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Potential Anti-Inflammatory Effects of *Jatropha curcas* L.: A Review

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Abstract
Inflammation is a biological process in response to infection, injury, or irritation. The increasing incidence and impact of inflammatory diseases have encouraged the search for new pharmacological strategies to face them. Jatropha curcas L. has been traditionally used as anti-inflammatory diseases, antipyretic, and wound healing. Therefore, we aimed to present a review regarding the current knowledge of the anti-inflammatory activity of Jatropha curcas L. This review provides the evidence in the literature of the in vitro and in vivo anti-inflammatory activity of Jatropha curcas L. from 2010 to August 2020. Three bibliographical databases were used as information sources (PubMed, ScienceDirect, and Google Scholar). The search terms were "Anti-inflammatory" OR "Antiinflammatory" OR "Inflammation" AND "Jatropha curcas." A total of 9 studies were included in this paper based on our eligibility criteria with 5 in vitro studies, and 4 in vivo studies performed to substantiate the anti-inflammatory. This review has demonstrated the importance of Jatropha curcas L. as the potential for the natural anti-inflammatory. The bioactivities of Jatropha curcas L. are exhibited through the downregulation of different types of inflammatory mediators. Jatropha curcas L. has been reported to be able to inhibit the activity of nitric oxide production, reduce edema, and reduce the recruitment of neutrophils.

Keywords— Anti-inflammatory; Inflammation; Inflammatory mediator; Jatropha curcas L.

1. Introduction
Inflammation is an essential immune response that enables survival during infection or injury and maintains tissue homeostasis under a variety of noxious conditions [1]. Many types of mediators are either synthesized or released during inflammatory responses [2,3]. Proinflammatory mediators, including cytokines such as IL-1β, IL-6, and TNFα are synthesized during the initial phase of inflammation. These mediators recruit neutrophils and macrophages to the inflamed area which in turn propagates the synthesis of nitric oxide (NO) and prostaglandins (PGE2) [4]. Changes in the level of pro-inflammatory mediators regulate various cellular changes such as mast cell degranulation, phagocytic uptake, and synthesis of reactive oxygen species. The formation of ROS usually results in lipid peroxidation of the membrane system. In addition, the formation of ROS above the physiological concentration triggers the synthesis of NO and nuclear factor kappa B (NFkB) which together with other mediators regulate the expression of cyclooxygenase (COX) -2 and induced nitric oxide synthase (iNOS) [5,6]. Downregulation of these mediators can provide anti-inflammatory activity. For these purposes, nonsteroidal anti-inflammatory drugs (NSAIDs) or SAIDS are used to inhibit the pathway of inflammatory mediators [6]. However, long-term clinical usage of steroids and nonsteroid anti-inflammatory drugs (NSAID) have shown many side effects such as gastrointestinal, renal, and cardiovascular disorders [7–13]. In recent years, ethnopharmacological remedies are increasingly used as an alternative treatment against inflammation due to their milder action and lower adverse effects [14,15]. 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 [16,17]. *Jatropha curcas* Linn. from the Euphorbiaceae family has been

used in many parts of the world for various medicinal purposes [18]. The leaf and latex extracts of J. curcas contained appreciable amounts of secondary metabolic compounds [19,20]. However, there is a lack of studies that summarize comprehensive information regarding the anti-inflammatory activity of *Jatropha curcas* L. In this review, we summarize current knowledge about the anti-inflammatory activity of *Jatropha curcas* L. from in vitro and in vivo studies published since 2010.

2. Methods

The present review was based on the data search performed in the scientific literature database: PubMed, ScienceDirect, and Google scholar. 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 *Jatropha curcas* L. In this update, the search terms were "Anti-inflammatory" OR "Antiinflammatory" OR "Inflammation" AND "*Jatropha curcas*", The publication dates covered were from 2010 to 2020 (through August 31st). 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.

3. Results and Discussion

The anti-inflammatory activity of *Jatropha curcas* L. has been demonstrated in both in vitro and in vivo studies. A total of 9 studies were included in this paper based on our eligibility criteria. The anti-inflammatory properties of *Jatropha curcas* L. are summarized in Table 1.

Table 1. ***Summary of anti-inflammatory properties of Jatropha curcas L.. (In vivo and In vitro studies)***

Type of extract/ Formulation	Plant part used	Dose/ Concentration	Methods used	Animal or Cell/specimen	Reported activity	Country	Ref.(s)
Aqueous extract	Leaves	150 mg·kg/ BW	Carrageenan-induced rat paw edema (In vivo)	Wistar rats	The aqueous extract showed significant anti-inflammatory activity	Nigeria	[21]
Ethanol extract fractions	Leaves	150, 300 and 600 mg / kg	Carrageenan-induced rat paw edema and observations of the neutrophils by histopathological observations (In vivo)	Male Wistar rats	The ethyl acetate fraction was the best anti-inflammatory potency at a dose of 300 mg/kg. histopathologically, Ethyl acetate fraction was also able to reduce the recruitment of neutrophils in inflamed foot tissue.	Indonesia	[22]
Alcoholic extract	Root, stem, and leaf	200 mg/kg BW	Carrageenan-induced rat paw edema (In vivo)	Albino rats	The roots alcoholic extract showed a significant reduction of the percentage of inflammation over the other alcoholic extracts	India	[23]
Methanolic crude extract, root extract partition, and isolated compounds	Leaves, fruits, stem, and root	1 mg/mL	IFN-γ (100 U/mL) and LPS (5 µg/mL)-induced RAW 264.7 (In vitro)	RAW 264.7 macrophage cells	Crude extract from root gave 100% of inhibition towards nitric oxide production. The hexane partition from root extract showed the highest anti-	Malaysia	[24]

					inflammatory activity. Hexadecanoic acid methyl ester, octadecanoic acid methyl ester, and octadecanoic acid could be responsible for the anti-inflammatory activity of the J. curcas root extract		
Root methanolic extract	Roots	1.0, 0.5, 0.25, 0.125 mg/mL	IFN-γ (100 U/mL) and LPS (5 µg/mL)-induced RAW 264.7 (In vitro)	RAW 264.7 macrophage cells	The nature of compounds presents in J. curcas root methanolic extract which possessed anti-inflammatory without cytotoxicity activity	Malaysia	[25]
Essential oil	Leaves	2% v/v	Egg-albumin induced rat paw edema (In vivo)	Wistar rats	The essential oil of J. curcas exhibited anti-inflammatory effects	Nigeria	[26]
Cream	Latex	10% and 15%	Immunohistochemical (In vitro)	CD68 monoclonal mouse antibody	The latex cream of *Jatropha curcas* exhibited anti-inflammatory activity in the wound healing process of mice skin	Indonesia	[27]
The isolated compound (Jatrophacine)	Roots	50 µM	LPS-induced RAW 264.7 macrophages (In vitro)	RAW 264.7 Macrophage cells	Jatrophacine exhibited anti-inflammatory activity	China	[28]
Methanolic extracts	Leaves, stem bark, root, and latex	3.1, 6.25, 12.5, 25, 50, 100, 200 µg/ml in 0.1 % DMSO	IFN-γ (200 U/mL) and LPS (10 µg/mL)-induced RAW 264.7 (In vitro)	RAW 264.7 macrophage cells	Root and latex extract indicated anti-inflammatory activities	Malaysia	[29]

3.1 *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) [5,30]. 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 [31] and can mediate tissue injury. Inhibiting the production or function of inflammatory cytokines and mediators is thought to be important in regulating inflammation [32]. The ability to regulate inflammatory mediators is thus a potential prerequisite for an anti-inflammatory agent. Various in vitro assay systems have been used to screen plant extracts and constituents of active plants for anti-inflammatory activity.

Othman *et al*. reported among the plant parts of J. curcas (leaves, fruits, stem, and root), crude extract from the root showed 100% of inhibition towards nitric oxide production. The further anti-inflammatory activity was carried out using different solvent partitions of J. curcas root. Among the four partitions tested, hexane fraction showed the highest inhibition compared to the positive control. Hexane fraction was chosen as it showed anti-inflammatory for column chromatography analysis using silica gel (0.06 – 0.2 mm/70– 230 Mesh ASTM). The

separation produced five single spots, labeled as H-1 to H-5. Spot H-4 and H-5 showed potent inhibition towards nitric oxide production by RAW 264.7 murine macrophage cells, while spots labeled as H- 1 and H-(2&3) showed lower inhibition when compared to the positive control. The 3 (three) major fatty acids identified by GC-MS were hexadecanoic acid methyl ester, 9-octadecanoic acid methyl ester, and octadecanoic acid. However, it also showed high cytotoxicity towards RAW 264.7 cells at 1 mg/mL. This finding suggests that hexadecanoic acid methyl ester, octadecanoic acid methyl ester, and octadecanoic acid could be responsible for the anti-inflammatory activity of the J. curcas root extract [24].

Another study by Othman *et al.* reported that the purification steps conducted with the methanolic extract of J. curcas produced an active anti-inflammatory fraction without cytotoxicity activity. The non-toxic property is an important consideration as the anti-inflammatory assay was based on the measurement of NO production and a decrease in NO quantity could also mean cell death [25]. As shown by the MTT assay from previous analysis, the hexane fraction caused cell death, while the Griess assay showed a reduction in NO production (as an indication of anti-inflammatory activity) of the RAW 264.7 macrophage cells [24]. After a series of purification steps, the fractions obtained (Fraction A and B), showed anti-inflammatory activity and were non-toxic towards RAW 264.7 macrophage cells. This indicates that the compounds extracted were actually inhibiting the NO production of the RAW 264.7 macrophage cells through inhibition of the NO signaling pathway[25].

Yang *et al.* conducted the study relating The anti inflammatory activity of the new compounds was tested with the model of lipopolysaccharide (LPS) induced RAW 264.7 mouse macrophages. This study reported that the compound 1 (Jatrophacine) strongly inhibited the production of nitric oxide (IC50 = 0.53 μM). Jatrophacine was non- toxic for LPS-induced RAW 264.7 cells with inhibitions of cell viability < 10% at 50 mM by the MTT assay. [28].

Similarly, in another in vitro study reported that the extracts of J. curcas Linn. root and latex extracts showed actively inhibited the iNOS in macrophages RAW 264.7 cell, induced by LPS and IFN-Ɣ. it indicated their potential as an anti-inflammatory agent [29].

The anti-inflammatory activity of the cream from the 10% and 15% latex of J. curcas has also been reported. The cream from the 10% and 15% latex of J. curcas revealed moderate immune reaction to CD68 on wound healing. In the study, J. curcas latex cream 15% is an optimum dose that could fasten the inflammatory phase wound healing process. The study clearly demonstrated that the CD68 expression on mice wound skins it can be seen that the J. curcas latex cream 15% have potential as an anti-inflammatory [27].

3.2 *In vivo studies*

Carrageenan induced hind paw edema is an acceptable preliminary screening method to evaluate the anti-edematous efficacy of new therapeutic agents. The carrageenan-induced paw edema is also time-dependent, biphasic inflammatory process, as numerous inflammatory mediators contribute to this reaction. The first phase of inflammation is related to the release of histamine, bradykinin, and serotonin, while the late phase of edema is accompanied by the infiltration of polymorphonuclear leucocytes, the release of prostaglandins, and the production of oxygen-derived free radicals [3,33]. The carrageenan-induced paw edema model in rats is known to be sensitive to cyclo-oxygenase inhibitors and has been used to evaluate the effect of non-steroidal anti-inflammatory agents, which primarily inhibit the cyclo-oxygenase involved in prostaglandin synthesis. It plays a major role in the development of the second phase of an inflammatory reaction [34].

Some researchers have conducted the in vivo study relating to The anti-inflammatory activity of *Jatropha curcas* Linn. The aqueous extract of J. curcas leaves at a dose of 150 mg·kg-1 exhibited significant anti-inflammatory activity in the carrageenan-induced rat paw edema model. The percentage inhibition in ascending order is J. curcas (60.7%) performed comparably to aspirin (64.3%), but indomethacin had the highest percentage inhibition value (83.9%). Indomethacin had the highest percentage inhibition of the paw volume (83.9%), aspirin caused (64.3%) inhibition while the extract of J. carcus caused (60.7%) inhibition of the increase in paw volume, a performance well comparable with the standard drug aspirin. The study suggests that aqueous extract of J. curcas leaves has an anti-inflammatory effect comparable to those of the standard drugs such as aspirin and indomethacin. [21].

In another study reported that the ethyl acetate fraction has the greatest anti-inflammatory activity compared with the chloroform fraction and insoluble fraction of n-hexane. The ethyl acetate fraction Jatropha leaves (J. curcas) has anti-inflammatory activity with 74.83 ± 3.40% at a dose of 300 mg/kg [22].

Nayak and Patel also reported that the extract of various parts of *Jatropha curcas* showed a significant inhibition in inflammation. Of all the alcoholic extracts, the root showed a significant reduction in the percentage of inflammation over the other alcoholic extracts. It is evident that, in the phasic phenomenon, first inflammatory mediators, i.e. histamine and serotonin releases at 0-2 hr contribute to inflammation antagonized by the alcoholic extract of the root (70%), stem (42.5%), and leaf (50%). Kinin release in the second phase at the 3rd hr. It is also called the plateau phase that was inhibited significantly by the alcoholic extract of the root (80.64%), stem (45.16%), and leaf (54. 83%). Prostaglandin release as the third phase. At 4th hr, all the alcoholic extracts showed significant inflammatory effects but lesser as compared to standard. Inhibitory effects at the end of 4th hr could be due to inhibition of prostaglandin synthesis via inhibition of enzyme cyclooxygenase [23].

In a study showed that the leaves essential oil exhibited the anti-inflammatory activity on Wistar rats using egg-albumin as phlogistic agent; significant inhibition ($P< 0.05$) was shown at a dose of 2%, v/v. Percentage inhibition of the anti-inflammation increased steadily to 76.6% in the 4th hour [26].

4. Conclusions and Future Prospects

This review has demonstrated the importance of *Jatropha curcas* L. as the potential for the natural anti-inflammatory. Various assays have been conducted and indeed show that *Jatropha curcas* L. has the capability to be developed into an anti-inflammatory agent. The bioactivities of *Jatropha curcas* L. are exhibited through the downregulation of different types of inflammatory mediators. The present review shows that *Jatropha curcas* L. has in vitro and in vivo anti-inflammatory activities. The in vitro activities of *Jatropha curcas* L. are mostly through their ability to inhibit the activity of nitric oxide production, and the in vivo activities of *Jatropha curcas* L. are mostly shown through their ability to reduced edema and the recruitment of neutrophils. However, most of the pharmacological studies conducted using the crude extracts of the species are at its preliminary stages. In addition, there are still lacking definitive evidence for the precise mechanism of action by which *Jatropha curcas* L. might ameliorate inflammatory diseases in humans. Thus, future research should focus on determining this mechanism. Subsequently, the extract and their active metabolites should also be subjected to more mechanistic studies, in vivo investigations in various animal models, including pharmacokinetic and bioavailability studies. In addition, more toxicity studies must be conducted before submission to clinical trials to define the safest concentration of the *Jatropha curcas* L. 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 *Jatropha curcas* L.

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