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Integrating Nutraceuticals into Cancer Care

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Abstract: ***Cancer remains a major global health challenge, consistently ranking as the second leading cause of mortality worldwide, despite significant advancements in research and technology, conventional treatments chemotherapy, radiotherapy and surgery, but often associated with several toxicity, drug resistance and reduced quality of life.[1]***
These limitations have encouraged Interest in Nutraceuticals. Nutraceuticals are nourishing components (hybrids of nutrition and pharmaceuticals) that are biologically active and possess the capability to maintain optimal health and benefits. Nutraceuticals like curcumin (from turmeric), resveratrol, sulforaphane, vitamin c, vitamin D,Garlic extracts,greenteaextract, Omega-3 fatty acids,probiotics, Quercetin, APE (Annurca Apple polyphenol extract), Anthraquinone, Flavonoids, lycopene, carnosol have shown the ability to stop cancer growth in different ways.[2]
This review summarizes the current evidence on the anticancer properties of nutraceuticals and their possible integration into cancer care settings. It covers the mechanism of action and anti-cancer roles (antioxidant, anti-inflammatory, probiotic, anti-proliferative, anti-angiogenic, and immune modulating) based on evidence from preclinical and clinical studies.
Overall, nutraceuticals represent promising adjuncts in integrative oncology, with the potential to improve treatment outcomes and quality of life in patients with cancer.
Further well-designed clinical studies, advanced delivery systems, and regulatory frameworks are essential to establish their evidence-based use in routine cancer therapies.
Keywords: Nutraceuticals, Cancer therapy, Curcumin, Resveratrol, Antioxidants, Phytochemicals.

I. INTRODUCTION

Cancer arises when normal cells within a specific tissue lose control over their growth and division. While cancers can differ in type and site of origin, they are uniformly characterized by continuous proliferation, where cells divide repeatedly rather than undergoing programmed cell death, ultimately forming abnormal cell populations.

In certain cases, malignant cells disseminate to distant sites via the bloodstream or lymphatic vessels, a process referred to as metastasis. For instance, if malignant cells originating from the breast colonize the liver, the disease is classified as metastaticbreast cancer, not primary liver cancer.

At the molecular level, cancer primarily develops due to DNA damage within cells. Under normal circumstances, the body's repair mechanisms correct such damage; however, in cancer cells, these mechanisms are impaired or absent. Damaged DNA may be inherited genetically, accounting for hereditary cancers, or may result from environmental exposures, such as tobacco use or carcinogenic substances.

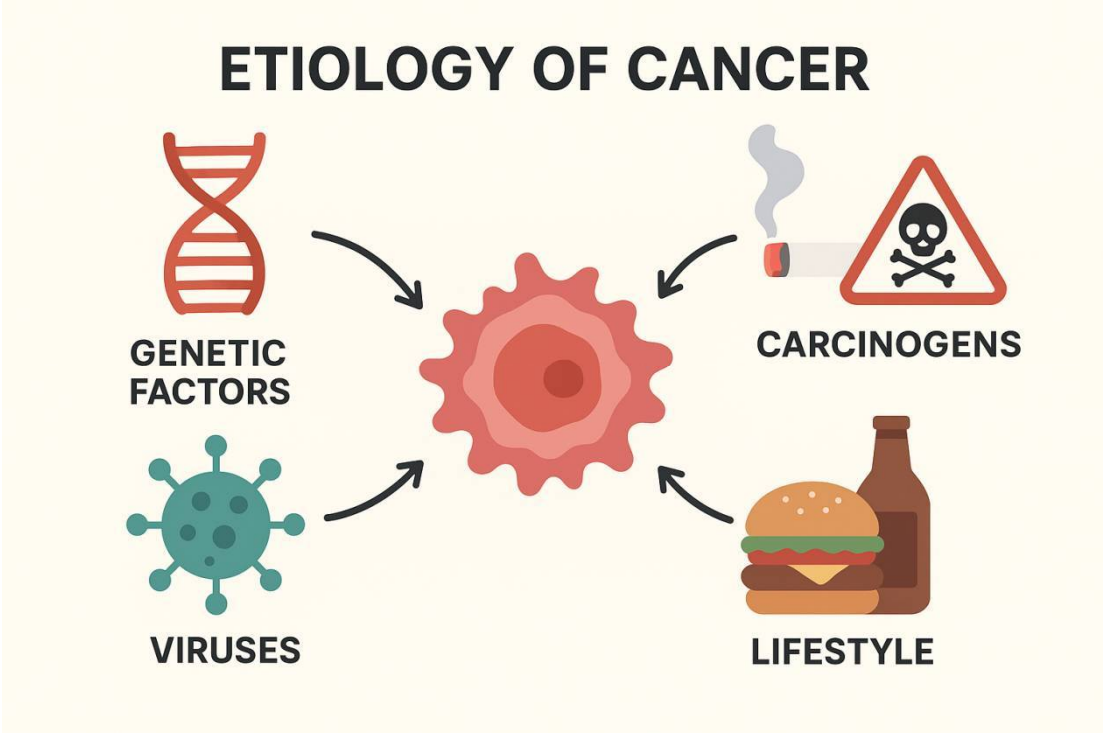
Recent investigations also emphasize the contribution of external risk factors in the initiation and progression of cancer, complementing advances in clinical diagnostics and therapeutic strategies.[3].

In most malignancies, cancer manifests as a solid tumor. However, certain hematological cancers, such as leukemia, do not form discrete tumor masses. Instead, leukemic cells infiltrate the blood and hematopoietic organs, subsequently disseminating to other tissues where they continue to proliferate. It is important to distinguish between malignant and benign tumors. Benign tumors are non-cancerous, remain localized, and typically do not pose a significant threat to life, whereas malignant tumors possess the capacity for invasion and metastasis.The biological behaviour of cancer cells varies considerably among different cancer types, influencing both prognosis and therapeutic response. Evidence indicates that the risk of several malignancies can be reduced through modifiable lifestyle factors, such as smoking cessation and adherence to a nutritionally balanced, low-fat diet.

Furthermore, early detection significantly improves clinical outcomes, as cancers identified at an initial stage are generally more amenable to treatment and associated with enhanced long-term survival rates.[4]

Many things can affect a person's chances of developing cancer. Factors like their age, gender, what they eat, their racial or ethnic background, where they live, and their genetic makeup all play a role. Because of these differences, cancer doesn't look the same everywhere—some regions or groups may face higher risks or different types of cancer.

According to the World Health Organization (WHO),cancer is one of the biggest health challenges around the world. It's responsible for millions of deaths every year—about 8.2 million people lose their lives to cancer, which makes up nearly a quarter of all deaths not linked to infectious diseases.



The most common cancers that lead to death include those affecting the lungs, liver, stomach, colon, and breasts. Sadly, the number of cancer-related deaths is expected to keep growing. Experts predict that by 2030, more than 13 million people could die from cancer — an increase of nearly 70% from today's numbers.[5]

A. Types of Cancer:

- Carcinoma- It is a type of cancer that begins in skin and tissues that lines and covers internal organs such as skin, lung, and colon.
- Sarcoma- It is a type that begins in bone, cartilage, fat, muscles, blood vessels and other connective tissues.
- Leukemia- It is a cancer that starts in blood forming tissues such as bone marrow and causes large number of abnormal blood cells to be produced and enter in blood.
- Lymphoma and Myeloma- It is a cancer that begins in cells of immune system that is T-cell and B-cell Lymphoma.
- Central Nervous system cancers- Cancers that begins in tissues of brain and spinal cord. For example,brain and spinal cord tumors, primitive neuroectodermal tumors. [6]

The conventional methods of cancer treatment, including surgery, radiation therapy, chemotherapy, immunotherapy, hormone therapy, and targeted therapy, are associated with a wide range of side effects. Common side effects include pain, infection, scarring, and functional impairments from surgery; skin irritation, fatigue, nausea, and damage to surrounding healthy tissues from radiation therapy; nausea, vomiting, hair loss, immune suppression, anaemia, and mouth sores from chemotherapy; flu-like symptoms, fever, fatigue, inflammation, and immune-related organ damage from immunotherapy; hot flashes, mood swings, weight gain, sexual dysfunction, and bone thinning from hormone therapy; and skin problems, liver issues, high blood pressure, and general fatigue from targeted therapy. These adverse effects can significantly impact patient well-being and quality of life;all these problems highlightthe need for supportive care and complimentary treatment strategies. All the above-mentioned problems have shifted the interestof patients towards nutraceuticals.

The term *nutraceutical* is a blend of "nutrition" and "pharmaceutical," highlighting its role at the intersection of food and medicine. Nutraceuticals encompass a wide range of products derived from food sources that offer health benefits beyond basic nutrition.

These products may include isolated nutrients, dietary supplements, herbal extracts, functional foods, and fortified foods that support overall health and prevent or manage diseases.

Nutraceuticals are known to influence and support normal physiological functions in the body. They play a significant role in modifying biological processes, boosting immune function, reducing inflammation, and improving metabolic activity. Regular consumption of nutraceuticals can enhance the body's defence mechanisms, promote better digestion, support cardiovascular health, and maintain bone strength, among other benefits.

The term **"nutraceutical"** was first introduced in 1979 by Stephen De Felice, who defined it as "a food or parts of food that provide medical or health benefits, including the prevention and treatment of disease." This concept goes beyond basic nutrition, emphasizing the therapeutic potential of certain foods and food components in promoting health and preventing illness.

The underlying principle of nutritional therapy is to complement conventional medical treatments by incorporating nutraceuticals into daily diets. Food, in this context, is not merely a source of energy and nutrients but also serves as a means of delivering bioactive compounds that offer medicinal benefits. Through regular consumption, nutraceuticals help support various physiological functions, enhance immune response, and improve overall well-being.

In addition to their preventive and therapeutic roles, nutraceuticals are recognized for their ability to detoxify the body, aid healthy digestion, and encourage balanced dietary habits. By assisting in metabolic regulation and supporting the body's natural healing processes, they contribute to maintaining long-term health and reducing the risk of chronic diseases.[7]

B. Typesof Nnutraceuticals

Nutraceuticals used in supporting the cancer therapy are curcumin (from turmeric), resveratrol, sulforaphane, vitamin c, vitamin D, Garlic extracts, green tea extract, Omega-3 fatty acids, probiotics, Quercetin, APE (Annurca Apple polyphenol extract), Anthraquinone, Flavonoids, lycopene, carnosol.

All the above-mentioned nutraceuticals support the cancer therapy and help to minimize the harmful effects of the traditional methods of therapy, all these shows different-different types of mechanism of action and anti-cancer roles (antioxidant, anti-inflammatory, probiotic, anti-proliferative, anti-angiogenic, and immune modulating).

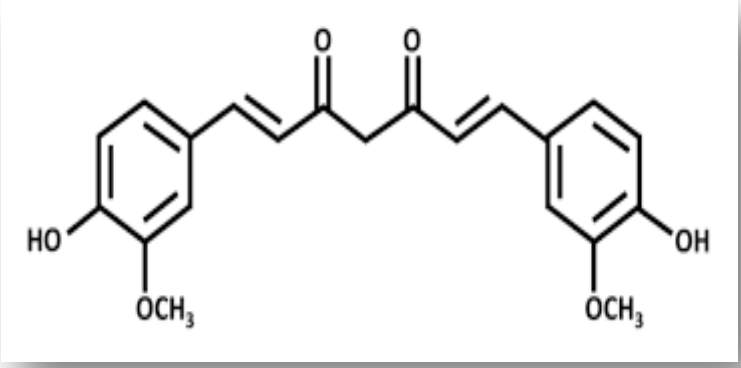
Table 1: Sources, Mechanisms, and Dosages of Common Nutraceuticals Used in Cancer Therapy

Nutraceutical	Source (Food/Plant/Compound)	Mechanism/Effect in Cancer Therapy	Typical Dosage*	Reference
Curcumin	Turmeric (Curcuma longa)	Anti-inflammatory, antioxidant, inhibits tumor growth and angiogenesis	500–2000 mg/day	[8]
Resveratrol	Grapes, berries, peanuts	Modulates cell signalling, induces apoptosis, prevents metastasis	150–500 mg/day	[9]
Sulforaphane	Broccoli, cabbage, cruciferous vegetables	Activates detox enzymes, induces apoptosis, inhibits proliferation	20–40 mg/day	[10]
Vitamin C	Citrus fruits, berries, vegetables	Antioxidant, enhances immune response, reduces oxidative stress	500–2000 mg/day	[11]

Vitamin D	Sunlight, fortified foods, supplements	Regulates cell growth, enhances apoptosis, modulates immune system	1000–4000 IU/day	[12]
Garlic extract	Garlic bulbs	Enhances detoxification enzymes, antioxidant, inhibitstumor formation	600–1200 mg/day	[13]
Green tea extract	Green tea leaves	Rich in catechins; inhibits cell proliferation, antioxidant, modulates signalling pathways	250–500 mg/day	[14]
Omega-3 fatty acids	Fish oil, flaxseeds, walnuts	Anti-inflammatory, enhances immune response, prevents tumor progression	1000–3000 mg/day	[15]
Probiotic	Yogurt, fermented foods	Modulates gut microbiota, enhances immune function, reduces inflammation	1–10 billion CFU/day	[16]
Quercetin	Apples, onions, citrus fruits	Antioxidant, inhibits proliferation, induces apoptosis	500–1000 mg/day	[17]
Aloe anthraquinone	Aloe vera leaf extract	Anti-inflammatory, antioxidant, may reduce cancer cell growth	100–300 mg/day	[18]
Flavonoids	Fruits, vegetables, herbs	Antioxidant, modulates cell signalling, reduces oxidative stress	200–1000 mg/day	[19]
Lycopene	Tomatoes, watermelon, pink grapefruit	Antioxidant, inhibits growth of cancer cells, supports immune function	10–30 mg/day	[20]
Carnosol	Rosemary, sage	Anti-inflammatory, antioxidant, induces apoptosis in cancer cells	50–200 mg/day	[21]

C. Roles of nutraceuticals in cancer prevention and treatment:

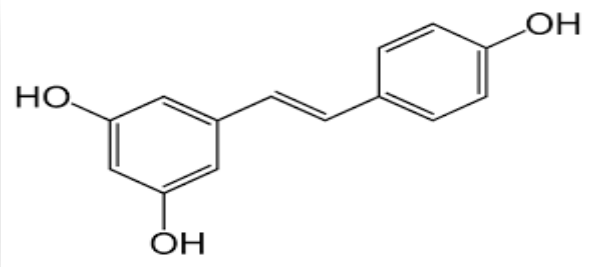
- Curcumin



Curcumin (diferuloylmethane) is a natural compound found in turmeric (curcuma longa).For the last 50 years, scientists have studied curcumin and found that it may be help both Prevent and treat cancer. Its anticancer effects mainly come from its ability to slow down or stop thegrowth of many types of cancer cells.[22]

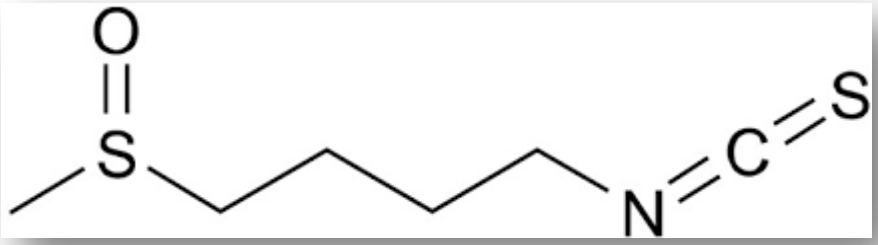
It is also a potent chemo preventive agent inhibiting tumor promotion against skin, oral, intestinal and colon carcinogenesis. Many studies using curcumin focused on its anti-inflammatory, antioxidant, anticarcinogenic, antiviral, and anti-infective activities. In addition, the wound healing and detoxifying properties of curcumin have also received considerable attention. Over the last decade, remarkable advances in our understanding of cancer biology have led us to the realization that apoptosis and the genes that control it have a profound effect on the malignant phenotype although apoptosis or programmed cell death is primarily a cell suicide program critical for development, tissue homeostasis, and protection against pathogens.[23]

- Resveratrol



Resveratrol, a natural stilbene and a non-flavonoid polyphenol, is a phytoestrogen that possesses anti-oxidant, anti-inflammatory, cardioprotective, and anti-cancer properties. It has been reported that resveratrol can reverse multidrug resistance in cancer cells, and, when used in combination with clinically used drugs, it can sensitize cancer cells to standard chemotherapeutic agents. Several novel analogues of resveratrol have been developed with improved anti-cancer activity, bioavailability, and pharmacokinetic profile. It has been shown that resveratrol has in vitro cytotoxic effects against a large range of human tumor cells, including myeloid and lymphoid cancer cells, and breast, skin, cervix, ovary, stomach, prostate, colon, liver, pancreas, and thyroid carcinoma cells. Resveratrol affects a variety of cancer stages from initiation and promotion to progression by affecting the diverse signal-transduction pathways that control cell growth and division, inflammation, apoptosis, metastasis, and angiogenesis.[24]

- Sulforaphane

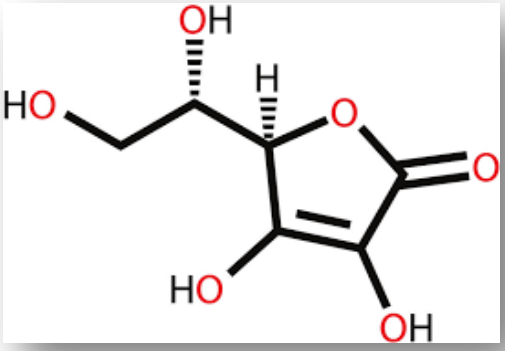


Sulforaphane is a biologically active phytochemical belonging to a diverse class of isothiocyanates derived from glucosinolates. Chemically, SFN is 1-isothiocyanato-4-(methyl sulfinyl)butane with a linear chemical expression of CH3–SO–(CH2)4–N=C=S. In plant cells, SFN is stored in the form of glucoraphanin which is its stable precursor. It is highly concentrated in the reproductive organs like seeds & inflorescence, young leaves, roots, and mature leaves.

Researchers use various tools to identify anticancer perspectives of bioactive compoundsinvolving activation of nuclear factor erythroid 2-related factor 2 (Nrf2) cell signaling pathway, modulation of xenobiotic pathways and epigenetic regulation.Nrf2 signaling pathway is of critical importance in biological cells where it regulates and controls the detoxification mechanisms of the environmental stress inducers .In normal conditions, Nrf2 transcription factor is held by Keap1 in cytoplasm facilitating its successive degradation via ubiquitination followed by proteolysis by 26S proteasomal complex. Under stressed conditions, nascent Nrf2 is translocated to the nucleus due to interruption in proteolysis.

Nrf2 then binds to antioxidant response element sequences present at the cytoprotective genes that encode for proteins and enzymes for regulation of redox homeostasis. In this way, the oxidative stress and other toxicants are diminished. [25]

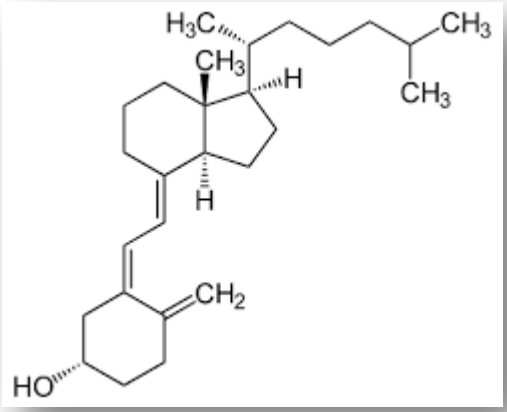
- Vitamin C



Vitamin C represents a redox system consisting of 2 L-isomers: ascorbic acid (vitamin C) in the reduced state and dehydroascorbic acid (DHA) in the oxidized state. Most of the vitamin's functionality in the human body is related to the role of vitamin C as an electron donor; hence, vitamin C is the active, stable form of vitamin C in tissues.[26]

Vitamin C is taken up by cells through sodium-dependent vitamin C transporters, whereas the oxidized form of vitamin C, dehydroascorbate (DHA), moves into cells via glucose transporters such as GLUT1.Once inside the cell, DHA is reduced back to vitamin C by glutathione (GSH), which consequently becomes oxidized glutathione (GSSG). Subsequently, GSSG is converted back to GSH by reduced nicotinamide adenine dinucleotide phosphate (NADPH). High doses of vitamin C can increase the amount of reactive oxygen species (ROS) in cancer cells and exert antitumorigenic activity.[27]

- Vitamin D

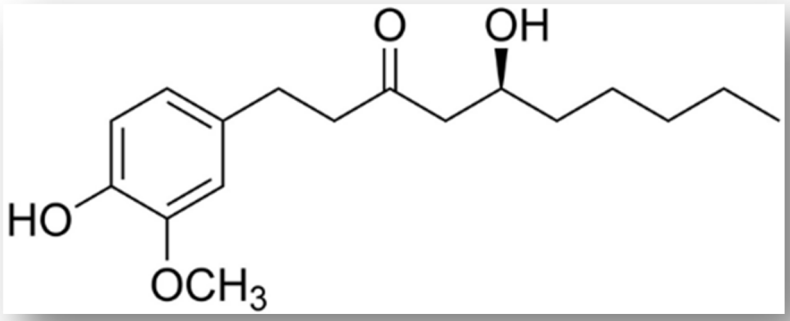


The vitamin D system consists of a family of fat-soluble compounds that function as prohormones along with their active metabolites. Naturally, vitamin D exists mainly in two forms: vitamin D_2 (ergocalciferol), produced in plants and fungi through photochemical reactions, and vitamin D_3 (cholecalciferol), generated in the skin of humans and animals when exposed to ultraviolet-B (UV-B) radiation within the wavelength range of 270–300nm. In most European and North American populations, it is estimated that around 90%of vitamin D is synthesized endogenously from 7-dehydrocholesterol in the skin following sunlight exposure, while the remaining 10% is supplied through dietary intake.[28]

Calcitriol(biologically most active form of vitamin D) has been found to promote apoptosis in several types of cancer cells, although this effect is not consistently observed across all malignancies.

In prostate and breast cancer cells, calcitriol primarily initiates the intrinsic apoptoticpathway, resulting in mitochondrialdysfunction, cytochromecrelease, and the generation of reactive oxygen species (ROS). These processes are linked to a reductioninanti-apoptotic proteins such as Bcl-2 and an increase in pro-apoptotic proteins including Bax and Bad. In certain cancer cell types, calcitriol may also activate caspases directly, thereby inducing apoptosis. Furthermore, calcitriol analogues have been shown to enhancethe susceptibility of cancer cells to chemotherapeutic agents and radiation therapy, leading to improved cell death responses.[29]

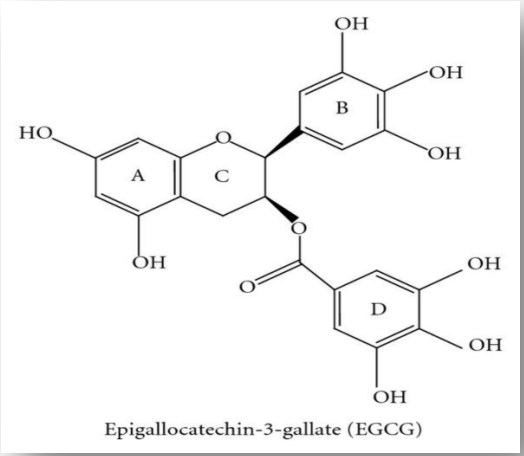
- Garlic extract



Garlic is obtained from the bulb of the plant Allium Sativum which belongs to the familyAmaryllidaceae.garlic is widely cultivated and used both as a culinary spice and medicinal herbduetoitssulfur-containng compoundssuch as allicin,which exhibit antibacterial,antifungal and anticancer properties.

Weisberger and Pensky demonstrated that preincubating sarcoma 180 tumor cells with diethyl thiosulfinate-a compound produced by the reactionof S-ethyl-L-cysteine sulfoxide with alliinase derived from fresh garlic—completely suppressed the tumor-forming ability of these cells in mice. In the same investigation, preincubation of Murphy-Sturm lymphosarcoma cells with diethyl thiosulfinate resulted in a marked reduction in tumor formation in rats. Furthermore, when animals were treated with the thiosulfinate concurrently with tumor cell inoculation, a significant inhibition of tumor growth was also observed.[30]

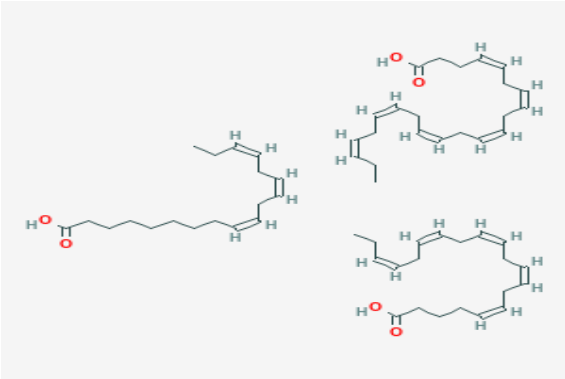
- Green tea extract



Green tea contains a rich composition of polyphenolic compounds, primarily catechins and flavonols, which together make up a significant proportion of its solid extract. The four principal catechins present in green tea include (-)-epicatechin, (-)-epicatechin-3-gallate, (-)-epigallocatechin, and (-)-epigallocatechin-3-gallate (EGCG). Among these, EGCG is the most abundant, representing approximately 40% of the total polyphenolic content. Typically, a single cup of green tea provides around 300–400 mg of polyphenols, which are generally regarded as non-toxic and safe for consumption.[31]

Research has shown that epigallocatechin-3-gallate (EGCG) and the chemo preventive agent sulindac can act synergistically to enhance anticancer effects. In one study, treatment with 75 μM EGCG combined with either 10 μM sulindac or its active metabolite, 1 μM sulindac sulfate, triggered apoptosis in the human lung cancer cell line PC-9 at a rate nearly 20 times higher than when either compound was used individually. Furthermore, co-administration of green tea extract and sulindac significantly suppressed tumor development in multiple intestinal neoplasiamice, producing a stronger inhibitory effect than either agent alone. These findings suggest that combining green tea constituents with established chemo preventive drugs may enhance therapeutic efficacy while reducing drug-related adverse effects, offering a more effective approach to cancer prevention.[32]

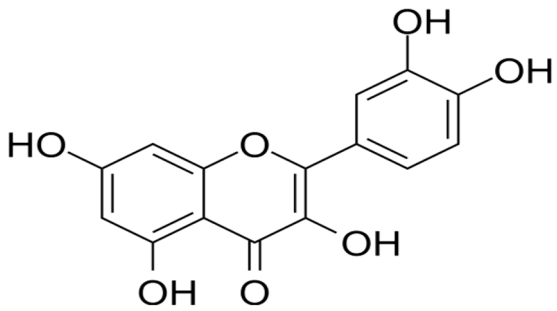
- Omega-3 fatty acids



Fatty acids are hydrocarbon chains with a carboxyl group at one end. In saturated fatty acids, all of the carbons are connected by single bonds, whereas unsaturated fatty acids have some carbons connected by double bond.

Evidence from animal studies suggests that the intake of omega-3 fatty acids can inhibit the growth of cancer xenografts, enhance the therapeutic efficacy of chemotherapy, and reduce its associated side effects as well as those caused by cancer itself. The beneficial effects of omega-3 fatty acids are believed to result from multiple molecular mechanisms, including the suppression of cyclooxygenase-2 (COX-2) expression in tumors, which leads to reduced cell proliferation and angiogenesis. They also downregulate oncogenes such as AP-1 and ras, which are involved in tumor promotion, and promote cancer cell differentiation. In addition, omega-3 fatty acids inhibit the activation of nuclear factor-κB (NF-κB) and lower the expression of bcl-2, thereby facilitating apoptosis. Another important effect is the reduction of cancer-induced cachexia. Taken together, these findings suggest that, following appropriate cancer therapy, dietary supplementation with omega-3 fatty acids could help suppress or slow metastatic tumor growth, extend patient survival, and improve overall quality of life.[32]

- Quercetin



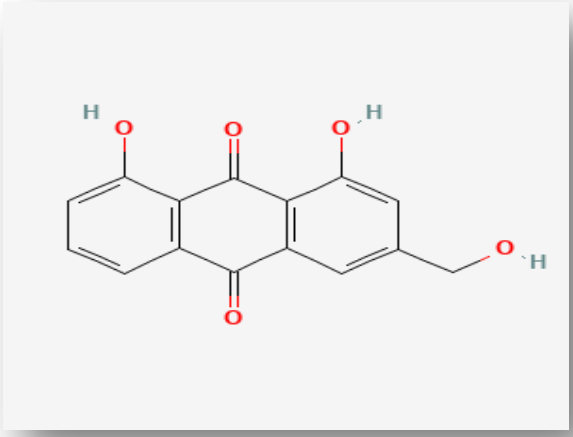
Quercetin (QUE; 3,5,7,3′,4′-pentahydroxyflavone) is a prominent compound belonging to the flavonol subclass of flavonoids. It is widely distributed in nature and occurs abundantly in a variety of fruits and vegetables, making it one of the most prevalent flavonols in the human diet.Onions are among the richest dietary sources of this flavonol. The concentration of quercetin in white and yellow onion varieties ranges from approximately 0.03 to 0.28 mg per 100 g of fresh weight (FW), while red onions contain the highest levels, reaching about 1.31 mg per 100 g FW.

Quercetin exhibits a broad spectrum of biological activities, including antioxidant, anticarcinogenic, anti-inflammatory, antidiabetic, and antimicrobial effects. In plants, quercetin primarily occurs as glycoside derivatives, which undergo enzymatic hydrolysis by intestinal β-glycosidases prior to absorption in the enterocytes. Within these cells, quercetin is further metabolized into various conjugated forms. However, its bioavailability remains relatively low, which limits its systemic efficacy and may account for the differences observed between in vitro and in vivo studies.

Under normal physiological conditions, healthy cells primarily generate energy through oxidative phosphorylation, shifting to glycolysis only when oxygen availability becomes limited. In contrast, cancer cells often rely predominantly on aerobic glycolysis even when oxygen is abundant—a phenomenon known as the Warburg effect. Recent evidence suggests that this metabolic reprogramming in malignant cells is driven not by mitochondrial dysfunction, but rather by an increased demand for glucose-derived intermediates required for biomass synthesis. From a therapeutic standpoint, targeting glycolysis is considered a promising strategy to suppress tumor growth. However, considering overall cellular energetics, simultaneous inhibition of glycolytic and mitochondrial ATP production may provide a more comprehensive approach to induce cancer cell death. Despite the development of several glycolytic inhibitors and mitochondria-targeted agents, few have advanced to clinical trials, mainly due to concerns regarding selectivity, efficacy, and safety. Therefore, identifying novel compounds that effectively disrupt cancer metabolism remains a major research focus.

In this context, quercetin (QUE) has been shown to interfere with both glycolytic and mitochondrial functions in cancer cells. Treatment with 26.5–50 μM quercetin significantly reduced glucose uptake and lactate production in breast cancer cell lines (HBL100, MDA-MB-231, and MCF-7) as well as in ascites tumor cells, indicating an inhibitory effect on glycolysis. Similarly, in colon cancer cell lines HCT-15 and RKO, quercetin at its IC_{50} concentrations (121.9 μM and 142.7 μM, respectively) caused a time-dependent decrease in glucose consumption and lactate generation over 4–10 hours in HCT-15 cells, while in RKO cells, only lactate production was reduced after 4 hours of exposure. Moreover, pre-treatment with quercetin at IC_{50} levels enhanced the glycolytic inhibition caused by 5-fluorouracil in both HCT-15 and RKO cells. These findings suggest that quercetin modulates glucose metabolism by inhibiting monocarboxylate transporter (MCT) activity, which is essential for the export of lactate and protons (H^+). By blocking this process, quercetin may lead to intracellular acidification, thereby promoting cell death in highly glycolytic cancer cells.[33]

- Aloe anthraquinone



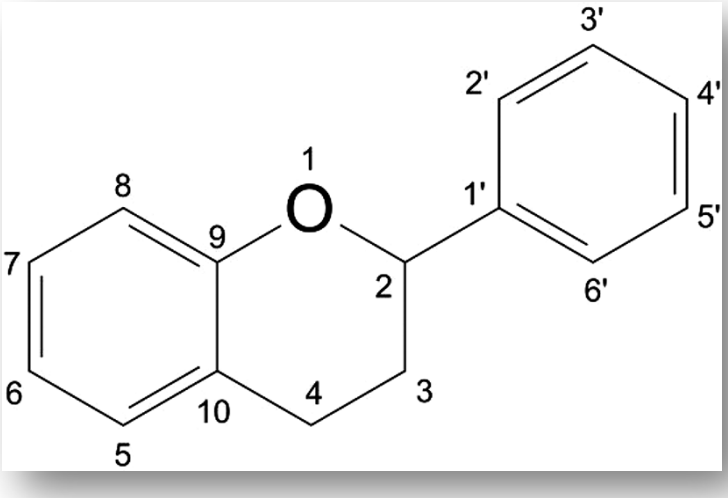
Aloe anthraquinones are naturally occurring bioactive compounds derived from species of the genus *Aloe*, particularly *Aloe vera*, *Aloe ferox*, and *Aloe barbadensis Miller*. These compounds are mainly concentrated in the latex or outer rind of the aloe leaves and include aloin (barbaloin), aloe-emodin, emodin, and chrysophanol. Anthraquinones are responsible for many of the plant's pharmacological activities, including laxative, antimicrobial, antioxidant, and anticancer effects.

Mechanistically, aloe anthraquinones exert their biological actions through several molecular pathways. Aloe-emodin and emodin, in particular, have been reported to induce apoptosis in cancer cells by activating the intrinsic mitochondrial pathway, which involves cytochrome c release, caspase activation, and downregulation of anti-apoptotic proteins such as Bcl-2. They also contribute to cell cycle arrest, often at the G_2/M phase, by modulating the expression of cyclins and cyclin-dependent kinases (CDKs).

Additionally, these compounds are known to generate reactive oxygen species (ROS), leading to oxidative stress and DNA damage in tumor cells, which enhances their cytotoxic potential. Beyond their anticancer activity, aloe anthraquinones exhibit anti-inflammatory effects by inhibiting NF-κB signaling and reducing the production of pro-inflammatory cytokines.

Overall, the anthraquinones from aloe act as multifunctional phytochemicals that regulate cell proliferation, apoptosis, and oxidative balance, contributing to their therapeutic potential in both cancer prevention and treatment.

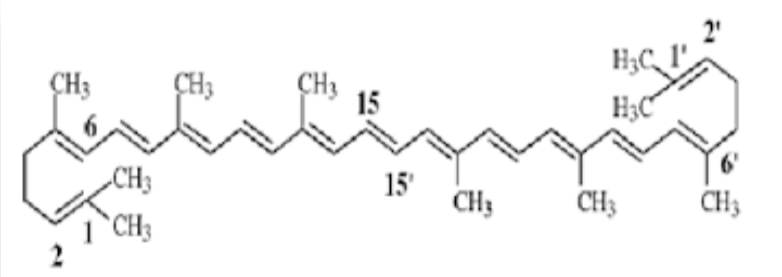
- Flavonoids



Flavonoids exert protective effects against cancer partly through their influence on the metabolic activation and detoxification of carcinogens. Many chemical carcinogens undergo phase I metabolism, primarily by cytochrome P450 (CYP) enzymes, to form reactive intermediates capable of binding to DNA and inducing mutations that may initiate carcinogenesis. These reactive metabolites are subsequently neutralized in phase II metabolism through conjugation reactions that render them water-soluble and facilitate their elimination from the body. Certain flavonols such as quercetin,kaempferol, and galangin, as well as the flavone apigenin, have demonstrated inhibitory activity toward CYP1A family enzymes, which are crucial in the metabolic activation of several human carcinogens, including polycyclic aromatic hydrocarbons and heterocyclic amines. Additionally, quercetin and naringin have been shown to inhibit CYP3A4, the predominant P450 enzyme in the liver that metabolizes numerous carcinogens and drugs, thereby contributing to the modulatory effects observed with grapefruit juice consumption.

Beyond their influence on xenobiotic metabolism, flavonoids also enhance the body's antioxidant defence mechanisms. Experimental studies have reported that tea catechins upregulate the activity of key detoxifying and antioxidant enzymes such as glutathione reductase, glutathione peroxidase, catalase, glutathione S-transferase, and quinone reductase. Moreover, several flavonoids, including quercetin, apigenin, and tea catechins, possess anti-inflammatory properties by inhibiting cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS), thereby reducing oxidative stress and inflammation associated with tumor promotion and progression.[35]

- Lycopene



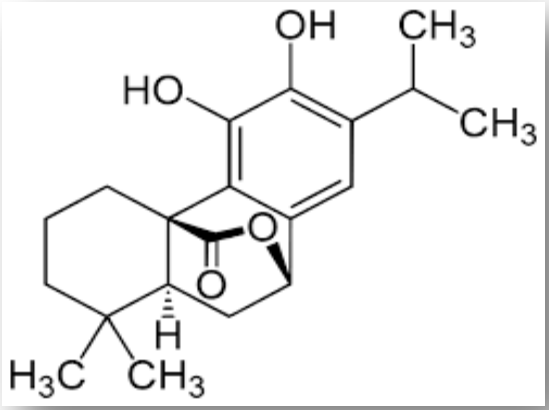
Lycopene (ψ, ψ-carotene) is the primary carotenoid responsible for the red coloration of tomatoes and is also present in several other fruits such as rosehips, watermelon, papaya, pink grapefruit, and guava. Unlike β-carotene, it does not contain a β-ionone ring and therefore lacks pro-vitamin A activity. Its structure, consisting of 11 conjugated and two non-conjugated double bonds, allows lycopene to interact readily with oxygen and free radicals. This strong antioxidant property is believed to play a significant role in its potential to help prevent cancer development.[36]

Lycopene helps cells stay connected by forming more *gap junctions*, which allow them to communicate properly. This connection is important for normal cell and organ function. Researchers have found that lycopene may help prevent cancer through two main actions — oxidative and non-oxidative mechanisms. It can block the activation of key control proteins like p53 and Rb, stopping abnormal cells from multiplying and keeping them in the G0–G1 stage of the cell cycle.

Studies also suggest that lycopene protects the liver by influencing an enzyme called cytochrome P450 2E1, which helps detoxify harmful substances. In laboratory experiments, lycopene was shown to reduce the rapid growth of cells triggered by insulin-like growth factors, which normally promote cell division.

In animal research, lycopene appeared to strengthen the immune system by improving T-cell development in the thymus, helping to slow down the growth of breast tumors. Overall, by supporting cell communication and controlling cell growth, lycopene plays a role in preventing the uncontrolled spread of cancer cells.[37]

- Carnosol



Carnosol is a natural compound known as a phenolic diterpene, found in the herb rosemary (*Rosmarinus officinalis* L.). It has shown strong potential in helping to prevent different types of cancer. Significant research progress has been made in understanding how carnosol works inside the body to provide these protective effects. Studies using both cell cultures and animal models have shown that carnosol can block the development of cancer caused by experimental agents. It also has powerful antioxidant, anti-inflammatory, and anti-proliferative actions, and it can trigger apoptosis (programmed cell death) in cancer cells. In addition, carnosol has been found to make drug-resistant cancer cells more responsive to chemotherapy treatments.

Carnosol has been shown to stop the growth and promote the death of various human cancer cells. It causes cells to pause at the G2/M phase of the cell cycle, which prevents them from dividing. In human colon cancer (Caco-2) cells, this effect is linked to an increase in cyclin B levels and a reduction in cell division. Similarly, in human prostate cancer (PC3) cells, carnosol also produces a G2/M phase arrest, and this effect becomes stronger as the concentration of carnosol increases.

The growth-inhibiting effect of carnosol on PC3 cells is due to the reduced activity of several cell cycle proteins, including cyclins A, D1, and D2, and cyclin-dependent kinases (Cdks) 2, 4, and 6. At the same time, it increases the levels of Cdk inhibitors p21 and p27, which help slow down cell division. Carnosol also triggers apoptosis (programmed cell death) in PC3 cells by activating caspase-8 and caspase-9, increasing Bax levels, and lowering Bcl-2 expression.

These effects are linked to greater phosphorylation of AMP-activated protein kinase (AMPK-α) and 4E-binding protein 1 (4E-BP1), along with reduced phosphorylation of mTOR, p70S6 kinase, and Akt, which are key proteins involved in cell growth and survival. In human leukemia (HL-60) cells, carnosol also prevents cell division by causing sub-G1 phase arrest, activating caspase-3, and promoting apoptosis.[38]

II. CHALLENGES AND LIMITATIONS

Although nutraceuticals show great potential in cancer prevention and treatment, several challenges limit their effective use. One major issue is the poor bioavailability of many natural compounds, as they are often unstable, poorly absorbed, or rapidly metabolized in the body, reducing their therapeutic impact. Another challenge is the lack of standardized formulations and dosages, which makes it difficult to compare study results and establish effective treatment guidelines. Many nutraceuticals also face limited clinical evidence, since most research is based on laboratory or animal studies rather than large-scale human trials. Additionally, interactions with conventional cancer drugs can occur, affecting drug metabolism or reducing their effectiveness. The variability in product quality, due to differences in plant sources and manufacturing methods, further complicates their use in clinical settings. Regulatory issues also pose a problem, as nutraceuticals are often classified as dietary supplements rather than therapeutic agents, leading to fewer quality control requirements. Overall, despite their promising benefits, more research, standardization, and clinical testing are needed before nutraceuticals can be reliably integrated into mainstream cancer therapy.

III. FUTURE DIRECTIONS OF NUTRACEUTICALS IN CANCER CARE (ORIGINAL VERSION):

The future of nutraceuticals in cancer care lies in advancing scientific understanding, improving formulations, and strengthening clinical validation. Future research should focus on enhancing the bioavailability and stability of active compounds through advanced delivery systems such as nanoparticles, liposomes, and phytosomes. Integrating genomic and metabolomic studies could help identify how individual genetic variations influence response to nutraceuticals, paving the way for personalized nutrition-based cancer therapy. More well-designed clinical trials are needed to confirm safety, efficacy, and optimal dosages, ensuring these compounds can complement standard cancer treatments. Collaboration between researchers, clinicians, and the pharmaceutical industry will be essential to develop standardized, evidence-based nutraceutical products. In addition, clear regulatory guidelines and quality control measures must be established to ensure product consistency and patient safety. With these advancements, nutraceuticals could evolve from supportive dietary components into scientifically validated, integrative tools for cancer prevention and management.

IV. CONCLUSION

Nutraceuticals represent a promising and evolving field in the prevention and management of cancer. Various natural compounds such as curcumin, lycopene, resveratrol, carnosol, and others have shown significant antioxidant, anti-inflammatory, and antiproliferative effects in both experimental and clinical studies. These bioactive agents not only help in reducing cancer risk but also enhance the effectiveness of conventional therapies while minimizing their side effects. However, challenges such as low bioavailability, lack of standardization, limited clinical evidence, and regulatory barriers continue to restrict their widespread clinical use. Future research focusing on advanced formulation technologies, personalized nutrition, and large-scale clinical trials will be essential to translate these natural products into reliable therapeutic tools. With continued innovation and scientific validation, nutraceuticals hold great potential to become integral components of comprehensive cancer prevention and treatment strategies.

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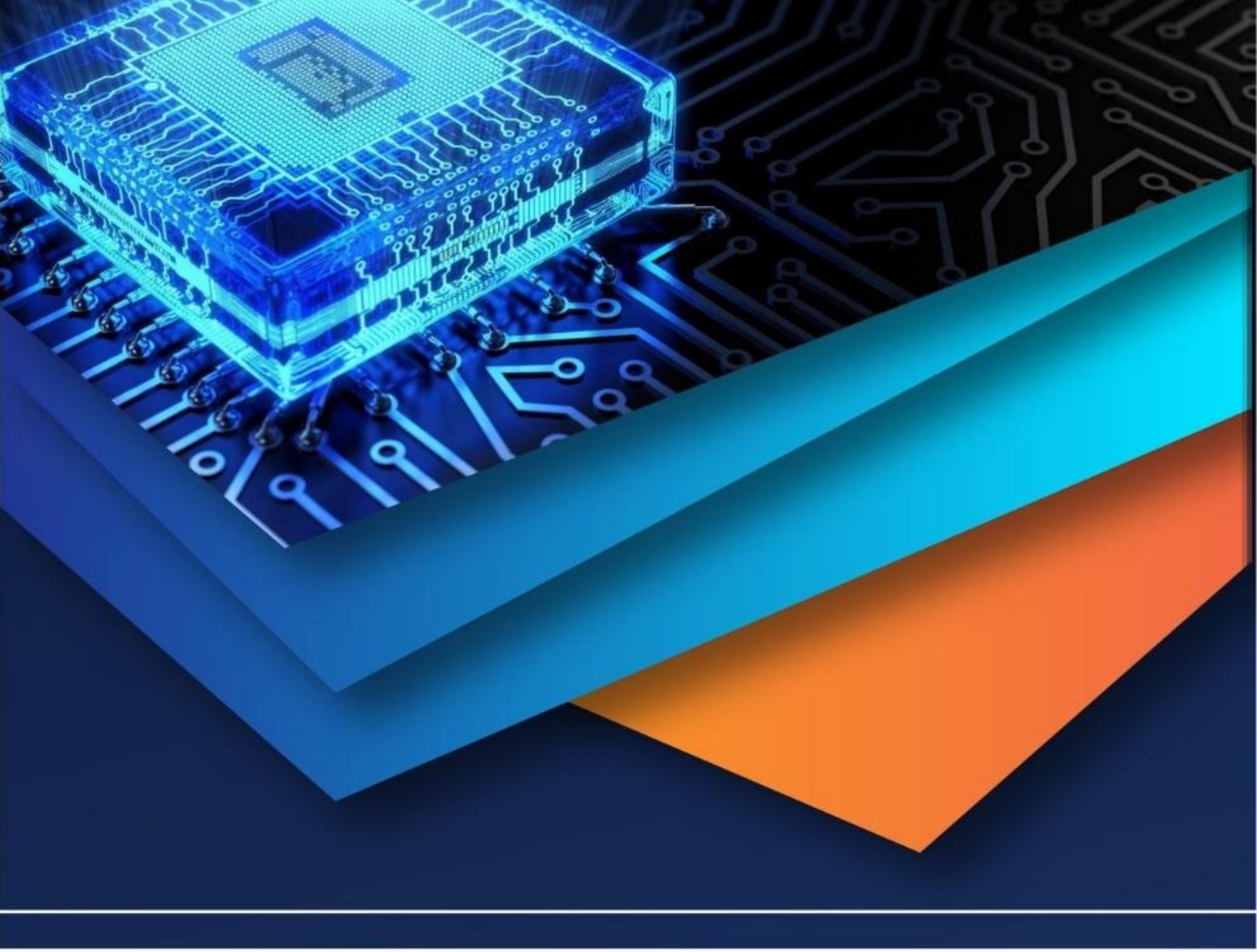

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