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Cancer's Natural Foe: Analysing the Devastating Impact Of Cancer And Unveiling The Anti-Cancer Potential Of Plant Compounds

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Abstract: In 2024, cancer remains a significant health challenge in India. The country sees over 1.5 million new cases a year. Breast and oral cancers are most prevalent among women and men, respectively. Sadly, many cases are diagnosed late, impacting survival rates. Improved awareness and access to healthcare are crucial. By 2030, cancer incidence is expected to surpass 1.7 million cases annually. Efforts to enhance prevention, early detection, and treatment access are crucial to mitigate this growing burden. The devastating effects of cancer and its impact globally is also explored in this research paper.

Natural products have long been a fertile source of cures for cancer, which is projected to become one of the major causes of death in this century. However, there is a continuing need for the development of new anticancer drugs, drug combinations, and chemotherapy strategies through the methodical and scientific exploration of the enormous pool of synthetic, biological, and natural products.

There are at least 2,50,000 species of plants, out of which more than one thousand have been found to possess significant anticancer properties. While many molecules obtained from nature have shown wonders, there are still a vast number of molecules that either remain untapped or have yet to be studied in detail by medicinal chemists. This paper reviews several such structures and their related chemistry, along with the recent advances in understanding the mechanisms of action and structure-function relationships of naturally derived anti-cancer agents at molecular, cellular, and physiological levels.

Index terms: **Cancer, anticancer drugs, chemotherapy strategies, natural products.**

INTRODUCTION

Cancer incidence rates are increasing at an alarming rate in India, and are anticipated to grow by 12% over the next five years. As a result, a detailed understanding of the current extent of the cancer problem is essential to developing a strategy for analyzing and regulating the impact of cancer across the country.
An assessment of the cancer burden in India attributed the increases to improved cancer diagnostics, cancer data gathering, and ongoing epidemiologic change. The incidence of tobacco-related, lifestyle-related, and aging-related cancers has grown over time in the tongue, mouth, colon, rectum, liver, lung, breast, corpus uteri, ovary, thyroid, prostate, gall bladder, pancreas, kidney, urinary bladder, brain and lymphoid leukemia. Meanwhile, cancer incidence rates have decreased in the hypopharynx, oesophagus, stomach, and cervix. Alcohol consumption (30.1%) was the most significant risk factor for pharyngeal cancer-related disability-adjusted life years (DALYs). Tobacco uses and air pollution (43% each) were risk factors for lung cancer DALYs, while dietary variables (43.2%) were associated with colorectal cancer.

Globally, the 65+ age group accounts for half of the cancer burden, whereas India accounts for one-third. However, half of the predicted cancer burden in India is among people aged 40 to 64. Childhood cancer affects 3% of boys and 1.8% of girls aged 0 to 14 years. The rural population in India reported a lower childhood cancer incidence rate, which could be attributable to underreporting. A study of teenage and young adult cancers found a considerable increase in incidence among males over time. The incidence of cancer cases is

expected to rise to 12.8% in 2025, compared to 2020. According to a recent NCRP (National Cancer Registry Programme**)** article, the cancer burden in India is expected to reach 29.8 million DALYs in 2025. (Alysha Mendossa, 2024)

In a healthy body, cells grow and divide to form new cells as needed. This process is tightly regulated by the body's systems. However, when this regulation fails, cells can grow uncontrollably, leading to cancer. Cancer can start almost anywhere in the human body, which is made up of trillions of cells. Normally, human cells grow and multiply (through a process called cell division) to form new cells as the body needs them. When cells grow old or become damaged, they die, and new cells take their place. Sometimes this orderly process breaks down, and abnormal or damaged cells grow and multiply when they shouldn't. These cells may form tumors, which are lumps of tissue.

Cancer cells differ from normal cells in many ways. For instance, cancer cells:

- grow in the absence of signals telling them to grow. Normal cells only grow when they receive such signals.
- ignore signals that normally tell cells to stop dividing or to die (a process known as programmed cell death, or apoptosis).
- invade into nearby areas and spread to other areas of the body. Normal cells stop growing when they encounter other cells, and most normal cells do not move around the body.
- tell blood vessels to grow toward tumors. These blood vessels supply tumors with oxygen and nutrients and remove waste products from tumors.
- hide from the immune system. The immune system normally eliminates damaged or abnormal cells.
- trick the immune system into helping cancer cells stay alive and grow. For instance, some cancer cells convince immune cells to protect the tumor instead of attacking it.
- accumulate multiple changes in their chromosomes, such as duplications and deletions of chromosome parts. Some cancer cells have double the normal number of chromosomes.
- rely on different kinds of nutrients than normal cells. In addition, some cancer cells make energy from nutrients in a different way than most normal cells. This lets cancer cells grow more quickly.

Cancer is caused by certain changes to genes, the basic physical units of inheritance. Genes are arranged in long strands of tightly packed DNA called chromosomes. The body normally eliminates cells with damaged DNA before they turn cancerous. But the body's ability to do so goes down as we age. This is part of the reason why there is a higher risk of cancer later in life. Each person's cancer has a unique combination of genetic changes. As the cancer continues to grow, additional changes will occur. Even within the same tumor, different cells may have different genetic changes.

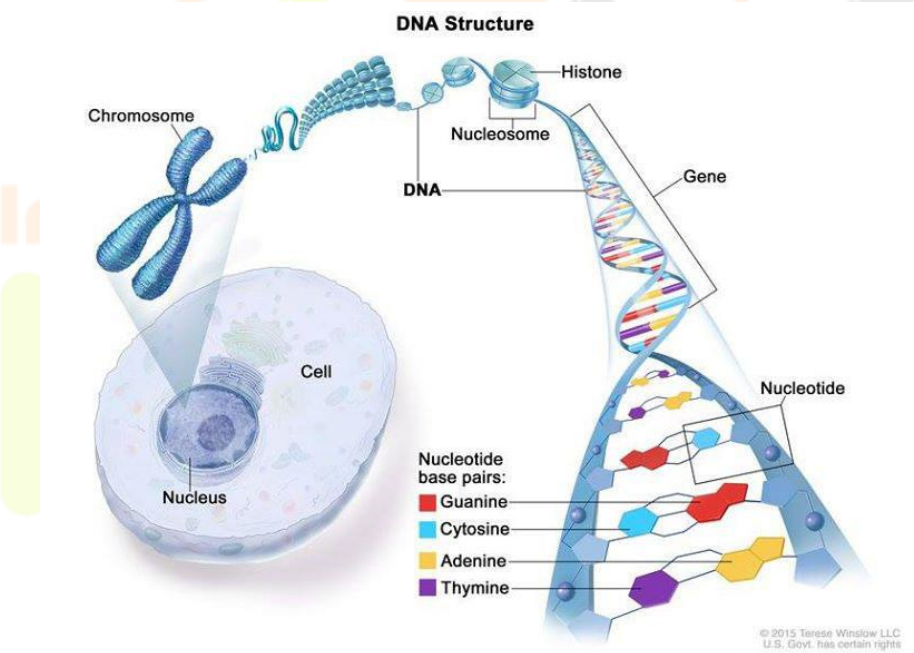


Figure 1: Long strands of tightly packed DNA (National Cancer Institute- What is Cancer?)

Many times, cancer cells rely so heavily on these abnormal behaviors that they can't survive without them. Researchers have taken advantage of this fact, developing therapies that target the abnormal features of cancer cells.
Cancer often begins with a genetic mutation in a cell's DNA. These mutations can be caused by various factors, including:

- Exposure to carcinogens (such as tobacco smoke, ultraviolet radiation, or certain chemicals)
- Genetic predisposition
- Random errors in DNA replication

As cancerous cells continue to divide and accumulate, they may form a mass called a tumor. Tumors can be benign (non-cancerous) or malignant (cancerous). Benign tumors typically do not invade surrounding tissues or spread to other parts of the body, while malignant tumors can invade nearby tissues and spread to other parts of the body. A cancer that has spread from the place where it first formed to another place in the body is called metastatic cancer. The process by which cancer cells spread to other parts of the body is called metastasis. (National Cancer Institute- What is Cancer?)

Metastatic cancer has the same name and the same type of cancer cells as the original, or primary, cancer. For example, breast cancer that forms a metastatic tumor in the lung is metastatic breast cancer, not lung cancer.

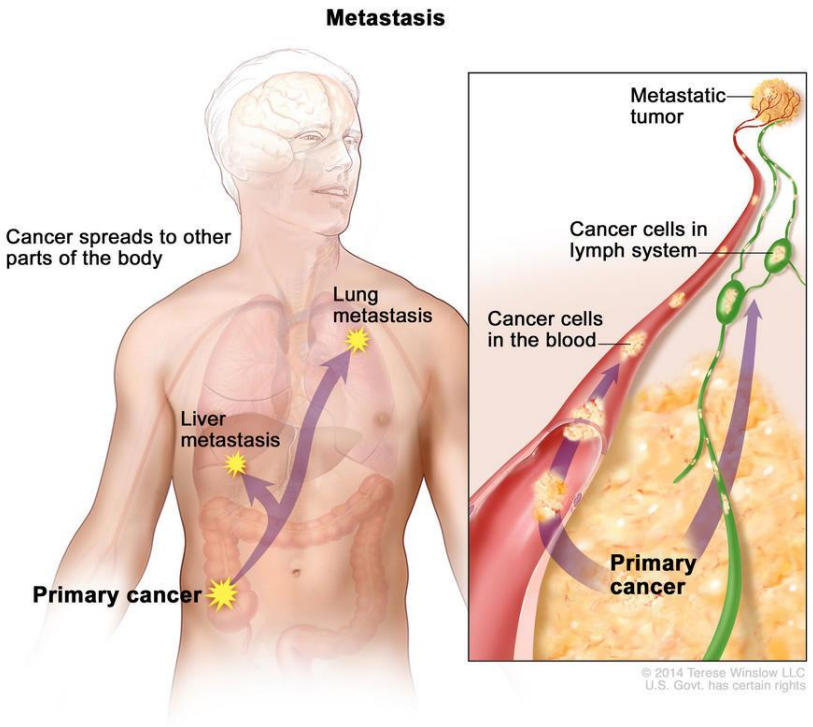


Figure 2: Metastasis (National Cancer Institute- What is Cancer?)

Symptoms of Cancer:

The symptoms of cancer vary depending on the type and location of the cancer. Common symptoms may include:

- Unexplained weight loss
- Persistent fatigue
- Changes in bowel or bladder habits
- Persistent cough or hoarseness
- Unexplained pain
- Presence of lumps or thickened areas in the body

Cancer is a large group of diseases that can start in almost any organ or tissue of the body when abnormal cells grow uncontrollably, invade adjoining parts of the body, and/or spread to other organs. This process of spreading is called metastasizing and is a major cause of death from cancer. A neoplasm and malignant tumor are other common terms for cancer.

Global Cancer Statistics:

Cancer is the second leading cause of death globally. Common types of cancer include:

- **In men:** Lung, prostate, colorectal, stomach, and liver cancer
- **In women:** Breast, colorectal, lung, cervical, and thyroid cancer

The cancer burden continues to grow globally, exerting tremendous physical, emotional, and financial strain on individuals, families, communities, and health systems. Many health systems in low- and middle-income countries are least prepared to manage this burden, and large numbers of cancer patients globally do not have access to timely, quality diagnosis and treatment. In countries with strong health systems, survival rates of many types of cancers are improving thanks to accessible early detection, quality treatment, and survivorship care. (World Health Organisation- Cancer Overview)

Cancer is not one disease, but a collection of related diseases that can occur almost anywhere in the body. At its most basic, cancer is a disease of the genes in the cells of our body. Genes control the way our cells work. But, changes to these genes can cause cells to malfunction, causing them to grow and divide when they should not—or preventing them from dying when they should. These abnormal cells can become cancer.

Understanding how genetic changes cause cancer is one way to understand this disease, while cancer statistics is another. Cancer statistics help scientists understand the burden of cancer on society. Statistics can tell us things such as how many people are diagnosed with and die from cancer each year and the number of people who are living after a cancer diagnosis. Changes in statistics over time can help scientists find areas where progress is needed. Cancer statistics also help scientists understand cancer health disparities. Examples of disparities include the higher cancer death rates, less frequent use of proven screening tests, and higher rates of advanced cancer diagnoses that are found in certain groups of people.

World Health Organisation releases latest global Cancer Data. The global cancer statistics, 2024, report from the American Cancer Society sheds light on world wide cancer facts, identifying trends and making predictions. Global cancer cases are predicted to rise by more than 75% by 2050, according to World Health Organisation. Cancer is the major contributor to global mortality, causing about 1 in every 6 deaths and affecting nearly every household. (Lydia Melisent, Cancer Global Statistics, 2024)

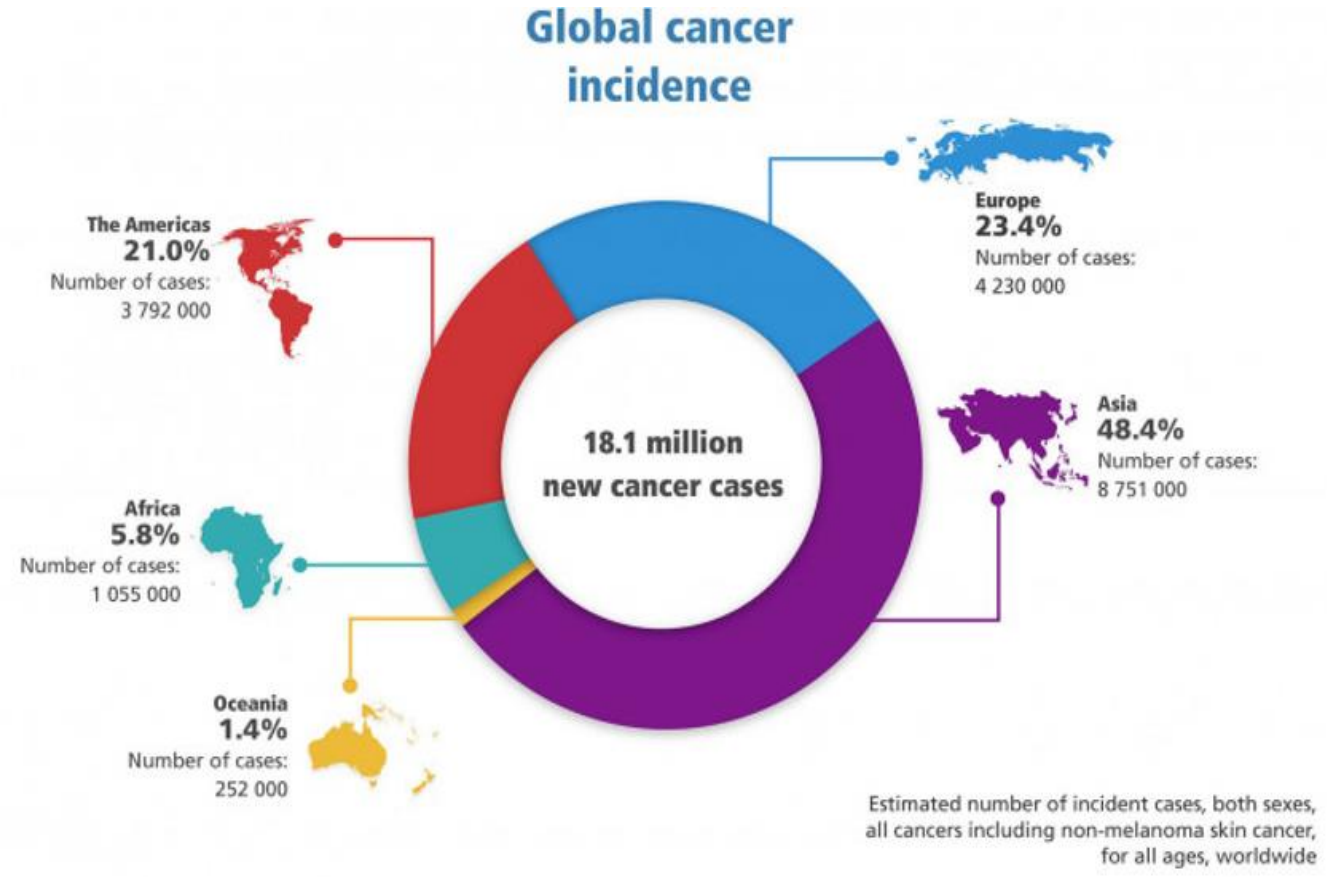


Figure 3: Global Cancer Incidence (Lydia Melisent, Cancer Global Statistics, 2024)

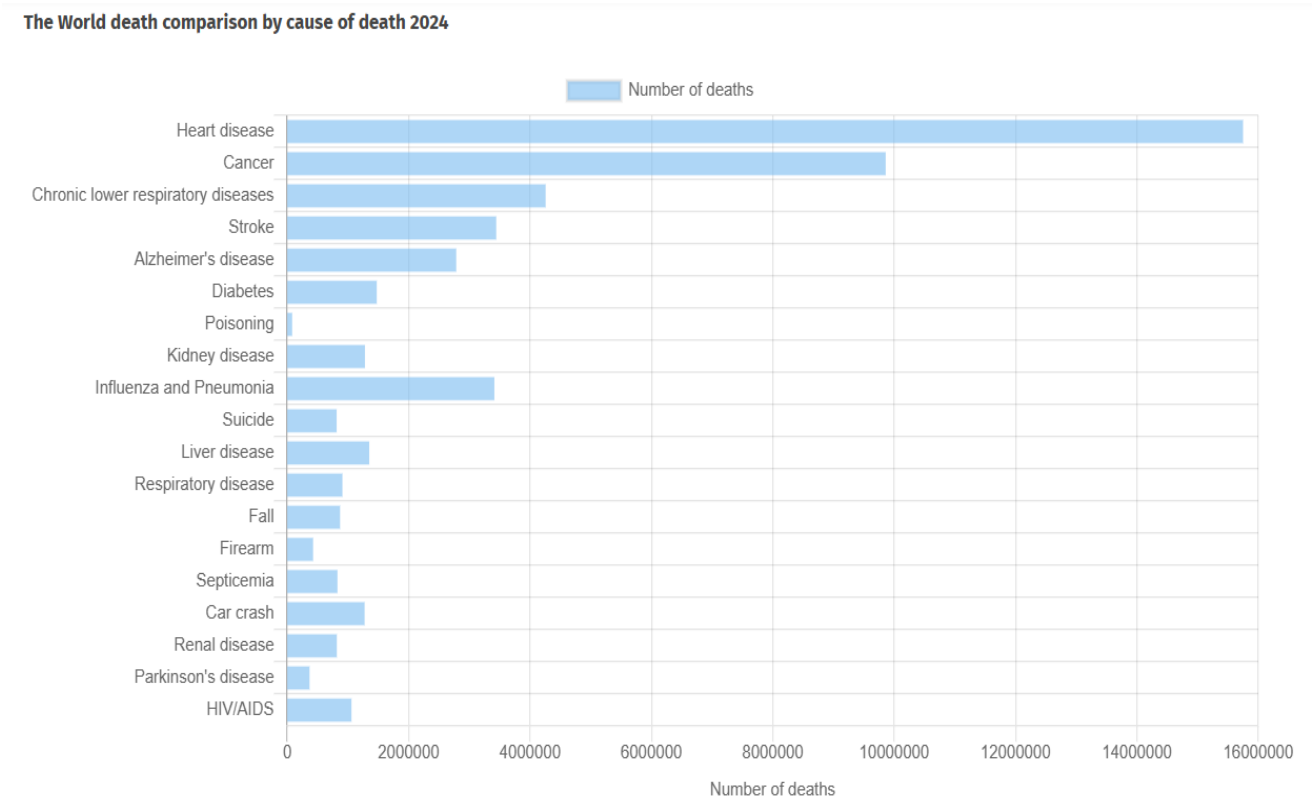


Figure 4: The World death comparison by cause of death 2024 (The World death statistics 2024)

Claims for hospitalisation under cancer saw the highest increase in incidence, with the number of cases rising by 12 per cent in 2024. In the case of cancer, the incidence- per cent of claims with respect to overall insured - has been observed to rise after the age of 40, with a steeper increase among women. "Women are observed to have a 1.2 – 1.5 times higher incidence rate with respect men, while data suggests that men have approximately a 1.3-1.5 times higher rate of cardiac ailments compared to women," Dhruv Rastogi, senior VP and Head of Data Science at MediAssist, said. (Mayur Shetty, January 2025)

Cancer is a significant health concern worldwide as explored earlier and India is no exception. As a nation, we are witnessing the rising incidence of several cancer types largely shaped by a combination of lifestyle and environmental factors. The top five most common cancers impacting Indians are explored to find the underlying reasons behind that. (India Today News, February 2024)

Breast Cancer:
Breast cancer is increasingly affecting younger women. Over half of the breast cancers in urban areas affect women younger than 50 years. Factors contributing to its high incidence include late marriages and childbirth, limited breastfeeding practices, and other lifestyle choices. Genetic predisposition also plays a role, with BRCA gene mutations being more prevalent in certain sections of Indian populations. Breast cancer does not affect women only but has a profound impact on their families and society as a whole. It is essential to understand the importance of regular breast self-examinations and screening mammograms for early detection and better treatment options.

Oral Cancer:
India is the oral cancer capital of the world, predominantly due to the rampant use of tobacco and alcohol. Smokeless tobacco, such as *gutka* and *paan* masala, is widely used and accounts for 90% of oral cancers. Poor oral hygiene practices and a diet low in fruits and vegetables further compound the problem. The high prevalence of oral cancer requires the urgent need for comprehensive tobacco control measures, including stricter regulations on the sale of tobacco products, public awareness campaigns, and easy access to smoking cessation programs.

Cervical Cancer:
Cervical cancer ranks high among women in rural India, primarily due to a lack of awareness and hygiene, limited access to healthcare facilities, and inadequate screening programs. Persistent HPV infection, early sexual activity, multiple partners and a lack of vaccination against HPV contribute to the high incidence. By vaccinating our youth, we not only protect the current generation but also pave the way for a healthier future where cervical cancer becomes increasingly rare.

Lung Cancer:
Lung cancer is closely linked to the rise in smoking habits, both in men and, increasingly, in women. Exposure to environmental pollutants and indoor air pollution from cooking fuels further elevates the risk, and we are seeing a significant number of lung cancer

patients who have never smoked. It is estimated that an average person in the National Capital Region (NCR) inhales environmental pollution that is equivalent to smoking 15 to 20 cigarettes daily. Delayed diagnosis is a significant concern, making early detection and smoking cessation crucial. The government needs to take proactive measures to curb air pollution. High-risk individuals like smokers, mine workers, should be subjected to regular screening for lung cancer.

Colorectal Cancer:
Colorectal cancer is on the rise in India, attributed to dietary shifts towards processed or junk food and reduced fibre intake. An inactive lifestyle, obesity, and genetic predisposition are other contributing factors. Promoting a balanced diet rich in fibre, regular physical activity, and routine screenings for those at risk can go a long way in preventing colorectal cancer.

The Importance of Awareness, Prevention and Early Detection

These top five cancers share a common thread – the potential for prevention and early detection. While genetic factors do contribute, lifestyle choices and environmental exposures are major contributing factors for up to 60-70% of cancers. Addressing the rising burden of cancer in India requires a multi-faceted approach involving public health campaigns about risk factors and lifestyle modifications, diligent implementation of tobacco control laws, nationwide screening programs and widespread access to quality healthcare.

Cancer may be a formidable adversary, but collaborative efforts by the government, healthcare providers, NGOs, and the community can develop effective strategies to prevent, detect, and manage cancers effectively. Let us unite in this cause for a healthier India by incorporating specific natural compounds found in certain foods into our daily diet.

PLANT COMPOUNDS

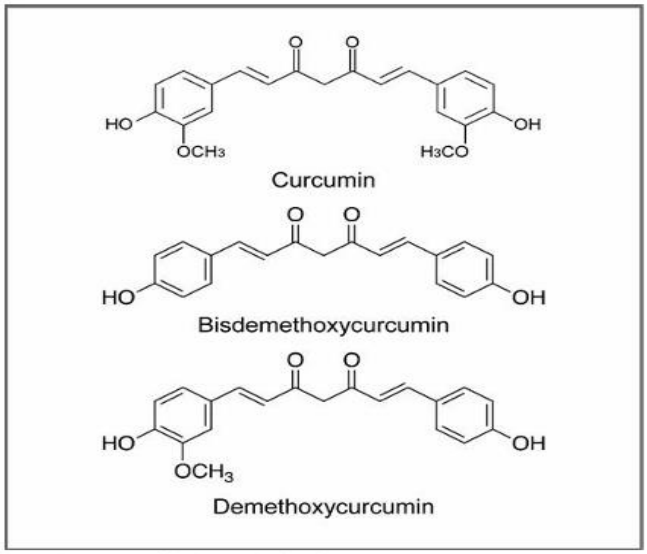
1] CURCUMIN (FOUND IN TURMERIC)

Curcumin, derived from ***Curcuma longa*** (turmeric), is a promising natural compound for cancer prevention. It modulates multiple molecular pathways involved in carcinogenesis and exhibits chemo-preventive effects through mechanisms such as promoting apoptosis, scavenging reactive oxygen species (ROS), and reducing inflammation. Despite its potential, curcumin's poor bioavailability limits its clinical application. Research continues to enhance its therapeutic efficacy through innovative delivery methods. (Wungki Park et al., May 2013)

Figure 5: Curcumin (Rebecca Park, 2018)

Mechanisms of Action:
- **Apoptosis Promotion**: Encourages programmed cell death in cancer cells.
- **Anti-inflammatory Effects**: Reduces inflammatory cytokines in the tumor microenvironment.
- **ROS Scavenging**: Neutralizes oxidative stress, which can lead to cancer progression.
- **Inhibition of Survival Signals**: Blocks pathways that promote cancer cell survival and proliferation.

Synergistic Applications:
1. **Prostate Cancer:** Combined with docetaxel, curcumin enhances therapeutic efficacy while reducing toxicity by modulating survival pathways such as NF-kB (Nuclear factor-kB).
2. **Hepatocellular Carcinoma**: In combination with metformin, curcumin suppresses tumor growth by targeting VEGF (vascular endothelial growth factor) and NF-kB pathways.
3. **General Chemotherapy**: Curcumin enhances the efficacy of drugs like doxorubicin and reduces multidrug resistance by inhibiting ABC transporters



Chemical structure of 3 polyphenols from *Curcuma longa*.

Figure 6: Chemical Structure of 3 polyphenols from *Curcuma longa* (Wungki Park et al., May 2013)

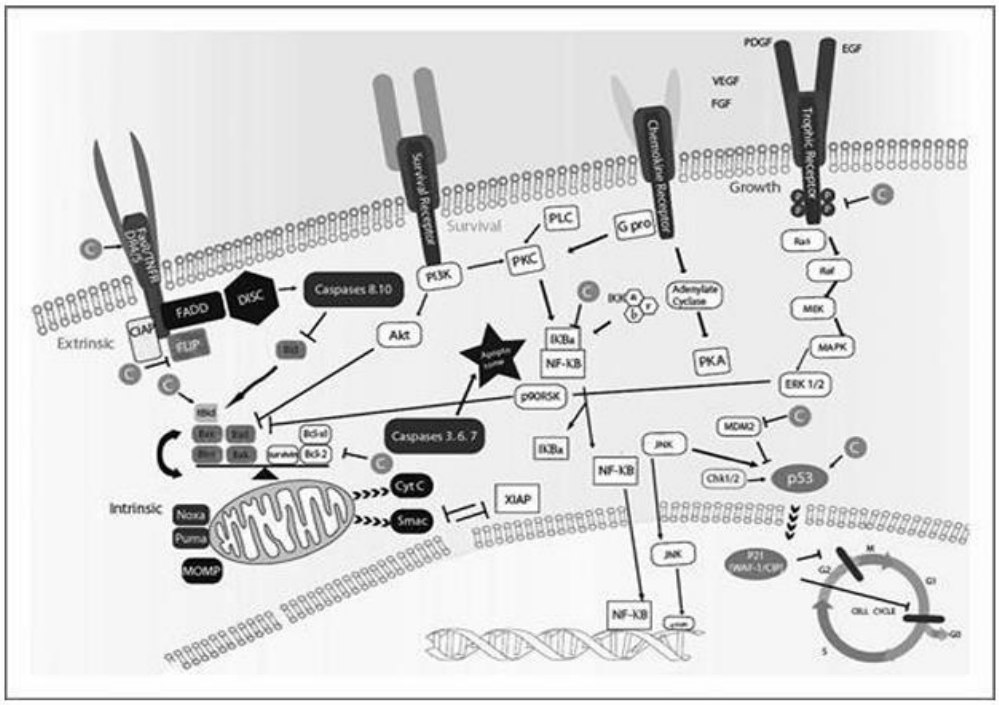


Figure 7: Molecular targets of curcumin. C, Curcumin; CIAP, cleavage inhibitor of apoptosis; FADD, Fas-associated protein with death domain; FLIP, FLICE-like inhibitory protein; DISC, death-inducing signaling complex; MOMP, mitochondrial outer membrane permeabilization; PKC, protein kinase C; PLC, phospholipase C; XIAP, X-linked inhibitor of apoptosis protein; VEGF, vascular endothelial growth factor; FGF, fibroblast growth factor; PDGF, platelet-derived growth factor; EGF, epidermal growth factor. (Wungki Park et al., May 2013)

Curcumin has been recognized to protect biomembranes against peroxidative damage. In general, lipid peroxidation is a free radical-mediated chain reaction that increased the damage of the cell membranes. Previous findings revealed that curcumin can inhibit the peroxidation through scavenging of reactive free radicals. The ability of curcumin confers greater protection against oxidative damage has been attributed to their functional groups, such as phenyl rings, carbon-carbon double bonds, and β-diketone group. (Bee Ling Tan and Mohd Esa Norhaizan, July 2019)

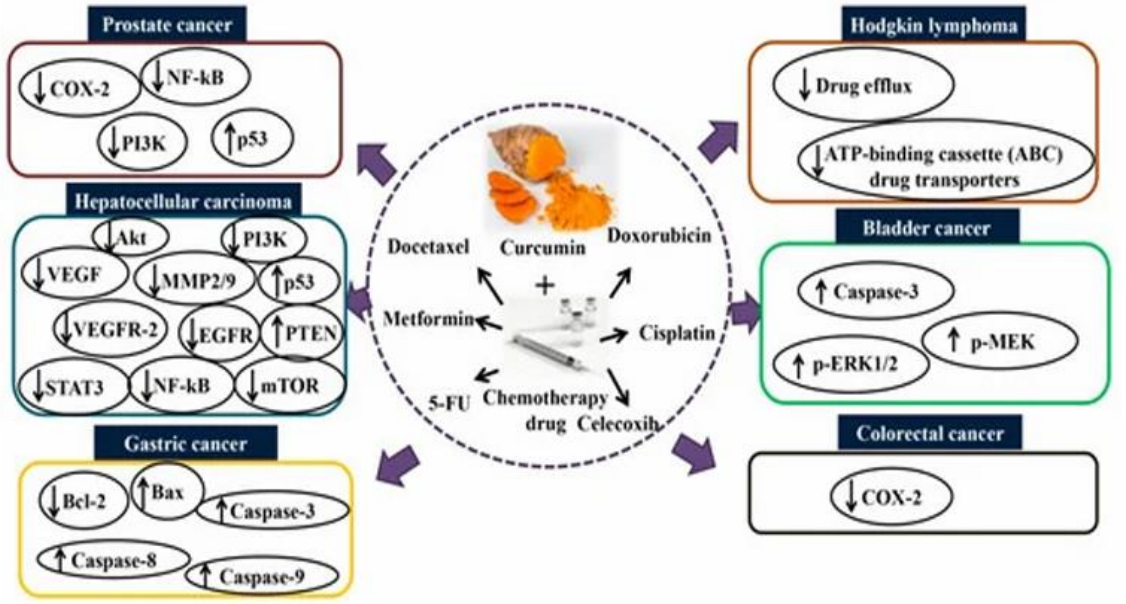


Figure 8: The Synergistic Effect of Curcumin Combination Chemotherapy (Bee Ling Tan and Mohd Esa Norhaizan, July 2019)

The figure explains the mechanisms of action of combination curcumin and chemotherapy drugs in vitro and in vivo. Co-treatment with curcumin and chemotherapy drugs such as docetaxel, metformin, 5-fluorouracil, doxorubicin, cisplatin, and celecoxib enhance the synergistic effect via modulating several signaling pathways and thus inhibit cancers such as prostate, hepatocellular, gastric, Hodgkin lymphoma, bladder, and colorectal. Akt: protein kinase B; COX-2: cyclooxygenase-2; EGFR: epidermal growth factor receptor; MMP2/9: matrix metalloproteinase-2/9; mTOR: mammalian target of rapamycin; NF-κB: nuclear factor kappa B; p-ERK1/2: phospho-extracellular signal-regulated kinase 1/2; PI3K: phosphoinositide 3-kinase; p-MEK: phospho-mitogen-activated protein kinase; STAT3: signal transducer and activator of transcription 3; VEGF: vascular endothelial growth factor; VEGFR2: vascular endothelial growth factor receptor 2. The combination of therapies with natural antitumor compounds was shown to enhance the effectiveness of drug treatment and decrease the toxic effect. (Bee Ling Tan and Mohd Esa Norhaizan, July 2019)

2] ELLAGIC ACID (FOUND IN BERRIES AND POMEGRANATES)

Ellagic acid is a naturally occurring polyphenolic compound found in fruits such as pomegranates, strawberries, raspberries, and blackberries. Known for its potent antioxidant and anti-inflammatory properties, ellagic acid has garnered significant attention for its anticancer potential. It inhibits tumor growth and induces apoptosis in various cancer cell types, making it a promising candidate for cancer prevention and therapy.

Figure 9: Foods rich in Ellagic acid (Adobe Stock)

Mechanisms of Action:

- **Antioxidant Activity:** Protects cells from oxidative damage by scavenging free radicals.
- **Induction of Apoptosis:** Triggers programmed cell death in cancer cells through caspase activation.
- **Anti-Angiogenic Properties:** Inhibits the formation of new blood vessels required for tumor growth.
- **Regulation of Gene Expression:** Modulates genes involved in cell cycle regulation and apoptosis, such as p53 and Bcl-2.

Applications in Cancer Treatment:

1. **Breast Cancer:** Ellagic acid suppresses estrogen receptor activity and inhibits the proliferation of hormone-dependent cancer cells.
2. **Colon Cancer:** Reduces tumor formation by modulating inflammatory pathways like NF-kB.

3. **Prostate Cancer:** Inhibits androgen receptor signaling, thereby reducing the growth of prostate cancer cells.

Synergistic Potential: Ellagic acid demonstrates enhanced anticancer activity when combined with other natural compounds like resveratrol and curcumin, as well as standard chemotherapeutic agents. This synergy improves therapeutic efficacy while minimizing side effects.

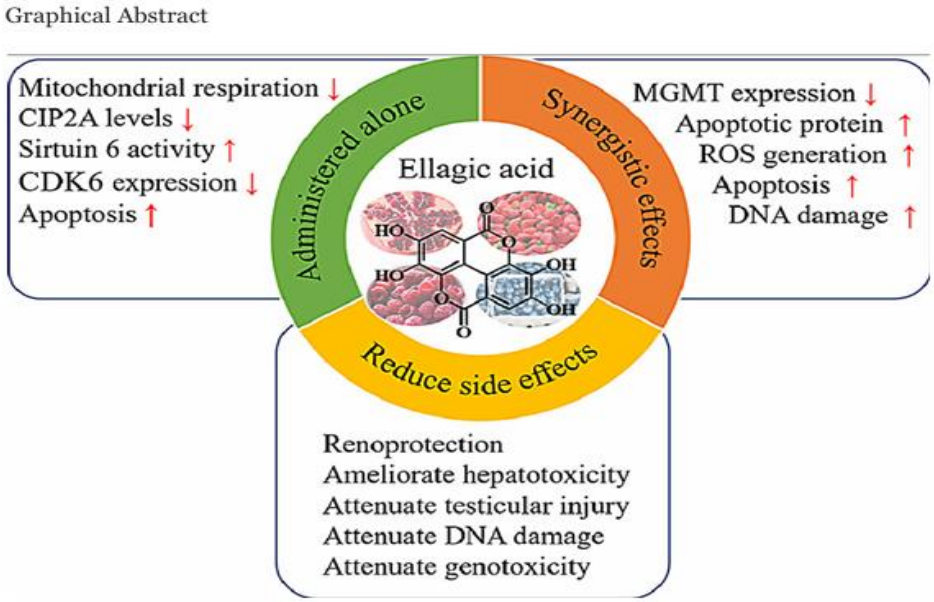


Figure 10: Effects of Ellagic Acids (Peiyu Xue et al., May 2022)

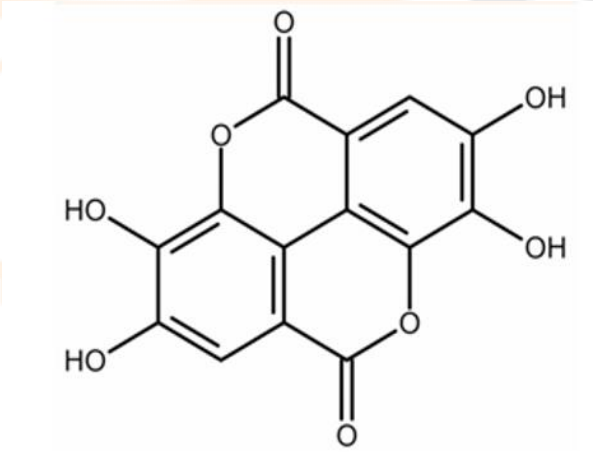


Figure 11: Structure of Ellagic Acids (EA)

EA's anti-inflammatory properties can influence the tumor microenvironment, making it more susceptible to radiation-induced cell death. It can potentially reduce inflammation-associated radio resistance, thereby enhancing the overall efficacy of radiotherapy. Many *in vitro* test results have shown that EA has anti-cancer activity, administered alone or in combination with radiotherapy/chemotherapy. (Peiyu Xue et al., May 2022)

3] BERBERINE (FOUND IN VARIOUS PLANTS LIKE GOLDENSEAL)

Berberine is a yellow-colored compound found in goldenseal root. Berberine, a natural plant-based alkaloid, shows promise as a therapeutic agent for breast cancer and other malignancies. Found in plants like *Berberis vulgaris* and *Coptis chinensis*, berberine inhibits cell proliferation and induces apoptosis in various cancer cell lines. Its anticancer effects are mediated through modulation of key signaling pathways, including MAP kinase and Wnt/β-catenin, which are critical for reducing cellular migration and growth factor sensitivity.

Figure 12: Goldenseal plant, flower and roots.

Mechanisms of Action:

- **Inhibition of Cell Proliferation:** Suppresses growth in breast, lung, colon, and liver cancer cells.
- **Apoptosis Induction:** Promotes programmed cell death via caspase activation.
- **Signaling Pathway Modulation:** Affects MAP kinase and Wnt/β-catenin pathways, reducing migration and sensitivity to growth factors.

Antioxidant/Oxidant Activity:

- **Antioxidant Effects:**
  1. **Scavenging Free Radicals:** Neutralizes reactive oxygen species to prevent oxidative damage.
  2. **Enhancing Antioxidant Enzymes:** Increases activity of enzymes like superoxide dismutase (SOD) and catalase.
  3. **Reducing Oxidative Stress:** Protects DNA, proteins, and lipids from oxidative damage.
- **Pro-Oxidant Effects:** At higher concentrations, berberine exhibits pro-oxidant activity, emphasizing the need for dose optimization.

Applications in Cancer Treatment:

1. **Breast Cancer:** Demonstrates efficacy in reducing tumor growth and improving outcomes in combination with other agents.
2. **Synergistic Effects:** Enhances the action of chemotherapeutics like vincristine and irinotecan while reducing toxicity.

Clinical Implications:

- **Cancer Prevention:** Berberine's antioxidant properties help prevent mutations leading to cancer.
- **Adjunct Therapy:** Its ability to mitigate oxidative stress complements conventional therapies, improving efficacy and reducing side effects.

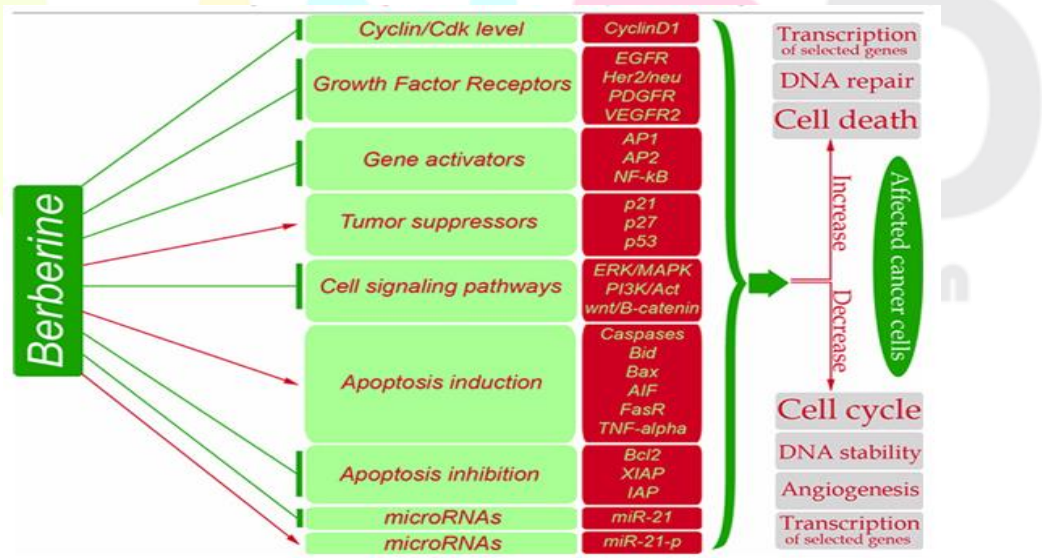


Figure 13: The effects of berberine on cancer cell (Parham J K. et al., October 2014)

● Berberine is a nitrogenous cyclic compound with a structure that is highly similar to that of intercalating agents (e.g., ethidium). Intercalating agents are often used as nucleic acid dyes to study cell functions, and berberine is a well-known alkaloid drug that is commonly used as a fluorescent dye. Berberine induces apoptosis and inhibits cell proliferation in various cell lines derived from breast, lung, colon, and liver cancer. However, berberine has been shown to have synergistic effects on cells treated in combination with more toxic drugs, including vincristine and irinotecan. Previous studies showed that the toxicity of vincristine towards hepatoma cells was reduced by combinatorial effects of berberine and cell resistance to drugs was decreased by combination treatments with berberine. (Parham J K. et al., October 2014)

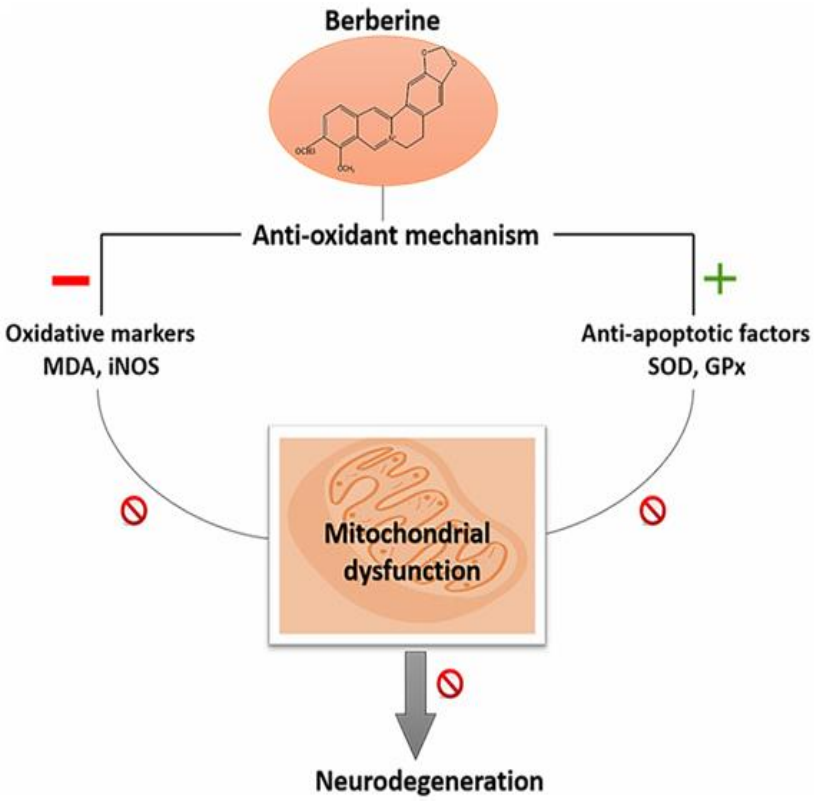


Figure 14: Schematic representation of antioxidant mechanism of berberine (Moazzama Akbar, September 2021)

4] PIPERINE (FOUND IN BLACK PEPPER)

Black pepper (Piper nigrum) is a widely used spice that has been used for centuries in traditional medicine. It's not only a common ingredient in cooking but also has medicinal properties known for centuries. One of the key bioactive compounds in black pepper is piperine, which is responsible for its characteristic pungent taste and aroma. Piperine exhibits notable anticancer properties. It inhibits cancer cell growth, induces apoptosis, and impairs metastatic processes. Research highlights its effectiveness in targeting triple-negative breast cancer (TNBC) cells and its potential as a complementary therapy to traditional treatments.

Figure 15: Piperine found in Black pepper (Codeage, Education, Blogs)

Mechanisms of Action:

1. **Anti-inflammatory Effects:** Reduces inflammation by inhibiting key factors and pathways linked to cancer development.
2. **Cell Cycle Arrest:** Inhibits progression in cancer cells, reducing proliferation and tumor growth.
3. **Induction of Cell Death:** Triggers apoptosis via mitochondrial pathways and caspase activation.
4. **Inhibition of Cancer Stem Cells:** Targets self-renewal pathways like Wnt /β-catenin, Hedgehog, and Notch.
5. **Anti-Invasion and Anti-Metastatic Effects:** Suppresses angiogenesis and reduces metastasis by downregulating matrix metalloproteinase-2 and -9 (MMPs) and vascular endothelial growth factor (VEGF).

Applications in Cancer Treatment:

- **Triple-Negative Breast Cancer:** Inhibits growth, cell migration, and tumor progression in TNBC models.
- **Combination Therapy:** Enhances the efficacy of γ-radiation and chemotherapeutic agents while reducing toxicity.
- **Cancer Prevention:** Prevents oxidative stress and inflammation, reducing cancer risk.

Clinical Significance:

- Piperine selectively inhibits cancer cells while sparing normal cells, suggesting a lower toxicity profile.
- Its dual role as a blocking and suppressing agent positions it as a promising candidate for future cancer therapies.

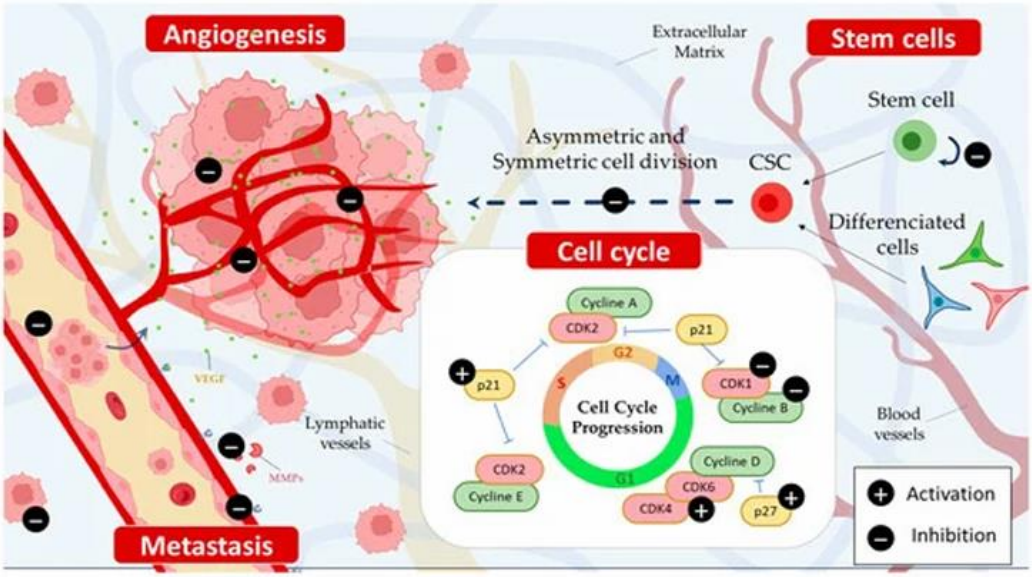


Figure 16: Piperine inhibits angiogenesis and metastasis by downregulating VEGF and MMP expression. It also impairs cancer stem cell self-renewal and induces cell cycle arrest at critical phases such as G1/S or G2/M.
(Salma Benayad, November 2023)

5] CATECHINS (FOUND IN GREEN TEA)

Catechins, particularly (−)-epigallocatechin-3-gallate (EGCG), found abundantly in green tea, have shown significant cancer-preventive activities in animal models and cell line studies. Catechins exhibit diverse mechanisms of action, including antioxidant and pro-oxidant properties, modulation of carcinogen metabolism, and interference with cancer signaling pathways.

Figure 17: Catechins found in green tea (Omad Diet, Blog)

Mechanisms of Action:

1. **Antioxidant Activity:** Catechins reduce oxidative DNA damage and quench reactive oxygen species (ROS) that contribute to carcinogenesis. In oxidative stress conditions, catechins display robust antioxidant effects.
2. **Pro-Oxidant Activity:** At high concentrations, EGCG generates ROS, inducing cancer cell apoptosis through mitochondrial pathways.
3. **Carcinogen Metabolism:** Modulation of enzymes via the Nrf2-mediated signaling pathway enhances cytoprotective enzyme expression.
4. **Inhibition of Cancer Pathways:** EGCG influences multiple cancer signaling pathways, targeting proteins like matrix metalloproteinases and vascular endothelial growth factors.

Applications in Cancer Prevention and Treatment:

1. **Epidemiological Insights:** Protective effects are evident against upper gastrointestinal cancers, particularly in non-smoking women. However, inconsistencies arise due to lifestyle differences and genetic variability.
2. **Animal Studies:** Demonstrate strong anti-tumor effects by inhibiting tumor growth and inducing apoptosis.
3. **Clinical Studies:** Evidence remains mild, suggesting the need for controlled trials to account for interfering variables.

Antioxidant and Pro-Oxidative Balance: Catechins maintain a dual role, acting as antioxidants under stress conditions but inducing pro-oxidative effects at higher concentrations. This delicate balance emphasizes the importance of dose optimization.

Safety Concerns: While EGCG supplementation enhances cytoprotective enzyme expression, excessive doses can lead to hepatotoxicity, similar to liver toxicity reported with high tea extract consumption for weight loss.

Tea catechins, such as EGCG, have been shown to reduce reactive oxygen species (ROS) such as superoxide radical, singlet oxygen, hydroxyl radical, peroxyl radical, nitric oxide, nitrogen dioxide and peroxynitrite. Among tea catechins, EGCG is most effective in reacting with the majority of ROS. Tea polyphenols are also strong chelators of metal ions such that the chelation of free metal ions prevents the oxidation of catechins and the formation of ROS. The vicinal dihydroxy or trihydroxy structures not only contribute to the antioxidant activity of tea catechins, but also increase their susceptibility to air oxidation under alkaline or neutral pH, especially in the presence of trace amounts of cuprous or ferric ion. (Chung S. Yang and Hong Wang, December 2016)

EGCG is known for its antioxidant effects, and it functions as an antiproliferative agent. Furthermore, there is evidence that EGCG functions synergistically against cancer cell proliferation in joint treatment with anticancer drugs such as enoxacin. Epigallocatechin gallate treatment causes down regulation of genes involved in the stimulation of adhesion, proliferation invasion and motility processes, and also play a lead role in the enhancement of numerous genes identified as having antagonist effects. Time-dependent exposure to Epigallocatechin gallate resulted in the reactivation of known tumor-suppressor genes in cancer cells due to marked changes in the methylation of the promoter regions of these genes. (Saleh A. A. et al., July 2020)

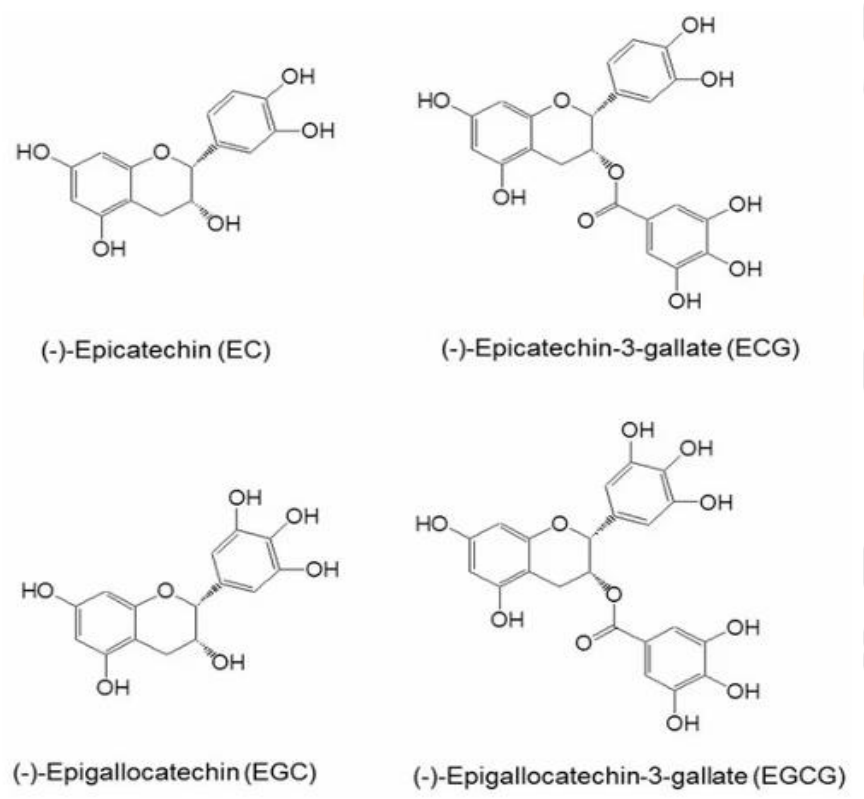


Figure 18: Structures of (−)-epigallocatechin-3-gallate (EGCG), (−)-epicatechin-3-gallate (ECG), (−)-epigallocatechin (EGC), and (−)-epicatechin (EC). (Chung S. Yang and Hong Wang, December 2016)

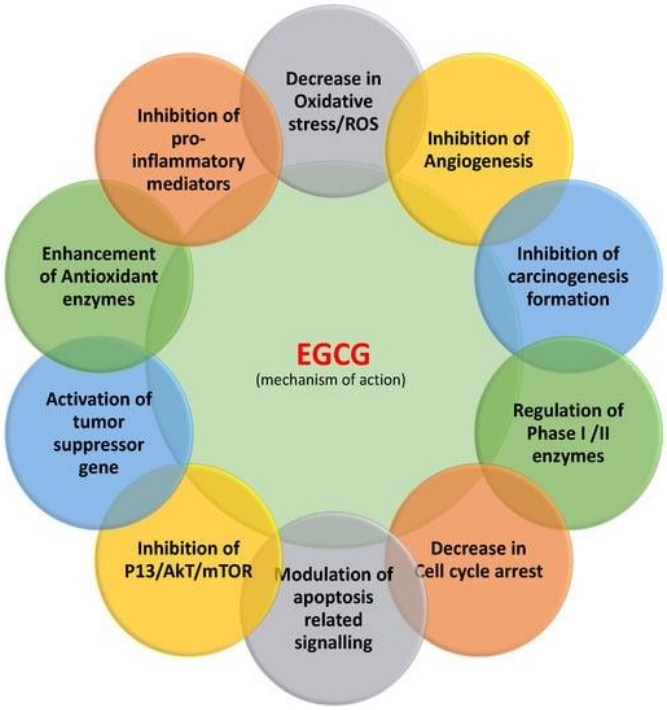


Figure 19: Mechanism of action of EGCG in cancer management through modulating various cell signaling pathways (Saleh A. A. et al., July 2020)

6] CAROTENOIDS (FOUND IN ORANGE COLOURED FRUITS AND VEGETABLES)

Carotenoids are a diverse group of over 600 fat-soluble pigments found in plants. These compounds can protect the skin from UV damage by scavenging harmful singlet molecular oxygen. Major carotenoids include β-carotene, lycopene, and lutein. Carotenoid levels in human skin can vary, with higher concentrations on the forehead compared to other areas. Oxidative stress, such as from smoking, can decrease these levels, while UV exposure also reduces carotenoids in both plasma and skin.

Figure 20: Foods that are high in carotenoids (Jessie Szalay, October 2015)

Animals cannot manufacture carotenoids themselves; they have to get it in their diets. Carotenoids need to be consumed with a fat in order for the body to absorb them. According to the Linus Pauling Institute at Oregon State University, carotenoids need to leave the food they came in and become part of mixed micelles, which are combinations of bile salts and lipids. The presence of a fat makes this process possible. β-Carotene, a red-orange pigment, is a precursor to vitamin A and a potent antioxidant. It inhibits free radicals and singlet oxygen-induced lipid peroxidation in liposomes and biological systems. As a photoprotective agent, β-carotene can quench photochemical reactions involving singlet oxygen and radicals generated by UV exposure, offering protection against UV-induced damage. (Jessie Szalay, October 2015)

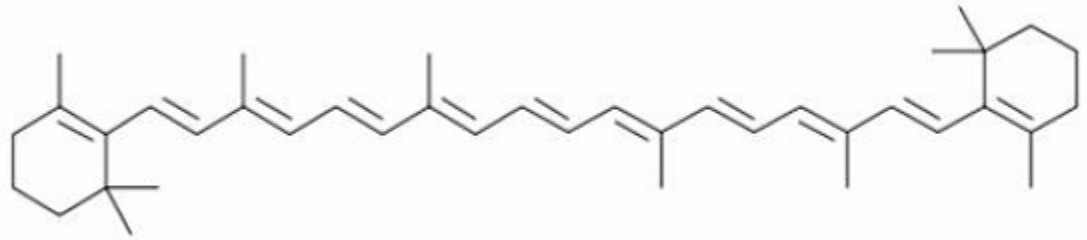


Figure 21: Chemical structure of β-carotene (Julie A. E. and Elizabeth J. J., August 2010)

The exceptional antioxidant properties of carotenoids channelize and orchestrate important pathways in animals, including photoprotection, cardiovascular protection, immunoprotection, anti-aging, cellular membrane stabilization, and oxidative stress modulation. In recent years, natural products have reemerged as biotherapeutic options, with several dietary carotenoids, viz. astaxanthin, fucoxanthin, siphonaxanthin, β-cryptoxanthin, α-carotene, β-carotene, and lycopene, developing as potential candidates for chemoprevention and chemotherapeutics of breast, colorectal, lung, and prostate cancers. The potent cytotoxic and antiproliferative effects of carotenoids against various cancer cells are mediated by a wide range of molecular mechanisms modulating oxidative stress and redox balance, mitogen-activated protein kinases (MAPK) and other cellular signaling proteins, transcription factors, caspase cascade pathways of apoptosis, cell cycle progression and proliferation, angiogenesis, metastasis, gap junction intercellular communication (GJIC), and multidrug resistance (MDR). This review discusses recent evidence demonstrating the crucial roles of carotenoids in these cellular and molecular events of cancer cell cytotoxicity. In addition, recent case-control and cohort studies are discussed to support the potential role of carotenoids in cancer prevention and therapy. (Ramesh K.S. et al., July 2020)

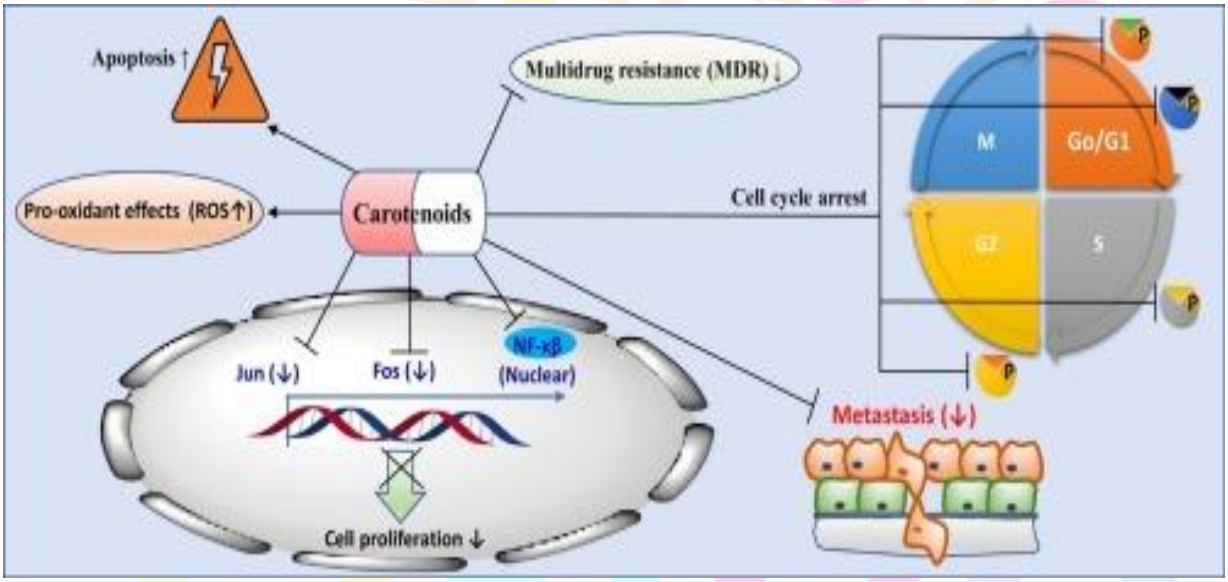


Figure 22: Effects of Carotenoids (Ramesh K.S. et al., July 2020)

7] GENISTEIN (FOUND IN SOYABEAN)

Soy isoflavones, particularly genistein, have been linked to reduced incidences of breast and prostate cancers, especially in Asian countries. Genistein is one of the numerous recognized isoflavones that may be found in a variety of soybeans and soy products, including tofu and tofu products. It inhibits carcinogenesis in animal models and human cancer cell growth. It modulates genes controlling the cell cycle and apoptosis, and inhibits NF-kB and Akt signaling pathways that regulate cell survival and apoptosis. Additionally, genistein antagonizes estrogen- and androgen-mediated signaling in carcinogenesis. With antioxidant properties, it inhibits angiogenesis and metastasis. Genistein shows promise in cancer chemoprevention and therapy, including reversing radio- and chemoresistance.

Figure 23: Genistein found in soyabean

Decades of research have shown that isoflavones, found in soy-rich diets, contribute to the lower rates of breast and prostate cancers observed in Asian countries like China and Japan. Genistein, the primary isoflavone in soy products, has been associated with reduced cancer risks in both pre- and postmenopausal women in Asia, though not in Western women. Studies also indicate that migration to Western countries leads to an increase in cancer incidence, suggesting that diet plays a significant role in cancer etiology. Genistein is effective in sensitizing cancer cells to radiotherapy and chemotherapy, creating new possibilities for cancer treatment.

Genistein and Cancer: Several epidemiological studies suggest a protective effect of soy isoflavones like genistein against breast and prostate cancer. This is particularly evident in Asian countries where soy consumption is high. Genistein's anticancer activity is attributed to its effect on various cancer types, including thyroid, pancreatic, breast, esophageal, liver, prostate, lung, cervical, and ovarian cancers. It blocks tumor formation and induces apoptosis in cancer cells, with its potency varying depending on the cancer type and the molecular target. Genistein also influences cellular signaling pathways, making it a potential adjunct in cancer therapy.

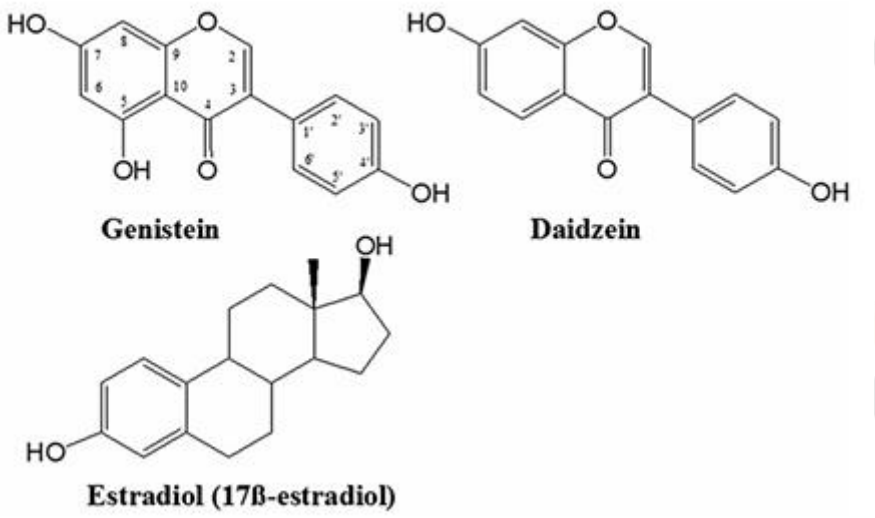


Figure 24: Chemical structure of genistein (Shenglin Hou, June 2022)

Genistein Anti-Cancer Activity: Genistein and related isoflavones inhibit the development of malignancies in various cancers. Studies have shown its effectiveness in preventing the division of cancer cells in vitro, with genistein inducing apoptosis in leukemia and other cancers. It also suppresses tumor development in animal models. Below is a summary of genistein's use against different cancer cell lines:

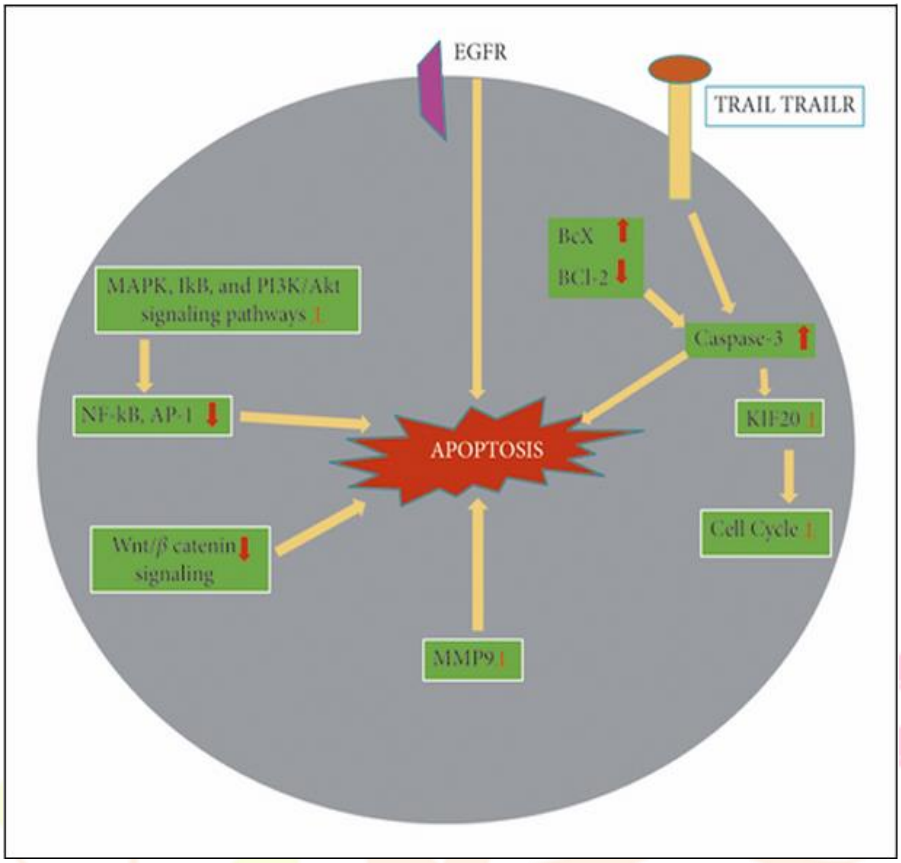


Figure 25: Summary of genistein's use against different cancer cell lines (Shenglin Hou, June 2022)

8] ALLICIN (FOUND IN GARLIC)

Allicin, a sulfur compound in garlic, has potent anticancer properties. It suppresses tumor growth across various types by targeting multiple molecular mechanisms such as DNA damage protection, apoptosis induction, and inhibition of cell proliferation and metastasis. Garlic has long been valued for its health benefits, including cancer prevention. Allicin is the key active compound, known for its ability to fight different cancers, such as leukemia, breast, lung, and prostate cancer.

Figure 26: Allicin found in Garlic (Cookist: Editorial team)

Mechanisms of Action

Allicin acts through several mechanisms:

- **DNA Protection**: Antioxidant effects that protect DNA.
- **Cell Death**: Promotes apoptosis in cancer cells.
- **Cell Proliferation**: Inhibits tumor cell growth.
- **Angiogenesis Blockage**: Prevents cancer spread by inhibiting new blood vessel formation.

In Vivo Studies

Animal studies show allicin reduces tumor burden in models like cholangiocarcinoma and colon cancer. Its mechanism involves modulating key signaling pathways such as STAT3.

Combination Therapy
Allicin enhances the effectiveness of other anticancer agents, potentially reducing toxicity and overcoming chemoresistance.

Selectivity Toward Tumor Cells
Allicin selectively targets tumor cells, making it a promising candidate for cancer treatment with minimal side effects. Those who regularly consume raw garlic are 44% less likely to get cancer, and this would also work on smokers, reducing the risk, in this case by 30%. (Cookist: Editorial team)

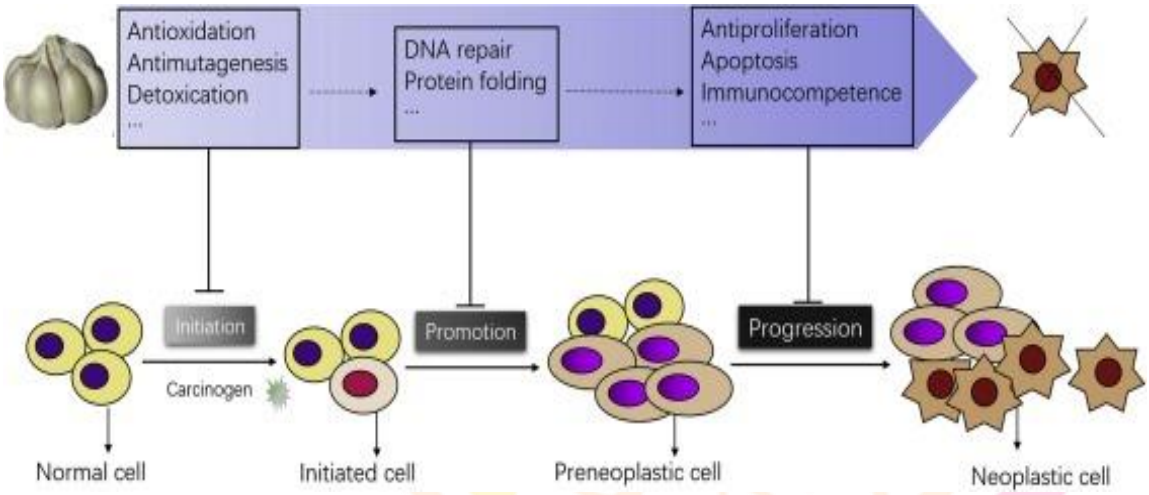


Figure 27: Anti-carcinogenic effect of garlic bioactive compounds in different stages of cancer progression. (Yan Zhang, March 2020)

In the initiation stage, blocking phytochemicals prevents the bioactivation of carcinogens through antioxidation, antimutagenesis and detoxication. In the promotion stage, suppressing phytochemicals inhibits the proliferation of clonal cells by modulating protein folding and DNA repair. In the progression stage, suppressing phytochemicals impedes the growth or metastasis of tumors by changing the cell behaviors, including antiproliferation, apoptosis and immunocompetence. (Yan Zhang, March 2020)

9] GINGEROL (FOUND IN GINGER)

Ginger, rich in compounds like gingerol, paradol, and shogaol, has shown promising anti-cancer, anti-inflammatory, and antioxidant effects. Cervical cancer, a leading gynecological cancer, is linked to factors like HPV infection, smoking, and immune dysfunction. Although surgery, chemotherapy, and radiotherapy are common treatments, they have significant side effects. The therapeutic potential of ginger in treating cervical cancer is widespread.

Figure 28: Gingerol found in Ginger (Knowledge Blogs, 2019)

Cervical cancer is the fourth most common cancer in women globally, with higher mortality rates in developing countries. Risk factors include Human Papillomavirus (HPV) infection, smoking, and immune dysfunction. While chemotherapy and surgery are primary treatments, they can have adverse effects. Alternative therapies with fewer side effects are being explored, and ginger has gained attention due to its anticancer properties.

Mechanisms of Action

Ginger compounds, especially gingerol, have been shown to:

- **Antioxidant Effects**: Protect cells from oxidative damage.
- **Anti-inflammatory Effects**: Reduce inflammation, a key factor in cancer progression.
- **Anti-cancer Properties**: Inhibit tumor growth, angiogenesis, and metastasis. Gingerol has demonstrated effectiveness in treating cervical, colorectal, pancreatic, and breast cancers by targeting various cancer pathways.

Ginger: Components

Ginger contains essential compounds like gingerols (e.g., 6-gingerol), shogaols, and oleoresin. These compounds exhibit multiple therapeutic effects, including anti-cancer, anti-inflammatory, and antioxidant properties. 6-gingerol is the most studied compound, known for its tumor-preventive effects, pain-relief, and cardiotonic properties.While extensive clinical trials on ginger's therapeutic effects exist, studies on its pharmacokinetics (absorption and efficacy of active compounds) in humans are lacking. Thus, the exact concentrations of gingerols and shogaols in the body and their therapeutic effectiveness remain underexplored.

This natural compound reduces cancer cell proliferation, arrests cell cycle, causes an imbalance in cellular redox homeostasis, and induces cell death. Additionally, ginger derivatives inhibit angiogenesis, EMT, and CSCs. Furthermore, they decrease multidrug resistance and enhance chemopreventive effects. ginger derivatives could play an important role in maintaining redox homeostasis: In some cases, by decreasing the quantity of ROS-induced tumor-promoting events, and in other cases, in contrast, by increasing oxidative stress and provoking cell death. Also, ginger derivatives seem to be potent anti-angiogenic substances that point to a possible role in preventing cancer from becoming malignant, presumably by selective inhibition of neovessel formation in tumor sites. (Mariia Zadorozhna and Domenica Mangieri, June 2021)

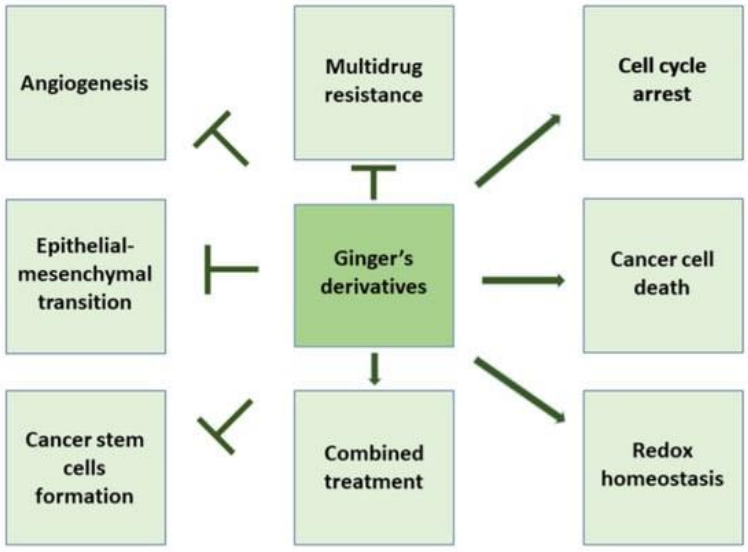


Figure 29: Schematic anti-cancer action of ginger and its phenolic derivatives
(Mariia Zadorozhna and Domenica Mangieri, June 2021)

10] LYCOPENE (FOUND IN TOMATOES)

Lycopene is a natural pigment produced by plants and microorganisms, acting as a powerful antioxidant. It plays a role in influencing cell growth and communication. Several mechanisms are proposed for its potential cancer-fighting properties, including inhibiting cancer cell growth, preventing DNA damage, and enhancing the breakdown of cancer-causing substances. Consuming lycopene or tomato juice has not been found to stimulate the immune system, but diets rich in carotenoids, like lycopene, are associated with a reduced risk of macular degeneration, cataracts, certain cancers, and heart disease. Lycopene protects against many chronic conditions. Chronic conditions include cancer, heart disease, male infertility, and cognitive decline. It is an antioxidant. It fights free radicals in the body. Lycopene is a member of the carotenoid family. It contributes to some fruits and vegetables' red and orange colours. Lycopene is high in the antioxidant potential of all carotenoids. It is also known as a non-provitamin A carotenoid. Our body is not able to convert it to vitamin A. It benefits our health by protecting us from oxidative damage. We find lycopene in the liver, testes, adrenal glands, and fatty tissues. There are lower kidney concentrations, ovaries, lungs, and prostate concentrations. Our body cannot manufacture lycopene, and its source is plant foods. Lycopene only occurs in plants. (Evidence-based whole foods, plant-based lifestyle- Blog, October 2023)

Figure 30: Lycopene found in tomatoes (Evidence-based whole foods, plant-based lifestyle- Blog, October 2023)

Mechanism of Action: Lycopene's cancer-preventive actions are linked to inhibition of cancer growth, modulation of cell cycles regulatory proteins, prevention of oxidative DNA damage, and enhancement of enzymes that break down carcinogens. In liver cancer cells, lycopene has shown anti-metastatic effects by downregulating NADPH oxidase 4, which produces reactive oxygen species (ROS). Other possible effects include immune enhancement and reduced risk of mutagenesis, transformation, and premalignant lesions. Lycopene's synergy with other treatments, such as docetaxel, is proposed through inhibition of IGF-I signaling and reduced levels of survivin, a protein associated with cancer cell survival.

Clinical Summary: Lycopene is primarily used for its antioxidant properties and in the prevention and treatment of cancer, heart disease, and macular degeneration. While some small trials suggest lycopene's potential in treating exercise-induced asthma and benign prostatic hyperplasia, no optimal dosage has been established.

Epidemiological studies suggest a reduced risk of cancers, particularly lung, stomach, prostate, and hormone-positive breast cancers, associated with lycopene consumption. The reported mechanisms of lycopene action in vivo included regulation of oxidative and inflammatory processes, induction of apoptosis, and inhibition of cell division, angiogenesis, and metastasis formation. The predominance of particular mechanisms seemed to depend on tumour organ localisation and the local storage capacity of lycopene. Aleksandra K. et al., December 2022)

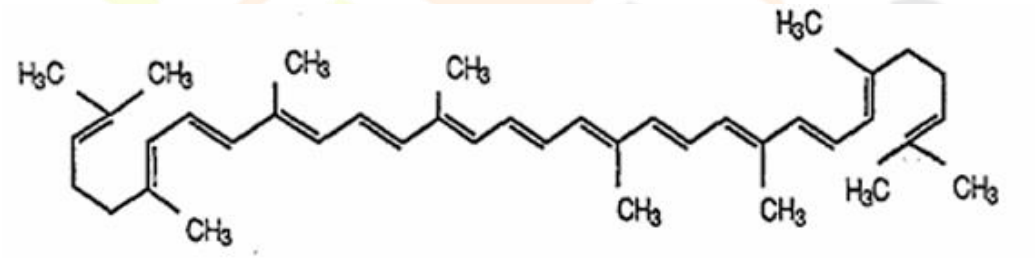


Figure 31: Chemical structure of Lycopene

Table 1: Plant Compounds and Their Impact on Cancer Treatment Duration

Plant Compound	Cancer Type	Normal Treatment Duration	Treatment Duration with Addition of Plant Compounds
Curcumin	Prostate, Breast, Colon, Pancreatic	6-12 months (chemotherapy/radiation)	3-6 months (faster tumor shrinkage, reduced chemotherapy cycles)
Ellagic Acid	Breast, Prostate, Colon, Skin	6-12 months (chemotherapy/radiation)	4-7 months (delays cancer progression, lowers recurrence rates)
Berberine	Colorectal, Liver, Pancreatic	6-9 months (chemotherapy/radiation)	4-6 months (reduced toxicity, quicker tumor response)
Piperine	Lung, Breast, Colon, Pancreatic	6-9 months (chemotherapy/radiation)	3-6 months (enhanced bioavailability of chemotherapy drugs)
Catechins	Prostate, Liver, Colon	6-12 months (chemotherapy/radiation)	4-8 months (improved tumor response, lower recurrence)

Beta-carotene	Lung, Breast, Prostate, Skin	6-12 months (chemotherapy/radiation)	5-8 months (reduced side effects, enhanced tumor suppression)
Genistein	Prostate, Breast, Colon, Lung	6-12 months (chemotherapy/hormone therapy)	4-7 months (synergistic effects, improved treatment response)
Allicin	Stomach, Colon, Lung, Liver	6-9 months (chemotherapy/radiation)	4-6 months (enhanced apoptosis and better chemotherapy outcomes)
Gingerol	Ovarian, Colon, Lung	6-12 months (chemotherapy/radiation)	4-7 months (increased apoptosis, improved chemotherapy efficiency)
Lycopene	Prostate, Lung, Breast, Endometrial	6-12 months (chemotherapy/radiation)	5-8 months (enhanced response, reduced side effects in chemotherapy)

Observations from the above table:

1. **Curcumin:** Typically, chemotherapy can last around 6-12 months, but with the addition of curcumin, the tumor responds faster, which can reduce the treatment cycle to 3-6 months. Curcumin enhances chemotherapy's effects and decreases side effects, allowing quicker treatment completion.

2. **Ellagic Acid:** Ellagic acid has been observed to delay tumor progression, leading to reduced recurrence and potentially shortening the duration of treatment. Typically, patients undergoing chemotherapy for 6-12 months could see results within 4-7 months with the addition of ellagic acid.

3. **Berberine:** Known to enhance chemotherapy effectiveness, berberine reduces the need for prolonged treatment cycles. Instead of the usual 6-9 months, patients may experience improvements in 4-6 months when combined with conventional cancer therapies.

4. **Piperine:** Piperine increases the bioavailability of chemotherapy drugs, making treatments more effective in a shorter time. With its addition, treatment durations may reduce to 3-6 months compared to the usual 6-9 months.

5. **Catechins:** These compounds, primarily found in green tea, have been shown to improve the response of tumors to chemotherapy. Therefore, the duration of chemotherapy may be reduced to 4-8 months from the typical 6-12 months.

6. **Beta-carotene:** The antioxidant effects of beta-carotene help in reducing side effects and improving the body's response to cancer treatment. Treatment may be shortened to 5-8 months compared to the usual 6-12 months.

7. **Genistein:** This is particularly useful in breast and prostate cancers, working synergistically with chemotherapy or hormone therapy. It has shown to improve the treatment response and can reduce the necessary treatment duration to 4-7 months.

8. **Allicin:** Known for its anticancer properties, allicin enhances apoptosis and boosts chemotherapy's effects, resulting in reduced treatment cycles of 4-6 months compared to 6-9 months.

9. **Gingerol:** Gingerol has been shown to reduce tumor growth and enhance the effects of chemotherapy, potentially shortening treatment duration from the usual 6-12 months to around 4-7 months.

10. **Lycopene:** Lycopene is particularly effective in prostate cancer, and when used alongside chemotherapy, it can reduce the duration of treatment to 5-8 months from the typical 6-12 months.

These durations are approximations based on current research and clinical observations, and results can vary significantly based on individual patient responses and cancer progression stages. Further clinical trials are necessary to establish more precise treatment durations with plant compounds.

CONCLUSION

In conclusion, cancer is a devastating disease that affects millions of lives, causing severe physical, emotional, and financial burdens. While conventional treatments like chemotherapy and radiation often lead to harmful side effects, plant-based products offer a promising alternative. With their natural compounds, medicinal plants provide effective cancer-fighting properties while causing minimal damage to healthy cells. Herbal remedies and plant-derived foods not only help in controlling cancer growth but also boost immunity and overall

well-being. As research continues to explore the potential of plant-based treatments, they stand as the safest and most sustainable solution in the fight against cancer.

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