Cassia alata (Linnaeus) Roxburgh for Skin

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Atopic dermatitis (AD) is an inflamed skin condition with relapsing pruritus and cutaneous physiological dysfunction. This skin disorder is widespread around the world and frequently affects infants, children and adults. Natural products with bioactive lead compounds are the source of natural medicines for complementary and alternative therapy in managing AD. *Cassia alata (Senna alata)* has been used traditionally as a remedy for a variety of health issues. *Cassia alata* is also known as ringworm cassia. This plant is perennial and is known as a 'candle bush' due to its shape and inflorescences.

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1. Introduction

Atopic dermatitis (AD), also referred to as eczema, is a chronic inflammatory skin condition that affects 1–3% of adults and 15–20% of children worldwide [1]. This chronic skin condition is frequently linked to allergic rhinitis, asthma and food allergies. The defining characteristic of AD is itchiness, which causes scratching, which further irritates the skin and may potentially make AD worse, because itchiness is a crucial component of the cycle of itch–scratch behaviour [2]. Due to its chronic nature, AD negatively impacts the sufferer's quality of life by increasing medical costs, causing absence from work and school, decreasing productivity and disrupting sleep [1][3].

The onset of AD is reported to mainly be at five years of age, often disappearing by adulthood. It is estimated that in the United States, 17% of children in the 6–12 year old age group suffer from AD [4]. However, the disease may persist in 10–30% of cases. There is a high percentage of adults in the United States who experience the onset of the disease during adulthood (≥18 years of age) (41.9%) and 24.4% after the age of 50 [5]. In Singapore, Malaysia and north-eastern Thailand, the lifetime prevalence of chronic rash in 5–15 year old children is about 12.5%, 17.6%, and 17.2%, respectively. The prevalence stabilised at the age of 12–15 in Singapore and 13–14 in Malaysia and north-eastern Thailand [4][6][7]. Hadi et al. reported the prevalence among children and adolescents in Taiwan, China, Japan, South Korea, and Malaysia, which differed according to age group and country (**Table 1**). Since the studies examined different age groups in populations, direct comparisons of the prevalence among children in these counties are difficult.

Table 1. Prevalence of atopic dermatitis in Asian countries.

Country	Prevalence of AD (%) (Age Group)			References
	Children	Adolescent	General Population	
Taiwan	10.7 (6–7 year old)	7.6 (13–14 year old)	6.7	[8][9][10][11][12]
China	12.95 (1–7 year old)	4.6	7.8	[13][14][15]
Japan	4.6 (7–12 year old) 10.9–19.6% (6–14 year old)		n.a	[16][17][18]
South Korea	15 (1–18 year old) 13.5 (7–18 year old)		n.a	[19]
Malaysia	13.4 (1–6 year old)		n.a	[1]

n.a.: data not reported.

Traditional medicine is believed to be generally safer when compared with synthetic medications and modern treatments due to fewer side effects. Traditional medicine mainly comprises plants or plant extracts as a natural source of medication arising from the wide range of phytochemicals and bioactive molecules present. *Cassia alata* (**Figure 1**), from the Leguminosae family, has been traditionally used to treat skin disorders. The plant is antipruritic and has traditionally been

used to treat ringworm, eczema, and scabies [20]. The plant is also well known for its laxative effect to treat constipation and gastrointestinal disorders [20]. It has potential as an alternative for managing AD due to the presence of phytochemicals such as carotenoids [21][22], polyphenols [23][24][25], flavonoids [23][26], alkaloids [23][26], terpenoids [21], anthraquinone derivatives [21][23][26], glycosides [23][26], fatty acids [23][27], and phytosterols [21]. These can have antimicrobial, antioxidant, anti-inflammatory and wound healing effects that can heal and alleviate AD. These pharmacological properties are extremely important in facilitating AD management.

Figure 1. Cassia alata plant. The figure is adapted from Chew et al. [6], under the Creative Commons Attribution License.

2. Botanical Description and Classification

C. alata (*Senna alata)* is also known as ringworm cassia (**Figure 1**). This plant is perennial and is known as a 'candle bush' due to its shape and inflorescences [6]. The term ringworm plant recognises the effectiveness and popularity of its leaves in the traditional treatment of ringworm [28]. This plant is also known as a craw-craw plant, ringworm bush, empress candle plant, emperor's candlesticks, yellowtop weed or seven golden candles, in various communities [26][29][30][31].

C. alata is a tropical shrub of 3 to 4 m tall. The flower is yellow and blooms from the bottom to the top. The petals are arranged in a vertical column. Each dark purple to black-coloured winged seed pod has four sides. The pod is 25 cm long and 2.8 cm in width. It holds 50–60 triangular to square-shaped seeds. The seeds are green in colour when they are unripe, turning black when they ripen [32]. *C. alata* has a rachis as the main stem of a compound leaf. The leaf has an oblong shape about 5–16 cm long and 3–8 cm wide. They exist in 6–12 pairs [33].

3. Ethnomedical Uses

C. alata offers many ethnomedicinal benefits. Various communities across many countries have used it as a traditional medicine to treat various diseases and complications, and for various purposes (**Table 2**).

Table 2. Ethnomedicinal uses of *Cassia alata*.

Plant Parts	Traditional Uses	References
Whole plant	**In Cuba, medical treatments include:** • Diuretic • Laxative—for constipation • Skin infections such as herpes ulcers **In Guatemala, Brazil, and Guinea, it is used for flu and malaria treatment.**	[26][33]

Plant Parts	Traditional Uses	References
Leaves	In Tanzania, Ghana, India, Indonesia, and Africa, the leaves are prepared as an infusion and decoction to treat constipation. The leaves are rubbed on the surface of the skin for the management of various skin diseases because of its various qualities: • Antifungal effect; management of ringworm and white-spot fungal skin infections • Antipruritic; reduction of itchiness and rashes • Antiviral; treatment against herpes simplex virus • Immunomodulatory; regulation of the production of white blood cells. Over-stimulated white blood cells production may cause psoriasis. In Nigeria, the fresh sap of leaves is rubbed into the skin for antifungal and ringworm treatment. The leaf decoction is also used for chronic lichen dermatosis management. In the Philippines, *C. alata* leaves are used on the skin for antibacterial, anti-inflammatory, analgesic and antifungal effects. The plant is also consumed to reduce blood glucose. In Togo and Gabon, the leaves are pounded and spread on the skin with palm oil for general skin disorder management. In India, the leaf decoction is used as: • An expectorant for the treatment of shortness of breath and bronchitis; • An astringent; • A skin wash for eczema; • To relieve discomfort associated with haemorrhoids; • For control of gastrointestinal parasitism; and • To control blood glucose levels.	[21][26][32][34][35]
Flowers	In Brazil, the leaves are used to promote menstruation and improve blood circulation in female reproductive organs. In Egypt, a leaf decoction is used as a laxative to relieve constipation. In Sierra Leone, the leaves are prepared to relieve pain due to childbirth and abortion. In Thailand, leaf decoction (consisting of a minimum of 0.5% hydroxyanthracene derivatives) is used to relieve constipation. In Peru, an infusion prepared from flowers is used for diuretic and urinary tract infection treatment. In the Amazon, the Tikuna Indians prepare decoction of the flowers and consume them once daily to relieve constipation.	[21]
Seeds	In China, the seeds are made into a tea to improve eyesight and asthma.	[26]
Wood	Decoctions are consumed to reverse liver damage caused by hepatotoxins and to treat gastrointestinal issues (e.g., loss of appetite). The leaves are ground into powder and rubbed directly on the skin to counteract problems correlated with fungal infections.	[34][36]
(Not defined)	In Africa, plant parts serve the following medicinal purposes: • To relieve stomach aches during gestation; • For treatment of dysentery; and • For treatment of haemorrhoids.	[21]

4. Phytochemistry

Numerous phytochemical compounds have been reported in *C. alata*, such as carotenoids, four phenolic acids, 20 flavonoids, two alkaloids, seven terpenoids, 17 anthraquinones, four glycosides, 28 fatty acids and two phytosterols (**Table 3**). Not all phytochemicals exist in all parts of the plant. Some are variously present in seeds, roots, and flowers, but most are reported in the leaves. Consequently, the leaves are the most used part of the plant for disease treatments.

These phytochemicals exhibit valuable pharmacological activities that support the management of AD. Selected phytochemicals with documented beneficial pharmacological activities are highlighted and discussed here.

Table 3. Phytochemical compounds in *Cassia alata*.

Class	Phytochemical Compounds	Parts of Plant	Reference
Carotenoids	β-carotene	Leaves	[21][22]
Polyphenols (Phenolic acids)	Gallic acid	Leaves	[23][24][25][37]
	Caffeic acid (3,4-Dihydroxycinnamic acid)		
	Chlorogenic acid		
Flavonoids	Kaempferol	Leaves, seeds, twig, roots	[23][26]
	Kaempferol-3-*O*-β-glucoside (astragalin)		
	trans-Dihydrokaempferol		
	Kaempferol-3-*O*-β-D-glucopyranosyl-(1→6)-β-D-glucopyranoside		
	Kaempferol-3-*O*-β-D glucopyranoside		
	Kaempferol 3-*O*-gentiobioside 50.0 ± 8.5 µM		
	3,5,7,4′-Tetrahydroxy flavone		
	2,5,7,4′-Tetrahydroxy isoflavones		
	5,7,4′-Trihydroflavanone		
	7,4′-Dihydroxy-5-methoxyflavone		
	Quercetin		
	Luteolin		
	Chrysoeriol-7-*O*-(2″-*O*-β-D mannopyranosyl)-β-D-allopyranoside		
	Rhamnetin-3-*O*-(2″-*O*-β-D-mannopyranosyl)-β-D-allopyranoside		
	ω-Hydroxyemodin		
	Ziganein		
	Apigenin		
	Naringenin		
	Propelargonidins		
	2, 5, 7, 4′-Tetrahydroxy isoflavone		
Alkaloids	Adenine	Leaves	[23][26]
	Cannabinoid alkaloid (4-butylamine 10-methyl-6-hydroxy cannabinoid dronabinol)		
Terpenoids	β-Caryophyllene	Leaves	[21]
	Germacrene		
	α-Selinene		
	Bicyclogermacrene		
	Limonene		
	α-Phellandrene		
	α-Bulnesene		

Class	Phytochemical Compounds	Parts of Plant	Reference
Anthraquinone derivatives	1,3,5-Trihydroxy-7-methylanthracene-9,10-dione	Leaves, stem	[21][23][26]
	1,5,7-Trihydroxy-3-methyl-anthra-quinone		
	Aloe-emodin		
	Rhein		
	Emodin		
	Chrysophanol		
	1,3,8-Trihydroxy-2-methyl anthraquinone		
	Hydroxymethyl anthraquinone		
	1,5-Dihydroxy-8-methoxy-2-methylanthraquinone-		
	Alatinone		
	Alatonal		
	Sennoside A		
	Sennoside B		
	Sennoside C		
	Sennoside D		
	Chrysophanic acid		
	Physcione		
Glycosides	Chrysoeriol-7-O-(2″-O-β-D-mannopyranosyl)-β-D-alopyranoside	Seed, stem, leaves	[23][26]
	3-O-Gentiobioside		
	Rhamnetin-3-O-(2″-O-β-D-mannopyranosyl)-β-D-allopyranoside		
	α-D-Galactopyranosyl		

Class	Phytochemical Compounds	Parts of Plant	Reference
Fatty acids	12-Methyltridecanoic acid	Seeds, leaves, flowers	[23][27][38][39]
	9-Hexadecenoic acid (Palmitoleic acid)		
	Hexadecanoic acid (methyl ester) (Palmitic acid)		
	n-Hexadecanoic acid (Palmitic acid)		
	cis-10-Heptadecenoic acid		
	Heptadecanoic acid		
	9,12-Octadecadienoic acid (Linoleic acid)		
	Octadecanoic acid		
	Octadecanoic acid methyl ester		
	9-Octadecenoic acid (Oleic acid)		
	9,12-Epithio-9,11-octadecanoic acid 11-eicosenoic acid		
	Eicosanoic acid (Arachidic acid)		
	15-Hydroxyl-9,12-octadecadienoic acid		
	9,10-Dihydroxyoctadecanoic acid 6,9,12-octadecatrienoic acid (γ-linolenic acid)		
	Heneicosanoic acid		
	9,10-Methylene-octadec-9-enoic acid (Sterculic acid)		
	Octadecanoic acid (Stearic acid)		
	20-Methylheneicosanoic acid		
	Tricosanoic acid		
	Tetracosanoic acid		
	Pentacosanoic acid		
	Hexacosanoic acid		
	Behenic acid		
	9-Dodecenoic acid		
	Nonadecanoic acid		
	3,11-Tetradecadien-1-ol		
	Octadecanal		
	9-Octadecenoicacid methyl ester		
Phytosterols	β-Sitosterol	Leaves	[21]
	Stigmasterol		

5. Pharmacological Properties

C. alata possesses numerous pharmacological properties, including antioxidant, antimicrobial, anti-inflammatory and wound healing. These pharmacological activities are essential in managing AD. In general, the antimicrobial activity of *C. alata* could prevent secondary infections caused by microbes, especially *Staphylococcus aureus* [40][41][42]. The antimicrobial activity also contributes to wound healing, closure, and recovery of AD skin lesions [43]. The plant has also been shown to inhibit inflammation through suppression of pro-inflammatory cytokines and through upregulation of the levels of anti-inflammatory-related transcription factors, enzymes, and cytokines [44]. Antioxidants such as phenolics, flavonoids and anthraquinones protect the skin from damage, scavenge free radicals, overcome oxidative stress and inhibit inflammation [45][46][47].

5.1. Antimicrobial Activity

AD patients often have dry and weakened skin barriers. The weakened barriers allow penetration of microorganisms and allergens through the skin. Microorganisms, including dermatophytes, parasitise the keratinised tissue of the skin. They exacerbate the condition due to secondary infection and play a significant role in the aetiology of AD. The skin condition is worsened due to microbial invasion and infection. According to many research studies, *S. aureus* is the most common microorganism that causes skin infection in AD [40][41][42]. This bacterium is closely associated with the pathogenesis and
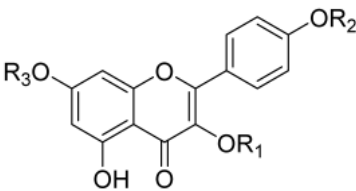
severity of the disease. When the patient's skin is massively colonised by *S. aureus*, it triggers a cascade of inflammatory responses on the skin by releasing high amounts of allergens [48]. As such, antibiotic therapy is one of the essential elements in managing AD [49]. However, the overuse of existing antibiotics could cause the emergence of antibiotic-resistant bacteria. The popularity of plant products with antimicrobial properties has increased in the past decade. They are rich in numerous phytochemicals, including tannins, terpenoids, alkaloids, and flavonoids, which exhibit antimicrobial properties. Some patients are turning to alternative therapies to manage the disease by using plant-derived ingredients as complementary and alternative treatments for AD.

C. alata has been used traditionally to treat various microbial infections. Several studies have proven that it has excellent antimicrobial activity against *S. aureus*. The alcoholic and aqueous extracts of roots, barks, stems and leaves exhibit moderate antimicrobial activity toward *S. aureus* [50][51][52]. Iraqui et al. formulated leaf fractions into a hydrogel and the antimicrobial activity was tested against *S. aureus* [53]. The formulated hydrogel exhibited prominent antimicrobial efficacy. Its antimicrobial effect was better than Renicol and Daktarin, two commercial antimicrobial formulations selected in the study [53]. The authors also performed the hydrogel's bioburden study in an in vivo model. They discovered that the tissue homogenate from the treatment group consisted of fewer microbial cells. This showed that it killed the wound-causing microbe and reduced the bacteria and fungus-causing infections. Since the reduction in the number of microbial cells in the excision wound was positively correlated with the number of infections [53], the wound would heal faster than the group treated with commercial antimicrobial formulations.

Several studies have investigated the antimicrobial activity of the phytochemicals recovered from *C. alata*, particularly towards *S. aureus*. Kaempferol and aloe emodin from *C. alata* exhibited excellent antimicrobial activity toward multidrug-resistant *S. aureus* (MIC_{50} 13.0 ± 1.5 µg/mL and 12.0 ± 1.5 µg/mL, respectively). In comparison with the other two flavonoids found in this plant, kaempferol 3-*O*-β-glucopyranoside (Astragalin) and kaempferol 3-*O*-gentiobioside had lower potency (MIC_{50} values of 83.0 ± 0.9 µg/mL and 560.0 ± 1.2 µg/mL, respectively) [54]. On the other hand, gallic acid, caffeic acid, cannabinoid dronabinol, rhein and fatty acids in the leaves and seeds could also exhibit antibacterial activity against *S. aureus* [24][39][55][56].

Some studies have reported the antimicrobial mechanism and the structure–activity relationship of *C. alata* phytochemicals. Phenolic acids in *C. alata* exhibited significant antimicrobial activity, either alone or in combination with antibiotics [56][57]. Gallic acid and caffeic acid of *C. alata* targeted the bacterial surface, affecting bacterial susceptibility, altering the membrane fluidity and integrity, and changing the physiochemical properties of the bacteria, resulting in potassium leakage and hence cell death [57][58][59][60]. Various studies have reported that the alkyl chain length of the phenolic acids is correlated with antimicrobial activity [56][57][58][61]. The longer the alkyl chain is, the stronger the antimicrobial activity toward *S. aureus* will be [56][57][58][61]. Other studies have also reported that the structure–activity relationship of the phytochemicals is closely associated with antimicrobial activity. For instance, a study by Hazni et al. evaluated the structure–activity relationship of kaempferol and its derivatives with antimicrobial potency against *S. aureus*. It was reported that the free hydroxyl group at the C-3 position of kaempferol and its derivatives is essential for exhibiting antimicrobial activity. In addition, the size of the R_1 side group of the kaempferol derivatives may affect the antimicrobial potency (**Table 4**). The bigger the group size at the R_1 position is, the weaker the antimicrobial potency [54].

Table 4. Structure of kaempferol, kaempferol 3-*O*-β-glucopyranoside and kaempferol 3-*O*-gentiobioside and their antimicrobial potency against MRSA.

Constituents	R_1	R_2	R_3	MIC Values (µg/mL) *			
				MIC_{10}	MIC_{30}	MIC_{50}	MIC_{80}
Kaempferol	H	H	H	6.0 ± 1.6	10.0 ± 0.7	13.0 ± 1.5	13.0 ± 1.5
Kaempferol 3-O-β-glucopyranoside (Astragalin)	Glucoside	H	H	40.0 ± 1.3	54.0 ± 1.2	83.0 ± 0.9	2000.0 ± 0.9
Kaempferol 3-O-gentiobioside	Gentibiosyl	H	H	110.0 ± 0.8	250.0 ± 1.1	560.0 ± 1.2	2000.0 ± 1.3

* MIC values obtained from Hazni et al. [54].

Quercetin in *C. alata* exhibited promising antibacterial activity. The activity was demonstrated by the multiple hydroxyl groups in the chemical structure [62][63][64][65]. Phosphorylation and sulfation of the hydroxyl groups exhibited antimicrobial activity affecting the functioning of peptides, proteins, and ion channels embedded in the membrane [64][66]. In addition, quercetin could also disrupt the cell wall and alter the bacterial cell membrane integrity, and causing the cell to die [67].

Rhein in *C. alata* also exhibited relatively strong antibacterial activity against *S. aureus* (MIC 4 µg/mL; MIC_{90} 8 µg/mL). It acts as the substrate for many transporters, where it regulates the expression of transporter genes [68], altering the bacteria's biological mechanism. The genes regulated by rhein include ferrichrome, siderophore, and heme transport. Upregulation of these genes suppressed the proliferation and killed the bacteria. Furthermore, rhein also inhibits aerobic and anaerobic respiration of bacteria. It regulates the metabolism of amino acids, detoxification, and pathogenic factors [68] which ultimately inhibit the growth of *S. aureus.*

5.2. Wound Healing

Wound healing is a natural process of regenerating dermal and epidermal tissue. A normal wound healing process goes through three phases in response to tissue injury: inflammatory, proliferative and remodelling phases [69]. Normal wound healing response is initiated immediately when the platelets come in contact with the exposed collagen at the injury site. Patients with AD flare-ups on their skin experience an itch–scratch cycle. Excessive scratching of the rash due to itchiness causes skin damage and injury [70] and slow wound recovery. Open wounds allow bacteria, viruses, and fungi to enter the skin, resulting in persistent infections. Consequently, wound healing for AD patients tends to be more challenging and complicated than for healthy individuals.

Wound healing is related to antimicrobial activity. Caffeic acid in *C. alata* has a broad spectrum of antibacterial activity, fighting both Gram-positive and Gram-negative bacteria. Antibacterial activity favours the wound-healing process [43]. An earlier study by Palanichamy et al. evaluated the antimicrobial effect of *C. alata* ethanolic leaf extracts in a rabbit wound healing model. The wound was inoculated with *S. aureus* so that the efficacy of the antimicrobial activity of the extract in wound closure could be evaluated. *C. alata* leaf extract was prepared in an ointment and applied to the treatment group animals for 21 days. The authors reported that the application of the ointment showed satisfactory wound healing. The wound surface area decreased significantly during the 21 days treatment period (58.8, 79.0, and 88.9% reduction in wound surface area after 7, 14, and 21 days, respectively) [71]. The negative control group (treated with ointment but without any antimicrobial agent) only showed a 57.1% decrease in wound surface area after 21 days. The positive control group treated with 0.2% nitrofurazone ointment had a 98.8% reduction in wound surface area after 14 days. Although the antimicrobial and wound-healing activities of *C. alata* leaf extract were not as prominent as those of nitrofurazone, it is an effective natural antimicrobial agent for AD wound management.

Another wound-healing study conducted by Midawa et al. also supported evidence that *C. alata* leaf extract facilitated wound closure in animal models [72]. Excision wounds in a rat model were treated with 125, 250, and 500 mg of leaf extracts twice daily until complete wound closure. They discovered that wound recovery had improved significantly. The wound healing rate was positively correlated with the amount of extract. The duration of epithelialisation (ca. 16 days) was significantly shorter than that of the negative control group (ca. 23 days). The authors commented that the promotion of wound healing could be due to the antimicrobial effect of *C. alata*, which is in agreement with Palanichamy et al. [71] and Iraqui et al. [53]. Iraqui et al. observed that wound recovery and epithelialisation improved significantly with the application of *C. alata* leaf hydrogel [53]. The authors also agreed that the antimicrobial properties promoted wound recovery. Wound infection by bacterial and fungal cells was also significantly reduced. Thus, whilst the wound-healing properties of *C. alata* have apparently been proven, the mechanism of tissue contraction during wound healing is not completely understood.

Alkaloids, terpenoids, flavonoids, anthraquinones and tannins could modulate the activity of fibroblasts and keratinocytes, promote collagen synthesis, and regulate the expression of cytokines and growth factors [6]. Oleic acid and linoleic acid in *C. alata* leaves modulate the inflammatory responses for tissue repair and wound closure [6][73][74]. They inhibit the accumulation of leukocytes at lesions and cationic serine protease activity in wounds, regulate the expression of metalloproteinase (MMP) and tissue inhibitor of MMP (TIMP) and promote wound closure in tissue remodelling [6][73][74]. The expression of TIMPs counter-regulate the MMPs and prevent exacerbated injury during inflammation [75]. Oleic acid also promotes angiogenesis, increases the collagen III expression during the final inflammatory phase of tissue repair and accelerates wound healing [73]. Wound healing is an essential aspect of managing AD.

5.3. Anti-Inflammatory

C. alata exhibits promising anti-inflammatory activity in both in vitro and in vivo models (**Table 5**). Excellent anti-inflammatory activity was noted in the carrageenan-induced mouse paw oedema model. Mice in the treatment group were fed orally with 5 mg/20 g *C. alata* extracts. Results showed a significant reduction in inflammation of the mouse paw after the treatment [76]. This finding is also supported by Lewis et al. [77], who studied the anti-inflammatory action of *C. alata* using the in vivo rheumatic arthritis model. *C. alata* leaves were found to inhibit the production of tumour necrosis factor-alpha (TNF-α) by immature dendritic cells in a dose-dependent manner. TNF-α regulates pro-inflammatory cytokine release and increases lipid signal transduction mediators, prostaglandins, and platelet-activating factors. It is crucial in the development of chronic inflammatory diseases. The leaves of *C. alata* have the ability to inhibit the inflammatory pathway, which includes TNF-α and other inflammatory cytokines. Astragalin in *C. alata* leaves regulates the anti-inflammatory pathways through controlling the levels of anti-inflammatory-related transcription factors, enzymes, and cytokines such as TNF-α, inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), prostaglandin E2 (PGE2), matrix metalloproteinase-1 (MMP-1), MMP-3, interleukin-1β (IL-1β), IL-4, IL-6, IL-8, IL-13 and interferon-gamma (IFN-γ) [44]. Other studies reported the anti-inflammatory activity of astragalin; some studies used in in vitro models, such as RAW

264.7, human gingival epithelial cells, and mouse uterine endometrial epithelial cells. Some studies of the anti-inflammatory action using animal models such as diabetic rats, BALB/c, and NC/Nga mice are reported in **Table 5**.

Table 5. Anti-inflammatory activities of astragalin in vitro and in vivo, reproduced from Riaz et al. [44]. The table reproduced is under the Creative Commons Attribution License.

Assays	Organism Tested	Dose/Concentration	Molecular Targets
LPS-induced mouse mastitis	**Mouse mastitis**	**10, 25 and 50 mg/kg**	**TNF-α ↓, IL-1β ↓, IL-6 ↓, p65 ⊥, and IκBα ⊥**
LPS-induced endotoxemia and lung injury in mice	**Mice (lung)**	**25, 50, and 75 mg/kg**	**TNF-α ⊥, IL-1β ⊥, and IL-6 ⊥**
LPS-induced macrophages in mice	**Mouse cells**	**1–100 µg/mL**	**IL-6 ↓, MIP-1α ↓, MCP-1 ↓, NF-κB p65 ⊥, IκBα ⊥, and NO ⊥**
LPS-induced RAW 264.7 cells	**Mice (RAW 264.7 cells)**	**1, 10, and 100 µM**	**NO ↓ and TNF-α ↓**
Inhibitory activity on the histamine release by KU812 cells	**KU812 cells**	**10 to 30 µmol/L**	**IL-4 ↓, IL-13 ↓, and (IFN- γ) no effect**
LPS-induced Inflammation in RAW 264.7 cells	**Mice (RAW 264.7 cells)**		**NO ⊥, IL-6 ⊥, and PGE2 ⊥**
P. gingivalis-induced human gingival epithelial (HGE) cells	**Human gingival epithelial cells**		**COX-2 ⊥, IL-6 ⊥, IL-8 ⊥, MMP-1 ⊥, MMP-3 ⊥, PGE-2 ⊥, and IL-4 ⊥**
Anti-inflammatory effects on _Leptospira interrogans_-induced inflammatory response	**Uterine and endometrial epithelial cells of mice**	**100 µg/mL**	**p38 ⊥, p-p38 MAPK ↓, ERK ⊥, JNK ⊥, and p-p65 ↓**
Protective effects against ovalbumin- (OVA-) induced allergic inflammation	**Mouse model of allergic asthma**	**0.5 mg/kg and 1 mg/kg**	**SOCS-3 ⊥, SOCS-5 ⊥, and IFN- γ ↑**
Alleviation in hepatic fibrosis function	**Diabetic rats and nondiabetic**		**PAR2 ⊥, IL-1β ↓, IL-6 ↓, TNF-α ↓, and TGF-β1 ⊥**
Prevention from atopic dermatitis	**NC/Nga mice**	**1.5 mg/kg**	**IgE ↓**

↑ Upregulation; ↓ downregulation; ⊥ inhibition.

5.4. Antioxidant Activities

Increased oxidative stress and a reduction in antioxidants are significant contributing factors in the pathogenesis of AD [78]. Free radicals are believed to disrupt the defence and restoration mechanisms, increasing lipid peroxidation and decreasing the levels of antioxidants. These contribute to skin damage and disorders. The supplementation of natural antioxidants such as phenolic compounds in AD management are expected to significantly improve the skin's condition, protect the skin from oxidative stress and inhibit the inflammatory response.

C. alata is rich in polyphenols, compounds that comprise aromatic rings bearing one or more hydroxyl groups. Some are simple phenols, i.e., phenolic acids and phenol derivatives. Some have complex structures, including flavones, flavonoids, anthocyanins, and anthraquinones. Polyphenols exhibit strong free radical and oxidative agent scavenging activity against nitric oxide, hydrogen peroxide, the superoxide anion, 1, 1-diphenyl-2-picrylhydrazyl (DPPH), and 2,2-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) [23][79][80][81][82]. Aqueous extract of _C. alata_ showed promising antioxidant activities. The extract inhibited 50% of the DPPH free radical at IC_{50} 2.25 ± 0.28 µg/mL. The scavenging activity was even more potent than the antioxidant standards, ascorbic acid (IC_{50} = 3.99 ±0.09 µg/mL) and Trolox (IC_{50} = 4.50 ± 0.08 µg/mL) [36]. Besides free radical scavenging, studies have also reported that _C. alata_ showed promising reducing power and lipid peroxidation inhibition effects [23][80]. Increased oxidative stress and free radical action can overwhelm the skin's defence and contribute to skin disorders.

Malondialdehyde (MDA) is an oxidant and a product of lipid peroxidation. MDA is the most frequently measured marker of oxidative stress. A significantly higher level of MDA and a lower level of antioxidant enzymes and antioxidants were noted in AD patients compared with healthy controls [45]. High serum MDA causes redox imbalances. Thus, restoring the redox balance is crucial for treating skin inflammation. Reduction of MDA may be achieved by supplementation of antioxidants with reducing power. Phenolics and flavonoids present in _C. alata_ potentially exhibit good antioxidant activities, such as free radical scavenging, hydrogen donating ability, and reducing power. Numerous antioxidants are present in _C. alata_, including gallic acid, caffeic acid, kaempferol and its derivatives, quercetin, luteolin, apigenin, naringenin, rhein, emodin and aloe-emodin. As reported by Vargas et al., hydroxyanthraquinones such as rhein, emodin, and aloe emodin are prominent antioxidative compounds [46]. The free radical and reactive oxygen species' scavenging abilities were evaluated

using isoluminol-enhanced chemiluminescence with horseradish peroxidase and luminol-enhanced chemiluminescence with hydrogen peroxide or ferrous iron. The reactive oxygen species released were reduced by these hydroxyanthraquinones. Emodin had the highest reactive oxygen species scavenging activity, followed by rhein and aloe emodin [46]. The free radical scavenging activity of these three hydroxyanthraquinones was also studied, with the scavenging activity being concentration dependent. Rhein and emodin exhibited more potent activity than vitamins C, and E. Lipid peroxidation is closely associated with the level of MDA and severity of AD [45]. The antioxidative activity delays lipid peroxidation by 10–15%.

Phenolic acids such as gallic acid, caffeic acid, quercetin, and naringenin were observed to reduce oxidative stress and improve skin condition and texture [47]. Nowak et al. recently reported that phenolic acids including gallic acid, chlorogenic acid, 3,4-dihydroxybenzoic acid, 4-hydroxybenzoic acid and caffeic acid could penetrate and accumulate in porcine skin tested via Franz diffusion cell measurements [83]. The concentration of antioxidants and free radical scavenging activity evaluated after skin extraction was higher than the acceptor fluid, which supported the proposal that phenolic acids could penetrate the skin, accumulate and exhibit antioxidant activity, suggesting improvement in the endogenous cutaneous protection system and a reduction in skin oxidative stress through the targeting of multiple pathways to overcome skin inflammation, manage bacterial skin infections and accelerate wound recovery. Sikora et al. developed a topical hydrating product formulated with *C. alata* [84]. A pilot clinical study tested the product's efficacy on human subjects. Subjects were exposed to harmful ultraviolet rays to induce oxidative stress in the skin. The study showed that antioxidants in *C. alata* could protect the skin against oxidative stress. Skin conditions improved significantly throughout the 12 weeks of treatment, including skin inflammation (24%), skin dryness (30%), and skin texture (18%). The antioxidative protection was mainly exhibited by the water-soluble, lipid-soluble and enzymatic antioxidants [84]. It is believed that the antioxidative effects would also effectively manage the skin condition in AD.

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