Alexandria Journal of Medicine (2018) **54**, 27–39

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Alexandria Journal of Medicine

http://www.elsevier.com/locate/ajme

ORIGINAL ARTICLE

Protective role of *Spondias mombin* leaf and *Cola acuminata* seed extracts against scopolamine-induced cognitive dysfunction

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Received 18 March 2016; revised 29 June 2016; accepted 11 August 2016
Available online 6 April 2017

KEYWORDS

Dementia;
Lipid peroxidation;
Nitrite;
Morris water maze;
Y-maze

Abstract The leaves of *Spondias mombin* L. (Anacardiaceae) when chewed with *Cola acuminata* (P. Beauv.) Schott & Endl. (Sterculiaceae) seeds have memory enhancing and anti-ageing properties. This study sought to investigate the protective effect of hydroethanolic leaf extract of *Spondias mombin* (SM) and *Cola acuminata* seed extract (CA) against scopolamine-induced cognitive dysfunction. SM or CA (50, 100 or 200 mg/kg, *p.o.*) or SM + CA (50 mg/kg, *p.o.*) was administered to rats for 3 consecutive days. One hour post-treatment on day 3, scopolamine (3 mg/kg i.p) was administered and 5 min later, the Y-maze test or Morris water maze test (MWM; days 3–7) was conducted. The rat's brains were isolated for the estimation of oxidative-nitritive stress status following the MWM task. The antioxidant capacity of SM and CA was also evaluated *in vitro* using the 1,1-diphenyl-2-picrylhydrazyl (DPPH), nitric oxide (NO) and ferric ion reducing power (FRAP) assays. Pretreatment of rats with SM, CA or SM + CA significantly ameliorated the learning and memory impairment induced with scopolamine as evidenced in Y-maze and MWM paradigms. Moreover, SM, CA or SM + CA significantly attenuated the oxidative-nitritive stress induced by scopolamine, evidenced in the decrease in malondialdehyde and nitrite levels and restoration of glutathione, catalase and superoxide dismutase levels. Furthermore, SM and CA showed promising free radical scavenging effect against DPPH and moderate antioxidant activity in NO and FRAP tests. This study showed that *Spondias mombin* and *Cola acuminata* have significant protective effect against scopolamine-induced memory deficit that could be attributed to their antioxidant properties.

1. Introduction

Dementia is a clinical syndrome caused by neurodegeneration and Alzheimer's disease (AD) being the most common, characterized by inexorably progressive deterioration in cognitive ability and capacity for independent living. AD is associated with the presence of intracellular neurofibrillary tangles and

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Peer review under responsibility of Alexandria University Faculty of Medicine.

http://dx.doi.org/10.1016/j.ajme.2016.08.001

extracellular amyloid-β plaques, loss of neuronal subpopulations, synaptophysin immunoreactivity of presynaptic terminals, loss of cholinergic fibres, mitochondrial dysfunction and proliferation of reactive astrocytes in the entorhinal cortex, hippocampus, prefrontal cortex and amygdala.[1,2] Extensive evidence indicates that disruption of cholinergic function is characteristic of ageing and AD, and experimental manipulation of the cholinergic system in laboratory animals suggests that age-related cholinergic dysfunction may play an important role in cognitive deterioration associated with ageing and AD.[3] Impaired cortical cholinergic neurotransmission may also contribute to β-amyloid plaque pathology and increase phosphorylation of tau protein, the main component of neurofibrillary tangles in AD[4]. The restoration of cholinergic function through prolongation of the availability of acetylcholine (ACh) released into the neuronal synaptic cleft by inhibiting acetylcholinesterase (AChE) activity, remains a rational target in the treatment of AD. Acetylcholinesterase inhibitors (tacrine, donepezil, and rivastigmine) are the mainstay in the treatment of AD, though effective but not without adverse effects.[5,6]

Scopolamine (muscarinic cholinergic receptor antagonist) impaired learning and memory, thus, used extensively to screen for potential antidementic drugs.[7,8] Several post-mortem and *in vivo* studies have demonstrated an accumulation of the products of reactive oxygen species (ROS) or reactive nitrogen species (RNS) damage in AD and scopolamine treated subjects; these substances can be considered biomarkers of oxidative and nitrosative damage, respectively.[9–11] Increased level of malondialdehyde (MDA) is a very reliable index of *in vivo* lipid peroxidation.[12] On the other hand, glutathione (GSH) (redox regulator in the maintenance of oxidant homeostasis and cellular detoxification of ROS in brain cells) depletion has been shown to affect mitochondrial function.[13] Thus, enhanced expression/activity of the endogenous antioxidant enzymes such as superoxide dismutase (SOD), catalase and GSH have been used as an index of brain oxidative stress.[12,14] Therefore, supplementation with antioxidants may delay the development of AD, and attenuate neuronal cell death induced by oxidative stress.[8,15]

Spondias mombin L. (Anacardiaceae) is a fructiferous tree, native to Nigeria, Brazil and several other tropical forests in the world and can reach a height of 15–22 m. A decoction of the mashed leaves with lemon is effective for worms in children and believed to expel calcifications from the bladder.[16] A tea made from the flowers and leaves is taken to relieve stomach ache, biliousness, urethritis, cystitis and eye and throat inflammations.[17] In Belize, a decoction of the young leaves is a remedy for diarrhoea and dysentery.[18] Interestingly, the antimicrobial,[19] sedative, antiepileptic, and antipsychotic properties[20] of *Spondias mombin* leaf extract have been reported. In an ethnobotanical survey by Elufioye et al.[21] they showed that the leaves of *Spondias mombin* when chewed with *Cola acuminata* (P. Beauv.) Schott & Endl. (Sterculiaceae) seeds have memory enhancing and anti-ageing properties. *C. acuminata* is a bitter brown seed found in the pod of evergreen trees native to Africa, commonly used stimulant in Nigeria, and has been reportedly used for the management of memory loss and other neurodegenerative diseases in folklore.[22] Niemenak et al.[23] reported that caffeine and theobromine were the major purine alkaloids in *C. acuminata* seeds while catechin and epicatechin were the predominant polyphenols. Oboh et al.[24] also reported anticholinesterase (anti-AChE) and anti-butyrylcholinesterase (anti-BuChE) activities of *C. acuminata* seed extract with median inhibitory concentrations (IC_{50}) of 14.60 and 96.20 μg/mL, respectively, in a dose-dependent manner. In this study, we examined the effect of *S. mombin* and *C. acuminata* on memory processes and oxidative stress status in the prefrontal cortex, striatum and hippocampus of scopolamine-treated animals.

2. Materials and methods

2.1. Plant material

The leaves of *S. mombin* were collected from Abatadu, Osun state, Nigeria, in May 2015 and seeds of *C. acuminata* were purchased from Mushin Herbal Market, Lagos state, Nigeria. The Botanical identification and authentication were done by Mr. Oyebanji, Department of Botany and Microbiology, University of Lagos, Akoka, Lagos state, Nigeria. The Voucher Specimens: LUH 6511 (*Spondias mombin*) and LUH 6905 (*Cola acuminata*) were deposited in the Herbarium of the Department for reference purposes.

2.2. Laboratory animals

Male Sprague-Dawley rats (150–170 g) and female Swiss albino mice (18–22 g) used in this study were obtained from the Laboratory Animal Centre, College of Medicine, University of Lagos, Lagos, Nigeria. The animals were housed six per cage, allowed access to water and food (Livestock Feeds, Lagos, Nigeria) *ad libitum*, and maintained at a constant temperature (23 °C ± 1 °C) and humidity (60% ± 10%) under a 12-h light/dark cycle (light on 07:00–19:00 h). The animals were maintained under laboratory conditions for an acclimatization period of 7 days before performing the experiment. Animal maintenance and treatment were carried out in accordance with the United States, National Institutes of Health Guidelines for Care and Use of Laboratory Animals in Biomedical Research (2011).

2.3. Preparation of the extract

The air-dried leaves of *S. mombin* were pulverized into powder (356 g). The powdered leaf was soaked in 6.25 L of 70% ethanol for 72 h at room temperature with intermittent agitation. The extract was filtered and the filtrate obtained was concentrated by Heidolph® Rotavapor (Switzerland) at 40 °C, and further oven-dried at 40 °C to give a deep green extract with a yield of 19 g (5.34% w/w).

The seeds of *C. acuminata* (2870 g) were chopped into small pieces and air-dried for 7 days. The dried seeds were pulverized into fine powder. The powdered seeds (1441 g) were soaked in 3.25 L of 70% ethanol for 72 h. The extract was filtered and the filtrate obtained was concentrated by Heidolph® Rotavapor (Switzerland) at 40 °C, and further oven-dried at 40 °C to give a deep brown extract with a yield of 149 g (10.34% w/w).

2.4. Drugs and chemicals

Ethanol, chloral hydrate, tacrine, glacial acetic acid, Folin-Ciocalteu reagent, scopolamine hydrobromide, phosphate buf-