Antiviral Plants in Marajó Island

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Viruses are a global threat and, in addition to health problems, cause serious social problems to humanity. Medicinal plants have been documented as a means of complementary treatments that are useful for a range of diseases. Among many islands around the world, the island of Marajó which is part of the Brazilian Amazon, is known to have several cultures formed by indigenous, quilombolas, and mestizo populations that make use of traditional knowledge of plants. The Amazon region also has a very wide plant diversity, being estimated to have from 25 to 30 thousand species of endemic plants, and some species are also associated with the treatment of diseases. In this sense, many plants from Marajó island are frequently used for the treatment of diseases, and could be a source of new specific bioactive compounds.

viral diseases plants extract medicinal plants

1. The Main Antiviral Plants Used to Treat Viral Diseases in Marajó Island

Many factors motivated the search for new antiviral agents from medicinal plants. From these, the biggest limitations are highlighted to the effectiveness of the drugs that are currently available on the market and, although there are several options for antiviral drugs with application in several existing viruses, many of them remain intractable with these drugs. In addition, many synthetic drugs can cause viral resistance and latency. In this sense, the knowledge and wisdom of the natives regarding medicinal plants continues to be a source for the discovery of new molecules with the potential for use as new or complementary antivirals in the treatment of diseases caused by viruses [1].

In the infield of research in the ethnopharmacological area on Marajó, reports of plants that have met the immediate needs of communities are found in this area. In this sense, interest in the diversity of the flora of the Marajó region is not recent, and has led to studies of prospective bioactive compounds from medicinal plants [2] with activity against viruses, such as those caused by Human Immunodeficiency Virus (HIV), Herpes Simplex Virus types 1 and 2 (HSV-1,2), Hepatitis A and B Virus (HAV/HBV), Poliovirus, influenza, and SARS-CoV-2. The influence of many people (Europeans, Africans, etc.), and the exchange of knowledge between such people, continues to reverberate, as can be seen through popular traditions of using medicinal plants [2].

In **Table 1**, there are some plants used in Marajó to treat diseases caused by viruses. This was narrated by researchers from this group, who are also natives of the region (P.W.P.G., E.G., and A.M.). In other places of the

world, these plants are empirically used for other purposes. All species have vernacular names, as well as an empirical therapeutic indication.

Table 1. The main plants cited to treat viral diseases in Marajó Island.

Species	Occurrence *		Native Name in Marajó	Part of Plant	Use and Indication
	Continent	Region			
Alpiniazerumbet L.	Southern America	Brazil	Vindicá	L, B	Infusion used to treat common viruses
Bixa Orellana L.	Europe, Southern America	Northern europe, Brazil	Urucum	L	Infusion used to treat flu
Citruslimon	Southern America	Brazil	Limãozinho	JF	Juice used to treat flu
Citrus limonum Risso	Southern America	Brazil	Limoeiro	BF	Infusion used to eliminate secretion from the lungs
Dysphania ambrosioides (L.)	Europe, Southern America	Northern europe, Brazil	Mastruz	L	Juice is used to eliminate secretion from the lungs in viral infections
Libidibia ferrea (Mart. ex Tul.) L.P.Queiroz	Southern America	Brazil	Jucá	S	Infusion used to treat flu
Ocimum gratissimum L.	Southern America	Brazil	Alfavacão	L	Tea used to treat flu and cough
Plectranthus amboinicus (Lour.) Spreng	South Africa, Southern America	Kenya, Angola, Mozambique, Swaziland, northern Natal, Brazil	Hortelã-Grande	L	Tea used to treat inflammation and sore throat
Spondias mombin L.	Southern America	Brazil	Taperebazeiro	L, B	Infusion used against herpes virus

2. Antiviral Compounds of Medicinal Plants from Marajó

Plants in general naturally have defense mechanisms against microorganisms, especially viruses, which are low-molecular-weight secondary metabolites with a level of toxicity. This factor can explain why such plants have been used therapeutically for viral diseases.

2.1. *Alpinia zerumbet L.*

Alpinia zerumbet L. is a medicinal plant used in many states in the north and northeast of Brazil [3]. In the Amazon, it has the vernacular name of “Vindicá”. More specifically, in Marajó, the leaves are used to prepare tea and baths that empirically help or bring some benefit for the treatment of flu and colds. To corroborate these antiviral reports, aromatic heterocycles of compounds isolated from the leaves and rhizomes of *Alpinia zerumbet* showed excellent antiviral activity for human immunodeficiency virus type 1 by the mechanism of inhibition HIV-1 integrase and neuraminidase activity [4]. Moreover, extracts from this species containing dehidrokavaina (DK), and dihydro-5,6-dehydrokawain (DDK) showed the same activity, with IC_{50} of values of 30 and 188 µg/mL. These data confirm and highlight the antiviral potential of that species, which is well distributed in the Marajó island.

2.2. *Bixa Orellana*

Another plant with antiviral properties is *Bixa Orellana*, also named “Urucum”. It is a very common plant in the northern region of Brazil; however it is also present in other countries of South America, such as Peru, Columbia, Ecuador and Mexico [5][6]. Two antiviral compounds have been isolated from this plant: Procyanidin B2 and Lutein. These compounds block the viral binding to the cell receptors for influenza and inhibit the HBV protease. In this sense, *B. orellana* is a promising source of compounds that could be applied in antiviral therapy [7][8][9].

2.3. *Citrus limon*

The *Citrus limon* species is known in the Marajó island as “Limãozinho”. It has many pharmacological properties as well as important natural chemical constituents, including citric acid and ascorbic acid [10]. For some time, the pharmacological properties of this species were associated with the presence of vitamin C. However, recent data confirm the participation of other supporting substances [10], such as Terpenes [11], Limonene, β-pinene, and γ-terpinene, which have been associated with reductions in hepatitis A virus (HAV) infectivity [12] by reducing HAV infectivity. These results reinforce the potential of this species and place it in the window of natural products with antiviral activities.

2.4. *Citrus limonum Risso*

Citrus limonum Risso is commonly called “Limoeiro” in the Marajó Island [13]. It belongs to the Rutaceae family and has round and acidic fruits called lemon. Tea from the peels of *Citrus limonum* fruits is used as a natural expectorant, which helps in the treatment of flu and viruses that cause the accumulation of secretions in the lungs. Recently, the literature reviewed the essential oils of *Citrus limonum*., and reported several therapeutic benefits, including antiviral activity [14]. To corroborate its empirical use in the Marajó, the literature has already highlighted a role that proves its activity as an expectorant agent [15]. Sheppard and Boyd observed that the expectorant property of lemon oil, when inhaled, is mainly due to limonene. Recent data reported its activity against influenza viruses [16] [17], as well as activity against Hepatitis A Virus (HAV), attributed to Proanthocyanidins, by a slight reduction in virus infectivity [12].

2.5. *Dysphania ambrosioides*

Dysphania ambrosioides, also known as “mastruz”, is widely used in Brazil as a medicinal plant. It has been reported to have beneficial effects against respiratory diseases. The literature [18] carried out a study with a computational approach (in silico), evaluating the potential of the compounds present in this species, and found that such compounds could inhibit the particles involved in the replication of the SARS-CoV-2 virus, responsible for causing SARS-CoV-2. The focus was on the flavonoid and derivative compounds that are present in this species. The results suggest that the substances Rutin and Nicotiflorin, two of the main “mastruz” flavonoids, and their compounds showed promising potential to block 3CLpro and RdRp proteins, and could play a key role in decreasing or inactivating SARS-CoV-2 infection [18][19][20][21]. The study points to Rutin as a possible alternative to low-molecular-weight heparin (LMWH), due to its anticoagulant and anti-inflammatory effects and its potential protection against acute lung injury (ALI). A computational study has its limitations. Therefore, it is necessary to conduct more in-depth studies, in vitro, in vivo, and clinical, to consolidate the use of these flavonoids or other detected substances, such as medicine.

2.6. *Libidibia ferrea*

Libidibia ferrea has been suggested to inhibit the replication of HSV-1 and PV viruses. One pioneer study [22] reported the antiviral effect of *L. ferrea*, and the effect of the sulfated polysaccharide obtained from the aqueous extract of *L. ferrea* seeds and its antiviral activity, as well as its ability to prevent viral replication, and viral fixation, and its direct effect on viral particles. The sulfated polysaccharide from *L. ferrea* extract has a polyanionic character, as sulfated polysaccharides are potent inhibitors of HSV binding to host cells competing with viral glycoprotein receptors. Thus, it is assumed that these substances end up solubilizing the virus envelope, which can also cause chemical changes and the inhibition of essential proteins reaching the virus envelope [22]. The same inhibition effect of this sulfated *L. ferrea* polysaccharide was observed for Poliovirus (PV), and was even stronger in this case, as it interfered in the initial stages of virus replication. Thus, this sulfated *L. ferrea* polysaccharide has potential as an antiviral, and these mechanisms are likely results of the action of the complex compounds in the extract composition, which may all act together to avoid virus replication [22].

2.7. *Ocimum gratissimum L.*

Plants of the genus *Ocimum* are widely used in African countries to treat HIV infection. The literature reported that *Ocimum gratissimum* leaf extract had 90% effective HIV inhibition after 2 h of infection, a better result than that obtained for AZT, a drug used in the treatment of SIDA, under the same conditions [23]. These results were attributed to Eugenol, Thymol, and ursolic acid caused by the inhibition of virus replication, and direct destruction of the virion mechanism. Moreover, a study conducted with *Ocimum* species reported activity of this species against Herpes Simplex Virus Type-1 (HSV-1) [24]. All pieces of evidence confirm the antiviral potential of *O. gratissimum,* as well as the antiviral reports by people from Marajó.

2.8. *Plectranthus amboinicus*

A flavonoid-rich fraction of the *Plectranthus amboinicus* showed antiviral activity against HIV-1 and the Herpes Simplex Virus type 1 [25]. It was checked for antiviral activity using the cleavage of peptide substrate method. It

showed excellent antiviral activity in cell analysis, with IC_{50} 100 µg/mL, and mechanisms of action for inhibiting HIV-1 protease, showing potential for use as an antiviral agent.

2.9. *Spondias mombin L.*

Spondias mombin L. is a medicinal plant known vernacularly as “taperebazeiro”, which belongs to the Anacardiaceae family and is found in almost all Brazilian territory (except in the South). This species has been reported to have antiviral activity against Herpes Simplex Virus type 1 (HSV-1) [26]. A fraction enriched with tannins and mainly geraniin showed promising anti-HSV-1 activity. The replication cycle of HSV is widespread in molecular biology (1. viral adhesion; 2. entry into host cells; 3. genome modification; 4. replication of genetic material; 5. creation of new capsids; 6. propagation of new viral particles). In this sense, data in the literature highlight that the natural products of split *S. mombin* may have their main effects in the early stages of HSV-1 infection, and show a better immune response when incubated with viral particles (glycoproteins gB and gD of HSV-1 surface).

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