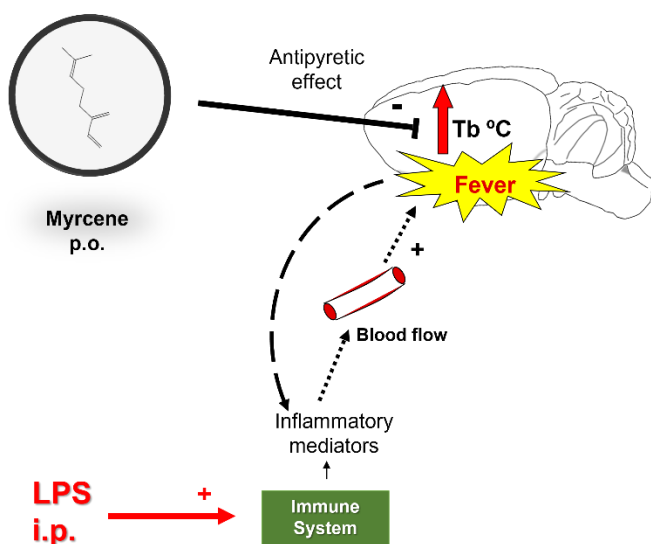


## Antipyretic effect of myrcene (MCN) as a potential therapeutic alternative for the treatment of systemic inflammation response (SI) in euthermic rats model

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### Graphical Abstract



### Abstract.

The new coronavirus pneumonia (COVID-19) is characterized by hemodynamic changes with a large release of inflammatory mediators, that inducing a systemic inflammation response (SI). Thus, SI can be induced by peripheral injection of lipopolysaccharide (LPS) in rodents, which promote the increase of systemic inflammatory mediators that induced an essential survival effector response, such as fever. Myrcene (MCN) is a monoterpene with anti-inflammatory, antioxidant, and analgesic actions are described. Our aim was to evaluate the MCN effect in euthermic rats against SI induced by low-dose LPS. Male Wistar rats were used to assess body temperature (Tb) by dataloggers. The animals were orally treated with Tween 80-1% (Tw; 10 mL/kg) or MCN (7.5 mg/kg) 30 min before the i.p. administration of induction with LPS (100 µg/kg) or Saline (1 mL/kg). After 360 min, the rats were sacrificed to evaluate the inflammatory mediators' levels through Multiplex assay. Rats in the Tw+LPS group present a significant increase in Tb when compared to the control group (Tw+Saline). The MCN treatment was

	able to significantly reduce Tb, demonstrated an antipyretic effect during SI-induced LPS. When investigating the inflammatory signaling caused by LPS administration, the demonstrated a significant increase in serum levels of MIP-1 $\alpha$ , MCP-1, IP-10, TNF- $\alpha$ , Fractalkine, IL-10, and IL-5. However, our treatment with MCN is not involved in peripheral signaling of inflammatory mediators during SI.
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## Introduction

The pandemic of new coronavirus pneumonia (COVID-19) is of great concern worldwide, due to the millions of deaths caused in the last year. COVID-19 is characterized by hemodynamic changes, such as venous thromboembolism and intravascular coagulation. In addition to a large release of inflammatory mediators, such as chemoattractant monocyte protein (MCP)-1, inflammatory macrophage protein 1- $\alpha$  (MIP1 $\alpha$ ), interferon gamma-inducible protein (IP)-10, that inducing a systemic inflammation response (SI) [1]. Thus, an important experimental model of SI is the peripheral injection of lipopolysaccharide (LPS) in rodents, which promote the production and release of peripheral inflammatory mediators [tumor necroses factor (TNF)- $\alpha$ , interleukin (IL)-5, IL-10 and fractalkine]. This inflammatory signaling promotes essential survival effector responses, such as an increase in deep body temperature (Tb), also known as fever [2–4]. The search for new drugs that alleviate this condition can alleviate in SI treatment, mainly, during COVID-19. Myrcene (MCN) is a monoterpene present in the Citrus aurantium essential oil, and their healing, anti-ulcer, anti-inflammatory, antioxidant, and analgesic actions are described in the literature [5]. However, the effect of this monoterpene during SI is unknown. Aim: To evaluate the effect of MCN in euthermic rats against systemic inflammation induced by low-dose LPS.

## Materials and Methods

Male Wistar rats (5-6 weeks, 230-280g, n= 7-8) were used to assess Tb by dataloggers implanted in the abdominal cavity [6]. The rats were orally treated with vehicle - Tween 80-1% (Tw; 10 mL/kg) or MCN (7.5 mg/kg) 30 min before the i.p. administration of induction with LPS (100  $\mu$ g/kg) or Saline (1 mL/kg). After 360 min of LPS injection, the rats were sacrificed to collected of serum to evaluate the inflammatory mediators' levels (MIP-1 $\alpha$ , MCP-1, IP-10, TNF- $\alpha$ , Fractalkine, IL-10 and IL-5) through Multiplex (Merck Milliplex; Millipore Corporation, Billerica, MA, USA) assay. Statistical significance was determinate by ANOVA followed Tukey post-hoc test ( $p < 0.05$ ) (CEUA-IBB/UNESP n $^{\circ}$  8259150621).

## Results and Discussion

Rats in the Tw+LPS group present a significant increase in Tb when compared to the control group (Tw+Saline) (Tw+Saline=  $53.42 \pm 5.42$   $^{\circ}$ C x min vs. Tw+LPS=  $197.4 \pm 12.6$   $^{\circ}$ C x min.). However, the MCN treatment was able to significantly reduce Tb when compared with the Tw+LPS group (Tw+LPS=  $197.4 \pm 12.6$   $^{\circ}$ C x min vs. MCN+LPS=  $137.1 \pm 15.6$   $^{\circ}$ C x min.), indicating an antipyretic effect of MCN during SI. When investigating the inflammatory signaling caused by LPS administration, the Tw+LPS group showed a significant increase in serum levels of MIP-1 $\alpha$ , MCP-1, IP-10, TNF- $\alpha$ , Fractalkine, IL-10, and IL-5, when compared to the control group ( $p < 0.05$ ). These factors are directly

related to thrombosis events and indicators of the systemic inflammatory response during COVID-19. However, our treatment with MCN did not act in the modulation of peripheral signaling to reduce the serum levels of inflammatory mediators, when compared with the Tw+LPS group ( $p > 0.05$ ).

### Conclusions

Our data demonstrate that MCN has an antipyretic effect after 360 min LPS administration. However, MCN was not able to reduce inflammatory signaling during SI. Possibly, the monoterpene effect may be involved in central nervous system mechanisms during the inflammatory response caused by LPS injection.

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