Academic Sciences

Asian Journal of Pharmaceutical and Clinical Research

Vol. 4, Issue 4, 2011 ISSN - 0974-2441

Research Article

ROLE OF INFLAMMATORY MEDIATORS IN ANTI-INFLAMMATORY ACTIVITY OF NONI *(MORINDA CITRIFOLIA)* ON ACUTE INFLAMMATORY PROCESS IN RATS

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Received: 28 July 2011, Revised and Accepted: 20 Aug 2011

ABSTRACT

Morinda citrifolia, commonly known as great morinda, Indian mulberry or noni. In recent years scientific studies have shown Noni to be an extraordinary supplement for promoting optimum health along with their therapeutic properties. In the present study the anti-inflammatory activity of Noni and its interaction with inflammatory mediator was evaluated. The inflammatory changes are brought about by the release of substances that can mediate various stages of inflammation. In addition, more than one mediator can bring about any one of these stages. Present study, therefore the interrelationship of 5-HT, histamine and prostaglandin with anti-inflammatory activity of aqueous & alcoholic extracts of *Morinda citrifolia*, was studied by pre-treating the animals with antagonist of mediators on acute inflammatory processes in rats. The alcoholic extract of Noni was more effective as compared to its aqueous extract on acute inflammatory process.

Keywords: Coscinium Noni, Morinda citrifolia, Inflammatory Mediators, Anti-Inflammatory, 5-hydroxytryptamine, Histamine.

INTRODUCTION

The inflammatory changes are brought about by the release of substances that can mediate various stages of inflammation. In addition, more than one mediator can bring about any one of these stages. During this complex inflammatory response, chemical mediators such as histamine, 5-hydroxytryptamine (5-HT), various chemotactic factors, bradykinin, leucotriens and prostaglandins are liberated locally. Histamine can facilitate inflammation by its effect on vascular permeability and also by inhibiting the effectors functions of many inflammatory cells.[1] 5-HT may also induce smooth muscle contraction and increase capillary permeability.[2] Prostaglandins have also been reported as strong reminiscent of inflammation.[3] Other mediators of inflammation like platlets activating factor, kinins and leucotrines etc are also produced in inflammatory response and further stimulate it.[4, 5]

A phyto-therapeutic approach to modern drug development can provide many invaluable drugs from traditional medicinal plants. Numerous plants and polyherbal formulations are used for the treatment of various infections, inflammations, to numb pain and to reduce body temperature. It is hoped that scientific evaluation of many potential medicinal plant extracts may provide safe and broad spectrum herbal formulations. The adverse effects of NSAIDS such as induced by opiates, limits the use of these drugs as anti-inflammatory and analgesic agents in all cases. This stimulated the search for new compound possessing potent anti-inflammatory activity with least toxic effect. Numbers of herbal agents have been found useful in different inflammatory conditions.

Morinda citrifolia (Noni), an indigenous medicinal plant has been reported to possess anti-inflammatory, analgesic and anti-ulcerogenic properties. In the present study, therefore the interrelationship of 5-HT, histamine and prostaglandin with anti-inflammatory activity of aqueous & alcoholic extracts of *Morinda citrifolia*, whose Polynesian name is Noni, was studied. The possible role of mediators of inflammation in anti-inflammatory activity of Noni was studied by pretreating the animals with number of antagonist of mediators namely, cyproheptadine (primarily block 5-HT_{2A} receptors and has additionally H1 antihistaminic properties), promethazine (a potent anti-histaminic), cimetidine (a reversible antagonist of histamine H2 receptors) and paracetamol (inhibits prostaglandin biosynthesis) on acute inflammatory models. The potency of anti-inflammatory response of aqueous & alcoholic extracts of Noni alone and with the combination of these antagonists was compared to generate a potent anti-inflammatory agent having least side effects.

METHODS

Procurement of animals

The experiment was conducted on 66 healthy adult albino rats of either sex, weighing between 120-150g. The rats were procured from small animal section of Vet. College HISSAR and maintained in polypropylene cages and housed in the lab animal section of the department under standard managemental conditions. Rats were fed standard ration ad libtum and free access to clean water. De-worming was done before the start of experiment by praziquantel @ 1 tablet per 10 kg body weight, single dose.

Treatment groups

Before experimentation rats were fasted overnight but water was given ad libitum. Aqueous extract (1000 mg/kg) and alcoholic extract (1000 mg/kg) of Noni were administered orally to six rats in each group. One group of rats were administered saline orally and kept as control. Standard blockers of mediators of inflammation were administered intra-peritoneally at the dose rate of cyproheptadine @ 10 mg/kg body wt.,[6] promethazine @ 10 mg/kg body wt.,[7] cemitidine @ 20 mg/kg body wt. [8] and paracetamol @ 100 mg/kg body wt. [9] in similar groups of rats.

The model of experiment on inflammation was as follows-

Group I	-	Aqueous extract of Noni
Group II	-	Alcoholic extract of Noni
Goup III	-	Cyproheptadine + aqueous extract of Noni
Group IV	-	Cyproheptadine + alcoholic extract of Noni
Group V	-	Promethazine + aqueous extract of Noni
Group VI	-	Promethazine + alcoholic extract of Noni
Group VII	-	Cemitidine + aqueous extract of Noni
Group VIII	-	Cemitidine + alcoholic extract of Noni
Group XI	-	Paracetamol + aqueous extract of Noni
Group X	-	Paracetamol + alcoholic extract of Noni
Group XI	-	Control

CarrageenIn induced rat paw edema (Acute inflammation)

Rat paw edema was produced by the method described by Winter *et al*.[10] Freshly prepared 0.05 ml suspension of carageenin (1.0 percent in 0.9 percent saline) was injected under the plantar aponeurosis of the right hind paw of each rat. The paw volume was measured before and at 1 hour interval for 4 hours after the injection of carageenin by the method of Bhatt *et al*.[11] The alcoholic and aqueous extract of Noni were administered half an hour before carageenin injection. Cyproheptadine, promethazine, cimetidine and

paracetamol were however, given half an hour before Noni. Percent anti inflammatory activity = 1- T/C × 100 where T is mean volume of edema in drug treated groups and C is mean volume of edema in control group.

Statistical analysis

The paw volume was measured before and at 1 hour interval for 4 hours after the injection of carageenin. The data obtained during study were analyzed, employing Completely Randomized Design (CRD) as described by Snedecor and Cocharan[12] with the assistance of statistician from the Department of Animal Breeding and Genetics.

RESULTS AND DISCUSSION

Noni has a broad range of therapeutic effects, including antibacterial, antiviral, antifungal, anti tumor, anti helminthes, analgesic, hypotensive, anti-inflammatory and immune enhancing effects.[13] The anti-inflammatory potency of both orally and intraperitonealy injected extract of Noni fruit juice has well documented.[14] There are not many reports available on the anti–inflammatory activity of Noni. The results of the present study indicated that both aqueous and alcoholic extracts of Noni produced significant anti–inflammatory activity on carrageenin induced rat paw edema model. The alcoholic extract of Noni has been found to be more effective on acute inflammatory model as compared to aqueous extract.

Anti–inflammatory activity of aqueous and alcoholic extracts of Noni on carrageenin induced acute rat paw edema

The results for mean edema volume (ml) in rats recorded at different hours for different treatments (control, aqueous extract and alcoholic extract of Noni) are summarized in table- 1A, and table- 2. The mean edema volume (ml) in control group were 1.1 ±0.11, 3.71±0.07, 5.0 ± 0.07 and 5.3±0.08, in aqueous extract of Noni were 0.84 ±0.04, 1.6±0.12, 1.1 ±0.09 and 0.68 ±0.07 and in alcoholic extracts of Noni were 0.81 ±0.01, 1.3 ±0.09, 0.83 ±0.03 and 0.5 ± 0.03 at the interval of 1st, 2nd, 3rd and 4th hour of administration respectively.

The percent anti-inflammatory activity was calculated at hourly interval for 4 hours against carrageenin induced acute inflammation .The aqueous extract of Noni produced 23.6, 56.87, 78.0 and 87.16 percent anti- inflammatory activity after 1st, 2nd, 3rd and 4th hour of administration respectively. The alcoholic extract of Noni produced 26.3, 64.95, 83.4 and 90.56 percent anti-inflammatory activity after 1st, 2nd, 3rd and 4th hour of administration respectively. The analysis of variance revealed that there was significant (P< 0.01) difference in mean edema volume observed at different time intervals in a treatment .Both alcoholic and aqueous extract were found to have significant anti–inflammatory action as compared to control. The findings are similar as found with the *Morinda officinalis* root (at 20 and 30 mg/kg/d) which significantly reduced acute paw edema by carrageenin in rats.[15] Similar findings were observed when arthritis was induced by injecting 0.1ml of 1% carrageenin per rat and Noni was administered after 30 minutes, 24 hours and 48 hours from injection.[16] The change of edema in carrageenin induced arthritic rats paw was measured after 1st hour, 5th hours, 24th hours and 48th hours from injection of carrageenin with Plethysmometer. Results showed that in the sample group, the rate of increase of paw edema was decreased as compared with that of control group but not significant.

Table 1: Analysis of variance for effect of carrageenin induced acute rat paw edema

A – On aqueous and alcoholic extracts of Noni

Source of variation	Degree of freedom	Sum of squares	Mean sum of squares	F-calculated value
Between treatment	2	128.32	64.16	8.22 *
Between hours within treatment	9	70.24	7.80	222.85 **
Error	60	2.11	0.035	

*, ** = Indicate treatment have significant effect at P< 0.05 and P< 0.01 respectively in relation to control.

B – On interaction of different antagonists of mediators of inflammation with aqueous extracts of Noni

Source of variation	Degree of freedom	Sum of squares	Mean sum of squares	F-calculated value
Between treatment	4	14.98	3.74	3.22 *
Between hours within treatment	15	17.46	1.16	28.2 **
Error	100	4.18	0.041	

*, ** = Indicate treatments have significant effect at P< 0.05 and P< 0.01 respectively in relation to aqueous extract on edema volume.

C – On interaction of different antagonists of mediators of inflammation with alcoholic extracts of Noni

Source of variation	Degree of freedom	Sum of squares	Mean sum of squares	F-calculated value
Between treatment	4	3.35	0.837	0.279 NS
Between hours within treatment	15	44.97	2.99	6.93 **
Error	100	43.18	0.431	

** = Indicate treatment has significant effect at P< 0.05 and P< 0.01 respectively in relation to alcoholic extract on edema volume.

NS: non significant.

Table 2: Anti–inflammatory activity of aqueous and alcoholic extracts of Noni on carrageenin induced rat paw edema

Treatment	Dose (mg/kg) Route	Mean edema volume (ml)				Percent increase in anti–inflammatory activity			
		1hr	2 hr	3 hr	4 hr	1hr	2 hr	3 hr	4 hr
Control (normal saline)	-	1.1 a ±0.11	3.71 b ±0.07	5 c ±0 .07	5.3 d ±0.08	-	-	-	-
Aqu. ext. of Noni	1000	0.84 a ±0.04	1.6 c ± 0.12	1.1 b ±0.09	0.68 a ±0.07	23.6	56.87	78.0	87.16
Alc. ext. of Noni	1000	0.81 b ±0.01	1.3 c ±0.09	0.83 b ±0.03	0.5 a ±0.03	26.3	64.95	83.4	90.56

Each treatment consists of six rats.Means in a particular class (row) with same superscripts do not differ significantly from each other.

Means in a particular class (row) with different superscripts differ significantly from each other.

Table 3: Interaction of different antagonists of mediators of inflammation with aqueous extracts of Noni on carrageenin induced acute rat paw edema

Treatment	Dose (mg/kg) Route	Mean edema volume (ml)				Percent increase in anti–inflammatory activity			
		1hr	2 hr	3 hr	4 hr	1hr	2 hr	3 hr	4 hr
Aqu. ext. of Noni	1000 oral	0.84 ^{a} ± 0.04	1.6 ^{c} ± 0.12	1.1 ^{b} ± 0.09	0.68 ^{a} ± 0.07	-	-	-	-
Prom. + Aqu. ext. of Noni	10 I/P + 1000 oral	0.76 ^{a} ±0.01	2.0 ^{d} ± 0.25	1.6 ^{c} ±0.17	1.0 ^{b} ± 0.11	9.52	25.0	45.45	47.05
Cime. + Aqu. ext. of Noni	20 I/P + 1000 oral	0.79 ^{c} ±0.02	0.81 ^{c} ± 0.01	0.40 ^{b} ± 0.01	0.16 ^{a} ±0.02	5.95	49.37	63.63	76.47
Cypro. + Aqu. ext. of Noni	10 I/P + 1000 oral	0.81 ^{a} ±0.01	1.95 ^{c} ± 0.23	1.63 ^{b} ±0.15	0.83 ^{a} ± 0.17	3.57	21.87	21.87	22.05
Para. + Aqu. ext. of Noni	100 I/P + 1000 oral	0.70 ^{bc} ± 0.02	0.73 ^{c} ± 0.01	0.49 ^{ab} ± 0.02	0.30 ^{a} ± 0.01	16.66	54.37	55.45	55.88

Each treatment consists of six rats.Means in a particular class (row) with different superscripts differ significantly from each other.

Means of a particular class (row) with at least one alphabet as common superscripts do not differ significantly from each other

Table 4: Interaction of different antagonists of mediators of inflammation with alcoholic extracts of Noni on carrageenin induced acute rat paw edema

Treatment	Dose (mg/kg) Route	Mean edema volume (ml)				Percent increase in anti–inflammatory activity			
		1hr	2 hr	3 hr	4 hr	1hr	2 hr	3 hr	4 hr
Alc. ext. of Noni	1000 oral	0.81 ^{ab} ±0.01	1.3 ^{b} ±0.09	0.83$^{a\,b}$ ±0.03	0.5^{a} ±0.03	-	-	-	-
Prom. + Alc. ext. of Noni	10 I/P + 1000 oral	1.0 ^{b} ±0 .01	2.0 ^{c} ± 0.15	1.58 ^{bc} ± 0.18	0.01 ^{a} ± 0.08	23.45	53.84	90.36	98.00
Cime. + Alc. ext. of Noni	20 I/P + 1000 oral	0.65 ^{a} ± 0.01	2.0 ^{b} ± 0.22	1.34 ^{ab} ± 0.20	0.82 ^{a} ± 0.11	19.75	53.84	61.44	64.00
Cypro. + Alc. ext. of Noni	10 I/P + 1000 oral	0.92 ^{a} ±0.02	1.91 ^{b} ±0.36	0.26 ^{a} ±0.02	0.15 ^{a} ±0.02	13.58	46.92	68.67	70.00
Para. + Alc. ext. of Noni	100 I/P + 1000 oral	0.91 ^{b} ±0.03	1.9 ^{c} ± 0.27	0.33 ^{ab} ± 0.01	0.16 ^{a} ± 0.06	12.34	46.15	60.24	68.00

Each treatment consists of six rats.Means in a particular class (row) with different superscripts differ significantly from each other.

Means of a particular class (row) with at least one alphabet as common superscripts do not differ significantly from each other.

Interaction of different antagonists of mediators of inflammation with aqueous extracts of Noni on carrageenin induced acute rat paw edema

The anti-inflammatory activity of aqueous extract of Noni (1000 mg/kg, orally) alone and in combination with antagonists of inflammatory mediators have been summarized in table- 1B and table- 3. The antagonist were administered, intraperitoneally, half an hour before the administration of aqueous extract of Noni. In all groups of rats, carrageenin was injected 30 minutes after aqueous extract administration and mean edema volume was measured at hourly intervals for four hours. The mean edema volume (ml) in promethazine with aqueous extract of Noni were 0.76 ±0.01 , 2.0 ± 0.25 , 1.6 ± 0.17 and 1.0 ± 0.11 , in cimetidine with aqueous extract of Noni were 0.79 ±0.01 , 0.81 ± 0.01 , 0.40 ± 0.01 and 0.16 ± 0.02 , in cyproheptadine with aqueous extract of Noni were 0.81 ±.01 , 1.95 ± 0.23 , 1.63 ± 0.15 and 0.83 ± 0.17 and in paracetamol with aqueous extract of Noni were 0.70 ± 0.03 , 0.73 ± 0.05 , 0.49 ± 0.02 and 0.30 ± 0.01 at the interval of 1st,2nd ,3rd and 4th hour of administration respectively.

The studies from this laboratory and elsewhere indicated that during complex inflammatory response, chemical mediators such as histamine, 5 HT, various chemotactic factors, bradykinin, leucotrines and prostaglandins are liberated locally.[17] In the present study, therefore the interrelationship of histamine, 5 HT and prostaglandin with anti-inflammatory activity of Noni was studied by pretreating the animals with antagonist of mediators of inflammation. All antagonists of mediators of inflammation used in the study showed a significant increase in anti-inflammatory activity of aqueous extract of Noni on carrageenin induced acute rat paw edema. Cemitidine (20 mg/kg body wt., I/P) was found to increase the anti–inflammatory activity of aqueous extract of Noni by 5.95, 49.37, 63.63 and 76.47 percent after 1st, 2nd , 3rd and 4th hours of treatment, respectively as compared to aqueous extract of Noni alone . Paracetamol (100 mg/kg body wt., I/P) was also found to increase the anti– inflammatory activity of aqueous extract of Noni by 16.66, 54.37, 55.45 and 55.88 percent after 1st, 2nd, 3rd and 4th hours of treatment, respectively. Promethazine (10 mg/kg body wt., I/P) increases the anti–inflammatory activity of aqueous extract of Noni by 9.52, 25, 45.45 and 47.05 percent after 1st , 2nd , 3rd and 4th hours of treatment respectively. Cyproheptadine (10 mg/kg body wt, I/P) do not produce significant increases in anti–inflammatory activity of aqueous extract of Noni in 2nd, 3rd and 4th hours of treatment which were 21.87, 21.87 and 22.05 respectively. The results indicated that the maximum increase in anti–inflammatory activity of aqueous extract of Noni has been produced with cemitidine which was found to persist for 4 hours followed with paracetamol and promethazine.

The aqueous extract of the stem bark of *Cussonia paniculata* at doses 50, 100 and 200 mg/kg body weight reduced significantly, the formation of edema induced by carrageenin and histamine.[18] The 50 mg/kg dose of the extract showed its highest activity at 2nd hr indicating that the extract may be more potent than the reference drug. The anti-inflammatory activity of the extract is possibly supported by its anti-histamine property. Since the extract effectively suppressed the edema produced by histamine, it showed that the extract exhibited anti-inflammatory actions by inhibiting the synthesis, release or action of inflammatory mediators such as histamine, serotonin and prostaglandins.

The results indicated that the maximum increase in anti–inflammatory activity of aqueous extract of Noni has been produced by cemitidine which was found to persist for 4 hours followed by paracetamol and promethazine. The analysis of variance revealed that there was significant (P< 0.01) difference in mean edema volume observed at different time intervals in a treatment. Aqueous extract of Noni showed significant anti–inflammatory activity with cimitidine, paracetamol and promethazine but not with cyproheptadine.

Interaction of different antagonists of mediators of inflammation with alcoholic extracts of Noni on carrageenin induced acute rat paw edema

The anti-inflammatory activity of alcoholic extract of Noni (1000 mg/kg, orally) alone and in combination with antagonists of inflammatory mediators have been summarized in table- 1C and table- 4. The antagonists were administered, as describe earlier and mean edema volume was measured at hourly intervals for four hours. The mean edema volume (ml) in promethazine with alcoholic extract of Noni were 1.0 ± 0.01, 2.0 ± 0.15, 1.58 ± 0.18 and 0.01 ± 0.08, in cimetidine with alcoholic extract of Noni were 0.65 ± 0.01 , 2.0 ± 0.22, 1.34 ± 0.20 and 0.82 ± 0.11, in cyproheptadine with alcoholic extract of Noni were 0.92 ±0.02 , 1.91 ±0.36 , 0.26 ±0.02 and 0.15 ±0.02 and in paracetamol with alcoholic extract of Noni were 0.91 ±0.03 , 1.9 ± 0.27, 0.33 ± 0.01 and 0.16 ± 0.06 at the interval of 1st, 2nd ,3rd and 4th hour of treatment respectively.

The administration of promethazine and alcoholic extract of Noni significantly reduced the paw volume in the carrageenin induced rat paw edema as compared to alcoholic extract of Noni administered alone. The increase in anti-inflammatory activity was 53.84, 90.36 and 98 percent after 2 nd,3 rd and 4 th hours of treatment respectively. Similarly, paracetamol produced 12.34 46.15 , 60.24 and 68 percent increase in anti– inflammatory activity of alcoholic extract of Noni after 1st, 2nd, 3rd and 4th hour of treatment respectively. Cyproheptadine and alcoholic extract of Noni produced 13.58, 46.92, 68.67 and 70 percent increase in anti–inflammatory activity after 1st, 2nd, 3rd and 4th hours of treatment respectively. Cimetidine and alcoholic extract of Noni produced 19.75, 53.84, 61.44 and 64 percent increase in anti– inflammatory activity after 1st, 2nd, 3rd and 4th hour of treatment respectively. The results indicated that the maximum increase in anti–inflammatory activity of alcoholic extract of Noni has been produced with promethazine which was found to persist for 4 hours followed by paracetamol , cyproheptadine and cimetidine.

The anti-inflammatory activity of 70% ethanolic extract of *Pongamia pinnata* leaves (PLE) in acute, sub acute and chronic models of inflammation assessed in rats. *Per os* (p.o.) administration of PLE (300 and 1000 mg/kg) exhibited significant anti-inflammatory activity in acute (carrageenin, histamine, 5-hydroxytryptamine and prostaglandin E_2-induced hind paw edema), sub acute (kaolin-carrageenin and formaldehyde-induced hind paw edema) and chronic (cotton pellet granuloma) models of inflammation.[19] The anti-inflammatory activity of aqueous and alcoholic extracts of *Valeriana wallichii* rhizomes at doses (100, 150 & 200 mg/kg) exhibited significant (P<0.05) anti-inflammatory effect as compared to saline control in the carrageenin induced paw edema.[20] The significantly high anti-inflammatory activity of both methanolic and aqueous extracts may be due to inhibition of mediators of the inflammation.

The results indicated that the maximum increase in anti–inflammatory activity of alcoholic extract of Noni has been produced by promethazine which was found to persist for 4 hours followed by paracetamol, cyproheptadine and cimetidine. The analysis of variance revealed that there was significant (P< 0.01) difference in mean edema volume observed at different time intervals in a treatment. Alcoholic extract of Noni showed significant anti–inflammatory activity with promethazine, cyproheptadine, cimetidine and paracetamol.

CONCLUSION

The conclusion of the study showed that during acute phase, the maximum increase in anti–inflammatory activity of aqueous extract of Noni was produced by cemitidine which was found to persist for 4 hours followed by paracetamol and promethazine but not with cyproheptadine. Thus anti-inflammatory effect aqueous extract of Noni might be due to the inhibition of endogenous histamine which was increased by pretreatment with cimetidine. The results further revealed that besides histamine, prostaglandins also play a role in controlling anti–inflammatory activity of Noni. Anti-inflammatory activity of Noni on transudative and proliferative stages of inflammation may be due to its blocking H_1 receptors, H_2 receptors and prostaglandins.

The results of the study showed that during acute phase the maximum increase in anti–inflammatory activity of alcoholic extract of Noni was produced by promethazine which was found to persist for 4 hours followed by paracetamol, cyproheptadine and cimetidine. Thus anti-inflammatory effect of alcoholic extract of Noni might be due to the inhibition of endogenous histamine, prostaglandins and 5 HT.

ACKNOWLEDGEMENT

The authors are thankful to the Dean, College of Veterinary Science and Animal husbandry, Mhow for providing research facilities and WNRF, Chennai for financial support and free supply of Noni fruits.

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