SUPPLEMENTS IN CANCER THERAPY

This Guide had been provided by Reliable Cancer Therapies (RCT) as a service to patients, to help patients and their relatives better understand the possible use of supplements in cancer therapy. We recommend patients to consult their doctor. The information described in this document is based on scientific research and has informative purposes only.

More information about Reliable Cancer Therapies: www.reliablecancertherapies.com

For words marked with an asterisk, a definition is provided at the end of the document.*

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DEFINITION OF SUPPLEMENTS

By definition, a supplement is intended to *supplement* the diet whenever needed. In a balanced diet, all essential nutrients (vitamins, minerals, fiber, amino acids and fatty acids) are abundantly present. However, the diet is often not ideally balanced and does not include sufficient intake of all nutrients. In this case, supplementation is required. In a broader sense, a supplement can also provide the body with beneficial components in an attempt to improve overall health or quality of life. Caffeine is an example of such a beneficial component present in several plants such as coffee and cola species. Caffeine is promoted to stimulate cognitive performance in aging people.

By definition, a supplement could never alter the outcome of a disease unless the disease is caused by a deficiency, for example scurvy, an illness caused by a lack of vitamin C. In earlier centuries, scurvy was common among sailors who were at sea for a long time and didn't have any access to fresh fruit and vegetables. In practice however, cancer patients often use supplements in an attempt to alter their prognosis*.

A wide range of products are available on the market as supplements for which therapeutic properties are often claimed. These products are often very popular with cancer patients. People take supplements for different reasons, including those linked to:

- Herbal medicines sold as supplements claimed to have the ability to fight cancer
- Antioxidants* which protect cells from oxidative damage*
- Supplements said to enhance the immune system*
- Supplements claimed to improve the effects of conventional medicine*

It is very important to understand the differences between a supplement and a drug so as to avoid misinformation when buying supplements. The main differences are explained below.

If you have any questions regarding a certain supplement or supplier, please contact RCT at info@reliablecancertherapies.com.

1. SUPPLEMENTS VERSUS DRUGS

1.1 Quality

Drugs need to be manufactured under Good Manufacturing Practices (GMP). This means that they are manufactured under carefully monitored conditions and packaged with complete information on the best dosage routine and schedule. The package information must include a list of all known side effects, contraindications (special conditions under which using the drug could be dangerous), or possible unsafe interactions with other drugs. There is strict control of the raw initial ingredients, intermediates and of the end product.

HACCP stands for Hazard Analysis and Critical Control Points. It is a system that addresses any chemical, biological and physicals hazards in the food industry. Supplements need to be manufactured according to the HACCP standards. This implies that possible contamination needs to be checked and it must be ensured that there are strict hygiene procedures during the production process.

The main differences between GMP and HACCP are that there is no monitoring of the end product in the case of HACCP, which means that the minimum and maximum tolerable content of the active ingredient(s) in the end product is not monitored and consequently not guaranteed. This control is obliged for registered drugs. Moreover, there is also no stability testing (whether or not the supplement remains stable until the expiry date and/or at higher temperature/humidity), as is obligatory for medicines.

1.2 Safety

Supplements from an unknown source like several websites, could be contaminated with germs, pesticides, toxins, toxic heavy metals or residual solvents. They could also contain more or less of the purported substance than mentioned in the product information. Some herbal supplements were found to contain prescription drugs. It is not surprising that the aforementioned product quality issues could have serious consequences for the health of the patient or customer.

A pharmacist is held responsible for the supplements he/she sells, while you are solely responsible for the supplement you are taking if it is purchased online.

It is very important to inform your pharmacist about the medication you are taking as it could harmfully interact with conventional drugs*.

“My pharmacist doesn’t provide the supplement. How can I distinguish good quality products from suspicious ones?”

It is difficult to be sure of the reliability of a supplement. When buying supplements, please keep the following in mind:

- A reliable supplier will clearly display the contact information of the manufacturer of the supplement on their website, product packaging or instructional leaflet.
- There must be clear information about the content of the supplement. Never trust "secret" herbs or combinations thereof.

1.3 Efficacy

A. The Situation in the US

In the United States, herbs and supplements are classified as a subcategory of food under the Dietary Supplement Health and Education Act (DSHEA). Unlike pharmaceutical drugs, herbs and supplements are not required to undergo a formal approval process. It is easy to misread the claims that are being made about products. The makers of dietary supplements are allowed to make 4 kinds of claims on the labels of their products.

These claims are explained below.

- **Nutritional claims**: These are statements about the general effects that dietary supplements, vitamins, and minerals have on diseases known to be caused by malnutrition, for example, "vitamin C prevents scurvy". These claims do not need to be approved by the authorities, but the label *must* state how many cases of the disease occur in the United States. Consumers must weigh up the risk of getting scurvy against the potential risks of the supplement itself.
- **Claims of wellbeing**: These include statements such as "it makes you feel better". These claims also do not require pre-approval by the authorities.
- **Health maintenance claims**: These are statements about evidence-based health benefits of certain compounds. For example, risk-reduction claims such as "folate may reduce the chance of pregnant women delivering an infant with neural tube defects" fall into this category.
- **Structure/function claims**: These are the most hotly debated and confusing to consumers. They are claims about the effect of the dietary supplement on the normal structure or function of the body and their role in growth development. Dietary supplements may not make any claims regarding the treatment of disease.

In the US, structure/function claims are not reviewed by the authorities. In fact, labels that carry them must also include the following disclaimer: "This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease."

B. The Situation in the EU

Since April 30, 2011, all health claims made for supplements in the European Union must be be revised and accepted by EFSA (European Food Safety Authority). To be accepted, all claims need to be clear and backed up by scientific evidence. This new legislation implies that in the coming years, many supplement manufacturers will need to remove the health claims on their product packaging or else take that supplement off the market. Herbal medicinal products that have already been in use for 30 years (of which at least 15 years have been in an EU country) can be registered under an alleged procedure called Traditional Use. With this new directive (2004/24 EC), customers are sure that they are buying a traditional herbal medicinal product that complies with all safety standards for which efficacy has been accepted on the basis of 30 years of use. Previously it was very difficult to find out whether you were buying an over-the-counter drug or a supplement with lower quality assurances.

Products that are proven to have a significant effect on any disease are considered drugs (by the Food and Drug Administration (FDA) for the USA and/or by the European Medicines Agency (EMA) for the EU) are strictly regulated and have to obtain a full Marketing Authorization (MA).

If a supplement sold over the internet is claimed to cure cancer, this claim is, without exception, false and illegal. If a product claims to be able to alter the outcome of a disease, it is, by definition, a drug and needs to obtain such a Marketing Authorization by the competent authority of a member state of the EU or of the entire European Community.

1.4 Research

An authorized medicinal product has proven to be safe and efficacious by preclinical* and clinical trials*. This means that the product has been tested in animals and in humans. It is approved by regulatory health authorities like the FDA/EMA or the national competent authorities. For more information on clinical trials* in humans, see the *Clinical Trials* tab on the RCT website.

2. DIETARY SUPPLEMENTS

It is very important to have a balanced diet that provides the body with all the necessary nutrients. If a balanced diet is achieved, it is not necessary to take extra supplements.

For more information on nutrition, see the guidance document on nutrition and physical activity on the *guides* tab of the RCT website.

The reality for cancer patients is often very different.

Malnutrition is very prevalent in cancer patients, ranging from 40-80% of cases, because cancer can alter metabolism and, therefore, the patient's need for proteins, carbohydrates, fat, vitamins and minerals. Malnutrition can also be caused by the side effects of cancer treatment. In turn, malnutrition also leads to increased toxicity from cancer treatment, lower quality of life and worse prognosis*.

Also, patients seem to require higher amounts of micronutrients* to enhance postoperative wound healing.

Vitamin and mineral deficiencies can be mostly traced through a blood analysis. Your GP can advise you on the vitamins and minerals that need to be supplemented and at what dosage.

2.1 Vitamins, trace elements and micronutrients* during chemotherapy*

It is very important to first discuss the use of supplements during chemo*- or radiotherapy* with your oncologist as some supplements may interact with conventional treatment*, making it less efficacious.

Supplementation of trace elements* such as selenium and zinc can delay cachexia* (general weakness and malnutrion) which suppresses the immune system*, thereby reducing the effect of chemotherapy*. Patients taking cisplatin may have magnesium and carnitine deficiencies, so supplementation may be recommended.

Pre-treatment with folic acid and vitamin B12 is crucial in patients who will be treated with pemetrexed.

It is also very important to monitor the Vitamin D-level of cancer patients and supplement it when necessary.

3. ANTIOXIDANTS

An antioxidant* is a substance that, when present at low concentrations compared with those of an oxidizable substrate, significantly delays or prevents oxidation of that substrate. An oxidizable substrate includes every type of molecule found in living organisms. In this way, antioxidants* protect the cells from damage by oxidizing substances. In biological systems, the most prevalent oxidizing substances are called reactive oxygen species (ROS) or reactive nitrogen species (RNS). ROS and RNS enter our body through consumption of drugs, a bad diet, environmental toxins and UV*-radiation.

Adding large amounts of antioxidants* to our diet seems to prevent tissue and organ damage by protecting our cells. But the presence of antioxidants* in the diet during cancer therapy is very controversial, because radiation therapy* and, to a lesser extent, chemotherapy* act by creating ROS to kill cancer cells. So, in theory, taking antioxidants* during radiotherapy* or chemotherapy* might inhibit the efficacy of the treatment because they could neutralize the ROS. There are several clinical trials* underway in an attempt to clarify this controversy, but no firm conclusions have been drawn yet. Clinical trials* exist which suggest that antioxidant* supplementation decreases the side effects and enhances the efficacy of conventional treatment*, but at the same time some clinical trials* saw a shorter survival time in patients taking antioxidants* during radiation therapy*.

It is important to mention that not all chemotherapies* act solely via the production of ROS. Chemical agents with this mechanism of action include anthracyclines* (e.g., doxorubicin), platinum-containing complexes (cisplatin, carboplatin), alkylating agents* (cyclophosphamide, ifosfamide), and cytotoxic* antibiotics* (bleomycin, mitomycin-C). Until there is clarification on the use of antioxidants* during radiotherapy*, it might be recommended to avoid them on the days of treatment (and two days before and after). For chemotherapy*, the same rule can be applied for the drugs mentioned above.

The American Institute for Cancer Research (AICR) states that taking dietary supplements during chemo- or radiation therapy* is considered safe as long as such supplements contain amounts of vitamins and minerals that are in the range of the recommended daily allowance according to official recommendations.

Below is a non-exhaustive list of supplements and foods containing large amounts of antioxidants* that are often used by cancer patients.

- Resveratrol
- Vitamin C
- Green tea
- Curcumin
- Selenium

- Vitamin E
- Coenzyme Q10
- Berries (blueberries, strawberries, raspberries, etc.)
- Vitamin A
- Beta-carotene
- Glutathione
- Melatonin
- Zinc
- Lycopene
- Lutein

4. IMMUNOSTIMULATING HERBS

The immune system* is the body's defense mechanism against infections and other harmful substances that enter the body. It is known that at a very early stage the immune system* can eliminate malignant cells and thereby retain the cells to form a tumor. However, once the tumor has developed, it applies different mechanisms to suppress the immune system*. Chemotherapy* and radiation therapy* are also known to be toxic to immune cells. The immune system* is often compromised in cancer patients. Cancer patients often seek treatments to improve this defense mechanism in order to tolerate chemotherapy* better and to avoid infections on top of their illness.

Several herbs are claimed to enhance the immune system*. The first papers describing the immunomodulatory* properties of compounds isolated from yeast, mushrooms, and plants were published in the 1970s. They could have a potential role in the prevention and treatment of cancer as an adjuvant immunotherapy*.

Although many plants could possibly act as immunostimulants*, for many it is not proven. Caution should be used when considering supplementation with immunostimulating* herbs. These herbs could also be toxic or there could be an interference with standard treatment. It is also important to inform yourself of the quality assurance activities of the supplier. When buying over the internet or from an unknown source, there could be a risk of contamination or of low quality plant material. This could cause side effects without any beneficial effect and is not caused by the plant itself but by the quality of the supplement. The list below describes several herbs with immunomodulatory* properties. More information on most of these plants can be found on the *Therapies* page on the RCT website.

- Herbs
  - Astragalus
  - Ginseng
  - Mistletoe
  - Cat's claw
  - Arabinogalactan
  - Echinacea
  - Rose hip
  - Goldenseal

- Mushrooms
  - Shiitake
  - Maitake mushrooms

- Vitamins
  - Vitamin A + beta-carotene (provitamin A)

- Vitamin B_6
- Vitamin D
- Vitamin E

- Minerals
  - Zinc
  - Copper

- Amino acids
  - Arigine/ L-arigine
  - Taurine

- Lipids
  - Amaranth oil
  - Gamma lineolic acid

- Miscellaneous
  - Bovine colostrum
  - Probiotic supplements
  - Thymus extract
  - Black currant seed oil

5. PROBIOTICS

Acidophilus* and some related bacteria are considered to be "probiotic" because they may help the body maintain or restore its normal balance of helpful bacteria.

Probiotics are living micro-organisms similar to the micro-organisms that are found in the human gut. Probiotics are harmless bacteria and help to maintain the natural balance of organisms (microflora) in the intestines. The normal human digestive tract contains about 400 types of bacteria that reduce the growth of harmful bacteria and promote a healthy digestive system. The largest group of probiotic bacteria in the intestine is lactic acid bacteria, of which *Lactobacillus acidophilus**, found in yogurt, is the most well-known. Other types of probiotics include different strains of *Bifidobacterium* and *Saccharomyces boulardii*. *Saccharomyces boulardii* has been described as a yeast probiotic, as it has been shown to antagonize disease-causing bacteria. Probiotics are available to consumers mainly in the form of dietary supplements and foods. Examples of foods containing probiotics are yogurt, fermented and unfermented milk, miso, tempeh (soybean cake), some juices (black currant juices containing probiotic cultures), and soy beverages (soy milk).

Probiotics should not be confused with **prebiotics**. Prebiotics are sugar derivatives (such as lactulose*, lactitol*, a variety of fructooligosaccharides*, and inulin*) that are used as fuel by bacteria (such as those from the genus *Bacteroides*) in the gut to stimulate their growth and activity while suppressing the growth and activity of harmful organisms. **Synbiotics** involves the co-administration of probiotics and prebiotics. Probiotics are thought to work by colonizing the small intestine and crowding out disease-causing organisms, thereby restoring proper balance to the intestinal flora. They compete with harmful organisms for nutrients and may also produce substances, such as ammonia, that inhibit the growth of harmful organisms in the gut. Probiotics may be used to treat problems in the stomach and intestines, including diarrhea. However, only certain types of bacteria or yeast have been shown to work in the digestive tract, including *Lactobacillus* and *Bifidobacterium*.

5.1 Evidence

Animal models suggest a positive effect on the gut mucosal integrity and on the healing of damaged intestinal epithelial cells.

Some clinical trials* with probiotics in cancer patients have been performed in the recent years. The effect of probiotics on diarrhea during radio*- or chemotherapy* was mainly investigated. All trials reported positive results: a decrease in diarrhea and an improvement in stool consistency. However, these were all small-scale trials so there is a need to confirm these results in large-scale controlled trials.

Probiotics are also used in colorectal cancer surgery. The idea behind this is that probiotic administration in surgical patients might compete with bacteria responsible for postoperative infections. It is also believed that probiotics can modulate the intestinal immune function. One trial found that Lactobacillus johnsonii, but not Bifidobacterium longum, affects the intestinal microbiota by reducing the concentration of pathogens and that it also modulates the immunity in the

intestines. Another trial with a mixture of probiotics suggested an improvement in the gut mucosal barrier by benefiting the faecal microbiota and a decrease in infectious complications in patients with colorectal cancer undergoing colorectomy.

5.2 Safety

Probiotics are considered safe if consumed in the amounts normally found in food as they are already a part of the normal digestive system.

Patients who are sensitive to or intolerant to dairy products should be cautious, as probiotics are often found in yoghurt, milk, etc. Lactose-intolerant patients may develop abdominal discomfort if they consume dairy products containing probiotics.

Probiotics may increase the risk of infections in patients prone to infections or with a compromised immune system*, like HIV patients, babies born prematurely or those with immune deficiency.

6. GLOSSARY

Acidophilus
Acidophilus or Lactobacillus acidophilus is a bacteria that occurs naturally in our intestines and provides a healthy intestinal flora.

Alkylating agent
A type of drug that is used in the treatment of cancer. It interferes with DNA and inhibits cell growth.

Anthracycline
Antibiotic* drug used in chemotherapy* to treat a wide range of cancers.

Antibiotic
A drug used to treat infections caused by bacteria and other micro-organisms.

Antioxidant
A substance that protects cells from the damage caused by free radicals. Free radicals may play a part in cancer, heart disease, stroke, and other diseases of aging. Antioxidants include beta-carotene, lycopene, vitamins A, C, and E, and other natural and manufactured substances.

Cachexia
A condition in which the patient loses weight and muscle tissue and is weak and tired. A loss of appetite is also associated.

Chemotherapy
A type of cancer treatment using drugs that kill cancer cells and/or limit their growth. These drugs are usually administered to the patient by slow infusion into a vein but can also be administered orally, by direct infusion to the limb or by infusion to the liver, according to cancer location.

Clinical trial
A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis, or treatment of a disease. Also called clinical study.

Conventional therapy
Therapies that have been approved by regulatory authorities and are now used in mainstream healthcare, also often called traditional or classical therapies.

Cytotoxic
Toxic to cells.

Fructo-oligosaccharides
These are oligosaccharide fructanes extracted from fruit and vegetables and used as an alternative sweetener because of their healthy and less caloric qualities. They are extracted from, amongst other things, bananas, tomatoes, onions, etc.

Inulin
Inulin is a kind of sugar extracted from the roots of vegetables like black salsifies and artichokes. In contrast to other sugars, inulin is not sweet, but it often contains elimination products and fructo-oligosaccharides* which give it a sweet taste. It is used as a substitute for glucose for the treatment of diabetes.

Immunotherapy
Treatment to boost or restore the ability of the immune system* to fight cancer, infections, and other diseases. Also used to lessen certain side effects that may be caused by some cancer treatments. Agents used in immunotherapy include monoclonal antibodies, growth factors, and vaccines. These agents may also have a direct antitumor effect. Also called biological response modifier therapy, biological therapy, biotherapy, and BRM therapy.

Immunomodulation
Change in the body's immune system*, caused by agents that activate or suppress its function.

Immunostimulant
A substance that increases the ability of the immune system* to fight cancer or infectious diseases.

Immune system
The immune system is a biological system of structures and processes that protects the body from diseases by identifying and killing tumor cells and foreign invaders such as viruses and bacteria.

Lactitol
Lactitol is a polyol or sugar-alcohol extracted from lactose (milksugar) and is often used as an artificial sweetener, for instance in bubble gum. It has a laxative effect in larger quantities.

Lactulose
Lactulose is a synthetic sugar used to treat constipation. It attracts moisture in the intestines, thereby softening the feces and making the transit easier.

Micronutrients
Micronutrients are nutrients of which less than 1 gram is needed a day, but which are essential to the human body. Subcategories are vitamins, minerals and trace elements*.

Oxidative damage
A condition in which antioxidant levels are lower than normal. It results in excessive levels of cytotoxic oxidants and free radicals which lead to damage to specific molecules with consequential injury to cells or tissue. It occurs as a result of fungal or viral infection, inflammation, ageing, UV* radiation, pollution, excessive alcohol consumption, cigarette smoking, etc.

Preclinical trial
Research using animals to find out if a drug, procedure or a treatment is likely to be useful. Preclinical studies take place before any testing in humans is done.

Prognosis

The likely outcome or course of a disease; the chance of recovery or recurrence.

Radiation therapy/radiotherapy

A therapy in which radiation is used in the treatment of cancer always oriented to the specific area of the cancer.

Trace elements

Trace elements are elements that are essential in very small amounts (micrograms to milligrams) for the development and functioning of a living organism. However, only small amounts are required, as they can be toxic in high amounts. Trace elements occur in nature in soil, plants and in the wild. Examples are copper, chromium, iodine, etc.

UV

Ultraviolet light is electromagnetic radiation with a wavelength shorter than that of visible light, but longer than X-rays, in the range of 400 to 10 nm.