MEDDOCS Open Access Publisher

Hematology and Oncology: Current Research

Open Access | Review Article

# Nutraceutical Oncology: A Review

***Okonkwo Cyril Onyedikachi*[1]*; Eze Emmanuel A*[2]**

[1]*Biotech Lab, Department of Biological Sciences, Godfrey Okoye University, Emene, Enugu, Nigeria.*

[2]*Department of Microbiology, University of Nigeria, Nsukka, Nigeria.*

***Corresponding Author(s): Okonkwo Cyril Onyedikachi**

Graduate Student, Medical Biotechnology programme, Department of Biological Sciences, Godfrey Okoye University, Ugwuomu-Nike, Enugu State. P.M.B. 01014 Thinker's Corner, Enugu, Nigeria.

Email: mastrecy123@outlook.com

Received: Aug 23, 2021

Accepted: Sep 16, 2021

Published Online: Sep 22, 2021

Journal: Hematology and Oncology: Current Research

Publisher: MedDocs Publishers LLC

Online edition: http://meddocsonline.org/



**Keyword:** Cancer; Chemoprevention; Chemotherapy; Nutraceutical; Oncology; Radiotherapy.

## Abstract

Cancer is a public health concern, and a major source of global morbidity and mortality. The conventional cancer therapies such as systemic therapy, surgery and radiotherapy have brought concomitant adverse effects such as multidrug resistance, cytotoxicity to adjacent normal cells and high financial burden in accessing them. Hence, there is the need for a better and cost-effective approach in cancer management. Nutraceuticals offer much better potentialities in effective chemoprevention and management of cancers. They are effective against cancers, are non-toxic, dosage friendly, safer and cheaper to afford. They offer a very big hope in cancer therapy. Scientists in the field should therefore work earnestly to straighten out the nuances involved in the production, uses and applications of different varieties of nutraceuticals both singly, synergistically and complementarily with conventional therapies. More preclinical and clinical studies should be carried out to validate some unverified claims, so that standardized approaches can be well established.

## Introduction

Cancer is a disease that is identified by its characteristic uncontrolled cell growth and proliferation. It is a situation where cells are no longer regulated by the body's normal growth control mechanisms and so have gained the ability to divide and proliferate indefinitely, resisting aging and normal programmed cell death. It is a product of multi-step process requiring the accumulation of many genetic and epigenetic changes over time [1,2]. Cancer is the second most common cause of death in the US and globally, exceeded only by cardiovascular disease [3]. According to American Cancer Society's Facts and Figure of 2019, 'cancer accounts for about one in every six deaths worldwide – more than HIV/AIDS, tuberculosis, and malaria combined' [3]. In 2018, there were an estimated 18.1 million new cancer cases diagnosed around the world and 9.6 million cancer deaths. About 20% of cancer cases occurred in low- and medium-human development index countries, many of which lacked the medical resources and health systems to support the disease burden. By 2040, the global burden is expected to reach 27.5 million new cancer cases and 16.3 million cancer deaths solely due to the growth and aging of the population [3-5].

**Cite this article:** Okonkwo CO, Eze EA. Nutraceutical Oncology: A Review. Hematol Oncol: Curr Res. 2021; 4(1): 1009.

In 2012, there were 14.1 million new cases and 8.2 million deaths globally [6]. According to National Cancer Institute's report on Cancer Statistics, 2018, 57% of new cancer cases reported in 2012 occurred in developing regions of the world that include Central America and parts of Africa and Asia with 65% of cancer deaths which was about 8.2 million worldwide also occurred in these regions [7]. According to a report [8], there is an average of 100, 000 new cases of cancer occurring in Nigeria every year, with high case fatality ratio. Also Global Cancer Observatory, 2019 reported that the number of new cancer cases in Nigeria in 2018 was 115, 950 with number of cancer-related deaths amounting to 70, 327 within the same year [9].

Cancer has become a public health concern and a major source of morbidity and mortality [10]. These reports show the amount and urgency of work needed to be done in the fight against cancer by all stakeholders both the in public and private sectors, in order to avoid being overrun by the disease.

The rich abundance of the physiological benefits that can be derived in nutraceuticals and functional foods needs to be exploited today in the bid to fight many health challenges and diseases including cancers. It was over 2500 years ago that Hippocrates, who is regarded as the father of medicine said, "Let food be thy medicine and medicine be thy food". This otherwise basic tenet of medicine was not until recently recognized as the best approach to prevention and treatment and/or management of diseases [11, 12]. Many health claims about the physiological benefits of most foods and foods components are being validated by scientific research evidences, and so can be used exclusively in the nearest future to treat many malignant ailments and diseases if appropriately prepared in the right amount [13, 14]. Nutraceuticals have been the subject of intensive study for their possible effects against heart disease and cancer. They also potentiate the general immune system activity. One study has also shown them to be effective in treating AIDS and in antimicrobial activity [15]. This review therefore seeks to present a comparative narrative of the conventional cancer therapies and the novel use of nutraceuticals.

**Oncology**

Oncology is the branch of medicine that researches, identifies, treats or manages cancer. It is the study of the science of cancer, its etiology, prevention, diagnosis, treatment and management [16]. The field of oncology has three major areas: Medical, surgical, and radiation [17, 18].

Medical oncology is concerned with the treatment of cancer using systemic medications such as chemotherapy or other targeted therapy like hormone therapy or immunotherapy. Surgical oncology deals with the removal of tumor and nearby infected tissue during surgery. Surgical oncologists also perform certain types of biopsies to help in the diagnosis of cancer. A radiation oncologist treats cancer using radiation therapy to shrink and kill the tumors [17].

Clinical oncologists are doctors who use radiotherapy and chemotherapy to treat and manage patients with cancer. They also use a range of other treatments against cancers, without using surgery. There are other specialties in oncology. A gynecologic oncologist treats gynecologic cancers, such as uterine, ovarian, and cervical cancers. A pediatric oncologist treats cancer in children. Some types of cancer occur most often in children and teenagers. This includes certain brain tumors, leukemia, osteosarcoma, and Ewing's sarcoma. Certain types of cancer more common in children sometimes also occur in adults. A hematologist-oncologist diagnoses and treats blood cancers, such as leukemia, lymphoma, and myeloma. Many other cancers such as breast, prostrate, lung, colorectal, stomach cancers and so on, have different specialist oncologists in those areas [18].

Cancers, or more appropriately neoplasms are benign when the cells divide rapidly but are still localized at their primary sites, without the capacity of spreading to secondary locations. Malignant neoplasms are more appropriately called cancers when they are capable of spreading through the body. It can be invasive malignant cancer if the cells migrate and penetrate to neighboring tissues. It is metastatic malignant cancer if the cancer cells are able to penetrate into lymphatic and blood vessels, circulate through the bloodstream, and invade other normal tissues in different parts of the body [16].

All cancers can be placed into six categories or groups based on the associated body organs of origin. They are carcinoma, sarcoma, leukemia, lymphoma, melanoma, and glioma. Carcinomas originate in epithelial tissues, such as the liver, lungs, glands (e.g., prostate or thyroid), bladder, kidney, breast, ovary, uterus, testes, colon, skin, and brain. Sarcomas originate in bone, muscle, cartilage, fat, and fibrous tissue. Leukemia's originate in the bone marrow; myeloma is a subset of leukemia, which is a cancer of plasma cells. Lymphomas originate in the lymphatic system, i.e. the lymph nodes. Melanomas are cancers that originate in skin cells called melanocytes (although melanomas can be found in organs other than skin); and gliomas are cancers of the nervous tissue, i.e. the brain and spinal cord [16].

**Causes of cancer**

Cancer is a genetic disease that is primarily caused by genetic transformation of a normal cell to a cancerous cell. The genetic transformation is a result of accumulation of mutations at specific regions of the genome. It involves stages of initiation, promotion and progression [19-20]. These occur when there is activation of proto-oncogenes to oncogenes. Proto-oncogenes are physiological regulators of cell proliferation and differentiation, while oncogenes are characterized by the ability to promote cell growth in the absence of normal mitogenic signals. This can happen through point mutation or gene amplification resulting in overproduction of growth factors, flooding of the cell with replication signals, uncontrolled stimulation in the intermediary pathways and cell growth by elevated levels of transcription factors. Some examples of oncogenes are Ras, Cyclins D, Cyclin E, CDK4 and C-MYC [1].

Cancer also occurs when there is deactivation of tumour-suppressor genes due to mutations. Tumour suppressor genes encode proteins that are:

- Receptors for secreted hormones that function to inhibit cell proliferation
- Negative regulators of cell cycle entry or progression
- Negative regulators of growth signalling pathways (e.g. APC)
- Checkpoint-control proteins that arrest the cell cycle if DNA is damaged or chromosomes are abnormal
- Proteins that promote apoptosis [1].

The transformation of a normal cell to a cancer cell is ac-

companied by the loss of function of one or more tumour suppressor genes and both gene copies must be defective in order to promote tumour development. Some examples of tumour-suppressor genes are p53, APC, Retinoblastoma (Rb), BRCA1 and BRCA2 [1].

Cancer can also result from defects in the genes involved in DNA repair systems. DNA repair genes are important in maintaining the integrity of the human genome, by fixing damage that may have occurred to the DNA. They minimize accelerated mutagenesis and thus prevent cancer. Principal DNA repair mechanisms include mismatch repair, base and nucleotide excision repair, repair of depurinated sites and repair of double-strand breaks. Examples of DNA repair genes are genes encoding DNA ligase, DNA polymerase l, DNA photolyases and DNA glycosylases [1].

**Predisposing factors of cancer**

These risk factors potentiate the probability for cancer development. They are chemical mutagens such as asbestos, components of tobacco smoke, aflatoxin (food contaminant) and arsenic (a drinking water contaminant); physical mutagens such as ultraviolet and ionizing radiations; biological mutagens, such as infections from certain viruses, bacteria, or parasites, hormonal dysfunction and hereditary factors [10]. Exposure to mutagens greatly increases mutation rate and thus, the probability of developing cancer. Chemical mutagens are a group of substances that modify DNA through various mechanisms, such as alkylation or deamination of DNA bases, intercalation between base pairs and formation of DNA adducts (e.g. aromatic hydrocarbons, tobacco etc.). Oxidative damage may also affect DNA integrity. X-rays and radioactive radiation tend to induce DNA double-strand breaks, whereas UV radiation results in the formation of pyrimidine dimers, by cross-linking of adjacent pyrimidine bases [1].

Certain viruses are able to induce cancer development. Highly oncogenic viruses are those viruses, which contain viral oncogenes in their genomes that are in most cases derived from cellular proto-oncogenes. Slowly transforming viruses are those ones, which do not contain such genes. They tend to use one of the following mechanisms to stimulate proliferation of their host cells: Insertion of a strong promoter in the vicinity of a host cell proto-oncogene, expression of proteins that neutralize host cell tumour suppressor proteins and expression of proteins that prevent or delay apoptosis [1].

Tumour viruses often establish persistent infections in the human host. They are rarely complete carcinogens, i.e. they require additional factors to fully activate carcinogenesis, and host factors such as immune suppression are important determinants in virus-induced carcinogenesis [10]. Examples of tumour viruses are Human Papilloma Virus (HPV), Human Herpes Virus 8 (HHV8), Epstein-Barr Virus (EBV), Hepatitis B virus, Human T-cell leukaemia virus, Human Immunodeficiency Virus (HIV) and Hepatitis C virus [1,21].

There is also inherited predisposition arising from germline mutation on the parent DNA. This usually occurs on the DNA repair genes and the tumour-repressor genes but not on the oncogenes [1,10,21].

Another important predisposition of cancer is aging. This is because the older one becomes, the more the accumulation of substantial amount of mutations that can trigger carcinogenesis [10,22].

Other risk factors of cancers include life styles such as chronic alcohol use, dietary factors including insufficient fruit and vegetable intake, overweight and obesity, and physical inactivity [3,22].

**Cancer staging**

Staging describes the extent or spread of cancer at the time of diagnosis. The two most common staging systems are described below, although some cancers (e.g., lymphoma) have alternative staging systems:

**a) The TNM system,** which is most often used by clinicians, assesses cancers in three ways: The size of the Tumor (T) and/or whether it has grown to involve nearby areas, absence or presence of regional lymph Node involvement (N), and absence or presence of distant Metastases (M). Once the T, N, and M categories are determined, the tumor is assigned a stage of 0, I, II, III, or IV, with stage 0 referring to a noninvasive cancer that is limited to the layer of cells where it originated, stage I being early stage invasive cancer, and stage IV being the most advanced stage [23, 24].

b) A second staging system, called **Summary Stage** involves classification of cancers as in situ, local, regional, or distant. Cancer that is present only in the original layer of cells where it developed is classified as in situ. If cancer cells have penetrated the original layer of tissue, the cancer is invasive and is categorized as local (confined to the organ of origin), regional (spread to nearby tissues or lymph nodes in the area of the organ of origin), or distant (spread to distant organs or parts of the body) [23].

In summary, there are seven major attributes of cancer as reported [25]. They are:

i. Self-sufficiency in growth signals,

ii. Insensitivity to anti-growth signals,

iii. Evading apoptosis,

iv. Limitless replicative potential with the presence of telomerase and non-diminutive telomeres,

v. Sustained angiogenesis,

vi. Tissue invasion and metastasis, and

vii. Genome instability.

**Diagnosis of cancer**

Cancer can be diagnosed through various methods, which include microscopic examination of biopsy, endoscopic examination of internal organs, radiography (i.e. x-rays), ultrasonography, Computed Tomography or CT scan, Positron Emission Tomography (PET) scan, and Magnetic Resonance Imaging (MRI). Additionally, blood tests can help to diagnose cancers. Some tumors have tumor markers that include genetic markers, cellular and tissue markers, and circulating markers that can be detected in the blood [16].

**Cancer prevention**

According to WHO of 2021, more than 30% of cancers are triggered by several lifestyle and environmental risk factors that are potentially modifiable [22]. So, by lifestyle changes, certain cancers can be prevented. This involves abstinence or controlled use of tobacco, promotion of healthy diet and physi-

cal activity, prevention of harmful use of alcohol, reduced exposure and promotion of protective actions against carcinogens in the environment and workplace, including ionizing and non-ionizing radiations and vaccination against tumour viruses [21, 26]. Functional foods and nutraceuticals can as well be used in preventing cancers [12,19,27,28].

**Treatment of cancers**

The most conventional methods of cancer treatment are by cancer surgery (surgical treatment), radiotherapy, chemotherapy and hormone therapy. Nowadays various immunological therapies and targeted drug delivery are also used. There is a variety of different cancer drugs available. They are usually used in combination. Cancer treatment is usually personalized, which is why treatments can vary depending on the type and stage of the disease, and on the genetic makeup of the patients. It can involve only surgery, or with radiotherapy and/or chemotherapy, called adjuvant and neoadjuvant therapy. Other treatment options include stem cell and bone marrow transplantation, antiangiogenetic, photodynamic and gene therapies [16,21]. Nutraceuticals are also being used recently in the treatment of various cancers [12,13,19,27,28].

**Nutraceuticals**

The word "nutraceutical" was coined by Stephen DeFelice, MD, founder and chairman of the Foundation for Innovation in Medicine (FIM), Cranford, NJ, in 1989. It was from the words "nutrition" and "pharmaceutical". He defined nutraceutical as a food or part of a food that can be used to provide medical or health benefits, including the prevention and/or treatment of a disease or ailment [12,19,29,30]. This definition previously covered functional foods. But more recent definitions by different groups and societies try to distinguish between nutraceutical and functional foods. Nutraceutical is defined as any product that is isolated from herbal products, dietary supplements, specific diets, and processed foods such as cereals, soups, and beverages that in addition to nutrition are also used as medicine [31]. Nutraceuticals are also defined as pharmaceutically blended products that possess both nutritional as well as the medicinal value that are intended to improve the physical health, fight against day-to-day challenges such as stress, increase longevity, slow down aging process and so on [15]. Health Canada defines nutraceutical as "a product prepared from foods, but sold in the form of pills, or powder (potions) or in other medicinal forms, not usually associated with foods" [30]. Functional foods are similar in appearance to conventional foods. They have physiological benefits and can reduce the risk of chronic diseases beyond basic nutritional functions, including maintenance of gut health, cancer prevention and so on. They are consumed as part of normal diet [29,32,33].

There is yet no legal and regulatory definition of nutraceuticals and functional foods. Different jurisdictions have their different definitions and treatments. The way they are defined and treated in US and Europe is quite different from that in Canada [30,33].

As reported [30], Nutraceuticals can be categorized in several ways. So based on food sources, mechanism of action and chemical nature, they can be classified as follows:

- Dietary Fibre
- Probiotics
- Prebiotics
- Polyunsaturated fatty acids
- Antioxidant vitamins
- Polyphenols
- Spices

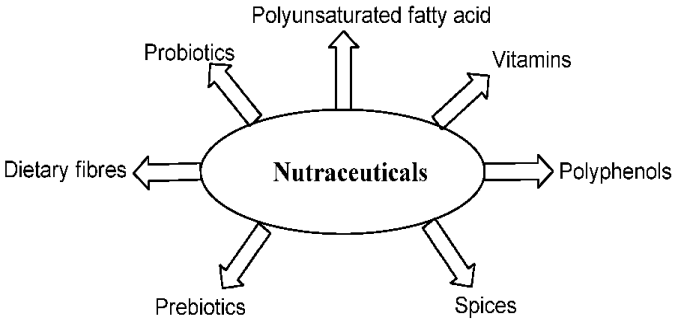


**Figure 1:** Classification of Nutraceuticals (Source: Chadha *et al* [34]).

In another point of view [30], nutraceuticals are also classified into two broad groups:

- Potential nutraceuticals
- Established nutraceuticals

A potential nutraceutical is one whose clinical claims have not been scientifically validated. It becomes an established nutraceutical only after efficient clinical data of its health and medical benefits have been obtained. Much of the nutraceutical products are still in the potential category [30].

Another report also has other classifications based on food availability, mechanism of action and chemical nature. Based on food availability, there are traditional and non-traditional nutraceuticals. Traditional nutraceuticals are natural and unprocessed food substances and food products [15]. They include:

- Chemical constituents (e.g. Nutrients, Herbals and Phytochemicals)
- Probiotic microorganisms
- Nutraceutical enzymes

Non-traditional nutraceticals are foods or food products that have been biofortified with bioactive components or that are biotechnological processed to boast their nutrient content and medicinal activities. They include fortified nutraceuticals and recombinant nutraceuticals.

Based on mechanism of action, they are further divided into antimicrobial, anti-inflammatory, and antioxidant nutraceuticals.

Finally, based on chemical nature, they are classified depending upon their primary and secondary metabolite sources such as fatty acids, carbohydrates, and amino acid-based substances, isoprenoid derivatives and phenolic substances [15].

**Nutraceutical approach in cancer: Nutraceutical oncology**

From the foregoing, it can therefore be said that nutraceutical oncology is the application of nutraceuticals and functional foods in cancer prevention, treatment and management. A lot of scientific breakthroughs have laid credence and credibility to the possibility of sole and complementary approach in preventing, treating and managing various kinds of cancers using

nutraceuticals and functional food. In recent times, researches have shown that about 64% to 81% of human cancer patients take various nutraceuticals supplements such as vitamins and minerals, or herbal supplements, even with about 68% of their physicians unaware of their supplement use [35, 36, 37]. More researches are also ongoing in the field both at preclinical and clinical stages. Research evidences have also proven that they do not produce negative side effects on the patients as are obtainable with chemotherapy and other forms of conventional cancer therapy. There are also no dosage problems associated with the use of nutraceuticals. Nutrceuticals can also be used in combination with other forms of cancer therapy [12, 14, 36, 38].

Foods low in simple carbohydrates with moderate amounts of high-quality protein, fiber, and fat (especially fats of the omega-3 fatty acid series) are beneficial for cancer patients. Also, certain supplemental micronutrients, nutraceuticals and functional foods have potential to reduce the risk of developing cancer, or retarding the rate of growth and metastasis of established malignant disease. They are also important in reducing toxicity associated with chemotherapy and radiation therapy, and may lead to better life conditions by reducing cancer cachexia. They inhibit cell proliferation and induce apoptosis in the cancer cells [19, 28, 39].

**Classifications of nutraceuticals and their anticancer mechanisms**

Below are some specific examples of scientific evidences of the applications of nutraceuticals in cancer preventions and management.

**Polyphenols**

Polyphenols are plant secondary metabolites that contain one or more hydroxyl group attached to a benzene ring in their structure. More than 8000 different polyphenols found in food (mainly wine, tea, coffee, cocoa, vegetables and cereals) are present in the human diet [28]. They are naturally occurring compounds found largely in fruits, vegetables, cereals and beverages. They are generally involved in defense against ultraviolet radiation and aggression by pathogens. Fruits like grapes, apple, pear, cherries and berries contain up to 200–300mg polyphenols per 100 grams fresh weight. The products manufactured from these fruits also contain polyphenol in significant amounts. Typically, a glass of red wine or a cup of tea or coffee contains about 100mg polyphenols. Cereals, dry legumes and chocolate also contribute to polyphenolic intake [20]. The basic classifications of polyphenols as reported [40], are given in the diagram below:

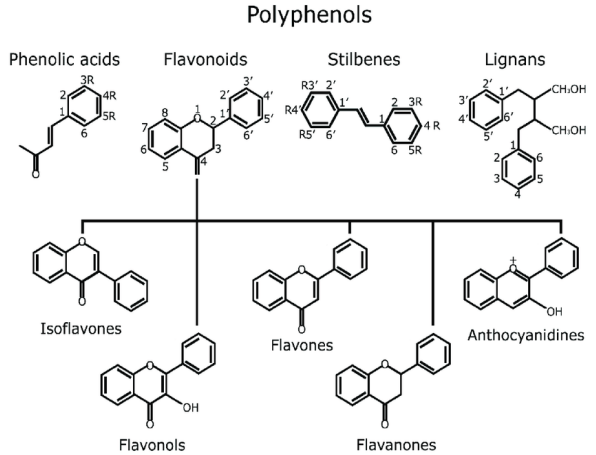


**Figure 2:** Classification of Phenols (Source: [40]).

**Phenolic acids** are divided into two classes: derivatives of benzoic acid such as hydroxybenzoic acids, and derivatives of cinnamic acid like hydroxycinnamic acids such as p-coumaric, caffeic, ferulic and sinapic acids.

**Flavonoids** comprise the most studied group of polyphenols. More than 4,000 varieties of flavonoids have been identified, many of which are responsible for the attractive colours of the flowers, fruits and leaves. They are divided into six subclasses: Favonols, flavones, flavanones, flavanols, anthocyanidines and isoflavones. Quercetin, myricetin, catechins etc., are some most common flavonoids.

Most **stilbenes** in plants act as antifungal phytoalexins, compounds that are synthesized only in response to infection or injury. One of the best studied, naturally occurring polyphenol stilbene is resveratrol (3, 4, 5-trihydroxystilbene), found largely in grapes. A product of grapes, red wine also contains significant amount of resveratrol.

Several **lignans** such as secoisolariciresinol are considered phytoestrogens. The richest dietary source is linseed, which contains secoisolariciresinol (up to 3.g/kg dry weight) and low quantities of matairesinol [20].

Many polyphenols, such as quercetin, catechins (e.g. epigallocatechin-3-gallate, EGCG), isoflavones, lignans, flavanones, ellagic acid, red wine polyphenols, resveratrol and curcumin have been tested against cancers, and all of them showed positive effects in some models although their mechanisms of action were found to be different. Polyphenols use various mechanisms which include estrogenic/antiestrogenic activity, antiproliferation, induction of cell cycle arrest or apoptosis, prevention of oxidation, induction of detoxification enzymes, regulation of the host immune system, anti-inflammatory activity and changes in cellular signaling pathways [20, 37].

**Antioxidant vitamins**

Antioxidants protect the body against the effects of free radicals and other substances, which produce toxic effects, such as xenobiotics. These therapeutic agents have other effects, however, which should be considered. They have beneficial effects on countering inflammation and immunosuppression, and other deleterious processes, which are very prevalent in patients with malignancies [41]. The role of antioxidant vitamins such as ascorbic acid, lycopene, beta-carotene, alpha tocopherol, retinoids and non-vitamin natural antioxidants (e.g. glutathione) in the prevention of cancer diseases had already been reported. Free radical production is a chain reaction and has 3 steps namely initiation, propagation and termination. These free radicals once produced, damage macromolecules by attacking at the double bonds. Oxygen radicals, especially the hydroxyl radical (.OH) modify nitrogen bases, split DNA, stimulate oncogene activators and probably in many other ways participate in carcinogenesis. These vitamins actions may be through the modulation of immune function or through antioxidant properties or by direct effect such as inhibition of N-nitrosamine formation or cell-to-cell interactions and modulation of the enzyme activities [19].

Antioxidant supplementation has however been seen to counteract other cancer therapy such as chemotherapy and radiotherapy. This is because these therapies cause cancer cell death through DNA damage by free radicals formed during irradiation and when certain drugs are metabolized. Guide should be given to cancer patients receiving chemotherapy and radio-

therapy by their oncologists in their supplementations with antioxidants to avoid a counteractive effect [36, 39].

**Lipids and polyunsaturated fatty acids**

The various subgroups include fats, waxes, glycolipids, phospholipids, and polyprenyl compounds. Steroids, fat-soluble vitamins, and isoprenoids (terpenoids) are polyprenyl compounds. Omega-3- and omega-6-PolyUnsaturated Fatty Acids (PUFAs) are essential fatty acids [42].

Isoprenoids enhance antioxidative power by improving receptor functionality. Farnesol (from floral essential oil) and geraniol (from citronella, geranium, lemon, palmarosa, and rose oils) have *in vivo* cytotoxicity against murine liver cancer, leukemia, and melanoma. Cell membrane phospholipid bi-layers are protected from free radicals by isoprenoids [42].

Omega-3-PUFAs are immune boosting, platelet aggregating, anti-inflammatory agents. They are consumed as DocosaHexanoic Acid (DHA) and EicosaPentanoic Acid (EPA). Omega-3-PUFAs bind Peroxisome Proliferator Receptor Activator (PPAR) gamma, thereby inhibiting cell proliferation and inducing cancer cell apoptosis. DHA has greater dose dependent pro-apoptotic activity against DU145 prostate carcinoma cells than does EPA. DHA's pro-apoptotic activity is mediated via MAPK, NF-κβ, p53, and PI3K-Akt signaling pathways [42]. Polyunsaturated fatty acids are also cancer cell membrane chemoradiation sensitizers [35]. Omega-3 PUFAs have direct cytotoxic effects against cancer cells. *In vitro*, they can reduce cellular proliferation, angiogenesis, and invasion and increased programmed cell death. They have been shown to be chemopreventative in patients predisposed to colon cancer and are being studied as part of combination therapeutic protocols for people with colon, breast, and prostate cancer [36].

**Spices**

Spices are substances, which are used as condiments because of their flavor, taste and color. Many of them have been used as medicinal plants in folk medicine for the treatment of various diseases because they contain many bioactive compounds and possess a lot of beneficial health effects. Scientific studies have shown the antioxidant, anti-inflammatory and immunomodulatory effects of these spices, which are utilized in prevention and treatment of several cancers, including lung, liver, breast, stomach, colorectum, cervix, and prostate cancers. Their main mechanisms of action include inducing apoptosis, inhibiting proliferation, migration and invasion of tumors, and sensitizing tumors to radiotherapy and chemotherapy [19, 35, 37, 43]. The tables below show some documented spices and their anticancer properties.

**Table 1:** Some Spices, their bioactive compounds and their anticancer properties (Source: [43]).

| Sites | Spices | Constituents | Anticancer Effects |
|---|---|---|---|
| Lung | Turmeric | Curcumin | Inducing apoptosis and DNA damage; inhibiting proliferation, migration, and the growth of cancer; decleasing cell growth and viability; inhibiting expression of DNA-repair-assouated proteins |
| | Black cumin | Seed extract and seed Oil; Thymoquinone | Reducing viability of human lung cancer; inhibiting proliferation, migration, and invasion Of lung cancer cells |
| | Ginger | | Decreasing tumorigenesis and the metastasis |
| | Garlic | Thiacremonone | Inhibiting tumor growth |
| | Saffron | Ethanolic extract, aqueous extract | Inducing cell death and apoptosis, inhibiting the cell proliferation |
| | Red chili pepper | Capsaicin | Restraining angiogenesis, inducing apoptosis and oxidative DNA damage |
| Liver | Turmeric | | Inhibiting the growth of hepatoma cells, inhibiting and reversing diethylnitrosamine-induced hepatocaltinogenesis |
| | Black cumin | Thymoquinone | Inhibiting cell proliferation |
| | Rosemary | Carnosic acid | Sensitizing TRAIL-mediated apoptosis, inducing autophagic cell death |
| | Clove | Eugenol | Improving the xenobiotic-metabolizing systems |
| | Galangal | Galangin | Inhibiting proliferation Of Cancer cells, |
| Cervix | Turmeric | Curcumin | Eradicating HPV* cancer cells without affecting non-cancerous tissue, inhibiting the proliferation and inducing apoptosis, inhibiting tumor growth and angiogenesis |
| | Black cumin | Thymoquinone, methanolic extract | Inducing apoptosis and inhibiting proliferation |
| | Clove | Eugenol | Enhancing the effect of gemcitabine, anticarcinogenic and anti-inflammatory activity |
| Prostate | | Curcumin | Targeting AR and histone modification, inhibiting the proliferation and growth |
| | Ginger | Ginger extract, 6-shogaol, 6-gingerol and 6-paradol | Inducing inhibiting prostate cancer cell proliferation and growth |
| | Saffron | Saffron extract | Antiproliferative properties, inhibiting cell invasion and migration |
| | Black pepper | Piperine | Reducing the androgen and androgen independent tumor growth, inhibiting proliferation |
| | Red chili pepper | icin | Reducing the metastatic burden, radio-sensitizing agent |

| | | | |
|---|---|---|---|
| | Rosemary | Rosemary extract | Promoting androgen receptor degradation and decreasing xenograft tumor growth |
| **Sites** | **Spices** | **Constituents** | **Anticancer Effects** |
| Breast | Turmeric | Curcumin | Inhibiting MCF-7 breast carcinoma cells, cell invasion, and sensitizing cancer cells to retinoic acid |
| | Black cumin | Thinone | Anti-proliferative and pm—apoptotic effects |
| | G inger | 6-Shogaol | Decreasing tumor and the metastasis |
| | Garlic | Dallyi disulfide. Dialiyl sulfide, Diallyl trisulfide, S—allyl me rcaptocysteine | Inhibiting prolifer cell growth, and metastasis; in-hibiti ng diethylstilbestrol in-duced DNA damage inducing apop-tosis; irr ation; inhibi tin g estrogen receptor-'x activity |
| | Sa ffron | Croce tin | Inhibiting invasiveness |
| | Bl ack pepper | Piperine | Inhibiting the growth and motility of cells, inducing apoptosis, en hancing the ef-ficacy of TRAIL-based therapy |
| | Red chili pepper | Capsaicin | Inducing cell death, inhibiting invasion and migration |
| | Rosemary | Supercritical fluid rosemary extract | Down regulating estrogen receptor-.and HER2 sensitizing TRAIL-mediated apoptosis |
| | Clove | Eugenol | Inducing apoptosis |
| | Coriander | Ethyl acetate extract | Inhibiting DNA damage and migration |
| | Wasabi | 6-MITC | Inducing apoptosis |
| Stomatch | Turmeric | Curcumin | Inhibiting proliferation and invasion, promoting apoptosis, supplessing lymphatic density, inhibiting cell growth |
| | Garlic | Diallyl disulfide | Causing G 2 / M arrest, promoting apoptosis, suppressing xenograft tumors |
| | Saffron | Cro cet in, crocin | antioxidant, anti-proliferative, and apoptotic activities |
| | Red chili pepper | Capsaicin | Inhibi ting cell proliferation, inhibiting cell , inducing apoptosis |
| | cardamom | Not mentioned | Inhibi ting forestomach p apillomagenesis |
| colorectum | Turmeric | Curcumin | preventing aberrant crypt foci, inducing apoptosis, inhibiting cell growth |
| | Black cumin | Thymoquinone | A ttenuating tu mor developmen t and growth, induci ng apoptosis, inducing au tophagic cell death |
| | Ginger | Ginger root/ leaf exlTact, 6-gingerol,shogaols | Reducing cel l viability and prol iferation, inducing apoptosis |
| | Garlic | Se-Methyl-L-selenocysteine garlicextract | lnducing apoptosis,suppressing cell proliferation |
| | Onion | Se-M ethyl-L-selenocystei ne | lnducing apoptosis |
| | Scallion | scallion extract | inhibiting tu mor growth |
| | Saffron | Crocin | Inducing apoptosis |
| | Black pepper | Piperine | lmpa iring cell cycle progression and inducing apoptosis |
| | Red chili pepper | Capsaicin | Inhibi ting cell proliferation and induci ng apoptosis |
| | Rosemary | Rosemary extract,camosic acid, diterpenes | Sensitizing ca ncer cells to 5-FU, inhibi ting cell migration, ind ucing apoptosis |
| | Clove | Clove extract | lnhibi ting tu mor growth and promoting cell cycle arrest and apoptosis |
| | Galangal | Galangin | Inducing cell death |
| | Cinnamon | Cinnama ldehyde | Regul ating d rug-metabol.i zing genes |

### Probiotics

The term "probiotic" was implied by Elie Metchnikoff in early 20th century but was later coined by Lilly and Stillwell in 1965 [44]. A probiotic is defined classically as a viable microbial dietary supplement that beneficially affects the host through its effects in the intestinal tract [12]. Probiotics are also defined as beneficial bacteria or other microorganisms that are/are added in foods, which add to the friendly microbial flora in the intestinal tract. Examples of common strains include *Lactobacillus* and *Bifidobacterium* families of bacteria. Some are naturally found in fermented foods like sauerkraut and yogurt; while some are added as nutraceutical ingredients in some foods usually displayed on the food's label [33]. They also enhance the growth

and functions of the beneficial intestinal microbial flora and keep down the toxic or pathogenic microorganisms. Their application are well boosted in modern medicine due to their ability to make the intestine more friendly for processes such as metabolism and absorption [15].

**Prebiotics**

Prebiotics are non-digestible foods in human digestive system (onions, garlic, bananas, Jerusalem artichoke, chicory root, beans, skin of apples, or other fiber) that have the capability to stimulate the favourable growth and activities of indigenous probiotic bacteria [12,45]. Examples of prebiotics are the inulin-type fructans, which include native inulin, enzymatically hydrolyzed inulin or oligofructose, and synthetic fructooligosaccharides.

There are also significant scientific evidences about anticancer activities of probiotics and prebiotics especially on colon cancer and associated inflammatory bowel disease. They are important in prevention of different kinds of cancers as reported by some works [46,47,48].

Probiotics and prebiotics function through various mechanisms such as modulating the gut microbiota, eliminating pathogens, reducing mutagenesis and genotoxicity of dietary carcinogens, suppressing xenobiotic enzyme activity, preventing the release and reabsorption of procarcinogenic substances, producing metabolites with anticancer properties, regulating apoptosis, and modulating immunity, confer protection against carcinogenesis in the host. Probiotics can be considered safe adjuvant strategy cancer therapy [49].

**Dietary fibers**

Dietary fibers are endogenous components of plant materials in the diet, which are resistant to digestion by enzymes produced by humans. Fibers can be broadly classified into soluble and insoluble fibers. Soluble fiber can be mainly derived from oat bran and fruit pectin. Wheat, rye, rice and most other grains are main sources of insoluble fibers. Legumes, beans, peas, certain fruits and vegetables are excellent sources of both soluble and insoluble fibers [12].

Dietary fibers have shown substantial evidence of positive effect. Insoluble fiber reduces rate of colon cancer and diverticulitis, an inflammatory condition of the colon [12]. Fibrous polysaccharides also bind carcinogens, lower bile acids, and modulate estrogen metabolism [42].

**Advantages of nutraceutical use over conventional cancer therapy**

Substances used as chemotherapy are majorly alkylating agents (e.g., cyclophosphamide, temozolomide, cisplatin, oxaliplatin), anti-metabolites (e.g., methotrexate, cytarabine, fluorouracil, capecitabine), anti-tumor antibiotics (e.g., doxorubicin, epirubicin, bleomycin), topoisomerase inhibitors (e.g., etoposide, irinotecan) and microtubule stabilizers (e.g., paclitaxel, docetaxel).Typically, they are not tumor specific and most times, their administration results in significant toxic effects to non-cancerous tissues, leading to some dangerous ailments such as cardiovascular diseases which are the most common causes of death to cancer survivors [50].

In radiotherapy, many tumor types remain insensitive to radiotherapy owing to intrinsic resistance or recurrence shortly after the treatment because of acquired resistance. Also, cancer radiotherapy is limited by the maximum tolerated dose of radiation to adjacent normal tissues. Thus, effective radiotherapy is considered in terms of how to maximize cancer cell killing capacity within the capacity of acceptable dose that adjacent healthy tissues can tolerate from radiation injury [51].

Surgery on its part can only be used on *in situ* noninvasive tumors. It cannot be used on metastatic cancers. And it is most times carried out with adjuvant and neoadjuvant therapies [16].

Generally, chemotherapy and radiotherapy have the limitations of multi drug resistance and non-specificity to tumors with adverse side effects to non-cancerous cells and the entire human body at large, hence the need for a more specific and targeted therapy. Treatments of cancer by nutraceuticals and their semi-synthetic analogues both *in vitro* and *in vivo* have shown promising results against different malignancies. Natural compounds such as sesquiterpenes, flavonoids, alkaloids, diterpenoids, saponins, and polyphenolic compounds can be substituted for, or applied in combination with existing drugs. They have shown to be non-toxic, more specific and are chemoradiation sensitizer when used in combination with conventional therapies [2, 14, 35, 37].

Nutraceuticals have also been found to be dosage friendly as there are no cases of dose toxicity to the body. They are generally safer than chemotherapeutic drugs and radiotherapy. They are also cost effective relative to conventional methods. [37, 52, 53].

**Limitations of nutraceutical oncology**

Notwithstanding the numerous positive potentials of nutraceuticals with respect to cancer management, there are some limitations to their efficacy and efficient use. There are ways that nutraceuticals can negatively affect conventional cancer treatment. For instance, antioxidant harm has been substantiated for cancer patients especially smokers receiving radiotherapy and chemotherapy [35, 36, 39, 41]. Lung and prostate cancer risks are significantly raised by vitamin E and high dose β-carotene. However, it is unclear the mechanism by which these risks occur [35]. Caution is paramount when considering certain plant-based supplements as they may antagonize the activity of therapeutic agents, or, alter their metabolism from efficacious forms thereby producing a counter activity and progression of the pathophysiology [37].

There are still insufficient clinical research findings on the appropriate use of nutraceuticals in cancer management. Most researches are mainly epidemiology and *in vitro* or animal model researches. There is the urgent need for aggressive researches in the field of nutraceutical oncology to substantiate the numerous claims available, and hence prescribe the appropriate uses of these physiologically important substances [37, 52].

Poor bioavailability is also another problem with some nutraceuticals. Some others however facilitate the uptake of poorly absorbed ones. Piperine for instance, a bioactive substance in pepper (*Piper nigrum*) has been reported to facilitate the uptake and bioavailability of curcumin and other tea polyphenols through its modulation of drug metabolism isoforms in the liver [37].

## Conclusion and perspectives

Nutraceutical oncology is a promising field of study, which requires more clinical researches to push it into the future. It is the future of cancer prevention, treatment and management. Scientists should endeavor seriously to work out the modalities

for a standardized nutraceutical oncology.

**Declaration of interest**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

**Funding:** This work did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## References


1. Bommer U, Perrow KL. Cancer Council Australia Oncology Education Committee. Cancer biology: Molecular and genetic basis, In: Sabesan S, Olver I, eds. Clinical Oncology for Medical Students, Sydney: Cancer Council Australia. 2014.
2. Mitra S, Dash R. Natural Products for the Management and Prevention of Breast Cancer. Evidence-Based Complementary and Alternative Medicine. 2018; 1: 23.
3. American Cancer Society. Cancer Facts & Figures. Atlanta: American Cancer Society. 2019.
4. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians. 2018; 68: 394-424.
5. GLOBOCAN, Switzerland: World Health Organization International Agency for Research on Cancer. 2018.
6. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. International Journal of Cancer. 2015; 136: E359-E386.
7. National Cancer Institute. Cancer Statistics. 2018.
8. Jedy-Agba E, Curado MP, Ogunbiyi O, Oga E, Fabowale T, et al. Cancer Incidence in Nigeria: A Report from Population-based Cancer Registries. Cancer epidemiology. 2012; 36: 271-278.
9. The Global Cancer Observatory. 2019.
10. Morounke SG, Ayorinde JB, Benedict AO, Adedayo FF, Adewale FO, et al. Epidemiology and Incidence of Common Cancers in Nigeria. Journal of Cancer Biology Research. 2017; 5: 1105.
11. Hasler CM. Functional Foods: Benefits, Concerns and Challenges—A Position Paper from the American Council on Science and Health. The Journal of Nutrition. 2002; 132: 3772-3781.
12. Ramaa CS, Shirode AR, Mundada AS, Kadam VJ. Nutraceuticals - An Emerging Era in the Treatment and Prevention of Cardiovascular Diseases. Current Pharmaceutical Biotechnology. 2006; 7: 15-23.
13. Pitchaiah G, Akula A, Chandi V. Anticancer potential of nutraceutical formulations in MNU-induced mammary cancer in Sprague Dawley rats. Pharmacognosy Magazine. 2017; 13: 46-50.
14. Aung TN, Qu Z, Kortschak RD, Adelson DL. Understanding the Effectiveness of Natural Compound Mixtures in Cancer through Their Molecular Mode of Action. International Journal of Molecular Sciences. 2017; 18: 656.
15. Chanda S, Tiwari RK, Kumar A, Singh K. Nutraceuticals Inspiring the Current Therapy for Lifestyle Diseases. Advances in Pharmacological Sciences and Pharmaceutical Sciences. 2019: 1-5.
16. Foote M. Oncology Basics. American Medical Writers Association Journal. 2005; 20: 52-58.
17. Cancer.net. Types of Oncologists. 2018.
18. Cancer Treatment Centers of America. What is the difference: Oncology specialties. 2018.
19. Tripathi YB, Tripathi P, Arjmandi BH. Nutracueticals and Cancer Management. Frontiers in Bioscience. 2005; 10: 1607-1618.
20. Pandey KB, Rizvi SI. Plant polyphenols as dietary antioxidants in human health and disease. Oxidative Medicine and Cellular Longevity. 2009; 2: 270-278.
21. Giaccone G. Grand Challenges in Oncology. Frontiers in Oncology. 2011; 1: 26.
22. World Health Organization. Cancer. 2021.
23. American Cancer Society. Cancer Treatment & Survivorship Facts & Figures 2016-2017. Atlanta: American Cancer Society. 2016.
24. Tan A, Cancer Council Australia Oncology Education Committee. Cancer diagnosis: staging and imaging. In: Sabesan S, Olver I, eds. Clinical Oncology for Medical Students. Sydney: Cancer Council Australia. 2014.
25. Idikio HA. Human Cancer Classification: A Systems Biology-Based Model Integrating Morphology, Cancer Stem Cells, Proteomics, and Genomics. Journal of Cancer. 2011; 2: 107-115.
26. Olver I, Cancer Council Australia Oncology Education Committee. Screening and prevention. In: Sabesan S, Olver I, eds. Clinical Oncology for Medical Students. Sydney: Cancer Council Australia. 2014.
27. Salami A, Seydi E, Pourahmad J. Use of nutraceuticals for prevention and treatment of cancer. Iranian Journal of Pharmaceutical Research. 2013; 12: 219–220.
28. Ranzato E, Martinotti S, Calabrese C, Calabrese G. Role of Nutraceuticals in Cancer Therapy. Journal of Food Research. 2014; 3: 18.
29. Cencic A, Chingwaru W. The Role of Functional Foods, Nutraceuticals, and Food Supplements in Intestinal Health. Nutrients. 2010; 2: 611–625.
30. Das L, Bhaumik E, Raychaudhuri U, Chakraborty R. Role of Nutraceuticals in Human Health. Journal of Food Science and Technology. 2012; 49: 173–183.
31. Nasri H, Baradaran A, Shirzad H, Rafieian-Kopaei M. New Concepts in Nutraceuticals as Alternative for Pharmaceuticals. International Journal of Preventive Medicine. 2014; 5: 1487–1499.
32. Bull E, Rapport L, Lockwood B. Nutraceuticals. The Pharmaceutical Journal. 2000.
33. El Sohaimy SA. Functional Foods and Nutraceuticals - Modern Approach to Food Science. World Applied Sciences Journal. 2012; 20: 691-708.
34. Chadha R, Bhalla Y, Vashisht MK, Chadha K. Cocrystallization in Nutraceuticals. In Glebovsky V, ed. Recrystallization in Materials Processing. 2015.
35. Nwanodi OB. Nutraceuticals: Chemoradiation Sensitizers and Adverse Effect Resolver. Herbal Medicine. 2017B; 3: 2.
36. Skorupski KA. Nutraceuticals: A Role in the Management of the Cancer Patient? Veterinary Meeting and Expo 2012 Proceeding. 2012.
37. Wargovich MJ, Morris J, Brown V, Ellis J, Logothetis B, et al. Nutraceutical use in late-stage cancer. Cancer Metastasis Rev. 2010; 29: 503–510.

38. Thani NAA, Keshavarz S, Lwaleed BA, Cooper AJ, Roopra HK. Cytotoxicity of gemcitabine enhanced by polyphenolics from Aronia melanocarpa in pancreatic cancer cell line AsPC-1. Journal of Clinical Pathology. 2014; 67: 949-954.

39. Burns KM. Therapeutic Foods and Nutraceuticals in Cancer Therapy. Veterinary Technician. 2019.

40. Echeberría ML, López MH, Micol V, Catalán EB. Polyphenols as Promising Drugs against Main Breast Cancer Signatures. Antioxidants. 2017; 6.

41. Jefferson Myrna Brind Center of Integrative Medicine. Integrative Medicine and Cancer: Treatment Strategies. 2006.

42. Nwanodi OB. Nutraceuticals: Curative Integrative Cancer Treatment. Alternative and Integrative Medicine. 2017A; 6: 240.

43. Zheng J, Zhou Y, Li Y, Xu D, Li S, et al. Spices for Prevention and Treatment of Cancers. Nutrients. 2016; 8: 495.

44. Bhuvan S, Saroj A. Probiotics: A Promising Anti-Cancer Agent. Advances in Biotechnology and Microbiology. 2018; 10: 555783.

45. Srivastava RK. Need of Nutraceuticals/Functional Food Products for Health Benefits to Worldwide People. Journal of Biotechnology and Biomedical Science. 2018; 1: 1-13.

46. Tarrah A, de Castilhos J, Rossi RC, Duarte V, Ziegler DR, et al. In vitro Probiotic Potential and Anti-cancer Activity of Newly Isolated Folate-Producing Streptococcus thermophilus Strains. Frontiers in microbiology. 2018; 9: 2214.

47. Motevaseli E, Dianatpour A, Ghafouri-Fard S. The Role of Probiotics in Cancer Treatment: Emphasis on their In Vivo and In Vitro Anti-metastatic Effects. International journal of molecular and cellular medicine.2017; 6: 66-76.

48. Kahouli I, Malhotra M, Alaoui-Jamali M, Prakash S. In-Vitro Characterization of the Anti-Cancer Activity of the Probiotic Bacterium Lactobacillus Fermentum NCIMB 5221 and Potential against Colorectal Cancer. Journal of Cancer Science & Therapy. 2015; 7: 224-235.

49. Devaraja G, Rashmi BS. Anti-Cancer Properties of Probiotics: A Natural Strategy for Cancer Prevention. EC Nutrition. 2016; 5: 1191-1202.

50. Palumbo MO, Kavan P, Miller WH, Panasci L, Assouline et al. Systemic cancer therapy: achievements and challenges that lie ahead. Frontiers in Pharmacology. 2013; 4: 57.

51. Chen H, Kuo MT. Improving radiotherapy in cancer treatment: Promises and challenges. Oncotarget. 2017; 8: 62742–62758.

52. Vadalà M, Laurino C, Palmieri L, Palmieri B. Shark Derivatives (Alkylglycerols, Squalene, Cartilage) as Putative Nutraceuticals in Oncology. European Journal of Oncology. 2017; 22: 5-20.

53. Block KI, Gyllenhaal C, Lowe L, Amedei A, Amin AR, et al. designing a broad-spectrum integrative approach for cancer prevention and treatment. InSeminars in cancer biology. 2015; 35: S276-S304.