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Original article

Antioxidant and anti-inflammatory activities of a commercial noni juice revealed by carrageenan-induced paw edema

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Abstract

This study aimed to investigate antioxidant and anti-inflammatory activities of a commercial product of noni (*Morinda citrifolia*) juice. Carrageenan-induced rat paw edema was employed as inflammatory model. One control and three experimental groups were formed. Experimental groups were administered noni juice alone, noni juice+carrageenan, and carrageenan alone. Oxidant and antioxidant capacity were determined by d-ROMs test and BAP test, respectively. Plasma concentrations of endothelin-1 and leptin were measured by ELISA. Measurements were performed at zero time and 2nd hour of inflammation. Oxidant capacity decreased in noni-received groups at 2nd hour ($p=0.019$). Antioxidant capacity of the group which received noni alone was found to be higher at 2nd hour ($p=0.036$). Plasma concentrations of endothelin-1 and leptin were notably lower in noni-received groups ($p=0.001$ and $p=0.021$, respectively). The results show that the commercial noni juice investigated has pronounced antioxidant and anti-inflammatory activities.

Key Words: carrageenan, noni (*Morinda citrifolia*), anti-inflammatory, antioxidant

Introduction

Due to bioactive compounds they contain, medicinal plants are still popular with a majority of human population to help prevent diseases and promote good health (Saminathan et al. 2013, Kannan et al. 2014, Murata et al. 2014, Krishnaiah et al. 2015). The genus *Morinda* (Rubiaceae) includes some 80 species native to Southeast Asia, Australia and Pacific Islands (Polynesia). The most popular species *Morinda citrifolia L.*, commonly known as noni in the Hawaiian language, is planted in tropical and subtropical regions including Polynesia, India, Cambodia, the Caribbean region, and Central and Northern South

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America for medicinal and nutritional purposes (Chan-Blanco et al. 2006, Serafini et al. 2015). Along with its consumption as food and a dye for traditional clothes (Palu et al. 2008, 2010), the fruit, leaf, root, seed, bark, stem and flower of this plant have been topically and internally used solely or combined in traditional medicine for over 2000 years in Polynesia to cure and prevent a broad range of human diseases which can be found in reviews by Wang et al. (2002), Mathivanan et al. (2005), Chan-Blanco et al. (2006), Pawlus and Kinghorn (2007), Singh (2012), Gupta and Patel (2013), Saminathan et al. (2013), Assi et al. (2015), Krishnakumar et al. (2015), Motshakeri and Ghazali (2015), Nerurkar et al. (2015), and Raja and Sreenivasulu (2015).

Noni has been globally commercialized since 1996. Among the commercial products are fruit juice, fruit drinks, fruit powder, capsules, lotions, soaps, oil, leaf powder and tea; fruit juice being the predominant formulation to consume (Yang et al. 2007, Singh 2012, Lin et al. 2013, Kannan et al. 2014, Krishnakumar et al. 2015). Today, numerous brands of noni products are available in the market, but they are not the same quality and chemical composition (Palu et al. 2005, West et al. 2006). Geographical origin and differences in varieties of noni plants, different growing conditions, stage of harvest, differences in post-harvest conditions such as maturation, harvesting, storage, transport, manufacturing processes, and formulation contribute to the differences in the quality and chemical composition of noni products (Deng et al. 2010, Motshakeri and Ghazali 2015, Nerurkar et al. 2015, Palioto et al. 2015).

Concerning biological and pharmacological activities of noni, most of the studies which have been conducted so far used laboratory prepared noni extracts, while commercial products were investigated in a few studies. Especially, to the best of our knowledge, studies on anti-inflammatory properties of noni products are quite limited. The present study therefore aimed to reveal antioxidant and anti-inflammatory activities of a commercial product of noni juice available on the Internet, based on photometric measurement of antioxidant capacity and ELISA-determined concentrations of inflammation markers endothelin-1 and leptin, by using a rat model of carrageenan-induced paw edema.

Materials and Methods

Animals

Provided by the Experimental Animal Center of Istanbul University, Turkey, 31 female Wistar albino rats weighing 150-200 g were employed in the present study. The experimental animals were housed in plastic cages in a controlled environment (a constant temperature of 22 ± 1°C, humidity of 60 ± 1%, and 12 h light-dark cycle), and maintained on standard rat pellet diet and water ad libitum. All experimental protocols were approved by Istanbul University Animal Experiments Native Ethical Committee (54-2008/30.04.2008).

Chemicals

Noni juice was purchased from Hanoju Europe Ltd. (Dinxperlo, The Netherlands). Carrageenan was purchased from Sigma-Aldrich (USA), while reagents for reactive oxygen metabolites-derived compounds (d-ROMs) test and biological antioxidant potential (BAP) tests from Diacron International s.r.l. (Grosseto, Italy), ELISA Kit for Endothelin 1 from USCN Life Science Inc. (Houston, USA) and Rat Leptin ELISA Kit from Crystal Chem Inc. (USA).

Carrageenan induced rat paw edema

Edema was induced by subcutaneous injection of 100 µl of a 1% solution of lambda carrageenan in 0.9% saline into plantar region of the left hind-paw, as was previously described (Morris 2003).

Experimental design

The animals were randomly divided into four groups: one control (n=7) and three experimental (n=8). Group 1 was the control group which received subcutaneous injection of 0.9% saline (0.2 ml) into the left hind-paw, while groups 2, 3 and 4 were experimental groups which were administered noni juice (2 ml/bw) alone by gavage, noni juice (2 ml/bw) by gavage + carrageenan (1% w/v) injection, and carrageenan (1% w/v) injection alone, respectively. Noni was given 30 min prior to the injection of carrageenan (Salvemini et al. 1996).

Determination of total oxidant and antioxidant capacity and inflammation markers

The blood was collected from the tail vein at zero time and from the heart of sacrificed animals 2 hours after carrageenan injection, and placed into heparinized tubes. The plasma was removed by centrifugation at 2400 rpm for 10 min within 1 hour after

venipuncture, and stored at -20°C until use. Oxidant capacity was determined by d-ROMs test, while antioxidant capacity by BAP test.

The d-ROMs test determines concentration of hydroperoxides (ROOH) in biological samples. While ROOHs are fairly stable molecules under physiological conditions, transition metals including Fe^{+2} and Fe^{+3} catalyze their decomposition, and correspondingly degradation of these compounds results in various secondary reactive radical species formation (Palmieri and Sblendorio 2007). The presence of ROOH in cells belonging to a broad class of Reactive Oxygen Metabolites (ROMs) points oxidative attack of ROS on various organic substrates such as carbohydrates, lipids, amino acids, proteins, or nucleotides (Sudhakar et al. 2015). Antioxidant capacity can be measured using the Ferric Reducing Ability of Plasma (FRAP) and Biological Antioxidant Potential (BAP), both of which ensure a global measurement of many antioxidants, including uric acid, ascorbic acid, proteins, α-tocopherol and bilirubin (Benzie and Strain 1996). Both tests were performed by means of an integrated analytical system, FRAS4 (H D s.r.l., Parma, Italy) which consists of a dedicated photometer with incorporate centrifuge. Briefly, for d-ROMs test, plasma was diluted in an acidic buffer solution (pH 4.8). Water solution of N,N,-diethyl-para-phenylenediamine, a compound which has the ability to change its color when is oxidized by hydroperoxyl and alkoxyl radicals, was then added to this solution. The resulting solution was incubated at 37°C for 5 minutes in the reading cell of the photometer, and quantified at 505 nm. The results were expressed as Carratelli Units (CARR U), where one CARR U corresponds to the oxidizing capacity of a solution containing 0.08 mg/100 ml hydrogen peroxide. For BAP test, plasma was dissolved in the colored solution, previously prepared by mixing a ferric chloride solution with a thiocyanate derivative reagent. After 5 min of incubation at 37°C, the absorbance of the solution was read at 505 nm. The results were expressed as (μEq/L) (Pasquini et al. 2008, Menichini et al. 2015). Plasma concentrations of inflammatory markers, endothelin-1 and leptin, were determined by enzyme linked immunosorbent assay (ELISA).

Statistical analysis

All data were analyzed using Statistical Package for the Social Sciences (SPSS) version 20.0. The Kruskal-Wallis test was used to compare differences between the groups, while the Mann Whitney U test for comparing two groups, and the Wilcoxon Signed Rank test for the comparison within the group. A value of $p<0.05$ was considered statistically significant. Outliers were rejected using Dixon's Q test.

Results

Analysis of total oxidant and antioxidant capacity and inflammation markers

Total oxidant and antioxidant capacity were determined from blood samples of the animals in all the groups before (zero time) and after (2nd hour) treatment with noni and carrageenan. Oxidant capacity of noni group was declined at 2nd hour when compared to zero time ($p=0.017$) (Fig. 1). However, oxidant capacity of carrageenan group was higher at 2nd hour in comparison with the value determined at zero time, being not statistically significant ($p=0.063$). There was a significant difference between oxidant capacities of

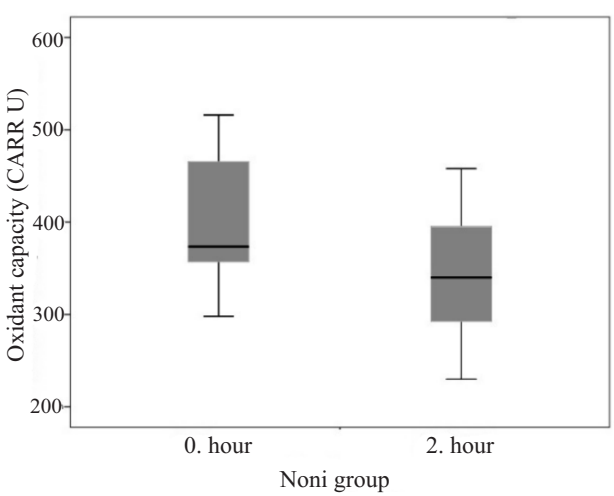

Fig. 1. Box plot of oxidant capacity of noni group at zero time and 2nd hour.

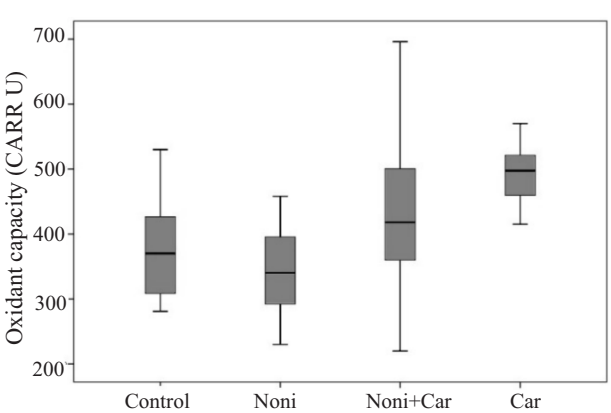

Fig. 2. Box plot of oxidant capacity of all groups at 2nd hour.

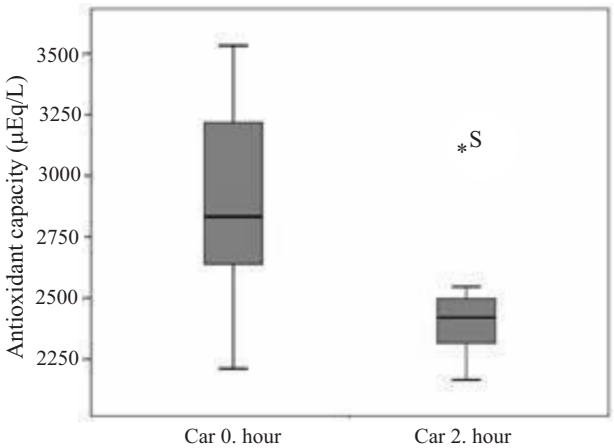

Fig. 3. Box plot of antioxidant capacity of carrageenan group at zero time and 2nd hour.

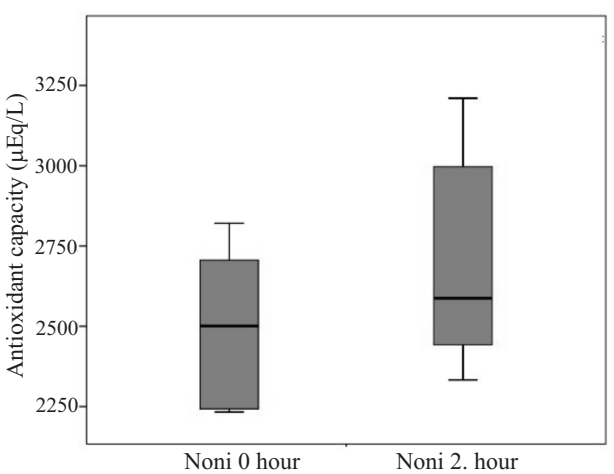

Fig. 4. Box plot of antioxidant capacity of noni group at zero time and 2nd hour.

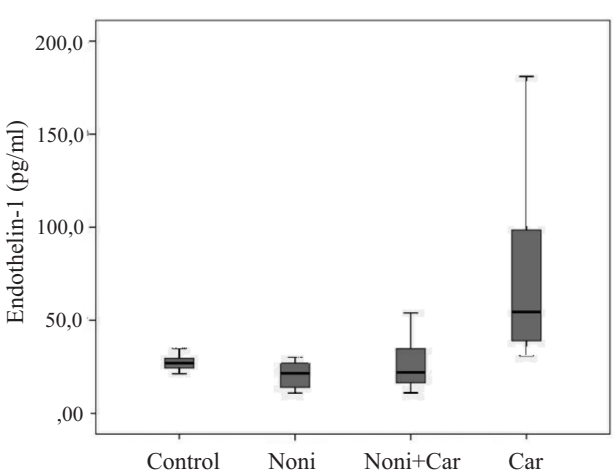

Fig. 5. Box plot of endothelin-1 concentrations of all groups at 2nd hour.

the groups at 2nd hour (p=0.019), in that oxidant capacity decreased and increased in noni and carrageenan groups (Fig. 2). As to the results related to antioxidant effect, antioxidant capacity of noni group was found to be higher at 2nd hour in comparison with that at zero time (p=0.036) (Fig. 4), whereas antioxidant capacity was significantly lower at 2nd hour by that at zero time in carrageenan group (p=0.028) (Fig. 3). Nevertheless, there was no difference between antioxidant capacities of the groups at 2nd hour (p=0.053). Taking inflammatory markers into consideration, plasma concentrations of endothelin-1 and leptin were notably lower in noni groups (p=0.001 and p=0.021, respectively) (Figs. 5, 6).

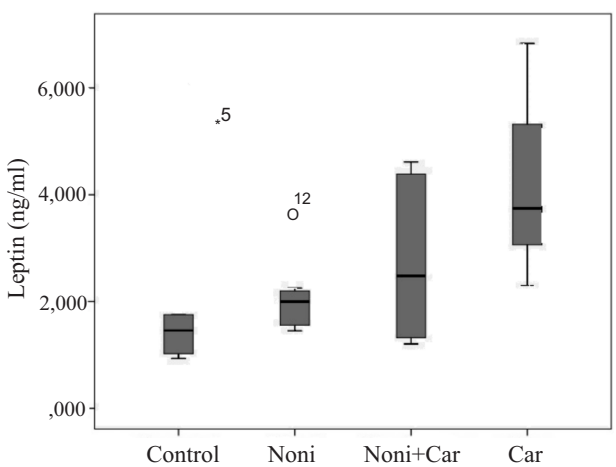

Fig. 6. Box plot of leptin concentrations of all groups at 2nd hour.

Discussion

With the large chemical diversity of secondary metabolites they contain, plants have always been among the common sources of new medicines for a great variety of diseases. Noni discovered as a medicinal plant by the ancestors of Polynesians 2000 years ago has been and is still used in traditional medicine, thus being a popular research object. Although first studies on this plant date back to the beginning of 1990s, with two publications in the years of 1907 and 1918 (Simonsen 1920), numerous *in vitro* and *in vivo* investigations and clinical trials have started with the advent of noni juice as a health and wellness drink in 1996 and its approval as a novel food by the European Commission in 2003 (Palu et al. 2008, Basar et al. 2010, Glang et al. 2013). Diverse bioactive and therapeutic properties of noni have recently been reviewed by Assi et al. (2015), Krishnakumar et al. (2015), Motshakeri and Ghazali (2015), Nerurkar et al. (2015), and Raja and Sreenivasulu (2015) comprehensively. In addition to its human health benefits, noni was reported to have beneficial effects on animal health and productivity (Retnani et al. 2014). However, most of the studies on noni are primarily based on labora-

tory prepared noni extracts, whereas there have been little scientific studies to reveal bioactive properties of commercial noni products. Therefore, the present study focused on antioxidative and anti-inflammatory properties of a commercial product of noni juice available on the Internet.

Noni possesses around 200 biologically and pharmacologically active compounds in widely varied structural classes, well documented by Singh (2012), Saminathan et al. (2013), Assi et al. (2015), and Krishnakumar et al. (2015). Of these, several phenolic compounds, vitamin C and some lignans were suggested to be responsible for antioxidative activity (Kamiya et al. 2004, Su et al. 2005, Dussossoy et al. 2011, Singh 2012, Saminathan et al. 2013, Krishnakumar et al. 2015). Furthermore, lipid soluble polyphenols, anthraquinones, α-tocopherol and β-carotene may give rise to part of the antioxidant activity. Yet, it is known that most of antioxidant compounds work synergistically with each other, producing a broad spectrum of effects against oxidative stress (Krishnakumar et al. 2015).

In recent years, a number of diverse methods have been developed for the detection of both oxidant and antioxidant status of biological systems. With good to excellent analytical performances, both d-ROMs test and BAP test have been proved to be reliable and suitable methods to assess the oxidative stress either in health or in ill subjects, before and after specific treatments and/or antioxidant supplements as indicated by numerous studies on humans and several animal species including mammals (Pasquini et al. 2008, Kotani and Yamada 2012, Finotello et al. 2014, Menichini et al. 2015). Therefore, the d-ROMs and BAP tests were chosen in this study due to their accuracy in measuring the whole oxidant capacity and the whole antioxidant biological potential of plasma, respectively.

The carrageenan-induced paw edema is a convenient *in vivo* model which has long been used to investigate the cellular and molecular mechanisms of inflammation, and to screen potential anti-inflammatory agents. Edema formation in this model is a biphasic response. An initial phase starts with the release of mediators including histamine, serotonin and bradykinins after carrageenan injection. A late phase is mediated by an eicosanoid like PGE2 and by neutrophil infiltration. Nitric oxide is also involved in carrageenan-induced edema, which reaches its maximum level at 1 h and after that it starts declining (Neha Mohan et al. 2013). The study by Dussossoy et al. (2011) showed that inhibitory effect of Costa Rican noni juice started at 1 h and lasted for 24 h, and they suggested that noni juice could deal in both the initial and late phases. However, our study assessed antioxidant and anti-inflammatory properties of noni juice at 2nd hour.

Endothelin-1 and leptin were used as inflammation markers in this study since their plasma concentrations are increased in inflammation processes. Endothelin-1, firstly described in endothelial cells and in vascular smooth muscle cells, was demonstrated to play a pivotal role in inflammation in several human diseases, by stimulating production of reactive oxygen species (Elisa et al. 2015, Kowalczyk et al. 2015). Leptin, produced mainly by the white adipose tissue, plays important roles in the activation of the immune system, and it is a mediator of inflammation (Gualillo et al. 2000, Fernández-Riejos et al. 2010, Paz-Filho et al. 2012).

This study suggests that anti-inflammatory activity of noni fruit may result from the presence of flavonoids such as quercetin, isoquercitrin and rutin, coumarins such as scopoletin and esculetin, and triterpenoid ursolic acid, which are most likely found in the noni juice product we investigated. As it is well known, these compounds exhibit anti-inflammatory activity through the nitric oxide and prostaglandins E2 pathways (Dussossoy et al. 2011, Kokturk et al. 2013, Motshakeri and Ghazali 2015).

In conclusion, the results of this study show that the commercial noni juice investigated has pronounced antioxidant and anti-inflammatory activities.

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