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Morinda citrifolia (Noni): A literature review and recent advances in Noni research¹

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ABSTRACT

Morinda citrifolia L (Noni) has been used in folk remedies by Polynesians for over 2000 years, and is reported to have a broad range of therapeutic effects, including antibacterial, antiviral, antifungal, antitumor, antihelmin, analgesic, hypotensive, anti-inflammatory, and immune enhancing effects. In order to reveal the nutritional and medicinal value of the Noni plant, and to summarize scientific evidence that supports the Polynesians' claim, a literature review and recent advances in Noni research is given below.

INTRODUCTION

Herbal and natural products of folk medicine have been used for centuries in every culture throughout the world. Scientists and medical professionals have shown increased interest in this field as they recognize the true health benefits of these remedies. "Let food be your medicine and let medicine be your food" was advised by the father of medicine, Hippocrates, over two millennia ago. It's still true today that "you are what you eat." Folk medicine in different cultures has a long history of ancestors creating primitive medicines during their struggles against natural calamity and disease. Tea is one of the first Chinese herbs mentioned in an-

cient literature. Tea supposedly originated in China, and was discovered to be an antidote for poisonous herbs by a great herbalist, Shen Nong, about 4700 years ago, when tasting unknown herbs to find plants with medicinal value. He is generally known as the "God of Agriculture" in China for his great achievements as both a pioneer and a leader in farming. His findings were compiled in a book in the Dong-Han dynasty (25-220 AD) called "Shen Nong's Herbs," which is still a classic herbal book today. While searching for food, the ancient found that some foods had specific properties of relieving or eliminating certain diseases, and maintaining good health. It was the beginning of herbal medicine^[1]. The same story occurred in Polynesia. Among the medicinal plants discovered by the ancestors of Polynesians, *Morinda citrifolia* L (Noni) is one of the traditional folk medicinal plants that has been used for over 2000 years in Polynesia^[2]. It has been reported to have a broad range of therapeutic and nutritional value^[3].

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LITERATURE REVIEW AND RECENT ADVANCES IN NONI RESEARCH

An edible and medicinal tropic plant —*Morinda citrifolia* L (Noni) The ancestors of Polynesians are believed to have brought many plants with them, as food and medicine, when they migrated from Southeast Asia 2000 years ago^[4]. Of the 12 most common medicinal plants they brought, Noni was the second most popular plant used in herbal remedies to treat various common diseases and to maintain overall good health^[5]. Noni is the common name for *Morinda citrifolia* L and is also called *Indian Mulberry*, *Ba Ji Tian*, *Nono* or *Nonu*, *Cheese Fruit*, and *Nhau* in various cultures throughout the world. It has been reported to have a broad range of health benefits for cancer, infection, arthritis, diabetes, asthma, hypertension, and pain^[6]. The Polynesians utilized the whole Noni plant in their medicinal remedies and dye for some of their traditional clothes. The roots, stems, bark, leaves, flowers, and fruits of the Noni plant are all involved in various combinations in almost 40 known and recorded herbal remedies^[7]. Additionally, the roots were used to produce a yellow or red dye for tapa cloths and fala (mats), while the fruit was eaten for health and food. There are numerous Polynesian stories of heroes and heroines that used Noni to survive from famine. There is one tale of Kamapua'a, the pig god, who loved Pele, the volcano goddess. He taunted Pele with a chant, "I have seen the woman gathering Noni /scratching Noni/pounding Noni." Supposedly, the chant referred to Pele's eyes becoming red, and she became so angry that she plunged into battle with him. A Tongan myth tells of the god Maui being restored to life by having Noni leaves placed on his body^[8].

Morinda citrifolia fruit has a long history of use as a food in tropical regions throughout the world. Written documentation of the consumption of this fruit as a food source precedes the twentieth century. Captain James Cook of the British Navy noted in the late 1700's that the fruit was eaten in Tahiti^[9]. An 1866 publication in London explained that *Morinda citrifolia* fruit was consumed as a food in the Fiji Islands^[10]. Later publications describe the use of this fruit as a food throughout the Pacific Islands, Southeast Asia, Australia, and India. In Rorotonga "the fruit was often eaten by the natives"^[9]. Australian Aborigines were reported to be "very fond" of the fruit^[11]. In Samoa, Noni fruit was common fare, and in Burma, the fruit was cooked in curries or eaten raw with salt^[12]. In 1943, Merrill de-

scribed *Morinda citrifolia* L as an edible plant in a technical manual of edible and poisonous plants of the Pacific Islands, in which the leaves and fruits could be used as emergency food^[13]. Abbott also reported that Noni had been used as a food, drink, medicine, and colorful dye^[14]. The medicinal history and accumulated scientific studies, to date, have revealed and confirmed the Polynesian's claim of the health benefits of Noni. The medical knowledge and pharmacopoeia of the Polynesians is now believed to have been fairly complex and modern scientific and medical communities are beginning to study the plants compiled from this knowledge base.

The Noni plant is a small evergreen tree found growing in open coastal regions at sea level and in forest areas up to about 1300 feet above sea level. The plant is often found growing along lava flows. It's identifiable by its straight trunk, large, bright green and elliptical leaves, white tubular flowers, and its distinctive, ovoid, "grenade-like" yellow fruit. The fruit can grow in size up to 12 cm or more and has a lumpy surface covered by polygonal-shaped sections. The seeds, which are triangular shaped and reddish brown, have an air sac attached at one end, which makes the seeds buoyant. This could explain, in part, the wide distribution of the plant throughout the Polynesian islands. The mature Noni fruit has a foul taste and odor^[15]. *Morinda citrifolia* L is not considered to be at risk in the wild.

Medicinal use of Noni plant The Polynesians utilized the whole Noni plant in various combinations for herbal remedies. The fruit juice is in high demand in alternative medicine for different kinds of illnesses such as arthritis, diabetes, high blood pressure, muscle aches and pains, menstrual difficulties, headaches, heart disease, AIDS, cancers, gastric ulcers, sprains, mental depression, senility, poor digestion, atherosclerosis, blood vessel problems, and drug addiction. Scientific evidence of the benefits of the Noni fruit Juice is limited but there is some anecdotal evidence for successful treatment of colds and influenza^[16]. Allen reported some information on the ethnobotanical properties of Noni. He said that the fruit is used as deobstruent and emmenagogue. This is one of the earliest articles on the medicinal benefits of Noni^[17]. Isabel Abbott, a former botanical chemist at the University of Hawaii, stated that, "People are crazy about this plant. They use it for diabetes, high blood pressure, cancer, and many other illnesses"^[18]. Bushnell reported that Noni was a traditional remedy used to treat broken bones,

deep cuts, bruises, sores, and wounds^[19]. Morton gave numerous references for medicinal uses of Noni^[12]. In addition, Polynesians are reported to have successfully used Noni to treat breast cancer and eye problems. Joseph Betz, a research chemist in the FDA's Division of Natural Products, Center for Food Safety and Applied Nutrition, stated that "*Morinda citrifolia* has been tested for a number of biological activities in animal and anti-microbial studies." He reports that the dried fruit has smooth muscle stimulatory activity and histaminergic effects^[20].

Major components A number of major components have been identified in the Noni plant such as scopoletin, octoanoic acid, potassium, vitamin C, terpenoids, alkaloids, anthraquinones (such as nordamnacanthal, morindone, rubiadin, and rubiadin-1-methyl ether, anthraquinone glycoside), β -sitosterol, carotene, vitamin A, flavone glycosides, linoleic acid, Alizarin, amino acids, acubin, *L*-asperuloside, caproic acid, caprylic acid, ursolic acid, rutin, and a putative proxeronine^[21-32].

A research group led by Chi-Tang Ho at Rutgers University in the US is searching for new novel compounds in the Noni plant. They have successfully identified several new flavonol glycosides, an iridoid glycoside from the Noni leaves, a trisaccharide fatty acid ester, rutin, and an asperulosidic acid from the fruit. Two novel glycosides and a new unusual iridoid named citrifolinolide have been shown to have an inhibiting effect on AP-1 transactivation and cell transformation in the mouse epidermal JB6 cell line^[33-38]. James Duke listed 23 different phytochemicals found in Noni as well as 5 vitamins and 3 minerals in an authoritative CRC handbook^[39].

Xeronine system Retired biochemist, Ralph Heinicke, states that the Noni fruit contains a natural precursor for Xeronine that he named Proxeronine. Proxeronine is converted to the alkaloid, Xeronine, in the body by an enzyme he calls Proxeroninase^[32]. His hypothesis is that Xeronine is able to modify the molecular structure of proteins. Thus Xeronine has a wide range of biological activities. When a protein such as an enzyme, receptor, or signal transducer is not in the appropriate conformation, it will not work properly. Xeronine will interact with the protein and make it fold into its proper conformation. The result is a properly functioning protein. Whenever a problem arises in the cell due to a protein structural problem, Xeronine's presence would be beneficial. His hypotheses may explain

why TAHITIAN NONI® JUICE (TNJ) can help in many health problems in different ways. He has obtained several patents for Xeronine. He states that the active ingredient in many of the pharmacologically active enzymes and in many of the effective folklore drugs is xeronine. This alkaloid is a critical normal metabolic coregulator. The ailments that he believes to be helped by Noni include high blood pressure, menstrual cramps, arthritis, gastric ulcers, sprains, injuries, mental depression, senility, poor digestion, drug addiction, and pain. "I have devoted much of my life to the study of this unique substance that I have named 'Xeronine'. I am convinced of the tremendous benefits achieved by furnishing the body with a proper supply of this material"^[40].

Biological activities of Noni products

Antibacterial activity Acubin, *L*-asperuloside, and alizarin in the Noni fruit, as well as some other anthraquinone compounds in Noni roots, are all proven antibacterial agents. These compounds have been shown to fight against infectious bacteria strains such as *Pseudomonas aeruginosa*, *Proteus morgani*, *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Salmonella*, and *Shigella*. These antibacterial elements within Noni are responsible for the treatment of skin infections, colds, fevers, and other bacterial-caused health problems^[41]. Bushnell reported on the antibacterial properties of some plants found in Hawaii, including Noni. He further reported that Noni was traditionally used to treat broken bones, deep cuts, bruises, sores and wounds. Extracts from the ripe noni fruit exhibited moderate antibacterial properties against *Ps aeruginosa*, *M pyrogenes* and *E coli*, and were also shown to have moderate antibacterial properties against *Salmonella typhosa*, *Salmonella montevideo*, *Salmonella schottmuelleri*, *Shigella paradys*, BH and *Shigella paradys*, III-Z^[19]. Leach demonstrated that acetone extracts obtained from *Cycas circinalis*, *Morinda citrifolia*, *Bridelia penangiana*, *Tridax Procumbens*, *Hibiscus tiliaceus*, and *Hypericum papuanun* showed antibacterial activity. The widespread medicinal use of these plants would suggest that they do contain pharmacologically active substances and alternative methods of extraction and screening should be utilized to find the major bioactive component in the plants for the purpose of new drug development^[42]. Locher reported that selected plants including *Morinda citrifolia* have a history of use in Polynesian traditional medicine for the treatments of infectious disease^[43]. These plants were

investigated for anti-viral, anti-fungal, and anti-bacterial activity *in vitro*. Their study using biological assays *in vitro* confirmed that some of the ethnobotanical reports of Hawaiian medicinal plants have curative properties against infectious diseases.

Recently, Duncan demonstrated that scopoletin, a health promotor in Noni, inhibits the activity of *E coli*, commonly associated with recent outbreaks resulting in hundreds of serious infections and even death. Noni also helps stomach ulcer through inhibition of the bacteria *H pylori*^[44].

Antiviral activity Umezawa and coworkers found a compound isolated from Noni roots named 1-methoxy-2-formyl-3-hydroxyanthraquinone suppressed the cytopathic effect of HIV infected MT-4 cells, without inhibiting cell growth^[45].

Anti-tubercular effects In the International Chemical Congress of the Pacific Basin Societies Meeting in Honolulu, Saludes and colleagues from the Philippines, reported that Noni has been found to kill *Mycobacterium tuberculosis*. A concentration of extracts from Noni leaves killed 89 percent of the bacteria in a test tube, almost as effective as a leading anti-TB drug, Rifampicin, which has an inhibition rate of 97 percent at the same concentration. Although there had been anecdotal reports of the native use of Noni in Polynesia as a medicine against tuberculosis, this is the first report demonstrating the antimycobacterial potential of compounds obtained from the Noni leaf. "I hope that pharmaceutical companies will pay attention to this research and explore the Noni plant as a potential source of drugs," said Saludes in Manila^[46,47].

Antitumor activity In 1992, Hirazumi, a researcher at the University of Hawaii, reported anticancer activity from the alcohol-precipitate of Noni fruit juice (noni-ppt) on lung cancer in C57 Bl/6 mice at the 83th Annual Meeting of American Association for Cancer Research. The noni-ppt was shown to significantly prolong the life of mice up to 75 % with implanted Lewis lung carcinoma compared with the control group^[48]. It was concluded that the noni-ppt seems to suppress tumor growth indirectly by stimulating the immune system^[49]. Improved survival time and curative effects occurred when noni-ppt was combined with sub-optimal doses of the standard chemotherapeutic agents such as adriamycin (Adria), cisplatin (CDDP), 5-fluorouracil (5-FU), and vincristine (VCR), suggesting important clinical applications of noni-ppt as a supplemental agent in cancer treatment^[50]. These results indicate that noni-

ppt may enhance the therapeutic effect of anticancer drugs. Therefore it may be of benefit to cancer patients by enabling them to use lower doses of anticancer drugs to achieve the same or even better results.

Recent unpublished study completed by Dr Wang and coworkers demonstrate that a cytotoxic effect of TNJ on cultured leukemia cell line at various concentration. The cytotoxicity of TNJ on cultured cancer cells showed a dose-dependent manner by inducing cancer cell necrosis at high doses and apoptosis at lower doses. The synergistic effects of TNJ with known anticancer drugs have been found. At a sub-optimum dose, both prednisolone and TNJ could induce apoptosis. When the dose of prednisolone was fixed, and the dose of TNJ increased, apoptotic cells were significantly increased. Therefore, TNJ is able to enhance the efficacy of anticancer drugs such as prednisolone. When a single dose of Taxol induced a lower percentage of apoptosis in leukemia cells, TNJ enhanced the rate of apoptosis to 100 %. This data indicates that TNJ is able to enhance the therapeutic effect of anticancer drugs such as Taxol. This finding may be significant for the combination of anticancer drugs with TNJ. It may allow one to decrease the dose of synthetic anticancer drugs, increase the tolerance of patients to the toxicity of anticancer drugs, and increase immune function. This creates a new method in treating cancer patients.

In 1993, Hiramatsu and colleagues reported in Cancer Letters the effects of over 500 extracts from tropical plants on the K-Ras-NRK cells. Damnacanthal, isolated from Noni roots, is an inhibitor of Ras function. The *ras* oncogene is believed to be associated with the signal transduction in several human cancers such as lung, colon, pancreas, and leukemia^[51].

Hiwasa and coworkers demonstrated that damnacanthal, an anthraquinone compound, isolated from the Noni root, was reported to have a potent inhibitory activity towards tyrosine kinases such as Lck, Src, Lyn, and EGF receptors. In his study, he examined the effects of damnacanthal on ultraviolet ray-induced apoptosis in ultraviolet-resistant human UVR-1 cells. Consequently, the ultraviolet light induced a concurrent increase in both phosphorylated extracellular signal-regulated kinases and stress-activated protein kinases. After pretreatment with damnacanthal, there was a stimulatory effect on ultraviolet-induced apoptosis^[52].

Dong reported that two glycosides extracted from

noni-ppt were effective in inhibiting cell transformation induced by TPA or EGF in the mouse epidermal JB6 cell line. The inhibition was found to be associated with the inhibitory effects of these compounds on AP-1 activity. The compounds also blocked phosphorylation of c-Jun, a substrate of JNKs, suggesting that JNKs are a critical target for the compounds in mediating AP-1 activity and cell transformation^[36,53].

Anthelmintic activity An ethanol extract of the tender Noni leaves induced paralysis and death of the human parasitic nematode worm, *Ascaris Lumbricoides*, within a day^[54]. A botanist via Morton reported that Noni has been used in the Philippines and Hawaii as an effective insecticide^[12].

Analgesic activity Joseph Betz reported that the Noni fruits possesses analgesic and tranquilizing activities^[20]. A French research team led by Younos, tested the analgesic and sedative effects of extracts from the *Morinda citrifolia* plant. The extract did “show a significant, dose-related, central analgesic activity in the treated mice.” They stated that “these findings validate the traditional analgesic properties of this plant.” The analgesic efficacy of the Noni extract is 75 % as strong as morphine, yet non-addictive and side effect free^[55].

In cooperation between University of Illinois College of Medicine and Henan Medical University, Wang and Fu examined the analgesic properties of TNJ in animal models. TNJ was tested for its analgesic properties by the “twisted method” animal model. The “twisted method” is a simple and reliable method to determine the analgesic effect of TNJ. Mice were divided into four groups: control group, 5 %, 10 %, and 20 % TNJ groups. TNJ was supplied in the drinking water for 10 d. The control group was only supplied with drinking water. A chemical named antimony potassium tartrate was administrated by ip which produces twisting due to pain. The number of twists within the first 15 min after injection is recorded to indicate the degree of pain. The number of twists was compared between the control and TNJ groups, using Student's *T*-test. There was an 82.30 %, 74.53 %, and 64.29 % decrease in the number of twists in the 20 %, 10 %, and 5 % TNJ groups, compared to the control. Clearly, the analgesic effect of TNJ in mice showed a dose-dependent manner. The analgesic effects of each TNJ group are statistically significant compared with that in the control group ($P < 0.01$, respectively). Additional unpublished research on the analgesic effect of TNJ has also been examined in female SD rats. Twelve fe-

male SD rats were divided into three groups, four in each: control, 20 % placebo, 10 % TNJ, and 20 % TNJ. Animals were supplied with placebo or TNJ in drinking water for seven days. On the last day, a hot plate assay was performed on individual animals from each group. The hot plate assay is a classical test to examine the animal's response to heat (55 °C). The response of the animals to the hot plate includes two phases, acute and lasting. The first sign of discomfort is that the rat sits up on its hind legs and laps its two front feet with its mouth. When the pain is too great to be borne by the back paws, the rat kicks its legs, dances, and tries to jump out of the beaker. The time of the acute and lasting phase was recorded, respectively. Compared with the placebo group, the toleration time in the first phase was delayed 276 % in the 10 % TNJ group and 419 % in the 20 % TNJ group. The toleration time of the second phase was delayed 162 % in the 10 % TNJ group and 212 % in the 20 % TNJ group, respectively. Clearly, the data from this experiment indicated that TNJ was able to make the animals tolerate more pain. Compared with the placebo group, the length of toleration time was dose-dependent.

Hypotensive activity Dang Van Ho of Vietnam demonstrated that a total extract of the Noni roots has a hypotensive effect^[56]. Moorthy and coworkers found that an ethanol extract of the Noni roots lowered the blood pressure in an anesthetized dog^[26]. Youngken's research team determined that a hot water extract of Noni roots lowered the blood pressure of an anesthetized dog^[57,58]. A Hawaiian physician reported that Noni fruit juice had a diuretic effect^[59].

Immunological activity Asahina found that an alcohol extract of Noni fruit at various concentrations inhibited the production of tumor necrosis factor-alpha (TNF- α), which is an endogenous tumor promotor. Therefore the alcohol extract may inhibit the tumor promoting effect of TNF- α ^[60]. Hirazumi found that noni-ppt contains a polysaccharide-rich substance that inhibited tumor growth. It did not exert significant cytotoxic effects in adapted cultures of lung cancer cells, but could activate peritoneal exudate cells to impart profound toxicity when co-cultured with the tumor cells. This suggested the possibility that noni-ppt may suppress tumor growth through activation of the host immune system. Noni-ppt was also capable of stimulating the release of several mediators from murine effector cells, including TNF- α , interleukin-1beta (IL-1 β), IL-10, IL-12, interferon-gamma (IFN- γ) and nitric ox-

ide (NO)^[50]. Hokama separated ripe noni fruit juice into 50 % aqueous alcohol and precipitated fractions that stimulated the BALB/c thymus cells in the [³H]thymidine analysis. It is suggested that inhibition of Lewis lung tumors in mice, in part, may have been due to the stimulation of the T-cell immune response^[60].

Wang and coworker in University of Illinois College of Medicine observed that the thymus in animals treated with TNJ was enlarged. The wet weight of the thymus was 1.7 times that of control animals at the seventh day after drinking 10 % TNJ in drinking water. The thymus is an important immune organ in the body, which generates T cells, involved in the aging process and cellular immune functions. TNJ may enhance immune function by stimulating thymus growth, and thus affecting anti-aging and anticancer activities, and protecting people from other degenerative disease.

Mental health and improved high frequency hearing A small human clinical trial of the effect of TNJ on auditory function and quality of life in the patients with decreased bone mineral density and auditory function has been conducted in UIC College of Medicine, Rockford, IL. This study showed that TNJ provided a positive benefit on mental health and improved high frequency hearing. The data suggests that increased amounts or extended duration of TNJ intake may be required to affect this disorder^[61].

Pharmacokinetic study of Noni Unpublished research on the pharmacokinetics of Noni was carried out at the UIC laboratory in Rockford, IL by Dr WANG. The frequency of consumption and the daily dose of TNJ are the questions asked most frequently by Noni juice users. The pharmacokinetics of Noni was studied in female SD rats after oral administration at a dose of 1 mL Noni puree per 100 g body weight. A known major component (scopoletin) in Noni was chosen as a marker and monitored in the plasma and in different organs over time by HPLC analysis in the cooperation with R & D Department of Morinda, Inc. The pharmacokinetics of scopoletin in Noni puree was calculated as follows: the plasma concentration reached a peak at 2 h after oral administration of Noni. The peak level of scopoletin decreased to 50 % in 4 h. Only 12 % and 2 % of the scopoletin was left in the plasma at 12 and 24 h, respectively. Absorption was rapid, with 50 % peak concentration reached in only 30 min. In order to maintain a higher blood level of scopoletin, TNJ should be taken every 2 to 4 h. For overall health maintenance, TNJ should be taken in one-ounce servings every 12 h.

The results demonstrate that the frequency of drinking TNJ is more important than the amount. The concentration of scopoletin in various organs indicates that Noni is absorbed into different tissues approximately one hour after administration. The peak concentration in different tissues occurred at about 3 h, with a rapid decline. Interestingly, the scopoletin level in breast tissue was relatively higher than any other extra-GI tract tissue.

Allergenicity and toxicity tests of TNJ Morinda Inc, makers of TNJ, sponsored acute toxicology studies in rats to assess the acute toxicity of TNJ. Fifteen thousand mg/kg was administered via gavage. The animals were observed for 14 d following treatment. All animals survived and no adverse clinical signs were noted. No signs of gross toxicity were seen in the organs after necropsy^[62].

Two studies using guinea pigs were performed to assess the allergenic risk of TNJ. Both study designs included an induction phase and a rest period, followed by a challenge with TNJ. The first study involved two test groups of six animals each, a positive control group, and a negative control group. Following the challenge, the animals were observed for 24 h. No allergic reactions to TNJ were seen in this study^[63].

The second study involved forty-five guinea pigs. The study consisted of several test groups using various forms and concentrations of TNJ with accompanying negative control groups. The test groups were induced three times each week for two weeks. After thirty-two days of rest, all animals were challenged and were observed for symptoms of an allergic response. No positive allergic reactions were seen in any Noni group of the animals following the challenge^[64].

A 13-week oral toxicity study in rats was performed to further assess the systemic safety of TNJ. Eighty Sprague Dawley rats were allocated into four groups; a control group and three dose groups. The daily gavage doses included 0.4 mL/kg, 4 mL/kg, and 8 mL/kg. The animals were observed for adverse clinical signs, food consumption, and weight gain. Additionally, blood samples were drawn for hematology and clinical chemistry at the study conclusion. Further more, selective organ weights were measured and tissue samples of 55 organs were taken for microscopic examination. All groups showed no treatment related differences in body and organ weights, food consumption, clinical examinations, blood chemistry, hematological measurements, and histological tissue examination^[65].

Morinda, Inc. sponsored a second 13-week oral toxicity study of TNJ. This study covers higher doses than the previous 13-week study. Three dose groups were included in this study. The samples evaluated were a single strength TNJ, a 2.5 times concentrated TNJ, and a 4 times concentrated TNJ. The concentrated samples were used to reach a dosing equivalent of 50 mL/kg body weight and 80 mL/kg body weight. The protocol and measurements for the second 13-week study were the same as the first. The results of this study demonstrate that the No-Observable-Adverse-Effect-Level (NOAEL) was above 20 mL of 4 times concentrated TNJ/kg/day. This is equivalent to 80 mL TNJ/kg/day. Perspectively, this amount is 8% of the animal's body weight^[53].

No upper limit for safe consumption has yet been determined from these studies. The data indicates that TNJ may be safely consumed in amounts that are typical for fruit juice beverages, though the results of these studies only apply directly to Morinda TNJ. Additional ingredients and processing methods are different for other commercial noni fruit juice products.

The major ingredient in TNJ, Noni fruit, has been safely consumed in other parts of the world for several hundred years^[6-7,10,66-74]. TNJ is demonstrated to be safe for human consumption through extensive chemical, microbiological, and toxicological analysis and evaluation.

Statistical clinical survey Recently, Neil Solomon, formerly Maryland's first Secretary of Health and Mental Hygiene, finished a statistical clinical survey that offers a fairly accurate picture of Noni's medicinal benefits. He has written books on Noni juice and visited more than 50 doctors and health professionals whose patients previously used or are using Noni to treat different conditions. After reviewing the results of the more than 10 000 Noni juice users, he determined that Noni possesses a variety of efficacious medical properties that modern medicine should not ignore. Sixty-seven percent of 847 people with cancer experienced significant lessening of their symptoms. Ninety-one percent of patients who used Noni juice noticed an increase in energy levels. Seventy-two percent of overweight patient lost weight. Eighty-seven percent of those drinking Noni juice for high blood pressure experienced a significant drop in blood pressure. Nearly ninety percent of those with chronic pain experienced a significant decrease in pain. Eighty percent of arthritis sufferers reported a lessening of arthritic

symptoms. Eighty percent of the people with heart disease experienced a decrease of their symptoms. Eighty-three percent of patients with Type 1 and 2 diabetes experienced a noticeable change in their condition. Eighty-nine percent of the people experienced improved digestion. Eight-five percent of people with allergies experienced a decrease in their symptoms. Seventy-seven percent of people with depression experienced lessening of symptoms. Side effects among all participants were minimal or nonexistent. He summarized the data and wrote several pamphlets and books explaining his findings^[75-79]. He indicated that nearly all the data comes from individuals using TNJ marketed by Morinda, Inc.

CANCER PREVENTION STUDY OF TNJ

“To take medicine only when you are sick is like digging a well only when you are thirsty —is it not already too late?” (Chi Po, c 2500 BC). This proverb suggests that prevention is more important than treatment^[80,81].

Cancer is the second leading cause of death in the US. According to the American Cancer Society, 1500 people per day die from cancer in the United States. Fighting against cancer is a great task for the scientists engaged in this field. The etiology of most cases of human cancer remains unknown^[82]. Environmental carcinogen exposure accounts for more than 90 % of human cancer^[83]. Cigarette smoke is the number one high-risk environmental factor^[84]. Although some cancers are preventable, a means to prevent most cancers is not yet known. Seeking a natural way to prevent human cancer is an urgent task for cancer prevention investigators.

The studies of food, diet, and cancer indicate that lifestyle changes include eating more fruits and vegetables, and quitting smoking will benefit cancer prevention. “A new plate” for America (75 % vegetables, 25 % meat) appeared at the 2001 annual conference of the American Institute for Cancer Research^[85]. Although TNJ possesses a broad range of therapeutic effects, the cancer preventive effect of TNJ remains unclear. A new hypothesis has been investigated; whether or not TNJ possesses a cancer preventive effect at the initiation stage of chemical carcinogenesis.

This hypothesis was examined using two carcinogenic animal models and one human clinical study of a group of current smokers at the University of Illinois

at Chicago, College of Medicine, Rockford, Illinois, USA. The animal models included the following: the DMBA-induced mammary gland tumorigenesis model^[86] and an acute liver injury model induced by a liver carcinogen, carbon tetrachloride (CCl₄)^[87]. These are classical extrinsic carcinogenic models. DMBA induced DNA adduct formation, in addition to histological examination by light and electron microscopy, was chosen as a sensitive biomarker to evaluate the preventive effect of TNJ at the initiation stage of multiple step carcinogenesis. In the mammary breast carcinogenic model, the focus was on the pathogenic changes after DMBA administration, to monitor the mechanisms of carcinogenesis and DMBA DNA-adduct formation in mammary tissue. In the acute liver injury model, the histopathological changes of liver tissue and the superoxide anion free radicals (SAR) and lipid hydroperoxide (LPO) levels after CCl₄ administration were the focus.

Carcinogen DMBA DNA-adduct formation was used as a marker to examine whether TNJ is able to prevent carcinogen induced DNA damage. Based upon scientific evidence, most chemical carcinogens need activation by our body enzymes to be transformed to an ultimate form that readily binds to genetic DNA to form DNA-adducts^[88]. Carcinogen-DNA adduct formation is an important "DNA damage" marker that predicts the possibility of cancer development. Most scientists agree that carcinogen induced DNA adduct formation is an early critical step in the multiple stages of carcinogenesis^[89]. Carcinogen-DNA adducts can be repaired by body enzymes. The unrepaired adducts will be fixed after one cell cycle^[90]. The unrepaired, fixed DNA damage will be responsible for mutation and the consequent cancer development^[91,92]. Therefore, preventing carcinogen-DNA adduct formation is a key step for cancer prevention at the initiation step of carcinogenesis^[93]. If TNJ can prevent and/or block the formation of carcinogen induced DNA adducts, it may prevent cancer at the initiation stage of multiple stage carcinogenesis.

Cancer preventive effect of TNJ at the initiation stage of mammary breast carcinogenesis The cancer preventive effect of TNJ at the initiation stage of mammary breast carcinogenesis, induced by DMBA, was examined in female Sprague-Dawley (SD) rats. The experiment was started at the 35th postnatal day with water in an age-matched control group, a DMBA group, and a 5 % TNJ group. DMBA (25 mg/kg) was administered by mouth at the 50th postnatal day in the

DMBA and TNJ groups. TNJ was continuously supplied for an additional 90 days after DMBA administration. All the animals were sacrificed at the 8th month after DMBA administration to examine the pathological changes in the mammary glands by light microscopy. Compared to controls, the DMBA treated group showed a variety of lesions, including epithelial hyperplasias (12.5 %), benign tumors (25 %), and *in-situ* carcinomas (25 %). No benign tumors or carcinomas were found in the TNJ group, which showed normal histology or mild hyperplasia. These results indicate that TNJ may prevent mammary breast cancer at the initiation stage of chemical carcinogenesis^[94].

Protective effect of TNJ on liver injury induced by a liver carcinogen (CCl₄) In this study, the preventive effect of TNJ on carbon tetrachloride (CCl₄)-induced liver injury in female SD rats was examined by light microscopy (LM) and electron microscopy (EM) examination. Liver sections in placebo and TNJ groups demonstrated normal lobular architecture and normal ultrastructure at the LM level. Liver sections in the placebo+CCl₄ group showed acute liver damage at the LM level: which includes focal vacuolated, lipid-containing or necrotic hepatocytes surrounding central veins and focal inflammatory cells scattered throughout the lobule. There was a significant decrease in the number of swollen, lipid containing, and apoptotic hepatocytes in the TNJ+CCl₄ group, compared to the placebo+CCl₄. At the EM level, glycogen depletion and lipid droplets in the cell plasma were observed in both CCl₄ treated groups. Swollen mitochondria, disorganization of rough endoplasmic reticulum (RER) with loss of ribosomes, and abundant focal areas of smooth endoplasmic reticulum (SER) were scattered throughout the cytoplasm. Interestingly, Golgi complexes in placebo+CCl₄ group contain small low-density vesicles. Golgi complexes in the TNJ+CCl₄ group contain large vesicles with increased electron density, and Golgi cisternal stacks were well developed. Those in the placebo+CCl₄ group were often swollen and diminished^[95].

Mechanism studies of the cancer preventive effect of TNJ

Prevention of chemical carcinogen-DNA-adduct formation Female SD rats were divided into two groups of six each. The control group was given regular drinking water and rat chow, ad libitum. The TNJ group was given 10 % TNJ in drinking water and rat chow, ad libitum. One week later, three animals from each group received intragastrically 25 mg/kg of DMBA

containing 5 % dimethylsulfoxide in corn oil. All animals were sacrificed 24 h later. DNA was isolated from liver, lung, heart, and kidney. The DNA adducts were analyzed by ³²P-postlabeling technique. After one week of consumption, the TNJ group showed a reduction in both the number and level of DMBA-DNA adducts from each of the four organs studied. The quantitative estimate after radioactive counting indicated that TNJ reduced the amount of DNA adduct formation by 80 % in kidney, 42 % in liver, 41 % in lung, and 26 % in heart. Even more dramatic experimental results were obtained using male C57 BL-6 mice. We found that TNJ was able to reduce the formation of DMBA-DNA adducts by 90 % in kidney, 70 % in liver, 60 % in heart, and 50 % in lung. This is the first finding of the cancer preventive effect at the initiation stage of carcinogenesis by TNJ^[96,97]. This preliminary data indicates that TNJ may prevent cancer at the initiation stage of carcinogenesis.

Antioxidant activity of TNJ In order to explore the mechanisms of the cancer preventive effect of TNJ, the antioxidant activity was examined. It is known that oxidative damage induced by reactive free radicals is involved in the development of cancer^[98]. Epidemiological studies demonstrated that consuming fruits and vegetable reduced free radical-induced oxidative damage and the consequent lipid peroxidation, therefore reducing cancer risk^[99,100]. It is believed that fruits and vegetable are major sources of antioxidants^[101,102]. Noni is a medicinal plant that helps different health conditions in many different ways. It was hypothesized that the antioxidant activity of TNJ may protect individuals from oxygen free radicals and consequent lipid peroxidation. In order to examine this hypothesis, the antioxidant activity of TNJ was analyzed. The study was designed to measure how well TNJ scavenged superoxide anion radicals (SAR) and quenched lipid peroxides (LPO) by TNB assay and LMB assay, respectively^[103-104]. SAR scavenging activity was examined *in vitro* by tetrazolium nitroblue (TNB) assay. In TNB assay, SAR reduces TNB into formazan blue, which absorbs at 602 nm. A SAR scavenger, such as TNJ, reduces the absorbency by reacting with SAR. In this assay, a standard curve is produced when SAR are generated from NADH under aerobic conditions, with phenazine methosulfate as a catalyst. In LMB assay, LPO oxidizes leucomethylene to methylene blue in the presence of hemoglobin. The resultant blue color can be quantified spectrophotometrically at 660 nm.

(a) *In vitro* TNJ showed a dose-dependent inhibition of both LPO and SAR. The SAR scavenging activity of TNJ was compared to that of three known antioxidants: Vitamin C, grape seed powder, and Pycnogenol at the daily dose per serving level recommended by US RDA's or manufacturer's recommendations. Under the experimental conditions, the SAR scavenging activity of TNJ was shown to be 2.8 times that of vitamin C, 1.4 times that of Pycnogenol, and 1.1 times that of grape seed powder. Therefore TNJ has a great potential to scavenge reactive oxygen free radicals^[105,106].

(b) *In an acute liver injury model induced by carbon tetrachloride* Carbon tetrachloride is a liver carcinogen and lipid hydroperoxidation inducer. To further confirm the antioxidant activity of TNJ *in vivo*, a carbon tetrachloride induced liver injury model in female SD rats was selected. Ten percent of TNJ in drinking water for 12 d was able to reduce the liver LPO and SAR levels to 20 % and 50 % of that observed in the placebo group 3 h after CCl₄ administration. In conclusion, TNJ may protect liver from an extrinsic carcinogenic CCl₄ exposure^[96,107].

(c) *In current smokers* Cigarette smoking has been implicated in the pathogenesis of emphysema, ischemic heart diseases, and cancer^[108-110]. A series of authoritative reports by the U.S. Public Health Service and other international scientific organizations has conclusively documented a causal relationship between cigarette smoking and cancer in men and women^[111]. There are 48 known chemical carcinogens among the 4000 compounds detected in cigarettes. Most recently, it was reported that 227 possible carcinogens exist in cigarettes. It was estimated that some 1×10^{17} oxidant molecules are present in each puff of cigarette smoke^[112]. Free radicals are known to cause oxidative damage and consequent lipid peroxidation, which are involved in the pathogenesis of human diseases. The induction of lipid peroxidation largely results from free radical reactions with polyunsaturated fatty acids in biological membranes. The unsaturated bonds undergo autocatalytic or enzymatic processing to form harmful lipid hydroperoxides. The active lipid hydroperoxides may be quickly converted to aldehydes, such as malondialdehyde, and alkenals, such as 4-hydroxynonenal. All of these are very active in DNA binding and are responsible for major indigenous cell damage^[113,115]. Epidemiological studies have demonstrated that consuming fruits and vegetables reduce free

radical-induced oxidative damage and lipid peroxidation in cigarette smokers, therefore reducing cancer risks^[116,117]. It is believed that fruits and vegetable are major sources of antioxidants. Consequently, it was hypothesized that antioxidants in TNJ may protect individuals from cigarette smoke by scavenging oxygen free radicals and quenching lipid peroxides.

In order to examine this hypothesis, a one-month double blinded, randomized, and placebo-controlled clinical trial was designed to test the protective effect of TNJ on plasma SAR and LPO in current smokers. The subjects were supplemented daily with two ounces of TNJ ($n=38$) or placebo ($n=30$), twice a day for 30 d. The plasma SAR and LPO levels were determined before and after trial by TNB and LPO assay, respectively. There was no effect observed on plasma SAR (0.23 ± 0.15 versus 0.21 ± 0.17 $\mu\text{mol/mL}$) and LPO (0.58 ± 0.22 versus 0.59 ± 0.21 $\mu\text{mol/mL}$) in the placebo group. The LPO and SAR levels in the TNJ group showed 23 % reduction (0.59 ± 0.21 $\mu\text{mol/mL}$ versus 0.45 ± 0.20 $\mu\text{mol/mL}$, $P=0.06$) and 27 % reduction (0.23 ± 0.18 $\mu\text{mol/mL}$ versus 0.17 ± 0.10 $\mu\text{mol/mL}$, $P<0.05$), respectively. These results indicate that TNJ may protect individuals from oxidative damage induced by tobacco smoke. Smoking specific, lipid peroxides and the related decomposed products such as malondialdehyde, induced DNA adducts will be analyzed soon.

The data from the *in vitro* study, CCl₄-induced liver injury model of female SD rats, and current smokers indicate that TNJ is a strong antioxidant which can scavenge reactive oxygen free radicals and quench lipid hydroperoxides, therefore reducing the cancer risk.

Anti-inflammatory activity

(a) Selective inhibition of COX-2 activity of TNJ

Accumulating evidence indicates that COX-2 inhibitors may be involved in breast, colon, and lung cancer development^[118-120]. Interest in cancer chemoprevention with COX-2 inhibitors has been stimulated by epidemiological observations that the use of aspirin and other non-steroidal inflammatory drugs (NSAIDs) is associated with the reduced incidence of colon and breast cancer^[121-123]. The main target of NSAID activity is the cyclooxygenase (COX) enzyme^[124]. Two isoforms of COX have been identified: COX-1, the constitutive isoform, and COX-2, the inducible form of the enzyme^[125]. COX-2 can undergo rapid induction in response to chemical carcinogens^[126]. It has been suggested that COX-2 overexpression may lead to increased angiogenesis and inflammatory reaction^[127,128]. There-

fore the inhibition of COX-2 might have a general cancer preventive effect via anti-inflammatory activity and decrease angiogenesis. In this study, the selectivity of COX-2 inhibition of TNJ versus COX-1 *in vitro* was investigated. The inhibitions of TNJ on COX-2 and COX-1 activities were compared with that of the traditional NSAIDs such as Aspirin, Indomethacin, and a known selective COX-2 inhibitor, Celebrex^[129-131]. The COX-1 and COX-2 activities were determined based upon the PGE₂ levels generated during the incubations of human platelets with tested compounds and/or vehicle by the Amersham ELA assay^[132]. The IC₅₀ of TNJ, Aspirin, Indomethacin, and Celebrex on COX-1 are 5 %, 4.55 $\mu\text{mol/L}$, 0.01 $\mu\text{mol/L}$, and 1.4 $\mu\text{mol/L}$, respectively, and that for COX-2 are 3.8 %, 595 $\mu\text{mol/L}$, 0.4 $\mu\text{mol/L}$, and 0.47 $\mu\text{mol/L}$ respectively. The data was converted into a ratio of IC₅₀ COX-2/COX-1. It was 0.76 for TNJ, 119 for Aspirin, 40 for Indomethacin, and 0.34 for Celebrex. These results show that the selectivity of COX-2 inhibition of TNJ is comparable with that of Celebrex. The discovery of the selective COX-2 inhibition of TNJ is very significant since TNJ is a natural fruit juice without side effects. This is the first scientific evidence for a strong anti-inflammatory activity in TNJ, which may also be one mechanism of cancer prevention^[133].

(b) *Anti-inflammatory of TNJ in acute liver injury induced by CCl₄* The anti-inflammatory activity of TNJ was observed in an acute liver injury model in female SD rats induced by CCl₄. A decrease in inflammatory foci and lymphocytes surrounding central vein areas were observed at 6 hours post CCl₄ administration in animals pretreated with 10 % TNJ for twelve days in drinking water compared with the CCl₄ group without TNJ^[96].

Ongoing study A pilot study including 68 current smokers was finished in early 2000. The clinical part of the extended study was closed in July 2002. An additional two hundred and seventy-four volunteers were recruited, which included 30 non-smokers. The volunteers were randomly divided into two groups: a one-ounce TNJ/day group and a two-ounces TNJ, twice/day group. Both groups followed their assigned regimen for one month. Plasma SAR, plasma LPO levels, smoking-specific DNA-adducts, lipid peroxide-related DNA-adducts, and malondialdehyde induced-DNA adducts in peripheral blood lymphocytes have been chosen as biomarkers to evaluate DNA-adduct prevention by TNJ. Results from this clinical trial will be pub-

lished next year. Cigarette-smoke is not only involved in cancer, but also involved in pulmonary, heart, and other degenerative diseases. Therefore drinking TNJ may be beneficial for the prevention of heart, lung, and brain diseases, as well as delaying the aging processing, and maintaining overall good health.

NONI: YIN & YANG

The Yellow Emperor of China (2695-2589 BC), Huang Di, an ancient Chinese physician born 2200 years earlier than Hippocrates (460.c-375 BC), created the principle of *Yin & Yang*. He taught “*Yin/Yang* are the way of Heaven and Earth, the great principle and outline of everything, the parents of changes, the root and source of life and death, and the palace of gods. Treatment of disease should be based upon the roots of *Yin/Yang*.” The theory of *Yin/Yang* indicates that every object in the universe consists of two opposite aspects, which are in continual mutual restriction and interaction. *Yin/Yang* theory has been used in many different ways in Chinese philosophy^[134], especially in biological and medical fields. According to Traditional Chinese Medicine (TCM), the human body is an integrated whole. Diagnosis and treatment is founded in the concept of an integral human body, and decided through careful identification of *Yin* and *Yang* based upon the signs and symptoms in an individual. A healthy body depends on the balance of *Yin* and *Yang*, and all diseases result from the imbalance of *Yin* and *Yang*. When these two forces are in balance, whether it occurs in a meal, a person, or in nature, harmony and equilibrium are achieved.

The basic nutritional theories of TCM arise through the concepts of *Yin/Yang* and Qi. *Yin/Yang* is a complicated philosophical concept. *Yin* literally translates as “in the shade,” and is considered to represent darkness, the moon, coldness, and passivity. *Yang*, “in the sunlight,” on the other hand, represents light, sun, heat, and activity. *Yin* represents all kinds of inadequate under-functioning such as cold, fatigue, and general weakness. *Yang* represents all kinds of detrimental over functioning such as fever, hyper-reactivity, and red swelling (skin). Qi is known as vital energy that represents various functions of the body. Blood is a conceptual term that refers to the material basis of Qi or the comprehensive material that represents all internal organs. Therefore, blood and Qi are often linked together. Keep in mind that this use of the word blood is different from the understanding with blood as it is used in modern medicine^[135].

When used properly, food can regulate *Yin*, *Yang*, Qi, and blood. According to TCM, each item of food has its own property (cool, cold, warm, hot, and plain). To simplify this concept the five categories have been collapsed to three-cool/cold, warm/hot, and plain. Cold and cool foods are used to treat diseases of a hot nature. Hot and warm foods are used in treating diseases with a cold nature. The plain foods such as apple, rice, and milk are used in treating both hot and cold diseases as general tonics. Food in TCM is applied in four ways: diet, tonic, medicine, and abstention. Food as a diet means that food provides the necessary substances for life, growth, and health. Food as a tonic refers to using food to treat individuals who have general weakness, but not a specific disease, or for those who are recovering from an ailment and need added strength. Food, as a medicine refers to using specific foodstuffs to correct imbalances that have led to disease states with particular signs and symptoms. Finally, food as an abstention refers to the practice of avoiding foods that would make a disease condition or imbalance in the body to worsen. For example: avoid eating hot pepper, old ginger, mutton, or liquor, which produces “fire” (heat) in the body, during acute inflammation, acute conjunctivitis, or high fever; because all these diseases are characterized by too much heat or excessive *Yang*^[136].

According to the *Yin/Yang*, five elements, and Zang Fu theories, human health is the results of a *Yin/Yang* balance^[137]. In any case, if the *Yin/Yang* balance is disrupted, harmony and balance broken, disease will occur as a consequence. There are millions of pairings of *Yin* and *Yang* in the human body; every element, cell, organ and system has its pair of *Yin* and *Yang*. The net results from the interaction of these *micro-Yin* and *Yang* pairings are manifested as *macro-Yin* and *Yang* of our health. They interact and strike a dynamic balance to achieve normal well-being. The Noni plant like other herbs acts as a *Yin/Yang* regulator from *micro-Yin* and *Yang* to *macro-Yin* and *Yang* to benefit many different health problems, sometimes benefiting two opposite health conditions such as diarrhea and constipation. Due to the limited scientific data, the *Yin/Yang theory* may be the best way to explain the beneficial effects of the Noni plant through the regulation of balance between *Yin* and *Yang*. That is why one simple plant can do so many things in so many different ways. Based upon TCM, the Noni plant is able to tonify Qi, clear heat and toxins, and invigorate the blood. The properties of this plant are sweet, stinky, and neutral. Noni enters the

lung, spleen, liver, and kidney meridians. Therefore Noni is beneficial for many different health conditions.

By TCM, the quality of the herb and nutritional components contained in the plants are directly related to the soil in which they grow. The terrain, the weather, geographic local, and other factors affect what are contained in the plants because they affect soil conditions. The tropical Noni plant grown in Tahiti is recognized as the best Noni because the air is clean, the water is pure, and the soil is rich in abundant micronutrients. The island group known as French Polynesia (Tahiti) is considered to be the source of the finest and most potent Noni in the world^[40].

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