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REVIEW ARTICLE

CANCER EPIGENETICS AND THE ROLE OF DIETARY ELEMENTS

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ABSTRACT

Cancer has been a fatal disease since many decades. Over the time, it is presented in multiple ways and is a matter of consideration as accounts for the high rate of mortality. The aim of the current review was to focus on the genetics, epigenetics factors and role of medicinal plants for the cure of this inimical disease. Related articles available in English language (2002-2018) were reviewed with help of different database, including PubMed, Springer Link, Medline, Google Scholar and ScienceDirect. In order to ensure credibility and accuracy of data only those articles were considered which are published in indexed journals i.e. Web of Science and Scopus. This project was conducted at the Department of Pharmacy, Government College University, Faisalabad, Pakistan from 02-01-2019 to 28-02-2019. The genetic machinery is vibrantly involved in the interpretation of the signals and is observed to be affected by various dietary factors. A sequence of modified activities is observed with use of these dietary elements. However, the modification is reviewed through the histone acetyltransferase (HAT), histone deacetylase (HDAC) and DNA methyl transferase (DNMTs), effecting the expression of gene. These modified genes, in turn then express the signals in multiple reformed ways. Different dietary elements that are used such as polyphenol, alkaloid and flavonoids are effective against cancer. The progression of disease involves genetics and epigenetics due to amplification, translocation and mutation during gene expression. Though, many studies have been conducted elaborating the role of plants and their ingredients which play a part in inhibition of cancerous cells by blockade of cell cycle and apoptosis; more in-depth investigations are still required to identify the new drug target and novel therapeutic modalities.

KEY WORDS: Cancer; Epigenetics; Histone Acetyltransferase; Histone Deacetylase; Medicinal Plants.

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INTRODUCTION

From the beginning of time, cancer has been presented in a variety of ways. Right from the time of Hippocrates, cancer was named following evidence of thick blood vessels feeding the tumor, acquiring a shape resembling the claw of a crab that grabs the tumor. Later in the era of Laennec, cancer was considered as a disease that is predisposed at the different stages of cell proliferation.[1] Last decade has shown up with the development of the genetic model of cancer. Boveri et al. was the first to link cancer with genetics due to the displacement of abnormal chromosome in cancer cells.[2]

Now a great deal of development has been done in the identification of the genes that are marked for the progression of cancer in different organs, like, mutations in ERBB2 and EGFR for the disposition of lung cancer, HER2/NEU mutations in breast cancer, BCR-ABL predisposition in chronic myelocytic leukemia. The studies have revealed the prevalence of disease on the basis of methylation in the DNA, whether it is hyper- or hypomethylation.[3] Methylation occurs on carbon no. 5 of cytosine. Also, summing up of different functional groups on the histone tails

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is observed. This is a common phenomenon in health and disease to express codes in genomes that vary in population .[4] This involves acetylation and deacetylation of histones. Histones are present as core entrapped in octamers of DNA chains made of 146 base pairs. Among these chains, one is a tetramer (H3-H4) and two chains are dimers (H2A and H2B). Each core is separated from other by almost 60 base-pairs in between. Histone acetylation in chromatin governs activation of genes for expression called as euchromatin while inactivated or closed chromatin doesnot express and is called heterochromatin. The base pairs of DNA are bound to the histone through epsilon-amino acid of lysine. This binding is aided by the enzyme called histone acetyltransferase (HAT). It helps to initiate the modification by acetylation of lysine residue in histones. Another enzyme involved is HDAC, histone de acetylase, meant for deacetylation of the lysine on histones.[5]

As the scenario predicts, epigenetics is concerned with the transfer of the heritable memory in genetics through meiosis and mitosis. The translational mechanistic of DNA is actually involved in the development of the human tissues and organs. The pluripotent cells are destined according to the memory they retain during the translation of DNA. In this process of transfer of heritage through genes: methylation of DNA, chromatin material reassembling and alterations and replacement of histone tails and histones, respectively, is involved. Irregularities in any of these stages may cause cancer lesions.[6]

Now, epigenetics is one of the primary cause in progression of malignancy. Epigenetic disease variations can be influenced by environmental and dietary factors. Animal studies have revealed that environment-induced epigenetic changes can be facilitated by diet. Different dietary elements that are used such as polyphenol and alkaloid are effective against cancer by acting on HDAC.[7]

In DNA methylation, variant other enzymes are involved such as DNMTs which cause DNA silencing and non-coding genomic regions. DNMT1 act as conservative methylating agent while DNMT3a and DNMT3b act to initiate de novo pathway. These are molecular targets in epigenetics for available anti cancer drugs that are approved by FDA.[8]

RNA silencing can occur in two ways: tracriptional and post-transcriptional. Post transcription silencing of genes occurs to produce hetrochromatin thereby wrapping up the chromatin material and the transcription sites. Connection of RNA silencing in different organisms has been studied in detail. For example, in the yeast (*Schizoaccharomyces pombe*) silencing of different components of the RNA machinery results in the inhibition of methylation of H3k9 along with disruption of centromere function.[9]

Epigenetics and Dietary components

Curcumin

Curcumin obtained from the rhizome of the *Curcuma longa*, and commonly called as turmeric. It's been used as a traditional drug in Chinese ayurveda medicine. It is under investigation for its beneficial properties.[10] It contains curcuminoid complex (80%), demethoxycurcumin (17%) and bisdemethoxycurcumin (3%). In cell culture of tumors, curcumin has shown to have potent inhibitory effects on profliferation of tumors. It also inhibits the tumor development in various xeno-transplant and ortho-transplant mouse models. It has shown anticancer activity with chemopreventive and chemotherapeutic effect with no observable side effects.[11]

HDAC inhibition

Curcumin is involved in modifying the various protein expressions. It inhibits the cell proliferation, angiogenesis and metastasis of different form of cancer. Curcumin has activity against HDAC. It stimulates apoptotic induced brain cell death through PRAP and caspase 3 by histone deacetylation.[12]

HAT inhibition

P300/CBP HAT activity is inhibited by curcumin, both, *in vivo* and *in vitro*. Curcumin strongly inhibits the H3 and H4 acetylation by p300/CBP. These findings are very important in cancer because HAT activity has a significant role in cancer.[13] Curcumin also reported as epigenetic modulator of TREM-1 gene expression, and this epigenetic modulation in TREM 1 promoter region done by inhibiting p300 activity, which causes hypoacetylation of histone 3 and 4.[14] HAT, p300 and acetylated CBP/p300 gene expression are down regulated by curcumin. Following reduction in gene expressions used to minimize various diabetic problems by inhibiting high glucose induced proinflammatory cytokines. Curcumin is very effective against the diabetes induced by streptozotacin in male Sprague dawley rats.[15]

Resveratrol

Red grapes, peanuts and pines are great sources for resveratrol. Dimethyl ether derivative of resveratrol is pterostilbene (3, 5-dimethoxy-4-hydroxystilbene). It is an ayurvedic medicine. These polyphenols have activity against the DNA methyltransferases (DNMTs) enzyme.[16]

HDAC Inhibition

It was found that when these two compounds are given in combination they inhibit the activity of

SIRT1, a type III histone deacetylase (HDAC).[17] Resveratrol causes inhibition of MTA1/NurD complex that is involved in the prostate cancer. This complex over expression in prostate cancer results in tumor aggressiveness. Resveratrol causes suppression of MTA1 protein and causes acetylation of P53.[18] Resveratrol regulates transcriptional activation and suppression of various genes including p53 and activation of SIRT1. SIRT1 has HDAC activity and thus it is effective against cancer.[19] Now efforts are being focused to increase bioavailability of resveratrol as it is very effective against cancer.[20]

DNMT Inhibition

Resveratrol has less DNMT inhibiting activity. However, it prevents epigenetic silencing of BRCA1 which is a tumor suppressor protein.[21] Another study revealed that resveratrol activating SIRT1 and p300, which are HDAC inhibitors. SIRT1 encoded protein are very important for the treatment of cancer and its chemo preventive action is meditated by resveratrol.[22]

Green tea

Epigallocatechin (EGCG) found in green tea is a polyphenol that could inhibit DNA methylation. EGCG produces a decrease in an enzyme activity which is called DNMT1. EGCG have anti-neoplastic, anti-inflammatory and antitumor effect.[23] EGCG may induce apoptosis and cell cycle arrest. EGCG has also been involved in regulation of many signal transduction pathways. The transduction pathway includes JAK/STAT, MAPK, NF-□B, and AP-1. Additionally, green tea has been involved in induction of tumor suppressor genes p53, p21 and p16.[24] EGCG induces apoptosis by over expression of TFPI-2. So it is an effective agent for the cure of renal cell carcinoma.[25] It is also involved in the reduction of expression of hTERT, a major catalytic unit of telomerase.[26,27]

DNMT AND HDAC Inhibition

Epigenetic regulation by EGCG is important in chemoprevention because of its DNA methyltransferases (DNMTs) and histone acetyltransferases (HATs) inhibition activities.[28] EGCG activity by inhibition of DNMTs has been shown to lead to global and local hypo methylation of a number of gene promoters.[29]

Genistein

Genistein (GE) isoflavones, are found in various plants including soya beans. It has anticancer and antiangiogenic activity. Genistein is involved in gene transcription and gene silencing activity by modifying epigenetic events.[30]

Genistein epigenetic modification involves not only in reactivation of tumor suppressor genes but also inhibits the expression of a tumor promoter gene such as hTERT. In human breast cancer cells it involves in transcriptional repression of hTERT expression. It was found that in low concentration, genistein moderately demethylated the GSTP1 tumor suppressor gene promoter and reactivated ts expression in MDA-MB-468 human breast cancer cells.[31]

Apoptosis mechanism

A study has reported that Genistein (GE) is involved in induction of apoptosis and reduction in proliferation in human prostate cancer. HT-29 and colo320 are suppressed by GE isoflavones. Additionally, other investigation showed that GE inhibits the growth of HCT 116 cells with a dose-dependent manner. Genistein inhibits the augmentation of breast cancer cell lines ADA/MB231, MCF-7 and HBL-100. Peterson and Barnes stated that GE (50 or 100 μM) inhibits ER-positive breast cancer cell growth in the human.[32] Numerous investigations have shown that GE causes apoptosis at 50-100 μM concentrations.[33]

Cell cycle arrest

GE causes cell cycle arrest at G2/M in ovarian cancer. In ovarian cancer, GE causes supression of cell cycle arrest at the G2/M phase. Some researchers have reported the relationship between GE and Bcl-2 family.[34]

Inhibition of Metastasis of cancer cells

Lee et al. investigated that GE can inhibit metastasis of cancer cells.[35] Another study showed by Zhang et al. and Chen et al. that use of foods rich in soy can decrease the frequency of ovarian cancer. With a high intake of genistein in the women leads to a lowering in the rate of cancer.[36]

Sulforaphane

Isothiocyanate is found mainly in cruciferous vegetables like cabbage sprouts. It has shown significant activity against the cancer.[37] Different studies have reported that increase utilization of cruciferous vegetables, expressively decreases cancer risk.[38] It has shown anticancer effect through various mechanisms, including cell cycle arrest, apoptosis and phase 2 detoxification enzyme.[39] Sulforaphane (SFN) involved in supression of HDAC activity, and this inhibition involves in epigenetic mechanism. SFN showed an irreversible cell arrest which causes inhibition of cellular growth. In LNCap prostate cancer cells an increase in the G2/M cell cycle arrest was observed after SFN incubation in a concentration and time dependent manner.[40] SFN induced cell death in different tumor cell lines by increased p53, activated caspase -3 proteins and decrease hypoxia inducible factor -1 alpha activation.[41] Apoptosis in human breast cancer MDA-MB-231 cells by SFN was initiated by induction of Fas ligand, which triggered the pathway caspase-8, caspase -3and PRAP.[37]

Lycophene

Lycopene is found in tomatoes, and other red fruits. It regulates the expression of various genes pertinent to cell cycle control. It also regulates DNA repair apoptosis in MCF-7 and MDA-MA-231 breast cancer cells.[42] Lycopene has antioxidant activity. A number of studies showed that it has activity against prostate adenocarcinoma (PCa).[43] Clinical investigation showed that treatment with lycopene supplementation in men with PCa, decreased DNA damage and serum prostate specific antigen concentrations.[44] Another study found that Lycopene demethylate is a promoter of the GSTP1 in a breast cancer cell line.[31]

Quercetin

Quercetin is a natural antioxidant flavonol, present in citrus fruits, onions, parsley, leaves and grains. Quercetin showed anti-cancer activity by regulating mitogenic signaling, cell cycle regulation, apoptotic signaling and metastatic steps in cancer.[45] It showed a concentration dependent effect on hyper methylation of $p16^{INK4a}$, a tumor suppressor gene, in human colon cancer cell lines (RKO). After 120 h of treatment with quercetin, it resulted in reversal of hypermethylation.[46] Quercetin is involved in stimulation of HAT and inactivation or supression of HDAC, both of which are involved in acetylation of H3 histone in leukemia HL60 cells and induces FasL dependent apoptosis. Several studies showed that *in vitro* anti-cancer activity of quercetin is linked to histone hyperacetylation. Quercetin can inhibit the DNMTs and thus DNA methylation indirectly by changing the concentration of SAM and SAH (S-adenosyl-L-homocysteine) intracellularly.[47] Quercetin has an effect on histone acetylation. Another study demonstrated that Quercetin decreases the level of COX-2 (cyclooxygenase-2) protein by hindering the binding of various transcription activators such as CREB2, NF-□B, p300, and c-Jun to the promoter of proinflammatory gene *COX2*, which results in its anti-neoplastic activity.[48]

Garcinol

Garcinol, a polyisoprenylated benzophenone is derived from Garcinia indica fruit rind. Garcinol strongly inhibits the histone acetyltransferases p300 and PCAF both in vivo and vitro. The kinetic investigation showed that it is a mixed type of inhibition with an augmented affinity for PCAF compared with p300. Garcinol intensely inhibited the HAT activity-dependent chromatin transcription. Additionally, it has been investigated that garcinol is a potent inducer of apoptosis, and it down regulates the global gene expression of HeLa cell lines.[49]

Lunasin

Lunasin is a 43 amino acid soy peptide. It has been investigated that it showed chemo preventive activity in mammalian cells and in a skin cancer mouse model against oncogenes and chemical carcinogens. As lunasin involved in inhibition of core histone acetylation, this activity of lunasin led to proposal of epigenetic mechanism. Soy lunasin and synthetic lunasin both are involved in inhibition of core histone acetylation in a dose-dependent manner.[50]

Parthenolide

Parthenolide (PN) is a sesquiterpene lactone obtained from *Tanacetumparthenium*. It has been investigated that parthenolide involved in induction of apoptosis and cell cycle arrest.[51] PN was shown to precisely deplete HDAC1. HDAC1 depletion was occurred through proteasomal degradation. PN led to depletion of HDAC1 which causes the ubiquitination of MDM2 result in activation of P53 and sustained DNA damage response.[52]

Anacardic acid

Anacardic acid 6 pentadecyl salicylic acid is an effective inhibitor of HAT. It inhibits p300 and p300/CBP-linked HAT activities.[53]

Garlic, Onions

They are members of the *allium* family that consist of a complex range of water-soluble and fat-soluble organ sulfur compounds. These organosulphur have activity against cancer and employed in cancer treatment.[54]

Garlic constitutes allyl derivatives which are amongst the first compounds having an impact on histone acetylation. Allyl mercaptan (AM), diallyl disulfide (DADS), *S*-allylcysteine (SAC), *S*-allylmercaptocysteine (SAMC) and allicin showed increased acetylation of histone (H3/H4) in human cancer cells.[55] AM responsible for causing H3 hyperacetylation and facilitated Sp3 and p53 binding on the *P21WAF1* promoter in human colon cancer cells.[56] Preclinical studies *in vitro* and *in vivo* showed the importance of garlic-derived organosulfur compounds in prostate cancer prevention.[57] DAD caused increase in histone acetylation and apoptosis in cancer like prostate cancer.[54] AM on human colon cancer cells causes rapid histone acetylation along with HDAC inhibition.[56]

Selenium

Selenium is an important trace element found generally in inorganic forms. While in its organic forms, it is found in Brazil within nuts and seafood. Selenium have an anticarcinogenic effect coming from its selenoprotein and importantly organoselenium metabolites.[58] It is a broad spectrum anticancer agent, found in lungs, ovarian, liver bladder and colon. Many of its forms are involved in epigenetic effect via histone modification.It decreases the HDAC activity and increases histone acetylation while many of its forms are involved in epigenetic changes. Some of the forms include sodium selenite, keto-methylselenobutyrate (KMSB), methyl selenocysteine (MSC), and methyl selenopyruvate (MSP).[59,54]

Silymarin (silibinin)

The flavonolignansilibinin is an active component of the milk thistle plant (*Silybummarianum)* that has been reported to increase acetylation of histones in hepatic cancer. Silibinin has exhibited increased acetylation of histone H3 and H4 *in vitro* in HuH7 cells[60] and *in vivo* in HuH7 xenografts in nude mice.[61] It also causes inhibition of HDAC activity and decreased HDAC levels and found to reduce DNMT activity in SW480 and SW620 cell lines following 72h of treatment. [62]

Rosmarinic Acid

Rosmarinic Acid is an ester of caffeic acid and naturally occurring phenolic compound. It has been reported that rosmarinic acid has a number of potential biological activities like anti-viral, antibacterial, anti-inflammatory and anticancer activities.[63] Rosmarinic acid has an inhibitory effect on DNA methyltrasnferase. In human breast cancer cell line MCF7 has shown decreased activity of methytransferase. [64] In cancer, DNA methylation undergoes aberrant changes resulting in variety of tumor suppressor genes undergoing promoter hypermethylation and becoming transcriptionally silent leading to tumor formation. Inhibition of DNA methyltransferase reverses the effect with rosmarinic acid having potential therapeutic effect against cancer. It has been investigated that rosmarinic acid may inhibit the bone metastasis from breast carcinoma by the NF kappaB ligand RANKL)/ RANK/osteoprotegerin (OPG with suppression of expression of interleukin 8. OPG factor is proangiogenic and through its inhibition, inhibition of metastasis of cancer cells can be achieved.[65]

Plumbagin

Plumbagin is a natural compound isolated from plants of the family Plumbaginaceae as well as from plants belonging to the family of Droseraceae. In India and China, plants extracts from these families have been traditionally employed in the treatment of an array of microbial and allergic diseases. The anti-cancer, anti-hyperlipidemic and anti-artherosclerotic actions of 5-hydroxy-2-methyl-1, 4-naphthaquinone (Plumbagin) is revealed by many research studies in the past. PL mediates an anti-tumorigenesis effect through the utilization of various molecular mechanisms including NF-□b and Bcl-2 inactivation, network of microtubule disruption and DNA breakage. In addition to these mechanisms, arresting of the cell cycle and reactive oxygen specie generation is also invovled.[66] The H460 lung cancer cell lines are more sensitive to plumbagin than A549 cells. The mechanism of action through which plumbagin targets H460 cells is the modulation of EGFR mediated AKt signaling pathway. Furthermore, the compound induces apoptosis through the arrest of G_2/M. The cell viability is also inhibited through the actions of PL.[67] In human breast cancer MCF-7 cell lines, PL induces potent cytotoxicity in a manner which is ROS dependent because a crucial role is played by ROS in the induction of cell dealth. [68] Plumbagin mediates its anti-cancer potential in a dose and time dependent manner. Human GC cells are also susceptible to the anti-cancer capacities of plumbagin. The human GC cells in response to therapy with the biologically active principle demonstrated growth inhibition, apotosis and an increase in chemosensitivity. [69]

Pomiferin

The osage orange fruit is the source of prenylated isoflavone known as Pomiferin which demonstrates, a remarkably potent free radical scavenging capacity. The photochemi-luminescence assay system of pomiferin exhibits a strong anti-oxidant activity against the superoxide anion. A selective anti-tumor growth against human breast cancer MCF-7 cell lines is observed *in vitro* with pomiferin[70] also showing a cytokeratin downregulation, in a proteomics approach. *In Vitro* studies involving Human-Dermal-Fibroblasts, it reveals its potent protein stimulant capabilities in the extracellular matrix. [71]

Sanguinarine

Sanguinarine demonstrates potent anti-proliferative activity against various types of cancer i.e. oral squamous cell **carcinoma.** It is an alkaloid belonging to the class of benzophenanthridine, demonstrating a selective action against prostate cancer cells through inhibition of survivin with negligible effects on normal prostate cells. The expression of survivin protein is inhibited through the degradation of proteins through the utilization of ubiquitin-proteasome system.[72] In addition to anti-invasive and anti-tumorigenisis effects, sanginarine also mediates anchorage independent cell growth inhibition.[73] The progression of prostrate cancer, which is castration resistant, is promoted by altered expression of survivin. The bioactive principle is also known to cause blockade of the cell cycle as well as apoptosis in human prostate cancer cells through the modulation of machinery of cell cycle and apoptosis. [72]

CONCLUSION

Cancer date backs to the era of Hippocrates, always known fatal to human life. It has shown up in multiple ways affecting almost all organs of the body. Its association to the genes has been thoroughly studied and evaluated for any possible counter. Genetics have contributed to cancer mortalities via signals and shown direct linked to diet related factors. Modified activities of genes are observed in association to these factors including histone acetyltransferase (HAT), histone deacetylase (HDAC), DNA methyl transferase (DNMTs) etc. effecting the expression in totality. Numerous studies have been conducted elaborating the role of plants and their ingredients play a part in inhibition of cancerous

cells by blockade of cell cycle and apoptosis or as the case may be.

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CONFLICT OF INTEREST
Authors declare no conflict of interest.
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The following authors have made substantial contributions to the manuscript as under:

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Acquisition, Analysis or Interpretation of Data:	FA, MS, SY, SQ, KA, SA, SA
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All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.