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Review Article

Ethnobotanical review of *Trichilia catigua* A. Juss

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Abstract: *Trichilia catigua* A. Juss (Meliaceae) has been widely used in Brazilian traditional systems of medicine for treatment of fatigue, stress, impotence and memory deficit. Recently, the plant extracts have been evaluated for their antidepressant, antioxidant, antibacterial and antiarrhythmic actions. It is also a component of herbal tonics that have widely been marketed in Brazil since the past twenty years. This review aims to provide a compilation of all available information about the plant including its botany, chemical constituents, and traditional uses, scientifically proven pharmacological activities, toxicological considerations and future prospects for research.

Keywords: Catuaba, Cognition, Cinchonain, Catiguanin, Vasorelaxation

Introduction

Plants and plant parts including their extracts prepared by traditional methods have been successfully used to treat a number of diseases since ages. It is widely believed that the inherent capability of these plants to protect themselves from undesirable microbial attacks due to presence of phytoconstituents is responsible for elimination of microorganisms and restoration of normal physiological activities. Ancient healers were in possession of this knowledge and used plants for "healing" powers. This knowledge was passed down the generations initially by word of mouth and later on by systematic documentation and records.

Sincere efforts on the part of botanists and traditional healers to highlight knowledge of herbs and their uses has led to the re-emergence of several herbal drugs as mainstream modalities of treatment. Amongst the different herbs that have been commercially exploited, majority of the plants have been indicated as a source of free radical scavengers, as antiinfectives and as immunostimulants. Very few herbal drugs have shown potent CNS activity. The primary reason for this could be the inability of the phytoconstituents to cross the blood-brain barrier. However, recent reports and scientific investigations of the plant *Trichilia catigua* have thrown light on its CNS activities. The purpose of this review which is the first of its kind on the plant is to compile all the available scientific information and to present it to the Scientific Community in order to generate interest in the plant.

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Brazilian traditional systems of medicine are replete with examples of herbs that are used for their adaptogenic properties [1]. The term "adaptogen" refers to those plants whose consumption can counteract stress and the resultant damage [2]. They are mainly used in conjunction with a balanced diet for a healthy lifestyle free of disease and illness [3]. A plant often mentioned in Brazilian texts is *Trichilia catigua* A. Juss (Meliaceae) commonly known as Catuaba [4]. The term "Catuaba" was coined by Brazilian Indians who have been using this herb as an aphrodisiac. The word Catuaba appears to have been modified from the local term "*catucaba*" which means kindness and health. Another likely explanation is that "*catu*" means good and "*apuaba*" means man, the term "good for man" being self-explanatory [5].

History, Distribution and Morphology

Figure.1: Leaves of *Trichilia catigua* A. Juss

Trichilia catigua has a wide distribution in South and Central America [6]. This species of *Trichilia* mainly occurs in the forest remnants in and near Maringa, Parana State and Brazil [7].The species *T. catigua* A. Juss is known as catigua, catigua amarelo, catigua branco, catigua vermelho, angelim rosa, mangalu-catinga, catagua, pombeiro, or veludo (Fig 1). The tree may reach a height of 3-8 m; the stem is branched, thickly covered with thin, almost smooth bark. Small trees are 2-4 m tall with diameter at breast height (DBH) of about 2-4 cm. The plant blooms from August to March showing the presence of yellow inflorescence [8]. Fruit production occurs two months later (Figure 2). Detailed morphology and anatomy of the flowers of *T. catigua* have been reported by various researchers [6,7,8].

Figure.2: Fruits of *Trichilia catigua* A. Juss

Microscopical evaluation of the bark of *T. catigua* revealed the presence of fibrous bark having grayish cork outside and reddish brown colour on the inner side. On the inner side of the cork layer were present a few rows of parenchymal cells containing calcium oxalate crystals. The inner layers consisted of stone cells and fibre bundles. The bark shows presence of brownish yellow secretion in parenchymal cells and interstitial spaces. In addition the bark contains many rounded, solitary and compound starch grains [9].

Traditional uses

T. catigua A. Juss (Meliaceae) is traditionally used in Brazil as a tonic for the treatment of physical and mental fatigue, stress, impotence, against memory deficits and also as a digestive and purgative [10,11]. Besides this, the bark of this plant is used by several pharmaceutical industries in Brazil to prepare tonic drinks which are utilized for their analgesic, CNS stimulant, aphrodisiac and vasorelaxant action [9,11]. Moreover, *T. catigua* also exhibits adaptogenic activity which helps to improve physical and cognitive performances that aid in attenuating source of related stress disorders [2,12]. In Brazil, the herbal product Catuama® whose constituents include 4 hydroalcoholic extracts, viz. *T. catigua* (28.23%), *Paullinia cupana* (40.31%), *Ptychopetalum olacoides* (28.23%) and *Zingiber officinalis* (3.26%) has also been commercially used as a remedy for neuromuscular asthenia and weakness disorders [11]. Phase I clinical trials of Catuama® carried out in healthy volunteers over a period of 28 days confirmed the absence of both adverse reactions and haematological and biochemical changes in humans [13,14,15,16].

Recently, studies carried out to evaluate pharmacological activity of various parts of the plant revealed that the plant elicits antidepressant, antiinflammatory and muscle relaxant properties.

Phytochemical constituents

Phytochemical investigations done on *T. catigua* extracts have revealed the presence of several chemical constituents which accounts for its wide range of pharmacological activities. Two phenylpropanoid-substituted epicatechins namely catiguanin A and catiguanin B (Fig 3) have been isolated from the stem bark of *T. catigua* [17]. Four compounds, cinchonain Ia, cinchonain Ib, cinchonain Ic and cinchonain Id (Fig 3) have been reported to be isolated from the bark [18,19,20]. Reviewed data also indicated that *T. catigua* extracts contained omega-phenyl alkanes, omega-phenyl alkanoic acids, omega phenyl-gamma lactones, alkyl-gamma-lactones, alkenyl-gamma lactones, sesquiterpenes, fatty acids ranging from C-14 to C-26, β-sitosterol, stigmasterol, campesterol and tannins [8, 21].

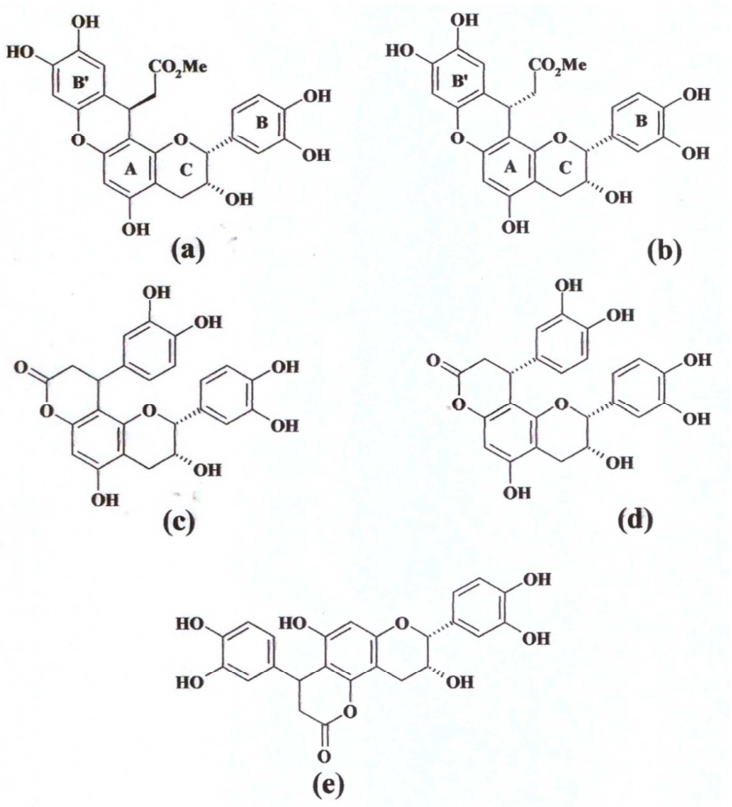

Figure.3: Phytoconstituents of *Trichila catigua* (a) Catiguanin A, (b) Catiguanin B, (c) Cinchonain Ia, (d) Cinchonain Ib, (e) Cinchonain Ic/Id. (Tang et al., 2007).

Materials and Methods

Pharmacological properties:

Numerous studies carried out on extractives of *T. catigua* have confirmed its therapeutic benefits in depression, ventricular fibrillation, cognition and pathogenic infections [21,22,23]. Scientists have attempted to unravel the underlying mechanisms and have come up with plausible explanations regarding the role of this herb in mitigating diseases. The pharmacological activities of this plant have been attributed to phytoconstituents such as phenylpropanoid substituted epicatechins like catiguanin A, catiguanin B and flavignans like cinchonain Ia, Ib, Ic and Id that were present in the extractives studied during bioassays. General protective mechanisms such as free radical scavenging activity due to flavonoids, tannins and phenylpropanoids are believed to be responsible for the beneficial effects demonstrated by the plant. This plant warrants further investigation into its traditionally claimed activities by scientifically validated biological experiments.

Antidepressant effect

Campos et al. (2000) evaluated that the antidepressant activity of hydroalcoholic extracts of dried barks of *T. catigua* by *in-vivo* and *in-vitro* tests [22]. Mice as well as rats dosed with 100, 200, 400 mg/kg of the hydroalcoholic extract were subjected to the forced swimming test. The extracts of *T. catigua* (200 and 400 mg/kg p.o.) and the standard drug used i.e. fluoxetine (32 mg/kg i.p.) significantly decreased the immobility time of mice. As compared to fluoxetine, animals treated with *T. catigua* extract (400 mg/kg p.o.) demonstrated enhanced climbing behaviour.

Investigations were carried out to unravel possible mechanisms that may have come into play [19,22]. Treatment rats were pretreated with one of the following drugs by i.p. route-Non-selective dopamine receptor agonist (Chlorpromazine 5 mg/kg), Dopamine $D_2/D_3/D_4$ receptor antagonist (Haloperidol 1 mg/kg), Selective dopamine D_2 receptor antagonist (Pimozide 2.5 mg/kg), Selective serotonin 5-HT_{1a} receptor antagonist (Spiroxatrine 1 mg/kg), Selective serotonin 5-$HT_{2\,a}$ receptor antagonist (Ketanserin 1 mg/kg) or neuronal serotonin store depleter (p. chlorophenyl alanine 100 mg/kg). All the drugs were administered 30 minutes before treatment with *Trichilia catigua* extract and animals were subjected to forced swimming test and tail suspension test. On the basis of the observations made, it was concluded that *T. catigua* extract was about two times more potent in inhibiting dopamine uptake as compared to serotonin uptake and did not affect synaptosomal uptake of noradrenaline. The *in-vitro* tests involved incubation of crude preparations of rat synaptosomal membranes in the presence of different concentrations of *T. catigua* extract (10-300 mcg/ml). These preparations were then incubated with radiolabelled serotonin, dopamine or noradrenaline. Non-specific uptake of neurotransmitters was then determined. The results clearly indicated that the hydroalcoholic extract of *T. catigua* produced a concentration-dependent inhibition of serotonin and dopamine uptake along with significant increase in release of both the neurotransmitters [22].

In another study, the step-down inhibitory avoidance test was used to evaluate memory enhancement capability of crude extract (CE) as well as ethyl acetate fraction (EAF) of the barks of *T. catigua* [12] Both CE (800 mg/kg) as well as EAF (200 and 400 mg/kg) significantly increased latency

indicating an increase in memory enhancing capacity as the probable mechanism involved. Similar behavioral studies were carried out that reconfirmed the earlier reported studies. Immunohistochemical techniques were used to evaluate the extent of cell proliferation and neurogenesis. The study concluded that *T. catigua* extract exerted anti-depressant like activity which was accompanied by neuronal proliferation in the hippocampal dentate gyrus [23].

Antinociceptive activity:

Catuama® has been evaluated for its antinociceptive effect using various animal models. It elicited time-dependent and long-lasting antinociception in acetic acid-induced writhing, formalin and capsaicin induced licking models as well as in tail-flick and hot plate assays in mice. This activity was countered by administration of naloxone. Evaluation of individual components of Catuama® revealed that *T. catigua* was partly responsible for the observed effects [24].

Detailed investigations into the antinociceptive mechanisms of *T. catigua* were carried out using hot plate test, mechanical hypersensitivity model, abdominal constriction model and reversal of apomorphine-induced hypothermia study [11]. The study was modified to include pretreatment with naloxone (non-selective opiod receptor antagonist) and selective dopamine D_1 and D_2 receptor antagonists, α_1-adrenergic receptor antagonist, GABA receptor antagonist and serotonin synthesis inhibitor. As compared to the fraction cinchonain II B, the hydroalcoholic extract was found to be more effective on the dopaminergic system. In the mechanical hypersensitivity model, significant decreases in the 50% paw withdrawal threshold were observed after preventive as well as therapeutic treatment regimens with hydroalcoholic extract of *T. catigua*. Activity of morphine and indomethacin, used as positive control in the study lasted for only 3-5 hours. However, the extract was unable to reduce paw edema formation elicited by carrageenan injection. Also, there was no change in levels of proinflammatory mediators namely IL-1β, TNF-α, PGE_2 and LTB_4. This indicated that *T. catigua* exerted a central analgesic rather than anti-inflammatory effect [11]. In another *in-vitro* study, *T. catigua* (120mcg/ml) inhibited the activity of inflammatory mediator phospholipase A_2 indicating that *T. catigua* may have anti-inflammatory activity [25].

Cardiovascular activity

Catuama® and hydroalcoholic extracts of its component plants were evaluated for their vasorelaxant properties by using isolated arteries from various animal models. Catuama® (1-3000mcg/mL) elicited vasorelaxant effect on rat thoracic aorta, guinea-pig pulmonary artery and guinea-pig mesenteric artery. Catuama® (1-3000mcg /mL) also produced partial relaxation in rings of rabbit mesenteric artery and rabbit pulmonary artery. Amongst the extracts of individual components evaluated by same methodologies, *T. catigua* was found to play an important role in attenuating vasorelaxation. The observed vasorelaxation in these studies was inhibited by nitric oxide (NO) synthase inhibitor, N-ω-nitro-L-arginine (L-NOARG, 100 μM) [26]. This indicates that the vasorelaxant effect was mediated via release of nitric oxide or nitric oxide-derived substances. This accounts for the beneficial role of Catuama® in cardiovascular disturbances.

As a component of Catuama®, *T. catigua* was responsible for reversing ventricular fibrillation in isolated rabbit heart, preventing reinduction and prolonging intraventricular conduction [26].

Antioxidant and Antimicrobial activity

The aqueous and ethanolic extracts and dichloromethane, ethyl acetate and n-butanol fractions of stem bark powder of *T. catigua* were evaluated for their antioxidant activity by DPPH assay. The observed IC_{50} values ranged from 9.17mcg /ml to 76.42mcg/ml with ethanolic extract being most effective. Although concentration of phenolics in above extracts and fractions was quantitated, the study could not establish any correlation between concentration of phenolics and observed antioxidant activity [7,28,29]. The extracts and fractions also had a significant inhibitory effect on Fe^{2+}-induced TBARS production in brain homogenates. The ability to complex Fe^{2+} was attributed to the presence of flavonoids such as quercetin and rutin. When studied using 2', 7'-dichlorofluorescein diacetate (DCFH-DA) fluorescence probe, the ethanolic extract was found to decrease reactive oxygen species production in isolated mitochondria. A concurrent decrease in mitochondrial membrane potential was also observed. This explains the role of *T. catigua* extracts and flavonoids such as quercetin, quercitrin and rutinin in protecting brain

mitochondria from Ca^{2+}-induced oxidative stress [27,28].

In the *in vitro* tests, isolated compounds (Fig. 3) exhibited potent DPPH radical scavenging activity with IC_{50} values ranging from 2.3 to 9.4 µM. However, the fractions were not as effective as the standard used in the study, catechin (IC_{50} 10 µM) [14]. In another study, the isolated compounds elicited significantly higher antioxidant activity than ascorbic acid in the DPPH radical scavenging assay. The influence of the number of hydroxyl groups in the polyphenols present in the extract on radical scavenging activity was demonstrated in this study [29,30].

The ethyl acetate extract of the stem bark of *T. catigua* inhibited the growth of gram-positive bacterium namely *Bacillus cereus* and *Staphylococcus aureus* ATCC 25923 with inhibition zones of 29 mm and 32 mm respectively. Gram-negative species such as *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853 were also incubated in presence of ethyl acetate extract and demonstrated inhibition zones of 18 mm and 30 mm respectively. Flavalignans cinchonain Ia and Ib isolated from this extract were more active against gram-positive bacterial strains. The values of minimum inhibitory concentration and minimum bactericidal concentration have also been reported [21].

Vasorelaxation of rabbit corpus cavernosal tissue

NO/cGMP pathway has been implicated in relaxation of corpus cavernosum leading to penile erection. In order to investigate the popular use of Catuama® as an aphrodisiac, a study aimed at determining effect of Catuama® and its individual components on isolated rabbit corpus cavernosum was carried out. The study revealed that *T. catigua* extract evoked long-lasting relaxations which were occasionally preceded by a brief contractile effect. This effect was significantly reduced by the soluble guanylate cyclase inhibitor ODQ (10 µM) indicating that *T. catigua* exerted its vasorelaxant effect via NO/cGMP pathway [31].This probably accounts for its mention as an aphrodisiac in Brazilian folklore.

Thus the potential of this plant to attenuate a host of diseases has been proven by scientific methodologies. It further needs to be tested clinically in humans. This will elevate its state from traditional medicine to mainstream medicine for alleviation of plethora of ailments.

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