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Ethnopharmacology of Q'eqchi' Maya antiepileptic and anxiolytic plants: Effects on the GABAergic system

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ABSTRACT

Ethnopharmacological relevance: The Q'eqchi' Maya possess a large selection of plants to treat neurological disorders, including epilepsy and *susto* (fright), a culture-bound illness related to anxiety disorders.
Aim of the study: To investigate the activity of antiepileptic and anxiolytic plants in the GABAergic system, and determine if there is a pharmacological basis for plant selection.
Materials and methods: Ethanol extracts of 34 plants were tested *in vitro* for their ability to inhibit GABA-transaminase (GABA-T) or bind to the $GABA_A$-benzodiazepine (BZD) receptor, two principal drug targets in epilepsy and anxiety. Pharmacological activity was correlated with relative frequency of use, based on informant consensus.
Results: Ten plants showed greater than 50% GABA-T inhibition at 1 mg/ml, while 23 showed greater than 50% binding to the $GABA_A$-BZD receptor at 250 μg/ml. Piperaceae, Adiantaceae and Acanthaceae families were highly represented and active in both assays. There was a significant positive correlation between GABA-T inhibition and relative frequency of use for epilepsy, and an even stronger correlation between $GABA_A$ binding and relative frequency of use for *susto* (fright).
Conclusions: Clearly, Q'eqchi' traditional knowledge of antiepileptic and anxiolytic plants is associated with the use of pharmacologically active plants. Based on the evidence, it is suggested that the mechanism of action for some traditionally used plants may be mediated through the GABAergic system.

1. Introduction

Epilepsy is the most common serious neurological condition during which brain dysfunction can result in unpredictable and spontaneous seizures (Shin and McNamara, 1994; Sander and Shorvon, 1996). There are approximately 50 million individuals worldwide who have epilepsy and it is estimated that approximately 80% do not have access to modern medical treatment (World Health Organization, 2005). The Q'eqchi' Maya traditional healers of Southern Belize recognize and treat epilepsy and its symptoms with over 40 species of medicinal plants (Bourbonnais-Spear et al., 2005; Treyvaud Amiguet et al., 2005). In fact, mental health and nervous system disorders (i.e., epilepsy/seizures, headaches, and *susto* (a culture-bound syndrome) are among the top-ranked categories of illnesses treated by the healers. The biological activities of many of these plants have yet to be established. In our meetings with the Q'eqchi' Healers Association, the healers requested research on their traditional medicines to determine their efficacy and safety in a modern context.

We have previously reported the anxiolytic activity of several plants used to treat the culture-bound illness *susto* in standardized animal behaviour paradigms (Bourbonnais-Spear et al., 2007), which provided evidence that *susto* may share a similar neurological basis as anxiety. However, the exact mechanism of action for these anxiolytic plants remains unclear. It is known that the neuropathology of anxiety and epilepsy is related, and often overlaps via several neurotransmitter systems (Nash and Nutt, 2005). In the present report, we attempted to determine the relation between traditional treatments for epilepsy and *susto* and pharmacological activity associated with the γ-aminobutyric acid (GABA) system.

Abbreviation: GABA, γ-aminobutyric acid.

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GABA is the principal inhibitory neurotransmitter in the mammalian central nervous system (CNS), and has an important role in epilepsy and anxiety (Shin and McNamara, 1994; Treiman, 2001). One of the main mechanisms for controlling hyperactive nervous disorders is increasing overall GABA levels; either by inhibiting the enzyme GABA-transaminase (GABA-T; 2-oxoglutarate aminotransferase; EC 2.6.1.19) (Beleboni et al., 2004), or by facilitating GABAergic transmission via the GABA receptors (Morimoto et al., 2004). GABA-T is an important pharmacological target for antiepileptic drugs (e.g., vigabatrin, a GABA-T inhibitor) (Sherif and Ahmed, 1995), while the $GABA_A$ receptor and its modulatory benzodiazepine (BZD) site is a primary target for anxiolytic and anticonvulsant drugs (e.g., diazepam, a $GABA_A$-BZD agonist) (Mohler et al., 2002). In this study, both the GABA-T enzyme and the $GABA_A$ receptor are examined as potential mechanisms by which Q'eqchi' antiepileptic and anxiolytic plants exert their effects.

Our specific objectives were the following: (1) to document traditional Q'eqchi' Maya plants used to treat epilepsy and anxiety/*susto*, and determine their relative frequency of use by using quantitative ethnobotanical methods; (2) to assess the pharmacological activity of selected plant extracts using *in vitro* assays to measure GABA-T inhibition and binding to the $GABA_A$ receptor; and (3) to characterize the relationship between relative frequency of use of plants and their activities in the GABAergic system. Our overall hypothesis was that plants used traditionally to treat epilepsy and (or) *susto* have a pharmacological basis and this activity may be correlated with frequency of use by the healers.

2. Materials and methods

2.1. Ethnobotanical analysis

The ethnobotanical study of the Q'eqchi' Maya healers previously described in Bourbonnais-Spear et al. (2005) and Bourbonnais-Spear (2005), was performed in collaboration with the Belize Indigenous Training Institute (BITI). The project was reviewed and accepted by the University of Ottawa Ethics Committee (Approval # H-06-03-01), and the Ministry of Natural Resources of the Government of Belize issued a permit for plant collection in June 2003 (Ref # CD/6-/9/03(18)). Close attention was paid to the respect of local customs, which was facilitated by working with two Q'eqchi' research collaborators, Pedro Maquin and Victor Cal, and the healers granted their consent individually for participation. The use of these plants is recognized as the intellectual property of the Q'eqchi' Healers Association and the information has been deposited at the Belize copyright office. Furthermore, utilization

Table 1
Plants identified by the Q'eqchi' healers to treat epilepsy and (or) *susto*. Selected plants were tested for activity in the GABA-T and $GABA_A$-BZD receptor assays.

Scientific name	Plant family	UOH voucher identification[a]	Traditional use[b]	Tested
Adelobotrys adscendens (Sw.) Triana	Melastomataceae	Spear 19747	Epilepsy	Yes
Adiantum latifolium Lam.	Adiantaceae	Spear 19731	Epilepsy, *susto*	Yes
Adiantum princeps T. Moore	Adiantaceae	Spear 19705	Epilepsy, *susto*	Yes
Adiantum tetraphyllum Humb. & Bonpl. ex Willd.	Adiantaceae	Spear 19750	Epilepsy, *susto*	Yes
Adiantum wilsonii Hook.	Adiantaceae	Spear 19755	Epilepsy	Yes
Aegiphyla sp.	Verbenaceae	Spear 19724	Epilepsy	No
Aphelandra sp.	Acanthaceae	Spear 19702	Epilepsy	No
Aristolochia grandiflora Sw.	Aristolochiaceae	Spear 19736	Epilepsy	No
Gonzalagunia rosea Standl.	Rubiaceae	Spear 19728	Epilepsy	Yes
Justicia albobracteata Leonard	Acanthaceae	Spear 19745	Epilepsy	No
Justicia aurea Schltdl.	Acanthaceae	Spear 19764	Epilepsy	Yes
Justicia pectoralis Jacq.	Acanthaceae	Spear 19720	Epilepsy	Yes
Lygodium heterodoxum Kunze	Schizaeaceae	Spear 19757	Epilepsy, *susto*	Yes
Lygodium venustum Sw.	Schizaeaceae	Spear 19758	Epilepsy, *susto*	Yes
Mollinedia sp.	Monimiaceae	Spear 19704	Epilepsy	No
Peperomia sp.	Piperaceae	Spear 19775	Epilepsy	Yes
Peperomia sp.	Piperaceae	Spear 19719	Epilepsy	No
Petiveria alliacea L.	Phytolaccaceae	Spear 19738	Epilepsy	Yes
Philodendron sp.	Araceae	Spear 19763	Epilepsy	No
Piper amalago L.	Piperaceae	Spear 19733	Epilepsy	Yes
Piper tuerckheimii C.DC. ex Donn. Sm.	Piperaceae	Spear 19710	Epilepsy, *susto*	Yes
Piper sp.	Piperaceae	Spear 19744	Epilepsy, *susto*	Yes
Piper sp.	Piperaceae	Spear 19770	Epilepsy	Yes
Piper sp.	Piperaceae	Spear 19772	Epilepsy	No
Piper sp.	Piperaceae	Spear 19742	Epilepsy, *susto*	Yes
Piper sp.	Piperaceae	Spear 19771	Epilepsy	Yes
Pityrogramma calomelanos (L.) Link	Adiantaceae	Spear 19751	Epilepsy, *susto*	No
Porophyllum ruderale (Jacq.) Cass.	Asteraceae	Spear 19711	Epilepsy	No
Pseudobaccharis trinervis (Lam.) V. M. Badillo	Asteraceae	Spear 19714	Epilepsy	No
Psychotria tenuifolia Sw.	Rubiaceae	Spear 19741	Epilepsy	Yes
Sabicea sp.	Rubiaceae	Spear 19774	Epilepsy	Yes
Selaginella af. stellata Spring	Selaginellaceae	Spear 19737	Epilepsy, *susto*	Yes
Selaginella sp.	Selaginellaceae	Spear 19743	Epilepsy	Yes
Solanum sp.	Solanaceae	Spear 19777	Epilepsy	Yes
Solanum sp.	Solanaceae	Spear 19776	Epilepsy	Yes
Stachytarpheta frantzii Pol.	Verbenaceae	Spear 19726	Epilepsy	No
Syngonium sp.	Araceae	Spear 19723	Epilepsy	No
N/A	Acanthaceae	Spear 19765	Epilepsy	Yes
N/A	Acanthaceae	Spear 19779	Epilepsy	No
N/A	Apocynaceae	Spear 19760	Epilepsy	No
N/A	Asteraceae	Spear 19739	Epilepsy	Yes
N/A	Gesneriaceae	Spear 19767	Epilepsy	Yes

Note: Preliminary data on 14 plants used for *susto* were published in Bourbonnais-Spear et al. (2007).

[a] University of Ottawa Herbaria.

[b] Ethnobotanical use of the same plant may be for more than one neurological disorder.