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Cancer Prevention by Epigenetic Modulation of Phytochemicals: A Review

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ABSTRACT

"Epigenetics," which emphasizes the impact of active dietary agents on the function of epigenetics, has become an exciting new field of study in recent years. Focusing on aberrant epigenetic alterations during earlier carcinogenesis has been considered in cancer chemotherapy research since, unlike genetic mutations, these differences are reversible. Genes that operate as signal transducers, nuclear receptors, cell cycle regulators, and transcription factors, among others, can be silenced by abnormal epigenetic processes such as DNA promoter methylation, histone changes, and post-transcriptional modifications mediated by miRNA. DNA, gene product maintenance, apoptosis-inducing, and ultimately result in carcinogenesis. An analysis of several natural phytochemicals has been performed on food and medicinal plants to recognize potential and develop anticancer agents that cause the minor lesion to normal cells and effectively destroy cancer cells. A study of several natural phytochemicals found in food and medicinal plants was conducted in order to identify potential and develop anticancer agents that cause a minor lesion in normal cells while effectively destroying cancer cells. According to this study, plant phytochemicals may be involved in the targeted epigenetic modulation of miRNAs, DNA methyltransferases, histone altering enzymes, and carcinogenesis.

Keywords: Dietary agents; microRNA, DNA methylation, epigenetics, cancer chemoprevention.

1. Introduction

Despite alterations in DNA sequence, expression of genes or cell phenotypes occurs [1]. Due to the reversible origin and early onset of cancer, epigenetic alterations are the promising target for cancer-eradication therapy. The main epigenetic pathways for gene expression are DNA methylation, chromatin modifications. Specific non-histone proteins and miRNAs can also be identified after translational alterations in histones and composition, which can disrupt or change mRNA translation [2]. The regulating of this epigenetic mechanism is essential standard cell functions at all levels,

except differentiation and growth [3], and allow adaptation to changes in the climate, such as changes in the food industry or Smoke, Chemicals, Radiation and Hormones Toxicity [4]. Updated epigenetic targets can potentially result in several diseases, including cancer [5].

2. DNA Methylation

S-adenosyl methionine (SAM) transfer to the cytosine is accelerated by the DNA methyltransferase (DNMT). 5-methylcytosine guanine, which is produced close to guanine by enzymes, is known as CpG dimers. While DNMT3b and

DNMT3a now methylate unmethylated DNA sequences, maintaining the DNMT1 enzyme DNA methylation during replication may also be important for the development of cancer (6). DNA sequences that repeat frequently from CG are known as CpG islands; these repeating sequences are highly methylated and stabilize chromosomes [7, 8]. Generally, unmethylated CpG can be found in a gene's promoter regions. more CpG methylation Gene promoters and gene deleters can silence the transcription of tumors; Even though he was a global figure, he repeatedly noted that DNA hypomethylation CpG Island may be the source of genomic instability in malignant cells [9,10].

3. Histone Modifications

Posttranslational modifications in the histone proteins also regulate the gene expression epigenetically, including methylation, ubiquitinylation, sumoylation, ADP ribosylation, acetylation, phosphorylation and sumoylation. Methylation and Histone acetylation are the most popular post-translation changes to histone proteins that lead to carcinogenesis [11]. Catalysis of histone acetylation by the class of acetyltransferases known as histones acetyltransferases (HATs), Although deacetylation of histone is being catalyzed by histone deacetylase (HDACs). Examples are that HDACs eliminate these groups of acetyl; HATs change the acetyl group to the lysine ϵ - amino group (K). Histone acetylation refers to an open configuration of chromatin and can be DNA binding transcription factors. On the contrary: Deacetylation results in a transcriptional and chromatinic condensation repressive steps. To date, there were 18-HDACs and 25-HAT proteins being identified. Histone deacetyltransferase is categorized into four groups— I, II, III and IV, Centred on subcellular expression, number, shape and homology of enzyme sectors [12]. The group of HDACs Class II are composed of 4, 5, 6, 7, 9 and 10HDACs; the HDACs of Class I include those of HDACs 1, 2, 3 and 8; the HDACs of class IV is composed of only one member – HDAC 11. Class III is not structurally connected with other groups, and NAD⁺ is a co-factor. Sirtuins 1-7 is seven members of this class [13]. HATs They were also classified into several the levels TAFII250 (TAFII250), SRC (SRC-1), p300/CBP (p300/CBP), MYST (MYSTand Tip60), and GNAT (hGCN5 and PCAF) depend on histone specificity, homology, and structure [14]. Histone methylation usually occurs in several lysines and arginines residues. Lysine methylation also might activate or become activated in

histones check the expression of the gene, refer to the lysine position residue with methyl groups; add methyl to H3K79, H3K4, and H3K36 as examples. Generally, it describes chromatin that is actively engaged in transcription on the opposing H4K20, H3K9, and H3K27 Methylation is aided by transcriptional inactivation. Lysine residue methylation on histones is mediated by the enzymes known as histone lysine methyltransferases (HMTs). Similar lysine acetylation, Methylation of lysine is not still isolated to histone proteins, since specific proteins that they non-histone subjected to add methylation [15].

4. MicroRNAs

A small 20–22 nucleotide non-coding RNA called a miRNA controls key biological processes by post-transcriptional gene expression ([16]. A complex protein system is manufactured with miRNAs, consisting of the Argonaute family proteins, Dicer ribonucleases and Drosha from RNA precursor system, and polymerase II-dependent transcription [17].

miRNAs monitor translation systems either through imperfect mRNA base pairing or through influencing mRNA stability. Each miRNA regulates many genes in related mechanisms and is involved at the beginning and development of tumours. They are also unregulated by genetic and epigenetic changes and deficiencies in processing during Carcinogenesis [18]. New research demonstrates that some regular dietary habits include phytochemical components from plants that are able to reverse epigenetic alterations prior to aggregation and ignite disease, for example, cancer [19]. Due to their incapacity to modify DNA methylation, miRNA expression, and histone changes, as well as the chemopreventive potential of the dietary phytochemicals system, we demonstrate the epigenomicalterability of specific nutritional polyphenols, Fig. 1.

4.1 Polyphenols of tea

Tea, the world's utmost commonly used after-water drink, is consumed differently, for example, black, oolong and green tea. Tea polyphenols, particularly the catechins in special tea like green one, the venture of numerous diseases, including cancer, is reduced. (–)-epigallocatechin-3-gallate (EGCG), (–)-epigallocatechin (EGC), (–)- epicatechin-3-gallate (ECG), and (–)-epicatechin (EC) are four main catechins in green tea; About 50% of the overall green tea-isolated

catechin was EGCG and was extensively studied for its anticancer effects. Invasion, metastasis, angiogenesis, the suppression of oxidative stress, and cell proliferation suppression through cell cycle induction apoptosis and detention are some of the anti-tumor properties of green tea polyphenols, which have been linked to a number of distinct pathways [20].

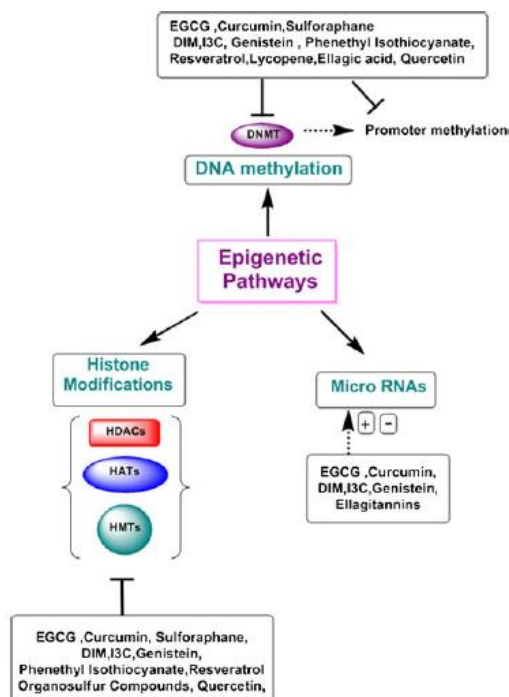


Fig. 1: Dietary compounds as epigenetic modulators

Epigenetic aberrations, for example, drive chromatin compaction, ubiquitination, some non-histone Proteins, HDACs class-I based on histones deacetylation, protein-based on methylation of histone, polycomb group (PcG), and tumour suppressor activity was shown to decrease, and cancer cell survival was increased; evidence indicates, by reversing such epigenetic changes in cancer cells green tea polyphenols achieve their anticancer impact. The B- and D-ring is proposed by structural analogues from the EGCG. The tea polyphenols structures were significant in inhibiting the activities of DNMT; This statement was followed by molecular modelling, EGCG could form hydrogen bonds with Arg(1309), Ser(1229), Cys(1225), Glu(1265), and Pro(1223) in the DNMT catalytic pocket. Both green tea catechins have also been reported to prevent DNMT1 in several ways, their IC₅₀ values range between 210 and 470

nM. In vitro research shows that polyphenols that include catechol prevent DNMTs by Dihydrofolate reductase enzyme activity, is directly inhibited, disrupt the folate cycle and raise the levels of SAM, DNMTs that specifically inhibit, Regardless of the position of methylation and enhanced formation of an effective non-competitive inhibitor, Catechol-methylate transferase enzyme S-adenosyl L-homocysteine is responsible for o-methylation of SAM (SAM). The final inhibition of DNMTs leads to DNA hypomethylation and protoOncogene re-expression or even other repressed genes [21].

First, DNA methylation was demonstrated by suppressing the expression of mRNA encoding tumour suppressor genes hMLH1, MGMT, and RAR in a human oesophageal cancer cell line (KYSE510) with a deficiency in tumour suppressor genes (hMLH1, MGMT, and RAR) due to a high level of methylation catalysts. 5 to 50 μM EGCG used for KYSE510 therapy during six days leading to a demonstrate of re-expression also MRNA hypermethylation and protein coded for the gene of tumour suppressor close to common inhibitors of DNMT zebularine and 5-aza-2'-deoxycytidine (5-Aza-dC). Related findings were also found in HT-29 cancer cells in the human colon and PC-3 Cells of prostate cancer [22].

The gene has been treated by LNCaP Prostate cells in humans with 1 to 10 μg per ml of GTP during one to 7 day's dose and period dependence-induced GSTP1 re-expression hypermethylated by its promoter, silenced in the majority of cancers. GSTP1 re-expression was linked to DNMT1 activity inhibition. GTP therapy also reduced mRNA and protein levels of MeCP2, MBD4, and MBD1, and reduced interaction between MBD2 and open attaching sites of Sp1, this results enhance binding and activate GSTP1 gene transcription. GTP therapy cannot lead to global improvements in the trend of hypomethylation. Instead, it supported genomic integrity preservation. In comparison to 5-Aza-dc cell exposure, caused either GSTP1 or S100P activation, therapy by GTP was inactivated by pro-metastatic gene S100P, demonstrate GTP specificities that only silenced tumour suppressor genes can be re-expressed, preserving genomic power. GTP processing also reduced the level of protein and messenger RNA in HDACs class I 1–3 and boosted H3 histone and acetylation of H4 simultaneously [23].

Global susceptibility to EGCG of human skin cancer A431 cells dose-dependent methylation of the DNA; 5-methylcytosine also decreased, the enzymatic activity of DNMTs and HDACs, H3 at Lysine 9 methylation, protein

levels, and DNMT1, 3a and 3b mRNA, Histone H3 increases in K 9 and 14, H4 histone increases in K 5, 12, and 16 in the same cells. As an extra factor, EGCG therapy repressed the p16, p21 mRNA and protein tumour suppressant genes that had in these cells been epigenetically muted (24).

Therapy by EGCG progressed to incremental demethylation of the hTERT promoter in MCF-7 breast cancer cells, including its Additionally down-regulated hTERT by inducing histone H3K9 hypoacetylation, to the hTERT promoter, a powerful inhibitor, this contributes to improved E2F-1 binding, E2F-1 binding sites. EGCG's hTERT epigenetic regulation of EGCG's is a cellular phenomenon, no related effect to breast cancer cells MCF-7 was seen for HL60 promyelocytic leukaemia cell therapy (25), While hTERT and inhibition of cell proliferation was identified in similar mechanisms in MDA-MB-231 (ER-) and MCF-7 (ER+) breast tumour cells [26].

Mouse model of intestinal cancer in azoxymethane-Apc Min/+, A substantial reduction in the methyl group of location 24 CPG in the promoter RXR Alpha gene location. Prostate cancer in human therapy by LNCaP cells PC-3 cells (lacking p53) and (Porting wild-type p53) with 10 to 80 µg/ml of GTP for twenty-four hours the dose-dependent inhibition resulted in the activity of Class I HDAC enzymes and improved HDAC class I protein proteomics degradation. GTP therapy of total cell chromatin culminated in the aggregation of acetylated histone H3; this results in greater accessibility of binding in conjunction with the cell cycle stop and apoptosis induction on both the p21/waf1 promoter sequences and Bax, independent of their p53 status [28].

Major constituent and GTPs, EGCG, LNCaP p53 activated human prostate cells increase their acetylation at K382 and K373 residues HDACs in their dosage- and time-dependent C terminus by inhibiting class I; The result of GTP or EGCG therapy has triggered acetylation depletion of p53. This EGCG or GTP therapy also improved binding of acetylated p53 with p21/waf1 or Bax promoters and elevated p21/waf1 and Bax protein and messenger RNA and expression the cycle of cell stoppage and cell lysis [29].

The PCG protein community enhances cell alive by controlling gene expression through epigenetic. Higher levels and better PcG protein activity result in increased methylation and a decline in histone acetylation in the tumour suppressor genes, causes decreased tumour suppressor activity and accelerated growth of cell and stay alive. Expression level in EZH2 and Bmi-1 two main PcG proteins, identified in both

the lines and keratinocytes of immortalized skin cancer cells; EGCG therapy decreased levels of Bmi-1 and EZH2 protein to SCC-13 cells for skin cancer, reduced overall survival has been correlated with reduced H3K27 trimethylation. Decreased PcG protein expression is also associated with decreased cell cycle developmental protein expression (i.e. cyclins, cdk) and improve inhibitory protein cell cycle expression. (i.e., p21, p27). As seen by enhancing case-9,-8 or -3, PARP cleavage, Bax-Bcl-xL relation, treatments with EGCG have also caused apoptosis. This analysis demonstrated that GTPs decrease survival in cells in skin tumours by affecting epigenetic regulatory pathways regulated by PcG [30].

The decrease in the PcG protein level was recorded later following GTP it is linked to its increasing ubiquitination and proteasome inhibitors may be blocked.

Green tea polyphenols can alter the gene expression of mi-RNAs in different individual cancers. Carcinoma of hepatocellular HepG2 human cell therapy with EGCG their miRNA meaning has been changed. In cells treated by EGCG, 13 miRNAs were upregulated, and 48 were downregulated relative to nontreated cells; TGFBR2, Bcl2, E2F, RAS, and the c-Kit is an upregulated miRNA target gene; Family proteins of HOX, including SNX19, PRPS1, ZNF513, SLC16A1, TTK, and MCL1 are the downregulated miRNA target genes. EGCG therapy for the downregulated expression of Bcl-2 protein; Anti miR-16 transfection repress the miR-16 statement and reciprocate downregulation and apoptosis in these cells with the effects of the EGCG on Bcl-2 [31].

The MCF-7 cells cure breast cancer using Polyphenone-60, initially highly expressed in these tumor cells, substantially altered the statement of 23 miRNAs, such as miR-21 and miR-27 down-regulation. EGCG therapy mediated apoptosis by increasing the miRNAs-16 expression in hepatocellular carcinoma cells, which led to decreases in proteins at Bcl-2 levels. EGCG therapy repressed transcriptional activation of androgen receptor (AR), which associated substantial decreases in male hormone (androgen) mediated miRNA-21 and the high regulation of tumourous suppressor, miRNA-330 and prevented tumour development, on a xenograft. Mouse model using LNCaP. Cells of prostate cancer [32].

The result was obtained with miRNA profiling showing that EGCG can exercise its biological functions by modulating miRNA expression.

4.2 Curcumin

Turmeric is a typical Indian spice linked to the prevention of cancer and many other health benefits. Its key active ingredient, Curcumin, has affected many intracellular processes, including proliferation, invasion and longevity [33].

Molecular dockings indicate curcumin interactions with DNMT1 indicate Curcumin could inhibit DNMT1 enzyme activity by binding it with the thiol group of C1226 acid by covalent blocking the catalytic site. This very same survey showed that Leukemia MV4-11 cells had global DNA Highly methylated following curcumin remedy. Still, epigenetically-silenced curcumin sequence-specific remove methylation in the promoter region was not demonstrated [34].

During prostate tumorigenesis in TRAMP mice, Nrf 2, a cellular antioxidant protection mechanism master regulator, has proved to be muted epigenetically. Curcumin therapy for TRAMP C1 cells direct to the nonmethylation of its first 5-CpGs in the promoter location at the Nrf2 gene and also to a new expression both of Nrf2mRNA and protein and improved presentation of the primary downstream wanted gene, NQO 1, as the enzyme of an antioxidant; This process may be responsible, in part, for curcumin chemoprevention [35].

Curcumin therapy was also vital to Neurog1, another gene linked to cancer that has been silenced by promoter hypermethylation. Curcumin also decreased the MeCP2 binding of the Neurog promoter dramatically in prostate tumour cells, by remove methylating the initial 14 CpG sites within its promoter1. Curcumin therapy increased HDAC1 levels, 4,5 and 8, but fell hdac3. HDAC function, H3K27me3 ranges and stick in the promoter area of Neurog1 were diminished following treatment, signalling Curcumin's potential to repress another gene silenced by epigenetic cancer alteration [36]. RARB2 promoter demethylation and its reactivation; the degree of demethylation increased in SiHa cells from 3 to 6 days with treatment time, while unmethylation in HeLa cells was observed six days later of therapy [37]. Because of its ability to model the enzymes' function in HAT and HDAC, Curcumin is also a possible modulator of histones. Marcu et al. [38]. It was shown that Curcumin is a CBP/p300 adoptive stopper that also indicates that alpha-beta unsaturated carbonyl group function as a Michael reaction site in the side chain of the Curcumin and that they are essential as a HAT inhibitor for activities. Also, Curcumin facilitated the degradation, without any impact on

the cells PCAF or GCN5, of proteasome-dependent CPB/p300 proteins.

Additionally, the activity of acetyltransferase of purification p300 with histone H3 or p53 as a substrate was studied [39]. Curcumin stopped successful HDAC inhibitor MS-275, Indicating all PC3-M and changes peripheral blood lymphocytes to histone hyperacetylation [40].

Curcumin therapy prevented HDAC1, HDAC3and p300/CBP in Raji cells, resulting in lower NF- κ B and Notch1 activation and contributing to a significant cell reproduction inhibition. The role of Curcumin for HDACs and HATs was even high prominent and partly because of the increased proteasomal degradation since MG-132 could partially reverse degradation protections via Curcumin [41]. It was also confirmed that Curcumin inhibited class IHDAC expression and increased histone H4 expression in Raji cells, respectively [42].

Using the HeLa nuclear extract and performing a molecular docking for a human enzyme HDAC8 in a fluorometric study, this group reported Curcumin more effective HDAC inhibition compared with sodium butyrate, a popular inhibitor for HDAC [43].

Curcumin in the DAOY, D283Med, and D341 cells of human medulloblastoma contributed to cell phases and cell apoptosis, decreased HDAC4 expression and activity, and increased acetylation of tubulin, resulting in mitotic tragedy. Curcumin therapy has reduced xenograft tumours' development in the Smo/Smo model, significantly improving mouse survival transgenic medulloblastoma [44].

In breast cancer cells the overexpression of zeste homolog enhancer 2 (EZH2) genes suggests bad prognosis; a dose- and time-dependent downregulating EZH2 expression was triggered by the curcumin therapy of MDA-MB-435 breast tumour cells which was also linked to decreased cell proliferation. Curcumin causes downregulation of EZH2, inducing anti-proliferation effects, such as MAPK, c-Jun NH2-terminal kinases, ERK and p38 [45].

The miRNA expression in cancer cells has been modulated by turmeric. Curcumin has changed the 29 miRNA expression in pancreatic cell human BxPC-3 cellulars, such as miRNA-22 upregulations which have caused the target genes SS1 and ESR1 to be suppressed [46]. The compound of curcumin effect on CFD, pancreatic cancer cells of human, sensitized MIAPaCa-EMIAPaCa-E, MIAPaCa-M & BxPC-3 cell lines are activated to gemcitabine, inactivating miR-21 and inducing NF- κ B,

COX-2 inhibition as well as downstream object molecules and miR-200b and miR-200c reactivation [47]. Therapy with Curcumin dramatically decreased miR- expression 186* in human lung adenocarcinoma cells multiresistant to A549/DDP and mediated cell autolysis [48]. Treatment with curcumin MCF-7 breast cancer cells led to reducing regulation of Bcl-2 and enhanced transcription of miR-15a and miR-16, and restored Bcl-2 expression by the silence of miR-15a and miR-16 with unique inhibitors, indicating a reduced level of Bcl-2 transcription in breast tumour cells following curcumin therapy because of its curcumin potential for upregulation of the expression of miR-15a and miRNA-16 [49]. Dose-based reductions in the function and name of the miR-21 promoter after curcumin therapy have been reduced as a result of decreased AP-1 binding and activation of the tumour suppressor gene (Pdc4) as a miR-21 goal and is highly expressed in colon cancer of human cells RKO or HCT116 and encourages incursion and deformation. Curcumin also normalized colorectal cancer statement from the tumour suppressor Pdc4 [50].

4.3 Sulforaphane

An additional bioactive phytochemical sulforaphane (PPS) was extensively investigated for its anticancer function, widely present in broccoli, spruces, chalk and poultry. SFN increases xenobiotic metabolism and induces cell cycle arrest and apoptosis in different human cancer cells [51]. SFN can also alter epigenetic events in cancer cells like many other plant polyphenols. SFN therapy contributed to the downregulation of DNMT1 activity in human colon cancer Caco-2 cells [52]. With MCF-7 and MDA-MB-231 cells, SFN therapy decreased DNMT1 and DNMT3a activity in the first hTERT exon and induced CpG demethylation in place in the first exon, promoting hTERT repression CTCF binding, and contributing to catalytic inhibition of the telomerase regulatory subunit. Treatment with SFN enhanced histone H3 in K9 and histone H4 acetylation and reduced dose-dependence trimethylation of histone H3 in K9 and K27. With this enhanced acetylation and decreased trimethylation of histones, the relation of her repressor proteins such as MAD1 and CTCF with the hTERT regulatory area was facilitated and increased, leading to cell proliferation autolysis [53]. SFN therapy reduced HDAC actuality while, raised 293 human embryonic kidney cells of a β -catenin reaction reporter (TOPflash). Even if β -catenin or HDAC protein levels have fixed and non-changeable, HDAC

actuality was decreased. The acetyl group addition of global and localized H3 and inflatables was enhanced, which acetylated the p21 promoter. At the other hand, the result was found at HCT116 cells colorectal cancer of human [54]. SFN therapy also inhibited HDAC function and consequently increased acetylated histone levels and its attachment to the promoter p21. And Bax genes, the mediated p21 expression, in prostate tumour cells acetylation of tubulin elevated and the arrest of cells and caspases dependent apoptosis in BPH1 benign prostatic hyperplasia LNCaP and PC3 prostate cancer cells HDAC6 over reversed SFN-induced cytotoxicity [55]. The human breast cancer lines of MDA-MB-231 with SFN exposure, MDA-MB-468, MCF-7, T47D triggered inhibition of the HDAC, enhanced histone acetylation, diminished ER, EGFR and HER-2 expression, mediated cycling of cell detention and cell autolysis [56].

Different inside body experiments on animal samples have shown that SFN Able minimizes HDAC activity and enhances histone protein acetyl group addition. With APC Min/C mice, treatment with SFN decreased tuberous development by increasing global histone acetylation, increased acetylated histone interaction with p21- and Bax-gene promoters, and increased Bax protein expression. A single oral dose of 10 μ M SFN Wilden C57BL/6 JC/C mice are substantially inhibiting HDAC production in the colonic mucosa with a concomitant but temporary rise in Histone H3 and H4 levels of acetylation [57]. Uses of 7.5 μ M SNF per mouse over 22 days has decreased by 40% xenograft tumour proliferation of PC-3 in the nude mice; Related to a considerable reduction in HDAC activity, the whole part growth Bax expression increased and histone acetylation in these animals in tumours and mononuclear blood cells [58]. A pilot study of three people feeding 68 g Broccoli Rich in the SFN, sprouts, demonstrated significant HDAC agility inhibition and accelerate histone H3 and H4 acetylation within 3 to 6 hours after ingestion in their peripheral blood mononuclear cells [58].

4.4 Diindolylmethane [DIM] and Indole-3-carbolic [I3C]

Indole-3-carbinol (I3C) is a glucosinolate yield found in cruciferous plants such as broccoli, cold clover, cauliflower, mortar, and radish. The reduction of glucosinolate to I3C is carried out by a myrosinase enzyme, which, through the stomach's acidic pH, converts I3C to diindolylmethane (DIM). All I3C and DIM were found to affect apoptosis by

the effects of multiple kinases and mediated signalling in several cancer cell lines from solid tumours of many bodies [59]. Research on cancer of human colon HCT-116, RKO, LS174T, and HT-29 and tumour xenografts Cell lines demonstrated proteasomal degradation mediates with DIM Class I HDAC degradation (1–3, 8), without influence on HDAC proteins class II. Class I decay of HDAC shows transcription inhibitions or enhanced expression of p21/waf1 and p27/Kip1 inhibitors, and the G(2) step of the cell cycle induced the cells to be an arrest. This study also revealed enhanced DNA damage linked to class I HDAC degradation and cell apoptosis induction following DIM therapy [60]. DIM treatment for human pancreatic cells withstand gemcitabine Aspc-1, Panc-1, and MiaPaCa-2 the upregulation has resulted in miR-200c miR-let-7e, miR-200b, and miR-let-7b. Also, the epithelial-cell marker high regulation, E-cadherin downregulation, and ZEB1 and vimentin downregulation [61]. Pancreatic cell therapy with DIM decreased the intrusive potential because of DIM's power to control miRNA-146, Reduced EGFR, MTA-2, IRAK-1 expression also NF- μ B pathway activity in these cells in turn [62]. DIM therapy was further shown how to decrease expression of CDK2, CDK4 and Cdc25A, caused by a cycle of cell arrests, through changing miR-21 both at human breast cancer cells, which are estrogen-dependent from MCF-7 or ER-negative p53 mutants; thus, DIM will induce a cycle of cell arrest at breast cancer cells by controlling miR-21 regardless of oestrogens and p53 status; This research also shows inhibition through DIM in an inside body xenograft model of human tumour growth [63].

Clinical disorders include vaginal itching, painful urination strawberry vagina (vaginitis), may leads to infertility due to endometritis in female. In male cause urethritis, painful urination and prostate secretion abnormality as described by Mehlhorn [10].

4.5 Genistein and Soy Isoflavones

Epidemiological studies indicate that the prevalence of a soy-rich diet having anticancer properties. The Genistein, an active ingredient in Soy, has protective effects on cancer by targeting different forms of producing cancer includes the breast and prostate [64]. A number of studies have demonstrated that genistein impacts transcription of other genes via multiple epigenetic processes, DNA-Methylated MGMT-based genistein suppresses p16INK4a, RAR, and human oesophageal cancer cell proliferation and cell growth.

RAR β ' reactivation by genistein hypermethylation also occurred in human prostate malignancy LNCaP and PC3 cells [65]. MDA-MB-468 low-genistein cells recovered GSTP1 gene expression by demethylating its promoter (66). Protein expression has been improved and the cell lines PC-3, DU-145 and LNCaP in human prostate cancer, The GSTP1 and EPHB2 promoters have been highly methylated, treating genistein and genistein soy isoflavones have been demethylating [67]. The BRCA1, GSTP1 and EPHB2 promoters showed similar outcomes: Protein toxicity and treatment with genistein or daidzein in prostate cancer of human DU145 and PC-3 lines [68].

Wnt signalling pathway plays a significant role in both natural epithelial and mammalian colon regeneration. Therapy of colorectal cancer of human SW1116 cells with genistein or Soy mediated WNT5a gene explanation by decreasing CpG island methylation in its proponent and cell inhibition development through cell proliferation inhibition [69]. Downregulated in kidney cancer due to promoter hypermethylation of the tumor suppressor gene, BTG3, was demethylated in A498 renal cell carcinoma, after treatment with genistein, reduced DNA Methyl-attaching regions Protein two(2) functions, also improved prostate cancer cell HAT activity [70]. The findings of genistein treatment outcomes are compatible with DNA methylation; Although in vitro studies show DNMT actuality and DNA methylation inhibition through the cancer cells, inside body (in vivo) studies have shown differently. A randomly, dual-blind experiment for the effects of isoflavones, including genistein in premenopause stable females (n = 34), Glycitein and daidzein took every day (40/140 mg) dose; genes are known to be silenced because of hypermethylation of the promoters of p16, RASSF1A, RARB2, ER, and CCND2 genes in brain cancer. In untranslated specimens after therapy associated with genistein concentration in the serum, RARB2 and CCND2 methylation is increased [71]. Genistein also has a histonemodic role, which has demonstrated epigenetic pathways involving active chromatin modulation, including the upregulation of HAT expression in human prostate cancer cell p21/waf1/cip1 and p16INK4a time suppressive genes [72]. Genistein, daidzein, and equol (a metabolite of daidzein) were found to promote ER-mediated histone acetyl adding by modulating HAT actuality and co-activating ER actuality [73]. LNCaP and PC-3 treatment hereditary cancer prostate cells by altering histone H3K9 after the translation has been carried out by many aberrantly silenced tumour suppressor

genes utilizing non-methylated promoters, such as PTEN, CYLD, p53, and FOXO3a. Inducing a major remodelling by demethylation and acetylation of H3K9, PTEN and CYLD genes were reactivate and inhibit the PI3K/Akt signal pathway. Genistein is also enhanced by downregulation of histone deacetylase SIRT1 in H3C9 in p53 and FOXO3a [74]. Ubiquitating AR protein in LNCaP cells has been increased after genistein therapy, HDAC6 inhibition, Hsp90 deacetylase and increased acetylation of Hsp90 due to reduced chaperone activity HDAC6 [75]. Soy isoflavones could also be capable of modulating miRNAs. New research discovered a collection of 53 independently regulated genes compared to the miRNA sequence of UL-3A and UL-3B treatment cells, formed with cancer of ovary patients. Untreated and genistein -treated cells. Genistein affected both mRNA and protein upregulation of ER α and ER β and decreased in contrast with untreated cells; the genistein treated cells show the migration potential and invasion. Unfortunately, this research has not evolved or attempted to characterize the function of miRNAs in ER α and ER β induction [76]. MiaPaCa-2, Panc-1 and Aspic-1 cell lines are human pancreases immune to gemcitabine. There was a strong connection among miRNA200 and the mesangial indicator like ZEB1, slug and vimentin, Genistein therapy. Genistein therapy has reversed the EMT transformation in these cells [61]. After treatment with genistein, LNCaP and PC-3 cells are seen in prostate cancer as upregulation of miRNA-1296 and cell aggregation step S of the cell cycle. Increasing miRNA1296 Control, Enables mRNA principles. And its target gene protein [MCM-2] is significantly decreasing [77]. The production of genistein by inhibiting the gene ZBTB10 via miRNA-27 was also suppressed by uveal melanoma C918 cells [78].

Phenethyl Isothiocyanate

Cruciferous vegetables are also rich in the isothiocyanate, such as horseradish, mouth-watering, radish, Brussel nasturtia, capers sprouts, and cress. This chemical community produces the characteristic flavours of these vegetables by the substitution of oxygen with sulphur. Phenyl isothiocyanate (PEITC) for its anticancer function is one of the most studied isothiocyanates. Apoptosis and cell cycle arrest have been reported for PEITC for various cancer affected cells [79]. PEITC demethylated a low methylated promoter of the GSTP1 gene, and GSTP1 reactivated in separate prostate cancer cell androgen-dependently. PEITC also inhibited the function and level of HDAC and induced selective

improvements in the acetylation and methylation patterns of histones. This dual-action in PEITC has been more successful than DNMT and HDAC pharmacologic inhibitors [80]. Allyl isothiocyanate therapy with DS19 mice erythroleukemia cells enhanced histone acetylation with really no influence on HDACs [81].

Histone acetylation can be almost undetected by high expression and activity in acute leukaemia patients. Cultivated patients displayed remarkable acetylation of histones in bone marrow from acute phenylexyl isothiocyanate, myeloid leukaemia (AML) and suggested inhibition of HDAC production phenyl hexyl isothiocyanates [82]. Phenylhexyl-isothiocyanate impaired cell growth and induced apoptosis in the treatment of hepatocellular carcinoma SMMC-7721, Increased H3K4 methylation and decreased the H3K9 methylation associated with accelerating acetylation of Histone H3 and H4 [83]. The inhibition of cell proliferation, differentiation, Ras, NF-Fraktion route, and angiogenesis inducing apoptosis, inducing reverse p53 and the abbreviation of the cigarette-inducing miRNA have been recorded in PEITC alone, or conjunction with other chemoprevention agents, PEITC. miR-125b, miR-146-pre, miR-222-pre let-7c, miR-192, miR-123 and miR-99 are a group of the cigarette smokeless regulated miRNA, treated in rats for their transmission for three days until they were exposed to cigarette smoke for 28 consecutive days, altered in rats treated with orally administered PEITCs [84]. The effect on miRNA expression was studied with liver and lung of the mice of PEITC and the glucocorticoid budesonide therapy alone or in combination. After birth or 2-weeks after weaning, therapy and resulting exposure to smoke is begun. PEITC therapy dramatically degraded nine and upregulated three miRNAs in the liver. The impact of the miRNA treatment in the lungs has been moderate. In contrast with the only treating party, the therapy dramatically upregulated 12 miRNAs and downregulated 11 miRNAs. These miRNAs were expressed differently about the stress-response genes, cell proliferation, protein repair, and inflammation [85].

4.6 Resveratrol

Resveratrol has antioxidative and anti-inflammatory properties. It has positive effects on cardiovascular, anti-inflammatory properties, and cancer, as found in red wine, peanuts, and some baits [86]. Resveratrol shows low DNMT inhibitory function in MCF7 breast cancer cells. The result is that some tumour suppressor genes have not been methylated

in reverse. Resveratrol enhanced adenosine analogues' efficiency to suppress RAR β 2 promoter methylation; however, it was not effective with Resveratrol alone. Resveratrol, with the combination of vitamin D3 anti-inflammatory properties, was incredibly successful in decline methylation of the PTEN promoter and persuaded PTEN explanation, In ER-positive MCF-7 breast cancer cells, the DNMT downregulation and controlling p21 but significant effects on three-negative breast cancer cells, MDA-MB-231, were observed [87].

The class III HDAC, sirtuin 1 (SIRT1) and p300 were further demonstrated as objectives of Resveratrol. Resveratrol stimulates the SIRT1 catalytic nucleus independently of the terminal areas, indicating an enzyme's catalytic centre for a resveratrol binding site. In mammary tumours of the mutant mice of BRCA1, low SIRT levels and high survival levels were observed; inducing expression from BRCA1 induced increased expression of SIRT1 by attaching to the BRCA1 to the SIRT1 promoter. Increased expression of SIRT1 inhibited the survival of histone H3K9 modulation. Resveratrol reduced acetylation of histoneH3K9 both in vitro and in vivo, inducing expression of SIRT1 and inhibiting survival from providing a BRCA1 Mutant Cancer Cells Profound inhibitory [88].

The number of intestinal polyps induced into arcmin mutation with the mouse did not affect the genotype SIRT1, but its polyp scale was much lower in vivo use of SIRT1-Null Mice. The incident and tumour loads of the skin did not affect SIRT1 genotype Butterflies. Topical applying of Resveratrol to the skin, tumorigenesis deeply reduced, but the effect of SIRT1 null mice has diminished, indicating that Resveratrol needs SIRT1 protein encoded to protect it [89].

Resveratrol has also prevented epigenetic silencing of the aromatic hydrocarbon receptors of tumour suppressor BRCA-1 in human cancer cells of MCF-7 by modulating H3K9 and H4 acetylation, combination in monomethyl-h3K9, DNMT1 and the BRCA-1 gene promoter and protein-2 methyl-binding region [90]. It has also been demonstrated that Resveratrol provides cancer protection by miRNAs. After treatment for Resveratrol, decreases of many oncogenic levels miRNAs in human SW480 colon cancer cells were identified to Dicer1 targets, PDCD4 and PTEN and core TGF β signalling route effectors were found. Treatment caused substantial upregulation and downregulation of 22 miRNA 26 miRNA phrase. Many of the high-regulated miRNA for colon tumours, such as miR-17, miR-21, miR-25,

miR-92a-2, have declined following resveratrol therapy. The miR-663, which has been shown to have improved cancer-suppressing roles, and TGF1 transcripts are targeted. The TGF β -signal pass elements, TGF β RI and RII and SMADs were decreased as miR-663 was also the target of resveratrol anticancer action [88].

4.7 Organosulfur compounds

To promote immunity and heart protection, microbial, x-rays, cancer prevention and hypoglycemic agents; allium plants, such as chives, garlic and leeks, have been used in traditional medicine. If allium vegetables are eaten daily, the risk of stomach and colon cancer is reduced significantly. Compounds of organosulfur that are released after treatment induce such plants' cancer action by disintegrating the highly unstable alliinase in the products that have formed after alliin and other alkyl alkane thiosulfonates are converted into allicin [91]. In vivo experiments, various organ cancers caused by chemicals are protected, and tumour development in xenografted models is inhibited. DADS is eventually metabolized into Allyl Mercaptan [AM] and other metabolites with the active metabolite S-lylmercaptocysteine [SAMC] [92]. DADS and SAMC. have been shown to cause histone acetylation and cell growth in DS19 erythroleukemia mouse cells. A more effective HDAC inhibitor was the A M metabolite. By conducting silico docking research and verifying HDAC's inhibitors' ability, the direct bending of AM to the catalytic position of the HDACs was expected. DADS therapy has enhanced global H3 and H4 histone acetylation and has strengthened its bonding with the p21 gene promoter. These activities were related to HDAC inhibition, upregulation and arrest of the cell cycle [81]. Caco2 cells in vitro breast tumour T47D species with SAMC increase histone acetylation by inhibiting allyl butyrate of HDAC activity [93]. The treatment of HDAC and HAT in DS19 cells decreased with s-Aylmer-captocysteine or isothiocyanate allyl. Hyperacetylation, P21 upregulation, arrest and differentiation of the cell cycle and apoptosis in various cancer cell lines linked to DADS therapy. HCA and increased histone acetylation of cells H3 and H4 associated with increased expression and cell arrest cycle p21/WAF1 Colon DADS showing cells Caco-2 or HT-29 decreased. [93].

4.8 Lycopene

Lycopene is primarily found in tomatoes. It is one of the regular and adequate antioxidant classes of tetraterpenoids. Inside body (In vivo) experiments with animal cancer samples demonstrated that, although not in effect to avoid colon, kidney and liver cancer, lycopene would suppress breast, prostatic and pulmonary tumours [94]. The GSTP1 tumour suppressor gene promoter in the MDAMB-468 line of breast cancer cells was partially demethylated by a single dose of 2 μ M lycopene and mRNA expression increased. However, in either MDA-MB-468 cells or MCF-7 breast cancer, the RAR β 2 gene has not been demethylated by lycopene therapy. Demethylation of RAR β 2 and HIN-1 genes was observed; however, after two weeks of lycopene therapy in immortalized non-tumorigenic MCF10A fibrocystic breast cells. The analysis reveals lycopene is specifically demethylated by DNA [66].

4.9 Quercetin

Polyphenols in dietary are multifaceted flavonoids with immense cancer prevention and therapeutic potential. [95]. Quercetin is one of the most widely occurring biflavonoid in buckwheat fruits and citrus. In wort, the NAD-dependent histone deacetylase SIRT1 is activated with quercetin. It prevented colon cancer development of RKO cells by dismantling its promoter by silencing the p16INK4a hypermethylated gene [96]. HL-60 caused FasL mediated Quercetin therapy for human leukaemia Caspase-8 activation, Bid cleavage, Bax combination shifts and cytochrome c be free, the extrinsic route through apoptosis. Quercetin enhanced histone H3 acetylation by HAT activation, which revealed quercetin mediated FasL-related apoptosis by transactivation by C-jun/AP-1 activation and HL-60 cell histone acetylation promotion [97, 98]. Recent research has shown that the combined administered of quercetin to hamsters painted by DMBA reduces the incidence and tumor pressure. In contrast, a substantial tumor growth delay was observed post-treatment. The administration of quercetin induced arrests and apoptosis of cells and prevented invasion and angiogenesis. This research indicates a positive association between quercetin and its anticancer properties, inhibiting HDAC1 and DNMT1 [99].

4.10 Ellagitannins

Ellagitannins are ellagic acid polyesters and a mode of sugar. There are few fruit and nuts, like grenades, raspberries, framberries, blackberries, nuts, and almonds found in popular food. Ellagitannins are commonly used for their antioxidant and antifreeze drugs and their anti-tumour, anti-tumour promotion and immunomodulatory properties. Ellagitannin is widely used in alternative therapy. Ellagitannins modulate different transcription factors and signalling pathways to prevent cancer cells from spreading and contributing to apoptosis [100]. Hepatic cancer HepG2 was isolated with ellagitannin (BJA3121) from balanophora japonica plant and inhibited cell growth and several miRNAs.

5. Summary and Future Directions

Prevention is more effective than rehabilitation, which applies to complex terminal illnesses like cancer. As already explained by methylation of the CpG islands on its promoters, epigenetic deregulation of essential tumour suppressor genes, significant cell components and cell expression levels, is deregulated for cancer. Abnormal post-translation changes by deregulation of acetylation/methylation and miRNA destruction of histone and specific non-histone proteins. Accumulating data suggests that dietary chemo preservation agents in cell culture trials and some human cancer models may inhibit or reverse such epigenetic alteration.

Table 1 provides a brief overview of these improvements. Future studies must be done on the transition in human and pre-clinical cancer models of the results of these food-borne phytochemicals. Since the group of consequences of these plant compounds are cell types or a specific organ, a particular disease prevention regime needs to improve and cure these variations' mechanism(s). Also, epigenetic defects will ultimately lead to not reversible genetic defects; it may be essential to take sufficient periods to act using nutritional chemopreventive agents that can delay cancer development. Therefore, it is significant to design and carry out effective tests to deal with these questions and efficiently evaluate the data collected. Epigenetic changes are an essential part of the production and division of cells, Adequate exposure period to interfere epigenetic mechanism is necessary for the dietary agent. More recent evidence shows that the combined impact of different phytochemicals is advantageous than an individual agent diet and that rigorous efforts are needed for exact determination. A combined method is used for dosage,

time and duration of the action. In conclusion, the development of dietary phytochemicals as effective chemopreventive and/or chemotherapeutic drugs is significantly more complex and convoluted than is well known and acknowledged by several research articles.

Although phytochemicals are particularly effective at preventing cancer, a number of problems must be answered before clinical studies based on scientific data may be conducted.

Table 1. Effect of dietary Polyphenols on Epigenetic Regulatory mechanism

Phytochemical/Dietary agent (source)	Epigenetic modification (s)	Mechanism(s)	References
Green tea polyphenol-epigallocatechin-3-gallate (EGCG) (green tea)	DNA methylation Histone modifications Differential miRNA modulations	DNMT inhibitor Promoter methylation↓ SAM, 5mC ↓ HDAC activity ↓ HAT exp ↑ Ac-H3, H3K9Ac, Ac-H4 ↑ HMT inhibitor BMI-1, SUZ12, EZH2, EED, H3K27me3 ↓, miR-16 ↑. miR-21 ↓. miR-27↓, miR-330 ↑	[21-32]
Curcumin (turmeric) words	DNA methylation Histone modifications Differential miRNA modulations	DNMT inhibitor Promoter methylation ↓ 5mC ↓ MeCP2 binding ↑ H3K27me3 ↑ HDAC1,HDAC3,HDAC0-8 ↓ p300 (HAT)↓ Ac-H3, Ac-H4 ↓ miR-22↑ . miR-186 ↓ miR-15a ↑. miR16 ↑	[34-50]
Sulforaphane (Broccoli)	DNA methylation Histone modifications	DNMT expression ↓ Promoter methylation ↓ HDAC inhibitor Ac-H3 and Ac-H4 ↑	[52-58]
Dindolylmethane (DIM) and Indole-3-carbinol (BC. Cruciferous vegetables- Brassica genus)	Histone modifications Differential miRNA modulations	Class I HDACs degradation ↑ HDAC-1,2,3 expression ↓ miR-let-7b, miR-146, miR- let-7e, miR-200b, and miR-200c.miR-21↑	[60-63]
Genistein (soy beans)	DNA methylation Histone modifications Differential miRNA modulations	DNMT inhibitor Promoter methylation↓ HDAC exp↓ HAT exp↑ AcH3, Ac-H4, Ac H3K9 ↑ H3K9me2↑ miR-200 ↓, miR1296 ↑. miR 27a↓	[61, 65-78]
Phenethyl Isothiocyanate (cruciferous vegetables)	DNA methylation Histone modifications	GSTP 1 Promoter methylation ↓ H3 and H4 acetylation↑, HDAC↓	[80-85]
Resveratrol (Grapes)	DNA methylation Histone modifications	DNMT inhibitor MBD2 recruitment ↓ Promoter methylation↓ MTA1/NuRD corepressor complex ↓	[87-90]
Organosulfur Compounds (Allium vegetables such as garlic)	Histone modifications	H3 and H4 acetylation ↑ HDAC↓	[81, 91, 93]
Lycopene (Tomatoes)	DNA methylation	Promoter methylation↓	[66]

Quercetin (Citrous fruits and Buck wheat)	DNA methylation Histone modifications	DNMT inhibitor Promoter methylation↓ Ac-H3 ↑ HDAC-1 ↓	[96-99]
Ellagitannins (Berries)	Differential miRNA modulations	miR-let-7e, miR-370, miR-373* and miR-526b ↑ let-7a, let-7c, let-7d ↓	[101]

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