Toxic Potential of Cerrado Plants on Different Organisms

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1. Introduction

Among the natural products found in plants, secondary metabolites are particularly important for humans [1]. These compounds exhibit different biological activities and have a wide range of uses. Secondary metabolites have been used as biopesticides, herbicides, medicines, and others due to their highly toxic potential. Thus, this review aims to present information about the toxicity of Cerrado plants. For this purpose, a review was performed using PubMed, Science Direct, and Web Of Science databases. After applying exclusion criteria, 187 articles published in the last 20 years were selected and analyzed. Detailed information about the extract preparation, part of the plant used, dose/concentration tested, model system, and employed assay was provided for different toxic activities described in the literature, namely cytotoxic, genotoxic, mutagenic, antibacterial, antifungal, antiviral, insecticidal, antiparasitic, and molluscidal activities. In addition, the steps to execute research on plant toxicity and the more common methods employed were discussed. This review synthesized and organized the available research on the toxic effects of Cerrado plants, which could contribute to the future design of new environmentally safe products.

Keywords: Brazilian savanna; chemical compounds; microorganisms; natural products; plant extract; tumor cells

Abstract: Cerrado has many compounds that have been used as biopesticides, herbicides, medicines, and others due to their highly toxic potential. Thus, this review aims to present information about the toxicity of Cerrado plants. For this purpose, a review was performed using PubMed, Science Direct, and Web Of Science databases. After applying exclusion criteria, 187 articles published in the last 20 years were selected and analyzed. Detailed information about the extract preparation, part of the plant used, dose/concentration tested, model system, and employed assay was provided for different toxic activities described in the literature, namely cytotoxic, genotoxic, mutagenic, antibacterial, antifungal, antiviral, insecticidal, antiparasitic, and molluscidal activities. In addition, the steps to execute research on plant toxicity and the more common methods employed were discussed. This review synthesized and organized the available research on the toxic effects of Cerrado plants, which could contribute to the future design of new environmentally safe products.

Keywords: Brazilian savanna; chemical compounds; microorganisms; natural products; plant extract; tumor cells

1. Introduction

Among the natural products found in plants, secondary metabolites are particularly important for humans [1]. These compounds exhibit different biological activities and have a wide range of uses. Secondary metabolites have been used as biopesticides, herbicides, cosmetics, and food additives, and have been used to improve human health significantly [1]. Secondary metabolites have been used in pharmaceutical product development, with approximately 50% of all drugs currently in clinical trials being derived from plants [2].

Although secondary metabolites are mainly used for beneficial biological activities, some are highly toxic [3]. The toxicity of a substance concerns its ability to cause harmful effects, which can be observed in a single cell, a group of cells, an organ system, or the entire body. Secondary metabolites can act by different mechanisms to exert toxic effects, making these natural compounds very useful in the pharmaceutical, agricultural, and food industries.

Identifying new natural compounds with specific toxicities is essential to reduce the use of synthetic chemicals that lead to increased resistance in pests or pathogens in both the agricultural and medical sectors. Drug discovery has developed significantly in recent decades but an urgent need remains for less toxic drugs with greater efficacy and economic accessibility. Plant-derived bioactive phytochemicals are promising novel
compounds that could address some of these problems. Therefore, there is a continuous need to explore new active molecules with different mechanisms of action within the plant kingdom. Secondary metabolites in plants are defensive toxic compounds capable of inhibiting vital processes when touched and/or ingested. Phytochemical biomolecules can maximize the effectiveness and specificity of future drug design because they often have specific or multiple targets, and are both economically and ecologically sustainable [4,5].

The vast and unique biodiversity of the Cerrado biome contains many bioactive compounds [6], which enable Brazilian researchers to carry out sustainable research and to develop innovative products based on these compounds. The Brazilian Cerrado has 5% of the world’s biodiversity and 44% of the Brazilian flora [7–9]. This biome comprises a mosaic of various types of vegetation consisting of plant formations ranging from grassland, savanna, and even forest physiognomies, such as dry forests and gallery forests [10]. This diversity of environments influences the abundance of herbaceous, shrub, arboreal, and vine plants, consisting of more than 12,000 species that occur spontaneously in the Cerrado domain, with a high degree of endemcity [9,11,12]. The Fabaceae, Myrtaceae, Melastomataceae, Lauraceae, and Rubiaceae families are the most prominent in this biome regarding species richness [13]. The Cerrado flora is used by traditional populations (quilombolas, riverside dwellers, healers, and indigenous people). Various Cerrado plants, such as *Caryocar brasiliense*, *Mauritia flexuosa*, *Hancornia speciosa*, *Dypteryx alata*, and *Eugenia dysenterica*, are used ancestrally by local people as food and for therapeutic purposes in the treatment of various diseases [14,15]. It is important to highlight that the knowledge of these traditional populations associated with the use and application of natural products from the Cerrado contributes to the institution of this biome as a national heritage of great importance.

Cerrado plants have many secondary metabolites that act alone or synergistically to produce beneficial or harmful bioactivities depending on the point of view. For example, a toxic activity of a Cerrado biomolecule against insects could be beneficial to humans because we could use this valuable information to develop products to control disease vectors or agricultural plagues. Thus, in this review, we aimed to synthesize the information available about the toxicity of Cerrado plants, especially the secondary metabolites, on different organisms. This information provides the basis for future studies to develop novel bioactive compounds based on these plants for the control of human diseases and agricultural pests, and highlights the importance and fragility of this biome. Ongoing conservation of the Cerrado biome is vital for sustaining local communities and preserving endemic plant biodiversity.

2. Results and Discussion

2.1. Toxic Activity of Cerrado Plants

Although Cerrado plants are used in traditional medicine (Table 1), their biological activity is often not scientifically determined and their toxicity is unknown. Based on the literature search, the most common toxic qualities of Cerrado plants are antibacterial, antiparasitic, cytotoxic, insecticide, antifungal, and antiviral activities (Figure 1a and Tables S1–S10). In total, 194 different plant species from the Cerrado biome with potential toxic activity were identified in this literature search (Tables S1–S10). The species *Cochlospermum regium* (Bixaceae) was mentioned in most studies (n = 14) and had the following bioactivities: antibacterial, antifungal, cytotoxic, and mutagenic (Figures 2 and 3). *C. regium* is a shrub widely distributed in Brazil and requires careful conservation based on the medicinal potential of its roots (Table 1). Since the harvesting of the roots kills the plant, it is in danger of being overexploited [16]. *E. dysenterica* (Myrtaceae) has the widest array of different bioactivities among plants included in the literature search, including antibacterial, antifungal, antiviral, cytotoxic, antiparasitic, molluscicide, and mutagenic activities (Figures 2 and 3). *E. dysenterica* is native to the Cerrado and is highly regarded by local populations for its medicinal uses [15]. Different parts of this plant are used in tradi-
Ethnobotanical data for the Cerrado biome plant species included in the present review.

| Family/Scientific Name | Popular Name | Popular Use | Reference |
|------------------------|--------------|-------------|-----------|
| **Anacardiaceae**       |              |             |           |
| Anacardium occidentale L. | Caju        | Treatment of malaria and yellow fever | [17]|
| Astrotium urundeuva (M.Allemão) Engl. | Aroeira    | Antiseptic for external ulcers | [18]|
| Schinus terebinthifolius var. radiatus Engl. | Aroeira-de-brejo and aroeira-da-praia | Treatment of leprosy and tumors | [19]|
| **Annonaceae**          |              |             |           |
| Araticum do cerrado or ata brava | Bananinha | Treatment of gripe and cold | [20]|
| Himatanthus obovatus (Müll. Arg.) Woodson | Araticum or marolo | Treatment of chronic diarrhea | [19]|
| **Apocynaceae**         |              |             |           |
| Graviola Brava | Pindaiba, Pindaiba, Pindaiba, Capreuva | Treatment of digestive problems and inflammation, and used as tonic and aphrodisiac | [22]|
| **Arecaceae**           |              |             |           |
| Attalea phalerata Mart. ex Spreng. | Bacuri | Pulmonary decongestant, anti-inflammatory for joints, and is antipyretic | [32]|
| Attalea speciosa | N/F | Treatment of burns and used as a potent vermifuge | [22]|
| **Aristolochiaceae**    |              |             |           |
| Aristolochia cymbifera Mart. & Zucc. | Caçáu | Treatment of oral diseases | [33,34]|
| **Asteraceae**          |              |             |           |
| Ageratum conyzoides L. | Menstrasto | Treatment of malaria, ulcers, dysentery, and yellow fever, and is a purgative, febrifuge, and antipyretic, and is an anti-microbial, and anti-lytic agent | [35]|
| Ageratum fastigiatum (Gardner) R.M.King & H.Rob. | Mata pasto | Caticrizing and anti-infiammatory, and is an analogic and antimicrobial agent | [36]|
| **Bignoniaceae**        |              |             |           |
| bigenio | N/F | Treatment of dermatitis, and used as an insecticide agent | [39]|

Table 1. Ethnobotanical data for the Cerrado biome plant species included in the present review.
Table 1. Cont.

| Family/Scientific Name | Popular Name | Popular Use | Reference |
|-----------------------|--------------|-------------|-----------|
| Arrabidaea brachypoda (DC.) Bureau | Cipó-una, tuntirete ou cervejinha do campo | Treatment of kidney diseases and painful joints (arthrits) | [42] |
| Callichlamys latifolia (Rich.) K. Schum. | Cipo-guanchana amarela | Treatment of intestinal colic and skin conditions | [43] |
| Cuspidaria sceptrum (Cham.) L.G.Lohmann | Lirio-do-campo | Depurative, antisyphilitic, and diuretic agents | [44] |
| Cryptanthus antiquispiloticus (Mart.) Mart. Distictella elongata (Vahl) Urb. | Ipê-branco, cincofolhas and pe'-de-anta | Treatment of kidney diseases | [43] |
| Fredericia chia (Borép.) L.G.Lohmann | Carnajuru ou guajuru-piranga ou Carijuru | Wound healing | [45] |
| Fredericia cincta (Bureau) L.G.Lohmann | Cipó-una, tuntirete ou cervejinha do campo | Treatment of kidney diseases | [43] |
| Fredericia formosae (Bureau) L.G.Lohmann | N/F | Treatment of kidney diseases | [46] |
| Fredericia gunniana (Bureau) L.G.Lohmann | Cipó-una, tuntirete ou cervejinha do campo | Treatment of kidney diseases | [42] |
| Fridericia chica (Bonpl.) L.G.Lohmann | Jacarandã, caroba, caiuá, caroba-branca, pau-de-colher, dacarandã-de-minas | Treatment of syphilis and gonorrhea, and is an antimycobacterial activity | [47] |
| Fridericia craterophora (Bureau) L.G.Lohmann | Djacumã, capit快乐urao-de-cerrado and cachaporra do gentio | General tonic and used to treat diarrheaa, vitilig, and coughing | [48] |
| Fridericia formosae (Bureau) L.G.Lohmann | N/F | Treatment of cancer and dermatosis | [49] |
| Fridericia formosae (Bureau) L.G.Lohmann | N/F | Treatment of ulcers, arthritis, intestinal infections, gynecological infections, and skin diseases | [50] |
| Fridericia formosae (Bureau) L.G.Lohmann | N/F | Anti-inflammatory, used for treatment of rheumatism, vein-related problems, hemorrhoids, gastric ulcers, pain, inflammation, diabetes, hypertension, and herpes | [51] |
| Fridericia formosae (Bureau) L.G.Lohmann | Pequi | Anti-parasitic, antifungal, antibacterial, and antimalarial, used for treatment of schistosomiasis and leishmaniosis | [52] |
| Fridericia formosae (Bureau) L.G.Lohmann | “pequi”, “pique”, “pequã”, “Thorn almond”, “horse bean” or “Brazilian almond” | Treatment of schistosomiasis, leishmaniasis, malaria, and both fungal and bacterial infections | [53] |
| Fridericia formosae (Bureau) L.G.Lohmann | N/F | Anti-inflammatory and used for treatment of high blood pressure | [54] |
| Fridericia formosae (Bureau) L.G.Lohmann | N/F | Anti-inflammatory and used to promote healing | [55] |
| Fridericia formosae (Bureau) L.G.Lohmann | N/F | Treatment of fever and edema | [56] |
| Fridericia formosae (Bureau) L.G.Lohmann | N/F | Treatment of pediculosis, kidney disease, gastric ulcers, skin cancer, malaria, chronic coughs, and headaches | [57] |
| Fridericia formosae (Bureau) L.G.Lohmann | N/F | Treatment of inflammation, pain, urinary infections, and other infections | [58] |
| Fridericia formosae (Bureau) L.G.Lohmann | N/F | Treatment of gastric ulcers, bronchitis and hemorrhages, ulcers, flux with fever, diarrheaa, inflammation, wounds, cramps, cancer, rheumatism, and body pains, and used as tranquiliier, diuretic, and anti-anxiety agent. Treatment of oral mucosa lesions by Candida strains, tumors (breast cancer), and diseases of the gastrointestinal tract (diarrheaa and gastritis) | [59] |
| Fridericia formosae (Bureau) L.G.Lohmann | N/F | Treatment of oral mucosa lesions by Candida strains, tumors (breast cancer), and diseases of the gastrointestinal tract (diarrheaa and gastritis) | [60] |
| Fridericia formosae (Bureau) L.G.Lohmann | N/F | Treatment of oral mucosa lesions by Candida strains, tumors (breast cancer), and diseases of the gastrointestinal tract (diarrheaa and gastritis) | [61] |
| Fridericia formosae (Bureau) L.G.Lohmann | N/F | Treatment of urinary infections and kidney stones | [62] |
| Fridericia formosae (Bureau) L.G.Lohmann | N/F | Astringent tonic and purgative, used for treatment of swellings, especially of the lymphatic nodes and testicles | [63] |
| Fridericia formosae (Bureau) L.G.Lohmann | N/F | Treatment of gastric problems | [64] |
| Fridericia formosae (Bureau) L.G.Lohmann | N/F | Treatment of gastric problems | [65] |
| Fridericia formosae (Bureau) L.G.Lohmann | N/F | Treatment of gastric problems | [66] |
Table 1. Cont.

| Family/Scientific Name       | Popular Name               | Popular Use                                                                 | Reference |
|------------------------------|----------------------------|------------------------------------------------------------------------------|-----------|
| **Euphorbiaceae**            |                            |                                                                              |           |
| *Alchornea triplinervia*     | Tapia                      | Treatment of gastric disturbances                                            | [67]      |
| *Croton heliotropifolius*    | velame                     | Treatment of influenza, general pain, inflammation, dermatitis, gastrointestinal disturbances, malaise, poor digestion, boils, and back pain, and used as a depurative agent | [21]      |
| *Croton urucurana*           | Sangra-d’água              | Treatment of cancer, prostate cancer, diabetes, stomach pain, gastritis, uterine inflammation, kidneys, and ulcers                           | [27]      |
| *Croton velutinus*           | Pimentinha                 | Treatment of cancer                                                           | [68]      |
| **Fabaceae**                 |                            |                                                                              |           |
| *Anadenanthera colubrina*    | Angico                     | Treatment of diabetes and infections, and used as an analgesic, anti-diarrheal, anti-inflammatory, and diuretic agent | [69]      |
| *Bauhinia holophylla*        | Pata-de-vaca               | Treatment of inflammation, respiratory problems related to infection (cough, influenza, and bronchitis), diarrhea, and泚疮疼 | [70]      |
| *Bowdichia virgilioides*     | Sucupira preta             | Anti-rheumatic, anti-inflammatory, and emollient agent; used as a general tonic; and used for treatment of wounds and infections of the bladder, inflammation, stomach aches, and uterine inflammation | [47]      |
| *Copaifera langsdorffii*     | Copaiba                    | Anti-rheumatic, anti-inflammatory, and emollient agent; used as a general tonic; and used for treatment of wounds and infections of the bladder, inflammation, stomach aches, and uterine inflammation | [71]      |
| *Dimorphandra mollis*       | Faveiro-de-anta            | Treatment of inflammation (swelling/pain)                                      | [56]      |
| *Dipteryx alata*             | Cumaru                     | Treatment of diarrhea, dysentery, intestinal colic, pulmonary weakness, and chronic cystitis | [27]      |
| *Eriosema crinitum*          | Pustemeira                 | Treatment of inflammatory diseases, including inflammatory skin disorders such as psoriasis | [72]      |
| *Hymenaea courbaril*         | Jatoba ORFarinheira        | Treatment of diarrhea, dysentery, intestinal colic, pulmonary weakness, and chronic cystitis | [63]      |
| *Hymenaea martiana*          | Jatoba-da-mata             | Treatment of diarrhea, infections, prostate cancer, anemia, leukemia, anxiety (tranquilizer), weakness, cataracts, eye irritation, asthma, bronchitis, flu, pneumonia, gastritis, gingivitis, ulcer, inflammation, rhinophath, uterine and ovary infections, prostate diseases, kidneys, wounds, bone fractures, body pain, throat infections, throat inflammation, coughing with catarh, and vomiting, and used as a depurative, expectorant, female intimate-cleaning, and lung-strengthening agent, and general tonic | [74]      |
| *Hymenaea stigonocarpa*      | Jatobá-do-cerrado          | Anti-inflammatory and anti-diarrheal, nasal decongestant, used for treatment of skin conditions and earaches, and for cleaning teeth | [75]      |
| *Inga laurina*               | Ingá Branco                | Treatment of hemorrhaging, swelling of injuries, liver, kidneys, and wounds   | [22]      |
| *Lachenia dendron viridiflorum* | Surucucu                 | Treatment of hemorrhaging, swelling of injuries, liver, kidneys, and wounds   | [22]      |
| *Platyhymenia reticulata*    | N/F                        | Treatment of gynecological problems, diarrhea, and decubitus ulcers            | [56]      |
| *Pieris eremophila*          | N/F                        | Treatment of inflammation and infection, and used to promote healing           | [63]      |
| *Styrophyllum chrysolepis*   | Barbatimão                 | Treatment of leucorhea and diarrhea; as an anti-inflammatory and antiseptic agent, and used to promote blood clotting and wound healing | [77]      |
| *Styrophyllum rotundifolium* | Barbatimão                 | Treatment of scabies and used as an antimalarial agent                          | [53]      |
| *Tachigali aurea*            | N/F                        | Treatment of diabetes                                                          | [78]      |
| *Vatairea macrocarpa*        | Amargoso, maleiteira and Angelim-do-Cerrado | Treatment of diabetes                                                          | [74]      |
| Family/Scientific Name | Popular Name | Popular Use | Reference |
|------------------------|--------------|-------------|-----------|
| Lamiaceae              |              |             |           |
| Hyptis crenata Pohl ex Benth. | Hortelá-brava or hortelá do campo | Treatment of gastrointestinal disturbances, including gastric ulcers | [79] |
| Hyptis passerina Mart. ex Benth. | N/F | N/F | [22] |
| Hyptis radicans (Pohl) Harley & J.B. Pastore | N/F | N/F | [22] |
| Lauraceae              |              |             |           |
| Axonos trinervis Meisn. | N/F | N/F | [22] |
| Nectandra amazonum Ness | Jiguia or Canelo or Louro | N/F | [80] |
| Nectandra gardneri Meisn. | N/F | N/F | [22] |
| Nectandra tilius (Ruiz & Pav.) Rohwer | N/F | N/F | [22] |
| Nectandra lanceolata Nees | N/F | N/F | [22] |
| Nectandra megapotamica (Spreng.) Meisn. | Canel-a-lora, canela-preta or canela-do-mato | Treatment of rheumatism and pain | [81] |
| Ocotea lancefolia (Schott) Mez | Canela pílosa and laurel n | N/F | [82] |
| Ocotea velicosa (Meisn.) Mez | N/F | N/F | [22] |
| Loganiaceae            |              |             |           |
| Styrelmus pseudoquinsta St. Hil. | Quina-quina | Treatment of digestive problems, anemia, diabetes, coughs, and headaches, and used as a vermifuge, depurative, and appetite-stimulating agent | [83] |
| Lythraceae             |              |             |           |
| Lafoesia pacari A. St-Hil. | Mangava-brava, pacari, dedaleiro, louro-da-serra | Treatment of inflammatory conditions, gastric ulcers, wounds, fevers, and various types of cancer | [84] |
| Malpighiaceae          |              |             |           |
| Banisteriopsis arengophylla (A. Juss.) B. Gates | Cipo-prata or cipó-folha-de-prata | Treatment of renal problems and used as an anti-inflammatory agent | [85] |
| Byrronima cocclobifolia Kunth | Murici de flor rósea, murici-do-cerrado | Treatment of diarrhea | [63] |
| Byrronima cruzii A Juss. | Murici-cascudo or Murici-vermelho | Treatment of snake bites, febrile illnesses, skin infections, diarrhea, and gastric disorders | [86] |
| Byrronima intermedia A. Juss. | Murici-pequeno | Treatment of fever and diarrhea, and used as an astrigent, purgative, and anti-inflammatory agent | [87] |
| Byrronima verbascifolia (L.) Richard | Murici de flor amarela, murici-cascudo | Treatment of fever and diarrhea, and used as an astrigent and mild laxative agent | [63] |
| Malvaceae              |              |             |           |
| Guazuma ulmifolia Lam | Mutamba, Chicomagro | Treatment of skin diseases and gastric ulcers | [88] |
| Melastomataceae        |              |             |           |
| Miconia albicans (SW.) Triana | Canel-a-develho | Treatment of rheumatoid arthritis, pain, and inflammation | [89] |
| Mouriri elliptica Martius | Puça-preto or jaboticaba-do-cerrado, comoa-de-frade or comoa | Treatment of gastric ulcers and gastritis | [90] |
| Mouriri pusa Gardner | N/F | N/F | [22] |
| Pleroma stenocarpum (Schrank et Mart. Ex DC.) Triana | Puça-preto, jaboticaba-do-cerrado | Treatment of gastric ulcers | [91] |
| Meliaceae              |              |             |           |
| Cabralea canjerana (Vell.) Mart. | Canjara-rana | Astringent, purgative, febrifuge, abortive, emetic, and anti-inflammatory agent | [92] |
| Guarea guandonia (L.) Sleumer | Açafrão | Antimalaric and used for treatment of stomach aches | [26] |
| Guarea kunthiana A Juss. | Jatuaiba | Antimalaric and used for treatment of stomach aches | [26] |
| Metteniusaceae         |              |             |           |
| Emmotum nitens Miers | Unha-do-anta, unha-de-anta | Treatment of hemorrhoids | [93] |
| Moraceae               |              |             |           |
| Brosimum geophilioides Trécul. | Inharé, mamacachorro, mamacadela | Treatment of infections, venereal diseases, furuncles, “impingem” (superficial skin mycoses), cancer, anemia, pneumonia, prickly heat, vitiligo, joint pain, inflammation, rheumatism, kidney diseases, and wounds, and used as a depurative and heart tonic agent | [93] |
| Myristicaceae          |              |             |           |
| Vireo sebifer L. | Ucuiuba-do-cerrado ou mucuuba ou Ucuiuba, ucuuba branca-de-folha grande | Treatment of wounds and rheumatism | [18] |
| Myrtaceae              |              |             |           |
| Blepharocalyx salicifólias (Kunth) O.Berg | Murta | Treatment of respiratory diseases, coughs, colds, hypotension, rheumatism, hypoglycemia, diarrhea, leukorrhea, urethritis, and bladders diseases | [94] |
| Campomanesia adantiomat (Cambr.) O. Berg | Gabiobra ou guabiobra-do-campo ou guavira | Antirheumatic, antidiarrheal, hypcholesterolemic, and anti-inflammatory, and used for treatment of cystitis and urethritis | [95] |
| Campomanesia sessilifora (O Berg) Mattos | N/F | N/F | [22] |
| Campomanesia velutina (Cambr) O. Berg | Gabiobra, guavira, cambuci | Treatment of diarrhea and intestinal cramps | [93] |
| Eugenia diphterica (Mart.) DC. | Cagaieteira, cagai | Purgative agent for treatment of diarrhea | [65] |
| Eugenia involucrata DC. | Pitanga vermelha ou cereja pitanga do cerrado | Hypotensive, diuretic, antidepressive, antihypertensive, and anti-inflammatory agent | [96] |
| Eugenia klotzschiana O.Berg | Pé-rá-do-cerrado, Cabacinha | Treatment of inflammatory conditions, gastric infections, diarrhea, and gastric disorders | [87] |
| Eugenia uniflora L. | N/F | N/F | [97] |
| Myrcia bella Cambess | Mercurinho | Treatment of gastrointestinal disorders and both hemorrhagic and infectious diseases | [98] |
| Myrcia linearifolia Cambess | N/F | N/F | [99] |

Table 1. Cont.
| Family/Scientific Name | Popular Name | Popular Use | Reference |
|------------------------|--------------|-------------|-----------|
| **Myrcia splendens (Sw.) DC.** | N/F | Treatment of gastrointestinal disorders and both hemorrhagic and infectious diseases | [99] |
| **Myrcia variabilis Mart. ex DC.** | Araçá | Treatment of influenza and fever | [22] |
| **Psidium buerjaniae Mart. ex DC.** | Goiabinha-araçá, araçá-do-campo, araçá-vermelho | Treatment of inflammation and gastrointestinal disorders, and used as a diuretic agent | [101] |
| **Psidium guianense Sw.** | Araçá | Treatment of cicastritation and diarrhea | [22] |
| **Psidium cattleyanum** | Araçá, araçá-cascudo | Adstringent, hepatoprotective, anti diarrheal, and analgesic agent | [102] |
| **Ouratea castaneifolia** | Farinha-seca, mangue-do-mato, tuiohy | Tonic and astringent | [20] |
| **Ouratea spectabilis** | Folha-de-serra, batiput | Treatment of diseases of the liver and skin | [103] |
| **Psychotria capitata** | N/F | Treatment of microbial, respiratory, and skin infections | [104] |
| **Psychotria deflexa** | N/F | Antimicrobial and antiseptic agent for the promotion of wound healing and for treatment of rheumatic conditions and diarrhea | [105] |
| **Psychotria hoffmannseggiana** | N/F | Tonic and anti-helminthic agent, and for treatment of hemorrhoids, diarrhea, ulcers, and gingivitis | [46] |
| **Piper aduncum L.** | N/F | Antipyretic, antiseptic, and contraceptive agent | [106] |
| **Piper aduncum** | N/F | Treatment of intestinal and non-specific blood disorders | [66] |
| **Piper aduncum** | N/F | Treatment of bronchitis, diabetes, and kidney disease | [27] |
| **Piperita** | N/F | Antifungal, diuretic, hypotensive, antiulcerogenic, cicatrizing, and anti-inflammatory agent, and for treatment of coughs, stomach aches, and kidney pains | [107] |
| **Piperita** | N/F | Stimulant and anti-helminthic agent, and for treatment of hemorrhoids, diarrhea, ulcers, and gingivitis | [46] |
| **Piperita** | N/F | Blood purgative and appetite-stimulating agent, and for treatment of renal and hepatic diseases, stomach aches, headaches, sore muscles, hepatic dysfunction, and rheumatism | [108] |
| **Piperita** | N/F | Antipyretic, antiseptic, and contraceptive agent | [106] |
| **Piperita** | N/F | Treatment of intestinal and non-specific blood disorders | [66] |
| **Piperita** | N/F | Treatment of bronchitis, diabetes, and kidney disease | [27] |
| **Piperita** | N/F | Antifungal, diuretic, hypotensive, antiulcerogenic, cicatrizing, and anti-inflammatory agent, and for treatment of coughs, stomach aches, and kidney pains | [107] |
| **Sapotaceae** | N/F | Blood purgative and appetite-stimulating agent, and for treatment of renal and hepatic diseases, stomach aches, headaches, sore muscles, hepatic dysfunction, and rheumatism | [108] |
| **Sapotaceae** | N/F | Antipyretic, antiseptic, and contraceptive agent | [106] |
| **Sapotaceae** | N/F | Treatment of intestinal and non-specific blood disorders | [66] |
| **Sapotaceae** | N/F | Treatment of bronchitis, diabetes, and kidney disease | [27] |
| **Sapotaceae** | N/F | Antifungal, diuretic, hypotensive, antiulcerogenic, cicatrizing, and anti-inflammatory agent, and for treatment of coughs, stomach aches, and kidney pains | [107] |
| **Sapotaceae** | N/F | Blood purgative and appetite-stimulating agent, and for treatment of renal and hepatic diseases, stomach aches, headaches, sore muscles, hepatic dysfunction, and rheumatism | [108] |
| **Sapotaceae** | N/F | Antipyretic, antiseptic, and contraceptive agent | [106] |
| **Sapotaceae** | N/F | Treatment of intestinal and non-specific blood disorders | [66] |
| **Sapotaceae** | N/F | Treatment of bronchitis, diabetes, and kidney disease | [27] |
| **Sapotaceae** | N/F | Antifungal, diuretic, hypotensive, antiulcerogenic, cicatrizing, and anti-inflammatory agent, and for treatment of coughs, stomach aches, and kidney pains | [107] |
| **Sapotaceae** | N/F | Blood purgative and appetite-stimulating agent, and for treatment of renal and hepatic diseases, stomach aches, headaches, sore muscles, hepatic dysfunction, and rheumatism | [108] |
| **Sapotaceae** | N/F | Antipyretic, antiseptic, and contraceptive agent | [106] |
| **Sapotaceae** | N/F | Treatment of intestinal and non-specific blood disorders | [66] |
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Table 1. Cont.

| Family/Scientific Name | Popular Name          | Popular Use                                                                 | Reference |
|------------------------|-----------------------|------------------------------------------------------------------------------|-----------|
| Smilax brasiliensis Sprengel | Salsaparrilha or japecanga | Diuretic, diaphoretic, stimulant, anti-hypertensive, and antisyphilitic agent, and for treatment of arthritis, rheumatism, and skin disorders | [117]     |
| Solanaceae             |                       |                                                                              |           |
| Solanum lycocarpum A. St.-Hil. | Lobeira or fruta-do-lobo | Treatment of diabetes, obesity, and hypercholesterolemia                       | [118]     |
| Solanum palinacanthum Dunal | Joa            | Treatment of skin diseases                                                   | [119]     |
| Styracaceae            |                       |                                                                              |           |
| Styrax cameronum Pohl | Laranjearia-do-mato | N/F                                                                           |           |
| Styrax ferrugineus Nees & Mart. | Laranjinha do campo | Treatment of gastrointestinal diseases and fevers                             | [22]      |
| Verbenaceae            |                       |                                                                              |           |
| Lippia laphina Cham.   |                       | N/F                                                                           |           |
| Lippia origanoides Kunth. | Salva-de-Marajo and alicrim d’Angola | Treatment of oral and throat infections General antiseptic agent for the mouth, throat, and wounds, and for treatment of infant colic, diarrhea, indigestion, flatulence, heartburn, nausea, vaginal discharges, menstrual complaints, and fever | [121]     |
| Lippia salviainfolia Cham. |                       | N/F                                                                           |           |
| Vitaceae               |                       |                                                                              |           |
| Cissus erosa Rich.     | Cipó-fogo             | Treatment of warts and external ulcers                                       | [20]      |
| Vochysiaceae           |                       |                                                                              |           |
| Qualea grandiflora Mart. | Pau-terra         | Treatment of diarrhea and pain                                               | [27]      |
| Qualea multiflora Mart. |                       | Treatment of external ulcers, gastric diseases, and inflammation             | [123]     |
| Qualea parviflora Mart. | Pau-terra, pau-ferro, pau-de-tucano | Treatment of diarrhea, blood diseases, intestinal colic, amebiasis, skin diseases, and inflammation, specifically ulcers and gastritis | [124]     |

N/F: Not Found.

2.2. Toxic Cerrado Plant Families

Diverse plant families can cause toxicity on different cells or organisms (Tables S1–S9). In the present review, we found 53 different plant families with toxic properties, the most represented of which were the Fabaceae and Myrtaceae families (Figure 1b). Fabaceae and Myrtaceae are the most frequently studied plant families in the Brazilian Cerrado and are also present in more than 80% of the localities sampled [13]. The large number of studies on these plant families may be due to their widespread occurrence, which means that they are easy to collect and more likely to be used as traditional medicine.

Some botanical families were significantly associated with bioactive properties (Figure 4). The Myristicaceae, Ericaceae, Polygonaceae, Vitaceae, and Ochnaceae families are associated with antiviral activity. The Siparunaceae, Phytolaccaceae, Euphorbiaceae, Aristolochiaceae, and Areaceae are related to antibacterial activity. Nyctaginaceae is associated with antifungal activity. Sapindaceae, Malvaceae, Ebenaceae, and Solanaceae are associated with antiparasitic activity, while the Metteniusaceae family is associated with a molluscicidal activity. Piperaceae and Meliaceae are associated with insecticidal activity. Sapotaceae, Erythroxylaceae, Costaceae, Clusiaceae, Lythraceae, and Celastraceae are associated with cytotoxicity, predominantly against tumor cells (Table S1).

Other than cytotoxicity against tumor cells, Cerrado plants had low genotoxicity, mutagenicity, and toxic effects in acute and chronic treatment regimens using murine models (Figure 4 and Tables S1–S3). This low toxicity against mammals suggests that medicinal plants originating from the Brazilian Cerrado are generally safe to handle and could be used to develop safe and effective drugs, such as insecticides, antimicrobials, and antiparasitic drugs.

2.3. Experimental Design for Evaluating Plant Toxicity

The toxicity of plants is often complex and requires a careful experimental design to evaluate and characterize this toxic potential (Figure 5). First, it is necessary to choose the target plant species and the more appropriate part of the plant. Various approaches have been proposed, including (i) random selection based on plant availability, (ii) chemotaxonomic or phylogenetic selection based on known chemical classes in a particular genus or species, and (iii) ethnopharmacological selection based on the prior use of a particular plant
in local or traditional medical practice [125]. In the present review, most studies focused on plants’ leaves, roots, and stems rather than fruit or seeds (Figure 1c). Secondary metabolites vary depending on the part of the plant consumed, with different amounts of specific secondary metabolites accumulating in different plant parts [126]. From a conservation perspective, it should be noted that the collection of root specimens usually leads to the death of the plant.

Figure 1. Summary of studies on the toxic activities of Cerrado plants included in the present review. The included manuscripts were screened to generate donut charts to visualize the proportions of (a) toxic activities studied, (b) plant families studied, (c) part of the plant studied, (d) type of extract or fraction studied, (e) classes of secondary metabolites studied, and (f) main techniques used to assess the toxicity of medicinal plants.

Figure 2. The bioactive properties of the Cerrado plant species that have been investigated in multiple studies. The most studied Cerrado species was Cochlospermum regium, while Eugenia dysenterica had the most diverse bioactive properties.
Figure 3. Most representative Cerrado species with toxic activity on different organisms according to this literature survey. (a) Cochlospermum regium (Mart. ex Schrank) Pilg. (“algodãozinho-do-campo”); (b) Annona crassiflora Mart. (“araticum”); (c) Cupania cinerea Poepp. and Endl; (d) Casearia sylvestris Sw. var. sylvestris (“guacatonga”); (e) Connarus suberosus Planch. (“bico de papagaio”); (f) Solanum lycocarpum A.St.-Hil. (“lobeira”); (g) Eugenia dysenterica (Mart.) DC (“cagaita”); (h) Pyrostegia venusta (Ker Gawl.) Miers (“cipó-de-são-joão”); (i) Serjania lethalis A.St.-Hil. (“cipó-timbó”); (j) Lafoensia pacari A.St.-Hil. (“pacari”); and (k) Stryphnodendron adstringens (Mart.) Coville (“barbatimão”). All photographs were obtained from the Herbário da Universidade Estadual de Goiás (HUEG) and are available at https://www.gbif.org/pt/dataset/bbb1f181-3221-4a10-ad52-14f1da0dca26 (accessed on 23 October 2021).

After selecting the plant species, it is crucial to choose the collection site by considering the environmental factors that affect the production of secondary metabolites, such as season, circadian rhythm, temperature, altitude, atmospheric composition, soil fertility, humidity, solar radiation, wind, herbivory, air pollution, and soil pollution [126,127]. After collecting the plant samples, the correct identification of the species should preferably be carried out by a botanist and an exsiccate must be deposited into an herbarium [125].

Quality control and standardization of all processing stages are fundamental to the successful characterization of plant-derived bioactive compounds. These steps ensure the reproducibility and safety of plant-derived products [15]. Therefore, the collected material must be dried with air circulation and stored in low humidity and temperature. Grinding should only be performed when preparing the extracts. Extracts are usually prepared by percolation (cold extraction method is commonly used), by a Soxhlet extractor (hot extraction method), or by an acid base. A polar solvent (methanol or ethanol) is generally used for single extractions (cold or hot). For multiple extractions, three types of solvents are usually used: non-polar (hexane or petroleum ether), moderate polarity (chloroform or dichloromethane), and polar (methanol or ethanol) [125]. However, it is important to highlight that organic solvents are often toxic and reuse is not always possible. As a result, great efforts are being made to replace conventional organic solvents with less toxic solvents, such as supercritical fluids, ionic liquids at room temperature, perfluorinated hydrocarbons, and water, to decrease the release of toxic solvents into the water, air, and
soil, and thus to reduce the amount of environmental pollution [128]. In the present review, most studies (31.85%) used ethanol as the extraction solvent (Figure 1d). Ethanol is a suitable solvent for polyphenol extraction and is considered safe for both human and environmental health [129].

In general, the liquid extract obtained must be concentrated. Once the concentrated extract is obtained, several quality parameters are essential for standardization, such as pH, solid content, density, chemical marker content, and viscosity. After considering the chemical and physical stability of the chemical extract, drying is the most commonly used preservation method to obtain a stable plant product [15]. At this point, the investigation into the chemical constituents and/or toxic activities of the plant material can begin (Figure 5).

Figure 4. Heatmap of the plant families included in the present review grouped according to the frequency of the important bioactive properties associated with each family.
Figure 5. Proposed workflow for the effective study of plant toxicity. The study of plant toxicity should be carefully designed with the following steps carefully considered: (a) Selection of species according to plant availability, chemotaxonomy/phylogenetics, or ethnopharmacology. (b) Selection of the part of the plant to be used. It is important to understand that environmental factors also affect the production of secondary metabolites in different parts of the plant. (c) Identification of species, collection, and deposition of the exsiccate into an herbarium. (d) Obtention of extracts by percolation, Soxhlet extractor, or acid-base strategies. Various quality parameters are used to standardize the preparation of samples (pH, solids content, density, content of chemical markers, and viscosity). At this stage, it is common to investigate the chemical constituents of the extract. (e) Toxicological analysis of the plant material using different experimental methods (in silico, in vitro, and/or in vivo).

The regulatory compliance of toxicity assessments is mainly handled globally by the Organization for Economic Cooperation and Development (OECD). Until recently, toxicological analyses were primarily performed using animal models. However, in vitro and in silico analyses are becoming more acceptable in regulatory settings as an alternative to animal testing [3,130], which can reduce the cost and duration of these tests, as well as reduce the number of experimental animals used [130]. Different toxic prediction tools have become more accurate and effective [130,131]. The “-omics era” (concerning genomic, transcriptomic, proteomic, and metabolomic data) has enabled researchers to derive hypotheses on the mechanisms of action and target identification of chemical compounds using high-throughput specialized instrumentation. These techniques offer whole-organism data rather than specific information on a particular pathway or target [132]. However, bioactive promiscuity, lack of complete genome sequence data, poor gene annotation, high costs, expensive and specific equipment, and the need for qualified, trained personnel remain as limiting factors in the use of omics technology in this field.

Different testing systems exist to determine if a substance is toxic and many different toxic endpoints may be considered such as cytogenotoxicity, carcinogenesis, hepatotoxicity,
renal toxicity, neurotoxicity, reproductive toxicity, endocrine toxicity, and immunotoxicity [133]. Toxicity assessments are essential for developing drugs, agrochemicals, cosmetics, food additives, and other important products.

The cytotoxic activity of plant extracts or isolated compounds can be determined using methods that evaluate (i) cell morphology variations using fresh cell preparations; (ii) cell membrane integrity using dye exclusion assays such as trypan blue and Congo red; and (iii) the inhibition of cellular metabolism using MTT and resazurin reduction assays, which evaluate the mitochondrial function of cells by measuring the activity of mitochondrial enzymes [125,134]. In the present review, the most commonly used method for determining the cytotoxic potential of Cerrado plants was the MTT assay (Figure 1f). This method to determine cytotoxicity and cell viability is easy to use, safe, and has high reproducibility [134].

A variety of laboratory methods can be used to evaluate or screen the in vitro antimicrobial activity of an extract or pure compound. The most well-known and simple methods to detect antibacterial and antifungal compounds are disk diffusion and broth or agar dilution methods. More sophisticated techniques, such as flow cytometric and bioluminescent methods, can be employed but they are not widely used because they require specific and expensive equipment [135]. In the present review, the broth microdilution assay was the most commonly used method to determine the antibacterial and antifungal properties of Cerrado plants (Figure 1f). Dilution methods are appropriate for determining the minimum inhibitory concentration (MIC) of a compound or extract, which is the lowest concentration of an antimicrobial that inhibits visible growth [135]. The methods commonly used for in vitro evaluation of antiviral activity are based on the ability of viruses to replicate in cultured cells because they are obligate intracellular symbiotes. Some viruses cause cytopathic effects or form plaques. Others can produce specialized functions or cell transformations. Viral replication can also be monitored by detecting viral products, such as viral DNA, RNA, or polypeptides [136]. The cytopathic effect inhibition assay is one of the most reliable and robust assays for screening natural antiviral compounds [137]; is a rapid and sensitive method; and has been extensively used to detect the antiviral potential of Cerrado plants (Figure 1f).

Unlike assays used to determine the antibacterial, antifungal, and antiviral activity of plant products, bioassays for parasites tend to be highly species-specific [136]. To improve the performance of antiparasitic assays, the following should be carefully considered: (i) the use of a well-characterized, drug-sensitive parasite strain, with validated model availability, which is safe for the researcher, and (ii) the use of sensitive endpoint-reading techniques [136]. The cytotoxic potential of natural products on \textit{Leishmania} spp. and \textit{Trypanosoma} spp. was evaluated by the MTT assay, which was widely used in the articles included in the present review (Figure 1f).

Similar to antiparasitic assays, bioassays for substances that control insects are highly variable due to the abundance and variety of insects and their life cycle stages [138]. Notably, the insects used in the assay should have been standardized concerning species, age, and physiological state [138]. In general, topical application is used to study the insecticide potential of natural products because it has a faster response than ingestion and is independent of insect activity. The disadvantages of topical application are that the compound may not overcome penetration barriers, the application process is tedious, and the process requires manual dexterity [139,140]. Tests on larvae are preferred because insecticides that are effective on larval stages can prevent the development of the next generation of insects [140]. Bioassays performed under conditions that simulate management applications are also required; however, formulated products should be used to ensure standardization. On-host applications or field tests should be considered but present a particular challenge because of the possible interactions with the host [139]. The larvicidal activity assay is one of the most commonly used assays when studying natural compounds with insecticide potential (Figure 1f). However, topical tests are scarce in Cerrado plants.
2.4. Toxicity of Secondary Metabolites

Secondary metabolites are organic molecules that are not involved in the normal growth and development of an organism. The absence of secondary metabolites does not result in immediate death but rather in a long-term impairment of the organism’s survivability, as they often play an essential role in plant defense. Toxicity is, therefore, an excellent strategy to inhibit the action of predators. Secondary metabolites act on the predators through multiple mechanisms (Figure 6). They can interact specifically or not specifically with proteins (enzymes, receptors, ion channels, and structural proteins), nucleic acids, biomembranes, and other cellular components [141,142]. The interaction with these different targets can disturb the vital components of the cellular-signaling system, resulting in dysregulated essential signaling in the nervous system (e.g., concerning neurotransmitter synthesis, storage, release, binding, re-uptake, receptor activation and function, and enzymes involved in signal transduction) or in interference with vital enzymes and blocking of metabolic pathways [143]. When interacting with nucleic acids, some secondary metabolites can have both mutagenic and antimutagenic roles, and act as a mutagen by directly binding to DNA, generating ROS, or inhibiting topoisomerase enzymes [144].

![Figure 6](image)

**Figure 6.** Mechanisms of action of secondary metabolites with cytotoxic effects. Secondary metabolites can interact specifically or not specifically with biomolecules, biomembranes, and other cellular components, disturbing the vital components of the cell.

Secondary metabolites can be simply classified into three main groups: (i) terpenes (such as plant volatiles, cardiac glycosides, carotenoids, and sterols); (ii) phenolics (such as phenolic acids, coumarins, lignans, stilbenes, flavonoids, tannins, and lignin); and (iii) nitrogen-containing compounds (such as alkaloids and glucosinolates) [145]. In the present review, 60 compounds with toxic activity were detected among the studied plants (Table S10 and Supplementary Material Figure S1). The most representative secondary metabolites isolated from Cerrado plants with toxic activities were terpenes, flavonoids, and alkaloids (Figure 1e). Many alkaloids are toxic and can cause death, even in small quantities. It seems that alkaloid function in plants and animals is linked to defense mechanisms, including antibiotic activities [145]. The beneficial antibiotic effects of plant secondary metabolites could therefore be similarly useful in human medical interventions, although care should be taken to establish safety profiles for plant-derived extracts.
3. Materials and Methods

The review was performed using the PubMed (n = 314), Science Direct (n = 2184), and Web of Science (n = 378) databases. In total, 2876 abstracts were selected using the following search terms: “Cerrado” AND “cytotoxic*” OR “genotoxic*” OR “insecticide*” OR “antiparasitic*” OR “antibacterial*” OR “antifungal*” OR “antiviral*” OR “chronic toxicity*” OR “acute toxicity*” OR “mutagenic*”. The asterisk (*) was used as a wildcard and enabled the search of any letters in its place. The inclusion criteria were species (i) native to the Cerrado biome and (ii) presenting toxic activity. Gray literature and review articles were excluded (PubMed (n = 93), Science Direct (n = 1963), and Web of Science (n = 157)). Studies that overlapped were also excluded (n = 34). Thus, 2665 articles were considered to be outside the scope of this review and were excluded. A total of 187 articles published between 2000 (first record within the inclusion and exclusion criteria) and December 2020 were selected and analyzed (Figure 7).

We extracted the species, part of the plant, type of extract, dose/concentration, activity, and extraction method used from each manuscript in our analysis. The plant species were then classified into their respective families according to the Flora do Brasil website [22]. The frequency of each type of toxic activity reported was associated with plant families by generating a heatmap in R [146] using the “pheatmap” package [147].

4. Conclusions

The present review summarizes the literature from the last two decades related to the toxicity of plant species from the Cerrado biome and the secondary metabolites that have been both identified and evaluated for their toxicity. The species and compounds reported in the present review have high cytotoxicity against tumor cells and low toxicity against non-tumor cells, indicating that Cerrado plants could be used to develop new anti-
cancer drugs. Plants from the Cerrado biome presented low genotoxicity, mutagenicity, and toxic effects on murine models in acute and chronic treatments. Moreover, Cerrado plants are effective against bacteria, fungi, viruses, insects, and parasites. In combination, these data suggest that Cerrado plants can be used to develop products that can be safely handled and administered (because of the low toxicity on mammals), including insecticides against urban and agricultural pests, antimicrobials, and antiparasitic products. The notable limitations of this review are the relatively low number of studies investigating the molluscicidal activity and the scarcity of associated omics data. We hope that this review supports the conservation of the Cerrado biome against anthropogenic activities, ensuring the preservation of the vast biodiversity and natural wealth provided by this unique biome.

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