

Original Paper

Establishment of NK Cell Natural Immunotherapy for Cancer Prevention and Treatment Using the Natural Terpenes Derived from Forest Phytoncide

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Abstract

The active ingredient of forest phytoncide has many remarkable biological activities, especially in the aspect of anti-tumor. It can activate NK cells, increase the number of NK cells and the expression level of anti-cancer protein in NK cells, induce the self-apoptosis of cancer cells, and help the human body effectively complete the cellular immune anti-cancer mechanism. If we replace ordinary air with natural forest air as a new pressurizing medium and input it into the hyperbaric oxygen chamber, after being processed by hyperbaric oxygen chamber oxygen production technology, the high pressure oxygen of forest phytoncide is generated. At this time, the high pressure oxygen inhaled into the body is different from natural forest air or ordinary air. The fundamental difference is that the high pressure oxygen inhaled into the body at this time contains both high concentration of oxygen and high concentration of phytoncide, moreover the phytoncide concentration and oxygen concentration are much higher than the natural forest air or ordinary air. After it is inhaled by the human body into the alveoli, it can reach the peripheral blood through the pulmonary circulation and systemic circulation, and the high concentration of the active component terpene of phytoncide has an opportunity to directly contact NK cells and fully play the biological activity of activating NK cells. The high pressure oxygen that enters the alveoli simultaneously with phytoncide gas also passes through the pulmonary and systemic circulation, reaches the peripheral blood, Oxygen is released from the oxygenated hemoglobin, passes through the cell membrane and enters the mitochondria in the cells to provide sufficient energy for the physiological activities of NK cells. By applying this basic principle, we can establish a satisfactory NK cell natural immunotherapy for cancer prevention and treatment that can be accepted by humanity in the long run.

Keywords

Forest phytoncide, biological activity, hyperbaric oxygen chamber, oxygen production technology, high pressure oxygen, natural terpene, natural killing activity of NK cell, NK cell natural immunotherapy

1. Immune Anti-cancer Mechanism of NK Cell

The anti-cancer mechanism of human Cell immunity is mainly realized by Natural Killer cells (NK cells). There are three types of cells in our blood: white blood cells, red blood cells and platelets. White blood cells include granular cells, lymphocytes and macrophages. Lymphocytes in turn include NK cells, T cells and B cells, all three of which are immune cells. NK cells have anti-tumor, anti-infection and immunomodulatory functions. They mainly operate in the peripheral blood and liver and spleen organs of the human body, they are natural killer cells specifically responsible for killing tumor cells, virus-infected cells, senescent cells and other abnormal cells in the body.

In fact, cancer cells are created in our bodies every day. Under normal immune function, NK cells are responsible for monitoring cancer cells and attacking them as soon as they appear in the body, the Perforin, GrA, GrB and GRN are directly released to cancer cells to induce self-apoptosis of cancer cells, thus inhibiting the production, growth and metastasis of cancer cells, and playing a vital role in maintaining human health without cancer. This is what we often call the cellular immune anti-cancer mechanism[1]. See the Figure 1 below.

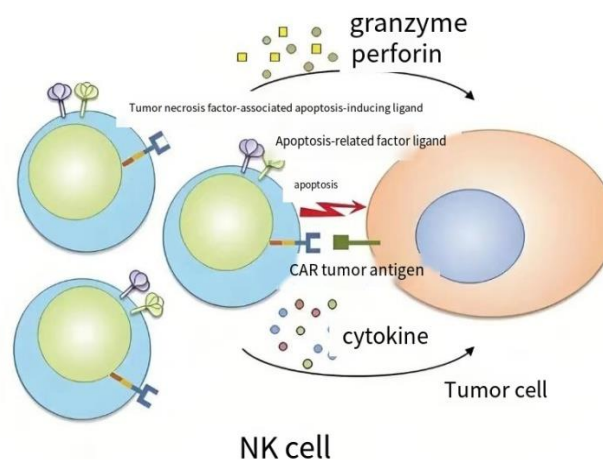


Figure 1.

2. The Importance of Maintaining the Number and Activity of NK Cells

However, the number of NK cells in our blood is limited, accounting for only 15% of the total number of lymphocytes, and from the age of 20, with the increase of age, its number and activity in the body gradually decreased, and after the age of 40, the decrease is more obvious. After reviewing a large number of clinical data, we have indeed witnessed this natural law. After middle age, with the decrease of the number and activity of NK cells, the human natural immunity also gradually decreases, which is

indeed prone to various serious diseases. In the case of cancer patients, the human natural immunity is even more rapid decline, prone to tumor spread and metastasis or postoperative recurrence of the original focus, the patient cachexia, near death, which brings great difficulties to clinical treatment[2] (see the Figure 2 below). These grim facts alert us that if we plan to schedule time for every adult over the age of 40 to increase the number and activity of NK cells which gradually decrease with age; Or, if we timely compensate for the natural killing activity lost by NK cells during the process to eliminate cancer, lesions and senescent cells in the body so as to maintain the normal operation of NK cell immune mechanism, we will have enough confidence to let the human body always maintain a healthy natural immunity, preventing and treating diseases, preventing and treating cancer[3].

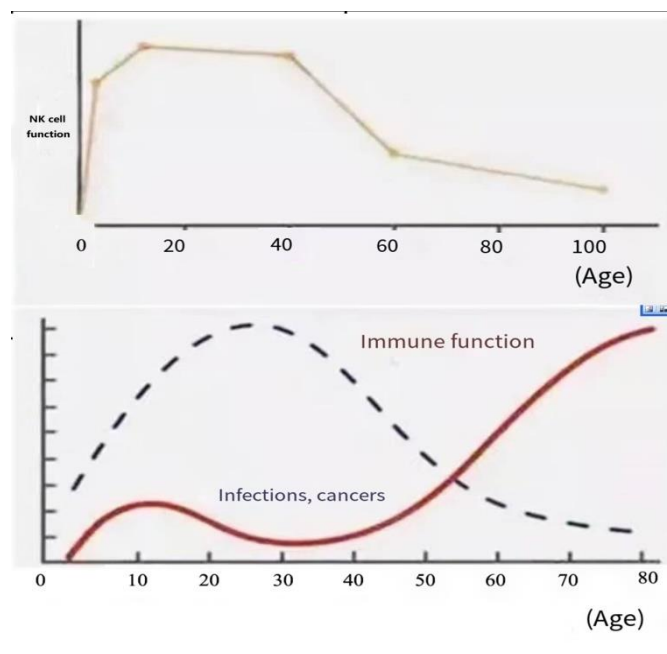


Figure 2.

3. What is Phytoncide

In 1930, the former Soviet Union Leningrad University professor of developmental biology Dr. B.P.Toknnh did an experiment, the onion, garlic leaves after cutting on the side of amoeba protozoa or typhoid fever, cholera, diphtheria and other pathogens, a few minutes later, these pathogens or amoeba protozoa were all killed. Thus, it was found that the plant itself has a complete defense system, which in the natural state will emit a gaseous bactericidal substance as self-defense, since then, this gaseous substance has been named phytoncide.

4. The Effect of Forest Bathing on the Number and Activity of NK Cells

4.1 Social Surveys

So what does phytoncide, which helps plants grow and survive, have to do with NK cells in humans?

Japan has done a social survey, people who often go to forest parks for a walk, the number and activity of NK cells in the body is about 50% higher than the average person. A similar study was conducted in Taiwan, China. A random selection of 100 urban white-collar workers and 100 forestry workers showed that the number and activity of NK cells in forestry workers were generally higher than those in urban white-collar workers, and they were less likely to get sick and cancer.

The Finnish Institute of Natural Resources reported that compared to urban kindergartens, in the forest kindergartens, after 28 days of classes, the immune indicators of 3-5 year old children generally increased.

Reported by the Daily mail in the UK, a Ph.D MaryCarol Hunter from the University of Michigan in the United States discovered, staying in a forest environment for 20-30 minutes can reduce the level of corticosteroids in the body by about 10%, this low pressure state in the body is very helpful for enhancing the human immune system

In 2008, a report on forest bathing was given by the Japanese medical university. When a person sit in the quiet forest, breathing the fresh forest air, the natural phytoncide gas that enters the body can activate NK cells, increase both the number and activity of NK cells in the body[4].

The above social surveys put forward the same opinion, that people who often walk, work or live in the forest have experienced forest bathing, and the phytoncide natural gas emitted by forest trees enters the body through respiratory circulation, causing an increase in the number and activity of NK cells[5]. These information give us an intuitive feeling about forest bathing.

4.2 Medical Literature Report

A). In November 2021, Sun Lijuan, Chen Yong, et al. published "Research Progress on constituents and Biological Activities of phytoncides from forest" in the Chinese Traditional and Herbal Drugs Journal. The paper pointed out that phytoncides are gaseous organic substances released naturally by the organs and tissues of forest plants, mainly aromatic terpenes, including monoterpenes, sesquiterpenes, diterpenes, etc. Among them, monoterpenes and sesquiterpenes have the strongest biological activities. Phytoncide not only protects plants from bacteria, fungi and parasites, but also has a wide range of positive effects on human health. This paper reviewed the types, chemical constituents, contents and biological activities of phytoncides from different tree species of pure forests and summarized the toxic components of harmful and toxic plants and flowers, which provided a very valuable biological basis and forest ecological environment investigation for further basic research on forest phytoncide. In a comprehensive and systematic way, the article explained 10 distinctive biological activities of the effective ingredients of phytoncide, including sedation and hypnosis, cough and asthma relief, cardiovascular system protection, anti-allergy, antibacterial, anti-inflammatory and analgesic, anti-oxidation and anti-aging, antiviral, hypoglycemic and anti-ester, and anti-tumor. Especially in the aspect of anti-tumor, the article pointed out, NK cells are very important lymphocytes in the natural immune system, which not only have anti-infection and anti-tumor immune functions, but also participate in immune regulation and transplantation rejection. NK cells can produce a variety of

chemokines, and participate in leukocyte chemotaxis and inflammation. In both blood circulation and tissues, NK cells can be involved in controlling tumor metastasis and inhibiting the growth of metastatic tumors through perforin-dependent mechanisms, but there are also perforin-independent mechanisms. phytoncide can activate NK cells, enhance human immunity and significantly inhibit the growth of cancer cells, which is related to the induction of NK cell proliferation in the peripheral blood and the expression of anti-cancer proteins in NK cells by the natural phytoncide[6].

B). Lin Jing, Jian Yi, Luo Z S, et al. conducted a “Study of Chemical Components and Contents in the Phytoncide from 5 Species of Forest Health Plants” in the Shichuan Forestry Science and Technology Journal, 2018, 39(6). The results showed that in the 5 species of forest health plants, main components released from living branches and leaves of Cupressus funebris, Pinus massoniana, Cryptomeria fortune and Cinnamomum septentrionale were monoterpenes and sesquiterpene, whose contents were more than 60% in the terpenes, which had stronger physiological function. The contents of alkane and a-pinene in the living branches and leaves of Pleioblastus amarus were the highest[7].

C). Dr. Li Qing, a Japanese Chinese expert in forest medicine, led his team to conduct a long-term exploration of forest bathing since 2004. Through the combination of laboratory research and human experiments, the biological activity of the active ingredients of forest phytoncide in cancer prevention and treatment has been explained with certain persuasively. The brief description is as follows:

The subjects were healthy adult men and women, who participated in a 3 days and 2 nights forest bathing tour. After the tour, they were also followed for 30 days to monitor immune indicators such as NK cell activity, NK cell number and anti-cancer proteins within NK cells. As a control group, healthy adult men and women were also followed up for 3 days and 2 nights in the city and 30 days after the tour. Below Figure 3 is a scene of the subjects taking a walk in the forest.



Figure 3.

The results showed that 3 days and 2 nights of forest bathing Tours not only increased the number and activity of adult NK cells, as well as anti-cancer proteins within NK cells, but also sustained this effect for up to a month[8,9].

Figure 3-1, 3-2 shows the statistical data of 12 healthy adult men and women after 3 days and 2 nights of forest bathing tour. Compared with before forest bathing, the number and activity of NK cells on the first and second days after forest bathing were significantly higher than before forest bathing. In addition, the number and activity of NK cells increased after consecutive 2 days of forest bathing compared with 1 day of forest bathing. On 7 and 30 days after forest bathing, the number and activity of NK cells were still higher than those before forest bathing (Figure 3-1), and the 4 anti-cancer proteins within NK cells also maintained an undecreased trend compared with those before forest bathing (Figure 3-2).

In the control group of urban tourism, the immune indexes of NK cells could not reach the satisfactory data of the group after forest bathing.

Figure 3-1 Forest bathing can effectively and continuously increase the activity and number of NK cells (male)*:p<0.05, **:p<0.01(before and after forest bathing), mean \pm standard deviation, n=12

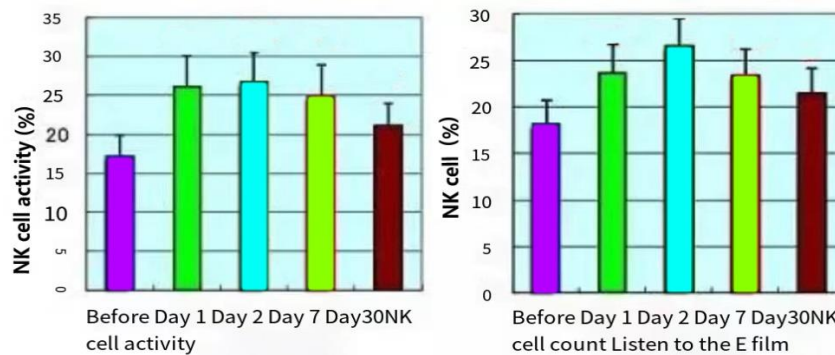
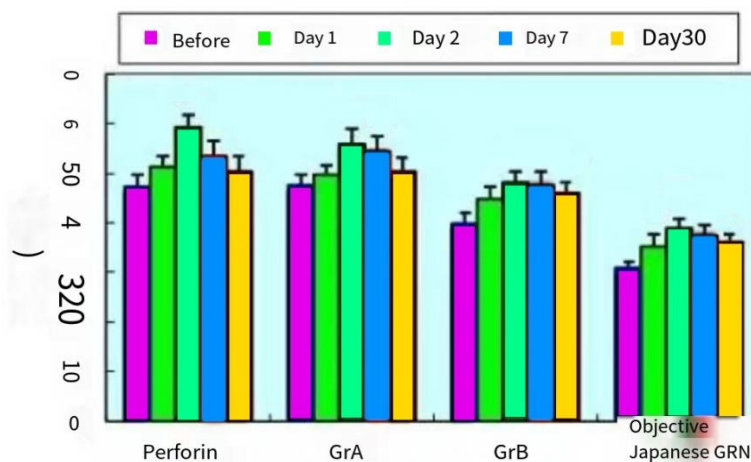


Figure 3-2 Forest bath effectively and consistently increases 4 anti-cancer proteins (male)

*:p<0.05, **:p<0.01(before and after forest bath), mean \pm standard deviation, n=12



D). In early July 2019, Liu Yanbo and other authors in China conducted also a similar experiment In Baihe District of Changbai Mountain, Jilin Province, the study screens and selects 12 healthy volunteers to have a three-day and two-night forest bathing. The percentages of CD56+NK cells and CD3+lymphocytes in their peripheral blood are monitored using flow cytometry, and the concentrations of Grs, GNLY and perforin in plasma are tested using Elisa assay before and after forest bathing. The results show that compared with the pretest conditions, the forest bathing produces a significant increase in percentage of CD3+lymphocytes and CD56+NK cells ($P < 0.05$), and also an obvious increase in the perforin, GrA, GrB and GNLY levels in plasma. The results suggested that forest bathing can significantly improve the human immune function to a certain extent[10]. See the Figure 4-1, 4-2, 4-3 below.

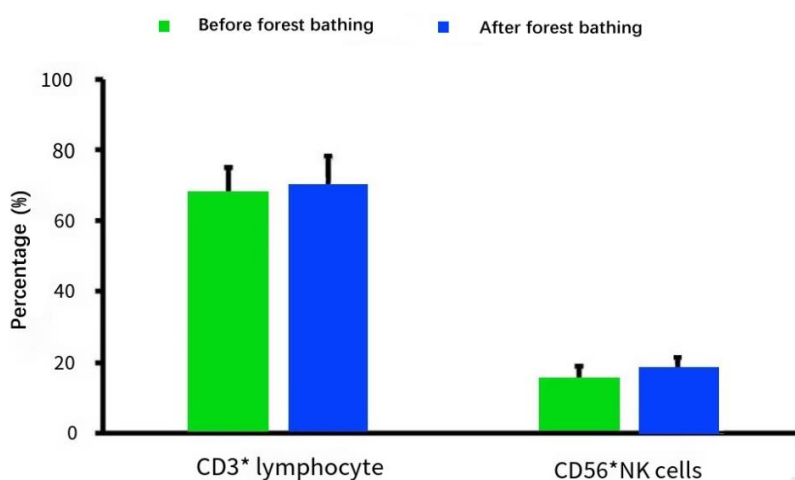


Figure 1. Effects of forest health care on percentage of peripheral blood lymphocytes and NK cells

Figure 4-1

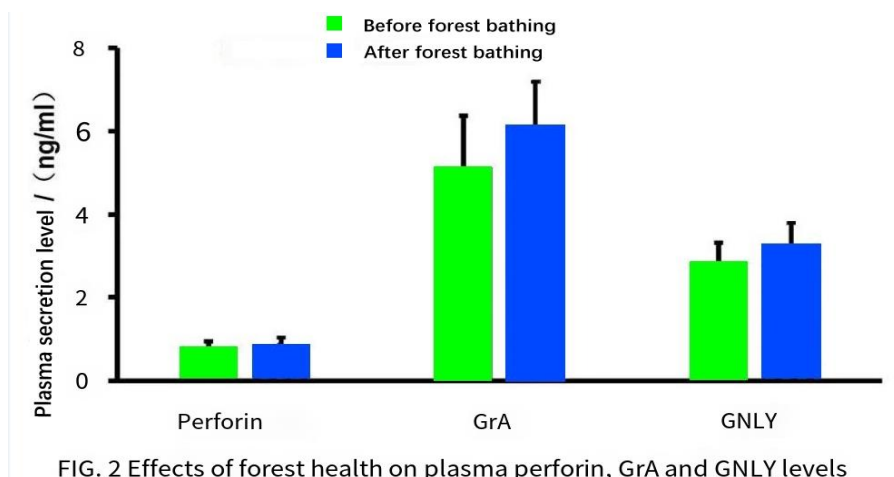


FIG. 2 Effects of forest health on plasma perforin, GrA and GNLY levels

Figure 4-2



FIG. 3 Effect of forest health care on plasma GrB level

Figure 4-3

5. The Active Ingredients and Biological Activities of Forest Phytoncide

The forest phytoncides are gaseous organic substances released naturally by the organs and tissues of forest plants, mainly aromatic terpenes, including monoterpenes, sesquiterpenes, diterpenes, etc. Among them, monoterpenes and sesquiterpenes have the strongest biological activities. Phytoncide not only protects plants from bacteria, fungi and parasites, but also has a wide range of positive effects on human health.

This is the identification of phytoncide released from live branches and leaves of 5 health plants using gas chromatography-mass spectrometry, its main components are monoterpenes and sesquiterpenes, both with a content of over 60%. Please refer to the Table 1, 2, 3 below.

Table 1.

BVOC, and relative content of phytoncides in leaves and branches of 5 species plants

Species of trees	Terpenes	Alcohols	Esters	Dehydes	Ketones	Alkanes	Summation
Species	Terpenes (%)	Alcohols (%)	Esters (%)	Aldehydes (%)	Ketones (%)	Alkane (%)	Totol (%)
Cypress wood	72.46	3.31	7.25	1.50	2.95	12.14	99.61
Masson Pine	83.29	5.82	2.35	1.03	1.53	5.23	99.25
Cryptomeria	72.27	2.51	5.96	3.06	5.18	9.85	98.83
Fragrant camphor tree	69.81	5.38	4.67	1.54	4.41	10.48	96.29
Bitter bamboo	34.61	5.13	11.86	4.95	2.13	37.76	96.44

Table 2.

Monoterpene and relative content of phytoncides in leaves and branches of 5 species plants

category	Classification	Compounds	Molecular Formula	Relative content (%)				
				The relative percentage (%)				
				Cedarwood	Masson Pine	Cryptomeria	Camphor tree	Bitter bamboo
Monoterpenes	Monoterpene	Alpha-pinene	alpha-pinene	42.63	46.47	30.18	27.24	13.64
		Beta-pinene	beta-pinene	1.33	11.61	1.62		2.12
		P-cymene	p-cymene	0.86	0.13	0.25	0.06	0.56
		Caene-3carene-3		0.27		2.25		
		tricycoene	β-Basil (E) β	0.36	0.31		0.11	
		-ocimene(E)		0.81			10.61	4.14
		sabinene	sabinene	20.59		23.34	17.86	1.89
		camphene		0.63	14.63	4.02	3.64	0.40
		Gamma-terpinene	γ-terpinene	0.15	0.10	0.25		
		Alpha-terpinene	alpha-terpinene	0.78	0.37	0.24		
Monoterpenes	Monoterpene	(+) -limonene	D-limonene	0.22	0.56	0.51	2.56	2.56
		terpinolene		0.24	0.24	0.17	1.08	0.75
		Total Totol(%)		68.87	74.42	62.83	63.16	26.06

Table 3.

category Classification	Compounds Compound	Molecular Formula Molecular formula	Relative content (%) The relative percentage (%)				
			Cedarwood	Masson Pine	Cryptomeria	Camphor tree	Sitter bamboo
Sesquiterpene Sesquiterpenes	cinnamene cinnamene	CoH16		0.48			1.31
	limonene Limonene				1.21	3.72	2.65
	thujene thujene					0.58	
	alpha-caryophyllene		0.18	0.10		0.72	1.32
	Beta-caryophyllene. Beta-caryophyllene		1.35	0.42		1.66	1.78
	alpha-thujene		1.32	0.08			
	Beta-thujene beta-thujene				0.62		
	Alpha-cubane alpha-cuparene				2.34		0.32
	alpha-cresine-alpha-phellandrene			4.48			
	Beta-cresine beta-phellandrene	C10H16		0.09			
Total Total(%)			2.85	5.65	4.17	6.68	7.38

The active ingredients of phytoncide are mainly eugenol, geranyl (maximum intake is 0-5.0mg/kg), carvacrol, thymoquinone, β -pinene, longifolene, isoprene, α -pinene, and bornol, which can inhibit the proliferation of human tumor cells such as endometrial cancer, oropharyngeal cancer, lung cancer, colon cancer, stomach cancer and leukemia. Studies have shown that α -pinene can activate NK cells by activating extracellular signal-regulated kinase (ERK) and protein kinase B (PKB/AKT) phosphorylation pathways. It can induce the release of perforin and attach to cancer cell membrane, open its surface, promote the proliferation of granzyme B protein and induce cell apoptosis. It can also enhance the spleen NK cell toxicity of mice and inhibit the growth of CT-26 colon cancer transplanted tumor in BALB mice. Lavender essential oil mainly contains linalool (the maximum intake is 0-0.5mg/kg, linalool acetate, etc.), which can inhibit the proliferation and induce apoptosis of human hepatocyte HepG2 cells. Forest bathing can increase the activity and number of NK cells and the expression level of intracellular anticancer protein in cancer patients, and this effect can continue until at least 7 days after forest bathing.

In recent years, the research progress on the anticancer effects of terpenes has been rapid, showing more and more scientific research achievements. For example, advances in study on antitumor activities of triterpenoids[11]. Research Advances in Triterpenes Antitumor Activities[12]. Biosynthesis and application of plant terpenoids[13]. Research progress in antitumor effect of natural terpenoids[14]. Ways to find new anticancer drugs from Chinese herbal and medicines[15]. Research on the anti-tumor effect and mechanism of terpenoids[16] and so on, have elucidated for us the anti-tumor activity of natural terpenoids, mechanism of action, structure-activity relationship, and principle of synergistic effect with other anticancer drugs.

All in all, summarizing the above multi-directional and multi-level data and biological data, we do see that forest phytoncide has many remarkable biological activities, especially in the aspect of anti-tumor. Its active ingredients, namely natural terpenes, can be directly related to the number and activity of human NK cells and the expression of anti-cancer proteins within NK cells, is a valuable natural resource that immune anti-cancer mechanism of our human body can rely on. If we elevate forest phytoncide from a simple natural gas for forest health to a clinical treatment platform to serve human

health, I think the biological activity of the active ingredients of forest phytoncide should have a higher level of display[17-22].

6. Establish a NK Cell Natural Immunotherapy for Cancer Prevention and Treatment

A. Conception

Imagine, if we set the hospital hyperbaric oxygen chamber in the forest, or collect forest air from the forest area, replace ordinary air with natural forest air as a new pressurized medium and input it into the hyperbaric oxygen chamber, after being processed by the pressure, filtration, cooling, molecular sieve and other oxygen production technology inside the hyperbaric oxygen chamber, the forest phytoncide high pressure oxygen is generated. Then, according to the pathological characteristics of malignant tumors and other related diseases, select different oxygen partial pressure, oxygen concentration and phytoncide concentration, as well as different forms of oxygen supply method for the subjects to inhale oxygen, and record the number and activity of the subjects NK cells before and after oxygen inhalation, as well as the anti-cancer proteins within the NK cells and other immune indicators and disease outcomes, we may get new revelations. Note that before officially starting the oxygen inhalation, we must do the following work: [23-28]

B. Steps[29]

- 1) What is the concentration of phytoncide in the high pressure oxygen of forest phytoncide produced after the treatment of hyperbaric oxygen chamber? Does it exceed the limit of intake allowed by the human body?
- 2) Do the concentration, temperature and pressure of the high pressure oxygen produced after the treatment of hyperbaric oxygen chamber comply with the actual operation regulations of the hyperbaric oxygen chamber? Oxygen poisoning, air pressure injury and decompression sickness caused by too high oxygen concentration and oxygen partial pressure should be avoided.
- 3) Is the maximum intake of citronellol, geraniol and linalool in the high pressure oxygen of phytoncide within the prescribed range of 0-5.0mg/kg?
- 4) Does the content of toxic and harmful plants/flowers in the high-pressure oxygen of phytoncide meet the relevant limit standards? [30.31.32]
- 5) Check whether there are contraindications for hyperbaric oxygen therapy among the subjects. For untreated malignant tumor patients, during early oxygen inhalation, oxygen should be administered under lower pressure as appropriate
- 6) According to the above test results, the duration of each oxygen inhalation, the frequency of oxygen inhalation per week, the concentration of oxygen, the concentration of phytoncide, the pressure of oxygen, and the method of oxygen supply are finally set with reference to the different pathological characteristics and personal physical conditions of various related diseases.

There are many forest plants, and the types and contents of phytoncide in different plants are different. We have listed the types and relative contents of phytoncide in common tree species. It can be seen that

the components of phytoncide in different tree species are mainly terpenes, and the types of terpenes in branches and leaves of different tree species are mainly monoterpenes and sesquiterpenes, the relative contents of which are as shown in the Table 1, 2, 3 above, it only records the active ingredients of phytoncide and relative contents of terpenes in our local area, when collecting forest air, everyone should consider the local distribution and emission time characteristics of phytoncide[33-38].

C. Historical background

At present, the main treatment methods for malignant tumors are surgery, radiation and chemotherapy. Patients spend pain and money in an effort to survive. Generally speaking, early detection and early treatment have a relatively high survival rate. In recent years, targeted drugs have come out, and the treatment of cancer is indeed very targeted, but it can not replace chemotherapy. The cutting-edge technologies of cell immunotherapy at home and abroad, such as human stem cell injection or local implantation, immune cell storage, in vitro culture, expansion and transfusion of homologous or allogeneic NK cells, including NK cells derived from the umbilical cord blood, have all made great progress. We are confident to look forward to the dawn of human overcoming cancer. However, safety and reliability of some technologies need to be further verified clinically[39-54].

D. Basic principle of NK cell natural immunotherapy for cancer prevention and treatment, and key points of the this therapy

Forest phytoncide is a natural resource given to human by nature, which is inexhaustible. This cheap natural resource is injected into the hyperbaric oxygen chamber as a new pressurizing medium, the high pressure oxygen generated after treatment with oxygen production technology. At this time, the high pressure oxygen inhaled into the body is different from natural forest air or ordinary air. The fundamental difference is that this forest phytoncide high pressure oxygen contains both high concentration of oxygen and high concentration of phytoncide, moreover the concentration of phytoncide and oxygen is much higher than that of natural forest air or ordinary air. The human body can use the oxygen inhalation setting in the hyperbaric oxygen chamber to let the high pressure oxygen of phytoncide enter the alveoli, and then diffuse to the capillaries outside the alveolar wall, and physically dissolve in the blood of capillaries in small amounts in turn, and then reach the peripheral blood through the pulmonary circulation and systemic circulation. High concentration of the active ingredient terpenes of phytoncide have an opportunity to directly contact NK cells, to give full play to the biological activity of activating NK cells. The high concentration of oxygen that enters the alveoli at the same time with phytoncide gas also diffuses into the blood of capillaries outside the alveolar wall, binds with the hemoglobin of red blood cells in the blood to oxygenated hemoglobin, and also reaches the peripheral blood through pulmonary circulation and systemic circulation. Oxygen is released from the binding of oxygenated hemoglobin, passes through the cell membrane, and enters the intracellular mitochondria, providing sufficient energy for NK cell physiological activities[29]. Exploring this hard won basic principle, we finally have the confidence to come out of the long-term clinical confusion. In the face of those patients who lose the number and activity of NK cells due to age or other pathological

factors, announce that we have found a NK cell natural immunotherapy for cancer prevention and treatment that can be accepted by humanity in the long run[55,56]. Briefly describe the key points as follows:

- 1) Schedule a regular oxygen therapy of forest phytoncide for every adult over the age of 40 to self enhance the number and activity of NK cells, and restore the natural immunity to a level of 20 years old which gradually decrease due to aging. The oxygen partial pressure during oxygen inhalation should be selected as 1-1.5 atmosphere depending on age and individual conditions.
- 2) Actively promote family style forest phytoncide oxygen bars to generally improve the natural immune system level per capita.
- 3) Timely and accurately apply hyperbaric oxygen therapy rich in natural terpenes of forest phytoncide to compensate for the natural killing activity lost by NK cells during the process of clearing cancerous, diseased and senescent cells in the body so as to maintain the normal operation of NK cell immune mechanism, allow the patients with weakened immunity caused by cancer or other diseases to regain a new natural immunity so that it is possible to gradually inhibit the growth, development and metastasis of cancer cells through one's own immune conditions until cancer is completely controlled or cured. At least, this natural immunotherapy of NK cells can replace postoperative chemotherapy of cancer to some extent[57].

E. Look into the future

The pace of modern urban life is tense, and there are few opportunities to go to forest parks to rest and relax. We can provide the oxygen bar service under the isobaric conditions of hyperbaric oxygen chamber and so on, so that the busy people in the city have the opportunity to enjoy the forest bathing and feel how forest phytoncide enables people to naturally acquire immunity in a comfortable and peaceful environment. I believe that it will certainly have a broad market prospects. Of course, if thousands of households know and accept the micro household forest phytoncide hyperbaric oxygen chamber, then in the future, our specialized organization responsible for the supply of natural forest air should be fully equipped to provide customers with bottled, canned compressed gas, liquefied gas and even install ventilation pipes in every household, plan to arrange family forest health, so as to achieve national fitness. To eliminate cancer [58-61].

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