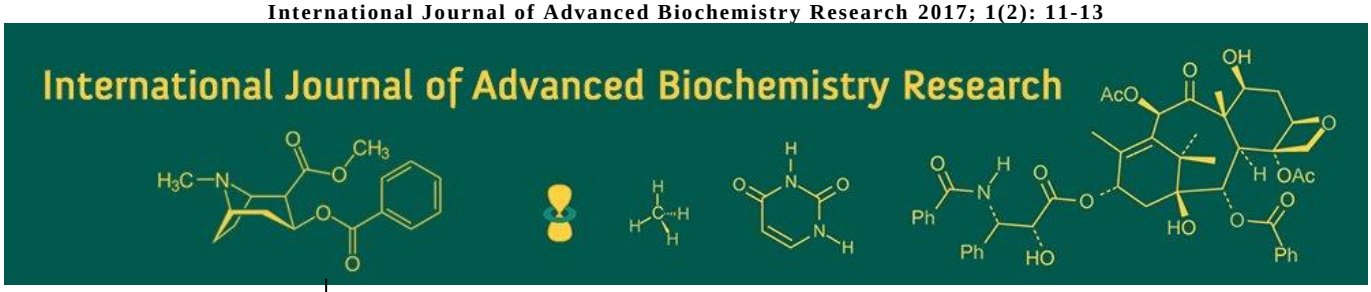

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Anti-pyretic effect of methanolic *Physalis micrantha* Link. extract

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Abstract
The present study aimed to investigate the anti-pyretic effect of *Physalis micrantha* methanol extract (MEPM) in *Mus musculus*. Findings suggest that MEPM at 250 and 500 mg/kg (p.o.) showed a significant anti-pyretic effect on the test system in comparison to the control (vehicle) groups. *Physalis micrantha* might be a good source of anti-pyretic agents. Further studies are needed to isolate and quantify chemical constituents present in this plant and to evaluate possible mechanisms of action for the anti-pyretic activity in suitable test systems.

Keywords: *Physalis micrantha*, *Mus musculus*, anti-pyretic effect

Introduction
Although antipyretic potential seems to be a feature of medications or chemicals that suppress prostaglandin manufacturing, it is a helpful tool for determining the overall antipyretic capabilities of biomass and synthesized pharmaceuticals (Habib *et al*., 2013)[7]. For well over a thousand years, antipyretics have been used to suppress feverish core temperatures (Mackowiak *et al*., 1998)[12]. Three vital hypotheses are established during administering antipyretic medication (Walsh *et al*., 2018)[15]. It may be that fever is toxic, at least partially, and indeed, the second would be that controlling fever would minimize, if not abolish, the unpleasant consequences of fever (Plaisance *et al*., 2000) [14]. Infants, primarily between the ages of three and five, are only one subset of people (Camfield *et al*., 2007)[3]. All other regions had rates as high as 14% (Hauser *et al*., 1994)[6]. Due to the obvious increased respiration requirements placed on either by higher temperatures, individuals having existing coronary or respiratory illnesses may be more sensitive to the negative consequences of infection (Mackowiak *et al*., 1997)[11]. The discharge of pyrogenic cytokines by provocative cells to a certain extracellular biological agent, initialization of cyclooxygenase (COX)-2 stimulation of both the eicosanoid sequence and augmented biosynthetic pathway of prostaglandin E2 (PGE2), besides pituitary gland vascular endothelium, are all essential components of the disease metabolic route (Hirtz *et al*., 1989; Kluger *et al*., 1996) [8, 10]. PGE2 raises the hypothalamus's thermal breakpoint via acting on temperature regulation synapses in the preoptic region of the frontal hypothalamus, inducing periphery and metabolic processes to elevate body temperature (Milton *et al*., 1971)[13]. Antipyretics might hypothetically disrupt the feverish sensitivity at whatever point somewhere along the route (de Sousa António *et al*., 2009)[4]. By blocking COX, acetaminophen, aspirin, or the other non-steroidal anti-inflammatory drugs (NSAIDs) seem to limit the enzyme that converts to PGE2 (Fiebich *et al*., 2000)[5]. This study evaluates the anti-pyretic effect of methanolic *Physalis micrantha* extract in *Swiss* mice.

Materials and Methods
Plant collection and identification
For this study, *P. micrantha* was collected from the hills of the Forest Research Institute; Chittagong and Rangunia; Chittagong, Bangladesh in October 2014 at day time and was identified by the Forest Research Institute; Chittagong, Bangladesh.

Extraction
The collected plant parts were separated from undesirable materials or plants or plant parts, sun dried at 35 to 50 °C, and ground into a coarse powder with the help of a suitable grinder. The powdered material (150 gm powder) was subjected to hot extraction with 97.7% methanol (800 mL) using a Soxhlet Apparatus (Quickfit, England). The obtained extract was collected, filtered, and made to evaporate the solvent below 50 °C.

Reagents and chemicals
Brewer's yeast was purchased from the local market in Chattagram, Bangladesh. GlaxoSmithKline Bangladesh Ltd. kindly provided paracetamol. Other required chemicals and reagents such as Tween-80 were purchased from Merck India Ltd.

Experimental animals
Young *Swiss* mice of either sex, with an average body weight of 18–21 gm, were purchased from the International Center for Diarrhoeal Diseases Research, Dhaka, Bangladesh (ICDDR, B), were used for this experiment. The animals were housed in a room with a temperature of 25 2 °C, a humidity of 50 5%, and a 12 hour dark/light cycle. Diet and water *ad libitum* were provided to the animals. They were subjected to this study after seven days (an acclimatization period). The animals were randomly grouped into the test and control groups, and the food was withdrawn 12 hours before the experimental hours.

Anti-pyretic activity study (*in vivo*)
Preparation of test samples
20% Brewer's yeast suspension was prepared with distilled water and stirred to the point to get a homogeneous suspension. Paracetamol solution was prepared at a dose of 150 mg/kg (p.o.) with distilled water, while MEPM at 250 and 500 mg/kg (p.o.) were prepared with 0.05% Tween-80 dissolved in 0.9% NaCl solution. 0.05% Tween-80 dissolved in 0.9% NaCl solution served as vehicle group (p.o.). Mice were treated at 10 mL/kg dose of test or controls. Each group contained five (5) mice.

Study design
This study was performed with a slight modification of the method described by Adams *et al*. (1968) [1]. Briefly, mice (fasted overnight with water) were subcutaneously (s.c.) treated with a 20% (w/v) Brewer's yeast suspension at a 10 mL/kg dose into the dorsum region of each animal. Seventeen hours after the injection, the rectal temperature of each mouse was measured using a digital thermometer (SK-1250MC, Sato Keiryoki Mfg. Co., Ltd., Japan). Only mice that showed an increase in temperature of at least 0.7 °C were used for this study. Mice were randomly divided into three groups: Gr-I (vehicle), Gr-II (standard, paracetamol) and Gr-III (test sample, MEPM two doses). After administration of the test or controls (described before), the rectal temperature of each mouse was measured at 0^{th}, 1^{st}, 2^{nd} and 3^{rd} hr.

Statistical analysis
Values are expressed as mean ± standard deviation (SD). One-way ANOVA (analysis of variance) followed by a *post hoc* test by using Graph Pad Prism software (version: 6.0) at a 95% confidence interval considering $p<0.05$.

Results and Discussion
The complex physiologic response, fever, is triggered by infectious or aseptic stimuli. It elevates our body temperature due to an increase in PGE2 concentrations within certain areas of the brain. The overall process alters the nerve firing rate, thus hampering the thermoregulation power of the hypothalamus. Besides providing a nonspecific immune response, fever is a source of discomfort. Normally, fever is suppressed with antipyretic medications (Aronoffand Neilson, 2001) [2]. Antipyretics such as aspirin and paracetamol are frequently used drugs for fever. However, these drugs have some side effects (Ishitsuka *et al*., 2020) [9]. Therefore, medicinal scientists are in a continuous search for new, safe and effective anti-pyretic agents. In this study, we evaluated the anti-pyretic effect of MEPM using yeast-induced hyperthermia. These findings confirm that perhaps the anti-pyretic effectiveness of MEPM was substantial. Only the mice showed at least an increase of about 1.26 of in rectal temperature 18 h after Brewer's yeast injection and were used in the anti-pyretic experiment. MEPM at 500 mg/kg significantly ($p<0.05$) reduced body temperature in experimental animals from the first hour of study and normalized temperature at the third hour. The standard drug, paracetamol (150 mg/kg), also significantly reduced body temperature similarly. However, MEPM at 500 mg/kg showed a better effect than the positive control group in comparison to the vehicle group. The MEPM showed a dose-dependent anti-pyretic effect in experimental animals (Table 1). The anti-pyretic effect of *P. micrantha* might be due to its reduction of prostaglandin synthesis, a temperature mediator.

Table 1: Rectal temperature (^{O}F) of mice recorded in test and control groups

Treatment groups (p.o.)	Basement temp. (^{O}F)	^{O}F after 18 hrs of yeast injection			
		0^{th} Hr	1^{st} Hr	2^{nd} Hr	3^{rd} Hr
Vehicle (10 L/kg)	94.30 ± 0.18	98.40 ± 0.02	99.00 ± 0.16	100.40 ± 0.08	100.45 ± 0.61
PC (150 mg/kg)	94.19 ± 1.11	99.00 ± 0.04	96.60 ± 0.97*	95.30 ± 1.06*	95.10 ± 0.41*
MEPM (250 mg/kg)	94.40 ± 1.08	98.30 ± 0.11	98.03 ± 0.11	97.08 ± 0.14*	96.14 ± 0.14*
MEPM (500 mg/kg)	94.20 ± 2.08	99.00 ± 0.08	97.33 ± 0.21*	96.77 ± 0.54*	94.40 ± 0.64*

Values are mean ± SD (n = 5); One-way ANOVA followed by *post hoc* test; *$p<0.05$ when compared to the vehicle group (0.05% Tween-80 dissolved in 0.9% NaCl solution); PC: Paracetamol; MEPM: Methanol extract of *Physalis micrantha*

Conclusion
MEPM showed a significant and dose-dependent anti-pyretic effect on *Swiss* albino mice. *P. micrantha* might be one of the good sources of anti-pyretic agents.

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Conflict of interest: None declared.

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