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A REVIEW ON POLYPHENOL USED IN CANCER

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ABSTRACT

Globally Cancer is a major health concern, after cardiovascular disease it is a second cause of death in noncommunicable diseases. it continues to be a extensive concern for public health systems worldwide. Recent years cancer death rate has been reduced by about 31%, by improve health status, healthier lifestyle habits. cancer occurs due to extensive DNA damage caused by ultraviolet radiations, therapeutic agents, ionizing radiations, environmental agents. Chemotherapeutic drugs are used to treat advanced stages of cancer or by following surgery. However, drug resistance developed to cancer cell it leading to failure of treatment and recurrence of the disease. Natural products like Plant-derived functional foods have a therapeutic potential and safety. Naturally derived polyphenols are beneficial in cancer treatment. it represents a structural class of mostly natural organic chemicals that consist of multiple phenol structural units. The helpful properties of polyphenols have been extensively studied for their antitumor, anti-inflammatory, and antibacterial effects, but their application extended due to their prebiotic role and their impact on the microbiota. The reported multiple anticarcinogenic properties of natually-derived polyphenols include the modulation of molecular events and signaling pathways associated with cell survival, proliferation of cancer cell, differentiation, angio- genesis, migration, hormonal activities, detoxification enzymes and immune responses. This review focused deep study of cancer, type of cancer, polyphenol as a anti-cancer agent and limitation in cancer treatment.

KEYWORD: cancer, polyphenols, Antineoplastic effects.

INTRODUCTION

Cancer is considered to be one of the most serious issues affecting humanity worldwide and is the second leading cause of mortality after cardiovascular diseases. Cancer is an uncontrolled division of ordinary cells in the body. Old cells do not demolish and continue to grow in an uncontrolled way, forming new abnormal cells.[1] These strange cells form a mass of tissue called tumor. Cancer may categorize into five major classes namely as carcinoma, leukemia, sarcoma, lymphomas, and central nervous system cancer. In particular, about 30-35% of cancer cases are associated with dietary factors: The Mediterranean diet represents one of the most popular dietary models now days under examination in the field of cancer prevention and treatment effect.[2] The most physiological and biochemical case of cancer are due to the ionized and ultraviolet radiations, viral infections, smoking, parasites, contamination of meal or beverages. This all cancer causing thinks cause the cancers, the most frequently diagnosed cancers are breast (12.5%), lung (15.9), colorectal (10.2%), and gastric cancer (8.5%).[3]

At present, there are multiple treatments for cancer, including surgery, chemotherapy, hormonal remedy, radiation, vulnerable remedy, targeted treatments, nanotechnology, and RNA rectifiers (microRNA and RNAi). Chemotherapeutics have been predominant for systemic cancer treatment; the maturity of these are acting to beget DNA damage in order to kill or to inhibit cells from an accelerated rate of division.[4] Chemotherapeutics are administered as single boluse or short curative at the minimal tolerable cure, followed by a treatment-free time that must be observed to allow for the recovery of normal cells. Despite the benefits of chemotherapy, it gives rise to adverse goods including hematological toxin, difference of gastrointestinal exertion, alopecia, diffreences of neurological exertion, anaphylaxis, hepatotoxicity, and nephrotoxicity.[5] The adverse goods of systemic chemotherapy are frequently severe and reduce the quality of life of cases. Although many adverse goods can be averted with acceptable prophylaxis, the toxin of some agents cannot be controlled; thus, a cure reduction becomes the only volition. In this regard, factory-deducted natural composites similar as polyphenols may arise as ideal furthers for single or attendant curative for cancer treatment with further effectiveness, safety, and lower toxin.[6] Factory-deduced natural composite has been

used for the for instalment and treatment of numerous condition. shops produce a wide range of secondary metabolites that confer on them great rigidity to act as antimicrobial agents, as growth enhancers, in resistance to water stress, as sun screeners, and as an aid to repel bloodsuckers.[7] Secondary metabolites include polyphenols with nearly, given members, composed of several sweet rings and multiple hydroxyl groups in their structure, with moderate water solubility and considerable antioxidant capacity. individualities gain roughly 1 g/ day of polyphenols from their diet; still, this varies according to socioeconomic factors, gender, and the region of the world where people live. further than 800 polyphenols have been linked in food sources, including cereals, cocoa, coffee, tea, wine, and berries.[8] Despite the advances in medicine discovery and development during the last decades, herbal drug continues to be used as primary remedy in many developing countries (nearly 4 billion persons.) Regular consumption of polyphenols has been related to salutary health goods, including regulation of the intestinal microbiota and antiaging goods, a threat reduction of atherosclerosis, a drop in the threat of colorectal cancer development, and the modulation of antioxidant enzymes through Nrf2 regulation.[9] One of the major challenges for the remedial use of polyphenols is their low oral bioavailability. The immersion, transportation, bioavailability, and bioactivity of polyphenols are of interest in terms of their use and as new medicine campaigners. After oral administration, polyphenols pass through the gastrointestinal tract (GI) with immersion in the stomach and small intestine, and some are biotransformed by gut microbiota or by those absorbed during the early stages of digestion by hepatic phase I/ II metabolism, Previous to reaching the systemic rotation, which may affect bioavailability and bioactivity.[10] Results of significance consider all of these processes and how they will affect the pharmacokinetics and pharmacodynamics of polyphenols. Still, availability, profitable significance, salutary health good, and the safety.[11]

Reactive Oxygen Species in Cancer Development

Currently Cancer has become a most health issues worldwide. According to WHO report millions of people died to cancer. about 30% of cancer case can be prevented and some of the most common cancers such as breast, colorectal, and cervical.[12] cancer are curable if treated promptly however the diagnosis tools, prognostic predictions, and conventional therapeutic strategies have reached to patient at higher level in recent years, there are still some challenges that remain to be solved such as the drug resistance and high treatment costs.[13]

Classification of polyphenols

Polyphenols are classified according to the number of phenol rings and the structural elements that bind them together. Polyphenols are mainly classified into flavonoids and phenolic acids. They are natural compounds that are all derived from phenylalanine and contain an aromatic ring with one or more hydroxyl groups.[14]

Table 1: Classification of polyphenols.

Classification		Representative Members	Major Dietary Sources
Flavonoids	Anthocyanins	delphinidin, pelargonidin, cyanidin, malvidin	berries, grapes, cherries, plums, pomegranates
	Flavanols	epicatechin, epigallocatechin, EGCG, procyanidins	apples, pears, legumes, tea, cocoa, wine
	Flavanones	hesperidin, naringenin	citrus fruits
	Flavones	apigenin, chrysin, luteolin,	parsley, celery, orange, onions, tea, honey, spices
	Flavonols	quercetin, kaempferol, myricetin, isorhamnetin, galangin	berries, apples, onions, broccoli, beans, tea
	Isoflavonoids	genistein, daidzein	soy
Phenolic acids	Hydroxybenoic acid	ellagic acid, gallic acid	pomegranate, grapes, berries, walnuts, chocolate, wine, green tea
	Hydroxycinnamic acid	ferulic acid, chlorogenic acid	coffee, cereal grains
	Lignans	sesamin, secoisolariciresinol diglucoside	flaxseeds, sesame
	Stilbenes	resveratrol, pterostilbene, piceatannol	grapes, berries, red wine

Polyphenols are a large family of natural 10,000 plant compounds, about 10000 source of polyphenols. This are known for their common structural features including the three-membered favan ring system and multiple phenol units.[15] Mainly Polyphenols classified in groups include phenolic acids, stilbenes, lignans, and flavonoids. Flavonoids have antioxidant and anti-inflammatory properties, which are found in legumes, fruits, vegetables, green tea, and red wine.[16] They are subdivided into six classes: anthocyanins, flavonols, flavones, flavanones, isoflavones, and flavanols. Flavonols are the most ubiquitous flavonoids that are abundant in fruits and leafy vegetables. The key members are quercetin and kaempferol, and the most abundant sources include leeks, and broccoli. Flavones consists chiefly of glycosides of luteolin and apigenin.

Flavanones are found in citrus, tomatoes, and other aromatic plants like mint. Isoflavones are flavonoids possessing structural similarities with estrogens and are mostly found in leguminous plants.[17] The primary source of isoflavones in the human diet is soya and its processed products. Among phenolic acids, hydroxybenzoic acids are found in tea, cinnamon, coffee, kiwis, blueberries, apples, plums, and cherries. Stilbenes are found in meager quantities in the human diet. Resveratrol is one of the well studied polyphenols for anticarcinogenic effects in medicinal plants.[18] Lignans are found in flax seeds, grains, legumes, cereals, algae, fruits, and certain vegetables. Anthocyanins occur in all tissues of plants, including stems, leaves, flowers, roots, and fruits. Flavanols are found in different types of fruits, chocolate, and green tea. The overall classification of polyphenols is illustrated in Table 1.[18]

The idea of using polyphenols for treating cancer patients is not new treatment. Early studies considering the anti-cancer effects of different polyphenols were conducted in the late twentieth century and our knowledge on these advantageous agents has been widely improved since then. What makes these agents greatly beneficial and interesting is that they attack cancer cells in a variety of ways and confront many cancer.[19]

Polyphenols as Anticancer Agents

Traditional anticancer treatment likes chemotherapy, targeted treatments, nanotechnology radiation, immune therapy available to treat the cancer. This therapies can be induce side effects and toxicity due to their specificity at a single target, mainly to organelle impairment around the cancerous cells and develop the drug resistance to tumor.[20] To inhibit, reverse and completely retard process of carcinomas, Cancer chemoprevention is a major field for prevention of carcinomas using different pharmaceutical, synthetic and natural compounds. Chemotherapatic compound are multi-target specificity, selectivity, and their cyto-friendly nature.[21]

Natural compounds has a potential anticancer properties, its become a interest topic for research. Polyphenols are most favored compounds for carcinogenesis therapies on the count of their anti-cancerous ability, ease of availability, potential to overcome the resistance, safety, and efficiency.[22] The plant kingdom is major source to anti-cancer drugs. Natural compounds has about 30 different anti-cancerous natural mixes have been separated from plants and more than 3,000 species of plants have been accounted in the treatment of cancer and clinical trials so far. Natural flavonoid compounds classified into six groups such as anthocyanidins, flavanols, flavanones, flavonols, flavones, and isoflavones.[23] These natural polyphenols compounds are found almost in all families of plant and it can be isolated from an aquatic submerged plant Myriophyllum spicatum that involved in allopathic interactions. Polyphenols also have ability to bind with the proteins and form soluble and insoluble protein-polyphenol complexes. The Polyphenols are a large family of 10,000 plant compounds that are known for their common structural features including the three-membered favan ring system and multiple phenol units. These natural compounds are mostly found in fruits, green and black tea, cofee, red wine, cocoa, and seeds.[24] These beneficial organic agents are categorized into several subclasses including catechins, favonoids (which contain favonols, favanols, and favones), anthocyanins, catechins, isofavones, chalcones, curcuminoids, and phenolic acids.[25]

Flavonoids Flavonoids compounds are a wide class of polyphenolic compound. Flavonoids rich source fragrance, color, and flavor of fruits, vegetables, seeds, flowers, and beverages, this foods has different quantity of anti-cancerous flavonoids.[26] In nature about 6,000 flavonoid-related compounds, this Flavonoids is their derivatives flavanones, flavones, isoflavones, flavanols, flavonols, and anthocyanidins. The natural flavonoid chemical structure is diphenylpropane (C6-C3-C6), which contain two aromatic rings at both corner and a three-carbon ring at the centre which forming an oxygenated heterocyclic.[27] Flavonoids compounds can occur as aglycones and as hydroxylated, methylated, and glycosylated derivatives and have great relevance for the sensory quality of citrus fruits. The best-known biological effects of natural flavonoids are prevention against cancer, inhibition of bone resorption, cardio-protective, and hormonal action.[28] In the metabolism and conjugation of total flavonoids inside the human, the gastrointestinal tract and the colonic micro-flora plays an important role and help the total flavonoids to circulate into the systematic circulation and liver. Flavonoids can also bind with the ATP-binding sites of proteins including mitochondrial ATPase, protein kinase A, protein kinase C, calcium plasma membrane ATPase, and topoisomerase.[29]

Flavanols

Flavanols are subclasses of flavonoid, it also called flavan-3-ols. Flavanols contain the 2-phenylchromanol skeleton, and also simple monomers, oligomers, and polymers. Flavanols can be commonly found in foodstuffs, vegetables, or some beverages, and shows various biological activities that made them useful for health.[30]

Epigallocatechin gallate (EGCG)

Epigallocatechin gallate (EGCG) is one of the most extensively investigated components of green tea, which have numerous advantageous impacts to lessen the tumor and cardiovascular diseases. EGCG founds in dried leaves of green tea, white tea and also found in black tea in very mute quantity.[31] EGCG virtually suppressed the invasion and migration of CL1-5 lung cancer cells by suppressing the matrix metalloproteinase-2 (MMP-2) expression at concentration of 5–20 mM (49). Banerjee (50) suggested that EGCG and theaflavins (TF) together

were assessed for their chemopreventive potential, these two compounds could activate the caspase-3, caspase-7, and Cox-2 expression, as a result of that, they lowered the incidence of pre-invasive lung cancer.[32]

Procyanidins

A study suggested that procyanidin C1 from Cinnamomi cortex might be able to prevent TGF-β-induced EMT in the A549 lung cancer cells. Another study found that hexmer form of procyanidins from cocoa inhibited the proliferation (50 and 100 μM), induced apoptosis and G2/M cell cycle arrest in several colorectal cancer cells, which was possibly mediated by the Akt pathway.[33] Procyanidins from Japanese quince also showed pro-apoptotic effects on Caco-2 colon cancer cells, with the oligomer enriched extract showing a more potent pro-apoptotic activity. Besides, data shows that in breast cancer cells, treatment of procyanidins from evening primrose (25–100 μM gallic acid equivalents) decreased cell viability by promoting apoptosis and reduced cell invasion by suppressing angiogenesis propensity.[34] Flavanones The chemical structure is based on two benzene rings, A–B (the flavan core), bound by a dihydropyrone ring C, chirality at C3 of the C ring, and the absence of double-bound at the C2–C3 position, with 100 glycosides and 350 aglycones as known. The principal flavanones comprise naringenin, hesperidin, eriodictyol, taxifolin, didymin, and eriocitrin, regularly found in citric fruits and juices such as oranges, mandarins, and lemon.[35] The beneficial health effects related to the consumption of citric fruits have been linked to flavanones such as naringenin through modulation of the PI3K/Akt pathway and the nuclear translocation of the Nrf2 transcription factor, promoting the expression of HO-1 (heme oxygenase-1) and improving antioxidant defence.[36]

Naringenin

In A549 lung cancer cells, naringenin treatment enhanced TRAIL-mediated apoptosis by up-regulating the expression of death receptor 5. Besides, in SGC-7901 gastric cancer cells, naringenin treatment inhibited cancer cell proliferation, invasion, and migration and induced apoptosis, which might be related to its inhibition of the Akt signaling pathway.[37] Another study in colon cancer cells suggested that the pro-apoptotic activity of naringenin was mediated by the p38-dependent pathway. In HCC cells, naringenin could suppress TPA-induced cancer cell invasion by down-regulating multiple signaling pathways, such as the NF-κB pathway, the ERK and c-Jun N-terminal kinase (JNK) signaling pathway. Besides, naringenin treatment to HepG2 liver cancer cells induced mitochondrial-mediated apoptosis and cell cycle arrest through up-regulation of p53.[38] In breast cancer cells, naringenin demonstrated anti-estrogenic activity in estrogen-rich status and estrogenic activity in estrogen-deficient status. In addition, oral administration of naringenin suppressed breast cancer metastases after surgery by modulating the host immunity.[39]

Hesperetin

In gastric cancer cells, hesperetin treatment (100–400 μM) decreased cell proliferation and induced mitochondria-mediated apoptosis via promoting intracellular ROS accumulation. Meanwhile, the compound (i.p. 20–40 mg/kg thrice a week) significantly suppressed the growth of xenograft tumors in mice model of gastric cancer.[40] Besides, dietary hesperetin showed anti-proliferative activities against chemical-induced colon carcinogenesis. Oral supplements of hesperetin (20 mg/kg/day) reduced the proliferating cell nuclear antigen, the formation of aberrant crypt foci induced by 1,2-dimethylhydrazine in rat.[41]

Flavones Chemical characteristics of these flavonoids include a double bond between C3 and C4, a keto group at C4, and no substitution in C3. Flavones have a characteristic yellow color or can be colorless; they act as primary pigments in white flowers, as copigments in combination with anthocyanidins in blueflowers, and as plant-signaling molecules. Relevant flavones include apigenin, diosmin, chrysin, tangeretin, luteolin, 7,8-dihydroxyflavone, and 6-hydroxiflavone.[42] Flavones are found in plants employed for preparing infusions such as chamomile and parsley. Apigenin glycosides are abundant in traditional teas (black, green, and oolong), while luteolin glycosides are found in rooibos tea. Important bioactivities have been related to flavones; apigenin has demonstrated health benefits including the inhibition of cell proliferation, apoptosis induction, the prevention of stem-cell migration through the upregulation of p21 and p27, and the downregulation of NF-κB and PI3K/Akt pathways.[43] Luteolin inhibits MCF-7 cell proliferation and cell-cycle arrest and activates apoptosis through the regulation of IGF-1-dependent IGF-1R and p-Akt without disruption of ERK1/2 phosphorylation.[44]

Isoflavones Isoflavones differ from flavones because of the phenyl group located in C3 instead of in C2 in the pyran ring, and some of their derivatives can form a D ring (e.g., rotenoid). Isoflavones represent the most abundant flavonoids in soybeans, in soy-derived products likes tofu, soymilk, soybean flour, and in green and mung beans.[45] In humans, isoflavones may act as estrogens because of their similarity to 17-β-estradiol. Isoflavones may be found as conjugated forms with acetyl, malonyl glycosides (e.g., genistin, daidzin, and glycitin), or aglycones (e.g., genistein, daidzein, and glycitein) (Zaheer and Humayoun Akhtar, 2017). Isoflavones may regulate cancerrelated signaling pathways.[46] Isoflavones compound in treatment of ovarian cancer cells inhibits invasion and cell migration in a dose-dependent manner. This signaling pathway through the downregulation of FAK and the PI3K/Akt/GSK and modulates p21 and cyclin D1 expression, related to the presence of Erβ. In Isoflavones has a genistein and daidzein sub compunds and its gained the most research attention.[46]

Daidzein

Daidzein(DAI) is a naturally found isoflavone, it is found in soy and soy based product. this dietary phytoestrogens such as the isoflavones daidzein and genistein are thought to protect against chronic diseases that are common in Western societies, such as cancer, osteoporosis, and ischemic heart disease.[47] Daidzein study indicates that an apoptosis inducer in liver cancer cells and treatment of daidzein at 200–600 μM caused mitochondrial-dependent apoptosis mediated by the Bcl-2 family. daidzein with metabolites R-equol and S-equol, suppressed the invasion of MDA-MB-231 expression. daidzein contain compound treatment up-regulated proto-oncogene BRF2 in ER-positive breast cancer cells but not ER-negative cells. In additional study on Female mice, this treated with a high-isoflavone commercial diet showed significantly increased BRF2 expression. Genistein inhibits ovarian carcinogenesis by pleiotropic mechanisms. A higher affinity to estrogen receptor β is one probable explanation for its ability to reduce the risk of ovarian cancer. Genistein also targets multiple cellular signal transduction pathways associated with cell cycle regulation and apoptosis.[48]

Genistein

Isoflavonoid contained in soy as well as soy products contain genistein is the most abundant component and is also a major active component of hormonal supplements for menopausal women. Genistein act like photoestrogens. genistein can be used as a chemo preventive agent in several types of cancers, especially for hormone dependent breast cancer. In H446 lung cancer cells, genistein treatment (25–75 μM) effectively suppressed the cell proliferation and migration, which was accompanied by induction of apoptosis and G2/M cell cycle arrest.[49] The Genistein compounds treatment that is survivin, cyclin B1 and Cdc25, suppressed the expression of Forehead box protein M1 and its target genes regulating cell cycle or apoptosis. hence, the effects of genistein were at least partly mediated by Forkhead box protein M1. genistein compounds treatment to gastric cancer cells suppressed the cancer cell stem-like abilities, including self-renewal, drug resistance and carcinogenicity, which might be due to down-regulation of stemness related genes as well as drug resistance gene ABCG2. genistein significantly decreased the weight and size of gastric cancer inoculated in nude mice. genistein at 25–100 μM exhibited anti-proliferative and pro-apoptotic effects on colon cancer cells.[50] The study indicated that inhibition of oncogenic miR-95, Akt and SGK as well as phosphorylation of Akt could be involved in these anticancer effects. also the genistein compound treatment to mice significantly decreased the weight and size of transplanted colorectal cancer. genistein also inhibited angiogenesis and suppressed metastasis of colorectal cancer to distant organs in mice.[51]

Flavonols Flavonols is a class of flavonoids, chemically it is a 3-hydroxy-2-phenylchromen-4-one. Flavonols founds in low concentration of in onions, red wine, apples, kale, teas, berries and apples. Flavonol-Rich dietary sources of flavonols are red onions, red wine, fresh capers, dried parsley, fresh cranberries, fresh figs. The flavonols classified into different subgroups likes quercetin, kaempferol, fisetin, isorhamnetin, and myricetin. Flavonols has a anti-cancer activities, antioxidant activity, interactions with proteins, and inhibit the enzymes (CYP2C9 and CYP3A4) that regulate the cancer cells.[52]

Quercetin

Quercetin involved in the anticancer effects of flavonoids. Quercetin is chemically consist of 2-phenyl4H-1-benzopyran-4-one, 2- phenylchromone. its shows anti-oxidant activities, the hydroxyl groups that attached at hetertocyclic ring B at carbon 3 and 5. its antiproliferative potential and also give good sensitivity against the free-radicals.[53] quercetin-3-O-glucuronide this are a metabolite of quercetin which is effective in inhibition the noradrenaline, which bind with 2-adrenegic by suppressing the DNA damage, that is induced during the treatment of human breast cancer cells (MCF-10A) by noradrenaline and 4-hydrooxyestradiol.[54]

Phenolic Acids

Polyphenol contain Phenolic acids, this compounds used for inhibiting cancers in vitro and in vivo. it are act as a antioxidant anti-inflammation capacity and repair the damage cells by free radical oxidation reaction. In body phenolic components absorbed through intestinal tract walls. Phenolic Acids mainly classified into two groups, hydroxybenzoic acid and hydroxycinnamic acid Lignans and Stilbenes.[55] Hydroxybenzoic acids class contains Ellagic acid, gallic acid, syringic acid. Hydroxycinnamic acid contain Ferulic acid, chlorogenic acid, caffeic acid. Stilbenes contains Resveratrol, pterostilbene, piceatannol, viniferins, Lignans contains Sesamin, secoisolariciresinol diglucoside, pinoresinol, lariciresinol, syringaresinol, hydroxymatairesinol, matairesinol. In natural source hydroxybenzoic acids compounds present in edible plants and are not considered to be of high nutritional interest. In common foods other phenolic acids are presents, but its consumption is highly variable, depending on intake of coffee.[56]

1. Ellagic Acid

Ellagic acid is a naturally occurring polyphenolic Acids detected the anticarcinogenic effects. ellagic acid prevent the development of colon cancer, it has a antiproliferative action in some cancers, also anti-inflammatory activity.[57] Natural source of ellagic acid (EA) is some fruits and nuts, including berries, pomegranates, grapes, and walnuts. Ellagic acid in 10–40 μg/mL dose showed growth inhibitory effects on MCF-7 breast cancer cells, which was conduct by G0/G1 cell cycle arrest. The modulation of TGF-β/Smads signaling pathway was propose to be the potential mechanism. The

non-cytotoxic dose of ellagic acid that is 25 and 50 µM to androgen independent prostate cancer cells markedly suppressed the cell invasion and motility. The effect might be the result of down-regulation of MMPs.[58] At other side, at higher dose this is 10–100 µM, treatment was found to induce growth inhibition and caspase-dependent apoptosis in PC3 prostate cancer cells in a dose responsive manner. It has a low bioavailability, with 90% remaining unabsorbed from the intestines until metabolized by microflora to the more bioavailable urolintins.[59]

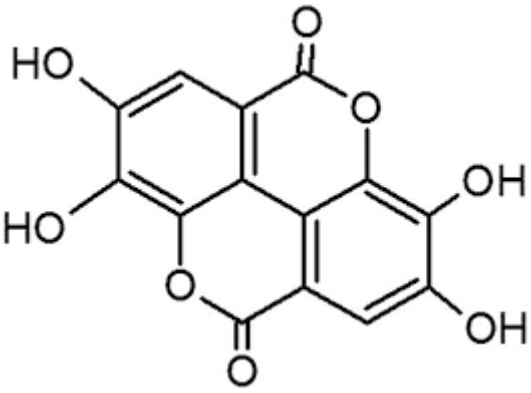

Fig. 1: Ellagic acid.

2. Gallic Acid

Gallic acid, is a plant-derived natural phenolic acid compound as well as part of hydrolyzable tannins. Gallic acid found in Blackberry, raspberry, walnuts, chocolate, wine, green tea and vinegar.[60] Gallic acid possesses various pharmacological activities, such as anti-microbial, anti-inflammatory and anticancer activities. This prevent the development and progression of various types of cancers. the anticancer effects and underlying mechanisms of Gallic acid alone and in combination with cisplatin in non-small cell lung cancer. Gallic acid show anticancer activity by regulation of apoptotic and anti-apoptotic proteins, suppression and promotion of oncogenes, inhibition of matrix metalloproteinases (MMPs).[61] gallic acid showing inhibited migration of AGS gastric cancer cells, GA may be mediated by up-regulation of RhoB as well as down-regulation of AKT/small GTPase signals and NF-κB activity. In addition to this, compared with the control, feeding with gallic acid solution significantly decreased tumor size and weight in mice models of gastric cancer. The ROS-dependent pro-apoptotic effects of gallic acid led to decreased viability of different cancer cells, such as HCT-15 colon cancer cells and LNCaP prostate cancer cells. gallic acid shows activity through the mitochondria-mediated apoptotic pathways by selectively inhibited growth of liver cancer cells.[62] Studies on MCF-7 breast cancer cells also showed that gallic acid treatment inhibited cell proliferation and induced apoptosis via both the extrinsic and intrinsic pathways. gallic acid suppressed the invasion and migration of PC-3 prostate cancer cells through down-regulation of MMP-2 and MMP-9. Treatment with gallic acid decreased cell viability, proliferation, invasion and angiogenesis HeLa and HTB-35 cervical cancer cells, but showed less cytotoxicity on normal cells indicating a potential role of the compound in cervical cancer treatment.[63]

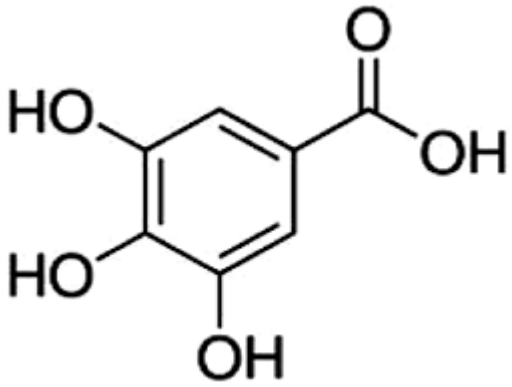

Fig. 2: Gallic Acid.

3. Ferulic Acid

Ferulic Acid, is a natural phenolic acid compound containing anticancer activity. ferulic acid are found in cereal grains, particularly the outer parts of grain. Ferulic Acid showing is a natural antioxidant with anti-cancer effect, on the human glioblastoma cells through molecular and Delayed Luminescence.[64] Ferulic Acid has a effective in cancer also in cardiovascular and neurodegenerative diseases showing therapeutic effect. Ferulic acid, isolated from Ferula foetida, a perennial herb, has shown antineoplastic activity on colon and lung cancer and central nervous system tumors. ferulic acid treatment resulted in decreased viability, increased apoptosis and suppression of metastatic potential in breast cancer cell line MDA-MB-231. Ferulic acid treatment caused cell cycle arrest in PC-3 cells (IC50 300 µM), and led to apoptosis in LNCaP cells.[65]

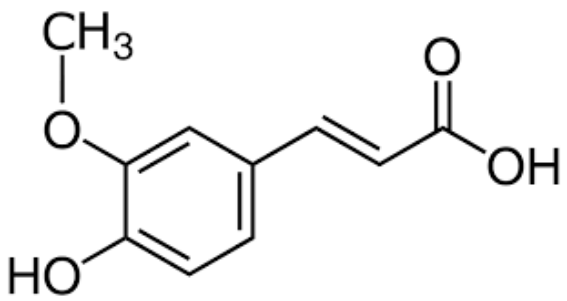

Fig. 3: Ferulic Acid.

Limitation of Polyphenols as Anticancer Agents

polyphenol compounds derived from plants, this are reach of Flavonoids and phenolic acid. anticancer activity studied due to they are able to modulate apoptotic genes. There is Limitation of Polyphenols compound use in cancer therapy. They has optimal pharmacokinetic, pharmacodynamic profile in human body. Same of the factors of this profile like low solubility, rapid release, poor permeability low bioavailability and susceptibility to environmental factors. The variable response to polyphenols compound

is influenced by dose, the cancer cell type, and the patient's genome.[66] This affect by the consumed quantity, and the type and stage of cancer. The polyphenol compounds has a low bioavailability because of very low efficiency of compound. The absorption, bioavailability transportation, and bioactivity of polyphenols compound are very important for their efficacy as new drug candidates. In therapy oral bioavailability of polyphenol compound are the challenge, this compound travel through the digestive system, being absorbed in the stomach and small intestine.[67] Active are biotransformed by the gut microbiota or by hepatic phase I/II metabolism, which may affect the bioavailability and bioactivity. This compound are naturally derived, they has a higher molecular weight hence not easily dissolve in body fluid so results in very poor absorption.[68] This compounds has a phenolic phytochemicals may degrade in body fluid due to various pH levels in the gastrointestinal tract. For example, EGCG is unstable in an acidic environment (stomach pH below 1.5) and at neutral pH such as in the intestine. Because no particular receptors have been identified to transport phenolic phytochemicals into cells via the surface of the small intestine epithelial cells, polyphenols have minimal intracellular penetration. As a result, paracellular and transcellular diffusions as well as passive diffusion serve as the primary basis for the mechanism of transportation through the epithelium. After being absorbed, phenolic phytochemicals go through an active efflux phase, whereby the majority of them are pushed back into the lumen.[69] To improve bioavailability and stability in Gastric pH, Polyphenols are load into carriers to increase their bioavailability and avoid these limitations. This carriers gives the biocompatibility improve bioavailability and avoids the environmental degradation. The nanocarriers use in cancer therapy to deliver polyphenol compounds to affected cell by use this encapsulating phenolic chemicals.[70]

CONCLUSION

The naturally derived compounds in treatment of disease are a most preferred way in current therapy. Cancer and related disease cases increased due to diet and changed lifestyle. As conventional therapy becomes less effective cost, increased toxicity, the development of drug resistance. The desire of new development chemical entities to battling cancer is still a challenge. The review describes current anticancer study, Reactive Oxygen Species in Cancer Development, classification of polyphenols, polyphenol compounds as anticancer agent and Limitation of Polyphenols as Anticancer Agents. This review study has shown that this therapeutic approach polyphenols has a low safety profile while showing minimal efficacy. Researchers has been an increased interest in natural compounds with antineoplastic and anticarcinogenic properties that are able to protect healthy tissues while destroying tumours without causing additional damage. In the future, more it is recommended that the synthesis of well-targeted and designed natural phenolic compounds, can lead to the development of clinically beneficial drugs with efficiency and selectivity in anticancer therapy.

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