

ROLE OF NUTRACEUTICALS IN CANCER THERAPY**Yahaya Mohammed, Yanlika Maina, Abba Abubakar, Mrutyunjaya Bhanja *****Faculty of Pharmacy, Kalinga University, Naya Raipur, Chhattisgarh India (492101)***Corresponding Author's E mail: mrutunjaya.bhanja@kalingauniversity.ac.in

Received 12 June. 2024; Revised 15 June. 2024; Accepted 21 June. 2024, Available online 10 July. 2024



Cite this article as: Mohammed Y, Maina Y, Abubakar A and Bhanja M. Role of nutraceuticals in cancer therapy. 2024; 13(3): 79-88.

<https://dx.doi.org/10.38164/AJPER/13.3.2024.79-88>**ABSTRACT**

Nutraceuticals are naturally occurring bioactive products that have nutritional value and show potential as treatments for a variety of illnesses. Cancer is a serious health issue that remains a significant cause of death worldwide. Currently available cancer treatments, includes; radiation, chemotherapy, and surgery, might have unforeseen side effects that compromising health and wellbeing of the patient. According to recent research, several plant-based substances might affect the cellular and molecular mechanisms that underlie the growth of tumours. However, some of these molecules might also play an antagonistic activity against classic therapeutic agents. The purpose of this article is to evaluate the existing understanding behind the use of nutraceuticals in cancer prevention and therapy.

Keywords: Nutraceuticals, Cancer, Phytochemicals, Curcumin, Gingerol.**INTRODUCTION**

Globally, cancer is a major health concern, with rising life expectancy, increasing urbanisation, and resulting changes in environmental and lifestyle conditions ¹. Every year, tens of millions of people worldwide are diagnosed with cancer, and more than 50% of these people eventually die as a result of it. Cancer is the second leading cause of death in many countries, after cardiovascular disease ². Cancer cases worldwide are expected to increase over the next two decades by 70% according to the World Health Organisation. The prevalence of cancer in India is estimated to be around 2.5 million, with about 8, 00,000 new cases and 5, 50,000 deaths per annum. It is believed that in near future the number of cancer patients will increase in the developing and under developed countries, which may rise up to 70%; a serious issue for all of us. The magnitude of cancer problem in the Indian Sub-continent (sheer numbers) is increasing due to poor to moderate living standards and inadequate medical facilities ³.

Cancer mortality is the top killer with breast and cervical cancer as the lead cause. Since the 2008 estimates, breast cancer incidence has increased by more than 20%, while mortality has increased by

14% and is the most frequently diagnosed cancer among women in 140 of 184 countries worldwide. Cervical cancer is the fourth most common cancer affecting women worldwide, after breast, colorectal, and lung cancers; it is most notable in the lower-resource countries of sub-Saharan Africa. Years of intense biomedical research and billions of dollars spent in cancer research have increased the understanding of the underlying mechanisms of tumorigenesis and cancer biology. One type of secondary prevention that lowers tumor growth and cancer-related mortality is cancer screening. The primary objectives of cancer treatment are to extend survival and improve quality of life. Given that most malignancies are diagnosed with a bad prognosis, the likelihood of survival and healing can be increased with an early diagnosis and targeted treatment.

Cancer is a condition where cells in the body grow and divide uncontrollably, invading tissues leading to the formation of tumours. Many years of dedicated and extensive efforts have been focused on detecting various risk factors for cancer. For certain types of cancer, aetiology has been influentially associated with specific environmental (acquired factors) such as radiation and pollution. On the other hand, unhealthy lifestyle choices such as smoking, eating an unbalanced diet, stress, and engaging in physical activity have a significant influence on determining the risk of cancer. These factors may act together to initiate or promote carcinogenesis in the human body and thus cancer is leading cause of death. Food and nutrients are essential to the body's normal functioning. They aid in the maintenance of an individual's health and the prevention of various diseases⁴. To date, chemotherapy represents the main pharmacological treatment. However, anticancer drugs have harmful effects on normal cells, carrying the risk of side effects that can sometimes cause serious complications and negate the benefits in terms of hospitalization and survival. Since the primary goal of anticancer treatments is to eliminate cancer cells without harming healthy cells, it is imperative to develop an effective treatment with anticancer properties and minimal side effects. Because cardiotoxicity and nephrotoxicity frequently necessitate the early discontinuation or replacement of treatment, the use of natural compounds as adjuvants of chemotherapy could lessen the necessity for these actions. Recently, from the literature, positive effects emerged with the combination of anticancer therapy and nutraceuticals products. Nutraceuticals are used daily to supplement nutrients that are lacking in the diet.

A large number of studies demonstrated that frequent consumption of vegetables and fruits decrease the risk of colon cancer, the third most common cancer in both men and women⁵. Diet, high intake of grains, fruits, legumes, vegetables and other edibles rich in phytoestrogen, high fibre and low fat diet can play a significant role in preventing colon cancer and others like breast cancer, prostate cancer and lung cancer

which are more prevalent in the developed countries ⁶. About 2000 years ago, Hippocrates well recognised father of medicine emphasised “Let food be your medicine and medicine be your food” ^{7,8}. There is currently increased global interest as it is recognised that "nutraceuticals" play an important role in health enhancement ⁹. Hundreds of natural and synthetic compounds have been shown to have cancer-preventive properties. Despite the fact that both the incidence and cure rates of cancer have not improved significantly, some medications have been developed to improve efficacy while minimising toxicity. Nowadays, there is a focus on the development of novel combination therapies/chemoprevention through nutraceuticals as components in multiple cancer targets. Many plant-derived products, when used in combination, have been found to improve cancer control efficacy and have a broader spectrum of activity. They may function synergistically to attack tumours by regulating distinct signalling pathways, or they may compensate for opposing features in cancer cells such as proliferation or apoptosis ¹⁰.

Aetiology of Cancer

Carcinogenesis is caused by the accumulation of several sequential mutations and alterations in nucleus and cytoplasm molecules, which eventually leads to invasive neoplasms ¹¹. The three stages of these events are initiation, promotion, and progression. The process, which includes carcinogen binding to the target and DNA damage, happens very quickly during the initiation phase. In the promotion phase, Tumour promoters function as mitogens, causing clones of initiated cells to proliferate. This process is usually reversible. Promotion is caused by the inactivation of regulatory proteins and cellular checkpoints that are required for proliferation and apoptosis. Progression is the stage at which phenotypically and genotypically altered cells undergo irreversible macroscopic changes. Progression and promotion both have lengthy timelines—possibly several years. By using this approach, chemo-preventive drugs can be conveniently categorised into categories according to their ability to either reduce promotion and progression or block initiation ¹².

TYPES OF CANCER

Breast cancer

Breast cancer remains the predominant cancer risk for women, with mortality of 53,5341 and disability adjusted life years of 14.8 million. In 2016, nearly 1.7 million cases of breast cancer emerged, making it globally the major cause of death and morbidity among females. Every year, over a million people are expected to be diagnosed with breast tumors globally and over 410,000 will die of the illness, accounting for 14% of women. There has been an overall rise in breast cancer diagnoses in recent years, due to many

contributing factors. In 2017, an analysis showed a 33% rise in cases from 2005 to 2015, while population growth was 12.6%, aging 16.4%, and age-specific cases 4.1%. Reproductive risk factors include the long history of menstruation, nulliparity, the present utilization of the postmenopausal hormone treatment, or contraceptives. The use of alcohol can also increase breast cancer risk ¹³.

Colorectal cancer

Colorectal cancer is fourth among males and the third among females in terms of prevalence. Colorectal cancer is primarily an elderly condition, with over 70% of people 65 years of age or older, and is a significant cause of illness and death in the aged. It is predicted that the number of cases will rise as age increases. It is the second most prevalent cancer in the United Kingdom. Australia, Canada, New Zealand, the US, and regions of Europe are among the nations that have the highest occurrence rates. India, China, and portions of Africa are among the lowest-risk countries. A substantial rise of 2–4 times in the occurrence of a colorectal tumor has occurred in Asian countries such as China, Japan, South Korea, and Singapore over the previous decades. Every year around the world 1.8 million new cases are diagnosed. Age, obesity, low intake of fruit and vegetables, lack of activity, smoking, excessive drinking of alcohol, and heavy consumption of refined or red meat are among the risk factors for colorectal cancer.

Lung cancer

About 100 types of cancer are categorized by organ and root tissue. Lung cancer is the primary cause of death of all these types. Every year, approximately 1.04 million new lung cancer cases are recorded globally, with the highest occurrence in North America and Europe. In some nations, this epidemic of lung cancer mortality has decreased where tobacco control results in smoking but in other countries, it is rising rapidly. Despite years of study, the outlook for lung cancer patients remains dysfunctional, with a survival rate of 14% across 5 years. However, in the early stages, lung cancer is treatable and most patients benefit from therapy, for example, prolonged lifespan or reduced symptoms. The chance of getting lung cancer is 20–30 times higher than that of a non-smoker in his or her lifetime. In developing nations, rates of lung cancer are increasing parallel to cigarette smoking.

Liver cancer

Liver cancer is the sixth-largest tumor diagnosed and the second largest cause of mortality around the globe. Around half the new cases and deaths were in China alone, with 466,100 cases and 422,100 deaths in 2015. In most countries, hepatocellular carcinoma (HCC) is the main histologic form of liver cancer and accounts for about 80% of total cases. The 2nd most frequent histologic form is intrahepatic

cholangiocarcinoma, which accounts for around 15% of total cases. There will be 1 million cases by 2030, and the burden of liver cancer is rising worldwide. Due to the highest prevalence of hepatitis B virus (HBV) infections in Sub-Saharan Africa and Asia, the morbidity of liver cancer is also high. The major causing factor for the HCC histological form of liver cancer is HBV and/or HCV infections. These causes have been identified as possible causing factors of liver carcinoma, such as dietary aflatoxin, betel nut chewing, alcohol intake, and smoking. Since major risk factors of liver cancer can be changed, there are good hopes that prevention interventions such as improvements to the diet and hepatitis immunization can decrease the occurrence and death from the disease. Some of its etiological factors such as hepatitis infection and cirrhosis can be easily identified through screening to decrease liver cancer growth ¹⁴.

Pancreatic cancer

Pancreatic cancer, with which death is nearly parallel, is an extremely lethal disease. More than 2,00,000 deaths annually occur from pancreatic cancer globally. Pancreatic cancer is less frequent from a global perspective than the lung, breast, stomach, liver, large bowel, and prostate tumors. The 4th common cause of carcinogenic mortality in developing countries is pancreatic cancer but forecasted to be the 2nd leading cause for cancer-related death in the next 10 years if the figures are not changed. Adenocarcinoma (accounts for nearly 85% of all cases) and pancreas endocrine tumors (represent fewer than 5% of all cases) are two primary forms of tumors in pancreatic cancer. Smoking, chronic pancreatitis family history, aging, male, diabetic mellitus, obesity, non-O blood type, occupational exposures, African-American ethnicities, heavy fat diet, meat-rich diet, poor vegetable, and folate-related diets, and potential *H. pylori* are the main factors for this malignant condition. Although the cause of pancreatic cancer is complicated, multifactorial, cigarette smoking, and family history are prevalent. Smoking rates raises the likelihood of pancreatic cancer, and it is suspected that smoking may be linked to as much as one in four cases of pancreatic cancer. Present screening practices are restricted to individuals with family history and those considered to raise the risk of catching the disorder, often done with MRI or endoscopic ultrasound ¹⁵.

Nutraceutical

In 1989, Stephen De Falice coined the term "nutraceutical. It is defined "as a food or parts of food that offer medical or health benefit including prevention and treatment of disease. Hippocrates, the well-known father of medicine, said over 2000 years ago, "Let food be your medicine, and medicine be your food," highlighting the links between nutrition and human health, particularly between appropriate food for health and their therapeutic benefits. Nutraceuticals can range from isolated nutrients, dietary

supplements, and diet to genetically altered "designed" foods, herbal products, and processed foods including cereals, soup, and beverages¹⁶. A nutraceutical is any non-toxic food extract supplement that has a considerable established health benefit for both prevention and treatment of illness. Some nutraceuticals are currently under clinical trials, but the majority have already approved clinical use. There are already over 470 nutraceuticals and functional food products available with established health benefits.

Depending on their emphases, these Nutraceuticals typically provide the required amount of vitamins, lipids, proteins, carbs, minerals, or other important components. Nutraceuticals can also regulate DNA transcription in tumours. They have several therapeutic benefits, including diabetes, sclerosis, anti-obesity effects, cardiovascular effects, immunological boosting, natural antioxidant activity, anti-inflammatory activity, and neurological problems. Some of the well studied phytochemicals in relation to tumour prevention includes curcumin (turmeric), gingerol (ginger), genistein (soya beans), resveratrol (grapes), caffeic acid phenyl ester (propolis from honey bee), capsaicin (green chilies), epigallocatechin gallate (green tea), sulforaphane (cruciferous vegetables), indole-3-carbinol (cabbage), tangeretin (citrus species), lycopene (tomatoes), emodin (aloes), diallyl sulphide (garlic), apigenin (tea, cabbage, garlic), allicin (garlic), quercetin (rhododendron cinnabarinum), anethole (fennel, camphor)¹⁷.

Nutraceuticals and Cancer

Epidemiology studies have repeatedly shown that nutrition is a major risk factor for chronic conditions such as cataract, type II diabetes, gallstones, neurological illnesses, cardiovascular disease, and a variety of cancers (including gastrointestinal cancer). A third of cancer-related deaths are thought to be avoidable through dietary and other lifestyle changes. The use of functional foods and nutraceuticals in the management, prevention, and treatment of cancer can be referred to as nutraceutical oncology for the reasons mentioned above. Numerous scientific advancements have given the prospect of using nutraceuticals and functional foods as a solo and complementary method in the prevention, treatment, and management of various types of cancer believability and credibility. Cancer patients benefit from eating foods that are low in simple carbohydrates and high in high-quality protein, fibre, and fat (particularly omega-3 fatty acid lipids). Furthermore, some micronutrients, nutraceuticals, and functional foods may be able to reduce cancer risk or slow the progression of pre-existing malignant diseases.

They play a critical role in reducing the side effects of chemotherapy and radiation treatment, and they may enhance quality of life by reducing cancer cachexia. They cause cancer cells to undergo apoptosis and suppress cell growth. Increasing antioxidant intake through diet may lower the chance of developing

diseases like cancer. The phytochemicals have demonstrated a variety of distinct modes of action at various cellular levels. The majority of them are well-known as diverse antioxidant sources that influence the signalling pathway for redox-mediated transcription factors.

Along the same lines, nutraceuticals may be useful in reducing toxicity associated with radiation and chemotherapy, as well as improving quality of life by reducing cancer cachexia. Nutraceuticals, functional foods, and supplemental micronutrients all have the ability to limit cancer cell proliferation and induce cancer cell death. Despite promising *in vitro* results using a variety of cell types, no mechanism-based preclinical studies have been conducted. The first extensive clinical studies of phytochemicals conducted in the 1990s were unsuccessful due to a lack of preclinical evidence. Botanicals have long been used to treat cancer. Vincristine and vinblastine, two alkaloids derived from the vinca species, as well as the Pacific yew *Taxus brevifolia* (*Taxol*), are among the numerous cancer treatment drugs derived from plants. Ancient societies all over the world used a variety of methods to cure and prevent illness, as well as to preserve health ¹⁵.

Possible mechanisms of action of nutraceuticals as chemo-preventive agent

Chemoprevention can be defined as the use of either natural or synthetic chemicals that inhibit, reverse, or eliminate the carcinogenesis process. Intraepithelial neoplasia or carcinoma *in situ*, which correspond to the promotion and progression stages, are typically used to diagnose early-stage solid cancer. Therefore, anti-promotion and ‘anti- progression’ agents may be of particular clinical interest. Ultimately, such agents prevent the growth and survival of cells already committed for malignancy. Gene expression regulation may be significantly impacted by bioactive components in food compounds, even at very low concentrations, as was previously underappreciated ¹⁶. Further research on the impact of nutraceuticals on gene expression should provide insight on the mechanisms underlying dietary interventions for the prevention of conditions like obesity, diabetes, atherosclerosis, hypertension, and cancer. Using a variety of genetically diseased animal models, a few recent studies on the effects of particular nutraceuticals on the activity of transcription factors like activator protein (AP-1), nuclear factor kB (NFkB), sterol response element binding proteins (SREBPs), peroxisome proliferator-activated receptor-gamma (PPARgamma), modulation of the expression of antioxidant genes like Bcl-2 as final targets in the signal transduction cascade, and gene regulation have paved the way for further in-depth investigations of these molecules ¹⁷.

NUTRACEUTICALS AND THEIR APPLICATIONS IN CANCER THERAPY

Curcumin

Curcumin is known to induce apoptosis in malignant cell lines by suppressing a number of key elements in cellular signalling pathways pertinent to growth, differentiation and malignant formation. It is one of the extensively investigated phytochemical, with regard to chemo-preventive potential. It inhibits the TNF- α induced COX-2 transcription and NF κ B activation by inhibiting the I κ B degradation, through down regulation of NF κ B inducing kinase (NIK) and I κ B kinase. Curcumin inhibited the catalytic activity of ERK 1/2 in different cell systems. Alternatively curcumin acts through another transcription factor NRF2, which normally exists in an inactive state as a consequence of binding to KEAP1 protein. Curcumin is unstable at neutral and basic pH and more than 90% of curcumin decomposes rapidly in buffer systems at this pH. It gets degraded to ferulic acid ([4- hydroxy-3-methoxy cinnamic acid]) and feruloyl methane (4-hydroxy-3- methoxycinnamoyl methane)¹⁸.

Resveratrol

Resveratrol is a naturally occurring polyphenol that can be found in a variety of foods, including grapes, wine, nuts, berries, and many other foods consumed by humans. Usually, it appears as a white powder that is just slightly soluble in water. Resveratrol is the most important stilbene related to cancer. It possesses a natural anti-proliferative activity due to its role as a phytoalexin (plant antibiotic). It is believed to have also multiple bioactivities including anti-cancer, anti-carcinogenesis and anti-inflammatory effects. The mechanisms by which resveratrol might produce these effects are not completely understood, but the main molecular mechanism seems to be the activation of sirtuin proteins. There is considerable interest in developing resveratrol for cancer prevention and treatment. The plasma pharmacokinetics of resveratrol in humans are now reasonably well defined, and studies have shown that repeated daily doses are safe and well tolerated. However, pharmacokinetics studies of resveratrol have shown a poor bioavailability (only 1%) due to extensive glucuronidation and sulfation as well as metabolism by gut bacterial enzymes¹⁹.

Capsaicin

Capsaicin is a pungent ingredient found in hot red chilli peppers (genus *Capsicum*, family Solanaceae). Its pre-treatment protects against free radical-induced pulmonary damage. It also has antiplatelet and anti-inflammatory properties, which are linked to its inhibition of phospholipase A2. By inhibiting plasma membrane NADH oxidase activity, it induces growth inhibition and apoptosis in transformed

human cells in culture, including ovarian carcinoma, mammary adenocarcinoma, and promyelocytic leukaemia (HL-60). Both Bcl-2 and the protein phosphatase calcineurin have been shown to regulate the apoptosis brought on by capsaicin ²⁰.

Epigallocatechin-3-gallate

EGCG (epigallocatechin-3-gallate) is the major catechin found in green tea (*Camellia sinensis*). Green tea consumption has been related to several health benefits in Asian countries, and it is recognised as the most effective cancer-preventive beverage. EGCG has been shown to have antitumor properties in multiple cancer cell lines, including less common tumours like anaplastic thyroid carcinoma and malignant mesothelioma. Clinical trials evaluating EGCG's efficacy should be carefully planned in order to better understand specific effects, as the majority of studies determining the anticancer drug properties of EGCG are preclinical. Low bioavailability and conversion into inactive methylated metabolites are the main drawbacks to green tea's therapeutic uses ²¹.

Genistein

Genistein (5,7-dihydroxy-3-(4-hydroxyphenyl)-4H-1-benzopyran-4-one) is an isoflavone obtained from soy beans that may have a role in soy's ability to prevent cancer. Among the few flavonoid and isoflavonoid compounds that have been studied, it is the only one that exhibits potent growth inhibitory and oestrogen agonist properties against breast cancer cells ²². It has demonstrated the ability to stop the growth of several cancer cells both in vivo and in vitro without harming healthy cells. The majority of studies have shown that genistein effectively chelates anti-metabolites such as gemcitabine and 5-FU. The FDA has approved erlotinib and gemcitabine as a combination treatment for advanced pancreatic cancer. The mechanism of action of genistein-mediated chemosensitization and chemoprevention is shown to be the down-regulation of key survival molecules such as NF- κ B, Akt, AMPK, TRAIL, MAPKs, etc ²².

Quercetin

Quercetin is a plant-derived compound that belongs to the flavonoid class and can be found in a variety of fruits and vegetables. Its daily intake in the human diet can reach up to 16–25 mg/day ²³. Numerous mechanisms are thought to be involved in the induction of cell apoptosis by quercetin. Oral administration of quercetin has been shown to prevent induced carcinogenesis, especially in the colon, and it can also inhibit the growth, invasion, and metastatic potential of melanoma, according to in vivo studies investigating its anticancer effects.

Lycopene

Lycopene is a prominent red-pigmented-carotenoid found in tomatoes and human plasma. It is an acyclic isomer of beta-carotene, which can also be found in watermelons, pink grapefruits, apricots, pink guavas, and papaya. Lycopene is found in microorganisms but is not found in animals. Lycopene primarily exhibits its anti-cancer properties through two distinct mechanisms: oxidative and non-oxidative. Singlet oxygen can be quenched by lycopene, maintaining cellular redox homeostasis.

Gingerol

Gingerol, 1-[4-hydroxy-3-methoxyphenyl]-5-hydroxy-3-decanone, isolated from Ginger (*Zingiber officinale* Family: Rosaceae), It has been discovered that it can inhibit invasion, motility, and adhesion in human breast cancer cell lines, human hepato-carcinoma cells, and other cell lines. It also exhibits strong anti-inflammatory activity. Ginger's ability to prevent nausea and vomiting, a common side effect of cytotoxic chemotherapy, has been acknowledged as a useful application, rather than its anticancer properties.

Polyphenols

Polyphenols are secondary metabolites found in plants that contain one or more hydroxyl groups attached to a benzene ring. More than 8000 different polyphenols found in food (mainly, wine, tea, coffee, cocoa, vegetables and cereals) are present in the human diet. In this context, the phenolic acid, flavonoid, stilbene, and curcuminoids groups are the most important due to their ability to inhibit the initiation of carcinogenic processes and suppress cancer progression ²⁴.

Pepper

Pepper (*Piper nigrum*), Piperine is one biologically active ingredient in black pepper. A common drawback of using natural plant-based products as medicines is that they are poorly absorbed. Piperine has been extensively researched for its potential to counteract this. Piperine modulates drug metabolism isoforms in the liver, improving the absorption and bioavailability of curcumin and tea polyphenols.

Chile pepper

Chile pepper (*Capsicum* sp.) is the active compound accounting for the pungency of red chilies, capsaicin, is biologically active. In vitro, capsaicin inhibits the growth of cancer cells, reduces inflammation, and may trigger apoptosis by affecting the GSK β 3 part of the beta-catenin pathway, which

is faulty in a lot of human cancers. The discovery that oral capsaicin can stop human pancreatic cancer cells grown as xenografts in naked mice is intriguing.

CONCLUSION

The incidence of cancer is continually rising. Concomitantly phytomedicines are growing increasingly important since they are used more readily. Numerous papers have been published on pharmacological activities and the clinical assessment of some of them in relation to cancer control. Although some studies have confirmed the positive response, their mechanisms of action are still not clear. Even though each of the above-mentioned nutraceuticals exhibit exceptional chemo-preventive and chemo-sensitizing efficacies, the major drawbacks of the clinical usage of these phytochemicals are their poor bioavailability and retention time inside the body. Low serum levels, poor tissue absorption and distribution, short half-life and rapid metabolism and elimination also contributes greatly to their failure in clinical scenarios. Intense research is carried out to increase the bioavailability of these compounds by incorporating chemical modifications, like nano-encapsulation, glucuronidation, polymerization etc. in order to enhance the therapeutic efficacy. The effective use of non-toxic nutraceuticals can enhance the efficacy of the chemotherapeutic drugs, by bringing down the optimal dose of the drug thereby minimising the cost and side effects of chemotherapy.

REFERENCES:

1. Ranzato E, Martinotti S, Calabrese CM and Calabrese G. Role of nutraceuticals in cancer therapy. *Journal of Food Research*. 2014;3(4):18.
2. Ma X and Yu H. Cancer issue: global burden of cancer. *The Yale journal of biology and medicine*. 2006; 79(3-4): 85.
3. Shreelaxmi G, Quazi S and Karpiński TM. Nanoparticles for cancer therapy: current progress and challenges. *Nanoscale research letters*. 2021;16(1): 173.
4. Chintale AG, Kadam VS, Sakhare RS, Birajdar GO and Nalwad DN. Role of nutraceuticals in various diseases: A comprehensive review. *Int. J. Res. Pharm. Chem*. 2013;3: 290-299.

5. Smith-Warner SA, Elmer PJ, Tharp TM, Fosdick L, Randall B, Gross M, Potter JD. Increasing vegetable and fruit intake: randomised intervention and monitoring in an at-risk population. *Cancer Epidemiol Biomarkers Prev.* 2000; 9: 307-317.
6. Tripathi YB, Tripathi P and Arjmandi BH. Nutraceuticals and cancer management. *Front Biosci.* 2005;10(1): 1607-1618.
7. Das L, Bhaumik E, Raychaudhuri U and Chakraborty R. Role of nutraceuticals in human health. *Journal of food science and technology.* 2012;49: 173-183.
8. Chintale AG, Kadam VS, Sakhare RS, Birajdar GO and Nalwad DN. Role of nutraceuticals in various diseases: A comprehensive review. *Int. J. Res. Pharm. Chem.* 2013; 3: 290-299.
9. Rajasekaran A, Sivagnanam G and Xavier R. Nutraceuticals as therapeutic agents: A Review. *Research Journal of Pharmacy and Technology.* 2008; 1(4): 328-340.
10. Shukla Y and George J. Combinatorial strategies employing nutraceuticals for cancer development. *Annals of the New York Academy of Sciences.* 2011; 1229(1): 162-175.
11. Danaei G, Vander HS, Lopez AD, Murray CJ and Ezzati M. Causes of cancer in the world: comparative risk assessment of nine behavioural and environmental risk factors. *The Lancet.* 2005; 366(9499): 1784-1793.
12. Weisburger JH. Antimutagens, anticarcinogens, and effective worldwide cancer prevention. *J Environ Pathol Toxicol Oncol.* 1999; 18: 85-93.
13. Tuomisto JT, Tuomisto J, Tainio M, Niittynen M, Verkasalo P, Vartiainen T and Pekkanen J. Risk-benefit analysis of eating farmed salmon. *Science.* 2004; 305: 476-477; author reply 476-477. <http://dx.doi.org/10.1126/science.305.5683.476>
14. Grimble RF. Nutritional therapy for cancer cachexia. *Gut.* 2003; 52: 1391-1392. <http://dx.doi.org/10.1136/gut.52.10.1391>
15. Ranzato E, Martinotti S, Calabrese CM and Calabrese G. Role of nutraceuticals in cancer therapy. *Journal of Food Research.* 2014; 3(4): 18.
16. Maurer M, Rosen K, Hsieh HJ, Saini S, Grattan C, Gimenez – Arnau A and Gimnez- Arnau AM. Omalizumab for the treatment of chronic idiopathic or spontaneous urticarial. *New England journal of medicine.* 2019; 381 (14):1321-1332.

17. Maurer M, Staubach P, Raap U, Richter-Huhn G, Bauer A, Rueff F and Magerl M. Attentus, a German online survey of patients with chronic urticarial highlighting real- life treatment and disease burden. *Allergy*. 2018; 73(7), 1564-1572.
18. Grattan C, Maurer M, Marinkovich MP, Bissonnette R, Gaul M, Nakonechna A and Staubach P. Child and Adolescent chronic spontaneous urticaria: A systematic review of characteristics. *Pediatric Allergy and immunology*. 2020; 31(7), 709-717.
19. Kim SH, Lee NR, Lee SH, Kim TW and Kim BE. Efficacy of levothyroxine Monotherapy for chronics idiopathic urticaria. *Journal of the American Academy of Dermatology*. 2021; 84(4), 1152-1153.
20. Vanbrant S, Vermeulen F, Stevens L, De Conick L, Lambert J, Mertens C and Gevert, P. Chronic spontaneous urticarial: comparison of theclinical profiles of patients treated in the university hospitals of Ghent and leuven. *Journal of the European Academy of Dermatology and venereology*. 2020; 4(9), 2045-2051.
21. Erbagci Z, and Erbagci, I. Effectiveness of Omalizumab in a patients with concomitant chronic spontaneous urticaria and Atopic dermatitis. *Dermatology and therapy*. 2016; 6(2): 291-295.
22. Jindal N, Arora G, Singh C and Dogra S. Low- dose rituximab therepy in refractory chronic idiopathic urticarial. *Journal of cutaneous immunology and Allergy*. 2017; 1(3): 128-132.
23. Rivas MF, Castells M and lopez, S. New and Emerging therapies for chronic spontaneous urticarial. *Drugs*. 2018; 78(15): 1645-1659.
24. Ardeleanu M, Marinescu C, Chiriac AE and Solovan C. Up-to[1]date management of chronic urticaria: An Evidence – based on review. *Dermatologic therapy*. 2021; 34(1):14624.