Tropical Journal of Pharmaceutical Research February 2018; 17 (2): 365-373
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v17i2.24

Review Article

Traditional uses, phytochemistry and biological activities of *Cotula cinerea* Del: A review

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Sent for review: 4 August 2017 *Revised accepted: 15 January 2018*

Abstract

Cotula cinerea Del. belongs to the family Asteraceae. It is widely used in the traditional medicinal system for the treatment of various ailments such as colic, cough, diarrhea, digestive disorders, rheumatism, urinary and pulmonary infections, fever and headaches. Cotula cinerea contains a wide range of phytochemical compounds such as saponins, essential oils, tannins, flavonoids, steroids, and terpenoids. This paper reviews information pertaining its traditional uses, phytochemistry and biological activities such as antibacterial, antifungal, antioxidant, herbicidal, anti-diarrheal and analgesic properties. It is hoped that the information presented here might stimulate further studies that will possibly lead to development of therapeutic agents from this plant.

Keywords: *Asteraceae, Cotula cinerea, Traditional uses, Phytochemistry, Biological activities*

Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, International Pharmaceutical Abstract, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

Herbs are largely used in ethnomedicine in the form of traditional preparations or derivatives of their pure active ingredients [1]. Medicinal plants represent natural sources of agents that can be used for the treatment of several diseases [2]. According to the World Health Organization (WHO), a large percentage of the people in developing countries depends mostly on medicinal plants for basic healthcare needs [3]. Medicinal plants have played a central role in the drug discovery process, due to their richness in bioactive natural products [4]. Indeed, several classes of bioactive compounds such as saponins, phenolics, lignans, glycosides, flavonoids, terpenes, and alkaloids have been used in the modern drug system, due to their potent therapeutic properties [5,6].

However, some information on plants used in traditional medicine are not readily available to the scientific community because they are presented in the language of the local population, and so are limited in circulation to those localities [7]. Many researchers have discussed the possibility of integrating traditional medicine into the public health system [8]. This requires collection, organization and wide publication of all information about traditional medicine.

Cotula cinerea is one of the most used plants in traditional medicine in the northern Sahara of

Algeria and in Morocco. The present review highlights the phytochemistry, and the various traditional uses and pharmacological properties of *C. cinerea.*

CLASSIFICATION OF *C. CINEREA*

The classification and vernacular names of *C. cinerea* are given in Table 1.

Table 1: Classification of *C. cinerea*

Kingdom	Plantae	Reference
Sub-kingdom	Tracheobionta	[9,10]
Super-division	Spermatophyta	
Division	Magnoliophyta	
Class	Magnoliopsida	
Sub-class	Asteridae	
Order	Asterales	
Family	Asteraceae	
Genus	*Cotula*	
Species	*Cinerea*	
Binomial name	*Cotula cinerea* Del	
Synonym	*Brocchia cinerea* Del	
Vernacular names	*Gartoufa, Gartoufa beida, Chouihiya, Chihia, Shihit El Ebel, Chiria, Robita*	[9,10,11,12]

GENERAL BOTANICAL DESCRIPTION OF *C. CINEREA*

Figure 1: General morphology of *C. cinerea* [15]

Cotula cinerea is a small annual plant (5 to 15cm in height) with a woolly appearance. It rarely reaches a height of 40cm and is characterized by a whitish-green stem, diffuse or erect and covered with small dense hairs. The leaves are small, whitish-green in color and covered with small, dense hairs (Figure 1). In addition, the leaves are entire, thick and velvety, and are cut into three to seven teeth (or fingers), resembling slightly closed hands [9,13,14]. The flowers are yellow and grouped into discoid hemispherical heads (6 to 10mm in diameter) at the tip of a short stem (Figure 2). The fruits of this species are small achenes, each of which does not exceed 5mm in diameter [14].

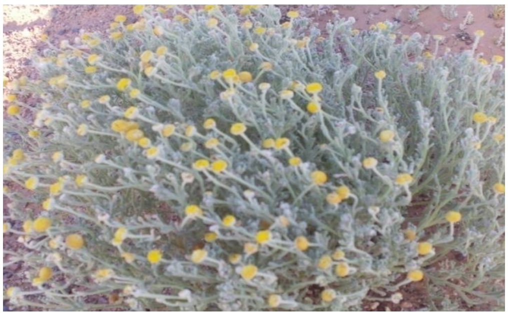

Figure 2: Photo of *C. cinerea* [16]

GEOGRAPHICAL DISTRIBUTION OF *C. CINEREA*

Cotula cinerea is a xerophytic plant; it thrives in desert conditions with an average annual rainfall of 100mm. The plant favors sand-loamy soils, and it is usually found on non-saline wadi beds on gravelly sandy soils [17]**.** Geographically, it is widely distributed in North Africa especially in the Saharan regions of Algeria and Morocco, Red Sea region, Sinai, Qattara Depression and Mali [18].

TRADITIONAL USES OF *C. CINEREA*

Traditionally, *C. cinerea* is extensively used to treat several diseases like colic, cough, diarrhea and digestive disorders. The plant is usually applied in the form of decoction, maceration, infusion and inhalation [19-21]. In traditional medical practice, it is used as an antiseptic, antipyretic, analgesic, and anti-inflammatory agent, and also for treating rheumatism [20,22]. The plant is also used in the treatment of fever and cough, and in the form of poultices against headaches and migraine [23]. In addition to its medicinal uses, the nomads use the plant as a tea additive for enhancement of the taste of tea. It is also used to filter goat butter, on account of its good preservative properties [24].

PHYTOCHEMISTRY OF *C. CINEREA*

Phytochemical screening of the aerial part of the *C. cinerea* showed the presence of saponins, essential oils, tannins, flavonoids, steroids and terpenoids [16,25].

It has been reported that the total phenolic content of the chloroform extract of the aerial parts of *C. cinerea* was 485mg of gallic acid equivalents/100g dry weight, while the total flavonoid content was 281.4 mg of quercetin/100g dry weight [24]. The plant sample used in that study was harvested in the region of Ouargla (Southeastern Algeria) during the flowering stage.

In another study on the flower parts of *C. cinerea* harvested in Adrar region, southern Algeria, Belyagoubi-Benhammou *et al* [26] obtained total phenolic content of 22.22 ± 0.41mg gallic acid equivalents (determined by spectrometry); flavonoid yield of 3.93 ± 0.06 mg (determined colorimetrically) and proanthocyanid in level of 8.61 ± 0.18 mg catechin equivalents (determined by vanillin assay). The chemical compositions of the hydro-ethanol extract of the aerial parts of *C. cinerea* harvested at the flowering stage in Tougourt (southeastern Algeria) have been studied by Dendougui *et al* [27]. Eighteen compounds were identified in the study. These included a new germacranolide-type sesquiterpene lactone, and seventeen new flavonoids for the genus *Cotula*: **(I)** chrysospenol-D, **(II)** chrysosplenetin, **(III)** oxyayanin-B, **(IV)** axillarin, **(V)** 3-methylquercetin, **(VI)** pedaletin, **(VII)** isokaempferid, **(VIII)** apigenin, **(IX)** luteolin, **(X)** 6-hydroxyluteolin, **(XI)** 3-glucosyli-sorhamnetin, **(XII)** 3-methyl-7-glucosylquercetin, **(XIII)** 7-O-β-D-glucosylapigenin, **(XIV)** 7-O-β -D-glucosylluteolin, **(XV)** 7-O-β-D-glucosyl-quercetin, **(XVI)** 7-O-β-D-glucosylaxillarin and **(XVII)** 7-O-β -D- diglucosylluteolin. The structures of these compounds were established by spectral methods.

Six sesquiterpenes lactones (three germa-cranolids, two guaianolides, and one eudesmanolide) have isolated from the chloroform extract **of** the aerial parts of *C. cinerea* [24]. Their structures were established by spectral methods.

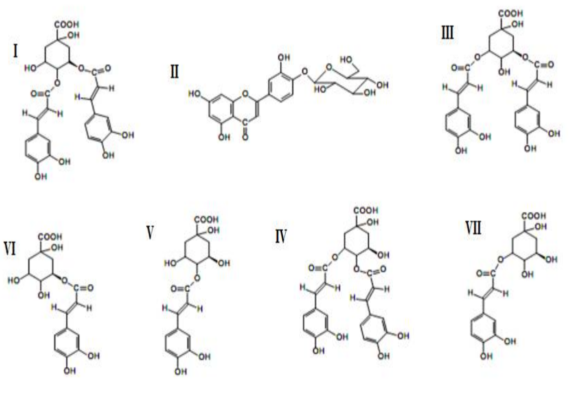

Figure 3: Structures of phenolic components of methanol extract of *C. cinerea*. **I**: 3, 4-dicaffeoylquinic acid; **II**: luteolin-4´-*O*-glucoside; **III:** 3, 5-dicaffeoylquinic acid; **IV**, 4,5-dicaffeoylquinic acid; **V:** cryptochlorogenic acid; **IV:** chlorogenic acid; **IIV:** neochlorogenic acid

Studies on the methanol extracts of the aerial parts of *C. cinerea* harvested from Errachidia (Morocco) at the flowering stage revealed that the major phenolic compounds were luteolin-4´-*O*-glucoside; 4,5-dicaffeoylquinic acid; 3,5-dicaffeoylquinic acid; 3,4-dicaffeoylquinic acid; cryptochlorogenic acid ; chlorogenic acid and neochlorogenic acid [24]. The structures of this compound were elucidated by HPLC-ESI-MS (Figure 3).

Table 2: Essential oil yield of *C. cinerea* from different geographical locations

Essential oil yield (v/w)	Area of harvest	*Harvest* season *or stage*	Reference
0.080%	Oued Souf (South-eastern Algeria)	Flowering	[29]
0.391%	Oued Souf (South-Eastern Algeria)	Fruiting	[29]
0.75 %	Ouargla (South-Eastern Algeria)	March	[24]
0.282%	Bechar (South-Western Algeria)	February and March	[30]
0.64%	Smara (Moroccan Sahara)	March	[31]
0.87%	Province Zagora (South of Morocco)	Flowering phase	[32]
0.30 %	Desert area between Cairo and Ismailia (Egypt)	Not stated	[33]

The essential oil of *C. cinerea* has also been subjected to many studies. The essential oil content of *C. cinerea* varies between 0.080 and 0.87% (Table 2). Samples of *C. cinerea* harvested in the region of Zagora (South Morocco) produced the highest oil yield. Many studies have been conducted to determine the effect of various factors on essential oil yield of *C. cinerea*. The oil essential yield is higher during the flowering period when compared to other periods [34], and the essential oil content increases with flowering [35]. The accumulation of essential oils during the full-flowering period has been related to the attraction of pollinators, and to the increase in antifungal defense system during this period [36]. The essential oil content also depends on precipitation, air movement, sunshine duration, relative humidity, and temperature [37]. Other factors that influence oil levels are the length of the day and altitude [38]; pedoclimatic conditions, as well as the ontogenic stage of the plant [39]. It has been reported that the yield of essential oil increases with accentuation of water deficit and decreases with increases in salt concentration [40]. In addition, essential oil content is influenced by the harvest stage, harvest time and mode of drying of the plant [41]. Generally, the yield of essential oils is influenced by intrinsic factors such as the condition of the plant, harvest period, genetic factors, as well as extrinsic issues such as the floral procession, insect pests, pollinators, climate and nature of the soil [29].

The physicochemical properties of essential oils from *C. cinerea* have also been investigated. It has been reported that the essential oil of *C. cinerea* is yellowish and viscous, and it is characterized by olfactory properties that resemble those of *Artemisia* [31]. Indeed, studies have indicated that at the fruiting stage, the essential oil of *C. cinerea* is characterized by a yellowish green color and viscous lingering odor, but at the flowering stage, the oil acquires a yellowish tinge [29]. In addition, the essential oil possesses a very agreeable aromatic odor. The physical properties of the essential oils have also been studied with respect to density, refractive index and rotatory power, resulting in values of 0.864, 1.4610 and +115°, respectively [24]. Moreover, numerous studies have been conducted on the composition of essential oils of *C. cinerea* essential oil from different geographical regions [24,29-33,42]. The major chemical compounds present in *C. cinerea* essential oil from different regions are listed in Table 3 and Table 4. The relative amounts of each component were determined by GC-MS analysis.

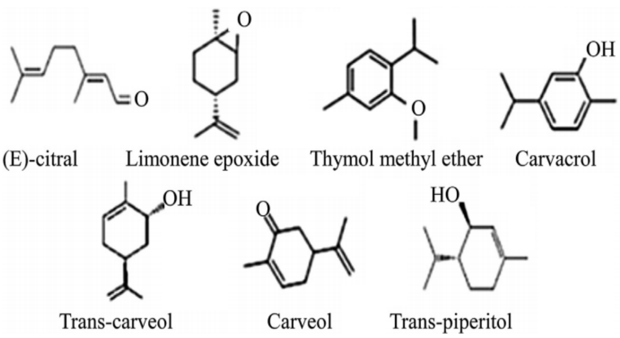

Figure 4: Major compounds of *C. cinerea* essential oil from Bechar area (southwest Algeria) [30]

Table 3: Major chemical components essential oils from *C. cinerea* from different geographical locations

Geographical region	**Major compound**	**Reference**
Ouargla (South-Eastern Algeria)	Thujone (47.72 %); camphor (10.54 %); santolinatriene (8.00%); eucalyptol (6.37 %); acetate (4.17 %), terpinen-4-ol (2.77 %).	[24]
Oued Souf (South-Eastern Algeria)	3-Carène (30.99%); thujone (21.73%); santolina triene (18.58%); camphor (6.21%); eucalyptol (2.79%); 7'-Oxaspiro[cyclopropane-1,4'tricyclo[3.3.1.0(6,8)] nonan-2'-one] (2.98%); terpinen-4-ol (3.64%); ρ-menth-1-en-8-ol (3.01%); trans-pinocarveol (1.28%).	[29a]
Oued Souf (South-Eastern Algeria)	Thujone (28.78%); 3-carène (15.90%); eucalyptol (15.13%); santolina triene (13.38%); camphor (7.49%), *M*-cymene (3.34%); 7'-oxaspiro [cyclopropane-1,4'-tricyclo[3.3.1.0(6,8)] nonan-2'-one] (3.31%); 4(10)-thujen-3-ol, stereoisomer (1.47%); terpinen-4-ol (4.26%) and *p*-menth-1-en-8-ol (1.65%); 3-thujanone (0.99%); isoborneol (0.61%); pinene (0.47%); camphene (0.37); *p*-cymen-8-ol (0.30); 1, 2, 2, 3-tetramethylcyclopent-3-enol (0.24%); origanene (0.23%); beta-phellandrene (0.21%).	[29b]
Bechar (Southwest Algeria)	(E)-citral (24.01%); cis-limonene epoxide (18.26%); thymol methylether (15.04%); carvacrol (15.03%); trans-carveol (13.79%); carvone (3.06%); trans-piperitol (2.54%).	[30]

a: sample harvested at flowering period; b: sample harvested at the fruiting period.

Table 4: Major chemical compounds in the essential oil of *C. cinerea* from different geographical locations

Geographical region	Major compound	Reference
Smara (Moroccan Sahara)	Iso-3thujanol (47.38%); Santolina triene (11.67%); camphor (10.95%); santolina alcohol (7.68%); borneol (5.49%); neo-iso-3-thujanol (3.74%); ß-pinene (2.98%).	[31]
Province Zagora (Morocco)	Trans-thujone (41.4%); cis-verbenyl acetate (24.7%); 1, 8-cineole (8.2%); santolinatriene (7.2%); camphor (5.5%).	[32]
Desert area between Cairo and Ismailia (Egypt)	Camphor (50%); alpha and beta-thujone (15%).	[33]

Results from analysis and identification of components showed that the main constituents of essential oil from the aerial parts of *C. cinerea* vary from region to region. The structures of some major compounds are given in Figure 4. The qualitative and quantitative differences in the chemical compositions of essential oil could be attributed to several factors. The chemical components of essential oils are influenced by several intrinsic and extrinsic factors [42].

Qualitative variation in oil composition is thought to be influenced by intrinsic genetic factors, whereas quantitative variation is influenced by extrinsic factors [43]. It has been revealed that the composition of the essential oils is influenced by a multiplicity of factors such as plant ontogeny, site of oil production, photosynthesis, plant growth regulators, plant density, soil salinity, harvesting stage, seasonal variations and climatic conditions [44].

PHARMACOLOGICAL ACTIVITIES OF *C. CINEREA*

Several pharmacological activities and medicinal applications of *C. cinerea* are widely known. A summary of the biological studies on this plant is presented below.

Antibacterial activity of *C. cinerea*

The antibacterial activity of *C. cinerea* extracts has been reported in a number of studies. Many researchers have investigated the antibacterial activity of essential oils from *C. cinerea* and reported that it possesses broad-spectrum antibacterial activity when tested by direct contact with pathogenic bacteria such as *Enterococcus faecalis, Salmonnella heidelberg, Staphyloccocus aureus, Klebsiella pneumoniae, Echerichia coli, Pseudomonas aeruginosa, Enterobacter cloacae, Enterococcus faecium*, *Morganella morganii, Citrobacter freundii, Proteus vulgaris, Acinetobacter baumannii, Bacillus subtilis* and *Micrococcus luteus* [29,31,45]. Some studies reported a relationship between the chemical structures of the major compounds in the essential oils of *C. cinerea* and its antibacterial activity. It has been reported that the ethylacetate and n-butanol extracts of the aerial parts of *C. cinerea* aerial part showed antibacterial activity against *Pseudomonas fluorescens, Pseudomonas savastanoui, Bacillus sp., Bacillus brevis* and *Bacillus sphaericus* [46], while the ethyl ether extract produced no antimicrobial activity against these bacterial strains. In another study, 70% ethanol, *n*-butanol, ethyl acetate and petroleum ether extracts of the aerial part of *C. cinerea* elicited antibacterial activities against *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Escherichia coli* [47].

Antifungal activity of *C. cinerea*

The essential oils of *C. cinerea* when tested by direct contact, suppressed the growth of *Aspergillus niger, Penicillium digitatum, Penicillium expansum, Gloeophyl lumtrabeum, Coniophora puteana, Poria placenta* and *Coriolus versicolo*r [31]. In another antifungal study, *Candida albicans* was inhibited by 70 % ethanol, *n*-butanol, ethyl acetate and petroleum ether extracts of *C. cinerea* [47]. Flavonoid and cell wall polysaccharide (hemicellulose and methylated pectins) extracts of the leaves and flowers of *C. cinerea* inhibited mycelia growth, germination and sporulation of the pathogenic fungi *Fusarium oxysporum* f.sp. *albedinis* [16]. In the same study, flavonoid extracts reduced the relative virulence, and inhibited the cellulase activity of the fungi. However, the synthesis of *Fusarium oxysporum* toxins was not affected.

It is important to point out that the antimicrobial effects of the major identified constituents of the essential oils from *C. cinerea* were not investigated in previous studies.

Many studies have demonstrated that the inhibitory effect of an essential oil results from a complex interactions between its different constituents: these interactions may produce synergistic, additive or antagonistic effects even with components present at low concentrations [48,49].

Antioxidant property of *C. cinerea*

The antioxidant properties of methanol extract of *C. cinerea* collected in Adrar region, Southern Algeria have been investigated through 1, 1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging, hydroxyl radical scavenging, reducing power and total antioxidant capacity [26]. The results showed that the plant exhibited strong antioxidant activity, with EC_{50} of 462.19 mg antioxidant/g DPPH (DPPH radical scavenging assay); EC_{50} of 0.66 ± 0.12 mg/ml (hydroxyl radical scavenging assay); IC_{50} of 1.174 ± 0.05 mg/ml (reducing power assay), and 17.190 ± 1.273 mg of ascorbic acid equivalents/g dry weight (total antioxidant capacity).

In another study, the antioxidant activity of the essential oil of *C. cinerea* collected from South Morocco was stablished using DPPH free radical-scavenging, ß-carotene/linoleic acid bleaching, and ABTS free radical scavenging assays [50].

In vivo* anti-diarrheal effect of *C. cinerea

Diarrhea is one of the most common causes of morbidity and mortality in many countries. In third world countries, it is responsible for the death of millions of people each year. Children are more susceptible to this disease which is considered as the second leading causes to death of children less than five years old [51]. Traditionally, *C. cinerea* plays an important role in the treatment of diarrhea and gastrointestinal disorders. However, there is limited scientific evidence supporting the use of this plant as an antidiarrheal agent. Aqueous extract of the aerial-part of *C. cinerea* (collected during the flowering period from the Errachidia Sahara region in Morocco) was tested for antidiarrheal activity using castor oil-induced diarrhea rat model, and also for gastrointestinal transit in mice [52]. The results showed that oral administration of the aqueous extract at doses of 50, 100 and 250 mg/kg significantly reduced fecal output of the rats by 30.17, 56.79 and 100 %, respectively, and increased the time taken to reach 100 mg/kg, while the reduction in fecal output by loperamide (10 mg/kg), was 100 % when compared with the untreated group. The results of gastrointestinal motility test revealed that small intestinal motility of charcoal meal in mice was significantly inhibited (48.57 %) at 250 mg/kg of the aqueous extract when compared to the control, while the inhibition produced by loperamide (10 mg/kg) was 78.5 %. The authors suggested that the antidiarrheal effect of the aqueous extract was probably exerted through an anti-secretory mechanism and/or anti-spasmodic effect which reduced intestinal contractions thereby allowing a greater time for absorption of water.

These results lend some credence to the widespread traditional use of *C. cinerea* as an antidiarrheal agent by the Northern Africa population.

Herbicidal effect of *C. cinerea*

The herbicidal activity of *C. cinerea* against *Melilotus indicus* (potential seed crop contaminant causing great loss in crop productivity) has been investigated [25]. The results showed that percentage germination, plumule and radicle lengths, and seedling dry weight were significantly inhibited by applying different concentrations of *C. cinerea* shoot extract. The authors also evaluated the effect of *C. cinerea* shoot powder mixed with different levels of sandy loam soils (on weight-to-weight basis), on some growth parameters, total available carbohydrates and total protein contents of *M. indicus*. It was revealed that the shoot and root lengths of *M. indicus* were significantly affected by different levels of *C. cinerea* shoot powder. The leaf area index and the total photosynthetic pigments were significant reduced in the recipient species by treatment with different levels *C. cinerea* shoot powder. On the other hand, carotenoid content was significantly increased with increase in *C. cinerea* shoot powder level. Total available carbohydrates and total protein contents of the recipient species were significantly decreased with increase in the amount of *C. cinerea* shoot powder.

Based on these results, there is a possibility of using the allelopathic potential of *C. cinerea* directly or in structure leads, for the discovery and development of environmental herbicides.

Analgesic properties of *C. cinerea*

Studies have been carried out on the possible analgesic effects of different extracts of *C. cinerea* (collected from Zagora, Morocco) [46]. Ethyl ether, ethyl acetate or n-butanol, and the reference drug acetyl salicylic acid, were orally administered to mice at a dose of 100 mg/kg, while mice in the control group received only water. After 1 h, 0.6 % acetic acid solution was injected intraperitoneally to the mice at a dose of 15 mL/kg. Nociception was evaluated 15 min after acetic acid injection by counting the number of abdominal constrictions for a period of 5 min. The results showed moderate analgesic effects of the ethyl acetate and n-butanol extracts, with constriction inhibitions of 50 and 40.21 %, respectively. In contrast, the constriction inhibition produced by the ethyl ether extract (62.49 %) was close to that of the reference drug (73.9 %).

Based on these results, it can be reasonably suggested that the isolation of the active compound(s) from these extracts may yield novel analgesic agents. Moreover, these findings justify the folkloric use of the plant for treating pain and inflammatory diseases.

Nutritional value of *C. cinerea*

Knowledge of dromedary-desert rangelands relationships is an essential element in the management and eco-development of the northwest Algerian Sahara which constitutes the habitat of various plants grazed by this animal. The dromedary is the only breeding species able to use these Saharan plants, making them valuable for the production of milk and meat, which constitute an important food resource for indigenous peoples [53]. The nutritional value (energy and nitrogenous values) of *C. cinerea* of the North Algerian Sahara have been evaluated [53]. The nutritional value assessment (based on chemical composition of this species) showed low values of fodder unit milk and of fodder unit meat (0.31 and 0.27, respectively). Nitrogenous value assessment of *C. cinerea* showed that the values of digestible protein in the small intestine limited by nitrogen (PDIN) and digestible protein in the small intestine limited by energy (PDIE) were 34.01 ± 1.14 g and 27.86 ± 2.72 g, respectively.

CONCLUDING REMARKS

This review is aimed at providing comprehensive and up-to-date information on research on the traditional uses, phytochemistry and biological activities of *C. cinerea.* The reported pharmacological properties of this species confirm its traditional uses. The plant possesses antibacterial, antifungal, antioxidant, herbicidal, anti-diarrheal and analgesic properties. Most of the therapeutic effects may be due to the presence of various phytoconstituents such as saponins, essential oil, tannins, flavonoids, steroids, and terpenoids. However, more investigations are needed to elucidate the exact mechanism(s) involved, as well as the nature of the bioactive components.

DECLARATIONS

Acknowledgement

The author thanks all the people who supported the writing of this paper.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The author declares that this work was done by the author named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by him.

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