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REVIEW ARTICLE

A review of *Hydrocotyle bonariensis*, a promising functional food and source of health-related phytochemicals

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Abstract *Hydrocotyle bonariensis* is an edible herb, that is also used for traditional medical purposes. It is high in antioxidants, phenols, and flavonoids. However, there is limited information on the nutritional composition and the mechanisms by which nutritional and functional constituents of *H. bonariensis* affect human metabolism. With an aim to identify gaps in evidence to support the mainstream use of *H. bonariensis* for health and as a functional food, this review summarises current knowledge of the taxonomy, habitat characteristics, nutritional value and health-related benefits of *H. bonariensis* and its extracts. Ethno-medical practices for the plant are supported by pharmacological studies, yet animal model studies, clinical trials and food safety assessments are needed to support the promotion of *H. bonariensis* and its derivatives as superfoods and for use in the modern pharmaceutical industry.

Keywords Functional food · Nutraceutical · Phytochemicals · Pharmacological · Therapeutic plant · Superfood

Introduction

Hydrocotyle bonariensis (*H. bonariensis*) is a wild species of large leaf marsh pennywort, previously assigned to the family Apiaceae, but now placed within the family Araliaceae of the order of Apiales (Nicolas and Plunkett 2009). The plant grows predominately in wetlands of temperate and tropical regions (Florinsiah et al. 2013; Masoumian et al. 2011) and is well distributed across many regions, including the southeastern part of the United States, Central America, South America, the Caribbean and sub-saharan Africa (Fig. 1). *H. bonariensis* can also be found in Asian countries, including China, India, Sri Lanka, Indonesia and Malaysia (Goh 2007). Regionally, *H. bonariensis* is known by an array of common names, such as pegaga embun in Malaysia (Ajani et al. 2009), karo in Nigeria (Ajani et al. 2012) as well as redondita de agua, paragüita, and tembladerilla in South America (Ouviña et al. 2009). The plant is semi-aquatic and can grow in soils ranging from inland damp, wet trenches and edges of ponds to saline beach dunes (Evans and Whitney 1992). A recent study showed the ability of *H. bonariensis* to successfully thrive in multiple habitats is mainly because of high phenotypic plasticity (Chiarello and Joesting 2018). *H. bonariensis* contains several bioactive components, including alkaloids, tannins, flavonoids, saponins, and phenolic compounds (Go et al. 2017). Among the bioactive components, phenolic acids and flavonoids are the core phenolics that constitute the total antioxidant content (Wojdyło et al. 2007). The antioxidant contents of *H. bonariensis* are reported to be higher than those of several other nutraceutical herbs such as *Barringtonia racemose* (powder-puff tree), *Kaempferia galanga* (aromatic ginger), *Piper sarmentosum* (wild betel) and *Cosmos caudatus* (Ulam raja) (Sumazian et al. 2010). Although the plant is rich in bioactive compounds, has a high antioxidant content and is easy to grow, *H. bonariensis* is not widely consumed in modern diets. To promote this plant as healthy food and for use in value-added nutraceutical and potentially pharmaceutical

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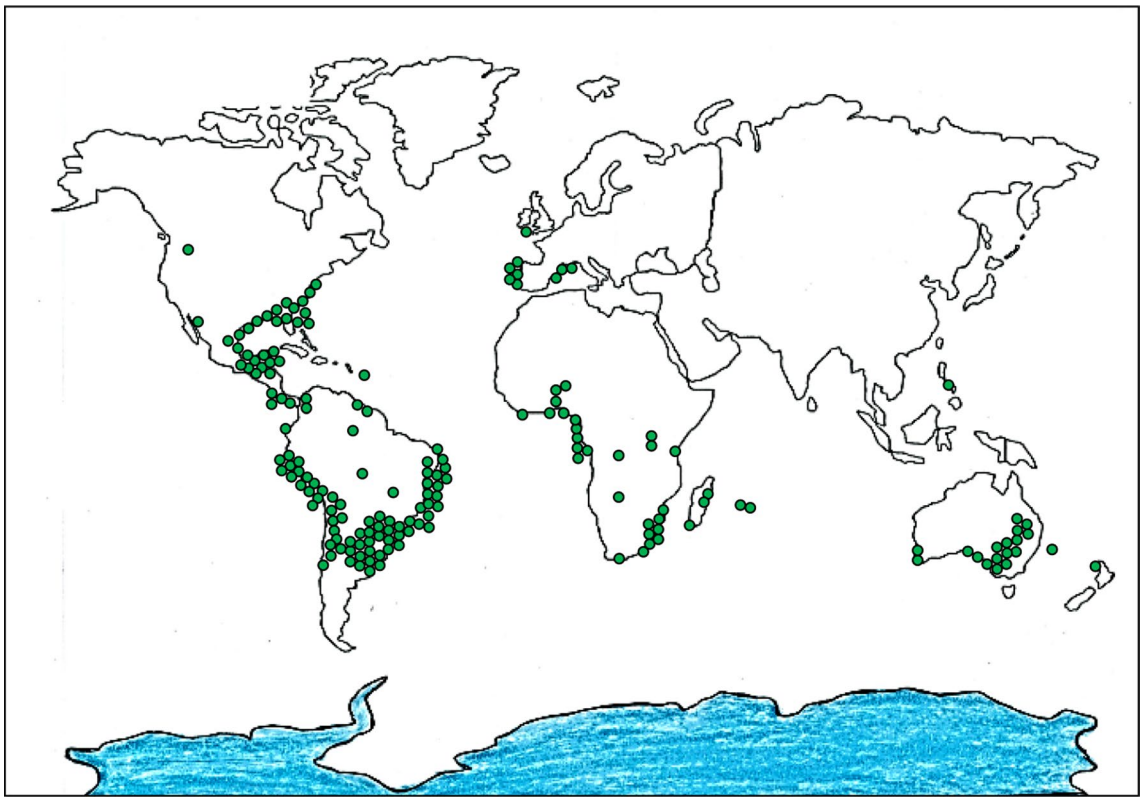


Fig. 1 Distribution of *H. bonariensis* across the world (Data source: Global Biodiversity Information Facility, https://www.gbif.org/species/3034611)

products, there is a need to collate the relevant information for *H. bonariensis*. Here, we considered the phytochemical and pharmacological value of *H. bonariensis*, also the taxonomy, habitat characteristics and reports of use as a functional food. Next, we discuss the prospects for the development of novel nutriceuticals and plant-based pharmaceuticals based on *H. bonariensis* and its derivatives. All information on *H. bonariensis* was retrieved from online searches using Google Scholar, Web of Science, ScienceDirect and PubMed. Global databases, including Integrated Taxonomic Information System (http://www.itis.gov), PopSet (https://ncbi.nlm.nih.gov/popset) and PubChem (https://pubchem.ncbi.nlm.nih.gov/) were used to validate the scientific names, define the evolution of *H. bonariensis* and verify chemical descriptions of phytochemicals present in the plant.

Taxonomy, molecular phylogeny and ecology of *H. bonariensis*

J. P. Tournefort was the first to introduce the genus *Hydrocotyle* (Hylander 1945). '*Hydrocotyle*' is derived from the Greek words 'hydro', for water and 'kotyle' for dish or plate, referring to the aquatic habitat and dish or plate-shaped leaf of the species (Bandara et al. 2011). The genus was later validated and expanded by C. Linnaeus in 1753 (Konstantinova and Yembaturova 2010). The species name *bonariensis* was derived from Buenos Aires, Argentina, where the plant is native and was first identified. *H. bonariensis* is a semiaquatic perennial herb with long stolons (runners), from which roots, leaves and inflorescences are produced at nodes (Fig. 2a). Nodes with an independent root system can act as physiologically independent units known as ramets and can be propagated vegetatively (Evans 1992). The leaves are circular to widely elliptical with palmate venation, arranged in small clusters of one to five glossy leaflets, 1.2 to 3 cm in diameter and attached by a petiole of 2 to 20.5 cm long (Fig. 2b). Inflorescences are produced at the nodes and opposite to the leaf (Fig. 2c). The inflorescence is umbelliferous, about 5.08 to 7.62 cm long, with clusters of white fragrant flowers. The hermaphroditic flower contains five sepals, five petals, six stamens and two separate carpels with an inferior ovary surmounted by a style and a stigma (Fig. 2c). The fruit emerges as a green schizocarp turning brown when mature (Fig. 2d, e) and containing brown to black seeds. Although

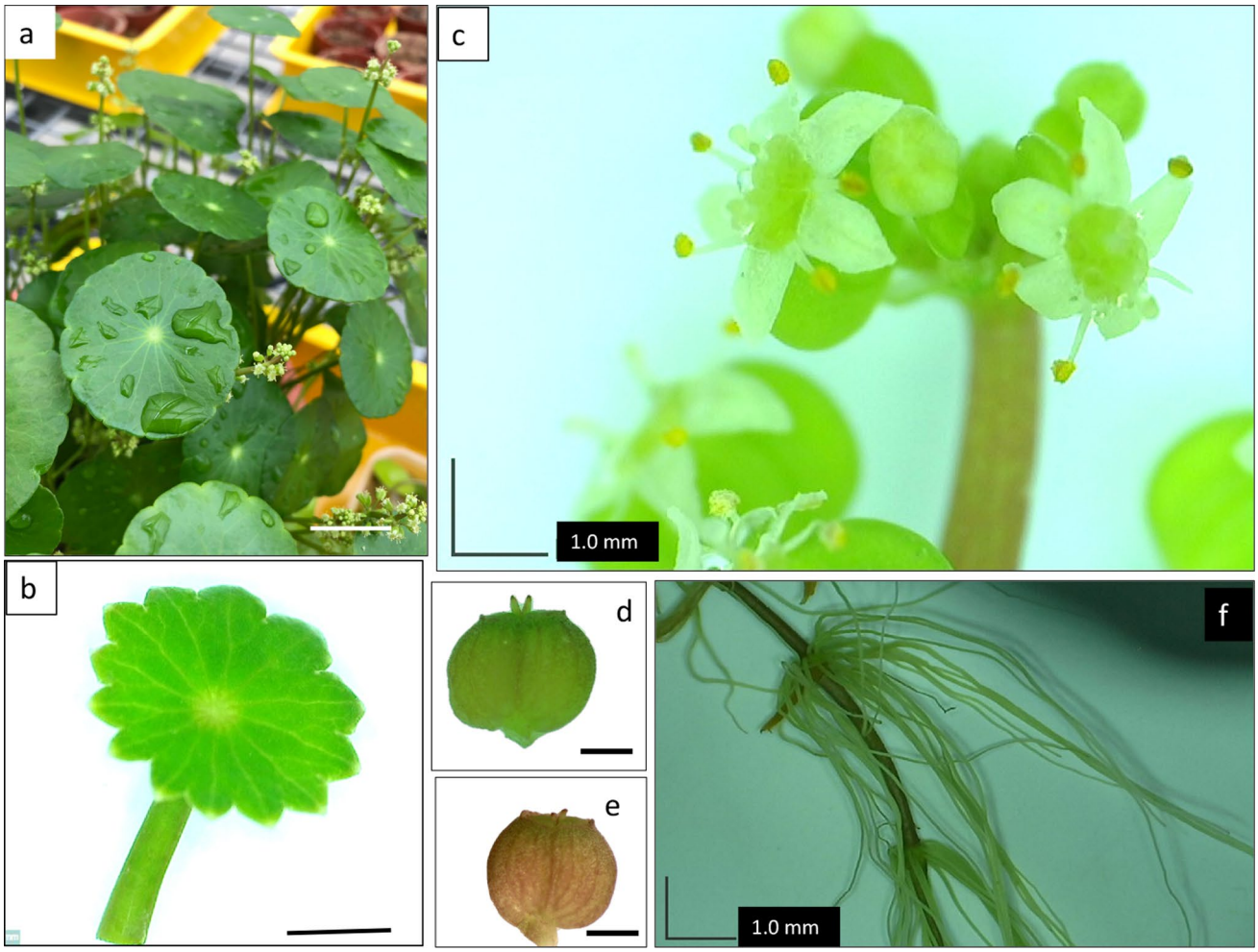


Fig. 2 *Hydrocotyle bonariensis* **a** Mature plant with inflorescence (bar = 40 mm), **b** Immature leaf (bar = 30 mm), **c** Compound umbel inflorescence (bar = 1 mm), **d** Indehiscent schizocarp (bar = 1 mm), **e** Mature schizocarp (bar = 10 mm), **f** Stolon with lateral roots (bar = 1 mm)

seed production occurs throughout the growing season, the seedling survival rate is reported to be less than 1% and hence vegetative reproduction through stolon (Fig. 2f) is the primary mode of reproduction for this plant (Evans 1992).

A few molecular phylogenetic and taxonomic studies have been undertaken to assess the evolutionary position of the *Hydrocotyle* taxa (Nicolas and Plunkett 2009; Danderson et al. 2018; Perkins 2019). The studies have assisted in the re-categorisation of *Hydrocotyle* from the family Apiaceae to the family Araliaceae in the order of Apiales based on chloroplast markers (Nicolas and Plunkett 2009; Danderson et al. 2018; Perkins 2019). There is little molecular phylogenetic or genomic information currently available for *H. bonariensis*, with only ten DNA sequence accessions of *H. bonariensis* in the National Center for Biotechnology Information (NCBI) database at the present time (Table 1). *H. bonariensis* can be found in two main distinct ecological environments; coastal sand dune and inland habitats. *H. bonariensis* growing in coastal sand dune environments is exposed to harsh growing conditions, including relatively higher temperatures of air and sand, higher intensity of sunlight due to lack of shading plants, and high salinity (Hesp 1991; Haddad and Mazzafera 1999). *H. bonariensis* in inland habitats have more favourable conditions of growth, such as the shade of a canopy and freshwater irrigation. In addition, inland soils are mainly loamy and consist of smaller particle sizes that hold more water and nutrients (e.g. organic matter, potassium, nitrate, and ammonium) compared to large-sized sandy soils (Chiarello and Joesting 2018). As a result, *H. bonariensis* grown on inland soil has been reported to have greater leaf area, petiole length, petiole thickness, petiole fresh weight, and abaxial stomata density compared to those grown on coastal sand dunes (Chiarello and Joesting 2018). In order to survive in sand dune habitats, *H. bonariensis* undergoes phenotypic adjustment, adopting a strategy of leaf inclination to withstand extreme weather conditions (Chiarello and Joesting 2018; Joesting et al. 2012). The capacity of *H. bonariensis* to

Table 1 GenBank sequence data of *H. bonariensis* (http://www.ncbi.nlm.nih.gov/)

Accession number	Sequence type	Size (bp)	Source	Description
KJ773564.1	DNA	1323	Chloroplast	*Hydrocotyle bonariensis* ribulose-1,5-bisphosphate carboxylase/oxygenase large subunit (rbcL) gene, partial cds
KJ772838.1	DNA	651	Chloroplast	*Hydrocotyle bonariensis* maturase K (matK) gene, partial cds
MH780008.1	DNA	914	Chloroplast	*Hydrocotyle bonariensis* tRNA-Leu (trnL) gene and trnL-trnF intergenic spacer, partial sequence
MH757450.1	DNA	456	Nuclear	*Hydrocotyle bonariensis* external transcribed spacer and 18S ribosomal RNA gene, partial sequence
KP057627.1	DNA	568	Chloroplast	*Hydrocotyle bonariensis* isolate P069 tRNA-Leu (trnL) gene, partial sequence
KP057626.1	DNA	564	Chloroplast	*Hydrocotyle bonariensis* isolate P008 tRNA-Leu (trnL) gene, partial sequence
JQ937322.1	DNA	308	Chloroplast	*Hydrocotyle bonariensis* psbA-trnH intergenic spacer, complete sequence
GQ243831.1	DNA	884	Chloroplast	*Hydrocotyle bonariensis* voucher Ware s.n. tRNA-Asp (trnD) gene, partial sequence; trnD-trnY intergenic spacer, tRNA-Tyr (trnY) gene, trnY-trnE intergenic spacer, tRNA-Glu (trnE) gene, and trnE-trnT intergenic spacer, complete sequence; and tRNA-Thr (trnT) gene, partial sequence
AF077894.1	DNA	619	Nuclear	*Hydrocotyle bonariensis* internal transcribed spacer 1, partial sequence; 5.8S ribosomal RNA gene, complete sequence and internal transcribed spacer 2, partial sequence
GQ244102.1	DNA	1007	Chloroplast	*Hydrocotyle bonariensis* voucher Ware s.n. rpl16 gene, intron

thrive in this environment suggests that the plant has good potential for cultivation in saline agriculture. However, such studies appear to be lacking. It would also be interesting to know how if and how such stress affects phytonutrient and active compound content in *H. bonariensis*. Because there is a general lack of information on diverse plant accessions and their diversity, there is also a lack of understanding in terms of nutrient variability, flavour, growth characteristics.

Traditional and current uses of *H. bonariensis* in food and medicine

In Indonesia, Malaysia and Taiwan, the leaves and stalks of *H. bonariensis* are consumed as a fresh salad (known in the Malay language as "ulam"), fresh juice, as a fermented vegetable, as a condiment sprinkled on food and as a herbal tea (Reihani and Azhar 2012). *H. bonariensis* is also recognised as a wild edible plant in Texas, U.S.A. (https://medivetus.com/botanic/hydrocotyle-bonariensis-beach-pennywort-edible-and-medicinal-uses/). Other than that, *H. bonariensis* is also recognised for being an excellent source of bioactive phytochemicals for traditional treatments of diseases. For example, indigenous people in the United States use this herb as an emetic, diuretic and laxative (Evans 1992), while the locals in South America use the aerial part of the plants for treating cutaneous erythema (Ouviña et al. 2009). In addition, *H. bonariensis* is used among local people in Western Nigeria for treatment of tuberculosis and ophthalmic diseases, for pain relief due to rheumatism and arthritis, as well as for longevity and enhancement of brain capacity (Masoumian et al. 2011). As there are only anecdotal sources, it is difficult to determine how widely the plant is used or cultivated for such use, but reports for other pennywort species suggest that overcollection from their natural habitats is an issue of concern and there is a need for more economically viable and sustainable solutions, such as farming on a larger scale (Hashim 2011).

Potential of *H. bonariensis* as a functional food and nutraceutical

Functional foods are foods either whole, fortified, enriched or enhanced forms of food that provide health benefits beyond basic nutrition (Hasler 2002). Functional foods have high global demand, with the revenue generated by the functional food market worldwide expected to rise substantially from about 174.75 billion U.S. dollars in 2019 to over 275.77 billion U.S. dollars in 2025 (Global functional food market revenue 2019−2025). From the nutritional aspect, *H. bonariensis* leaves contain high amounts of choline (3.20 mg/L) compared to other pennyworts such as *Centella asiatica* and *H. sibthorpioides* (Maulidiani et al. 2012). Choline is an essential nutrient involved in the production of acetylcholine, a neurotransmitter which is associated with memory, muscle and liver functions (Wallace et al. 2018). According to the Food and Nurition Board of the U.S.A. Institute of Medicine, the recommended daily intake for choline has been set at 425 mg per day for women and 550 mg per day for men (Zeisel and Da Costa 2009). Humans can produce choline via the hepatic phosphatidylethanolamine N-methyltransferase pathway in the liver, but the amount naturally synthesised is not sufficient to meet human needs (Jacobs

et al. 2010). Hence, dietary intake of food rich in choline is essential to prevent deficiency (Wallace et al. 2018).

Also, essential micronutrients such as calcium (Ca) (60%), magnesium (Mg) (35%), iron (Fe) (3%), zinc (Zn) (1%) and copper (Cu) (1%) calculated as the percentage of the dry weight of leaves were also found to be higher in *H. bonariensis* compared to *Centella asiatica* and *H. sibthorpioides* (Monyn et al. 2016). These minerals are essential for human health and thus deficiencies in the minerals can lead to certain health risks (Mehri 2020). For example, a dietary Ca deficiency was reported to be epidemiologically linked to bone diseases (Almaghamsi et al. 2018), Mg deficiency may increase risks of atherosclerosis and endothelial dysfunction (Kostov and Halacheva 2018), Cu (Myint et al. 2018) and Fe (Gooding et al. 2019) deficiencies are common causes of anaemia, and Zn deficiency is associated with hypogeusia (Gooding et al. 2019). Eating a well-balanced diet, such as by consuming foods rich in Ca, Mg, Cu, Fe, and Zn can fulfil nutritional needs and prevent mineral deficiencies and so the inclusion of *H. bonariensis* in the diet can address this need.

Several parts of the plant, including roots, petioles and leaves (Haida et al. 2021) of *H. bonariensis* were reported to have a high amount of polysaccharides (1.00 mass/mass ratio) which can serve as a source of dietary fibre (Dantas-Santos et al. 2012). Plant-derived fibre, which primarily comprises plant-cell wall polysaccharides, is important in the diet for human health as a source of energy and to minimize risk factors of chronic diseases (Lovegrove et al. 2017). The fresh aerial part of *H. bonariensis* was reported to have relatively higher total reducing sugar (1.94 mg g^{-1}FW) and hydrolysed sugar (3.84 mg g^{-1}FW), total phenolics (0.96 mg GAE g^{-1}FW) and total flavonoids (13.79 mg CE g^{-1}FW) and antioxidant activities (45.45% 2,2-diphenyl-1-picrylhydrazyl inhibition) compared to *Centella asiatica* (Haida et al. 2021). Polyphenols such as flavonoids inhibit or delay oxidative damage of cells by scavenging the free radicals (peroxide or hydroperoxide) and thus reduce the risk of degenerative diseases (Chandra et al. 2014). Yet, despite the widespread traditional use, other than these sparse reports, there is a distinct lack of information on the nutritional and health-related content of *H. bonariensis*, which is surely worthy of attention. Studies to document the nutritional profile would enable accurate comparisons with other herbs and could lead to more widespread cultivation and use. While *H. bonariensis* is noted as a traditional herb among several communities around the world, it appears that its use is very localised to those specific communities and it has yet to reach sufficient interest for export trade as either a food or medicinal ingredient. The potential for wider use and even export will require enhancing production by larger-scale cultivation, including indoor cultivation. A recent study showed indoor cultivation of *H. bonariensis* under red and blue LED light with a higher blue irradiance (R: B = 83: 65) can enhance plant growth and biomass by twofold compared to plants grown under natural light conditions (Nair et al. 2021). Other than large scale cultivation, it is also important to develop post-harvest processes that retain health-promoting phytochemicals in the end-product to better serve the export potential for this herb. There is only one report on post-harvest processing of *H. bonariensis*, in which leaves were dried using a multi-chamber dehumidified-air drying system with an airflow rate of 50 L/min and temperature at 50 °C (Go et al. 2017). Leaves dried with this system retained 84.9% of the phenolic and 66.5% of the flavonoid contents, comparing favourably with commercial methods requiring higher temperatures, such as hot air drying, drum drying and spray drying (Go et al. 2017). Further research on processing and shelf-life for food and nutraceutical use will be of great value to develop markets for *H. bonariensis* products.

Potential of *H. bonariensis* for human health use

Phytochemicals have protective qualities for human health. Few studies have been conducted to analyse and quantify the phytochemical content in *H. bonariensis*, with the majority examining leaf tissue extracts (Table 2). A total of sixteen bioactive compounds have been reported for *H. bonariensis*, mainly belonging to three major groups of phytochemicals: saponins, flavonols and triterpenes (Table 2). Table 3 shows the chemical structures of phytochemicals present in *H. bonariensis*, constructed using ChemDraw® program (https://www.perkinelmer.com/product/chemdraw-professional-chemdrawpro). Previous studies using in-vitro and in-vivo approaches have demonstrated that the phytochemical compounds reported in leaves and roots of *H. bonariensis* have unique biological and pharmacological functionalities such as antioxidants and for the treatment of health-related conditions including inflammation, cataract development, arthritis and cancer (Table 4).

Anti-inflammatory activity

Scientific studies on *H. bonariensis* extracts suggest the plant to have anti-inflammatory potential, which could be developed as an alternative to synthetic anti-inflammatory drugs that present adverse effects when used in the long term (Wongrakpanich et al. 2018). For example, topical application of infusion and methanolic extracts from the total aerial part of *H. bonariensis* showed 30% to 58% inhibition of mouse ear oedema (a local swelling), suggesting the effectiveness of the plant extract to reduce inflammation in the mouse model (Ouviña et al. 2009). The potency of anti-inflammatory effects of *H. bonariensis* was further elucidated by evaluating the hexane extracts of the leaf containing

Table 2 Various extraction methods used to isolate phytochemicals from different plant parts of *H. bonariensis*

Plant part	Extraction method	Phytochemicals	Quantity	References
Leaf	100% aqueous	Tannic acid	0.38 μ mol^{-1}	Marino et al. (2009)
Leaf	100% aqueous	Flavonoids	3.32 mg/g DW	Sumazian et al. (2010)
		Phenols	9.3 mg/g DW	
		Ascorbic acid	0.70 mg/g FW	
Root	70% aqueous methanol	Saponins	Not determined	Tabopda et al. (2012)
Leaf	70% aqueous methanol	Phenols	28.6 mg GAE/100 g DW	Maulidiani et al. (2014)
		Flavonoids	0.759 mg/100 g of extract	
		Triterpenes glycosides	Not determined	
Leaf	Hexane	Saponins	47.20 ± 1.600% FW	Obaseki et al. (2016)
		Phenols	1.07 ± 0.003 mg(GE)/g	
		Flavonoids	1.36 ± 0.042 mg(QE)/g	
		Tannins	18.74 ± 0.050% FW	
		Terpenoids	Not determined	
		Sterols	Not determined	
Leaf	Ethylacetate: methanol	Flavonoids (quercetin)	Not determined	Ajani et al. (2017)

FW Fresh weight, *DW* Dry weight

active compounds hexadecenoic acid methyl ester, falcarinol and phytol (Obaseki et al. 2016). The hexane extract was tested in human red blood cell (HRBC) membrane stabilisation studies as the red blood cell membrane is similar to lysosomal membranes that influence the inflammatory process. The anti-inflammatory effect was observed with an increase in hexane extract concentration from 30.1% to 71.3% in membrane stabilisation (half maximal inhibitory concentration; IC_{50} of 117.37 μg/ml), suggesting that the plant extract has membrane stabilisation properties that may contribute to the potency of the anti-inflammatory agent (Obaseki et al. 2016). Membrane stabilisation is critical for limiting the anti-inflammatory response, as it prevents the release of lysosomal components such as proteases that cause more tissue inflammation and damage after extracellular release (Obaseki et al. 2016). The anti-inflammatory property of the plant was further assessed against protein denaturation, which is an important cause of inflammation. The inhibition protein denaturation assay confirmed the inhibitory effect of *H. bonariensis* on heat-induced bovine serum albumin (BSA) denaturation and was reported to act in a concentration-dependent manner, ranging from 26.50% to 69.23% with an in vitro IC_{50} value of 44.84 μg/ml compared to the standard non-steroidal anti-inflammatory drug diclofenac sodium (46.15% to 85.47% inhibition with an IC_{50} value of 10.68 μg/ml) (Obaseki et al. 2016). The anti-inflammatory activity of H. *bonariensis* was also evaluated using the arthritis-induced rat paw oedema model, which confirmed the potent anti-inflammatory effect at a dose of 250 mg/kg body weight (Obaseki et al. 2016).

Antioxidant activity

Oxidative stress is induced by the excessive production of reactive oxygen species (ROS) and/or a decrease in antioxidant defenses (Siddeeg et al. 2021). Excessive ROS can damage DNA, RNA, proteins and lipids, resulting in an increased risk for chronic diseases, including cancer, neurodegenerative, diabetes and cardiovascular diseases (White et al. 2014). Antioxidants such as polyphenols and flavonoids (Hunyadi 2019) can slow down or prevent oxidative damage by directly or indirectly scavenging and/or controlling ROS production (Lü et al. 2010). The mechanisms of action for antioxidants, including polyphenols and flavonoids, have been reported previously in the literature (Leopoldini et al. 2011). *H. bonariensis* possesses antioxidant activities, owing to the plant's rich content of polyphenols and flavonoids (Ajani et al. 2017). Based on 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activity, fractionated phenolic leaf extracts showed antioxidant potential through their ability to scavenge free radicals, leading to the disappearance of colour and therefore expressing high antioxidant activity (Maulidiani et al. 2014). Antioxidant properties were further assessed in fractionated extracts of *H. bonariensis* leaves, which were partitioned using different solvents of increasing polarity, namely hexane, chloroform, ethyl acetate and methanol (Ajani et al. 2017). The antioxidant activity assessment was conducted using DPPH radical scavenging assay, metal chelating activity, free radical (OH, H_2O_2 and NO) scavenging activity and reducing power assay. The tests showed that methanol and aqueous fractions had the highest free radical scavenging activity while the aqueous fraction had the highest metal chelating activity (35.5%) and

Table 3 Chemical descriptions of phytochemicals present in *H. bonariensis*

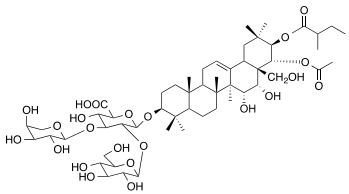
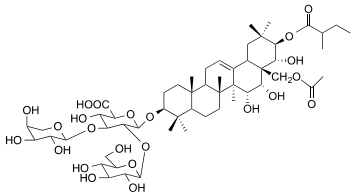
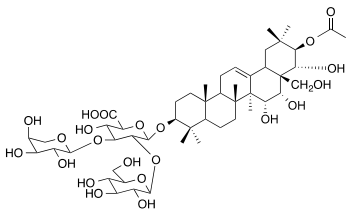
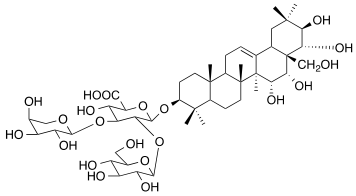
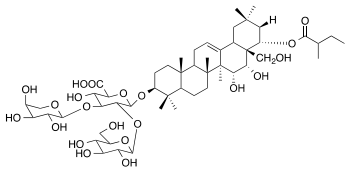
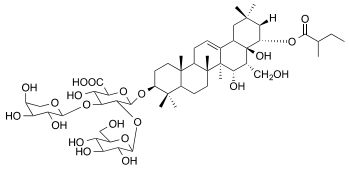
Group	Chemical structure	Molecular formula/ (Molecular weight)	Chemical Name (Common name, if available)	Reference (PubChem CID, if available)
Saponins		$C_{54}H_{86}O_{23}$ (1103.26 g/mol)	3-*O*-{β-D-glucopyranosyl-(1 → 2)-[α-l-arabinopyranosyl-(1 → 3)]-β-D-glucuronopyranosyl}-21-*O*-(2-methylbutyroyl)-22-*O*-acetyl-R_1-barrigenol (Common name: bonarienoside A)	Tabopda et al. (2012) (PubChem CID: 56,951,544)
		$C_{54}H_{86}O_{23}$ (1103.26 g/mol)	3-*O*-{β-D-glucopyranosyl-(1 → 2)-[α-l-arabinopyranosyl-(1 → 3)]-β-D-glucuronopyranosyl}-21-*O*-(2-methylbutyroyl)-28-*O*-acetyl-R_1-barrigenol (Common name: bonarienoside B)	Tabopda et al. (2012) (PubChem CID: 56,951,656)
		$C_{49}H_{78}O_{22}$ (1019.14 g/mol)	3-*O*-{β-D-glucopyranosyl-(1 → 2)-[α-l-arabinopyranosyl-(1 → 3)]-β-D-glucuronopyranosyl}-21-*O*-acetyl-R_1-barrigenol (Common name: bonarienoside C)	Tabopda et al. (2012) (PubChem CID: 56,951,657)
		$C_{47}H_{76}O_{21}$ (977.10 g/mol)	3-*O*-{β-D-glucopyranosyl-(1 → 2)-[α-l-arabinopyranosyl-(1 → 3)]-β-D-glucuronopyranosyl}-R_1-barrigenol (Common name: bonarienoside D)	Tabopda et al. (2012) (PubChem CID: 56,949,673)
		$C_{52}H_{84}O_{21}$ (1045.22 g/mol)	3-*O*-{β-D-glucopyranosyl-(1 → 2)-[α-l-arabinopyranosyl-(1 → 3)]-β-D-glucuronopyranosyl}-22-*O*-(2-methylbutyroyl)-A_1-barrigenol (Common name: bonarienoside E)	Tabopda et al. (2012) (PubChem CID: 56,949,674)
		$C_{52}H_{84}O_{21}$ (1045.22 g/mol)	21-*O*-[2-methylbutanoyl]-3β, 15α, 16α, 21β, 22α, 28-hexahydroxyolean-12-ene 3-*O*-[α-L-arabinopyranosyl(1 → 3)]β-D-glucopyranosyl (1 → 2)-beta-D-glucuronopyranoside (Common name: saniculoside-R1)	Tabopda et al. (2012); Schöpke et al. (1998) (PubChem CID: 9,491,771)

Table 3 (continued)

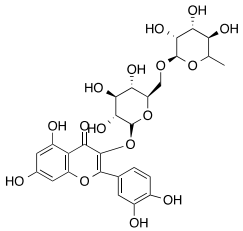
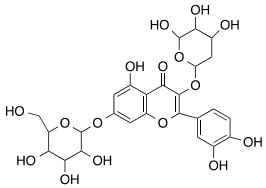
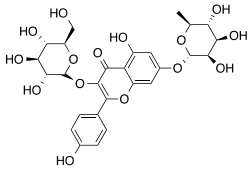
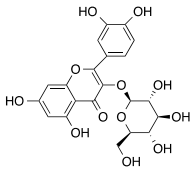
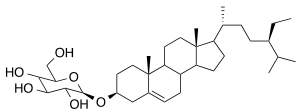
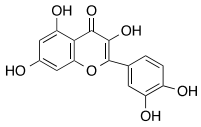
Group	Chemical structure	Molecular formula/ (Molecular weight)	Chemical Name (Common name, if available)	Reference (PubChem CID, if available)
Flavonols		$C_{27}H_{30}O_{16}$ (610.52 g/mol)	Quercetin-rutinoside	Maulidiani et al. (2014) (PubChem CID: 124,221,768)
		$C_{26}H_{28}O_{16}$ (596.49 g/mol)	Quercetin-3-*O*-pentosyl-7-*O*-hexoside	Maulidiani et al. (2014) (PubChem CID: 133,053,374)
		$C_{27}H_{30}O_{15}$ (594.52 g/mol)	Kaempferol-3-*O*-glucoside 7-*O*-rhamnoside	Maulidiani et al. (2014) (PubChem CID: 14,035,324)
		$C_{21}H_{20}O_{12}$ (466.39 g/mol)	Quercetin-3-*O*-glucoside	Maulidiani et al. (2014) (PubChem CID: 5,280,804)
		$C_{35}H_{60}O_6$ (576.86 g/mol)	3-*O*-β-D-glucopyranosyl-sitosterol	Ajani et al. (2017) (PubChem CID: 5,742,590)
		$C_{15}H_{10}O_7$ (302.24 g/mol)	Quercetin	Ajani et al. (2017) (PubChem CID: 5,280,343)

Table 3 (continued)

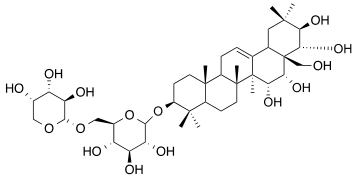
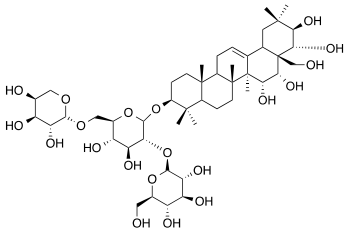
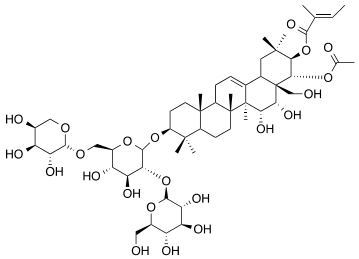
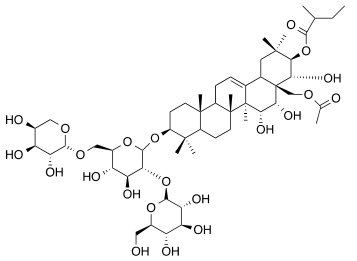
Group	Chemical structure	Molecular formula/ (Molecular weight)	Chemical Name (Common name, if available)	Reference (PubChem CID, if available)
Tripertenes		$C_{41}H_{68}O_{15}$ (800.98 g/mol)	3β,15α,16α,21β,22*x*,28-hexahydroxy-Δ^{12}-oleanane-3-*O*-[α-L-arabinopyranosyl-(1 → 6)]-β-D-glucopyranoside (Common name: Ranuncoside I)	Maulidiani et al. (2014); Greca et al. (1994) (PubChem CID: 101,672,524)
		$C_{47}H_{78}O_{20}$ (963.12 g/mol	)3β,15α,16*x*,21β,22α,28-hexahydroxy-Δ^{12}-oleanane-3-*O*-[α-L-arabinopyranosyl-(1 → 6)]-β-D-glucopyranosyl-(1 → 2)- β- D-glucopyranoside (Common name: Ranuncoside II)	Maulidiani et al. (2014); Greca et al. (1994) (PubChem CID: 101,673,080)
		$C_{54}H_{86}O_{22}$ (1087.26 g/mol)	3β,15α,16α,21β,22α,28-hexahydroxy-Δ^{12}-oleanane-21-*O*-tigloyl-22acetyl-3-*O*-[α-L-arabinopyranosyl-(1 → 6)][β-D-glucopyranosyl-(1 → 2)]-β-D-glucopyranoside (Common name: Ranuncoside IV)	Maulidiani et al. (2014); Greca et al. (1994) (PubChem CID: 101,672,525)
		$C_{54}H_{88}O_{22}$ (1089.28 g/mol)	3β,15α,16α,21β,22α,28-hexahydroxy-Δ^{12}-oleanane-21-*O*-[2-methylbutyroyl)-28-*O*-acetyl-3-*O*-[α-L-arabinopyranosyl-(1 → 6)][β-D-glucopyranosyl-(1 → 2)]- β- D-glucopyranoside (Common name: Ranuncoside V)	Maulidiani et al. (2014); Greca et al. (1994) (PubChem CID: 101,672,526)

Table 4 Pharmacological activities of phytochemicals and extracts of *H. bonariensis*

Phytochemicals	Biochemical analysis/ biological assays	Pharmacological activity	Reference
Not mentioned[a]	1. Thiobarbituric acid reacting substances test 2. Reduced glutathione activity 3. Superoxide dismutase activity 4. Colorimteric assay of catalase	Anticataract potential	Ajani et al. (2009)
Not mentioned[a]	1. Triglyceride GPOPAP kit 2. Cholesterol CHODPAP kit 3. High Density Lipoprotein Cholesterol precipitant determination 4. Low Density Lipoprotein Cholesterol calculation 5. Atherogenic risk index 6. Thrombin physicochemical transformation	Cardioprotective effects	Ajani et al. (2012)
Not mentioned[a]	Patch clamp experiments for IK currents recording	Potential for management of cardiac arrythmias	Kaboua et al. (2021a)
Saponins (bonarienoside derivatives)	MTT ([3–(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] cytotoxicity assay	Anti-cancer potential	Tabopda et al. (2012)
Oleanane-type triterpenes	1,1-Diphenyl-2-picrylhydrazyl (DPPH) radical scavenging assay	Antioxidant activity	Maulidiani et al. (2014)
Flavonoids/ polyphenols	1. DPPH radical scavenging assay 2. Metal chelating activity 3. Nitric oxide (NO) radical scavenging activity 4. Hydrogen peroxide (H_2O_2) scavenging activity	Antioxidant activity	Ajani et al. (2017)
Not mentioned[a]	12-O-Tetradecanoylphorbol-13 acetate (TPA)-induced ear edema in a mouse model	Anti-inflammatory effects	Ouviña et al. (2009)
Hexadecanoic acid methyl ester, falcarinol, phytol	Heat-induced albumin denaturation, human red blood cell (HRBC) membrane stabilization assays, haematological assessments, liver function tests	Anti-inflammatory effects	Obaseki et al. (2016)
Not mentioned[a]	MTT cytotoxic assay Antichlamydial activity assays	Inhibitory activity against *Chlamydia trachomatis* and *Chlamydia pneumoniae*	Entrocassi et al. (2021)
Dibenzylbutyrolactone lignans	MTT cytotoxic assay Haemolytic activity test	Inhibitory activity against *Trypanosoma cruzi*	Souza et al. (2021)

[a]Not mentioned as total leaf extracts were used

free radical scavenging activity and reduced power activity compared to other fractionated extracts (Ajani et al. 2017).

Preventive activity against ophthalmic diseases

Potent antioxidant activities of *H. bonariensis* leaf extracts may be beneficial in reducing cataract progression by preventing oxidative damage in eye lens tissue. Cataract disease has resulted from increased peroxidation and reduced antioxidant enzymatic activity of catalase, superoxide dismutase and lower glutathione levels in eye lens tissue (Ajani et al. 2009). The oral treatment of lyophilised leaf extracts restored the activity of catalase and superoxide dismutase, increased glutathione levels, and simultaneously reduced the level of peroxidation in galactose-fed, weanling albino rat lens tissues (Ajani et al. 2009). Although the leaf extract administration has reduced the progression of cataracts, it has not reversed cataractogenesis. These results are promising for the use of *H. bonariensis* extracts as active ingredients for cataract prevention and/or treatment.

Preventive activity against cardiovascular diseases

The potential use of *H. bonariensis* extract as an active ingredient for therapeutic use for cataracts is further assessed to evaluate the possible cardiovascular disease (CVD) risk associated with its administration. An experimental animal model has shown that aqueous extract of *H. bonariensis* is effective in reducing CVD risk, which is often associated with increased dietary galactose that can result in cataract progression. Following the oral administration of the extract to cataract-affected weanling albino rats at 500 mg/kg and 1000 mg/kg, the plasma lipid profile, fibrinogen and platelet counts of galactose-fed rats showed low-dose *H. bonariensis* leaf extracts (500 mg/kg) to be more effective in reducing plasma fibrinogen and platelet counts than diets either supplemented with 1000 mg/kg leaf extract or with no leaf extract (Ajani et al. 2012). A recent study showed the potential of hydro-ethanolic leaf extract of *H. bonariensis* to selectively block the potassium current which controls cardiac repolarization (Kaboua et al. 2021a). This effect was comparable to the effects of class III anti-arrhythmics drugs, indicating the potential use of *H. bonariensis* in the management of cardiac arrhythmia.

Anticancer activity

H. bonariensis is also reported to have anticancer properties. The anti-tumour potential was reported in Tabopda et al. (2012), which showed that two plant saponin derivatives (Bonarienosides A and Bonarienosides B) isolated from the leaf extract displayed toxicity (IC_{50} 24.1 and 24.0, 83.0 µM and 83.6 µM, respectively) against two colon cancer cell lines (HCT 116 and HT-29). Saponins have potent anticancer activities by inducing cell cycle arrest and apoptosis (Man et al. 2010). Interestingly, *H. bonariensis* extract does not show any cytotoxicity effect on normal cells. In a cellular toxicity study based on the survival of shrimp larvae, the hydroethanolic extract of *H. bonariensis* was considered non-toxic for average lethal concentrations (LC) ≥ 0.1 mg/ml as the obtained LC was 0.12 mg/ml, which is higher than the limit. An orally administered extract was also reported to be toxicologically safe in a mammal model, as negligible acute and subchronic toxicity signs were observed in the treated Wistar rats compared to the control batch (Kaboua et al. 2021b).

Antimicrobial activity

The exploration of *H. bonariensis*' antimicrobial activity has been limited, however, antiviral, antibacterial, and antiprotozoal activity have been reported: Antiviral activity was demonstrated for a *H. bonariensis* methanol extract and water infusion against bovine viral diarrhea virus type 1 (Ruffa et al. 2004); A dicholoromethane extract of aerial parts of *H. bonariensis* was able to inhibit the growth of bacterial pathogens *Chlamydia trachomatis* (causative agent of sexually transmitted disease Chlamydia) and *Chlamydia pneumoniae* (causative agent of neonatal conjunctivitis and pneumonia) in LLC-MK2 or HeLa cells culture (Entrocassi et al. 2021); A methanol extract of *H. bonariensis* leaves was shown to inhibit the protozoan parasite *Leishmania infantum* with 100% lethality at 500 µg/ml concentration (Tempone et al. 2008). Also, hexane extract of the aerial part of *H. bonariensis* was reported to inhibit the protozoan parasite *Trypanosoma cruzi* with 100% lethality at 300 µg/ml concentration (Souza et al. 2021). The antimicrobial activity of *H. bonariensis* extracts may be related to the high flavonoid and polyphenol content: Flavonoids extracted from plants have been shown to have antiviral (Ninfali et al. 2020), antibacterial (Adamczak et al. 2020) and antifungal activities (Al Aboody and Mickymaray 2020), while polyphenols in plant extracts have been reported to have antimicrobial and antiviral properties that can be useful in the food industry (Olszewska et al. 2020). While there are no reports of the antimicrobial or anti-inflammatory effects of including *H. bonariensis* in the human diet, the health-promoting effects of foods rich in flavanols are widely reported (Barreca et al. 2021) therefore, it is likely that mechanisms of action of *H. bonariensis* flavonoid compounds will be a fruitful area of research.

As a rich source of several saponins, flavonols and triterpenes (Table 3), *H. bonariensis* possesses a promising health benefit potential. The chemical structures that we have generated using ChemDraw® (Table 3) may serve as a resource for predicting their molecular targets and studying molecular interactions. Isolating or synthesising these phytochemicals and testing their activity in in vitro and in vivo conditions will be useful for further exploration of the mechanism of each individual compound in promoting human health.

In-vitro studies for enhancement of phytochemical production in *H. bonariensis*

A diet enriched with health-promoting phytochemicals reduces disease incidence, thus it is recommended for general health, particularly to reduce the incidence of non-communicable diseases (Chang et al. 2016). From a pharmaceutical perspective, in most cases, plants are used to discover of novel compounds that are then more cost-effective to produce synthetically or semi-synthetically, as production directly from plant materials is often not sustainable (Zhao et al. 2019). However, several strategies have been explored to enhance the content of beneficial phytochemicals in crop

plants, ranging from the exogenous application of light (Kim et al. 2021), chemical inducers (Alothman et al. 2009) to genetic manipulation of associated genes in metabolic pathways (Singh 2016). For phytochemical enhancement in *H. bonariensis,* Masoumian et al. (2011) have accelerated the flavonoid production in in vitro leaf-callus tissues by supplementing precursors of flavonoids such as phenylalanine, proline, glutamine and naringenin at different concentrations. *H. bonariensis* callus produced the highest flavonoid content when grown on media containing either 3 mg/l phenylalanine (11.4 mg/g dry weight), 4 mg/l proline (10.7 mg/g dry weight), 1 mg/l of glutamine (10.5 mg/g dry weight) or 4 mg/l naringenin (10.1 mg/g dry weight). Overall, the study suggested that an optimum concentration of flavonoid precursors can be used to elevate the phytochemical concentration in *H. bonariensis*. While there remains much room to improve the detailed understanding of plant secondary metabolite biosynthetic pathways, genomic, transcriptomic and metabolomic approaches are narrowing this gap in knowledge (Saito 2013; Nielson et al. 2019; Delfin et al. 2019). Nair et al. (2021) reported the enhancement of total antioxidant content, total phenol and total flavonoid content of *H. bonariensis* when plants are grown under red and blue LED with a higher level of blue irradiance compared to plants grown under natural light conditions. The study suggested that specific LED spectra can be used to increase the phytochemical content of *H. bonariensis*. Future research on the secondary metabolite biosynthesis, its genetic regulation and its association with photoreceptors in *H. bonariensis* would be useful to enhance its potential as a functional food and for pharmaceutical use.

Conclusion and future perspectives

The main phytochemical compounds found in *H. bonariensis* are saponins, phenols, triterpenes and flavonoids. A rich phytochemical content, robust growth characteristics and adaptability to extreme environmental conditions (Chiarello and Joesting 2018) make *H. bonariensis* worthy for inclusion as a mainstream edible functional food crop. *H. bonariensis* also has a great potential to be used in the pharmaceutical industry, as inferred from pharmacological activities. Prolonged traditional dietary and ethnomedicinal use suggest the plant is safe for consumption and pharmacological studies provide evidence of biological activity, however, much research is still needed to quantify the bioactive compounds of fresh and processed plant materials along with systematic animal and clinical trials to evaluate safety and efficacy both for edible and pharmacological use.

Research highlights

1. *H. bonariensis* has wide traditional and potential functional food uses.
2. Cell and animal studies show anti-inflammatory, antimicrobial, anti-tumoural and antioxidant activity.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval Not applicable.

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