

## Dietary Phytochemicals as Epi-drugs: Role in Modulating the Epigenetic Mechanisms of Human Diseases

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### ABSTRACT

Epigenetic therapy is emerging as a promising approach against numerous human diseases. Though, the epigenetic mechanisms are essential for normal cellular functions, the aberrant epigenetic mechanisms, such as promoter DNA methylation, histone modifications, and miRNA-mediated post-transcriptional alterations contributes to the life style related diseases. Unlike genetic modification, the epigenetic modifications are reversible and often identified in early stages of diseases. Thus, targeting aberrant epigenetic modification has gained considerable attention in diseases prevention especially in cancer therapy and diagnosis.

The concept of “epi drugs” is at the forefront of drug discovery which some are either approved or under clinical trials. The global demand for safe, cost effective and readily available therapeutics has a renewed interest in plant based drug leads which allow chronic use. A wide spectrum of secondary metabolites extracted from fruits, vegetable, teas and medicinal plants are known to regulate the epigenetic mechanisms and exhibit low toxicity in chronic administration. The applicability of major phytochemical groups such as polyphenols, terpenoids, organosulfur and alkaloids as epi-drugs against cancer and other diseases are experimentally established. Hence, the present review summarizes therapeutic potential of common dietary phytochemicals and their influence on major epigenetic mechanisms associated with human diseases, mostly against cancer and emphasizes their potential application as epi-drugs.

**Keywords:** Epigenetics, Epi-drugs, methylation, histone, acetylation, miRNA, dietary phytochemicals, polyphenols, Cancer

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### INTRODUCTION

The non-communicable diseases (NCD) are increasing at alarming rates globally and represent a leading threat to human health<sup>1</sup>. Common, chronic diseases such as diabetes, coronary heart disease and cancers constitute the major burdens in almost all countries<sup>1</sup>. Most NCDs are multifactorial in nature where, both genetic and environmental factors are involved in the onset and progression of diseases<sup>2</sup>. Sequencing the human genome revolutionized the understanding of genetic background of human diseases<sup>3</sup>. However, it is now becoming apparent, non-genetic factors such as environmental toxins, nutrients and life style play a pivotal role in developing NCDs<sup>4</sup>. A novel concept of “epigenetics” explains the influence of environmental factors on genetic alteration contributing to the development of NCDs<sup>5</sup>. Though, epigenetic processes are essential in the regulation of normal functions of the cell during all stages, aberrant epigenetic alteration could lead to various diseases, including cancer<sup>6</sup>. During last two decades epigenetic modifications and the development of cancers have been extensively studied. The term epigenetic refers to the study of heritable alteration in

gene expression without changes in the deoxyribonucleic acid (DNA) sequence<sup>7</sup>. Methylation of cytosine bases in DNA, covalent modification of histone proteins and post transcriptional gene regulation by micro ribonucleic acid (miRNAs) are the key processes of epigenetic modifications<sup>7</sup>. Change of diet, environmental toxins, life style factors, chronic stress etc, promotes aberrant epigenetic modifications which subsequently lead to acquired genetic alteration<sup>8</sup>. Unlike genetic mutations which are perpetual, epigenetically modified genes can be changed and restored, and thus providing a promising area of therapeutic interventions<sup>9</sup>. Small molecules that reverse epigenetic mechanisms are now undergoing clinical trials. Accordingly, some of these molecules have been approved for cancer treatment by the Food and Drug Administration (FDA)<sup>10,11</sup>. These mainly include inhibitors of DNA methyltransferases (DNMTs) [5-azacitidine (5AC) and 5-aza-2'-deoxyazacytidine (DAC), Procainamide] and histone deacetylases (HDAC) [(Trichostatin A, Suberoylanilide hydroxamic acid (SAHA))<sup>10, 12</sup>. The vast number of clinical trials underlines the promising use of these drugs in treating human diseases. Combination therapy with traditional

chemotherapy in preclinical settings has shown promising results<sup>10</sup>. However the long term administration of synthetic drugs is contentious considering their adverse side effects, narrow specificity and high cost<sup>13</sup>. Experimental evidence accumulated in the recent years from various preclinical and clinical studies clearly support the idea that dietary and medicinal phytochemicals have potentially beneficial effects on multitude of health conditions, including cancer, and cardiac diseases<sup>13</sup>. The mere fact that currently a plethora of dietary phytochemicals are being characterized from an “epi drugs” perspective reflecting an understanding of the concept of safe, cost effective and natural agents as chemo preventives for many diseases. Although, the health effects of dietary phytochemicals in humans are generally considered promising, the knowledge of the underlying molecular mechanisms is still in its infancy. This article provides a comprehensive review of literature on current knowledge and underlying mechanisms of the most common dietary phytochemicals and their influence on major epigenetic mechanisms associated with disease interventions.

#### *Epigenetic mechanisms*

Epigenetic mechanisms can be classified into three distinct types: DNA methylation, histone modifications, and non-coding RNAs or micro RNA interference<sup>14</sup>. All of these are crucial mechanisms that regulate gene activity and expression during development and differentiation of mammalian cells<sup>14</sup>.

#### *DNA methylation*

Methylation of DNA molecule is the most widely studied epigenetic modification. In mammalian cells, DNA methylation occurs by covalent addition of a methyl group at the 5' carbon of the cytosine ring, primarily at cytosine–guanosine dinucleotides (CpGs)<sup>15</sup>. Genomic regions with CpG rich sequences are called as CpG islands<sup>15</sup>. Most of the CpG dinucleotides in the human genome are methylated<sup>15</sup> however, these islands are typically found in or near promoter regions of genes, where transcription is initiated<sup>15</sup>. The modification at 5-methyl cytosine is catalyzed by enzyme DNA methyltransferases (DNMTs)<sup>16</sup>. Mammalian cells are equipped with several classes of DNMT including DNMT1, DNMT2, DNMT3a, and DNMT3b and DNMT3L<sup>16,17</sup>. DNMT1 is crucial for keeping genomic integrity in higher eukaryotes by maintenance of established patterns of DNA methylation<sup>17</sup>. DNMT3a and 3b mediate establishment of new, or *de novo*, DNA methylation patterns<sup>18</sup>. DNMT2 is methylating transfer ribonucleic acid (tRNA) with weak DNMTase activity<sup>16,19</sup>. The third member of the DNMT3 family: DNMT3L acts as a regulatory factor for DNMT3a and induces *de novo* DNA methylation of imprinted genes in mammalian germ cells by recruiting or activating DNMT3a<sup>19</sup>. Distinct methylation patterns are established during embryonic development and maintained through many cellular divisions. This faithful maintenance of normal DNA methylation patterns is disrupted in cancer<sup>20</sup>. Generally CpG islands within the promoter regions of a gene are unmethylated and increased

methylation of CpG within gene promoters can lead to transcriptional silencing of genes including many tumor suppressive genes<sup>20</sup>. Thus, Promoter hypermethylation of critical pathway genes could be potential biomarkers and therapeutic targets for many cancers<sup>21</sup>. Therefore, demethylation-based therapy can aggravate the hypemethylation status in cancer cells making them more susceptible to demethylate than normal ones. Some of the epigenetic alterations are experimentally proven or being translated into clinically practice as personalized treatment approach against cancer and other NCDs<sup>22</sup>.

#### *Histone modification*

Epigenetic regulation of gene expression is also mediated by histone post translational modification. Histones are major structural proteins of chromosomes. They serve as building blocks to package eukaryotic DNA into higher order chromatin fibers<sup>23</sup>. Each nucleosome encompasses ~146 base pair (bp) of DNA wrapped around an octamer made out of core histone proteins H2A, H2B, H3 and H4<sup>23</sup>. The histone proteins coordinate the changes between tightly packed DNA (or heterochromatin), which is inaccessible to transcription, and loosely packed DNA (or euchromatin)<sup>23</sup>. Histone modifications typically occur as post-translational modifications at the N-terminal tail of histones<sup>24</sup>. These modifications include acetylation, methylation, phosphorylation, biotinylation, and ubiquitination, and so on, and are essential for folding and functional state of the chromatin fiber<sup>24</sup>. Acetylation and methylation are the most widely studied covalent modification of histones<sup>24</sup>. In most cases, histone acetylation enhances transcription while histone deacetylation represses transcription<sup>24</sup>. Histone acetylation is maintained by the interplay of histone acetyl transferases (HATs) and histone deacetylases (HDACs). HATs transfer acetyl groups from acetyl-Coenzyme (Aacetyl-CoA) to the e-amino group of lysine (K) residues in histone tails<sup>24</sup>. Histone acetyltransferase (HAT) enzymes can be classified into several groups, including the often possess distinct histone specificity. Subgroups include the Gcn5-related N-acetyltransferase (GNAT), MYST, p300/CBP, Steroid receptor coactivator SRC and transcription initiation factor TFIID 250 (TAFII250) families<sup>25</sup>. In contrast to histone acetylation, histone deacetylation generally leads to chromatin condensation and transcriptional repression. So far, 18 proteins with HDAC activity have been classified and HDACs 1–11 are subdivided into three classes – I, II, and IV – based on homology, size, sub-cellular expression etc<sup>26</sup>. These site-specific acetylation or deacetylation leads to locally restricted activation or repression of transcription, respectively<sup>27</sup>. Histone methylation takes place at lysine and arginine residues. Both activating and repressive effect of gene expression is associated with histone lysine methylation dependent on the site (lysine residue) that is methylated (e.g., K4, K9, K27, K36, K79 in H3), and the status of methylation status (mono-, di-, or tri-methylation)<sup>27</sup>. Methylation at H3K4, H3K36, and H3K79 is generally associated with transcriptional active chromatin (euchromatin), whereas methylation at H3K9, H3K27, and H4K20 is frequently associated with

transcriptional inactive heterochromatin<sup>27</sup>. Several families of histone methyltransferases (HMTs) have been identified that catalyze the methylation of specific arginines or lysines in histones H3 and H4<sup>28</sup>. Alterations in the function of histone-modifying complexes are believed to disrupt the pattern of histone marks and consequently deregulate the control of chromatin-based processes, ultimately leading to oncogenic transformation and the development of cancer. Especially, abnormal activity of both HATs and HDACs has been linked to the pathogenesis of cancer.

#### Micro RNA

Micro RNA (miRNA) are small non-coding RNAs of 20–22 nucleotides that inhibit gene expression at the posttranscriptional level to regulate key biological processes including development and differentiation<sup>29</sup>. They are transcribed by RNA polymerase II (Pol II) into primary miRNAs and subsequently processed in the nucleus by the RNase III Drosha and DGCR8 (microprocessor complex) into the precursor miRNAs<sup>30</sup>. These miRNAs bind to their target mRNAs and down-regulate their stabilities and/or translation. Each miRNA is predicted to have many targets, and may be regulated by more than one miRNA<sup>30</sup>. To date, there are more than 460 known human miRNAs<sup>30</sup>. These miRNA genes can be epigenetically regulated by DNA methylation and/or histone modifications<sup>31</sup>. Micro RNAs have been implicated in cancer initiation and progression, and their expression is often down-regulated during carcinogenesis<sup>31</sup>. Importantly, miR-9, miR-148, miR-124, miR-137, miR-34, miR-127 and miR-512 reportedly can be silenced by CpG hyper methylation in cancers<sup>32</sup>.

#### Dietary phytochemicals as potential in disease prevention

The effect of dietary phytochemicals on health status has been recognized since antiquity. During last few decades there has been a surge of interest in dietary phytochemicals as ethno medicines against chronic diseases such as cancer, diabetes, and cardiovascular disease<sup>33</sup>. Phytochemicals are described as non-nutritive components in the plant-based diet<sup>33</sup> and mainly include carotenoids, phenolic compounds (flavonoids, phytoestrogens, phenolic acids), phytosterols and phytostanols, tocotrienols, organosulfur compounds (allium compounds and glucosinolates), terpenoids, saponins, alkaloids and non-digestible carbohydrates (dietary fiber and prebiotics)<sup>34-36</sup>. Experimental evidences suggest that consumption of dietary agents can alter normal epigenetic states as well as reverse abnormal epigenetic mechanisms which may avert onset and progression of cancer and other NCDs<sup>37</sup>. We summarize herein, some of the popular dietary phytochemicals and their chemo preventive role in cancer and other NCDs by regulating the epigenetic mechanisms.

#### Polyphenols

Polyphenols are the most numerous and ubiquitous groups of phytochemical present in plant diet. These chemical compounds are highly diverse with one or more (poly-) phenolic structures<sup>38</sup>. Polyphenols are present in fruits and plant-derived beverages such as fruit juices, tea, coffee, and red wine. In addition, vegetables, cereals,

chocolate, and dry legumes also contribute to the total polyphenol intake<sup>39</sup>. Polyphenols possess strong antioxidant properties and suggests a role of preventing cardiovascular diseases, cancers, osteoporosis, neurodegenerative diseases and diabetes mellitus<sup>38</sup>. Polyphenols are mainly categorized into phenolic acids, flavonoids, polyphenolic amides, stilbenes and lignans<sup>40</sup>. Flavonoids are the largest and best characterized polyphenols including flavonols, flavones, catechins, flavanones, anthocyanidins, and isoflavonoids<sup>41</sup>. The role of dietary polyphenols in regulating epigenetic mechanisms and the expression of various tumor suppressor genes have been extensively studied during the last decade<sup>42,24</sup>.

#### Tea polyphenols

Tea is a popular beverage globally and has a significant therapeutic potential. Tea polyphenols are most studied dietary phytochemicals for its *in vitro* and *in vivo* anticancer, antioxidant and anti-inflammatory properties and other chronic diseases<sup>43</sup>. Most of the polyphenols in green tea are flavanols, commonly known as catechins; the major catechins in green tea are (–)-epicatechin, (EC) (–)-epicatechin-3-gallate (ECG), (–)-epigallocatechin (EGC), and (–)-epigallocatechin-3-gallate (EGCG)<sup>44</sup>. In black teas, the major polyphenols are theaflavin and thearubigin<sup>44</sup>. Experiments on laboratory animals (rats, mice and hamsters) have demonstrated that tea consumption protects against numerous chemical carcinogen induced cancers such as lung, fore stomach, esophagus, duodenum, pancreas, liver, breast, colon, and skin cancers<sup>45,46</sup>. Accumulating experiment evidence suggests that the anticancer properties of tea polyphenols could be attributed to the modulation of epigenetic mechanisms. Over the past decade, several reports highlighted the role of EGCG as a DNMT inhibitor<sup>45</sup>. Biochemical experiment revealed tea polyphenols and bioflavonoids inhibit prokaryotic SssI DNMT- and human DNMT1-mediated DNA methylation in a concentration-dependent manner in *in vitro* system<sup>45</sup>. It was also reported EGCG inhibits DNMT activity and reactivates methylation-silenced genes (P16(INK49), RAR $\beta$ , MGMT and hMLH1) in human esophageal cancer, esophageal cancer cell line (KYSE 510) cells, colon cancer, human colon adenocarcinoma cells (HT-29) and prostate cancer (PC3) cells<sup>46</sup>. Green tea consumption has also reduced the methylation of CDX2 and bone morphogenetic protein-2 (BMP-2) genes associated with gastric carcinoma<sup>47</sup>. It was reported that the EGCG treatment reduces the DNA methylation and induced the activity of forkhead box P3 (Foxp3) which is a transcription factor that serves as the master switch which controls the regulatory T cell function in Jurkat T cells<sup>48</sup>. Molecular modeling studies proposed, the gallate moiety of EGCG forms hydrogen bonding between Glu1265 and Pro1223; the two catalytic residues of DNMT1. Further A and B rings of EGCG form hydrogen bonds with Ser1229 and Cys1225 and prevent DNA methylation by blocking the entry of the key nucleotide cytosine into its active site<sup>49</sup>. In addition to DNMT inhibition, several reports highlighted the effect of EGCG on histone modification.

Treatment of human breast adenocarcinoma cell line (MCF-7) and MDA-MB-231 breast cancer cell lines with EGCG has significantly reduced Enhancer Of Zeste 2 Polycomb Repressive Complex 2 Subunit (EZH2) and HDAC1 levels and increased the transcription activation of tissue inhibitor of metalloproteinases-3 (TIMP-3) gene which subsequently suppresses the pathogenesis of breast cancers. In prostate cancer, chromatin changes on the Glutathione S-Transferase Pi 1 GSTP1 promoter have been shown to have effects on the tumor progression. EGCG inhibits HDACs 1–3 activity and increase in levels of acetylated histone H3 at lysine 9 and 18, and in overall H4 acetylation and increase the GSTP1 promoter transcription by increasing the access by facilitating chromatin unfolding<sup>50</sup>. This study highlights the importance of EGCG as both DNMT inhibitor and chromatin remodeler<sup>50</sup>.

#### Curcumin

Curcumin (diferuloylmethane), a component of the Indian spice *Curcuma longa*, commonly known as turmeric<sup>51</sup> is known to modulate epigenetic mechanisms associated with diseases<sup>52</sup>. Curcumin has the potential to demethylate the DNA methylation of first 5 CpGs in the promoter region of Nrf2 gene in murine prostate cancer TRAMP C1 cells which is epigenetically silenced during the progression of prostate cancers in TRAMP mice<sup>53</sup>. Curcumin has been reported to reverse CpG methylation of the promoter region of Neurog1, a cancer methylation marker known to be highly methylated and whose expression is perturbed in human prostate cancer LNCaP cells<sup>54</sup>. Curcumin has been reported to modulate the activities of HDAC and HAT<sup>55</sup> and especially HDAC 1, 3, and 8 protein levels were significantly lowered by curcumin which indirectly related to increase acetylation of histone H4<sup>56,57</sup>. Curcumin is a natural inhibitor of HAT p300/CREB-binding protein (CBP) and this inhibition abrogate histone and p300-mediated p53 acetylation leading to induction of apoptosis of Hela cells<sup>58</sup>. Moreover, curcumin induces apoptosis of ovarian cancer SKOV3 cells through inducing the MiRNA-9 – mediated phosphorylation fork head box protein O1 (FOXO1) pathway<sup>59</sup>. Curcumin effectively induced histone H3/H4 hypoacetylation in brain cancer cells, and this effect was associated with neuronal stem cell fate controlling<sup>60</sup>. Another study revealed, unlike 5-aza-2'-deoxyazacytidine (DAC) mediating global hypomethylation, curcumin induces methylation at subset of partially methylated genes, proving insight into potent therapeutic lead<sup>61</sup>. Curcumin modulates miRNAs (miR-15a, miR-16, miR-21, miR-22, miR-26, miR-101, miR-146, miR-200, miR-203, and let-7) and their multiple target genes<sup>55</sup> and thereby regulate epigenetic events associated with human diseases.

#### Resveratrol

Resveratrol (3,5,40 -trihydroxystilbene) is a common polyphenol of blueberries, mulberries peanuts and grapes<sup>62</sup>. Several properties of resveratrol including anti-aging, anti-carcinogenic, anti-inflammatory, and antioxidant properties have been scientifically justified using biochemical, *in vitro* and *in vivo* assays<sup>63</sup>.

Regulation of epigenetic mechanisms by resveratrol, especially the activation class III histone deacetylases: sirtuins (SIRT1) has been extensively studied<sup>64</sup>. However, another study has recognized resveratrol can mediate epigenetic effect through ER (estrogen receptor) and are independent of SIRT1 regulation<sup>65</sup>. It was reported resveratrol reverse the epigenetic silence of Breast Cancer 1, Early Onset (BRAC1) gene expression involves in breast cancer<sup>66</sup>. The recruitment(s) of HDAC1, DNMT1, Methyl-CpG Binding Domain Protein 2MBD2, and mMH3K9 contributing to the epigenetic silencing of BRCA-1 induced by (aromatic hydrocarbon receptor) AhR agonists such as 2,3,7,8 tetrachlorobenzo(p)dioxin (TCDD) was antagonized by dietary intake of resveratrol<sup>66</sup>. Resveratrol down regulates the metastasis associated proteins 1 (MTA1) which is overexpressed in progressive prostate cancers<sup>67</sup>. Resveratrol destabilized the metastasis associated proteins 1/nucleosome remodeling deacetylation MTA1/ NuRD complex by down regulating MTA1 and subsequently allowing acetylation of p53. Thus, increased acetylation of p53 favors the cell cycle arrest and apoptosis of prostate cancer<sup>67</sup>. *In vitro* analyses of overall HDAC inhibition and a detailed HDAC profiling showed that resveratrol inhibited all eleven human HDACs of class I, II and IV in a dose-dependent manner<sup>68</sup>.

#### Quercetin

Quercetin is a flavonol, ubiquitously present in dietary plant sources but predominantly present in citrus fruits and buckwheat<sup>69</sup> with strong antioxidant and antitumor properties<sup>70</sup>. It is also demonstrated that quercetin activates histone acetyltransferase (HAT) and inhibition of histone deacetyltransferase (HADAC), both of which contributed to histone acetylation H3 in HL-60 leukemia cells. This study shows quercetin induces apoptosis of Human promyelocytic leukemia (HL-60) cells is FasL-related and activates extracellular signal-regulated kinase (ERK) and jun N-terminus kinase (JNK) signaling pathway<sup>71</sup>.

#### Anacardic acid

Anacardic acid (AA) is an active compound found in cashew nuts<sup>72</sup>. Anacardic acid inhibits the Tip60 HAT in *in vitro* system and blocks the Tip60-dependent activation of the Ataxia telangiectasis mutated (ATM) and DNA-PKcs protein kinases (which are differentially participate in DNA damage responses) and increase the sensitivity of tumor cells to radiation and stimulates cytotoxicity<sup>73</sup>. Anacardic acid effectively inhibits UV-induced cancer formation and premature skin aging by inhibiting UV-enhanced levels of *c-H2AX*, *p53*, and acetylation of H3 lymphoid and myeloid leukemia cells<sup>76</sup>.

#### Caffeic acid

Caffeic acid (3,4-dihydroxycinnamic acid) is a phenolic phytochemical present in many foods, including coffee<sup>74</sup>. Recent studies suggested that Caffeic acid exerts anticarcinogenic effects. Caffeic acid partially inhibits the methylation of the promoter region of the RAR $\beta$  gene in MCF-7 and MAD-MB-231 human breast cancer cells<sup>75</sup>. Inhibition of DNA methylation is regulated through a non-competitive mechanism, where formation of S-

adenosyl-L-homocysteine (SAH, a potent inhibitor of DNA methylation) was increased by Caffeic acid resulting from the catechol-O-methyltransferase (COMT)-mediated O-methylation<sup>75</sup>.

#### Gallic acid

Gallic acid (3,4,5-trihydroxybenzoic acid) is a polyhydroxyphenolic compound which is abundant in natural products such as nuts, tea leaves, apple peels, berries, pineapples, bananas, lemons, and in red and white wine<sup>76</sup>. In *in vitro* experiment it was found Gallic acid inhibited p300-induced acetylation hyperacetylation of p65 *in vitro* and reversed the Lipopolysaccharides (LPS)-enhanced acetylation of p65 in adenocarcinomic human alveolar basal epithelial cells (A549 cells)<sup>76</sup>.

#### Genistein

Genistein is the major isoflavone in soya beans (*Glycine max*)<sup>77</sup>. Chemopreventive activity of Genistein has been demonstrated in *in vitro* and animal models for ovarian, skin, stomach, colon cancer, prostate and breast cancer<sup>78</sup>. It is known to antagonize estrogen- and androgen-mediated signaling pathways in the processes of carcinogenesis<sup>78</sup>. It was reported Genistein significantly stimulated TCR  $\alpha$  enhancer (E $\alpha$ ) mediated histone acetylation<sup>79</sup>. Genistein treatment induced HAT1 activity which increased H3K9 acetylation and explained reasons for Wnt inhibitory genes such as SRY (Sex Determining Region Y)-Box 7 (SOX7) to be slightly induced when treated<sup>80</sup>. Genistein treatment reduced the growth of breast cancer cells suggesting apoptosis is mediated thorough inhibition of human telomerase reverse transcriptase (hTERT) by epigenetic mechanisms by increasing trimethyl-H3K9 but decreasing dimethyl-H3K4 in the hTERT promoter<sup>81</sup>.

#### Isothiocyanates

Isothiocyanates are sulfur-containing compounds found in cruciferous vegetables<sup>82</sup>. Sulforaphane (SFN) is one of the bioactive isothiocyanate, abundant in vegetables such as broccoli, cabbage and Brussels<sup>83</sup>. Sulforaphane suppresses DNA methylation of the nuclear factor erythroid 2-related factor 2 (Nrf2) promoter in TRAMP C1 cells via down regulating the DNMTs (DNMT1, DNMT3a and DNMT3b) and HDACs (HDAC1, HDAC2, HDAC3 and HDAC4)<sup>84</sup>. Sulforaphane stimulates ubiquitination and acetylation of SUV39H1 within a C-terminal nuclear localization signal peptide motif and decrease in global trimethyl-histone H3 lysine 9 (H3K9me3) levels<sup>85</sup>.

#### Triterpenoids

Terpenoids are group of phytochemicals traditionally claimed for numerous medicinal properties<sup>86</sup>. Both *in vitro* and *in vivo* models discusses the anti-proliferative, anti-inflammatory and pro-apoptotic activities of terpenoids<sup>86</sup>. More than 40 000 terpenoids compounds are exist in nature and few compounds have been extensively investigated<sup>87</sup>.

#### Parthenolide

Parthenolide (PTL), a sesquiterpene lactone (SL) originally purified from the shoots of feverfew (*Tanacetum parthenium*)<sup>88</sup>. Experimental evidence supports that it is a potent anticancer and anti-

inflammatory compound<sup>88</sup>. Parthenolide inhibits DNMT1 possibly via alkylation of the proximal thiolate of Cys (1226) of the catalytic center by its gamma-methylene lactone or by interrupting transcriptional factor Sp1 binding to the promoter of DNMT1<sup>89</sup> and exhibits an anti-cancer properties.

#### Lycopene

Lycopene, is type of terpenoid which is naturally abundant in tomato<sup>90</sup> and was found to enhance the antioxidant response of prostate cells and inhibit proliferation<sup>91</sup>. Lycopene partially and directly demethylates the promoter of the glutathione S-transferase pi gene (GSTP1) tumor suppressor gene in MDA-MB-468 cells<sup>92</sup>.

#### Triptolid

Triptolide is a diterpenoid triepoxide the active constituent in extracts from the Chinese herb *Tripterygium wilfordii* Hook.F<sup>93</sup>. Triptolide inhibited the proliferation of multiple myeloma cell line RPMI8226 in a time- and dose-dependent manner, induced G0/G1 cell cycle arrest and apoptosis<sup>94</sup>. Triptolide exert anti myeloma activity by decreasing HDAC8 activity which increases acetylation of H3 and H4<sup>94</sup>.

#### Alkaloids

Alkaloids are nitrogen atoms containing phytochemicals with marked medicinal properties<sup>95</sup>. Despite the traditional claims, very few alkaloid based drugs exists in modern medicine<sup>96</sup>. Mahanine, Sanguinarine and Matrine are few plant alkaloids which have been extensively studied for anti-cancer properties.

#### Mahanine

Mahanine (3,11-dihydro-3,5-dimethyl-3-(4-methyl-3-pentenyl)-pyrano[3,2-a]carbazol-9-ol) is a carbazole alkaloid and is a major constituent of the edible parts of the Thai vegetable *Micromelum minutum*<sup>97</sup>. Mahanine treatment restores the expression of RASSF1A gene which is hypermethylated in advance grade prostate cancer cells<sup>98</sup>. The degradation of DNMT1 and DNMT3B via the inactivation of protein kinase B (Akt) by mahanine, facilitates the demethylation of the RASSF1A promoter and restores its expression in prostate cancer cells<sup>98</sup>.

#### Sanguinarine

Sanguinarine (13-methyl[1,3]benzodioxolo[5,6-c]-1,3-dioxolo [4,5-i] phenanthridium) is another plant alkaloid, derived from the root of *Sanguinaria Canadensis*<sup>98</sup> with an antioxidant, anti-inflammatory and anti-microbial properties<sup>99</sup>. Sanguinarine is reported as a DNA binding anticancer agent due to its ability to bind to DNA. Moreover, sanguinarine binds to both DNA and to core histones and induces chromatin aggregation<sup>99</sup>.

#### Matrine

Matrine is another alkaloid recommended against breast cancer treatment especially in China. It is extracted from *Sophora flavescens*<sup>100</sup>. Matrine induces the apoptosis of human breast adenocarcinoma cells (MCF-7) by down regulating the expression of miRNA; miR-21 which in turn up-regulates the phosphate and tensin homologue (PTEN) protein<sup>100</sup>. The PTEN then dephosphorylates Akt and inhibits the cell proliferation<sup>100</sup>.

**CONCLUSION**

The process of drug discovery and development has evolved strikingly over the past few decades. The therapeutic potential of naturally occurring dietary phytochemicals are at the spotlight in both clinical and experimental fields. Dietary phytochemicals with the potential of modulating the epigenetic mechanisms are a particular interest in prevention of cancer and other life-style related diseases. Aberrant epigenetic modifications such as promoter hypermethylation of tumor suppressor genes, abnormal post translation modifications of histone and some non-histone proteins by deregulation of acetylation/methylation, and miRNA perturbation are found to be associated with numerous human diseases including cancers. The epi-drugs originated from natural source such as plants offer a great promise over single synthetic regimen which is costs effective and safe in chronic administration. However, more precise understanding of underlying mechanisms is required prior to evidence- based clinical trials.

**CONFLICT OF INTREST**

The authors do not have any conflict of interest to declare.

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