

Effects Of Bioactive Compounds Obtained From Fruits to Act Against Various Kind of Cancer: Molecular Mechanism and Oxidative Stress Conditions

Dr.Anamika PK, Dr.V.Sandhiya, Dr.N Deepa, G Vijayamma, Jaisudha

Associate professor, Department of pharmacology, Sree Balaji medical College and hospital campus BIHER
Associate professor, Department of pharmaceutics, Sree Balaji medical College and hospital campus BIHER campus

Abstract:

The leading cause of death in the world today is cancer. The results of cancer patients have significantly improved with the development of surgery, radiotherapy, and pharmaceuticals. Cancer's basic mechanisms, nevertheless, are still poorly understood. Natural remedies have recently been demonstrated to be helpful for a number of ailments and have been crucial in the development of innovative therapies. A significant body of research indicates that bioactive substances may benefit cancer patients' prognoses through a number of routes, including endoplasmic reticulum stress, epigenetic alteration, and oxidative stress reduction. Here, we discuss the most recent research on bioactive substances found in natural products for the treatment of cancer and provide an overview of the pathological process' underlying mechanisms.

Keywords: Bioactive compounds, Molecular mechanism, polyphenols, Phenolic acids, cancer

Introduction

A malignant disease known as cancer is characterised by uncontrollable cell proliferation and unregulated cell expansion [1]. It is still one of the major killers on the planet. The International Agency for Research on Cancer (IARC) predicts that in 2022 there will be 19.3 million new cancer cases, 10.0 million cancer-related deaths, and that in 2030 there will be 28.4 million new cases of cancer worldwide, a 47% increase from 2020. Lung, liver, and stomach cancers were the most frequent causes of cancer deaths worldwide [2], followed by female breast cancer, lung, and prostate cancer. In recent decades, there have been dramatically fewer deaths from cancer thanks to higher rates of early detection and treatment. Additionally, over the past 15 years, methods of therapy for cancer have changed as a result of advances in our knowledge of molecular biology and tumour biology. Figure 1 shows a number of the pathological characteristics of cancer. The biological abilities of cancer cells to support proliferative signalling, insensitivity to antigrowth signals, resistance to cell death, unlimited replication potential, inducing angiogenesis, active invasion, and metastasis, deregulation of cellular energetics, and resistance to immune destruction are among them. Tumor-associated inflammation, which can supply bioactive chemicals to the tumour microenvironment (TME), and the genomic instability of cancer cells are both necessary for the acquisition of the aforementioned characteristics [3]. The extracellular matrix, cytokines, growth factors, chemokines, and other compounds that support reciprocal heterotypic signaling interactions during the progression of malignancies make up the TME, which

is a portion of tumours that is integrated with neoplastic cells such as cancer stem cells, cancer-associated fibroblasts, endothelial cells, pericytes, and immune-inflammatory cells [4]. These distinct traits suggest that tumour cells have an infinite capacity for expansion, invasion, and metastasis. Numerous treatments have been created that particularly target these characteristics. However, the majority of currently available anticancer medicines only offer modest therapeutic benefits and have serious side effects. Small amounts of food-derived molecules known as bioactive compounds have the potential to be medicinal agents as well as having nutritional value. They can be found in a wide variety of plants, including whole grains, fruits, and vegetables [5]. The majority of bioactive substances have residues of amino acids and can have a variety of physical effects, including antioxidant, antithrombotic, and antihypertensive actions . Numerous substances have more than one of these outcomes [6].

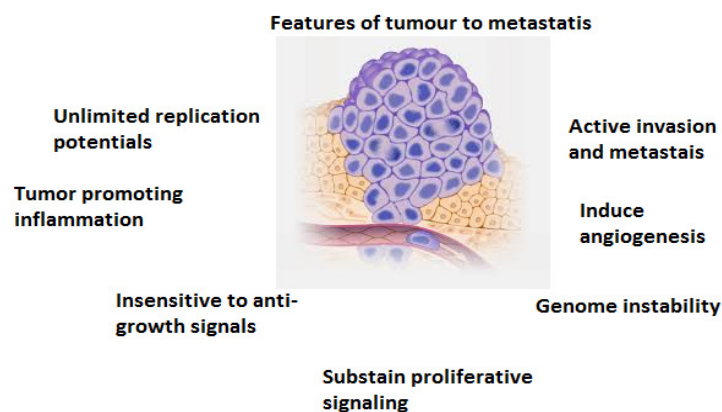


Fig 1: Tumor to metastatis

Bioactive substances are becoming more and more credible as cancer preventative and therapeutic agents, according to mounting data [7]. The 26 anticancer foods listed in the "Global Diet and Cancer Research Report" were recently updated by the American Institute for Cancer Research (AICR). The report defines strong evidence as research that clearly establishes a causal link between cancer and the condition, while limited evidence denotes that while the overall conclusions are generally supported by the data, the evidence is rarely sufficient to support recommendations for cancer risk reduction. Additionally, we will go into more detail about the drugs' anticancer mechanisms in the following section. In conclusion, changing one's diet could stop many tumours' destructive processes. In this review, we will first talk about a few typical bioactive substances before summarising their impacts on cancer and the cancer-related pathways.

Table 1 : bioactive compound against cancer

Bioactive compounds	Natural products	Against cancer
Triterpenoid compounds	Apples	Colorectal cancer
Vit c, chlorogenic acid, proanthocyanidins	Blue berries	Colorectal cancer
Flavonols, folate	Asparagus	Breast cancer
Carotenoids, lutein	Broccoli and cruciferous vegetables	Colorectal cancer
Carotenoids,phenolic acid	Carrots	Lung cancer

Anthocyanins, phenolicacids	melatonin,	Cherries	Colon cancer
Terpenes, flavanones	coumarins,	Grapefruit	Breast cancer
Flavonones		Orange	Stomach cancer
Ellagitannins,anthocyanins		Raspberries	Lung cancer
Stilbenes, resveratrol		Strawberries	Esophageal cancer
Lycopene, beta-carotene		Tomatoes	Lung and stomach cancer

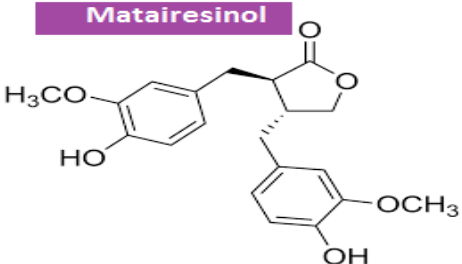
Bioactive compounds

Polyphenols

A wide range of naturally occurring substances with various phenolic activities are known as polyphenolic compounds[8]. These substances are widespread in plants and are essential for protecting against pathogen attacks and controlling cell growth. Numerous clinical investigations are being conducted right now to clarify their beneficial effects in warding against ageing, metabolic dysfunction, and cardiovascular disorders. More studies have concentrated on polyphenols' anticarcinogenic characteristics (such as reducing tumour growth, metastasis, and angiogenesis) as a result of an in-depth understanding of these compounds. The polyphenolic chemicals are typically divided into four classes based on the number of phenol rings and molecular structures: phenolic acids, stilbenes, lignans, and flavonoids.

Table2:Phenolic acids with example

Phenolic compounds	Example	Structure
Flavanoids	Flavones, anthocyanine, isoflavanoids	<p>ANTHOCYANIN STRUCTURE</p>
Stilbenes	Resveratrol	<p>Resvetatrol</p>
Phenolic acids	Benzoic acid, cinnamic acid	<p>CINNAMIC ACID CHEMICAL STRUCTURE</p>

Lignans	Matairesinol	
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The majority of food-derived polyphenols exist as polymers, esters, or glycosides; when entering the body, polyphenols are first hydrolyzed by bacteria in the intestines before being absorbed [9]. Polyphenols then participate in the processes of methylation, sulfation, and glucuronidation . All of these polyphenolic compounds could be found in blood, but not in organic foods. The rate of absorption, metabolism, and excretion are only a few of the variables that affect how the polyphenols behave biologically. Additionally, hepatic activity not only controls polyphenol metabolism, but also controls how quickly they reach cells and tissues . Dietary polyphenols have been shown to inhibit a variety of biochemical processes , including oxidation, tumour cell apoptosis, immune system activation, and anti-inflammatory properties . These and other biochemical processes will be covered in more detail in the following sections.

Phenolic acids

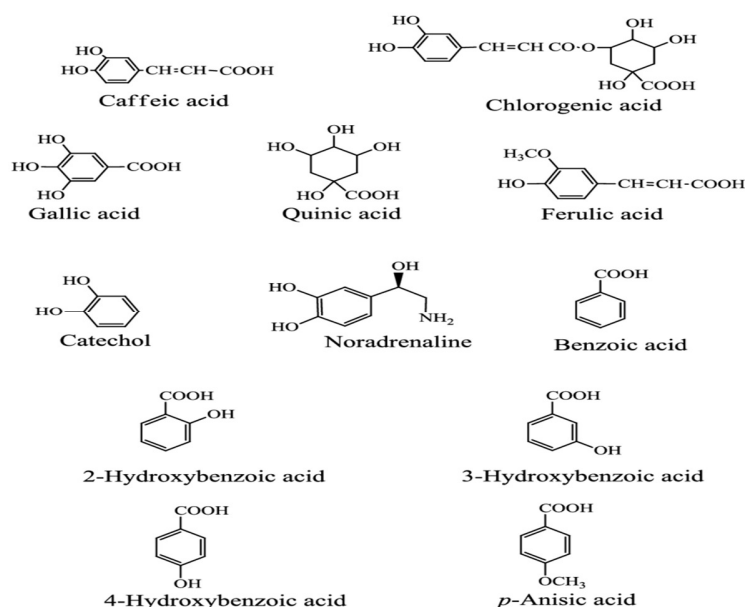


Fig 2: phenolic compounds

Effects of phenolic acid against various types of cancer

Solanum lycopersicum

The tomato (*Solanum lycopersicum*), which is a popular vegetable around the world and has many health advantages, is an important component of the human diet. It belongs to the family Solanaceae. The plants produce small to large, spherical, green fruits that turn red as they ripen.

Tomato fruit is an excellent reserve of carotenoids including

- lycopene,

- β -carotene, and
- Lutein

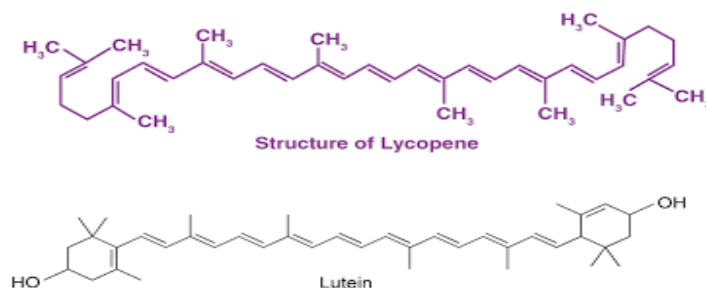


Fig 3: structure of Lycopene and lutein

As a powerful antioxidant with anti-tumor capabilities, lycopene is regarded as the primary bioactive component of tomatoes. Tomatoes include a number of bioactive substances that lower the risk of cancer formation, including fibre, Vitamins C and E, flavonoids, sterols, and phenolics[10]. Phenolics, which are present in varying levels in various tomato cultivars, exhibit antioxidant action that inhibits cellular damage as well as cancer cell proliferation.

The most prevalent substances included

caecic acid, chlorogenic acid, ferulic acid, rosmarinic acid, quercetin, and naringenin. Sterols, along with -sitosterol, stigmasterol, and campesterol, are one of the main substances in tomatoes despite being present in lesser concentrations.

The water-insoluble pigment lycopene is in charge of giving tomatoes their red hue. According to statistics from certain sources, lycopene is 10 times more effective and has ten times the antioxidant activity of vitamin E because it has a long-chain structure with dienes and a higher proportion of conjugated double bonds than vitamin E. Data from numerous studies have demonstrated a protective association between tomato consumption and cancer risk. Lycopene administration produced several beneficial effects, including accelerated prostate-specific antigen concentration and death of cancer cells.

Effects of ferulic acid , bioactive obtained from tomato on various types of cancers:

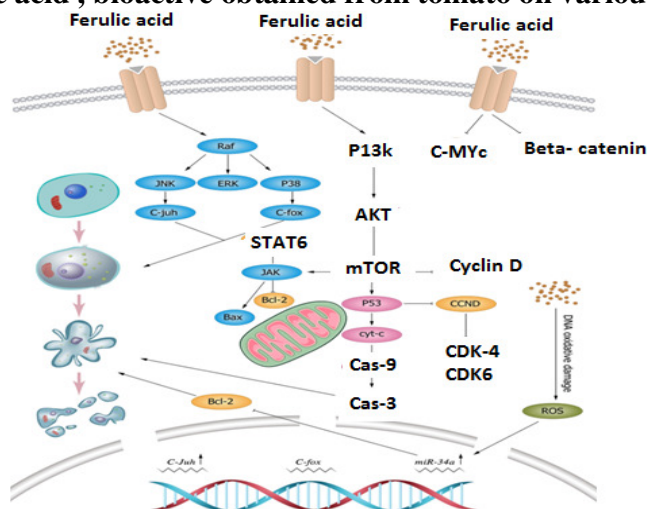


Fig 4: Ferulic acid against cancer

The mechanism by which FA and its byproducts cause the demise of cancer cells. FA upregulates P53 expression, downregulates cyclin D1 and cyclin-dependent kinase (CDK) 4/6 expression, upregulates Mir-43a expression, suppresses Bcl-2 expression, and activates the apoptotic pathway to cause cell death [11]. FA causes DNA oxidative damage and apoptosis by causing the production of ROS. JNK is also known as the enzyme extracellular signal-regulated kinase (ERK), STAT signal transduction and transcriptional activator, C-fox forkhead box C, JAK the Janus kinase, Bcl-2-associated X (Bax), BCL-2 (B-cell lymphoma-2), and AKT protein kinase B. Other names for JNK include tumour protein 53 (P53), caspase cysteinyl aspartate

Quercetin against cancer

Pharmacological role

There are antioxidant qualities to quercetin.

Cells are helped to resist oxidative damage by antioxidants. When the body's antioxidant defences are outnumbered by the body's excess free radicals, oxidative damage takes place. This is referred to in medicine as oxidative stress.

Free radicals are erratic molecules in the body that can hasten ageing and raise the risk of disease. Free radicals are created by the body during routine metabolic functions like energy synthesis.

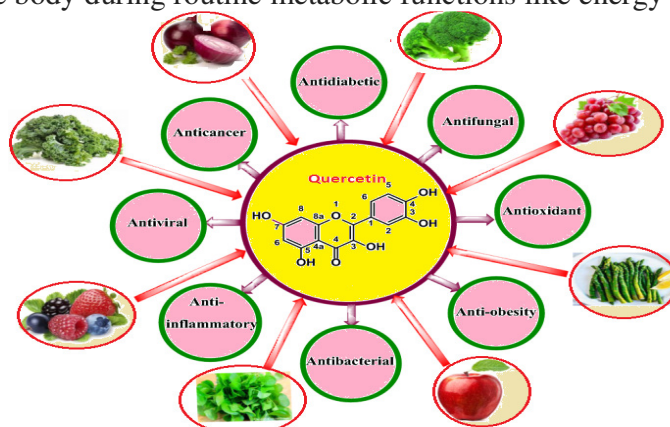


Fig 5: Therapeutical role of quercetin

Molecular Mechanism

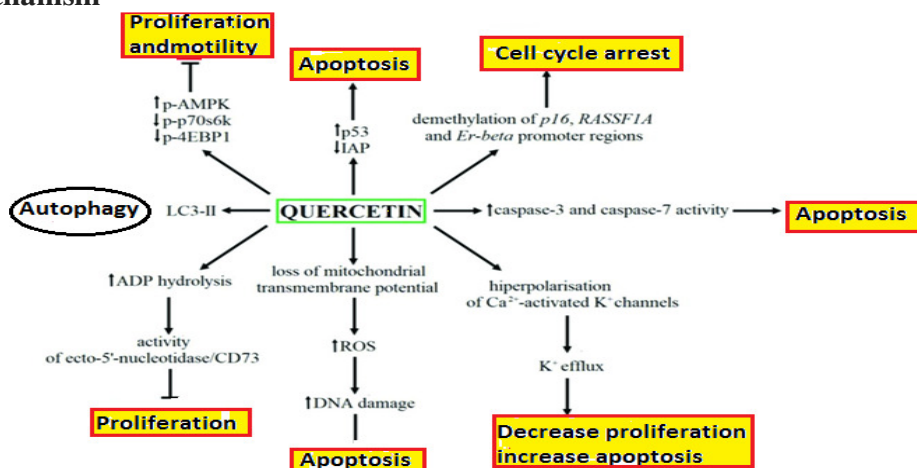


Fig 6: molecular mechanism of quercetin

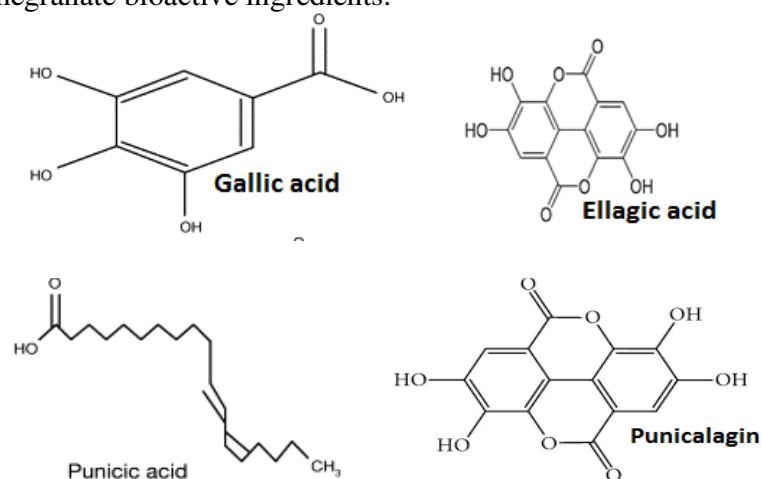
Quercetin boosted the apoptosis-inducing factors such as DNA fragmentation, subG0/G1 cell percentage, and caspase 3/7 activities. However, autophagy might be the cause of the quercetin-induced reduction in cell viability. After quercetin exposure, the amount of a particular autophagy marker, such as LC3-II, was elevated in human BC cells. On the other hand, quercetin plus an autophagy inhibitor (bafilomycinA1) may be used in combination to more effectively suppress the growth of bladder cancer cells by improved apoptosis[12]. According to an in vivo study, quercetin may cause BC cells to undergo apoptosis through controlling p53. According to literature reviews, quercetin administration led to a decrease in the expression of the mutant P53 protein (mutP53). Additionally, this therapy was linked to a decreased expression of survivin. It is also possible that quercetin's antiproliferative action on bladder transitional cell carcinoma is mediated, at least in part, by abnormalities in the extracellular catabolism of nucleotides[13,14]. These abnormalities may be brought on by AMP buildup or quercetin-blocked adenosine receptors. (The primary) Ecto-50-nucleotidase AMP hydrolysis into adenosine is catalysed by the enzyme of nucleotide catabolism, which has been identified as a key substance implicated in the progression of cancer, regulation of cell proliferation, maturation, differentiation, treatment resistance, and tumour promotion. According to an in vivo investigation, quercetin enhanced ADP hydrolysis, inhibited the activity of ecto-50-nucleotidase and CD73, had no impact on the production of any proteins, and ultimately reduced cell proliferation.

Effects of bioactive compounds obtained from pomegranate on various types of cancers

Punica granatum

The pomegranate (*Punica granatum* L.), a member of the Lythraceae family, is a spherical berry that contains between 250 and 1500 white seeds when it is unripe and deep red or purple seeds when it is ripe. Due to the tannins and anthocyanins present, the edible seeds have anti-inflammatory and antioxidant qualities. Since ancient times, pomegranates have been utilised as medicine for a variety of illnesses. It has antiparasitic properties and can be used to treat ulcers and diarrhea[15,16]. The Unani system of medicine, another conventional medical system, has even gained recognition for its efficacy in the management of diabetes. In addition to the fruits, it is also known that the bark, leaves, roots, and other sections contain significant amounts of molecular components that have medicinal effects. There are several

It contains a bioactive substance that is known to have an impact on a number of signalling pathways involved in inflammation, the start of carcinogenesis, hyperproliferation, cellular transformation, angiogenesis, and ultimately metastasis. Various transcription factors, pro- and anti-apoptotic, cell cycle-regulating molecules, protein kinases, cell adhesion molecules, proinflammatory mediators, and growth factors have all been found to be modulated by pomegranate bioactive ingredients.



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Fig 6: Structure of bioactive compounds obtained from pomegranate

Role of punnic acid against oxidative stress

Effect of punnic acid in various cancers

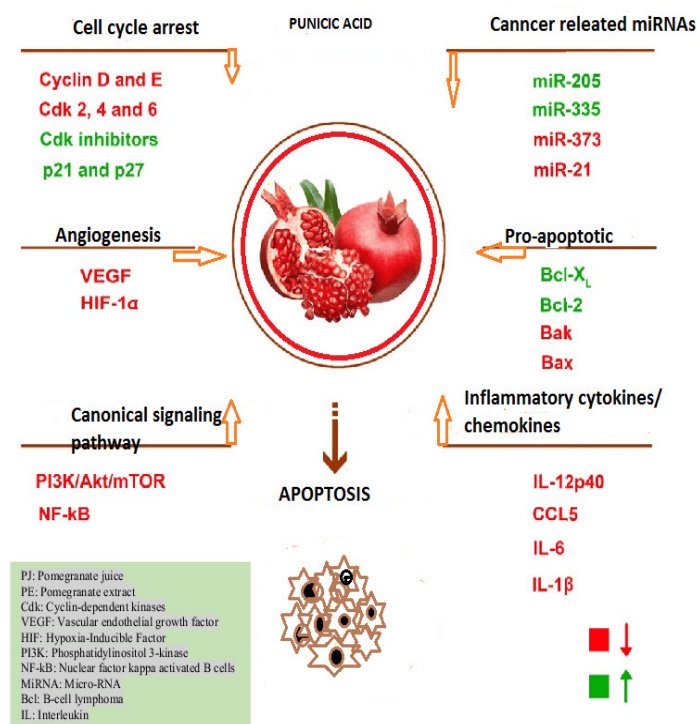


Fig 7: molecular signaling pathways of punnic acid

The majority of skin cancer cases are caused by exposure to the sun. UVB light stimulates a number of signalling pathways in the skin and is therefore a significant risk factor for skin cancer[17,18]. All three pomegranate products—pomegranate fruit extract (PFE), pomegranate juice (PJ), and pomegranate seed oil (PSO)—have the capacity to guard against UVB-induced skin cancer. They have all been put to the test using skin cancer-related animal models, reconstituted human skin models, and cell culture. The phosphorylation of the UVB-induced Mitogen-Activated Protein Kinases (MAPK) in Normal Human Epidermal Keratinocytes (NHEK) was demonstrated to be blocked by PFE. Leukocyte infiltration and epidermal cell hyperplasia were prevented by oral treatment of PFE coupled with

Breast cancer: According to reports, polyphenols from the PJ, pericarp, and PSO inhibited the conversion of testosterone to oestrogen by blocking aromatase activity and hence have a significant role in breast cancer[19]. These polyphenols were also found to have an adverse influence on the proliferation of the cell lines MCF-7 and MB-MDA-231 in addition to their anti-estrogenic actions. According to the results of another study, pomegranate ellagitannin derivatives have anti-proliferative effects on breast cancer cells. Because of their pro-apoptotic and antioxidant qualities, PFE and its components are of the utmost relevance for chemoprevention against breast cancer, according to studies. Punnic acid, which is present in PSO, was also discovered to trigger apoptosis in the breast cancer cell lines MDAMB-231 and MDA-ER-7, which are both estrogen-sensitive and insensitive.

Effect of caffeic acid

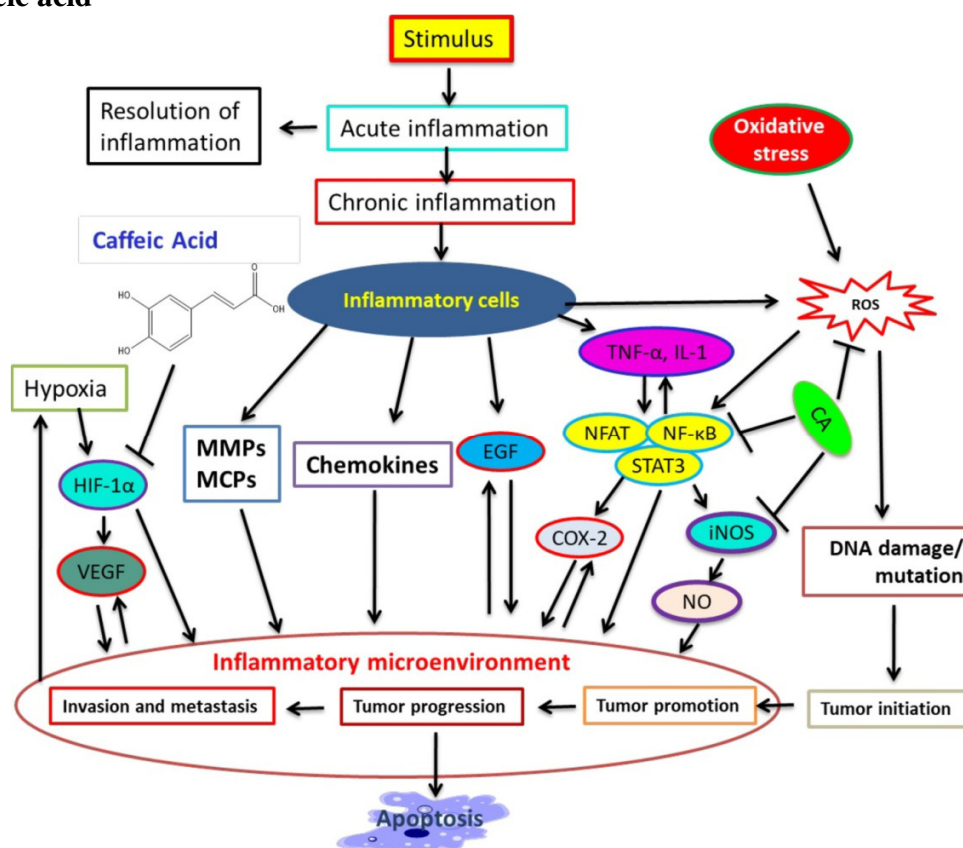


Fig 8: Molecular signaling pathway of caffeic acid

CA has demonstrated its ability to downregulate IL-6, IL-1, and NF- κ B in the inflammatory response, as well as its significance as a powerful 5-lipoxygenase inhibitor. CA significantly inhibits STAT3 activity [20,21], which in turn inhibits HIF-1 activity. It possesses promising STAT3 inhibitors and suppresses tumour angiogenesis by inhibiting STAT3 activity as well as VEGF and HIF-1 expression. CA prevented the phosphorylation of ERKs, transactivation of NF- κ B and AP-1. However, CA inhibits tumour metastasis and neoplastic cell transformation by targeting MEK1 and TOPK. In fact, it interacted with ERK1/2 and in vitro inhibited ERK1/2 activity.

Effect of ellagic acid

Ellagic acid (EA) is a bioactive polyphenol that many plant species naturally produce as a secondary metabolite. The pomegranate (*Punica granatum* L.), as well as the wood and bark of several tree species, contain significant amounts of EA. EA is structurally a dilactone of the widely dispersed class of secondary metabolites known as ellagitannins, which is formed mostly by the hydrolysis of hexahydroxydiphenic acid (HHDP), a dimeric gallic acid derivative. The antioxidant, anti-inflammatory, antimutagenic, and antiproliferative qualities of EA are drawing attention.

Pharmacological activity of ellagic acid

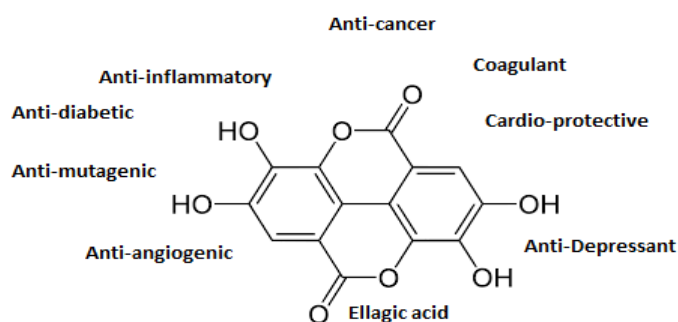


Fig 9: Therapeutic uses of ellagic acid

Molecular mechanism of ellagic acid

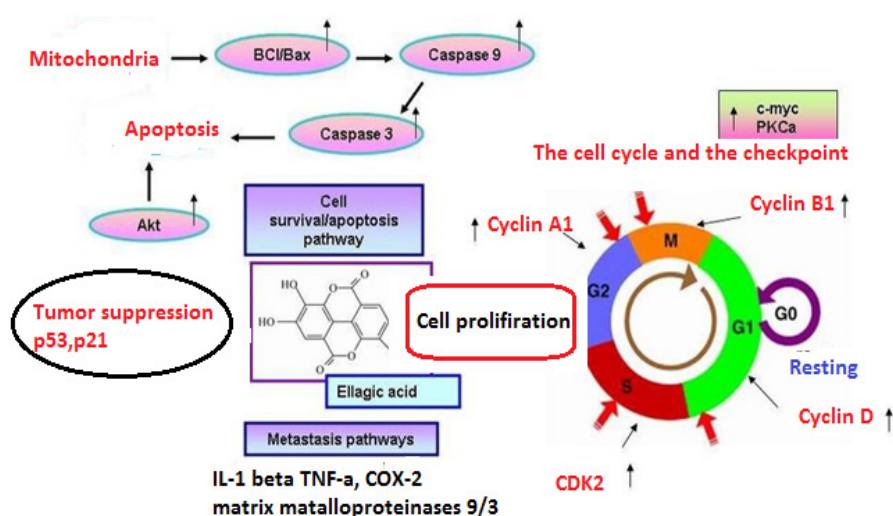


Fig 10: Molecular mechanism of ellagic acid

Blackberries, cranberries, raspberries, strawberries, wolfberries, grapes, pomegranates, pecans, and walnuts contain ellagic acid, a benzopyranoid. According to reports, ellagic acid and its metabolites exhibit anti-cancer effect against cancer cells. Specifically, signalling pathways' regulation is modulated[22]. The different signalling pathways involved are the cell tumour suppressor pathway (p53, p21), the cell proliferation pathway (cyclin dependent kinase 2, cyclin A2, cyclin B1, cyclin D1, c-myc, PKCa), the survival/apoptosis pathway (Bcl-XL, Bax, Caspase 9/3, Akt), the angiogenesis pathways (VEGF), the inflammatory metastasis pathways (IL-1 beta, T

Emblica officinalis

Commonly called Indian gooseberry in English and amla in Hindi, *Emblica officinalis* Gaertn. or *Emblis myrobalans* is a medium-sized deciduous tree belonging to the family Euphorbiaceae. All parts of the plant show health benefits and are used in tending to various ailments, but the fruit is of colossal use in many traditional systems of medicine along with serving a great deal in culinary uses.

In Ayurveda, amla is appraised to be a potent Rasayana or rejuvenator as it is useful in stalling senescence, promoting longevity, benefitting the eyes, enhancing digestion and treating constipation, preventing peptic ulcers, reducing fever, purifying the blood, along with possessing hepatoprotective, cardioprotective, diuretic, antiinflammatory properties[23]. It is used for curing a diversity of disorders such as anemia,

hyperacidity, diarrhea, eye inflammation, leucorrhoea, jaundice, nerve debility, liver complaints, cough, and hair loss.

Amla is a rich source of vitamin C, tannins, alkaloids, and phenolic compounds.

The fruit contains

- Gallic acid,
- Ellagic acid,
- Corilagin
- Chebulinic acid,
- Chebulagic acid,
- Emblicanin a, emblicanin b, punigluconin, pedunculagin, citric acid, ellagitannin, trigalloyl glucose, pectin, 1-ogalloyl-b-d-glucose, 3,6-di-ogalloyl-d-glucose, corilagin, 1,6-di-o-galloyl-b-d-glucose, 3 ethylgallic acid (3 ethoxy 4,5 dihydroxy benzoic acid), and isostrictiniin along with flavonoids like quercetin, kaempfero etc.

Amla as an antineoplastic agent: The antiproliferative action of amla extract in the human tumor cell lines of different histological origins like human erythromyeloid K562, B-lymphoid Raji, T-lymphoid Jurkat, MCF7, and MDA-MB-231 breast cancer cell lines was observed to be very functional. A concentration-dependent cytotoxic effect on L 929 cells in vitro and apoptosis in Dalton’s lymphoma ascites and CeHa cell lines was also seen upon administration of its aqueous extract [24]. The most important difference between normal cells and cancer cells is the loss of differentiation, unlimited replicative ability, increased invasiveness, and metastasis. Constituents of amla show metastasis prevention and its aqueous extract are effective in preventing the MDAMB-231 cell invasion in the in-vitro matrigel invasion assay. Kaempferol, an amla bioactive, has been reported to inhibit stromelysin 1 (MMP-3) expression in the MDA-MB-231 breast cancer cell line. Gallic acid, a polyphenol is also reported to show inhibitory effects on gastric adenocarcinoma cell migration, and metastasis of P815 mastocytoma cells to the liver of DBA/2 mice

Gallic acid

A naturally occurring polyphenolic substance called gallic acid (3, 4, 5-trihydroxybenzoic acid) can be found in processed beverages like red wines and green teas. Plants contain it as hydrolysable tannins1-2, free acids, esters, catechin derivatives, and free acids. The pharmacological activity of these compounds as radical scavengers is the reason for the interest in them[25]. It has been demonstrated to have potential therapeutic and preventive effects in a number of illnesses where oxidative stress has been linked, including ageing, cancer, cardiovascular disease, and neurological disorders.

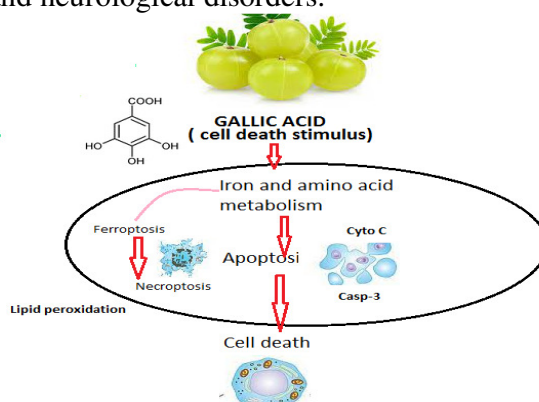


Fig 11: Molecular mechanism of gallic acid

proposed mechanisms for cell death brought on by gallic acid. Through the stimulation of the apoptotic, ferroptotic, and necroptotic pathways, gallic acid causes cell death[26,27]. The iron chelator DFO can decrease certain types of cell death, proving that they are iron-dependent. Even when used in combination, the inhibitors of three distinct cell death pathways, including the apoptosis inhibitor Z-VAD-FMK, the ferroptosis inhibitors AOA and Fer-1, and the necroptosis inhibitors Nec-1 and NSA, are unable to prevent the gallic acid-induced cell death. This finding suggests that cell death may occur via an unidentified downstream route.

Chebulinic acid

Pharmacological activity of chebulinic acid

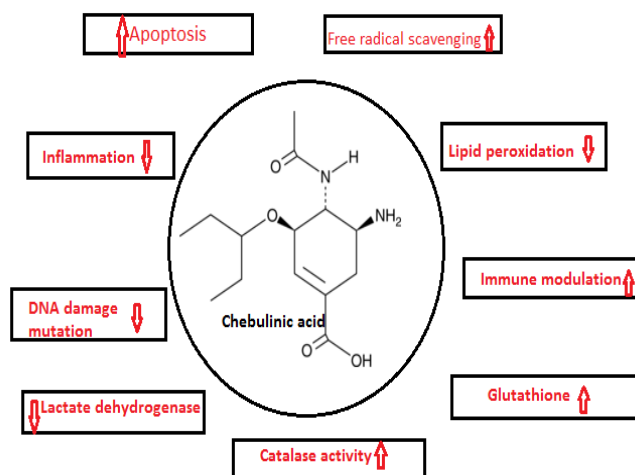


Fig 12: Therapeutic uses of chebulinic acid

Corilagin

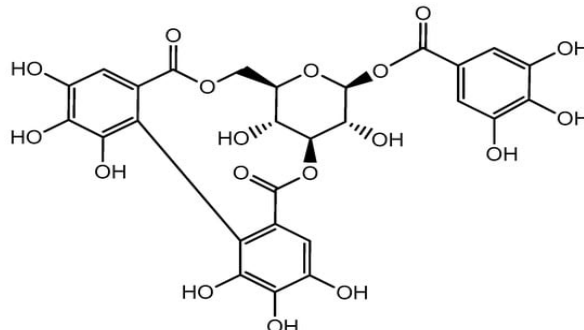


Fig 12: Structure of corilagin

A natural ellagitannin (ET) called corilagin, also known as 1-O-galloyl-3,6-(R)-hexahydroxydiphenoyl-d-glucose, is present in a variety of plants. Corilagin has recently been shown to have a wide range of biological and pharmacological properties, including antioxidant, anti-inflammatory, hepatoprotective, antibacterial, antihypertensive, and anticancer activity. It has substantial antistaphylococcal activity and reduced the reverse transcriptase activity of RNA tumour viruses. Multiple mechanisms, including cell cycle inhibition, apoptosis via the mitochondrial pathway, and self-destruction after replication, have been proposed as the causes of ET's antiproliferative effect.

Molecular mechanism of corilagin against cancer

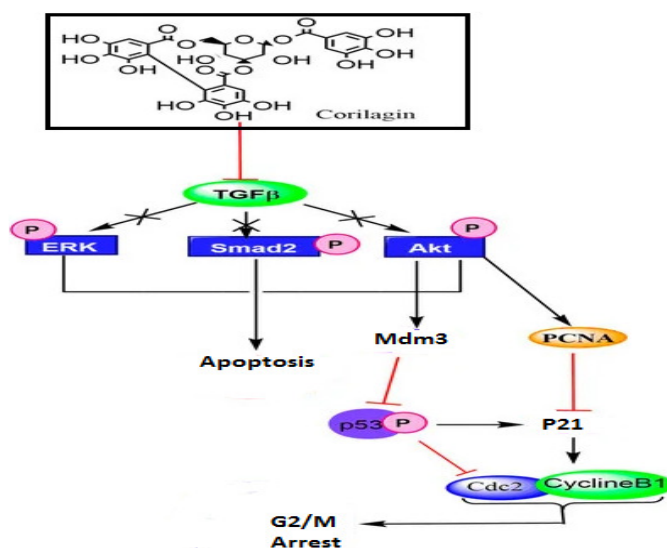


Fig 13: Molecular mechanism of Corilagin against cancer

Different isoforms of TGF- cause the pro-matrix metalloproteinase (MMP) to be secreted from cancer cells, which results in cell-to-cell contact loss, elevation of N-cadherin and downregulation of E-cadherin, and the development of a fibroblastoid phenotype. The epithelial-mesenchymal transition is consistent with all of these processes. Additionally, type I (ThRI) and type II (ThRII) receptors are associated with TGF-. After ThRII binds to its ligands, ThRI is activated, which results in the phosphorylation of receptor-regulated Smads. The co-Smad and Smad4 are then bound by the phosphorylated Smads. Further movement of this complex alters gene expression in the nucleus. PI3K and MAPK family members, such as c-Jun-NH2-kinase, TAK1, p38, and extracellular signal-regulated kinase, are involved in the Smad-independent pathways that TGF- also activates.

Corilagin may stop the cell cycle in the S- and G2/M phases by inhibiting the cyclin B1/cdc2 complex, which is crucial for controlling the transition from the G2 to the M phase in SKOV3ip cells.

Conclusion

The biggest cause of sickness and mortality in the world is cancer. To stop cancer from getting worse, it is vital to create more effective and targeted treatment plans. Chemotherapeutic and chemopreventive medicines for the treatment of cancer have been identified as bioactive chemicals. Additionally, it has been suggested that a number of mechanisms, including ROS, ER stress, and epigenetic changes, modulate the impact of bioactive chemicals on cancer. We will conduct more experimental research to better understand the mechanisms underlying the anticancer effects. The development of synergistic combinations to attain greater efficacy may benefit from this information.

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Data is contained within the article

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Conflict of interest

The authors declare no conflict of interest

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