Epigenetic Modifications in Neurological Diseases: Natural Products as Epigenetic Modulators a Treatment Strategy

Omkaram Gangisetty and Sengottuvelan Murugan

Abstract Epigenetic modifications, including DNA methylation, covalent histone modifications, and small noncoding RNAs, play a key role in regulating the gene expression. This regulatory mechanism is important in cellular differentiation and development. Recent advances in the field of epigenetics extended the role of epigenetic mechanisms in controlling key biological processes such as genome imprinting and X-chromosome inactivation. Aberrant epigenetic modifications are associated with the development of many diseases. The role of epigenetic modifications in various neurodegenerative disorders including Alzheimer's disease, Parkinson's disease, Huntington disease, epilepsy, and multiple sclerosis is rapidly emerging. The use of epigenetic modifying drugs to treat these diseases has been the interest in recent years. A number of natural products having diverse mechanism of action are used for drug discovery. For many years, natural compounds have been used to treat various neurodegenerative diseases, but the use of such compounds as epigenetic modulators to reverse or treat neurological diseases are not well studied. In this chapter, we mainly focus on how various epigenetic modifications play a key role in neurodegenerative diseases, their mechanism of action, and how it acts as a potential therapeutic target for epigenetic drugs to treat these diseases will be discussed.

Keywords DNA methylation • Histone deacetylases (HDACs) • Neurological diseases • Epigenetic modulators • Dietary products

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Introduction

The eukaryotic genome is organized and packed into chromatin, which is a complex structure composed of DNA, histone, and nonhistone proteins. Chromatin remodeling is a dynamic process that modulates gene expression. Chromatin exists either in a condensed, inactive, transcriptionally repressive state called heterochromatin or transcriptionally active state called euchromatin. The term epigenetics is defined as heritable change in gene expression without altering the DNA sequence. Epigenetic modifications regulating gene expression are reversible and have long lasting effects. These epigenetic modifications control the gene expression during cellular development through DNA methylation, histone code modifications, and small noncoding RNAs (Costa 2008; Kouzarides 2007). All the three mechanisms regulate gene expression without altering the DNA sequence. There is a complex interplay between these three processes to regulate the gene expression (Fig. 1). These epigenetic modifications are involved in a number of essential cellular processes such as transcription, cellular differentiation, development, X-chromosome inactivation, gene imprinting, and cellular responses to environmental stimuli (Guibert and Weber 2013; Klose and Bird 2006; Smith and Meissner 2013; Subramaniam et al. 2014). Aberrant epigenetic modifications have been extensively reported in cancer. In recent years, the upcoming interest is developing on studying the role of epigenetic modifications in a number of neuropsychiatric and neurodegenerative diseases including schizophrenia (Grayson et al. 2005; Veldic et al. 2004, 2005) epilepsy, Alzheimer's disease (AD), Huntington's, and Parkinson's diseases (PD). Abnormal epigenetic mechanisms also have been reported in a number of mental disorders such as Rett, ICF, Fragile-X, and ATRX syndrome (Egger et al. 2004).

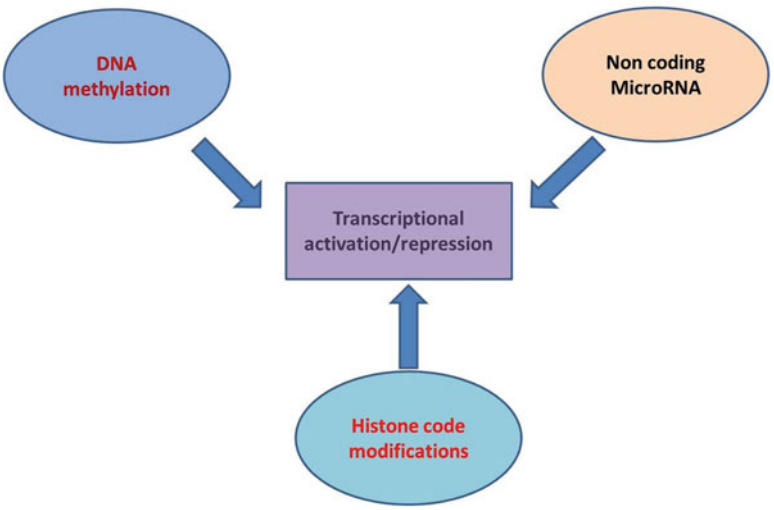


Fig. 1 Epigenetic regulation of gene expression. DNA methylation, histone code modifications, and noncoding microRNAs control gene expression without altering the DNA sequence. There is a complex interplay between the three epigenetic modifications to regulate gene activation or repression

DNA Methylation

DNA methylation is one of the most classically studied epigenetic modifications and involves covalent modification of cytosine residue in the CpG back ground by the addition of a methyl group at the fifth carbon position on its pyrimidine ring. The CpG dinucleotide rich regions are called CpG islands and are found in the promoter regions of the gene. The Promoter CpG island methylation plays an important role in regulating the gene expression by preventing transcription factors binding on to the promoter and thereby recruiting transcriptional repressors on to the promoter regions (Cedar and Bergman 2012). DNA methylation is also involved in silencing of imprinted genes in which only one allele, either paternal or maternal, is expressed (Reik et al. 2001; Edwards and Ferguson-Smith 2007). It is also involved in X chromosome inactivation in women (Jaenisch and Bird 2003). DNA methylation is also associated with maintenance of chromosomal stability and translocation prevention (Bird 2002). In human genome, most of the methylated CpGs occur in repetitive sequences such as long interspersed transposable element 1 (LINE1) and Alu repeats (Edwards and Myers 2008).

DNA Methyl Transferases

DNA methyl transferases catalyze the addition of a methyl group onto the cytosine nucleotide by utilizing *S*-adenosyl methionine (SAM) as the methyl donor. There are about five DNA methyl transferases reported that play a crucial role in establishing and maintaining DNA methylation. They are DNMT1, DNMT3A, DNMT3B, DNMT3L, and DNMT2. They share common structural similarities of having an N terminal regulatory and C terminal catalytic domain. Of all the five members of the DNMT family, DNMT1, 3A, and 3B are required to establish and maintain the genome methylation (Fig. 2).

DNMT1 is most abundant in mammalian cells and first murine DNMT cloned (Bestor 1988). DNMT1 plays an important role in methylating newly synthesized DNA during replication. It has a preference toward hemimethylated DNA and is responsible for copying preexisting methylation patterns to the newly synthesized DNA strand. It is also called maintenance methyl transferase. It is a large protein with around 1620 amino acids in length. It has an N terminal regulatory domain and C terminal catalytic domain. DNMT1 plays an essential role in development. DNMT1 knockout mice results in early embryonic lethality (Li et al. 1992).

DNMT 3A and 3B are other groups of DNMTs that effectively methylate unmethylated DNA de novo. They are considered as de novo DNA methyl transferases. They are encoded by two different genes and have structural homology with N terminal regulatory domain and C terminal catalytic domain. They play an important role in germ cell development and embryogenesis. In addition to redundancy in de novo methylation, these enzymes have different functional roles. DNMT3A is

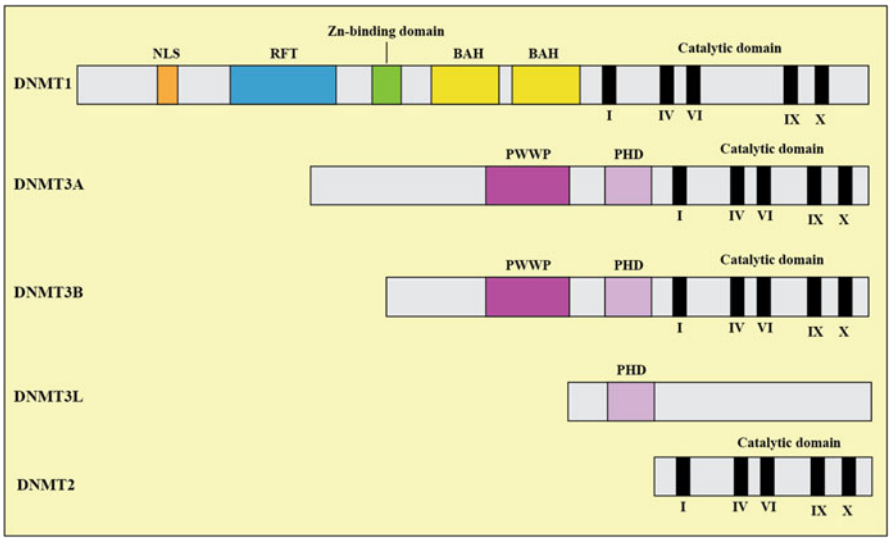


Fig. 2 A schematic representation of DNA methyl transferases (DNMTs). The five member family of DNMTs includes DNMT1, DNMT2, DNMT3A, 3B, and 3L. They all share conserved methyl transferase motifs indicated by *roman numerals* in the catalytic domain at C terminus. The regulatory N terminal domain is represented with NLS (nuclear localization signal), RFT (replication foci targeting domain), BAH (bromo-adjacent homology domain), PWWP (proline–tryptophan–tryptophan–proline) motif, and PHD (plant homeodomain). DNMT3L lacks methyl transferase motifs and is catalytically in active. DNMT2 lacks N terminal regulatory domain

ubiquitously expressed and DNMT3B is expressed at low levels except in testis, thyroid, and bone marrow (Xie et al. 1999). DNMT3B expression is increased in tumor cell lines and focused on methylating CpGs in repetitive sequences of pericentric regions of the chromosome (Hansen et al. 1999; Xu et al. 1999).

DNMT3L is another member of DNA methyl transferase that lacks the methyl transferase activity. It may cooperate with other de novo DNMTs and thereby increase the activity of that enzyme. It plays an important role in genomic imprinting since targeted disruption of DNMT3L resulted in biallelic expression of genes imprinted and expressed from one parental origin (Bourc'his et al. 2001).

DNMT2 was cloned based on its sequence homology with other DNMTs. It is the most conserved and its targeted disruption in ES cells did not detect any effect on global methylation suggesting it is not an essential for DNA methylation (Okano et al. 1998).

DNA Demethylation

DNA methylation has long thought to be a permanent epigenetic mark and is irreversible. However, it is a dynamic process during early mammalian development and alteration of methylation is also important for normal development (Shemer

and Razin 1996). There is considerable evidence supporting genome-wide active demethylation found in zygotes (Mayer et al. 2000; Oswald et al. 2000), primordial germ cells (Morgan et al. 2005; Hajkova et al. 2002), and locus-specific active demethylation observed in somatic cells such as neurons (Ma et al. 2009) and T lymphocytes (Bruniquel and Schwartz 2003). However, the mechanism of active demethylation is not clearly understood. Recent studies showed 5-hydroxymethylcytosine (5hmC) is likely to have an important implication in mammalian genome for active demethylation. The substantial amount of 5hmC has been detected in mouse purkinje neurons (Kriaucionis and Heintz 2009) and in ES cells (Tahiliani et al. 2009) In humans, TET family of proteins, TET1, TET2, and TET3, have been identified to catalyze the conversion of 5mC to 5hmC (Tahiliani et al. 2009).

Histone Code Modifications

In the eukaryotic cell nucleus, DNA is packed with histone octomer composed of two copies each of H2A, H2B, H3, and H4. Chromatin remodeling in the brain is characterized by posttranslational modification of histones. The specific amino acid residues such as lysine, arginine, serine, and threonine at the N terminal tail of histones subjected to potential modifications such as acetylation, methylation, phosphorylation, ubiquitination, and sumoylation. These modifications are associated with transcriptional activation or repression depending on the site of residue and the type of modification thereby forms the histone code. Posttranslational modification of histones is a dynamic and reversible process mediated by two different sets of enzyme complexes that add or remove a particular chemical group in a site-specific manner.

Histone Acetylation and Deacetylation

Histone acetylation is associated with positive transcription. Histone acetylation of lysine residue is one of the well-studied histone modifications. Histone H3 and H4 acetylation increases gene expression by promoting open configuration of chromatin. It is mainly catalyzed by histone acetyl transferases (HATs). They catalyze the transfer of acetyl group from acetyl co-A to lysine residues of histones. These acetyl groups neutralize positive histone charge, thereby opening up the chromatin for transcriptional activation. Some of the HATs include GCN5-related *N* acetyl transferases, MYST HATS, p300/CBP HATS, TATA binding protein-associated factor II (TAF II), RE1 silencing transcription factor (REST), nuclear factor kappa B (NFkB), etc. Acetylation is a transient mark and is vital for precise temporal transcription control. There are a number of acetylation sites on histone residues dynamically regulated by HATs and Histone deacetylases (HDACs). The most important acetylation sites of histone H3 are H3K9, K14, K18, and K56. The histone H4 acetylation sites are H4K5, K8, K12, and K16. Another histone H2B lysine residues are also

acetylated at K7, K16, and K17. All these histone code modifications play a role in transcriptional activation (Strahl and Allis 2000). Histone deacetylation involves removal of acetyl groups of lysine residues in the conserved tails of core histone proteins, thereby altering the negative to the positive charge. This results in the tight interaction of histones with negatively charged DNA, thereby facilitating the closed chromatin structure. It is associated with transcriptional repression catalyzed by HDACs. There are two major family proteins with HDAC activity. Sir2 (silent information regulator-2) or sirtuin (sir2-like protein) family of NAD-dependent HDACs (Class III HDACs) and classical HDAC family protein (De Ruijter et al. 2003; Yang and Seto 2008). The classical HDAC family proteins comprise three different classes such as class I, II, and IV. The class I HDACs includes HDAC1, 2, 3, and 8 which are smaller proteins. The class II HDACs includes HDAC 4, 5, 6, 7, 9, and 10 which are larger proteins (Bjerling et al. 2002; Fischle et al. 2002). The class IV HDAC member includes HDAC11 which has sequence similarity to class I and II HDACs (Gregoretti et al. 2004).

Histone Methylation and Demethylation

Histone methylation is associated with both transcriptional activation and repression depending on the modified amino acid residues. It occurs mainly on lysine and arginine residues either as mono-, di- and, trimethylation. Methylation of H3K4 and H3K36 are associated with transcriptional activation. H3K9, K27, and H4K20 methylations are associated with transcriptional repression (Barski et al. 2007). Histone methyl transferases (HMTs) which catalyze H3K9, K27, and H4K20 include G9a, GLP (Tachibana et al. 2002, 2005), SUV39H1, EZH2 (Cao et al. 2002), and PR-SET7 (Nishioka et al. 2002). However, SET7/9 mediates H3K4-specific methylation (Wang et al. 2003). These enzymes catalyze the transfer of the methyl group from *S*-adenosyl-L-methionine to the lysine residues of histones. Like other histone modifications, histone demethylation also plays an important role in the regulation of gene expression. Lysine-specific demethylase1 (LSD1) is the first reported histone demethylase which act on mono- and dimethylations (Shi et al. 2004). Jumanji domain containing protein is another histone demethylase that acts on trimethylated as well as mono- and dimethylated lysine's (Tsukada et al. 2006; Klose et al. 2006).

The overall epigenetic modification machinery including DNA methylation, demethylation, and various histone code modifications regulate gene expression either positively or negatively constitute the whole epigenome as it is represented in Fig. 3.

Epigenetic Dysregulation in Neurological Diseases

DNA methylation has been implicated in regulation of gene activity in the adult brain. It is linked to activation or repression of genes by synaptic activity. Such mechanisms regulate the expression of specific sets of neuronal genes that are

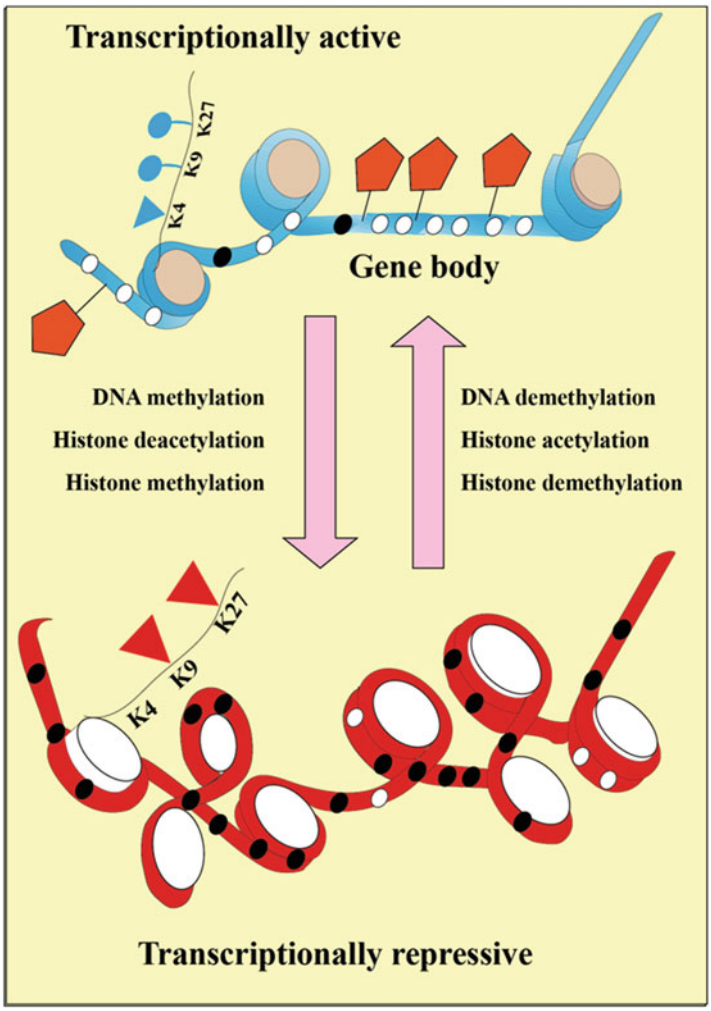


Fig. 3 Euchromatin- and heterochromatin-associated epigenetic modifications. Transcriptionally active euchromatin is represented in *blue* at *top*. DNA wrapped around histones. Unmethyl cytosine residues are represented in *open circles* on DNA. The hydroxyl methyl cytosine was represented as *pentagon structure* on the DNA. The N terminal tail of histone3 (H3) is represented with methyl group (*filled blue inverted triangle*) at K4 and acetyl group (*filled blue circles*) at K9 and K27. Transcriptionally inactive heterochromatin is represented in *red* at *bottom*. DNA wrapped around histones. Methyl cytosine residues are represented in *closed circles* (*filled black circles*). The N terminal tail of H3 is represented with methyl group (*filled red inverted triangle*) at K9 and K27

important for neural activity, survival, and morphology of neurons. DNA methylation patterns were altered in schizophrenia, Alzheimer's, Parkinson's, and other related psychiatric diseases. There is growing evidence that DNA methylation is involved in the pathophysiological mechanism of depression and addiction (Table 1).

Table 1 Epigenetic modifications associated with neurological diseases

Neurological disease	Epigenetic modification	Reference
Schizophrenia		
DNA methylation	Hypermethylation of GADD67 and Reelin in GABAergic neurons.	Veldic et al. (2004), Grayson et al. (2005), Ruzicka et al. (2007)
	Over expression of DNMT1 in GABAergic neurons.	
	Increased plasma homocysteine levels.	Applebaum et al. (2004), Levine et al. (2002), Adler Nevo et al. (2006)
Histone modifications	Increased H3K9 and H3R17 di- and trimethylation at GAD1 promoter.	Akbarian (2010)
	Loss of H3K4 methylation marks and excess of H3K27 methylation at GAD67 promoter.	Huang et al. (2007)
	G9a, GLP, and SETDB1 are increased across genome in lymphocytes.	Wang et al. (2003), Zee et al. (2010)
	HDAC1 expression is increased in prefrontal cortex of schizophrenia patients.	Sharma et al. (2008)
Alzheimer's disease		
DNA methylation	Genome-wide hypomethylation in AD patients.	Mastroeni et al. (2011)
	SAM levels were significantly reduced in AD.	Bottinglieri et al. (1990), Morrison et al. (1996)
	Repetitive Alu elements were hypomethylated with aging but not the repetitive long interspersed transposable elements (LINE-1).	Bollati et al. (2009)
Histone modifications	Accumulation of phospho-H2AX in AD.	Myung et al. (2008)
	Tip60 a HAT acetylates H4 necessary for correct repair of DNA is important in AD.	Stante et al. (2009)
	HDAC2 deficiency results in increased synapse number and memory facilitation supporting the role of histone acetylation and deacetylation in AD.	Guan et al. (2009)
Parkinson's disease		
DNA methylation	Hypomethylation of SCNA gene promoter with increased expression of α-synuclein which aggregates to form Lewy bodies which is hall mark of PD.	Ammal Kaidery et al. (2013) Pieper et al. (2008)
	TNF-α promoter hypomethylation with its increased expression induces dopaminergic neuronal death in substantia nigra in PD	
Histone modifications	α-Synuclein associate with sirt2 a class III HDAC inhibitor inhibit the histone acetylation.	Outeiro et al. (2007)
Epilepsy		

(continued)

Table 1 (continued)

Neurological disease	Epigenetic modification	Reference
DNA methylation	Global hypermethylation in epileptic rats.	Kobow et al. (2013)
	Hypermethylation of calcium calmodulin protein kinase with its reduced expression in epileptic rats.	
Histone modifications	Transient phosphorylation of histone H3 and sustained acetylation of histone H4 were observed in hippocampal neurons in animal model of epilepsy.	Sng et al. (2006)
	Histone H3 and H4 are rapidly deacetylated at promoter of glutamate receptor subtype GluR2 lead to reduced expression after seizure development.	Huang et al. (2002)

Schizophrenia

Schizophrenia is a psychiatric disorder with the positive symptoms such as delusions, hallucinations and disorganized thoughts, social withdrawal, and apathy. There is an evidence that epigenetic mechanisms are involved in pathogenesis of schizophrenia disease. One of the global methylome study identified numerous DNA methylation changes at differentially methylated regions in schizophrenia and bipolar disorder (Xiao et al. 2014). GADD67 and Reelin genes were extensively studied in psychiatric disorders. These genes are downregulated in GABA neurons of the prefrontal cortex of schizophrenia and bipolar disorder patients (Impagnatiello et al. 1998; Guidotti et al. 2000; Fatemi et al. 2000). The downregulation of these gene expressions leads to a decrease in GABAergic transmission, which is an important pathological mechanism that underlies the clinical manifestation of schizophrenia and bipolar disorders (Akbarian et al. 1995; Guidotti et al. 2005; Eastwood and Harrison 2006). Hypermethylation of promoters of GADD67 and Reelin are associated with reduced expression of these genes in GABAergic neurons. There is a characteristic overexpression of DNMT1 in GABAergic neurons responsible for downregulation of GADD67 and Reelin in schizophrenia and bipolar disorder patients (Veldic et al. 2004, 2005; Grayson et al. 2005; Ruzicka et al. 2007). DNMTs utilizes the SAM as a substrate to transfer the methyl group to cysteine there by converting SAM to *S*-adenosyl L-homocysteine (SAH) which is subsequently hydrolyzed to form homocysteine. The plasma homocysteine levels were also reported to be increased in schizophrenia patients (Applebaum et al. 2004; Levine et al. 2002; Adler Nevo et al. 2006). The accumulation of homocysteine has been shown to cause neural damage and cognitive dysfunctions (Krebs et al. 2009).

Histone code modifications are another epigenetic regulators which plays a role in schizophrenia disease. Increased levels of GAD1 promoter H3K9 and H3R17 di- and trimethylation are associated with its reduced expression in

cortical neurons and adjacent nonneuronal cells of post-mortem tissue of schizophrenia patients and are typically associated with neuronal metabolism (Akbarian 2010). GAD67 a GABA synthesis enzyme expression is downregulated in cerebral and cerebellar cortex of schizophrenia, depression, or autism patients and may be contributing to desynchronization of cortical networks and cognitive dysfunction due to defective GABAergic inhibition. The promoter that regulates GAD67 expression is associated with altered histone code modifications, including loss of H3K4 methylation marks and excess of repressive marks such as H3K27 methylation (Huang et al. 2007). The three HMTs G9a, GLP, and SETDB1 that mediate H3K9 di- and trimethylations are increased across the genome in lymphocytes from schizophrenia patients (Wang et al. 2003; Zee et al. 2010). H3K4 methylation levels are reduced at nearly 600 loci, including near multiple NMDA receptor subunits and genes involved in neurodevelopment. HDAC1 expression is increased in the prefrontal cortex of schizophrenia patients (Sharma et al. 2008).

Alzheimer's Disease

Alzheimer's disease (AD) is the age-related most common type of dementia with characteristic features of loss of memory, language, ability to focus, reasoning skills, and visual perception (Blennow et al. 2006). The amyloid precursor protein (APP) which is a membrane protein that is expressed throughout the brain and particularly concentrated in neuronal synapses cleaved to produce β-amyloid plaques is a hallmark of AD. The hyperphosphorylated microtubule-associated protein tau that is expressed in neurons is capable of forming neurofibrillary tangles is another hallmark of AD (Voss and Gamblin 2009). There is a growing evidence suggesting epigenetic mechanisms mediate the risk for AD. Genome-wide hypomethylation has been reported in AD patients (Mastroeni et al. 2011). Global DNA hypomethylation was reported in the entorhinal cortex of AD patients compared to controls (Mastroeni et al. 2010). Studies also reported that folate and SAM levels were significantly reduced in AD (Bottiglieri et al. 1990; Morrison et al. 1996). CpG islands become more methylated with aging, while loci not in CpG islands were hypomethylated (Christensen et al. 2009). Repetitive Alu elements were also hypomethylated with aging, but not the repetitive LINE-1 elements (Bollati et al. 2009). APP and tau genes involved in pathophysiology of AD are affected by epigenetic regulation. In addition to DNA methylation, histone code modification plays an important role in AD. The cleavage of APP generates APP C-terminal peptide (AICD) in addition to Aβ peptide. AICD translocates to the nucleus and acts on specific genes and modify their expression. Over expression of AICD in rat primary cortical neurons associated with increased acetylation of histones H3K14 and H4K5. Fe65 is a binding partner of APP and its interaction with AICD recruits Tip60 to DNA strand breaks. Tip60 an HAT acetylates H4 which is necessary for the correct repair of DNA and

this process could be important in AD (Stante et al. 2009). In AD, an accumulation of phospho-H2AX, an indicator of DNA strand breaks, has been described (Myung et al. 2008). HDAC2 deficiency results in increased synapse number and memory facilitation supporting the role of histone acetylation and deacetylation in human diseases associated with memory impairment such as AD (Guan et al. 2009).

Parkinson's Disease

Parkinson's disease (PD) is another common neurodegenerative disease characterized by progressive loss of substantia nigra dopamine neurons and striatal projections. The typical symptoms include muscle rigidity, tremor, bradykinesia, and postural instability. Genome-wide DNA methylation studies in the brain and blood samples of PD patients were reported to have differential methylation pattern of several genes associated with PD pathology supporting the role of epigenetic dysregulation in PD (Masliah et al. 2013). The presence of Lewy bodies (structures containing aggregates of α-synuclein encoded by gene SNCA) which accumulate at sites where neuronal loss is found is a hallmark of PD. The epigenetic regulation of SNCA gene plays an important role in the pathogenesis of PD. The increased α-synuclein production is associated with PD may result from increased expression of the SNCA gene as a consequence of hypomethylation of this gene (Ammal Kaidery et al. 2013). It has also been reported that α-synuclein sequesters DNMT1 in cytoplasm, leading to global DNA hypomethylation in PD and dementia with characteristic accumulation of Lewy bodies found in post-mortem brains and in transgenic mouse models (Desplats et al. 2011). Another study reported hypomethylation of TNFα promoter and its overexpression induces dopaminergic neuronal cell death in substantia nigra in PD (Pieper et al. 2008).

α-Synuclein can associate with histones and inhibit their acetylation. It is largely associated with Sirt2, a type of NAD-dependent class III HDAC. The inhibition of Sirt2 using siRNA rescued α-synuclein toxicity (Outeiro et al. 2007). Another epigenetic hallmark associated with PD is dopamine depletion observed in this disease is associated with reduction in H3K4me3. Over all epigenetic regulation might have an important role in the pathogenesis of this disease.

Epilepsy

Epilepsy is another common brain disorder affecting millions of people worldwide. In epilepsy, certain brain regions such as the hippocampus is susceptible to electrical discharge that promote some morphological changes such as cell death in the CA1 and mossy fiber sprouting and dispersion of granule cell layer that are thought to be involved in recurrent excitatory circuits that contribute to seizure

susceptibility (Heck et al. 2004). DNA methylation is one of the epigenetic modifications involved in epilepsy (Kobow et al. 2009; Miller-Delaney et al. 2012; Zhu et al. 2012). Kobow et al. 2013 reported global DNA methylation pattern in chronic epileptic rats using methyl seq and showed global hypermethylation of the DNA. They also confirmed hypermethylation of calcium calmodulin-dependent protein kinase with its reduced expression involved in calcium signaling in pilocarpine induced epileptic rat model.

Histone modifications have also been altered in epilepsy induced animal models. In kainic acid induced animal model of epilepsy, transient phosphorylation of histone H3 and sustained acetylation of histone H4 were observed in hippocampal neurons (Sng et al. 2006). Other promoter-specific histone code modifications in epilepsy include hyperacetylation of histone H4 on BDNF promoter which correlate with its increased expression. Histone H3 and H4 are rapidly deacetylated at the promoter of glutamate receptor subtype GluR2 correlated with its reduced expression after seizure development (Huang et al. 2002).

The importance of DNA methylation in association with other neurological disorders such as Rett syndrome and the ICF syndrome has been reported. Rett syndrome is one of the most common mental retardation diseases in females. Mutations of methyl CpG binding protein2 (MeCP2) have been found in 80 % of Rett syndrome patients (Amir et al. 1999). Mutations of DNMT3b have been reported in about 60 % of ICF syndrome patients (Hansen et al. 1999). ICF syndrome patients are characterized with immune defects, chromosomal instability, and neurological defects including mental retardation.

Epigenetic Modulatory Drugs to Treat Neurological Diseases

The most widely studied epigenetic modulatory drugs include DNA methylation inhibitors and HDAC inhibitors. 5-AZA deoxycytidine, zebularine are DNA methylation inhibitors more widely used to treat cancer. These drugs incorporate in to target DNA and bind to DNMT1 during DNA replication to inhibit its activity and therefore require DNA replication to be active (Wu and Santi 1985). However, the use of these drugs for treating brain disorders has limitation since most of the neurons are postmitotic. The mechanism of action of demethylation in postmitotic neurons is not clearly understood. However, the recent study used RG108, a small molecule DNA methylation inhibitor in epilepsy therapeutics suggesting a novel epigenetic modulatory drug to treat neurological diseases (Machnes et al. 2013).

HDAC inhibitors show a promise for cognitive improvement and are being considered for drug development in neurological diseases. Hence, HDAC inhibitors could be used as promising therapeutic agents for diseases associated with dementia and cognitive impairments. The class I HDAC inhibitors such as sodium valproate and sodium butyrate improve memory in AD mouse model (Kilgore et al. 2010). Valproic acid is also used as an anticonvulsant in epileptic patients and as a mood stabilizer in bipolar disorder patients (Phiel et al. 2001). Sodium butyrate and Sirtuin

HDAC siRNA inhibitors are effectively used in a Drosophila model of PD (St Laurent et al. 2013; Outeiro et al. 2007). The use of Valproic acid in the treatment of schizophrenia and bipolar disorders has also been reported (Weaver et al. 2006).

Natural Products as Epigenetic Modulators in Neurological Diseases

Most of the human diseases are significantly influenced by diet in a varying degree. Except the inherited one, some are almost purely influenced by dietary components like the vitamin and mineral deficiency. In the last decade, a new wealth of information has emerged to explain how nutrition and diet affect different diseases to varying degrees. Nutrition and diet have little impact on some diseases, but strongly affects others. Considering the role of epigenetics in human diseases; here, we discuss how the diet affects long-term health by altering the epigenome and how one can prevent degenerative conditions by consuming of diets rich in antioxidants and anti-inflammatory components. This part of the chapter mainly focuses to discuss the promising epigenetic effects of dietary factors (phytochemicals) and their effects in neurodegeneration and neuroprotection.

Phytochemicals

Phytochemicals are considered as nonessential complex chemicals found in plants, particularly in fruits and vegetables. Even though, phytochemicals do not fall under the category of essential nutrients for humans, they are contributing greatly to health and well-being. So far, in nature more than 3000 phytochemicals have been discovered and here we have provided a noncomprehensive list of phytochemicals and examples of how they are broadly subclassified (Liu 2004).

1. *Terpenoids (Isoprenoids)*
   (a) *Carotenoid terpenoids* (lycopene, beta-carotene, alpha-carotene, lutein, zeaxanthin, and astaxanthin)
   (b) *Noncarotenoid terpenoids* (perillyl alcohol, saponins, terpeneol, and terpene limonoids)
2. *Polyphenolics*
   (a) *Flavonoid polyphenolics* (anthocyanins, catechins, isoflavones and hesperetin, naringin, rutin, quercetin, silymarin, tangeretin, and tannins)
   (b) *Phenolic acids* (ellagic acid, chlorogenic acid, *P*-coumaric acid (*para*-coumaric acid), phytic acid, ferulic acid, vanillin, cinnamic acid, and hydroxycinnamic acids)

   (c) *Nonflavonoid polyphenolics* (curcumin, resveratrol, pterostilbene, lignans, and coumestans)

3. *Glucosinolates*

   (a) *Isothiocyanates* (phenethyl isothiocyanate and sulforaphane)
   (b) *Indoles* [Indole-3-Carbinol (I3C)]

4. *Thiosulfonates*
5. *Phytosterols* (beta-sitosterol)
6. *Anthraquinones*

   (a) *Senna*
   (b) *Barbaloin*
   (c) *Hypericin*

7. *Capsaicin*
8. *Piperine*
9. *Chlorophyll* (chlorophyllin)
10. *Betaine*
11. *Pectin*
12. *Oxalic acid*

In recent years, the role of epigenetic modifications in neurodiseases and degeneration has been well established through systematic studies. Many studies have shown that essential nutritional compounds like vitamin B_{12} or folic acid play key role in the modulation of epigenetic changes. Increasing scientific evidence suggests that oxidative stress (cellular and metabolic) has crucial implications for the pathogenesis of many neurodegenerative diseases, including PD, AD, and many others via epigenetic changes (Andersen 2004). Therefore, nonnutritional compounds such as polyphenols have attracted the scientific world as epigenetic modulators mainly through its antioxidant properties. In addition to plant based natural products (compounds), certain secondary metabolites derived from marine and terrestrial micro- and macro-organisms are discovered as drugs that have epigenetic targets such as HDACs. Although, many natural compounds have been shown to possess potential epigenetic modulatory effects in diseases like cancer and atherosclerosis, only fewer natural products inhibitors have been documented in modulating epigenetic pathways in brain-related diseases.

Dietary Factors as Modulators of HDAC Activity

Diet derived bioactive components are able to modulate epigenetic events and their epigenetic targets. For example, genistein, diallyl sulfide, vitamin D3, or all-*trans* retinoic acids have been shown to impact DNA methylation by altering histones and chromatin structure (Bassett and Barnett 2014). Here, we provided a brief

Table 2 Partial list of dietary compounds as HDAC modulators

Inhibitors of HDACs	Inducers of HDACs
• Butyrate	• Theophylline
• Diallyl disulfide	• Resveratrol
• Sulforaphane	
• Isothiocyanates	
• All-*trans* retinoic acid	

introduction of some important bioactive natural compounds and how they target the epigenetic events in disease conditions. Table 2 gives a partial list of dietary compounds that are known to modulate HDAC activity.

Genistein

Genistein is mainly a soy-derived compound classified under the category of isoflavones (Fig. 4). Many anticancer studies have shown that genistein affects tumorigenesis/carcinogenesis through epigenetic regulations (Zhang and Chen 2011). Reports suggest that genistein may be involved in inhibiting the DNMTs and can regulate gene expression by erasing DNA methylation at promoter levels. Genistein has been proved to prevent breast cancer risk and promotes DNA demethylation of SF1 promoter in endometrial stromal cells (Khan et al. 2012), a type of cells that is present in the endometrium (the innermost lining) of the uterus. Recently, it has been shown that genistein, inhibits neuroblastoma (NB) growth and tumor microvessel formation in vivo by decreasing hypermethylation levels of tumor suppressor genes (TSGs) such as CHD5 and enhances the expression of CHD5 as well as p53 (Li et al. 2012). In addition, genistein acts as an inhibitor to significantly decrease the expression of DNMT3b in NB model and thereby suggest that genistein could be used as an adjuvant therapeutic agent for NB treatment.

Also, genistein induces chromatin remodeling and DNA methylation, which leads to the activation of TSGs and thereby suppression of the cancer cell survival. Genistein has also been shown to inhibit the DNMT activity, which causes inhibition of DNA methylation and thus may be acting as an anticancer agent (Li and Tollefsbol 2010). Genistein has been observed to enhance the acetylation of histones H3 and H4 in the transcription sites of p21 and p16, thereby, it upregulates the TSGs in prostate cancer cells (Zhang and Chen 2011). Prenatal exposure to genistein possesses estrogenic activity and affects the erythropoiesis in the fetus and alters the gene expression and DNA methylation in hematopoietic cells (Vanhees et al. 2011). Also, genistein causes modulation of the HAT activity and extents the acetylation of histone (Piaz et al. 2011). In breast and prostate cancer cell lines, genistein has been shown to inhibit the proliferation (Moyad 1999) and to compete with estrogen, it prevents the estrogen receptor mediated cell growth (Wang et al. 1996). Another study shows that genistein is positively associated with modulation of DNA methylation at CpG islands of certain genes in prostate of a mouse.

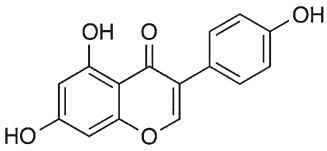


Fig. 4 Structure of genistein

Genistein seems to reduce the hypermethylation status of RARβ, p16, and MGMT genes in vitro and inhibit the activity of DNA methyltransferases dose dependently, showing that genistein can reactivate methylation-silenced genes, via inhibiting DNA methyltransferase (Fang et al. 2005). Supplementation of genistein during the gestation period modulated the site-specific DNA methylation of offspring and changed coat color of heterozygous yellow agouti (Avy/a) pups to black pseudoagouti by reducing the DNA methylation status of the agouti locus (Dolinoy et al. 2006).

Epigallocatechin-3-gallate (EGCG)

Epigallocatechin gallate (EGCG) is a type of catechin (Fig. 5) found highly in green tea and exists in nature as the ester form of epigallocatechin and gallic acid. Trace amounts of (EGCG) are found in plums, onions, hazelnuts, and apple skin. Numerous studies have shown that EGCG has beneficial effects in a broad range of disorders including cancer. Preliminary research shows that EGCG is an inhibitor of various enzymes in epigenetic pathways, such as histone acetyltransferase (Choi et al. 2009) DNA methyltransferase (Choi et al. 2009) or tyrosinase (No et al. 1999).

Decaffeinated green tea and black tea extracts are rich in EGCG and has been shown to inhibit 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)-induced DNA methylation in lung cancer model in A/J mice (Shi et al. 1994). In cancer cells, EGCG reactivated methylation-silenced genes by inhibiting DNMTs and suggest the potential use during carcinogenesis (Fang et al. 2003). In addition, a study demonstrated that EGCG and other tea polyphenols (e.g., catechin and epicatechin) and bioflavonoids (quercetin, fisetin and myricetin) can inhibit Dnmt 1-mediated DNA methylation in a concentration-dependent manner (Lee et al. 2005).

Lycopene

Lycopene is a tetraterpene (carotenoid), possess potent antioxidant property (Fig. 6). Lycopene is mainly present in fruits and vegetables, including tomatoes, watermelon, pink grapefruit, pink guava, and papaya. As an antioxidant, lycopene knows to modulate the expression of many genes that are associated with cell cycle, DNA repair, and apoptosis. Also, it has been shown to alter DNA methylation and upregulate the GSTP1 gene in the breast cancer cell line (King-Batoon et al. 2008). It seems

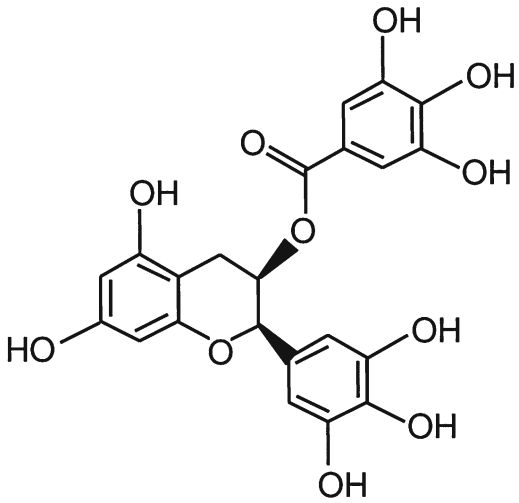


Fig. 5 Structure of epigallocatechin gallate (EGCG)

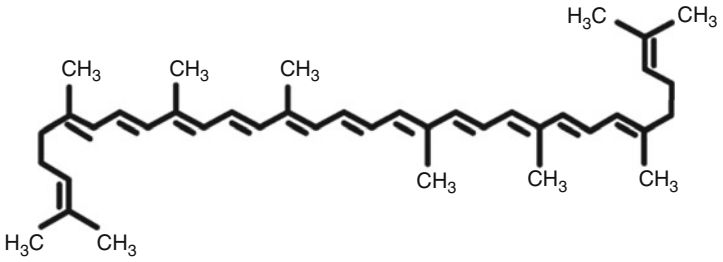


Fig. 6 Structure of lycopene

that lycopene affects gene expression by modifying gene-specific methylation. It has been reported to demethylate the promoter of RARβ2 and HIN-1 genes (King-Batoon et al. 2008).

Resveratrol

Resveratrol is more famous by the name "French Paradox" by preventing many diseases, including neurological disorders such as AD, PD, and stroke. Studies have shown that the potential beneficial effects of resveratrol (Fig. 7) are not only because of its antioxidant and anti-inflammatory action but also due to activation of sirtuin 1 (SIRT1). It is well known that at least in animal models, caloric restriction has been shown to prevent the development of various cancers through sirtuins as a target. Sirtuins are nicotinamide adenine dinucleotide (NAD(+))-dependent HDACs which are involved in aging and reverted significantly in transformed cells. Resveratrol is known to activate the sirtuin 1 (SIRT1), a class III HDAC (Baur 2010) and thereby preventing aging and cancer cell proliferation.

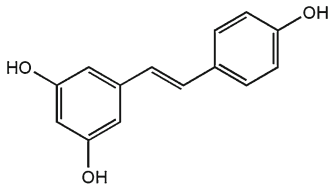


Fig. 7 Structure of resveratrol

In cell lines, resveratrol acts as a weak inhibitor of DNMT activity (Paluszczak et al. 2010) and acts synergistically with adenosine analogues to inhibit methylation of retinoic acid receptor beta 2 gene and thereby increases its expression (Stefanska et al. 2010).

Curcumin

Curcumin is the principal active compound of turmeric and known to have an anti-disease effect in various animal models and in humans (Fig. 8). Effects of curcumin to induce apoptosis in cancer cell lines are well characterized and recently it has been shown to inhibit certain epigenetic enzymes (such as HATs, HDAC1, HDAC3, and HDAC8) in vitro (Reuter et al. 2011; Vahid et al. 2015). The mode of induction of apoptosis by curcumin may vary from cell to cell. For example, in cervical cancer, curcumin inhibits the acetylation of histone and p53 through specific inhibition of p300/CBP (Balasubramanyam et al. 2004b).

In addition, it also induces histone hypoacetylation, activation of poly (ADP) Ribose polymerase- and caspase-3-mediated apoptosis in brain glioma cells (Kang et al. 2006) were observed. In addition, curcumin decreased histone H3 and H4 acetylation and thereby controls the fate of neural stem cells (Kang et al. 2006).

Anacardic Acid

Anacardic acid falls under the category of phenolic lipids and are highly present in the shell of the cashew nuts (Fig. 9). Anacardic acids seem to arrest the growth of cancer cells by inhibiting acetylation, nuclear translocation of p65 and through modulation of NF-kappaB signaling pathway. (Sung et al. 2008). Anacardic acid can inhibit HATs such as p300, PCAF, and Tip60. Also, anacardic acid has been shown to specifically inhibit HAT (Balasubramanyam et al. 2003; Sun et al. 2006).

Garcinol

Garcinol is a highly cytotoxic polyprenylated benzophenone from the fruit G*arcinia indica* (Fig. 10). Garcinol is also a potent inhibitor of different HATs, such as p300 and PCAF (Mai et al. 2006; Chandregowda et al. 2009; Balasubramanyam et al.

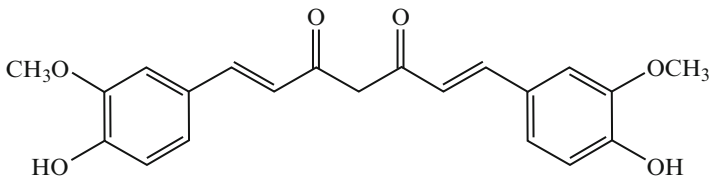
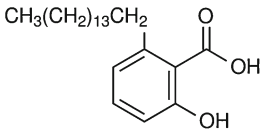


Fig. 8 Structure of curcumin

Fig. 9 Structure of anacardic acid



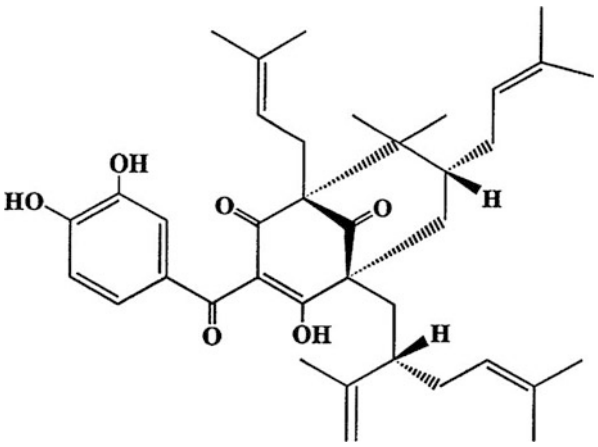


Fig. 10 Structure of garcinol

2004a). Many derivatives of garcinol have been synthesized (1) iso-garcinol (IG), (2) 14-isopropoxy IG (LTK-13), (3) 14-Methoxy IG (LTK-14), and (4) disulfoxy IG (LTK-19). LTK-13, LTK-14, and LTK-19 selectively inhibit p300 and LTK-14 act as a noncompetitive inhibitor of acetyl-coA and histones (Mantelingu et al. 2007).

Plumbagin

Plumbagin is another compound, derived from a root extract of the plant *Plumbago rosea* (Fig. 11), which has been found to potently inhibit HAT activity (Ravindra et al. 2009). Plumbagin and its derivatives possess HAT inhibitory activity and serves as a noncompetitive inhibitor for p300. The single hydroxyl group seems to be crucial for the HAT inhibitory activity.

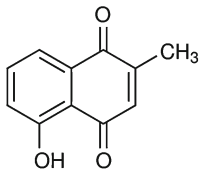


Fig. 11 Structure of plumbagin

Conclusion

A growing body of research suggests that epigenetic defects (epimutations) play a considerable role in human conditions that are strongly influenced by changes in the lifestyle, environment, diet, and pharmacological intervention. Therefore, it is possible that the discovery of novel synthetic and natural dietary compounds or testing the molecules that are already known, may be an effective strategy to treat the epigenetic changes or correct epimutations of various disease states. Although, a variety of compounds have been discovered as epigenetic modulators on various human diseases, such as cancer, obesity, and insulin resistance, only a few compounds (natural or synthetic) are known to target various epigenetic factors in brain disorders which are associated with epigenetic changes. So there is an urgent need in the investigation of phytochemicals as epigenetic modulators in the treatment of neurological diseases.

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Compliance with Ethics Requirements The authors declare that they have no conflicts of interest.

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