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Research paper

Screening and identification of neuroprotective compounds relevant to Alzheimer's disease from medicinal plants of S. Tomé e Príncipe

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ABSTRACT

Ethnopharmacological relevance: Alzheimer's disease (AD) neuropathology is strongly associated with the activation of inflammatory pathways, and long-term use of anti-inflammatory drugs reduces the risk of developing the disease. In S. Tomé e Príncipe (STP), several medicinal plants are used both for their positive effects in the nervous system (treatment of mental disorders, analgesics) and their anti-inflammatory properties. The goal of this study was to determine whether a phenotypic, cell-based screening approach can be applied to selected plants from STP (*Voacanga africana*, *Tarenna nitiduloides*, *Sacosperma paniculatum*, *Psychotria principensis*, *Psychotria subobliqua*) in order to identify natural compounds with multiple biological activities of interest for AD therapeutics.
Materials and methods: Plant hydroethanolic extracts were prepared and tested in a panel of phenotypic screening assays that reflect multiple neurotoxicity pathways relevant to AD—oxytosis in hippocampal nerve cells, *in vitro* ischemia, intracellular amyloid toxicity, inhibition of microglial inflammation and nerve cell differentiation. HPLC fractions from the extract that performed the best in all of the assays were tested in the oxytosis assay, our primary screen, and the most protective fraction was analyzed by mass spectrometry. The predominant compound was purified, its identity confirmed by ESI mass spectrometry and NMR, and then tested in all of the screening assays to determine its efficacy.
Results: An extract from the bark of *Voacanga africana* was more protective than any other plant extract in all of the assays ($EC_{50}s \leq 2.4$ μg/mL). The HPLC fraction from the extract that was most protective against oxytosis contained the alkaloid voacamine (MW=704.90) as the predominant compound. Purified voacamine was very protective at low doses in all of the assays ($EC_{50}s \leq 3.4$ μM).
Conclusion: These findings validate the use of our phenotypic screening, cell-based assays to identify potential compounds to treat AD from plant extracts with ethnopharmacological relevance. Our study identifies the alkaloid voacamine as a major compound in *Voacanga africana* with potent neuroprotective activities in these assays.

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1. Introduction

Alzheimer's disease (AD) is the most common form of dementia in the elderly. It is characterized by the presence of senile plaques, neurofibrillary tangles and neuronal loss associated with other age-related detrimental events such as increased oxidative stress, reduced energy metabolism and inflammation (Schubert and Maher, 2012). Therefore, AD is multi-factorial in the sense that there are a large number of mechanisms that can contribute to the disease and, specifically, nerve cell death. Many, if not most, of these mechanisms can be reproduced in cell culture assays. The

Abbreviations: Aβ, amyloid beta peptide; AD, Alzheimer's disease; APP, amyloid precursor protein; ATP, adenosine triphosphate; BBB, blood–brain barrier; CLogP, lipophilicity; CNS, Central nervous system; DMEM, Dulbecco's modified Eagle's medium; ESI, Electrospray ionization; FCS, fetal calf serum; GSH, glutathione; HBA, hydrogen bond acceptor; HBD, hydrogen bond donor; HPLC, High-performance liquid chromatography; HT22, mouse hippocampal nerve cells; IAA, iodoacetic acid; LPS, lipopolysaccharide; MC65, human nerve cells; MTT, 3-(4, 5-dimethylthiazolyl-2)-2, 5-diphenyltetrazolium bromide; MW, molecular weight; N9, mouse microglial cells; NGF, nerve growth factor; NMR, nuclear magnetic resonance; Opti-MEM, Opti-minimal essential media; PC12, rat pheochromocytoma cells; ppm, parts per million; STP, S. Tomé e Príncipe; TLC, thin layer chromatography; TMS, tetramethylsilane; tPSA, topological polar surface area

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current single-target approach to the development of anti-AD therapies has been unsuccessful (Frautschy and Cole, 2010). An alternative approach is to identify small molecules that have a broad range of biological activities that are relevant to AD (Schubert and Maher, 2012). Our laboratory has developed a set of cell-based phenotypic screening assays that reflect multiple pathological features associated with AD (Schubert and Maher, 2012). Importantly, by means of these assays we have successfully identified compounds that present beneficial therapeutic efficacy in *in vivo* models of AD (Ishige et al., 2001; Sagara et al., 2004; Liu et al., 2008; Chen et al., 2011; Chiruta et al., 2012; Schubert and Maher, 2012; Prior et al., 2013, Currais et al., 2014). However, there is a great need for additional compounds that have a therapeutic potential for the treatment of AD. Although we have previously applied our phenotypic screening approach to test pure natural compounds and their derivatives, we have never taken advantage of the rich ethnopharmacological knowledge available from historically relevant plants to directly test crude extracts and identify active components.

Traditional herbal medicines have been used for a long time in many countries all over the world as memory enhancers or to treat dementia-related disorders, and have recently become more popular. *Ginkgo biloba* leaf and *Lycium barbarum* fruit extracts are used as memory enhancers, and also have strong anti-oxidant and anti-inflammatory effects (Kim and Oh, 2012). A few clinical studies have been conducted to address the potential of herbal medicines or natural compounds to treat AD but to date none has been conclusive (Kim and Oh, 2012).

S. Tomé e Príncipe (STP) is part of the Guinean Forests of West Africa Hotspot, one of the eight biodiversity hotspots in Africa (Hotspots, 2014), and is endowed with a unique endemic plant diversity. Traditional medicine plays a crucial role in STP as the population has few means of accessing modern medical treatment. Medicines prepared from plants have been used for centuries in STP and have been proven to be safe and efficient (Madureira et al., 2008). The evolution of the local traditional medicine in STP benefited from the privileged location of the islands which were an important crossroads of culture and knowledge between the Mediterranean, Africa, South America and Asia during the Age of the Discovery in the 15th century (Madureira et al., 2008). Since 1993 several ethnopharmacological surveys have been conducted in STP with the collaboration of the Ministry of Health. Vernacular names and the specialized therapeutic use of more than 325 plants were documented, including over 1500 detailed medical recipes. Fieldwork was carried out with the collaboration of more than 50 traditional healers from both islands. Information about the medical ideology, including basic conceptual and philosophical aspects, classification of diseases and treatments, was recorded (Madureira et al., 2002, 2008; Madureira, 2006).

In this study, five different species of plants—*Voacanga africana, Sacosperma paniculatum, Psychotria subobliqua, Psychotria principensis* and *Tarenna nitiduloides,* previously collected, were selected based on ethnopharmacological data or pre-existing biological and pharmacological information. *Voacanga africana*, *Sacosperma paniculatum* and *Psychotria subobliqua* were selected for their local medicinal properties in STP, namely their positive effects in the nervous system (NS) and their anti-inflammatory activities (Madureira et al., 2002, 2008; Madureira, 2006) (Table 1). There is strong evidence from both biochemical and neuropathological data for an activation of inflammatory pathways in the brains of AD patients, and long-term use of anti-inflammatory drugs is linked with a reduced risk of developing the disease (Wyss-Coray and Rogers, 2012). Therefore, plants with anti-inflammatory properties represent good candidates for the treatment of AD, and this was one of our primary criteria in selecting the above plants for further study. Of these species, *Voacanga africana* is the only one whose medicinal properties have been examined (Koroch et al., 2009). *Voacanga africana* is traditionally used to treat a wide range of conditions in Africa, including leprosy, diarrhea, generalized edema, mental disorders and as an analgesic and anti-inflammatory (Burkill, 1985; Olaleye et al., 2004; Koroch et al., 2009). In STP, *Voacanga africana* is also used as a hypotensive and to reduce body aches and trauma (Madureira et al., 2002; Madureira, 2006). *Sacosperma paniculatum* is used in Africa to treat arthritis and rheumatism (Burkill, 1985), and in STP as a body analgesic and to treat intestinal cramps, liver disease and hernias (Madureira et al., 2002, 2008; Madureira, 2006). *Tarenna nitiduloides* and *Psychotria principensis* are two species endemic to STP that are not used by the local healers but that were selected because of their affinity (Rubiaceae family) to *Psychotria subobliqua*, which is locally used to treat toothaches and mouth inflammation (Madureira et al., 2002, 2008; Madureira, 2006). Several Rubiaceae, namely *Psychotria* species, present analgesic and anti-inflammatory properties (Burkill, 1985) and have been studied in the context of neurodegenerative diseases (Passos et al., 2013). Since *Tarenna nitiduloides* and *Psychotria principensis* have no reported ethnopharmacological relevance, they were chosen as negative controls.

Table 1
Descriptions of the extracts from the five STP medicinal plants selected based on their potential positive effects in the CNS and anti-inflammatory activity used in this study.

Extract	Botanical name (family)	Local name	Therapeutic use	Plant part used	Voucher No. (COI)
A	*Voacanga africana* Stapf (Apocynaceae)	Cata-manginga, Cata-kiô	Leprosy, diarrhea, generalized edema, mental disorders, analgesic, anti-inflammatory (Burkill, 1985; Olaleye et al., 2004; Koroch et al., 2009), hypotensive, body aches/trauma (Madureira et al., 2002; Madureira, 2006)	Leaves + stems	46 MCM/2011
B	*Voacanga africana* Stapf (Apocynaceae)	Cata-manginga, Cata-kiô	Same as A	Bark	46 MCM/2011
C	*Tarenna nitiduloides* G. Taylor (Rubiacea)	–	–	Leaves + stems	19A;19B MCM/2011
D	*Sacosperma paniculatum* (Benth.) G. Taylor (Rubiaceae)	Gligô-d'obô	Arthritis, rheumatism (Burkill, 1985), analgesic, intestinal cramps, liver disease, hernias (Madureira et al., 2002, 2008; Madureira, 2006)	Leaves + stems	50 MCM/2011
E	*Psychotria principensis* G. Taylor (Rubiaceae)	–	–	Leaves + stems	20 MCM/2011
F	*Psychotria subobliqua* Hiern (Rubiaceae)	Kuako-maguita	Toothaches, mouth inflammation (Madureira et al., 2002, 2008; Madureira, 2006)	Leaves + stems	49 MCM/2011
G	*Psychotria subobliqua* Hiern (Rubiaceae)	Kuako-maguita	Same as F	Fruits	49 MCM/2011

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