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*Chinese Journal of Natural Medicines* 2017, **15**(3): 0202–0209

**Chinese Journal of Natural Medicines**

# Anti-inflammatory and membrane stabilizing properties of methyl jasmonate in rats

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Available online 20 Mar., 2017

**[ABSTRACT]** The present investigation was carried out to evaluate anti-inflammatory and membrane stabilizing properties of methyl jasmonate (MJ) in experimental rat models of acute and chronic inflammation. The effects of MJ on acute inflammation were assessed using carrageenan-induced rat's paw edema model. The granuloma air pouch model was employed to evaluate the effects of MJ on chronic inflammation produced by carrageenan in rats. The number of white blood cells (WBC) in pouch exudates was estimated using light microscopy. The levels of biomarkers of oxidative stress, such as malondialdehyde (MDA), glutathione (GSH) and activity of antioxidant enzymes in the exudates, were determined using spectrophotometry. The membrane stabilizing property of MJ was assessed based on inhibition of hemolysis of rat red blood cells (RBC) exposed to hypotonic medium. Our results indicated that MJ (25−100 mg·kg$^{-1}$, i.p.) produced significant anti-inflammatory activity in carrageenan-induced paw edema in rats ($P < 0.05$). MJ reduced the volume of pouch exudates and the number of WBC in carrageenan-induced granulomatous inflammation. It also exhibited potent antioxidant and membrane stabilizing activities. In conclusion, these findings suggest the therapeutic potentials of methyl jasmonate in disease conditions associated with inflammation and its anti-inflammatory activity may be related to its antioxidant and membrane stabilizing activities.

**KEY WORDS]** Methyl jasmonate; Granuloma air pouch model; Anti-inflammatory; Antioxidant; Membrane stabilizing property

**CLC Number]** R965 **[Document code]** A **[Article ID]** 2095-6975(2017)03-0202-08

## Introduction

Inflammation is a response of body tissues to injury, which helps limit the degree of damage and promote wound healings [1]. There are several components through which inflammatory reaction mediates tissue injury and worsens symptoms associated with chronic diseases of inflammation origin. The main components involved in the pathogenesis of chronic diseases of inflammatory origin include edema formation, WBC infiltrations, and release of chemical mediators including reactive oxygen species (ROS) [2-5]. Edema, which limits body function, is due to synergism between several inflammatory mediators that increase vascular permeability accompanied by accumulation of fluid in the interstitial tissues [1, 4]. Increased vasodilatation encourages WBC infiltrations to the site of injury, whose activity leads to the release of inflammatory mediators and other cytotoxic products including ROS [1-2, 4]. The activity of WBC-mediated release of ROS plays a key role in the onset and progression of chronic inflammatory diseases like rheumatoid arthritis (RA).

The carrageenan-induced paw edema model, which is mediated through the release of histamine, serotoinin, bradykinin, and prostaglandins, is widely used for evaluation of acute inflammation [1, 4]. The granuloma air pouch model of chronic inflammation closely mimics the pathology of RA and shares similar features with the disease, such as patterns of tissue destructions, infiltrations of WBC, and released mediators [3, 5-7]. Thus, inhibition of infiltrations of WBC, stabilization of lysosomal membrane and prevention of WBC-mediated release of ROS may be effective approaches

**[Received on]** 17- Apr.-2015
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These authors have no conflict of interest to declare.

to the treatment of RA. However, the drugs currently used for the management of inflammatory conditions especially RA, have limited efficacies and are also compromised by incidence of adverse effects after prolonged use [2-3, 8]. Thus, the current research effort is centered on the development of safer drugs of plant origin that could be efficacious for the treatment of chronic inflammatory disorders.

Methyl jasmonate (MJ) is a naturally occurring bioactive compound originally isolated from the essential oil of *Jasminum grandiflorum,* but now obtained commercially through pharmaceutical synthesis [9]. MJ has won international recognition over the years, as a potential source of new drug for the treatment of a wide range of human cancers [10-11]. Several studies have shown that MJ selectively kills cancer cells, leaving normal cells intact, thus raising the hope of its development as an effective and safe chemotherapeutic agent against several neoplastic diseases [10]. Moreover, *in vivo* studies have also confirmed that MJ does not cause significant local or systemic adverse effects, regardless of the route of exposure in humans and experimental animals [12].

The notable absence of toxicity of MJ *in vitro* and *in vivo* studies indicates that it could be used safely in cancer chemotherapy [10, 12] and deserves further pharmacological investigations as a novel therapeutic agent for the treatment of other ailments as well. In recent years, there is an increasing interest in the development of MJ as a therapeutic agent for the treatment of inflammatory disorders [10]. This interest stems from the observation that MJ shares a similar chemical structure with anti-inflammatory prostaglandins [13]. Based on this observation, the anti-inflammatory potentials of MJ and its derivatives have been investigated in culture macrophage cells [13-14]. The results of these studies have confirmed that MJ and its derivatives have significant anti-inflammatory property by decreasing the release of pro-inflammatory cytokines due to inhibition of the NF-B pathway [13-14]. Moreover, the rise in the levels of MJ in plants following injury [10-11] also indicates a crucial role in the fight against inflammatory processes. In our previous studies, we reported that MJ significantly reduced nociceptive responses associated with inflammatory conditions in animal models of pain [15]. However, literature search revealed that no studies have been carried out to establish anti-inflammatory property of MJ *in vivo* animal models of inflammation. Thus, the present study was designed to examine the effects of MJ on animal models of acute and chronic inflammation that closely mimic the pathology of RA, while also describing its effect on hyposaline-induced rat RBC hemolysis.

## Materials and Methods

### *Animals*

Male Wistar rats weighing 160−200 g were obtained from the Central Animal House, University of Ibadan, Ibadan. They were kept in cages at room temperature of 22 ± 2 °C under light/dark (12 : 12) cycle and had access to commercial food pellets and water *ad libitum*. They were acclimatized for one week before commencement of the experiments. The experimental procedures were carried out in compliance with National Institutes of Health Guide for Care and Use of Laboratory Animals (Publication No.85-23, revised 1985). All efforts were made to minimize the suffering of the animals.

### *Drugs and chemicals*

Methyl jasmonate (Sigma Aldrich, Germany), acetylsalicylic acid (aspirin, Sigma, Germany), carrageenan (Sigma, Germany), indomethacin (Sigma, Germany), 5, 50 dithio-bis-2-nitrobenzoic acid (DTNB, Sigma, Germany), triochloroacetic acid (TCA, Sigma, Germany), thiobarbituric acid (TBA, Sigma, Germany), sodium carbonate (British Drug House, Medspeak, United Kingdom), potassium carbonate (BDH), sodium chloride (BDH), Lurk solution (Sigma, Germany) and methylene blue (Sigma, Germany) were used in the study.

### *Preparation of methyl jasmonate soultion*

MJ of 95% purity was prepared according to the procedure previously described by Umukoro and Olugbemide [15]. Briefly, MJ was dissolved in 95% ethanol and this solution was further diluted with distilled water. The final concentration of ethanol in the solution used for the study did not exceed 1%. The doses of MJ used in the study were selected based on the results obtained from preliminary investigations.

### *Carageenan-induced rat paw oedema model*

The effects of MJ on acute inflammation was evaluated using the carrageenan-induced rat paw edema model, according to the method previously described [16]. The rats were randomly distributed into five treatment groups (6 per group). The first 3 groups were treated with MJ (25, 50 or 100 $mg \cdot kg^{-1}$, i.p.), whereas the fourth and fifth groups received aspirin (100 $mg \cdot kg^{-1}$, i.p.) and vehicle (10 $mL \cdot kg^{-1}$ of 1% ethanol, i.p.) respectively. At 30 min after treatment, the right hind paw volume of each rat was determined before induction of acute inflammation with sub-plantar injection of 0.1mL of 1% carrageenan [16]. The paw volumes were then measured using a plethysmometer (Ugo Basile) at 0 (before injection of carageenan) and 3 h post-carrageenan administration. The increase in paw volume was determined as the difference between the paw volume at 0 and 3 h. The percentage inhibition was calculated as previously described [1].

### *Assay of inflammatory exudates*

The inflammatory exudates were produced using the granuloma air pouch model of chronic inflammation according to the technique previously described [17] and as reported by Boris and Stevenson [18]. The rats were randomly divided into 5 groups (6 per group) and anesthetized with ether in a transparent glass box. Thereafter, the dorsal intrascapular region was shaved and disinfected. Air pouch was then created at the shaved portion of the back by injection of 20 mL of sterile air. Then, 1 mL of 20% carrageenan suspension in sesame oil was injected into the pouch at 30 min after treatment with MJ (25−100 $mg \cdot kg^{-1}$), aspirin