



A review on traditional uses and applications of *Cordia* spp. (Boraginaceae) as a natural polymer in the development of food and pharmaceutical products

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Review

Abstract

Background: The growing demand for natural polymers useful for food and drug production has prompted the search for new plant sources to replace synthetic polymers. Unlike synthetic polymers, natural ones have advantages such as low toxicity, biocompatibility, and non-toxicity to the environment. Among the plant sources investigated as biopolymers, we find gums and mucilage, which have achieved a remarkable position in the additive market due to their applications in the paper, cosmetic, food, and pharmaceutical industries, to name a few. The genus *Cordia* L. is traditionally known for its medicinal use, however, in recent years the fruit mucilage has been studied as a biopolymer. This review aims to compile and analyze the research conducted with species of the genus *Cordia* L., especially the ones that studied the mucilage of its fruits, including the methods applied to obtain, identify, and characterize it. Besides, talking about its application in new groundbreaking fields.

Methods: Relevant information was selected from articles, books, theses, and patents published in databases such as Scopus, ScienceDirect, PubMed, Google Scholar, Google Patents, Patentscope, Patent Inspiration, and Espacenet.

Results: The research data showed that the biopolymer obtained from fruit mucilage of the genus has attractive physical and chemical properties, and may be suitable for the design of drugs, nanoparticles, coatings, and food products. In addition, specific studies revealed the presence of some flavonoids and terpenes as active ingredients of the genus *Cordia* L., which are associated with their ancestral medicinal use.

Conclusion: The possible use of mucilage of the genus *Cordia* L. is evidenced by its addition, substitution, or combination with other biopolymers to improve and design new products. Likewise, study alternatives are presented for countries where species of this genus are found and have not yet been considered for experimentation.

Keywords: mucilage, gum, biomaterials, pharmaceutical industry, food industry, medicinal use.

Background

The genus *Cordia* L. belongs to the Boraginaceae family, which consists of approximately 2300–2700 species, 300 of which belong to this genus (Gupta & Gupta 2015). Its distribution is widespread in the tropical zone of some countries in Africa, America, and Asia (Matias *et al.* 2015). Different ancestral medicinal properties have been attributed to the genus due to its antibacterial, antioxidant, anthelmintic, anti-inflammatory, and analgesic activity presented by its leaves, roots, flowers, and fruits (Hojjati & Beirami-Serizkani 2020, Rezende *et al.* 2020). However, in recent years, the mucilage from the fruit of some species of the genus has been evaluated as a biopolymer for the development of pharmaceutical and food formulations, such as oral and dermal drug delivery systems (Duppala *et al.* 2016, Pawar *et al.* 2014), nanoparticles (Saidu *et al.* 2019), edible coatings (Castro 2019, El-Mogy *et al.* 2020), food additives (Hasani & Yazdanpanah 2020), among others. Both mucilage and gums are considered hydrocolloids, polysaccharides of high molecular weight, useful for the elaboration of various products in the pharmaceutical, food, cosmetic, and paint industries (Amiri *et al.* 2021, Singh & Barreca 2020). Gums of vegetable origin, which have been mostly exploited since the early days of the industry, include gum Arabic (*Acacia senegal* (L.) Willd.), karaya gum (*Sterculia urens* Roxb.), chewing gum (*Astragalus gummifer* Labill.), as well as others (Whistler 1982). These gums have been mainly used as stabilizers, thickeners, gelling agents, emollients, and emulsifiers (Singh & Barreca 2020).

It is estimated that, in 2021 worldwide, the exported value of natural gums, resins, balsams, and other natural oleoresins, was US\$ 911 million, corresponding to more than 300 tons (International Trade Centre (ITC) 2019). It is also mentioned that France (US 156 million), India (US 126 million), Sudan (US 117 million), and Afghanistan (US 95 million) were the countries that most exported these products worldwide. In the same year, the exported value of mucilage and thickeners derived from vegetable substrates (excluding agar-agar, guar seeds, and carob seeds) was 1.53 billion dollars, being China (US 531 million), the Philippines (US 207 million), Spain (US 115 million) and Indonesia (US 107 million), the countries with the highest exports (International Trade Centre (ITC) 2019). The accelerated population growth, the consequent need to increase food and drug production, as well as the current trend to use natural compounds instead of synthetic ones, are some of the causes that lead to investigating new sources of vegetable gums and mucilage to fulfill the needs of international markets. Unlike natural polymers, synthetic polymers have a certain downside because they are usually high in cost, not biodegradable, not biocompatible and an environmental pollutant during their synthesis (Jani *et al.* 2009). Therefore, there is a constant search for new sources of natural polymers that are efficient enough to be incorporated into the industry (Choudhary & Pawar 2014). The mucilage obtained from the plant fruit of species of the genus *Cordia* L. (Boraginaceae) could be evaluated as a new natural polymer option for countries where these species are distributed, especially where experimental trials have not been developed. In this context, the objective of this review is to collect and analyze research carried out with different plant parts of *Cordia* spp., with a strong emphasis on their fruits. In this way, the methods previously used to obtain, identify and characterize extracts and mucilage will be presented. In addition, the applications given to the genus worldwide will be included, both in the medicinal aspect and in the elaboration of industrial products. Aiming to propose new uses in countries where these species are found and available but have not been investigated or exploited. Consequently, Fig. 1. resumes the whole content of this study.

Materials and Methods

Relevant information was selected from articles, books, and theses published in PubMed, ScienceDirect, Scopus, and Google Scholar. The keywords "*Cordia* medicinal", "*Cordia* fruit gum", and "*Cordia* fruit mucilage" were used to search for information in the first 3 databases mentioned. Additionally, in Google Scholar, the search terms "*Cordia* fruto goma" and "*Cordia* fruto mucilago" were included, in order to find information published in Spanish. No specific range of years was established to search for the information due to the low number of documents obtained in the preliminary literature compilation. In addition, the Plant of the World Online (POWO) database and the NCBI Taxonomy browser were used to identify the synonyms of the scientific names of the different species of the genus *Cordia* L. mentioned in this review. Patents found in Google Patents (<https://patents.google.com>), Patent Inspiration (<https://app.patentinspiration.com>), Patentscope (<https://patentscope.wipo.int>) and Espacenet (<https://worldwide.espacenet.com>) were included in this analysis.

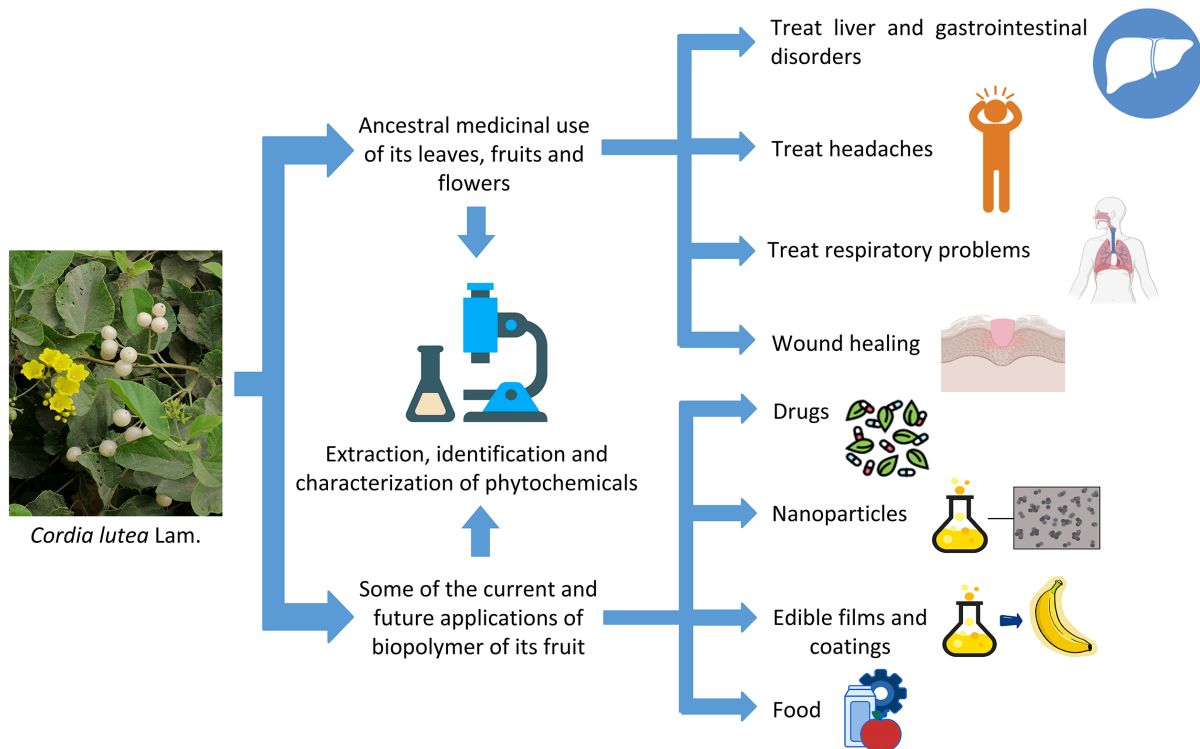


Figure 1. Summary of the activities carried out to obtain pharmaceutical and food products using a species of the genus *Cordia* L.

Results and Discussion

Distribution of collected documents

The documents found in the search show a distribution of publications of 57% in Asia, 29% in America, and 14% in Africa, with India being the country with the most publications (Fig. 2). Of the documents found, 86% belong to research articles published in scientific journals, 5% to patents, 5% to theses and 3% to book chapters. In the American continent, Peru, and Brazil, top the list of countries with the largest number of publications on the genus *Cordia* L., highlighting its medicinal activity and the active components responsible for it. In the literature search by country, no articles related to medicinal and industrial applications of *Cordia* L. were found in Ecuador; instead, theses published in university repositories were included in the present analysis. Of the total number of research articles found, 47% include studies on the medicinal effect and its related biological activity, 18% on extraction and characterization, 10% on the use of mucilage as a food additive and 10% as a pharmaceutical additive, in addition to other smaller percentages presented in Fig 3. For each of these categories, more information is provided in the following items.

The documents produced in Asian and African nations exhibit a greater tendency of publications involving the use of the mucilage of the genus as a biopolymer for its application in pharmaceutical and food formulations. Nonetheless, in Fig. 4 was included other areas where the genus *Cordia* is currently used/studied according to the data presented in Scopus from the first literature research. In this figure, it can be visualized the wide range of applications that this species can have, which the primary ones are the Pharmacology, Toxicology and Pharmaceutics, Medicine and Agricultural and Biological Sciences sectors. Fig. 4 also makes a distinction between the terms used in the research. The first ring corresponds to the term "cordia fruit mucilage" which has record of studies since 1964. The second ring is related to the term "cordia fruit gum" with studies since 2002, and the third ring matches the term "cordia medicinal" including studies throughout 1962 and 2023.

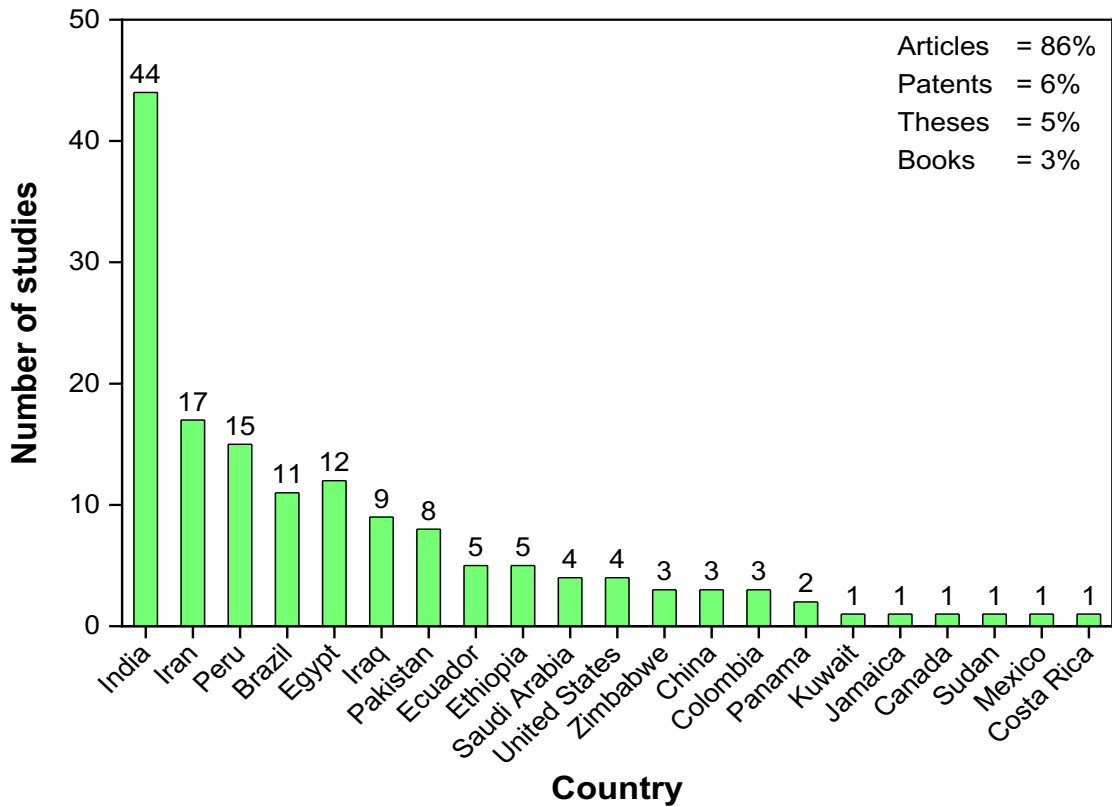


Figure 2. Number of published documents (articles, patents, books, and theses) found by country according to the methodology used.

Categories of the articles included in this study

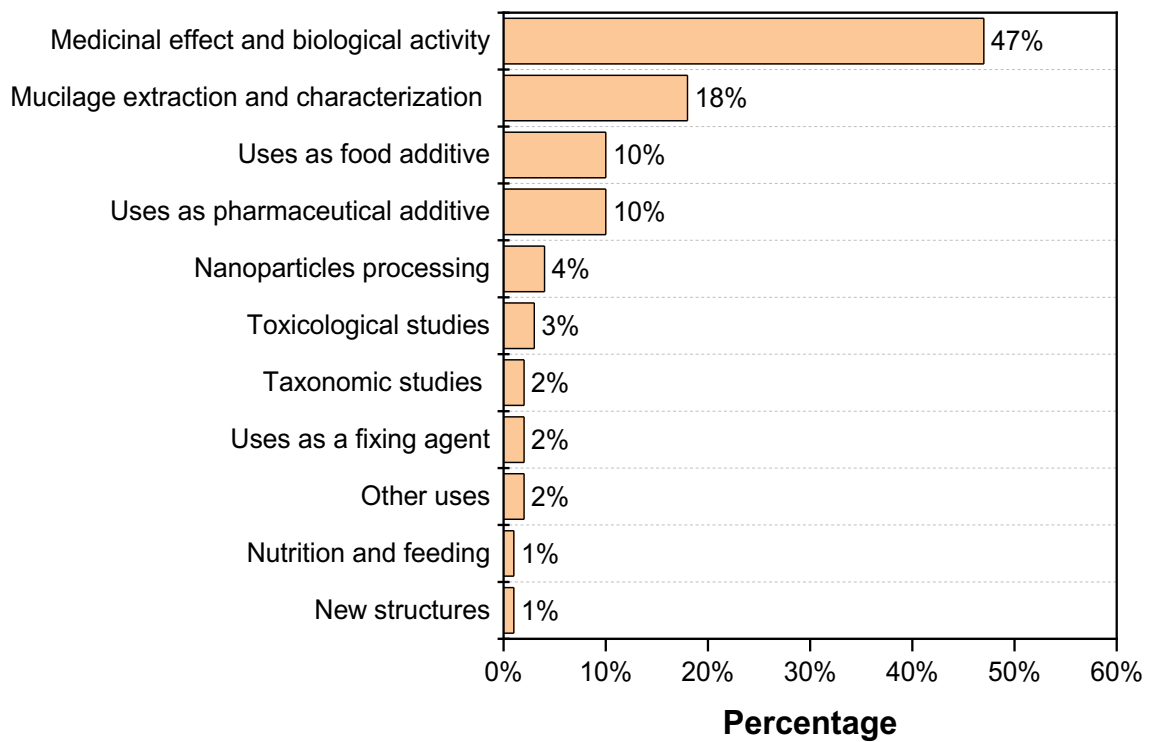


Figure 3. Percentage of articles included by category of interest. The category named "other uses" include uses of this species for wastewater treatment, bioremediation and for agroforestry systems.

Percentage of published documents according to subject areas

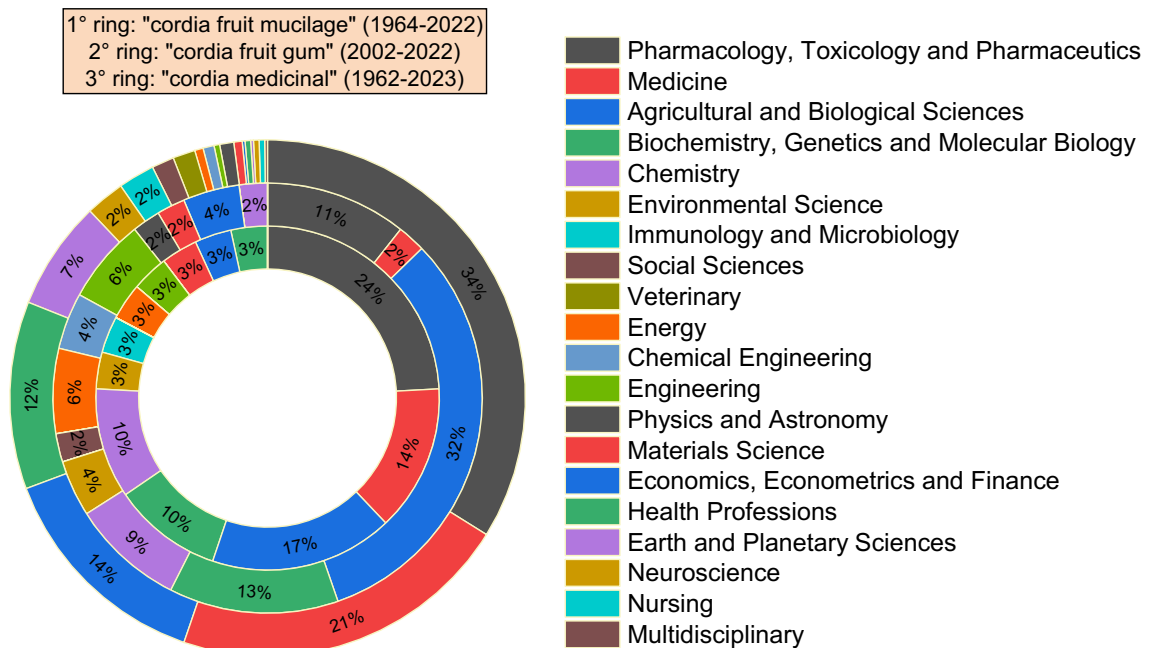


Figure 4. Percentage of published documents according to subject areas extracted from the literature search in Scopus with the terms "cordia fruit mucilage", "cordia fruit gum", and "cordia medicinal".

Botanical description of the genus *Cordia* L.

The genus *Cordia* L. is one of the 156 accepted genera of the family Boraginaceae, which records more than 2000 species (Royal Botanic Garden 2022). Species of this genus have been discovered in warm areas of some countries in Africa, America, and Asia, and the most common forms have been identified as trees and shrubs (Oza & Kulkarni 2017). In Ecuador, it is estimated that there are about 25 species of this genus distributed in the 4 natural regions that comprise it (Ulloa & Moller 2002). Some of them have been used ancestrally for their medicinal effect, however, the metabolites behind this activity are not scientifically known (Luzuriaga-Quichimbo *et al.* 2019, Vacas *et al.* 2015). In addition, the fruits of one of the species of this genus have been traditionally used as glue and natural hair fixative (Castro 2015). This is similar to the use given to other species of the same genus native to Asia, where multiple products have been developed from this property in the food and pharmaceutical industry (Mukherjee & Dinda 2008, Rahayu *et al.* 2016, Tripathi 2020, Al-Musawi *et al.* 2022).

The height of species of the genus can range from 50 cm to 15 m, depending on the species (Estrada 2019). They are sympodial growing plants with alternate leaf arrangements (Taroda 1984). The ovary has four lobes with one oculus each (Oza & Kulkarni 2017). The stamens are slender; thus 6 to 15 whitish stamens can be placed in a flower (Taroda 1984). Actinomorphic flowers with orange, white, yellow, or red colors tend to have an average length between 24 to 45 mm (Amer *et al.* 2016). Generally, the fruits are ovoid drupaceous with viscid matter containing a seed inside with folded cotyledons. These are supported by a calyx that completely or partially covers the fruit (Taroda 1984). The calyx may be tubular or bell-shaped and has three to five septa (Oza & Kulkarni 2017).

Ancestral medicinal uses of the genus *Cordia* L.

Worldwide, medicinal plants have been used for both prophylactic and therapeutic purposes, being recorded as a source of antibiotics, antivirals, analgesics, and antineoplastic agents, among others (Mawalagedera *et al.* 2019). One of the current public health challenges is microbial resistance to conventionally used antimicrobial drugs (Serra 2017). In 2019, an estimated 1.27 million deaths occurred worldwide due to antimicrobial resistance (Murray *et al.* 2022). By 2050, this number is estimated to exceed 10 million deaths per year (Thomas & Wessel 2022). Some of the most common resistant pathogens include *E. coli*, *S. aureus*, *K. pneumoniae*, *S. pneumoniae*, *Acinetobacter baumannii*, and *P. aeruginosa* (Murray *et al.* 2022). In recent years there has been an increased interest in exploring antimicrobials, based on ethnobotanical knowledge, as an alternative to those antimicrobial drugs (Gupta & Birdi 2017). Throughout this review, some studies on the use of species of the genus *Cordia* L. as antimicrobials are presented. Likewise, species of the genus *Cordia* L. have been evaluated for their anti-inflammatory, and

antidepressant activity in rats (Al-Awadi *et al.* 2001, Schezaro-Ramos *et al.* 2020, Zakerin *et al.* 2021), as well as for their antitumor, analgesic, and antitussive activity in mice (Ibrahim *et al.* 2019, Salimimoghadam *et al.* 2019).

Traditionally, the flowers of *Cordia lutea* Lam. have been used for the preparation of infusions useful for treating respiratory, gastric, hepatic, and allergic disorders. (Arroyo-Acevedo *et al.* 2016, Trelles 2019, Rojas-Armas *et al.* 2020). In Peru, dried flowers of this species are commonly sold for the preparation of infusions. (San Fernando, 2022). Roncagliolo *et al.* 2018 proposed the study for the export of flowers of this species from Peru to Chile. Although in Ecuador the flowers of this species are used to treat the same disorders, no sales records have been found. The fruits of *Cordia lutea* Lam. are not usually consumed by humans due to their stickiness and taste, however, they have traditionally been consumed to treat coughs, as well as the fruits of *Cordia dichotoma* native to Asia (Raghuvanshi *et al.* 2022, Quinde 2020). Birds and bears have been seen to feed on this species (Martos *et al.* 2009, Figueroa 2013). The infusion of the bark of the *Cordia nodosa* Lam. tree has been used in South American countries, including the Amazon region of Ecuador, to treat snake and spider bites, to reduce inflammation and prevent gangrene. (De Filippis *et al.* 2004, De la Torre *et al.* 2008, Luzuriaga-Quichimbo *et al.* 2019). The infusion of the leaves of *Cordia verbenacea* DC. has been used to treat coughs, influenza, headaches, as well as for wound healing (Matias *et al.* 2013, Schroeder & Burgos 2017). This species is mostly known to treat skin disorders and inflammation, including bruises and wounds, as well as to treat arthritis (Hernandez 2007, Martim *et al.* 2021). Similarly, the ointment made from the seeds of *Cordia alliodora* (Ruiz and Pav.) Oken. has been used for skin conditions. (Oza & Kulkarni 2017). Another species used medicinally is *Cordia myxa* L., whose macerate has been used as a beverage to treat trypanosomiasis (de Filippis *et al.* 2018). Medicinal plants have not only made it possible to treat and/or cure diseases, but they are also an economic livelihood for many families that commercialize them, either for direct sale to the consumer or to industries that process them (Iannicelli *et al.* 2018). For this, the first step is to know which organ plant is responsible for the active compound that will confer the specific medicinal property. The following are examples of some species of the genus *Cordia* L. used medicinally, classified according to the type of plant and part used.

Leaves

Erva-baleeira (*Cordia verbenacea* DC.)

This species is distributed in xeric zones of the neotropics, especially in Colombia and Brazil (Estrada 2019). It is one of the species of the genus *Cordia* L. most investigated for the anti-inflammatory, analgesic, and antibacterial activity of its leaves (Matias *et al.* 2015, Passos *et al.* 2007). Tannins, flavonoids, mucilage, and essential oils have been mainly found in this species (de Carvalho *et al.* 2004). Some of the metabolites identified in its leaves include monoterpenes (α -pinene), sesquiterpenes (β -caryophyllene, α -humulene, trans-caryophyllene, δ -cadinene), and triterpenes (Fernandes *et al.* 2007, Rezende *et al.* 2020). From the research of its leaf extract, Acheflan® topical cream was developed, which is used for muscle pain and inflammation (Thirupathi *et al.* 2008). In South American countries, the decoction of its leaves has been used as an analgesic, anti-inflammatory, and anti-rheumatic agent (Oza & Kulkarni 2017). The ethanolic extract of this species has been used to protect the skin against damage caused by ultraviolet B (UVB) radiation. In this case, topical and oral administration of the extract has been evaluated in mice, giving as a result the decrease in the inflammatory process and oxidative stress (Melo *et al.* 2021a, Melo *et al.* 2021b). The essential oil of this species has also demonstrated its medical relevance in combating parasitosis caused by *Leishmania brasiliensis* and *Trypanosoma kuzi* (Pereira *et al.* 2021). High Performance Liquid Chromatography (HPLC) has been used to identify the components present in the methanolic extract of *Cordia verbenacea* DC. leaves (Matias *et al.* 2013). The results provided a chromatogram with defined peaks detecting gallic acid, chlorogenic acid, caffeic acid, rutin, and quercetin. These compounds have shown antioxidant activity in films prepared with the extract of this specie (Bodini *et al.* 2020). The chemical structures of some compounds found in this specie leaves are shown in Fig. 5.

Laurel (*Cordia alliodora* (Ruiz and Pav.) Oken)

Laurel is known in several countries in the tropical zone of Latin America and the Caribbean. Its properties, such as the hardness and smoothness of wood surfaces, are useful for making furniture and handicrafts (Guamán 2018, Marulanda *et al.* 2011). Its geographic distribution includes areas of humid and dry tropical forests. It is the most widely dispersed species of the genus *Cordia* L., found from northern Mexico to South America (The International Tropical Timber Organization 2022). It is a valuable species in agroforestry systems and is usually found next to sugarcane, coffee, banana, and cocoa plantations (Somarrriba *et al.* 1998, Pineda-Herrera *et al.* 2018). In this context, laurel avoids the negative effects caused by monoculture in this type of plantation, and also provides shade for crops. (Cerdeira 2008, Cañadas *et al.* 2015, Andrade & Segura 2016). However, studies are being carried out to determine how close these trees should be planted, since it has been observed that a level of shade greater than

60% in coffee plantations can reduce coffee production by up to 39%. (Farfán-Valencia & Urrego 2004). The decoction of laurel leaves has been used for the treatment of colds and pulmonary conditions, while the powdered seeds of its fruits have been used to treat skin diseases (Liegel & Stead 1990). Some triterpenoids have been isolated from its leaves (Oza & Kulkarni 2017), and it has been shown that these have anti-inflammatory, analgesic, antipyretic, hepatoprotective, and antitumor activities (Bishayee *et al.* 2011, Seo *et al.* 2020). In addition, one of these triterpenoids, the compound 3 α -Hydroxyolean-12-en-27-oic acid, has been shown to have repellent activity against ants (Chen *et al.* 1983). This and other triterpenes isolated from laurel leaves are shown in Fig. 6.

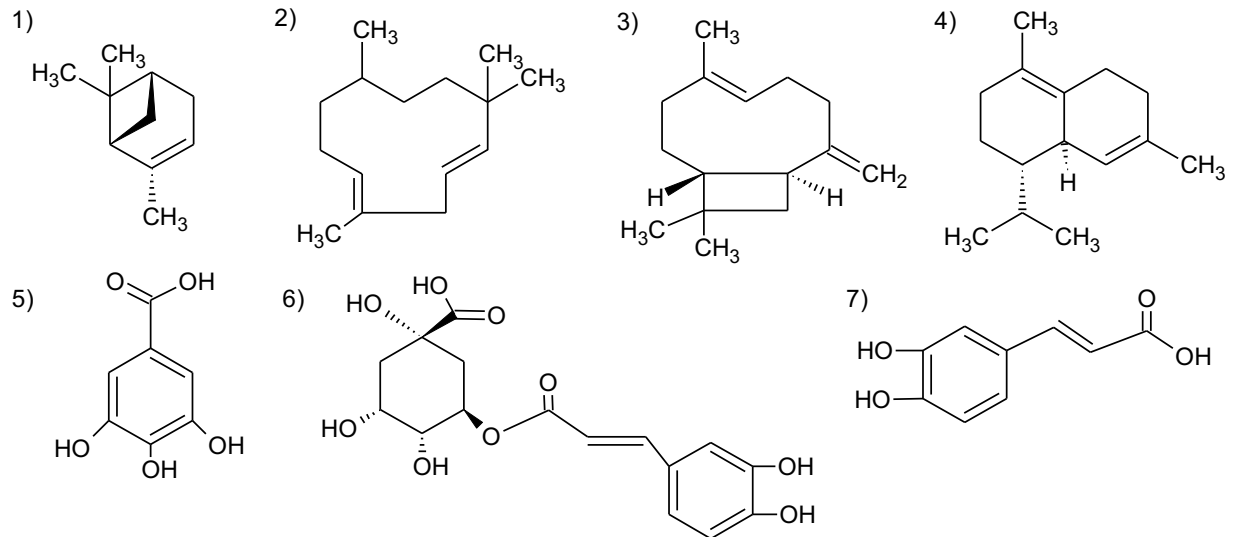


Figure 5. Chemical structures from components identified from *Cordia verbenacea* DC. leaves. Terpenes: 1) α -pinene, 2) α -humulene, 3) Trans-caryophyllene and 4) δ -cadinene. Phenolic compounds: 5) gallic acid 6) chlorogenic acid and 7) caffeic acid

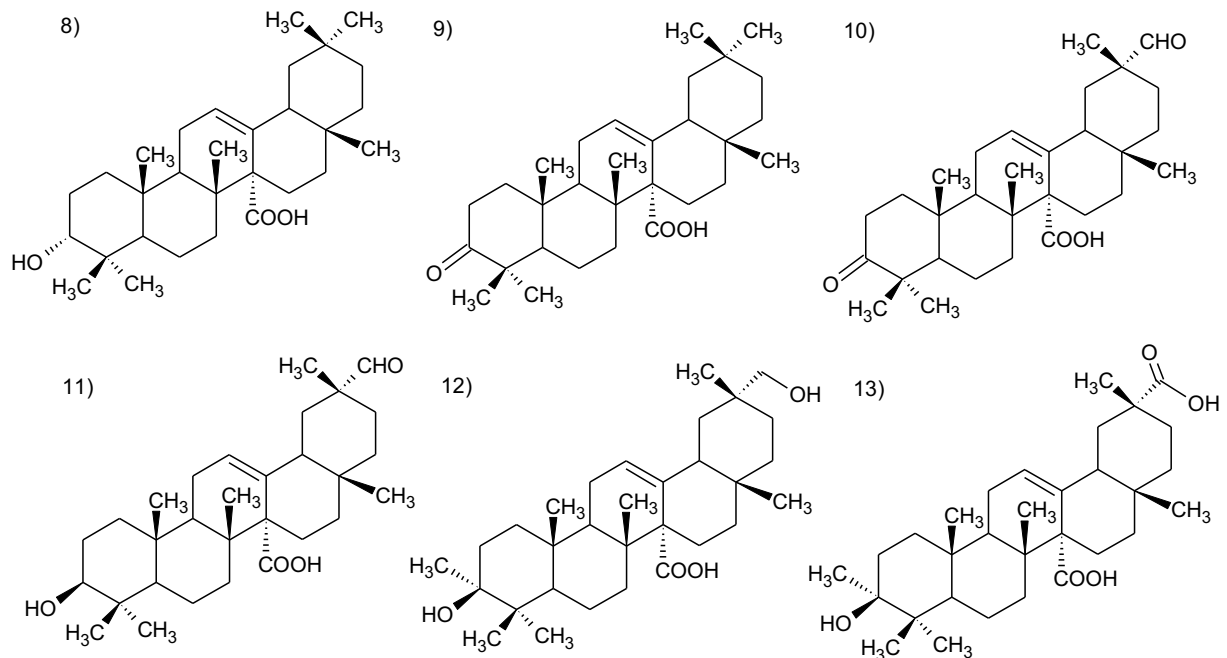


Figure 6. Chemical structures from components isolated from *Cordia alliodora* (Ruiz and Pav.) Oken leaves. 8) 3 α -Hydroxyolean-12-en-27-oic acid, 9) 3-Oxoolean-12-en-27-oic acid, 10) 3,29-Dioxoolean-12-en-27-oic acid, 11) 3 α -Hydroxyolean-29-en-27-oic acid, 12) 3 α , 29-Dihydroxyolean-12-en-27-oic acid and 13) 3 α -Hydroxyolean-12-en-27,29-oic acid.

Assyrian plum (*Cordia myxa* L.)

It is a common species in Asian and African countries (Al-Ati 2011). Its distribution is centered in India, including arid and semi-arid regions (Meghwal *et al.* 2014). *Cordia myxa* L. leaves have been used to treat trypanosomiasis as well as mosquito bites (Freiburghaus *et al.* 1996, Oza & Kulkarni 2017). However, no scientific evidence was found to corroborate this activity. Significant antioxidant, anti-inflammatory, analgesic, antipyretic, and antidiabetic activities were obtained from ethanolic extract of *C. myxa* leaves, while it was tested in *in vitro* and *in vivo* experimental models (Abdel-Aleem *et al.* 2019). This study also corroborated the non-toxicity of its fruits and leaves up to a dose of 2500 mg/kg, using albino rats as an animal model. Leaf extracts of *C. myxa* L. and *C. francisci* Ten. Have reported significant analgesic and anti-inflammatory activities in rats (Karami *et al.* 2014). Compounds such as lutein, violaxanthin, chlorogenic acid and other antioxidant compounds have been identified from the leaves of *C. myxa* and have been attributed with the following properties (Oza & Kulkarni 2017, Singh *et al.* 2022).

Indian cherry (*Cordia dichotoma* G. Forst.)

It is a species distributed in tropical and subtropical regions of India (Oza & Kulkarni 2017). Some of the components recorded in its leaves and fruits include coumarins, flavonoids, terpenes, and sterols (Pawar *et al.* 2014). Its medicinal uses include the treatment of ulcers and headaches (Gupta & Gupta 2015, Gupta & Kaur 2015). In addition, extracts of its leaves have been shown to have anticarcinogenic and antioxidant properties (Rahman & Hussain 2015, Rahman *et al.* 2017, Rajashekar *et al.* 2014). Christian Dior, S.A., has registered a patent (expired) for extracts with leaves of this species for the manufacture of cosmetics for their firming effects on the skin (Renimel *et al.* 1997).

Clammy Cherry (*Cordia obliqua* Willd.)

Its geographic distribution includes countries with tropical and subtropical climates, such as India, Egypt, and The Philippines, growing mostly in ravines and humid valleys (Jamkhande *et al.* 2013). Additionally, this species has been reported from The Caribbean islands such as Barbados, Cuba, and Jamaica (Aimey *et al.*, 2020). Additional information establishes *Cordia obliqua* Willd. as a synonym of *Cordia dichotoma* G. Forst (Royal Botanic Gardens Kew 2022). However certain studies refer to them as different species due to the different fruit sizes that can be found (Aimey *et al.* 2020). Due to its phytochemical compounds such as flavonoids and terpenes, different applications have been studied in the area of medicine (Raghuvanshi *et al.* 2022). A gel with anti-inflammatory properties was prepared from the methanolic extract of the leaves of this specie (Gupta & Gupta 2015). This result was a product with properties similar to the standard diclofenac sodium gel, which showed favorable outcomes for the treatment of edema. Another product was developed by the IES Institute of Pharmacy, whose inventors were granted the patent for a polyherbal toothpaste formulation, which included the extract of clammy cherry, useful for the prevention of dental disorders (Yadav *et al.* 2022). Some of the compounds identified in the leaves of this species include quercetin, rutin, kaempferol-3-O-rutinoside, rosmarinic acid, among others (Oza & Kulkarni 2017, Raghuvanshi *et al.* 2022). Some of these structures are shown in Fig 7.

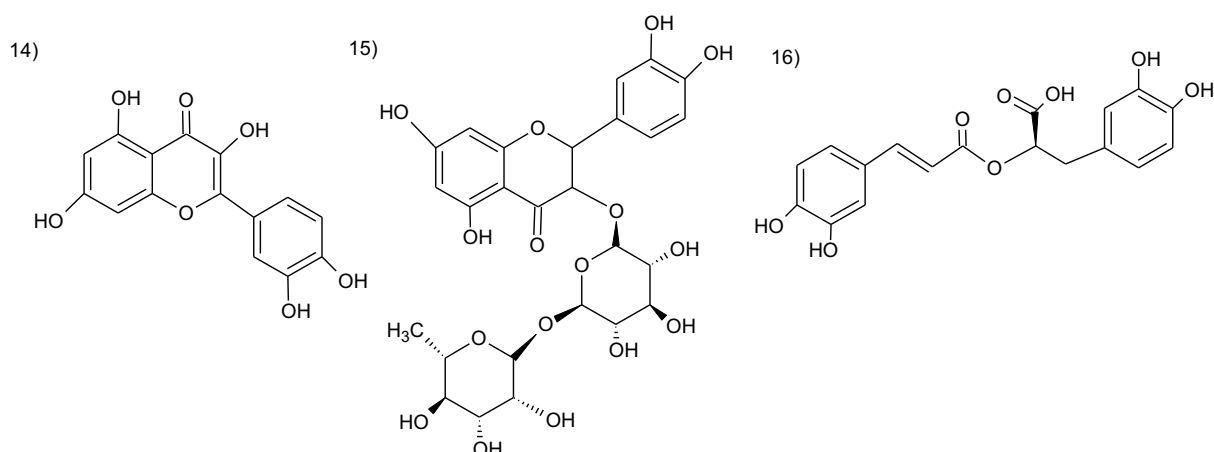


Figure 7. Chemical structures from components isolated from *Cordia obliqua* Willd. leaves. 14) quercetin, 15) rutin and 16) rosmarinic acid.

Palo de araña (*Cordia nodosa* Lam.)

This species is distributed in several South American countries, including Brazil, Colombia, Peru, Venezuela, and Ecuador (Luzuriaga-Quichimbo, 2017). In the Ecuadorian Amazon, the fruit, stem, root, and leaf of this specie have

been traditionally used to treat cough, spider bites, and snake bites and as an energizer (Saltos *et al.* 2016, Vacas *et al.* 2015). The antiophidic properties of this specie have been demonstrated by molecular coupling between the quercetin in its extract and toxins obtained from different snakes (Luzuriaga-Quichimbo *et al.* 2019). The chemical structure of quercetin is shown in Fig. 7. Likewise, the neutralizing effect of the extract of this species against the venom of the snake *Bothrops atrox* has been demonstrated (Yarlequé *et al.* 2012).

Bugre (*Cordia ecalyculata* Vell.)

This specie is distributed in Latin-American areas such as Brazil, Argentina, and Paraguay. It has been traditionally used as a cardiotoxic, diuretic, weight loss nutraceutical and agent that helps to reduce triglycerides in blood levels (Caparo-Assed *et al.* 2005, Dias *et al.* 2006). Compounds as (+)-spathulenol and β -sitosterol have been identified from its leaves (Menghini *et al.* 2008, Oza & Kulkarni 2017). Among the activities attributed to (+)-spathulenol are: anticholinesterase (Karaya *et al.* 2020), anti-mycobacterial (de Jesus Dzul-Beh *et al.* 2019), antioxidant and anti-proliferative (do Nascimento *et al.* 2018), among others. On the other hand, β -sitosterol has been shown to act in the prevention and lowering of high cholesterol (Shi *et al.* 2011, Desai *et al.* 2016). Both (+)-spathulenol and β -sitosterol have also been identified on the leaves of *Cordia verbenacea* DC. where they showed inhibition of the growth of gram-negative bacteria (Michielin *et al.* 2009, Martim *et al.* 2021). The chemical structure of this compounds is shown in Fig. 8. Additionally, its leaf extract has been evaluated as an antiophidic against the venom of the **yararacusú** snake (*Bothrops jararacussu*) and **Olfers'** snake (*Philodryas olfersii*), which improved the first symptoms of envenomation in rats in the research conducted by Scherazo-Ramos and collaborators (2020). Moreover, studies with the leaf extract of this species, in Wistar rats, showed no significant changes in biochemical and hematological assays at doses up to 400 mg/kg for 90 days (Caparroz-Assef *et al.* 2005).

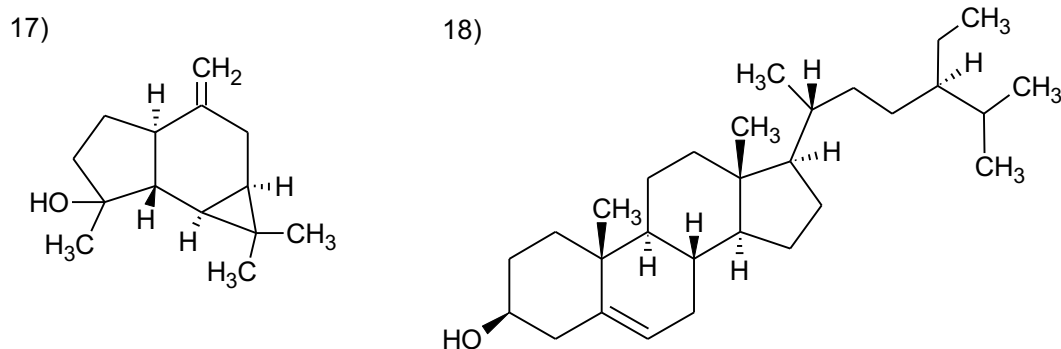


Figure 8. Chemical structures from components isolated from *Cordia ecalyculata* Vell. leaves. 17) (+)-spathulenol and 18) β -sitosterol

Cordia abyssinica R.Br. (*SynCordia africana* Lam.)

This is a species of the genus *Cordia* L. found in dry areas of Ethiopia and other African countries (Nigussie *et al.* 2021). Traditionally, leaf extracts of this species have been used for antidiarrheal purposes. This effect has been tested in mouse models with 80% (v/v) methanolic extracts at doses of 100, 200, and 400 mg/kg, causing a decrease in the prolongation of diarrhea as well as a decrease in stool water content (Ferede *et al.* 2021). However, no information was found regarding the compounds responsible for this activity. In addition, the leaves of this species were traditionally used in a mixture with butter to treat wounds and burns (Jansen 1981, Teklay *et al.* 2013). This is related to its proven anti-inflammatory and antioxidant activity, which is believed to be due to its high antioxidant content (Isa *et al.* 2016, Zemichael *et al.* 2019). Leaf extracts of this species, with different solvents, showed antimalarial activity in mice at doses between 400 - 600 mg of extract/kg body weight (Wondafrash *et al.* 2019). Extracts of these fruits have also been evaluated as pesticides (Abdelrahim *et al.* 2016). In this case, about 10 compounds could be separated, 3 of which had higher pesticidal activity, however, these compounds were not specifically identified.

Flowers

Muyuyo (*Cordia lutea* Lam.)

The **muyuyo** (*Cordia lutea* Lam.) is a native species of Peru, Colombia, and Ecuador, including the Galapagos Islands (Bernal *et al.* 2019). Its flowers have been used for the treatment of yellow fever, anemia, headache, and stomach pain, among others (Castro 2015). Experimental trials have been recorded with *Cordia lutea* extract to treat liver damage induced in rats (García *et al.* 2016, Olivera 2018, Ruiz-Reyes *et al.* 2020, Semple *et al.* 2016, Vásquez 2015),

employed for prostate cancer as a chemo-preventive (Rojas-Armas *et al.* 2020), as a protector of the gastric mucosa (Swain *et al.* 2019), and as a healing agent for oral wounds (Crisologo 2020). An important anti-allergic effect has been evidenced in floral extracts of *Cordia lutea* Lam. together with **soursop** flowers (*Annona muricata* L.) and **turmeric** rhizome (*Curcuma longa* L.) (Arroyo-Acevedo *et al.* 2016). In addition, the same extract mixture has been applied for the treatment of liver diseases and as a protector of gastric mucosa (Swain *et al.* 2019). The effective results obtained with this mixture led to the publication of a patent for the prevention and treatment of hepatitis (Cabanillas-Coral 2010). Catechins, reducing sugars, triterpenes, quinones, phenolic compounds, and anthocyanidins have been identified in ethanolic and methanolic extracts of the flowers of muyuyo (Mendocilla-Risco *et al.* 2019, Venegas 2019). Moreover, some secocycloartane glycosides isolated from the ethanolic extract of the flowers of this species have been shown to have antimicrobial activity against *Helicobacter pylori* and *Staphylococcus aureus* (I. Castro *et al.* 2019). Furthermore, rutin, a bioflavonoid of great importance in medicine, was isolated from **muyuyo** flowers with a purity of 97.55% and a yield of 8% (Venegas 2019). Fig. 9 shows images of **muyuyo**, native plant of Ecuador, taken by the authors in the province of Manabí.

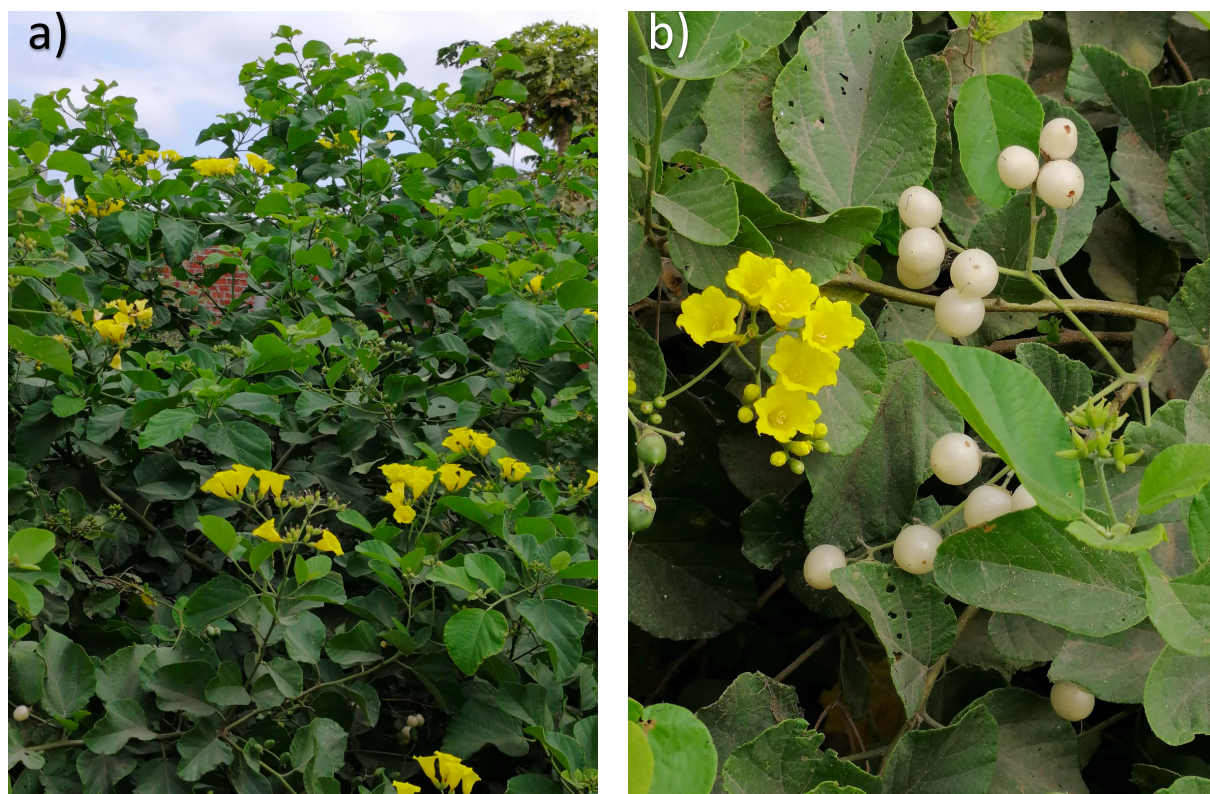


Figure 9. Images of a) shrub, b) flowers and fruits of **muyuyo** (*Cordia lutea* Lam.)

The flowers of other species of the genus, such as *Cordia myxa* L., *Cordia dentata* Poir and *Cordia macleodii* Hook, have been studied regarding the antioxidant activity of their flavonoids (Thirupathi *et al.* 2008). The mixture of fruits and flowers of *Cordia dichotoma* G. Forst has been utilized successfully for the treatment of sunburn (Melo *et al.* 2021b). The quantification of total phenols and flavonoids of some species of the genus *Cordia* L. are shown in Table 1. It is believed that the antioxidant activity of species is attached to these compounds. Therefore, a patent developed by Shuge *et al.* (2014) has been accomplished to establish a method to identify the number of polyphenols in order to quantify the quality of *Cordia dichotoma* G. Forst fruits.

Roots

Laurel *Cordia alliodora* (Ruiz and Pav.) Oken. and **Erva-baleeira** *Cordia verbenacea* DC.

From the root of *Cordia alliodora* (Ruiz and Pav.) Oken. and *Cordia verbenacea* DC. antifungal and larvicides compounds were isolated, including a phenylpropanoid derivative, hydroquinones and naphthoquinones (Ioset *et al.* 2000a, Ioset *et al.* 2000b). The chemical structures of these compounds are shown in Fig. 10. In this research, antifungal activity was observed against *Cladosporium cucumerinum*, a pathogen that affects cucumber crops and larvicidal activity against larvae of *Aedes aegypti*, the mosquito vector of yellow fever. Furthermore, these compounds have significant antimicrobial activity against Gram-positive and Gram-negative bacteria, including *S. aureus* and *K. pneumoniae*, respectively (Fouseki *et al.* 2016).

Cordia africana Lam.

Both leaves and roots of this species have been used to treat diarrhea (Teklay *et al.* 2013, Ferede *et al.* 2021). Asrie *et al.* (2016) verified this activity, where they concluded that the methanolic extract decreases intestinal fluid accumulation by 51.66% when a dose of 400 mg/kg of this extract is used. Here it is proposed that the secondary metabolites found in the root, such as flavonoids, terpenoids and saponins are responsible for this activity. The terpenoids identified in the root include triterpenoids as oleanolic acid, 3- β -lup-20(29)-en-3-ol and stigmast-5,22-dien-3 β -ol, a hydroquinone and benzaldehyde derivate and an isoflavone; 7-hydroxi-4'-methoxyisoflavone (Abate 2019, Nigussie *et al.* 2021). Some of the chemical structures of these compounds are shown in Fig. 10.

Table 1. Flavonoids and total phenols content found in species of the genus *Cordia* L

Species	Used part	Catechin content	Quercetin content	Routine content	Gallic acid content	Reference
<i>Cordia myxa</i> L.	Leaf	---	---	13.09 \pm 0.11-811.91 \pm 0.07 mg/g dry weight	4.54 \pm 0.04-31.03 \pm 0.15 mg/g dry weight	(Abdel-Aleem <i>et al.</i> 2019)
	Fruit	---	68.9 \pm 0.002 mg/g dry extract ^E	---	113.71 \pm 0.04 mg/g dry extract ^E	(Al-Musawi <i>et al.</i> 2022)
	Fruit	25.59 \pm 1.78 mg/g extract ^E	69.68 \pm 4.20 mg/g extract ^E	---	112.72 \pm 8.38 mg/g extract ^E	(El-Massry <i>et al.</i> 2021)
<i>Cordia dichotoma</i> G. Forst	Fruit	25.65 \pm 1.80 mg/g extract ^E	69.76 \pm 4.18 mg/g extract ^E	---	112.71 \pm 8.40 mg/g extract ^E	(Ibrahim <i>et al.</i> 2019)
<i>Cordia lutea</i> Lam.	Flower	---	0.56 \pm 0.59 mg/g dry weight ^M	54.73 \pm 0.07 mg/g dry weight ^M	---	(Venegas Casanova 2019)
			0.65 \pm 3. mg/g dry weight ^E	60.63 \pm 0.34 mg/g dry weight ^E		
<i>Cordia africana</i> Lam.	Bark	---	3.91 mg/g extract ^M	---	43.71 mg/g extract ^M	(Isa <i>et al.</i> 2016)
	Leaf	---	2.75 mg/g extract ^H	---	2.56 mg/g extract ^H	
	Fruit	---	---	---	---	2317 \pm 104 mg/100 g fruit

*^E: ethanolic extract, ^M: methanolic extract, ^H: hexane extract

Fruits

Indian cherry (*Cordia dichotoma* G. Forst.)

The fruits of *Cordia dichotoma* G. Forst have traditionally been used for the treatment of cough, diabetes, lung and liver conditions (El-Newary *et al.* 2016, Mishra & Prasad 2011, Sulieman *et al.* 2014). Its antitumor effectiveness has been proven in rats, which is thought to occur due to its high content of flavonoids (quercetin and catechin), phenols and glucuronic acid (Ibrahim *et al.* 2019). Additionally, their effect against wound healing has been evaluated, showing in mice an acceleration of the wound epithelialization process, attributing this effect to the flavonoid content and their action against free radicals produced during the damage process (Kuppast & Vasudeva 2006). About forty phenolic compounds were isolated from the extract with ethyl acetate of *Cordia dichotoma* G. Forst fruits. This provided a significant increase in antioxidant and antimicrobial activities against *Candida albicans*, *Escherichia coli* and *Staphylococcus aureus* (Yaermainaiti *et al.* 2021). It should be noted that these antioxidant and antimicrobial activities of plant extracts are currently being investigated to incorporate them into improved food formulations allowing to extend products shelf life (Hashemi *et al.* 2020). In contrast, the impact on fertility in rats was evaluated, for 56 days, using a hydro-ethanolic extract with fruits of this species in doses of 125, 250 and 500 mg extract/kg of weight (El-Newary *et al.* 2022). At the end of the experiment it was observed, with the highest concentration of the extract, a decrease in sperm quality. However, this effect was reversible when the extract was no longer administered over one month. *Cordia dichotoma* leaf extract has been evaluated for its antifertility activity (Sharma *et al.* 2015). Results of this study show a percentage of 81.22% of anti-implantation activity in

female rats, which demonstrates such activity. Fruits of this specie showed positive outcomes as a hepatoprotective agent in rats, exhibiting non-toxicity at doses up to 3000 mg/kg body weight (Tharun *et al.* 2020).

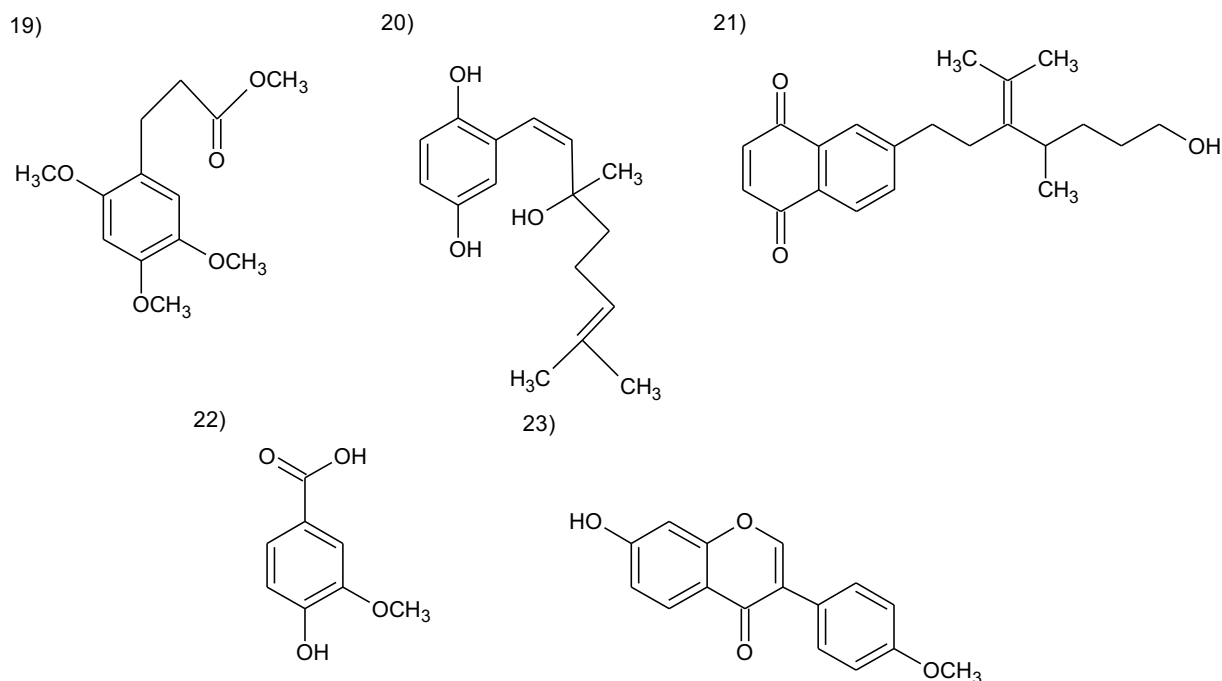


Fig. 10. Chemical structures of compounds found in *Cordia* spp. roots. Compounds identified in *Cordia alliodora* (Ruiz and Pav.) Oken. roots: 19) 1-(3'-methoxypropanoyl)-2,4,5-trimethoxybenzene, 20) 2-(2Z)-(3-hydroxy-3,7-dimethylocta-2,6-dienyl)-1,4-benzenediol, *Cordia verbenacea* DC. roots: 21) Cordiaquinone A and *Cordia africana* Lam. roots: 22) 4-hydroxy-3-methoxy-benzaldehyde and 23) 7-hydroxy-4'-methoxyisoflavone.

The hepatoprotective, gastroprotective and immunomodulatory effect has been tested *in vivo* with extracts of *Cordia myxa* L fruits (Abdallah *et al.* 2011, Ali *et al.* 2015, Hassan & Karbon 2020). Traditionally, the fruits of this species are consumed for their properties, specifically to treat respiratory and urinary infections, wounds, as well as for their anthelmintic and diuretic activity (Al-Hamdani & Al-Faraji 2017, Oza & Kulkarni 2017). The mucilage of this species has shown nephroprotective activity in rats with induced nephrotoxicity, which can be attributed to its antioxidant capacity (Ghavamizadeh *et al.* 2020, Meghwal *et al.* 2021). Some of the compounds that have been identified in the fruits of this species include linoleic acid, stigmastanol, phytol and sitosterol (Shwaish & Al-Imarah 2017). Chemical structures of these compounds are shown in Fig. 11. In addition, the fruit of these species have presented anti-Leishmania effect, mainly against *L. infantum* and *L. major*, under in vitro conditions (Saki *et al.* 2015). Similarly, *Cordia verbenacea* DC. has been used to treat the infection caused by this kind of protozoa but using the essential oil of its leaves (Pereira *et al.* 2021). Fruits extracts of *Cordia myxa* have shown antibacterial activity in wounds, which is related with its healing properties due to its antioxidant content (Aljeboury 2021, Seyedian *et al.* 2021). The fruits of *Cordia myxa* L. have been shown to have an average content of 63.9% carbohydrate, 8.6% protein, and 9.9% fat (Al-Hamdani & Al-Faraji 2017). Within the fat content found, it has about 12.4% oleic acid, which is important to both human nutrition and health (Sales-Campos *et al.* 2013). Furthermore, in this study, the aqueous extract with fruits of *Cordia myxa* L. (200 mg/ml) displayed antimicrobial activity against *Pseudomonas fluorescens*, *Salmonella* and *E. coli*, with inhibition zones of 26 mm, 25 mm, and 24 mm, respectively. Therefore, *Cordia myxa* L. extract presented a larger inhibition zone compared to the control group established with 15 mg of erythromycin.

During the pandemic caused by SARS-CoV-2 infection, multiple natural medicine alternatives were sought to control the effects. From the fruits of *Cordia myxa* and other medicinal plants ancestrally used, a syrup was elaborated whose results proved to improve the symptoms after the infection (Borujerdi *et al.* 2022, Hasheminasab *et al.* 2022). Conversely, there is a lack of studies that corroborate their effectiveness. Larki *et al.* (2020) established a method for the preparation of a syrup from *Cordia myxa* fruits, obtaining a product with phenolic compounds. The phenol content recorded in *Cordia myxa* L. is approximately 113.71 ± 0.04 mg gallic acid/g dry extract, while the flavonoid content is 68.9 ± 0.002 mg quercetin/g dry extract and 25.59 ± 1.78 mg catechin/g extract (Al-Musawi

et al. 2022, El-Massry *et al.* 2021, Murthy *et al.* 2019). More information on the content of phenolic compounds is shown in Table 1. Using fruits of this specie, antimicrobial activity was observed against *S. aureus*, *E. coli*, *S. enterica*, *B. subtilis* and *P. aeruginosa*, exhibiting inhibition zones between 13 and 17 mm (Al-Musawi *et al.* 2022). Similar results were obtained by Aljeboury (2021), who tested *Cordia myxa* fruit extract against infection with *P. aeruginosa*, showing similar results to those presented by the use of gentamicin in wound healing.

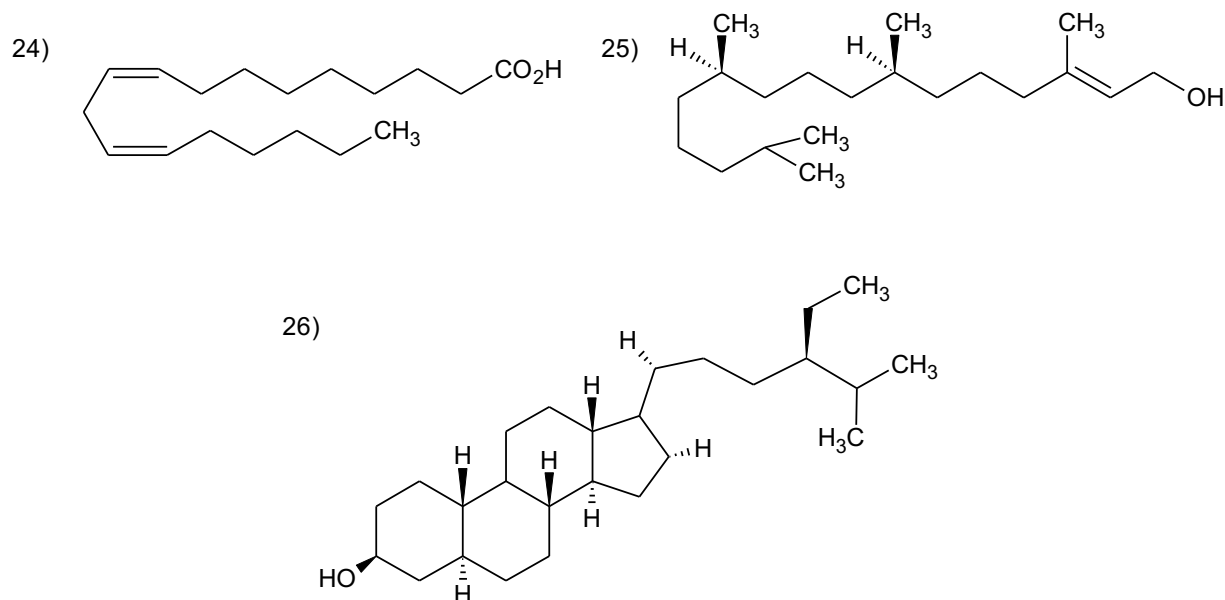


Figure 11. Chemical structures of compounds found in *Cordia myxa* L. fruits. 24) linoleic acid, 25) phytol and 26) stigmastanol.

Cordia africana Lam.

The fruit of *Cordia africana* Lam. is consumed in several regions of Africa due to its nutritional content in iron, vitamin A and C, as well as calcium, magnesium, phosphorus, and antioxidants (Mokria *et al.* 2022, Tewolde-Berhan *et al.* 2015). An average value of total phenols of 2317 ± 104 mg gallic acid/100 g fruit in this specie has been reported (Tewolde-Berhan *et al.* 2013).

Mucilages and gums

Plant-derived polysaccharides, such as pectin, cellulose, gums, mucilages and starch, have been investigated for their application in multiple industries (Amiri *et al.* 2021, Choudhary & Pawar 2014). Specifically, gums and mucilage are composed of heteropolysaccharides (Bisulca *et al.* 2016), which have a variety of usages in the pharmaceutical and food industry as binding agents, thickeners, emulsifiers, and stabilizers (Amiri *et al.* 2021, Saha *et al.* 2017). The preference to use gums and mucilage, compared to synthetic polysaccharides for industrial use, lies in the fact that they are non-toxic, biocompatible, inexpensive, and environmentally friendly (Jani *et al.* 2009, Prajapati *et al.* 2013). Gums are originated as pathological products according to external stimuli, including physical injuries, contact with insects, and unfavorable environmental conditions (Choudhary & Pawar 2014, Wadhwa *et al.* 2013); while mucilage originates naturally as part of plant metabolism (Amiri *et al.* 2021, Prajapati *et al.* 2013). Mucilages are usually extracted from the outer layer of the seeds, leaves, and roots of certain plant families (Wadhwa *et al.* 2013). Gums can be collected directly from the site they were produced, whereas to obtain mucilage the plant material is first collected and then it must go through different artisanal or industrial processes to obtain it (Bisulca *et al.* 2016). Although in some cases "gums" and "mucilage" are used interchangeably, criteria have been established for their differentiation. Examples of this ambiguity are polysaccharides extracted from guar (*Cyamopsis tetragonoloba* L.) and Tara seeds (*Caesalpinia spinosa* (Mol.) O. Kuntze), which have been given the name of guar gum and Tara gum, respectively (Saha *et al.* 2017). By definition, both products should be called mucilages; however, commercially they are known as gums (Bisulca *et al.* 2016). Besides this fact, it has been proposed to name dry mucilages as "gums", which could explain the indistinct use of both terms (Wadhwa *et al.* 2013).

Mucilages and gums can also be differentiated by their solubility in water. Gums dissolve easily in water meanwhile mucilages form viscous masses (Amiri *et al.* 2021, Choudhary & Pawar 2014, Jani *et al.* 2009). A higher proportion of branched polysaccharides than linear polysaccharides in the composition of gums and mucilages results in

higher viscosity due to the space occupied by these structures (Singh & Barreca 2020). The high content of hydroxyl groups and other polar functional groups present in the structure of both biopolymers increases the amount of hydrogen bonds, which gives the materials a higher cohesion and film formation capacity (Saha *et al.* 2017, Troncoso *et al.* 2017). Consequently, the latter turns out to be an attractive property for the development of new materials in the pharmaceutical and food industry (Amiri *et al.* 2021, Choudhary & Pawar 2014, Duppala *et al.* 2016). On the other hand, gums can be classified according to their charge, they can be nonionic or anionic gums (Prajapati *et al.* 2013). Some authors classify the gum obtained from the fruit of species of the genus *Cordia* L. as an anionic (negative charge) gum (Ahuja *et al.* 2013, Haq *et al.* 2015, Yadav & Ahuja 2010). Similarly, Arabic, karaya and gellant gums belong to the same classification, which allows scientists to know how a material will behave in a given application (Prajapati *et al.* 2013).

Methods of extraction, identification, and characterization of mucilage from *Cordia* spp.

Methods of mucilage extraction

Regarding extraction methods, some authors establish as a first step which is the separation of the seed (Castro 2019, Duppala *et al.* 2016). Although other authors propose the use of the complete fruit (Haq *et al.* 2015, Pawar & Jadhav 2015, Yadav & Ahuja 2010). The internal seed of the fruits could be a disadvantage for obtaining mucilage on a large scale, since in some methods manual compression extraction is proposed (Castro 2019). Among the methods for obtaining mucilage, extraction with hot water and subsequent precipitation is recommended either with 1% hydrochloric acid or with 95% ethanol (Haq *et al.* 2015). Fig. 12 presents a summary of the process carried out for the extraction of mucilage from the genus *Cordia* L. It should be added that in each methodology of the analyzed documents variations are exposed, such as the use of different species of the genus *Cordia* L., state of maturity of the fruit and other technical modifications of the mucilage extraction process (Hasani & Yazdanpanah 2020, Hussain *et al.* 2020). The advantage observed in the processes where hot water is used is related to the color of the mucilage obtained (less dark), since due to the temperature the enzyme polyphenol oxidase (PPO) is inactivated, causing the browning of some fruits (Haq, Hasnain, Jamil, *et al.* 2014).

Another way to extract mucilage is from dried fruits (Gupta & Gupta 2015, Hojjati & Beirami-Serizkani 2020, Toliba 2018). In this process, the dried fruits go through a grinder, then distilled water is added and the mixture is heated (Larki *et al.* 2020). The product obtained is filtered, then precipitated and filtered again for subsequent drying and storage. Petroleum ether and chloroform have been used to remove chlorophyll and other pigments from dried fruits before mixing with distilled water (Singh & Barreca 2020). In general, as a method of extraction of gums and mucilages, microwave extraction is proposed (Choudhary & Pawar 2014). Despite this, this method was not found for the extraction of mucilage from species of the genus *Cordia* L.

Methods of mucilage identification

The o-toluidine reaction has been used to identify both gums and mucilages (Choudhary & Pawar 2014). The reaction of gums and mucilages having aldohexoses and uronic acids results in a green color, in the case of aldopentose produces a red color and a mixture of both phenomena gives a reddish-brown coloration (Bisulca *et al.* 2016). The search conducted did not find the application of this reaction for the identification of mucilage of species of the genus *Cordia* L. However, its applicability was found for the identification of gum gate, gum Arabic, gum tragacanth and some mucilages (Bisulca *et al.* 2016). Therefore, the author suggest it could be applied in future studies as a simple method to visually recognize the mucilage components of species of the genus *Cordia* L. Molisch's test indicates the presence of carbohydrates, and it is confirmed by the presence of a violet ring (Gupta *et al.* 2015). This test has been used as a preliminary study to identify gums and mucilage, including the mucilage of *Cordia dichotoma* G. Forst species (Singh & Barreca 2020). In addition to the detection of gums and mucilage, a phytochemical screening can be performed to analyze the presence of impurities such as alkaloids, saponins, fats, steroids, among other compounds that can affect the quality of the product for commercialization (Shwaish & Al-Imarah 2016).

Methods of mucilage characterization

Once the mucilage has been identified, other analyses can be performed for its characterization, including scanning electron microscopy (SEM), high-performance liquid chromatography (HPLC), gas chromatography coupled to mass spectrometry (GC-MS), and Fourier transform infrared spectroscopy (FTIR) (Singh & Barreca 2020). Before applying any of the chromatographic techniques mentioned before, a hydrolysis should be performed to identify the monosaccharides present in the sample (Prajapati *et al.* 2013). A higher proportion of compounds such as galactose, glucose, rhamnose and a lower proportion of mannose, arabinose and uronic acids have been identified in *Cordia dichotoma* mucilage using HPLC (Haq, Hasnain, Jamil, *et al.* 2014), in contrast with another research where

a higher concentration of glucuronic acid, followed by glucose and fructose content were found (Ibrahim *et al.* 2019). In this same study it was seen that uronic acids have shown to have antioxidant capacity, the most potent being polygalacturonic acid followed by glucuronic acid. In *Cordia myxa* L. mucilage, a higher percentage of glucose, fructose, sucrose, maltose, and ribose (descending order) was found (Hojjati & Beirami-Serizkani 2020). The components found in the mucilage of *Cordia* L species are similar to those in other mucilages and gums of high industrial value (Amiri *et al.* 2021, Maisale *et al.* 2010). By FTIR, different functional groups have been identified in the mucilage of fruits of the genus *Cordia* L. (see Table 2). The values resulting from the FTIR analysis show a spectrum with defined peaks similar to the ones observed with polysaccharides (Keshani-Dokht *et al.* 2018). It has been shown that the carboxyl groups present in biopolymers can interact with some ions, which modifies the viscosity of hydrocolloids (Keshani-Dokht *et al.* 2018). The amount of hydrogen bonds and polar groups is related to the good bioadhesive capacity of mucilage (Troncoso *et al.* 2017). Moreover, the peak obtained at a frequency of 1030 cm^{-1} has been associated with the existence of uronic acids in *Cordia myxa* L. mucilage of (Keshani-Dokht *et al.* 2018). Uronic acids are potential antioxidants because of their ability to release hydrogen from hydroxyl functional groups (Ibrahim *et al.* 2019).

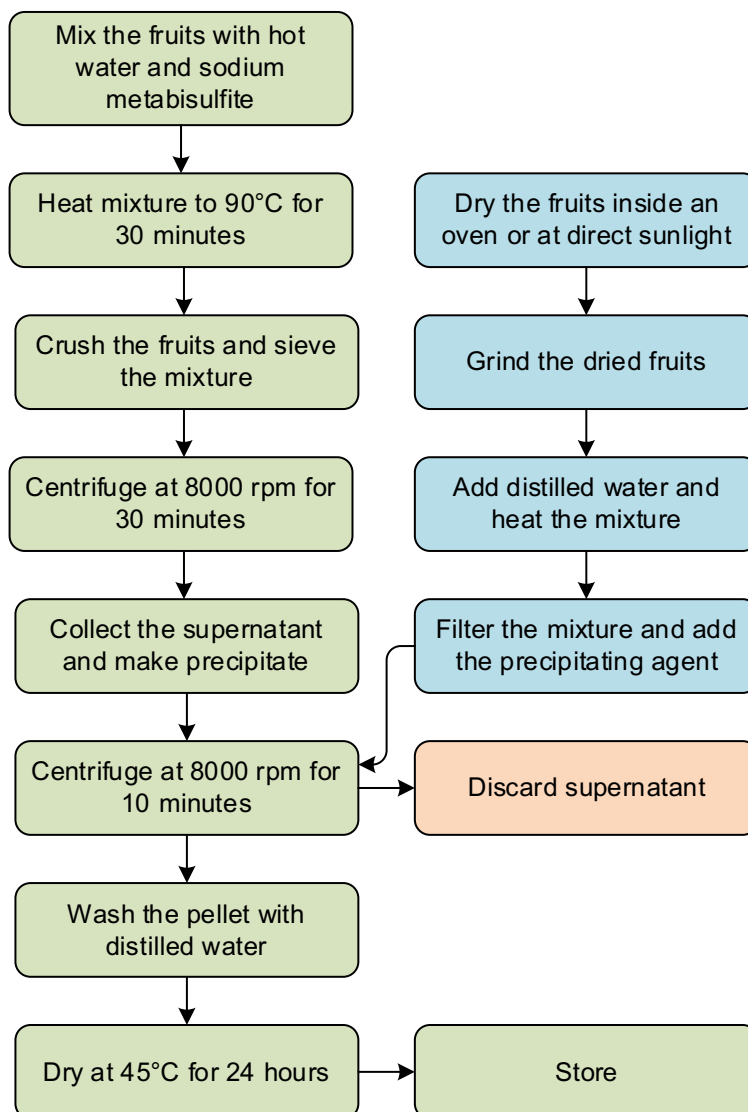


Figure 12. Process diagram of mucilage extraction from fresh fruits (process in green) and with dried fruits (process in blue) of species of the genus *Cordia* L. Created by the author from the information written in Haq *et al.* (2014) and Gupta *et al.* (2015).

Table 2. Functional groups identified by FTIR in the mucilage of fruits of the genus *Cordia* L.

Species	Identified functional groups (Frequency)				Reference
	-OH	-CH	-COOH	C-O	
<i>Cordia myxa</i> L.	3438.81 (cm ⁻¹)	2921.91 (cm ⁻¹)	1635 (cm ⁻¹)	950-1200 (cm ⁻¹)	(Keshani-Dokht <i>et al.</i> 2018)
	3442.19 (cm ⁻¹)	2925.26 (cm ⁻¹)	1412.3 (cm ⁻¹)	---	(Hojjati & Beirami-Serizkani 2020)
<i>Cordia dichotoma</i> G. Forst	2852.75 (cm ⁻¹)	2929.87 (cm ⁻¹)	1728 (cm ⁻¹)	1170.57 (cm ⁻¹)	(Pawar <i>et al.</i> 2018)
	----	2985.48 (cm ⁻¹)	1733.1 (cm ⁻¹)	---	(Gupta <i>et al.</i> 2015)
	3247 (cm ⁻¹)	---	1719 (cm ⁻¹)	----	(Saidu <i>et al.</i> 2019)
<i>Cordia lutea</i> Lam.	3270 (cm ⁻¹)	2929 (cm ⁻¹)	---	1050 (cm ⁻¹)	(Troncoso <i>et al.</i> 2017)

Organoleptic parameters such as flavor and color, as well as some rheological parameters were evaluated (Gupta *et al.* 2015). In exchange the rheological and thermal properties of *Cordia lutea* Lam. fruits have been assessed by Keshani-Dokht and collaborators (Keshani-Dokht *et al.* 2018). Results indicated that the viscosity of the analyzed samples decreased with increasing shear rate, showing a non-Newtonian pseudoplastic behavior (shear-thinning). Another study suggested that at concentrations less than 0.8% of the mucilage of *Cordia myxa* L. there is a Newtonian fluid behavior, whereas when the concentration increases, there is a pseudoplastic behavior (Keshani-Dokht *et al.* 2018). Similar behavior was observed in rheological studies of gum Arabic as well (Dauqan & Abdullah 2013).

Current applications of mucilage of the genus *Cordia* L. in the pharmaceutical area

Drug Delivery Systems

In the pharmaceutical industry, it is common to use excipients in the preparation of drugs to give them the desirable weight, volume and consistency (Pifferi & Restani 2003). However, when adding excipients, additional characteristics such as time and concentration of the drug to be administered, safety, stability and bioavailability of the drug, as well as the ease of manufacture and patient acceptability must be taken into consideration (Tekade & Chaudhar 2013). Some of the problems observed during drug development are their low water solubility and low membrane permeability of the active ingredient, which as a result influences the bioavailability of the drug (van der Merwe *et al.* 2020). In recent years, plant excipients have marked territory in pharmaceuticals due to their non-toxic, biocompatible, cost-effective and environmentally friendly characteristics (Singh & Barreca 2020). Plant mucilage and gums have been recognized as useful natural excipients for enhancing drugs properties (Amiri *et al.* 2021, Choudhary & Pawar 2014).

Some of these evaluated plant excipients include guar gum (Prakash *et al.* 2014), khaya gum (Odeku & Itiola 2002), aloe vera mucilage (*Aloe vera* L.) (Hamman 2008, Rahman *et al.* 2016) and pectin (Bansal *et al.* 2014, Ravindrakullai & Manjunath 2013). The mucilage of *Cordia myxa* L. and *Cordia dichotoma* G. Forst has been used in the design of drug delivery systems, including oral, mucoadhesive and transdermal approaches (Table 3 explores this information in-depth) (Dinda & Mukherjee 2009). Improved drug release time and texture have been reported in these studies. Drug development patents have been published using mucilage of the genus *Cordia* L. Controlled and sustained release of drugs is the main purpose of these patents (Dhiman *et al.* 2017, Mukherjee & Dinda 2007). Furthermore, increasing the concentration of mucilage used in the analyzed pharmaceutical formulations, increases the release time of the active ingredient due to the formation of a viscous layer that hinders its diffusion, which is favorable for the design of some slow-release drugs (Ahuja *et al.* 2013).

Table 3. Uses of mucilage of the genus *Cordia* L. for drug design.

Species	Country	Use of mucilage	Drug administered	Results	Reference
<i>Cordia dichotoma</i> G. Forst.	India	Mucoadhesive patch	Ramipril	10% mucilage with 53% release in the first 6 hours	(Pawar A <i>et al.</i> 2014)
		Transdermal films	Alfuzosin	16% mucilage with 44% release at 6 hours	(Duppala <i>et al.</i> 2016)
		Mucoadhesive discs	Fluconazole	Optimal mucilage/lactose formulation with a radius of 0.86	(Ahuja <i>et al.</i> 2013)
		Transdermal films	Neomycin	10% mucilage with 0.20% plasticizer demonstrated significant anti-inflammatory activity against induced edema in rats	(Shahapurkar & Jayanthi 2011)
		Oral tablets	Glimepiride	Swelling and controlled release time up to 12 hours later	(Ahad <i>et al.</i> 2009)
		Oral tablets	Diclofenac	Formulation with 2% mucilage presented a dissolution profile similar to the commercial product	(Mukherjee <i>et al.</i> 2008)
<i>Cordia myxa</i> L.	Pakistan	Oral tablets	Paracetamol	Purified and hydrolyzed mucilage is compared to the quality of tablets made with HPMC	(Tahir <i>et al.</i> 2019)
		Mucoadhesive tablets	Chlorhexidine	Faster drug release compared to HPMC use	(Moghimipour <i>et al.</i> 2012)
	Iran	Mucoadhesive tablets	Chlorhexidine	Faster drug release compared to HPMC use	(Moghimipour <i>et al.</i> 2012)

*HPMC: Hydroxypropyl methylcellulose

Topical wound creams

It is estimated that approximately one third of the traditional medicine applied to the treatment of skin wounds and burns comes from plants (Wadhwa *et al.* 2013). Some factors that contribute positively to the healing process include proper patient feeding, addition of amino acids to the diet for collagen synthesis, application of skin and mucosal grafts, as well as the use of topical dressings and creams (Morishima & Inagawa 2018). The latter have been used to locally administer medications, such as analgesics and/or anti-inflammatory drugs, avoiding first-pass metabolism (Anchal *et al.* 2021).

Natural hydrocolloids, such as gums and mucilage, have been used as dressings for the treatment of wounds and burns due to their ability to cover mucous membranes, avoiding the stimulation of nerve terminals (Amiri *et al.* 2021). From rheological and thermal studies applied to *Cordia lutea* Lam. Mucilage, it was confirmed that this material has useful properties for the development of biomaterials related to wound treatment and drug delivery systems (Troncoso *et al.* 2017). Some of these properties involve thermal degradation of mucilage around 158°C, high water retention capacity and mucoadhesion. In addition to the physical characteristics presented, it has been proposed that the flavonoid content present in the mucilage of species of the genus could be related to their healing attributes (Ibrahim *et al.* 2019, Keshani-Dokht *et al.* 2018, Kuppast & Vasudeva 2006).

The preparation of a topical cream with mucilage of *Cordia myxa* L. exhibited physical and microbiological characteristics suitable for commercialization after 3 months of storage (Karami *et al.* 2014). No microbial growth of *Pseudomonas aeruginosa* was observed in the creams. Nevertheless, this study does not include the results of *in vitro* or *in vivo* tests, only the method of preparation and evaluation of the final product.

Nanoparticles

Nanoparticles are one of the best options for achieving greater bioavailability and biological distribution of active ingredients to be administered (Amiri *et al.* 2021). The mucilage of species of the genus *Cordia* L. has been used for the elaboration, by green synthesis, of polymeric and metallic nanoparticles. Green (biological) synthesis of metal nanoparticles or metal oxide differs from chemical synthesis in that the chemical reductant is replaced by an extract of a biological product (plants or microbial agents), providing a sustainable, alternative, free of chemical contamination, less expensive and useful for mass production (Hussain *et al.* 2016). *Cordia obliqua* Willd. fruits were used in the preparation of fluconazole nanoparticles for ophthalmic use (Yadav & Ahuja 2010). The resulting product was compared via *in vitro* test with a commercial formulation, revealing no significant difference in the percentage permeation of the drug. An antitussive effect has been observed in mice with nanoparticles synthesized with *Cordia myxa* L. extract at a concentration of 750 mg/Kg, resulting in a similar effect to the use of dextromethorphan with a dose of 10 mg/kg (Salimimoghadam *et al.* 2019). The antioxidant and cytotoxic activities of micro and nanocapsules made with *Cordia myxa* L. extract have been evaluated because of its current and potential uses in the food industry (El-Massry *et al.* 2021). In this study, the cytotoxicity of crude, micro and nanoencapsulated mucilage was evaluated. There was no cytotoxicity on normal THLE-2 liver cells (IC₅₀ > 100 µg/ml); however, reduced viability of hepatocellular carcinoma cells (HepG-2) was observed. In other investigations, *Cordia obliqua* Willd. fruits were used for the synthesis of silver nanoparticles (Bharathi *et al.* 2018, Saidu *et al.* 2019). In both cases, antibacterial activity was observed against *Staphylococcus aureus* and *Escherichia coli* compared to commonly used antibiotics employing nanoparticle concentrations between 30 to 100 µg/mL. Additionally, antibacterial activity against *Bacillus circulans* and *Pseudomonas aeruginosa* have been shown (Saidu *et al.* 2019). These nanoparticles inhibited biofilm formation of 92% and 95% against *S. aureus* and *E. coli*, respectively, using a concentration of 100 µg/mL of the nanoparticles produced (Bharathi *et al.* 2018). Additionally, nanoparticles synthesized using *Cordia dichotoma* and *Cordia myxa* leaves have shown photocatalytic degradation as well as antibacterial and antioxidant activity (Kumari *et al.* 2016, Samari *et al.* 2019). Silver nanoparticles synthesized with raw and modified *Cordia myxa* L. mucilage showed antibacterial activity against *E. coli* and *S. aureus*, as well as fungicidal activity against *Fusarium solani* and *Aspergillus niger* (Tahir *et al.* 2021).

Current applications of mucilage of the genus *Cordia* L. in food industry

Edible films and coatings

Currently, most of the packaging used in the food industry is produced from petroleum derivatives (Castro 2019). Consequently, in recent years initiatives have been established to develop packaging and coatings that have non-polluting biodegradable polymers in their formulation (Saha *et al.* 2017). An edible coating consists of a thin layer made of edible materials that can be used to protect food from environmental and physical factors that could influence its quality, while an edible film consists of structures that can be consumed independently (Falguera *et al.* 2011). *Cordia myxa* L. gum has been used in laboratory tests to coat artichokes (*Cynara cardunculus* L.) and chilgoza (*Pinus gerardiana*) (El-Mogy *et al.* 2020, Haq *et al.* 2013). In both studies, increased shelf life was observed during storage, and in some treatments, improvements were observed when antioxidants were incorporated into the edible coating; Table 4 includes the use of this kind of mucilage for the design of films and edible coatings. In addition to this, films made with mucilage of the genus *Cordia* L. have shown protection against UV light, which is useful to prevent food spoilage (Haq *et al.* 2016, Saha *et al.* 2017).

Table 4. Uses of the genus *Cordia* L. mucilage for the design of films and edible coatings.

Species	Country	Product made with mucilage	Results	Reference
<i>Cordia myxa</i> L.	Pakistan	Edible film	Improved optical film properties in relation to control	(Haq <i>et al.</i> 2016)
		Edible coating for peanuts	Coating supplemented with antioxidants (BHA, BHT, AA) increased shelf life by 290%	(Haq <i>et al.</i> 2015)
		Edible coating for peanuts	Coating supplemented with CFE increased shelf life by 122%	(Haq & Hasnain 2014)
		Edible coating for chilgoza (<i>Pinus gerardiana</i>)	95% increase in chilgoza shelf life	(Haq <i>et al.</i> 2013)
		Edible film with beeswax	No significant effect of beeswax was observed	(Haq <i>et al.</i> 2016)

Species	Country	Product made with mucilage	Results	Reference
		Edible film with different plasticizers	Film with better properties was obtained using glycerol, followed by sorbitol and PEG.	(Haq <i>et al.</i> 2014)
	Egypt	Edible coating for artichoke (<i>Cynara cardunculus</i>)	Film made with ascorbic acid and calcium dichloride (CaCl ₂) showed reduction in weight loss and browning rate	(El-Mogy <i>et al.</i> 2020)
<i>Cordia dichotoma</i> G. Forst.	Iran	Edible film with essential oil from <i>Salvia Mirzaiani</i> leaves	Film with 2% of the essential oil showed greater antimicrobial activity against <i>L. monocytogenes</i>	(Hasheminya & Dehghannya 2021)
	Ecuador	Edible coating	The combination of mucilage with chitosan improved the mechanical and antimicrobial properties of the coating	(Castro 2019)
<i>Cordia lutea</i> Lam.	Peru	Chitosan films	Not positive result was obtained with <i>Cordia</i> mucilage compared to other natural plasticizers evaluated	(Gonzaga <i>et al.</i> 2019)

*BHA: Butylated hydroxyanisole, BHT: Butylated hydroxytoluene, AA: Ascorbic acid, CFE: *Cordia* fruit extract, PEG: Polyethylene glycol

Food additives

Food additives are substances that are intentionally added in order to improve the physical and/or chemical properties of foods (Blekas 2016). They can be antioxidants, preserving agents, stabilizers, emulsifiers, thickeners, acidity regulators, antibiotics, among others (Karunaratne & Pamunuwa 2017). Some gums, including guar gum, arabica, karaya, tragacanth, have been considered safe for human consumption (Singh & Barreca 2020). Although information has been collected on the uses of mucilage of the genus *Cordia* L. as a food additive, no evidence has been found to endorse the safety of its use or consumption (Hashemi *et al.* 2020). Traditionally, certain populations in Asia and Africa include the fruit of some species of the genus *Cordia* L. in their regular diet (Gupta & Gupta 2015, Thirupathi *et al.* 2008). The mucilage from the fruit of *Cordia myxa* L. has been used as a hydrocolloid to modify the properties of corn starch, which result in a formulation with enhanced textural, rheological, and stability properties (Hussain *et al.* 2020). An example of this statement is shown in the research conducted by Hasani and Yazdanpanah (2020), in which *Cordia myxa* L. mucilage was added to an apple jelly and resulted in a significant increase of antioxidants and an improvement of the evaluated viscoelastic parameters. In addition, sensory properties such as texture, flavor and appearance were acceptable to the evaluators. Mixing *Cordia myxa* L. mucilage with wheat flour could prove to be an innovative alternative for bread making, in a way that uses a low-cost and easily accessible hydrocolloid (Mahmood *et al.* 2015, Mahmood *et al.* 2018). The fruit mucilage of *Cordia abyssinica* R. Br. has been analyzed for its emulsifying properties (Mudadi Albert Nhamoiesu Benhura & Chidewe 2004). At neutral pH with 1% *Cordia* mucilage, emulsions are formed. These could be useful for application in food processing. It has been shown that mucilage from species of the genus *Cordia* L. improves the organoleptic and nutritional properties of food products, some examples are shown in Table 5.

Other applications and future trends

The carbohydrate content recorded in the fruits of species of the genus *Cordia* L. ranges from 18% to 75% (Keshani-Dokht *et al.* 2018, Patra & Chand 2017, Pawar *et al.* 2018). In countries where little is known about them, these could be used to make jams, wines, juices, and other products, just like other fruits. However, there is a limitation due to the lack of studies demonstrating the non-toxicity of the fruits of some species of the genus. Another alternative that could be evaluated is the use of mucilage as a substrate to produce specific microorganisms useful in some industries. In the present review, we have found no studies where mucilage of species of the genus *Cordia* L. is employed as a substrate. Nonetheless, cocoa mucilage was found to be successfully exploited as a nutrient for *Lactobacillus bulgaricus* and *Pichia kudriavzevii* in the production of lactic acid and ethanol, respectively (Arias *et al.* 2009, Romero *et al.* 2018). Additional information stipulates that the carbohydrate content of cocoa mucilage is estimated to be between 67% and 69% (Martínez *et al.* 2012). At this point, it is important to identify whether the carbohydrates of the fruit mucilage of the genus *Cordia* L. are fermentable, since this will affect the yield of the

final product (Swain *et al.* 2019). Therefore, the possible use of mucilage from the fruits of species of the genus *Cordia* L. as a source of nutrients for the growth of useful microorganisms in industry could be evaluated. In certain regions, where these species have no defined edible or commercial use, people could benefit from this advantage. Silver nanoparticles made with *Cordia obliqua* Willd. mucilage has been used both to prevent microbial growth and to catalytic degrade dyes. Catalytic activity against the violet crystal has been evaluated, methyl orange and rhodamine blue obtaining favorable results for its degradation (Saidu *et al.* 2019, Seyedian *et al.* 2021). Likewise, *Cordia obliqua* Willd. fruits have been used to remove heavy metals from waste waters (Bhuvanewari *et al.* 2015). Therefore, products could be designed with *Cordia* mucilage, for the removal of heavy metals and colorants that contaminate the water. On the other hand, the mucilage of *Cordia myxa* L. has been used to fix animal tissues in replacement of Mayer's albumin (Al-Shammary 2014). In this assay, the mucilaginous substance gave excellent results as an adhesive to promote adequate tissue fixation and visualization under the microscope. The fruit of *Cordia lutea* Lam. has also been used in capillary fixators, where a fixative was obtained with an action similar to the ones obtained with commercial fixators (Castro 2015). In the same way, the gel-forming properties of *Cordia africana* Lam. have been well studied (Benhura & Katayi 2011, Benhura & Katayi-Chidewe 2000, Benhura & Chidewe 2002). The use of mucilage from species of the genus as a glue for paper and cardboard has also been reported (Gupta & Gupta 2015, Ponce *et al.* 2017). A patent has been published to produce a *Cordia* mucilage powder to coat different materials for example tubes or tanks (Angus & Gayner Pneumatic Company LTD 1920). Future studies could evaluate this mucilage to produce bags and packaging that replace conventional plastics.

Table 5. Uses of the genus *Cordia* L. mucilage as food additive

Species	Country	Modified product	Results	Reference
<i>Cordia myxa</i> L.	Saudi Arabia	Corn starch	Improvement in texture and stability	(Hussain <i>et al.</i> 2020)
		Wheat flour	Improvement in the fermentation process and reduction in cooking temperature	(Mahmood <i>et al.</i> 2018)
	Iran	Apple jellies	Improvement in viscoelastic parameters	(Hasani & Yazdanpanah 2020)
		Milk ice cream	Product with improved nutritional and sensory properties	(Elkot <i>et al.</i> 2017)
<i>Cordia dichotoma</i> G. Forst	Egypt	Chocolate	Product with better sensory properties	(Toliba 2018b)
		Yoghurt	Increased viscosity and stability during 4 weeks of storage using	(Abdel-Galeele <i>et al.</i> 2013)

Conclusions

Knowing the scientific evidence that supports the traditional use of plants is essential from a medical, economic, and social point of view, especially in countries with high levels of biodiversity. Specific studies revealed the presence of some flavonoids and terpenes as active ingredients of the genus *Cordia* L., which is associated with their ancestral medicinal uses. Quercetin and rutin are phenolic compounds found in common in some species of the genus *Cordia* L., to which their antioxidant effect has been attributed. Both terpenes and phenolic compounds have been shown to have anti-inflammatory, healing, analgesic, antimicrobial, antidiarrheal, and other activities. All these biological activities are promising for the development of new products for both the pharmaceutical and food areas. In addition, an important aspect within this genus is the mucilage found in the fruits of some species. Vegetable gums and mucilage are sustainable materials that, due to their chemical, biological and mechanical properties, are being used mainly by the pharmaceutical and alimentary industries. According to the data found, the market for these hydrocolloids is worth millions of dollars, as European and Asian countries are the largest exporters of these components. On the other hand, the ancestral medicinal use of the genus *Cordia* L. is well known in the countries where it is widespread, as well as new applications of its mucilage are currently being explored. From the information gathered, it was found that most of the research on the mucilage of the genus is focused on Asian countries like India, Iran, and Iraq. In the Americas, Peru and Brazil are the countries with the most research on this subject. Most of the papers found on the genus *Cordia* L. use the term "gum" to refer to what, by definition, corresponds to the mucilage of the fruit. In addition, these studies expose mucilage from species of this genus as

a possible substitute for synthetic polymers. Among the advantages of the application of natural mucilage and gums are their non-toxicity (lower probability of generating adverse side effects), bioadhesion, biodegradation, bioavailability, and local availability. It is important to mention that more *in vitro* and *in vivo* studies are needed to recognize and quantify their efficacy and toxicity.

The ancestral uses of these species have allowed the study of the medicinal effects of some species of the genus, which has led to the development of products that are currently commercialized such as anti-inflammatory and cosmetic creams, toothpastes and some more. This shows that the phytochemical constituents present in species of the genus could continue to be evaluated to develop more products. Likewise, the evidence collected highlights other potential applications of mucilage of the genus *Cordia* L. in other activities, such as substrates for the culture of microorganisms, tissue fixing agent, hair fixative, reducing and stabilizing agent for the synthesis of nanoparticles or as a glue. The possible use of mucilage of the genus *Cordia* L. is evidenced by its addition, substitution, or combination with other biopolymers to improve and design new products. Finally, it should be noted that the scientific articles and theses found open the possibility of new studies on the previously described applications and new potential projects based on *Cordia* L. mucilage.

Declarations

List of abbreviations: E.: *Escherichia*, K.: *Klebsiella*, S.: *Streptococcus*, P.: *Pseudomonas*, HPLC.: High Performance Liquid Chromatography, L.: Carl Linnaeus, G. Forst.: George Forster, Vell.: Vellozo, DC.: Augustin Pyramus de Candolle, S.: *Staphylococcus*, S.: *Salmonella*, B.: *Bacillus*, Lam.: Lamarck, Cham: Adelbert von Chamisso, Ten.: Michele Tenore, Pav.: José Antonio Pavon, Oken.: Lorenz Oken, O.: Carl Ernst Otto, mm.: millimeters, spp.: several species, R. Br.: Robert Brown, S.A.: Société Anonyme, HPMC.: Hydroxypropyl methylcellulose, BHA.: Butylated hydroxyanisole, BHT.: Butylated hydroxytoluene, AA.: Ascorbic acid, CFE.: *Cordia* fruit extract, PEG.: Polyethylene glycol.

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