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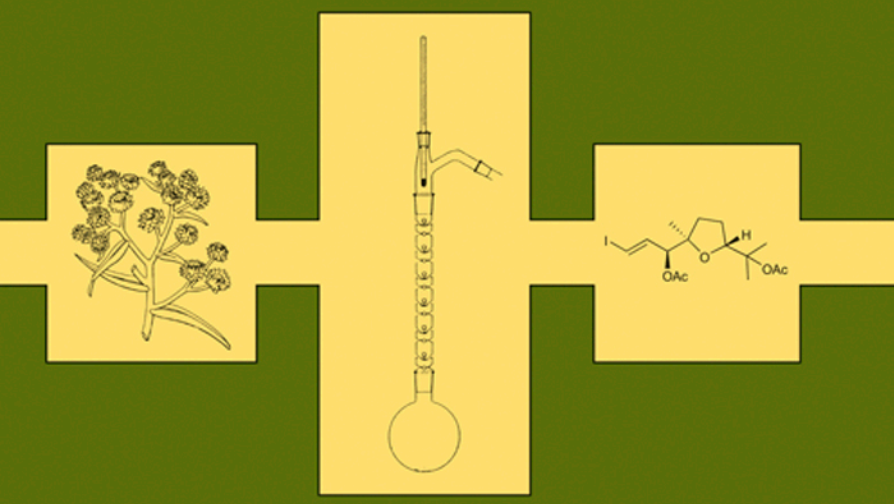

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PLANTS WITH POSSIBLE ANXIOLYTIC AND/OR HYPNOTIC EFFECTS INDICATED BY THREE BRAZILIAN CULTURES - INDIANS, AFRO-BRAZILIANS, AND RIVER-DWELLERS

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ABSTRACT: This study shows that, in spite of the great biological and cultural potential in Brazil, there is, even today, no phytomedicines originating from this flora, as an alternative to allopathic anxiolytics and hypnotics prescribed by psychiatry. Thirty-nine plants with potential anxiolytic effects and 28 hypnotics were indicated in the course of ethnopharmacological surveys carried out with Afro-Brazilians and/or Quilombolas, the Caboclo population (river-dwellers), and Indians in Brazil. Practically no pharmacological studies have been found in the scientific literature as evidence of their popular use. From the phytochemical point of view, it is of interest to observe that flavonoids, essential oils, phenolic acids, and alkaloids are the chemical constituents predominantly present in these species, both in those indicated as anxiolytic, and the hypnotic.

INTRODUCTION

Biological and Cultural Aspects in Brazil

The interest in flora in Brazil can be traced back to the 16th century: countless European botanists and naturalists visited the country to study the landscape and flora as from the 17th century and on, until the end of the 19th century [1,2].

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In this contact, some of the medicinal uses of plants were brought to Brazil, above all, by the Portuguese: rosemary (*Rosmarinus officinalis* L.), while some of the Indian habits were taken from here to the European and African continents: consumption of peanut (*Arachis hypogaea* L.) is an example of this [3].

Brazil, with 8,547,403.5 km^2, possesses the richest flora in the world, with over 56,000 species of plants - almost 19% of the world flora. Estimates today point to 5-10 species of gymnosperms, 55,000-60,000 species of angiosperms, 3,100 species of bryophytes, 1,200-1,300 species of pteridophytes, and some 525 species of marine algae [4,2].

These species are distributed over five main types of biomas: the cerrado savannahs, the Mata Atlântica rain forest, the Amazon forest, pantanal wetlands, and caatinga semiarid scrublands, as can be seen in Fig. (**1**). In spite of all this wealth, the first two are among the ecosystems regarded as hotspots in South America [5].

Brazil is rich not only from the point of view of biodiversity, but also of cultural diversity and is inhabited by, at least, three types of population that live in the rural areas of the biomas cited above, many of them isolated geographically from official medical assistance.

Indigenous Ethnic Groups

Estimates show there are 218 Indian groups inhabiting Brazil - a total of some 370 thousand persons, approximately 0.2% of the total population of Brazil, speaking 180 different languages [6]. This population in Brazil was once, however, much greater. It is difficult to say for sure how many Indians there were in Brazil before colonization by Portugal in 1500 - an estimated 5 million. Three centuries subsequent to this contact with Europeans, this number was reduced to 1 million [7].

Specialists in healing in these ethnic groups are the shamans, that generally use plants that will alter their perception, above all, in rituals for healing, known by the academic community as shamanism. In addition to consuming these plants, that we refer to as hallucinogens, they prescribe as many more, with varied therapeutic purposes, to the sick that seek them out: this process is generally carried through with spiritual aid. In shamanism, a shaman may be in a state of trance, brought on by one of the hallucinogenic plants, and may extracts the disease from the sick in a materialized form.

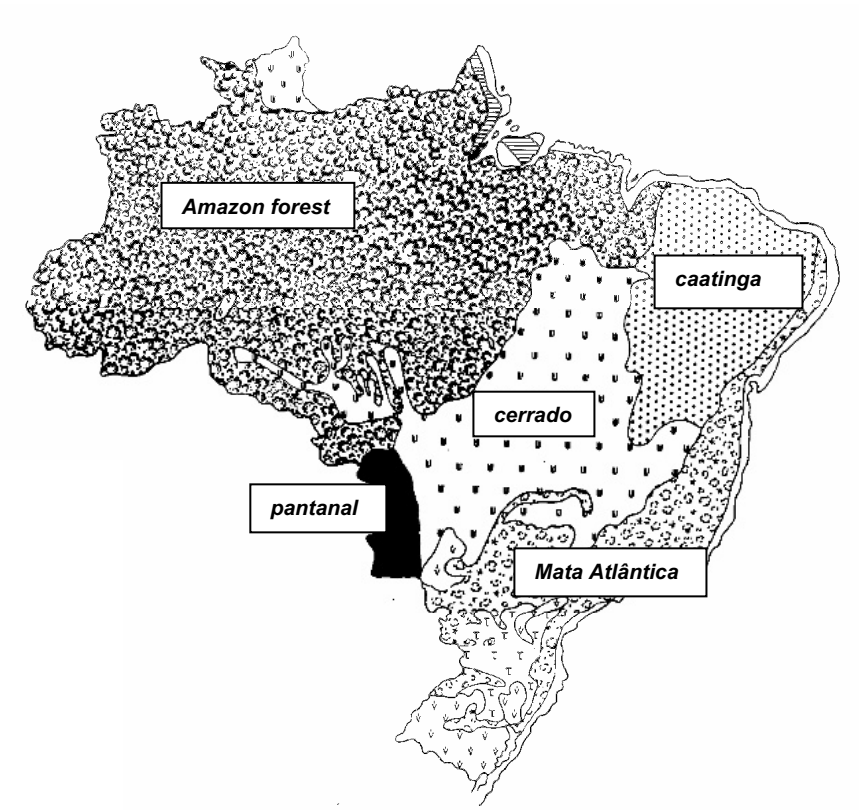

Fig. (1). The five main biomas in Brazil, prior to human interference. Today, different parts of each of these have ceased to exist and made way for soybean monoculture, human occupancy, and grazing lands, amongst others.

A review by Rodrigues et al [8] shows there are ethnopharmacological surveys concerning 26 indigenous groups in Brazil, some of them occupy the borders of other South American countries [9-38]. The use of 307 plants with possible action on the CNS, with 25 classified as "hallucinogens" were recorded [8]. This review also includes 10 plants with potential anxiolytic and 7 with hypnotic effects, to be presented in the present study, below.

Quilombolas and Afro-Brazilian Groups

There are in Brazil an estimated 178 groups of descendants of Afro-Brazilian runaway slaves, called Quilombolas, who sought hideouts in

areas named Quilombos [39]. In addition, rural and urban areas in Brazil are occupied by Afro-Brazilians, resulting from slavery in Brazil from the 16th until the 19th century. An estimated 3,216,800 African slaves are believed to have been brought to Brazil at this time [7].

The slaves found great biodiversity in Brazil and set about deciphering same, to survive both physically and culturally. Adaptation to the new habitat and the new social conditions gave way to substitution of indispensable plants that were not found here [40]. When it was not possible to find these plants, the Black population developed strategies so that these species could be brought from Africa [40]. Species such as *Cola acuminata* (P. Beauv.) Schott & Endl. (obí), *Garcinia kola* Heckel (orobô kola nut) and *Elaeis guineensis* Jacq. (dendê oil palm) were introduced in Brazil [41].

This ethnic group includes a wealth of experts in healing: faith healers, mediums, "pai-de-santo" priests, "mãe-de-santo" priestesses, "babalorixás", among others. Rituals for healing may also vary, most of them occurring during the "candomblé" and "umbanda" ceremonies. These rituals involve spiritual therapy, divination, healing baths, and incenses [41]. In this therapy, a great number of plants are mixed together to make up each formula in a manner similar to that observed among the Caboclo population (river-dwellers), as opposed to that observed among the Indians [42].

Some studies on the therapeutic use of plants by the Black population have been carried out in Brazil: [3,40,41,43,44,45,46,47,48] and, recently, by Rodrigues & Carlini [49,50].

Mestizo Populations: River Dwellers

Derived from the miscegenation of European, Indian, and Black (including such as: Caboclo river dwellers, coastal Caiçara fishermen, Seringueiro rubber tappers and Jangadeiro raftsmen).

The Caboclo river dwellers living in the Amazon region inhabit the banks of the rivers and live from hunting, fishing, fruit-gathering, and subsistence agriculture. They usually possess a great deal of knowledge on the therapeutic use of plants and animals available to them within their environment [51].

Until ten years ago, over one half of the original population of Amazon Caboclos had been dislodged from their settlements and forced into nearby towns. In these cases all of the thousand-year adaptive wisdom

this population had acquired from the Indians to survive in a site as inhospitable as the Amazon forest, has been lost [7].

Specialists in healing among the Caboclo population include: faith healers, midwives, and healers, among others. In the course of healing practices, in addition to prescribing medicinal plants and animals, rituals are used: prayers, during which branches of specific plants such as vassourinha broom (*Scoparia dulcis* L.) are shaken around the body of the sick.

A record of plants utilized by Caboclos in the Amazon region for medicinal purposes has been compiled by some Brazilian researchers [52-59].

The ethnopharmacology was defined by Schultes [33] as a sub-area of the ethnobotany and refers to the medical or pseudomedical use of plants and animals by pre-literate societies.

Ethnopharmacological studies carried out in Brazilian forests are promising instruments for the discovery of new drugs: the high indices of biodiversity and endemism associated to a process of intense miscegenation resulted in considerable wealth of knowledge on the flora.

In addition, ethnographical work with these groups has shown us that the use of certain categories of plants by any one specific culture is related to their day-to-day needs. Use of hallucinogenic plants is more common, for instance, among Afro-Brazilians and Indians [42]; in healing ceremonies, Shamanism or "Umbanda"rituals, that require the use of plants to facilitate communication with spiritual guides [3,60].

Anxiolytic and Hypnotic Drugs: Psychopharmacology and Psychiatry

Psychoactive substances (including plants) are those that alter some aspect of the mind including behavior, mood, anxiety, cognition, and well-being [61]. They may be classified in three types: a) depressors of Central Nervous System (CNS) activity, such as neuroleptics, anxiolytics, and hypnotics; b) CNS stimulants - antidepressives and amphetamines, mainly; and, finally, c) disturbers of the CNS - hallucinogens [62].

Anxiolytics are substances that, as the name suggests, precipitate a break (lise) in anxiety, and hypnotics are substances that induce sleep. One same substance will generally serve both to reduce anxiety and induce sleep, depending on the dose employed. These drugs are classified

as CNS depressors, producing slower mental processes, reduced reflexes, deficient attention, and memory impairment. On prescribing this medication, the patient must be informed of the risks in driving and operating machinery. Because they are psychotropic drugs, they may potentially induce tolerance and dependence [63,64]. On prescribing a benzodiazepine (BDZ), a doctor should restrict use of same to short periods of time - from 2 to 4 weeks at the most, and only within the framework of severe anxiety or insomnia [65]. In addition, the risk of interaction with other substances is high, particularly with alcohol [66]. The search for new substances to reduce anxiety, that will entail fewer damages than the BDZs are promising prospects in the field of medical therapeutics.

Anxiolytics act together with the gabaergic receptors facilitating coupling to Gama Amino Butiric Acid (GABA) - the main neurotransmissor inhibitor to the CNS, to GABA A receptors. This is an ionotropic receptor that, coupled to GABA, opens channels of chloride, increasing the influx of these anions and rendering the neuron hyperpolarized, reducing nervous transmission [67].

BDZs are among the most prescribed drugs worldwide. Consumption of these drugs is believed to double every five years [68]. In 1999, Brazilian consumption of BDZs was approximately of 20 DDDS (defined daily doses), similar to that of the U.S. [69].

A recent review reported by Ernst [70] assesses the conditions of the various plants, amongst these Blue skullcap (*Scutellaria lateriflora* L.); Gotu kola (*Centella asiatica* (L.) Urb.); Guaraná (*Paullinia cupana* Kunth); Kava-kava (*Piper methysticum* G. Forst.); Lemon grass (*Cymbopogon citratus* (DC.) Stapf); Passion flower (*Passiflora incarnata* L.) and Valerian (*Valeriana officinalis* L.). Only the use of Kava-kava seems consistent as to an anxiolytic effect, comparable to that of BDZs. The author concludes stating that today there are no well documented studies on alternatives to conventional anxiolytics [70]. Several studies have reported the safety and advantages of the use of Kava-kava in relation to the BDZs in that they do not induce dependence and are well tolerated by the patients [71]. There are, however, in scientific literature, reports of cases of hepatitis and hepatic failure produced by chronic use of Kava-kava or even ataxia with acute use of same [72]. Finally, kavalactones from extracts of Kava-kava have been identified as powerful inhibitors of various enzymes of the CYP450 system, which may result in

severe complications in the use of this plant with certain types of medication [73].

Synergism produced by concomitant use of two or more plants popularly recommended as "tranquilizers" is of interest as, for instance, simultaneous use of Kava-kava extract and Passiflora extract [74]. The tendency is to mix extracts from various plants into one single product, also a practice in Brazil. One example is a medication advertised wholesale in the media in Brazil to spread the message that: to feel "ever so relaxed", just take *Passiflora alata* Ailton, *Erythrina mulungu* Mart. ex Benth, and *Crataegus oxyacantha* Linné. The product described as phytomedicine does not include one fundamental piece of information - namely, a 16% alcoholic content. So, what exactly does bring on the relaxed feeling: the plant extracts or the alcohol?

The Phytochemical Approach in the Study of Medicinal Plants

Plants are regarded as an important source of biologically active natural products, many of which are models for synthesis of a great number of medicines. Researchers of natural products are impressed by chemical constituents found in nature in an almost unbelievable range of structures and physico-chemical and biological properties [75]. With the prospect of obtaining new medicines, two aspects distinguish products of natural origin from the synthetic: molecular diversity and biological function. Molecular diversity of natural products is much superior to that derived from processes of synthesis, that in spite of considerable advances, are as yet limited. In addition, as the product of organisms that are very similar to the metabolism of mammals, natural products often show properties additional to the antimicrobian associated to them [76]. The quality of a phytomedicine is ensured through the characterization of their chemical constituents, or pharmacological activity. None of the alternatives are swift or of rapid execution. The most secure option would be to identify and determine the concentration of active substances, which is not always possible because of the great number of components present in the extract. Use of marker substances, listing, for instance, the concentration of the more abundant substances, or that of chemical groups with biological activity is an alternative to be validated.

Anxiolytic Drugs: Animal Models for Study

Several animal models have been developed in the study of anxiety in order to verify the effectiveness of new drugs, study their mechanisms of action, or investigate the pathophysiological phenomena involved in anxiety. These models are based on punishment-conflict procedures, such as the Geller and Steifer model [77], or, as the model for discrimination of the convulsive effects of penthylenotetrazol, or, as yet, in exploratory behaviors such as the Elevated Plus Maze (EPM) [78] model, and also fear of a new situation such as a neophobic reaction in rats. Amongst the most utilized, we may cite the EPM, the neophobia test, and the open field.

The EPM was utilized for the first time by Handley and Mithani, in 1984, as from the model developed by Montgomery, in 1955. They observed that rats placed in an elevated maze, consisting of two open arms and two closed arms showed a preference for the closed arms. In addition, these authors observed that anxiolytic drugs such as diazepam (a BDZ) increased the number of entrances of the animals into the open arms of the maze, where anxiogenic drugs reduced the number of entrances into these arms. Among the advantages of this model are simplicity of use, low cost of assembly and maintenance, allowing an assessment both of the anxiolytic and of the anxiogenic substances [79].

Another very simple test to evaluate substances with anxiolytic action is the Test of Neophobia in Rats [80]. When rats are exposed to new food in their natural habitat, or when their usual food is placed in a new environment, or when both occur, namely, food and environment are both new, the animals' intake of food is reduced (neophobic reaction). This seems to be the result of a reaction of "fear" or of "anxiety" on the part of the animal to external stimuli: ultimately, the anxiolytics should be able to block the reaction, as, in fact, they do.

A response to anxiety is a subjective answer inherent to the human species; for this reason, the term "emotionality" or "emotional response" has often been used to refer to the association of responses generated by animals exposed to new situations or that are elicited by several noxious stimuli.

The open field is one of the oldest models used for the study of emotionality in animals, and was used for the first time in 1934 by Hall. The procedure consists in observing locomotor activity, rearing, freezing, and defecation by animals subjected to a circular arena divided into 12

peripheral and 6 central quadrants. In addition, some of the variables present in the environment as, for instance, continuous noise or increased lighting, increase the emotional reactivity in animals and, for this reason, are part of the procedure most commonly utilized for open field [81,82]. Open field, as in the case of other tests formerly described, is also a model characterized by simplicity and ease of application - much utilized to assess possible anxiolytic action of one specific substance.

To evaluate the hypnotic effect, the same models can also be utilized, besides one more specific, the sleeping time.

Plants with possible anxiolytic and/or hypnotic effects indicated by three Brazilian cultures - Indians, Afro-Brazilians, and River-Dwellers.

As in a previous review [8], one strong limitation to analyzing the data found in this study resides in the interpretation of the researchers concerning the uses indicated by the cultures involved in each one of the ethnopharmacological surveys. To correlate one term in ethnomedicine with one in official use is not always an easy task: for some terms, researchers must resort to a type of "translation", a type of "ethnopharmacological puzzle" where one of the greatest challenges to researchers is the absence of medical professionals to follow up on field works and thus contribute to establish this correlation.

Twenty-three publications were consulted for this review: 10 scientific articles, 8 books, and 5 Master's degree and Ph.D. degree theses. Of studies carried out amongst Indians, Afro-Brazilians and/or Quilombolas, and Caboclos that inhabit 4 of the 5 principal biomas in Brazil (caatinga, the Amazon forest, cerrado and Mata Atlântica) almost one half (10) are studies among Afro-Brazilians and/or Quilombolas; another 7 among Indians, and 6 among Caboclos. These data must be considered in analyzing the contributions from each group to the present study.

Plants with Possible Anxiolytic Effects

Table 1 shows that 39 species were indicated for uses with apparent anxiolytic effect/action. The main uses described in literature seem synonymous - as a tranquilizer, as a tranquilizer for children, for anxiety, a tranquilizer for nerves, for nervous excitation, nervous disturbances, to

relax, for child nervousness, children crying for feeling unwell, for emotionally unstable people, for irritability, for nervous diseases, and nervousness.

These 39 species belong to 22 taxonomic families, the most important being: Asteraceae (5 species indicated), Fabaceae (4), and Melastomataceae (4); with 48.7% of these native to Brazil.

The species most often cited in the publications consulted were *Lippia alba* (Mill) N.E.Br. (cited in 7 of these) and *Passiflora edulis* Sims. (4).

Among the plants indicated for anxiety, 21 were indicated by Afro-Brazilians and/or Quilombolas; 15 by Caboclos and by 10 Indian groups with some species indicated by more than one culture. Most of the publications available and consulted in this study focus on the first ethnic group.

Table 1: Thirty-nine (39) plants with possible anxiolytic effects utilized by three cultures in Brazil - Indians, Afro-Brazilians and Caboclos - and respective pharmacological and phytochemical studies published in the scientific literature.

Family (n. species) *Species* - vernacular name	**Use described in the literature consulted**	**Part utilized and form of use as described in the literature consulted**	**Cultures cited in the literature consulted**	**Phytochemical studies found in the literature**	**Pharmacological studies found in the literature**
Amaranthaceaea (1)					
Celosia argentea L. - suspiro	Tranquilizer	No information	Quilombolas [48]	Betalains [84,85]	Anti-diabetic activity [248]; anti-metastatic and immunomodulating properties [249]; immunostimulating activity [250]; hepatoprotective effects [251]
Annonaceae (2)					
Annona muricata L. - graviola	Tranquilizer	No information	Caboclos [59]	Acetogenins [86,87]; neurotoxic benzylisoquinoline derivatives [88]; essential oil [89,90]; alkaloids [91,92]; flavonoids and terpenoids [93]	striatal neurodegeneration [252]; atypical parkinsonism [253]; antileishmanial activity [254]; antidepressive activity [91]
Guatteria scandens Ducke [N] - Cipó-luira, cipó-iuira	As a tranquilizer for children	Bark (bathing)	Caboclos [52]	Alkaloids [94,95]	
Apiaceae (1)					
Pimpinella anisum L. - erva-doce	For anxiety	Raw leaves to be chewed or leaf tea, for flatulence	Afro-Brazilians [41]	Flavonoids [96]; essential oil [97,98]; coumarins [99]	
Apocynaceae (1)					
Tabernaemontana sananho Ruiz & Pav. [N]	For a calming effect		Indians from the Brazilian Amazon [83]	No phytochemical data	
Asteraceae (5)					
Baccharis uncinella DC. [N] -vassoura-do-campo	Tranquilizer for the nerves	Leaves and flowers (decoction , ingested)	Xokleng Indians [36]	No phytochemical data	
Lactuca sativa L. -	Nervous	Leaf (Infusion)	Afro-Brazilians	Phenolic acids [100]; triterpenoids,	

alface	disturbances		(Northeast Brazil) [45,46]	saponins [101,102]; flavonoids [103]	
Matricaria chamomilla L. - camomila	Nervous disturbances	Flower (infusion)	Afro-Brazilians (Northeast Brazil) [45,46]	Flavonoids [104,105]; essential oil [106]; acylglycerols, linoleic and linolenic acids [107]; coumarins [108,109]; sesquiterpene lactone [110]	inhibits both development of morphine dependence and expression of abstinence syndrome [255,256]; anxiolytic effect [257]; sedative as well as spasmolytic effects [258]
Mikania amara (Vahl) Willd. [N] - Cipó-catinga)	As a tranquilizer	Leaf (bathing)	Caboclos [52]	No phytochemical data	
Tagetes erecta L. - cravo-de-defunto	Diseases of the nerves	Flowers (infusion, ingested)	Caboclos [56]	Fatty acids [111,112,113]; essential oils [114,115]	
Caryophyllaceae (1)					
Dianthus caryophyllus L. - cravo-branco	Nervous disturbances	Flower (Infusion)	Afro-Brazilians (Northeast Brazil) [45,46]	Phenolic acids [116]; essential oils [117]; anthocyanins [118,119]	
Crassulaceae (1)					
Kalanchoe brasiliensis Cambess. [N] - folha-da-costa	As a tranquilizer	Leaf	Afro-Brazilians [43]	Flavonoids [120]	Immunomodulatory and anti-inflammatory effects [259,260]
Fabaceae (*sensu lato*) (4)					
Erythrina corallodendron L. - mulungu	As tranquilizer for nervous excitement	Bark	Afro-Brazilians [44]	No phytochemical data	
Erythrina poeppigiana (Walp.) O.F. Cook - mulungu	To relax	Leaf (tea)	Afro-Brazilians [41]	Isoflavonoid [121,122,123]; arylbenzofuran [124], erythrinan alkaloids [125,126]	Antibacterial properties [121]; antimicrobial activity [123]
Erythrina velutina Willd. [N] - mulungu	As a tranquilizer	Relief bathing and bottled brews (ingestion)	Afro-Brazilians [44]	Flavonoids [127,128]	Anti-nociceptive activity [261,262] ; central nervous system effects [263,264]
Mimosa camporum Benth. - juqueri-manso	As a tranquilizer for children	Leaves and roots (bathing)	Caboclos [52]	No phytochemical data	
Lamiaceae (3)					

Melissa officinalis L. - erva-cidreira	Irritability	Tea	Terena Indians [13]	Flavonoids [129,130]; essential oils [131,132,133,134]; phenolic acids [135,136,137]	
Mentha piperita subsp. *citrata* Briq. - hortelã	Tranquilizer	Branch (infusion, ingested)	Caboclos [57]	Essential oils [138,139]; flavonoid glycosides [140,141]; menthol [142]; menthofurolactone [143,144]; pyridine-derivatives [145]; mintlactone [146]; flavones [147]; triterpenes [148]; terpenoids [149]; sesquiterpenic hydrocarbons [150]; menthofuran [151,152].	Antimicrobial and antioxidant activities [138,265]; antiallergic effect [140]; **a**nti-nociceptive and anti-inflammatory effects [266]
Pogostemon cablin (Blanco) Benth. – oriza, patchouli, patcholi, patchuli	Tranquilizer, for a calming effect	Leaf (decoction or infusion, ingested)	Caboclos [51,56]	Essential oils [153,154,155,156]; patchoulic alcohol [157,158]; sesquiterpene hydroperoxides [159]; flavonoids [160,161]; tetracyclic sesquiterpene [162,163,164].	
Malpighiaceae (1)					
Camarea ericoides A. St.-Hil. [N] - erva-doce-do-campo	Tranquilizer	The whole plant (decoction, ingested)	Quilombolas*	No phytochemical data	
Melastomataceae (4)					
Henriettea granulata O. Berg & Triana [N] – Pöra	Irritability in children, children crying	Leaves (infusion, bathing)	Tiriyó Indians [14]	No phytochemical data	
Miconia holosericea (L.) DC. [N] - Pöra-imö	Irritability and for children who are unwell	Leaves (decoction, bathing)	Tiriyó Indians [14]	No phytochemical data	
Miconia rubiginosa (Bonpl.) DC. [N] - pöra-imö	Irritability and for children crying because they are unwell	Leaves (decoction, bathing)	Tiriyó Indians [14]	Triterpenoids [165]	
Tococa formicaria Mart. [N]	As a tranquilizer	Branches (bathing)	Pareci Indians [25]	No phytochemical data	
Meliaceae (1)					
Cedrela odorata L. [N] - Chega-te-a-mim	As a tranquilizer	Bark (bathing)	Caboclos [52]	Essential oils [166,167]; flavonoids [168,169]; tetranortriterpenoids [170]; triterpenoids [171,172]	Antimalarial activities [168,169]
Monimiaceae (1)					

Siparuna guianensis Aubl. [N] - capitiú	Tranquilizer for children	Leaf (bathing the body)	Caboclos [51]	Essential oil [173,174]; oxoaporphine alkaloids [175]; flavonoids [176]	
Moraceae (1)					
Ficus doliaria (Miq.) Miq. [N] - gameleira	For a calming effect	Latex	Afro-Brazilians	No phytochemical data	
Nymphaeaceae (1)					
Nymphaea alba L. - òsibàtà	As a tranquilizer	Leaf	Afro-Brazilians [40]	Anthocyanins [177]	
Passifloraceae (1)					
Passiflora edulis Sims [N] - maracujá, maracujá-de planta	Tranquilizer, irritability	Flower or leaf (decoction, ingested)	Caboclos [53,57,59]; Xokleng Indians [36]	Flavonoids, glycosides, alkaloids [178]; triterpenoids [179]; saponins [180]; norterpenoids derivatives [181]; Cyanogenic glucosides [182]; carotenoids [183]; 3-Methyl-2-butanone [184]; phenolic compounds [185]	
Poaceae (1)					
Cymbopogon citratus (DC.) Stapf - capim-santo, capim-cidró	Tranquilizer, for a calming effect on the nerves, irritability	Leaf or the whole plant (decoction, ingested)	Quilombolas [50,54]; Xukuru Indians [37]; Caboclos [57,59]	Flavonoids [186,187]; essential oils [188,189]; triterpenoids [190]	
Rutaceae (3)					
Citrus aurantifolia (Christm.) Swingle - lima	Tranquilizer	No information	Caboclos [59]	Essential oils [191,192]; flavonoids [193,194]	
Citrus aurantium L. - laranja	Nervous disturbances	Leaf (Infusion)	Afro-Brazilians (Northeast Brazil) [45,46]	Alkaloids [195,196]; adrenergic amines [197,198]; flavonoids [199,200]; Coumarins, fatty acids [201,202]; polyphenolic compounds [203]; essential oils [204,205]	Suppressive effect [267]; ischemic stroke [268]; cardiovascular changes [269]; weight loss [267]; induction of apoptosis [270]; anxiolytic and sedative effects [271]; adrenergic agonists [272], antiobesity [273,274]; anti-inflammatory activity [275]
Citrus sinensis (L.) Osbeck - laranjeira, laranja	Tranquilizer	Leaf (infusion or decoction, ingested)	Caboclos [57,59]; Quilombolas [54]	Flavonoids [206,207]; essential oils [208,209]; phenolic compounds; Coumarins, fatty acids [210,201]; quinoline alkaloids [211,212];	Radical scavenging activity [276]; antioxidant activity [277]; inotropic effect [278]

				anthocyanins [213,214]	
Schizaeaceae (2) - ferns					
Lygodium venustum Sw. [N] - abre-caminho	For emotionally unstable people who are irritable	The whole plant (relief bathing)	Afro-Brazilians (Northeast Brazil) [47]	No phytochemical data	
Lygodium volubile Sw. [N] - abre-caminho	For emotionally unstable people who are irritable	The whole plant (relief bathing)	Afro-Brazilians (Northeast Brazil) [47]	No phytochemical data	
Solanaceae (1)					
Physalis angulata L. [N] - camapu	Nerve diseases	Root (tea, ingested)	Caboclos [56]	Steroids [215,216]; flavonoids [217]; alkaloids [218]	
Verbenaceae (2)					
Lippia alba (Mill.) N.E. Br. [N] - cidreira, erva-cidreira, melissa, carmelitana	A calming effect, to relax, tranquilizer	Leaves (decoction)	Afro-Brazilians [3,41]; Xukuru Indians [37]; Caboclos [52,56,59]; Quilombolas [48]	Alkaloids [219]; saponins [220]; sterols, flavonoids [221]; essential oils [222,223]; prenylated naphtoquinones [224]; iridoids [225]; terpenoids [226,227]; phenolic acids [228]	
Vitex agnus-castus L. - alecrim-de-angola	Tranquilizer	Flowers and seeds (prepare a beverage)	Afro-Brazilians [3]	Phenolic compounds [229]; essential oil [230,231]; iridoidal glycosides [232,233]; flavonoids [234,235]; glucosides [236]; diterpenoids [237,238]; labdane diterpene lactam [239]; phenolic acids [240]; ketosteroids [241]	Induces apoptosis [279,280]; dopaminergic activity [281]; treatment of disorders of the female sexual cycle [282]
Zingiberaceae (1)					
Alpinia zerumbet (Pers.) B.L. Burtt & R.M. Sm. - leopoldina	Nervousness	Tea	Afro-Brazilians [41]	Essential oils [242,243]; kava-pyrones [244]; flavonoids [245]; labdane diterpenes [246,247]	

[N] native to Brazilian flora.

* Personal information obtained by author E.R., in a study not yet published.

A survey made on the main data base and an extensive analysis of the scientific literature available, showed that some plants with an anxiolytic and/or hypnotic effect utilized by the three Brazilian cultures exert an effect confirmed by scientific studies. Outstanding among these plants are those of the genus *Erythrina* - a genus well known in Brazil and in various parts of the world. Some authors [283,284] described the depressor activity on the CNS. Vasconcelos et al. [264] found that the hydroalcoholic extracts of *E. velutina* Wild and *E. mulungu* Mart. ex Benth did not interfere with the results of the EPM and did not, therefore, present an anxiolytic effect; however, the data obtained by these authors showed a depressor action on the CNS, in that rats subjected to the Open Field test subsequent to the administration of these plants; the animals showed a reduction in locomotor activity, in rearing and grooming. Onusic et al [285], on the other hand, observed an anxiolytic effect in rats subsequent to acute administering of a hydroalcoholic extract of *E. mulungu* Mart. ex Benth. The action of another plant of this genus (*E. poeppigiana* (Walp) O.F.Cook), utilized by Afro-Brazilians as an anxiolytic, is not confirmed in scientific literature: on the other hand, reports concerning this plant emphasize its antibacterial and muscular block action [286,287].

Melissa officinalis L. is a plant widely utilized for its mild sedative/hypnotic properties [288,289], and is also employed as an anxiolytic by Brazilian cultures related to this study. In high doses, this plant may present peripheral analgesic activity, obtained by reducing the acetic acid-induced pain (writhing test) [288]. Its essential oils possess an antioxidant and anti-tumoral effect [290,291]. Clinical studies with this plant [292-294] also showed that administering same on healthy volunteers reduced stress induced in a laboratory, in addition to modulating mood and augmenting calmness, although it may produce damage to cognitive functions. Some studies show that the extract of *Melissa officinalis* L. also acts as a stimulant of the immune system [295].

One other plant much cited (7 citations) by the cultures, in addition to being widely utilized in popular Brazilian medicine, is *Lippia alba* (Mill) N.E.Br. as to its sedative properties [296,297]. Some studies reported that this plant also has a myorelaxing effect [296] and its essential oils may present both a possible anxiolytic [298] and anticonvulsant effect [299].

The genus *Passiflora* includes approximately 500 species and, as per the last two plants cited (*Melissa officinalis* and *Lippia alba*), is a genus well known [178]. In the specific case of *Passiflora edulis* Sims., some studies have shown its anxiolytic effect when assessed through the EPM [300]. A comparative study involving two species of this genus by Dahwan et al [301] showed that, although the methanolic extract of *P. edulis* Sims. presented an anxiolytic effect, this effect is less potent if compared to that observed with *Passiflora incarnata* L.

Some of the plants listed as anxiolytic by the three cultures are also listed as hypnotic, amongst these, *Lippia alba* (Mill) N.E.Br., the species of the *Citrus* and of the *Erythrina* genus. This is owing to the fact that, often, the hypnotic and anxiolytic effects are similar, in that one and the same substance may present both effects, depending on the dose utilized. On the other hand, some plants listed in Table 1 did not have an anxiolytic effect confirmed by the survey in literature, and others have apparently not been studied up to the present time.

A Phytochemical Approach

The phytochemical survey carried out with the species indicated, to which were attributed an anxiolytic effect showed that the main constituents found were the flavonoids, essential oils, as shown in Fig. (**2**), followed by the phenolic acids, sesquiterpenoids, triterpenoids, and alkaloids.

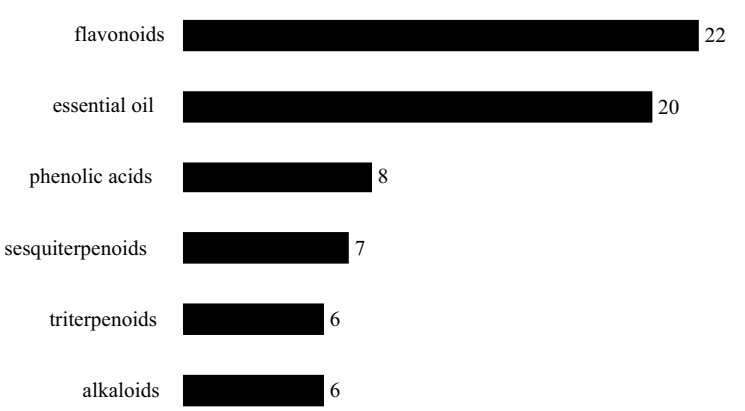

Fig. (2). Number of species with possible anxiolytic effects indicated by the cultures under study that present respective chemical constituents (in this figure represented only by those constituents with at least six species cited).

The flavonoids represent one of the most important and diversified phenolic groups among products of natural origin. This class of compounds is broadly distributed in the plant kingdom. Flavonoids such as 6-Methylapigenin and hesperidin exert activity on the CNS [302]. *Passiflora incarnata* L. has been used to cure anxiety and insomnia since time immemorial. The flavonoids of *P. incarnata* L. [301] and of *Turnera aphrodisiaca* Ward showed anxiolytic activity [303]. The behavioral effects of acute administration of two flavonoids, apigenin and chrysin, contained in *Matricaria chamomilla* L. and in *P. incarnata* L., respectively, were studied in rats. Chrysin exhibited a clear anxiolytic effect [255].

According to the chemical structure, the anxiolytic agents used in allopathic medicine may be divided into three classes: carbamate of propanodiol and related compounds, BZDs and several others compounds. The most effective are the BDZs Chlordiazepoxide, Fig. (**3**), which was commercialized in 1960 as a therapeutic innovation for the treatment of anxiety. As from the identification of its property, dozens of new BDZs derivates were commercialized, including diazepam, Fig. (**3**), one of the medicines most prescribed worldwide.

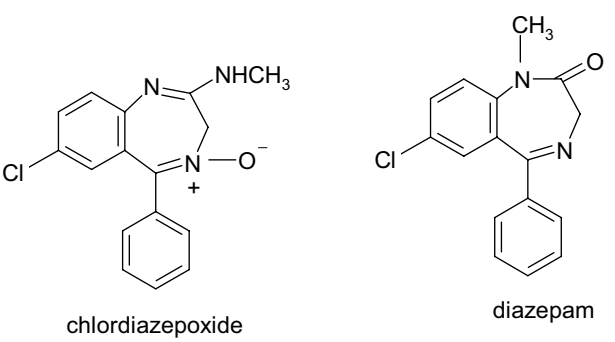

Fig. (3). Chemical structures of chlordiazepoxide and diazepam.

Flavonoids: A New Family of BDZ Receptor Ligands

BDZs are the most widely prescribed class of psychoactive drugs in current therapeutic use, despite the important unwanted side-effects that they produce such as sedation, myorelaxation, ataxia, amnesia, ethanol and barbiturate potentiation, and tolerance. The existence of a new family of ligands with a flavonoid structure was recently demonstrated in the

search for safer BDZ-receptor (BDZ-R) ligands. First isolated from plants used as tranquilizers in folk medicine, some natural flavonoids have proved to possess a selective and relatively mild affinity for BDZ-Rs and a pharmacological profile compatible with a partial agonistic action. As a logical extension to this discovery, various synthetic derivatives of those compounds, such as 6,3'-dinitroflavone, were found to have a very potent anxiolytic effect, not associated with myorelaxant, amnestic or hypnotic actions [304].

A large number of structurally different classes of ligands, many of them sharing the main characteristics of the BDZ nucleus, are active in the modulation of anxiety, sedation, convulsion, myorelaxation, hypnotic and amnesic states in mammals. These compounds have a high affinity for the BDZ binding site (BDZ-bs) of the GABA(A) receptor complex. Flavonoids found to be ligands for the BDZ-bs have been compared with the classical BDZ diazepam [305]. Structure-activity relationships utilizing synthetic flavonoids with different 2' substituents on the flavone backbone supported that 2'-hydroxyl-substitution is a critical moiety on flavonoids with regard to BDZ receptor affinities [306].

Volatile oils are compound mixtures of volatile, lipophylic substances that are generally odoriferous and liquid. The name volatile oils is derived from some of their physico-chemical characteristics such as, for example, to being generally liquid and oily in appearance at room temperature. Their main characteristic is volatility. Another important characteristic is a pleasing and intense aroma for the majority of volatile oils - also known as essences. In water, volatile oils present limited solubility, but that is sufficient to aromatize aqueous solutions [307]. Angelica essential oil (*Angelica officinalis* Moench.), as does diazepam, exhibits an anxiolytic-like effect [308]. Essential oil from *Tagetes minuta* L. may exert a negative modulation on the GABAergic function without affecting the learning ability [309].

No article was found reporting anxiolytic activity of phenolic acids. However, the anxiolytic activity of the alkaloids is known. Anxiolytic properties may be a crucial feature of newer antipsychotics associated with the improvement of negative symptoms in schizophrenic patients. The indole alkaloid alstonine acts as an atypical antipsychotic in behavioral models, but differs in its dopamine and serotonin binding profile [310]. Behavioral effects of psychollatine, a glycoside indole monoterpene alkaloid isolated from *Psychotria umbellate* Thonn., was investigated in models of anxiety, depression, memory, tremor, and

sedation related to 5-Hydroxytryptamine (5-HT) and/or GABA neurotransmission. The effects of psychollatine on the CNS involve serotonergic 5HT2 (A/C) receptors [311].

Plants with Possible Hypnotic Effects

Twenty-eight species were indicated for the following uses: insomnia, severe insomnia, sedative, hypnotic, sedative for children, for the elderly who find difficulty in sleeping, to induce sleep (Table 2).

These species belong to 17 taxonomic families, the most important being: Fabaceae (6 species cited) and Rutaceae (3); 57% of these belong to the Brazilian flora. The species with greater frequency of citation in the publications consulted were: *Lactuca sativa* L., *Lippia alba* (Mill.) N.E.Br. and *Citrus aurantium* L. (3 citations each).

In the same way as in the category of anxiolytic plants, the majority of plants were indicated by the Afro-Brazilians and/or Quilombolas (15 in all), with 8 indicated by Indians, and 6 by Caboclos.

Table 2: Twenty-eight (28) plants with possible hypnotic effects utilized by three cultures in Brazil - Indians, Afro-Brazilians and Caboclos - and respective pharmacological and phytochemical studies published in the scientific literature.

Family (n. species) *Species* - vernacular name	**Use described in the literature consulted**	**Part utilized and form of use as described in the literature consulted**	**Cultures cited in the literature consulted**	**Phytochemical studies found in the literature**	**Pharmacological studies found in the literature**
Annonaceae (1)					
Annona muricata L. - graviola	Severe insomnia	Leaves (infusion or decoction, ingested)	Caboclos [56,57]	Acetogenins [86,87]; neurotoxic benzylisoquinoline derivatives [88]; essential oil [89,90]; alkaloids [91,92]; flavonoids and terpenoids [93]	Striatal neurodegeneration [252]; atypical parkinsonism [253]; antileishmanial activity [254]; antidepressive activity [91]
Asteraceae (2)					
Lactuca sativa L. - alface	Insomnia, sedative	Leaf (tea)	Terena Indians [13]; Afro-Brazilians (Northeast Brazil) [45,46]	phenolic acids [100]; triterpenoids, saponins [101,102]; flavonoids [103]	
Matricaria chamomilla L. - camomila	Sedative	Flower (Infusion)	Afro-Brazilians (Northeast Brazil) [45,46]	Flavonoids [104,105]; essential oil [106]; acylglycerols, linoleic and linolenic acids [107] ; coumarins [108,109]; sesquiterpene lactone [110]	Inhibits both development of morphine dependence and expression of abstinence syndrome [255,256]; anxiolytic effect [257]; sedative as well as spasmolytic effects [258]
Burseraceae (1)					
Commiphora leptophloeos (Mart.) J.B. Gillett [N] - emburana	Insomnia	Seeds (decoction, ingested)	Quilombolas*	No phytochemical data	
Caryophyllaceae (1)					
Dianthus caryophyllus L. - cravo-branco	Sedative	Flower (Infusion)	Afro-Brazilians (Northeast Brazil) [45,46]	Flavonoids [313,314]; phenolic acids [116]; essential oils [117]; anthocyanins [118,119]	

Fabaceae (*sensu lato*) (6)					
Cassia multijuga Rich.[N] - topeiuia	As a sedative for children	Leaves	Tenharins Indians [56]	Anthraquinones [315,316]; anthraquinones glycosides [317]; chromone glycosides [318,319]; flavonol glycoside [320]	
Erythrina mulungu Mart. ex Benth[N] - mulungu	Hypnotic and sedative	Bark (decoction)	Afro-Brazilians [44]	No phytochemical data	
Erythrina poeppigiana (Walp.) O.F. Cook - mulungú	Soporific	Leaf (tea)	Afro-Brazilians [41]	Isoflavonoid [121,122,123]; arylbenzofuran [124]; erythrinan alkaloids [125,126]	
Erythrina speciosa Andrews [N] - mulungu	Hypnotic and sedative	Bark (decoction)	Afro-Brazilians [44]	Flavonoids [321]	Antibacterial activity [321]
Mimosa hirsutissima Mart. var *barbigera* (Benth) Barneby [N] - durme-durme	Insomnia	Leaves (decoction, ingested)	Quilombolas*	No phytochemical data	
Mimosa pudica L. [N] - cipó-dorme-dorme	Insomnia	Leaves and vines (decoction, ingested)	Xokleng Indians [36]	Tannins, steroids, alkaloids, triterpenes [322,323]; flavonoids [324,325,326,327,328]; saponins [329]; bufanolide [330]; mimopudine [331,332]	
Flacourtiaceae (1)					
Casearia sylvestris Sw. [N] - chá-de-frade	Insomnia	Leaf (decoction, ingested)	Quilombolas*	Terpenes [333]; essential oil [334,335]; diterpene [336]; clerodane diterpenoids [337,338]	Antiulcer activity [354]; abortive activity [338]
Lamiaceae (1)					
Pogostemon cablin (Blanco) Benth. - oriza, patchouli, patcholi, patchuli	Sedative	Leaves (infusion, ingested)	Caboclos [56]	No phytochemical data	
Malpighiaceae (1)					
Camarea ericoides A. St.-Hil. [N]	Against insomnia	The whole plant	Quilombolas*	No phytochemical data	

- erva-doce-do-campo		(decoction, ingested)			
Malvaceae (2)					
Hibiscus rosa-sinensis L. - pampola	Against insomnia	Flowers (infusion)	Caboclos [56]	Phenolic acids [339]; fatty acid methyl esters [340,341]; anthocyanins [342]	Against oxidative damage [355,356]; hypoglycemic activity [357,358]
Urena lobata L.	Sedative	No information	Indians of the Brazilian Amazon [312]	No phytochemical data	Antibacterial activity [359]
Marcgraviaceae (1)					
Marcgraviastrum elegans de Roon [N] - no-tê-wê-tá	For the elderly who find it difficult to sleep	Leaves and flowers (tea)	Kubeo Indians [83]	No phytochemical data	
Monimiaceae (1)					
Siparuna guianensis Aubl. [N] - negramina-branca	Insomnia	Leaf (decoction, ingested)	Quilombolas*	Essential oil [173,174]; oxoaporphine alkaloids [175]; flavonoids [176]	
Passifloraceae (2)					
Passiflora coccinea Aubl. [N] - maracujá-do-mato	Sedativo	Leaves (tea, ingested)	Caboclos [56]	Cyanogenic glycoside [343]	
Passiflora laurifolia L. [N]	To induce sleep	Leaves (decoction)	Kubeo Indians [83]	No phytochemical data	
Poaceae (1)					
Saccharum officinarum L. - cana-de-açucar	Insomnia	Culm (suco)	Caboclos [56]	Flavonoids [344,345]; long-chain aliphatic acids [347]; fatty acids [346,348]; phenolic compounds [349]; glycans [350]; triterpenoids and steroids [351]	Anti-inflammatory and analgesic effects [348]; antidiabetes [350]
Rubiaceae (2)					
Palicourea rigida Kunth [N] - erva-molar-fêmea	Insomnia	Leaf (decoction, ingested)	Quilombolas*	Alkaloids and iridoid glucosides [352]	
Rudgea viburnoides (Cham.) Benth. [N] - erva-molar-macho	Insomnia	Leaf (decoction, ingested)	Quilombolas*	No phytochemical data	
Rutaceae (3)					
Citrus aurantium L. - laranja-da-terra, laranja	Sedative	Leaf (Infusion)	Afro-Brazilians (Northeast Brazil) [41,45,46]	Alkaloids [195,196]; adrenergic amines [197,198]; flavonoids [199,200]; coumarins, fatty acids [201,202];	

				polyphenolic compounds [203]; essential oils [204,205]	
Citrus sinensis (L.) Osbeck (laranjeira)	Insomnia	Leaf (decoction, ingested)	Quilombolas*	Flavonoids [206,207]; essential oils [208,209]; phenolic compounds; coumarins, fatty acids [210,201]; quinoline alkaloids [211,212]; anthocyanins [213,214]	Radical scavenging activity [276]; antioxidant activity [277]; inotropic effect [278]
Pilocarpus pennatifolius Lem.[N] - ibirarta-iba	Sedative	No information	Indians of the Brazilian Amazon [312]	Essential oils[353]	
Solanaceae (1)					
Brugmansia insignis (Barb. Rodr.) R.E. Schult.	Sedative	Leaves	Indians of the Brazilian Amazon [83]	No phytochemical data	
Verbenaceae (1)					
Lippia alba (Mill.) N.E. Br.[N] - cidreira, erva-cidreira	To sleep, to induce sleep	Leaves (infusion or decoction, ingested)	Caboclos [51,52,57]	Alkaloids [219]; saponins [220]; sterols, flavonoids [221]; essential oils [222,223]; prenylated naphtoquinones [224]; iridoids [225]; terpenoids [226,227]; phenolic acids [228]	

[N] native to Brazilian flora.

* Personal information obtained by author E.R., in a study not yet published.

A Pharmacological Approach

Some plants utilized as hypnotics and/or anxiolytics by the Brazilian cultures such as, for instance, *Citrus aurantium* L., were the object of contradictory studies. According to Carvalho-Freitas & Costa [271], the essential oils of this plant exert sedative and anxiolytic effects, whereas the hexane and dichlomethanic fractions present only the former effect. The anxiolytic effect of the essential oils of this plant was later confirmed by Pultirini et al. [360].

Although *Lactuca sativa* L. is one of the species most cited in this survey, there is no clear pharmacological evidence that this plant exerts a significant hypnotic effect. According to Bang et al [361], phytol, a diterpenoid isolated from the ethanolic fraction of this plant would raise the levels of GABA in the CNS by inhibiting the action of one of the enzymes responsible for degradation of this neurotransmitter, succinic semialdehyde dehydrogenase (SSADH). The result is a sedative effect on the body; in any case, other studies would be necessary to confirm the sedative action attributed to this plant.

Few studies have been found concerning the sedative effect of *Annona muricata* L. [362]: this plant appears to be potentially toxic, which would render use of same difficult [363].

Other plants have either been commented because they are in Table 1 or possibly, have been described in the item referring to the phytochemistry in this chapter, as a result of knowledge or isolation of some chemical component with a known pharmacological action already described. Those species that were not commented have not, as far as we have been able to ascertain, been the object of pharmacological studies.

A Phytochemical Approach

Mankind has, down the ages, made use of psychoactive plants and plant-derived products for spiritual, therapeutic, and recreational purposes. An investigation of psychoactive plants such as *Cannabis sativa* L. (marijuana), *Nicotiana tabacum* L. (tobacco) and analogues of psychoactive plant derivatives such as lysergic acid diethylamide (LSD) have provided insight into our understanding of neurochemical processes and diseases of the CNS. Many of these compounds are currently being used to treat a variety of diseases such as anxiety as, for instance, Kava-kava [364].

Kava-kava is a well-established hypnotic drug with a rapid onset of effect, adequate duration of action and minimal morning after-effects. As mentioned previously, however, reports of serious hepatotoxicity with this preparation have led to its being banned in most countries worldwide [365]. Kava-kava extract produced a significant increase in delta activity during non-REM sleep in sleep-disturbed rats, whereas a significant decrease in delta power during non-REM sleep was observed with flunitrazepam, a BDZ utilized as hypnotic [366].

In this review, the phytochemical studies found in the scientific literature for the plants included in Table 2, with possible hypnotic effects, also showed a prevalence of the flavonoid and essential oil, as shown in plants in Table 1, with possible anxiolytic effects, as can be seen in Fig. (**4**). These results emphasize the importance of these constituents in the treatment of diseases related to some deficiencies of the CNS, once more followed by the phenolic acids and alkaloids as shown in Fig. (**4**). These substances may act producing two effects, both as anxiolytics and as hypnotics, the difference being only in the dosage of the drug, as formerly cited.

Several studies describe the hypnotic activity of flavonoids. Apigenin is a flavonoid that showed sedative and antidepressant activity [367]. The flavonoids and indole alkaloids of *P. incarnata* L., also showed sedative effects [368]. Linarin, a flavonoid-isolated from *Valeriana officinalis* L. showed sedative and sleep-enhancing properties (Fernandez et al., 2004). The nonvolatile fraction of *L. alba*, extracted in ethanol, presented sedative and myorelaxing effects: among the extracts tested, these possess the highest flavonoid content [296].

Essential oils also present sedative activity, as do those from *Lippia alba* (Mill.) N.E.Br. and *Matricaria chamomilla* L. [255,257]. Citral, myrcene and limonene, constituents of essential oils from *Lippia alba* produced a potentiation of pentobarbital-induced sleeping time in mice which was more intense in the presence of citral [370].

No studies were found on the hypnotic activity of the phenolic acids; however, the hypnotic activity of alkaloids is known. D1-Tetrahydropalmatine (d1-THP), a naturally occurring alkaloid, has been intensively studied for its sedative and hypnotic effects. A putative explanation for its mechanism and target of action involves the dopaminergic neurotransmission system [371]. Reserpine, an alkaloid from *Rauwolfia serpentina* Benth. ex Kurz, was widely used for its antihypertensive action. However, its use has been reduced because of its

sedative symptoms [372]. Alkaloid rotundin [373] and the peptide alkaloids from *Zizyphus* spp. species exhibited sedative effects [374].

Fig. (4). Number of species with possible hypnotic effects, indicated by the cultures under study, that present the respective chemical constituents (only those constituents with at least four species cited have been shown in this illustration).

Alkaloids of the *Erythrina* Species

The *Erythrina* genus belong to the Fabaceae family and are in popular use in Brazil for their effects on the CNS.

Erythrina velutina Willd. at lower doses interferes with the mnemonic process for different tasks, while the sedative and neuromuscular blocking actions are the main effects at higher doses [263]. The hydroalcoholic extracts of *E. velutina* and *E. mulungu* Mart. ex Benth have depressant effects on the CNS which, at least partially, corroborates the popular use of these species as tranquilizers in Brazilian popular medicine [264].

Through an analysis of four species of *Erythrina* (*E. mulungu*; *E. corallodendron* L.; *E. speciosa* Andrews and *E. velutina*), Camargo [44] explains that the use of these different species does not interfere with the results desired by users, since all of them presented alkaloids responsible for hypnotic and sedative effects in varying doses.

The study of alkaloids of the *Erythrina* genus is of assistance in grouping species, but only some of the species have been carefully examined [375]. Alkaloids are compounds, generally with heterocyclic nitrogen in the molecule, biosynthesized as from aminoacids.

Erythrina alkaloids, Fig. (**5**), have a structure which is very different, strictly speaking from the curares, but are substances with curare-like activity. Naturally-occurring curares are non-depolarizing (or competitive) neuromuscular blocking agents. Active only by the parenteral route, they compete with acetylcholine for the cholinergic receptors at the motor end-plate and prevent the formation of action potential, without modifying nerve conduction elsewhere, and without preventing muscular contraction in response to direct stimulation [376]. No phytochemical data were found for species *E. corallodendron* L. and *E. mulungu* Mart. ex Benth.

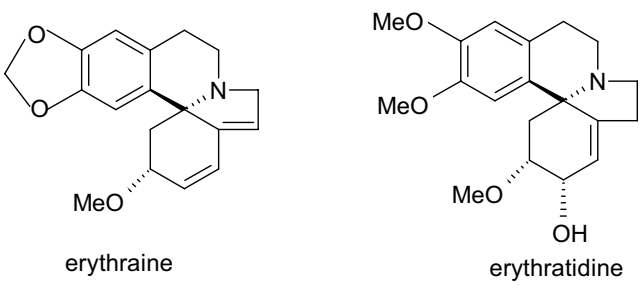

Fig. (5). Erythrina alkaloids

Essential Oils

Essential oils were the second class of chemical constituents most recurrent among the species analysed in this review, both for anxiolytic and for hypnotic effects. The essential oil from *Citrus aurantium* L., commonly used as an alternative treatment for insomnia, anxiety, and epilepsy, showed anxiolytic and sedative effects [271].

There is some evidence that aromatic substances present in essence/volatile oils from certain plants might exert an anxiolytic or a relaxing effect, with improved mood.

In an interesting study developed by Almeida et al [377], the anxiolytic effects of inhaling rose oil on rodents was assessed, with diazepam as gold standard. Results showed that, subsequent to inhaling this essential oil, rats explored the open arms of the EPM more, as compared to the placebo group.

Studies with essential oils in human beings have also shown beneficial effects. For instance, anxiolytic effects were observed in patients awaiting dental care treatment in a waiting room previously aromatized with essential oils from *Citrus sinensis* (L.) Osbeck [378]. In another controlled study, 14 patients undergoing hemodyalisis benefited from hiba and lavender aromas and presented a feeling of calm [379]. Several studies on aromatherapy have attracted the attention of researchers in a study of chemical, pharmacological, and therapeutic properties of these substances [380].

According to this line of reasoning, Ballard et al [381] verified that aromatherapy with essential oils from *Melissa officinalis* L. was very effective in reducing the agitation normally observed in patients with several dementia, with consequent improved quality of life for these people.

One fact that is worthy of note relates to *Cymbopogon citratus* Staf. This is one of the plants most utilized in popular medicine in Brazil: many studies have been carried out with this plant. Some studies show that this plant produces evidence of an absence of hypnotic and anxiolytic effects [382], with no effect on nervous and gastrointestinal disorders [383]: it is a plant with no toxicity [384]. Anti-inflammatory action was observed [385], in addition to an analgesic effect confirmed by different authors [386-388]. Palmieri [389], however, observed an anxiolytic effect utilizing the essential oils of the plant, while studies by Leite et al. [382] and Carlini et al. [383] which did not verified this effect, utilized hydroalcoholic extract.

Since it is known that the potentiation of GABA(A) receptors by BDZ, barbiturate, steroids, and anesthetics induces the anxiolytic, anticonvulsant, and sedative activity or anesthetic effect, these results suggest the possibility that the intake of perfume or phytoncid through the lungs, the skin, or the intestines modulates the neural transmission in the brain through ionotropic GABA(A) receptors and changes the human frame of mind as do alcohol or tobacco [389]. Aromatherapy is an anecdotal method for modifying sleep and mood. The inhalation of essential oils may induce stimulative or sedative effects in mice [390], as a nonphotic method for promoting deep sleep and for producing gender-dependent sleep effects [391].

Within this framework, the attribution of essential oils to anxiolytic activity might relate not only to the oral route for administering, but also as an inhalant route: as the tea is being imbibed, mostly taken hot, part of

its active principles, essential oils, for instance, volatilize and may thus come into contact with the neurons of the vomeronasal organ which is considered an accessory olfactory system which can detect odorants and pheromones [392].

Cultural Peculiarities in the Therapeutic Use of Plants

Forms of Use

Some of the publications consulted for this review offered insufficient description of use, lacking information about route of administration and the recipes concerning the “medicines”, as can be observed in Tables 1 and 2. In the cases in which they are described, recipes may include: teas (infusion or decoction), bottled brews, or extract - in natura. While, route of administration may be: ingestion and topical (in the form of bathing).

One of the uses frequently described during ethnopharmacological surveys is bathing, associated or not to the consumption of plants in the form of teas, bottled brews, etc. The liquid utilized in these cases is produced as from decoction, infusion, or even maceration prepared with the leaves, bark, roots, or other parts - in most cases with appropriate times for bathing: in the morning, at midday, or in the late afternoon. In some cases, the site on the body to be bathed is specified: only the head (in the cases of flu or headache) or the entire body (usually fever and flu). The brew is allowed to dry on the body post bathing.

Albuquerque and Chiappeta [47] explain that the Afro-Brazilians (of northeast Brazil) prescribe "relief bathing" for people who are emotionally unstable, and nervous: two ferns are used for this purpose *Lygodium volubile* Sw. and *Lygodium venustum* Sw.

Amarozo and Gely [52] call attention to the fact that the practice of bathing is most important among Caboclos. Furthermore, belief in the effectiveness of applying medication topically (bathing, poultice) is so great that, instead of taking some allopathic medicines by mouth, Caboclos usually dissolve tablets together with plants in the bath water to counteract flu and headache.

The effects against nervous excitation caused by the action of alkaloids and of some species of *Erythrina* spp. in baths have not yet been studied from the scientific point of view, but both the Afro-Brazilians and the Indians of the Amazon region resort to them [44].

Table 1 and another review [8] show that the therapeutics for the Pareci and Tiriyó Indians involve a considerable number of baths.

How can bathing be interpreted from the pharmacological point of view? These processes would lead to dermic absorption similar to the action of slow-release patches, since in bathing, the formula is allowed to dry on the body ?

Lipophylic substances such as diterpenoids, fatty acids, essential oils themselves, triterpenoids, of greater affinity with the skin which is lipophylic [393], are known to be absorbed by the skin. However, it is difficult to explain just how these constituents may be transported to the CNS, although lipophylic substances do cross the hematoencephalic membrane easier than the hydrophylic substances which are polar.

Number of Plants per Formula

A number of plants make up the composition of each formula in Afro-Brazilian and/or Quilombola therapeutics: the species *Erythrina velutina* Willd. in bottled brews is mixed with another three species: *Anadenanthera colubrina* (Vell.) Brenan (angico), *Stryphnodendron* sp (barbatimão), and *Schinus* sp (aroeira pepper tree) [44]. In "relief bathing", Afro-Brazilians also add another three plants to *Lygodium volubile* Sw. and *L. venustum* Sw.: *Petiveria alliacea* L (guiné), *Ruta graveolens* L. (arruda rue), and *Rosmarinus officinalis* L. (alecrim rosemary) [47].

In a similar way, an ethnopharmacological survey among the Caboclos of the Jaú National Park, in the Amazon forest, showed that every formula may present from one up to six ingredients (parts of plants and/or animals) [51].

This was also observed in Africa, among the Yorubas [394]; in India, in Ayurveda therapeutics [395], and among the Chinese [396]. Verger, (1996) tries to explain this logic: "The single plant may perhaps be compared to one letter in a word: on its own, it has no significance, but associated to other words, it contributes to the significance of the word." From the pharmacological point of view, this may signify that the association of plants could well have a synergic effect, as explained by some authors [397,398].

On the other hand, among the Indian ethnic groups, the opposite occurs, namely, the use of one single plant for each prescription and, in general, specifically, for one use [42].

A predominance was observed in the use of plants introduced into Brazil by Afro-Brazilians and/or Quilombolas (48.3%) and Caboclos (50%) in relation to Indians (28%), as can be observed in Table 3.

This peculiarity in the use of plant resources can be explained, in part, by the history of the occupation of Brazil itself, in that the ascendants came from other continents (Europe and Africa) and brought with them multiple influences, as also plant resources that, even today, are incorporated to the therapeutics of the Caboclos and Afro-Brazilians and/or Quilombolas

Among the Indians, 72% of the plants indicated by them in this study are native to the Brazilian flora. These data are congruent with a study carried out among the Krahô Indians where 100% of the plants used by them are originally from Brazil [49]. One of the reasons for this difference is the fact that the Indians invariably had recourse to "a stock of plants on Brazilian territory", and thus, investigated and still do investigate the plants; furthermore, they did not have to move across other continents in the course of history, different from the Afro-Brazilians and/or Quilombolas.

Table 3. Number of native plants and of plants introduced in Brazil utilized by each culture under analysis, with possible anxiolytic and/or hypnotic effects, as also the frequency with which species introduced were utilized.

Culture	Native	Introduced	Total	% introduced
Afro-Brazilian and/or Quilombola	15	14	29	48.3
Caboclo	10	10	20	50
Indian	13	5	18	28

Other Pharmacological Effects

A review of the literature showed that many of the plants cited by the three cultures cited in this survey present other pharmacological effects that are not necessarily anxiolytic or hypnotic, although, in the majority of cases, these plants exert action on the CNS, as can be observed in Tables 1 and 2. Thus *Lactuca sativa* L. exerts an antioxidating, [399] analgesic, and anti-inflammatory effect [101]; *Miconia rubiginosa* (Bonpl.) DC has an analgesic effect [165]. Molina et al., [400], working

with *Mimosa pudica* L., verified its antidepressive effect on the CNS, but could not confirm the anxiolytic effect of this plant. In a later study, Bum et al [401] reported anticonvulsant action of this plant, an effect that was also observed in *Pimpinella anisum* L. [402].

Analgesic and anti-inflammatory effects were reported for species *Sacharum officinarum* L. [403] and *Casearia sylvestris* Sw. [404]. Studies were also found showing the following pharmacological effects for some of the plants cited in this study: *Kalanchoe brasiliensis* Cambess., anti-inflammatory [405] and immunomodulator [406]; *Vitex agnus-castus* L., a dopaminergic effect [407]; *Mentha piperita* L., gastric antispasmodic action [408]; *Hibiscus rosa-sinensis* L., anticonceptional effect [409,410]; *Nymphaea alba* L., renal protector [411] and antinociceptive [412]; finally an anti-hypertensive effect [413] for *Alpinia zerumbet* (Pers.) B.L. Burtt & R.M. Sm.

FINAL CONSIDERATIONS

Among the plants indicated in this survey, 67% were investigated from the phytochemical point of view: the flavonoids, essential oils, and alkaloids are important constituents for the anxiolytic and hypnotic effects attributed to these plants by popular lore.

Fifty per cent were investigated from the pharmacological point of view: among the pharmacological effects studied, only 25% referred to anxiolytics or hypnotics.

These sparse pharmacological data found in the scientific literature concerning the native species in Brazil agree with that observed in a previous study conducted by Rodrigues and Carlini [414]. They developed a bibliographical survey conducted on Databases such as LILACS (Latin-American and Caribbean Literature in Health Studies) and MEDLINE (PUBMED), in order to verify the number of studies on plants (pharmacological and phytochemical) developed about South American plants in reference to the psycholeptic and psychoanaleptic effects. Results of this search showed that only 15 and 16 pharmacological studies, respectively, had been carried out to investigate the anxiolytic and hypnotic effects of plants in South America. A total of 863 studies and of 1,160 studies concerning anxiolytic and hypnotic plants, respectively, were recorded in the rest of the world.

These observations corroborate the idea that it is necessary to carry out more studies that will focus on plants with action/effect on the CNS since

this field of study is as yet extremely incipient. Even with so many studies worldwide, as cited above, up to the present time, it has not been possible to develop anxiolytic or hypnotic phytomedicines to substitute the allopathic medication prescribed by psychiatry.

ABBREVIATIONS

CNS = Central Nervous System
BDZs = Benzodiazepinies
EPM = Elevated Plus Maze
GABA = Gama Amino Butiric Acid

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