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Morinda citrifolia (Noni) Fruit Juice Inhibits Endocannabinoid Degradation Enzymes

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Abstract

Morinda citrifolia (noni) fruit juice has been shown to have a wide variety of potential health benefits in human clinical trials. It may also influence the endocannabinoid system of the body. Since the main ingredient of the product studied in these clinical trials was juice made from noni fruit puree from French Polynesia, it was evaluated for its ability to inhibit the two major endocannabinoid degradation enzymes *in vitro*. Noni fruit juice inhibited both fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) in a concentration-dependent manner, suggesting that it may help maintain anandamide and 2-arachidonoylglycerol levels. Samples of the puree were also analyzed for the presence of characteristic phytochemical markers of authentic noni fruit such as scopoletin, rutin, quercetin, deacetylasperulosidic acid and asperulosidic acid, all of which were present. Also present was scandoside, which is reported for the first time as being identified in noni fruit or its juice. Some of these compounds may contribute to the FAAH and MAGL inhibiting activity of noni juice. These results reveal another set of mechanisms by which noni juice possibly supports mental health, maintains joint health, relieves discomfort and modulates the immune system.

Keywords

Morinda citrifolia, Endocannabinoid System, Fatty Acid Amide Hydrolase, Monoacylglycerol Lipase

1. Introduction

The endocannabinoid system (ECS) serves an important regulatory function within the human body. It influences the nervous and immune systems extensively and has an impact on digestion, reproduction and bone mass [1] [2]. The ECS also has interrelations with the respiratory, renal, endocrine and cardiovas-

cular systems [3] [4]. Indeed, the ECS has a wide effect on the body and helps maintain overall health. The ECS is composed of G protein-coupled receptors (GPCRs) within cell membranes, lipid signaling molecules (endocannabinoids) and the enzymes responsible for endocannabinoid synthesis and catabolism. The two most prominent ECS receptors are cannabinoid receptor type 1 (CB1) and cannabinoid receptor type 2 (CB2). Other GPCRs, currently designated as orphan receptors, have been more recently discovered. There are two main endocannabinoids produced by the body, N-arachidonoylethanolamine (anandamide or AEA) and 2-arachidonoylglycerol (2-AG). AEA and 2-AG are synthesized from arachidonic acid derivatives, N-arachidonoyl phosphatidylethanolamine (NAPE) and diacylglycerol, by phospholipases and diacylglycerol lipases. AEA is eventually degraded by fatty acid amide hydrolase (FAAH) to arachidonic acid and ethanolamine. 2-AG is hydrolyzed by monoacylglycerol lipase (MAGL) and FAAH [5]. AEA and 2-AG are CB1 and CB2 ligands, and it is through their interactions with these receptors that many of their physiological effects are mediated [6].

Morinda citrifolia is a small to medium sized tree that grows in tropical regions. It is commonly known as noni or Indian mulberry. The tree produces fruit year-round, which has been used as both food and medicine [7]. The leaves and other plant parts also had significant roles in the Pacific, South Asian, Southeast Asian, and the Caribbean traditional medicine [8]. The noni tree was reportedly the most important and widely used Polynesian medicinal plant prior to the European era [9]. Various parts of the plant were used by local healers for a broad range of health conditions [10] [11] [12]. Traditional perceptions of the health benefits of noni appear to be validated by the results of human clinicals trials, especially those involving noni fruit juice. Among the recorded effects of noni juice ingestion are control of inflammation, improved joint mobility, relief of discomfort, immune system modulation, protection against oxidative damage, maintenance of bone health, and improved mental health outcomes [13].

The array of noni juice benefits observed in human studies suggests that it interacts with multiple bodily systems, among which the ECS may have a significant role. In fact, we have previously reported that noni juice exhibits CB2 receptor agonist activity [14]. But as the major endocannabinoids produce effects within the body that are similar to those reported for noni juice, we further investigated noni juice's interaction with the ECS by assessing its potential to maintain AEA and 2-AG levels through FAAH and MAGL inhibition.

2. Materials and Methods

Noni fruit was harvested in French Polynesia and allowed to fully ripen. The fruit was then processed into a puree by mechanical removal of the seeds and skin, followed by pasteurization at a good manufacturing certified fruit processing facility in Mataiea, Tahiti. This source of noni fruit puree was approved by the European Commission in 2003 as a safe novel food for use in pas-

teurized beverages [15]. It was also later approved as a safe novel food ingredient for use in a wide variety of food categories within the European Union [16]. For our study, the noni fruit puree was centrifuged to remove insoluble fiber. The resultant clarified juice was then filtered through a 0.45 μm PTFE filter.

Samples of this filtered noni juice were analyzed by high performance liquid chromatography (HPLC), according to a previously validated method, for iridoid markers of authentic noni fruit, including deacetylasperulosidic acid (DAA) and asperulosidic acid (AA) [17]. As we have since discovered the presence of scandoside in noni fruit by LC-MS analysis, we included this in our HPLC analyses. Samples were diluted with methanol-H_2O (1:1) and filtered through a 0.45 μm nylon membrane filter. Chromatographic separation was performed with a C-18 column (4.6 mm × 250 mm; 5 μm, Waters Corporation, Milford, MA, USA). Two mobile phases were used: A; acetonitrile (MeCN), and B; 0.1% formic acid in H_2O (v/v). The elution rate was 0.8 mL/min. with consecutive linear gradients of 100% B for 0 - 5 min. followed by 70% B and 30% A for 40 min. A photodiode array (PDA) detector was used to monitor the eluted compounds within 210 - 400 nm. Sample injection volume was 10 μL, and column temperature was 25˚C.

Analyses of scopoletin, rutin, and quercetin—additional phytochemical markers of authentic noni fruit—were also performed by HPLC according to a previously validated method [18]. Chromatographic separation was performed on a Waters 2690 separations module, coupled with a Waters 996 photodiode array (PDA) detector, and a C-18 column. Three solvents were used to compose the mobile phase. These were MeCN (solvent A), MeOH (solvent B), and 0.1% formic acid in H_2O (solvent C). The following linear gradient was used for the separation: 0 min. of 10% A, 10% B, and 80% C; 15 min. of 20% A, 20% B, and 60% C; 26 min. of 40% A, 40% B, and 20% C; 28 - 39 min. of 50% A, 50% B, and 0% C; and 40 - 45 min. of 10% A, 10% B, and 80% C. The flow rate was 1.0 mL/min. Chromatograms were integrated at 365 nm. In both HPLC methods, retention times and peak areas were compared against standards to determine analyte concentrations in the samples.

The total polyphenol content of each sample was determined by the Folin-Ciocalteu method [19]. Samples were centrifuged and diluted 1:10 with deionized water. Next, 10 μL of each sample was mixed with 50 μL Folin-Ciocalteu (2N) and an additional 800 μL deionized water. The mixture was incubated at room temperature for a few minutes, followed by addition of 150 μL Na_2CO_3 (saturated) and incubation at room temperature for 2 hours. Gallic acid standards were prepared with the same procedure. Afterwards, the absorbance of each sample and standard was measured at 765 nm with a microplate reader. Sample absorbance vs. gallic acid concentration was used to determine the total phenol content of the samples, expressed as gallic acid equivalents (GAE).

FAAH and MAGL inhibition assays were carried out as previously described, but with some modifications [20]. Human recombinant FAAH, human recom-

binant MAGL, 7-amino-4-methyl coumarin-arachidonamide (AMC-AA), and 4-nitrophenylacetate were obtained from Cayman Chemical Company (Ann Arbor, MI, USA). For the FAAH inhibition assay, the recombinant FAAH was diluted with Tris-HCl buffer (125 mM, pH 9.0) containing 1 mM EDTA. Noni juice samples were added in varying volumes to separate wells of a black plastic 96-well microplate, with deionized water also being added to make up a total volume of 10 µL. Vehicle control (no inhibitor) wells did not receive noni juice, only water. Inhibitor (noni juice) and control wells received 10 µL FAAH solution as well as additional 170 µL of buffer. Background fluorescence wells, to which no FAAH was added, received 180 µL buffer. The microplate was then incubated for five minutes at 37˚C. Ten µL of AMC-AA solution was then added to each well with a final concentration of 20 µM. The microplate was then incubated again at 37˚C for 30 minutes. Following incubation, the fluorescence intensity of each well was measured in a Synergy™ HT microplate reader (BioTek Instruments, Winooski, VT, USA) with 360 ± 40 nm excitation and 460 ± 40 nm emission. All samples and the control were evaluated in triplicate. The relative increase in fluorescence intensity was determined by the ratio of the intensities of the inhibitor well and its corresponding background well. Percent FAAH inhibition was calculated from the difference between the relative increase in fluorescence intensity of the vehicle control and the sample divided by that of the vehicle control alone. DAA, the major phytochemical constituent of noni fruit, was also evaluated in this assay but with DMSO as the solvent and vehicle control.

In the MAGL inhibition assay, the recombinant MAGL was diluted with Tris-HCl buffer (10 mM, pH 7.2) containing 1 mM EDTA. Noni juice samples were added in varying volumes to separate wells of a clear plastic 96-well microplate, with deionized water added to make up a total volume of 10 µL. As in the previous assay, vehicle control (no inhibitor) wells only received water. Inhibitor (noni juice) and control wells received 10 µL MAGL solution as well as additional 150 µL of buffer. Background absorbance wells, with no MAGL, received 160 µL buffer. The microplate was then incubated at room temperature for five minutes. Enzymatic reactions were then begun by the addition of 10 µL of 4-nitrophenylacetate in ethanol (236 µM in final reaction solution), which proceeded at room temperature for 10 minutes. Absorbance at 405 nm was then read with an EL_X800 microplate reader (BioTek Instruments, Winooski, VT, USA). All samples and the control were evaluated in triplicate. Absorbance values were corrected by subtracting background well values from those of corresponding sample wells. Percent MAGL inhibition was calculated from the difference between control and sample absorbance divided by that of the absorbance of just the control. Mean results, as well as standard deviations, were calculated for each set of replicate samples in both the FAAH and MAGL inhibition assays.

3. Results and Discussion

HPLC analyses revealed that our noni juice samples contained phytochemical

constituents that are present in a commercial source of authentic noni juice that has been reported to protect lymphocyte DNA, improve serum lipid profiles, and reduce high-sensitivity C-reactive protein (hs-CRP) and homocysteine levels of cigarette smokers [21] [22]. The concentrations (mean ± standard deviation) of DAA, AA, scopoletin, rutin, and quercetin were, respectively, 1.3827 ± 0.0170, 0.4033 ± 0.0057, 0.0463 ± 0.0006, 0.0136 ± 0.0005 and 0.0014 ± 0.0001 mg/mL. Scandoside, which is reported here for the first time in noni fruit or juice, was present at 0.0823 ± 0.0153 mg/mL. The total polyphenol content was 0.8903 ± 0.0243 mg GAE/mL.

Noni juice inhibited FAAH activity in a concentration dependent manner, Figure 1. Between 2.50 and 8.33 μ/mL, inhibition vs. noni juice concentration is linear—reducing AMC-AA hydrolysis by (mean ± standard deviation) 25.22% ± 5.43% to 68.75% ± 5.03%. But above this range, the incremental decrease in FAAH activity is much less, with suppression of 82.55% ± 0.55% enzyme activity at 16.66 μL/mL. There was also a concentration-dependent suppression of MAGL activity by noni juice, Figure 2. The lowest concentration, 2.78 μ/mL, reduced hydrolysis of 4-nitrophenylacetate by 32.88% ± 3.62%. MAGL activity is

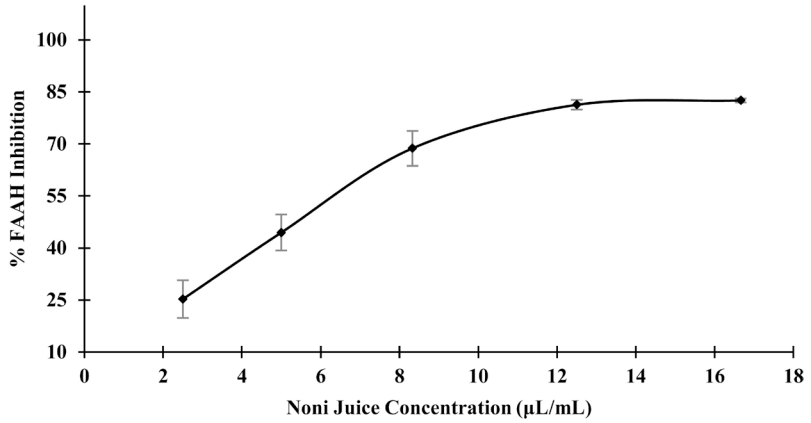

Figure 1. Inhibition of fatty acid amide hydrolase (FAAH) by increasing concentrations of noni juice. Note: % inhibition by vehicle control (water) is zero.

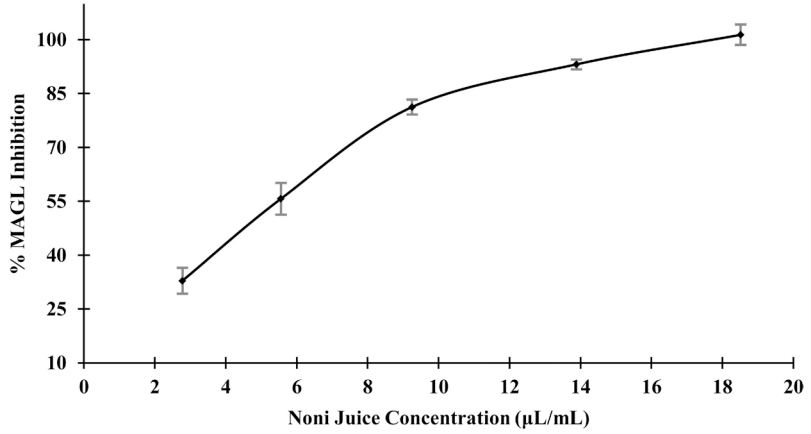

Figure 2. Inhibition of monoacylglycerol lipase (MAGL) by increasing concentrations of noni juice. Note: % inhibition by vehicle control (water) is zero.

reduced by 55.71% ± 4.40% with 5.56 μL/mL and continues to decline until it is completed prevented with 18.52 μL noni juice/mL.

These enzyme inhibition assays reveal that noni juice has the potential to influence AEA and 2-AG levels or prolong their interactions with CB1, CB2, and the orphan G-protein receptors. This maintenance of endocannabinoid tone, or levels, likely contributes to pain management since endocannabinoids accumulate at sites of injury and inflammation where they interact with cannabinoid receptors, transient receptor potential vanilloid 1 (TRPV1) ion channels and G protein-coupled GPR55 receptors to produce analgesia and anti-inflammatory effects [23] [24] [25]. Mice with a genetic deletion for FAAH had increased pain tolerance in the tail flick test and the formalin and carrageenan models of inflammation [26]. A selective FAAH inhibitor, URB597, reduced neuropathic pain in Sprague-Dawley rats. This analgesic effect was reduced when CB1 receptor and peroxisome proliferator-activated receptor alpha (PPAR alpha) antagonists were administered before URB597 [27].

Selective MAGL inhibitors significantly reduced neuropathic pain (allodynia) resulting from chronic constriction injury of the sciatic nerve [28]. The dual FAAH/MAGL inhibitor JZL195 reduce allydonia, motor incoordination, and catalepsy in C57BL/6 mice subjected to chronic constriction injury [29]. The reduction in neuropathic pain in these animals was greater with the dual FAAH/MAGL inhibitor than with selective FAAH or MAGL inhibitors alone. This suggests that substances which impact both AEA and 2-AG levels are more effective in treating pain and can do so at much lower doses, thus reducing the potential for side effects.

The antinociceptive properties of noni juice have been demonstrated in multiple in vivo studies and in human clinical trials. Mice fed noni fruit puree for four days experience reduced pain sensitivity; an effect comparable to the central analgesic drug tramadol [30]. This was only partial reversed by naloxone, revealing the involvement of other non-opioid mechanisms. The authors of this study also reported that a noni fruit extract reduced matrix metalloproteinase-9 (MMP-9) from human monocytes following lipopolysaccharide (LPS) stimulation and suggested that this is one immunomodulating mechanism responsible for the analgesic and anti-inflammatory action of noni. Interestingly, MMP-9 levels in CB2 knockout mice reached significantly higher levels following LPS challenge than those in normal mice [31]. This provides supportive in vivo evidence for noni's potential MAGL and FAAH inhibitor activities since 2-AG is the principle ligand for CB2.

Clinical trials of noni juice have also been conducted in patients with osteoarthritic conditions in which MMP-9 expression has a contributing role [32] [33]. The first of two open-label clinical trials to demonstrate the potential joint health benefits of noni juice reported pain reduction and improved range of motion (flexion, extension, lateral flexion, and rotation) in patients suffering from cervical spondylosis after four weeks [34]. In this study, 90 patients were ran-

domly assigned to either a standard physiotherapy treatment group (positive control), a noni juice treatment group, or a combined treatment group (physiotherapy plus noni juice). Measurements of pain intensity and neck flexibility (cervical range of motion) were compared among the treatment groups. Before the trial, all subjects in the noni juice group fell within the 5 - 7 (moderate to severe) pain intensity range. But the pain intensity range of this group decreased to 0 - 4 (none to very moderate) after four weeks, with complete relief of neck pain in 60% of patients. The combined treatment group also experienced significant reduction in pain symptoms, experiencing even greater reduction in pain intensity. Range of motion improved among all three treatment groups. Lateral flexion and rotation doubled in the noni juice group.

In the second open label intervention study, 82 osteoarthritis (hip and/or knee) patients drank 88.5 mL noni juice daily for 90 days [35]. Arthritis Impact Measurement Scales (AIMS2) were used to measure pain/discomfort levels. The Short Form-36, version 2 (SF-36 V2) was used to measure patient quality of life. Noni juice ingestion significantly improved mean quality of life measurements. These included reduced duration of arthritis pain, including a 23.7% decrease in the frequency of severe pain, and a 16.4% decrease in pain severity. Improvements in average mobility and patient psychological state also occurred. Satisfaction with personal health increased by approximately 19%. The improved symptoms observed in these two human studies provide further support for the MAGL and FAAH inhibitory effect of noni juice, since compelling evidence points to the active involvement of the ECS in mitigating the progress osteoarthritis [36].

The ECS is an important regulator of stress and mental health [37]. As mentioned briefly above, noni juice ingestion significantly improved AIMS2 mental health scores of patients in the 90-day osteoarthritis trial, especially those that rate anxiety levels and overall mood. A similar effect was reported in post-menopausal women in a three-month placebo-controlled pilot study [38]. When compared to the placebo group, drinking 59 mL noni juice twice per day significantly improved the average SF-36 mental health subgroup score.

Feeding of noni juice from Tahiti to rabbits for four weeks resulted in increased sleep duration after receiving general anesthesia as well as improved basal heart and respiration rates [39]. Further, sponteneous movements were reduced while under anesthesia, and animals receiving noni juice had smoother inductions and smoother recoveries. The authors of this study reported that noni juice increased calmness, muscle relaxation, and reduced anxiety in the anesthetized rabbits. Another study evaluated the influence of noni juice on stress-induced impairment of cognitive function of male ICR mice [40]. Those that had been fed noni juice performed better in a Morris water maze (MWM) test following chronic restraint stress (CRS). Immunohistochemical analysis revealed that noni juice prevented stress-induced reduction in blood vessel density in the dentate gyrus of the hippocampus, but the underlying mechanism of ac-

tion for this was not elucidated. Even so, CRS increases FAAH activity and lowers AEA concentrations in the amygdalas of C57/Bl6 mice, as well as causes changes in amygdalar structure and increases anxiety-like behavior. But these changes are absent in FAAH deficient mice [41]. Further, testing with MAGL knockout mice in hippocampus-dependent learning paradigms indicate that 2-AG signaling is important for learning and memory [42]. Therefore, the inhibition of FAAH and MAGL by noni juice may also be responsible for improved MWM performance following CRS.

In our study, DAA inhibited FAAH activity modestly at 28.26% ± 4.61%. Other compounds may also have contributed to the activity of noni juice in our assays. Quercetin is reported to be a weak FAAH inhibitor, although kaempferol is reportedly more active [43]. Both of these compounds are in noni fruit and inhibit 5- and 15-lipoxygenases, with quercetin also weakly inhibiting cyclooxygenase-2 (COX-2) [44]. It is worth noting that COX-2 and lipoxygenases degrade AEA and 2-AG [45]. Noni fruit juice inhibited these enzymes *in vitro* and dramatically reduced the expression of COX-2 in neonatal foals, thereby revealing another set of pathways by which noni juice may influence endocannabinoid levels [46] [47]. An extract from noni fruit significantly reduced time-to-recovery following epileptic seizures in Wistar albino rats, with accompanying restoration of serotonin, dopamine and noradrenaline levels in the forebrain [48]. Similar anti-epileptic effects have been reported for cannabidiol, a known FAAH inhibitor, in human clinical trials [49] [50]. However, no such phytocannabinoid compounds occur in any part of the noni plant. Further, cannabidiol is reported to be an ineffective MAGL inhibitor [51]. Therefore, the phytochemical constituents in noni juice modulate endocannabinoid levels in a different manner with dual FAAH/MAGL inhibition. Noni fruit juice is a source of polyphenols and contains many other biologically active compounds [52]. So, any number of these may contribute to FAAH and MAGL inhibition, including the lignans [53]. Therefore, additional phytochemical studies are needed to determine which compounds in noni fruit are responsible for inhibiting endocannabinoid hydrolysis enzymes.

4. Conclusion

The results of this study provide another possible explanation as to why noni juice has been observed to have such a broad range of therapeutic effects. The ability of noni juice to reduce FAAH and MAGL activity *in vitro* indicates the possibility that ingesting it may subsequently elevate AEA and 2-AG levels or prolong their interactions with CB1, CB2, and orphan G-protein receptors. The increased opportunity for receptor agonism by these endocannabinoids elicits physiological responses that have also occurred with repeated daily noni juice consumption. The presence of phytochemicals with FAAH and MAGL inhibitory potential lends further credence to the hypothesis that noni juice promotes health and wellbeing by interacting with the body's ECS. However, further *in vi-*

tro research should be conducted to confirm this.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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