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The effects of *Morinda citrifolia* L. (noni) on the immune system: Its molecular mechanisms of action

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Abstract

The aim of this study was to investigate the mechanisms involved in the immunomodulatory effects of *Morinda citrifolia* L. (noni) in vitro and in vivo in mice. In vitro, Tahitian Noni® Juice (TNJ) and Noni fruit juice concentrates (NFJC) (1, 5 mg/mL) potently activate cannabinoid 2 (CB_2), but inhibit cannabinoid 1 (CB_1) receptors in a concentration-dependant manner. In vivo, oral administration of TNJ *ad libitum* for 16 days decreased the production of IL-4, but increased the production of IFN-γ. These results suggest that noni modulates the immune system via activating of the CB_2 receptors, and suppressing of the IL-4, but increasing the production of IFN-γ cytokines. It may also exert beneficial immunomodulation effects in conditions involving inadequate immune responses.

Keywords: *Morinda citrifolia*; Rubiaceae; Immunomodulation; IL-4; IFN-γ; CB_2

1. Introduction

Morinda citrifolia L. (noni) from the family Rubiaceae has been used by Polynesians for over 2000 years for two main purposes. First, the roots and the barks have been used as a dye for traditional and ceremonial clothes. Second, every part of the plant has been used medicinally in treating a variety of ailments (Wang et al., 2002; Palu et al., 2004).

The advent of Tahitian Noni® Juice (TNJ) in 1996 fuelled an increase in scientific research into its possible effects on human health. In addition to traditional uses, recent research (Hirazumi et al., 1994, 1996; Hirazumi and Furusawa, 1999) on the effect of the polysaccharide-rich ethanol-insoluble precipitate of noni (noni-ppt) in the Lewis Lung Carcinoma in mice, has prompted studies into the possible mechanisms involved in its anticancer activity and immunity-enhancement effects. Hirazumi et al. (1996) reported that noni-ppt may exhibit anti-tumor effects in mice by acting as an immunomodulator.

Concerns have recently been raised about the safety of the noni fruit juice for consumption (Mueller et al., 2000; Carr et al., 2004; Millonig et al., 2005; Stadlbauer et al., 2005). However, the "sketchy details and limited number of cases reported are inadequate to draw any conclusion" (West et al., 2006). Further, noni fruit juice was subjected to an official safety evaluation by the European Union and found to be acceptable for human consumption (European Commission, 2002). They concluded that, "there is not convincing evidence for a causal relationship between the acute hepatitis observed in the case studies reported and the consumption of noni juice" (European Food Safety Authority, 2006).

Our study reports on the effects of noni on the immune response in vitro and in vivo in mice, and its effect on the cannabinoid receptors as underlying mechanisms for its immunomodulatory activity.

Abbreviations: TNJ, Tahtian Noni® Juice, a commercial noni fruit juice brand; CB_2/CB_1, cannabinoid receptors 1 & 2; IFN-γ, interferon gamma; IL-4, interlukin 4; NFJC, noni fruit juice concentrates; CHO, Chinese Hamster Ovary; PEC, peritoneal exudates cells; RPMI, a type of media for culturing human cells first developed in Roswell Park Memorial Institute which utilizes a bicarbonate buffering systems; LPS, lipopolysaccharide; Con A, concanavalin A; FCS, fetal calf serum; DMSO, dimethyl sulfoxide.

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2. Methods

2.1. Noni samples

We used noni fruit juice concentrates (NFJC, Lot# 100275) obtained from noni (*M. citrifolia* L.) fruits grown in French Polynesia and provided by Tropical Resources Inc. The TNJ (Lot# 2004-06029) was obtained from Tahitian Noni® International Inc. The noni-ppt was isolated from the noni fruit puree from French Polynesia provided to us by Tropical Resources Inc., and the isolation was in accordance with established protocol (Hirazumi et al., 1994). Briefly, about 19 L of noni fruit puree were partitioned into about 32 aliquots of 580 g each, loaded into four anodized-aluminium cups (Beckman, CH-3.8), and then centrifuged (Beckman GS-6 Centrifuge). This process was repeated until all aliquots had been centrifuged, yielding a total of about until 4 L of juice. The juice was decanted and the pulp discarded. Two litres of the juices were mixed with 2.0 L of 200 Proof Ethanol (Fisher Scientific, USA) and mixed well using T-Line 106A Laboratory Stirrer (Talboys Engineering Corp., Montrose, PA, USA) for 1 h, after which, the precipitates were discarded. An equal volume of 200 Proof Ethanol was again mixed with the supernatant and mixed well as described above for another hour. The noni-ppt precipitate was then collected and air-dried under the hood yielding about 16.27 g.

2.2. Radioligand binding assay for CB_1

The binding affinities of the noni samples (NFJC and TNJ) for CB_1 receptors were investigated using membranes containing CB_1 receptors obtained from human recombinant HEK-293 cells that were stably transfected with a plasmid encoding the human cannabinoid CB_1 receptors in triplicate, 0.5 nM [^{3}H] CP-55,940 as a ligand, and 10 μM R(+)-WIN-55,212-2, as a non-specific ligand. A 1% solution of DMSO was used as the carrier vehicle with a 90 min incubation time at 37 °C. All reactions were carried out in an incubation buffer containing 50 mM Tris–HCl, pH 7.4, 1 mM EDTA, 3 mM $MgCl_2$, and 0.5% BSA, in accordance with established protocol (Compton et al., 1993; Rinaldi-Carmona et al., 1996).

2.3. Radioligand binding assay for CB_2

Binding affinities of noni samples for CB_2 receptors were determined using membranes CB_2 receptors obtained from human recombinant CHO (Chinese Hamster Ovary) K1 cells that were stably transfected with a plasmid encoding the human cannabinoid CB_2 receptors in triplicate, 2.4 nM [^{3}H] WIN-55,212-2 as a ligand and 10 μM R(+)-WIN-55,212-2, as a non-specific ligand with 1% DMSO as a carrier vehicle. All reactions were carried out in an incubation buffer containing 5 mg/mL BSA in 10 mM HEPES, and pH 7.0 and in accordance with established protocol (Munro et al., 1993).

2.4. TNJ immune stimulation in C57B/6J mice

A group of 10 C57BL/6J male mice (Jackson Lab, Bar Harbor, ME, USA) weighing approximately 14–18 g, was divided into two groups of five each (control and treatment). Their handling and treatment was conducted in accordance with the US guidelines for care and use of laboratory animals (NIH publication 85–23, 1985). Each day, for 15 days, the control and treatment groups were provided with clean bottles containing 100 mL of fresh water or TNJ, respectively. On day 16, the animals were sacrificed and the spleens and peritoneal exudate cells (PEC) were harvested as described by Delves (1994).

2.5. Collection of peritoneal exudate cells and isolation of spleen

Peritoneal was soaked with 70% ethanol and approximately 3 mL of peritoneal exudate cells was withdrawn, washed three times with cold RPMI (Sigma, USA) and centrifuged to yield approximately 2×10^6 cells. The spleen was removed and placed in a sterile Petri dish containing RPMI 1640 and 10% FCS. It was next cut into several small pieces and carefully massaged between two glass slides. A small portion of the cell suspension was then aspirated for microscopic determination of cell viability.

2.6. ELISA analysis of IL-4, IFN-γ and IL-12p70 in splenocytes and peritoneal exudate cells

Splenocytes and peritoneal exudate cells (PEC) from water- and TNJ-treated mice were cultured in the presence of LPS, Con A and noni-ppt for 16 h. They were then centrifuged and the supernatant collected. Aliquots of the supernatant were partitioned for cytokine testing. The IL-4, IFN-γ and IL-12p70 cytokines present in the supernatant were quantified using ELISA (Endogen®, Rockford, IL, USA) assay kits EMIL4 (IL-4), EM1001 (IFN-γ), and EMIL12 (IL-12) in accordance with the manufacture's instructions without any modifications of any of the instructions in these bioassay kits. Briefly, 50 μL of Plate Reagent was added to each well and 50 μL of standards and samples were added to their respective wells. The plate was covered and incubated for 2 h at 37 °C. After which, the plate was washed five times then 100 μL of prediluted conjugate reagent was added to each well, the plate was covered and incubated for 1 h at 37 °C. The plate was washed five times then 100 μL of premixed TMB substrate solution was added to each well and then the plate was developed in the dark at room temperature for 30 min. A 100 μL of stop solution was added to each well to stop the reaction and the absorbance was measured and results were calculated.

3. Results

3.1. CB_1 and CB_2 ligand binding assays

TNJ produced inhibition of [^{3}H] CP-55,940 binding. At concentrations of 1 and 5 mg/mL, the CB_1 receptors showed inhibitions of 14 and 10%, respectively. The CB_2 receptors, at the same concentrations, showed stimulations of 54 and 160%, respectively.

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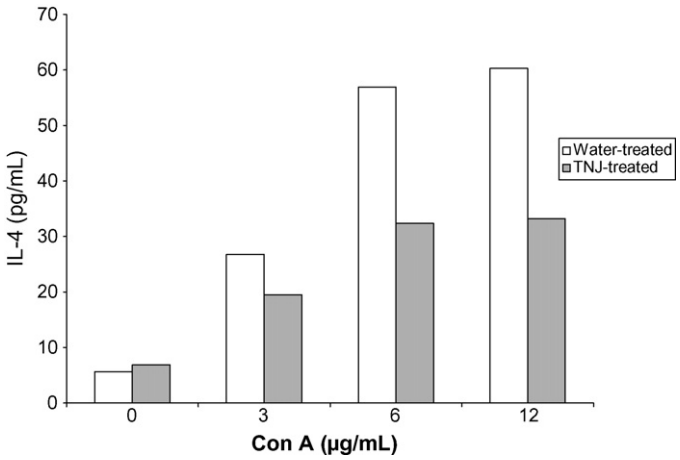

Fig. 1. The production of IL-4 in water- and TNJ-treated mice from their splenocytes incubated for 72 h with Con A. PEC were cultured with different concentrations of Con A (0, 3, 6, 12 μg/mL) in the presence of LPS (0.5 μg/mL).

NFJC produced stimulation of [^{3}H] WIN-55,212-2 binding. At concentrations of 1 and 5 mg/mL, the CB_1 receptors showed inhibitions of 13 and 172%, respectively. The CB_2 receptors, at the same concentrations, showed stimulations of 132 and 224%, respectively.

3.2. IL-4 production from splenocytes

TNJ-treated mice showed suppressed production of IL-4 compared to water-treated mice (Fig. 1).

3.3. IFN-γ Production from PEC

PECS from water- and TNJ-treated mice were evaluated for IFN-γ production using ELISA. Both water- and TNJ-treated mice showed an increase in the IFN-γ production. However, cells from TNJ-treated mice appear to have more IFN-γ production than from water-treated mice (Fig. 2) when culturing with media, TNJ, and LPS. Surprisingly noni-ppt seemed to have a suppressing effect on IFN-γ production whereas LPS increased the production of IFN-γ in the TNJ-treated mice.

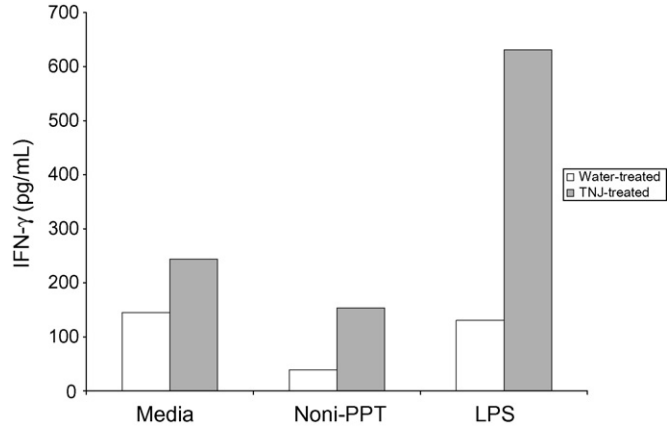

Fig. 2. The production of IFN-γ from PEC incubated for 16 h in the presence of media, noni-ppt and LPS.

4. Discussion

The development and pathogenesis of both inflammation and autoimmune diseases are deeply correlated with the immunological status of the host. Concomitantly, the cannabinoid receptors, specifically CB_2, are also involved in: (1) mediating the protective signals that counteract the proinflammatory responses (Massa et al., 2004), (2) inhibiting neuropathic pain (Ibrahim et al., 2003) without psychoactive effects (Malan et al., 2003), (3) suppressing microbial activation (Ehrhart et al., 2005) and (4) protecting hippocampal neurons from excitotoxicity (Shen and Thayer, 1998). Perhaps more relevant to this study, is the ability of herbs such as *Echinacea* to activate CB_2 receptors and other cytokines involved in the immune systems (Raduner et al., 2006).

In this study, 1 and 5% TNJ and NFJC, respectively, clearly activate CB_2, but inhibit CB_1 receptors. The binding activity of TNJ for CB_1 was basically the same at each concentration, even when the concentration increased fivefold. However, a significant selectivity for CB_2 binding/activation was observed at both TNJ concentrations for CB_2 receptors. The increase in TNJ concentration (1–5 mg/mL) also increased the binding/activation of CB_2 receptors by about threefold. However, the binding activity of NFJC was different than that of TNJ with respect to CB_2 receptors. At 1 mg/mL, NFJC inhibited the binding of the ligand to CB_1 receptors by 13%, but increased the binding/activation of the ligand ([^{3}H] WIN-55,212-2) to CB_2 receptors by 132%, a 10-fold increase. Interestingly, unpublished data from fractionation of the crude noni fruit juice in our lab revealed that the activity is mostly concentrated in the petroleum ether extract, with a CB_2 binding activity of 25% at 100 μg/mL concentration. This is especially noteworthy, since this concentration is only one-tenth that of TNJ, but has a corresponding activity of approximately one-half of its effect on CB_2 receptors at a concentration of 1 mg/mL. Therefore, it seems that the active noni compound(s) that show the immunomodulatory effects may be concentrated within the petroleum ether extract. The selective binding/activation effects of NFJC and TNJ on the CB_2 receptors might explain another possible mechanism whereby noni fruit juices may modulate the immune systems, in addition to those described here.

The activation of CB_2 receptors is shown in the scientific literature to be involved in immunomodulation and anti-inflammation. It has been reported that activation of CB_2 receptors is involved in mediating the protective signals that counteract the pro-inflammatory responses (Bonhaus et al., 1998; Thomas et al., 1998; Howlett et al., 2002; McKallip et al., 2002; Massa et al., 2004; Raduner et al., 2006). The CB_2 receptor is localized, predominantly, in peripheral tissues such as the spleen and hemopoietic cells (Munro et al., 1993). Microbial pathogens that invade tissues are subsequently recognized by the host cells as foreign. Consequently, the host triggers the activation of both innate and adaptive immune responses. However, the activation of the inflammatory response to the infection depends on the amount of pro-inflammatory cytokines and chemokines being released. This inflammatory response is known to be tightly regulated to avoid tissue damage in the host

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and to maintain and/or return to homeostasis. Immune cells, after being activated, in both humans and animals, have been shown to increase the production of endocannabinoids in response to LPS and other stimuli. Hence, it is not surprising that metabolites similar to arachidonic acid, such as endocannabinoid AEA, are produced and released by activated immune cells. In fact, in vitro studies have shown that stimulation with LPS increases the production of anadamide in the immune cells, which seems to suggest that CB_2 is involved in the immune cell and cytokine biology (Di Marzo et al., 1999; Klein et al., 2000a,b; Klein, 2005).

An aberrant increase in expression of IL-4 has been shown in the literature to be involved in allergic responses and airway inflammation (Ricci et al., 1997; Okano et al., 2000; Bergeron et al., 2003; Nonaka et al., 2004). Increasing expression of IL-4 is correlated with increased severity of the allergy. However, the opposite effect between IFN-γ and IL-4 is well documented (Nguyen and Benveniste, 2000). The treatment with agents that down-regulate IL-4 production, since it up-regulates MHC II in asthma conditions, will lead to a reduction in the allergy (Kips et al., 2001). Our studies showed that TNJ suppressed the production of IL-4 compared to water. This agrees with the previous report by Hirazumi et al. (1994), that noni-ppt suppressed the IL-4 production in LLC-infected mice. TNJ increased the production of IFN-γ, which is known to be involved in activating macrophages. The suppressive effects of TNJ on IL-4 production from splenocytes, in conjunction with its increased production of IFN-γ, suggest that TNJ modulates the immune system.

This is the first known report of the effects of *M. citrifolia* noni on the cannabinoid, CB_1 and CB_2, systems. It elucidates another possible mechanism by which noni may modulate the immune system, which complements the earlier reports of Hirazumi et al. (1994, 1996) and Hirazumi and Furusawa (1999), on stimulation of the immune cytokines. Our results show that both TNJ and NFJC potently activate CB_2, but inhibit CB_1 receptors. Also, TNJ suppressed IL-4, but increased the production of IFN-γ. These findings suggest a modulation of the immune system. The mechanism described warrants further clinical research into the effects of noni on the cannabinoid systems in vivo. Such studies could thus clarify the dosage and actual mode of action on this system and CNS in general for its possible effects on the signal transduction pathways in humans.

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