Biomedicine & Pharmacotherapy 86 (2017) 414–425

Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com/en

Original article

Antidepressant like effects of hydrolysable tannins of *Terminalia catappa* leaf extract *via* modulation of hippocampal plasticity and regulation of monoamine neurotransmitters subjected to chronic mild stress (CMS)

Y. Chandrasekhar, E.M. Ramya, K. Navya, G. Phani Kumar*, K.R. Anilakumar

Applied Nutrition Division, Defence Food Research Laboratory, DRDO, Mysore 570011, Karnataka, India

ARTICLE INFO

Article history:
Received 8 November 2016
Received in revised form 29 November 2016
Accepted 5 December 2016

Keywords:
Chronic mild stress
Terminalia catappa
Hippocampus
BDNF
Hydrolysable tannins

ABSTRACT

Terminalia catappa L. belonging to Combretaceae family is a folk medicine, known for its multiple pharmacological properties, but the neuro-modulatory effect of TC against chronic mild stress was seldom explored. The present study was designed to elucidate potential antidepressant-like effect of *Terminalia cattapa* (leaf) hydro-alcoholic extract (TC) by using CMS model for a period of 7 weeks. Identification of hydrolysable tannins was done by using LC–MS. After the CMS exposure, mice groups were administered with imipramine (IMP, 10 mg/kg, i.p.) and TC (25, 50 and 100 mg/kg of TC, p.o.). Behavioural paradigms used for the study included forced swimming test (FST), tail suspension test (TST) and sucrose preference test (SPT). After behavioural tests, monoamine neurotransmitter, cortisol, AchE, oxidative stress levels and mRNA expression studies relevant to depression were assessed. TC supplementation significantly reversed CMS induced immobility time in FST and other behavioural paradigms. Moreover, TC administration significantly restored CMS induced changes in concentrations of hippocampal neurotransmitters (5-HT, DA and NE) as well as levels of acetyl cholinesterase, cortisol, monoamine oxidases (MAO-A, MAO-B), BDNF, CREB, and p-CREB. It suggests that TC supplementation could supress stress induced depression by regulating monoamine neurotransmitters, CREB, BDNF, cortisol, AchE level as well as by amelioration of oxidative stress. Hence TC can be used as a complementary medicine against depression-like disorder.

1. Introduction

Terminalia catappa Linn (Combretaceae) is also known as Indian almond. The phytochemicals of *T. catappa* leaf contain chebulagic acid, corilagin, kaempferol, punicalagin, punicalin, quercetin, tercatain, tergallagin, terflavin A, and terflavin B [1]. Early studies indicate that *T.catappa* has multiple pharmacological properties such are anticancer, wound healing, antidiabetic, anti-inflammatory, analgesic, immunomodulatory, hepatoprotective, and aphrodisiac [2]. The leaves of this plant have been used as a folk medicine for treating dermatitis and hepatitis in India and Philippines, but the neuro-modulatory effect of TC against chronic mild stress was seldom explored.

Depression is more prevalent in aged people and considered as one of the serious psychiatric disorders [3]. World health organisation (WHO) has revealed that depression is fourth leading cause of disability worldwide and it also predicts that depression will be second leading cause by 2020 [3]. Stress can be characterised by changes in mental status induced by psychological, physiological or environmental stressors which leading to a state of threatened homeostasis [4]. Chronic mild stress (CMS) is an experimental rodent model aimed at evaluating the progress of stress patho-physiology induced by to mild and unpredictable stressors [5]. CMS model of depression has high validity, since CMS exposed animal exhibits a wide variety of behavioural changes mimicking features of most human depressive states [6,7].

Depressive disorders are generally characterized by hyperactivity of hypothalamic–pituitary–adrenal (HPA) axis and

* Corresponding author.
E-mail addresses: sekhar268@gmail.com (Y. Chandrasekhar), phani_bot@rediffmail.com (G. Phani Kumar), anilakumarkr@gmail.com (K.R. Anilakumar).

http://dx.doi.org/10.1016/j.biopha.2016.12.031
0753-3322/

neurotrophin dysfunction [8]. CMS induced alterations in HPA axis may be a result of increased glucocorticoid levels that alter negative feedback control in the hippocampus and prefrontal cortex [9,10]. Early studies have revealed that the deficiency of monoaminergic transmitters in the neurons such as noradrenaline (NE), serotonin (5-hydroxytryptophan; 5-HT), dopamine (DA) *etc*., play a key role in depressive disorders [11,12]. Oxidative stresses, brain-derived neurotrophic factor (BDNF) and cyclic AMP reactive elemental binding protein (CREB) are targeted in mood elevating disorders [13–15]. In the recent decade, considerable attention is directed in ascertaining suitable evidence to establish that depressive disorders are accompanied by elevated levels of pro-inflammatory cytokines and a reduction in antioxidant enzymes [16,17].

Several antidepressants like selective serotonin reuptake inhibitors, monoamine reuptake inhibitors and monoamine oxidase inhibitors are in use to treat patients suffering from depression. Unfortunately, these anti-depressant drugs need longer time to produce therapeutic responses and many of depressed patients have shown resistance to these drugs. Synthetic antidepressants have adverse reaction by showing side effects [18]. Therefore, recent studies have put more efforts on development of herbal based drugs for the treatment of mood elevating disorders and found that herbal medications have comparatively less or no adverse side effects when compared to synthetic anti-depressants [19]. In the present study, *T. catappa* is evaluated for its beneficiary effect against depressive disorder on experimental mice model to understand the mechanism of action for the first time.

2. Material and methods

2.1. Preparation of Terminalia catappa extract

Fresh tender leaves of *Terminalia catappa* were collected in the premises of Defence Food Research Laboratory (DFRL), Mysore and were authenticated by Department of Botany, Mysore University. A voucher specimen (AND 1379) is kept in our laboratory for future reference. The leaves were shade dried at room temperature and powdered using dry grinder and screened with sieve no 40. The powder of *T. catappa* leaves were packed in a soxhlet apparatus and extracted with 70% alcohol for 12 h then followed by flash evaporation under reduced pressure (Heidolph, Germany). The lyophilized extract powder was used for further studies.

2.2. LC–MS analysis for hydrolysable tannins

Terminalia catappa hydro alcoholic leaf extract (TC) was analysed for polyphenols detection by using Agilent 1260 LC–MS and the chromatographic conditions were DL temperature of 250 °C, scan range of 100–1500 *m*/*z*, 2 Hz scan speed, 0.8 kV detector voltage and mobilizing gas flow of 7l/min was used for MS analysis of the samples.

2.3. Experimental animals

Balb/c female mice, weighing between 25 ± 3 g were selected from the stockpile colony, Defence Food Research Laboratory (DFRL), Mysore, India. Mice were housed on a 12 h light/dark cycle under controlled temperature (22 ± 2 °C) and humidity (50 ± 10%) with standard pellet 'chow' feed and water were provided *ad- libitum*. The procedures in this study were conducted in accordance with the institute animal ethical committee (IAEC) regulations approved by the committee for the purpose of the control and supervision of experiments on animals (CPCSEA) with the IAEC approval no. 28/1999/CPCSEA.

2.4. Drug administration and experimental design

Thirty six Balb/c female mice were randomly divided into the following six experimental groups: Control group, chronic mild stress group (CMS), imipramine group (IMP) and three treatment groups. Different doses of hydro-alcoholic extract of TC were orally administered to the mice groups separately such as, TC-25, 50 and 100 mg/kg p.o, respectively) for a period of seven weeks. Imipramine group was kept as positive control and received imipramine at 10 mg/kg p.o for the same duration. Control and CMS groups were received equal amount of saline orally during the experimental period. Except control group, all mice groups were exposed to CMS, sucrose preference test, tail suspension test and forced swimming test were scheduled as per the protocol (Fig. 1).

2.5. Chronic mild stress (CMS)

The CMS procedure was performed as described by [20] with minor modifications. The mice were subjected to a variety of following stressors in a week period: (Day-1) fasting for 24 h, (Day-2) water deprivation for 24 h, (Day-3) empty water bottle for

Experimental groups			Test procedure for CMS*		
Groups	Treatment	CMS	Test	Duration	Day
CON	Vehicle	No	Food deprivation	24 h	1st
CMS	Vehicle	Yes	Water deprivation	18 h	2nd
IMP	Imipramine, 10 mg kg bwt^{-1}	Yes	Empty water bottle	01 h	3rd
			Cage tilt	18 h	4th
TC-25	TC, 25 mg kg bwt^{-1}	Yes	Damp saw dust	21 h	5th
TC-50	TC, 50 mg kg bwt^{-1}	Yes	Cold water swimming	5 min	6th
TC-100	TC, 100 mg kg bwt^{-1}	Yes	Overnight illumination	13 h	7th

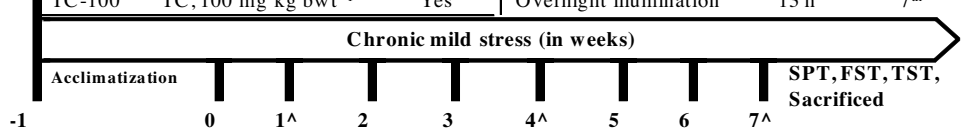

Fig. 1. Experimental design and CMS protocol. n = 6; control (CON) and chronic mild stress group (CMS) received saline water; Imipramine (IMP; 10 mg/kg., p.o), TC-25, TC-50 and TC-100 (Hydro-alcoholic extract of *T.cattapa*, 25 mg/kg., p.o, 50 mg/kg., p.o and 100 mg/kg., p.o, respectively) supplemented to mice groups orally for a period of seven weeks.
'*' Mice groups, except CON were subjected to daily chronic mild stress over a time period of 7 weeks in an unpredictable manner.
'^' Mice were allowed for sucrose preference test (SPT), force swimming test (FST) and tail suspension test (TST) scheduled on 1st, 4th and 7th week of CMS period.