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Preliminary Investigation of the Anti-inflammatory Properties of an Aqueous Extract from *Morinda citrifolia* (Noni)

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The fruit juice of *Morinda citrifolia* (noni, Indian mulberry, duppy soursop) is commonly used as a "miracle" cure in many tropical countries including Tahiti, Hawaii, and the Caribbean islands. In Jamaican folklore practice, noni juice is used to treat diverse conditions, including hypertension, diabetes mellitus, bronchial asthma, rheumatoid arthritis, some cancers, and sexual dysfunction. Evidence has recently been presented for the presence of a polysaccharide-rich substance with anti-tumor activity in noni fruit juice [1]. It has also been reported that an extract from the root of the noni plant exhibited significant analgesic activity in the CNS of mice [2].

In local practice, noni juice is sometimes used in combination with other plant substances, such as garlic and pepper, which are purported to increase the efficacy of noni. More often, noni is commercially marketed as a tonic prepared from fermented ripe fruit. The leaves of the plant are also used occasionally for direct application to the skin to relieve pain and swelling.

The noni fruit has a lumpy appearance and varies in size. The skin of the fruit is waxy and semi-translucent when it is ready for use, and the color changes from green through yellow, to off-white when fully ripened. The ripe fruit has a characteristic rancid taste and smell, which may be partially improved on fermentation. Folklore practitioners often add the juice of other fruits to improve palatability of the noni juice.

Despite the extensive use of noni juice to treat inflammatory joint diseases and other illnesses in Jamaica, the therapeutic benefits of the juice in inflammation has not been verified. This study was therefore undertaken to investigate the potential of noni juice to protect against the development of acute inflammation in response to bradykinin and carrageenan.

METHODS:

Extraction of noni juice. Ripe fruits were washed, the skin and pulp were crushed and the resulting slurry left to percolate overnight in distilled water. The juice collected was freeze-dried and used to prepare aqueous extracts of 50 mg/ml and 200 mg/ml.

Inflammation studies (rat paw edema model). Female Wistar rats (8 per group) were injected (ip) with 0.2 ml of saline (0.9%) or noni juice (50 mg/ml). Each animal also received an injection (0.1 ml) of a pro-inflammatory agent in the sub-plantar region of the left hind limb 10 min later. Pro-inflammatory agents used were bradykinin (0.1

mM) and carrageenan (1%). The effect on carrageenan-induced edema was also investigated in the presence of higher concentration of noni extract (200 mg, ip). Changes in paw volume were measured with a plethysmometer (Ugo Basile) at 30 min intervals over a 4-h period.

In two additional groups of rats (6 each), the experiment was modified to investigate the effectiveness of noni juice in inhibiting inflammation via the oral route. Each group of rats received either saline (1.0 ml, 0.9%) or noni juice (1.0 ml, 200 mg/ml) orally 30 min prior to injection of bradykinin (0.1 ml, 0.01 mM) into the left hind paw of each rat. Volume changes in the paws were measured as stated above at 30 min intervals for 3.5 h.

Results are presented as means \pm SEM. Significant differences with a probability of $p < 0.05$ were determined from the use of the unpaired "t" test.

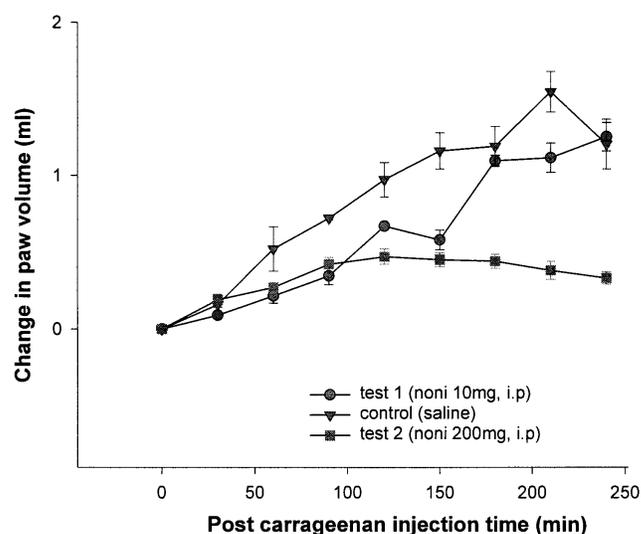


Figure 1. Effects of noni fruit juice extract (10 mg & 200 mg, ip) on the development of carrageenan-induced rat paw edema. Values represent the means \pm SEM for 8 animals in each group.

RESULTS: In the rat paw model of inflammation, carrageenan (1%) produced greater maximum change in paw volume (1.55 ± 0.13 ml) in the control group of rats compared to bradykinin (0.1 mM) which increased paw volume by 1.18 ± 0.11 ml. The rate of development of edema was greater with bradykinin, which produced a maximum response in 1 h, whereas carrageenan produced the maximum response in 3.5 h. These responses were not significantly reduced 4 h after administration of the inflammatory agents.

In the treated groups of rats, 10 mg ip of noni extract

had minimal effect on carrageenan-induced inflammation (Fig. 1), whereas the extract inhibited bradykinin-induced maximum increase in paw volume by 40% and completely relieved the edema within 4 h (Fig. 2). By contrast, a higher dose of noni extract (200 mg, ip) was required to completely inhibit the inflammatory response to carrageenan (Fig. 1).

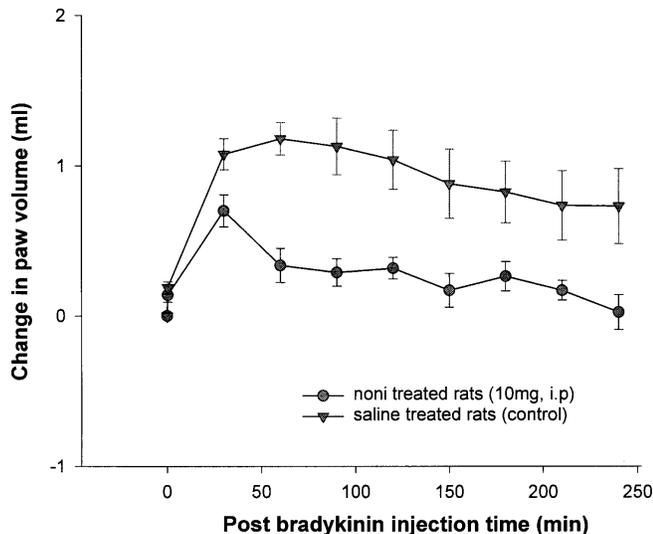


Figure 2. Effects of noni fruit juice extract (10 mg, ip) on the development of bradykinin-induced edema in the rat paw. Values are means \pm SEM, n = 8 for each group.

Oral administration of the noni extract (200 mg) also inhibited the bradykinin-induced inflammatory response (Fig. 3). However, it should be noted that for experiments involving orally administered noni extract, a high concentration of the extract (200 mg) was required to inhibit edema induced by relatively low concentration of bradykinin.

Additionally, there were no observable toxic effects within 24 h of oral administration of 200 mg noni juice extract to mice and rats. There was also no evidence of ulceration of the stomach or other gross toxicological effects after 9 weeks of daily treatment of rats with noni extract (200 mg/day, orally).

DISCUSSION: The characteristic swelling of the paw that occurs in the rat paw model of inflammation is due to edema formation [3]. Endogenous mediators of inflammation include bradykinin, histamine, hydroxytryptamine and prostaglandin [3]. It has been reported that injection of bradykinin into the rat paw produced edema, which was potentiated by co-administration of low doses of prostaglandin, hydroxytryptamine and substance P. However there was no potentiation of inflammation with co-administration of histamine [4].

The carrageenan-induced rat paw edema model is widely used to investigate mechanisms of inflammatory

processes and also to screen potential anti-inflammatory agents. However, the precise mechanism by which carrageenan produces inflammation in the rat paw is unclear.

Di Rosa *et al.* [5] reported that there are three distinct phases involved in carrageenan-induced inflammation: an initial phase mediated by histamine and hydroxytryptamine; an intermediate phase involving the activity of kinins; and a third phase in which the mediators are most likely prostaglandins. Further support for the involvement of bradykinin as a mediator in carrageenan-induced rat paw inflammation was presented by Capasso *et al.* [6]. In contrast, it has been reported that histamine and bradykinin do not mediate events in the pathway to carrageenan-induced rat paw edema [7]. More recently, evidence has been presented for the involvement of nitric oxide as a key mediator in carrageenan-induced rat paw inflammation [8].

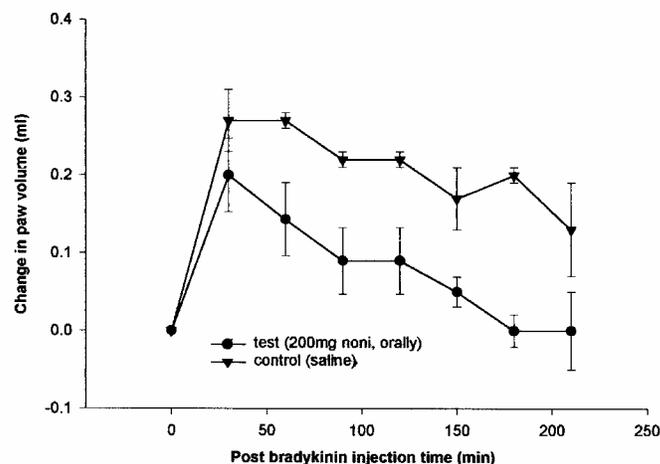


Figure 3. Effects of noni fruit juice extract (200 mg, orally) on the development of bradykinin-induced edema in the rat paw. Values are means \pm SEM for 6 animals in each group.

In the present study, the acute inflammatory response was demonstrated with bradykinin and carrageenan. More importantly, the bradykinin-induced inflammatory response was inhibited and subsided rapidly in rats that were pretreated either orally or ip with noni fruit juice extract. This effect of the juice extract may have resulted from interference with the B₂ receptor-mediated mechanism by which bradykinin was reported [4] to induce rat paw edema.

In further studies, the fruit juice extract partially inhibited at low dose, and totally suppressed at high dose, paw edema produced by carrageenan. This effect of the fruit juice may reflect a more extensive action against several inflammatory mediators such as histamine, hydroxytryptamine, bradykinin, prostaglandin and nitric oxide, all of which are reported to be involved in carrageenan-induced edema [5,6,8].

The specific mechanism that underlies the noni fruit juice effect against both bradykinin-induced and carrageenan-induced edema was not determined in this study. Nevertheless, the results from this initial study provide the basis for further investigation of the anti-inflammatory effect of the noni fruit juice extract, especially through identification and isolation of the biologically active component.

CONCLUSION: The results of this study have clearly indicated the anti-inflammatory potential of both orally and ip administered noni fruit juice extract. The results also suggest that there is a high probability for therapeutic effectiveness of the fruit juice against some inflammatory conditions as claimed by folklore practitioners in Jamaica. This suggestion is reinforced by the demonstrated absence

of toxic effects when the juice extract was given acutely and chronically via the oral route in rats.

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