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A review of botany, medicinal uses, phytochemistry and biological activities of *Cotyledon orbiculata*

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Abstract

Cotyledon orbiculata is a succulent shrub widely used as herbal medicine throughout its distributional range in southern Africa. This study is aimed at providing a critical review of the botany, biological activities, phytochemistry and medicinal uses of *C. orbiculata*. Documented information on the botany, biological activities, medicinal uses and phytochemistry of *C. orbiculata* was collected from several online sources which included BMC, Scopus, SciFinder, Google Scholar, Science Direct, Elsevier, Pubmed and Web of Science. Additional information on the botany, biological activities, phytochemistry and medicinal uses of *C. orbiculata* was obtained from pre-electronic sources such as book chapters, books, journal articles and scientific publications sourced from the University library. This study showed that the leaves, leaf sap and roots of *C. orbiculata* are mainly used as herbal medicines for earache, epilepsy, infertility, respiratory problems, sexually transmitted infections, skin problems, sores and wounds, toothache, ulcers and worms. Phytochemical compounds identified from *C. orbiculata* include cardiac glycosides, flavonoids, gallotannin, phenols, reducing sugar, saponins, tannins and triterpene steroids. Pharmacological research revealed that *C. orbiculata* extracts have anthelmintic, antibacterial, antifungal, anticancer, anticonvulsant, antinociceptive, anti-inflammatory, Aβ42 protein reduction, $GABA_A$ benzodiazepine receptor-binding, antioxidant and cytotoxicity activities. Future research should focus on evaluating the phytochemical, pharmacological and toxicological properties of *C. orbiculata* crude extracts as well as compounds isolated from the species.

Keywords: *Cotyledon orbiculata*, Crassulaceae, ethnopharmacology, herbal medicine, indigenous pharmacopeia

INTRODUCTION

Cotyledon orbiculata L. is a succulent shrub belonging to the Crassulaceae or stonecrop or orphine family. *Cotyledon orbiculata* is an important ornamental plant throughout the world.[1-6] Cotyledon orbiculata is listed as a weed in the global collection of weeds by Randall[7] and the species is naturalized and categorized as an invasive species in Australia, California, New Zealand, Portugal and Spain.[4-8] In Portugal and Spain, *C. orbiculata* has escaped from gardens and occurs on slopes where it reproduces both sexually and vegetatively.[4,5,8] In Australia, California and New Zealand, *C. orbiculata* is well-established on rocks in coastal areas and spreading in coastal sage scrub and bushland, and invading natural and semi-natural habitats as well as managed afforested areas and maritime protected areas.[6] In South Africa, *C. orbiculata* is managed in home gardens in the Limpopo and North-West provinces as an ornamental plant and source of traditional medicines.[9-13] The leaves of *C. orbiculata* are sold as herbal medicines in the informal herbal medicine markets in the Eastern, Gauteng and Western Cape provinces of South Africa.[14,15] Moreover, *C. orbiculata* is one of the valuable medicinal plant species in South Africa, and the species is included in the book "medicinal plants of South Africa," a photographic guide to the most commonly used traditional medicines in the country, including its botany, major medicinal applications and active phytochemical compounds.[2] It is within this context that this review was undertaken aimed at reviewing the botany, medicinal uses, phytochemistry and biological activities of *C. orbiculata* so as to provide baseline data required in evaluating the therapeutic potential of the species.

Botanical profile of *Cotyledon orbiculata*

The genus name "*Cotyledon*" is derived from the Greek word "*kotyledon*" which means "cup-shaped hollow" in reference to the leaves of some species of the genus.[16] The species name "*orbiculata*" is derived from the Latin word meaning "round" or "circular" in reference to the shape of the segments. The English common names of the species include "cotyledon", "pig's ear" and "round-leafed navel-wort". *Cotyledon orbiculata* is a complex species, divided into five varieties, namely, *C. orbiculata* var. *dactylopsis* Tölken, *C. orbiculata* var. *flanaganii* (Schönland & Baker f.) Tölken, *C. orbiculata* var. *oblonga* (Haw.) DC., *C. orbiculata* var. *orbiculata* and *C. orbiculata* var. *spuria* (L.) Tölken.[17] These varieties are separated based on differences in leaf and flower shape, shape and size of the corolla tube and their geographical distribution patterns.[17] *Cotyledon orbiculata* var. *flanaganii* is categorized as Near Threatened in South Africa,[18] this is a poorly known taxon likely to occur in less than 10 locations in the country and potentially threatened by overgrazing and trampling by livestock.[19] *Cotyledon orbiculata* is a succulent shrub with woody branches, thick and fleshy leaves which may vary from green to grey in colour, often with a red line around the leaf margins and covered with a waxy layer on the surface.[2,16] The leaves are obovate to narrowly ovoid in shape. The flowers are yellow to orange-red in colour, usually hanging, tubular and bell-shaped, carried in clusters on the ends of an elongated flower stalk. *Cotyledon orbiculata* has been recorded in Angola, Lesotho, Mozambique, Namibia, South Africa and Swaziland in sandy or in rocky soils or rocky outcrops in depressions, river banks, grassland, scrub, fynbos and karoo biomes at an altitude ranging from 50 m to 3000 m above sea level.[16,17,20-26]

Medicinal uses of *Cotyledon orbiculata*

Leaves, leaf sap and roots of *C. orbiculata* are mainly used as traditional medicines for earache, epilepsy, infertility, respiratory problems, sexually transmitted infections, skin problems, sores and wounds, toothache, ulcers and worms (Table 1, Figure 1). The roots of *C. orbiculata* are mixed with those of *Commelina africana* L. as traditional medicine for female infertility in Lesotho.[27,28] In Lesotho, the leaves of *C. orbiculata* are mixed with those of *Senecio asperulus* DC. as traditional medicines for sore throat and ulcers.[27]

Table 1: Medicinal uses of *Cotyledon orbiculata*

Medicinal use	Parts used	Country	References
Aching feet	Roots	South Africa	Mogale et al.[15]
Diarrhoea	Leaves and roots	South Africa	Masafu et al.[29];
Earache	Leaf sap	Leostho and South Africa	Van Wyk et al.[2]; Duarte et al.[3]; Harris[16]; Moteetee and Van Wyk[27]; Lum[30]; James[31]; Jacot Guillarmod[32]; Schmitz[33]; Bhat and Jacobs[34]; Hutchings et al.[35]; Thring and Weitz[36]; Amabeoku et al.[37]; Van Wyk and Gericke[38]; Van Wyk[39]; Aremu et al.[40]; Moffett[41]; De Beer and Van Wyk[42]; Amabeoku and Kabatende[43]; Ndhlala et al.[44]; Wintola and Afolayan[45]; Kumari et al.[46]; Terblanche et al.[47]; Hulley and Van Wyk[48]; Moteetee et al.[49]; Ondua et al.[50]
Epilepsy	Leaf sap	South Africa	Van Wyk et al.[2]; Duarte et al.[3]; Harris[16]; Lum[30]; Hutchings et al.[35]; Thring and Weitz[36]; Amabeoku et al.[37]; Van Wyk and Gericke[38]; Van Wyk[39]; Amabeoku and Kabatende[43]; Ndhlala et al.[44]; Kumari et al.[46]; Terblanche et al.[47]; Watt[51]; Sobiecki[52]; Stafford et al.[53]; Philander[54]; Masondo et al.[55]; Thakur et al.[56]
Eye problems	Leaves	Lesotho	Dyubeni and Buwa[57]
Fractures and sprains	Leaf sap	South Africa	Thring and Weitz[36]
Haemorrhoids	Leaves	South Africa	Hulley and Van Wyk[48]
Infertility	Roots mixed with those of *Commelina africana* L.	Lesotho	Moteetee and Van Wyk[27]; Moteetee and Kose[28]
Insect bite	Leaf sap	Lesotho	Moteetee and Van Wyk[27]
Respiratory problems (flu and sore throat)	Leaf sap and roots	South Africa and Swaziland	Mogale et al.[15]; Van Wyk and Gericke[38]; Van Wyk[39]; Long[58]
Sore throat	Leaves mixed with those of *Senecio asperulus* DC.	Lesotho	Moteetee and Van Wyk[27];
Sexually transmitted infections (gonorrhoea, syphilis and venereal diseases)	Leaves, leaf sap and roots	South Africa	Mogale et al.[15]; Masafu et al.[29]; Lum[30]; Hutchings et al.[35]; Thring and Weitz[36]; Kumari et al.[46]; Terblanche et al.[47]; Watt and Breyer-Brandwijk[59]; Erasmus et al.[60]; Semenya et al.[61]; Semenya et al.[62]
Skin problems (abscesses, boils, burns, corns, inflammation, rash and warts)	Leaves and leaf sap	Lesotho, South Africa and Swaziland	Van Wyk et al.[2]; Duarte et al.[3]; Maroyi and Mosina[11]; Harris[16]; Moteetee and Van Wyk[27]; Lum[30]; James[31]; Bhat and Jacobs[34]; Hutchings et al.[35]; Thring and Weitz[36]; Amabeoku et al.[37]; Van Wyk and Gericke[38]; Van Wyk[39]; Aremu et al.[40]; De Beer and Van Wyk[42]; Amabeoku and Kabatende[43]; Ndhlala et al.[44]; Wintola and Afolayan[45]; Kumari et al.[46]; Terblanche et al.[47]; Hulley and Van Wyk[48]; Philander[54]; Long[58]; Watt and Breyer-Brandwijk[59]; Felhaber[63]; Mabona and Van Vuuren[64]; Mabona et al.[65]; Nortje and Van Wyk[66]; Xaba and Buwa[67]; Moteetee and Kose[68]; Adebayo and Amoo[69]; Sagbo and Mbeng[70]
Sores and wounds	Leaves and leaf sap	South Africa	Thring and Weitz[36]; De Beer and Van Wyk[42]; Hulley and Van Wyk[48]; Nortje and Van Wyk[66]
Toothache	Leaf sap	South Africa	Van Wyk et al.[2]; Duarte et al.[3]; Harris[16]; Moteetee and Van Wyk[27]; Lum[30]; James[31]; Hutchings et al.[35]; Thring and Weitz[36]; Amabeoku et al.[37]; Van Wyk and Gericke[38]; De Beer and Van Wyk[42]; Amabeoku and Kabatende[43]; Ndhlala et al.[44]; Wintola and Afolayan[45]; Kumari et al.[46]; Terblanche et al.[47]; Hulley and Van Wyk[48]; Ondua et al.[50]; Philander[54]; Akhalwaya et al.[71]
Ulcers and mouth ulcers	Leaves	Lesotho and South Africa	Moteetee and Van Wyk[27]; Nortje and Van Wyk[66]; Moteetee and Kose[68]
Ulcers	Leaves mixed with those of *S. asperulus*	Lesotho	Moteetee and Van Wyk[27]
Worms	Leaves and leaf sap	South Africa and Swaziland	Van Wyk et al.[2]; Duarte et al.[3]; Harris[16]; Van Wyk and Gericke[38]; Aremu et al.[40]; Ndhlala et al.[44]; Wintola and Afolayan[45]; Terblanche et al.[47]; Long[58]; Cock et al.[72]

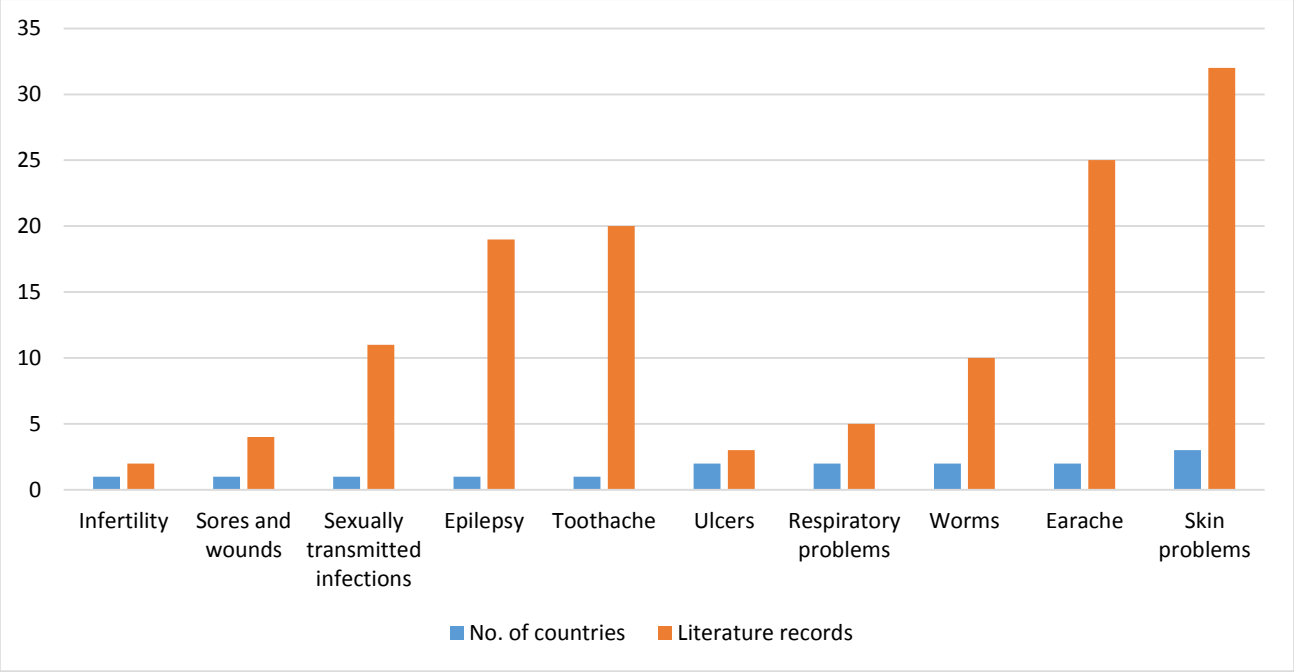

Figure 1. Medicinal applications of *Cotyledon orbiculata* derived from literature records

Phytochemistry and biological activities of *Cotyledon orbiculata*

Cotyledon orbiculata contains several cardiac glycosides of the bufadienolide type[2,38,55,73,74] and these compounds are known to be poisonous and causes acute or chronic diseases in domestic animals.[2,38,75,76] Other compounds that have been identified from the leaves and stems of *C. orbiculata* include flavonoids, gallotannin, phenols, reducing sugar, saponins, tannins and triterpene steroids.[37,40,50,67,77] The following biological activities have been reported from the leaf, shoot and stem extracts of *C. orbiculata*: anthelmintic,[40,77] antibacterial,[40,46,65,71,78,79] antifungal,[40,65,71,78,79] anticancer,[80] anticonvulsant,[37] antinociceptive,[43] anti-inflammatory,[40,43,50] Aβ42 protein reduction,[56] $GABA_A$ benzodiazepine receptor-binding,[81] antioxidant,[50] cytotoxicity and toxicity[76,82,83] activities.

Anthelmintic activities

Molefe et al.[77] evaluated the anthelmintic activities of acetone and water extracts from the shoots of *C. orbiculata* using the egg hatch, larval development and larval mortality assays using nematode species of *Haemonchus, Oesophagostomum, Trichostrongylus* and *Teladorsagia*. The water extracts at 7.5 mg/ml prevented nematode eggs from hatching with 82.6% success and suppressed nematode larval development at 85.3% when the concentration of 2.5 mg/ml was used, and the extract was able to kill all larvae at 2.5 mg/ml within 48 hours to 96 hours.[77] Aremu et al.[40] evaluated the anthelmintic activities of petroleum ether, dichloromethane, water and ethanol leaf and stem extracts of *C. orbiculata* var. *dactylopsis* and *C. orbiculata* var. *orbiculata* using an *in vitro* colourimetric assay used in the determination of free-living nematode larvae viability of *Caenorhabditis elegans* var. *bristol* with levamisole as a positive control. The organic leaf extracts of both varieties exhibited the best activities with the minimum lethal concentration (MLC) values ranging from 0.3 mg/ml to 1.0 mg/ml which were higher than 40.0 µg/ml exhibited by the positive control.[40]

Antibacterial activities

Aremu et al.[40] evaluated the antibacterial activities of petroleum ether, dichloromethane, water and ethanol leaf and stem extracts of *C. orbiculata* var. *dactylopsis* and *C. orbiculata* var. *orbiculata* against *Bacillus subtilis, Staphylococcus aureus, Escherichia coli* and *Klebsiella pneumoniae* using the microtitre plate dilution technique with neomycin (100 µl; 0.4 mg/ml) as a positive control. The extracts of both varieties exhibited activities with minimum inhibitory concentration (MIC) values ranging from 1.6 mg/ml to >12.5 mg/ml.[40] Mabona[78] and Mabona et al.[65] evaluated the antibacterial activities of aqueous and dichloromethane : methanol (1:1) leaf extracts of *C. orbiculata* using the microtitre plate assay against dermatologically relevant pathogens such as *Brevibacillus agri, Propionibacterium acnes, Pseudomonas aeruginosa, Staphylococcus aureus* and *Staphylococcus epidermidis* with ciprofloxacin as a positive control. The extracts exhibited activities with MIC values ranging from 0.3 mg/ml to >16.0 mg/ml.[65,78] Kumari et al.[46] evaluated the antibacterial activities of ethanol extracts of different tissue types of *C. orbiculata* from in vitro culture (callus, shoots and plantlets) and leaves from ex vitro plants against *Enterococcus faecalis, Micrococcus luteus, Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae* and *Pseudomonas aeruginosa* using microtitre microbial bioassays with neomycin as a positive control. The extracts exhibited activities with MIC values ranging from 0.1 mg/ml to 6.3 mg/ml.[46] Akhalwaya[79] and Akhalwaya et al.[71] evaluated antibacterial activities of

aqueous and dichloromethane : methanol (1 : 1) leaf and stem extracts of *C. orbiculata* against *Streptococcus mutans, Streptococcus sanguis, Lactobacillus acidophilus, Lactobacillus casei, Porphyromonas gingivalis* and *Fusobacterium nucleatum* using the microtiter plate dilution assay with ciprofloxacin (0.1 mg/mL) as a positive control. The extracts exhibited activities with MIC values ranging from 0.5 mg/mL to >8.0 mg/mL.[71,79]

Antifungal activities

Aremu et al.[40] evaluated the antifungal activities of petroleum ether, dichloromethane, water and ethanol leaf and stem extracts of *C. orbiculata* var. *dactylopsis* and *C. orbiculata* var. *orbiculata* against *Candida albicans* using the microtitre plate dilution technique with amphotericin B (100 µl; 0.25 mg/ml) as a positive control. The extracts of both varieties exhibited activities with MIC and minimum fungicidal concentration (MFC) values ranging from 3.1 mg/ml to >12.5 mg/ml and 6.3 mg/ml to >12.5 mg/ml, respectively.[40] Mabona[78] and Mabona et al.[65] evaluated the antifungal activities of aqueous and dichloromethane : methanol (1:1) leaf extracts of *C. orbiculata* using the microtitre assay against dermatologically relevant pathogens such as *Candida albicans, Microsporum canis* and *Trichophyton mentagrophytes* with amphotericin B as a positive control. The extracts exhibited activities with MIC values ranging from 0.3 mg/ml to >16.0 mg/ml.[65,78] Akhalwaya[79] and Akhalwaya et al.[71] evaluated antifungal activities of aqueous and dichloromethane : methanol (1 : 1) leaf and stem extracts of *C. orbiculata* against *Candida albicans, Candida glabrata* and *Candida krusei* using the microtiter plate dilution assay with amphotericin B (0.01 mg/mL) as a positive control. The extracts exhibited activities with MIC values ranging from 0.5 mg/mL to >8.0 mg/mL.[71,78]

Anticancer activities

Fouché et al.[80] evaluated anticancer activities of dichloromethane : methanol root extracts of *C. orbiculata* subsp. *oblonga* against sixty human cancer cell lines organized into subpanels representing leukemia, melanoma and cancer of the lung, colon, kidney, ovary, and central nervous system. The extracts exhibited a moderate growth inhibition of above 50% for two or more of the cell lines (GI_{50}) with values ranging from >0 µg/mL to 1.1 µg/mL.[80]

Anticonvulsant activities

Amabeoku et al.[37] evaluated the anticonvulsant activities of aqueous and methanol leaf extracts of *C. orbiculata* on seizures induced by pentylenetetrazole, bicuculline, picrotoxin and N-methyl-DL-aspartic in male albino mice. The extracts at 50 mg/kg to 400 mg/kg administered intraperitoneally, exhibited anticonvulsant properties by reducing the incidences of seizures, delaying the onset of seizures or prolonging the onset of tonic seizures. These results suggest that *C. orbiculata* has anticonvulsant activities and thus, lend pharmacological justification to the use of the plant species in the treatment of epilepsy.[37]

Antinociceptive activities

Amabeoku and Kabatende[43] evaluated the antinociceptive activities of leaf methanol extract of *C. orbiculata* using acetic acid writhing and hot-plate tests in male albino mice. The extract at 100 mg/kg to 400 mg/kg administered intraperitoneally significantly inhibited acetic acid-induced writhing and significantly delayed the reaction time of mice to the hot-plate-induced thermal stimulation.[43]

Anti-inflammatory activities

Aremu et al.[40] evaluated the anti-inflammatory activities of petroleum ether, dichloromethane, water and ethanol leaf and stem extracts of *C. orbiculata* var. *dactylopsis* and *C. orbiculata* var. *orbiculata* using cyclooxygenase (COX-1 and COX-2) inhibition assays. The highest COX-1 and COX-2 inhibition was exhibited by the dichloromethane extracts of both varieties with inhibition ranging from 46.7% to 98.0%.[40] Amabeoku and Kabatende[43] evaluated the anti-inflammatory activities of leaf methanol extract of *C. orbiculata* using the carrageenan-induced oedema test in male albino mice. The extract at 50 mg/kg to 400 mg/kg administered intraperitoneally significantly attenuated the carrageenan-induced rat paw oedema.[43] Ondua et al.[50] evaluated the anti-inflammatory activities of hexane, acetone, ethanol, methanol and water leaf extracts of *C. orbiculata* using the 15-lipoxygenase (15-LOX) inhibitory and the nitric oxide (NO) inhibition assays using lipopolysaccharide (LPS)-activated RAW 264.7 murine macrophages with quercetin as a positive control. The acetone, ethanol and methanol extracts exhibited the best activities with half maximal inhibitory concentration (IC_{50}) values ranging from 18.1 µg/mL to 63.9 µg/mL while hexane and water extracts exhibited IC_{50} values which were >100.0 µg/mL. The extract exhibited good nitric oxide inhibitory activity with 84.3% NO inhibition and cell viability of 84.1% at 50 µg/mL.[50]

Aβ42 protein reduction activities

Thakur et al.[56] evaluated the Aβ42 protein reduction activities of dichloromethane: methanol (1:1) leaf and stem extracts of *C. orbiculata* using ELISA - sAPPα, sAPPβ and Aβ peptide assays. The extract reduced the secreted level of Aβ42 in a dose-dependent manner compared to the control by 77.5%. The extract also decreased the levels of Aβ40, sAPPβ-sw and sAPPα in a dose-dependent manner.[56]

$GABA_A$ benzodiazepine receptor-binding activities

Stafford et al.[81] evaluated the $GABA_A$ benzodiazepine receptor-binding activities of ethanolic leaf extracts of *C. orbiculata* by assessing the binding of ^{3}H-Ro 15-1788 (flumazenil) to the benzodiazepine site. The extract showed weak dose-dependent activities.[81]

Antioxidant activities

Ondua et al.[50] evaluated the antioxidant activities of hexane, acetone, ethanol, methanol and water leaf extracts of *C. orbiculata* using the free radical scavenging DPPH (2,2-diphenyl-1-picrylhydrazyl) and electron reducing

ABTS (2,2′-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) assays with trolox and vitamin C as positive controls. The acetone, ethanol and methanol extracts exhibited the best activities with IC_{50} values ranging from 2.0 μg/mL to 23.5 μg/mL while hexane and water extracts exhibited IC_{50} values which were >100.0 μg/mL.[50]

Cytotoxicity and toxicity activities

Cotyledon orbiculata is regarded as one of the most important poisonings of small stock in South Africa.[2,38,74-76,82-85] Four poisonous bufadienolides, namely orbicusides A, B and C and tyledoside C have been isolated from *C. orbiculata*.[76,82] About 14g of dried leaves of *C. orbiculata* given over a period of 25 days have resulted in toxicity in goat and it has been shown that the toxins have a cumulative effect.[76,83] The median lethal dose (LD50) of the major bufadienolides of *C. orbiculata* involving subcutaneous injection in guinea pigs was found to vary between 0.1 mg/kg and 0.25 mg/kg.[76,82] Akhalwaya[79] and Akhalwaya et al.[71] evaluated toxicity activities of aqueous leaf extracts of *C. orbiculata* using the brine shrimp lethality assay with potassium dichromate (1.6 mg/mL) as a positive control. The extract exhibited 35.3% mortality in brine shrimp assay after 24 hours of exposure in comparison to 100% exhibited by the positive control, and therefore, the species considered non-toxic.[71,79]

CONCLUSION

The present review summarizes the botany, medicinal uses, phytochemistry and biological activities of *C. orbiculata*. Based on presented information, there is not yet enough data correlating the ethnomedicinal uses of the species with its phytochemical and pharmacological properties. Since *C. orbiculata* contain potentially toxic compounds, future studies should include the identification of toxic compounds, possible side effects caused by taking *C. orbiculata* as herbal medicine, and mechanisms of how potential toxic components of the species can be managed. Detailed studies on the pharmacokinetics, in vivo and clinical research involving both extracts and compounds isolated from the species are required.

Conflict of interest

The author declares that there is no conflict of interest regarding the publication of this paper.

REFERENCES

[1] Van Jaarsveld, E., *Veld Fl.* 1999, 85, 82-83.
[2] Van Wyk, B.-E., Van Oudtshoorn, B., Gericke, N., *Medicinal Plants of South Africa*, Briza Publication, Pretoria 2013.
[3] Duarte, L.M.L., Alexandre, M.A.V., Rivas, E.B., Galleti, S.R., Harakava, R., Chaves, A.L.R., *J. Pl. Path.* 2014, 96, 143-149.
[4] Silva, V., Laguna, E., Guillot, D., *Bouteloua* 2015, 20, 76–96.
[5] Silva, V., Figueiredo, E., Smith, G.F., *Bradleya* 2015, 33, 58–81.
[6] Weber, E., *Invasive Plant Species of the World: A Reference Guide to Environmental Weeds*, CAB International, Boston 2017.
[7] Randall, R.P., *A Global Compendium of Weeds*, Department of Agriculture and Food, Perth 2017.
[8] Verloove, F., Salas-Pascual, M., Marrero Rodríguez, Á., *Fl. Medit.* 2018, 28, 119-135.
[9] Lubbe, C.S., Siebert, S.J., Cilliers, S.S., *Sci. Res. Essays* 2010, 5, 2900-2910.
[10] Molebatsi, L.Y., Siebert, S.J., Cilliers, S.S., Lubbe, C.S., Davoren, E., *Afr. J. Agr. Res.* 2010, 5, 2952-2963.
[11] Maroyi, A., Mosina, G.K.E., *Indian J. Trad. Knowl.* 2014, 13, 665-672.
[12] Mosina, G.K.E., Maroyi, A., Potgieter, M.J., *Ethno. Med.* 2015, 9, 43-58.
[13] Nortje, J.M., Van Wyk, B.E., *S. Afr. J. Bot.* 2019, 122, 120–135.
[14] Loundou, P.-M., *Medicinal Plant Trade and Opportunities for Sustainable Management in South Africa*, MSc Dissertation, University of Stellenbosch 2008.
[15] Mogale, M.M.P., Raimondo, D.C., Van Wyk, B.-E., *S. Afr. J. Bot.* 2019, 122, 90–119.
[16] Harris, S., Cotyledon orbiculata L., Free State National Botanical Garden, 2004, available from: http://pza.sanbi.org/cotyledon-orbiculata, accessed on: 11 September 2019.
[17] Tölken, H.R., *Bothalia* 1979, 12, 615-620.
[18] Victor, J.E., Dold, A.P., *S. Afr. J. Sci.* 2003, 99, 437-446.
[19] Raimondo, D., Von Staden, L., Foden, W., Victor, J.E., Helme, N.A., Turner, R.C., Kamundi, D.A., Manyama, P.A., *Red List of South African Plants*, Strelitzia 25, South African National Biodiversity Institute, Pretoria 2009
[20] Fernandes, R., in: Launert, E. (Ed.), *Flora Zambesiaca vol* 7, part 1, Royal Botanic Gardens, London 1983, pp. 3-74.
[21] Tölken, H.R., in Leistner, O.A., *Flora of Southern Africa*, Botanical Research Institute, Pretoria 1985, pp. 1-244.
[22] Germishuizen, G., Meyer, N.L., *Plants of Southern Africa: An Annotated Checklist*, Strelitzia 14, National Botanical Institute, Pretoria 2003.
[23] Bandeira, S., Bolnick, D., Barbosa, F., *Wild Flowers of Southern Mozambique*, Universidade Eduardo Mondlane, Maputo 2007.
[24] Figueiredo, E., Smith, G.F., *Plants of Angola*, Strelitzia 22, South African National Biodiversity Institute, Pretoria 2008.
[25] Manning, J., Goldblatt, P., *Plants of the Greater Cape Floristic Region 1: The Core Cape Flora*, Strelitzia 29, South Africa National Biodiversity Institute, Pretoria 2012.
[26] Snijman, D.A., *Plants of the Greater Cape Floristic Region, Vol 2: The Extra Cape Flora*, Strelitzia 30, South Africa National Biodiversity Institute, Pretoria 2013.
[27] Moteetee, A., Van Wyk, B.-E., *Bothalia* 2011, 41, 209–228.
[28] Moteetee, A., Kose, L.S., *J. Ethnopharmacol.* 2016, 194, 827–849.
[29] Masafu, M.M., Mbajiorgu, C.A., Nemadodzi, L.E., Kabine, E.S., I*ndian J. Trad. Knowl.* 2016, 15, 363-369.
[30] Lum, E.A., *The Sci. Monthly* 1951, 72, 183-185.
[31] James, T., *Arch. Dis. Child.* 1963, 38, 75-76.
[32] Jacot Guillarmod, A., *Flora of Lesotho*, Cramer, Lehre 1971.
[33] Schmitz, M.O., *Wild Flowers of Lesotho*, ESSA, Roma 1982.
[34] Bhat, R.B., Jacobs, T.V., *J. Ethnopharmacol.* 1995, 48, 7–12.
[35] Hutchings, A., Scott, A.H., Lewis, G., Cunningham, A., *Zulu Medicinal Plants: An Inventory*, University of Natal Press, Scottsville 1996.
[36] Thring, T.S.A., Weitz, F.M., *J. Ethnopharmacol.* 2006, 103, 261–275.
[37] Amabeoku, G.J., Green, I., Kabatende, J., *J. Ethnopharmacol.* 2007, 112, 101–107.
[38] Van Wyk, B.E., Gericke, N., *People's Plants. A Guide to Useful Plants of Southern Africa*, Briza Publications, Pretoria 2007.
[39] Van Wyk, B.-E., *J. Ethnopharmacol.* 2008, 119, 331–341.
[40] Aremu, A.O., Ndhlala, A.R., Fawole, O.A., Light, M.E., Finnie, J.P., Van Staden, J., *S. Afri. J. Bot.* 2010, 76, 558–566.
[41] Moffett, R.O., *Sesotho Plant and Animal Names and Plants Used by the Basotho*, Sun Press, Stellenbosch 2010.
[42] De Beer, J.J.J., Van Wyk, B.-E., *S. Afr. J. Bot.* 2011, 77, 741–754.
[43] Amabeoku, G.J., Kabatende, J., *Adv. Pharmacol. Sci.* 2012, art ID 862625.
[44] Ndhlala, A.R., Ncube, B., Okem, A., Mulaudzi, R.B., Van Staden, J., *Food Chem. Toxicol.* 2013, 62, 609–621.
[45] Wintola, O.A., Afolayan, A.J., *Afr. J. Trad. Compl. Alt. Med.* 2015, 12, 112-121.
[46] Kumari, A., Baskaran, P., Van Staden, J., *Plant Cell Tiss. Organ Cult.* 2016, 124, 97–104.
[47] Terblanche, U., Semakalu, C.C., Mtunzi, F., Pillay, M., *Int. J. Pharmacogn. Phytochem. Res.* 2017, 9, 303-312.
[48] Hulley, I.M., Van Wyk, B.-E., *S. Afr. J. Bot.* 2019, 122, 225-265.
[49] Moteetee, A., Moffett, R.O., Kose, L.S., *S. Afr. J. Bot.* 2019, 122, 21–56.

[50] Ondua, M., Njoya, E.M., Abdalla, M.A., McGaw, L.J., *J. Ethnopharmacol.* 2019, 234, 27–35.
[51] Watt, J.M., *Lloydia* 1967, 30, 1–22.
[52] Sobiecki, J.F., *Trans. Roy. Soc. S. Afr.* 2002, 57, 1-24.
[53] Stafford, G.I., Pedersen, M.E., Van Staden, J., Jäger, A.K., *J. Ethnopharmacol.* 2008, 119, 513–537.
[54] Philander, L.A., *J. Ethnopharmacol.* 2011, 138, 578– 594.
[55] Masondo, N.A., Stafford, G.I., Aremu, A.O., Makunga, N.P., *S. Afr. J. Bot.* 2019, 120, 39–64.
[56] Thakur, A., Chun, Y.S., October, N., Yang, H.O., Maharaj, V., *J. Ethnopharmacol.* 2019, 231, 363–373.
[57] Dyubeni, L., Buwa, L.V., *J. Med. Pl. Res.* 2012, 6, 2721-2726.
[58] Long, C., *Swaziland's Flora: SiSwati Names and Uses*, Swaziland National Trust Commission, Mbambane 2005, available from: http://www. sntc.org.sz/index.asp, accessed on 21 September 2019.
[59] Watt, J.M., Breyer-Brandwijk, M.G., *The Medicinal and Poisonous Plants of Southern and Eastern Africa*, Livingstone, London 1962.
[60] Erasmus, L.J.C., Potgieter, M.J., Semenya, S.S., Lennox, S.J., *Afr. J. Trad. Compl. Alt. Med.* 2012, 9, 591-598.
[61] Semenya, S.S., Potgieter, M.J., Erasmus, L.J.C., *S. Afr. J. Bot.* 2013, 87, 66–75.
[62] Semenya, S.S., Potgieter, M.J., Erasmus, L.J.C., *Afr. J. Pharm. Pharmacol.* 2013, 7, 250-262.
[63] Felhaber, T., *South African Traditional Healers' Primary Health Care Handbook*, Kagiso Publishers, Cape Town 1997.
[64] Mabona, U., Van Vuuren, S.F., *S. Afr. J. Bot.* 2013, 87, 175–193.
[65] Mabona, U., Viljoen, A., Shikanga, E., Marston, A., Van Vuuren, S., *J. Ethnopharmacol.* 2013, 148, 45–55.
[66] Nortje, J.M., Van Wyk, B.E., *J. Ethnopharmacol.* 2015, 171, 205–222.
[67] Xaba, V.M., Buwa, L.V., *S. Afr. J. Bot.* 2016, 103, 355.
[68] Moteetee, A., Kose, L.S., *Afr. J. Trad. Compl. Alt. Med.* 2017, 14, 121-137.
[69] Adebayo, S.A., Amoo, S.O., *S. Afr. J. Bot.* 2019, 123, 214–227.
[70] Sagbo, I.J., Mbeng, W.O., *Indian J. Pharmacol.* 2019, 51, 140–149.
[71] Akhalwaya, S., Van Vuuren, S., Patel, M., *J. Ethnopharmacol.* 2018, 210, 359–371.
[72] Cock, I.E., Selesho, M.I., Van Vuuren, S.F., *J. Ethnopharmacol.* 2018, 220, 250-264.
[73] Kamerman, P., *S. Afr. J. Sci.* 1926, 23, 185.
[74] Tustin, R.C., Thornton, D.J., Kleu, C.B., *J. S. Afr. Vet. Ass.* 1984, 55, 181–184.
[75] Steyn, P.S., Van Heerden, F.R., Vleggaar, R., Anderson, L.A.P., *J. Chem. Soc. Perkin Trans.* 1986, 1, 1633–1636.
[76] Van Wyk, B.-E., Van Heerden, F., Van Oudtshoorn, B., *Poisonous Plants of South Africa*, Briza Publication, Pretoria 2005.
[77] Molefe, N.I., Tsotetsi, A.M., Ashafa, A.O.T., Thekisoe, O.M.M., *J. Med. Pl. Res.* 2013, 7, 536–542.
[78] Mabona, U., *Antimicrobial Activity of Southern African Medicinal Plants with Dermatological Relevance*, MSc Dissertation, University of the Witwatersrand, Johannesburg 2013.
[79] Akhalwaya, S., *The Antimicrobial Investigation of Indigenous South African Medicinal Plants Against Oral Pathogens*, MSc Dissertation, University of the Witwatersrand, Johannesburg 2017.
[80] Fouché, G., Khorombi, E., Kolesnikova, N., Maharaj, V.J., Nthambeleni, R., Van der Merwe, M., *Pharmacologyonline* 2006, 3, 494-500.
[81] Stafford, G.I., Jäger, A.K., Van Staden, J., *J. Ethnopharmacol.* 2005, 100, 210–215.
[82] Anderson, L.A.P., Schultz, R.A., Kellerman, T.S., Kotze, S.M., Prozesky, L., Erasmus, G.L., Labuschagne, L., *Onderstepoort J. Vet. Res.* 1985, 52, 21-24.
[83] Kellerman, T.S., Coetzer, J.A.W., Naudé, T.W., *Plant Poisonings and Mycotoxicoses of Livestock in Southern Africa*, Oxford University Press, Cape Town 1988.
[84] Terblanche, M., Adelaar, T.E., *J. S. Afr. Vet. Med. Ass.* 1965, 36, 555-559.
[85] Vahrmeijer, J., P*oisonous Plants of Southern Africa That Cause Stock Losses*, Tafelberg Publishers, Cape Town 1981.