



SUPPLEMENTS IN CANCER THERAPY

This Guide had been provided by the Anticancer Fund 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 the Anticancer Fund: www.anticancerfund.org

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, fibers, amino acids, sugars, and fatty acids) are sufficiently present. However, the diet is often not ideally balanced and does not include sufficient intake of all nutrients. As a result, supplementation is required. In a broader sense, a supplement can also provide the body with benefits to help improving quality of life and possibly general health. As an example, caffeine is a beneficial component present in several plants such as coffee and cola species. Caffeine stimulates cognitive performance (to think, to interpret, to observe, and to remember) in aging people.

Also by definition, a supplement could never alter the outcome of a disease unless the disease is caused by a deficiency. An example is 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 did not have any access to fresh fruit and vegetables.

A wide range of products is available on the market with various claims. Some supplements are even promoted as having therapeutic properties against cancer. These products are very popular with cancer patients who regularly use supplements in an attempt to alter their prognosis.

In general, cancer patients take supplements for some or all of the following reasons:

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

It is very important to understand the differences between a supplement and drug to avoid misinformation when buying supplements. The main differences are explained further in this guide.

Homeopathy is not being discussed in this guide. In homeopathy, one or more active substances are diluted in alcohol or water until or past the point where none of the original substances remain. In contrast, supplements still contain a certain amount of one or more active substance(s) on which the mechanism of action is based. In homeopathy it is said that the therapeutic activity increases by diluting and shaking. You can find a summary about homeopathy at <http://www.anticancerfund.org/therapies/homeopathy>.

If you have any questions regarding a certain supplement or supplier, please contact the Anticancer Fund at info@anticancerfund.org.



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.

A system that addresses any chemical, biological and physical hazards in the food industry is Hazard Analysis and Critical Control Points (HACCP). 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 is no monitoring regarding the end product of HACCP. This means that the minimum and maximum tolerable content of the active ingredient(s) in the end product is not monitored and, consequently, not guaranteed. In contrast, this control is required for registered drugs. Moreover, there is also no stability test of HACCP verifying whether or not the supplement remains stable until the expiry date and/or at higher temperature/humidity, which is obligatory for medicines.

1.2 Safety

There are several risk factors regarding supplements that people need to be aware of.

Supplements bought from an unknown source through certain manufacturers and some websites could be contaminated with germs, pesticides, toxins, toxic heavy metals, or residual solvents. They could also contain more, less, or even none of the purported substance/s mentioned in the product information. Some herbal supplements were even found to contain prescription drugs. These product quality issues could have serious consequences for the health of the patient or other consumers.

A pharmacist is held responsible for the supplements he/she sells, while the purchaser is solely responsible for the supplement purchased online and from other sources.

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



“My pharmacist does not provide the supplement. How can I distinguish good quality products from suspicious ones?”



It might be quite challenging to know whether or not a certain supplement is reliable. When buying supplements, please keep in mind the following:

- 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.
- Never trust promises of cures. If something sounds too good to be true, such as so-called wonder drugs, it probably is..

1.3 Efficacy

Before entering the market, a drug has gone through a series of clinical trials in people that have shown a positive effect compared to placebo or standard of care. These trials have also been reviewed by the regulatory agencies to evaluate approval, and are therefore trustworthy. There are some clinical trials with food supplements in cancer, but these are sporadic and not of the same extent as the clinical trials performed with registered drugs. As a consequence, without extensive clinical trials, efficacy claims made for supplements are often false or exaggerated.

In this chapter, claims for supplements in the US and the EU will be explained separately since the regulations on both continents differ.

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 manufacturers 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 assess the risk of getting scurvy against potential risks of vitamin C supplementation.
- **Claims of wellbeing:** These include statements such as "it makes you feel better". These claims do not require pre-approval by the authorities either.

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- **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" belong to this category.
- **Structure/function claims:** These are the most hotly debated and most confusing for consumers. They are claims about the effect of the dietary supplement on the normal structure or function of the body and its 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 revised and accepted by the EFSA (European Food Safety Authority). To be accepted, all claims need to be clear and corroborated 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 remove that supplement from the market.

Herbal medicinal products that have already been in use for 30 years (of which at least 15 years have been in a EU country) can be registered under an alleged procedure called Traditional Use. With this new directive (2004/24 EC), customers will know 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 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) or the national competent authorities for the EU). They are strictly regulated and have to obtain a full Marketing Authorization (MA).

If a supplement sold over the internet claims to cure cancer, without exception this claim is 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 a MA by a competent authority.



1.4 Research

Authorized medicinal products have been proven to be safe and efficacious by preclinical* and clinical trials*. This means that the product has been tested in animals and in humans. The approval happens 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 Anticancerfund website.

 Websites often report on promising cancer research but do not mention clearly that the research has been performed on cancer cells only, not in people. Besides, at high doses almost everything kills cancer cells. A treatment should only be postulated to show promise once it has been tested in people. If you read news reports about spectacular cancer treatments, fully evaluate any published research findings to learn if and how accurate, these promising study results were achieved.



2. DIETARY SUPPLEMENTS

For more information on nutrition, see the guidance document on nutrition and physical activity on the *Guides* tab of the Anticancerfund website www.anticancerfund.org.

A balanced diet provides the body with all the necessary nutrients. If a balanced diet has been achieved, extra supplements are not necessary, unless your doctor tells you so.

The reality for cancer patients is often very different.

Malnutrition is very prevalent in cancer patients, ranging from 40-80% of cases. Cancer can alter metabolism, which increases dietary needs for more proteins, carbohydrates, fat, vitamins, and minerals. Malnutrition can also be caused by the side effects of cancer treatment. In addition, malnutrition leads to increased toxicity to cancer treatment that lowers quality of life and worsens prognosis*.

Patients undergoing surgery often require higher amounts of micronutrients* to enhance postoperative wound healing.

Vitamin and mineral deficiencies can be mostly traced through a blood analysis. Your GP (General Practitioner) 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

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 with trace elements* such as **selenium** and **zinc** can delay cachexia* to address symptoms of general weakness and malnutrition. Cachexia also suppresses the immune system* and reduces the effect of chemotherapy*.

Patients taking cisplatin may have magnesium and carnitine deficiencies; therefore, supplementation may be recommended.

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

Most cancer patients absolutely benefit from monitoring their **Vitamin D**-level and taking the necessary supplements if needed.



Recently, several studies with **fish oil** supplements in cancer patients were published. In non-small cell lung cancer, fish oil supplementation with standard chemotherapy improved the therapy response by two-fold. Patients in the supplement group were also able to receive on average an additional 3 weeks of chemotherapy. Another study in non-small cell lung cancer patients suggests that adding a fish oil supplement to standard treatment improves quality of life, physical function, cognitive function, and global health status.

In breast cancer patients, chemotherapy outcomes improved when adding a daily fish oil supplement to anthracycline-based chemotherapy. However, in oesophago-gastric cancer patients no improvement occurred.

The effect of fish oil supplements on cancer cachexia was studied in several cancer types with mixed results. The type of cancer appears to play a role, with gastrointestinal cancer patients gaining a significant amount of weight compared to lung cancer patients. In general, many studies report an improved quality of life.

As for non-cancer patients, a systematic review has shown that fish oil supplements do not treat nor prevent cognitive decline.

2.2 Supplements during cancer therapy: an overview

The table below consists of a non-exhaustive list of frequently used supplements and the effect in combination with a cancer treatment such as: surgery, radiotherapy*, stem cell transplantation, hormone therapy and different types of chemotherapy*. The color code used in the table gives on research based advice on each combination of supplement and therapy.

	Vincalkaloids *(O)	Taxanes *(N)	Platinum analogs *(M)	Monoclonal antibodies *(L)	Imatinib *(K)	Gemcitabine *(J)	Epidodophyllotoxines *(I)	EGFR-inhibitors *(H)	Dacarbazine *(G)	Cyclophosphamide *(F)	Camptothecines *(E)	Bortezomib *(D)	Antitumor antibiotics *(C)	Antimetabolites *(B)	Anthracyclines *(A)	Chemotherapy in general	Stem cell transplantation	Hormone therapy	Radiotherapy	Surgery	Supplements		
Aloe vera																							
Beta-glucanes																							
Co-enzyme Q10																							
Combination of supplement antioxidants, vitamins and minerals																							
Echinacea																							
Garlic																							
Ginger																							
Ginkgo																							
Ginseng																							
Grape stone extract																							
Green tea																							

Hop			Red																	
Mistletoe	Green	Green	Green		Green															
Milk thistle	Yellow	Yellow	Red		Yellow			Yellow												
Omega 3 or fish fatty acid EPA/DHA	Yellow			Green	Yellow	Green	Green	Green	Green	Yellow	Green	Green	Green	Green	Green	Green	Green	Yellow	Green	
Quercetin	Yellow	Yellow				Red		Yellow									Red			
Resveratrol	Yellow	Yellow	Yellow		Yellow			Yellow	Yellow	Red	Red	Red	Red	Red				Red	Red	
Selenium		Yellow						Yellow												
St-John's wort	Yellow		Red		Red		Red			Red						Red			Red	
Soya/Isoflavones/Phyto-estrogens			Yellow		Yellow															
Turmeric	Yellow	Yellow			Yellow	Yellow	Green	Yellow		Red	Red			Red	Green				Green	
Valerian	Yellow	Yellow	Red					Yellow		Red	Red	Red	Red	Red					Red	Red
Vitamin B6 B12						Green	Green											Green		Green
Vitamin E	Yellow	Yellow	Green		Yellow			Yellow										Yellow	Yellow	
Zinc		Yellow			Yellow			Yellow												

Source: Stichting tegen Kanker: http://www.kanker.be/sites/default/files/overzichtstabel_voedingssupplementen_vriend_of_vrijand.pdf
(Translated by the Anticancer Fund)



Legend of table:

*

- A. Anthracyclines (Adriplastina, Caelyx, Doxorubicine, Myocet,...)
- B. Antimetabolites (5FU, Capecitabine, Emthexate, Ledertrexate, Leustatin, Metoject, Methotrexate, Pemetrexed, Xeloda...)
- C. Antitumor antibiotics (Bleomycine, Mitomycine- C,...)
- D. Bortezomib (Velcade,...)
- E. Camptothecines (Campto, Irinosin, Irinotecan,...)
- F. Cyclophosphamide (Endoxan,...)
- G. Dacarbazine
- H. EGFR-inhibitors (Iressa, Tarceva,...)
- I. Epipodophyllotoxines (Celltop, Eposin, Vepesid,...)
- J. Gemcitabine
- K. Imatinib (Glivec,...)
- L. Monoclonal antibodies (Avastin, Herceptin,...)
- M. Platinum analogs (Carboplatine, Cisplatine,...)
- N. Taxanes (Docetaxel, Paclitaxel, Paclitaxin, Taxotere, Tevadocel,...)
- O. Vincalkaloids (Eldisine, Vinblastine, Vincrisin, ...)

Color code
Positive effect
Use with great care
Avoid
Neither known positive nor known negative effect



3. ANTIOXIDANTS

Antioxidants are substances that may protect cells against damage through interaction with and stabilization of free radicals to help blocking unstable molecules. High levels of free radicals develop from oxidative stress. Oxidation involves the loss of an electron from an atom or molecule. In this process, free radicals can attack the mitochondria, damage DNA, and initiate cancer development and growth.

An oxidizable substrate includes every type of molecule found in living organisms. This way, antioxidants* protect the cells from damage by oxidizing agents. 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 as it protects our cells. But the presence of antioxidants* in the diet during cancer therapy is very controversial since radiation therapy*, and to a lesser extent chemotherapy*, acts by means of creating ROS to kill cancer cells. Therefore, in theory, antioxidants* during radiotherapy* or chemotherapy* might inhibit the efficacy of the treatment through neutralization of the ROS. There are several clinical trials* ongoing in an attempt to clarify this controversy, but no firm conclusions have been drawn yet. Some clinical trials* suggest that antioxidant* supplementation decreases the side effects and enhances the efficacy of conventional treatment*, yet other clinical trials* indicate a shorter survival time in patients taking antioxidants* during radiation therapy*. Other clinical trials* suggest that antioxidants* could diminish the efficacy of the conventional treatment*. On the other hand, antioxidant* compounds can also protect healthy tissue against the damaging free radicals produced by the cancer therapy; these compounds are called radioprotectants. To date only a small number of radioprotectants such as curcumin are used in clinical trials* to diminish therapy-induced toxicity. Several promising compounds are emerging but further studies should investigate their effect and safety.

Important to note in this evaluation of antioxidants during conventional cancer treatment, is the fact 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).

It is possible to find in the literature numerous articles that discuss the effect of antioxidants* and cancer therapies, but there are many compounds and drugs for which this kind of studies has not been performed yet. Future research will be helpful to establish concrete recommendations for patients, but until there is clarification on the use of antioxidants* during radiotherapy*, some researchers recommend avoiding them on the days of treatment (as well as two days before and after). For chemotherapy*, the same rule can be applied for the drugs mentioned above.

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

- Vitamins and derivatives: vitamin A, C, E, K, beta-carotene, lycopene in berries, vegetables, citrus fruits, some herbs and spices, etc.
- Minerals: selenium, zinc
- Polyphenols*: quercetin, genistein, resveratrol in fruits, soy, berries etc.
- Coenzyme Q10, glutathione, melatonin,
- Plant derivatives: curcumin, green tea

For ascorbate (ascorbic acid, vitamin C) recently a small clinical trial* indicated that potentially only through parenteral* administration therapeutic doses are attainable in the human body. Intravenous* ascorbate was found to be safe and well tolerated when added to the gemcitabin and erlotinib chemotherapy* of patients with metastatic stage IV pancreatic ductal adenocarcinoma. Larger trials are necessary to confirm these results. Also the potential synergistic action of ascorbate with radiation therapy* in pancreatic cancer and the impact of ascorbate on therapy side effects in several cancers is of interest. Despite numerous clinical trials*, the anti-cancer property of vitamin C remains controversial and some authors opine that overall reports of toxicity are variable, poorly graded, and therefore inconclusive. More information on intravenous* high-dose vitamin C can be found on the Anticancer Fund website.

Vitamin supplementation (vitamin C and E, beta-carotene) in recommended daily doses in patients with cervical cancer increased quality of life at different stages of disease. This clinical trial* examined patients receiving chemotherapy* combined with radiation* and chemotherapeutical* cisplatin.

In a small clinical trial*, selenium administration for 6 months resulted in a greater tumor regression* in cervical intraepithelial neoplasia grade 1 patients than in patients without selenium administration. Selenium could also reduce upper limb lymphedema* following surgery and radiation* treatment in breast cancer patients, and had a protective effect against radiation*-induced dermatitis*. Selenium has important toxic side effects so further research and large trials* are necessary.

Melatonin might be an ideal protective agent during radiotherapy* but the suitable dose for humans in radiotherapy* treatments is an issue that has to be investigated in more depth. The results of a couple of trials on melatonin as adjuvant in chemotherapy* indicated potentially less therapy-induced side effects, more tumor regression* and longer patient survival but larger clinical trials* should dig into it further.



4. IMMUNOSTIMULATING HERBS

The immune system* is the body's defense mechanism against infections and other harmful substances in the body. At a very early stage, the immune system* can recognize and eliminate malignant cells. However, once the tumor has been developed, it applies different mechanisms to suppress and compromise the immune system* in cancer patients. Chemotherapy* and radiation therapy* are also known to be toxic to immune cells. Therefore cancer patients often seek treatments to improve their immune system defense mechanisms in order to tolerate chemotherapy* in a better way and to avoid infections on top of their illness. Some cancer patients also try to improve their immune system* with the goal of provoking anticancer activity.

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. These can play a potential role in the prevention and treatment of cancer as an adjuvant immunotherapy*. Nowadays, a lot of effort is put into the development of immunotherapy* for cancer patients because they have been proven to be successful therapeutic strategies in a broad spectrum of tumors. A lot of ongoing clinical trials* are trying to define the appropriate tumor type, therapeutic setting, treatment combination and patients populations in order to maximize clinical benefit from immunotherapeutic* agents.

Although many plants could possibly act as immunostimulants*, for many of those plants proof is lacking. Caution should be used when considering taking supplementation with immunostimulating* herbs. These herbs could also be toxic or interfere with standard treatment. Check 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 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* tab on the Anticancer Fund website.



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

- Mushrooms
 - Shiitake
 - Maitake

- Vitamins
 - Vitamin A + beta-carotene (provitamin A)
 - Vitamin B₆
 - Vitamin D
 - Vitamin E

- Minerals
 - Zinc
 - Copper

- Amino acids
 - L-arginine
 - Taurine

- Lipids
 - Amaranth oil
 - Gamma linolenic acid

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



5. PROBIOTICS

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

This area of research, called microbiome, receives more and more attention. In the coming years, there will be additional knowledge available on this matter.

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 the group of the lactic acid bacteria, of which *Lactobacillus acidophilus**, found in yoghurt 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 that has been shown to antagonize disease-causing bacteria. Probiotics are available to consumers mainly in the form of dietary supplements and food products. Examples of food products containing probiotics are yoghurt, 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*) 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 act 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, which 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 healing of damaged intestinal epithelial cells.

Several clinical trials* with probiotics in cancer patients have been performed in recent years. The effect of probiotics on diarrhea during radio*- or chemotherapy* has mainly been investigated. All trials reported positive results with a decrease in diarrhea and an improvement in stool consistency. Specifically *St. thermophiles*, *B. breve*, *B. longum*, *B. infantis*, *L. acidophilus*, *L. plantarum*, *L. casei* and *L. bulgaricus* administration decreased the incidence and frequency of radiation* therapy-induced diarrhea.



In colorectal cancer, the gut microbiota has been shown as compromised and unbalanced. In a clinical trial in colorectal cancer patients, the administration of probiotics increased the counts of beneficial bacteria and lowered the counts of pathogenic bacteria.

Probiotics are also used in colorectal cancer surgery. The reason is that probiotic administration in surgical patients might compete with bacteria responsible for postoperative infections. 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 modulating 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 decreasing infectious complications in patients with colorectal cancer undergoing proctocolectomy*.

Constipation is a common side effect for those advanced cancer patients on opioids or patients with previous surgery. Several new anti-constipating medications are under investigation in randomized clinical trials* and probiotics are one of them.

Chemotherapy* alters the intestinal microbiome which is the onset of constipation, weight loss and even mucositis*. This mucositis* can often necessitate chemotherapy* treatment breaks or dose reductions, thus compromising survival outcomes. Clinical trials* indicate that *Lactobacillus* indeed can be used as an intervention for mucositis*, resulting in the *Mucositis* Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology* guidelines suggesting that this may be beneficial for the treatment of chemotherapy*- and radiotherapy*-induced mucositis*-related diarrhea. Currently the decision to recommend probiotic therapy ultimately depends on the clinical scenario, patient interest and clinician preference.

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 sensitive or intolerant to dairy products should be cautious since 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*, including HIV patients, babies born prematurely or those with immune deficiency.

Despite the positive results, probiotics such as lactobacilli must be administered with great care because we do not have enough information about the long-term genetic stability and safety. The widespread clinical trial* use of lactobacilli has also highlighted potential mutations and untoward effects such as sepsis*, endocarditis* and bacteremia*. Always follow the advice of your doctor.



6. GLOSSARY

Acidophilus

Acidophilus or Lactobacillus acidophilus is a bacterium 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 that 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.

Bacteremia

The presence of bacteria in the blood. The response of the immune system can be sepsis and even a deadly septic shock can occur.

Cachexia

A condition in which the patient loses weight and muscle tissue and is weak, tired and suffers from a loss of appetite.

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 infusion to the liver, according to cancer location.

Clinical trial or Clinical study

A type of research study that tests whether new medical approaches are therapeutic in people. These studies test new methods of screening, prevention, diagnosis, or treatment of a disease.

Conventional therapy

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

Cytotoxic

Toxic to cells.

Dermatitis

Dermatitis or eczema is a group of conditions where the skin is inflamed and characterized by itchiness and a red skin.

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**Endocarditis**

Situation where the inner layer of the heart is inflamed.

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 that gives 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 have a direct antitumor effect. They are also named biological response modifier therapy (BRM), biological therapy, and biotherapy.

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.

Intravenous

Drugs often are administered intravenously. This means a liquid drug is delivered immediately into a vein. This is an parenteral route of administration.

Lactitol

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

Lactulose

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

Lymphedema

Condition where tissue swells due to localized fluid retention. Often caused by a compromised lymphatic system.

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.

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Mucositis

Painful inflammation and ulceration of the mucous membranes that line the digestive tract. This is usually an adverse effect of chemotherapy or radiotherapy treatment for cancer.

Oxidative damage

A condition in which antioxidant levels are lower than normal. It results in excessive levels of cytotoxic oxidants and free radicals that lead to damage of 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.

Parenteral

Route of drug administration like into a vein, into bone marrow, under skin, into muscle. Drug is given by any route but the enteral one which includes passage through the gastrointestinal tract. So not by mouth, through tube feeding or with suppository.

Polyphenols

Class of chemicals with a typical phenol structural unit. Polyphenols play an important role in most plants. They were traditionally used as dyes.

Preclinical trial

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

Proctocolectomy

Surgical removal of the colon and the rectum.

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 and which is always oriented to the specific area of the cancer.

Regression

Characteristic of disease to show lighter symptoms without completely disappearing. At a later point, symptoms may return.

Sepsis

Life-threatening condition caused by an overreaction of the body due to an infection. The body's reaction harms its own organs and tissues.



Scurvy

Disease caused by a lack of vitamin C.

Trace elements

Trace elements providing elements are essential in very small amounts (micrograms amounts) for the development and functioning of a living organism. However, only small amounts are required since 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.