Overview of Tabebuia avellanedae

This section introduces the botanical data, benefits and research trends of Tabebuia avellanedae, commonly known as “Taheebo”.

I. Basic Data

■Introduction

Tabebuia avellanedae (hereinafter abbreviated as "TA") is a medicinal plant of the Bignoniacese family that is native to South America. Its bark has been used in Brazilian folk medicine since long ago, even as far back as the Inca Empire whose advanced civilization spread across South America over 500 years ago. Early settlers worshipped the tree as a blessing of the gods and called it Taheebo, meaning "light," from whence it gets its name today.

Tabebuia avellanedae (Taheebo) tree

■Scientific Name

Bignoniaceae Tabebuia avellanedae Lor.ex.Gris

■Common Name Taheebo (Ipe Roxo)

■Habitat Brazil (Amazon River Basin), Northern Argentina, some areas of Paraguay

■Characteristics

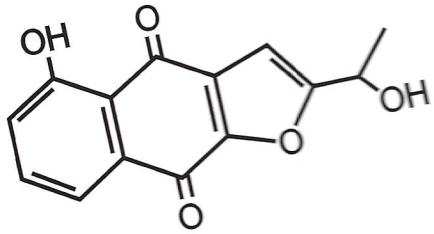
With a trunk diameter of 1.5 m and height of about 30 m, a mature tree is mammoth in size. Its wood is hard and heavy, to the extent that it does not float on water. Its flowers are reddish-violet in color and bloom between mid-July and August. Because of the climate, soil and other habitat conditions it requires, it is a difficult tree to cultivate.

■Similar Trees

There are over 100 species of tree in the Tabebuia genus. In Brazil, they are known as Ipe, Ippe, Ippi, Pau d'arco, Ipe Uba, etc. They are flowering trees that bloom in white, yellow, pink, crimson, violet, orange and other colors, but are mainly classified into white, yellow and violet. The yellow species, called ipe amarelo, is the national flower of Brazil. Within the Tabebuia genus, it is the ipe roxo (ipe violet), a species classified as violet in color, which is the most numerous at over 50 species. TA blooms a reddish-violet flower, so it is a variety of ipe roxo.

■Efficacy

Botanists, pharmacists and chemists have verified through years of scientific research that TA contains a naphthoquinone-based compound active ingredient, code-named "NQ801" in drug development, and its benefits have drawn the attention of the medical world in recent years. In research done by the late Dr. Shinichi Ueda (1932–1996), assistant professor at the Faculty of Pharmaceutical Sciences of Kyoto University, and Professor Harukuni Tokuda of the Department of Pharmacology at the Kyoto Prefectural University of Medicine, NQ801 was found to inhibit the growth of 21 types of cancer cells, first and foremost of note being lung cancer. It has also been identified as being selectively toxic in that, in doses that are effective against cancer, it has almost no impact on healthy cells. Dr. Takusaburo Ebina formerly of the Miyagi Cancer Center (currently Professor at Tohoku Fukushi University) announced in an academic paper that TA containing NQ801 was effective towards suppressing the invasive metastasis of cancer cells, inducing apoptosis and inhibiting angiogenesis.
Moreover, South American botanist Dr. Walter Radamés Accorsi (1912–2006, Professor Emeritus at The University of São Paolo) reported in his research that TA has various benefits beside anticancer activity, specifically including anti-inflammatory, pain relief and diuretic effects.



[Figure 1]
Chemical structure of NQ801
(2-[1-hydroxyethyl]-5-hydroxynaphtho [2, 3-b]-furan-4, 9-dione)

■Scientific Research Begun by Dr. Accorsi

Over the course of 50 years of investigation and research of medicinal plants, Dr. Accorsi discovered the effect that TA has on leukemia and cancer, and that TA growing in a specific region of the Amazon River Basin has a higher effect than trees of the same species that grow elsewhere. Later, a research team of Dr. Ueda and Professor Tokuda backed Dr. Accorsi's work by identifying a naphthoquinone compound that inhibits the growth of cancer cells in the inner bark of TA harvested from that specific area*.

* It must be noted that, even natural plants of the same species can have markedly different components due to habitat conditions (climate, soil, etc.).

Tabebuia avellanedae (Taheebo) flower

II. A Tree from the Gods

Since ancient times, people have conveyed to their descendants through word of mouth that which is healthy for the body. Through folklore especially, they have handed down medicinal plants of long proven efficacy against illnesses and ailments. TA is one of those plants and, because its effect has been recognized, it has been know through to today as a "tree from the gods." In fact, since no record of epidemic can be found in historical reviews of areas where settlers have known of TA, TA is believed useful towards preventing epidemics, etc.

Known as "taheebo", TA is used widely throughout Japan, with the most common way of ingesting it being by boiling the powder of the inner bark and drinking it. More recently, a spray-dried extract powder and soft capsules containing the extract have become available. Amongst users are many persons with a diversity of conditions who seek the benefits of TA.

In recent years, up-to-date scientific explanations for household remedies like TA have become necessary, so researchers focused on TA are conducting analyses via human cells and animal tests. Furthermore, due to the importance of food safety, clinical tests have been underway alongside these analyses towards revalidating efficacy and safety in humans.

III. Effective Component

About 20 years ago, Professor Wagner et al. of Germany identified many compounds of various species of the Tabebuia genus through component and structural analyses. Amongst those found were many naturally occurring aromatics, which launched hopes of the tree's efficacy as a bioresource. Of the compounds contained in this tree, attention in recent years has turned to those classified as quinone natural pigments, many of which are important as medicines. Wagner et al. isolated lapachol, a naphthoquinone, as a biologically active substance and aggressively researched it, but their only conclusion was that it had about the same activity as existing antitumor drugs, so research into anticancer drugs was halted and remains on hold to this day. Nevertheless, lapachol is sold today as a reagent and used as a biological activity reference material for the leading antitumor drug Mitomycin that belongs to the same benzoquinones. In Japan, the previously mentioned team of Ueda et al. took the inner bark of TA growing in the specific area and isolated an effective component – 2-(1-hydroxyethyl)-5-hydroxynaphtho(2, 3-b)-furan-4, 9-dione (code-named "NQ801" in drug development) – possessing a chemical structure of stronger biological activity (Fig. 1) than lapachol. They then tested and verified the efficacy of powder from the inner bark and NQ801 on its own against "cancer".

They subsequently patented NQ801 as a pharmaceutical preparation for cancer patients in Japan, the USA, Taiwan and China. They also researched its organic synthesis, eventually establishing and patenting a method of asymmetric synthesis for chemically producing the natural compound of NQ801, which is serving pharmaceutical research.

Chemically synthesized NQ801

IV. Basic Experiments and Applications to Humans

Professor Tokuda has conducted tests using a reagent taken from TA bark with the objective of applying it to cancer patients. Employing a simple method and human-derived lymphoma, he looked at the antitumor action on healthy human organs and cancer cells in search of a cancer preventing effect, and analyzed the maximum efficacy in small dosages. With that same reagent, he also carried out detailed analyses of the distinctive dynamics of the signal transduction system that is closely related to cancer cell growth.

On a higher level, he also selectively infected small animals – genetically stable mice in particular – with a substance known to cause cancers in humans, and analyzed the efficacy in humans using that same approach. Results showed promise in terms of cancer prevention.

In order to further evaluate that function in humans, Professor Tokuda analyzed TA-derived substances in serum. He examined its efficacy for application to humans by reviewing data from numerous prior cellular and animal tests and the premises in reported cases of persons who drank a beverage brewed from TA bark. From that work, he concluded that determinations without adequate evidence were still being carried out within the bounds of Western medicine. Yet, as a recently reported case on the digestive track showed progress that predicts cancer regression without any significant side effects, he is providing consumers with useful information by accumulating such evidence.

V. Importance for Cancer Patients

Japan has enacted the Basic Act on Cancer Control Measures in recognition of the importance of measures for controlling cancer, but the number of individuals contracting this disease continues to grow. At the present time, one in every two people in Japan has some form of cancer and there are those who will die from it, resulting in cancer being designated a national disease. In particular, there has specifically been a marked increase in lung cancer. Though there are many possible causes, there is much that is unknown about its origin and an improvement effect has yet to be observed.

The 60 trillion cells that make up the human body go through a repeated cycle of incessant destruction and regeneration in many locations. Perhaps it is the fate of higher order animals, but it has been pointed out in numerous reports that, as this situation progresses, a malignant cancer is likely to appear somewhere in our bodies.

In a report from the USA some years ago, it was also pointed out that the fine complexities of cancer differ considerably by organ, tissue and patient, and there was still great difficulty in identifying them all. Professor Tokuda has advocated the peaceful coexistence and coprosperity with cancer rather than aggressively fighting it. To that end, it is important that information on efficacy vis-à-vis cancer be provided, that we come to clearly understand meaningful information like that, and that we make it a part of our daily life.

The TA discussed in this document is very promising and effective as a complementary and alternative treatment for dealing with cancer. From the perspective of coexisting and coprospering alongside cancer as well, consuming a brewed beverage of TA bark on a daily basis should be useful towards maintaining one's health. Basic and applied research on TA will be promoted widely and actively in the future, with the hope for its possibilities and of developing the efficacy unobtainable by modern medicine.

Action and Benefits of Components Contained in Tabebuia avellanedae

Tests are underway with animals and human cells to study the action and benefits of the components found in Tabebuia avellanedae. Several examples are presented in this section.

I. Tests on Cultured Human Cancer Cells and Healthy Human Cells

The anticancer efficacy and safety of NQ801* contained in Tabebuia avellanedae was tested as described below. The cancer cells ① to ⑳ in Table 1 were collected by trypsinization (technique for isolating cells from tissue by trypsin separation), while those of ㉑ to ㉓ were collected by suspension culture (suspension and culturing of cells in a solution similar to animal body fluid). The healthy cells in ㉔ were collected by trypsinization, those of ㉕ and ㉖ by direct extraction, and those of ㉗ by sampling peripheral blood from healthy adults.

To observe and measure these cells to a high degree of accuracy, the cells were transferred to a 96-well microplate at a constant density (10 x 10 cm3 cell/㎠), disseminated in DMEN and RPMI-1640 culture medium containing the fetal bovine serum needed for cell growth, and cultured for 24 hours according to protocol. After culturing, NQ801 that had been dissolved in DMSO (dimethyl sulfoxide solution) was added to the wells in a consistent quantity. Cell counts were checked after 24, 28, 48 and 72 hours.

■Test Results

Table 1 Effect of NQ801 on Malignant Tumors and Safety of Healthy Cells

Units: ng/ml

	Cell	LD50, IC50
Malignant cancer cells	① Human lung adenocarcinoma A549 cells	9.5
	② Human lung adenocarcinoma VMRC-LCD cells	13.0
	③ Human lung adenocarcinoma SK-LU-1 cells	17.0
	④ Human lung squamous cell carcinoma Calu-1 cells	17.0
	⑤ Human colon adenocarcinoma WiDr cells	11.0
	⑥ Human prostatic carcinoma LNCaP cells	1.7
	⑦ Human vaginal squamous cell carcinoma A431 cells	21.0
	⑧ Human cervical cancer HeLa cells	18.0
	⑨ Human biliary carcinoma HuCC-T1 cells	20.0
	⑩ Mouse skin melanoma B16 (M4) cells	6.7
	⑪ Human pancreatic carcinoma ASPC-1 cells	17.0
	⑫ Human neuroblastoma IMR-132 cells	10.0
	⑬ Human lung small cell carcinoma SCCH-194 cells	10.0
	⑭ Human bladder cancer T24 cells	21.0
	⑮ Human renal adenocarcinoma VMRC-RCW cells	19.0
	⑯ Human stomach cancer NUGC-2 cells	17.0
	⑰ Human thyroid cancer 8305C cells	25.0
	⑱ Human liver cancer HuH-7 cells	5.5
	⑲ Human ovarian carcinoma TYK-nu cells	17.0
	⑳ Human choriocarcinoma BeWo cells	18.0
	㉑ Human breast cancer MRK-nu-1 ce	12.0
	㉒ Human malignant lymphoma B cells	5.6
	㉓ Human chronic myelocytic leukemia K562 cells	14.0

	Cell	LD50, IC50
Healthy cells	㉔ Human normal fibroblast N6KA cells	84.0
	㉕ Human normal tracheal epithelial cells	>55.0
	㉖ Human normal nephrocytes	65.0
	㉗ Human normal peripheral blood lymphocytes	84.0

* LD50 and IC50 indicate the concentration at which NQ801 inhibits 50% growth of malignant tumor cells and healthy cells in humans and mice.

■Observations and Conclusions

NQ801 strongly inhibited the growth of and killed malignant tumors ① to ㉓ in low concentrations of 5.5 to 22 ng/ml, while that effective dose did not restrict the growth of or kill healthy human cells. These results confirm that NQ801 is selectively toxic to malignant tumor cells.

II. Stage-2 Lung Cancer Suppression Tests in Mice

The effect of NQ801 contained in Tabebuia avellanedae to suppress lung cancer in mice was tested as follows.

Tests were conducted with 15 ICR male mice placed in a single cage and allowed to freely ingest solid feed and water. After raising the mice for one week prior to testing, a reagent of 4-nitroquinoline N-oxide (4NQ0) dissolved in a 20:1 solution of olive oil and cholesterol was injected subcutaneously into the back of 6-week old mice, at a quantity of 10 mg per kg of body weight. Then, from the fifth week after that, the mice were allowed to freely and orally ingest 8% glycerol as a tumor promoter.

For 25 weeks, the positive control group that did not take NQ801 was fed 8% glycerol in addition to the 4NQ0 treatment, while the test compound group that was fed NQ801 was allowed to freely ingest 8% glycerol that contained 0.1 ng/ml of NQ801. In the thirtieth week after the start of testing, the mice were subjected to cervical dislocation then dissected, where their lungs were removed and preserved in formalin solution. Adenomas that formed in the lungs were observed and counted under microscope, and comparisons were made between the positive control group and the group that ingested NQ801.

■Test Results

Table 2 Adenoma Count and Incidence in Mice Lungs

Test group	Adenomas	Adenomas per mouse	Mice with adenomas
Ⅰ Given only water to drink	0	0	0
Ⅱ Given only 8% glycerol to drink	0	0	0
Ⅲ Given only water to drink after ingesting 4NQ0	3	0.2	13.3
Ⅳ Given only 8% glycerol to drink after ingesting 4NQ0	48	3.2	100
Ⅴ Given 8% glycerol solution containing 0.1 ng/ml of NQ801 to drink after ingesting 4NQ0	9	0.6	33.3

■Observations

In the thirtieth week after the start of testing, the test group that ingested NQ801 developed 1/3 less adenomas than the positive control group, thereby confirming the effect that NQ801 has on suppressing lung adenoma formation.

III. Stage-2 Skin Cancer Suppression Tests in Mice

The effect of NQ801 contained in Tabebuia avellanedae to suppress skin cancer in mice was tested as follows.
Tests were conducted with 15 ICR male mice placed in a single cage and allowed to freely ingest a commercially available solid feed and water until testing was completed.
The next day, the backs of 6-week old mice were shaved and a 0.1 ml acetone solution of 390 mol of 7, 12-dymethylbenz[a]anthracene (DMBA) was coated on the shaved location as a cancer initiator. After 1 week, a 0.1 ml acetone solution of 1.7nmol of 12-0-tetradecanoylphorbol 13-acetate (TPA) was similarly coated twice a week, for 20 weeks, on the same location as a cancer promoter. As the test drug, one group of 15 mice was coated with 0.1 ml of acetone, and another group of 15 mice was coated with a 0.1 ml acetone solution containing 85 nmol of NQ801 one hour before the promoter application, and the suppressive effect was observed in the group treated with NQ801. Results were recorded as the percentage of mice in each group with papillomas of 1 mm or more, and the number of papillomas per mouse.

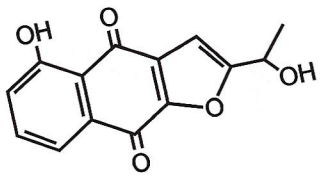
■Test Results

Charts 1 and 2 show the effect of NQ801. Charts 3 and 4 show the effect of lapachol.

■Observations and Conclusions

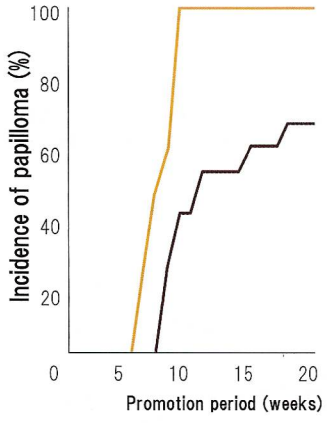
It was determined that NQ801 can be used as a tumor promotion inhibitor and possibly used as a cancer prevention drug.

* 2-(1-hydroxyethyl)-5-hydroxynaphtho(2,3-b)-furan-4, 9-dione (code-named"NQ801"in drug development)

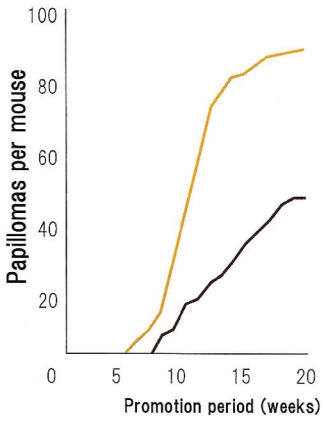


【Stage-2 skin cancer suppression tests in mice】

[Chart 1]

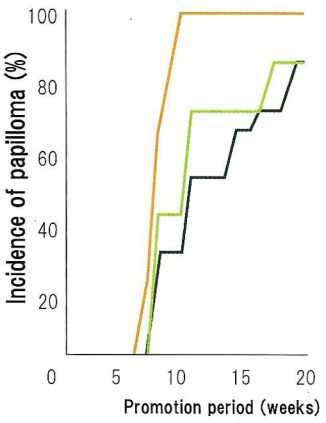


[Chart 2]

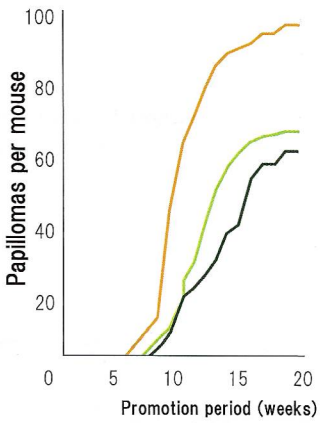


DMBA (390nmol) + TPA (1.7nmol)
DMBA (390nmol) + NQ801 (85nmol) +TPA (1.7nmol)

[Chart 3]



[Chart 4]



DMBA (390nmol) +TPA (1.7nmol)
Post-treatment with lapacoal (85nmol) 60 minutes before TPA
Pretreatment with lapacoal (85nmol) 60 minutes before TPA

IV. Tests on Human Lung Cancer Cells

The effect of NQ801 contained in Tabebuia avellanedae on human lung cancer cells was tested as follows.

■Observations

As shown by Charts 5 to 8, it was verified that the human lung cancer cells were almost completely suppressed by the addition of 11.2 to 16.8 ng/ml of NQ801, while almost all of the cancer cells were killed by a concentration of 33.5 to 55.4 ng/ml.

■Conclusions

As can be seen by the given test results, NQ801 exhibited a good antitumor effect on various types of cancer and can be used safely. It was also understood that NQ801 works in the promotion stage, which is an important process when normal cells transition into cancer cells because of chemical carcinogens or viruses.

【Effect on human lung adenocarcinoma cells】

Chart 5 Growth inhibition and lethal affect of NQ801 on human lung adenocarcinoma A549 cells

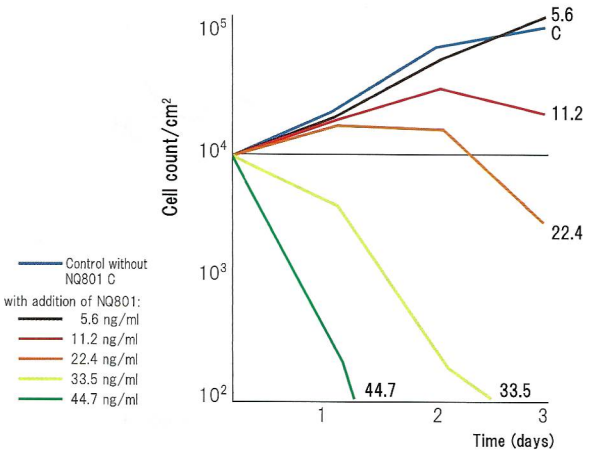


Chart 6 Growth inhibition and lethal affect of NQ801 on human lung adenocarcinoma VMRC-LCD cells

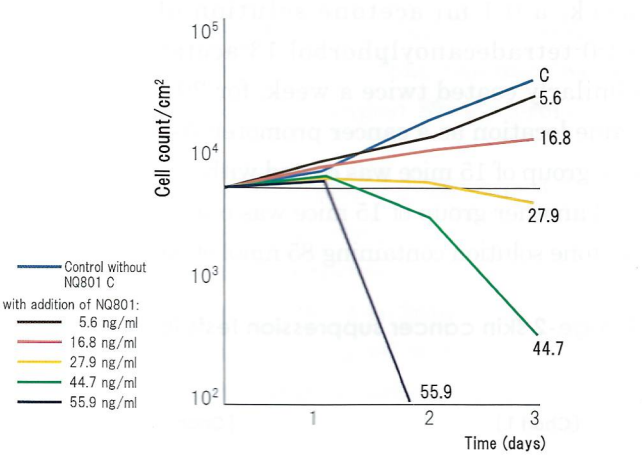


Chart 7 Growth inhibition and lethal affect of NQ801 on human lung adenocarcinoma SK-LU-1 cells

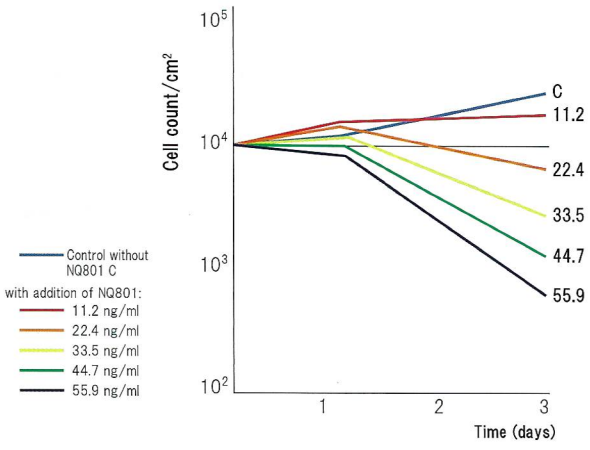
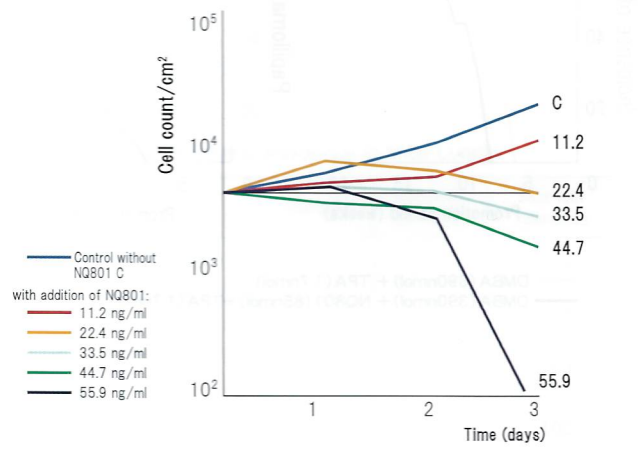
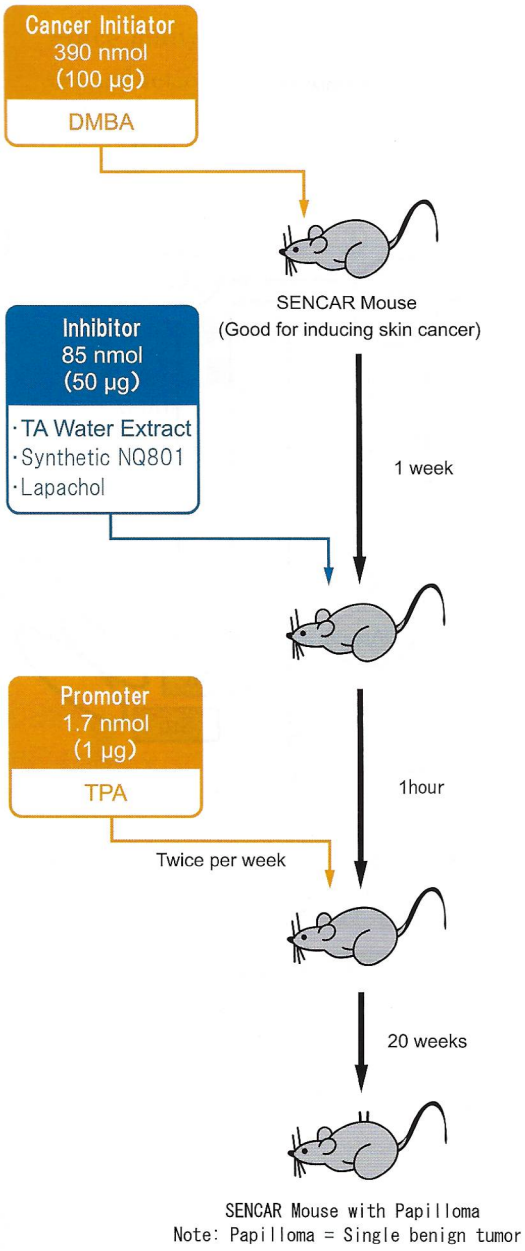
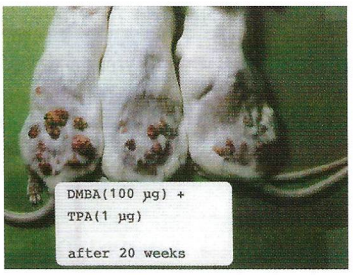


Chart 8 Growth inhibition and lethal affect of NQ801 on human lung squamous cell carcinoma Calu-1 cells



V. Effects of Tabebuia avellanedae (TA) Water Extract, Synthetic NQ801 and Lapachol on Stage-2 Skin Cancer in Mice





Untreated

Injected with Tabebuia avellanedae water extract

Chart 9 Effect of Tabebuia avellanedae water extract on stage-2 skin cancer in mice

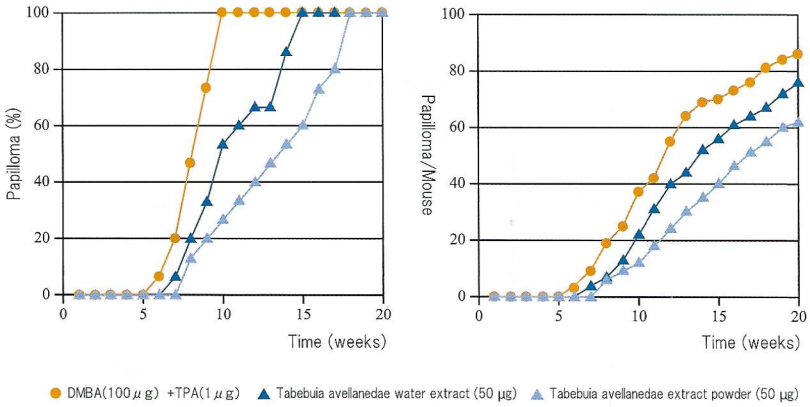


Chart 10 Effect of naphthoquinone containing Tabebuia avellanedae water extract on stage-2 skin cancer in mice

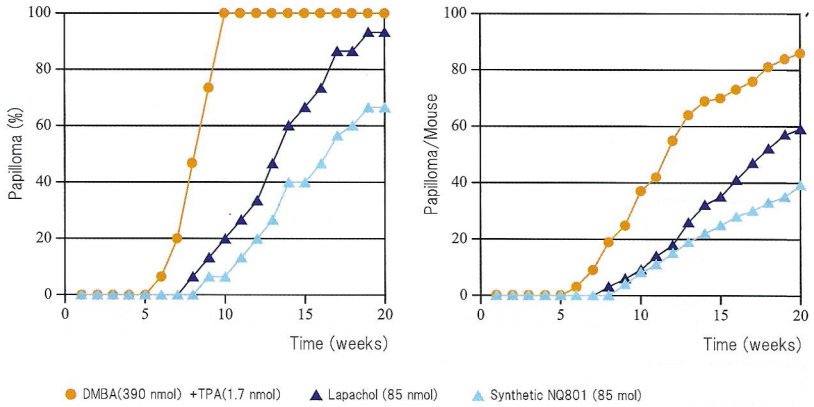


Table 3 Cancer growth suppression effect of Tabebuia avellanedae(TA) water extract

Survival rate (%)

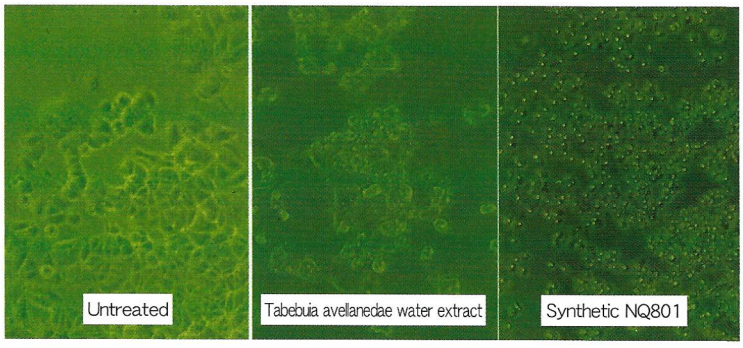
Dosage (mg)	MCF-7 (Human breast cancer cell)		SVCT-M12 (Human normal mammary gland cell)	
	TA water extract	NQ801-fortified taheebo extract powder	TA water extract	NQ801-fortified taheebo extract powder
3	40	0	60	40
1.5	90	20	100	80
0.15	100	50	100	100
0.015	100	100	100	100
0.010	100	100	100	100

Table 4 Cancer growth suppression effect of synthetic NQ801

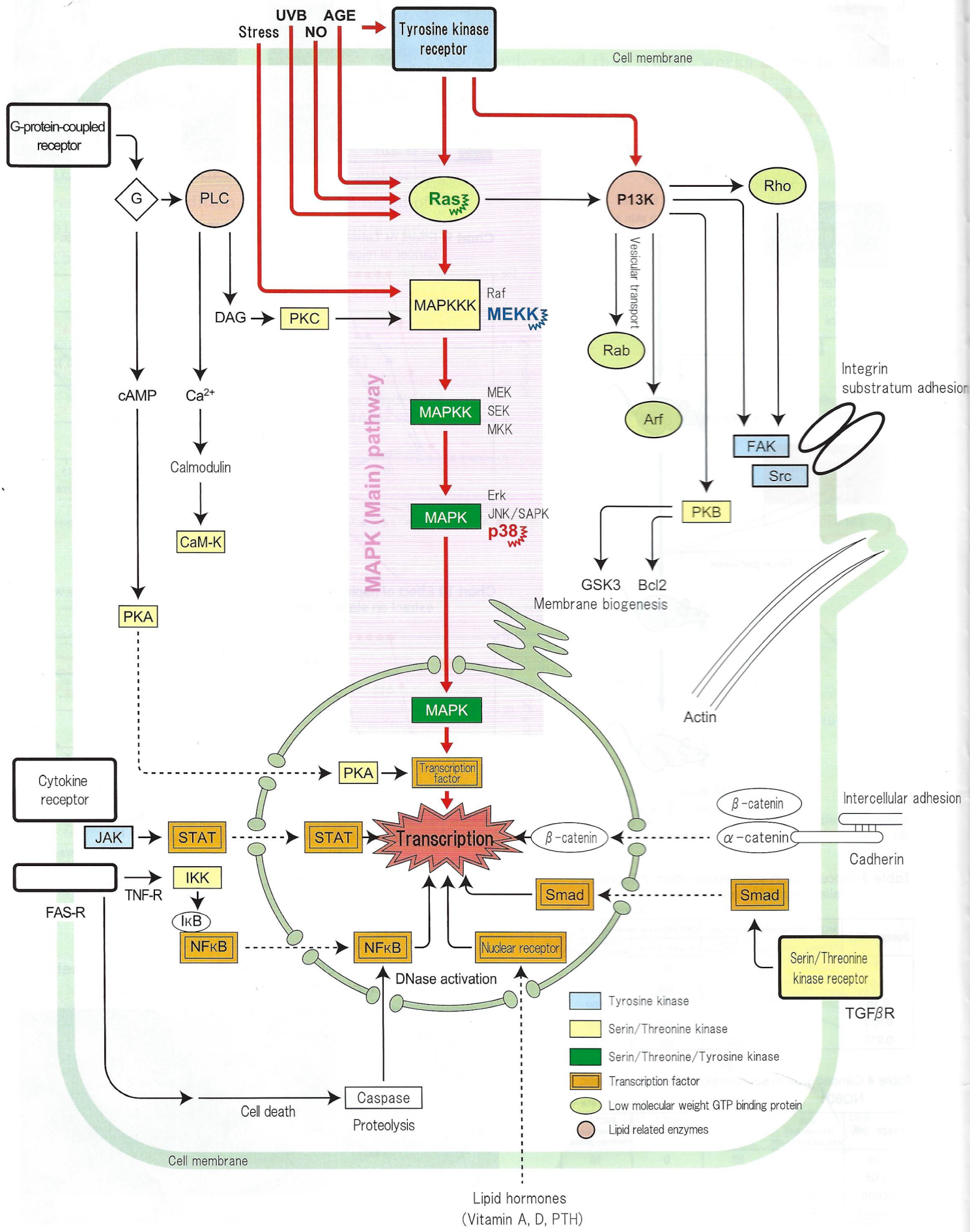
Survival rate (%)

Dosage (mM)	A549 (Human lung adenocarcinoma cell)	Hs888Lu (Human normal lung cell)	MCF-7 (Human breast cancer cell)	SVCT-M12 (Human normal mammary gland cell)
0.05	0	20	0	10
0.005	20	60	10	50
0.0005	60	90	50	90
0.00005	90	100	80	100

Effect of Tabebuia avellanedae water extract and synthetic NQ801 on MCF-7 cells (human breast cancer cells)



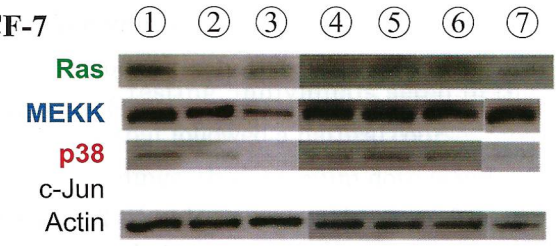
VI. Outline of Signal Transduction in Cells



Ⅶ. Analysis of Signal Transduction in Cellular Malignant Transformation

It has been established that genetic changes occur in the process of a cell becoming cancerous. Since many of those products have been found to function as transmitters, analyzing signal transduction as the detailed nature of this malignant transformation is now understood to be logical and effective.

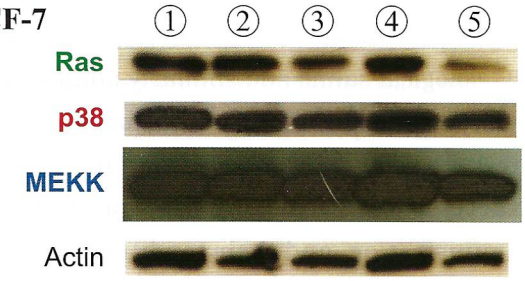
【1】 MCF-7



① Untreated
② Reaction 1 day after administering 1.5 mg/ml of TA extract powder
③ Reaction 1 day after administering 0.0025 mM of NQ801
④ Reaction 1 day after administering 0.3 mg/ml of TA extract powder
⑤ Reaction 1 day after administering 0. 5 mM of aspirin
⑥ Reaction 1 day after administering 3 mg/ml of TA extract powder (without dextrin)
⑦ Reaction 3 days after administering 1.5 mg/ml of TA extract powder

Human breast cancer cells (MCF-7) were treated with NQ801 and protein levels were analyzed as a useful test for analyzing the effect of NQ801 on breast cancer, which is very frequent amongst women in Japan and the USA. By examining protein levels, it became clear that NQ801 acted on p38 at a midpoint of the MAPK (main) signal transduction pathway that takes part in the malignant transformation process. It was also learned that it acted on Ras. (See the diagram on P2-6.) These findings suggest that the detailed mechanism that actually acts on breast cancer patients acts on the MAPK pathway and leads researchers to believe that the active mechanism of NQ801 is a prerequisite of inhibiting growth of breast cancer cells.

【2】 MCF-7



① Untreated
② Reaction 3 days after administering 150 mg/ml of TA extract powder
③ Reaction 3 days after administering 0.00025 mM of NQ801
④ Reaction 3 days after administering 0.0025 mM of NQ801
⑤ Reaction 1 days after administering 0.025 mM of NQ801

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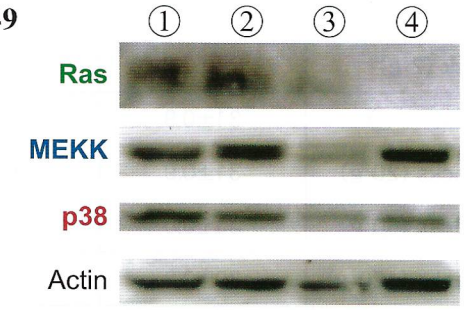
Even under modified conditions, studies of the MAPK pathway of breast cancer cells suggest that NQ801 acts on Ras and p38. These findings verified NQ801 as a more detailed effect mechanism for breast cancer.

【3】 A549



① Untreated
② Reaction 1 day after administering 0.0025 mM of NQ801
③ Reaction 3 days after administering 0.005 mM of NQ801
④ Reaction 3 days after administering 0.0005 mM of NQ801

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Similar studies were done on A549 human lung cancer cells as lung cancer is very prevalent in Japan. As thought, changes were observed in the MAPK pathway with action at p38 and so forth, suggesting that the biological activity of NQ801 provides a more detailed mechanism of inhibiting growth of lung cancer cells.

Ⅷ. Physical Effect on Mice Orally Administered NQ801-fortified taheebo extract powder

■Outline

It has been found that an NQ801-fortified taheebo extract powder, which adds high concentration natural NQ801 to commercially available TA extract powder, has helped mainly to reverse or slow the malignant process in cancer patients.

Just the commercially available TA extract powder alone reduced cancer growth a slight amount, but when the NQ801-fortified taheebo extract powder was used, a marked preventative effect was seen in cancer-induced mice.

Studies were done to identify the most effective and adequate dose of this NQ801-fortified taheebo extract powder. SENCAR mice were forcefully administered physiological saline and a solution of the NQ801-fortified taheebo extract powder for 3 consecutive days and were then observed for a few days. In this test, 1 pack of NQ801 contained 2g of fortified taheebo extract powder. As a result of administering 60 packs (120 g) to humans, very little difference from the normal state was observed, while after administering 30 packs (60 g), absolutely no difference was seen from the controls that were administered only physiological saline. From these findings, less than 60 packs were estimated appropriate for force-feeding to mice, and that dose is viewed as useful towards both treating and preventing cancer inducement and cancer risk.

■Overview

Surgical intervention, immunological treatment, chemotherapeutic treatment and variations thereof have been developed as trial treatments for fighting cancer.

However, treatment with medicinal plants is an undeveloped area of cancer therapy that is stirring hopes. With this approach, the intake or dosage of medicinal plant components is important, as weight loss, physical discomfort and other side effects constitute risk factors to maintaining a normal physical condition.

For this reason, various studies have been conducted for the purpose of identifying the appropriate amount to administer. Commercially available TA extract powder is currently used an NQ801-fortified taheebo extract powder that was developed to be more effective by including a higher concentration of NQ801 extract in a designer food configuration.

■Materials and Method

The following suspensions of physiological saline and the NQ801-fortified taheebo extract powder (packaged from TA extract powder) were used as the test articles.

1 mg/0.2 ml saline … (equates to 2 g/pack when converted into human intake)
3 mg/0.2 ml saline ····· 3 packs (6 g)
8 mg/0.2 ml saline ····· 10 packs (20 g)
24 mg/0.2 ml saline ····· 30 packs (60 g)
48 mg/0.2 ml saline ····· 60 packs (120 g)

To the untreated mice that served as the control, 0.2 ml of physiological saline alone were forcefully administered, while the test articles were prepared as suspensions of the specified amount of the NQ801-fortified taheebo extract powder in 0.2 ml of physiological saline and similarly administered for 3 consecutive days. After that, the mice were observed for 1 week and then processed for examination exactly 1 week from the first day of test article administration, and their condition was evaluated. Each group had 5 mice.

■Results

Dose	Final body weight (g)	Individual physical condition
Physiological saline	31±0.5	−
1 pack (2 g)	31±0.3	+*
3 packs (6 g)	31±0.9	+
10 packs (20 g)	31±0.9	+
30 packs (60 g)	31±0.6	+
60 packs (120 g)	30±0.8	+**

−: No abnormalities
+: Affected only by forced administration
++: Slowed activity
+++: Inactive
*: Affected by forced administration for 3 consecutive days
**: No abnormalities observed on final test day

■Conclusions

In general, attention is given only to the effect of health products, but it is important to first and foremost establish their safety. These tests looked for the optimum dose of NQ801-fortified taheebo extract powder in groups of 5 mice. In detailed observations of all individuals, no marked disorders were detected during the test period even after administering quantities 20 times the currently recommended dose, and, at the end of testing, individuals acted in the same way as mice that followed a natural course.
Based on these findings, this optimum dose is judged adequate and reliable. Future research will be directed at further elucidating safety and efficacy.

■Cautions in Using NQ801-fortified taheebo extract powder

It should be noted that the aforementioned data was obtained from tests with mice maintained in a controlled environment with controlled activities and feeding conditions. Therefore, consideration must be given to other factors in using NQ801-fortified taheebo extract powder.

An Examination of Supplement Dose Dependence and Safety in Integrative Medicine for Cancer: Based on the Experience of Tabebuia avellanedae, a South American Medicinal Plant Commonly Known as Taheebo

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【Abstract】

Clinical research of NQ801 extracted from Taheebo was tested for anti-tumor effects, dose dependence and safety of cancer patients. 4 advanced cancer patients were given daily NQ801 by oral ingestion during 3 months, and afterwards 3 times dose NQ801 were taken during more 3 months. As a result, NQ801 made to reduce the tumor in 3 patients in 4. In addition dose dependence effect of NQ801 was seen. And also no negative side effects were seen in this clinical examination.

The "NQ801" is suggested from above that it is the anti-tumor effects, dose dependence and safety of cancer patients.

Key words : Integrative medicine for cancer, NQ801, Dose dependence, safety of cancer patient

Introduction

Supplements have various roles in integrative treatment of cancer, such as improving effects on the body' s internal environment (improvement of the gut environment, antioxidant effect, detoxifying effect, nutrient supplementation, and enhancement of the metabolism), and also immunostimulatory effect, inhibition of neovascularization, induction of cancer cell apoptosis, analgesic effect, etc. Various basic studies have been carried out on the effects of such supplements, and the results of clinical studies have also been reported from many medical institutions.

NQ801 is extracted from the inner bark of the tree Tabebuia avellanedae (common name taheebo), a medicinal plant native to South America that grows naturally in certain regions. NQ801 is the code name for the effective component, 5-hydroxy- 2-(1-hydroxyethyl)-naphtho[2,3-b]furan-4,9-dione1), which has a chemical structure that gives strong biological activity, and was isolated by a Kyoto university research group. The anticancer activity of NQ801 has been studied. It is reported to have (1) direct effects[2),3)] (selective toxicity, induction of apoptosis, inhibition of neovascularization, and suppression of metastasis and infiltration), (2) indirect effect[2),3)] (immunostimulation), and (3) auxiliary effects (antioxidant effect[4)], analgesic and sedative effect, and anti-inflammatory effect), on cancer cells[5),6),7)].

In the present study, we examined the anticancer effect of NQ801 clinically in cancer patients. We also carried out clinical investigations on the dose dependence of NQ801' s effect, and its safety, using the newly developed product X6. X6 is a fortified taheebo extract powder prepared by adding a group of fractionated and extracted components that includes NQ801, called "NQ801 fraction", at six times (1.8 mg) the standard dose (0.3 mg) of NQ801 so far used in clinical studies.

I. Methods

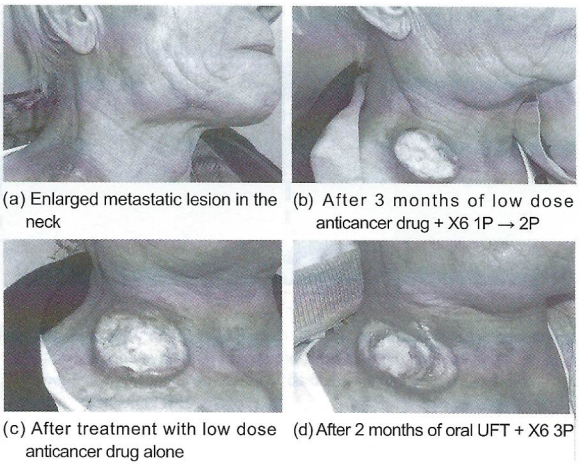
Four terminal cancer patients (Case 1: Cancer of the tongue metastasized into the neck, Case 2: Cancer of the upper jaw and buccal mucosa, Case 3: Cancer of the upper jaw, and Case 4: Rectal cancer), who had been informed by other hospitals that all their treatment options had been exhausted, were treated by giving 1.8 mg (1P)/day of X6 (NQ801-fortified taheebo extract powder) for three months, after explaining the treatment to them and obtaining written consent. During the next three months, the dose was raised to 3P (5.4 mg) /day, and the anticancer effect, effect on QOL and safety of the X6 supplement were evaluated clinically. Low doses of anticancer drugs, etc that the patients were taking before the start of the X6 treatment were continued so that the patients would not be deprived of the benefits of the integrative treatment. But, no additional supplements, which the patients were not taking earlier, were given. One patient (Case 3), as desired by him, continued the high dose vitamin C drip that he was receiving before the X6 treatment.

II. Results

【Case 1】 Tongue cancer metastasized into the neck (80-year-old male)

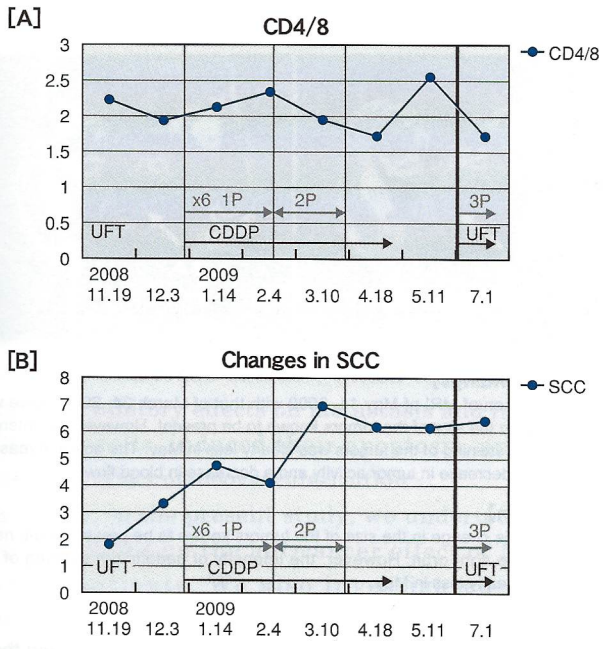
The patient had T2N2 cancer of the tongue in the year X, and had severe tongue pain and eating disorder. He underwent only partial resection of the tongue cancer because of his advanced age and his alcoholic hepatitis. He was taking only UFT 400 mg orally for the metastatic foci in the neck lymph nodes, and he was under observation. However, in the year X+1, the metastatic foci in the neck started to increase in size (Fig. 1-a). Therefore, low dose of anticancer drug (CDDP 5 mg/body, iv drip, once a week) treatment concurrently with 1P/day of X6 was given for two months. But, as the metastatic foci in the neck continued to enlarge, the dose of X6 was increased to 2P/day and the concurrent treatment continued for another month. But,the

metastatic foci in the neck continued to grow (Fig. 1-b) and the tumor marker SCC increased (Fig. 2 [B]) during that time. However, the QOL did not decline and the patient could go on family trips to Guam and Okinawa from Hokkaido. Despite the increase in size of the metastatic foci, the CD4/8 ratio was maintained, which suggested that there was no decrease in immunocompetence (Fig. 2 [A]), and the QOL was maintained with improved liver function. No X6 was given during the next four months, and only the low dose treatment with the anticancer drug was continued. The metastatic foci increased in size (Fig. 1-c), and the CD4/8 ratio (immunocompetence) also worsened. Therefore, the low dose treatment with the anticancer drug (CDDP 5 mg/body, iv drip, once a week) was stopped. Instead, oral administration of UFT 400 mg concurrently with the increased dose of 3P/day of X6 was started. After two months of this treatment, the tumor in the neck was localized, as shown in Fig. 1-d, and the QOL during this period remained good.



(a) Enlarged metastatic lesion in the neck
(b) After 3 months of low dose anticancer drug + X6 1P → 2P
(c) After treatment with low dose anticancer drug alone
(d) After 2 months of oral UFT + X6 3P

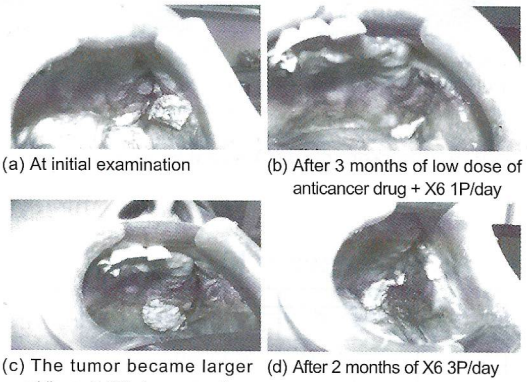
(Fig.1) Case 1: Neck lymph node metastasis of tongue cancer



(Fig.2) Case 1: Changes in immunocompetence (CD4/8 ratio) and tumor marker (SCC) in the course of changing the dose of X6 , 1P→ 3P

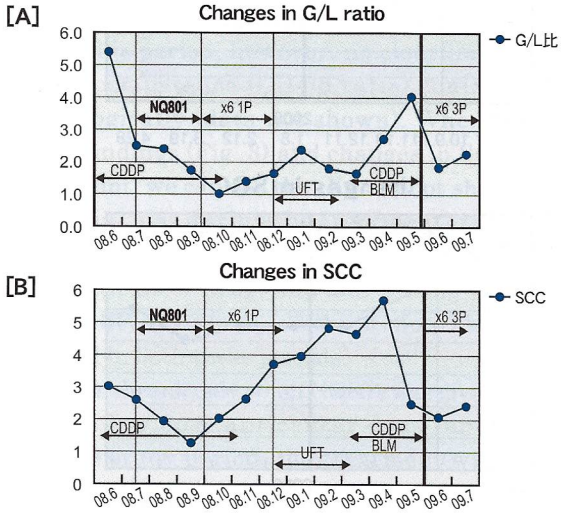
[Case 2] Cancer of the left upper jaw and buccal mucosa (60-year-old)

The patient was first given a low dose of anticancer drug (CDDP 5 mg/body, iv drip, once a week) for the cancer (Fig. 3-a). After that, concurrently with the anticancer drug, the standard dose of NQ801 was given for two months, and then X6 was given at 1P/day for three months (Fig. 4). This improved the granulocyte/lymphocyte (G/L) ratio (parasympathetic dominant state) (Fig. 4 [A]). Along with this change, the tumor also shrank (Fig. 3-b). She was coming for hospital visits in Sapporo from a far away location. As it was winter, the visits were temporarily halted and she was put on oral UFT 400 mg (Fig. 4). Three months later she returned to the hospital with an enlarged tumor (Fig. 3-c). She was put on low doses of anticancer drugs (CDDP 5 mg/body, once a week, plus BLM 5 mg/body, iv drip, once a week) for two months (Fig. 4). The SCC decreased once but the G/L ratio increased as the lymphocyte count decreased, and the tumor increased in size. Even though the anticancer drugs were being given at low doses, she lost appetite and therefore the anticancer drugs (CDDP and BLM, iv drip) were discontinued. Instead, X6 3P/day was started (Fig. 4). Two months after the start of the X6 3P/day treatment, the tumor did not show rapid increase in size though there was no shrinkage either (Fig. 3-d). The G/L ratio improved again (Fig. 4 [A]), and the QOL did not worsen during this period.



(a) At initial examination
(b) After 3 months of low dose of anticancer drug + X6 1P/day
(c) The tumor became larger while oral UFT alone was given
(d) After 2 months of X6 3P/day

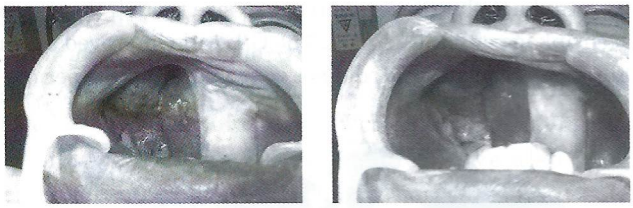
(Fig.3) Case 2: Cancer of the upper jaw and buccal mucosa



(Fig.4) Case 2: CDDP 5 mg/day + NQ801 (2 months) → X6 1P (3 months) → 3P

[Case 3] Recurrence after surgery for cancer of the upper jaw (70-year-old)

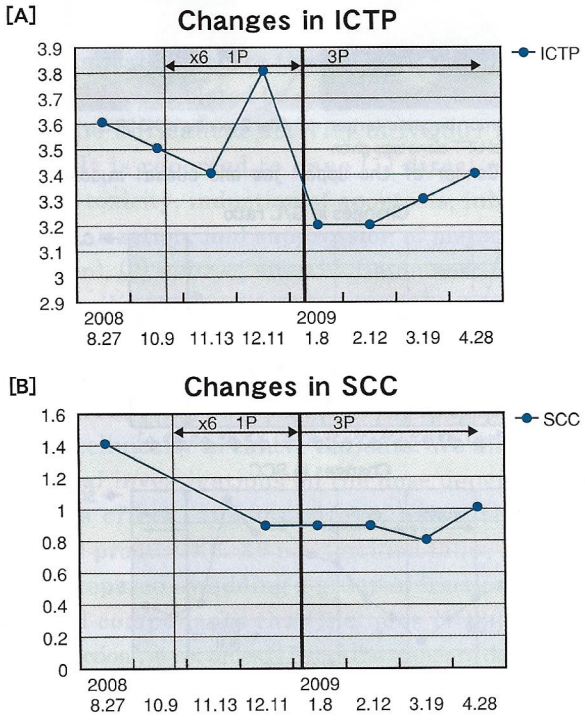
The patient had recurrence of cancer after the surgery and was told in the year X that he would live only for another 6 months, and all treatments were stopped. Since then, the patient received no anticancer treatment or radiotherapy, and volunteered to have Gerson' s diet therapy along with yoga therapy and hot spring therapy. After that, he also had high dose vitamin C drips once or twice a week. The progression of the tumor became very slow, and the patient visited our hospital for the first time in the year X + 3. However, the tumor continued to advance, and the patient started taking X6 1P/day concurrently (Fig. 5-a) from the year X+3. Three months from the start of the X6 treatment, MRI showed that the tumor had not increased in size form the previous observation, and thus the cessation of tumor enlargement could be confirmed for the first time through imaging. After that, X6 was continued at the increased dose of 3P/day, and concurrently, the diet therapy and high concentration vitamin C drip once or twice a week were also continued.



(a) Immediately before the start of the X6 oral treatment

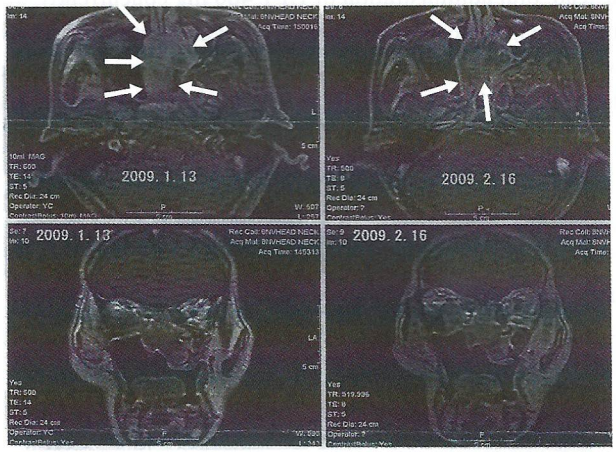
(b) After X6 1P (3 months) and 3P (3 months)

Changes in tumor markers during X6 oral treatment 1P → 3P



(Fig.5) Case 3: Cancer of the upper jaw

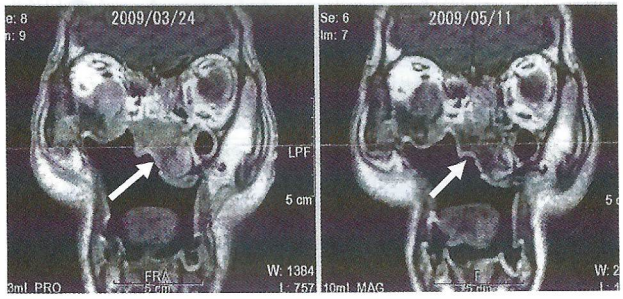
After one month on X6 3P/day, MRI showed shrinkage of the tumor (Fig. 6) for the first time. The MRI finding (Fig. 7) after two months on X6 3P/day led to the comment, "Staining of the tumor by gadolinium has clearly decreased, which suggested decreased tumor activity or decreased blood flow, intravenous injection of gadolinium was smooth, and there was no leakage of the contrast agent". During this period, the tumor marker ICTP increased once and then decreased sharply, whereas SCC decreased continuously (Fig. 5 Bottom). Intraoral observations also showed that the tumor that had been advancing slowly had shrunk (Fig. 5 Top) three months after the dose of X6 was increased form 1P to 3P/day.



【Imaging findings】
In a comparison of MRI of February 16, 2009 with that of January 13, 2009, the residual tumors in the nasal septum, the right orbit, etc appeared to have shrunk slightly.
The post imagining staining intensity also appeared to be slightly less in February.

【Impression】
The residual tumors in the nasal septum, ethmoid sinus, right orbit, etc appeared to have shrunk, though only slightly.

(Fig.6)
Case 3: MRI findings one month after the start of the X6 3P treatment



【Imaging findings】
In a comparison of MRI of May 11, 2009 with that of March 24, 2009, there was little change in the size of the tumors known to be present. However, the intensity of gadolinium staining of the tumors was clearly less in May. The possible reasons for this are a decrease in tumor activity and a decrease in blood flow

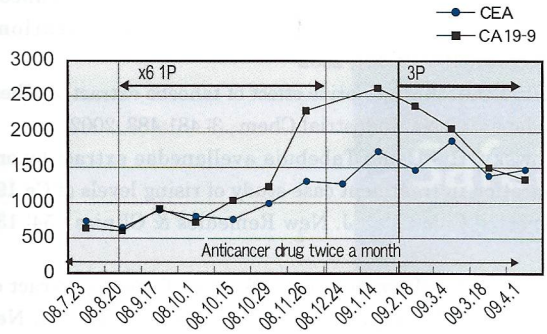
【Impression】
There was little change in the size of the tumors known to be present in the nasal cavity and the right orbit. However, the intensity of gadolinium staining of the tumors was clearly less in May.

Note : The intravenous injection of gadolinium was smooth, and there was no leakage of the contrast agent.

(Fig.7)
Case 3: MRI findings three months after the start of the X6 3P treatment

【Case 4】Rectal cancer metastasized into the lung (46-year-old)

The patient was under treatment at another hospital with anticancer drugs for Stage IV rectal cancer metastasized into the lung. He was then given concurrent treatment of X6 1P/day for four months. There was no sign of tumor shrinkage, and the level of the tumor marker also increased (Fig. 8). However, the QOL was maintained during this period, and the treatment with anticancer drugs was continued. In the following four-month period, when he did not take X6, the tumor further enlarged and the tumor marker also increased. Therefore, X6 was resumed at the higher dose of 3P/day concurrently with the ongoing treatment with anticancer drugs. One month later, the tumor marker decreased, the tumor was seen to have shrunk, and the QOL improved sufficiently for him to return to work.



The tumor marker levels decreased only when the dose of X6 was increased to 3P.

(Fig.8) Case 4: Lung metastasis of Stage IV rectal cancer (46-year-old patient)
Anticancer drug → X6 1P → 3P
(The patient received anticancer drug treatment from the Department of Gastrointestinal Medicine of another hospital, and that hospital provided the data).

Ⅲ. Conclusion

Ueda, Tokuda and coworkers[8),9)] had reported that NQ801 inhibited proliferation of 21 types of cancer cells in vitro, including lung cancer cells, and had selective toxicity, with little effect on normal cells at a dose that was effective against cancer cells. Ebina[2),3)] had reported that T. avellanedae extract, which contains NQ801, showed inhibitory effects on metastasis and infiltration of cancer cells, induced their apoptosis, and had an inhibitory effect on neovascularization.

Therefore, in the present study, we undertook clinical investigations on the anticancer effect of NQ801 in cancer patients. We also investigated the dose dependence of the anticancer effect of NQ801, and its safety, using the newly developed product X6 (NQ801-fortified taheebo extract powder), which contains six times the standard dose of NQ801 so far used in clinical studies. The following conclusions were reached.

【Conclusions from Case 1】

X6 showed anticancer effect, as the tumor became localized in the eighth week after the dose of X6 was increased to 3P/day (Fig. 1), although the disease remained as PD when the dose was 1P/day. The immunocompetence (CD4/8 ratio) was maintained while the patient was taking X6, and showed maximum decrease when the X6 treatment was withheld (Fig. 2 [A]). Along with this decrease, the metastatic foci in the neck also showed the maximum enlargement. The tumor marker SCC showed a temporary decrease when he was under combination therapy of CDDP 5 mg/body and X6 1P/day, and also under combination therapy with 2P/day of X6. But, overall it increased (Fig. 2 [B]). Nevertheless, his QOL was maintained during this period, and he could travel from Hokkaido to far away places without incident. Based on the above results, it was concluded that the X6 form of NQ801 had an immunostimulatory effect, an indirect anticancer effect, apart from its direct anticancer effects. The direct anticancer effects, in particular, showed dose dependence, and blood samples tested during the study did not reveal any biochemical abnormalities. But, there was a gradual increase in anemia with the advancement of the cancer.

After the study, the cancer worsened, the patient was hospitalized for palliative care, X6 was discontinued, and he died in the third week of hospitalization.

Thus, in spite of the terminal cancer, the patient' s QOL was maintained while he was taking X6, and the period spent in hospital for palliative care was short.

【Conclusions from Case 2】

Concurrent use of X6 1P/day with low dose of the anticancer drug for three months lowered the G/L ratio (parasympathetic dominant state) and there was no adverse reaction or loss of appetite even while she was on the anticancer drug. The X6 1P/day treatment, especially with the concurrent use of the anticancer drug, increased lymphocytes and improved parasympathetic dominance (decreased the G/L ratio; Fig. 4 [A]), and the QOL was maintained.

During this period, however, no clear improvement in immunocompetence (CD4/8 ratio) could be detected hematologically (data not shown). When we take the clinical findings (Fig. 3) and changes in SCC (Fig. 4[B]) into account, we can see that X6 did not show anticancer effect (Fig. 5-a) during the treatment with X6 1P/day alone for three months following the drip administration of the anticancer drug, and also during the treatment with X6 3P/day alone for three months, as the SCC increased in both these periods.

The tumor shrunk only when NQ801 was given concurrently with the low dose anticancer drug for two months. After the study period, the treatment with X6 3P/day concurrently with the low dose of anticancer drug was started and is continuing until now, but the tumor is showing signs of enlargement, although the QOL is maintained.

[Conclusions from Case 3]

The tumor markers ICTP and SCC decreased after the X6 treatment started (Fig. 5 Bottom, ICTP decreased after increasing once) and clinically also the tumor was seen to have shrunk, for the first time. After three months on X6 3P/day, the MRI showed a clear decrease in uptake of the contrast agent, which suggested lowered activity of the tumor (Fig. 7). The X6 3P/day treatment changed into parasympathetic dominance favorably (decreased the G/L ratio) (data not shown). Besides this, the patient showed no biochemical or clinical abnormality during the X6 treatment.

The results of this case also suggested dose dependence of the effect of NQ801 and its safety.

The patient continues to be on X6 3P/day concurrently with diet therapy and high dose vitamin C drip, and the tumor is shrinking and has reached about half its former size.

[Conclusions from Case 4]

Treatment with X6 1P/day for four months did not improve the tumor marker level. But, the tumor marker decreased, and the QOL improved, after increasing the dose to 3P/day.

This case also suggested the dose dependence of NQ801' s effect, and its safety.

Afterwards, as his physical condition improved, the patient was treated with a not yet approved anticancer drug in another hospital. He died three months later from adverse reactions to the anticancer drug.

As discussed above, NQ801 showed anticancer effect in cases 1, 3; and 4. Suppression of cancer proliferation was noticed when patients received 3P/day of X6, which showed the dose dependence of the effect of NQ801. Besides this, NQ801 showed better anticancer effect when used in combination with an anticancer drug than when used singly. This effect was particularly clear in Case 2. In spite of all the patients having advanced cancer, treatment with NQ801 improved parasympathetic dominance, and also immunocompetence. The QOL as either maintained or improved in all the cases of advanced cancer studied here. It is expected that treatment with NQ801 would improve or maintain QOL in advanced cancer patients for whom all other treatments have been given up, and in patients on palliative care. There were no abnormal clinical or biochemical findings when patients are given X6, which has six times the normal dose of NQ801, even at the high dose of 3P/ day.

IV. Areas for future studies

Clinical investigations of the present study have suggested that the anticancer effect of NQ801 is dose dependent, and confirmed the safety of NQ801 up to 5.4 mg/day. In the future, it is necessary to investigate the dose requirement of NQ801, when used in combination with anticancer drugs in specific cases, by using it on a larger number of patients in integrative treatment of cancer.

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