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Botanicals as epigenetic modulators for mechanisms contributing to development of metabolic syndrome

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Abstract

Epigenetics refers to heritable changes in gene expression that are not attributable to changes in DNA sequence and impacts many areas of applied and basic biology including developmental biology, gene therapy, somatic cell nuclear transfer, somatic cell reprogramming, and stem cell biology. Epigenetic changes are known to contribute to aging in addition to multiple disease states. Epigenetic changes can be influenced by environmental factors that in turn can be inherited by daughter cells during cell division and can also be inherited through the germ line. Thus, it is intriguing to consider that epigenetics, in general, may play a role in human conditions that are strongly influenced by changes in the environment and lifestyle. In particular, metabolic syndrome, a condition increasing in prevalence around the world, is one such condition for which epigenetics is postulated to contribute. Epigenetic defects (epimutations) are thought to be more easily reversible (when compared with genetic defects) and, as such, have inspired efforts to identify novel compounds that correct epimutations or prevent progression to the disease state. These efforts have resulted in the development of a rapidly growing new field being referred to as *epigenetic therapy*. To date, 2 classes of drugs have received the most attention, that is, DNA methyltransferase inhibitors and histone deacetylase inhibitors; but recent data suggest that botanical sources may be a rich source of agents that can potentially modulate the epigenome and related pathways and potentially be useful in attenuating the progression of many factors related to development of metabolic syndrome. This review will provide an overview of the field of epigenetics, epigenetic therapy, and the molecules currently receiving the most interest with respect to treatment, and review data on botanical compounds that show promise in this regard.

1. Introduction: role of epigenetics in disease

An epigenetic contribution to disease was first realized more than 20 years ago by Feinberg and Vogelstein [1] who distinguished human cancer from normal tissues based on DNA methylation levels. To date, it appears that malignancy represents most of the diseases for which epigenetic defects have been shown to contribute to disease pathogenesis. However, over the recent past, epigenetics has been demonstrated to be a major contributor in the pathogenesis of several other diseases and disorders including schizophrenia and bipolar disorder [2], aging [3], fragile X syndrome [4], leukemia [5], Beckwith-Weideman syndrome [6], and Angelman syndrome [7]. The relevance of epigenetics to more common diseases, for example, diabetes and cardiovascular disease, has been less conspicuous. There is growing consensus however that many conditions that characterize metabolic syndrome, that is, insulin resistance, carbohydrate intolerance, regional adiposity, dyslipidemia, hypertension, and eventual development of cardiovascular disease, are characterized by aberrant "epigenetic programming" during fetal and postnatal development (and possibly as early as preimplantation development). These changes are postulated to be associated with inadequate maternal nutrition and metabolic disturbances during these periods and during their lifetime [8]. Thus, there is great interest to identify

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epigenetic-based therapeutic strategies as a means to prevent development and possibly treat these related conditions. Increasing our understanding of epigenetics and the role that molecules such as nutrients and drugs can play in reversing and/or preventing disease-associated epigenetic patterns (eg, de-repressing gene expression) should provide important future directions to develop novel strategies to treat the growing worldwide epidemic of metabolic syndrome.

When one considers molecules that may have an effect on epigenetic patterns, it is interesting to note that plants have been known to harbor regenerative capacity for some time. For example, numerous plants retain plasticity that provides regenerative capabilities [9]. This plasticity, which, for the most part, appears to be generalizable to the plant kingdom, involves epigenetic mechanisms; but limited knowledge is actually available. Both methylation and chromatin changes have been observed. The plant protoplast system appears to be an invaluable experimental tool to further understand mechanisms associated with plasticity and regenerative capability. In this system, terminally differentiated mesophyll cells can be isolated, induced to reenter the cell cycle, and form masses of dividing cells from which roots and stems emerge. The transition of a differentiated mesophyll cell into the cell cycle involves acquisition of pluripotential (dedifferentiation) followed by signal-dependent reentry into the cell cycle, a process also referred to as *reprogramming*. The plasticity observed in the protoplast system suggests the presence of important molecules and pathways that, if identified and characterized, could be used to induce reprogramming processes as a basis for therapy in humans. The diversity of plants present on this planet also implies a potentially rich source of highly evolved compounds that could be discovered.

2. Mechanisms that regulate epigenetic memory

Epigenetic mechanisms ensure heritable characteristics of cells and functional differences between cell types without changing DNA sequence and is often referred to as *cellular memory*. Epigenetic mechanisms modify chromatin (DNA and associated proteins) in ways that change the availability of genes to transcription factors required for their expression. Two of the most studied epigenetic phenomena are histone modifications and DNA methylation.

2.1. Histone modifications

The basic building block of chromatin is the nucleosome, which is based on an octamer of histone proteins. Histone tails protrude out of the nucleosome and undergo several posttranslational modifications including acetylation (and deacetylation) and methylation of lysines, phosphorylation, ubiquitylation, sumoylation, adenosine diphosphate ribosylation, glycosylation, biotinylation, and carbonylation [10]. Histone modifications can distinguish euchromatin from heterochromatin and influence associations of proteins and protein complexes that regulate gene transcription or repression by altering the availability of genes to transcription factors. A brief summary of several histone modifications and associated enzymes is presented in Table 1.

2.2. DNA methylation

The DNA molecule can be modified at the 5′ position of cytosine rings present in CG (cytosine, guanine) dinucleotide sequences by addition of a methyl group [11]. Patterns of cytosine methylation are distinct for each cell type and confer cell type identity [12]. The DNA methylation patterns are known to be established during mammalian development and subsequently maintained by the maintenance DNA methyltransferases (DNMTs).

The DNA methylation patterns are closely linked to chromatin structure. Unmethylated DNA is typically associated with an active chromatin configuration, whereas methylated DNA is associated with inactive chromatin. The DNMTs catalyze de novo and maintenance DNA methylation. These enzymes catalyze the transfer of a methyl group from the methyl donor *S*-adenosylmethionine (SAM) onto the 5′ position of the cytosine ring found in CpG (CpG notation used to distinguish a cytosine and guanine separated by a phosphate) dinucleotides. Not all CpGs are methylated, and patterns are tissue and time specific. Five enzymes have been identified: DNMT1, DNMT2, DNMT3a, DNMT3b, and DNMT3L.

DNMTs 2 and 3L lack enzymatic function because of an amino-terminal regulatory domain in DNMT2 and the catalytic domain in DNMT3L [13]. DNMT1 is regarded as a maintenance methyltransferase and recognizes hemimethylated DNA. DNMTs 3a and 3b are classified as de novo methyltransferases; they bind to both hemimethylated and unmethylated CpG sites and add methyl groups to previously unmethylated cytosines. DNTM3L has been reported to participate in de novo methylation of retrotransposons [14] and establishing maternal imprints [15].

Table 1
Classes of histone modifying enzymes

Class	Modification	Gene expression	Enzymes
HATs	Acetylation	Permissive	Superfamilies: GNAT P300/CBP MYST
HDACs	Deacetylation	Repressive	3 Classes based on localization: I: HDAC1, 2, 3, and 8 II: HDAC4, 5, 6, 7, 9, and 10 III: Surtin enzymes 1-7
HMTs	Methylation	Permissive and repressive	4 Subgroups: SUV1 SUV2 SUV3 RIZ

3. Methylation and methyl group metabolism

In the process of methylating molecules such as cytosines in CpG dinucleotides and histones, methyltransferases convert SAM to *S*-adenosylhomocysteine (SAH) (Fig. 1). Regulating the supply and utilization of methyl groups is accomplished by the enzymatic activity of a key regulatory protein, glycine *N*-methyltransferase (GNMT). Glycine *N*-methyltransferase optimizes the ratio of SAM and SAH molecules by catalyzing the conversion of SAM and glycine to SAH and sarcosine [16] (Fig. 1). Because SAH is a potent inhibitor of methyltransferase activity [17], optimizing the SAM/SAH ratio serves to regulate the transmethylation capacity of the cell [18].

4. Methyl group metabolism and relevance to carbohydrate metabolism

Both type 1 and type 2 diabetes mellitus states have been identified as pathological factors in the modulation of methyl group metabolism in rat models [19,20]. Metabolic dysregulation as observed in diabetic states leads to the disruption of hepatic methyl group metabolism, characterized by elevations in GNMT activity and abundance. Up-regulation of GNMT expression and activity would reduce methylation capacity of cells and induce hypomethylation.

5. Epigenetic therapy: correcting epigenetic defects

Epigenetic therapy is a new and rapidly developing area of potential intervention aimed at correcting epigenetic defects. Epigenetic therapy is a potentially very useful form of therapy because epigenetic defects are thought to be more easily reversible when compared with genetic defects. It is also possible that epigenetic therapeutic agents may prevent disease. Currently, several epigenetic-based drugs are undergoing preclinical and clinical trials. Most target various types of cancers such as solid tumors and hematologic malignancies. Targets include enzymes such as histone acetyltransferases (HATs), histone deacetylases (HDACs), DNMTs, and histone methyltransferases (HMTs) [21,22].

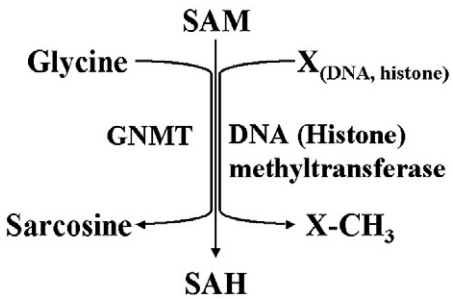

Fig. 1. Regulation of SAM and SAH pools by GNMT.

6. Epigenetic modifying compounds

Table 2 lists principal classes of epigenetic modifiers and representative compounds within each class. A brief summary follows:

6.1. DNMT inhibitors

There are 2 classes of DNMT inhibitors: nucleoside analogues and non-nucleoside analogues (Table 2). The classic DNMT inhibitor is 5-azacytidine, a derivative of the nucleoside cytidine. The inhibitor was discovered more than 40 years ago [23], and its demethylating activity was discovered subsequently because of its ability to influence cellular differentiation in vitro [24] 5-Azacytidine is a nucleoside inhibitor that can be incorporated into DNA and can be methylated by DNMTs. The DNMT, however, becomes covalently trapped because the intermediate cannot be resolved, inactivating the enzyme. As the enzyme is depleted, genomic DNA is demethylated as a result of continued DNA replication. To become incorporated into DNA, 5-azacytidine must be modified to a deoxyribonucleoside triphosphate before incorporation into DNA. Before modification, 5-azacytidine can become incorporated into RNA, resulting in a variety of consequences including cytotoxicity. An analogue of 5-azacytidine, 5-aza-2′deoxycytidine (AKA, decitabine), does not require modification and is thought to be less cytotoxic, but still has severe cytotoxic affects [25]. For example, decitabine has been used in clinical trials and has shown promise for treatment of myeloid malignancies [26,27], but also has toxic effects including myelosuppression and neutropenic fever [25].

Several non-nucleoside compounds also inhibit DNMT activity. Two compounds have been reasonably characterized, whereas compounds representing 3 subclasses are less understood. The 2 characterized compounds include (−)-epigallocatechin-3-gallate (EGCG), the key polyphenol in green tea [28], and RG108, a molecule identified in an in silico screening assay [29]. (−)-Epigallocatechin-3-gallate inhibits DNMT activity in protein extracts and human cancer cell lines [30] and is thought to block the active site of DNMT1. Degradation of EGCG results in production of hydrogen peroxide, a strong oxidizing agent [31] that may result in cytoxicity. In contrast, RG108 appears to have low toxicity and has been demonstrated to inhibit the catalytic activity of recombinant DNMTs. The inhibitory activity appears to be direct and specific for DNMTs [29].

6.2. HDAC inhibitors

The original discovery that trichostatin A (TSA) had antileukemia properties due to inhibition of HDAC enzymes [32] has inspired the discovery of additional HDAC inhibitors that have been proposed as possible therapeutic agents for a variety of diseases. There are 4 classes of HDAC inhibitors: short-chain fatty acids,

Table 2
Classification of pharmacological epigenetic modulators

A.	DNA methylation inhibitors: nucleoside analogues	
	1.	5-Azacytidine
	2.	5-Aza-2′-deoxycytidine
	3.	5-Fluoro-2′deoxycytidine
	4.	5,6-Dihydro-5-azacytidine
	5.	Zebularin
B.	DNA methylation inhibitors: non-nucleoside analogues	
	1.	Hydralazine
	2.	Procainamide
	3.	EGCG
	4.	Psammaplin A
	5.	MG98
	6.	RG108
C.	HDAC inhibitors: short-chain fatty acids	
	1.	Butyrate
	2.	Valproate acid
D.	HDAC inhibitors: hydroxamic acids	
	1.	CBHA
	2.	Oxamflatin
	3.	PDX101
	4.	Pyroxamide
	5.	Scriptaid
	6.	SAHA
	7.	TSA
	8.	LBH589
	9.	NVP-LAQ824
E.	HDAC inhibitors: cyclic tetrapetides	
	1.	Apicidin
	2.	Depsipeptide
	3.	TPX-HA analogue
	4.	Trapoxin
F.	HDAC inhibitors: benzamides	
	1.	C1-994
	2.	MS-275
G.	HAT inhibitors	
	1.	LysCoa
	2.	H3CoA20
	3.	Arachidonic acid
	4.	Garcinol
	5.	Curcumin
	6.	γ-Butyrolactone MB-3
	7.	MC1823
	8.	MC1626
	9.	MC1752

hydroxamic acids, cyclic tetrapeptides, and benzamides. Short-chain fatty acids are typically not potent inhibitors of HDACs. In contrast, hydroxamic acids and cyclic tetrapeptides are potent inhibitors of HDACs (for review, see Yoo and Jones [22]).

6.3. HAT inhibitors

Several transcription factors contain HAT activity, and the proteins are grouped into distinct classes based on sequence homologies and functionality [33]. It has been shown that some HAT genes are misregulated in cancer. For example, it has been demonstrated that p300 is an E1A binding protein; and p300 missense and deletion mutations have been identified in breast, colorectal, gastric, and epithelial cancers [34], suggesting that identification of HAT inhibitors may have therapeutic value. To date, relatively few HAT inhibitors have been identified and include the bisubstrate analogues Lys-CoA and H3-CoA-20 [35] and natural small molecules such as arachidonic acid [36], garcinol [37], and curcumin [38]. Synthetic small molecules having HAT inhibitory activity include γ-butyrolactone MB-3 [39], isothiazolones [40], and quinolines MC1823, MC1626, and MC1752 [41-43], of which MC1823 is 10-fold more potent than MC1626 and MC1752.

6.4. HMT inhibitors

To date, identification of inhibitors of HMTs is in its infancy; but it is likely that a growing interest will develop over the next several years.

7. Combining epigenetic therapeutic strategies

Deoxyribonucleic acid methylation and histone modification are tightly linked; and more recently, combined approaches aimed at inhibiting DNMTs as well as HDACs are showing promise as a strategy for cancer treatment. For example, it has recently been reported that the HDAC inhibitor TSA in combination with a low dose of the DNMT inhibitor decitabine induced expression of 4 hypermethylated genes in cultured colorectal carcinoma cells [44]. In addition, a combination of decitabine and the HDAC inhibitor phenylbutyrate had a synergistic effect in preventing lung cancer induced in mice by tobacco carcinogen [45].

8. Botanical extracts as epigenetic modulators

Recently, our laboratory has reported that the peptide nucleoplasmin induces up-regulation of several hundred genes in a somatic cell nuclear transfer reprogramming model [46]. Many of the genes were previously silenced in the somatic cell donor cell line. We also reported that exposure of mammalian somatic cells growing in culture to all-*trans* retinoic acid up-regulates expression of Gnmt, inducing global demethylation, increased expression of the pluripotency gene Oct4, and restoration of differentiation potential [47]. Moreover, we have reported that down-regulating Dnmt1 and/or 3b of cells in culture has similar effects [47]. These results indicate that compounds or activities can be identified that target key components of epigenetic pathways and alter gene expression patterns typically thought to be “fixed” or permanent. As stated previously, it has been recognized that plants are characterized by remarkable plasticity that is associated with epigenetic changes. Thus, we have been investigating whether activities could be identified in plants that could also target expression of key epigenetic regulatory genes in mammalian cells. Our initial screens have focused on Gnmt,

Dnmt1, and Dnmt3b gene expression because changes in expression of these genes have been demonstrated by us and others to induce alterations in DNA methylation and gene expression. In addition, we have assessed expression of the pluripotency gene Nanog, typically silenced or expressed at very low levels in mammalian somatic cells and associated with promoter hypermethylation. To date, we have screened approximately 50 botanical extracts; and extracts were evaluated using NIH/3T3 fibroblast cells cultured in 6-well culture dishes. The particular botanicals evaluated consisted of extracts of *Allium tuberosum* L, for example, Chinese chives or garlic chives; *Ligustrum lucidum* L, for example, glossy privet; and *Artemisia dracunculus* L, for example, Russian tarragon. Extracts of *A tuberosum* L, that is, ALT-S, and *L lucidum* L, NZ-01 (assessed at concentrations ranging from 100 μg/mL to 1 mg/mL for 48 and 96 hours and 1 and 2 weeks), were obtained from the Louisiana State University Agricultural Center (Baton Rouge, LA), whereas subfractions of *A dracunculus* L, that is, PMI 5011 (evaluated at concentrations of 10 and 100 μg/mL for 48 and 96 hours), were obtained from the Botanical Core Laboratory of the Botanical Research Center of the Pennington Biomedical Research Center and Rutgers University. The cells were harvested at the conclusion of the time points, and messenger RNA was obtained using the RNeasy Mini Kit (Qiagen, Valencia, CA). Quantitative reverse transcriptase–polymerase chain reaction (RT-PCR) was performed to examine the relative expression levels of the genes Gnmt, Dnmt1, Dnmt3b, and Nanog as compared with Gapdh. Results from the 3 botanical sources (PMI 5011, NZ-01, and ALT-S) are described.

PMI 5011 (*A dracunculus* L) was originally identified from a screening of extracts for hypoglycemic activity in diabetic mice as the most promising candidate for the development of a nutritional supplement for diabetes and is described in detail in other articles as part of this supplement. The active compounds in the preparation are believed to be members of the sesquiterpene lactone or flavanoid groups, of which the *Artemisia* family is well known. Preliminary data further suggest that PMI 5011 may have significant effects to improve carbohydrate metabolism by enhancing molecular events of insulin action in skeletal muscle. We have identified 3 subfractions that down-regulate Dnmt1 or Dnmt3b and one subfraction that up-regulates Nanog expression (Fig. 2A-D). Specifically, exposure of NIH3T3 cells to 100 μg/mL of subfraction 7-6-2 for 48 hours reduced

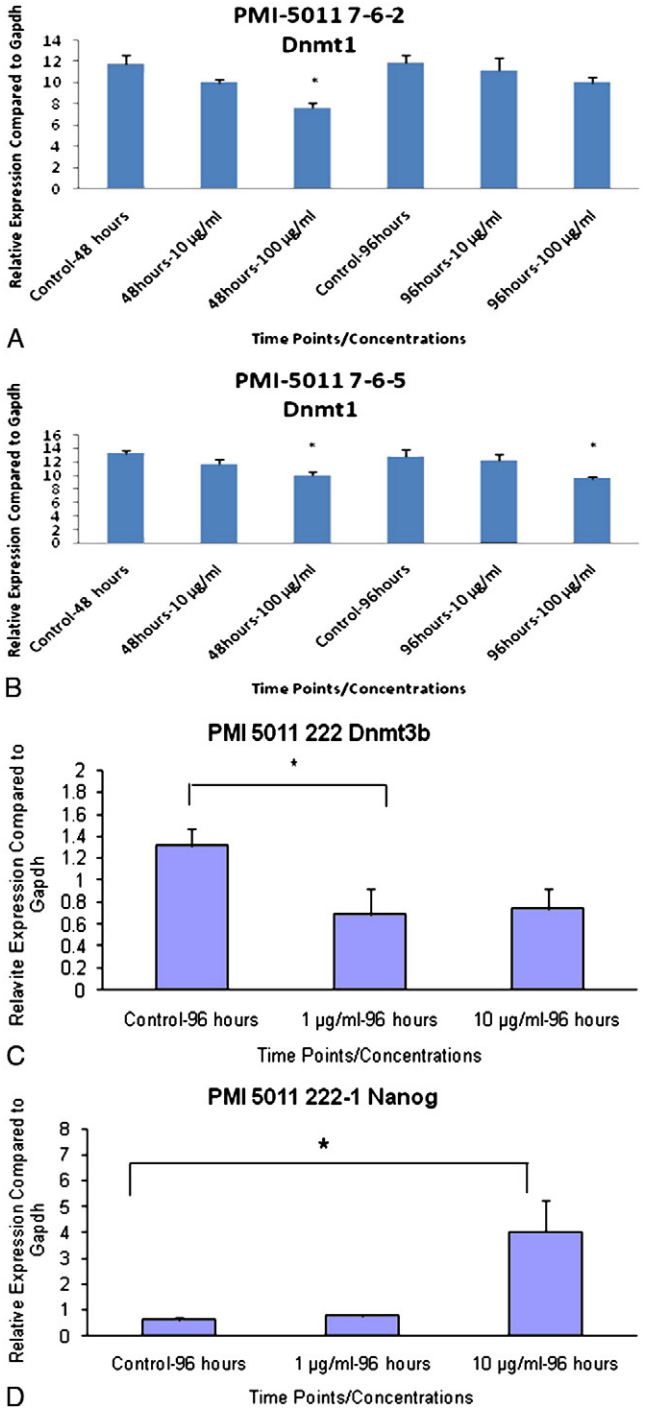

Fig. 2. A, Effects of botanical extract PMI 5011 7-6-2 on relative expression levels of Dnmt1 as compared with Gapdh. Expression in NIH/3T3 murine fibroblast cells that were treated with 10 and 100 μg/mL of compound levels of PMI 5011 7-6-2 for 48 and 96 hours. Significant decrease shown in relation to untreated, control cultures. Statistical analyses were performed by a 2-sample, equal-variance, 2-tailed *t* test. **P* < .05. B, Effects of botanical extract PMI 5011 7-6-5 on relative expression levels of Dnmt1 as compared with Gapdh. Expression in NIH/3T3 murine fibroblast cells that were treated with 10 and 100 μg/mL of compound levels of PMI 5011 7-6-5 for 48 and 96 hours. Significant decrease shown in relation to untreated, control cultures. Statistical analyses were performed by a 2-sample, equal-variance, 2-tailed *t* test. **P* < .05. C, Effects of botanical extract PMI 5011 222 on relative expression levels of Dnmt3b as compared with Gapdh. Expression in NIH/3T3 murine fibroblast cells that were treated with 1- and 10-μg/mL subfractions of PMI 5011 222 for 96 hours. Significant decrease shown in relation to untreated, control cultures. Statistical analyses were performed by a 2-sample, equal-variance, 2-tailed *t* test. **P* < .05. D, Real-time RT-PCR quantitative analysis of Nanog messenger RNA levels. Expression in NIH/3T3 murine fibroblast cells that were treated with 1- and 10-μg/mL subfractions of PMI 5011 222-1 for 96 hours. Significant increase shown in relation to untreated, control cultures. Statistical analyses were performed by a 2-sample, equal-variance, 2-tailed *t* test. **P* < .05.

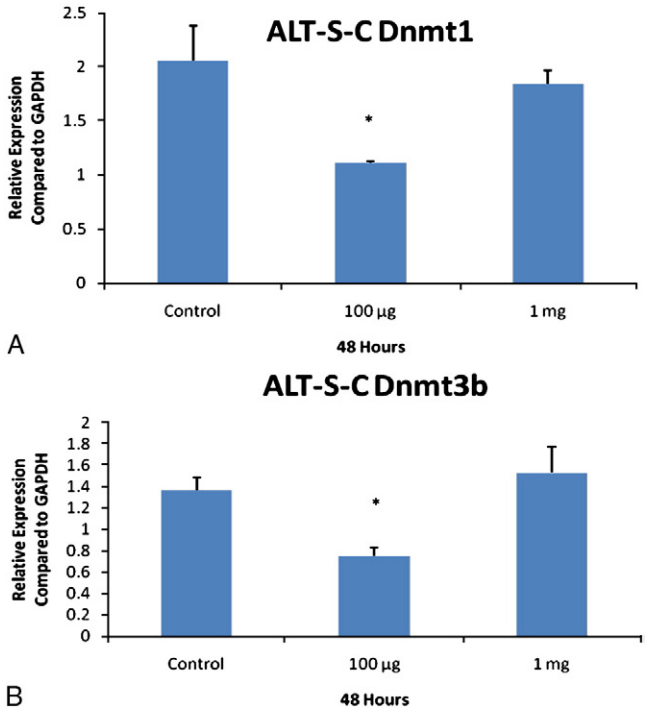

Fig. 3. A, Effects of botanical extract ALT-S-C on relative expression levels of Dnmt1 as compared with Gapdh. Significantly decreased expression in NIH/3T3 murine fibroblast cells that were treated with crude botanical extract ALT-S-C at 100 μg/mL and 1 mg/mL for 48 hours. Fold decrease shown in relation to untreated, control cultures. Statistical analyses were performed by a 2-sample, equal-variance, 2-tailed t test. *$P < .05$. B, Effects of botanical extract ALT-S-C on relative expression levels of Dnmt3b as compared with Gapdh. Significantly decreased expression in NIH/3T3 murine fibroblast cells that were treated with crude botanical extract ALT-S-C at 100 μg/mL and 1 mg/mL for 48 hours. Fold decrease shown in relation to untreated, control cultures. Statistical analyses were performed by a 2-sample, equal-variance, 2-tailed t test. *$P < .05$.

DNMT1 gene expression ($P < .05$) (Fig. 2A). Similar decreases were observed after exposure to 100 μg/mL of subfraction 7-6-5 for 48 and 96 hours ($P < .05$) (Fig. 2B). Exposure of NIH3T3 cells to 1 μg/mL of subfraction 222 reduced Dnmt3b expression ($P < .05$) (Fig. 2C). In contrast, Nanog expression was up-regulated ($P < .05$) in NIH3T3 cells after exposure to 1 and 10 μg/mL of PMI 5011 subfraction 222-1 for 96 hours (Fig. 2D). No changes in Gnmt expression were detected after treatment with any of the subfractions.

ALT-S (*A tuberosum* L) was identified in a random screen from a collection of a variety of botanicals located at the Louisiana State University. Since that time, we have learned that *A terbosum* is being investigated for anticancer activity [48]. We treated NIH3T3 cells with 100-μg/mL or 1-mg/mL extracts of ALT-S for 48 or 96 hours. Quantitative RT-PCR demonstrated down-regulation of both Dnmt1 and Dnmt3b ($P < .05$) at 48 hours after treatment with 100 μg/mL (Fig. 3A, B).

NZ-01 (*L lucidum* L) was also identified in our random screen of botanicals and has also been reported to have antidiabetic [49], anticancer [50], antioxidant [51], and neuroprotective [52] activities. Up-regulation of Gnmt gene expression was detected in NIH3T3 cells by quantitative RT-PCR after treatment with 750 μg/mL of NZ-01 extract for 48 and 96 hours ($P < .05$) as well as 1 mg/mL for 96 hours

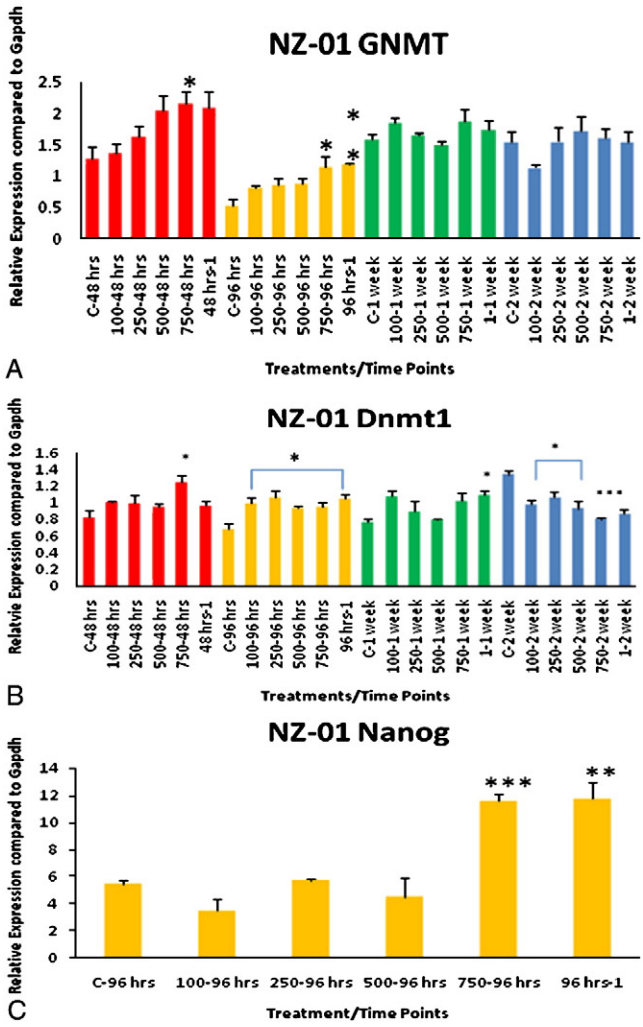

Fig. 4. A, Effects of botanical extract NZ-01 on relative expression levels of Gnmt as compared with Gapdh. Expression in NIH/3T3 murine fibroblast cells that were treated with 100 μg/mL, 250 μg/mL, 500 μg/mL, 750 μg/mL, and 1 mg/mL of crude extract NZ-01 for 48 hours, 96 hours, 1 week, and 2 weeks. Significant increase shown in relation to untreated, control cultures. Statistical analyses were performed by a 2-sample, equal-variance, 2-tailed t test. *$P < .05$; **$P < .01$. B, Effects of botanical extract NZ-01 on relative expression levels of Dnmt1 as compared with Gapdh. Expression in NIH/3T3 murine fibroblast cells that were treated with 100 μg/mL, 250 μg/mL, 500 μg/mL, 750 μg/mL, and 1 mg/mL of crude extract of NZ-01 for 48 hours, 96 hours, 1 week, and 2 weeks. Significant increases and decreases shown in relation to untreated, control cultures. Statistical analyses were performed by a 2-sample, equal-variance, 2-tailed t test. *$P < .05$; ***$P < .001$. C, Effects of botanical extract NZ-01 on relative expression levels of Nanog as compared with Gapdh. Expression in NIH/3T3 murine fibroblast cells that were treated with 100 μg/mL, 250 μg/mL, 500 μg/mL, 750 μg/mL, and 1 mg/mL of crude extract of NZ-01 for 96 hours. Significant increase shown in relation to untreated, control cultures. Statistical analyses were performed by a 2-sample, equal-variance, 2-tailed t test. **$P < .01$; ***$P < .001$.

($P < .01$) (Fig. 4A). Interestingly, Dnmt1 expression was up-regulated at 48 hours after treatment with 750 μg/mL of extract ($P < .05$) and at 96 hours after treatments with 100, 250, 500, and 750 μg/mL of extract ($P < .05$), but was significantly down-regulated after 2 weeks of exposure to 100, 250, and 500 μg/mL of extract ($P < .05$) and 750 μg/mL and 1 mg/mL ($P < .001$) (Fig. 4B). Nanog expression was also induced by NZ-01 treatment for 96 hours at 750-μg/mL ($P < .001$) and 1-mg/mL ($P < .01$) concentrations (Fig. 4C).

Taken together, the above data provide compelling evidence that modulators of epigenetic patterns are found in botanical sources. Specifically, data presented above clearly indicate that botanical extracts may contain activities that can modulate gene expression levels of components relevant to establishing and maintaining the epigenome in mammalian cells and are likely important sources for mammalian epigenetic modifying activities that may have therapeutic and other applications. More importantly, the observation that particular extracts that modulate epigenetic patterns may have an effect also to enhance insulin action provides intriguing associations and, as such, provides templates for future studies in the goal to prevent human related conditions such as obesity and insulin resistance.

8.1. Future directions

It is becoming increasingly clear that epigenetic processes play important roles in numerous diseases including cancer and developmental syndromes. More recently, epigenetic processes have been implicated in other complex diseases including type 2 diabetes mellitus, cardiovascular disease, and obesity. It is possible that a variety of compounds may prove to be efficacious to treat the epigenetic-based contributions to these diseases, in addition to playing a role in the prevention of other human disease states such as obesity and insulin resistance. The regenerative capabilities, or plasticity, observed in plants are thought to be associated with epigenetic reprogramming mechanisms and suggest a possible source to identify molecules and activities that could prove beneficial for the treatment of a variety of conditions associated with epimutations.

Acknowledgment/Conflict of Interest

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