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Traditional Uses, Phytochemistry, and Antimicrobial Activities of *Eugenia* Species – A Review

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ABSTRACT

Antimicrobial resistance is a critical health problem, and pathogens responsible for common infections have developed resistance to antimicrobials, posing a threat to global health and placing a huge burden on health services. During the past two decades, the search for new bioactive agents in nature has become extremely important for promoting health and in the development of more efficient antimicrobials. The genus *Eugenia* is one of the largest in the Myrtaceae family, comprising approximately 1000 species from Mexico to Argentina, with a few species distributed in Australia and Africa. *Eugenia* species are used in folk medicine, with antidiabetic, antirheumatic, antipyretic, anti-inflammatory, antidiarrheal, antifungal, and antibacterial properties. This study systematically reviews the *Eugenia* species to compile the phytochemical composition and antimicrobial effects. In addition, we provide information regarding the traditional uses and cytotoxic activity of *Eugenia* species. We conducted a systematic literature search of specialized databases (Web of Science, Scielo, Lilacs, Pubmed, Science Direct, Scopus) and selected articles published between 1973 and 2015 using *Eugenia* and antimicrobial activity, *Eugenia* and toxicity, and *Eugenia* and chemical composition as key words. Ninety-three studies were included, and the phytochemical analyses from these studies show that *Eugenia* species are a rich source of flavonoids, tannins, triterpenes, and sesquiterpenes. Chemical constituents play an apparent role in the antimicrobial effects and reinforce the known antimicrobial potential of the *Eugenia* genus. It is worth mentioning that some *Eugenia* species cause significant cytotoxicity.

Introduction

The Myrtaceae family is a group of dicotyledonous plants comprising approximately 130 genera and 3800–5800 species of shrubs or trees. It has been found in all continents except Antarctica, with predominance in the tropical and subtropical regions of the world [1–3]. Approximately one-third of the species in this family belong to the genus *Eugenia*, with around 1000 species distributed from southern Mexico to northern Argentina. It is estimated that 350 species are native to Brazil, with a small number of species being found in Africa. The plants of this genus are perennial trees or shrubs with spherical and edible fruits [4, 5] that have diverse pharmacological activities, including antidiabetic, antirheumatic, antidiarrheal, antipyretic, anti-inflammatory, antifungal, antibacterial, antioxidant, and cytotoxic properties. In addition, they have also been used to treat diseases of the stomach [6, 7].

Several known species from the *Eugenia* genus have been reported for their medicinal uses and chemical constituents, as well as antimicrobial and cytotoxic activities, including *Eugenia axillaris* (SW.) Willd., *Eugenia beaurepaireana* (Kiaersk.) D.Legrand, *Eugenia brasiliensis* Lam., *Eugenia dysenterica* DC., *Eugenia punicifolia* (Kunth) DC., *Eugenia pyriformis* Cambess., *Eugenia rigida* DC., *Eugenia sulcata* Spring ex Mart, *Eugenia umbelliflora* O.Berg, and *Euge-*

▶ **Table 1** Data on the traditional use of *Eugenia* species in the studies selected through this systematic review.

Species	Extracts and/or part of the plant	Traditional uses	References
E. axillaris (SW.) Willd.	Decoction of the leafy branch tips	Aphrodisiac, antidiarrheic, and for bathing women after childbirth	[17, 18]
E. beaurepaireana (Kiaersk.) D.Legrand	No date	Anti-inflammatory, antidiarrheic, diuretic, antirheumatic, anti-febrile, antidiabetic, and antirheumatism	[7]
E. brasiliensis Lam.	Leaves, fruits, and bark infusions	Stomach diseases, antirheumatic, anti-inflammatory, antidiarrheic, and diuretic	[4, 7, 19]
E. dysenterica DC.	Leaves	Anti-inflammatory, antimicrobial, antihypertensive, antidiarrheic, purgative	[7, 8, 16, 18]
E. punicifolia (Kunth) DC.	No date	Hypoglycemic activity	[8]
E. pyriformis Cambess.	Leaves	Treatment for gout	[20]
E. rigida DC.	No date	Leukemia	[5]
E. sulcata Spring ex Mart	No date	Fever treatment and antidiarrheic	[21]
E. umbelliflora O.Berg	Aerial parts	Infections, inflammation, and diabetes	[22]
E. uniflora L.	Leaf and fruit infusions, hydro-alcoholic leaves extract	Exciting, febrifuges, antidysenteric, antidiarrheic, antihypertensive, antirheumatic, anti-inflammatory, hyperlipidemia, hypotriglyceridemic, hypoglycemic, bronchitis, coughs, fevers, anxiety, diuretic, stomach diseases, digestive disorders, verminosis, gout, vaso-relaxant, antioxidant, and with antimicrobial property	[7, 8, 11, 14–16, 23–31]

nia uniflora L., among others. Thus, the aim of the present study was to develop a systematic review to analyze whether plants in the *Eugenia* genus have antimicrobial and cytotoxic properties *in vitro*, as well as the chemical composition of the various species. This review demonstrates the importance of the *Eugenia* genus in providing secondary metabolites of pharmacological interest and establishes that further research of many species would be beneficial.

Search Strategy

This systematic review was carried out using bibliographic research in 2016, and includes articles published from 1973 to 2015. We used specialized databases (Web of Science, Scielo, Lilacs, Pubmed, Science Direct, Scopus, and an article selected from Google Scholar) and included *Eugenia* and antimicrobial activity, *Eugenia* and toxicity, and *Eugenia* and chemical composition as key words for the literature searches. The articles included in this manuscript were original articles. Further, articles containing isolated compounds identified via spectroscopic techniques and articles reporting antimicrobial and cytotoxic activity were included. Species of the genus *Eugenia* were selected according to the classification of *Kew Royal Botanic Garden* and *The Plant List*, excluding species not belonging to the genus. Duplicate items or items that were not within the review area of interest were excluded. The three major compounds identified in the species studied were selected for the chemical composition of the essential oil. The Endnote program was used to store the selected articles. Initially, two researchers selected articles by titles, and article abstracts were evaluated. Finally, the complete articles were read in whole, and references that met the inclusion criteria were included in the review. Disagreements were resolved through consensus among researchers, and in the case of nonagreement, a third reviewer was consulted.

Initially, 1057 articles were selected. We excluded 227 duplicate articles, 53 of which were excluded with the help of an Endnote tool and 174 of which were manually excluded. Of the original 1057 articles, 673 did not fit the inclusion criteria and were excluded after reading the titles and abstracts, while 64 were excluded after reading the complete article. As such, this review includes 93 articles that reported the isolation of phytoconstituents, as well as the antimicrobial and cytotoxic properties of species from the genus *Eugenia*.

The *Eugenia* Genus

The *Eugenia* genus is considered the fourth most important genus of the family Myrtaceae for the production of essential oils after the *Eucalyptus, Melaleuca*, and *Psidium* genera. Essential oils from *Eugenia* species comprise approximately 300 compounds that have been previously identified, with cyclic sesquiterpenes predominating and monoterpenes found in smaller quantities. A few species produce aliphatic and aromatic compounds. These various types of terpenoid compounds are used in the pharmaceutical, cosmetic, and agrochemical industries [6, 8]. In addition to essential oils, flavonoids, triterpenoids, and tannins have also been identified in *Eugenia* species. Among the flavonoids, there is a predominance of polyhydroxy flavanols, and most of the isolated pentacyclic triterpenes have a lupan or oleanane skeleton [4].

The most studied *Eugenia* species are *E. uniflora* L. and *E. brasiliensis* Lam., which produce exotic fruits such as “pitanga” (*E. uniflora* L.) [9] and “grumixama” or “Brazilian cherry” (*E. brasiliensis* Lam.) [10]. These fruits are consumed fresh or in the form of juices and jellies and have high nutritional value, as well as being rich

▶ **Table 2** Chemical composition of essential oils from *Eugenia* species in the studies selected through this systematic review.

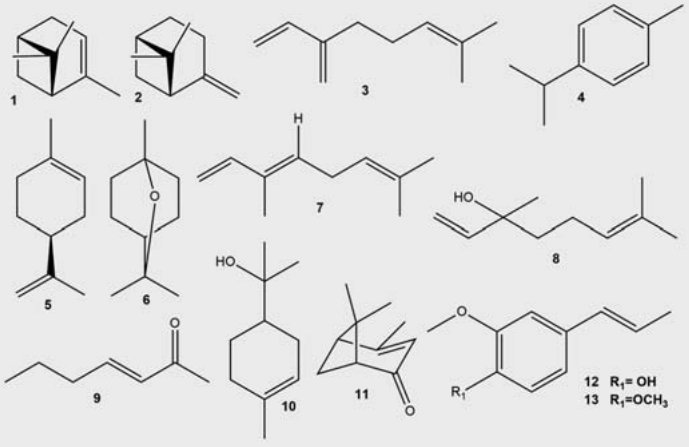
N_o	Species	Part of plant	Major components	References
1	*E. arenosa* Mattos	Leaves	Farnesyl acetate (70.4%) **59**, Aromadrendene (11.7%) **20**, Globulol (7.1%) **42**	[31]
2	*E. argentea* Bedd.	Leaves	*β*-Caryophyllene (18.0%) **17**, *δ*-Cadinene (7.8%) **32**, Germacrene D (7.1%) **24**	[15]
3	*E. austin-smithii* Standl.	Leaves	Trans-2-hexenal (33.6%) **9**, *α*-Terpineol (7.8%) **10**, Germacrene D (7.1%) **24**	[32]
4	*E. axillaris* (SW.) Willd.	Leaves	Guaiol (35.4%) **44**, *α*-Pinene (15.5%) **1**, Germacrene D (12.1%) **24**	[17, 33]
5	*E. bacopari* D.Legrand	Leaves	*δ*-Cadinene (15.8%) **32**, Aromandrendene (12.2%) **20**, Viridiflorene (7.9%) **27**	[34]
6	*E. beaurepaireana* (Kiaersk.) D.Legrand	Leaves	Bicyclogermacrene (14.3%) **29**, Germacrene D (8.6%) **24**, *β*-Caryophyllene (8.0%) **17**	[35, 36]
7	*E. biflora* (L.) DC.	Leaves	*β*-Pinene (27.85%) **2**, *α*-Pinene (27.34%) **1**, *β*-Caryophyllene (15.36%) **17**	[37]
8	*E. brasiliensis* Lam.	Leaves	Cubenol (33.1%) **52**, Trans-*α*-Bergamotene (19.0%) **18**, Sphatulenol (18.17%) **40**	[10, 19]
9	*E. burkartiana* (D.Legrand) D.Legrand	Leaves	Bicyclogermacrene (14.2%) **29**, Germacrene D (8.8%) **24**, *β*-Caryophyllene (7.8%) **17**	[34]
10	*E. calycina* Cambess.	Leaves	Bicyclogermacrene (19.3%) (**29**), Spathulenol (21.36%) **40**, *β*-Caryophyllene (8.57%) **17**	[7]
11	*E. candolleana* DC.	Leaves	*δ*-Elemene (13.87%) **14**, Muurola-4,10(14)-dien-1*β*-ol (8.68%) **49**, 1-Epi-cubenol (7.59%) **48**	[38]
12	*E. cartagensis* O.Berg.	Leaves	Trans-2-hexenal (31.2%) **9** (E) *β*-Ocimene (16.2%) **7**, Germacrene D (12.3%) **24**	[39]
13	*E. catharinensis* D.Legrand	Leaves	Ethyl palmitate (10.5%) 63, Trans-*α*-Bergamotene (6.5%) **18**, *α*-Humulene (5.9%) **22**	[34]
14	*E. chlorophyla* O.Berg.	Stem	Caryophyllene oxide (17.2%) **41**, Globulol (16.5%) **42**, t-Muurolol (16.8%) **51**	[40]
		Leaves	Globulol (22.5%) **42**, *α* -Cadinol (9.4%) **35**, 1,10-di-epi-Cubenol (9.8%) **46**	
		Flowers	*β*-Caryophyllene (12.8%) **17**, *α*-Cadinol (10.1%) **35**, Caryophyllene oxide (8.9%) **41**	
15	*E. copacabanensis* Kiaersk.	Leaves	*β*-Pinene (50.4%) **2**, *α*-Pinene (20.2%) **1**, 1,10-di-epi-Cubenol (14.24%) **46**	[8, 38]
16	*E. cuprea* (O.Berg) Nied.	Leaves	Spathulenol (12.1%) **40**, *β*-Caryophyllene (9.2%) **17**, Caryophyllene oxide (8.7%) **41**	[31]
17	*E. dimorpha* O.Berg.	Leaves	*α*-Pinene (22.4%) **1**, *α*-Humulene (12.9%) **22**, 1,8-Cineole (9.9%) **6**	[34]
18	*E. dysenterica* DC.	Leaves	*γ*-Cadinene (27.0%) **31**, *β*-Caryophyllene (14.8%) **17**, *δ*-Cadinene (13.0%) **32**	[41]
19	*E. flavescens* DC.	Leaves	*α*-Curcumene (14.95%) **23**, *α*-Selinene (11.72%) **28**, *δ*-Cadinene (5.71%) **32**	[37]
20	*E. foetida* Pers.	Leaves	Caryophyllene oxide (14.8%) **41**, Caryophyllene alcohol (9.1%) **39**, *α*-Cadinol (6.0%) **35**	[42]
21	*E. haberi* Barrie	Leaves	*α*-Pinene (29.0%) **1**, *α*-Terpineol (19.4%) **10**, trans-2-Hexenal (11.2%) **9**	[32]
22	*E. hiemalis* Cambess.	Leaves	Bicyclogermacrene (37.7%) **29**, *β*-Caryophyllene (7.4%) **17**, Germacrene D (7.0%) **24**	[43]
23	*E. involucrata* DC.	Leaves	*β*-Caryophyllene (10.1%) **17**, Spathulenol (7.8%) **40**, *β*-Bisabolene (7.2%) **30**	[44]
24	*E. joensonii* Kausel	Leaves	5-epi-Paradisiol (8.4%) **45**, *δ*-Selinene (7.9%) **26**, *β*-Selinene (7.2%) **25**	[34]
25	*E. klappenbachiana* Mattos & D.Legrand	Leaves	Globulol (8.7%) **42**, Viridiflorene (6.9%) **27**, Spathulenol (5.9%) **40**	[45]
26	*E. langsdorfii* O.Berg	Leaves	Epi-Longipinanol (13.6%) **37**, *γ*-Eudesmol (12.3%) **58**, Limonene (11.8%) **5**	[46]
		Fruits	10-epi-Eudesmol (35.7%) **47**, 1,10-di-epi-Cubenol (15.6%) **46**, Caryophyllene oxide (7.5%) **41**	
27	*E. melanadenia* Krub & Urb.	Leaves	1,8-Cineole (45.3%) **6**, *α*-Terpineol (10.6%) **10**, p-Cymene (8.2%) **4**	[47]
28	*E. monteverdensis* Barrie	Leaves	*α*-Pinene (92.0%) **1**, Linalool (30.4%) **8**, trans-2-Hexenal (22.5%) **9**	[32, 48]
		Fruits	*α*-Pinene (55.1) **1**, Linalool (22.7%) **8**, Limonene (7.7%) **5**	
29	*E. moraviana* O.Berg.	Leaves	*β*-Caryophylene (14.5%) **17**, *β*-Elemene (11.8%) **16**, *α*-Copaene (7.9%) **15**	[45]
30	*E. multicostata* D.Legrand	Leaves	*α*-Pinene (16.1%) **1**, Spathulenol (10.7%) **40**, Globulol (8.7%) **42**	[31]
31	*E. neonitida* Sobral	Leaves	Bicyclogermacrene (24.3%) **29**, Germacrene D (18.7%) **24**, *β*-Caryophyllene (12.5%) **17**	[49]
32	*E. octopleura* Krug & Urb.	Leaves	*α*-Pinene (43.0%) **1**, Limonene (23.6%) **5**, (E)- *β*-Ocimene (5.1%) **7**	[50]
33	*E. patrisii* Vahl	Leaves	*β*-Bisabolene (16.52%) **30**, (E)-Muurola-3,5-diene (13.28%) **21**, *β*-Caryophyllene (11.07%) **17**	[37]
34	*E. piauhiensis* O.Berg	Leaves	*γ*-Elemene (17.48%) **19**, *β*-Caryophyllene (16.46%) **17**, Bicyclogermacrene (8.11%) **29**	[51]
35	*E. pitanga* (O.Berg) Nied.	Leaves	Germacrene D (29.3%) **24**, Bicyclogermacrene (22.4%) **29**, (E)-*β*-Ocimene (10.5%) **7**	[31]
36	*E. platysema* O.Berg	Leaves	*β*-Selinene (17.9%) **25**, Aromandrene (12.6%) **20**, 7-epi-*α*-Selinene (10.4%) **33**	[52]
37	*E. pluriflora* DC.	Leaves	(E)-nerolidol (24.6%) **36**, *α*-Pinene (24.0%) **1**, 1,8-Cineole (12.7%) **6**	[52]
38	*E. protenta* McVaugh	Leaves	Selin-11-en-4*α*-ol (18.3%) **54**, *β*-Elemene (16.9%) **16**, Germacrene D (15.6%) **24**	[53]

continued

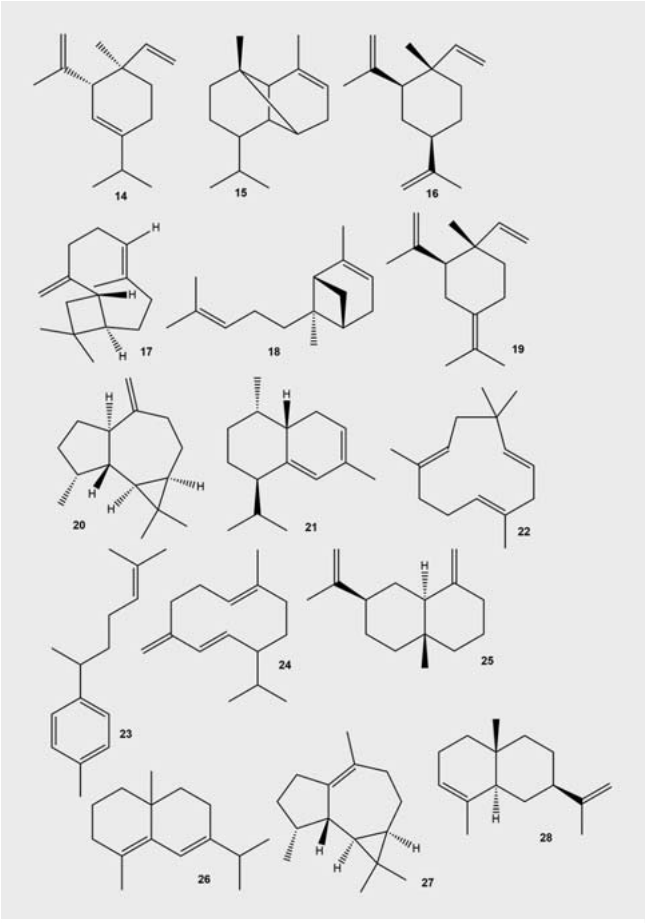
▶ **Table 2** *Continued*

N_o	Species	Part of plant	Major components	References
39	*E. punicifolia* (Kunth) DC.	Leaves	Linalool (61.2%) **8**, β-Caryophyllene (22.7%) **17**, α-Cadinol (10.6%) **35**	[54, 55]
40	*E. pyriformis* Cambess.	Leaves	β-Pinene (25.7%) **2**, Limonene (22.0%) **5**, 1,8-Cineole (14.7%) **6**	[56]
41	*E. ramboi* D.Legrand	Leaves	β-Elemene (10.6%) **16**, Bicyclogermacrene (9.7%) **29**, β-Caryophyllene (8.2%) **17**	[52]
42	*E. repanda* O.Berg	Leaves	β-Caryophyllene (16.3%) **17**, α-Humulene (10.2%) **22**, Bicyclogermacrene (9.4%) **29**	[45]
43	*E. rhombea* (O.Berg) Krug & Urb.	Leaves	Cubenol (12.6%) **52**, α-Cadinol (12.5%) **35**, α-Pinene (12.1%) **1**	[57]
44	*E. riedeliana* O.Berg	Leaves	Valerianol (28.1%) **53**, 10-epi-Eudesmol (12.6%) **47**, β-Caryophyllene (10.9%) **17**	[58]
45	*E. rocana* Britton & P.Wilson	Leaves	Caryophyllene oxide (57.7%) **41**, 14-hydroxy-9-epi-β-Caryophyllene (10.3%) **55**, Verbenone (10.2%) **11**	[59]
46	*Eugenia* sp.	Leaves	β-Caryophyllene (49.0%) **17**, 1,8-Cineole (26.0%) **6**, Zingiberene (24.7%) **34**	[10, 32]
47	*E. speciosa* Cambess.	Leaves	α-Pinene (47.3%) **1**, Limonene (23.0%) **5**, Bicyclogermacrene (11.1%) **29**	[31]
48	*E. stigmatosa* DC.	Leaves	Physeteric acid (90.5%) **62**, δ-Tetradecalactone (2.2%) **60**, γ-Tetradecalactone (1.3%) **61**	[43]
49	*E. stitipata* McVaught	Leaves	Germacrene D (38.3%) **24**, β-Caryophyllene (22.7%) **17**, Caryophyllene oxide (15.4%) **41**	[60, 61]
50	*E. sulcata* Spring ex Mart	Leaves	α-Pinene (34.2%) **1**, β-Caryophyllene (24.6%) **17**, 1,8-Cineole (19.0%) **6**	[21, 31, 55]
51	*E. supraaxilaris* Spreng.	Leaves	Limonene (21.8%) **5**, β-Pinene (17.4%) **2**, α-Humulene (8.7%) **22**	[1]
		Fruits	Eugenol (35.5%) **12**, *Methyl* eugenol (32.8%) **13**, Myrcene (12.8%) **3**	
52	*E. umbeliflora* O.Berg	Leaves	α-Pinene (24.7%) **1**, Viridiflorol (17.7%) **43**, β-Pinene (13.2%) **2**	[52, 62]
53	*E. uniflora* L.	Leaves	Curzerene (47.3%) **38**, Selina1,3,7(11) trien-8-one (43%) **50**, Selina-1,3,7(11)-trien-8-one epoxide (29.0%) **57**	[13, 63]
		Fruits	Selina1,3,7(11) trien-8-one (48.2%) **50**, Curzerene (42.6%) **38**, Germacrone (17.3%) **56**	[27, 64]
54	*E. uruguayensis* Cambess.	Leaves	α-Pinene (23.5%) **1**, β-Pinene (11.8%) **2**, β-Caryophyllene (9.5%) **17**	[52]
55	*E. xiririicana* Mattos	Leaves	Spathulenol (15.4%) **40**, β-Pinene (14.1%) **2**, Globulol (8.6%) **42**	[31]
56	*E. zuchowskiae* Barrie	Leaves	α-Pinene (28.3%) **1**, β-Caryophyllene (13.2%) **17**, α-Humulene (13.1%) **22**	[18, 32]

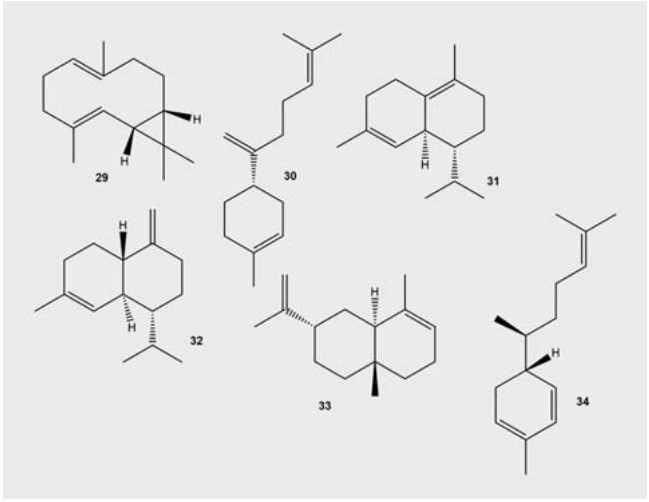
Arabic numeral in bold corresponds to the chemical structures shown in ▶ **Figs. 1–6**



▶ **Fig. 1** Chemical structures of monoterpenes α-pinene (**1**), β-pinene (**2**), myrcene (**3**), cymene (**4**), limonene (**5**), 1,8-cineole (**6**), (E)-β-ocimene (**7**), linalool (**8**), trans-2-hexenal (**9**), α-terpineol (**10**), verbenone (**11**), eugenol (**12**), and *Methyl* eugenol (**13**) isolated from *Eugenia* species.



▶ **Fig. 2** Structures of sesquiterpene hydrocarbons δ-elemene (**14**), α-copaene (**15**), β-elemene (**16**), β-caryophyllene (**17**), trans-α-bergamotene (**18**), γ-elemene (**19**), aromandrene (**20**), (E)-muurola-3,5-diene (**21**), α-humulene (**22**), α-curcumene (**23**), germacrene d (**24**), β-selinene (**25**), δ-selinene (**26**), viridiflorene (**27**), and α-selinene (**28**) isolated from *Eugenia* species.



▶ **Fig. 3** Structures of sesquiterpene hydrocarbons bicyclogermacrene (**29**), β-bisabolene (**30**), γ-cadinene (**31**), β-cadinene (**32**), 7-epi-α-selinene (**33**), and zingiberene (**34**) isolated from *Eugenia* species.

in calcium, phosphorous, provitamin A, vitamin C, carotenoids, and phenolic compounds (anthocyanins) [11]. In addition, these compounds have therapeutic properties that are widely used in folk medicine, such as diuretic, antirheumatic, antipyretic, antidiarrheal, and antidiabetic properties [12, 13]. The essential oils are used in the Brazilian cosmetic industry, attributable to their astringent properties and pleasant smell [14].

Traditional uses

In traditional medicine, most of the plants of the genus *Eugenia* have been used to treat a wide variety of ailments such as infectious diseases, intestinal infections, and gastrointestinal disorders, as well as in the treatment of wounds or as repellents or insecticides against domestic and agricultural pests [15, 16]. The traditional uses of *Eugenia* species are described in ▶ **Table 1**.

Phytochemical constituents of *Eugenia* genus

An investigation of the chemical constituents of *Eugenia* species resulted in the isolation and identification of sesquiterpenes, monoterpenes, aliphatic compounds, triterpenes, flavonoids, tannins, and cyanidins.

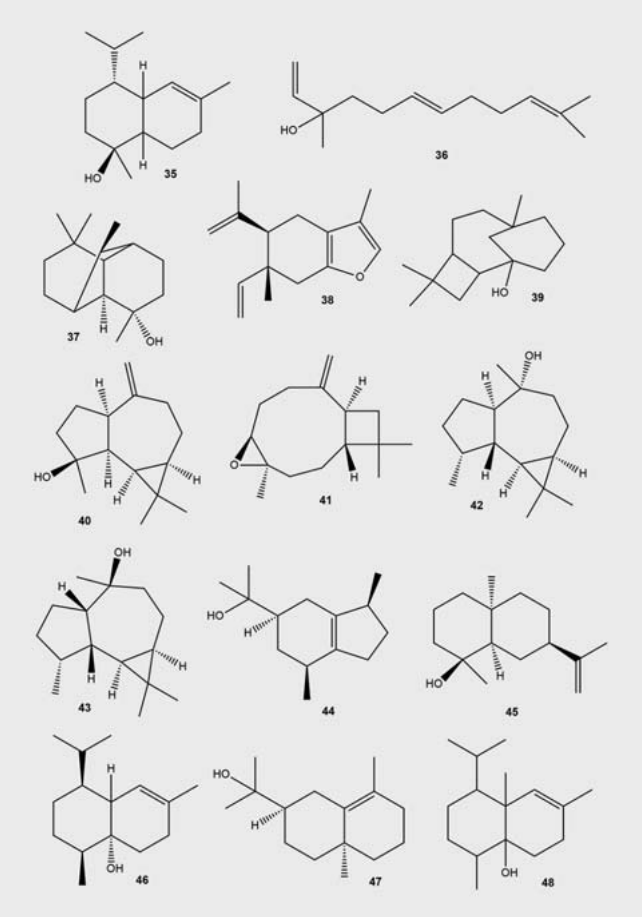
Essential oils

To obtain the essential oils, fresh samples of *Eugenia* species are collected and then identified, and an exsiccated sample is deposited in an herbarium. Most reports focus on the composition of essential oils from the plant leaves, however, in some studies, the stem, fruit, and flowers were analyzed. The most commonly used extraction processes were hydrodistillation and supercritical fluid extraction. The compounds were characterized using mass spectrometry, retention indexes, and retention times. We compared the results of each study to the current literature and spectra from databases.

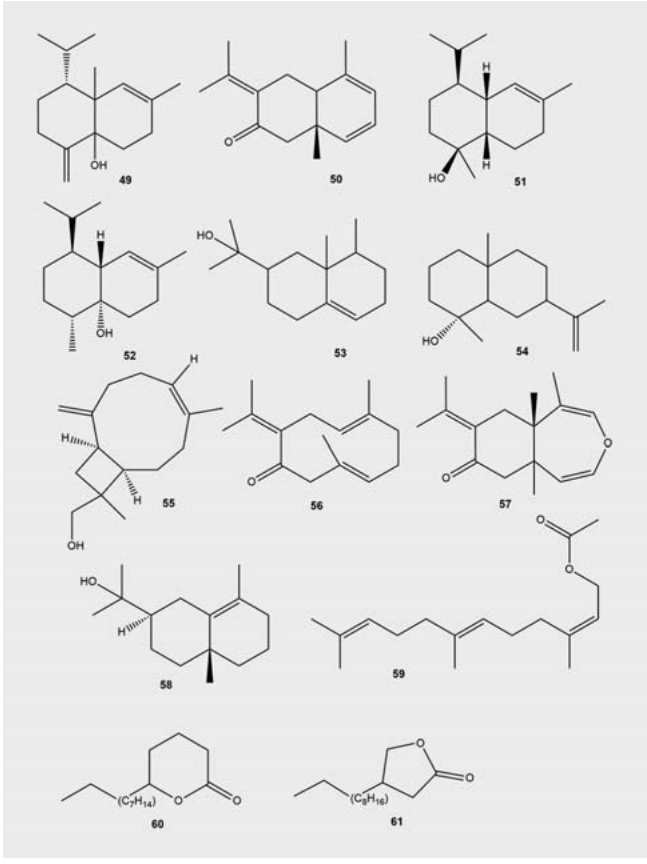
The essential oils from 56 species of *Eugenia* were analyzed, and approximately 500 compounds were identified. Sesquiterpenes (hydrocarbons and oxygen derivatives) were found and classified as the main class of volatile constituents, together with monoterpenes in smaller amounts. Some species produce small amounts of aromatic and aliphatic compounds, with concentrations below 1%. However, 90.0% of the compounds identified in *Eugenia stigmatosa* DC. were aliphatic compounds. Further, the aliphatic compounds from *Eugenia burkatiana* D.Legrand (7.9%), *Eugenia catharinensis* D.Legrand (10.5%), and *Eugenia joensonii* Kausel (14.6%) differed from the other species analyzed. The amount of each component is given as a percentage of the total oil and, in general, 80–90% of the oil was identified. The essential oils from *Eugenia* species are characterized by chemical diversity (▶ **Table 2**), and their molecules are shown in ▶ **Figs. 1–6**.

Triterpenes

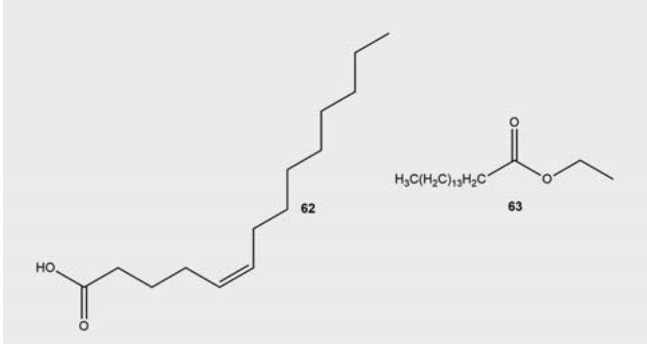
The reported triterpenes were isolated from the stem and leaves of five species of *Eugenia* and are described in ▶ **Table 3**, and their structures are shown in ▶ **Fig. 7**. The triterpenic acids present in



▶ **Fig. 4** Structures of oxigenated sesquiterpene α-cadinol (**35**), (E)-nerolidol (**36**), epi-longipinanol (**37**), Curzerene (**38**), Caryophyllene alcohol (**39**), Spathulenol (**40**), Caryophyllene oxide (**41**), Globulol (**42**), Viridiflorol (**43**), Guaiol (**44**), 5-epi-paradisiol (**45**), 1,10-di-epi-cubenol (**46**), 10-epi-Eudesmol (**47**), and 1-epi-cubenol (**48**) isolated from *Eugenia* species.



▶ **Fig. 5** Structures of oxigenated sesquiterpene muurola-4,10(14)-dien-1β-ol (**49**), selina1,3,7(11) trien-8-one (**50**), t-muurolol (**51**), cubenol (**52**), valerianol (**53**), selin-11-en-4α-ol (**54**), 14-hydroxy-9-epi-β-caryophyllene (**55**), germacrone (**56**), selina-1,3,7(11)-trien-8-one epoxide (**57**), γ-eudesmol (**58**), farnesyl acetate (**59**), tetradecalactone (**60**), and γ-tetradecalactone (**61**) isolated from *Eugenia* species.



▶ **Fig. 6** Structures of aliphatic compounds physeteric acid (**62**) and ethyl palmitate (**63**) isolated from *Eugenia* species.

many botanical families have also been isolated from species in the *Eugenia* genus, including betulinic acid, which has several biological properties, including cytotoxic and anticancer potential [65]. Other compounds, such as α, β-amirins, have been identified in *Eugenia* species. The structural characteristics of the compounds were determined via ^{1}H and ^{13}C nuclear magnetic resonance spectroscopy and are compared to experimental data described in the literature.

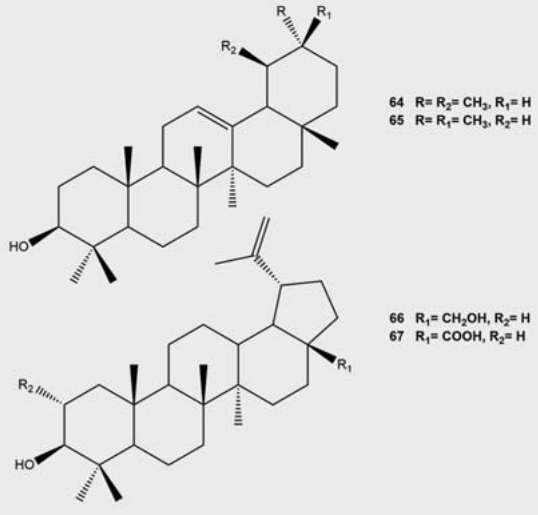
Polyphenols and cyanidins

Several species of *Eugenia* are used in traditional medicine as antibacterial and anti-inflammatory agents, attributable to high concentrations of polyphenolic compounds, hydrolysable tannins, and flavonoids. Natural phytoalexins (also called stilbenes) having several important biological activities, including anticancer properties, were isolated from *E. rigida*. The first stilbene reactant isolated from the genus *Eugenia* was (Z)-3,4,3′,5′-tetramethoxystilbene [5]. Further, euglobals were found in *E. umbelliflora*. Euglobals are substances that occur exclusively in the *Eucalyptus* genus of the family Myrtaceae and have known biological activities, including chemoprotective, antileishmanial, and antimalarial properties [67]. These compounds are described in ▶ **Table 3**, and their chemical structures are shown in ▶ **Figs. 8–10**.

▶ **Table 3** Isolated compounds from *Eugenia* species in the studies selected through this systematic review.

Species	Part of plant	Components	References
E. beaurepaireana (Kiaersk.) D.Legrand	Leaves	*α*-Amirin **64** *β*-Amirin **65**	[36]
E. brasiliensis Lam.	Leaves	*α*-Amirin **64** *β*-Amirin **65** Betulin or 3*β*,28-dihydroxy-lup-20(29)-ene **66** Quercetin or 3,5,7,3′,4′-Pentahydroxyflavone **70** Catechin or (+)-(2*R*,3*S*)-5,7,3′,4′-Tetrahydroxyflavan-3-ol **68** Gallocatechin or (+)-(2*R*,3*S*)- 5,7,3′,4′,5′-Pentahydroxyflavan-3 ol **69**	[4]
E. dysenterica DC.	Leaves	Procyanidin-B1 **71** Catechin **68** Dimeric procyanidin gallate **72**	[66]
E. florida DC.	Leaves	Betulinic acid **64**	[65]
E. rigida DC.	Leaves	(Z)- 3,4,3′,5′ -Tetramethoxystilbene **73**	[5]
		(E)- 3,4,3′,5′ -Tetramethoxystilbene **74**	
		(Z)- 3,5,4′ -Trimethoxystilbene **75**	
		(E)- 3,5,4′ -Trimethoxystilbene **76**	
E. umbelliflora O.Berg.	Leaves	Taxaferol Mixture of *α*- and *β*-Amirin **64** and **65** Mixture of Betulin and Betulinic acid **66** and **67** Betulinic acid **67**	[22]
	Fruits	Trimethoxy ellagic acid **77** Eugenial A similar to Euglobal A **78** Eugenial B similar to Euglobal B **79** Delphinidin 3-O-*β*-glucopyranoside **80** Cyanidin 3-O-*β*-glucopyranoside **81** Petunidin 3-glucoside **82** Pelargonidin 3-glucoside **83** Peonidin 3-glucoside **84** Malvidin 3- glucoside **85**	[22, 67, 68]

Arabic numeral in bold corresponds to the chemical structures shown in ▶ **Figs. 7–10**



▶ **Fig. 7** Structures of triterpenes isolates *α*-amirin (**64**), *β*-amirin (**65**), betulin (**66**), and betulinic acid (**67**) isolated from *Eugenia* species.

Biological activities

Antimicrobial activity

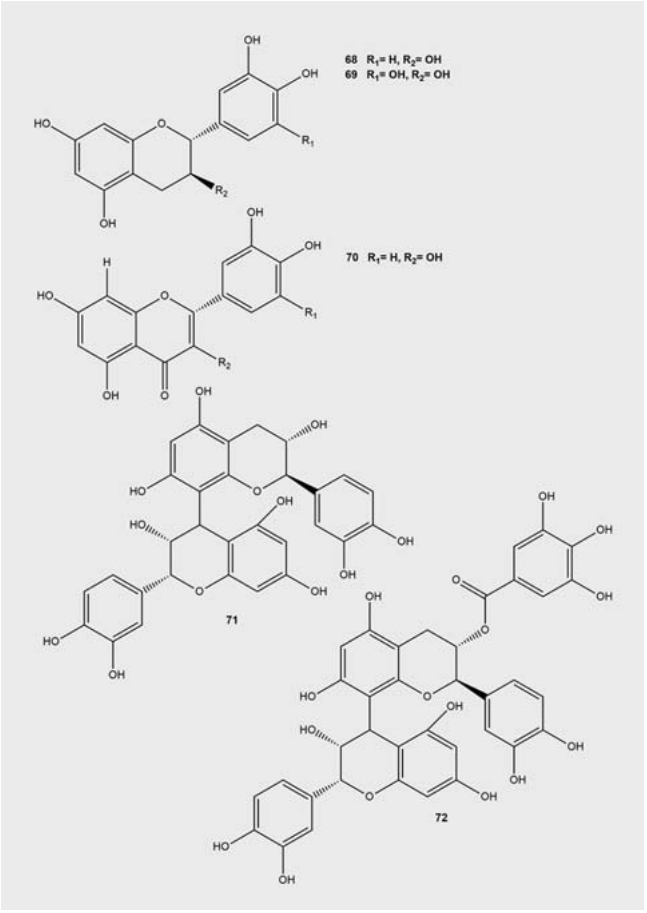
Some *Eugenia* species were investigated for their antibacterial and antifungal activities. Studies of the antimicrobial activity of *Eugenia* species are reported in ▶ **Table 4**.

Preparations of essential oils, leaf extracts, stems, and seeds of *Eugenia* species have been widely researched for their activities against gram-positive and gram-negative bacteria, as well as some species of yeast-like fungi, and compared to the activity of standard drugs. There are few studies on the antimicrobial activity of the isolated compounds.

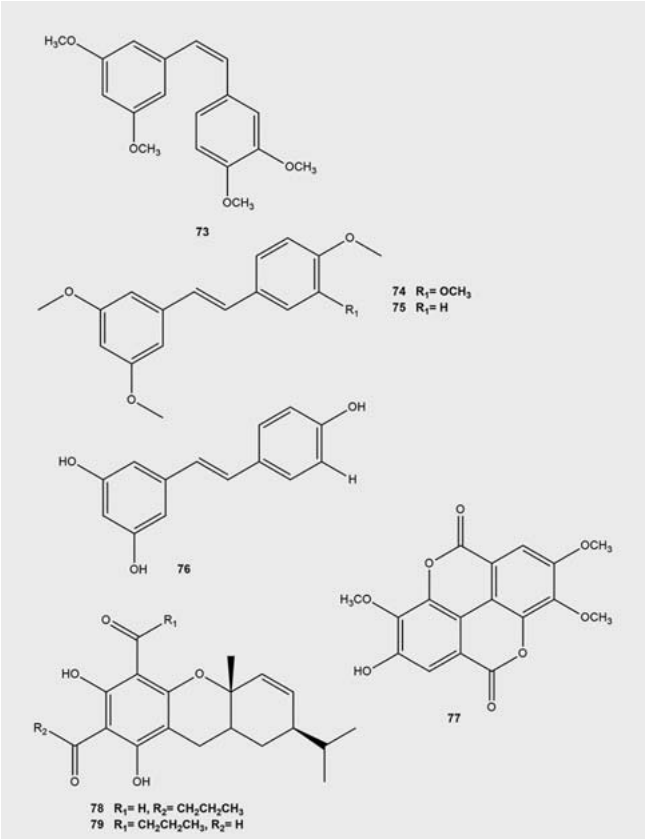
Different antimicrobial activity assays with different antibiotic and antifungal controls were used, including agar diffusion, disc diffusion, bioautography, macrodilution, and microdilution.

Eugenia species were tested against ATCC and clinical isolates of gram-positive and gram-negative bacteria, as well as yeast-like fungi.

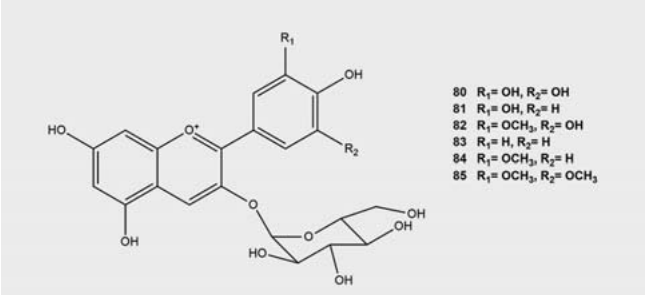
When the results were analyzed, the minimum inhibitory concentration (MIC) values were classified as having good inhibitory potential (less than 100 µg/mL), moderate inhibitory potential (between 100 and 500 µg/mL), weak inhibitory potential (between 500 and 1000 µg/mL), or the absence of inhibitory potential (above 1000 µg/mL) [20].



▶ **Fig. 8** Structures of polyphenolic compounds isolates catechin (**68**), gallocatechin (**69**), quercetin (**70**), procyanidin-B1 (**71**), and dimeric procyanidin gallate (**72**) isolated from *Eugenia* species.



▶ **Fig. 9** Structures of polyphenolic compounds isolates (Z)-3,4,3′,5′-tetramethoxystilbene (**73**), (E)-3,4,3′,5′-tetramethoxystilbene (**74**), (Z)-3,5,4′-trimethoxystilbene (**75**), (E)-3,5,4′-trimethoxystilbene (**76**), trimethoxy ellagic acid (**77**), eugenial A (**78**), and eugenial B (**79**) isolated from *Eugenia* species.



▶ **Fig. 10** Structures of cyanidins isolates delphinidin 3-O-*β*-glucopyranoside (**80**), cyanidin 3-O-*β*-glucopyranoside (**81**), petunidin 3-glucoside (**82**), pelargonidin 3-glucoside (**83**), peonidin 3-glucoside (**84**), and malvidin 3-glucoside (**85**) isolated from *Eugenia* species.

According to this established profile, the *Eugenia calycina, E. pyriformis, E. umbelliflora, E. uniflora*, and *Eugenia uruguayensis* species demonstrated good inhibitory potential against gram-positive and gram-negative bacteria, as well as yeast-like fungi. Samples of ethanolic, methanolic, and ketonic extracts and essential oil evaluated against strains of several microorganisms showed MIC values ranging from 7 to 100 µg/mL. The antimicrobial activity observed has been attributed to the presence of different bioactive compounds that have an impact on the growth and metabolism of microorganisms. Medicinal plants are known to produce antimicrobial substances belonging to many chemical classes, such as alkaloids, lignins, phenolic compounds, and terpenoids [20].

Moderate antimicrobial potential was observed against strains of gram-positive and gram-negative bacteria, as well as yeast-like fungi, with MIC values ranging from 156.2 to 500 µg/mL in several *Eugenia* species.

Antimicrobial activity in the presence of standard antibiotics

The compounds present in plants are capable of retarding or inhibiting the growth of bacteria, yeasts, and yeast-like fungi when used alone. However, there is also the possibility of using them in combination with conventional antimicrobials to improve their effectiveness [20]. The MIC of an *E. uniflora* ethanolic extract was reduced in the presence of the antibiotics amikacin, gentamicin, kanamycin, neomycin, and tobramycin at concentrations of 16 and 32 µg/mL when tested against clinical isolates of *Staphylococcus aureus*, demonstrating a synergistic effect [23]. However, the same samples evaluated against clinical isolates of *Escherichia coli*

▶ **Table 4** Antimicrobial activity of *Eugenia* species selected through this systematic review.

Eugenia species	Extraction/isolation procedure	Antimicrobial activity assay/control	Microrganisms and results	References
E. axillaris (SW.) Willd.	Essential oil of leaves/ hydrodistillation	Microdiluition method/ gentamicin sulfate and amphotericin B	*Bacillus cereus* ATCC 14579 = 625 µg/mL *Staphylococcus aureus* ATCC 29213 = 625 µg/mL *Pseudomonas aeruginosa* ATCC 27853 = 625 µg/mL *Escherichia coli* ATCC 25922 = 625 µg/mL *Candida albicans* ATCC 10231 = 625 µg/mL *Aspergillus niger* ATCC 16401 = 625 µg/mL	[17]
E. bacopari D. Legrand	Essential oil of leaves/ hydrodistillation	Agar diffusion method/ no date	*Staphylococcus aureus* ATCC 6538 p = 7–11 mm	[69]
E. beaure-paireana (Kiaersk.) D. Legrand	Essential oil of leaves/ hydrodistillation	Microdiluition method/ gentamycin	*Staphylococcus aureus* ATCC 25923 = 1110 µg/mL *Escherichia coli* ATCC 25922 = 556.6 µg/mL *Pseudomonas aeruginosa* ATCC 27853 = 278.3 µg/mL	[62]
E. brasiliensis Lam.	Essential oil of leaves/ hydrodistillation	Microdiluition method/ no date	*Staphylococcus saprophyticus* = 500–1000 µg/mL *Staphylococcus aureus* = 1000 µg/mL *Escherichia coli* = 1000 µg/mL *Pseudomonas aeruginosa* = 500–1000 µg/mL	[19]
	Essential oil of leaves/ hydrodistillation	Microdiluition method/ gentamycin	*Staphylococcus aureus* ATCC 25923 = 156.2 µg/mL *Escherichia coli* ATCC 25922 = 624.9 µg/mL *Pseudomonas aeruginosa* ATCC 27853 = 624.9 µg/mL	[62]
	ethanol extract/ maceration Fractions: hexane, dichloromethane, and ethyl acetate	Microdiluition method/ gentamycin	*Staphylococcus aureus* ATCC 25923 = 1560–6250 µg/mL *Escherichia coli* ATCC 25922 = 390–6250 µg/mL *Pseudomonas aeruginosa* ATCC 27853 = 780–6250 µg/mL	[4]
E. calycina Cambess.	Ethanol extract of bark and leaves/maceration Fractions were prepared from the ethanolic extracts (hexane, dichloromethane, and ethyl-acetate)	Microdiluition method/ vancomycin, gentamycin, and itraconazole	*Bacillus cereus* ATCC 14579 = 250–2000 µg/mL *Bacillus subtilis* ATCC 6633 = 1000–2000 µg/mL *Micrococcus roseus* ATCC 1740 = 1000–2000 µg/mL *Micrococcus luteus* ATCC 9341 = 1000–2000 µg/mL *Staphylococcus epidermidis* ATCC 12229 = 1000–2000 µg/mL *Staphylococcus aureus* ATCC 6538 = 500–2000 µg/mL *Staphylococcus aureus* ATCC 25923 = 1000–2000 µg/mL *Enterobacter aerogenes* ATCC 13048 = 1000–2000 µg/mL *Escherichia coli* ATCC 11229 = 1000–2000 µg/mL *Pseudomonas aeruginosa* ATCC 9027 = 2000 µg/mL *Pseudomonas aeruginosa* (clinical isolate) = 2000 µg/mL *Salmonella* spp. ATCC 19430 = 1000–2000 µg/mL *Serratia marcenscens* ATCC 14756 = 1000–2000 µg/mL *Candida parapsilosis* ATCC 22019 = 250–2000 µg/mL *Enterobacter cloacae* (clinical isolate) = 1000–2000 µg/mL *Candida parapsilosis* (clinical isolate) = 250–2000 µg/mL *Candida albicans* (clinical isolate) = 500–2000 µg/mL *Cryptococcus sp*. D (clinical isolate) = 15.62–2000 µg/mL *Cryptococcus gatti* (clinical isolate) = 31.2–2000 µg/mL *Cryptococcus neoformans* (clinical isolate) = 31.2–2000 µg/mL	[6]
E. chlorophyla O.Berg	Essential oil of leaves, steam, and flowers/ hydrodistillation	Microdiluition method/ bacitracina and ketocona-zole	*Streptococcus mutans* ATCC 15175 = 50–500 µg/mL *Streptococcus sobrinus* (clinical isolate) = 50–500 µg/mL *Staphylococcus aureus* ATCC 6538 = 500 µg/mL *Kocuria ryzophila* ATCC 9341 = 100–500 µg/mL *Staphylococcus* aureus ATCC 6538 = 500 µg/mL *Candida albicans* ATCC 1023 = 500 µg/mL	[40]
E. dysenterica DC.	Essential oil of leaves/ hydrodistillation	Microdiluition method/ fluconazole, amphotericin B and itraconazole	*Criptococcus neoformans* = < 250 µg/mL *Criptococcus gatii* (clinical isolate) = < 250 µg/mL	[70]
E. mansoni O.Berg	Ethanolic, acetonic, and chrororform extract of leaves/maceration	Agar diffusion method Microdiluition method/ nystatin and gentamicin	*Pseudomonas aeruginosa* ATCC 27853 = resistant *Staphylococcus aureus* ATCC 6538 p = sensitive (+) *Listeria inocua* (clinical isolate) = sensitive (+) *Aspergillus niger* ATCC 2601 = sensitive (+) *Mycobacterium tuberculosis H37Rv*ATCC 27294 = sensitive (+)/200 µg/mL	[71]

continued

▶ **Table 4** *Continued*

***Eugenia* species**	**Extraction/isolation procedure**	**Antimicrobial activity assay/control**	**Microrganisms and results**	**References**
E. monteverdensis Barrie	Essential oil of leaves/ hydrodistillation	Microdiluition method/ gentamycin	*Bacillus cereus* ATCC 14579 = 1250 µg/mL *Staphylococcus aureus* ATCC 29213 = 1250 µg/mL *Escherichia coli* ATCC 25922 = 1250 µg/mL	[48]
E. pyriformis Cambess.	Ethanolic extracts of leaves, flowers, roots, stems, and fruits/ maceration	Microdiluition method Agar diffusion method/ chlorhexidine and rifamycin	*Candida albicans* ATCC 10231 = 12.5–50 µg/mL *Saccharomyces cerevisiae* ATCC 2601 = 25–50 µg/mL *Bacillus subtilis* ATCC 6633 = 25–50 µg/mL *Bacillus cereus* ATCC 11778 = 12.5–50 µg/mL *Micrococcus luteus* ATCC 9341 = 25–50 µg/mL *Enterococcus faecalis* ATCC 51299 = 50 µg/mL *Staphylococcus aureus* ATCC 6538 = 12.5–25 µg/mL *Escherichia coli* ATCC 25922 = 12.5 µg/mL *Pseudomonas aeruginosa* ATCC 27853 = 50 µg/mL *Proteus mirabilis* ATCC 25922 = 50 µg/mL *Salmonella typhimurium* ATCC 14028 = 2–50 µg/mL *Enterobacter cloacae* (clinical isolate) = 12.5–50 µg/mL *Serratia marcescens* (clinical isolate) = 25–50 µg/mL	[30]
	Ethanolic extract fractions: hexane, chloroform, and ethyl acetate, hydroalcoholic. Acetonic extract/Soxhlet	Microdiluition method/ vancomycin and fluconazole	*Enterococcus faecalis* ATCC 29212 = 62.5–1000 µg/mL *Stapylococcus aureus* ATCC 25923 = 62.5–250 µg/mL *Escherichia coli* ATCC 25922 = 250–1000 µg/mL *Klebsiella pneumoniae* ATCC 700603 = 250–1000 µg/mL *Pseudomonas aeruginosa* ATCC 27853 = 250–1000 µg/mL *Candida albicans* ATCC 40175 = 7.81–62.5 µg/mL *Candida krusei* ATCC 40147 = 7.81–31.25 µg/mL *Candida parapsilosis* ATCC 40038 = 7.81–62.5 µg/mL	[20]
E. pluriflora DC.	Essential oil leaves of leaves/hydrodistillation	Agar diffusion method/ no date.	*Staphylococcus epidermidis* ATCC 12228 = 7–11 mm *Staphylococcus aureus* ATCC 6538 p = 7–11 mm *Candida albicans* ATCC 10231 = 7–11 mm *Micrococcus luteus* ATCC 9341 = 11–16 mm *Saccharomyces cerevisae* ATCC 160 = 11–16 mm	[69]
E. repanda O.Berg	Ethanolic extract/ maceration	Agar diffusion method Microdiluition method/ nystatin and gentamicin	*Psudomonas aeruginosa* ATCC 27853 = resistant *Staphylococcus aureus* ATCC 6538p = resistant *Listeria inocua* (clinical isolate) = sensitive (+) *Aspergillus niger* ATCC 2601 = sensitive (+) *Mycobacterium tuberculosis H37Rv* ATCC 27294 = sensitive (+)/200 µg/mL	[71]
E. stipitata McVaugh	Essential oil of leaves/ hydrodistillation	Agar diffusion method/ tetracycline	*Listeria monocytogenes* ATCC 7973 = 12 mm *Staphylococcus aureus* ATCC 25923 = 14 mm *Pseudomonas aeruginosa* ATCC 27853 = 11 mm	[60]
E. umbelliflora O.Berg	Essential oil of leaves/ hydrodistillation	Microdiluition method/ gentamycin	*Staphylococcus aureus* ATCC 25923 = 119.2 µg/mL *Escherichia coli* ATCC 25922 = 477 µg/mL *Pseudomonas aeruginosa* ATCC 27853 = 477 µg/mL	[62]
	Methanol extracts of leaves and fruits/ maceration Fractions: dchloromethane and ethyl acetate	Microdiluition method/ ketoconazole	*Aspergillus flavus* ATCC 9170 = > 1000 µg/mL *Aspergillus fumigatus* ATCC 26934 = > 1000 µg/mL *Aspergillus niger* ATCC 9092 = > 1000 µg/mL *Rhizopus sp* (clinical isolate) = > 1000 µg/mL *Microsporum canis* (clinical isolate) = 300 > 1000 µg/mL *Microsporum gypseum* (clinical isolate) = 300– > 1000 µg/mL *Trichophyton mentagrophytes* ATCC 9972 = 600– > 1000 µg/mL *Trichophyton rubrum* (clinical isolate) = 400– > 1000 µg/mL *Epidermophyton floccosum* (clinical isolate) = 300– > 1000 µg/mL *Cryptococcus neoformans* ATCC 32264 = > 1000 µg/mL *Candida albicans* ATCC 1023 = > 1000 µg/mL *Candida tropicalis* ATCC 7349 = > 1000 µg/mL	[72]
	Methanol extracts of leaves and fruits/ maceration Fractions: dchloromethane and ethyl acetate	Microdiluition method/ vancomycin	*Bacillus cereus* ATCC 14579 = 7–300 µg/mL *Enterobacter cloacae* ATCC 35030 = 900 µg/mL *Escherichia coli* ATCC 11775 = 900 µg/mL *Pseudomonas aeruginosa* ATCC 27853 = 900 µg/mL *Salmonella typhimurium* ATCC 14028 = 900 µg/mL *Staphylococcus aureus* ATCC 6538P = 6–100 µg/mL *Staphylococcus saprophyticus* ATCC 35552 = 10–200 µg/mL *Streptococcus agalactiae* ATCC 13813 = 2–400 µg/mL	[73]

continued

▶ **Table 4** *Continued*

Eugenia species	Extraction/isolation procedure	Antimicrobial activity assay/control	Microrganisms and results	References
E. uniflora L.	*n*-Hexane fraction of leaves/maceration	Disc diffusion/trimethoprim, sulfamethoxazole, and para-chlorocresol	*Escherichia coli* = 5.000 µg/mL *Aspergillus flavus* = 5.000 µg/mL	[24]
	Essential oil leaves of leaves/hydrodistillation	Disc diffusion/ketoconazole	*Epidermophyton floccosum* = 12–18 mm *Trichophyton mentagrophytes* = 16–18 mm *Trichophyton rubrum* = 15–20 mm	[74]
	Essential oil of leaves/hydrodistillation	Agar diffusion method Microdiluition method/sulphadiazine and cephalotine	*Candida albicans* (clinical isolate) = 208.3 µg/mL *Candida parapsilosis* (clinical isolate) = 208.3 µg/mL *Candida guilhermondii* (clinical isolate) = 109.4 µg/mL *Candida globosa* (clinical isolate) = 187.5 µg/mL *Candida lipolytica* (clinical isolate) = 93.7 µg/mL *Candida laurentii* (clinical isolate) = 208.3 µg/mL *Trichosporon asahii* (clinical isolate) = 312.5 µg/mL	[75]
	Essential oil leaves/hydrodistillation	Disc diffusion Microdiluition method/fluconazole and chloramfenicol	*Candida dubliniensis* ATCC 7978 = 230 µg/mL *Candida tropicalis* ATCC 13803 = 900 µg/mL *Candida albicans* ATCC 18804 = 1.800 µg/mL *Candida glabrata* ATCC 90030 = 930 µg/mL *Candida parapsilosis* (clinical isolate) = 3.750 µg/mL *Candida grubii* KN99 (serotype A) = 450 µg/mL *Candida gattii* R265 (serotype B) = 220 µg/mL *Cryptococcus neoformans JEC21* (serotype D) = 110 µg/mL *Saccharomyces cerevisiae* BY4742 = 220 µg/mL	[76]
	Ethanol extract/maceration	Microdiluition method/amphotericin B and itraconazole	*Candida krusei* = 250 µg/mL *Aspergillus fumigatus* = > 500 µg/mL	[77]
	Essential oil leaves/hydrodistillation	Microdiluition method/no date	MIC90 Clinical Isolates: *Staphylococcus* aureus methicillin-resistant (MRSA), *Staphylococcus* aureus methicillin-sensitive (MSSA), *Escherichia* coli, Pseudomonas *aeruginosa, Salmonella typhimurium, Salmonella enteritidis* = 50.800–92.400 µg/mL	[78]
	Essential oil leaves/hydrodistillation	Macrodiluition method/no date	*Paracoccidioides brasiliensis* = 62.5–250 µg/mL	[27]
	Ethanolic extracts of leaves/maceration	Microdiluition method/pennicilin G and eritromicin	*Micrococcus roseus* ATCC 1740 = 2.187 µg/mL *Micrococcus luteus* ATCC 9341 = 273 µg/mL *Bacillus cereus* ATCC 14576 = 1.094 µg/mL *Bacillus stearothermophylus* ATCC 1262 = 2.187 µg/mL *Bacillus subtilis* ATCC 6633 = 2.187 µg/mL *Enterobacter aerogenes* ATCC 13048 = 17.500 µg/mL *Escherichia coli* ATCC 8739 = 17.500 µg/mL *Staphylococcus aureus* ATCC 6538 = 2.187 µg/mL *Staphylococcus aureus* ATCC 25923 = 2.187 µg/mL *Staphylococcus epidermidis* ATCC 12228 = 273 µg/mL *Pseudomonas aeruginosa* ATCC 27853 = 8.750 µg/mL *Serratia marcescens* ATCC 14756 = 35.000 µg/mL *Enterobacter cloacae* (clinical isolate) = 17.500 µg/mL *Candida albicans* (clinical isolate) = 547 µg/mL	[28]
	Ethanolic extracts of leaves/maceration Fractions: hexane, chloroform, and ethyl acetate	Agar diffusion method Microdiluition method/no date	n = 80, *Pseudomonas aeruginosa* (clinical isolate) = 1.090–17.500 µg/mL	[79]
	Ethanolic extracts of leaves/maceration	Agar diffusion method Microdiluition method/ceftriaxone	*Staphylococcus aureus* ATCC 25923 = 250 µg/mL *Staphylococcus epidermidis* ATCC 14990 = 52 µg/mL *Pseudomonas aeruginosa* ATCC 27853 = 14 mm *Escherichia coli* ATCC 14942 = 11 mm	[80]
	Ethanolic extracts of leaves/maceration	Microdiluition method/amphotericin B, mebendazole, nystatin and metronidazole	*Candida albicans* = > 1.024 µg/mL *Candida krusei* = > 1.024 µg/mL *Candida tropicalis* = 1.024 µg/mL	[81]

continued

▶ **Table 4** *Continued*

Eugenia species	Extraction/isolation procedure	Antimicrobial activity assay/control	Microrganisms and results	References
	Methanolic extracts of leaves/maceration	Microdiluition method/ no date	*Pseudomonas aeruginosa* = 10 µg/mL *Shigella sonnei* = 156 µg/mL *Bacillus cereus* = 39 µg/mL	[25]
	Methanolic extracts of leaves/maceration	Agar diffusion method/ chloramphenicol and nystatin	*Staphylococcus aureus* ATCC 6538P = sensitive (+) *Bacillus subtilis* ATCC 6633 = sensitive (+) *Micrococcus luteus* ATCC9341 = sensitive (+++) *Staphylococcus epidermidis* ATCC12228 = resistant *Escherichia coli* ATCC 25922 = resistant *Candida albicans* ATCC 10231 = resistant	[82]
	Hydroalcoholic extracts of leaves/maceration process with ethanol-water (90–10%)	Microdiluition method Bioautography method/ tetracycline, vancomycin, penicillin and nistatin	*Escherichia coli* ATCC 25922 = 500 µg/mL *Pseudomonas aeruginosa* ATCC 15442 = > 1000 µg/mL *Bacillus subtilis* ATCC 6623 = > 1000 µg/mL *Staphylococcus aureus* ATCC 25923 = 250 µg/mL *Candida albicans* (clinical isolate) = > 1000 µg/mL *Candida krusei* (clinical isolate) = 31.2 µg/mL *Candida parapsilosis* (clinical isolate) = 125 µg/mL *Candida tropicalis* (clinical isolate) = 31.2 µg/mL	[83]
	Hydroalcoholic extracts/ percolation	Microdiluition method/ ampycilin and nistatyn	*Staphylococcus aureus* ATCC 6538 = 80 µg/mL *Salmonella choleraesuis* ATCC 10708 = 100 µg/mL *Pseudomonas aeruginosa* ATCC 15442 = 400 µg/mL *Candida albicans* ATCC 10231 = 500 µg/mL *Aspergillus niger* ATCC 16404 = 900 µg/mL	[29]
E. uruguayensis Cambess.	Extracts/maceration with EtOH/H_2O 70:30, acetone and $CHCl_3$	Microdiluition method/ no date	*Staphylococcus aureus* ATCC 6538 p MSSA = 31.3 µg/mL *Staphylococcus aureus* ATCC 700699 MRSA = 31.3 µg/mL *Staphylococcus aureus* ATCC 43300 MRSA = 31.3 µg/mL *Staphylococcus aureus* USA 100 MRSA = 31.3 µg/mL	[84]
	Essential oil of leaves/ hydrodistillation	Agar diffusion method/ no date	*Staphylococcus epidermidis* ATCC 12228 = 11–16 mm *Escherichia coli* ATCC 25922 = 11–16 mm *Saccharomyces cerevisae* ATCC 160 = 10–16 mm	[69]

at a concentration of 128 µg/mL showed no synergistic effects [85]. An ethanolic extract from *E. uniflora* leaves evaluated against *Candida tropicalis* (ATCC 13803) alone and in combination with the antifungal metronidazole reduced the MIC of metronidazole from 128 to 32 µg/mL, a fourfold reduction [81].

The checkerboard method was used to evaluate synergistic interactions between *E. pyriformis* and vancomycin or fluconazole. A combination of the hydroalcoholic fraction from the *E. pyriformis* leaves and vancomycin exhibited synergism against *Enterococcus faecalis*, with a fractionated inhibitory concentration index (FICI) of 0.37. FICI values are interpreted as synergistic (FICI < 0.5), additive (0.5 < FICI > 4), or antagonistic (FICI > 4) [20]. In addition, combinations of fluconazole with an *E. pyriformis* crude leaf extract and acetone extract showed activity against *Candida krusei* and *Candida parapsilosis*, with FICI values between 0.24 and 0.50. Further, a synergistic interaction was observed when an ethyl acetate fraction of *E. pyriformis* leaves was combined with vancomycin or fluconazole to treat *Candida albicans, C. krusei*, and *C. parapsilosis* resulted in FICI values between 0.24 and 0.37 [20].

Cytotoxicity

The cytotoxic activity of *Eugenia* species is reported in ▶ **Table 5**. In these studies, several extraction methods were used to obtain extracts, fractions, and essential oils from leaves, fruits, and seeds of some *Eugenia* species. Effective results against growth in different tumor cell lineages and *Artemia salina* were observed. Specimens of *A. salina* Leach (brine shrimp), a marine microcrustacean, were used as target organisms to detect bioactive compounds in plant extracts, and toxicity tests against these animals have shown a good correlation with antitumor activity [86]. Medium lethal concentrations (LC_{50}) were used to estimate the toxicity of *A. salina*, providing a general toxicity analysis, and several studies correlated this method with antiviral, antiparasitic, and antitumor activity [87–89]. The essential oil of *Eugenia zuchowskiae* Barrie was cytotoxic, with 100% death when used to treat cell lines at 100 µg/mL [18]. *E. zuchowskiae* Barrie extracts comprise α-pinene, β-caryophyllene, and α-humulene compounds. α-Pinene has exhibited cytotoxic activity in Hep G2 human hepatocellular carcinoma cells, and α-humulene has been shown to be active in several tumor cell lines [90].

Conclusions, Discussion, and Future Perspectives

Species of *Eugenia* have been investigated in recent decades, revealing a great diversity in chemical composition. Hydrocarbons and oxygenated derivatives have been identified in the essential oils of *Eugenia* species, while in extracts of the aerial parts, the compounds triterpenes, flavonoids, tannins, and cyanidins have

▶ **Table 5** Cytotoxic activity of *Eugenia* species in the studies selected through this systematic review.

Species	Extraction	Cytotoxicity assays	Cell lineages	Cytotoxic activity	Reference
E. axilaris (SW.) Willd	Essential oils of leaves/ hydrodistillation dichloromethane extraction	*In vitro* cytotoxicity assay MTS	PC-3 (human prostatic adenocarcinoma) MDA-MB-231 (human mammary adenocarcinoma) MCF7 (human mammary adenocarcinoma) Hs 578T (human ductal carcinoma) Hep G2 (human hepatocellular carcinoma)	PC-3 = 67.47 % MDA-MB-231 = 42.66 % MCF7 = 30.21 % Hs 578 T = 95.79 % Hep G2 = 92.21 % Cytotoxicity expressed as percentage kill at 250 µg/mL for Hs 578T and Hep G2; and at 100 µg/mL for PC-3, MDA-MB-231 and MCF7	[17]
E. calycina Cambess.	Essential oils of leaves/ hydrodistillation Fractions obtained of Dichloromethane: F1, F2, F3, and F4	*In vitro* cytotoxicity assay MTT cervical cancer cell lines	Cervical cancer cell lines (HeLa ECACC 93021013)	EO CC50 = 137.4 ± 9.6 µg/mL F1 CC50 = 120.0 ± 9.4 µg/mL F2 CC50 = 117.6 ± 9.6 µg/mL F3 CC50 = 151.1 ± 8.3 µg/mL F4 CC50 = 139.2 ± 5.1 µg/mL	[7]
E. cartagensis O.Berg	Essential oils of leaves/ hydrodistillation	*In vitro* cytotoxicity assay MTT	Colorectal carcinoma cells (HCT-15 and SW 620) Malignant melanoma cells (MCF7, M-14 and SK-Mel-28) Malignant melanoma cells (Malme-3M and UACC-257) Mammary adenocarcinoma cells (MDA-MB-231) Mammary ductal carcinoma cells (MDA-MB-435) Ovarian adenocarcinoma cells (OVCAR-5 cells)	Cytotoxic against HCT-15 and SW 620 cells at a concentration of 100 µg/ mL, with 100 and 84.1 % cell death, respectively. These oils were less active against MCF7 (73.5 %), M-14 (45.3 %), and SK-Mel-28 (41.3 %) cells and were inactive against MDA-MB-468 cells, Malme-3M and UACC-257 cells, MDA-MB-231 cells, MDA-MB-435 cells, and OVCAR-5 cells.	[39]
E. dysenterica DC.	Ethanolic extract of leaves/maceration	*In vitro* cytotoxicity in *Rhesus neonato* monkey cells	*Rhesus neonato* monkey cells (MA-104)	Disruption of the cell layer observed at a concentration of 5000 µg/mL	[16]
E. monteverdensis Barrie	Essential oils of leaves and fruits/hydrodistillation	*In vitro* cytotoxicity assay MTT	Human MDA-MB-231 breast adenocarcinoma cells Human Hs 578T breast ductal carcinoma cells	MDA-MB-231 or Hs 578 T human tumor cells (0 % killing at 100 µg/mL)	[48]
E. uniflora L.	Ethanolic extract of leaves/maceration	Brine shrimp lethality bioassay	*Artemia salina* Leach eggs varying concentrations 1 to 1000 µg/mL	LC_{50} values above 250 µg/mL, with a 95 % confidence interval (194.2–433.7)	[88]
	Methanolic extract of leaves/maceration	Brine shrimp lethality bioassay	*Artemia salina* Leach eggs varying concentrations 10 to 1000 µg/mL	LC_{50} values above 250 µg/mL	[25]
	Ethanolic extract of leaves/maceration	*In vitro* cytotoxicity assay	J774 macrophages	8 % cytotoxic activity in J774 macrophages at a concentration of 100 µg/mL	[91]
	Ethanolic extract of fruits/maceration	MTT assay Tritiated thymidine incorporation assay GRX MitoTracker Green MitoTracker Flow cytometry assays Cell	HSC line was obtained from livers of C3H/HeN mice that were infected by transcutaneous penetration of cercariae from the *Schistosoma mansoni* BH strain (GRX)	Viability cell was significantly decreased on cells treated with 50 µg/mL of extract for 72 h and on cells treated with 100 µg/mL for 48 and 72 h. Proliferation cell: The reduction of cell proliferation was dose dependent at the cell counting assay and the cells treated with 100 µg/mL of extract visually, not increased in three days of treatment. Mitochondrial content was significantly reduced in GRX cells treated with 50 and 100 µg/mL of an extract at all times studied. The cells treated with 50 and 100 µg/mL of extract for 24 h showed a 13 % increase in the number of GRX cells in the G0G1 phase and a reduction in the S phase. We did not observe an increase in apoptosis in cells treated for 24 and 48 h. However, the percentage of necrotic cells increased significantly in cells treated with 50 and 100 µg/mL for 48 h.	[26]

continued

▶ **Table 5** *Continued*

Species	Extraction	Cytotoxicity assays	Cell lineages	Cytotoxic activity	Reference
	Methanolic extracts of leaves and seeds Fraction: ethyl acetate, *n*-butanol and aqueous fraction	*In vitro* cytotoxicity assay splenocytes from BALB/c mice	Splenocytes from BALB/c mice Each sample was evaluated in six concentrations (1, 5, 10, 25, 50, and 100 g/mL) in triplicate	Ethyl acetate fraction of leaves = 50 and 100 µg/mL Ethyl acetate fraction of seeds = 25, 50, and 100 µg/mL Butanol fraction of seeds = 100 µg/mL Control saponin	[92]
	Essential oils of leaves/ hydrodistillation	*In vitro* cytotoxicity assay MTT	Vero cell line	IC_{50} = 117.4 ± 11.9 µg/mL	[77]
	Essential oils of leaves/ hydrodistillation	*In vitro* cytotoxicity assays (3T3 cells) neutral red	Balb/c 3T3 fibroblast	IC_{50} = > 1 mg/mL (no potential cytotoxic at concentrations > 1 mg/mL)	[93]
E. supraaxillaris Spreng.	Essential oils of leaves and fruits/hydrodistillation	*In vitro* cytotoxicity assay tumor cell lines	Tumor cell lines (cervices, colon, larynx, liver, and breast)	Cervices IC_{50} = 0.62 µL leaves and 1.30 µL fruits Colon IC_{50} = 0.43 µL leaves and 0.43 µL fruits Larynx IC_{50} = 0.54 µL leaves and 0.87 µL fruits Liver IC_{50} = 0.40 µL leaves and 0.38 µL fruits Breast IC_{50} = 0.40 µL leaves and 1.40 µL fruits	[1]
E. zuchowskiae Barrie	Essential oils of leaves/ hydrodistillation	*In vitro* cytotoxicity assay MTT	MCF-7, MDA-MB-468, and UACC-257 human tumor	MCF-7 = 100% kill MDA-MB-468 = 100% kill UACC-257 = 100% kill Expressed as % kill at 100 µg/mL concentration	[18]

been identified. In view of the chemical diversity described, *Eugenia* species are likely a promising source of bioactive compounds. Of the *Eugenia* species known, only 350 have been investigated for their chemical composition and biological activity, demonstrating a shortage of studies for this genus. *E. uniflora* was the most studied species, attributable to its popular use. It is important to consider that *Eugenia* species are used in folk medicine, and several therapeutic properties have been reported, including antibacterial and antifungal activity against various microorganisms. Several studies evaluating the antimicrobial activity of extracts and derivatives used in combination with commercial antimicrobials revealed synergistic effects against microorganisms, potentializing the efficacy of these agents. However, some studies evaluating the bioactivities did not present a positive control or use a comparator to infer value to the results obtained, such as MIC or IC_{50} values. Finally, we observed that cytotoxicity studies performed with *Eugenia* species presented wide methodological variations, making it difficult to compare the observed biological effects.

Studies exploring the association between the various phytochemicals and their biological activities may lead to the discovery of new bioactive compounds with therapeutic potential in *Eugenia* species that are native to Brazilian flora. Natural sources should be further explored and may result in the discovery of chemically diverse and biologically active compounds, including promising drugs in the search for new antimicrobial agents. Detection of these agents is important, as the increase in pathogen resistance to commercially available antimicrobials is a global health problem. Thus, this review suggests that species in the *Eugenia* genus have promising biological activities, supporting the need for future research on the development of drugs from the extracts and chemical constituents.

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Conflict of Interest

The authors declare no conflict of interest.

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