



## Research report

## Investigation of the effects of vanilloids in chronic fatigue syndrome



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## ABSTRACT

**Aim of the study:** To assess the effectiveness of TRPV1 modulators in animal model of Chronic fatigue syndrome (CFS). To assess central and peripheral behavioral activity of TRPV1 modulators.

**Material and methods:** CFS was induced by forcing the rats to swim for 10 min for 21 consecutive days. The rats were treated with capsaicin (TRPV1 agonist, 2.5 mg/kg) and *n-tert*-butylcyclohexanol (TRPV1 antagonist, 10 mg/kg) for 21 days 30 min before the exposure to stress procedure. The behavioral consequence of CFS was measured in terms of immobility time, grip strength, locomotor activity, and anxiety level using Rota rod, Actophotometer, and Elevated plus maze model respectively. The other parameters include Plasma corticosterone, adrenal gland and spleen weight, complete blood count, blood urea nitrogen (BUN), Lactate dehydrogenase (LDH), Lipid peroxidation, catalase and reduced glutathione (GSH).

**Results and discussion:** TRPV1 modulators reversed ( $p < 0.05$ ) the increase in immobility period, anxiety, spleen weight, BUN and LDH levels, and MDA levels along with decrease in grip strength, locomotor activity, plasma corticosterone, adrenal gland weight, catalase, and GSH. There was also significant increase in total WBC count when compared with the disease control group. The reversal was attributed to modulation of HPA axis, oxidative stress, anaerobic respiration product, muscle degradation product.

**Conclusion:** The present study reveals the effectiveness of *n-tert*-butylcyclohexanol and capsaicin against chronic fatigue syndrome. The mechanism of action can be attributed to inhibition of TRPV1 channel and thereby modulating pain perception, neuroendocrine function, oxidative stress and immune function.

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## 1. Introduction

Chronic fatigue syndrome (CFS) is characterized by numerous symptomatic changes occurring in various body system (Meeus et al., 2011). It is closely related with immunosuppression either due to physical or psychological fatigue or both. Many studies have shown that there is potential involvement of central and autonomic nervous system; as well as there is generalized immune activation and selective immune dysfunction (Prinsen et al., 2012; Pariente, 2009). The oxidative stress is associated with expression of symptoms in patients of CFS (Maes et al., 2011). The free radicals generated in the process leads to lipid peroxidation of the membranes and thus alters the interaction between proteins and lipids and it results in deactivation of enzymes (Gupta et al., 2010). The rise in oxidative stress and reduced antioxidant defense contribute to the expression of CFS symptoms.

Recently, TRPV1 channels are studied for their central and peripheral actions widely. Basically these channels act as heat sen-

sors and are distributed throughout the body. Vanilloids are the compounds producing their action via TRPV1 channels. At present, TRPV1 channels are reported to be associated with schizophrenia (Almeida et al., 2014), depression, anxiety (Chahl, 2011), obesity (Hsu and Yen, 2007), superoxide formation, nitrous oxide release, immunity (Southall et al., 2003; Basu and Srivastava, 2005), auditory function (Zhou et al., 2006), pain perception (Starowicz et al., 2008), etc. The agonist capsaicin can activate the channel at low dose, while at higher doses it desensitize the channel and cause its inhibition. The antagonist of TRPV1 channel are used in ointments as pain reliever.

In the light of above discussion, it was worth evaluating and establishing the mechanism of action of TRPV1 channel modulators like capsaicin and *n-tert*-butylcyclohexanol against experimental procedures using modafinil as standard drug.

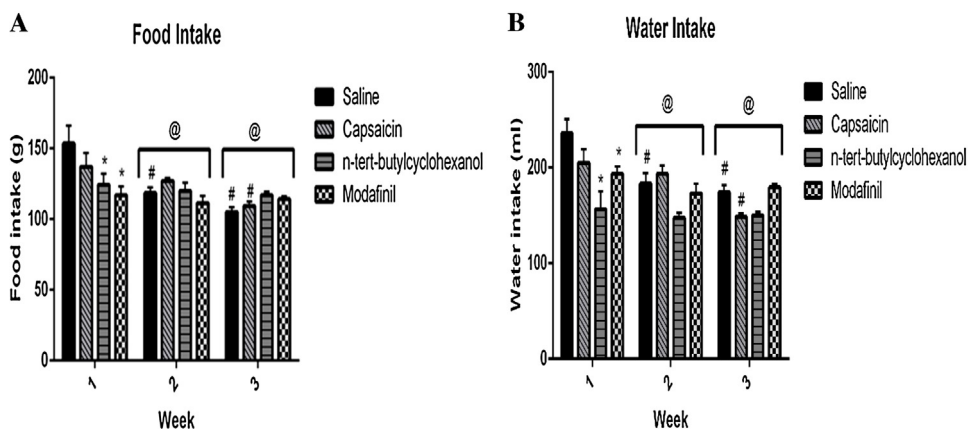
## 2. Materials and methods

## 2.1. Animals

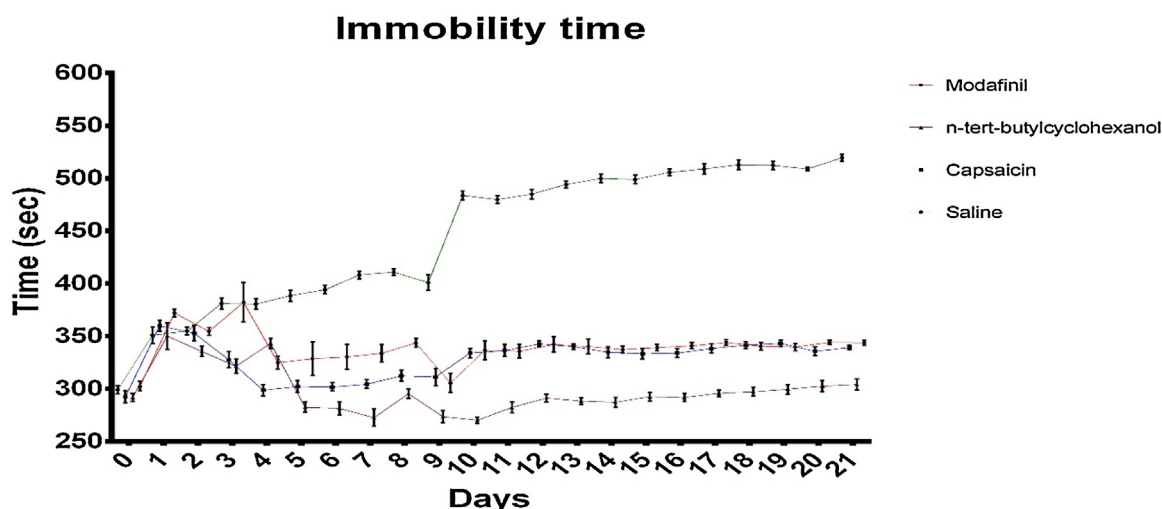
Wistar rats weighing 250–300 gm used in the study were maintained on a constant temperature ( $22 \pm 2^\circ\text{C}$ ), a constant relative

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**Fig. 1.** (A) Effect of treatment groups on Food intake (B) Effect of treatment groups on Water intake. The bars represent Mean  $\pm$  SEM (n = 6) values. Two-way ANOVA followed by Tukey's multiple comparison test. \*P < 0.05 when compared with the disease control group of respective week. #P < 0.05 when compared with respective treatment per week. @P < 0.05 when compared with first week.



**Fig. 2.** Immobility time. The points represent Mean  $\pm$  SEM (n = 6) values.

humidity ( $55 \pm 10\%$ ) and automatically controlled 12:12 h light dark cycle (light on at 07:00 h). They were fed with a standard laboratory food and water ad libitum. The animal handling protocols were based on the CPCSEA guideline. The experimental protocols were approved by the Institutional Animal Ethics Committee (IAEC) of L.M. College of Pharmacy, Ahmedabad.

## 2.2. Drugs

Capsaicin and n-tert-butyl-cyclohexanol (Sigma-Aldrich) were dispersed in tween 80 and diluted with normal saline. Modafinil was dissolved in distilled water. Capsaicin (2.5 mg/kg) and n-tert-butylcyclohexanol (10 mg/kg) were administered intraperitoneally using injection, while modafinil (13 mg/kg) was administered orally daily using oral gavage 30 min prior to forced swimming. All other chemicals were of analytical grade procured from local supplier.

## 2.3. Experimental procedure

The animals were divided into 4 groups each consisting of 6 animals in it. Group I (negative control) consisted of animals given saline via I.P. route. Group II (standard treated) consisted of animals treated with modafinil (13 mg/kg, orally). Group III

(agonist treated) and Group IV (antagonist treated) consisted of animals treated with capsaicin (2.5 mg/kg, I.P.) and n-tert-butylcyclohexanol (10 mg/kg, I.P.) respectively. All groups were given treatment 30 min prior to forced swimming for 28 days. Various parameters were divided as daily, weekly, hematological and brain parameters.

## 2.4. Daily parameters

### 2.4.1. Food & water Intake (Sachdeva et al., 2011)

The amount of food & water consumption in groups of animals is noted on daily basis. The amount of consumption is calculated by subtracting amount of food & water remained from amount given for 24 h.

### 2.4.2. Immobility time (Surapaneni et al., 2012; Singh et al., 2002)

Animals were placed one after another in container filled with water in such a way that animal cannot escape the container. The animals were considered immobile when they stopped moving their front legs and float on water surface without showing movement. The immobility time was recorded from fixed duration of 10 min.

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