Original Research Article

The Pharmacological Properties and Medicinal Potential of *Chromolaena odorata*: A Review

Nur Amirah Aziz[1], Mashani Mohamad [2], Hannis Fadzillah Mohsin[3], Nurul Aqmar Mohamad Nor Hazalin[2], Khuriah Abdul Hamid[1*]

[1]Department of Pharmaceutics, Faculty of Pharmacy, Universiti Teknologi MARA (UiTM), 42300 Bandar Puncak Alam, Selangor, Malaysia.
[2] Department of Pharmaceutical Life Sciences, Faculty of Pharmacy, Universiti Teknologi MARA (UiTM), 42300 Bandar Puncak Alam, Selangor, Malaysia.
[3]Department of Pharmacology and Chemistry, Faculty of Pharmacy, Universiti Teknologi MARA (UiTM), 42300 Bandar Puncak Alam, Selangor, Malaysia.

Abstract

Chromolaena odorata Linn (L.) King and Robinson, which is locally known as 'Pokok Kapal Terbang' is one of the most gradual invasive weeds in Asia. The *C. odorata* species is distributed extensively in many areas and grow well in a wide range of habitats, especially moist and cold areas. The species, mainly the biotype found in Asia and West Africa, have been vastly used as a medicinal herb and are well-accepted among Asians over the past few decades for its medicinal properties. The literature revealed remarkable ethnopharmacological properties of this plant such as antibacterial, anti-inflammatory, antioxidant and analgesic activity. Other medicinal uses include its potential in wound healing treatment, skin infection as well as to treat stomach problems. The presence of various active chemical constituents such as phenolic, essential oils and flavonoid compounds in the leaves and root extracts of *C. odorata* is reported to have essentially contributed to its medicinal properties. Therefore, this review aims to give an overview of the phytochemical constituents, the bioactivities and potential medicinal properties of *C. odorata*.

Keywords: *Chromolaena odorata*, invasive weed, medicinal herb, antibacterial, anti-inflammatory, wound healing

**Corresponding author*

Khuriah Abdul Hamid
Department of Pharmaceutics,
Faculty of Pharmacy, Universiti Teknologi MARA
Cawangan Selangor, 42300 Puncak Alam
Selangor, Malaysia
khuriah@uitm.edu.my

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1.0 Introduction

Chromolaena odorata Linn (L.) King and Robinson is formerly known as *Eupatorium odoratum* L. belongs to the kingdom Plantae (plants), family Asteraceae (Aster family), genus Chromolaena (Thoroughwort), and species *Chromolaena odorata* L. (1). The family Asteraceae or Compositae (known as the aster, daisy, or sunflower family) is the largest family of flowering plants represented by about 950 genera and 20,000 species over the globe (2). *C. odorata* plants are distributed all over the world in almost all habitats (3). The common names for these plants are Siam weed, devil weed, eupatorium, Jack in the bush, Jack-in-the-bush, kingweed, paraffinbush, and paraffinweed (4).

C. odorata has been introduced extensively to tropical Asia, West Africa and some parts of Australia (5). In general, this plant is able to grow in a wide range of soil pH (6).However, it seems to grow best at acidic soil areas that contain a high amount of potassium and phosphorus.

Herbal plants are known to be rich sources of phytochemical ingredients that contribute to healthcare management (7). Thereby, the demand for plant-based medicinal treatment using natural herbal plants has been shown to rise worldwide (7). At the beginning of the 21st century, more than half of all the drugs used in clinical applications contained natural products in their medication treatment. Furthermore, various herbal drugs from natural products such as plants, animals, microorganisms, and fungi have been approved in medical treatments (7). Besides, natural products also serve as an essential source for developing new drug products.

In recent decades, people are more attracted to drugs from plant origin as they are highly biocompatible and produce lesser side effects than synthetic drugs. However, productivity and quality of these natural products are not satisfactory due to the slow rate of multiplication, overexploitation, and habitat degradation that is a drawback in meeting the ever-increasing market demand.

Nevertheless, among the variety of plant species available worldwide, only a few plants have been studied for its phytochemical constituents and biological activity (9) that may serve as potential alternative sources of therapeutic agents.

C. odorata has been commonly and widely used in traditional medicine because of its property that can give therapeutic effects on the body. The leaf extracts of *C. odorata* has been shown to possess antioxidant, anti-inflammatory, analgesic, antimicrobial, cytoprotective and many other medicinally significant properties (9).

The phytochemical components of *C. odorata* include alkaloids, flavonoids, flavanone, essential oils, phenolics, saponins, tannins, and terpenoids. The other essential constituents of this plant are chromomoric acid, quercetagetin, and quercetin, all of which contribute to its medicinal properties (10).

For instance, it has been reported in several studies that these phytochemicals are able to exhibit a wide spectrum of pharmacological activities including antioxidant activity, hypoglycaemic and hypocholesterolemic effects in animals (3) as well as modulation in wound healing stages (4).

This work aims to present a review of the current knowledge and evidence available on *C. odorata* and its attribution in medicinal practices. Published information about *C. odorata* was compiled using various database platforms, including Google Scholar, Science Direct, SciFinder and Scopus. The selection process included all the papers that cited *C. odorata* and its weed status, distribution, or beneficial attributes.

2.0 Habitats of *Chromolaena odorata*

2.1 Distribution of Chromolaena odorata

This plant is native to North America and is widely spread from the southern USA to northern Argentina, including Central America and the Caribbean. Besides, *C. odorata* plant has also been extensively introduced to tropical Asia, West Africa and some parts of Australia (11), pacific region (12) and subsequently distributed to Asian country including Indonesia, Malaysia, China, Thailand, Taiwan, Laos, Sri Lanka, Bangladesh, Cambodia and India (9).

It was grown as medical herbs and ornamental plant and it is also a serious weed in plantation crops globally as it is highly allelopathic and suppresses the vegetation of the neighbouring plants (5).

This plant is able to live in many countries due to its large tolerance to adapt to a variety of climates. Besides, it is extensively found in the raw forest, dry slopes or abandoned fields. It was revealed that sites with high biotic pressure, maximum temperature variation, open forest canopy, and free from herbivory are the most suitable habitat for the growth of *C. odorata*. Furthermore, an elevated level of phosphorus, potassium, magnesium, soil organic matter, and nitrogen as well as acidic soil encourages further invasion of *C. odorata* (12,13).

Based on the factors mentioned earlier, *C. odorata* plants have also been reported to be found in Australia where the plants can grow extensively on buildings, in the garden, and along borders of the canal due to its highly invasive behaviour (14). Collectively, the most suitable habitat for *C. odorata* to grow well includes the moist, humid, warm, cold, and abandoned areas. These features provide a suitable and favourable area for *C. odorata* plants to grow in a wide range of habitats (6).

2.2 Invasive Weed properties

Although *C. odorata* plants preferably invade areas with a higher amount of moisture content (6), it does not prevent the plants from growing at other sites due to its ability to grow on soil with pH ranging from 4 to 8. It has been shown that *C. odorata* plants not only invade soil that contains potassium and phosphorus, but it can also increase the nutrient contents in the soil, namely potassium, phosphorus, calcium, nitrogen, and magnesium (13). Another study also revealed a significant increase in soil nutrients such as nitrogen and soil organic matter (SOM) from all invaded sites (6). The rise of the amount of nitrogen and soil organic solvent (within the 10 cm layer) of the soil showed that *C. odorata* plants have the potential to invade all fallow areas (15).

It is reported that *C. odorata* plants are one of the world's most gradually invasive weeds in Southeast Asia, India, Pacific Islands, Australia as well as west and central Africa (16). Besides, most of the roots of *C. odorata* plants are spread laterally and superficially in all plots. However, only some of the roots can penetrate deeper into the soil between 15 to 20 cm in length. Although the plants are highly invasive, they do not favour dry and sandy soil (6). *C. odorata* plant is shown in Figure1.

Figure 1: *Chromolaena odorata* plant

3.0 Phytochemical Constituents of *Chromolaena odorata*

3.1 Phenolic Compounds

Phenolic compounds are among the largest group of phytochemicals in plants. Many studies have reported that this compound to be responsible for the antioxidant property (17). Phenols have been reported as one of the essential constituents in *C. odorata*. The structure contains a hydroxyl group, a property that gives the scavenging effects in this plant (18). Figure 2 shows the chemical structure of phenolic compounds; *p*-coumaric and *p*-hydroxybenzoic from *C. odorata* leaves. Other phenolic compounds isolated from *C. odorata* includes protocatechuic, vanillic and ferulic acids. These phenolic groups were reported to be promising in protecting cultured skin cells against oxidative damage (19).

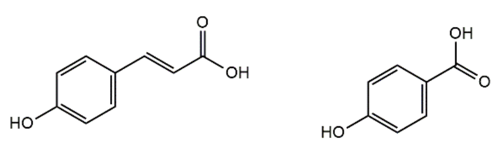


Figure 2: Chemical structure of *p*-coumaric (left) and *p*-hydroxybenzoic (right) from *C. odorata* leaves.

The extraction of *C. odorata* leaves yielded the highest amount of total phenolic compounds compared to other parts of the plant such as the stem and the roots. It is also shown that the aqueous extraction of the *C. odorata* leaves produced a higher amount of phenolic content than ethanol extraction. Specifically, after 24 hours of extraction, the highest amount of total phenolic compounds from the aqueous extract was 198.02 ± 3.96 mg of gallic acid (20). The compound is expressed as mg of Gallic Acid Equivalent (GAE) per gram of extract. The total phenolic content obtained from the methanolic extract of *C. odorata* was 455.55 mg GAE/g (21).

Hanphakphoom et al. (22) has reported the highest total phenolic compounds was found in the ethanol leaves extract, followed by water, methanol, and hexane. However, the water extract has the highest content of gallic acid compared to the others.

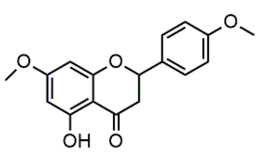
3.2 Flavonoid

Flavonoids are the major group of phytonutrients, with more than 6,000 types that exist in the aerial parts of *C. odorata* (23). Among the known and common flavonoids isolated from *C. odorata* plants includes quercetin-7-methyl ether, kaempferol-4-methyl ether, naringenin-4-methyl ether, scutellarein-6,4-dimethyl ether, luteolin-3,4-dimethyl ether, quercetagetin-6,4-dimethyl ether and taxifolin-4-methyl ether (17). The crude methanolic extract from the aerial parts of *C. odorata* fractionated by silica gel column chromatography gave rise to a new flavanone and six known flavonoids; 5-hydroxy-6,7,4′- trimethoxyflavanone, eriodictyol-7,3′,4′-trimethyl ether, alyssifolinone, aromadendrin-7-dimethyl ether, dihydro-kaempferide, and apigenin-7,4′-dimethyl ether (23). Beside the known flavonoids, quercetagetin-6,4′-dimethyl ether, a very unusual flavonoid, has been discovered in *C. odorata*. This flavone was recently identified in *C. odorata* plants and has only been detected in other plant species such as *Brickella laciniata* and in two *Arnica* species. Aromadendrin-7,4′-dimethyl- ether, isolated from *C. odorata* leaves has only been identified from the bark of *Cephalantus spathelliferus* (24).

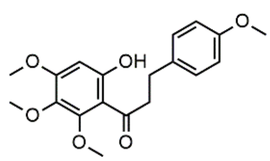
Kouamé et al. (2013) reported that three compounds were isolated from the hexane fraction of *C. odorata* leaves with two known compounds identified as 5-hydroxy-7,4′-dimethoxyflavanone and 2′-hydroxy-

4,4′,5′,6′-tetramethoxychalcone along with one new compound namely 1,6-dimethyl-4-(1-methylethyl) naphthalene or known as cadalene (Figure 3). All the three compounds were also reported for their cytotoxicity and anticancer properties. Compound 2′-hydroxy-4,4′,5′,6′-tetramethoxychalcone was found to be both cytotoxic and anticlonogenic and to act synergistically with the Bcl2 inhibitor ABT737 to enhance apoptosis in Cal51 breast cancer cells (25).

Additionally, the study conducted by other researchers also found that flavonoid compounds such as eriodictyol-7-4′-dimethyl ether, naring-enin-4′-methylether and 2′,4-dihydroxy-4′,5′,6′,-trimethoxychalcone have high efflux inhibitory action towards methicillin-resistant *Staphylococcus aureus* (MRSA). Thus, they can be good efflux inhibitors for MRSA (26).



(a)



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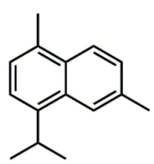

(c)

Figure 3: Chemical structure of; (a) 5-hydroxy-7,4′-dimethoxyflavanone; (b) 2′-hydroxy-4,4′,5′,6′-tetramethoxychalcone; and (c) 1,6-dimethyl-4-(1-methylethyl) naphthalene.

3.3 Essential Oils

Extraction of *C. odorata* leaves which was collected during hot weather has been shown to contain essential oils such as geijerene, pregeijerene, germacrene D, α-pinene, β-caryophyllene, α-humulene, sabinene, δ-cadinene, and β-cubebene (Figure 4) (27).

Meanwhile, extraction from the leaves of *C. odorata* that were collected during the cold weather was revealed to have a greater concentration of β-caryophyllene, pregeijerene, geijerene, germacrene D, together with α-pinene, β-pinene, (E)-β-ocimene,α-humulene, bicyclogermacrene, δ-cadinene, α-cadinol and viridiflorol (28). However, the concentration of other constituents was reported to be less than 1% (29).

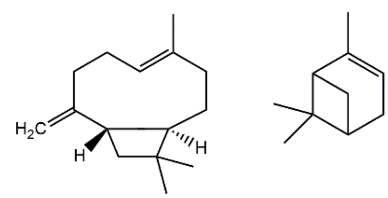

Figure 4: Chemical structure of β-caryophyllene (left) and α-pinene (right) from *C. odorata.*

In addition, the essential oils of *C. odorata* plants include other nine monoterpene hydrocarbons, 15 sesquiterpene hydrocarbons, one oxygenated monoterpenes, seven oxygenated sesquiterpenes as well as two phenyl derivatives that consist of 34 constituents of the total oil compounds (30). It has been reported that 64 essential oil compounds were present in the *C. odorata*, and it is dominated by the constituents of sesquiterpenes and hydroxy derivatives.

The aerial parts of *C. odorata* were also shown to have volatile constituents. The constituents include about 31% of oxygenated sesquiterpenes, 30% sesquiterpene hydrocarbons, 10% oxygenated monoterpenes, and 7% of mono-terpene hydrocarbons, as well as 15% of two phenyl derivatives. The main essential oils analysed from the aerial part oil of *C. odorata* were pregeijerene, 10-epi-γ-eudesmol, cubebol, epi-cubebol, δ-cadinene, cissabinene hydrate, and germacrene-D-4-ol. (30).

4.0 Pharmacological Properties of *Chromolaena odorata*

4.1 Antibacterial Activity

The *C. odorata* leaves extracts from ethanol, methanol, and hexane extraction have been reported to exhibit strong inhibitory effects against both Gram-positive (*Bacillus cereus, Enterococcus faecalis, Staphylococcus epidermidis, Staphylococcus aureus, Streptococcus pyogenes* and *Propionibacterium acnes*) and gram-negative (*Proteus vulgaris*) bacterial strains (31).

In addition to leaves extract, hexane extract of *C. odorata* stem showed greater inhibitory activity against *Pseudomonas aeruginosa, B. cereus* and *Klebsiella pneumoniae*, while hexane root extract showed high inhibitory activity against *Enterococcus faecalis* and *K. pneumoniae*. The findings also reported that the ethanolic and methanolic leave extracts produced high extraction yield and high contents of both total phenolics and flavonoids. Besides, it has been reported these extracts exhibited good antibacterial activity against the gram-positive bacteria *Staphylococcus S. aureus, S. pyogenes* and *Staphylococcus epidermidis* and the gram-negative bacteria *P. vulgaris*. The results obtained suggested that the ethanolic, methanolic and hexane leaves extracts of *C. odorata* are promising to be further developed in treating bacterial skin infections (31).

Furthermore, it was reported that *C. odorata* leaves extracts from four different solvents: cyclohexane, dichloromethane, ethyl acetate and butanol displayed antibacterial activities against four bacteria that causes intestinal tract infection including *Klebsiella oxytoca, Salmonella enterica, Shigella sonnei* and *Vibrio cholera*. This further validates the traditional use of this plant in the treatment of intestinal infectious diseases (17).

A recent study by Udayaprakash et al. (32), demonstrated that acetone extract of *C. odorata* exhibited high inhibitory activity against *S. aureus* and *P. aeruginosa*. Meanwhile, ethyl acetate extract of *C. odorata* recorded the maximum zone of inhibition against *Bacillus subtilis* and chloroform extract demonstrated strong inhibition against *Streptococcus mutans*. It is worth noting that the extracts of the direct solvent extraction method were shown to possess better antibacterial compounds when compared to the sequential extraction method (32).

4.2 Anti-inflammatory Activity

The *C. odorata* plants also have been shown to exhibit anti-inflammatory property. It was reported that the aqueous and ethanolic extracts of *C. odorata* could retard the inflammatory reaction. The anti-inflammatory activities exhibited by *C. odorata* may be due to the presence of phenolic compounds in these extracts (17).

Besides, it has also been shown that the chloroform extract of *C. odorata* exhibits significant inhibition on the production of nitric oxide (18). Nitric oxide (NO) is a free radical produced naturally in the body, however overproduction of NO may cause many types of the inflammatory process in the body (18). Therefore, inhibition of NO could prevent or reduce the inflammatory effects in the body (18).

Furthermore, the acid derivatives such as coriolic acid, linoleamide and didehydrocoriolic acid from the extracts of *C. odorata* were shown to be a natural inhibitor of NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells). NF-κB is a crucial mediator of inflammation. Therefore, inhibition of NF-κB transcriptional factor is considered a therapeutic target for anti-inflammatory treatment by the fatty acid components of *C. odorata* (33).

Flavonoid compounds such as chalcones were reported to be associated with a potent anti-inflammatory activity, which is also targeting the NF-κB signaling pathway. Chalcones were shown to exhibit anti-inflammatory activity by suppressing the activation of NF-κB signaling pathways, resulting in the reduction of proinflammatory cytokines in LPS-activated macrophages. This action justifies the role of chalcone in reducing inflammation (34).

In addition, based on the anti-inflammatory test conducted, the aqueous extract of *C. odorata* was able to consistently produce high levels of anti-inflammatory activities in acute and chronic models of inflammation (35). It is postulated that the flavonoid compounds of *C. odorata* may be responsible for the anti-inflammatory activities in the body (35).

4.3 Antioxidant Activity

Antioxidant is an important substance in the body that works by protecting the body from any harm or injury that is eventually caused by oxidative stress due to free radicals (18). The natural antioxidants present in the *C. odorata* plants such as polyphenols play an important role in preventing the body from oxidative damage (18). This is because the ideal chemical structure of polyphenols compound makes the plants more effective as an antioxidant against a free radical-scavenging activity as compared to any other compounds such as ascorbate and tocopherols (18).

C. odorata was also able to stimulate the production of antioxidant at the wound site by avoiding tissues from oxidative damage and providing a favourable environment for tissue healing (1). Basically, the reactive intermediates (ROS) can cause a delay in wound healing. Phytochemical compounds of *C. odorata* such as alkaloids and flavonoids were also shown to have antioxidant activity that can reduce or regulate the oxidative damage caused by ROS generation. Furthermore, *C. odorata* could enhance antioxidant enzyme levels, in which these enzymes can quench the superoxide radical and avoid the free radical-mediated damage to cells. Thus, it can support the wound healing mechanism (1).

In addition, the polyphenols are able to exhibit antioxidant properties due to the high reactivity of polyphenol compounds that can act as either an electron or hydrogen donors and its ability to stabilise and remove the unpaired electron (18). The phenolic compound that can be found in crude extracts of *C. odorata* essentially can work as a metal chelator, reducing agent, free radical quenchers, as well as a hydrogen donor. This function is due to their redox properties that enable the phenolic compounds in this plant to exhibit antioxidant properties (18).

The common solvents for extraction of *C. odorata* plants that exhibit antioxidant activity include chloroform, ethanol, methanol, and petroleum ether. Overall, the ethanol extract of the leaves demonstrated the most effective antioxidant property (17).

4.4 Analgesic Activity

Substances that relieve pain can be defined as analgesics (painkillers). Analgesics works through various mechanisms and function either centrally (opioids receptor agonism) or peripherally. In recent years, there has been an impetus on the use of traditional medicinal plants with analgesic effects worldwide due to its natural origin and lesser side effects (36).

A study by Owoyele et al. (35) reported that *C. odorata* ethanolic extraction was shown to exhibit analgesic activity through hot plate latency assay and formalin paw licking tests. There were significant increases in the reaction time from 1.80 ± 0.37 to 4.0 ± 0.55 min after 60 min of 100 and 200mg/kg oral administration in the hot plate latency assay. While in the formalin-induced paw licking assay, doses of 25– 200 mg/kg *C. odorata* ethanolic extract significantly inhibited the early and late phase licking time. The number of writhing incidents also significantly decreased from 16.0 ± 0.37 to 7.0 ± 0.26 at doses between 25 and 200 mg/kg extract administration in the acetic acid-induced writhing test. It is postulated that the fraction of *C. odorata* ethanolic extract contains high amounts of active constituents that is responsible in inhibiting both the centrally and tonic pain induced by hot plate assay and formalin test.

The effectiveness of *C. odorata* extracts to exhibit the analgesic properties might be due to its active phytochemical constituents (37). The main active constituents responsible for the analgesic property include glycosides, terpenes, flavonoids, steroids, tannins, alkaloids as well as saponins (38). The effectiveness of *C. odorata* plant extract on the analgesic properties was reported to be approximately similar to the pentazocine drug. Pentazocine is an opioid pain medication which is sometimes referred to as a narcotic. This drug also works as an analgesic which eventually interacts with k-receptors which in turn causes sedation (37).

5.0 Medicinal Uses of *Chromolaena odorata*

5.1 Wound healing

Substances that relieve pain can be defined as analgesics (painkillers). Analgesics works through various mechanisms and function either centrally (opioids receptor agonism) or peripherally. In recent years, there has been an impetus on the use of traditional medicinal plants with analgesic effects worldwide due to its natural origin and lesser side effects (36).

The presence of the phenolic compound in the *C. odorata* leaf extracts works as an antioxidant, which helps increase the efficacy of *C. odorata* in wound healing. This antioxidant property works by increasing the efficiency of preserving the growth of keratinocytes and fibroblasts on the wounds (10). The presence of several active phytochemical compounds possesses a synergistic wound healing activity. It has been proven that the active constituents from the *C. odorata* extract are able to enhance and improve wound healing in laboratory animals including rats (40). Besides, there were no adverse side effects such as exudate, wound haemorrhage, inflammation, or oedema when *C. odorata* leaves extracts were used for the treatment of wound healing. Based on a study by Vijayaraghavan & Rajkumar (40), the most potent concentration of *C. odorata* for wound treatment is at 5% w/w, where it has been proven to heal the area of the wounds significantly faster than control (petroleum jelly) and Betadine-treated groups. In addition, the aqueous extraction of *C. odorata* has been found to accelerate healing in excision wound model in rats (40).

The *C. odorata* plant extracts can induce wound healing primarily by enhancing the regulation of thromboxane synthase, heme oxygenase 1, and anti-platelet aggregator genes. On the other hand, the anti-platelet aggregator which is matrix metallopeptidase 9 (MM9) was reduced with the treatment using *C. odorata* leaf extracts (10).

5.2 Treatment of Skin Infection

C. odorata is a traditional medicinal plant that has been used for its many medicinal properties including external application to treat skin infections. For instance, the West and Central African exploited the plant for the management of a wide range of medical conditions, despite this being a non-native species. Besides, it was reported that the stem extract of *C. odorata* plants has been demonstrated to be effective for the treatment of skin infections, particularly caused by the *Propionibacterium acnes* (41).

The extract from the leaves of *C. odorata* has also been widely used in countries such as Vietnam and other tropical countries to treat skin infections and rashes (42). Besides, in other countries such as Thailand and India, this plant has been extensively used as a traditional herb to treat skin infection (1).

5.3 Treatment of Stomach Related Problems

The species of *C. odorata* plants, found in the West of Africa and Asia were also found to be useful in reducing stomach-ache (17). The phenolic compound in *C. odorata* leaves extract has been shown to prevent internal bleeding from diathesis and stomach ulcers. Equally important, is that this compound also preserved the keratinocytes from being damaged and reduces the internal bleeding from the stomach ulcer (43).

In addition to phenolic compounds, the presence of other active constituents such as flavonoids and tannins have demonstrated to be essential in arresting internal bleeding from stomach ulcers and minimising the bleeding diathesis in heparin-induced mouse model. Moreover, oral administration of *C. odorata* extract was proven to protect the bone marrow cells from busulfan, thereby elevating the platelet count and improving thrombocytopenia conditions (43).

6.0 Conclusion

In summary, the review and analysis of literature on *C. odorata* shows that the plant species are invasive to a wide range of habitats including the grasslands, at the roadsides, agricultural lands, forest margins, as well as in the disturbed forests. Despite its invasive properties, this plant is useful as a medicinal herb. The uses of *C. odorata* in traditional practice give rise to many research studies that are currently ongoing to further validate its medicinal properties. This review also provides an understanding of the medicinal properties and uses of *C. odorata* particularly in treating diseases such as skin infections, stomach problems, and wound healing management. Therefore, considering the above-mentioned aspects, this review could enhance our knowledge on the beneficial attributes of this plant and create awareness among the local population on its medicinal uses.

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Conflict of interest

Authors declare no conflict of interest in the present work.

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