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Noni Juice and Hydrolyzed Fish Collagen Supplement Improves Skin Elasticity

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Abstract: *Morinda citrifolia*, more commonly known as noni, is a tropical tree with fruit that has a wide variety of traditional uses and biological effects. It had been used for the maintenance of skin health by Pacific Islanders and has been found to promote collagen deposition in vivo. Oral ingestion of hydrolyzed collagen has also been shown to improve skin quality. A 21-day human intervention study was conducted to evaluate a dietary supplement containing a combination of noni fruit juice and hydrolyzed marine collagen, as well as other ingredients, on skin viscoelastic properties in healthy Japanese adults. Daily ingestion of the supplement significantly improved net elasticity and biological elasticity measurements of the cheek. This also accompanied a trend for lowered skin autofluorescence, a measurement of skin glycation. The results indicate that the combination of noni fruit juice and hydrolyzed collagen improved skin biomechanical properties through enhanced collagen and elastin deposition in the skin, reduced skin glycation and improved skin hydration, possibly from increased hyaluronic acid concentration. Noni fruit juice also effectively scavenged cumene hydroperoxide in vitro. The positive effects on skin quality are likely due, in part, to the antioxidant and antiglycative properties of the supplement, as well as its ability to induce fibroblast proliferation and influence extracellular matrix protein gene expression.

Keywords: *Morinda citrifolia*, Noni, Hydrolyzed Marine Collagen, Skin Elasticity, Collagen, Elastin

1. Introduction

The skin is a major protective organ of the body, providing a barrier to the environment. It also performs many other functions which are necessary for the maintenance of life. The skin is composed of multiple layers, each with a unique structure and function. The dermis is the middle layer of the skin, lying below the epidermis. Collagen is a major component of the dermis, providing resistance to mechanical stress and deformation. The dermis also contains elastin that allows the skin to be stretched without being damaged. Collagen and elastin are synthesized by fibroblasts, cells responsible for producing the extracellular matrix of the dermis. The proper function of all these components is essential for maintaining skin health.

Morinda citrifolia, commonly known as noni, is a tropical fruit bearing tree that has a long history of food use [1]. The fruit is an ovoid syncarp, which the tree produces throughout the year, Figure 1. While sailing with Captain James Cook in 1769, Sydney Parkinson recorded that Tahitians ate noni fruit [2]. This was likely the first written description of its use as a food. Other naturalists have recorded similar observations since that time. Rarotongans frequently ate the fruit, while the Burmese prepared curries with it [3, 4]. The Aborigines of northern Australia consumed noni fruit during the cool-dry season [5, 6]. Tahitians wrapped fish in noni leaves for baking to enhance the flavor [7]. Noni leaves were also included in meals in Java and Thailand [8].

Prior to the arrival of Europeans, noni was the most important and widely used medicinal plant among Polynesian people [9]. In the past two decades, noni juice has become a globally popular health supplement. In more than 80 nations, over 106 million liters of noni juice have been consumed [10]. It was the first fruit juice approved as a safe novel food after the passage of the European Union's 1997 novel food regulations [11]. One commercial source of noni juice was also approved by the Chinese government as a safe new food

resource and was granted status as a functional food that can enhance immunity [12].

Noni fruit was used in traditional remedies for inflammation, abscesses, angina, diabetes, ranula, abdominal fibromas and scorpionfish stings [13, 14]. In French Polynesia, it was used to treat osteoarthritis, rheumatism, backache, joint problems and hemorrhoids [15]. European consumers of Tahitian Noni Juice report that the most common health benefits are improved sleep, improved digestion, increased energy, improved well-being, reduction of pain, fewer infections, and reductions in allergy and asthma symptoms [16].

Traditionally, noni was frequently used to promote skin health [17]. Noni fruit juice promotes skin collagen synthesis in vivo, likely through increased expression of extracellular matrix protein (collagen I and III, laminin, and fibronectin) genes [18, 19]. It also increases fibroblast proliferation in vitro [20]. Further, noni juice inhibits the formation of advanced glycation end products (AGEs) in the skin [21].

Ingestion of hydrolyzed collagen was found to suppress the activity of matrix metalloproteinases (MMPs), while increasing type 1 collagen skin deposition in vivo [22]. This effect was also reported in a placebo-controlled clinical trial of hydrolyzed collagen where dermal collagen density increased by 8.83% and dermal collagen network fragmentation decreased by 31.2% [23].

Skin firmness and elasticity depend on the quality of dermal collagen and elastin networks [24]. As such, combined ingestion of noni fruit juice and hydrolyzed collagen peptides may have a positive influence on skin elasticity and other skin quality parameters. Therefore, an open-labelled pilot study was conducted to evaluate the effect of a noni juice and collagen dietary supplement on skin elasticity and AGE content of adult volunteers.

Figure 1. *Noni fruit and leaves in Tahiti. Immature and ripe fruit grow on the same branch.*

2. Materials and Methods

Ten adult volunteers (ages 38 to 49 years, 9 females and 1 male) from the Tokyo, Japan area were enrolled in this study. Participants were healthy, had no existing skin conditions that would interfere with measurements and were willing to comply with the study protocol and provide informed consent. The investigational product used in this pilot study was a dietary supplement, TeMana Noni+Collagen (Morinda, Inc., American Fork, Utah, USA). This product contains noni fruit juice, 10000 milligrams of hydrolyzed marine collagen peptides and other ingredients.

The participants were instructed to drink 1 bottle of investigational product every day for 21 days. Pre and post-trial skin elasticity was measured with the Cutometer dual MPA 580 (Courage+Khazaka, Cologne, Germany) using mode 1, with a probe (model CT580MP) aperture of 2 mm and 350 mbar negative pressure (suction). Immediate skin deformation (Ue), immediate skin retraction (Ur), and final skin deformation (Uf), all measured in millimeters, were used to calculate skin elasticity R values. Net elasticity (R5) is the ratio Ur/Ue, while biological elasticity (R7) is the ratio Ur/Uf [25]. Advanced glycation end product measurements were made with the TruAge mini-scanner (Morinda, Inc.). This scanner uses skin autofluorescence to measure AGE levels (score) and is based on clinically validated methods [26]. Both elasticity and AGE measurements were made on the left cheek at the intersection of the zygomatic and infraorbital regions.

Summary statistics, such as means and standard deviations, of pre and post-trial (before and after) measurements were calculated. Student's *t*-test was used to compare pre and post-trial mean values after a Shapiro-Wilk test revealed that the data are normally distributed [27, 28]. Pearson's product moment correlation coefficients were calculated to evaluate the relationships between changes in R5, R7, and AGE scores, followed by two-tailed calculations of their *t* distributions [29].

The ability of noni fruit juice to protect against hydroperoxide oxidation was evaluated in vitro. To accomplish this, noni fruit was collected from the island of Tahiti in French Polynesia. Individual fruit samples, representing four different sizes of ripe fruit, were mashed. The seeds were separated from fruit pulp with a wire strainer. The pulp was then centrifuged, with the supernatant (or juice) subsequently filtered through a 0.45 μm Teflon syringe filter. The filtered noni juice samples were tested in duplicate for lipid hydroperoxide scavenging activity in the cumene hydroperoxide assay. In this assay, cumene hydroperoxide oxidizes N-benzoyl leucomethylene blue (LMB) to methylene blue in the presence of hemoglobin. Methylene blue absorbs light at 660 nm. Lipid hydroperoxide scavengers will decrease absorbance at this wavelength by reacting with the cumene hydroperoxide.

N-benzoyl leucomethylene blue was obtained from TCI America (Portland, Oregon, USA). Cumene hydroperoxide, N, N-dimethyl formamide, hemoglobin (bovine), potassium hydroxide, potassium phosphate and Triton X-100 were purchased from Sigma-Aldrich (St. Louis, Missouri, USA). Ninety-two mL of hemoglobin reagent was prepared with a 0.05 M potassium phosphate buffer (pH 5.0) containing 1.5% (v/v) Triton X-100 and 5.5 mg bovine hemoglobin. To this was added 8 mL of 2.19 mM LMB in N, N-dimethyl formamide to create a LMB color reagent. A 0.0526 μM

cumene hydroperoxide standard was prepared in methanol. The assay was performed by combining 10 µL of the cumene hydroperoxide solution with 3 mL LMB color reagent, adding 21 µL of noni juice or water blank, incubating the mixture for 10 minutes at room temperature, then reading its absorbance at 600 nm with a spectrophotometer. Unreacted hydroperoxide concentration was calculated from absorbance at this wavelength, against a cumene hydroperoxide generated standard curve. Noni juice results were compared against the blank to calculate the scavenging activity, expressed as scavenging percentage.

3. Results and Discussion

Daily ingestion of noni fruit juice and collagen had a positive influence on skin quality. At the beginning of the trial, the average cheek AGE score was 142 arbitrary units (AU). As the cheek was the site measured and not the volar forearm, there is no direct correlation to population studies which allows us to calculate the AGE associated age (ASA). But the initial facial AGE measurements of all but two participants were actually lower than those expected for the volar forearm for people in the 38 to 49 yr. age range. This demonstrates that this group was generally healthy, with lower than expected AGE accumulation. After three weeks of consuming the investigational product, there was a trend of further improvement, with the average AGE score dropping to 123 AU. Additionally, the AGE scores of all participants had decreased to values much lower than expected for their age range. These results are consistent with previous findings and indicate that the antiglycative effects of noni juice ingestion occur in facial skin, not just in the forearm.

Skin elasticity improved during the trial. The initial average, ± standard deviation (SD), net elasticity (R5) was 0.53 ± 0.05, Figure 2. This changed to 0.70 ± 0.08 ($p < 0.001$), which is a 32% increase. Biological elasticity (R7) also improved significantly during the course of the trial from a mean ± SD of 0.37 ± 0.05 to 0.45 ± 0.04, Figure 3. This is a 21.6% increase ($p < 0.001$). It is important to note that for every participant, R5 and R7 values increased after three weeks.

No significant correlation was found between the changes in R5 and R7 values. This suggests that the underlying biochemical changes that influence these values may be independent. No significant correlation was observed between changes in R5 and AGE scores. As discussed above, this group of volunteers already had lower than expected AGE scores. This may account for the weak association between R5 increase and AGE decrease. However, there was a strong linear association between improved biological elasticity (R7) and the lowered AGE values ($r = 0.73$, $p < 0.05$).

Net elasticity is reported to be the most useful parameter for quantifying the progress of skin aging. This is because it is independent of skin thickness, and immediate skin retraction (Ur) tends to decrease as our age increases [30]. R5 values represent the elasticity of the extracellular matrix fibers, such as those composed of collagen and elastin, and do not account for the influence of hydration status [31]. As such, the increased R5 values of every person in the trial reveal that collagen and elastin deposition was enhanced with ingestion of Noni+Collagen.

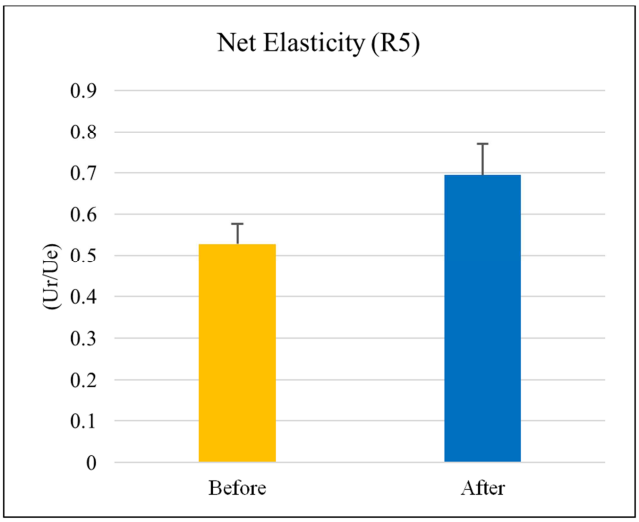

Figure 2. *The effect of TeMana Noni+Collagen on net skin elasticity (R5) of the cheek. The increase in mean R5 was significant ($p < 0.001$) after 3 weeks of daily ingestion.*

Biological elasticity (R7) is a viscoelastic measurement that accounts for both elastic fiber and fluid (or water) responses to mechanical stress [25]. Skin hydration state is positively correlated with elasticity [32]. Hyaluronic acid binds water in the skin, thereby maintaining better hydration which subsequently improves the skin's viscoelastic response [33]. Therefore, the increased R7 values suggest that TeMana Noni+Collagen elevated hyaluronic acid content of the skin. Such an effect is not surprising since asperulosidic acid, found in noni fruit juice, inhibits hyaluronidase activity after β-glucosidase treatment [34, 35]. Lower hyaluronidase activity should increase hyaluronic acid concentration.

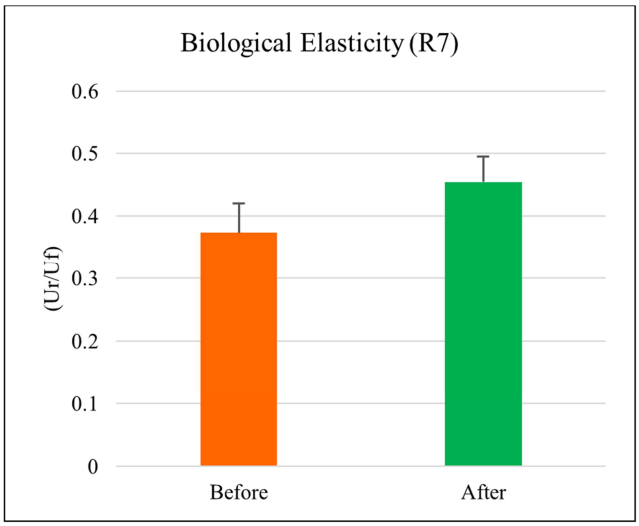

Figure 3. *The effect of TeMana Noni+Collagen on biological elasticity (R7) of cheek skin. The increase in mean R7 was significant ($p < 0.001$) after 3 weeks of daily ingestion.*

AGE-associated skin autofluorescence increases, but skin elasticity decreases, with advancing age [36, 37]. Negative correlations exist with age and R5 and R7 measurements at various locations of the body, with facial R7 values demonstrating the most significant declines [38]. The reason for this is that AGEs decrease skin elasticity and collagen fibril organization [39]. The "classical" pathway of AGE formation involves the initial glycation of protein by reducing sugars, where the carbonyl group is subject to nucleophilic attack by the amino group. This produces a Schiff's base that undergoes eventual Amadori rearrangement. Amadori products are susceptible to involvement in a variety of additional reactions which produce AGEs and other AGE precursors [40, 41]. Where collagen is the targeted protein, AGE formation involves the glycation of the lysine residue [42]. Collagen-AGE and elastin-AGE compounds are capable of aberrant crosslinking with other proteins, thereby altering the biomechanical properties of collagen-elastin fibers [43]. This leads to the stiffening of tissues [44].

The results of the cumene hydroperoxide scavenging assay reveal that noni juice has remarkable in vitro antioxidant activity, Figure 4. All samples were able to neutralize more than 99% of the available cumene hydroperoxide.

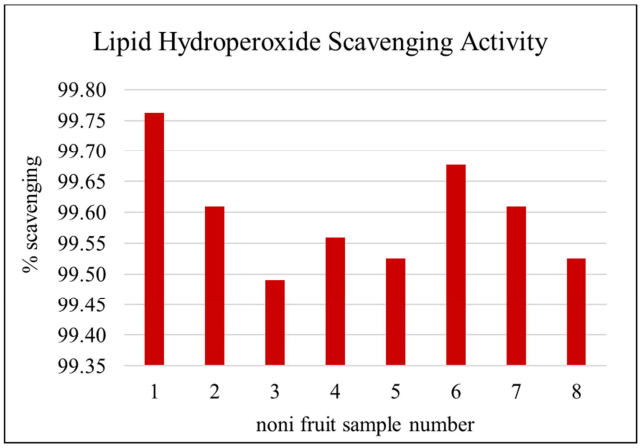

Figure 4. *The effect of noni fruit juice on LMB oxidation by cumene hydroperoxide. All noni fruit samples displayed significant lipid hydroperoxide scavenging activity, >99%.*

As mentioned briefly above, noni juice ingestion inhibits AGE formation in the skin [21]. In vitro studies provide some insight into how noni fruit may be helpful in controlling the formation of AGEs and reducing their adverse effects. For example, an extract from noni fruit collected in French Polynesia inhibited the formation of glucose-collagen AGEs and exhibited AGE-crosslink breaking activity [45]. Breakage of collagen-AGE and elastin-AGE crosslinks will certainly restore some of the elastic biomechanical properties of the skin. The extract also prevented AGE-induced reactive oxygen species (ROS) generation in human umbilical vein endothelial cells [46]. Elevated ROS are capable of inducing further AGE formation [47]. Noni juice has excellent antioxidant properties and effectively controls ROS generation within the body [48]. Consequently, ROS-induced AGE formation is limited.

The antioxidant properties of noni juice may also prevent direct oxidative damage to collagen and elastin fibers. The skin is frequently exposed to ultraviolet (UV) light. UV-exposed collagen undergoes cleavage of peptide bonds and scission of its triple helix. This is due to the generation of ROS from the decomposition of hydrogen peroxide, which is inhibited by radical scavengers [49]. Elastin is also susceptible to damage by UV-generated ROS in the skin [50]. Noni juice induces superoxide dismutase and catalase activities which, in turn, lower available ROS [51]. These are just two of several mechanisms by which noni juice impacts skin quality.

In this study, we demonstrated that noni fruit juice may directly scavenge hydroperoxides. This is yet another antioxidant mechanism that is very relevant to maintaining healthy collagen, as well as limiting further potential ROS generation. Hydroperoxides may form in type 1 collagen that is exposed to oxidative stress, such as that generated by Fenton reactions [52]. Proteins that are exposed to peroxides are more susceptible to proteolytic action, which may lead to increased tissue destruction [53]. The hydroperoxide scavenging potential of noni juice protects against this type of damage.

The results of the trial reflect the utility of combining noni fruit juice and hydrolyzed marine collagen. As noted in the introduction, noni fruit juice promotes collagen synthesis. This possibly involves the proliferation of fibroblasts, which are responsible for collagen and elastin synthesis, as well as the induction of extracellular matrix (ECM) protein gene expression [19, 20]. These fibroblasts, with their increased ECM gene expression levels, are able to improve collagen and elastin synthesis from amino acids made available by the ingestion of hydrolyzed marine collagen.

4. Conclusion

Daily ingestion of TeMana Noni+Collagen significantly improved net elasticity and biological elasticity measurements of the cheek and appeared to mitigate AGE accumulation. These results suggest that a combination of noni fruit juice, hydrolyzed collagen peptides and other ingredients, such as artichoke extract, are useful for maintaining or improving skin biomechanical properties, especially elasticity. These effects occurred within three weeks. It is expected that longer use of the supplement will result in further increases in skin collagen and elastin quality and should serve as a useful component of any antiaging regimen.

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