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Review Article

Role of Polyphenols and Flavonoids as Anti-Cancer Drug Candidates: A Review

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ABSTRACT

Natural drug-based chemotherapeutic have advanced at an unprecedented rate over the past decade. Owing to protective roles in vegetation, and exceptional antioxidant qualities, polyphenols and flavonoids have demonstrated promising clinical implications in malignancies amongst other plant metabolites. It is widely debated how dietary flavonoids and polyphenols can prevent cancer. Flavonoids are believed to execute a significant role in cancer prevention and treatment, as corroborated from experimental studies, epidemiological research, and human clinical trials. Carcinogen deactivation, antimutagenic, cell cycle arrest, apoptosis and differentiation, suppression of vasculature, oxidative stress, and reversion of multidrug resistance are among the many mechanisms of action that have been discovered. The present review outlines the classification of various polyphenols and flavonoids and their potential as anticancer therapeutic agents.

Keywords: Cancer, Secondary metabolites, Polyphenols, Flavonoids, Reactive oxygen species.

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INTRODUCTION

Cancer is a class of disorders that comprises abnormal growths of cancerous cells with the ability to spread to or infiltrate other body regions. The lifestyle and behaviours of an individual have a significant impact on the risk of augmenting cancer as well as other conditions like cardiovascular disease and obesity.[1,2] The external variables including smoking, overweight, eating processed foods, radiotherapy, genetic predisposition, anxiety, and environmental factors contribute to cancer development. According to the WHO, there will be more than 13 million cancer-related fatalities worldwide by 2030.[1-4] The normal cells divide uncontrollably in case of malignancy. Older cells mostly don't disintegrate; instead, they keep multiplying uncontrollably and generates aberrant cells. Ionic and UV radiations, viral diseases, cigarette smoking, parasitic infections, tainted food or drink, and pathogenic micro-organisms are the leading biochemical and physical determinants of cancer.[4]

Although, identifying the appropriate medication for every kind of cancer remains challenging due to delayed diagnoses, insufficient approaches to combat extensive metastasis, and a dearth of therapeutic techniques to fight cancer that is resistant to several drugs.[5,6] Numerous medicines are accessible to cure cancer, but because of specific focus on a particular target, they can be hazardous and can cause adverse effects. Cancer chemotherapeutics is a critical element in the management of carcinoma cells that uses various pharmacological, synthetic, and natural substances to totally obstruct or impede the development of cancerous cells.[5]

Currently, whenever cancerous cells are removed, normal cells will also be annihilated together with the tumour cells owing to the general non-specific properties and inherent cytotoxicity of chemotherapeutic drugs. Detrimental complications are frequently experienced when treating malignancies with common medications and techniques like chemotherapy and radiation therapy.[7,8] Furthermore, the creation of novel medicines that are less hazardous to the person is one of the major objectives of cancer research. Natural chemicals can be extremely beneficial on this process.[9] Nature has always provided mankind with an endless supply of natural resources. Additionally, in order to create beneficial techniques and biopolymers, scientists should attempt to replicate the apparent natural patterns.[10,11] Developing or creating novel medicines with minimal toxicity to normal tissues and parallelly exhibiting potent anti-cancer properties is of utmost importance. The anti-cancer capabilities of natural substances have been considered valuable. It is anticipated that substances that are obtained from nature will serve as anticancer medications as they are widely accessible, affordable, physiologically effective, and only marginally toxic.[12-14]

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Phytoconstituents are secondary metabolites created by plants that are usually promotes growth and are employed in defence mechanism against infections or predators. Presently, utilizing phytonutrients, particularly polyphenols and flavonoids, as a substitute for standard chemotherapeutic drugs has potential to be employed as anticancer therapeutics because they lessen or reduce the complications of these therapies engendered by the standard counterparts.[15,16] Additionally, our bodies become resistant to some standard cancer treatments due to medication. interactions. As flavonoids and polyphenols are harmful to cancerous cells but harmless to normal cells, they have been suggested as prospective chemotherapy regimens. Natural drug-based chemotherapeutics have advanced at an unprecedented rate over the past decade.[17] Owing to their protective roles in vegetation, their use as dietary supplements, and their exceptional antioxidant qualities, polyphenols and flavonoids have demonstrated potent pharmacological applications in cancer treatment.[18,19] Accordingly, a wide variety of polyphenols and flavonoids that have been researched for potential use in various cancer treatments are presented in this review.

POLYPHENOLS AS ANTI-CANCER AGENTS

Plants synthesize polyphenols as a secondary metabolite. Berries (strawberries, cranberries, blueberries), grape vines, plums, olive oil, chocolate, almonds, nuts, and other vegetables and fruits are the primary sources of polyphenols.[17,18] Polyphenols are categorized into a wide range of classes and subclasses depending on the number of phenolic rings. Figures 1 and 2 outlines the major polyphenolic categories and their plant sources. Investigation and articles on the promising applications of polyphenolic substances in cancer treatment have expanded in the past decade.[20] The exploration of these substances as possible anticancer drugs will be facilitated by the fact that polyphenols can be isolated utilizing inexpensive, environmentally friendly methods, including ultrasound-assisted extraction, and that upon sterilization, polyphenols retain the preponderance of their characteristics. Among diverse plant species, over 8000 polyphenolic metabolites have been discovered. Studies evaluating the potential health advantages of polyphenols, such as prevention of oxidative stress cardiovascular problems, hypoglycaemia, bronchitis, neurological condition, and even ageing, have been undertaken in significant numbers.[21] The pursuit of new chemoprotective medicines that are safer than current treatments have sparked a deep interest on research centralized on naturally occurring plant compounds. As a result, this class of compounds has been investigated for their potential to inhibit the development and growth of tumours, migration, inflammatory processes, and cell death.[22]

The majority of polyphenols are digested in a regular pathway and are reported in food products of esters, glycosides, or polymers. Polyphenols are initially hydrolyzed by digestive enzymes or colonic bacteria before being absorbed.[23] The colon can only digest aglycones. Following substantial transformations by conjugation in intestinal epithelium polyphenols undergo

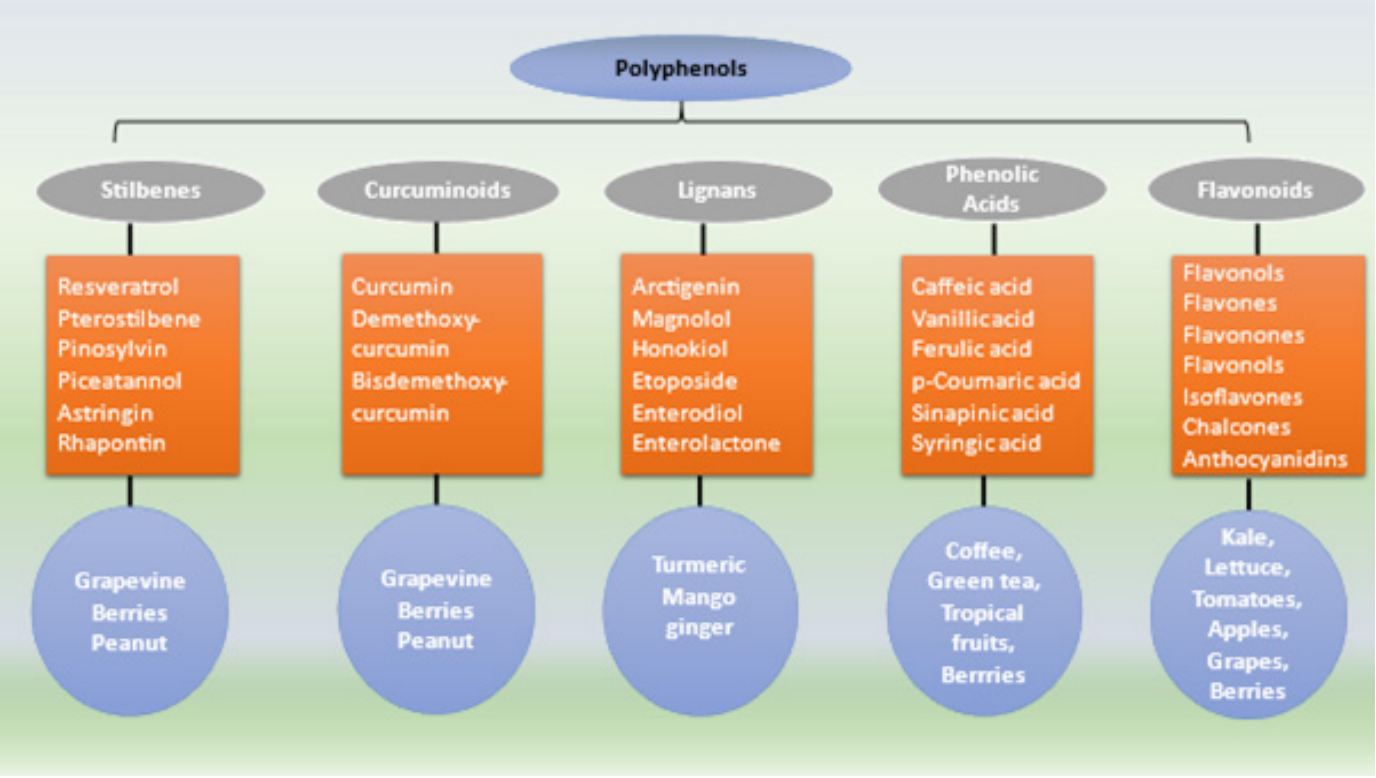

Figure 1: Different classes of Polyphenols and their source.

additional modifications in the hepatic cells to facilitate their absorption. Furthermore, not all polyphenols are equally prevalent in the food or equally physiologically effective. Polyphenol digestion is influenced by intestinal absorption, metabolic activity, and excretion rate.[24] Polyphenol derivatives travel through the blood bonded with proteins, primarily albumin, and their structural properties play a significant role in the complex formation. Protein complexation may impact how efficiently they reach cells and tissues.[23,24] Polyphenolic compounds can enter cells and are especially effective in the hepatic and colon cells, where they are processed. Citrus fruit flavanones have fairly high concentrations, while flavanols and isoflavones have lower levels. In order to evaluate the health consequences of polyphenols, it is crucial to comprehend their solubility and bioavailability.[25,26]

Polyphenolic compounds have the ability to influence and alter a wide range of biological mechanisms and events implicated in the development of cancer. Additionally, they can serve as pharmacological enhancers that enhance immune response operation and buffer living tissue from oxidative stress induced damages.[27] Despite widespread evidence linking the polyphenols to the cancer management, only a small number of the preventive consequences of specific chemicals have been solidly established in clinical trials as a result of variations in dosage, duration, and other extraneous variables.[28,29]

Polyphenols have been demonstrated to have an influence on a number of cancer-preventive processes, such as the signal transduction pathway immune system function, xenobiotics purification, activation of apoptotic processes, protection from oxidative stress (Figure 3). The majority of research has centred on particular polyphenols in an attempt to unravel the cellular and molecular pathways underlying their anticancer effectiveness.[30,31] The interplay between these substances and other biological elements, both at the subcellular and organ levels, greatly affect the impact that these substances eventually generate.[17,18] Some important research assessing the effectiveness of various polyphenols in preventing cancer are presented below.

Stilbenes

Stilbenes, also known as stilbenoids, are hydroxylated metabolites of stilbene that are synthesized in a diverse range of plants, including cannabis, berries, vines, and nuts. Additionally, trees produce stilbenes as additional by-products, which have antibacterial and antioxidant properties.[31-33] Resveratrol is the most well-known member of the stilbene family and provides a number of medical advantages and there have been several investigations on them.[34,35] According to research, resveratrol inhibits the growth of a wide variety of human malignancies *in vitro*, including those of the mammary, epidermis, ovarian, gastrointestinal, prostrate, colorectal, hepatic, pancreatic, cervical, laryngeal, nasopharyngeal, lymphoid, and myeloid cancers.[35] Resveratrol captures hydroxyl group, superoxide anion, and free radicals created in cells, to safeguard DNA against oxidative stress, which are typically associated with the development of cancers. Additionally, resveratrol is an effective against hepatocellular carcinoma.[36,37] Mice were administered resveratrol (30 mg/kg, three times per week) orally, which decreased prostate cancer spread and angiogenesis and triggered cell death.[38] Chemotherapy with resveratrol (150-250 μM) resulted in cell cycle inhibition and cell death in a majority of cervical carcinoma cells.[39]

Pterostilbene is prevalent in blueberries and is a naturally occurring derivative of resveratrol. In the intestines, pinostilbene dramatically reduced the proliferation of human colon carcinoma cells at therapeutically appropriate doses (20 and 40 μM), as well as triggered cell death and S phase arrest.[40]

Additionally, breast cancer cells were able to undergo cell death when treated with pterostilbene (25–75 μM).[41,42] In prostate cancer mouse models, pterostilbene (50 mg/kg/day) suppressed the formation of tumours.[43]

Curcuminoids

Curcumin is well-known for its anti-inflammatory and antioxidant qualities. Curcumin's ability to reduce tumorigenesis aand angiogenesis and decrease cellular proliferation has been established in different cancer models.[44-46] Curcumin derivatives are helpful in the treatment of colon cancer cells. According to research by Anand, curcumin can influence cancer proliferation and invasion in besides controlling tumorigenesis, angiogenesis, and triggering cell death.[47] Numerous research centralized on pulmonary carcinoma, indicate that curcumin affects signal transduction restriction and Stat3 network activation. Because to its associations with arachidonate pathway in addition to its *in vivo* anti-angiogenic capabilities, curcumin may exert anti-tumour effects.[48-51] Curcumin has proven benefits against a number of malignancies, particularly colon, pancreas, ovarian, prostrate, pulmonary, myeloma, and squamous cell carcinoma, according to Gupta *et al*., who surveyed clinical trial data on curcumin.[52-54]

Lignans

Lignans are diphenolic chemicals that can be detected in very modest levels plants, such as cabbage, legumes, beans, wheat, seeds (sesame, pumpkin, flax) and various berries. Lignans, is well recognized for its strong antioxidant capabilities. Owing to their potential to imitate the actions of human hormones, lignans could be employed as anticancer medications.[55,56] Lignans have been shown in several rat experiments to inhibit the formation of prostate and breast carcinomas.[57-60] A naturally occurring lignan called secoisolariciresinol diglucoside is transformed into biologically active lignans by bacteria found in the intestine. Due to their structural similarity to estradiol, these lignans portray anticancer properties against tumors, including breast, prostate, and colorectal cancer.[61,62] The three lignans that have been the

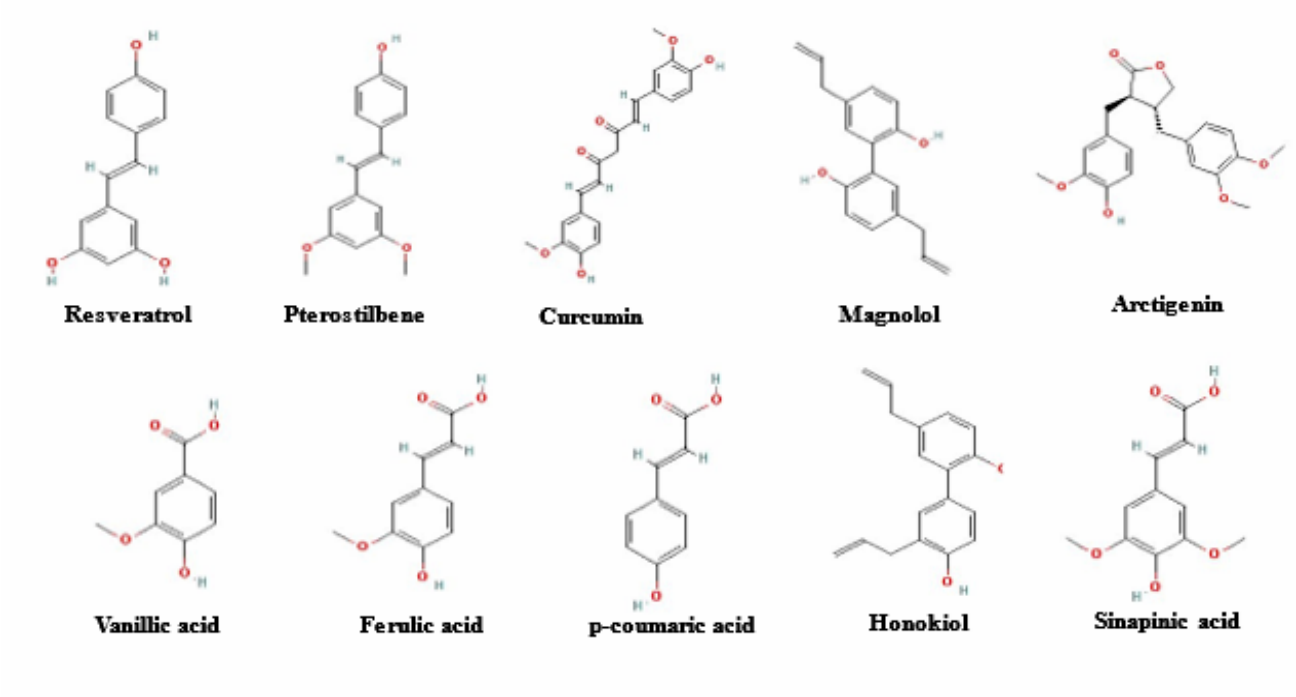

Figure 2: Structures of some common polyphenols.

focus of the most medical research are arctigenin, magnolol, and honokiol. However, etoposide, a commercial compound from the podophilotoxin subfamily, is employed in the management of several cancers.

According to several research, arctigenin prevents the proliferation of immune cells. The caspase-3 protein, which is essential for the destruction of cancerous cells, is activated more actively in response to the presence of arctigenin.[63,64]

Traditional medical practices have used concoctions made from magnolia bark.[65] Magnolol administered to treat colorectal cancer, decreases protein kinase C delta type phosphorylation.[66] Together with magnolol and obovatol as analgesics, honokiol has been prescribed in conventional treatments to address depression and anxiety issues.[67] Multiple studies have discovered that honokiol has the capacity to destroy tumour cells in various types of cancer.[68-70]

Phenolic acids

Phenolic acids are a distinctive subclass of polyphenols that are present in many foods, particularly dried fruits and berries. These substances are distinguished by having an organic carboxylic acid and a phenolic ring.[71] The two types of phenolic acids are either benzoic acid derivatives or cinnamic acid derivatives.[72] P-coumaric acid is the phenolic acid that has so far demonstrated therapeutic benefits that make it a viable option in the therapeutic strategies for the management of cancer. A multitude of fruits and vegetables contain the natural component p-coumaric acid, which is formed from cinnamic acid and has been shown to have anticancer and antioxidant effects.[73]

Many plants contain significant quantities of vanillic acid, which has been utilized in traditional medicine for a number of ailments.[74] The plant metabolites, vanillic acid, has been investigated for the treatment of colon cancer by operating on a different cellular process.[75,76] Vanillic caid has demonstrated to exert anti-proliferate and anti-angiogenetic effects on the cancerous cells.[77] Ferulic acid has demonstrated antineoplastic effect in a variety of malignancies, including colon and lung cancer as well as tumours of the nervous system.[78,79] Ferulic acid may trigger cell death in LNCaP cells while it may induce cell cycle interruption in PC-3 cells.[80] Its optimization approaches in preventing tumour metastasis are yet uncertain. The plant metabolite ferulic acid is condensed to create poly ferulic acid, which functions as a drug delivery carrier and has anticancer activities.[81,82]

FLAVONOIDS AS ANTI-CANCER AGENTS

Isoflavonoids, flavanols, flavonols, flavones, and anthocyanidins are the major flavonoids subclass found in plants (Figures 4 and 5). The primary food sources of flavonoids include fruits, green leafy vegetables, and beverages made from plants, including tea, wines, and those produced from cocoa.[83] Flavonoids possess a wide range of chemotherapeutic actions, including modulating the activity of enzymes that scavenge reactive oxygen species, participating in cycle arrest, inducing cell death and autophagy, and reducing the multiplication and pervasiveness of cancerous cells.[84]

Flavonoids operate as antioxidants under normal circumstances and are strong pro-oxidants in the cancerous cells, stimulating

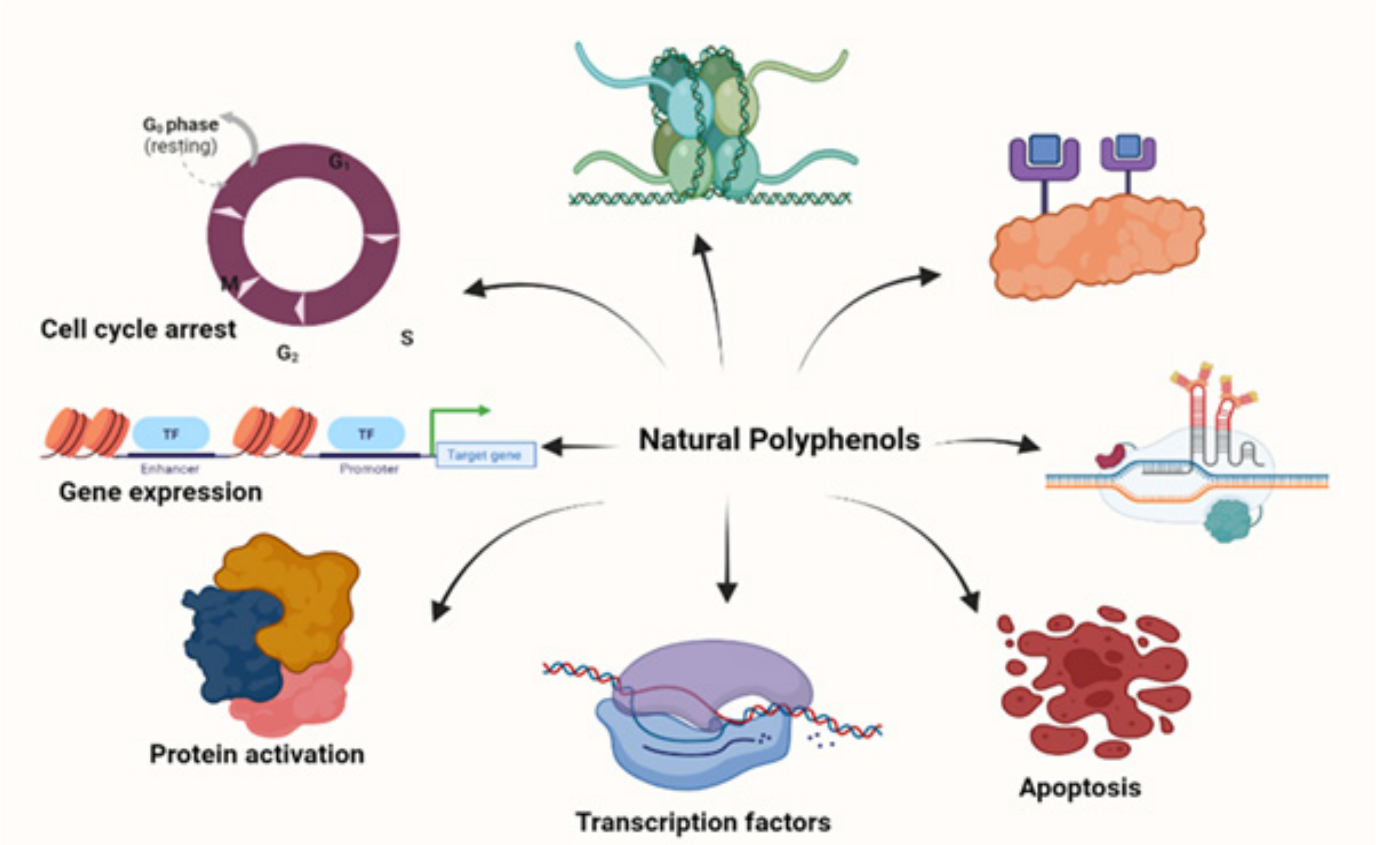

Figure 3: Anticancer properties of naturally occurring plant polyphenols.

the cell apoptosis and by the decreased expression of pro-inflammatory signaling pathways.[85,86] Due to their limited hydrophobicity, flavonoids have the ability to permeate cellular and mitochondrial membranes and function as protonophores.[87] Because of the inhibition of carbohydrate hydrolyzing enzymes and the glucose transporters in the brush border cells, flavonoids can engage with several other micronutrients and restrict the uptake of carbohydrates. Through enhanced bile salt production, which promotes micellar assimilation of flavonoids, consuming fat promotes flavonoid availability and boosts their digestibility.[88] Following intake, gastrointestinal bacteria can solubilize glycated flavonoids into their corresponding lipophilic aglycones, hence simple diffusion is important for their passage to the intestinal epithelium subsequent to reception.[89]

Following absorption, flavonoids go through metabolic derangements in the intestine, hepatic tissues, and kidney before reaching the bloodstream and, ultimately, the cells, where they may have a consequence on their bioactivity. Multiple studies have demonstrated that flavonoids can excavate free radicals, control cell functions, and shield against illnesses driven by oxidative stress.[90] Flavonoids have a wide range of antitumor actions, including modulating the functions of reactive oxygen species scavenging enzymes, participating in cycle arrest, inducing autophagy, and inhibiting the multiplication and intrusiveness of cancerous cells. The following section outlines the anti-cancer potential of some major flavonoids.[86]

Flavanols

Flavanols, which are primarily found in foods like apples, grapes, cereals, oats, peaches, oranges, berries, red onion, cruciferous vegetables, eggplants, cabbage, peppers, potatoes, spinach, Aloe Vera, thyme, soybean.[90,91]

Quercetin is considered one of the most effective antioxidants in the flavonoid family, according to numerous *in vitro* and *in vivo* experiments, making it a prime contender for a chemotherapeutic medication. Chemotherapy of A549 lung cancer cells with quercetin (IC_{50} 2.30 ± 0.26 μM) resulted in cell death, which inhibited cell proliferation. Similar patterns of quercetin (8.4 mg/kg) on lung tumour progression were observed in nude mice.[92] Additionally noted is a decrease in the docetaxel sensitivity of cancerous cells when quercetin is added to docetaxel chemotherapy for prostate cancer. As a consequence of intensifying cancer cell apoptosis and decreasing tumour development, cancer therapy becomes more effective.[93] Numerous studies conducted over the past few years have produced additional evidence of kaempferol's anticancer processes, both *in vitro* and *in vivo*.[94] The identification of these pathways has made it possible to analyse and comprehend kaempferol's function as an anticancer agent, and it may ultimately result in the creation of specific

drug delivery systems that contain kaempferol. Kaempferol therapy prevented TGF-beat-1 induced EMT and movement in A549 lung cancer cells by preventing the activation of smad3 by AKT1.[94] In another study, kaempferol therapy had a substantial anti-proliferative impact on the stomach cancer cells MKN28 and SGC7901 despite appearing to have any negative effects on healthy intestinal epithelial cells.[95]

Flavones

Herbs, red or purple plants, and vegetables primarily contain flavones. Flavones often function in plants as defence mechanisms against disease caused on by infections. The most prominent example is luteolin, which has been employed as a yellow pigment since olden days. Wool has also been dyed with apigenin.[96,97] Wogonin is also well-known for being one of the key components in Japanese herbal medicines. Nevertheless, due to their effective antibacterial, antioxidant, antimicrobial, anti-inflammatory, antitumor, and anticancer properties, this family of flavonoids has attracted medical attention.[98]

Apigenin has been extensively utilized as a herbal medicine for many years. The research of this natural compound's potential as an antitumor medication has been motivated by its excellent properties. In addition, different positive benefits of apigenin dosage, either alone or in conjunction with other chemotherapeutic agents, were outlined in various investigations for diverse types of cancer therapy.[99] According to reports, apigenin causes cancer cell lines to die, initiates senescence and cell death, inhibits cancer cell growth and migration, and causes cancer growth arrest. Treatment with apigenin (40–160μM) led to DNA damage, cell death, and enhanced reactive oxygen species generation in H460 lung carcinoma cells.[100] According to research, apigenin (30–60 mg/kg/week) can stop the progression of stomach cancer and the atrophic gastritis caused by *Helicobacter pylori*.[101] It is believed that luteolin could play a significant role in the treatment of cancer because of its positive impacts on the human body, including its antioxidant properties and anti-inflammatory properties, capacity to neutralize free radicals, promotion of glucose metabolism, and ability to modulate the immune response. This flavone is typically used with other cancer medications to strengthen the anticancer properties of luteolin.[102] By enhancing the activity of the caspase-3 and Bax proteins, the administration of luteolin along with oxalipatlin, a traditional anticancer medication was advantageous in preventing the growth of cancer cells, and inhibited the multiplication of gastric cancer cells *in vitro*.[103]

Flavanones

Flavone is the source of the colourless ketones known as flavanones. Because of their antioxidant capacity, radical scavenging ability, cardioprotective, anti-inflammatory, antimicrobial, and anticarcinogenic activities, flavanones have been more significant in medicine during the recent decades. Most frequently, hesperetin and naringenin are tested as potential anti-cancer medications. However, several studies were conducted

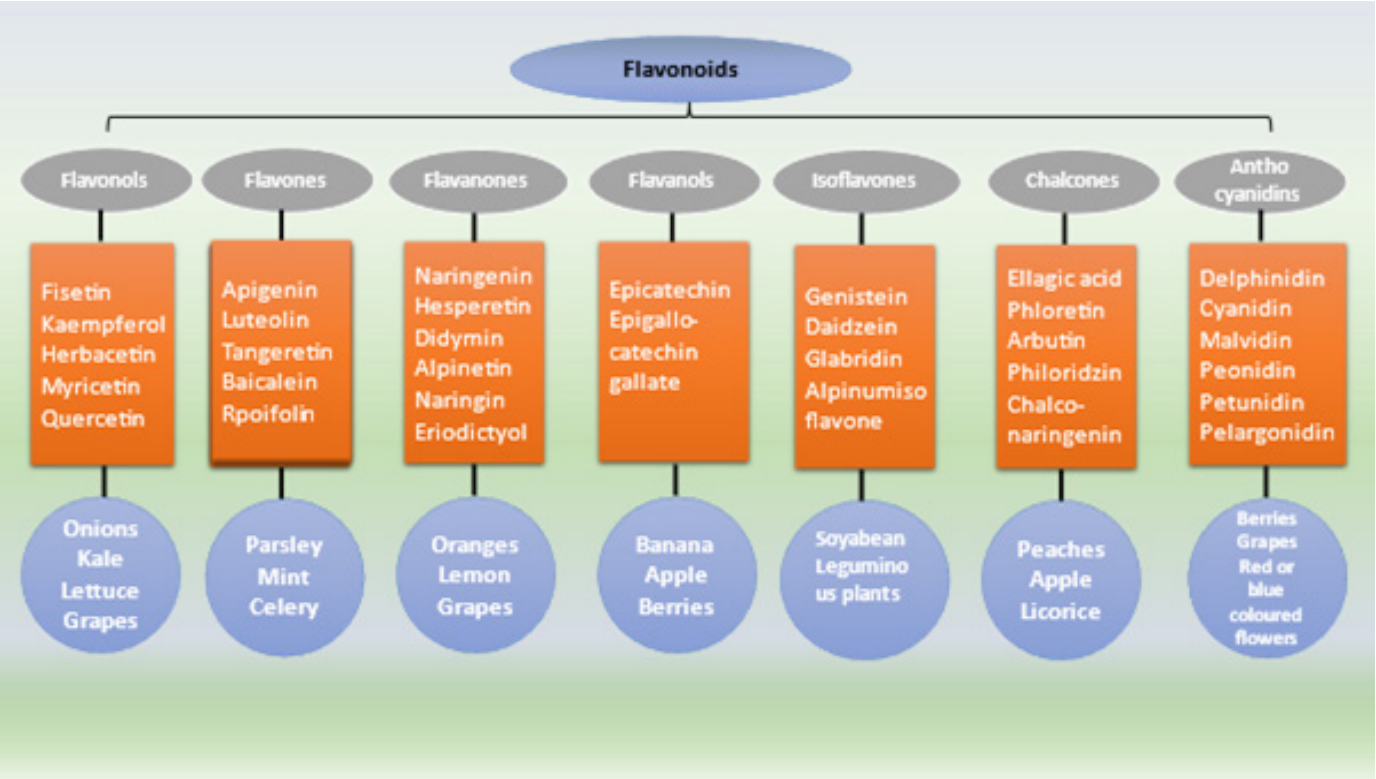

Figure 4: Classification of natural flavonoids.

utilizing additional flavanones, such as didymin and alpinetin. An abundant flavanone in grapefruit and *Citrus* fruits is naringenin. Naringenin promotes cytotoxicity in many malignant cells of mammary, gastrointestinal, hepatic, cervical, pancreatic, colon tumours as demonstrated in numerous investigations. However, naringenin's poor solubility and dispersion in physiological environment restrict its use in medicine.[104]

The anticancer effects of hesperetin on particular malignancies have been extensively studied and published in a number of journals. It prevents the uptake of glucose by different cancer cell lines, lowers NF-κB activity, which slows the growth of tumours, and improves lethality by causing the production of intracellular ROS.[105] In another investigation, hesperetin was found to enhance the anticancer medication cisplatin's activity in the treatment of pulmonary cancer. Hesperetin was shown to suppress the multidrug resistance protein, which has been linked to the tolerance to cisplatin that has evolved in a significant percentage of patients receiving cancer treatment.[106] Interestingly, experiments evaluating the anticancer benefits of naringenin and hesperetin administration were conducted *in vitro* and *in vivo* for human pancreatic cancer. According to the study, naringenin and hesperetin together could be employed as a viable non-toxic cancer therapeutic approach to halt the growth of pancreatic cancer.[107]

Flavanols

Flavanols include catechin and its derivatives. Flavanols are abundant in tea and chocolate. These substances offer protection from perilous intruders like micro-organisms, fungus, bugs, and herbivorous animals. The advantages of flavanols for human well-being have so been extensively researched. Discovering a correlation between drinking green tea and an increased risk of developing malignancy has been the subject of extensive research.[108] An apparent illustration is the study's confirmation that drinking up to seven cups of green tea (catechin) per day somewhat lowers the risk of developing prostate cancer.[109] Even though epigallocatechin gallate is a flavanol that is frequently present in nature, its usefulness in cancer therapy is restricted by issues with poor stability, poor absorption, and liver toxicity. Therefore, encapsulating epigallocatechin gallate may be a potential way to address the limitations of epigallocatechin gallate.[110,111] Epigallocatechin gallate increased the activity of the transferrin receptor, a protein that serves as a transporter for transferrin, in HT-29 colorectal cell lines while decreasing the function of the ferritin-H protein.[112]

Isoflavones

In terms of potential therapeutic uses, genistein and daidzein are the subgroup's most extensively researched substances. But other isoflavones, such as glabridin and alpinum isoflavone, have sparked interest as promising cancer treatments for numerous

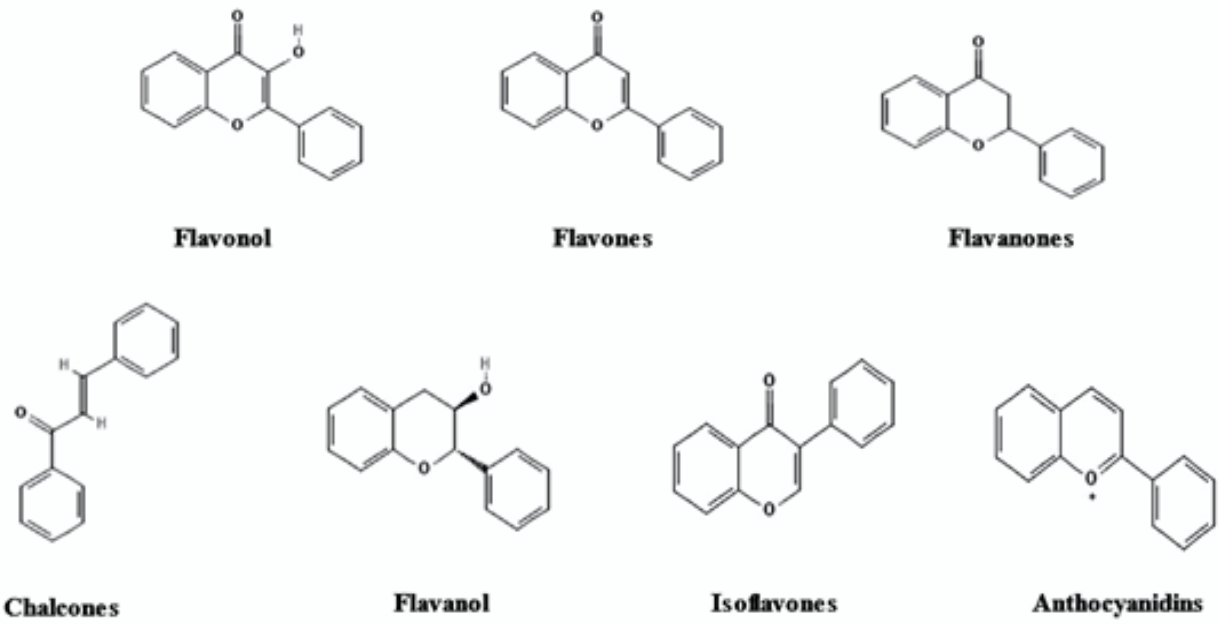

Figure 5: Structures of flavonoids subclasses.

tumours.[113] Genistein has been shown to play a role in the controlling of several genes linked to the development of cancer through a number of mechanisms. Additionally, other research has looked into how genistein interacts with other anticancer medications.[114] Cisplatin and genistein combinations at various doses as a potential anticancer therapy for cervical cancer cells have been proven effective from previous investigations.[114,115] In breast cancer cell lines, daidzein decreased the expression of multidrug resistance-associated protein 1.[116] Oral daidzein was given to mice for 22 days after they had been injected with 4T1 breast cancer cells. The greatest dose of daidzein was necessary in this instance to see a sizable reduction in tumour size. The authors also noted that the combination therapy including daidzein and consistent exercise stimulates apoptosis in breast cancer cells.[116]

Chalcones

Chalcones can be found in a wide range of vegetables and fruits including apples, cherries, shallots, onions, and green beans, as well as in some culinary herbs like liquorice.[117] Ellagic acid, which has been researched as a potential anticancer agent, is the chalcone that has received the greatest interest in the field of medicine. Through the comparison of many possibilities, the advantages of using ellagic acid to cure tumors have been researched for decades. Few researchers have attempted to encapsulate ellagic acid in order to boost its poor permeability as well to improve its regulated distribution.[118] Two distinct biopolymers were used to nano encapsulate ellagic acid, which were subsequently evaluated against MCF-7 breast cancer cells. In comparison to non-capsulated ellagic acid, the cytotoxicity of encapsulated was enhanced by the controlled release of ellagic acid. Additionally, it slowed the growth of malignant cells.[119]

Anthocyanidins

Plants contain water-soluble compounds called anthocyanidins. The hues of the fruits, blossoms, and foliage are due to them. Anthocyanins are present in berries and other fruits that are consumed by people. Owing to their physicochemical characteristics, these kinds of phytochemicals are also widely employed in the pharmaceutical industries to lower the risk of developing different ailments like overweight, enhance cognition and age-related impairments, or strengthen the immune system.[120] Anthocyanidins from the plant *Cyanomorium coccineum* have demonstrated anticancer properties, and studies on various leukaemia cell lines have shown that they have an inhibitory effect on cell proliferation. Numerous studies have shown delphinidin to have antitumor properties. Delphinidin boosted the activation of Caspase-3, Caspase-7, and Caspase-8, effectively promoting the death of cancer cells, according to studies that examined the effectiveness of the compound against prostate cancer.[121]

CONCLUSION

Polyphenols are strong contenders for compounds utilized in various categories of chemotherapeutics due to their great antioxidant properties qualities. Apparently, preclinical animal models and *in vitro* cancer cells have been used mostly for research on the anticancer properties of various phytochemicals substances, specifically polyphenols and flavonoids. However, there aren't many clinical studies concerning the use of polyphenols or flavonoids as chemotherapy regimens. The preponderance of these clinical investigations is currently ongoing. Research on various polyphenol families' potential anticancer properties, especially flavonoids, has led to the creation of alternative remedies that are relatively less aggressive than anticancer medications that are currently on the market. In fact, numerous studies have shown that polyphenols and flavonoids can be employed as chemotherapy adjuvants in the treatment of cancer. Further research is necessary to determine the processes by which polyphenols work against cancer and how they interact with tumours, for these organic substances to enhance the real treatment approaches.

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CONFLICT OF INTEREST

We declare that the authors have no conflict of interest.

ABBREVIATIONS

WHO: World Health Organization; **DNA:** Deoxyribonucleic acid; **LNCaP:** Lymph Node Carcinoma of the Prostrate; **PC-3:** Prostate cancer **A549:** Adenocarcinoma human alveolar basal epithelial cells; **IC_{50}:** Inhibitory Concentration; **TGF:** Transforming Growth Factor; **EMT:** Epithelial Mesenchymal Transitions; **SMAD 3:** Suppressor of Mothers against Decapentaplegic; **ROS:** Reactive Oxygen Species; **AKT1:** Alpha Serine/Threonine protein kinase 1; **BAX:** Bcl-2 associated X protein; **NF-κB:** Nuclear Factor kappa B; **HT-29:** Human colorectal adenocarcinoma cell line; **MCF-7:** Michigan Cancer Foundation-7.

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