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REVIEW ARTICLE

NOVEL APPROACHES OF NUTRACEUTICALS IN CANCER CHEMOPREVENTION

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ABSTRACT:

Epidemiology studies have repeatedly demonstrated that nutrition is a major risk factor for chronic conditions such as cataracts, type-II diabetes, gallstones, neurological illnesses, cardiovascular diseases, and a number of cancers. Dietary choices and foods directly affect health and disease. Modern cancer treatments have greatly increased patient survival rates in recent years. This improvement in the survival rate demonstrates advancements in the use of combination treatment and early-stage diagnosis. Natural antioxidants work in concert with some chemotherapy drugs, according to clinical research. In this article, novel approaches of nutraceuticals in cancer chemoprevention has been discussed.

KEYWORDS: Nutraceuticals, Cancer, Chemoprevention.

INTRODUCTION:

The word’s "nutrition" and "pharmaceutical", describing this term as "the food components or active ingredients present in food that have positive effects for well-being and health, including

the prevention and treatment of diseases". Foods, dietary supplements, and medicinal foods all fall under the category of nutraceuticals, which have a special effect on health through illness prevention and/or treatment. An expanding field of study understands the use of nutraceuticals in the prevention and management of chronic diseases, but a longer-term clinical trial is required to validate their benefits in terms of treating disease. [1]

Alkaloids, different terpenoids, and polyphenols (anthocyanins, flavones, flavanols, isoflavones, stilbenes, ellagic acid, etc.) are examples of bioactive phytochemicals that are important sources of nutraceutical components. The majority of phytochemicals produced by plants have specific pharmacological effects on human health, including antioxidant, anti-inflammatory, anti-allergic, antibacterial, antifungal, chemopreventive, hepato-protective, neuroprotective, hypotensive, and antiaging effects in diabetes, osteoporosis, DNA damage, cancer, and heart diseases.

NUTRITIONAL SUPPLEMENTS WITH CANCER CHEMOPREVENTION:

Humans have developed a comprehensive and cooperative system of antioxidant defense mechanisms against hazardous oxygen intermediates through eating, according to biochemical and epidemiological evidence. Increased antioxidant consumption through diet may reduce the risk of illnesses like cancer. The ability to limit cancer cell proliferation and induce cancer cell apoptosis exists in nutraceuticals, functional foods, and supplemental micronutrients. Many organic dietary supplements have demonstrated a possible impact in cancer prevention and therapy and are regarded as useful tactics. Natural and dietary nutraceuticals may have anticancer properties. Examples include carotenoids, which boost "connexin 43" to promote gap-junctional communication in vitro; flavonoids, which regulate phase I and phase II xenobiotic detoxification; and vitamin E, which blocks protein kinase C, a key enzyme in the development of some cancers. In 126, 110, and 35 clinical trials, respectively, curcumin, resveratrol, and berberine have all been investigated. These compounds have demonstrated a wide range of activities in treating a variety of human pathologies, including age- related macular degeneration, cardiovascular disease, diabetes, cancer, Alzheimer's disease, and various types of cancer. According to numerous reports, phytochemicals (found, for example, in cumin, red pepper, and ginger) may be able to prevent cancer by blocking the nuclear transcription factor-B (NF-B) pathway, which has been linked to both cancer and a number of inflammatory disorders. NF-B is a highly desirable therapeutic target for polyphenols and nutraceuticals made from plants. According to reports, RES can reduce the

activities of cyclooxygenase and the cytochrome P450 isoenzyme (CYPA1), which can both affect NF-B activity. RES may also affect other biochemical processes involved in metabolism, including fatty acid oxidation, mitochondrial biogenesis and respiration, and gluconeogenesis. TNF-a, IL-17, and other pro-inflammatory cytokines may be suppressed, and activated T cells may undergo apoptosis as a result of RES. It has therefore been suggested that it might be helpful in auto-immune illnesses. With their anti-cancer effects, such as the reduction of cell proliferation, anti-invasive activity, and inhibition of angiogenesis in vitro, curcumin and its analogues have gained significant attention as cancer-preventive medicines. Through the activation of Nrf2 enzymes, the promotion of the tumour suppressor p53, and the reduction of TGF- and COX-2, curcumin prevents mouse liver lymphoma. Many foods, including soy, pomegranate, mangosteen, citrus fruits, apple, grape, mango, cruciferous vegetables, ginger, garlic, black cumin, edible macro-fungi, and cereals, could have an impact on the onset and progression of breast cancer (BC). Their anti-breast cancer effects involve a variety of mechanisms of action, including down regulating ER-expression and activity, preventing breast tumor cell migration, proliferation, metastasis, and angiogenesis, inducing cell cycle arrest and apoptosis, and making breast tumor cells more susceptible to chemotherapy and radiotherapy. Following a cancer diagnosis, 20% to 85% of patients take dietary supplements. As prostate, colorectal, and lung cancer are the most often diagnosed adult cancers, BC survivors and patients with these diseases are the ones who use supplements the most frequently. Dietary supplement use is hotly contested, especially while patients are receiving treatment, because it is unclear whether supplements have an impact on how well treatments work. [2]

NUTRACEUTICALS ON EPIGENETIC PHENOMENON:

In the past ten years, research has concentrated on specific categories of botanical elements that have bioactive qualities that can affect epigenetic processes. The "epigenetic diet" refers to the combination of these bioactive substances that can be included in a person's diet. Several human diseases, including cancer, are thought to be prevented by some dietary elements having qualities that affect epigenetic processes. Numerous dietary and organic phytochemicals, including curcumin, genistein, quercetin, and resveratrol, have been shown to have potent anti-tumor effects by reversing epigenetic changes caused by oncogene activation and tumour suppressor gene inactivation. They can also modulate the mammalian epigenome by controlling the mechanisms

and proteins involved in chromatin remodeling. Early ingestion of specific epigenetic diets may result in an epigenetic modification and can lower the risk of developing certain diseases, according to human epidemiological research and animal studies. Experimental investigations have investigated how plant-derived substances, such as phytochemicals, which are involved in changing epigenetic mechanisms and sculpting the epigenome, can alter the function of proteins and ncRNAs, demonstrating that they may soon play a significant role in pharmacogenomics. It has been demonstrated that they influence ncRNAs, particularly miRNAs and long ncRNAs, and hence contribute to DNA methylation, histone modifications, and post- transcriptional control of genes. If adequate dietary recommendations are followed, these food components may help avoid conditions including diabetes and cancer. [3] Numerous foods consumed by people contain epigenetic dietary elements, including genistein, a naturally occurring isoflavone found in soybean products; sulforaphane, an isothiocyanate found in broccoli sprouts or cabbage; and EGCG, the main polyphenol in green tea, which has been linked to a lower risk of developing many common cancers. The main factors controlling gene expression through epigenetic mechanisms such as DNA methylation, histone modification through histone acetyl transferases (HATs), and histone deacetylases are dietary chemicals (HDACs). Long-term ingestion of bioactive chemicals may cause epigenome alterations, which can help build dietary plans to prevent and treat metabolic illnesses. These alterations serve as an essential memory mechanism throughout embryogenesis and are a persistent and heritable part of epigenetic control. At least three independent DNA methyltransferases (DNMTs), DNMT1, DNMT3a, and DNMT3b, maintain DNA methylation patterns and are necessary for cellular differentiation during early embryonic development. Accordingly, the right exposure to epigenetic modulators from the diet that target DNA methylation may result in early epigenetic reprogramming that is beneficial and may prevent disease in later life. Typically, chemo- radiotherapy medicines, kinase inhibitors, individualized antibodies, and substances that activate the immune system are used in cancer therapy. By undoing the abnormal epigenetic modifications formed during cancer, demethylating medications and histone deacetylase inhibitors can change how genes are expressed. Current research suggests that natural compounds and dietary supplements may be able to restore the normal epigenetic marks that are lost during carcinogenesis, and phytochemicals may constitute an alternative therapeutic strategy for the treatment of cancer. [4] The most studied phytochemicals for cancer are EGCG, quercetin, RES, curcumin, and sulphorane, which inhibit tumour growth and spread by focusing

on critical signaling pathways such as epigenetic machinery control (regulation of DNMTs and HDACs activities). Using molecular modelling studies, Khan et al. demonstrated that EGCG directly binds to the enzymatic substrates of DNMT3b and HDAC1, inhibiting their activity and activating tumor suppressor genes such as the retinoic acid receptor, cadherin 1, and death-associated protein kinase-1. In a different study, Lee Y.H. et al. found that EGCG inhibited the androgen receptor's sensitivity to hormones by lowering its acetylation, which in turn reduced cell proliferation and encouraged cell death in the LNCaP prostate cancer cell line. DNMTs and HDACs may be modified epigenetically by EGCG in cervical and skin malignancies, restoring epigenetically repressed genes. In skin cancer cells, EGCG reduced the levels of the proteins DNMT1, DNMT3a, and DNMT3b and altered the HDAC activities, which allowed the transcriptional activation of genes known to prevent tumor growth, including p16 INK4a and Cip1/p21. Curcumin, a different phenolic compound, is used extensively in China and India as a medicine and for its anti-inflammatory, anti-proliferative, anti-angiogenic, and antioxidant qualities. It is regarded as a top-notch, non-toxic hypomethylating medication for BC treatment. For instance, in the estrogen-positive MCF-7 breast cancer cell line, curcumin lowered cell proliferation and the development of breast tumours in vivo. It also restored the function of RASSF1A by restoring promoter hypomethylation. Curcumin treatment inhibited the formation of tumours when A549 lung cancer cells were implanted in naked mice, and this effect was achieved by upregulating RAR and downregulating DNMT3b expression. Curcumin, on the other hand, inhibited astrocyte differentiation and promoted neural differentiation associated with hypoacetylation of H3 and H4 in brain cancer cells and triggered histone hypoacetylation and death related to PARP activity. [5] Curcumin reduced the expression of DNMT1 in in vivo and ex vivo investigations using various cell line models of acute myeloid leukaemia while restoring the expression of p15INK4b by hypomethylating its promoter, causing cell cycle arrest at the G1 phase and apoptosis. In vivo, JNK signaling is inhibited by curcumin, and the epigenetic mark H3K4me3 is suppressed, which encourages the death of LNCaP prostate cancer cells. RES is a phytoalexin that has anti-cancer properties through controlling biological processes such as cell division, proliferation, apoptosis, angiogenesis, and metastasis. By blocking the MTA1/HDAC complex and the Akt pathway in vivo, RES encourages the acetylation and reactivation of PTEN. Because PTEN is negatively regulated by the MTA1/HDAC complex, prostate cancer development and tumour cell survival are encouraged. The ability of phytochemicals to modify the functioning of

epigenetic pathways through nutritional intervention, as well as their involvement in preventing the development or recurrence of cancer, are still up for dispute.

NUTRACEUTICALS AND CHEMOPREVENTIVE ACTIVITIES WITH A SPECIAL FOCUS ON THERAPEUTICAL APPROACHES:

An increase in response rates was seen in patients receiving vitamin A supplements in addition to either doxorubicin or cyclophosphamide in a randomized trial on 100 patients with a diagnosis of BC. A thorough investigation concluded that two patients had been diagnosed with advanced epithelial ovarian cancer. Paclitaxel and carboplatin were given to both individuals. Prior to carboplatinum, patient 1 received an oral antioxidant cocktail (vitamins C, E, b-carotene, coenzyme Q-10, and a multivitamin/mineral), whereas patient 2 received the same cocktail of chemotherapy, antioxidants, and parenteral ascorbic acid but not consolidation paclitaxel. According to the findings, antioxidants and chemotherapy work together synergistically to induce remission in both individuals. Also, it showed that, as compared to drug-alone treatment, modest doses of Vitamin C and Decitabine have synergistic effects on proliferation, apoptosis, TET2 expression, and activity in HL60 and NB4, both in cell lines in vitro and in clinical studies. After one cycle of chemotherapy, safety analyses revealed that patients who got the Decitabine regimen (DCAG) in combination with intravenous vitamin C saw a greater rate of full remission. It was also discovered that, when compared to patients receiving the same treatment but not taking vitamin D supplements, women receiving a little over 10,000 IU/week (around 1500 IU/d) of vitamin D during chemotherapy for BC had a statistically significant enhanced disease-free survival. [6]

The main causes of death and disability are chronic diseases. Although some studies have found some discrepancies, many studies have linked nutraceutical phytochemicals to preventive effects against chronic illnesses. Cancer treatment may be impacted by a variety of possible drug- nutrient interactions. Due to their plentiful sources, low cytotoxicity, and safe ingestion, people have been paying special attention to the role of nutraceuticals in tumour prevention and cancer therapy during the past ten years. Many patients are currently advised by oncologists to refrain from taking dietary supplements with antioxidant properties, such as vitamins, while receiving cancer treatments. As practically all foods—including fruits, vegetables, beans, and nuts— contain

antioxidants, vitamins, or other comparable compounds, this type of warning is difficult to understand. The daily consumption of high amounts of phytochemical extracts may not be safe or may have harmful effects. The physiologic (nutritional) dose must be distinguished from the pharmacological dose. Two opposing theories have been put forth regarding the utilization of phytochemicals with antioxidant capabilities during radiation and chemotherapy. One study suggests that taking supplements containing high doses of several dietary antioxidants, such as vitamins C and E and carotenoids, may increase the tumor's response to radiation or chemotherapy while lowering its toxicity. The alternative theory contends that using antioxidants (dietary or endogenously produced) during radiation therapy is not recommended because they would shield cancer cells from radiation damage. The paucity of clinical evidence is the key factor in the debate over whether antioxidant supplements should be taken concurrently with chemotherapy; the strength of the scientific evidence on this issue is not clear. [7]

Instead of treating localized lesions, chemotherapy is typically used to treat systemic illnesses. Antineoplastic drugs that disrupt cellular activity are used in chemotherapy to kill tumor cells (including replication). This medication therapy damages DNA fatally, which promotes more malignant cell death by apoptosis. Chemoprevention is the use of non-toxic chemicals to stop the growth of cancerous cells. Chemopreventive phytochemicals in plant-derived diets have the capacity to alter the NF-kB-mediated signal transduction pathways that promote the growth of cancer. NF-kB is a transcription factor that modifies the genes involved in cell proliferation, differentiation, adhesion, and survival, which aids in the development of cancer. Among the chemopreventive phytochemicals known to suppress carcinogenesis by blocking NF-kB activation, there are curcumin (turmeric), catechins (tea), caffeic acid, capsaicin (red chilli), resveratrol (red grapes, peanuts, and berries), lycopene (tomato), beta-carotenes (carrots), 6-gingerol (ginger), ursolic acid (rosemary), ellaglic acid (in pome Dietary phytochemicals contain anti-oxidative and anti-inflammatory qualities that may aid in chemopreventive actions. [8]

Some chemotherapy drugs produce free radicals in order to kill healthy cells and necrotize cancerous ones, but these ROS frequently have side effects that last throughout the course of treatment. Nutritional supplements can work against cancer therapy because they can affect cancer in its later stages and may change the way it spreads to other parts of the body. For example, ginger and ginkgo supplements might interact with warfarin, and garlic can stop blood from clotting. The

metabolism of the painkiller acetaminophen by cytochrome P4502E1 may be inhibited by the interaction between garlic and its organ sulfides. Doctors advise against using non-steroidal anti-inflammatory medicines before surgery for this reason. Chemotherapy drugs produce a lot of OS in order to kill cancer cells, and this mechanism may lessen the effectiveness of the treatment. The important reason is that chemotherapy kills cancer cells precisely during cell replication, which means that decreasing cell replication lowers chemotherapy efficacy. OS decreases the process of cell replication. One strategy is to increase the patient's intake of particular antioxidants at predetermined levels to reduce OS and increase the efficacy of the chemotherapeutic treatment. Certain antioxidants can lessen the production of aldehydes during oxidative stress brought on by chemotherapy in order to boost the antioxidant activity of cancer treatment. Based on the different doses used—low doses for a preventive treatment and high doses for a therapeutic treatment—phytochemical nutraceuticals with antioxidant activity play a controversial role and have different effects in cancer therapies. According to the data, the therapeutic dose suppresses tumour cell proliferation but not that of normal cells, whereas the preventative dose protects both tumour and normal cells. According to the majority of preliminary clinical research, antioxidants do not appreciably lessen the impact of chemotherapy. The question of whether antioxidant supplements used during chemotherapy could shield normal cells without interfering with tumour control has been the subject of numerous articles. Additional recent analyses have demonstrated that concurrent administration of antioxidants protects healthy tissues, improves patient survival, and enhances treatment outcomes without interacting with chemotherapy. Angiogenesis, which is triggered by the growth of new blood vessels from endothelial cells with continuous oxygen and nutrition supply, is one of the major steps in the development of cancer. A novel idea called "angio-prevention" examines the mechanisms through which and for what reasons chemopreventive drugs might exercise their antiangiogenic effects. Angio-prevention tries to stop the growth of tumours by utilizing both organic and artificial chemopreventive medicines. [9]

Curcumin, resveratrol, and genistein are polyphenols with potent antiangiogenic effects. They exhibit antioxidant characteristics that directly scavenge ROS, which can impede the growth of new blood vessels. Angiogenesis-related molecules, vascular endothelial growth factor (VEGF), and platelet-derived growth factor (PDGF) receptors are known to be inhibited by anthocyanidin and ellagic acid, a natural polyphenol present in many fruits and nuts. Its simultaneous inhibition of VEGF and PDGF inhibits angiogenesis in both in vitro and in vivo experiments, showing that

phytochemicals' antiangiogenic properties play a critical role in their cancer-preventive effect by limiting the growth of new blood vessels. Late-stage cancer patients exhibit a compromised immunophysiological state, which includes decreased natural killer (NK) cell activity and cytokine output. Nutraceuticals can significantly increase the production of cytokines in this advanced stage of cancer, including tumour necrosis factor, interferons, and interleukins, as well as possibly activate natural killer cells, T lymphocytes, and macrophages. Chen and colleagues examined the impact of Ganoderma lucidum (Lingzhi), a medicinal mushroom popular among Asians, on a few immunological functions in adults with advanced colorectal cancer in this study. After receiving the polysaccharide fraction from G. lucidum treatment (three times per day for 12 weeks), the immune-modulating effect was examined in 41 assessable cancer patients. In this study, this herb had a tendency to increase mitogenic reactivity to phytohemagglutinin, counts of CD3, CD4, CD8 and CD56 lymphocytes, plasma concentrations of IL-2, IL-6, interferon, and NK activity while decreasing plasma concentrations of IL-1 and tumour necrosis factor (TNF), although statistical significance was not seen when a comparison was made between baseline and those values after a 12-week treatment. For instance, increases in IL-1 and IL-2 were linked with changes in IL-6, CD8 and NK activity, IFN-, CD3, CD4, and NK activity, respectively (p 0.05). According to the current study's findings, G. lucidum may enhance host defense in people with advanced colorectal cancer. Many therapy modalities advocate phytoestrogens and soy isoflavone (such as genistein, daidzein, and biochanin) with the goal of regulating the expression of the IL-6 gene to stop the spread of cancer. The synthetic selective oestrogen receptor modulators (SERMs), which are now used in hormone replacement therapy, are thought to have some competition from soy isoflavone (HRT). Phytochemicals may be used to treat NF-B-related inflammatory illnesses as well as cancer chemoprevention since they combine hormonal ligand actions and interference with signaling cascades. A pharmaceutical adjustment of IL-6 gene expression levels may be therapeutic in humans to stop cancer progression because excessive IL-6 production promotes carcinogenesis (in breast, prostate, lung, colon, and ovarian cancer). The IL-6 gene is expressed primarily via the transcription factor NF-B, whose activity is controlled at various levels. Vitamins C and E were linked to a lower risk of BC recurrence, and vitamin E use was linked to a lower risk of all-cause mortality. On the other hand, frequent use of combination carotenoids was linked to a higher risk of both BC and all-cause mortality. A protective link between vitamin C and vitamin E consumption and death from all causes and BC recurrence was found, supporting the notion that

different types of antioxidant supplements would have distinct impacts on outcomes. It was also noted that frequent use of vitamins C and E after diagnosis was associated with a reduced risk of all-cause mortality, death from BC, and BC recurrence. Data also showed that frequent use of combination carotenoids in the period following diagnosis was associated with an increased risk of death from BC and all causes, but not BC recurrence. Moreover, vitamin E has demonstrated the ability to boost the effectiveness of chemotherapy and has been found to trigger apoptosis in experimental tumor lines. In a different trial, vitamin E was found to lessen the side effects of chemotherapy and, when combined with omega-3 fatty acids, to extend patients' lives. Because of the rising use of phytochemicals in chemoprevention, the nutraceutical industries have boosted production of many phytochemicals that contain nutraceuticals; however, the use of phytochemicals in cancer is poor because most research is done in vitro. [10]

CONCLUSION:

As already revealed by epidemiologic and animal model research, nutraceuticals, which are mostly phytochemicals derived from dietary or medicinal plants like soya bean, garlic, ginger, tea, as well as propolis, honey, and others, may have chemopreventive actions. These results indicate that their capacity to lower cancer incidence is probably connected to apoptosis. Many in-vitro studies on the biological effects of nutraceuticals in cultured human cells have been conducted as a result of the possibility for employing them as chemopreventive drugs. Chemotherapy is the use of chemicals, primarily synthetic ones, to treat or relieve the symptoms of cancer. Chemoprevention is the use of tiny molecules, including dietary or herbal chemicals, to prevent malignancies. Investigating the potential for employing phytochemicals or other dietary compounds as chemopreventive agents is therefore interesting. Additionally, the molecular basis for these phytochemicals' anti-tumor efficacy is provided by the research of their biological effects at the cellular level, which also lays the groundwork for the development of more potent chemopreventive and even chemotherapeutic drugs. Apoptosis is engaged in a wide range of normal physiological processes, such as immune defense, tissue homeostasis and development, and any tipping of the life-death scale within an organism that may prevent or make diseases worse. As a result, a number of functional deficiencies and degenerative diseases, including Alzheimer's disease, Parkinson's disease, Huntington's disease, multiple sclerosis, myocardial infarction, arteriosclerosis, chronic inflammation, rheumatoid arthritis, sterility, or cataract, may be

significantly impacted by the loss of vital cells of post-mitotic tissues as a result of enhanced cell death. Apoptosis, on the other hand, can be seen as a proactive self-defense mechanism of a live organism that eliminates defective cells, such as the progenitors of cancer cells that spread to other parts of the body, without causing secondary oxidative stress as a result of inflammation. A malfunction in the apoptotic pathway is acknowledged as a key factor in the development of cancer. Cancer cannot emerge from deregulation of proliferation alone; there must also be a reduction of apoptotic signals. By overexpressing antiapoptotic proteins (Bcl-2, IAPs, and FLIP) and/or by down regulating or mutating proapoptotic proteins, cancer cells can develop resistance to apoptosis (Bax, Apaf-1, caspase-8, and death receptors). In more than 50% of malignancies, antiapoptotic Bcl-2 and Bcl-xL are overexpressed. More than 4000 polyphenolic chemicals collectively referred to as flavonoids are found naturally in meals derived from plants. These substances share a phenylbenzopyrone structure, and they can be divided into flavones, flavonols, isoflavones, flavonols, flavanones, and flavanonols based on the saturation and opening of the central pyran ring. For their potential to be used in chemoprevention, tea polyphenols, quercetin, and genistein have all received much research. In human lymphoid leukaemia cells and human carcinoma cells, some flavonoids were first demonstrated to induce apoptosis. Similar findings have since been applied to cervical cancer cells, breast cancer cells, prostate cancer cells, stomach cancer cells, brain tumour cells, colon cancer cells, and cell lines from lung tumours. Recent epidemiological studies have found a strong link between eating foods rich in carotenoids and a lower risk of developing cancer and cardiovascular disorders. Many carotenoids are abundant in tomatoes. The tomato's precursor to-carotene, lycopene, builds up after the lycopene cyclase gene is suppressed during ripening. Malignant lymphoblast cells and prostate cancer cells can both undergo apoptosis when exposed to lycopene and beta-carotene. An active phenolic substance isolated from honey bee propolis called caffeic acid phenethyl ester prevents carcinogenesis in a two-stage mouse skin cancer model. It has been noted that the caffeine phenethyl ester induces apoptosis in mouse epidermal JB6 Cl 41 cells and HL-60 leukemic cells. Colon cancer, leukaemia, prostate cancer, melanoma, and breast cancer cells all undergo apoptosis when exposed to curcumin. Garlic has a long history of use as a cancer preventative. Garlic-derived allyl sulphur compounds exhibit strong anti-proliferative effects on human malignancies. In addition to prostate cancer and breast cancer cells, diallylsulfide and diallyldisulfide cause apoptosis in non-small cell lung cancer cells.

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