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Research Article

EFFECT OF NANOSTRUCTURED EXTRACT *MORINDA CITRIFOLIA* L (NONI) IN THE TREATMENT OF ABDOMINAL SEPSIS IN RATS

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ABSTRACT

Medicinal plants are inexhaustible sources of bioactive compounds with varied pharmacological properties. Among them, the *Morinda citrifolia* L. (Rubiaceae), popularly known as *Noni,* looked to the scientific community because of their anti-inflammatory and immunomodulatory effects. The rational use of drugs and herbal medicines, it is considered major pharmacological properties of validation by means of preliminary studies *in vitro* and *in vivo*. The study evaluated formulated nanostructured base hydroalcoholic extract *Morinda citrifolia* L. (Noni) conveyed in enteral form, in an experimental model of septic cecal ligation and puncture (CLP). The study consisted of 2 groups of 6 animals, where the controls were treated with 0.9% saline solution (C) and the abdominal sepsis group (CLP) treated with 5 mg/mL/Kg Noni nanoemulsion (SME-FC5). Orally by gavage 12h and 2h before the experiment. Treatment response was assessed by blood count, inflammatory markers and biochemical dosages, including hepatic histopathological analysis. There was a reduction of inflammatory markers, maintenance of normal hematological parameters in addition to the preservation of laboratory functions, and histologically. It was concluded therefore that the structured nano extract *Morinda citrifolia* L (Noni) positively influenced the organic reactions in the presence of sepsis, reducing the production of proinflammatory cytokines, preventing tissue injury and attenuating the systemic inflammatory response against the experimental model of polymicrobial sepsis.

INTRODUCTION

Sepsis is the main cause of admission to intensive care unit (ICU) and in-hospital mortality. It presents high morbidity and mortality, compromises around 20-30% of the patients hospitalized in ICU; Those who survive have functional impairment and cognitive decline, as well as mood disorder and a worsening of quality of life[1].

Sepsis is defined as the presence of the two signs and symptoms of Systemic Inflammatory Response Syndrome (SIRS) secondary to an infectious process: temperature >38°C or <36°C; heart rate>90 beats per minute; respiratory rate>20 movements per minute; number of leukocytes in peripheral blood>12,000/mm^3 or <4,000/mm^3 or even the presence of>10% of juveniles on mobile blood count (sticks)[2]. According to the severity of the signs and symptoms

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can be classified into sepsis, severe sepsis and septic shock to evolve[1,2]. Sepsis is a syndrome involving the systemic host response to an inflammatory or infectious stimulus. Despite intensive research efforts, mortality rates in sepsis have not declined significantly[3]. In sepsis, an overwhelming inflammatory response characterized by the activation of inflammatory cells and excessive production of proinflammatory cytokines leads to tissue injury, multiple organ failure, and death[1,4].

The rationale for selecting cecal ligation and puncture (CLP) model of the septic is that it induces effects analogous to the perforated peritonitis with appendicitis. The cardiovascular response to polymicrobial sepsis induced by cecal ligation and puncture (CLP) is characterized by an early hyperdynamic phase (increased cardiac output and tissue perfusion, reduced vascular resistance) followed by a late, hypodynamic phase (reduced cardiac output and tissue perfusion)[3]. Peritonitis causes severe local damage to intra-abdominal organs due to overproduction of various proinflammatory mediators such as factor tumor necrosis (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6) and cyclooxygenase products. It is now considered that these mediators bring about systemic microcirculatory injury which is thought to be the main mechanism responsible for damage in sepsis[1-3]. The host defense responses to sepsis may promote generalized increase in leukocyte recruitment and accumulation in the tissues, which may lead to subsequent endothelial damage, leaky capillaries, and organ dysfunction and failure[5]. The organic lesion begins in the lungs, progressing to the anguish respiratory syndrome, followed by kidney and liver failure because of damage caused in the architecture of these organs. Heart failure occurs in late stage septicemia[3].

The pathophysiology of sepsis induced by the cecal ligation and puncture (CLP) is widely used in animal models and well established in the literature, and is a viable way of analyzing therapeutic options. The technique will result in a peritonitis, generating an ideal model for the therapeutic trial with Noni[1-3]. Medicinal plants influence the health conditions of the people, in part due to the increase of studies with phytotherapeutics, leading to a confirmation of the therapeutic action of several popular plants, a fact that proves Phytotherapy as part of the culture of the population, being used and widespread for many generations[4].

In Brazil, the use of medicinal herbs has its bases in the indigenous practice, which influenced by the African and Portuguese culture, generated a vast popular culture[5]. With the technological advances of allopathic medicine and the pharmaceutical industry in recent years, herbal medicines have been placed in the background, being something allied to popular belief and without scientific bases[6]. However, due to side effects and the high cost of medicines, Phytotherapy is again highlighted and scientific studies with medicinal plants are being resumed[7].

Among the species for herbal treatment highlights the *Morinda citrifolia L.* (Rubiaceae), popularly known as Noni. Information on its therapeutic benefits has gone through the world causing great demand as a medicinal product[7,8].

Scientific studies attest biological activities of *Morinda citrifolia L (Noni)* described by the polynesians as: antioxidant, anti-inflammatory, analgesic, antibacterial and anti-tumor[6]. In scientific studies conducted for the isolation of fixed compounds of the plant, about 200 active substances have already been isolated, where the presence of anthraquinones, triterpenes, iridoids, among others[9]. The anti-inflammatory activity of Noni has been studied *in vivo* and *in vitro* by inhibiting the activity of COX-1 enzymes and COX-2, and the release of chemical mediators from macrophages (nitric oxide (NO) and prostaglandin 2 - PGE-2)[10].

Morinda citrifolia L. (Rubiaceae), popularly known as Noni appears as high healing power agent, whose empirical knowledge of the population has made the fruit is constantly present in the diet[9,10]. Despite the great success and international demand for Noni products, Brazil has reduced the amount of research carried out to obtain more data on this plant species, although scientific articles and papers mention that Morinda citrifolia L (Noni) has phytotherapeutic activity of analgesic, antimicrobial, antitumor, anti-inflammatory and antioxidant effects[11-13]. In this sense, products using biotechnology in the form of nanoparticles or nanostructured compounds, can have excellent results, since, due to their reduced diameter, the substance can be used in smaller doses, avoiding the toxic effect of the plant and maintaining its phytotherapic action.

Purpose

The objective of this study was to observe the protective and repairing effect of Noni's nano-emulsified extract (SME-FC5) in the presence of induced sepsis, by ligation and puncture of the cecum in rats, using the dosage and subsequent blood count, inflammatory markers and biochemical measurements, including histopathological analysis of the compared to the control group treated with 0.9% saline solution.

METHODS

The experimental protocol was approved by the *Ethics Committee on the Use of Animals - ECUA, number 034/2016, Brazil*. Animals were handled in accordance with the *Guide for the Care and Use of Laboratory Animals, US National Research Council, 1996*. The Institutional Committee on Ethics in the Use of Animals approved the research project under protocol. The care with the use of the animals followed the standards of the Brazilian legislation for the scientific use of animals (Law 11.794 / 2008 CONCEA).

Experimental design

We used 12 Wistar male rats with three months of age, randomly divided into 2 groups, kept in individual cages with food and water standard (Labina-Purina®) is rodents, *ad* libitum. In the experimental group (n=06) rats received 5mg/mL/Kg (EMS-FC5) noni extract via the probe/gavage 18 and 2 hours prior to cecum ligation and puncture (CLP), the remainder rats (n=6) Were treated with oral saline solution at 0.9%, 18 and 2h prior to CLP.

Preparation of the vegetable extract

The hydroalcoholic extract of *Morinda citrifolia* L. was prepared from the aerial parts (stem, leaves, and fruits) of fresh adult plants. The collected material was placed at room temperature; then crushed and placed in the oven for 24 hours ata temperature ranging from 45°C to 50°C to remove

moisture. Then the material was ground to obtain the powder, weighed and deposited in a glass vessel with the addition of 70% hydroalcoholic solution in the ratio of 1:3 of the powder. The resulting mixture was allowed to stand for 12h and stirred for five minutes every two hours under two simple filtration procedures under reduced pressure to give the crude extract which was concentrated in a rotary evaporator under reduced pressure at a temperature between 55°C and 60°C, for total solvent elimination. The product obtained after concentration in paste form was diluted in distilled water until the hydroalcoholic extract at 5mg/mL concentration was obtained in the refrigerator and kept at 10°C until it was used.

Surgical model

After 12h of fasting, the rats were anesthetized with for the induction of anesthesia general, the solution of Zoletil® 50, the anesthetic dissociative, will be used in the dose of 0.3mL/100 mg intramuscularly in the region of the quadriceps, with disposable syringes of 1mL of insulin and needle 27F and operated under aseptic conditions.

They breathed spontaneously throughout the procedures. After shaving, the abdominal skin was disinfected with 0.2% chlorhexidine. All procedures were performed under sterile conditions. In the CLP (control) and CLP + Noni (EMS-FC5) rats, a midline laparotomy was 2cm performed and the cecum was exposed, ligated with 2-0 silk (Ethicon®, Brazil) 1cm distally to the ileocecal valve to avoid intestinal obstruction. Four cecal punctures were performed with an 18F needle, squeezed gently to force out a small amount of feces, and then it was returned to the abdominal cavity. The abdominal incision was closed with 4-0 nylon suture (Ethicon®, Brazil) and, 24 hours after the procedure, reopened to the attainment of biopsies and blood collection. The peritonitis was clinically diagnosed when the animals had lethargy, frizzed hair and periorbital dark halo. After surgical intervention, postoperative pain control was done with intramuscular meperidine. At a dose of 10mg/Kg once daily for the first three days. The animals were kept under observation for five days, during which weight loss parameters were observed through digital weighing (Toledo®, São Paulo, Brazil), with sensitivity for variation from 1gram. After the procedures, the rats were killed by injection of anesthetic intracardiac overdosage.

***Treatment Morinda citrifolia* L**

In the experimental group, rats (n=6) will receive 05mg/mL/Kg Noni extract via probe (SME-FC5), 18 and 2 hours prior to cecum ligation and puncture (CLP), remaining (n= 6) will be treated with oral saline solution 18 and 2 hours before the CLP (2mL)

Laboratory analysis.

After 24 hours of conclusion of the procedures under anesthesia and aseptic conditions, blood was collected by cardiac puncture to measure the cytokines and transaminases. Samples of blood were treated with EDTA and the plasma was separated by centrifugation at 2000rpm and stored in -80°C for later measurement of tumor necrosis factor (TNF-a) interleukin-6 (IL-6) andinterleukin-1b (IL-1b) by the ELISA (enzyme-linked all immunoassay kits from PeproTech® (Rocky Hill, NJ, USA) according to the manufacturer's recommended protocols. The fluorescence was measured by a Bio-Tec Instruments EL 808 ultra microplate reader, using KC4-V3.0 analysis software. The sensitivity of detection was 3pg/mL for all cytokines. For counting leukocytes and red cells using an automated cell counter (Abbott Cell-Dyn 3500R CD® 5L-3500, USA). For albumin, alkaline phosphatase, gamma-glutamyl transferase (GGT), glutamic-oxalacetic transaminase (AST), glutamic-pyruvic transaminase (ALT), total bilirubin and fractions, erythrocyte sedimentation rate (HSV) blood was treated with EDTA.

Histopathology

For the histopathological analysis, samples of the liver were fixed in formalin to 10%. Sections made with thickness of 4mm were dehydrated, embedded in paraffin and stained with hematoxylin and eosin through conventional technique. All the slides were examined by the same pathologist, so blind. The histopathological data (swelling, congestion, inflammatory reaction, cell degeneration and necrosis) were graded according to the following scale: absent (0), lightweight (1), moderate (2) and severe (3).

Statistical analysis

Data on continuous quantitative variables are the mean ± expresso standard deviation. In the variables that did not present normal distribution, the logarithm transformation method was adopted. These variables are represented by their respective logarithms.

To verify if the differences between the Experimental (SME-FC5) and Control groups were statistically significant, the Student's *t*-test for independent samples was used. The statistical package SPSS®21 was used. For animal weight analysis, data on continuous quantitative variables were expressed the mean ± standard deviation. Initially, the normality assumption was assessed through the Shapiro-Wilk and Kolmogorov-Smirnov tests. For the variable weight two Student *t*-tests were used, the first for independent sample, comparing the groups; and the other of paired samples, which compared the before and after. The level of significance was 5%.

RESULTS

The Group CLP + Noni (SME-FC5) showed significantly lower values of TNF-α and IL-1β when compared to the CLP group. The IL-6 levels in group CLP + Noni, were lower than found in Group CLP ($p < 0.05$) (Table 1).

Table 1 Plasma levels of cytokines

GROUPS	TNF-α (pg/mL)	IL-1β (pg/mL)	IL-6 (pg/mL)
CLP (Control)	39.0±8.9**	76.0±10.9**	20.7±2.8**
CLP + Noni	14.3±1.9	6.7±2.0	9.5±2.0§

* P <0.05 compared with CLP; ** p <0.05 compared with CLP + Noni; § p <0.05 compared with control. Noni (Morinda citrifolia L); CLP, cecal ligation and puncture.

Noni was able to maintain and modulate the inflammatory reaction in the experimental group, which was proven through normality in the hematological dosages. There was also a significant reduction in the number of total leukocytes, which did not generate immunosuppression in experimental animals, but control the systemic inflammatory response in the presence of induced abdominal sepsis. A trend towards normality was

observed in the other cellular parameters measured in relation to the control group (Table 2).

Table 2 Descriptive and inferential statistics of hemogram results

Parameter	Group		*p*-value[1]
	Experimental	Control	
Hemogram			
Hemoglobin (g/dL)	14,20±1,19	14,13±0,56	0,904
Hematocrit (%)	43,00±3,65	42,48±1,68	0,759
Blood cells (x10^6/µL)	5,46±1,05	5,25±0,48	0,668
RDW	14,12±3,92	15,63±1,14	0,385
Leukogram			
Leukocytes (x10^3/ µL)	5,57±0,84	8,82±1,06	<0,001
Segmented (%)	24,50±6,35	31,50±7,71	0,117
Eosinophils (%)	2,00±1,26	2,17±0,75	0,787
Lymphocytes (%)	64,67±7,37	58,00±7,59	0,154
Monocytes (%)	11,67±2,42	7,83±1,72	0,010
Platelets (10^6/mm^3)	0,77±0,14	0,79±0,19	0,847

Mean ± standard deviation / 1 - p-value Student's *t* test

Regarding the biochemical parameters, the nanoemulsified Noni extract maintained normal hepatic enzymes as well as erythrocyte sedimentation rate, with an elevation of albumin levels significantly in relation to the control group. This demonstrates a hepatoprotective effect of the extract, even under adverse conditions. (Table 3). This phenomenon was confirmed in the histopathological analyzes, in which in the experimental group, the Noni maintained the hepatic architecture within its normality, when compared to saline group, where intense inflammatory infiltrate was observed due to a probable transfections hepatitis, evidenced by the significant elevation of the enzymes hepatic diseases (Table 3 / Figure 1)

Table 3 Descriptive and inferential statistics of the biochemical parameters of the animals

Parameter	Group		*p*-value[1]
	Experimental	Control	
Albumin (g/dL)	3,19±0,21	2,45±0,23	<0,001
Alkaline phosphatase LOG (U/L)	2,31±0,09	2,43±0,09	0,037
Gammaglutamyltransferase/GGT (U/L)	43,33±11,86	60,33±15,44	0,058
Glutamic-oxalacetic transaminase LOG (U/L)	2,13±0,07	2,28±0,11	0,018
Glutamic-pyruvic transaminase LOG (U/L)	1,87±0,05	2,02±0,09	0,006
Total Bilirubin	1,53±0,18	1,42±0,32	0,457
Direct Bilirubin	0,67±0,82	0,58±0,17	0,309
Indirect Bilirubin	0,87±0,12	0,83±0,16	0,696
Erythrocyte sedimentation rate	6,20±2,28	7,00±4,05	0,705

Mean ± standard deviation / 1 - p-value Student's t test

weights of the experimental group, but there was a significant reduction of the weights of the animals of the group Control (saline solution) compared to the group that used the nanostructured Noni formulation in the presence of induced abdominal sepsis (Table 4).

Table 4 Descriptive and inferential statistics of the weight of the animals

Variables	Groups		*P-value*
	Controle	Experimental	
Weight before (g)	323,5±25,13	316,7±35,59	0,709[1]
Weight after (g)	265,5±8,46	309,4±36,2	0,030[1]
p-value	0,001[2]	0,004[2]	

Mean ± standard deviation
1 - *p*-value of Student's *t* test for independent samples, comparison between groups.
2 - *p*-value of Student's *t* test for paired samples, comparison between before and after.

DISCUSSION

The use of medicinal plants for the treatment of diseases has been occurring since the dawn of civilization[14]. The development of methodologies for the isolation of active substances has made it possible to identify substances in complex samples such as plant extracts. In this way, the interest for compounds of vegetal origin that could be used as prototypes for the development of new drugs resurfaced[15].

Medicinal plants represent the main raw material used for the synthesis of medicinal products, besides being used as therapeutic agents. Plant consumption is overvalued in traditional use based on its medicinal benefits[16].

Noni (*Morinda citrifolia L.*) has become a promise of the cure for a variety of diseases, ranging from simple hypertension to malignant tumors; even provokes the cure of syndromes, still incurable such as AIDS and other viral diseases[12]. There are studies referencing Noni as a natural drug, although many of the effects are not scientifically proven; some cite cases of hepatitis and even cases of need for liver transplantation related to the indiscriminate use of the vegetable[14].

The popular use and wellbeing attributed to Noni make the industry commercially explore Morinda citrifolia *L* products, often without scientific evidence[12].

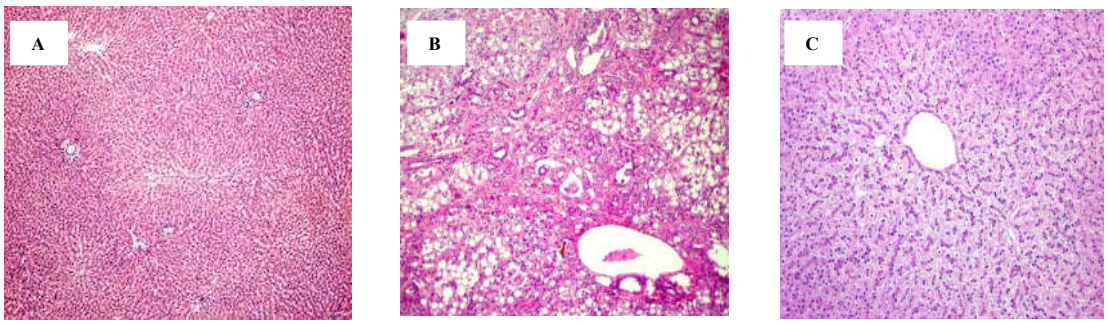

Figure 1 A Normal liver structures are demonstrated. B: hepatic section from a septic rat with vehicle (normal saline) treatment. Patches of hepatocytes show necrosis with eosinophilic cytoplasm nuclei that are condensed and intensely stained with hematoxylin. C: section from a septic rat with *Morinda citrifolia* L (Noni) treatment. Liver structures appear normal. (HE,100 x /100 µm).

Based on the analysis of weight of the animals, comparing intragroup and through the analysis between the control and experimental groups, it was observed the maintenance of the

There are cases that evidence possible toxic properties of Noni, which cannot be neglected[11]. Therefore, the use must be rational to avoid undesirable events, and that only the benefits

of plant products are widely exploited in the treatment of diseases and recovery of health[13].

In this context, the use of biotechnology transforming Noni into a nanostructured compound, has the advantage of using the plant's medicinal properties, reducing its toxicity, keeping its bioactive principles beneficial to health[15-17].

Antimicrobial activity of Noni has already been reported in the literature. Studies have shown that noni inhibited growth *in-vivo* and *in-vitro* bacterial strains such as *Staphylococcus aureus, Pseudomonas aeruginous, Bacillus subtilis, Escherichia coli, Helicobacter pylori, Salmonella* and *Shigella*[6,7]. In addition, Noni has already been studied on its effect against *Plasmodium falciparum*, believed to be due to the presence of anthraquinones, acubin, L-asperuloside, alizarin, scopoletin, among other substances[18-21].

It has also been found that ethanol and hexane extracts of noni have an antitubercular effect since they inhibit by 89-95% the growth of Mycobacterium tuberculosis[22]. The major components identified in the hexane extract were E-phytol, cycloartenol, stigmasterol, b-sitosterol, campesta-5,7,22-trien-3-b-ol, and the ketosteroids, stigmasta-4-en-3-one and stigmasta-4-22-dien-3-one[23-25].

Moreover, they showed that the anti-microbial effect is highly dependent on the stage of ripeness and on processing, being greater when the fruit is ripe, without drying[26].

The limiting factor for the use of Noni as an herbal remedy is that most of the studies previously found in the literature, administer the extract in the alcoholic or hydro-alcoholic form, which may, through prolonged use, mainly cause hepatotoxicity[27-29].

With this in mind, the present study makes its scientific contribution to demonstrate that with the use of biotechnology in the formulation of a nanostructured extract of Noni, such undesirable side effects were abolished, maintaining the active principles of the vegetable under analysis[16,17,30].

This phenomenon was confirmed in the present study, where a reduction in the total leukocytes and polymorphonuclear levels was observed, maintaining normal hemoglobin and hematocrit levels in the experimental group, which used Noni in the presence of induced abdominal sepsis[31,32].

Based on this phenomenon, it is possible to infer that Morinda citrifolia L. has an immunomodulatory action, since it was able to maintain stable and within normal limits hematometry and leucometry of animals under sepsis, associated to the reduction of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) when compared to the control group.This phenomenon occurs due to the different substances in Noni, already proven by other scientific studies[33,34].

In the nanostructured form, it was observed in the present study that Noni maintained its antibacterial, anti-inflammatory and anti-oxidant properties, without presenting toxic activity, mainly hepatic, providing an increase in albumin production (structure) in relation to the control group, maintenance of hepatic function and weight of the animals of the experimental group within normal, evidencing a hepatoprotective effect of Noni when nanoemulsion, which contradicts other studies, in which the use of the same, caused important cellular damages[32-34].

CONCLUSION

In conclusion, the present study demonstrated that Noni's nanoemulsified extract acted as an immunomodulatory agent in the presence of induced abdominal sepsis, reducing the systemic inflammatory response, stimulating the immunity of experimental group animals, preserving liver function and maintaining its bioactive principles beneficial to the experimental model used.

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