Why you and your family should use Divine Noni ?
Reason 3

Noni has very powerful antimicrobial action which helps to kill the bacteria in co-infection in SARS CoV viral including pneumonia caused by Klebsella pneumonia and other respiratory pathogens including TB (Mycobacterium TB)

Scientific Reference :

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

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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 ancient 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].

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*, C*heese 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 Roratonga "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 described *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- □ -methyl ether, anthraquinone glycoside), □ -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 lycosides, an iridoid glycoside from the Noni leaves, a trisacharide fatty acid ester, rutin, and an asperulosidic acid from the fruit. Two novel glycosides and a new unusual iridoid named citrifolinoside 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 morgaii, Staphylococcus aureus, Baciillis subtilis, Escherichia coli, Salmonella,* and *Shigela.* 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, Rifampcin, 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 (nonippt) 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 nonippt 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 apotosid 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]. Hiwas a 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 hosphorylation 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 activites[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 l5 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 dosedependent 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 female 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 ºC). 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-□□, which is an endogenous tumor promotor. Therefore the alcohol extract may inhibit the tumor promoting effect of TNF-□□60]. Hirazumi found that nonippt 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-□, interleukin-1beta (IL-1□), IL-10, IL-12, interferon-gamma (IFN-□) and nitric oxide (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. Seventyseven 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 phamplets 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 h as 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 administrated by mouth at the 50th postnatal day in the MBA and TNJ groups. TNJ was continuously supplied for an ad dition al 90 days a fter 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 *insitu*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 % dimethysulfoxide 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 USRDA'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[96,1 07]. *(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 1×1017 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 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 □mol/mL) and LPO (0.58±0.22 versus 0.59±0.21 □mol/mL) in the placebo group. The LPO and SAR levels in the TNJ group showed 23 % reduction (0.59±0.21 □mol/mL versus 0.45±0.20 □mol/ mL, P=0.06) and 27 % reduction (0.23±0.18 □mol/mL versus

0.17±0.10 □ 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]. Therefore 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 □ mol/L, 0.01 □ mol/L, and 1.4 □ mol/L, respectively, and that for COX-2 are 3.8 %, 595 □ mol/L, 0.4 □ mol/L, and 0.47 □ 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 peroxiderelated 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 published 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 Y*in*/*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].

REFERENCES

1. Zhu YP, Woerdenbag HJ . Traditional Chinese herbal medicine. Pharm World Sci 1995; 17: 103-12.

2. Whistler WA. Traditional and herbal medicine in the cook islands. J Ethnopharm 1985; 13: 239-80.

3. Singh Y, Ikahihifo T, Panuve M, Slatter C. Folk medicine in Tonga. A study on the use of herbal medicines for obstetric and gynacological conditions and disorders. J Ethnopharm 1984; 12: 305-25.

4. Tabrah FL, Eveleth BM. Evaluation of the effectiveness of ancient Hawaiian medicine. Hawaii Med J 1966; 25: 223-30.

5. Krauss B. Plants in Hawaiian culture. Honolulu: University of Hawaii Press; 1993. p103, p252.

6. Whistler W. Tongan herbal medicine. Isle Botanica, Honolulu, Hawaii, 1992. p 89-90.

7. Bruggnecate JT. Native plants can heal your wounds. Honolulu Star-Bulletin Local News 1992 Feb 2.

8. Neal M. Gardens of Hawaii. Honolulu, Hawaii: Bishop Museum Press; 1965. p 804.

9. Cheeseman TF. The flora of raratonga, the chief island of the cook group. v 6. London: Linnean Soc;1903. p 261-313.

10. Seemann B. Flora V. A des cription of the plants of the Vitior Fiji is lands with an account of their history, uses , and properties. London: L Reeve and Co; 1866. p 1865-73.

11. Maiden JH. Useful native plants of Australia including Tasmania. Sydney: Tuner and Henderson Publisher; 1889.p 45.

12. Morton JF. The ocean-going Noni, or Indian mulberry *(Morinda citrifolia,* Rubiaceae) and some of its 'colorful' relatives. Economic Botany 1992; 46: 241-56.

13. Merrill ED. Noni (*Morinda citrifolia*) as an edible plant. In: Technical manual: emergency food plants and poisonous plants of the islands of the pacific. Washington DC: US Government Printing Office; 1943.

14. Abbott IA. La'au Hawaii' traditional Hawaiian uses of plants. v 3. Honolulu, Hawaii: Bishop Museum Press; 1992. p 97-100.

15. Swanholm CE, St John H, Scheuer PJ. A survey of alkaloids in Hawaiian plants. Pacific Science 1959; 13: 295-305.

16. Solomon N. The tropical fruit with 101 medicinal uses, NONI juice. 2nd ed. Woodland Publishing; 1999.

17. Allen WH, London C. Some information on the ethnobotanical properties of Noni (*Mor inda citr ifolia*). In: The useful plants of india; 1873.

18. Abbott IA. The geographic origin of the plants most commonly used for medicine by Hawaiians. J Ethnopharmacol 1985; 14: 213-22.

19. Bushnell OA, Fukuda M, Makinodian T. The antibacterial properties of some plants found in Hawaii. Pacific Science 1950; 4: 167-83.

20. Pride Publishing, Noni: Polynesia's natural pharmacy. 1997.p 13.

21. Levand O, Larson HO. Some chemical cons tituents of *Morinda citrifolia*. Planta Med 1979; 36: 186-7.

22. Farine JP, Legal L, Moreteau B, Le Quere JL. Volatile components of ripe fruits of *Mor inda citr ifolia* and their effects on Drosophila. Phytochemistry 1996; 41: 433-8.

23. Higa I, Fuyama Y. Genetics of food preference in Drosophila sechellia. 1. Responses to food attractants. Genetica 1993; 88: 129-36.

24. Peerzada N, Renaud S, Ryan P. Vitamin C and elemental compos ition of some bushfruits. J Plant Nutrition 1990; 13: 787-93.

25. Budavari S, O'Neil MJ, Smith A, Heckelman PE. In: The Merck Index. An encyclopedia of chemicals, drugs , and biologicals. 11th ed. Merck & Co Inc, Rathway, New Jersey, 1989.

26. Moorthy NK, Reddy GS. Preliminary phytochemical and pharmacological study of *Morinda citrifolia*, Linn. Antiseptic 1970; 67: 167-71.

27. Daulatabad CD, Mulla GM, Mirajikar AM. Riconoleic acid in *Morinda citrifolia* seed oil. Oil Technologists' Association of India 1989; 21: 26-7.

28. Balakrishna S, Seshadri TR, Venkataramani B. Special chemical component of commercial woods and related plant materials: Part X-Heartwood of *Morinda citrifolia* Linn. J Sci Industrial Res 1961; 20B: 331-3.

29. Legal L, David JR, Jallon JM. Molecular basis of *Morinda citrifolia* (L.): toxicity on Drosophila. J Chem Ecolog 1994; 20: 1931-43.

30. Singh J, Tiwari RD. Flavone glycosides from the flowers of Morinda citrifolia. J Indian Chem Soc 1976; 53: 424.

31. Simonsen JL. Note on the constituents of *Morinda citrifolia*. J Chem Soc 1920; 117: 561-4.

32. Heinicke R. The pharmacologically active ingredient of Noni. Bulletin of the National Tropical Botanical Garden, 1985.

33. Wang M, Kikuzaki H, Csiszar K, Boyd CD, Maunakea A, Fong SF, *et al.* Novel trisaccharide fatty acid ester identified from the fruits of Morinda citrifolia (Noni). J Agric Food Chem 1999; 47: 4880-2.

34. Sang S, He K, Liu G, Zhu N, Cheng X, Wang M, *et al.* A new unusual iridoid with inhibition of activator protein-1 (AP-1) from the leaves of Morinda citrifolia L. Org Lett 2001; 3: 1307-9.

35. Sang S, Cheng X, Zhu N, Wang M, Jhoo JW, Stark RE, *et al.* Iridoid glycosides from the leaves of Morinda citrifolia. J Nat Prod 2001; 64: 799-800.· 1139 Wang MY *et a l* / Acta Pharmacol Sin 2002 Dec; 23 (1 2): 1127 - 1141 ·

36. Liu G, Bode A, Ma WY, Sang S, Ho CT, Dong Z. Two novel glycos ides from the fruits of Morinda citrifolia (noni) inhibit AP-1 transactivation and cell trans formation in the mouse epidermal JB6 cell line. Cancer Res 2001; 61: 5749-56.

37. Sang S, Cheng X, Zhu N, Stark RE, Badmaev V, Ghai G, *et al.* Flavonolglycosides and novel iridoid glycoside from the leaves of Morinda citrifolia. J Agric Food Chem 2001; 49: 4478-81.

38. Wang M, Kikuzaki H, Jin Y, Nakatani N, Zhu N, Csiszar K, *et al.* Novel glycosides from noni (Morinda citrifolia). J Nat Prod 2000; 63: 1182-3.

39. Duke JA. Handbook of phytochemicals. Boca Raton, FL: CRC Publishing; 1992.

40. Heinicke R. The Xeronine sys tem: a new cellular mechanism that explains the health promoting action of NONI and Bromelian. Direct Source Publishing; 2001.

41. Atkinson N. Antibacterial substances from flowering plants. 3. Antibacterial activity of dried Australian plants by a rapid direct plate test. Australian J Exper Biol 1956; 34: 17-26.

42. Leach AJ, Leach DN, Leach GJ . Antibacterial activity of some medicinal plants of Papua New Guinea. Sci New Guinea 1988; 14: 1-7.

43. Locher CP, Burch MT, Mower HF, Beres tecky J , Davis H, Van Poel B, *et al.* Anti-microbiol activity and anti-complement activity of extract obtained from s elected Hawaiian medicinal plants. J Ethnopharm 1995; 49: 23-32.

44. Duncan SH, Flint HJ, Stewart CS. Inhibitory activity of gut bacteria against Es cherichia coli 0157 mediated by dietary plant metabolites. FEMS Microbiol Lett 1998; 164: 283-58.

45. Umezawa K. Isolation of 1-methoxy-2-foremyl-3-hydroxyanthraquinone from *M citrifolia* and neoplasm inhibitors containing the same. Japan Kokai Tokyo Koho JP 06 87, 736 (94-87, 736) Appl 1992; 92/264, 311 07.

46. American Chemical Society: Noni plant may yield new drugs to fight tuberculosis. Press releas e the 2000 International Chemical Congress of Pacific Basin Societies. 2000.

47. Author unlis ted. Noni plant may help TB. AIDS patient care STDS 2001; 15: 175.

48. Hirazumi A, Furusawa E, Chou SC, Hokama Y. Anticancer activity of Morinda citrifolia (noni) on intraperitoneally implanted Lewis lung carcinoma in syngeneic mice. Proc West Pharmacol Soc 1994; 37: 145-6.

49. Hirazumi A, Furusawa E, Chou SC, Hokama Y. Immunomodulation contributes to the anticancer activity of *Morinda citrifolia* (noni) fruit juice. Proc West Pharmacol Soc 1996; 39: 7-9.

50. Hirazumi A, Furus awa E. An immunomodulatory polysaccharide- rich substance from the fruit juice of *Morinda citrifolia* (noni) with antitumour activity. Phytother Res 1999; 13: 380-7.

51. Hiramatsu T, Imoto M, Koyano T, Umezawa K. Induction of normal p henotypes in ras -trans fo rmed cells by damnacanthal from *Morinda citrifolia*. Cancer Lett 1993; 73: 161-6.

52. Hiwasa T, Arase Y, Chen Z, Kita K, Umezawa K, Ito H, *et al.* Stimulation of ultraviolet-induced apoptos is of human fibroblast UVr-1 cells by tyrosine kinas e inhibitors. FEBS Lett 1999; 444: 173-6.

53. Sang S, He K, Liu G, Zhu N, Cheng X, Wang M, *et al.* A new unusual iridoid with inhibition of activator protein-1 (AP-1) from the leaves of Morinda citrifolia L. Org Lett 2001; 3: 1307-9.

54. Raj RK. Screening of indigenous plants for anthelmintic action against humanAscaris Lumbricoides: Part-II. Indian J Physiol Pharmacol 1975; 19: 47-9.

55. Younos C, Rolland A, Fleurentin J, Lanhers MC, Miss lin R, Mortier F. Analgesic and behavioural effects of *Morinda citrifolia*. Planta Med 1990; 56: 430-4.

56. Youngken HW, Jenkins H J, Butler CL. Studies on *Morinda citrifolia* L. II. J Am Pharm Assoc 1960; 49: 271-3.

57. Youngken HW. A study of the root of *Morinda citrifolia* Linn, I. J Am Pharm Assoc 1958; 47: 162-5.

58. Davison C. Hawaiian medicine. The Queen's Hospital Bulletin with Palama Clinic Section 1927; 4: 2-5.

59. Asahina AY, Ebesu JSM, Ichinotsubo D, Tongson J, Hokama Y. Effect of okadaic acid (OA) and Noni fruit extraction in the synthesis of tumor necrosis factor-□□ (TNF-□) by peripheral blood mononuclear (PBN) cells *in vitro*. The Procedings of the International Symposium of Ciguatera and Marine Natural Products; 1994. p 197-205.

60. Hokama Y. The effect of Noni fruit extract (*Morinda citrifolia*, Indian mulberry) on thymocytes of BALB/c mouse. FASEB J 1993; 7: A866.

61. Langford J , Doughty A, Wang MY, Clayton L, Babich M. Effects of Morinda citrifolia on auditory function and quality of life in patients with decreas ed bone mineral density and auditory function. J Complementary & Alternative Med Submitted, 2002.

62. Acute oral toxicity s tudy in rats -limit test: TAHITIAN NONI® Juice. 1999 Oct 6. Product Safety Labs (Eurofins Scientific, Inc). East Brunswick, New Jersey, USA.

63. Kaaber K. TAHITIAN NONI® Juice: active systemic anaphylaxis test in the guinea pig. 2000 Feb 18 . Scantox Biologisk Laboratorium A/S, DK-426, Lille Skensved, Denmark.

64. Guinea pig antigenicity study. TAHITIAN NONI® juice. 2000 Feb 29. Product Safety Labs (Eurofins Scientific, Inc). East Brunswick, New Jersey, USA.

65. Glerup P. TAHITIAN TNJ: A 13-week oral (gavage) toxicity study in rats. 2001 May. Scantox Biologisk Laboratorium A/S, DK-426. Lille Skensved, Denmark.

66. Degener O. In: Plants of Hawaii national park illustrative of plants and cus toms of the south seas . Photo-Lithoprint Reproductions, Braun-Brumfield, Inc. Ann Arbor, Michigan. 1973.

67. Rock JF. In: The indigenous trees of the Hawaiian islands.Patronage. Honolulu, Hawaii. 1913.

68. Stone BC. "Morinda Linnaeus". Micronesica 1970; 6: 551-2.

69. Sturtevant EL. Sturtevant's notes on edible plants (Hedrick UP, editor). Albany, New York: JB Lyon Co; 1919. p 368.

70. Terra JA. Tropical Vegetables. Ams terdam: Knoninklyk Ins tituut voor de Tropen; 1996. p 61.

71. Turbott IG. Diets , Gilbert and Ellice Islands Colony. J Polynesian Soc 1949; 58: 36-46.

72. Uhe G. In: Wayside plants of the south pacific. Stockton House R.D. 3. Albany, New Zealand. 1974.Wang MY *et al* / Acta Pharmacol Sin 2002 Dec; 23 (1 2): 1127 -114· 1140 · 1

73. Wilder GP. In: The flora of Makatea. Bernice P. Bishop Museum Bulletin 120. Honolulu, Hawaii: Bishop Museum Press; 1934.

74. Yuncker TG. In: The flora of Niue Island. Bernice P. Bishop Museum Bulletin, 178. Honolulu, Hawaii: Bishop Museum Press; 1943.

75. Solomon N. Nature's amazing healer, Noni. Pleas ant Grove, Utah: Woodland Publishing; 1998.

76. Solomon N. The Noni phenomenon. Discover the powerful tropical healer that fights cancer, lowers high blood pressure and relieves chronic pain. Direct Source Publishing; 1999.

77. Solomon N. TAHITIAN NONI Juice: How much, how often, for what. Direct Source Publishing; 2000.

78. Solomon N. TAHITIAN NONI® Juice—The pain fighter (arthritis/pain). Direct Source Publishing; 2001.

79. Sharps J. NONI juice, A pres cription for the good health. Integrated Health Service; 2000.

80. Veith I. Translated "Yellow Emperor's Classic of Internal Medicine" (2500 BC); 2002.

81. Du B, You S. Present situation in preventing and treating liver fibrosis with TCM drugs. J Tradit Chin Med 2001; 21: 147-52.

82. American Cancer Society: Statistics of cancer incidence. 2002.

83. Lichtenstein P, Holm NV, Verkas alo PK, Iliadou A, Kaprio J, Koskenvuo M, *et al.* Environmental and heritable factors in the causation of cancer — analys es of cohorts of twins from Sweden, Denmark, and Finland. N Engl J Med 2000 343: 78-85.

84. Perera P. Molecular epidemiology and prevention of cancer. Environ Health Perspect 1995; 103 (Suppl 8): 2336.

85. American Ins titute for Cancer Research: 11th Annual Research Conference on Diet, Nutrition and Cancer. Washington DC. 2001.

86. Rus so J , Russo IH. Experimentally induced mammary tumors in rats . Breast Cancer Res Treat 1996; 39: 7-20.

87. elSisie AE, Hall P, Sim WL, Earnest DL., Sipes IG. Characterization of vitamin A potentiation of carbon tetrachlorideinduced liver injury. Toxicol Appl Pharmacol 1993; 119: 280-8.

88. Santella RM. DNA damage as an intermediate biomarker in intervention studies. Proc Soc Exp Biol Med 1997; 216: 166-71.

89. Kens ler TW, Groopman JD. Carcinogen-DNA and protein adducts: biomarkers for cohort selection and modifiable endpoint in chemoprevention trials. J Cell Biochem Suppl 1996; 25: 85-91.

90. Rabes HM. DNA adducts and cell cycle. J Cancer Res Clin Oncol 1986; 112: 189-95.

91. Hemminki K. DNA adducts , mutations and cancer. Carinogenesis 1993; 14: 2007-12.

92. Poirier MC, Weston A. Human DNA adduct measurements: state of the art. Environ Health Perspect 1996; 104 Suppl 5: 883-93.

93. Slaga TJ. Multistage skin carcinogenesis: an useful model for the s tudy of the chemopreventionn of cancer. Acta Pharmacol Toxicol 1984; 55 Suppl 2: 107-24.

94. Wang MY, Anderson G, Nowicki D. Preventive effect of Morinda citrifolia (Noni) at the initiation stage of mammary breas t cancer induced by 7,12-dimethylbenz(a)-anthracen (DMBA) in female Sprague-Dawley rats. The Proceedings of the Frontiers in cancer prevention research, AACR, Boston, 2002 Oct 17.

95. Wang MY, Nowicki D, Anderson, G. Protective effect of *Mor inda citr ifolia* on hepatic injury induced by a liver carcinogen. The Proceedings of 93rd Annual Meeting of American Association for Cancer Research 2002; 43: 477.

96. Wang MY, Su C, Nowicki D, Jensen J, Anderson G. *Morinda citrifolia* and cancer prevention. J Nutrition 2001; 131 (11S):3151S.

97. Pryor WA. Cigarette smoke radicals and the role of free radicals in chemical carcinogenicity. Environ Health Perspect 1997; 105 Suppl 4: 875-82.

98. Bartsch H, Nair J. New DNA-das ed biomarkers for oxidative stress and cancer chemoprevention studies. Eur J Cancer 2000; 36:1229-34.

99. Wang MY, Lieher, JG. Induction by estrogens of lipid peroxidation and lipid peroxide derived malondialdehyde- DNA adducts in male Syrian hams ters : role of lipid peroxidation in estrogen-induced kidney carcinogenesis. Carcinogenesis1995; 16: 1941-5.

100. Diplock AT, Charleux JL, Crozier-Willi G, Rice-Evans C, Roberfroid M, Stahi W, *et al.* Functional food science and defense against reactive oxidative species. Br J Nutr 1998; 80 Suppl 1: S77-112.

101. Weisburger JH, Rivenson A, Garr K, Aliaga C. Tea, or tea and milk, inhibit mammary gland and colon carcinogenesis in rats. Cancer Lett 1997; 114: 323-7.

102. Nishikimi M, Rao NA, Yagi K. The occurrence of superoxide anion in the reaction of reduced phenazine methosulfate and molecular oxygen. Biochem Biophys Res Commun 1972; 46: 849-54.

103. Auerbach BJ , Kiely JS, Cornicell JA. A spectrophotometric microtiter-based assay for the detection of hydroperoxy derivatives of linoleic acid. Anal Biochem 1992; 201: 375- 80.

104. Wang MY, Su C. Cancer preventive effect of *Morinda citrifolia* (Noni). Ann NY Acad Sci 2001; 952: 161-8.

105. Wang MY, Su C. Cancer preventive effect of Morinda citrifolia. The proceedings of the Strang International Cancer Prevention Conference. 2000 Nov 10-11, New York.

106. Wang MY, Su C, Nowicki D, Jensen J, Anderson G. Protective effect of Morinda citrifolia in carbontetrachloride-induced liver injury model: A light and electron microscopic study. The Proceedings of the Eicosanoids and other Bioactive Lipids in Cancer, Inflammatory and Related Diseas es, the 7th Annual Conference, 2001 Oct 16. Loews Vanderbilt Plaza, Nashville, Tennessee, USA.

107. Burns DM. Cigarette smoking among the elderly: disease consequences and the benefits of cess ation. Am J Health Promot 2000; 14: 357-61.

108. Meerson FZ, Kagon VE, Kozolov YP, Belkina IM, Penko A. The role of lipid peroxidation in pathogenes is of ischemic damage and the antioxidant protection of the heart. Basic Res Cardiol 1982; 77: 465-85. · 1141 Wang MY *et a l* / Acta Pharmacol Sin 2002 Dec; 23 (1 2): 1127 -1141 ·

109. Chow CK. Cigarette smoking and oxidative damage in the lung. Ann NY Acad Sci 1993; 686: 289-98.

110. US Department of Health and Human Services. Reducing the health consequences of smoking 25 years of progress. A report of the Surgeon General. DHHHS Publ# (CDC) 1989; 89: 8411.

111. Kozumbo WJ, Trush MA, Kens ler TW. Are free radicals involved in tumor promotion? Chem Biol Interact 1985; 54: 199-207.

112. Hemminki K, Kumar R, Bykov VJ, louhelainen J, Vodicka P. Future research directions in the use of biomarkers. Environ Health Perspect 1996; 104 Suppl 3: 459-64.

113. Wang MY, Dhingra K, Hittelman WN, Lieher JG, Andrade M, Li D. Lipid peroxdation-induced putative malondialdehyde- DNA adducts in human breast tissues. Cancer Epidemology, Biomarkers & Prevention 1996; 5: 705-10.

114. World Cancer Research Fund and American Institute for Cancer Res earch: Food, nutrition, and the prevention of cancer: a global perspective. Published by the American Institute for Cancer Research, 1997.

115. Fontham ET. Protective dietary factors and lung cancer. Int J Epidemiol 1990;19 Suppl 1:S32-42.

116. Wang MY, Nowicki D, Anderson G, Su C, Jensen J. Protective effects of *Morinda citrifolia* on plasma superoxides (SAR) and lipid peroxides (LPO) in current smokers. The Proceedings of XIth Biennial Meeting of the Society for Free Radical Research International. July 16-20, 2002. Ren'e Des cartes University. Paris, France. in press.

117. Natarajan K, Mori N, Artemov D, Bhujwalla ZM. Exposure of human breast cancer cells to the anti-inflammatory agent indomethacin alters choline phospholipid metabolites and Nm23 expression. Neoplasia 2002; 4:409-16.

118. Yao M, Song DH, Rana B, Wolfe MM. COX-2 selective inhibition revers es the trophic properties of gas trin in colorectal cancer. Br J Cancer 2002; 87: 574-9.

119. Takahashi T, Kozaki K, Yatabe Y, Achiwa H, HidaT. Increas ed expres sion of COX-2 in the development of human lung cancer. J Environ Pathol Toxicol Oncol 2002; 21: 177-81.

120. Langman MJ, Cheng KK, Gilman EA, Lancashire RJ. Effect of anti-inflammatory drugs on overall risk of common cancer: case-control study in general practice research database. BMJ 2000; 320: 1642-6.

121. Decensi A, Cos ta A. Recent advances in cancer chemoprevention, with emphasis on breast and colorectal cancer. Eur J Cancer 2000; 36: 694-709.

122. Schreinemachers DM, Everson RB. Aspirin use and lung, colon, and breast cancer incidence in a prospective study. Epidemiology. 1994; 5: 138-46.

123. Brigati C, Noonan DM, Albini A, Benelli R. Tumors and inflammatory infiltrates: friends or foes? Clin Exp Metastasis 2002; 19: 247-58.

124. McMurray RW, Hardy KJ. COX-2 inhibitors: today and tomorrow. Am J Med Sci 2002; 323: 181-8.

125. Dermond O, Ruegg C. Inhibition of tumor angiogenesis by non-steroidal anti-inflammatory drugs : emerging mechanisms and therapeutic perspective. Drug Resist Updat 2001; 4: 314-21.

126. Marrogi AJ, Travis WD, Welsh JA, Khan MA, Rahim H, Tazelaar H, *et al*. Nitric oxide synthase, cyclooxygenase 2, and vascular endothelial growth factor in the angiogenesis of no-small cell lung carcinoma. Clin Cancer Res 2000; 6: 4739-44.

127. Colville-Nash PR, Gilroy DW, Potential adverse effects of cyclooxygenase-2 inhibition: evidence from animal models of inflammation. Biodrug 2001; 15: 1-9.

128. Donnan GA, Davis SM. Aspirin therapy should be first line: probably, but watch this this space. Stroke 2002; 33:2139-40.

129. Komoike Y, Takeeda M, Tanaka A, Kato S, Takeuchi K.. Prevention by parenteral aspirin of indomethacin-induced gastric lesions in rats: mediation by salicylic acid. Dig Dis Sci 2002; 47: 1538-45.

130. Koki AT, Masferrer JL. Celecoxib: a specific COX-2 inhibitor with anticancer properties. Cancer Control 2002; 9 (2 Suppl): 28-35.

131. Horton JK, Williams AS, Smith-Phillips Z, Martin RC, O'Beirne G. Intracellular measurement of prostaglandin E2: effect of anti-inflammatory drugs on cyclooxygenase activity and prostanoid expression. Anal Biochem 1999; 271:18-28.

132. Su C, Wang MY, Nowicki D, Jensen J, Anderson G. Selective COX-2 inhibition of *Morinda citrifolia* (Noni) *in vitro*. The proceedings of the Eicosanoids and other bioactive lipids in cancer, inflammation and related disease. The 7th Annual Conference, 2001 Oct 14-17. Loews Vanderbilt Plaza, Nashville, Tennessee, USA.

133. Zhang LD, Zhang YL, Xu SH, Zhou G, Jin SB. Traditional Chinese medicine typing of affective disorders and treatment. Am J Chin Med 1994; 22: 321-7.

134. Chang IM. Anti-aging and health-promoting constituents derived from traditional oriental herbal remedies: information retrieval using the TradiMed 2000 DB. Ann NY Acad Sci 2001; 928: 281-6.

135. Chen J, Weng W. Medicinal food: the Chinese perspective. J Med Food 1998; 1: 117-22.

136. Weng WJ, Chen JS. The eastern perspective on functional foods based on traditional Chinese medicine. Nutrition Rev 1996; 54: S11-6.

137. Cheng TO. Hippocrates , cardiology, Confucius and the yellow emperor. Int J Cardiol 2001; 81: 219-33.