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Plants from Solanaceae family with possible anxiolytic effect reported on 19th century's Brazilian medical journal

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Abstract: In the beginning of the 19th century, the first Brazilian scientific knowledge journal on medicinal plants the Gazetas Médicas was launch reporting Brazilian medicinal plants belonging to several botanical families. The aim of this study was research the Solanaceae species that were described as anxiolytics in the 19th century's Brazilian Medical Gazettes and to make a revision about these species in literature. A taxonomic update, together a careful research about ethnopharmacological, pharmacological and phytochemical, patent process and reports of phytomedicines, was carried out for these Solanaceae species. In this research were found thirteen plants, but the taxonomic update reduced this number to six species. Among them, *Physalis angulata* L. and *Solanum nigrum* L. were studied and showed depressor activity on central nervous system (CNS) as described in Gazetas Médicas. This research showed that Solanaceae species reported in this study has potential as anxiolytic drugs and should be investigated more deeply.

Introduction

In the beginning of the 19th century, Brazilian's fauna and flora were practically unknown. Brazil was a Portuguese colony between 1500 and 1822. In 1808, when the Portuguese Royal Family moved to Rio de Janeiro, this situation changed. The 13 years that they lived in Brazil was characterized by notable progress in the country's economy, culture and science. An improvement of scientific knowledge was also obtained thanks to naturalists that contributed greatly to the growing knowledge of South-American biodiversity and led to significant advances in the study of medicinal plants, which were the main health resources of the Brazilian medicine in the beginning of the 19th century.

Another important advance was the reorganization of the Medical Academies, in 1832 (Fonseca, 2002), and the creation of the first Medical School in Salvador city, Bahia. These Academies carried out several scientific researches in Brazil, mainly the study of the medicinal properties of several indigenous plants (Debret, 1949), which led to the publication of the Brazilian Medical Journal: the Medical Gazettes. Both, the Medical Gazettes from Rio de Janeiro and Bahia were published for the first time in the 19th century (1862 and 1868 respectively), and their objectives was disseminate the main scientific research among the medical community and inform some curious clinical observations (Gazeta Médica do Rio de Janeiro, 1976). The main Gazettes' topics were reports of cases (diseases or surgical proceedings); discussions of illness inside and outside Brazil; prescriptions of medicines made from chemical substances, minerals and animals, besides studies from medicinal plants.

Some botanical families, such as Solanaceae, had their medicinal uses described for a long time. It comprises 2800-3000 species belonging to 85-90 genera of herbs, shrubs, and a few trees (Woodland, 1997); cosmopolitan, occurring around the world except in the Artic area. The major part of species is located in South America (Schultes & Raffauf, 1990; Agra & Berger, 2009). The anxiolytic properties of the Solanaceae family are also well known empirically for long time. Freire Allemão, in Medical Gazette of Rio de Janeiro (1862), explained that the word *Solanum* comes from the Latin word *Solari*, which means "to relieve". The author also says that "the vegetable which deserves this denomination have been employed for its tranquillizer property for a long time" (Allemão, 1976). The bioactive chemical constituents found in this family are tropane, pyrrolidine and pyrrolic alkaloids; protoalkaloids; glycoalkaloids; nicotine; cardenolides; capsaicinoids; kaurene-type tetracyclic diterpenes; steroidal glycosides; withasteroids, withanolides, and physalins (Pomilio et

al., 2008).

Psychoactive substances (including plants) are those which alter aspects of the mind including behavior, mood and cognition (Bertolote & Girolamo, 1993). They may be classified in three types: disturbers of the Central Nervous System (CNS); stimulants and depressors (Chaloult, 1971). Anxiety is an emotion experienced in several threat situations day by day; however, there are many stressful situations that cause inadaptable responses, leading to some types of anxiety disorders (Stahl, 2002). The therapies for anxiety are accompanied with medication, using anxiolytics, which are psychoactive substances that, as the name suggests, precipitate a break (lysis) in anxiety. Thus, anxiolytics act as depressors of CNS. The first drugs used to treat anxiety were barbiturates, toxic compounds that produced a variety of adverse effects, which have mainly been replaced by benzodiazepines (BDZ), the most common anxiolytic drugs. Benzodiazepines (BDZ) are the main anxiolytics drugs today. As side effects, they produce slower mental processes, reduced reflexes, deficient attention and memory impairment. Beside this, as psychotropic drugs, may potentially induce tolerance and dependence (Hardman et al, 2001; Lader, 1999).

Type A α-aminobutyric acid (GABAA) receptors are the major inhibitory neurotransmitter receptors in the CNS (Macdonald & Olsen, 1994). Anxiolytics facilitate the coupling of GABAergic receptors to GABAA and produce their pharmacological effect by binding to a benzodiazepine recognition site on the GABAA receptor complex. Research on flavonoids has increased because they have been identified as a new type of neuromimetic ligand with *in vivo* anxiolytic properties. Flavonoids have been shown to have effects on rodent behavior with anxiolytic potency comparable to that of typical BDZ agents. Beside this, unlike BDZ, the flavonoid anxiolytics did not induce sedation concurrent with their anti-anxiety activity (Herrera-Ruiz et al., 2008). Flavonoids glycosides, have been shown to exert CNS mediated activities, particularly as sedative-hypnotics, analgesics and anxiolytic (de Castro et al., 2007). Thus, the researches for new anxiolytic substances that will entail fewer damages than the BDZ are promising prospective in the field of medical therapeutics.

The aim of this study was research the botanical species of Solanaceae family described as anxiolytic in the 19th century's Brazilian Medical Gazettes and to make a comparison with data reported update for these same species.

Methods

Information about Solanaceae species was obtained from the three volumes of "Gazeta Médica do Rio de Janeiro", which reported plants with anxiolytic and/or hypnotic effects.

Gazeta Médica do Rio de Janeiro (Tomes I, II and III): published from June 1862 to May 1864. São Paulo. Brasiliensia Documenta (X), 1976.

The taxonomic information for Solanaceae species reported as possessing anxiolytic effect were update, according to the International Code of Botanical Nomenclature, by the consult of taxonomists and specialized literatures; or yet, by the taxonomic databanks available online. Species without references about their origin were not included. The presence of any synonymies was checked at the site of the Missouri Botanical Garden (www.tropicos.org).

An extensive search in the scientific literature (20th and 21st centuries) were carried out in order to find recent results concerning the phytochemistry and pharmacological effects of these plants, focusing their actual use with medicinal purpose, using scientific and popular names, as well as its synonyms. The research about its ethnopharmacological uses were conducted in Scopus, Dr. Duke's Phytochemical and Ethnobotanical Database and in the articles of the Center of Ethnopharmacological Studies' collection (CEE–Unifesp).

Efforts were made in the attempt to found modern pharmacological studies, that could validate some of the possible effects mentioned in the Gazeta Medica, which were carried out in Scopus, Pubmed and Web of Science databases and in all of the Annals of the Brazilian Symposium of Medicinal Plants (from 1968 until 2010), one of the most relevant sources available in Brazil.

A complete list of pharmaceutical products was consulted on line into Anvisa (National Agency for Sanitary Vigilance) - a regulatory agency for Brazilian medication, through the site (www.anvisa.gov.br), to verify if any of the Solanaceae species is commercialized on the market of Brazil, as pharmaceutical products. The survey about registry of patents in Brazil, the United States, and Europe, was carried out in the following sites, for the United States Patent Office - USPTO (http://www.uspto.gov) and for the European Patent Office - Espacenet (http://www.ep.espacenet.com), which possess patent processes of several countries of Europe, Japan and Brazil. This search was carried out in November 2008, in agreement with the ethical proceedings, and it was approved by the Ethic Committee of the Federal University of São Paulo (CEP 0601/06).

Results

The three volumes of the "Gazeta Médica do Rio de Janeiro" could be read, thanks to a re-publication facsimile of the original Gazettes, being found citation

of thirteen medicinal plants belonging to the Solanaceae family. Of these, twelve were cited by the scientific name, and one was cited by the genus. The taxonomic update reduced this number to six species, because in three cases the species equivalent was not found as described in Gazettes. All species cited in Table 1, contain their scientific names in the 19th century, the respective names after the taxonomic update and its synonyms. The Gazettes of Bahia also were read, but, in this case, it was not found Solanaceae species with anxiolytic report.

Despite the long tradition of these species as medicinal plant, only a few reports were found about ethnopharmacology, pharmacology and phytochemical data. However, nowadays two species of Solanaceae family, *Physalis angulata* L. and *Solanum nigrum* L. were reported as possessing potential CNS-depressant action (Perez et al., 1998), as described in 19th century's. None of them have records of phytomedicines or patent registered in Brazil (Anvisa, 2008). The results of this search are described below.

Physalis angulata L.

Vernacular name: Timbó.

Synonyms: *Physalis angulata* L.; *Physalis brasiliensis* Sendtn.; *Physalis pubescens* L.

Part of use: whole plant.

Report in the 19th century: little active narcotic principle, tranquilizer, tonic.

Current literature: Ethnopharmacology: analgesic, sedative, narcotic, to treat fever, nausea, and to "sleep disorder" (Dr. Duke's Phytochemical and Ethnobotanical Database, 2010). Pharmacology: anticolinergic (Fonteles et al., 1990); analgesic (Bastos et al., 2006); antioxidant (Choi & Hwang, 2005), anti-inflammatory effects (Bastos et al., 2008). Phytochemical: seco-steroids (physalins) (Soares et al., 2006; Abe et al., 2006; Kuo et al., 2006; Magalhães et al., 2006a; Magalhães et al., 2006b; Damu et al., 2007), alkaloids (Edeoga et al., 2005), tannins and flavonoids (Edeoga et al., 2005; Wollenweber et al., 2005), the withanolides withangulatin (Lee et al., 2008) and physagulins (He et al., 2007). Patents that were reported, both in the European Patent Office and the Brazilian National Institute of industrial Property databases, most of which concern inflammatory, allergic, parasitic, infectious or digestive diseases, including extracts from *P. angulata* (Balbani et al., 2009).

Solanum americanum Mill.

Vernacular name: Carachichú.

Synonyms: *Solanum americanum* var. *nodiflorum* (Jacq.) Edmonds; *Solanum caribaeum*. Dunal; *Solanum nodiflorum* Jacq.

Part of use: not mentioned.

Report in the 19th century: sedative baths.

Current literature: Ethnopharmacological, pharmacological studies or patent processes were not found for this plant. Phytochemical: The sapogenin tigogenine and the steroidal alkaloids solasodin and solasonine (Aldana & Lima, 1999), alpha-solamargine

Table 1. Scientific names of the plants in the 19th century; the names after the taxonomic update, and its synonyms.

Scientific name cited in the 19th century	Scientific name after the taxonomic update	Synonyms
Cestrum L.	*Cestrum* L.	-
Physalis heterophylla Nees	*Physalis angulata* L.	*Physalis angulata* L.; *Physalis brasiliensis* Sendtn.; *Physalis pubescens* L.
Solanum guaraquinha	Not identified	-
Solanum guaraquinhaçu Vell.	Not identified	-
Solanum guineense Lam.	*Solanum scabrum* Mill.	*Solanum intrusum* Soria; *Solanum melanocerasum* All.
Solanum morella	*Solanum nigrum* L.	-
Solanum nigrum L.	*Solanum nigrum* L.	-
Solanum nigrum var. *aguariquya*	*Solanum chenopodioides* Lam.	*Solanum gracile* Dunal; *Solanum gracilius* Herter; *Solanum sublobatum* Willd. ex Roem & Schult.
Solanum nodiflorum Jacq.	*Solanum americanum* Mill.	*Solanum americanum* var. *nodiflorum* (Jacq.) Edmonds; *Solanum caribaeum* Dunal; *Solanum nodiflorum* Jacq.
Solanum oleraceum Dunal	*Solanum americanum* Mill.	*Solanum americanum* var. *nodiflorum* (Jacq.) Edmonds; *Solanum caribaeum* Dunal; *Solanum nodiflorum* Jacq.
Solanum prodomus	Not identified	-
Solanum pterocaulon Dunal	*Solanum chenopodioides* Lam.	*Solanum gracile* Dunal; *Solanum gracilius* Herter; *Solanum sublobatum* Willd. ex Roem & Schult.
Solanum toxicarum Rich.	*Solanum stramoniifolium* Jacq.	-

(Al Chami et al., 2003) and anthocyanins (Bobbio et al., 1987) were isolated from *Solanum americanum* Mill.

Solanum chenopodioides Lam.

Vernacular name: Herva Moira.

Synonyms: *Solanum gracile* Dunal; *Solanum gracilius* Herter; *Solanum sublobatum* Willd. ex Roem & Schult.

Part of use: not mentioned.

Report in the 19th century: sedative baths.

Current literature: Ethnopharmacology: to treat fever (Dr. Duke's Phytochemical and Ethnobotanical Database, 2008). Pharmacological, phytochemical studies or patent registrations were not found for this plant.

Solanum nigrum L.

Vernacular name: Carachichú.

Part of use: not mentioned.

Report in the 19th century: tranquilizer.

Current literature: Ethnopharmacology: analgesic, depurative, to treat fever, tonic, tranquilizer and CNS depressor (Dr. Duke's Phytochemical and Ethnobotanical Database, 2008), sedative (Adesina, 1982; Dr. Duke's Phytochemical and Ethnobotanical Database, 2008). Pharmacology: antinociceptive property (Zakaria et al., 2006); can cause a central nervous system depression which may be correlated with an increased parasympathetic tone (Perez et al., 1998), antioxidant (Al-Fatimi et al., 2007); antipyretic and anticancer agent (Hsieh et al., 2008; Hsu et al., 2009; Yang et al., 2010; Li et al., 2008; Li et al., 2009), mutagenic activity (Almeida et al., 2010). Phytochemical: glycoalkaloids (El-Ashaal et al., 1999), tropane alkaloids (Oksman-Caldentey, 2007; Grynkiewicz & Gadzikowska, 2008; Nash et al., 1993), nicotine alkaloids (Oksman-Caldentey, 2007; Boswell et al., 1999), flavonoids (Wollenweber et al., 2005; Huang et al., 2010), sterols (Amir & Kumar, 2004), steroidal saponins (Ikeda et al., 2000; Nakamura et al., 2008; Zhou et al., 2006; Ferreira et al., 1996), pregnane saponins (Zhou et al., 2007), volatile oils and anthocyanins (Jainu & Devi, 2006), steroidal alkaloids, such as solamargine, solasonine and solanine (Sanchez-Mata, et al., 2010; Cornelius et al., 2010; Suthar & Mulani, 2008; Chen et al., 2010) and deacetoxysolaphyllidine-3-*O*-β-D-glucopyranoside (Colmenares et al., 2010); phenolic compounds with strong oxidative effects (Mimica-Dukic et al., 2005; Lin et al., 2007; Huang et al., 2010; Yang et al., 2010); hydroxycinnamic acid amides (Henriques et al., 2006); steroidal glycosides (Ando et al., 1999) and oligosaccharides of 2-deoxy sugars, which have been reported to possess immunomodulating, antitumor, and anticancer activities (Chen et al., 2009). The cuticular waxes of the leaves of Solanaceae plants are unusual, because they contain significant quantities of branched-chain hydrocarbons in addition to normal hydrocarbons (Szafranek & Synak, 2006). Patent: benzodiazepine compound (USPTO, 2008), weight gain (Espacenet, 2008).

Solanum scabrum Mill.

Vernacular name: Carachichú.

Synonyms: *Solanum intrusum* Soria; *Solanum melanocerasum* All.

Part of use: not mentioned.

Report in the 19th century: tranquilizer.

Current literature: Ethnopharmacological, pharmacological, phytochemical studies or patent processes were not found for this species.

Solanum stramoniifolium Jacq.

Vernacular name: not mentioned.

Part of use: not mentioned.

Report in the 19th century: tranquilizer; paralyzing; narcotic.

Current literature: Ethnopharmacological, pharmacological, phytochemical studies or patent processes were not found for this species.

Discussion

Social factors underlying the traditional medical practices, such as a familiar historical background in traditional medicine, play a crucial role in the transmission and survival of this important knowledge in communities. Understanding the dominant medical-belief system of a community is essential to any ethnobotanical survey of medicinal plants, as had been suggested by traditional healers in South America.

The use of traditional medicinal knowledge in drug discovery seems so promising that recently even large pharmaceutical companies have begun to show interest (Kate & Laird, 1999). Important studies about the plants used as medicinal in the last centuries were reported by Heinrich et al. (2006) and Pollio et al. (2008). Botanical and medicinal knowledge in Brazil colonial was documented in Medical Gazettes, but this source of knowledge has been neglected and consequently, these Solanaceae species did not evaluate pharmacologically. One of the reasons for neglecting is the difficulty of accessing Medical Gazettes nowadays, which can not be removed from their libraries.

Researches carried out with data reported in the past centuries require a special careful. It is necessary to observe the context of the report, to understand the exact taxonomic concept that was used in the past period, because certain terms may be used in different contexts at

different occasions. If the taxonomic aspects had not been considered, could be concluded that some species were not studied and consequently their data were not published, when in fact the scientific names mentioned are not valid or not used today. It is known that in the past, researchers used taxonomic concepts which are not considered correct for species from the genera *Solanum* nowadays. For instance, the botanical characteristics mentioned on the "Gazeta Médica" for *Solanum nigrum* L. belong to the specie *S. americanum* Mill. This "taxonomic confusion" was reported by Edmonds & Chweya (1997), and showed the importance of the process of taxonomic update. Some other limitations must be considered in spite of the careful survey. The historic literature sometimes did not specify the part used of plant, or the method of utilization (tea, pomade etc).

The importance of Solanaceae family is due to the presence of alkaloids among their secondary metabolites, being known for their high alkaloid content. Alkaloids are found in all plant parts like roots, stems, leaves, flowers, fruits and seeds and are known for their antimicrobial activity (Kumar et al., 2009). Beside this, chemical constituents such as flavonoids, tannins and steroids were also found and are important secondary metabolites. Many plants belonging to the Solanaceae family have been used as a source of pharmaceuticals for centuries due to the presence of tropane and nicotine alkaloids, as principle actives. Tropane alkaloids, atropine, hyoscyamine and scopolamine, are among the oldest drugs used in medicine (Oksman-Caldentey, 2007; Hashimoto et al., 1993, Reina et al., 2010). Hyoscyamine, anisodamine (6-β-hydroxyhyoscyamine) and scopolamine were traditionally used due to anticholinergic activity. Atropine and scopolamine are considered to be model anticholinergic drugs, continues to provide inspiration in the search for more selective muscarinic receptor antagonists. Anisodamine is gaining attention due to the wide range of therapeutic applications (Cardillo et al., 2010). Pharmaceutical industry manufactures more than twenty active pharmaceutical substances containing tropane moiety in their structure, which are applied as mydriatics, antiemetics, antispasmodics; anesthetics and bronchodilators (Grynkiewicz & Gadzikowska, 2008). Nicotine alkaloids had only recently gained attention as a backbone for novel potential alkaloids to be used for certain neurological diseases (Oksman-Caldentey, 2007).

Some *Solanum*-genera plants have traditionally been used as anti-cancer and anti-herpes agents from olden times (Ikeda et al., 2003). Steroidal alkaloids, such as solamargine induces apoptosis (Shiu et al., 2009) and also solanine induced apoptosis in HepG(2) cells (Ji et al., 2008). Solamargine and solasonine, exhibited an inhibitory effect on serum glucose levels in oral sucrose-loaded rats, and this effect could be relevant for the prevention and treatment of diabetes (Yoshikawa et al., 2007). α-Chaconine, α-solanine, and α-tomatine inhibited normal human liver HeLa (Chang) cells (Lee et al. 2004). β-Solamargine is the main antineoplastic agent in *S. nigrum* (Hu et al., 1999). Pregnane saponins had been effective in treating diseases such as osteoporosis and premenstrual syndrome in women (Noguchi et al., 2006).

Psychoactive drugs that act as depressors, decrease the activity of the CNS, and can exhibit anxiolytic activity (Walesiuk et al., 2010). Among the species cited, only *Physalis angulata* and *Solanum nigrum* were reported as possessing potential CNS-depressor activity, as described in Brazilian Medical Gazettes. In a study made by Perez et al. (1998), an ethanol extract of the fruit of *S. nigrum* did not show any sedation and motor coordination, but decreased the spontaneous motor activity of the experimental animals and potentiated the pentobarbital-induced hypnosis, indicating a central depressant effect. *S. nigrum* contain many polyphenolic compounds (Lin et al., 2007), including gallic acid, protocatechuic acid, catechin, caffeic acid, epicatechin, rutin, and naringenin, besides other flavonoids such as, luteolin, quercetin, apigenin, kaempferol and hesperetin (Huang et al., 2010). Flavonoids could to be a subtype-selective partial agonist of GABAA receptors that exhibit anxiolytic effects without sedative, amnesic, myorelaxant, motor incoordination, or anticonvulsant effects, being a promising drug candidate for the treatment of anxiety-like disorders. Glycosilation can influence transport of flavonoids through haemato-encephalitic barrier modifying the entrance into the brain tissue and consequently its neuropharmacological properties (Ren et al., 2010). Luteolin and apigenin were found among the constituents of *S. nigrum*, and the flavones homoorientin, orientin, vitexin, and isovitexin, derived of apigenin and luteolin, exhibited anxiolytic activity, through positive modulation of GABAA receptor (Grundmann et al., 2008; Fernandez et al., 2009). Quercetin and kaempferol derivatives, such as tiliroside also exhibited anxiolytic-like response and the anxiolytic activity of three Mexican *Tilia* species was attributed for these flavonoids occurrence independently of the kind of glycosides present in the samples (Aguirre-Hernandez et al., 2010). Tiliroside was isolated from *Solanum crinitum* Lam (Cornelius et al. 2010). The effects of flavonoids as CNS active substances probably are related to the dose administered, because anxiolytic-like activity was observed at lower dose while sedative-like activity was observed at higher dose (Deng et al., 2010).

Complex interactions can exist among the flavonoids and between them and several other psychoactive plant constituents to produce the anxiolytic effects (Coleta et al., 2008). It is interesting to observe that in plants of Solanaceae family such as *Solanum tuberosum* was found the presence of endogenous

BDZ from cultivated tissues (Kavvadias et al., 2000). *S. tuberosum* exhibited after HPLC separation a series of compounds identified as N-desmethyldiazepam (temazepam) and diazepam by Mass Spectra analysis. According to Corsi et al. (2004), the presence of such molecules in vegetables might not just be a coincidence because these molecules seem to be likely involved in the basic metabolic pathway of plant cells. Temazepam and diazepam were found in amounts of about 0 to 450 ng/g cell tissue of *S. tuberosum* (Kavvadias et al., 2000). The low content of diazepam in the potato extracts could not sustain the anticonvulsant activity of potato juice, *in vivo*. But, according to Muceniece et al. (2008), potato juice might contain GABA(A) receptor GABA-site active compounds, suggesting that potato juice as well as potato taken as food may have the capacity of influencing brain GABA-ergic activity (Muceniece et al., 2008). Besides benzodiazepines derivatives other compounds were identified in potato. The two major glycoalkaloids in potato are α-solanine and α-chaconine, which together comprise approximately 95% of tuber glycoalkaloids (Shakya & Navarre, 2006). Three flavonols, which were identified by HPLC-DAD-ESIMS as quercetin 3-rutinoside, quercetin 3-diglucoside, and quercetin 3-glucosylrutinoside, together with chlorogenic acid as the main caffeic acid derivative were also found and quantified in potato cultivars (Tudela et al., 2002).

Physalis angulata and *Solanum nigrum* have studies in the recent literature that suggested an anxiolytic activity (Perez et al., 1998). Active principles that could be exhibited anxiolytic activity, such as flavonoids and endogenous benzodiazepines were found in Solanaceae family and this fact could be a strong evidence of the anxiolytic effect of these plants, but more specific studies must been conduced to confirm this activity.

The present article shows that the research based on historic literature can be an important tool on the selection of plants with biological activity. This article also pointed the great importance of the taxonomic update in species cited in historic literature researches.

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