial uses.

2 Methodology

A high quality and reliable information were retrieved only from PubMed (Medline) and Google Scholar using keywords "*Centella asiatica*", "triterpenoid", "asiatic acid", "asiaticoside", "madecassic acid", "madecassoside", "determination of triterpenoid", and "triterpenoid analysis". We searched the databases since the year 2000 up to the latest information.

3 Triterpenoids in CA as bioactive constituents

3.1 Types of triterpenoids in CA

For thousands of years, natural substances have been utilized as important ingredients of medication for preventing and curing diseases (Razali et al. 2019). The fact that approximately 34% of developed modern medicines originated from natural substances from 2000 to 2014, emphasizes the importance of exploring various natural substances and their bioactive ingredients for developing and utilizing natural medications (Newman and Cragg 2016). The term secondary metabolites means natural products that are not required for growth, development, and reproduction but are produced by organisms, including bacteria, fungi, plants, and animals, often to regulate the ecological interactions between them and their environment (James and Dubery 2009). These secondary metabolites might even potentiate or synergize the effectiveness of other ingredients in the preparations, whether utilized individually or in combination, can be used safely and effectively act even when synthetic drugs fail (Gorlenko et al. 2020; Seca and Pinto 2019). In plants, secondary metabolites are also called specialized metabolites, because each plant synthesizes its own unique set to control its interaction with its environment (Tugizimana et al. 2015). Previous studies reported 57 kinds of CA secondary metabolites which can be clustered into four groups: triterpenoids, volatile terpenes, flavonoids, and trace components (Sangwan et al. 2013; Suntornsuk and Anurukvorakun 2005; Zainol et al. 2003). In another recent study, Shin et al. (2021) reported the analytical condition and quantification of 12 secondary metabolites in CA into three types: triterpenes, polyphenolic acids, and flavonoids. Nevertheless, the most abundant and well-studied compounds in CA are generally accepted to be pentacyclic triterpenes, organic compounds containing 30 carbon atoms and whose basic structure consists of a skeleton of five six-membered rings (Gallego et al. 2014; Jia and Lu 2008; Xu et al. 2004).

3.2 Chemical structure of triterpenoids in CA and their determination

The fundamental skeleton of the triterpenoids is characterized by the methyl substitution pattern on the C_{19} and C_{20} carbon atoms, defining two subtypes, the oleane- and ursane-type components (James and Dubery 2009; Kim et al. 2017). Oleane-type pentacyclic triterpenes include terminolic acid, asiaticoside B, centellasapogenol A, centellasaoinin D, and so on; ursane-type pentacyclic triterpenes include oleanolic acid, glycyrrhizic acid, saikosaponin, maslinic acid, asiatic acid, asiaticoside, asiaticoside C, asiaticoside D, asiaticoside E, asiaticoside F, brahmol, centellasaponin B, isothankuniside, madaciatic acid, madecassic acid, madecassoside, methyl brahmate, and so on (James and Dubery 2009). The most famous triterpenoid metabolites found in CA are the ursane-type triterpenoids asiatic acid and madecassic acid and their glycosides asiaticoside (madecassol) and madecassoside (asiaticoside A) (Fig. 1) (Kim et al. 2005; Sun et al. 2020). Asiaticoside and madecassoside as terpenoid glycosides are formed by the combination of basic triterpenoid structure (asiatic acid or madecassic acid) with three sugar residues (two glucose units and one rhamnose unit) (Li et al. 2023). This means that asiaticoside and madecassoside produce asiatic acid and madecassic acid, respectively, when they were hydrolyzed chemically or enzymatically (Awathale et al. 2021). In general, the most abundant triterpenoid components in CA are asiaticoside and madecassoside, but there are also several minor triterpenoids, such as thankuniside, scheffoleoside, and centellasaponins (Azerad 2016). In addition, the triterpenoid composition of CA may considerably change depending on the geographical location and the environmental conditions (Azerad 2016).

To separate and identify these pentacyclic triterpenoids, various methodologies and technologies are now available (Tan et al. 2021), such as TLC (Bonfill et al. 2006), HPLC-UVD (da Rocha et al. 2017; Rafamantanana et al. 2009; Shin et al. 2021), HPLC-ELSD (Kwon et al. 2011; Yang et al. 2009; Zhang et al. 2008), and mass spectroscopy (Bonfill et al. 2006; Han et al. 2012; Nagoor Meeran et al. 2018). Using these methods, several studies reported the variation

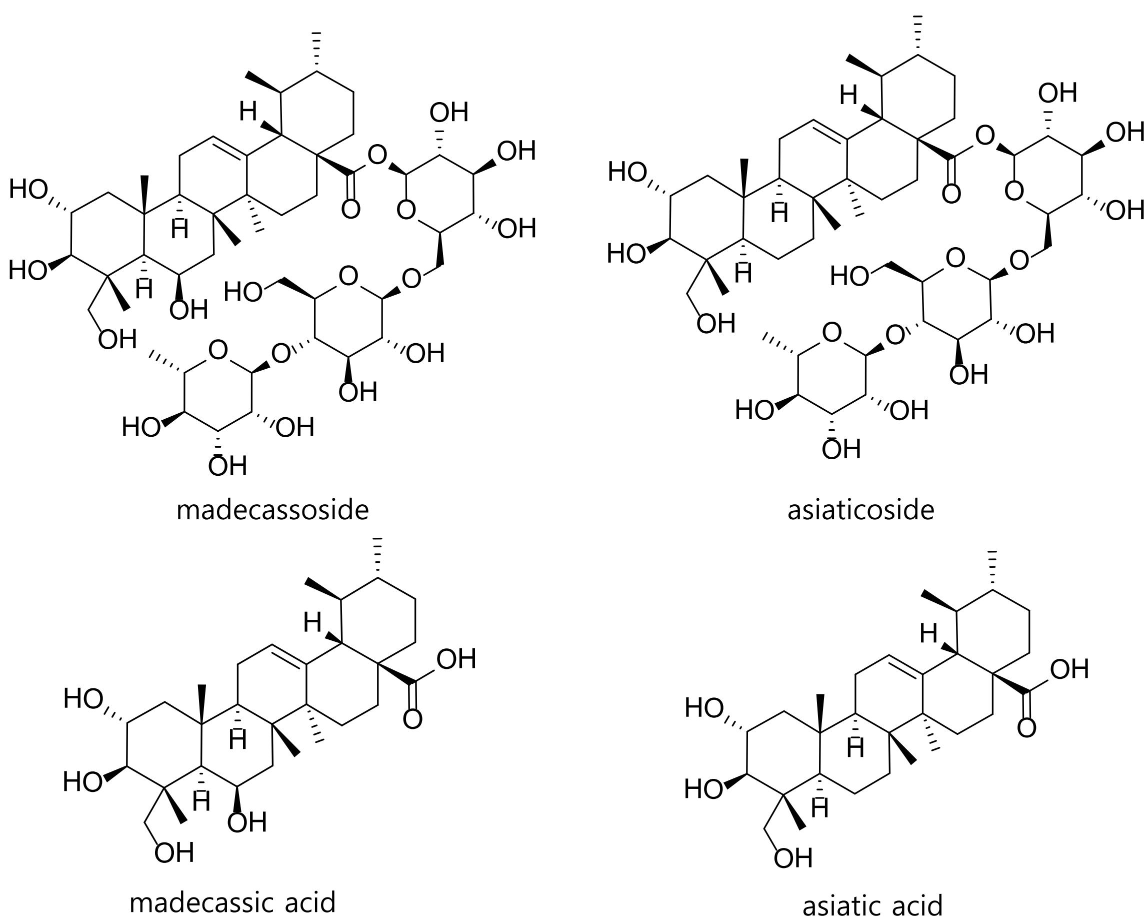

Fig. 1 Chemical structures of the major pentacyclic triterpenoids in CA

in composition and contents of triterpenoids in different parts of CA (Alqahtani et al. 2015; Azerad 2016; da Rocha et al. 2017; Hashim et al. 2011; Luo et al. 2015; Shin et al. 2021).

3.3 Pharmacological activity of key triterpenoids in CA

Because of the variety of its pharmacological properties, CA has long been used for curing skin damage, such as wounds and burns, as well as for treating various human diseases, such as leprosy, stomach ulcers, degenerative arthritis, eczema, diarrhea, fever, genital diseases, hepatitis and jaundice, physical fatigue and mental fatigue, and to promote detoxification (Brinkhaus et al. 2000; Bylka et al. 2014; Gohil et al. 2010; Sabaragamuwa et al. 2018; Siddiqui et al. 2007). In addition, recent scientific evidence elucidated that CA has antioxidant, antimicrobial, anti-inflammatory, neuroprotective, memory improvement, immunomodulatory, and antidepressant activities (Gohil et al. 2010; Goo et al. 2018; Harun et al. 2019). Its verified medicinal properties have contributed to its approval as a natural medicine both in Western countries, such as England, France, Italy, Netherlands, Germany, and Poland, and in Asian ones, such as China (Bylka et al. 2013; Shin et al. 2021).

Triterpenes and their derivatives are the second most abundant group of secondary metabolites in nature, with more than 20,000 types of metabolites reported. Pentacyclic triterpenoids, a subgroup of triterpenoids, have important applications for human health and are widely distributed in organisms, especially plants (Li et al. 2023). Their well-known and remarkable medicinal and pharmacological effects are useful for various human diseases, such as diabetes, liver diseases, inflammatory diseases, oxidative stresses, cancer, cardiac disorders, and infectious diseases (Li et al. 2023). Specific plant kingdom, including Araliaceae, Leguminosae, Compositae, Aesculaceae, Polygalaceae, Oleaceae, Akebiaceae, Cucurbitaceae, Euphorbiaceae, Campanulaceae, Caryophyllaceae, and Poaceae can synthesize and produce pentacyclic triterpenoids (Li et al. 2023). Here, we introduce and discuss the four most abundant pentacyclic triterpenoids in CA: asiatic acid, madecassic acid, asiaticoside, and madecassoside. Although the secondary metabolite contents of plants, including CA, is significantly influenced by genetic and environmental factors (Kunjumon et al. 2022b), it is generally accepted that triterpene glycoside forms (asiaticoside and madecassoside) are more accumulated in CA than aglycone forms (asiatic acid and madecassic acid) (Kunjumon et al. 2022b). Notably, the pharmacological efficacy of CA is significantly affected by the glycoside-to-aglycone ratio (Gajbhiye et al. 2016; Puttarak and Panichayupakaranant 2012; Rafamantanana et al. 2009).

3.3.1 Asiaticoside

Asiaticoside, the representative ursane-type triterpene glycoside, is the most abundant secondary metabolite in CA. Its molecular formula is $C_{48}H_{78}O_{19}$ and its molecular weight is 959.12 Da (Gajbhiye et al. 2016; Shin et al. 2021). The content of asiaticoside in CA increases gradually since spring, reaching a peak in October (Kil et al. 2018). Asiaticoside exhibits various physiological effects, such as anticancer, neuroprotective (nervous system injury, Alzheimer's disease, and Parkinson's disease), hepatoprotective, cardiovascular protective, skin protective, pulmonary protective, anti-inflammatory, anti-diabetic, anti-fibrotic, anti-allergic, antiviral, and immunomodulatory effects (He et al. 2023). A well-organized, systematic review article on the pharmacokinetic and pharmacological effects of asiaticoside is available in the recently published literature (He et al. 2023). Above all, the most widely investigated effect of asiaticoside is its protective effect on the skin. There are three main effects achieved by asiaticoside and underlying skin function improvement: wound healing, by increasing angiogenesis and collagen synthesis; improved appearance of hypertrophic scars and keloids, by regulating inflammatory reactions; and improvement appearance of aged skin, by promoting collagen synthesis and inhibiting melanogenesis (He et al. 2023). In general, asiaticoside has prominent skin function-promoting properties, including the promotion of collagen formation and tissue regeneration, that result in increased skin strength.

Asiaticoside facilitates the secretion of insulin through pancreatic β cell stimulation, thus exerting significant anti-diabetic activity (Zhang et al. 2022). It is known to inhibit pulmonary fibrosis via suppressing profibrotic and inflammatory signaling pathways (Dong et al. 2017). Anti-cancer effects have also been reported, specifically asiaticoside can significantly reduce the expression of TNF-α and IL-1β, improve anti-tumor activity through apoptosis, and trigger autophagy through signal transducer and transcriptions 3 pathway suppression to resist proliferation, migration, and invasion of drug-resistant multiple myeloma cells (Tan et al. 2021). Moreover, asiaticoside has a reported beneficial role in ameliorating diseases in the central nervous system, such as Parkinson's disease, Alzheimer's disease, and dementia (He et al. 2023).

3.3.2 Madecassoside

Madecassoside is another representative ursane-type triterpene glycoside in CA. Its molecular formula is $C_{48}H_{78}O_{20}$ and its weight is 975.12 Da (Loc and An 2010). Compared with asiaticoside, madecassoside has one more oxygen atom attached to its C_6 position on the second pentacyclic ring. Analytical results using HPLC show that madecassoside content begins to increase gradually in spring and is the highest in October (Kil et al. 2018). Because of its similar structural characteristic, madecassoside has the same medicinal and pharmacological effects as asiaticoside, and it has similarly been used as a therapeutic and functional ingredient (Bylka et al. 2013). The prominent beneficial effects of madecassoside are exerted on tissue damage, including skin, liver, kidney, and lung, and in the context of systematic disorders, such as cardiovascular disease, rheumatoid arthritis, neurological disease, diabetes, and cancer (Tan et al. 2021). Madecassoside treatment improved the healing of burn wounds by increasing antioxidant activity, reducing infiltration of inflammatory cells, and improvement of the barrier function due to dermal proliferation of fibroblasts (Liu et al. 2008). Madecassoside also protected umbilical vein endothelial cells (HUVECs) from hydrogen peroxide-induced lipid peroxidation and cell death, by protecting the mitochondrial membrane and downregulating the activation of caspase-3 and p38 MAPK (Bian et al. 2012). In addition, madecassoside showed an antioxidant effect in human melanocytes exposed to hydrogen peroxide, exhibiting a therapeutic effect on cells exposed to leukopenia repigmentation and hyperpigmentation after inflammation (Jung et al. 2013). Madecassoside was shown to inhibit the generation of wrinkles by inhibiting the expression of metalloproteinase (MMP) under membrane potential in fibroblast-like synovial cells induced by IL-1β (Tan et al. 2021). Furthermore, it has been reported that madecassoside is effective in neurodegenerative diseases by reducing the production of reactive oxygen species (ROS) and lowering the expression of genes and proteins of neuroinflammation-related biomarkers (Hafiz et al. 2020).

3.3.3 Asiatic acid

Asiatic acid is an active component that is isolated from CA and has a pentacyclic triterpenoid structure in the ursane skeleton. Unlike asiaticoside, asiatic acid doesn't have three glycoside residues, but a simple ursan-type triterpenoid skeleton with molecular formula $C_{30}H_{48}O_5$ and weight of 488.72 Da (Gallego 2014). The absence of glycosides means that asiatic acid has a lower solubility and bioavailability than asiaticoside (Lv et al. 2018). Mohammadparast et al. (2014) demonstrated a method for increasing asiatic acid contents in CA employing organic elicitors. The content of asiatic acid in CA increases gradually in spring, and is highest in July (Kil et al. 2018). Despite its low bioavailability, asiatic acid showed prominent potential as therapeutic and preventive ingredient in various inflammatory responses in many studies (Lv et al. 2018). It has an analgesic and anti-inflammatory effect, which has been associated with an induction of nitric oxide synthase and with an increase in antioxidant activity (Lv et al. 2018). In addition, it has been shown that the anti-inflammatory action of asiatic acid is induced through the activity of antioxidants and the inhibition of the NF-κB and MAPK signaling pathways (Lv et al. 2017). Aside from its anti-inflammatory effects, asiatic acid is effective in healing skin wounds (Jeong 2006). Specifically, it is known to promote wounds and nerve regeneration in skin wounds and burns (Bylka et al. 2014). Studies have shown that pharmacological effects prevail in connective tissue disorders, leading to gene expression to prevent skin damage through antiglycemic action (Sun et al. 2020). Asiatic acid also has important anti-bacterial effects in wounds and burns: by causing irreversible damage to the membrane of bacterial cells, it causes the release of genetic information, thus inhibiting bacterial proliferation (Tan et al. 2021).

In addition, asiatic acid is known to protect myocardial cells from reperfusion that occurs when blood containing oxygen and glucose is suddenly supplied in ischemia, which is associated with low oxygen and glycoside in tissues through various channels such as protein kinase B (Akt), glycogen synthase kinase-3β, and Hypoxia Inducible Factor-1α (HIF-1α) (Yi et al. 2022). It can also protect myocardial cells by lowering oxidative stress and suppressing ROS-mediated mitochondria-dependent apoptosis (Yi et al. 2022). In addition, regulation of miR-1290, HIF3α, and HIF-1α increases the viability of myocardial cells against apoptosis due to hypoxia, and also suppresses mitochondrial-dependent apoptosis pathways in heart failure, reducing epilepsy and inflammatory responses (Fong et al. 2016). Asiatic acid is known to have preventive effect in heart damage caused by diabetes by weakening glycation and coagulation disorders, which change proteins by combining carbohydrates and proteins. It can also play a role in treating early atherosclerosis by interfering with the endothelial permeability of blood vessels (Tan et al. 2021). Furthermore, it has been reported to increase cell proliferation in the hippocampus in the brain, stimulate spatial working memory, increase neuron cells, and prevent spatial memory impairment (Sun et al. 2020). Asiatic acid is also known to improve glucose absorption into skeletal muscles through the phosphatidylinositol 3 kinase-Akt signaling pathway, thereby exhibiting antihypertensive blood glucose activity and accelerating glycogen synthesis (Sun et al. 2021).

3.3.4 Madecassic acid

Madecassic acid is another aglycone of the ursane-type tetracyclic triterpenoid group, one of the major active components in CA. Unlike its saponin glycoside, madecassoside, madecassic acid doesn't have any glycosides, so it has a simple ursan-type triterpenoid skeleton with molecular formula $C_{30}H_{48}O_6$ and weight of 504.72 Da (Gallego et al. 2014). Compared with asiatic acid, madecassic acid has one more oxygen atom attached to its C_6 position on the second pentacyclic ring. Analytical results using HPLC show that madecassoside content starts to increase gradually in spring and is highest in July (Kil et al. 2018; Xing et al. 2009). Chemically, madecassic acid has one carboxyl group at C_{28} and four OH groups at C_2, C_3, C_6, and C_{23} positions in its ursane skeleton.

In an interesting study, madecassic acid was mixed with asiatic acid and then administered topically to the skin tissue or orally to reach the subcutaneous layer, observing antioxidant activity and wound healing. The study also showed that madecassic acid increases proline levels, stimulates the synthesis of type I collagen in human skin fibroblasts, and is effective in ameliorating inflammatory reactions (Bylka et al. 2013, 2014). Based on its efficacy to promote skim, madecassic acid has been used as an ingredient in some skin cosmetic products to promote moisture and cell regeneration (Bylka et al. 2013). Another study reported that madecassic acid downregulates inducible nitric oxygen synthase (iNOS) and cyclooxygenase 2 (COX-2) gene expression and then inhibits the production of corresponding inflammatory mediators, nitric oxide (NO) and prostaglandin E2 (PGE2) (Won et al. 2010). Madecassic acid also inhibited the production of pro-inflammatory cytokines, such as TNF-α and IL-6 (Harun et al. 2019). Madecassic acid is also known to help controlling blood glucose levels, lowering plasma lipids, suppressing oxidative and inflammatory stresses, and improving insulin resistance and blood vessel homeostasis (Tan et al. 2021).

4 Conclusions and perspectives

Many commercial products containing CA extracts or their isolated triterpenoids are easily found on the market. Many commercial products make use of CA extracts as active ingredients because of their wound healing and anti-inflammatory effects. One example is Madecassol® (Barnes et al. 2007; Bylka et al. 2013). This famous topical dermatologic drug has been used to cure skin wounds and burns for over 20 years. Moreover, an intravenous improvement agent which contains the main components of the titrated CA extracts is also commercially marketed as a medicine for treating venous diseases, specifically for treating symptoms related to lymphatic failure such as vein circulatory disturbance, pain, and restless legs syndrome (Cesarone et al. 2001). Most of all, CA extracts are currently widely applied as main ingredients in many skincare products, so much so that it is difficult to find natural cosmetics that do not contain CA extracts or their components. CA is thus considered a valuable ingredient that can be used and developed as a key raw material for medicines and cosmeceuticals.

Despite the numerous pharmacological properties of CA and its active pentacyclic triterpenoids, it is still difficult to find examples of its application aside from skin health products. As stated earlier, triterpenoids, key bioactive ingredient in CA, have been found to have a variety of health functionalities in addition to skin physiological activity. We think that, despite the outstanding pharmacological effectiveness of CA, its active ingredients, the pentacyclic triterpenoids, have some limitations in terms of industrial application, because of their weak solubility in water and low absorption rate and bioavailability to human (Anukunwithaya et al. 2017; Boonyarattanasoonthorn et al. 2022; He et al. 2023). To solve these shortcomings, various attempts have been made using process techniques such as encapsulation, particularization, nanonization, cyclization, and complexation (He et al. 2023; Khoshnevisan et al. 2018; Paolino et al. 2012; Soe et al. 2020; Wannasarit et al. 2020). In addition, more in vivo and clinical studies are necessary to confirm the safety of CA and its active ingredients.

Acknowledgements This research was supported by a grant of Natural Product Institute of Science and Technology, Anseong, Korea.

Author contribution D-HM, Y-BY, T-HK: investigation and document search; HK: writing; SL: design, writing and editing.

Declarations

Conflict of interest There is no conflict of interest.

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