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Review / Revisión

Phytochemical composition and biological activities of the plants of the genus *Randia*

Composición fitoquímica y actividades biológicas de las plantas del género *Randia*

Manrique Ojeda-Ayala[1], Soila Maribel Gaxiola-Camacho[1] and Francisco Delgado-Vargas[2,3]*

[1] Laboratorio de Parasitología, Doctorado en Ciencias Agrícolas, Facultad de Medicina Veterinaria y Zootecnia, Universidad Autónoma de Sinaloa (UAS), Culiacán, Sinaloa, México.
[2] Unidad de Investigaciones en Salud Pública "Dra. Kaethe Willms", Facultad de Ciencias Químico-Biológicas, UAS, Ciudad Universitaria, Culiacán, Sinaloa, México.
[3] Laboratorio de Química de Productos Naturales, Posgrado en Ciencia y Tecnología de Alimentos, Facultad de Ciencias Químico-Biológicas, UAS, Ciudad Universitaria, Culiacán, Sinaloa, México.
*Corresponding author: fdelgado@uas.edu.mx

Abstract
Background: The genus *Randia* L. (Rubiaceae) is native to Americas and highly distributed in tropical areas. Some *Randia* species are used in traditional medicine in some countries to treat diverse illnesses/symptoms of kidney, circulatory system, lungs, diabetes, cancer, inflammation, and against the bites/stings of snakes and other poisonous animals.
Questions: What are the phytochemical compounds previously identified in *Randia*? What biological activities do they present?
Data description: Twenty-eight studies on chemical composition and biological activities of *Randia* were reviewed. Species names were corroborated in Plants of the World Online and World Flora Online.
The site and studied years: Studies of *Randia* of Americas from 1991 to 2021.
Methods: Database reviewed were PubMed, Scopus, Scielo, BVS, DAOJ, Science Direct, Springer Link, Web of Science, and Google Scholar, employing the keywords *Randia* and its synonym *Basanacantha*.
Results: Six species are the most studied (*R. aculeata*, *R. echinocarpa*, *R. ferox*, *R. hebecarpa*, *R. matudae*, and *R. monantha*). Ethnopharmacology information of 12 species was recovered. One hundred compounds in *Randia* have been identified (phenolic acids, terpenes, sterols, and others), and diverse biological activities reported in 24 studies (*e.g.*, antimutagenic, antioxidant, and antivenom) have demonstrated for nine species.
Conclusions: Biological activities found in some species of *Randia* support their traditional uses, but only the antivenom effect of *Randia aculeata* has been demonstrated. *Randia* species could be a source of bioactive compounds; however, knowledge must be expanded to demonstrate their traditional uses and contribute to the development of strategies for their preservation and rational use.
Keywords: Bioactive compounds, ethnopharmacology, herbal medicine, natural compounds, Rubiaceae.

Resumen
Antecedentes: El género *Randia* L. (Rubiaceae) es originario de América y está altamente distribuido en zonas tropicales. Algunas de sus especies son utilizadas en la medicina tradicional de algunos países para tratar diversos padecimientos/síntomas: renales, circulatorios, pulmonares, diabetes, cáncer, inflamación y contra las mordeduras/picaduras de serpientes y animales ponzoñosos.
Preguntas: ¿Cuáles son los compuestos fitoquímicos identificados en *Randia*? ¿Qué actividades biológicas presentan?
Descripción de datos: Se revisaron 28 estudios sobre composición química y actividades biológicas de *Randia*. La nomenclatura se corroboró en Plants of the World Online y World Flora Online.
Sitio y años de estudio: Estudios de *Randia* de América desde 1991 a 2021.
Métodos: Las bases de datos revisadas fueron PubMed, Scopus, Scielo, BVS, DAOJ, Science Direct, Springer Link, Web of Science y Google académico, empleando las palabras clave *Randia* y su sinónimo *Basanacantha*.
Resultados: Seis especies de *Randia* son las más estudiadas (*R. aculeata*, *R. echinocarpa*, *R. ferox*, *R. hebecarpa*, *R. matudae* y *R. monantha*). Se recuperó información etnofarmacológica de 12 especies. Cien compuestos han sido identificados en *Randia* (ácidos fenólicos, terpenos, esteroles y otros) y demostrado diversas actividades biológicas en 24 estudios (*e.g.*, antimutagénica, antioxidante, antiveneno) para nueve especies.
Conclusiones: Las actividades biológicas de especies de *Randia* soportan sus usos tradicionales, pero solo está demostrada la actividad antiveneno de *R. aculeata*. Especies de *Randia* podrían ser fuente de compuestos bioactivos, pero su conocimiento debe incrementarse para demonstrar sus usos tradicionales y contribuir al desarrollo de estrategias para su preservación y uso racional.
Palabras clave: Compuestos bioactivos, compuestos naturales, medicina herbolaria, etnofarmacología, Rubiaceae.

The genus *Randia* L. is native to America, belongs to the Gardeniae tribe in the Rubiaceae family. The species of *Randia* are bushy, arboreal, or some lianas (POWO 2019). Three neotropical genera have been related to *Randia*: *Basanacantha*, *Rosenbergiodendron*, and *Glossostipula* (Hooker 1873, Gustafsson 1998, Lorence 1986). *Randia* and *Basanacantha* have been considered synonyms since 1919 (Stranczinger *et al.* 2007); whereas *Rosenbergiodendron* and *Glossostipula* are independent genera (Lorence 1986, 1999). The species of *Randia* grow in wooded areas at 0-3,300 m above sea level, in tropical and subtropical areas (Lorence 1986, Gustafsson 1998, 2000, Borhidi 2006). The morphological and molecular characterization of *Randia* spp. show the following characteristics: some are woody and dioecious, pollen in permanent tetrads, monolocular ovary with two parietal placentas, fruit with abundant seeds in a juicy pulp of black color, and short lateral branches with thorns in the knots. However, some exceptions include monoecious and hermaphrodite species (Lorence & Dwyer 1986, Burger & Taylor 1993, Gustafsson 2000). Analysis of the Gardeniae genera (*i.e.*, vegetative, floral and fruit morphology, anatomy, and palynology) indicates that paleotropical species previously assigned to *Randia* belong to other genera (Keay 1958, Lorence & Nee 1987). The re-classified species are *Randia dumetorum* (*Catunaregam spinosa* (Thunb.) Tirveng.), *Randia spinosa* (*Catunaregam spinosa* (Thunb.) Tirveng.), *Randia formosa* (*Rosenbergiodendron formosum* (Jacq.) Fagerl.), *Randia siamensis* (*Oxyceros horridus* Lour.), *Randia ruiziana* (*Rosenbergiodendron longiflorum* (Ruiz & Pav.) Fagerl.), *Randia tetrasperma* (*Himalrandia tetrasperma* (Wall. ex Roxb.) T. Yamaz.), and *Randia nilotica* (*Catunaregam nilotica* (Stapf) Tirveng.) (POWO 2019, WFO 2021). Thus, *Randia* comprises 106 species distributed in Americas. Mexico is a center of diversity with 62 species (58.5 % of the total) and 44 of them are endemics (41.5 %) (Villaseñor 2016, POWO 2019, WFO 2021). Seven species have been identified since 2012 (Borhidi *et al*. 2013, Jiménez & Cruz 2013, Borhidi & Soto-Nuñez 2014, Borhidi & Salas-Morales 2014, Borhidi & Martínez-Salas 2015).

Traditional medicine includes the knowledge and practices based on theories, beliefs, and experiences of indigenous people of different cultures to maintain health and prevent/treat physical and mental diseases, including the traditional use of medicinal plants (OMS 2013). In traditional medicine, the used parts (leaves, stem, root, flower, or seed) depend on the plant, and its activity is associated with the content of secondary metabolites (Balandrin *et al.* 1993). Approximately 80 % of the world's population employs traditional medicine, but most uses are not supported with scientific information (Vides & Alvares 2013). Mexico has a high floristic richness, and Mexican herbal traditional medicine includes a great diversity of phytotherapeutic treatments, including about 4,500 species, representing the second country with more registered medicinal plants globally (Barragán-Solís 2006).

People of different countries in America (*e.g.*, Mexico, Colombia, Panama, and Brasil) use the leaves, stems, and fruit of several species of *Randia* in traditional medicine against a wide range of diseases (*e.g.*, renal, respiratory, circulatory, cancer, malaria, snake bites) and symptoms (*e.g.*, inflammation, pain, diarrhea) (Bye *et al.* 1991, Borhidi & Diego-Pérez 2008, Méndez-Valenzuela & Hernández-Martínez 2009, Erbano & Duarte 2011, Gallardo-Casas *et al.* 2012). In Mexico, ethnobotanical uses of *Randia* are known since 1,777 with records of Tarahumaras Indians that consumed the fruits of *Randia echinocarpa* Moc. & Sessé ex DC. and *R. laevigata* Standl., and scraps of the *R. echinocarpa* husks were used to prepare a sacramental maize beer (batari) (Irigoyen-Rascón & Paredes 2015). Besides, the early twentieth century reports indicate that *R. echinocarpa* preparations were used to treat diarrhea, malaria, and other kidney maladies (Martínez 1939). In this regard, most ethnopharmacological uses of the *Randia* species have not been scientifically demonstrated. However, biological activities of plants are due to their chemical constituents, so phytochemical characterization is essential. On this subject, the chemical studies of *Randia* are scarce despite the ethnobotanical importance of several of its species in America and particularly Mexico, where the genus is widely diversified. This review analyses the published information about ethnobotany, phytochemical characterization, and tested biological activities of *Randia*. The information presented here is useful to support future studies on developing supplemental foods or new phytotherapeutic agents.

Materials and methods

Systematic searches on the databases PubMed, Scopus, Scielo, Health Virtual Library (BVS), Directory of Open Access Journals (DOAJ), Science Direct, Springer Link, Web of Science, and Google Scholar were conducted, including dates from January 1940 to November 2021. The employed keywords were *Randia* and its synonym *Basanacantha*. The recovered information was classified accordingly to inclusion and exclusion criteria. Inclusion criteria: original papers, reviews, and books including information about ethnobotany, chemical characterization, and biological activities. Exclusion criteria: Original papers, reviews, theses, posters, and books on species originally classified as *Randia* but later reclassified into another genus.

A total of 6,914 results were discriminated as follows: first screening, 423 duplicates were removed; second screening, the titles of documents recovered were analyzed according to the selection criteria, and 6,344 results were eliminated; third screening, 30 results were removed by abstract reading; 147 full papers were reviewed, but 89 were excluded because the studied species were reclassified to other Rubiaceae genera (POWO 2019, WFO 2021). After discrimination, 28 original papers were recovered. Additionally, we included six books and two original papers not retrieved in the searches.

Results

Our review data included 30 original papers and six books with ethnobotanical, phytochemical, and biological activities studies for 15 of the *Randia* species, 14 % of the total richness of the genus (106 spp.). Scientific studies that validate the traditional uses of *Randia* species and evaluate their phytochemical composition have been conducted in Mexico, Brazil, Panama, and the United States of America. Mexico has the highest number of scientific publications (21), followed by Brazil (5), Panama (1), and the United States of America (1).

Ethnobotany of Randia. Reports of traditional uses were found for 12 species of *Randia* (*e.g.*, antivenom and to treat dysentery, kidney ailments, and cancer) (Table 1), and scientific studies of biological activities (*e.g.*, antioxidant, antimicrobial, antivenom) were reported for nine of them (8.5 %) (Table 1).

Phytochemical studies on Randia. Eight species of *Randia* have been studied by qualitative phytochemical screening to establish the presence of families of compounds. *R. armata* (Sw.) DC., *R. echinocarpa, R. laevigata,* and *R. nitida* (Kunth) DC are the best studied, and their main families are phenolic acids, flavonoids, terpenes/sterols, and saponins (Table 2). On the other hand, identification of specific compounds has been reported in seven research papers for six species (*R. aculeata L., R. echinocarpa, R. ferox* (Cham & Schtdel) DC., *R. hebecarpa* Benth, *R. matudae* Lorence & Dwyer, *R. monantha* Benth.) (Table S1, Figure S1). One hundred compounds have been characterized in *Randia*: 32 phenolic acids, 28 terpenes, three sterols, one alkaloid, and 36 others (sugars, fatty acids, aldehydes, alcohols, and ketones). Most compounds were characterized by liquid chromatography or gas chromatography coupled with mass spectrometry (UPLC-MS/MS or GC-MS). However, compounds of *R. echinocarpa* have been purified and characterized by instrumental techniques (*e.g.*, infrared, mass spectrometry, nuclear magnetic resonance). Several identified compounds in *Randia* have shown a range of biological activities (*e.g.*, anticancer, antiinflammatory, antimicrobial) (Table S2) that could support some of their traditional uses.

Biological activities. Considering the ethnobotanical uses of *Randia*, fruit was the main employed part reported for 12 species (Table 1, Figure 1). On the other hand, scientific studies of nine species register 14 biological activities, and *Randia echinocarpa* is the most studied (Appendix 1). Seven documents show the antimicrobial and antiparasitic activities of five species; six studies indicate the antioxidant activity of four species; and three papers study the toxicity of three species. On the other hand, compounds identified in *Randia* have antioxidant, antiinflammatory, antimicrobial, and antiobesity properties. Such properties have been associated with chronic-degenerative and infectious diseases; thus, these compounds could be responsible for the ethnobotanical uses and demonstrated biological activities of samples obtained from species of *Randia* (Table S2).

Table 1. Traditional uses and demonstrated biological activities of *Randia* species.

Plant	Part of the plant/ traditional uses	Demonstrated biological activities
Randia aculeata L.	Fruit/ Against the snake's bites[1]	Antinociceptive[2], antifungal[3], antivenom[1,4], nematicide[5], toxicity[2]
Randia armata (Sw.) DC.	Leaves/ Leaf decoction to sleep better[6]	Antioxidant[8], antiparasitic[7]
Randia capitata DC.	Not specified/ To treat cough[9]	ND
Randia cinerea (Fernald) Standl.	Fruit and leaves/ To clear the urinary tract (bladder and kidneys)[9]	ND
Randia echinocarpa Moc. & Sessé ex DC.	Fruit/ To treat cancer, malaria, diabetes, peptic ulcers, and diseases of kidney, circulatory and lung [10]	Antibacterial[11], antidiabetic[12,13], antimutagenic[14,15], antioxidant[13,14,16], cicatrizing[17], diuretic[18], nematicide[19], antiproliferative[16], toxicity[20]
Randia ferox (Cham & Schltdl) DC.	Leaves/ To treat diarrhea, intestinal colic and pneumonia[21]	Antioxidant, cytotoxicity and genotoxicity[22]
Randia hebecarpa Benth.	Stem-roots/ Infusion to treat rheumatism[23]	Antioxidant and antiinflammatory[24]
Randia laevigata Standl.	Fruit/ To treat gastric discomforts and malaria[25]	ND
Randia longiloba Hemsl.	Bark/ Infusion to treat dengue[26]	Antifungal[3] and nematicide[5]
Randia monantha Benth.	Fruit/ Against bites of snakes and other poisonous animals[27]	Antioxidant[28] and toxicity[27]
Randia nitida (Kunth) DC.	Vegetative parts/ To heal wounds, antiinflammatory, and antispasmodic[29,30]	Antifungal[31]
Randia tetracantha (Cav.) DC.	Fruit/ To treat dysentery[9]	ND

[1]Gallardo-Casas *et al.* 2012, [2]Pérez-Espinosa *et al.* 2015, [3]Gamboa-Angulo *et al.* 2008, [4]Torres-Schwartz *et al.* 2018, [5]Cristóbal-Alejo *et al.* 2006, [6]Zamora-Martínez & Nieto de Pascual-Pola 1992, [7]dos Santos *et al.* 2013, [8]Chaves *et al.* 2015, [9]Borhidi & Diego-Pérez 2008, [10]Bye *et al.* 1991, [11]Salinas-Sánchez *et al.* 2009, [12]Alarcón-Aguilera *et al.* 1998, [13]Cuevas-Juárez *et al.* 2014, [14]Santos-Cervantes *et al.* 2007, [15]Cano-Campos *et al.* 2011, [16]Montes-Avila *et al.* 2018, [17]Pérez *et al.* 1993, [18]Vargas-Solís & Pérez-Gutiérrez 2002, [19]López-Aroche *et al.* 2008, [20]Gil-Avilés *et al.* 2019, [21]Carvalho 2008, [22]Pappis *et al.* 2021, [23]Agra *et al.* 2008, [24]Nazari *et al.* 2006, [25]Irigoyen-Rascón & Paredes 2015, [26]Trejo-Torres *et al.* 2014, [27]Méndez-Valenzuela & Hernández-Martínez 2009, [28]Juárez-Trujillo *et al.* 2018, [29]Erbano & Duarte 2011, [30]Pott & Pott 1994, [31]Cruz-Silva *et al.* 2016, ND: Not determined.

Table 2. Phytochemical screening test in some species of the genus *Randia.*

Species[1]	Extract/ Fraction	Alkaloids	Coumarins	Flavonoids	Tannins	Saponins	Terpenes/ sterols	Free anthracenic derivatives	Phenolics	Anthraquinones
Randia echinocarpa Moc. & Sessé ex DC. [4,a]	ME	-	+	+	+	+++	+	-	ND	ND
	HF	-	+	-	-	++	++	-	ND	ND
	CF	-	-	+	+	+	++	-	ND	ND
	AQF	-	+	+	+	-	-	+	ND	ND
	AEF	-	-	+	+	-	-	++	ND	ND
Randia nitida (Kunth) DC.[3,a]	ME	++	++	+++	+++	+	+++	ND	+++	ND
	HF	-	-	+	-	-	+++	ND	-	ND
	DMF	++	++	++	-	-	++	ND	+++	ND
	AEF	++	++	+++	++	+	++	ND	+++	ND
Randia laevigata Standl.[5,a]	HE	-	ND	-	+	+	ND	ND	-	-
	DME	-	ND	-	-	+	ND	ND	-	-
	ME	+++	ND	+++	-	+++	ND	ND	+++	+++
Randia aculeata L. [6,c]	ME	ND	ND	+	ND	+	ND	ND	ND	ND
Randia. mira Dwyer [2,b]	CE	-	ND	ND	ND	ND	ND	ND	ND	ND
Randia altiscandens (Ducke) C.M. Taylor [2,b]	CE	++	ND	ND	ND	ND	ND	ND	ND	ND
Randia aculeata L.[2,b]	CE	+	ND	ND	ND	ND	ND	ND	ND	ND
Randia armata (Sw.) DC. [2,b,*]	CE	+++	ND	ND	ND	ND	ND	ND	ND	ND
Randia lasiantha (Standl.) Standl. [2,b]	CE	+	ND	ND	ND	ND	ND	ND	ND	ND

[1]Species with highest diversity of compounds is ordered first. [2]Soto-Sobenis *et al.* 2001; [3]Cruz-Silva *et al.* 2007; [4]Cano-Campos *et al.* 2011; [5]Jiménez-Ortega *et al.* 2020; [6]Martínez-Ceja *et al.* 2022. CE, chloroform extract; CF, chloroform fraction; DME, dichloromethane extract; DMF, dichloromethane fraction; EAF, ethyl acetate fraction; HE, hexane extract; HF, hexane fraction; ME, methanol extract. [a]The relative quantity of metabolite is established as abundant (+++), moderate (++), poor presence (+), and complete absence (-); [b]It is shown the intensity of the orange developed, color ranges from light (+) to very dark (++++); [c] + indicates presence; - indicates absence; ND, not determined.

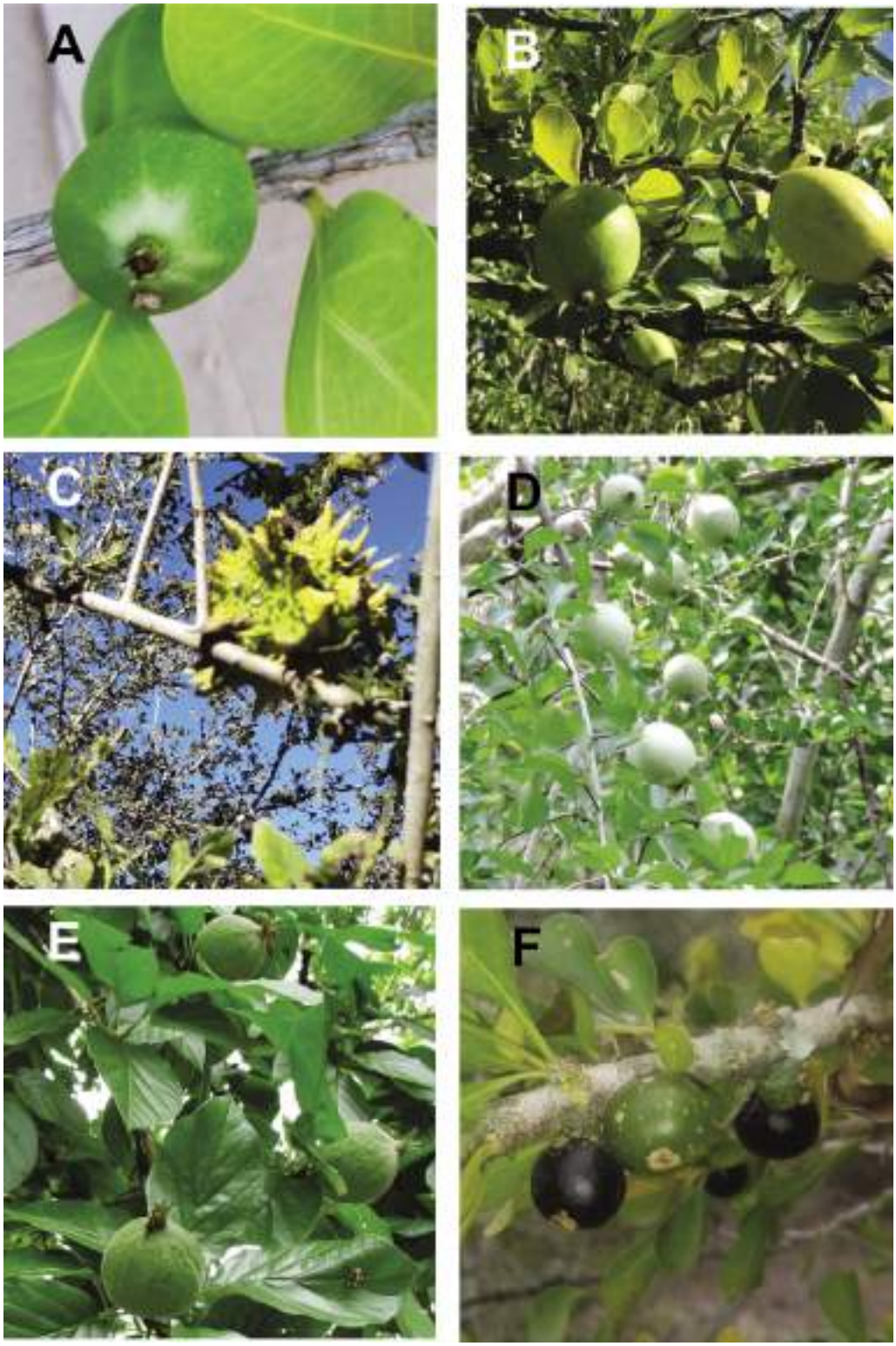

Figure 1. Fruit of *Randia* species employed in traditional medicine: (A) *Randia aculeata*, (B) *Randia armata*, (C) *Randia echinocarpa*, (D) *Randia longiloba*, (E) *Randia monantha*, and (F) *Randia obcordata*. Images from iNaturalist.org, credits: (A) Minerva Reyes, (B) Hailen Ugalde, (D) Joaquín Cauich Pool, (E) Alfredo Dorantes Euan, and (F) Lex García.

Discussion

Mexico has the highest number of species richness, endemism, and publications of *Randia*, parameters that must be associated.

Ethnobotany of Randia. This review shows that most *Randia* species have not been studied. However, ethnobotanical reports about traditional medicine uses are indicated for 12 species (Table 1). Bye *et al.* (1991) studied the ethnobotany of *Randia echinocarpa*, through systematical collection of data and plant specimens from markets in Mexico City. Their results show that *R. echinocarpa* is known by different common names depending on the country region: granjel is the most common, and others are kakawari, telocoche, xacua, and papache. The most common traditional use of *R. echinocarpa* is to treat renal diseases, including renal pain, kidney stones, and cystitis. In Mexico, the entire fruit is prepared as infusion or decoction and consumed three times per day or instead of drinking water. Fruit or leaf infusions of *R. echinocarpa* are also used to treat cough, circulatory ailments, diabetes, diarrhea, malaria, and stomach and intestine cancers.

Gallardo-Casas *et al.* (2012) reported the traditional medicinal use of *Randia aculeata* L. in Japama, Veracruz, Mexico, to treat snake bites (Table 1). The plant common names are "crucetillo" or "crucetillo macho". Fruit is used to prepare drinks, seven fruits (sometimes including the peel) are mixed with 1 L of cherry wine, beer, or cane liquor for one week. This preparation is used orally or topically against the venoms of *Bothrops asper*, *Crotalus* spp., *Micrurus* spp., *Apis* spp., *Latrodectus* spp., and *Centruroides* spp. *Randia monantha* is distributed in Mexico and Central America, where it is employed to treat snakebites (Méndez-Valenzuela & Hernández-Martínez 2009, POWO 2019). In some communities of Veracruz, Mexico, *R. monantha* is commonly known as crucetillo and used against the *Bothrops asper* venom and other poisonous animal bites. The ripe fruit with or without peel is mixed with cane liquor and left to stand. The employed dose depends on the bite or sting of the poisonous animal. This preparation is known since the first settlers' medicine cabinet of those localities (Méndez-Valenzuela & Hernández-Martínez 2009).

Randia armata is distributed in Mexico and South America, where leaves decoction is employed to better sleep (Zamora-Martínez & Nieto de Pascual-Pola 1992, POWO 2019). Chaves *et al.* (2015) studied the chemical composition and antioxidant activity of *R. armata* in four communities in the Buriti dos Montes and Cocal municipalities, Piauí, Brazil; this species is usually consumed as food. The common name of *R. armata* is taturapé, and the fruit pulp is consumed directly. Another study analyzed the use of *R. armata* by the ethnic group Chayahuia from Peru; in its medical system, this plant is commonly known as Kahpari werun, and its leaves are used to treat diarrhea. Leaves are prepared by decocting for 0.5 h to drink three times per day (Odonne *et al.* 2013).

Randia hebecarpa is native to South America, where it is employed as traditional medicine in Brazil, Colombia, Guyana, and Paraguay (Nazari *et al.* 2006, POWO 2019). Agra *et al.* (2008) reported that *R. hebecarpa* is used to treat rheumatism in the Northeast region of Brazil, where it is known as "limaozinho".

Randia nitidia is distributed in Brazil, Colombia, Ecuador, Guyana, Paraguay, Peru, and Venezuela. Plant preparations have been traditionally used for wound healing and as antiinflammatory and antispasmodic agent. *R. nitida* has several common names: "indigoberry", "roseta (rosete")", or "veludo-despinho" (Pott & Pott 1994, Erbano & Duarte 2011, POWO 2019).

Randia ferox is distributed in Argentina, Brazil, and Paraguay, where it has been traditionally employed to treat diarrhea, intestinal colics, and pneumonia; *R. ferox* is commonly known as "limao-do-mato" or "limoneiro-do-mato" (Carvalho 2008, POWO 2019). The infusion of the leaves is traditionally employed to treat diarrhea, intestinal colics, and pneumonia (Carvalho 2008).

Medicinal uses of other species of *Randia* are reported. *Randia longiloba* Hemsl. is endemic to Southwestern Mexico, and its bark infusion has been traditionally employed to treat dengue (Trejo-Torres *et al.* 2014, POWO 2019). *Randia capitata* DC. to treat cough and is commonly known as "zapote prieto" (Borhidi & Diego-Pérez 2008); *R. tetracantha* (Cav.) DC. to treat dysentery and is known as "cruzetillo" (Borhidi & Diego-Pérez 2008).

Randia cinerea (Fernald) Standl. is distributed in Mexico, Guatemala, and Honduras, where is known as "crucetillo", "crucillo", "rangel", or "caporal and used to clean the urinary tract (Borhidi & Diego-Pérez 2008, POWO 2019).

Phytochemical studies on Randia. Most *Randia* species have not been characterized, but the first chemical studies appeared in the 1990s and were conducted on *R. echinocarpa* (Bye *et al.* 1991). The qualitative phytochemical studies are limited and incomplete for eight species, being flavonoids and tannins the most found (Table 2). Moreover, compounds have been isolated and identified only in six *Randia* species (Table S1 and Figure S1) (Nazari *et al.* 2006, Setzer *et al.* 2006, Cano-Campos *et al.* 2011, Juárez-Trujillo *et al.* 2018, Pappis *et al.* 2021, Martínez-Ceja *et al.* 2022), and many of them have demonstrated biological activities (Table S2). The following paragraphs describe the main compounds identified in *Randia*, and bold numbers in parentheses after the compound name correspond to the respective structure in Figure S1.

Phenolics.- The phenolic compounds in *Randia* are numerous and include flavonoids, coumarins, and phenolic acids (*e.g.*, phenylpropanoids) (Table S1 and Figure S1). The seeds of *R. monantha* have the highest phytochemical compound diversity, and the most representatives are the following: flavonoids, *e.g.*, rutin (**9**); coumarins, *e.g.*, scopoletin (**12**); phenylpropanoid acids, *e.g.*, chlorogenic acid (**16**); and phenolic acids, *e.g.*, vanillic acid (**22**) (Juárez-Trujillo *et al*. 2018). Phenolic acids are the main compounds in flower essential oil of *R. matadue*: benzyl benzoate (**25**) and trans-methyl isoeugenol (**30**) (Setzer *et al*. 2006). Kaempferol glycosides (3-6) are abundant in *R. hebecarpa* (Nazari *et al*. 2006). Phenylphosphonic acid (**32**) is identified in leaves of *R. aculeata* (Martínez-Ceja *et al.* 2022).

Terpenes.- The species of *Randia* contain terpenes (Table S1 and Figure S1). In the flowers' essential oil of *R. matudae* the main terpenes are oxygenated monoterpenes (46 %) and sesquiterpenes (2.3 %), highlighting the presence of the monoterpenes α-terpineol (**41**) and linalool (**47**) (Setzer *et al.* 2006). Two triterpene saponins are identified in the ethyl acetate and hydromethanolic fractions of *R. hebecarpa* leaves: cincholic acid 3-*O*-β-D-quinovopyranosil-28-*O*-β-D-glucopyranoside (**53**) and quinovic acid 3-O-β-quinovopyranosyl-28-O-β-D-glucopyranoside (**54**) (Nazari *et al.* 2006). In the ethyl acetate fraction of the *R. echinocarpa* fruit, five triterpenes are identified, being the most abundant quinovic acid (**57**) and oxoquinovic acid (**56**) (Bye *et al.* 1991, Cano-Campos *et al*. 2011). In the hexane, dichloromethane, and methanol extracts of *R. aculeata* leaves were identified the diterpene phytol (**52**) and triterpenes squalene (**59**) and cycloartenol (**60**) (Martínez-Ceja *et al.* 2022).

Sterols.- *Randia echinocarpa* and *R. aculeata* are the only species where sterols have been reported (Bye *et al.* 1991, Cano-Campos *et al.* 2011, Martínez-Ceja *et al*. 2022). In the hexane fraction of *R. echinocarpa* fruits and the hexane, dichloromethane, and methanol extracts of *R. aculeata* leaves are identified three sterols, and β-sitosterol (**61**) is the most abundant (Table S1 and Figure S1) (Cano-Campos *et al.* 2011, Martínez-Ceja *et al*. 2022).

Others.- Other identified compounds in *Randia* species are sugars, fatty acids, aldehydes, alcohols, and ketones (Table S1 and Figure S1). The main fatty acids in the essential oils of seeds of *R. monantha* are linoleic (**69**), oleic (**71**), and palmitic (**67**) (Juárez-Trujillo *et al.* 2018). The fruit pulp of *R. echinocarpa* contains linoleic (**69**) and palmitic (**67**) acids, and the last one is the most abundant (Cano-Campos *et al.* 2011). The main alcohols in flower essential oils of *R. matudae* are *cis*-3-hexenol (**78**) and *trans*-3-hexenol (**79**) (Setzer *et al*. 2006). Three aldehydes have been registered for *R. echinocarpa*, being pentadecanal (**97**) the most abundant (Cano-Campos *et al.* 2011). The mannitol (**81**) has been identified in *R. echinocarpa* and *R. hebecarpa* (Bye *et al.* 1991, Nazari *et al.* 2006, Cano-Campos *et al.* 2011). The main polyalcohols in the leaves extracts of *R. aculeata* are ribitol (**85**) and glucitol (**86**) (Martínez-Ceja *et al.* 2022).

Biological activities. Among the biological activities demonstrated for the 12 species of *Randia* used in traditional medicine, the antioxidant activity is reported for five species (Table 1 and Appendix 1). Oxidative stress and inflam-

mation have been associated with the etiopathogenesis of different diseases (*e.g.*, cancer, cardiovascular, metabolic, neurodegenerative), and plant antioxidants can be health protective by preventing lipid oxidation, protein denaturation, DNA damage, and improving the DNA repair and detoxification mechanisms (Munialo *et al*. 2019). Phenolics and flavonoids are common components of *Randia* (Table S1); these compounds have been proposed as an adjuvant therapy to treat inflammation, activity associated with the antioxidant activity and inhibition of enzymes involved in the production of eicosanoids (Hussain *et al.* 2016). Therefore, the antioxidant activity of *Randia* compounds could be relevant in the prevention and treatment of diseases. In general, biological activities demonstrated for *Randia* support some of their traditional uses (Table 1 and Appendix 1). *Randia echinocarpa* has been the most studied species. It is endemic to Mexico, where it has been used to treat cancer, malaria, diabetes, and peptic ulcers, as well as renal, circulatory, and pulmonary diseases (Bye *et al.* 1991). The acetone extracts of stems/leaves of *R. echinocarpa* have low activities against *Staphylococcus aureus, Streptococcus faecalis, Escherichia coli, Proteus mirabilis, Salmonella enterica* serovar Typhi, and *Candida albicans*; the Minimal Inhibitory Concentrations (MIC) are ≥ 8 mg/mL (Salinas-Sánchez *et al*. 2009); besides, the fruit acetone extract shows nematicidal activity against *Haemonchus contortus* L3, inducing up to 37 % death after incubation for 48 h (López-Aroche *et al*. 2008). Moreover, the aqueous extract of *R. echinocarpa* has antimutagenic activity in *Salmonella enterica* serovar Typhimurium YG1024, acting by desmutagenic (damage prevention) and bioantimutagenic (damage repair) mechanisms. In this regard, a bioguided assay of an antimutagenic methanolic extract of *R. echinocarpa* showed greater activity in its hexane fraction, and the responsible compounds were β-sitosterol, linoleic acid, and palmitic acid (Santos-Cervantes *et al*. 2007, Cano-Campos *et al.* 2011). Aqueous and non-polar extracts of *R. echinocarpa* fruit showed similar antioxidant activities by the β-carotene discoloration method; the aqueous extract has low content of phenolics and authors suggested that synergic effects (*e.g.*, between β-sitosterol and phenolics) are contributing with the antioxidant activity of *R. echinocarpa* (Santos-Cervantes *et al.* 2007). The insoluble melanins of *R. echinocarpa* fruit have high antioxidant activity by the FRAP (1,098.41 ± 11.43 μmol TE/g, TE means Trolox Equivalents) and ABTS (1,333.5 ± 8.45 μmol TE/g) methods. They show cellular antioxidant activity in the *Saccharomyces cerevisiae* BY4741 strain (Montes-Avila *et al.* 2018). A dose-response effect was observed with better results at the two lowest melanin concentrations (0.01 and 0.1 mg/mL) than with ascorbic acid. Melanins are ubiquitous biological pigments produced by oxidation and polymerization of phenolics, and in alive organisms are involved in thermoregulation, chemoprotection, camouflage, sexual attraction, and photoprotection (Bilinska 1996, Krol & Liebler 1998). It must be emphasized that melanin-containing food has been associated with antioxidant and immunostimulatory properties (Pugh *et al.* 2005, Huang *et al.* 2011). In particular, the insoluble melanins of *R. echinocarpa* fruit showed immunomodulatory activity by increasing the splenocyte proliferation, and authors suggested that the immunostimulant effect was due to phenolic structures in melanins (Montes-Avila *et al.* 2018). It was suggested that phenolics induce endogenous enzymes (*e.g.*, superoxide dismutase, catalase, glutathione peroxidase) and chelate metals (*e.g.*, iron and copper) (Montes-Avila *et al.* 2018).

Soluble melanins (impure and purified) from fruit of *Randia echinocarpa* have shown a higher α-glucosidase inhibitory activity (αGI) than acarbose, a drug commonly employed to treat type II diabetes (Cuevas-Juárez *et al.* 2014). Furthermore, the purified melanins showed the highest αGI, suggesting that the components/structure of soluble melanins are essential for the activity. The αGI values were not correlated with the content of phenolics or antioxidant activity, albeit these three parameters increase with purification; consequently, sample composition is differentially affecting such parameters (Cuevas-Juárez *et al.* 2014). However, fruit decoction of *R. echinocarpa* did not show anti-hyperglycemic activity in rabbits (Alarcón-Aguilera *et al.* 1998). Thus, *R. echinocarpa* extracts have antioxidant, immunomodulatory, and antimutagenic activities that have been considered essential to treat various diseases, including malaria and cancer (Munialo *et al.* 2019), and support the traditional uses of the species. Supporting the potential of *R. echinocarpa* as a source of phytotherapeutic compounds, toxicity assays in mice showed that soluble melanins from fruit were innocuous, and treated mice showed normal behavior, weight, and healthy organs (Gil-Avilés *et al.* 2019).

Randia hebecarpa is traditionally used to treat rheumatism (Nazari *et al.* 2006). The methanol extract of leaves and its fractions have *in vitro* antioxidant activities evaluated by the DPPH (2,2-diphenyl-1-picrylhydrazyl) and lin-

oleic acid peroxidation methods. Activities of the methanol extract, ethyl acetate fraction, and hydroxymethanol fraction were similar to the positive control butylated hydroxytoluene (inhibition percentage of 89.4 %) in linoleic acid peroxidation. In the DPPH method, ethyl acetate fraction shows the best activity (IC_{50} = 60.8 µg/mL). In the most active fractions were identified five flavonoids, two triterpenes, and mannitol. Authors suggested that flavonoids are responsible for antioxidant activity (Nazari *et al.* 2006). The methanol extract of *R. hebecarpa* leaves is active against *Mycobacterium tuberculosis* (250 < MIC < 500 µg/mL) (Araujo *et al.* 2014) and lacks antiinflammatory activity in the carrageenan or dextran murine models (Nazari *et al.* 2006).

Randia monantha is traditionally employed to treat snakebites (Méndez-Valenzuela & Hernández-Martínez 2009). The aqueous, methanol, and ethanol extracts of pulp and seeds of their fruits show high *in vitro* antioxidant activity evaluated by the ABTS (2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)), DPPH, FRAP (Ferric Reducing Antioxidant Power), and reducing power methods; seed extract shows higher DPPH activity than pulp extract, and it is suggested that flavonoids are the active compounds (Juárez-Trujillo *et al.* 2018). By contrast, the aqueous extract of pulp was more active than that of seeds by the FRAP method, proposing that pulp antioxidant activity was due to the synergy of phenolics, vitamin C, and melanins (Juárez-Trujillo *et al.* 2018).

The ethanol extract of *R. aculeata* fruit is effective against the venoms of the *Crotalus simus* and *Bothrops asper* snakes: the extract decreases the tissue damage of skeletal and cardiac muscles and the loss of red blood cells (Gallardo-Casas *et al.* 2012). It is suggested that extract inhibits the proteolytic enzymes involved in the venom hemotoxic effects. The *R. aculeata* ethanol extract was also useful as an adjuvant of the polyvalent drug therapy in mice lung tissue against the *Bothrops asper* venom (Torres-Schwartz *et al.* 2018). Compared with venom-treated mice, mice treated with venom followed by the polyvalent serum had decreased atrophy and bleeding in the lungs. However, those treated with venom, polyvalent serum, and extract did not show these symptoms. Therefore, it was suggested that extract neutralizes the venom toxins. The ethanolic extract of *R. aculeata* was innocuous in mice (LD_{50} > 1,000 mg/kg b.w.) and was able to reduce the number of acetic acid-induced contortions, thus suggesting that it has an analgesic effect at the visceral level (Pérez-Espinosa *et al.* 2015). Martínez-Ceja *et al.* (2022) evaluated the *in vitro* antiinflammatory, antibacterial, and antioxidant activity of methanol, hexanic, and dichloromethane extracts of *Randia aculeata* leaves. At the tested concentrations, none of the extracts showed activity against *Staphylococcus aureus*, *Staphylococcus aureus*-MRSA, *Streptococcus pyogenes*, *Escherichia coli*, and *Salmonella* Typhimurium. The methanol extract of *Randia aculeata* showed high *in vitro* antioxidant activity with the following IC_{50} values: 92.92 ± 0.91 µg/mL in DPPH and 14.27 ± 0.20 µg/mL in ABTS. The extracts did not affect the RAW 267.4 cells viability and showed a concentration-dependent inhibition of the nitric oxide (NO) production, being most active the hexane (26.25 ± 2.62 % at 20 µg/mL) and dichloromethane (35.38 ± 4.35 % at 40 µg/mL) extracts. It is suggested that *Randia aculeata* may be a promising medicinal resource.

Randia armata is traditionally employed to better sleep (Zamora-Martínez & Nieto de Pascual-Pola 1992). An ethanol-water (7:3 v/v) extract of *R. armata* aerial parts shows moderate antiparasitic activity against Larvae of *Rhipicephalus (Boophilus) microplus* (75 % efficacy at 40 % extract concentration) (dos Santos *et al.* 2013). In addition, the *in vitro* antioxidant activity of the methanolic extract of *R. armata* has been high due to its elevated concentration of phenolics and carotenes (Chaves *et al.* 2015).

Randia nitida is traditionally used for wound healing (Pott & Pott 1994, Erbano & Duarte 2011). Methanolic extract of leaves and its fractions show antifungal activity against *Colletotrichum truncatum*, *Rhizoctonia solani*, and *Sclerotinia sclerotiorum*. This activity may be related to their main flavonoid, steroid, and triterpene components (Cruz-Silva *et al.* 2016).

Randia longiloba has been traditionally employed to treat dengue (Trejo-Torres *et al.* 2014). The ethanol extract of leaves, stems, and roots of *R. longiloba* show nematicidal activity (Cristóbal-Alejo *et al.* 2006).

Randia obcordata S. Watson is distributed from Texas to Venezuela, and it has no information on medicinal uses (POWO 2019) nor phytochemical characterization. The ethanol extract of *R. obcordata* leaves inhibits the growth of the fungi *Alternaria tagetica*, *Colletotrichum gloeosporioides*, and *Rhizopus* sp. In contrast, the root extract only inhibits the growth of *Rhizopus* sp. (Gamboa-Angulo *et al.* 2008). In addition, the ethanol extracts of leaves, stem,

and roots of *R. obcordata* were nematicidal against *Meloidogyne incognita* J2, and the highest mortality was obtained with the extract of leaves (60 % at 500 ppm) (Cristóbal-Alejo *et al.* 2006).

Randia ferox is traditionally employed to treat diarrhea, intestinal colics, and pneumonia (Carvalho 2008). The aqueous extract de *R. ferox* leaves show high *in vitro* antioxidant DPPH activity (IC_{50} = 79.26 µg/mL). The cytotoxicity and genotoxicity of the *R. ferox* extract were evaluated in different cell lines. Peripheral blood mononuclear cells treated for 24 h showed normal cell viability. All evaluated concentrations reduced the Reactive Oxygen Species (ROS) levels without affecting the Nitric Oxide (NO) levels. In addition, most tested concentrations did not affect the release of double-strand DNA (dsDNA). Thus, it is suggested that aqueous extract *R. ferox* is safe and has the potential to treat diverse illnesses/ symptoms (Pappis *et al.* 2021).

Increasing knowledge about phytochemical composition and biological activities is necessary to produce high-value products through modern biotechnological tools. Based on the demonstrated characteristics of *R. echinocarpa*, plant cell tissue culture was employed to produce calli and plantlets toward the *in vitro* production of antioxidants and other bioactive metabolites (Valenzuela-Atondo *et. al.* 2020).

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Supplementary material

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Appendix 1. Biological activities of extracts and compounds of *Randia* species.

Biological activity	Plant	Part of the plant	Type of extract/ Preparation	Model/Method	Result	Reference
Antibacterial	*Randia echinocarpa* Moc. & Sessé ex DC.	Leaves and stems	AE	*Staphylococcus aureus, Streptococcus faecalis, Escherichia coli, Proteus mirabilis, Salmonella* Typhi and *Candida albicans*	MIC = 8 mg/mL for *S. aureus* and *S. faecalis*, MIC > 8 mg/mL for the rest	Salinas- Sánchez *et al.* 2009
	Randia aculeata L.	Leaves	ME, HE and DME	*Staphylococcus aureus, Staphylococcus aureus*-MRSA, *Streptococcus pyogenes, Escherichia coli and Salmonella* Typhimurium	None of extracts had an inhibitory affect	Martínez-Ceja *et al.* 2022
	Randia hebecarpa Benth.	Leaves	ME	*Mycobacterium tuberculosis*	MIC > 250 µg/mL	Araujo *et al.* 2014
Antiparasitic	*Randia armata* (Sw.) DC.	Plant	HEE	Larvae of *Rhipicephalus* (*Boophilus*) *microplus*	25, 28, and 75 % efficacy at [5], [20] and [40] % of HEE	dos Santos *et al.* 2013
Antifungal	*Randia longiloba* Hemsl.	Leaves	EE	*Alternaria tagetica, Colletotrichum gloeosporioides, Fusarium oxysporum* and *Rhizopus* sp.	Only active against *Rhizopus* sp.	Gamboa-Angulo *et al.* 2008
	Randia obcordata S. Watson	Stems and root	EE	*Alternaria tagetica, Colletotrichum gloeosporioides, Fusarium oxysporum*, and *Rhizopus sp*.	Effect against *A. tagetica, F. oxysporum* and *Rhizopus* sp.	
	Randia aculeata var. aculeata L.	Leaves and root				
	Randia nitida (Kunth) DC.	Leaves	ME, HF, DMF, and EAF	*Colletotrichum truncatum*, *Rhizoctonia solani* Kühn and *Sclerotinia sclerotiorum*	Activity order was as follows: EAF>DMF>HF, evaluated at [160 µg/mL]	Cruz-Silva *et al.* 2016
Nematicide	*Randia echinocarpa* Moc. & Sessé ex DC.	Flowers	AE	*Haemonchus contortus* L3	Effect at [20 mg/mL], % larval mortality 3.33 ± 1.76, 37 ± 11.83, and 25.33 ± 3.38 after 24, 48, and 72 h respectively	López-Aroche *et al.* 2008
	Randia longiloba Hemsl.	Leaves, root, and stems	EE	*Meloidogyne incognita* J2	The EE of leaves induced higher mortality at 72 h: 95% at 500 ppm and 25% at 250 ppm	Cristóbal-Alejo *et al.* 2006
	Randia obcordata S. Watson				The EE of stems induced higher mortality at 72 h, 63% at 500 ppm	
	Randia aculeata L. *var. aculeata*				The EE of leaves show higher % mortality of 95 and 8 at [500] and [250] ppm at 72 h	

Biological activity	Plant	Part of the plant	Type of extract/ Preparation	Model/Method	Result	Reference
Antioxidant	*Randia echinocarpa* Moc. & Sessé ex DC.	Fruit	ME, HE, CE, and AQE	β-carotene bleaching	AQE showed the highest AA *in vitro*	Santos-Cervantes *et al.* 2007
			Partially purified soluble melanins	ABTS and FRAP	High AA *in vitro*	Cuevas-Juárez *et al.* 2014
			Purified insoluble melanins	FRAP, ABTS and *Saccharomyces cerevisiae*	High AA *in vitro* and showed no dose-response effect on the oxidizing agent H_2O_2	Montes-Avila *et al.* 2018
	Randia ferox (Cham & Schltdl) DC.	Leaves	AQE	DPPH	High AA *in vitro*	Pappis *et al.* 2021
	Randia aculeata L.	Leaves	ME, HE and DME	DPPH and ABTS	High AA *in vitro*	Martínez-Ceja *et al.* 2022
	Randia hebecarpa Benth.	Leaves	ME, AQF, HF and EAF	DPPH and linoleic acid peroxidation	ME, AQF, and EAF showed the same effect as BHT, and EAF had the best IC_{50} = 60.8 µg/mL	Nazari *et al.* 2006
	Randia monantha Benth.	Pulp and seed	ME and EE	FRAP, DPPH, ABTS and reducing power.	High AA *in vitro*	Juárez-Trujillo *et al.* 2018
	Randia. armata (Sw.) DC.	Pulp	HME	DPPH and ABTS	High AA *in vitro*	Chaves *et al.*2015
Anti-inflammatory	*Randia hebecarpa* Benth.	Leaves	ME	Albino rats	No significant effect on inflammation reduction	Nazari *et al.* 2006
	Randia aculeata L.	Leaves	ME, HE and DME	RAW 264.7 cell line	All extracts showed a dose-dependent effect in the inhibition of NO production	Martínez-Ceja *et al.* 2022
Cicatrizing	*Randia echinocarpa* Moc. & Sessé ex DC.	Fruit	AQE, CE, and BE	Wistar rats	AQE increased healing and clotting time	Pérez *et al.* 1993
Antidiabetic	*Randia echinocarpa* Moc. & Sessé ex DC.	Fruit	Aqueous decoction	Rabbits	Not significant decrease in hypoglycemic peak	Alarcón-Aguilera *et al.* 1998
			Partially purified soluble melanins	Inhibition of α-glucosidase	High inhibition of α-glucosidase IC_{50}= 1.00 ± 0,010 and 1.17 ± 0.069 mg / mL extracted at room and boiling temperature, acarbose IC_{50}= 8.38 mg / mL.	Cuevas-Juárez *et al.* 2014
Antimutagenic	*Randia echinocarpa* Moc. & Sessé ex DC.	Fruit	AQE	*Salmonella enterica* serovar Typhimurium YG1024	Inhibited the 1-NP mutagenicity by 32 and 56%	Santos-Cervantes *et al.* 2007
			ME, AQF, HF, EAF, and CF	*Salmonella enterica* serovar Typhimurium YG1024	The HF was the most active and contains palmitic acid, linoleic acid, and β-sitosterol compounds	Cano-Campos *et al.* 2011

Biological activity	Plant	Part of the plant	Type of extract/ Preparation	Model/Method	Result	Reference
Proliferative	*Randia echinocarpa* Moc. & Sessé ex DC.	Fruit	Purified insoluble melanins	Splenocytes of BALB/c mice	It showed a significant difference of [25 µg/mL] with respect to LPS and PHA positive controls	Montes-Avila *et al.* 2018
Diuretic	*Randia echinocarpa* Moc. & Sessé ex DC.	Fruit	AQE	Wistar rats	Increased urine volume	Vargas-Solís & Pérez-Gutiérrez 2002
Antinociceptive	*Randia aculeata* L.	Fruit	EE	Wistar rats	Analgesic effect at visceral level	Pérez-Espinosa *et al.* 2015
Antivenom	*Randia aculeata* L.	Fruit	EE	CD1 mice	Decreased atrophy and bleeding in the lungs	Torres-Schwartz *et al.* 2018
					Decreased tissue damage and red blood cells	Gallardo-Casas *et al.* 2012
Toxicity	*Randia monantha* Benth.	Fruit, leaves, and stems	EE	*Artemia salina* L.	No toxicity up to 1 mg/mL	Méndez-Valenzuela & Hernández-Martínez 2009
	Randia aculeata L.	Fruit	EE	Mice	No toxicity up to 1000 mg/kg b.w.	Pérez-Espinosa *et al.* 2015
	Randia echinocarpa Moc. & Sessé ex DC.	Fruit	Partially purified soluble melanins	BALB/c mice	No toxicity up to 5 g/kg b.w.	Gil-Avilés *et al.* 2019
Cytotoxicity and Genotoxicity	*Randia ferox* (Cham & Schltdl) DC.	Leaves	AQE	Cell lines Vero, RAW 267.4 HFF-1, and U-87 MG	The extract did not affect cellular proliferation, decreased ROS, and increased NO.	Pappis *et al.* 2021
					Extract concentration did not affect dsDNA release compared to untreated cells	

AA, antioxidant activity; AE, acetonic extract; AQE, aqueous extract; AQF, aqueous fraction; BE, benzene extract; BHT, butylated hydroxy toluene; CE, chloroformic extract; CF, chloroformic fraction; DME, dichloromethane extract; DMF, dichloromethane fraction; dsDNA, doble stranded DNA; EAF, ethyl acetate fraction; EE, ethanolic extract; HE, hexanic extract; HEE, hydroethanol extract; HF, hexanic fraction; HME, hydromethanol extract; LPS, lipopolysaccharide; ME, methanol extract; NO, nitric oxide; PHA, phytohemagglutinin; ROS, reactive oxygen species.