

# Potential Anti-inflammatory Effects of *Lantana camara* L.: A Review

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**Abstract**— Inflammatory diseases affect a large portion of the worldwide population, and chronic inflammation is a major risk factor for several dangerous pathologies. Increasing incidence and impact of inflammatory diseases have encouraged the search for new pharmacological strategies to face them. *Lantana camara* L. has been traditionally used as anti-inflammatory diseases, antipyretic, anti-ulcer, and wound healing property. Therefore, we aimed to obtain a comprehensive review regarding the anti-inflammatory activity of *Lantana camara* L. This review provides the evidence in the literature of the *in vitro* and *in vivo* anti-inflammatory activity of *Lantana camara* L. from 2010 to July 2020 without language restriction. Three bibliographical databases were used as information sources (PubMed, ScienceDirect, and Google Scholar). The search terms were “Anti-inflammatory” OR “Antiinflammatory” OR “Inflammation” AND “*Lantana camara*”. A total of 8 studies were included in this paper based on our eligibility criteria with 2 *in vitro* studies, 5 *in vivo* studies, and 1 study, a combination of *in vivo* and *in vitro* performed to substantiate the anti-inflammatory. This review has demonstrated the importance of *Lantana camara* L. as the potential for the natural anti-inflammatory. The set of pharmacological studies reported evidence of the *Lantana camara* L. potential for the treatment of diseases associated with an inflammatory response. Studies have also affirmed the *in vitro* and *in vivo* anti-inflammatory properties of *Lantana camara* L., with several molecular mechanisms. *Lantana camara* L. has been reported to be able to inhibit Cox-2, LOX, NO, ROS, NF- $\kappa$ B, and reduce edema.

**Keywords**— Anti-inflammatory; Inflammation; Inflammatory mediator; *Lantana camara* L.

## I. INTRODUCTION

Inflammation is a process caused by different types and levels of cytokines, growth factors, NO, and prostaglandins, i.e. produced by activated macrophages and other immune system cells [1]. Pro-inflammatory mediators are the key regulators of physiological process, but uncontrolled production of pro-inflammatory mediators can maintain or amplify the inflammatory response leading to chronic inflammation. Cyclooxygenase is present in two isoforms; COX-1 and inducible form COX-2 [2]. Although the inflammatory process promotes the elimination of damaging stimuli, the inflammatory process itself may also contribute to damage of neighboring tissues and can in some cases increase the severity of pathology [3]. Clinically inflammatory disorders are usually managed by steroidal (betamethasone) and the non-steroidal anti-inflammatory drugs (NSAIDs; acetylsalicylic acid), however, chronic administration of such drugs can cause gastrointestinal, renal and cardiovascular disorders [4]. Ethnopharmacology-based research is regarded as a valuable strategy for the discovery of new agents with therapeutic potential [5]. In recent years, ethnopharmacological remedies are increasingly used as an alternative treatment against inflammation due to their milder action and lower adverse effects [6]. Consequently, there is a strong need for natural products with minimum side effects. Data indicated that plants possess diverse therapeutic activities including anti-inflammatory activities [7].

*Lantana camara* L., commonly known as red sage from Verbenaceae family, is a noxious weed [8]. *Lantana camara* L. has been well studied chemically. Two active toxic principles lantadene  $\alpha$  and  $\beta$  are considered the most important. In addition, two new pentacyclic triterpenoids lancamarinic acid and lancamarinin have been obtained from

the aerial parts of *Lantana camara* L. [9]. Different parts of this plant are used in traditional medicine for the treatment of febrile illness, skin infections, and diarrhea [8]. However, Only a small proportion of the *Lantana camara* L. have been tested to confirm their anti-inflammatory activity. To date, no comprehensive literature is available concerning their usage as an anti-inflammatory. It is thus important to preserve valuable herbal knowledge which could be useful for future drug discovery efforts. The aim of the present review was to compile extensive literature evidence of both *in vitro* and *in vivo* studies that reported the anti-inflammatory activity of *Lantana camara* L.

## II. METHODS

A comprehensive search of papers was conducted to find evidence in the literature about the *in vitro* and/or *in vivo* anti-inflammatory activity of *Lantana camara* L. in three different online bibliographical databases: PubMed, ScienceDirect, and Google scholar. In this update, the search terms were “Anti-inflammatory” OR “Antiinflammatory” OR “Inflammation” AND “*Lantana camara*”, The publication dates covered were from 2010 to 2020 (through July 31<sup>st</sup>). No restriction by language. All abstracts and full-text articles were collected, examined, summarized, and conclusions made accordingly. The most relevant articles were selected for screening and inclusion in this review.

## III. RESULTS AND DISCUSSION

The anti-inflammatory activity of *Lantana camara* L. has been demonstrated in both *in vitro* and *in vivo* studies. A total of 8 studies were included in this paper based on our eligibility criteria. The studies consisting of 1 study on active isolates (leaves and aerial parts), 3 ethanol extracts (leaves, bark, roots), 1 ethanol extract of leaves, 1 aqueous extract of leaves,

and 1 study on essential oils (leaves, flowers, fruits, and stems) of *Lantana camara* L.. The anti-inflammatory

properties of *Lantana camara* L. are summarized in Table I.

TABLE I. Summary of antiinflammatory properties of *Lantana camara* L. (In vivo and In vitro studies).

Type of extract/ Formulation	Plant part and Source used for studies	Dose/ Concentration	Experimental Model	Animal or Disease models / Cell specimen	Reported activity	Region	Ref.(s)
All isolates (in vitro)  Isolates (Lantrieuphene B and C) (in vivo)	Aerial parts (in vitro, In vivo)	24.00, 27.98, 34.16 μM (in vitro) 24.00, 27.98 μM (in vivo)	Inhibiting NO release in LPS-induced murine microglial BV-2 cells (in vitro) and An LPS-induced zebrafish model (in vivo)	Murine microglial BV-2 cells (in vitro) and zebrafish embryos (in vivo)	All the isolates exhibited anti-inflammatory effects in cellular model by inhibited NO release (in vitro method). The active compounds (Lantrieuphene B and Lantrieuphene C ) had anti-inflammatory effects by inhibiting ROS and NO formation (in vivo method).	China	[10]
Essential oils	leaves, flowers, fruits, and stems	100 μL l and 0.05 mL	Lipoxygenase Inhibition Assay with some modifications and Bovine Serum Protein Denaturation Method (In vitro)	Cell and the bovine serum protein	LOX inhibitory activity results (IC50) showed that all essential oil samples presented high activitie and the leaf samples displaying higher anti-inflammatory activities than the flower essential oil.	Belgium	[11]
Ethanol extract	leaves	100, 200, 400 mg/kg BW	Carrageenan-induced rat paw edema method and COX-2 was determined by using the Enzyme-Linked Immunosorbent Assay (ELISA) (In vivo)	Male white rats	The ethanol extract of Temblekan leaves has anti-inflammatory effects and inhibitory effect against COX-2	Indonesia	[12]
Methanol extract	leaves and bark	100 and 200 mg/kg	Carrageenan and histamine induced paw edema (In vivo)	wistar albino rat	The methanol extract of <i>Lantana camara</i> (MELC) showed great potential for anti-inflammatory activity	india	[13]
Aqueous extract	Fresh leaves	25, 50, and 100 mg	Carrageenan-induced lung edema and pleurisy mice (In vivo)	Swiss Albino mice	The aqueous extract showed significant anti-inflammatory Effect	Kenya	[14]
Methanol extract	leaves	750, 1000, 1250, dan 1500 mg/kg BW	Carrageenan-induced paw edema (In vivo)	Male white rats	<i>Lantana camara</i> L. leaves extract has decreased paw edema. however, the effective dose of tembelean leaf extract is 1500mg / kg BW which has better anti-inflammatory activity	Indonesia	[15]
Methanol extract	Roots	200 and 400 mg/kg BW	Carrageenan-induced paw edema (In vivo)	rats	The methanol extracts showed inhibition of edema volume at the end of 4h.	India	[16]
The isolated compounds	Leaves	0,64 μmol and 0,76 μmol	The inhibition of TNF-α-induced NF-kB activation in the A549 lung adenocarcinoma cell line The evaluation of COX-2 activity by the quantitation of PGE2 (in vitro)	The human lung adenocarcinoma A549 cell line And mouse macrophages	The lead compound 14 (3b,22b-Di(2-(2-(2,6-dichlorophenylamino)phenyl)acetoyloxy)-olean-12-en-28-oic acid) inhibited both NF-kB and COX-2	India	[17]

A. In Vitro Studies

During the inflammatory response, immune cells secrete many types of mediators, including cytokines (e.g., interferons, interleukins, and TNF-α), chemokines (e.g., monocyte chemoattractant protein 1), and eicosanoids (e.g., prostaglandins and leukotrienes) [7]. Those mediators of inflammation are responsible for eliminating the invading

pathogen and initiating repair processes. Failure to resolve acute inflammation leads to the development of chronic inflammation, which is characterized by excessive levels of pro inflammatory mediators [18] and can mediate tissue injury. Inhibiting the production or function of inflammatory cytokines and mediators is thought to be important in regulating inflammation. The ability to regulate inflammatory

mediators is thus a potential prerequisite for an anti-inflammatory agent [19].

The anti-inflammatory properties of *Lantana camara* L. (LC) essential oils have been evaluated by the lipoxygenase (LOX) inhibition assay and by the bovine serum protein denaturation method. In the first method, the ability of essential oils to inhibit LOX, an enzyme involved in the inflammation process, was evaluated in vitro. LOX inhibitory activity results (IC<sub>50</sub>) showed that all essential oil samples presented high activities. The lowest value was observed with LC (Flowers) J1 which had an IC<sub>50</sub> value of  $17.23 \pm 0.10$   $\mu\text{g/mL}$ . Quercetin was used as a reference (IC<sub>50</sub>:  $13.54 \pm 0.01$   $\mu\text{g/mL}$ ). In the second method, the in vitro anti-inflammatory effect of *L. camara* essential oils was evaluated based on the denaturation of bovine albumin. The results showed that *Lantana camara* essential oils have an interesting IC<sub>50</sub> at  $15.45 \pm 0.04$ ,  $15.82 \pm 0.07$ , and  $17.75 \pm 0.07$   $\mu\text{g/mL}$  for LC (leaves) J12, LC (leaves) J1, and LC (Flowers) J1, respectively. Diclofenac was used as the reference standard; its IC<sub>50</sub> value was  $15.31 \pm 0.17$   $\mu\text{g/mL}$ . The study showed that all essential oils had interesting anti-inflammatory activities, the leaf samples displaying higher anti-inflammatory activities than the flower essential oil [11]. The high anti-inflammatory activity of the LC (leaves) J12 sample is probably due to the high proportions of (E)- $\beta$ -caryophyllene and  $\alpha$ -humulene, which are particularly effective [20].

Suthar *et al.* reported that the lead compound 14 (3b,22b-Di(2-(2-(2,6-dichlorophenylamino)phenyl)acetoxy)-olean-12-en-28-oic acid) from *Lantana camara* L. Leaves can suppress the TNF- $\alpha$ -induced activation of NF- $\kappa$ B by inhibiting IKK activation and I $\kappa$ B $\alpha$  degradation. Compound 14 also inhibited the NF- $\kappa$ B regulated protein expression of COX-2, which regulates inflammation and cyclin D1, which in turn regulate the proliferation. Compound 14 inhibited the proliferation of lung adenocarcinoma A549 cells in a dose-dependent manner [17]. On the preliminary Phytochemical screening, the methanolic extract of *Lantana camara* Linn was found to contain flavonoids and triterpenoids. Flavonoids are known to target prostaglandins that are involved in acute inflammation [9], [21]. A strong relationship has been found between inflammation and cancer, suggesting that inflammation can lead to cancer [22]. Nuclear factor NF- $\kappa$ B is an important target that has been shown to mediate inflammation and suppress apoptosis, and it is commonly over-expressed in cancer cells [23]. Similarly, COX-2, an inducible form of cyclooxygenase, serves as an interface between inflammation and cancer. The aberrant induction of COX-2 has been implicated in the pathogenesis of various types of malignancies. COX-2 promotes the breakdown of arachidonic acid to produce a series of prostaglandins, which are key mediators of inflammatory responses [24]. In another in vitro study, Wu *et al.* reported ten isolates of *Lantana camara* L. were evaluated for their anti-inflammatory effects by inhibiting NO release in LPS-induced BV-2 cellular model, all the isolates exhibited anti-inflammatory effects in this cellular model, Lantrieuphene B, Lantrieuphene C, and 19 $\alpha$ -hydroxyoleanonic acid seemed to be more active, whose IC<sub>50</sub> values were less than 40  $\mu\text{M}$  [10].

### B. In Vivo Studies

The in vivo zebrafish experiments showed that compounds Lantrieuphene B and Lantrieuphene C had anti-inflammatory effects by inhibiting ROS and NO formation in a concentration-dependent manner. The assay using a zebrafish model indicated the potential medicinal applications of active compounds as anti-inflammatory agents for inflammatory diseases. The anti-inflammatory screening revealed that compounds Lantrieuphene B, Lantrieuphene C, and 19 $\alpha$ -hydroxyoleanonic acid were more active for the inhibition of NO production. All the in vitro and in vivo biological experiments demonstrated that compounds Lantrieuphene B and Lantrieuphene C with strong anti-inflammatory effects are expected to be useful for inflammatory diseases [10].

Another study demonstrated The ethanol extract of *Lantana camara* L. leaves at doses 100, 200, and 400 mg/kg B.W showed significant anti-inflammatory activity and COX-2 inhibitory effect ( $p < 0.05$ ) [12]. The anti-inflammatory potential of *Lantana camara* L. leaves may be due to the presence of active phytoconstituents such as flavonoids. The previous report describes that different subclasses of flavonoids can modulate in several stages of inflammation [21], [25]. The flavanol quercetin was found to suppress the expression of COX 2 mRNA in the pouch exudates cells of a rat paw, indicating that the anti-inflammatory action of quercetin may partly due to suppressing the up-regulation of COX-2 [26].

The bark and leaves extract-treated animals showed significant ( $P < 0.01$  and  $P < 0.05$ ) reduction in paw volume induced by Carrageenan at 100 and 200mg/kg dose when compared with the standard group from 2 h onwards. Both the extracts showed anti-inflammatory action up to 5h of both the doses. The extract treatment reduced inflammation in a dose-dependent manner [13]. The indomethacin, leaves, and bark extract at both the doses showed significant ( $P < 0.01$  and  $P < 0.05$ ) reduction in histamine induced paw edema from 2h onwards as compared to the control group. Both the extract showed anti-inflammatory action up to 5h of both the doses. The extract showed dose-dependent anti-inflammatory actions [13].

Millycent *et al.* treated Swiss Albino mice with 25, 50, and 100 mg of the aqueous plant extracts and found all the doses exhibited highly significant edema diminishing effect. The 25 and 100 mg doses of the herb showed a very significant reduction in the number of white blood cells infiltration in the pleural fluid. However, the 50 mg dose showed no effect [14]. In this study carrageenan attenuated both edema and pleurisy development by the 4th hour just like diclofenac [14]. Hence, it can be postulated that both activities may have been inhibited via inhibition of COX activity. However, it is also possible that it may have acted via inhibition of white blood cell mobilization.

The roots methanolic extract at a dose of 200 and 400mg/kg body weight showed a significant and dose-dependent decrease in the mean paw volume increased by carrageenan. The maximum percentage inhibition was 35.92 and 46.80% by methanolic extract at 200 and 400mg/kg



bodyweight respectively at 4hr. However, standard (Diclofenac, 50mg/kg body weight) showed highly significant inhibition at the same time [16]. In another study, all dose of *Lantana camara* L. leaves methanolic extract has decreased paw edema. however, the effective dose of *Lantana camara* L. extract is 1500mg / kg BW which has better anti-inflammatory activity [15].

#### IV. CONCLUSION

Natural products provide important leads for the development of pharmaceuticals, including anti-inflammatory agents. This review has demonstrated the importance of *Lantana camara* L. as the potential for the natural anti-inflammatory. The set of pharmacological studies reported evidence of the *Lantana camara* L potential for the treatment of diseases associated with an inflammatory response. Studies have also affirmed the in vitro and in vivo anti-inflammatory properties of *Lantana camara* L., with several molecular mechanisms. The bioactivities of *Lantana camara* L. are exhibited through the downregulation of different types of inflammatory mediators. *Lantana camara* L. has been reported to be able to inhibit COX-2, LOX, NO, ROS, NF- $\kappa$ B, and reduce edema. However, advanced investigations are needed to understand its metabolism in the body and the contribution of metabolites in anti-inflammatory action and possible interactions in receptors related to inflammation to provide leads for novel anti-inflammatory drugs in the future. In additions, Future studies of the anti-inflammatory activity of *Lantana camara* L. must provide a clear source and specifications of material used, especially when plant extract is used. Moreover, the methods and conditions used in in vitro and in vivo studies must be validated to avoid bias and ensure the anti-inflammatory activity of *Lantana camara* L..

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