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Review Article

Role of Nutraceuticals in Cancer Management

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ABSTRACT

In recent years, there has been growing interest in exploring alternative and complementary approaches to conventional cancer therapy. Cancer remains a global health challenge, demanding innovative therapeutic strategies beyond conventional approaches. Nutraceuticals, defined as bioactive compounds derived from natural sources, are gaining prominence for their potential application in cancer therapy. This review aims to comprehensively examine the evolving landscape of nutraceuticals in cancer treatment, elucidating their mechanisms of action and exploring their role as complementary agents to conventional therapies by analyzing the current literature, this study highlights the diverse compounds found in nutraceuticals that exhibit anticancer properties, on their potential as adjunctive therapies. Through a comprehensive evaluation of the scientific evidence, this review aims to contribute to a better understanding of the role of nutraceuticals in the cancer treatment.

INTRODUCTION

Natural bioactive supplements known as nutraceuticals provide nutritional benefit and show promise as treatments for a number of ailments. According to Stephen De Felico's original definition from 1989, a nutraceutical is "a food, food ingredient, or dietary supplement that demonstrates specific health or medical benefits, including the prevention and treatment of disease beyond basic nutritional functions." Later, nutraceuticals became recognized as potential food based natural sources of cancer prevention [1]. The goods that are separate from herbal products, supplements, certain diets, and processed foods including cereals, soups, and beverages are known as nutraceuticals.[2]

The use of pharmaceutical and nutraceutical substances to treat or prevent disease is possible,

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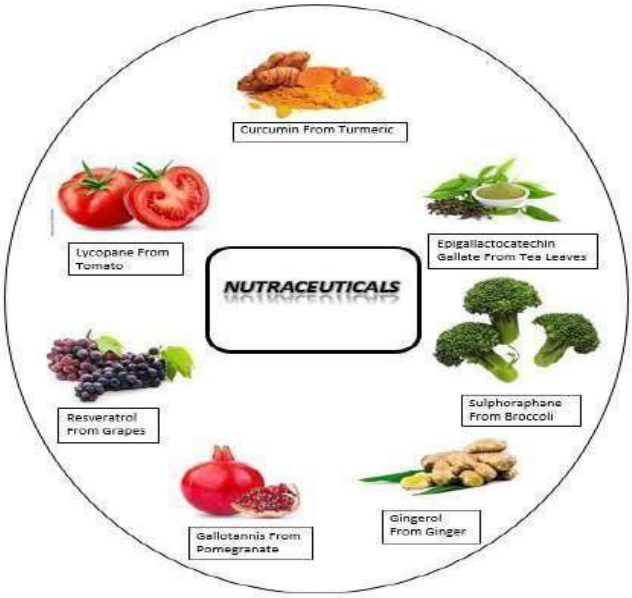
but only pharmaceuticals are approved by the government.[3] Due to their potential, nutritional value, safety, and therapeutic effects, that supplied the body's necessary daily requirement for energy. To avoid goiter, for instance, various food manufacturers started adding iodine to salt in the early 19th century. This is an example of an attempt to design a useful component. As the usage of nutraceuticals for self-prescription increased, it was later understood how important they were in treating various nutritional diseases. The acceptance of nutraceutical medicine as a new branch of "complementary and alternative medicine" (CAM) and the great growth in awareness of nutraceuticals as strong nutraceuticals have recently attracted a lot of attention. [4] Up to the year 1990, the idea of nutraceuticals was viewed as simply natural foods therapeutic supplements in the new century are both evident[5]. With the consistent increase in life expectancy, rising urbanization, and ensuing changes in lifestyle and environmental factors, cancer is a significant global health concern. Depending on the process of isolation, the plant products have been classified as foods, food supplements, functional foods, and nutraceuticals. While semi-purified plant products consumed as supplements rather than as food are referred to as functional foods, pure extracted Phyto molecules are known as nutraceuticals [6].

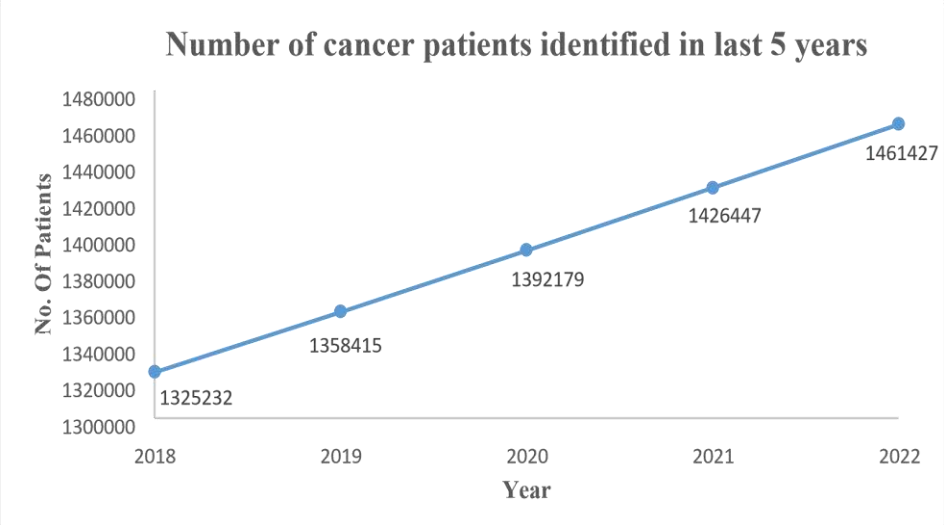
Some of the well-studied phytochemicals in relation to tumour prevention includes-



curcumin (turmeric) [7], capsaicin (green chilies) [8], epigallocatechin gallate (green tea) [9], gingerol (ginger) [10] , genistein (soyabeans) [11], John’swort [17] ,indole-3-carbinol (cabbage) [18], tangeretin(citrus species) [19], apigenin (tea, cabbage, garlic) [20] ,allicin (garlic) [21], lycopene (tomatoes) [22] , emodin(aloes) [23] , diallyl sulfide (garlic) [24], resveratrol (grapes) [12] ,caffeic acid phenylester (propolis from honey bee) [13], sulforaphane [14] (cruciferous vegetables) [15] , silibinin [16], St. quercitin(rhododendron cinnabarium) [25] ,anethole (fennel,camphor) [26], ß-carotene [27].

Chemotherapy, radiation, and surgery are some of the current cancer treatments that have unwanted side effectsthat endanger the patients’ health and wellbeing. 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. By using nutraceuticals, the risk of experiencing systemic side effects could be decreased, leading to the intended anti-proliferative effect [29]. According to the National Care Registry initiative, 14,61,427 new cases of cancer are expected to occur in India in 2022[28].



MODE OF ACTION -

Nutraceuticals act by following ways -

1. **Cancer prevention:**
   A few nutraceuticals may have the ability to prevent the development of cancer. Vegetables, fruit-rich diets, and whole grains, for instance, have all been associated with a lower risk of developing various malignancies. These foods contain a variety of bioactive substances such as antioxidants, polyphenols, and dietary fibers, which may help protect cells from harm and stop the growth of cancer. [30]
2. **Supportive care:**
   During cancer treatment, patients often experience side effects such as nausea, fatigue, hair loss and loss of appetite. certain nutraceuticals such as ginger and turmeric have been studied for their potential to alleviate these symptoms and improve the health of cancer patients. [31]
3. **Anti-cancer properties :**
   Some nutraceuticals have been shown promise in preclinical studies for their potential anti-cancer effects. For example, Resveratrol found in grapes and red wine has investigated for its potential to interfere with cancer cell signaling pathways. Curcumin from turmeric has been studied for its ability to inhibit cancer cells growth and induced apoptosis. [32]
4. **Immune modulation :**
   Some dietary supplements may have immunomodulatory effects, which means they may alter how the immune system reacts to cancer cells. In patients with advanced cancer, nutritional supplements can considerably increase tumor necrosis factor (TNFa) and natural killer cell (NK cell) activity. In patients with advanced cancer, it has been proposed that an aggressive combination of immuno-active nutraceuticals can significantly increase NK cell function, other immunological markers, and hemoglobin. [33]

5. **Potential interactions with conventional cancer treatments :**
   Some studies indicate that certain nutraceuticals may interact with certain treatments, either improving their effects or decreasing their efficacy.

Rational of nutraceuticals in cancer treatment-

Nutraceuticals' potential to help traditional cancer therapies and enhance general health and wellbeing is the justification for their use in cancer treatment. Nutraceuticals, however, should not be viewed as a stand-alone cancer treatment; rather, they should be considered complimentary methods that help improve the overall management of the condition.

Some of the justifications for using dietary supplements to treat cancer include the following:

1. **Antioxidant Properties:**
   Many nutraceuticals are rich in antioxidants, which can help neutralize free radicals that can cause cellular damage and potentially lead to cancer development. [34]
2. **Anti-Inflammatory Effects:**
   Chronic inflammation is linked to cancer development and progression. Some nutraceuticals possess anti-inflammatory properties that may help in reducing cancer-related inflammation.
3. **Immunomodulation:**
   Certain nutraceuticals can modulate the immune system, enhancing the body's natural defense mechanisms against cancer cells. [35]
4. **Angiogenesis Inhibition:**
   Some nutraceuticals may inhibit the formation of new blood vessels that feed tumors, a process known as angiogenesis, thus preventing tumor growth.
5. **Apoptosis Induction:**
   Nutraceuticals have been studied for their potential to induce apoptosis (programmed cell death) in cancer cells, helping to eliminate them.
6. **Chemoprevention:**
   Nutraceuticals may play a role in cancer prevention by interfering with carcinogenesis at various stages.
7. **Enhancement of Conventional Therapy:**
   In some cases, certain nutraceuticals may enhance the efficacy or reduce the side effects of traditional cancer treatments like chemotherapy and radiation therapy.

Advantages of nutraceuticals –

1. **Health benefits:**
   Nutraceuticals can provide various health benefits, such as supporting immune function, improving cardiovascular health, and promoting overall well-being
2. **Natural sources:**
   Many nutraceuticals are derived from natural sources like plants and herbs, making them a potentially safer option compared to synthetic pharmaceuticals.
3. **Preventive approach:**
   Nutraceuticals are often used as a preventive measure to maintain good health and reduce the risk of chronic diseases.
4. **Minimal side effects:**
   Due to their natural origins and often gentle action, nutraceuticals generally have fewer side effects than conventional drugs.
5. **Personalized approach:**
   Nutraceuticals can be tailored to individuals' specific health needs and can complement a personalized healthcare regimen.
6. **Easily accessible:**
   Many nutraceuticals are available over-the-counter or as dietary supplements, making them convenient for consumers to incorporate into their daily routine.
7. **Long term well-being:**
   Regular consumption of nutraceuticals can contribute to long-term health and wellness, supporting a holistic approach to healthcare.

Disadvantages of nutraceuticals-

1. **Limited scientific evidence:**
   Many nutraceuticals lack comprehensive clinical trials and robust scientific evidence to support their claimed benefits. Without well-established data, their efficacy and safety can be uncertain
2. **Interaction with medications:**
   Nutraceuticals can interact with prescribed medications, potentially reducing their effectiveness or causing harmful side effects. It's crucial to inform healthcare providers about any supplements you are taking.
3. **Allergies and sensitivities:**
   Some nutraceuticals may trigger allergic reactions or sensitivities in certain individuals, which can lead to adverse effects.

Commonly used Nutraceuticals -

CURCUMIN

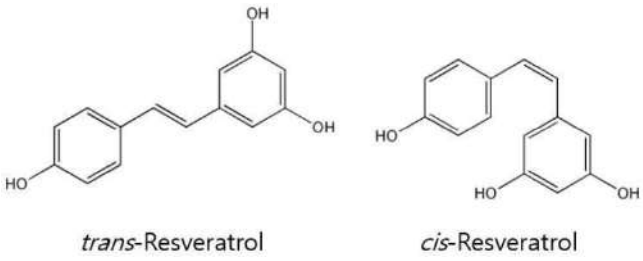
Curcumin

Turmeric, also known as Curcuma longa, is also referred to as Haldi. It is made from the Zingiberaceae plant species Curcuma longa. In South Asia, Indonesia, China, Pakistan, and India, it occurs naturally. [36,37] Among the secondary metabolites produced by the plant are flavonoids, alkaloids, tannins, and phenolic acids, with curcumin, an active hydrophobic polyphenol, drawing particular attention for the first time, pure crystalline curcumin was isolated from the turmeric plant in 1870.[38] Both on its own and in combination with other antineoplastic medicines, curcumin has demonstrated promising effects in the treatment of several cancers. It has an impact on a number of signaling pathways and can therefore successfully alter both the initiation and progression of certain cancers. Curcumin has been shown to have anticancer properties against breast cancer, lung cancer, head and neck squamous cell carcinoma, prostate cancer, and brain tumors in several investigations [39]. Due to their biofunctional qualities, such as their anti-tumor, anti-oxidant, and anti-inflammatory actions, curcumin and its derivatives have attracted a lot of attention [40]. Curcumin's distinct anticancer activity is primarily mediated by inducing apoptosis and reducing tumor growth and invasion by blocking a number of cellular signaling pathways. [41] A powerful nutraceutical for the treatment of cancer is curcumin. Curcumin has been shown in pre-clinical tests to decrease carcinogenesis at every stage, including angiogenesis, metastasis, and proliferation, in a variety of malignancies, including pancreatic, colorectal, prostate, gastric, and hepatic cancer. When used in conjunction with chemo- and radiotherapies to treat cancer, it is significantly more successful. By inhibiting a number of essential components in cellular signaling pathways important for proliferation, differentiation, and the development of malignant cells, curcumin is known to cause apoptosis in malignant cell lines. Regarding its capacity to prevent chemo, it is one of the widely studied phytochemicals. Several kinds of cancer are brought on by chronic inflammatory conditions and infectious illnesses [42] Reactive oxygen species (ROS), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-Kb), cytokines, AKT, transcription factor activator protein-1 (AP-1), and cyclooxygenase-2 (COX-2) are examples of pro-inflammatory molecules that are produced

during the inflammatory process and are involved in the development of tumours. [43] Some of curcumin's anticancer activities are the result of how it affects the control of several immune modulators. ROS are oxygen-derived molecules that can function as secondary messengers in a number of cellular signalling pathways. They contribute to cell survival, differentiation, and proliferation as well as inflammation, which advances several cancers [44]. Some cancer types may experience a reduction in development and spread as a result of curcumin's direct binding to ROS scavengers. [45]

Tumour necrosis factor alpha (TNF) synthesis and cell-mediated signalling from TNF- in different cell types are both blocked by curcumin, which also inhibits proinflammatory pathways. Studies conducted in vitro and in vivo have demonstrated that curcumin has the ability to directly block TNF- by attaching to and inactivating this molecule. The expression of several proteins, including cytokines and interferons, is regulated and controlled by the NF-B factor. These proteins have a tight connection to the development of cancer and inflammation. [46] Tumours are suppressed and apoptosis is induced by curcumin's inhibitory impact on the NFB dependent pathway. [47,48] Cells can interact with one another across short distances thanks to cytokines, which also regulate leucocyte proliferation, survival, differentiation, and death. The effect of curcumin on the interaction of nuclear proteins with interleukins or interferons has been found to downregulate the production of pro-inflammatory cytokines. [49] Curcumin inhibits the expression of the transcription factor AP-1, which has been linked to both pro and anti-apoptotic effects in many cancer types. [50] Curcumin was found to reduce the expression of COX-2 in microglial cells, while melanoma cancer cells showed a concentration-dependent reduction in COX-2. [51,52] More than 90% of curcumin degrades quickly in buffer systems at neutral and basic pH levels because curcumin is unstable at these levels. As a result, ferulic acid and feruloyl methane are produced.

RESVERATROL-

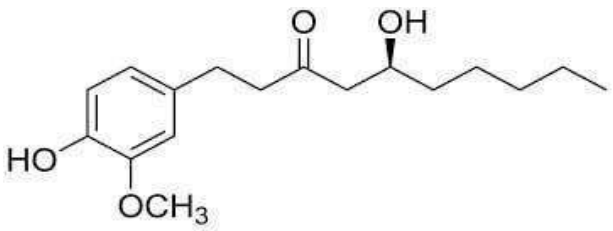


trans-Resveratrol *cis*-Resveratrol

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. [53] Usually, it appears as a white powder that is just slightly soluble in water. It has been established that resveratrol, a natural polyphenol, has a wide range of biological actions, including anti-inflammatory, antioxidant, antiviral, antifungal, and anti-aging effects. [54] A variety of human tumor cells, including myeloid and lymphoid cancer cells, as well as breast, skin, cervix, ovary, stomach, prostate, colon, liver, pancreatic, and thyroid carcinoma cells, have been demonstrated to be sensitive to resveratrol in vitro. [55] Due to its ability to both prevent and treat cancer; resveratrol is becoming more popular. [56] By influencing the various signal-transduction pathways that regulate cell growth and division, inflammation, apoptosis, metastasis, and angiogenesis, resveratrol influences various phases of cancer, from initiation and promotion to

progression The anti-oxidant properties of resveratrol are varied. Its antioxidant properties are due to its capacity to scavenge and neutralize free radicals, unstable chemicals that can harm cells' DNA, proteins, and lipids. Resveratrol reduces cellular damage and promotes overall cell health by disarming these free radicals. Resveratrol not only directly neutralizes free radicals but also stimulates a number of cellular defines mechanisms, such as boosting the activity of antioxidant enzymes including superoxide dismutase (SOD) and catalase. These enzymes are essential for scavenging free radicals and guarding cells against oxidative damage. Additionally, it guards against DNA deterioration brought on by ROS and lipid peroxidation within cell membranes [57]. Oxidative stress can harm cells and be a factor in a number of health problems, such as aging and some cancers. OS is a major factor in the development of cancer[58]. In addition to chromatin proteins, ROS can interact with DNA, which can lead to a variety of DNA damage [59, 60].As an antioxidant, it aids in preventing oxidative stress, which is brought on by an imbalance between the body's capacity to fight off free radicals and their damaging effects. Additionally, it has been demonstrated that resveratrol inhibits the proliferation of cancer cells by inducing apoptosis in these cells [61–62]. Additionally, cyclin A and E levels were shown to rise in response to resveratrol, and cell cycle arrest in the G2/M and S phases was seen [63,64]. Resveratrol appears to stop cell cycles and activate the p53-dependent pathway, according to similar studies. [65–66] An essential component of transcription is the tumour-suppressor protein p53, which is also strongly linked to the control of apoptosis and cell proliferation. p53 also functions as a crucial mediator in the prevention of carcinogenesis. [67]

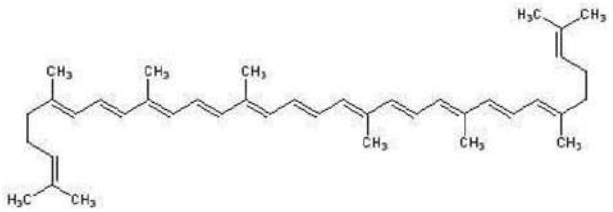
GINGEROL-



The rhizome of Zingiber officinale, a member of the Zingiberaceae family, is the source of gingerol. is a common spice used all across the world, especially in the majority of Asian countries.[68] Skin, ovarian, colon, breast, cervical, oral, renal, prostate, gastric, pancreatic, liver, and brain cancer are among the conditions for which it is utilized as a treatment. Anti-inflammatory qualities found in gingerol can aid in lowering chronic inflammation in the body. An elevated risk of cancer onset and progression is linked to chronic inflammation. Gingerol may aid in slowing the growth of cancer cells by lowering inflammation. renowned for its antioxidant qualities, which have the ability to squelch reactive oxygen species and free radicals. Free radicals can harm cells and alter DNA, which can result in the growth of cancer. Gingerol may shield cells from oxidative stress and stop the development of cancer by functioning as an antioxidant Apoptosis, or "programmed cell death," has been demonstrated to be induced by gingerol in cancer cells. Gingerol's capacity to cause cancer cells to undergo apoptosis might be useful in preventing tumor growth. According to reports, it causes cancer cells to develop DNA damage, which can lead to apoptosis as a

biological response to irreversible DNA defects. The PI3K/Akt and NF-B signaling pathways, as well as other signaling pathways involved in cell survival and death, can be affected by gingerol. Gingerol aids in the activation of apoptosis in cancer cells by blocking these pro-survival pathways and activating pro-apoptotic ones. Certain cell cycle-promoting factors that are necessary for cell division can be inhibited by gingerol's ability to limit their production and activity. This stops cancer cells from moving through the cell cycle by upsetting the strictly controlled cell cycle machinery. Protein complexes called cyclins and cyclin-dependent kinases (CDKs) control how the cell cycle develops. It has been demonstrated that gingerol alters the expression and activity of particular cyclins and CDKs, producing abnormalities in the normal progression of the cell cycle and cell death.The tumor suppressor protein p53, a key regulator of cell cycle checkpoints and apoptosis, has been shown to be activated by gingerol in several studies. Gingerol may cause problems with cell cycle regulation is regulated by a number of signaling pathways, including the PI3K/Akt and MAPK pathways. Gingerol interferes with the signals that encourage cell cycle advancement by focusing on certain pathways, which results in cell cycle arrest in cancer cells. Several signaling pathways involved in the initiation and progression of cancer may be affected by gingerol. Gingerol works by focusing on these pathways to stop the spread of cancer cells. [69]

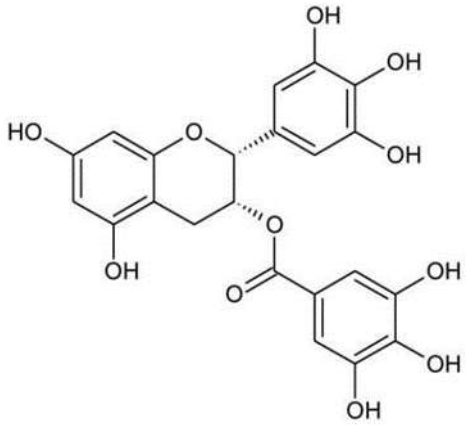
LYCOPENE



A carotenoid nutraceutical called lycopene improves defenses against diseases like cancer, inflammation, hypertension, neurological disorders, and cardiovascular disease. [70] It occurs naturally primarily as the trans isomer in tomatoes, as well as in other red fruits and vegetables such red carrots, watermelons, grapefruits, and papayas, in different amounts. [71] In addition to tomatoes, other red fruits and vegetables such as red carrots, watermelons, grapefruits, and papayas also contain lycopene, a carotenoid that is not a precursor to vitamin A. [72,73] Depending on the species and ripening stage, tomatoes can contain 0.88 to 7.74 milligrams of lycopene per 100 grams. [74] It possesses strong anti-inflammatory, anticancer, antioxidant, and anti-diabetic activities. [75] It has been linked to a lower risk of several different cancers, including breast, prostate, stomach, ovary, and lung cancer [76]. It should be emphasized that the human body is unable to manufacture lycopene. Consequently, it needs to be included in a daily diet [77]. Lycopene is the most effective antioxidant and has a synergistic impact with medications used to treat cancer. [78, 79] It is a crucial ROS (reactive oxygen species)

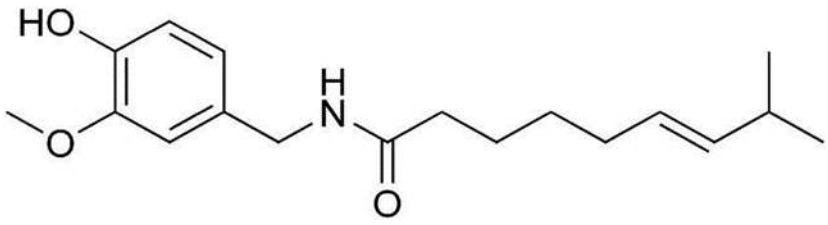
deactivator. Reactive oxygen species (ROS), which are principally responsible for oxidative stress and are recognized as a major risk factor for cancer, are well-documented [80]. Unchecked ROS generation can interact with biological components such DNA, proteins, and lipids and may result in harm that promotes the growth of cancer [81]. It is highly reactive against oxygen and free radicals because of its polyene structure and plenty of conjugated double bonds.

EPIGALLOCATECHIN GALLATE-



A chemopreventive polyphenol called epigallocatechin gallate (EGCG) was found in green tea. Common phytochemical EGCG is the most researched member of the flavonol class and is rich in physiologically active components. One of the most potent molecules with anti-oxidant capabilities is a catechin conjugated with gallic acid, and it is thought to be one of the most active molecules. The Camellia sinensis plant, which produces green tea, has a lot of EGCG. [82] Epigallocatechin has been shown to have an additive or synergistic impact with chemopreventive drugs by reducing toxicities and enhancing anti-cancerous benefits. The cancer-preventive and other anti-cancer activities of tea preparations have been proven in a variety of animal models over the past 25 years, including those for cancers of the mouth, esophagus, stomach, small intestine, colon, liver, pancreas, lung, bladder, skin, prostate, and mammary glands. [83]vThrough the suppression of the initiation, promotion, and development of carcinogenesis, EGCG has been demonstrated to have chemo-preventive effects. [84] The generation of oxidative stress and the activation of death in tumor cells brought on by these pro-oxidant actions may account for some of catechins' anti-cancer effects. The natural antioxidant defense mechanisms in healthy tissues that offer protection against mutagenic damage may also be activated by these pro-oxidant effects. [85] Tumor necrosis factor has been discovered to be inhibited by EGCG. In many cancer cell lines, it plays a crucial part in preventing proliferation and inducing apoptosis. Additionally, it affects both pro- and anti-apoptotic proteins as well as cell cycle regulator proteins to cause apoptosis. [86] Numerous cell cycle-related genes had their mRNA levels reduced by EGCG, while the expression of the cell cycle inhibitor p21 and the apoptosis-related death receptor 5 is increased. [87] Cyclooxygenase (COX)-2 modulation is a critical component of cancer therapy. EGCG inhibits cyclooxygenase-2 without changing the mRNA and protein expression of COX-1, [88]

ALLICIN-



Freshly crushed garlic (Allium sativum), as well as various other allium species, contain the primary active component allicin. It is applied to treat colorectal cancer, mammary cancer, chest cancer, stomach cancer.pancreatic cancer and liver cancer. The prevention of DNA damage, the activation of cell death, the suppression of cell proliferation, and the prevention of angiogenesis and metastasis formation are the mechanisms through which allicin exerts its anticancer effects. Allicin can cause cancer cells to generate DNA ladders and apoptotic bodies. [89] Additionally, it's been discovered that allicin can cause redox changes in cultured the activation of the mitochondrial apoptotic pathway in human cells route [90] Alliin, which is the precursor to allicin, exhibits anti-proliferative properties in humans.

It has been established that the gastric adenocarcinoma cell line does not affect.

Limitations of Nutraceuticals in Cancer-

Herbal supplements have potential to interfere with drug therapy.

- Curcumin may interfere with effectiveness of certain chemotherapy drugs such as irinotecan or docetaxel.
- Resveratrol can interact with chemotherapy drugs like etoposide and paclitaxel, and also interfere with blood thinning medications such as warfarin.
- Allicin may interact with certain chemotherapy drugs such as cyclophosphamide, by potentially affecting their effectiveness

CONCLUSION:-

The incidence of cancer is increasing, so it is important to control them. The nutraceuticals are becoming popular as they are safe and natural food constituents. Nutraceuticals provide chemo preventive effects with negligible toxicity. Although some studies have confirmed the positive response but their mechanism of action still not clear. Many of them have same mechanism and can be grouped together, based on that pathway.

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