e-ISSN:2582-7219

INTERNATIONAL JOURNAL OF MULTIDISCIPLINARY RESEARCH IN SCIENCE, ENGINEERING AND TECHNOLOGY

Volume 5, Issue 12, December 2022

INTERNATIONAL STANDARD SERIAL NUMBER INDIA

Impact Factor: 7.54

International Journal Of Multidisciplinary Research In Science, Engineering and Technology (IJMRSET)

| ISSN: 2582-7219 | www.ijmrset.com | Impact Factor: 7.54|

| Volume 5, Issue 12, December 2022 |

| DOI:10.15680/IJMRSET.2022.0512015 |

Polyphenols: Remedy for Cancer

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ABSTRACT: Cancer is a major health concern as the incidence is growing worldwide and still lacks successful therapies. Plant-derived functional foods are getting considerable attention, primarily due to their safety and therapeutic potential. Polyphenols are a group of mostly natural, water-soluble organic compounds. Here, we review the functions of selected polyphenols and their anticancer properties on numerous cancer cell lines and their mechanisms. The literature search was performed using the electronic database PubMed, Google scholar up to June 2020, with the following keywords—polyphenol, polyphenol anticancer, quercetin anticancer, resveratrol anticancer, curcumin anticancer, and kaempferol anticancer. Chemical structures of the selected polyphenols were obtained using the ChemDraw program. The initial search identified 40,554 polyphenols papers and among that, 2,559 were limited to polyphenol and cancer, 987 quercetin and cancer, 2,174 curcumin and cancer, 1,079 resveratrol and cancer, and 226 were limited to kaempferol and cancer. A total of 84 papers are included in this review paper. Most studies report the multiple anticarcinogenic properties of plant-derived polyphenols, including its inhibitory effects on the proliferation of cancer cells, tumor expansion, angiogenesis, inflammation, and metastasis. Besides, some studies shows potential synergistic effects when polyphenol treatment combined with chemotherapeutic agents. Anticancer effects of polyphenolic compounds like quercetin, curcumin, resveratrol, and kaempferol are investigated on numerous cancer cell lines and have shown prominent results.

KEYWORDS: cancer, polyphenols, anticarcinogenic, inhibitory effects, chemotherapeutic, tumor, organic, therapy

I. INTRODUCTION

Globally, there were approximately 14.1 million new cancer cases in 2012, and the number was estimated to reach 25 million in 2032. Aside from the high incidence, cancer is also one of the leading causes of death. In 2012 alone, there were about 8.2 million cancer-related deaths, which were mainly attributed to lung, gastric, colorectal, liver, breast, prostate and cervical cancer . The situation urges the research of cancer prevention and treatment.[1] In the last two decades, the anticancer effects of natural polyphenols have become a hot topic in many laboratories. [1]Meanwhile, polyphenols are potential candidates for the discovery of anticancer drugs. Polyphenols are defined as compounds having at least one aromatic ring with one or more hydroxyl functional groups attached. Natural polyphenols refer to a large group of plant secondary metabolites ranging from small molecules to highly polymerized compounds . Polyphenols are widely present in foods and beverages of plant origins (e.g., fruits, vegetables, spices, soy, nuts, tea and wine) .[2] Based on chemical structures, natural polyphenols can be divided into five classes, including flavonoids, phenolic acids, lignans, stilbenes and other polyphenols. [2]Flavonoids and phenolic acids are the most common classes, and account for about 60% and 30% of all natural polyphenols, respectively . A plethora of studies have documented the anticancer effects of natural polyphenols . Noteworthy examples include anthocyanins from blueberries, epigallocatechin gallate (EGCG) from green tea, resveratrol from red wine and isoflavones from soy[3]. The anticancer efficacy of natural polyphenols has largely been attributed to their potent antioxidant and anti-inflammatory activities as well as their abilities to modulate molecular targets and signaling pathways, which were associated with cell survival, proliferation, differentiation, migration, angiogenesis, hormone activities, detoxification enzymes, immune responses, etc.[3]

| ISSN: 2582-7219 | www.ijmrset.com | Impact Factor: 7.54|

| Volume 5, Issue 12, December 2022 |

| DOI:10.15680/IJMRSET.2022.0512015 |

Table 1

The classification of natural 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, 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

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II. DISCUSSION

Polyphenols: Their Chemistry and Their Importance in Human Health

Relevant Members of the Polyphenol Family

Polyphenols are classified as derivatives of shikimic acid/phenylpropanoids (derived from tyrosine and phenylalanine) and polyketide (lacking functional groups related to nitrogen) pathways. For shikimic acid derivatives, phenylpropanoid units serve as the basis for multiple types of polyphenols, such as cinnamic (C6–C3), benzoic acids (C6–C1), flavonoids (C6–C3–C6), proanthocyanidins [(C6–C3–C6)n], stilbenoids (C6–C2–C6), and lignins [(C6–C3)n] [4]

Phenolic Acids

Phenolic acids are the simplest phenolic compounds, formed of only one phenolic ring with multiple hydroxy or methoxy groups attached to their backbone. Hydroxycinnamic acids are aromatic carboxylic acids with unsaturation in the side chain (commonly of trans-configuration) and are more abundant than hydroxybenzoic acids. Cinnamic acids work as phytohormones, which are important components of lignin and the precursors of chalcones, flavonoids, anthocyanins, and stilbenes . Hydroxycinnamic acids are considered potent antitumor agents due to the presence of α, β-unsaturation, acting as Michael acceptors . Relevant hydroxycinnamic acids include caffeic, [5]ferulic, p-coumaric, and sinapic acids, and the most representative hydroxybenzoic acids include gallic, vanillic, syringic, protocatechuic, and p-hydroxybenzoic acids. Phenolic acids can be found in vegetable-derived foods including cereals, legumes, soybeans, coffee, tea, rosemary, thyme, apples, various berries, plums, cherries, and citrus fruits . Different health effects have been related to phenolic acids. Chlorogenic acid has exhibited its anticancer potential by inducing differentiation through an increase of KHSRP, p53, and p21, a decrease of poor differentiation-related genes c-Myc and CD44, and downregulation of oncogenic miRNA-17 family members in cancer cell lines .Other mechanisms involve epigenetic regulation; gallic acid inhibits DNMT1 activity through the negative regulation of p-Akt, reducing the nuclear import and stability of DNMT1. [4]Potential epigenetic targets include CCNE2, CCND3, CDKN1A, and CCNB1 genes, which play important roles in the GADD45 signaling pathway .[6]

Flavonoids

Flavonoids are ubiquitous compounds in plants that are responsible for the fragrance, color, and flavor of fruits, seeds, and flowers, with important roles in pollination and protecting plants from ultraviolet (UV) light and acting as detoxifying agents and as signaling molecules, and they may play important roles in cold and heat acclimation . There are nearly 6,000 flavonoid-related compounds, including their derivatives flavanones, flavones, isoflavones, flavanols, flavonols, and anthocyanidins. Benzo-γ-pyrone is the basic chemical structure of flavonoids characterized by the presence of 15 carbon atoms as the base skeleton, organized in the form C6–C3–C6 (A+C–B) (two benzenic rings A and B) [7]and linked by a unit of three carbons that may or not form a third-ring structure (pyran ring C).[5] Flavonoids can occur as aglycones and as hydroxylated, methylated, and glycosylated derivatives and have great relevance for the sensory quality of citrus fruits. For example, flavonoids such as naringerin and neohesperidin are responsible for bitterness .Regular consumers of tea may have intakes of over 1,000 mg/day; however, normal diets only provide between 20 and 200 mg/day , and a regular dietary intake of flavonoids (500 mg/day) has been related to a diminished mortality risk .[8]

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 members . [6]The principal flavanones comprise naringenin, hesperidin, eriodictyol, taxifolin, didymin, and eriocitrin, regularly found in citric fruits and juices such as oranges, mandarins, and lemon.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 defense .[9]

Flavones

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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 blue flowers, and as plant-signaling molecules. Relevant flavones include apigenin, diosmin, chrysin, tangeretin, luteolin, 7,8-dihydroxyflavone, and 6-hydroxiflavone[10]. Flavones are found in plants employed for preparing infusions such as chamomile and parsley. Apigenin glycosides are abundant in traditional teas[7] (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 . 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 .[11]

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 (tofu, soymilk, soybean flour) ,and in green and mung beans. In humans, isoflavones may act as phytoestrogens 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) .[8] Isoflavones may regulate cancer-related signaling pathways. Genistein and daidzein treatment of ovarian cancer cells inhibits invasion and cell migration in a dose-dependent manner through the downregulation of FAK and the PI3K/Akt/GSK signaling pathway and modulates p21 and cyclin D1 expression, related to the presence of ERβ .[12]

Flavonols

Constituted of a 3-hydroxyflavone backbone, flavonols entertain an unsaturation between C2 and C3, an OH− at C3, and a carbonyl group at C4, and along with flavones and anthocyanidins, they act as copigments to strengthen the color of flowers .Flavonols are usually found as β-O-glycoside conjugates to facilitate storage in vacuoles (glucose being the most common conjugate) . Flavonol-rich dietary sources include fresh capers, dried parsley, elderberry juice, rocket lettuce, red onions, fresh cranberries, fresh figs, apples, red wine, and tea. The principal flavonols include kaempferol, quercetin, fisetin, isorhamnetin, and myricetin, and their consumption has been related to a broad spectrum of health benefits. Different mechanisms are involved in the anticancer effects of flavonoids.[9] Quercetin-3-O-glucoside inhibits cell growth, arrests the cell cycle in phase S, induces apoptosis through caspase-3 activation, and inhibits topoisomerase II activity in human hepatic-cancer cells. Other mechanisms include apoptosis induction through modification of the BAX/Bcl-2 ratio and evoking paclitaxel chemosensitization by the downregulation of MDR-1 (associated with paclitaxel resistance) in myricetin-treated ovarian cells .[13]

Flavanols

Flavanols (also known as flavan-3-ols or catechins) have a pyran ring with an OH− at C3, the B ring is bound to C2, and there is a lack of a double bond between C2 and C3 (allowing for two chiral centers). Flavan-3-ols are found either in free form or as gallic acid esters in different food sources such as apples, black tea, green tea, dark chocolate, and red wine .Relevant flavanols include the following:[10] (+)-catechin; (+)-gallocatechin; (−)-epicatechin; (−)-epigallocatechin; (−)-epicatechin 3-gallate; (−)-epigallocatechin 3-gallate; theaflavin; theaflavin 3-gallate; theaflavin 3′-gallate; theaflavin 3,3′-digallate; and thearubigins . Several health benefits have been related to flavanols. Lung cancer cells treated with (−)-epigallocatechin 3-gallate decreased the cell migration induced by human neutrophil elastase and induced α-1 antitrypsin through PI3K-pathway regulation.[14]

Proanthocyanidins

Proanthocyanidins (condensed tannins) are linked by C–C (sometimes by C–O–C) bonds, varying in the degree of polymerization .According to interflavan linkages, proanthocyanidins are classified as type A or type B. Type A lacks interflavan linkage but possesses another bond between the OH- from A ring and the C2 of C ring (C2–O–C7 or C2–O–C5) and type B with bonds between the C4 of B ring and either C6 or C8 of C ring (C4–C6 or C4–C8) . Proanthocyanidins, which are composed of catechin or epicatechin subunits, are known as procyanidins; if they are composed of epigallocatechin subunits, they are called prodelphinidins. Proanthocyanidins confer astringency and bitterness and are regularly found in natural sources such as the fruits/seeds/peels of *Vitus vinifera, Punica granatum*,

| ISSN: 2582-7219 | www.ijmrset.com | Impact Factor: 7.54|

| Volume 5, Issue 12, December 2022 |

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and *Theobroma cacao*, the leaves of *Fructus crataegi* and *Eucalyptus* spp.[11], the flowers of *Rosa rugosa* and *Nymphaea tetragona,* and the roots/stems of *Rheum palmatum* and *Ipomoea batatas* .Procyanidins along with flavones possess high antioxidant activity. Catechin-related compounds are the most powerful flavonoids against reactive oxygen species (ROS), with a broad spectrum of health benefits. Grape proanthocyanidins have been associated with a decrease of UVB-induced photocarcinogenesis in SKH-1 mice through the regulation of immunosuppression by decreasing the expression of IL-10 and increasing that of IL-12 .Proanthocyanidins also inhibit cell proliferation by means of the modulation of miRNA expression .[15]

Anthocyanidins

Anthocyanidins are composed of ring A linked to ring C, which is bound in C3 to ring B, with no carbonyl group in C4 and two unsaturations in ring B at the O–C2 and C3–C4 positions. Anthocyanidins are salt derivatives from the flavylium cation with a positive charge in the oxygen atom. Their color is pH-dependent, with red predominating under acidic conditions, whereas blue predominates under alkaline conditions . Anthocyanidins can be found as aglycones, but when they are conjugated into a glycoside, they are known as anthocyanins . Anthocyanidins act as naturally occurring pigments found in the flowers and fruits of many plants that confer red, pink, blue, or violet shades , and that occur in the outer cell layer of many edible products including blueberries, strawberries, raspberries, red wine, and red onion. The most representative anthocyanidins are cyanidin, delphinidin, pelargonidin, peonidin, malvidin, and petunidin .[12] Many anthocyanidin-rich plants have been employed in traditional folk medicine and their effects have been extensively studied. A phase 0 clinical trial showed that an anthocyanin-rich raspberry lozenge administered to patients with oral squamous cell carcinomas (OSCC) for 14 days caused a reduction in the expression of prosurvival genes AURKA, BIRC5, and EGFR, and downregulation of proinflammatory genes NFKB1, PTGS1, and PTGS2 .[15]

Stilbenoids

Stilbenoids are nonflavonoid polyphenols derived from the phenylpropanoid pathway, in the form of hydroxylated derivatives of stilbene backbone C6–C2–C6 (two aromatic rings linked by a methylene bridge), with two possible planar configurations (cis or trans). Stilbenoids are usually found as aglycones, glycosidic/methoxyl conjugates, or oligomeric units (viniferins). Stilbenoids act as phytoalexins and 1,000 of these compounds have been identified to date .Stilbenoid-rich sources include the plants of the Gnetaceae, Pinaceae, Cyperaceae, Fabaceae, and Dipterocarpaceae families; however, their content is <10% of that found in the Vitaceae family, and the richest sources of stilbenoids are wine, berries, and grape juice .Resveratrol represents by far the most important compounds of its kind[13], followed by gnetol, piceid, astringin, pterostilbene, piceatannol, viniferins, etc. The bioactivities of stilbenoids include anticancer effects. Pterostilbene has shown upregulation of PTEN in prostate cancer cells and xenografts through the reduction of levels of oncogenic miR-17, miR-20a, and miR-106b,thus highlighting the potential health effects of stilbenoids in terms of their being promising candidates as novel therapeutic agents.[16]

Absorption and Metabolism of Polyphenols

There are several considerations for the development of new drugs, including bioaccessibility and bioavailability. Bioaccessibility is the fraction released from the food matrix into the intestinal milieu, rendering the drug bioavailable , whereas bioavailability is the extent of the drug absorbed that reaches the systemic circulation, with the drug becoming available at the site of action .Ingested polyphenols are subjected to biotransformation in the GI tract by either digestive enzymes or the gut microbiota and may impact their bioactivities. The majority of polyphenols are released in the stomach (65%) and small intestine (10%) . The main sites of polyphenol absorption include the intestine and the colon (5–10% of the ingested polyphenols), whereas unabsorbed polyphenolics accumulate at mM concentrations in the large intestine, where the gut microbiota will exert biotransformation because complex polyphenols cannot be absorbed without modifications . The gut microbiota involved in the biotransformation of polyphenols includes *Eubacterium* spp., *Clostridium* spp., *Bifidobacterium* spp., and *Lactobacillus* spp. Biotransformed polyphenols are absorbed through the intestinal wall, transported to the liver where hepatic enzymes will break down (phase I metabolism) or conjugate (phase II metabolism) polyphenolics[14], and then they are distributed to target organs or eliminated in urine. The biotransformation of polyphenols may limit biological effects, and this may explain the discrepancy between in vitro and in vivo effects. For example, although many metabolites of anthocyanins can be found in urine, parent compounds are not detectable, possibly due to full metabolization .Another example is curcumin, which has low bioavailability and poor absorption, and the majority of the ingested curcumin is detected in the form of phase II metabolism-derived products, whereas the parent compound is scarcely detectable in the organism [17]. The gut microbiota plays a significant role in the metabolism of curcumin, especially Escherichia coli, which converts curcumin into

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| DOI:10.15680/IJMRSET.2022.0512015 |

tetrahydrocurcumin.Biotransformation is not always linked to the loss of bioactivity; the oxidative metabolites of curcumin possess important biological effects . However, like the majority of polyphenols, after passing through the GI, 90% of curcumin is excreted;is significant in that 10% of the ingested curcumin is responsible for its biological effects. The low bioavailability and complex metabolism of polyphenols render it difficult to present recommendations concerning their daily intake. The high variability of results of in vivo experiments and clinical trials is attributed to the poor absorption and metabolism of polyphenols; however, their safety and the ease of obtaining make them ideal candidates for the treatment of many diseases.[18]

Anticancer Activities of Polyphenols Against the Foremost Malignant Tumors

Cancer constitutes an important public health concern worldwide with 19.3 million new cases and 10 million deaths in 2020. Principal cancer types include lung, colorectal, stomach, liver, breast, esophagus, prostate, and cervix uteri .Cancer development is closely related to unhealthy nutritional habits; the low consumption of fruits and vegetables (<800 g/day) has been related to an increase of 30–50% in the incidence of colorectal cancer . Plant-derived compounds are widely utilized by individuals due to their cost accessibility, the belief in better effectiveness compared to medical prescription drugs, and the trend toward the use of products of natural origin. The contribution of plant-derived natural compounds[15] to the pharmaceutical field is extensive; important examples include aescin, morphine, paclitaxel, and vincristine and, in the most recent two decades, more than 30% of US Food and Drug Administration (FDA)-approved drugs are derived from natural compounds .Polyphenols may act as antioxidants through two main mechanisms as follows: first, phenolic groups accept an electron to form relatively stable phenoxyl radicals, preventing oxidative damage in cellular components. Second, OH− groups act as hydrogen donors and interact directly with reactive nitrogen species (RNS) and ROS , which could explain their preventive role in oxidative damage.[19]

Polyphenols provide protection from cancer risk factors, including tobacco, alcohol, unhealthy diets, sedentarism, and even those related to carcinogenic infections caused by pathogens such as the hepatitis B/C virus (HBV; HCV), the Epstein-Barr virus, and the human papillomavirus (HPV).[16]

Nicotine represents the most toxic factor of tobacco, may lead to excessive cell proliferation through an increase in oxidative stress, and also has been related to an improvement of the invasiveness of lung and breast cancer cells . Resveratrol prevents nicotine-induced cell proliferation through the MAPK signaling pathway by means of the downregulation of p-ERK in pancreatic cells . Alcohol consumption has been related to the development of colorectal cancer .Epigallocatechin 3-gallate (EGCG) inhibits ERK and activates JNK, thus fostering apoptotic cell death by the release of cytochrome c in human colon cancer cells . Healthy food habits improve the health status of persons[17]. The kaempferol present in apples and onions suppresses the expression of MMP-9 (related to metastasis progression) via the inactivation of the MAPK/AP-1 pathway in breast cancer cells .HCV promotes the proteasomal degradation of pRb through the E6 ubiquitin-dependent mechanism, thus interfering with cell-cycle regulation and the response to cellular DNA damage. Treatment with theaflavins prevents the entry of HCV into hepatocytes but does not prevent viral replication ,however, it represents a promising preventive approach for future malignancy induced by HCV infection. High-risk HPV represents other infectious agents of relevance for the development of malignant tumors; they account for approximately 25% of cases of HNSCC (HPV-16), and virtually all cervical cancers are caused by high-risk HPV . The combination of TriCurin polyphenols (curcumin, epicatechin 3-gallate, and resveratrol) reduces mRNA and the protein levels of E6 and E7, leading to the accumulation of p53 and pRb, thus decreasing tumor weight and cell proliferation by 86.3 and 19.9%, respectively.The effects of TriCurin on HNSCC appear promising, considering that this cancer is the sixth most prevalent malignancy worldwide .[20]

Despite the fact that the bioactivities of polyphenols can often be limited by bioavailability, the detoxification metabolism, and the individual variability index, their wide range of health benefits is not limited to a single type of cancer or to a single mechanism of action. Therefore, polyphenols represent promising therapeutic agents for different cancers.[11]

III. RESULTS

Cancer cells are distinguished by several distinct characteristics due to cumulative epigenetic changes of multiple genes and associated cell signalling pathways, some of which are linked to inflammation. Immune cells infiltrate tumours and are engaged in a cross talk with neoplastic cells; thus, inflammation might affect responses to cancer therapy[18] . Studies on a wide spectrum of various bioactive polyphenols that regulate multiple cancer-inflammation pathways and epigenetic cofactors exhibit low toxicity and are readily available .The anti-inflammatory properties of many reported

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polyphenols are associated with their ability to induce HDAC activity .Since several polyphenols can modulate both HDAC and HAT, there may be a common underlying mechanism. For instance, curcumin, a known antioxidant as well as a free radical, may regulate both acetylation and deacetylation through the modulation of oxidative stress. Rahman et al. have shown that oxidative stress can induce NF-κB pathway through the activation of intrinsic HAT activity, resulting in the expression of proinflammatory mediators, but it can also inhibit HDAC function.The role of polyphenols in regulation of epigenetic pathways including sirtuin 1 (SIRT1) modulation has been investigated . Sirtuins are a subclass of HDACs that have been shown to modify metabolism, inflammation, aging,[13] or cellular apoptosis in many pathological processes. The epigenetic effect of SIRT1 is due to its ability to deacetylate many transcriptional factors such as p53, NF-κB, forkhead box class O (FOX), and histone proteins .Sulforaphane (SFN) is a bioactive polyphenol present in cruciferous vegetables such as broccoli, cabbage, and kale . It has been previously shown that SFN induces the expression of phase-II detoxification enzymes , and expression of glutathione transferase in murine hepatocytes.Furthermore SFN stimulates phase-II detoxification through activation of nuclear factor E-related factor 2 (NRF2) localized in the cytoplasm .In response to oxidative stress, NRF2 translocates to the nucleus and binds to the antioxidant responsive element (ARE) promoting expression of antioxidant enzymes .In a xenograft murine model, oral administration of SFN significantly reduces tumour size and increases apoptosis. These results indicated that SFN anticancer effects are exerted via inhibition of oxidative stress induced by NRF2-mediated pathways .[19] In addition, SFN promotes anticancer effects through the inhibition of HDAC activity. For instance, in HCT116 colon cancer cell line, SFN inhibits HDAC activity in a dose-dependent manner . A ten-week diet supplementation with SFN induces acetylation of histones in the ileum, colon, and prostate C57BL/6J mice tissues .Moreover, sulforaphane-N-acetylcysteine (SFN-NAC) and sulforaphane-cysteine (SFN-Cys), two metabolites of SFN generated via the mercapturic acid pathway, may mediate the inhibitory effects on HDAC activity .[15]

Isothiocyanate, such as phenethyl isothiocyanate (PEITC), has been shown to inhibit carcinogenic process by growth arrest of many types of cancer cells through induction of apoptotic pathway . Treatment of human prostate cancer cell lines, with PEITC modulated histone acetylation and methylation pathways, in particular restored GSTP1 expression through demethylation of specific gene promoter and inhibited the activity of HDACs.Curcumin, a polyphenol extracted from the most popular Indian turmeric spice (*Curcuma longa*), has antioxidant and anti-inflammatory properties which have been associated with multiple health benefits including cancer prevention.In liver of lymphoma bearing mice long term effect of curcumin leads to prevention of cancer, by inducing phase-II antioxidant enzymes via activation of NRF2 signalling, restoration of tumour suppressor p53, and modulation of inflammatory mediators like TGF-β and COX2. These results suggest antioxidant and anti-inflammatory properties of curcumin .[20]

Curcumin is a potential modulator of histones affecting both the HAT and HDAC enzyme activities .Several in vitro studies, performed on cancer cell lines derived from various tissues, have demonstrated that curcumin has the potential to specifically downregulate p300/CBP HAT activity. In particular, such inhibition suppresses histone acetylation as well as acetylation of nonhistone protein like p53 . Furthermore, curcumin exposure led to a significant reduction of histone acetylation via inhibition of HAT activity without changing HDAC levels in hepatoma cultured cells .In hematopoietic cell lines, curcumin repressed the HAT activity of p300/CBP as well as the activity of various classes of HDACs, which in turn limits the proliferative capacity of cells and induces apoptosis . Antitumour activity of curcumin has been also linked to its ability to modulate miRNA expression level in cancer cells. To this purpose, curcumin has shown to reduce the expression of the antiapoptotic protein Bcl-2 in a breast cancer cell line, MCF7, by upregulating miR-15a and miR-16 .Green tea polyphenols are known to have high antioxidant properties and consequent beneficial functions, including anti-inflammation and cancer prevention. On the other hand,[17] some studies have demonstrated their gastrointestinal toxicity when used at high doses, presumably due to their prooxidant properties.Among green tea polyphenols, ECGC has been extensively studied. A treatment of high doses of this catechin may aggravate colon carcinogenesis in mice and induce hepatotoxicity in experimental animals and in humans as reported by epidemiological observations .Importantly, it has been reported that EGCG can reduce cisplatin-mediated side effects treatment, in particular nephrotoxicity. Cisplatin, a cancer chemotherapeutic drug, induces kidney specific mitochondrial oxidative stress and impaired antioxidant defense enzyme activity. Treating mice with EGCG reduces cisplatin induced mitochondrial oxidative stress leading to an improved renal function compared to the counterparts. EGCG may be a potential and promising adjuvant agent for cisplatin cancer therapy.Additionally these bioactive compounds are extensively studied from an epigenetically point of view. It has been shown that treatment on a human prostate cancer cell line altered DNA methylation levels and chromatin modelling and reduced the activity of Class I HDACs [90]. EGCG remarkably inhibits HAT activity, whereas other polyphenols derivatives, such as catechin, epicatechin, and epigallocatechin, exhibited low anti-HAT effects. EGCG acted as a HAT inhibitor and reduced the binding of p300/CBP to the promoter region of interleukin-6 gene with an increased recruitment of HDAC3, which highlights the importance of the balance between HATs and histone deacetylases in the NF-κB-

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| Volume 5, Issue 12, December 2022 |

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mediated inflammatory signalling pathway Nandakumar and colleagues demonstrated that EGCG-treatment of skin cancer cells modulated the levels of DNA methylation and histone modifications. [19]These findings resulted in reexpression of tumour suppressor genes $p16^{INK4a}$ and $p21^{CIP/WAF1}$.[17]

A combination of green tea polyphenols, a dietary DNA methyltransferase inhibitor and sulforaphane, a dietary histone deacetylase inhibitor leads to the epigenetic reactivation of silenced tumour suppressor genes such as $p21^{CIP/WAF1}$ and KLOTHO through active chromatin modifications in breast cancer cell lines . These findings are relevant for understanding the potential of synergistical activity of polyphenol therapeutic combinations.

Treatment of various human cancer cell lines with EGCG caused a concentration and time-dependent reversal of hypermethylation of $p16^{INK4a}$, p15, RARβ, MGMT, and hMLH1 genes [94, 95]. Furthermore, EGCG partially reversed the hypermethylation status of tumour suppressor gene RECK and enhanced the expression of RECK mRNA, which correlated with reduced expression of matrix metalloproteinases MMP-2 and MMP-9 involved in the invasive ability of cancer cells .[20]

Aberrant promoter methylation of Wnt inhibitory factor-1 (WIF-1) is a fundamental mechanism of epigenetic silencing in human cancers. EGCG has been reported to directly reactivate the WIF-1, through the promoter demethylation in lung cancer cell lines .EGCG modulated miRNAs in lung cancer and hepatocellular carcinoma where the expression of several miRNAs was changed . One of the upregulated miRNAs, miR16, specifically targets antiapoptotic protein Bcl-2 . Altogether these pieces of data indicate that EGCG may be effective in different cancer cell types through different epigenetic pathways.Coffee and tea polyphenols are also demethylating agents in human breast cancer cell lines where caffeic acid or chlorogenic acid inhibited DNMT1 activity, in a concentration-dependent manner .Resveratrol (RV), a natural polyphenol found in blueberries, cranberries, nuts, red grapes, and wine, exerts anti-inflammatory and anticancer effects .It has the ability to modulate signalling pathways that control cell growth, apoptosis, angiogenesis, and tumour metastasis processes.Furthermore, RV is gaining attention for its antioxidant capabilities and influence on glucose metabolism. Oxidative stress and high glycolytic flux are common characteristics of cancer cells. It has been demonstrated that RV inhibits intracellular ROS level and suppresses cancer cell glycolytic metabolism[12] .

Since anticancer biological activities are already demonstrated for RV and curcumin, to investigate the combined chemopreventive potential of these two polyphenols has been of great interest. It has been shown by Malhotra and colleagues that curcumin and RV when supplemented in combination regulate drug-metabolizing enzymes and antioxidant enzymes, during lung carcinogenesis in mice.[18]

RV activates the protein deacetylase SIRT1 leading to the formation of inactive chromatin and changes in gene transcription .On the other hand, RV activates p300/CBP HAT that participates in the formation of an active chromatin structure .Furthermore, Tili and his group [106] have shown that RV also inhibits oncogenic miRNAs while inducing tumour suppressor miRNAs. These multiple epigenetic alterations by RV exposure can partially explain the activation of some tumour suppressor genes.[14]

In breast cancer, the tumour suppressor gene BRCA1 is associated with lower levels of SIRTs expression. It has been reported that in in vitro and in vivo experimental models RV can increase the expression of BRCA1 by inhibiting Survivin expression and activating SIRT1. These findings suggest that resveratrol treatment serves as a potential strategy for targeted therapy for BRCA1-associated breast cancer . Furthermore, RV in combination with black tea polyphenols suppresses growth and development of skin cancer in mice by inhibiting the MAPK and p53 pathways .Isoflavones are compounds found in soy beans and act like estrogens. Among them, genistein and daidzein have gained the most research attention. Many studies have reported that genistein can be used as a chemopreventive agent in several types of cancers, especially for hormone-dependent breast cancer . Genistein has been shown to bind both the estrogen receptor alpha (ERα) and the estrogen receptor beta (ERβ). The ERα/ERβ ratio is a prognostic marker for breast tumours, and ERα expression could indicate the presence of malignant tumours. It has been reported that in human breast cancer cell lines genistein effects depend on ERα/ERβ ratio for oxidative stress regulation, mitochondrial functionality, and modulation of antioxidant enzymes, and sirtuins . Genistein is also involved in the regulation of gene transcription by modification of epigenetic events including DNA methylation and histone modifications. Genistein has been shown to cause reversal of DNA hypermethylation and reactivated methylation-silenced genes, including tumour suppressor gene $p16^{INK4a}$ in human esophageal squamous carcinoma cell line . In renal carcinoma, the cell tumour suppressor gene BTG3 is transcriptionally downregulated. This inhibition is due to promoter CpG island methylation. The methylation-silenced BTG3 gene can be reactivated by genistein treatment that causes CpG demethylation, inhibition of DNMT activity[19], and induction of active histone modifications .[16]

| ISSN: 2582-7219 | www.ijmrset.com | Impact Factor: 7.54|

| Volume 5, Issue 12, December 2022 |

| DOI:10.15680/IJMRSET.2022.0512015 |

Moreover, genistein treatment has shown the ability to modulate miRNAs expression level. For instance, in prostate cancer cells, genistein caused an increase of miRNA-1296 and accumulation of cells in the S phase of the cell cycle along with a significant downregulation of minichromosome maintenance gene (MCM-2), target of miRNA-1296 .Quercetin, a dietary polyphenol present primarily in buckwheat and citrus and onions , is known to reduce intracellular ROS levels in various cell types by modulating detoxifying enzymes, such as superoxide dismutase 1 (SOD1) and catalase (CAT). Low concentration of quercetin attenuates the therapeutic effects of cisplatin and other antineoplastic drugs in ovarian cancer cells, by reducing ROS damage. The study concluded that quercetin supplementation during ovarian cancer treatment may detrimentally affect therapeutic response .Quercetin activates SIRT1 deacetylase, through inhibition of HDAC and DNMT1, and has been shown to inhibit the cell cycle and induce apoptosis, thus suppressing tumour growth and angiogenesis .Artichoke polyphenolic extracts had cytotoxic and apoptotic effects on colorectal cancer cells. It has been found that the proapoptotic BAX gene expression and a cell cycle inhibitor $p21^{CIP/WAF1}$ were induced in the presence of artichoke polyphenols . Polyphenolic extracts from the edible part of artichoke (AEs) exhibited cancer cytotoxic activity on a human hepatoma cell line, as well as on other cell lines derived from various human tissues. It triggered apoptosis in a dose-dependent manner on a human breast cancer cell line without any effects on normal breast epithelial cell line. Furthermore, cell motility and invasion capabilities were remarkably inhibited by AEs treatment .Furthermore AEs induce DNA hypomethylation and increase lysine acetylation levels in total proteins . Importantly, the authors have shown that AEs have a prooxidant activity in breast cancer cells and an antioxidant effect on normal hepatocytes .[18]

From another point of view, chemopreventive polyphenols may indirectly modulate chromatin dynamics and epigenetic effects upon interference with global cancer metabolism .To this purpose, the important role of sirtuins as principal intracellular mediators of the beneficial effect of the Mediterranean diet has been recently highlighted .[20]

IV. CONCLUSIONS

Cancer remains a second leading cause of deaths and major public health problem. It occurs due to extensive DNA damage caused by ultraviolet radiations, ionizing radiations, environmental agents, therapeutic agents, etc. Among all cancers, the most frequently diagnosed cancers are lung (12.7%), breast (10.9%), colorectal (9.7%), and gastric cancer (7.81%). Natural compounds are most favorable against cancer on the count of their anti-cancerous ability, easy to avail and efficient. Among natural compounds, polyphenols (flavonoids, catechin, hesperetin, flavones, quercetin, phenolic acids, ellagic acid, lignans, stilbenes, etc.) represent a large and diverse group used in the prevention and treatment of cancer. Natural flavonoids are derived from different plant sources and from various medicinal plants including Petroselinum crispum, Apium graveolens, Flemingia vestita, Phyllanthus emblica, etc. Natural flavonoids possess antioxidant, anti-inflammation, as well as anti-cancerous activities through multiple pathways, they induce apoptosis in breast, colorectal, and prostate cancers, lower the nucleoside diphosphate kinase-B activity in lung, bladder and colon cancers, inhibit cell-proliferation and cell cycle arrest by suppressing the NF-kB pathway in various cancers, etc.[20]

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| ISSN: 2582-7219 | www.ijmrset.com | Impact Factor: 7.54|

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