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## Dietary natural products as epigenetic modifiers in aging-associated inflammation and disease

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Chronic, low-grade inflammation is linked to aging and has been termed "inflammaging". Inflammaging is considered a key contributor to the development of metabolic dysfunction and a broad spectrum of diseases or disorders including declines in brain and heart function. Genome-wide association studies (GWAS) coupled with epigenome-wide association studies (EWAS) have shown the importance of diet in the development of chronic and age-related diseases. Moreover, dietary interventions e.g. caloric restriction can attenuate inflammation to delay and/or prevent these diseases. Common themes in these studies entail the use of phytochemicals (plant-derived compounds) or the production of short chain fatty acids (SCFAs) as epigenetic modifiers of DNA and histone proteins. Epigenetic modifications are dynamically regulated and as such, serve as potential therapeutic targets for the treatment or prevention of age-related disease. In this review, we will focus on the role for natural products that include phytochemicals and short chain fatty acids (SCFAs) as regulators of these epigenetic adaptations. Specifically, we discuss regulators of methylation, acetylation and acylation, in the protection from chronic inflammation driven metabolic dysfunction and deterioration of neurocognitive and cardiac function.

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## 1. Introduction: aging-associated inflammation

"Inflammaging" is a phenomena of chronic low grade inflammation experienced with advanced age that is closely linked with the severity and progression of a variety of diseases.<sup>1,2</sup>

Inflammation is a tightly controlled and broadly conserved defensive response to injury and infection. The inflammatory response can be superficially characterized as swelling, redness, pain, heat and dysfunction around the affected area.<sup>3</sup> On a cellular level, several mediators act to isolate the affected area, attack foreign pathogens and clear damaged cells or irritants. These mediators include immune cells (e.g., macrophages and leukocytes), recognition receptors (e.g., toll-like receptors (TLR)) and signaling molecules (e.g., pro-inflammatory cytokines and chemokines). These signals activate intracellular cascades, such as necrosis factor kappa B (NF- $\kappa$ B), mitogen-activated protein kinases (MAPKs) and Janus Kinase/Signal Transducer and Activator of Transcription (JAK/STAT) pathways, to upregulate the inflammatory response.<sup>4</sup> Ultimately, in healthy individuals, this response leads to tissue repair, which triggers resolution of inflammation and restoration of homeostasis. Over time, however, as observed in aging, the inflammatory response loses its ability to properly reach resolution, which results in a progressive state of chronic inflammation, *i.e.*, chronic, low-grade inflammation (CLGI). CLGI can cause cellular/molecular dysregulation as observed with cell senescence, disrupted proteolysis and apoptosis and subsequent tissue dysfunction and degeneration.<sup>5</sup> Conversely, a homeostatic inflammatory environment promotes health and longevity.<sup>6,7</sup>

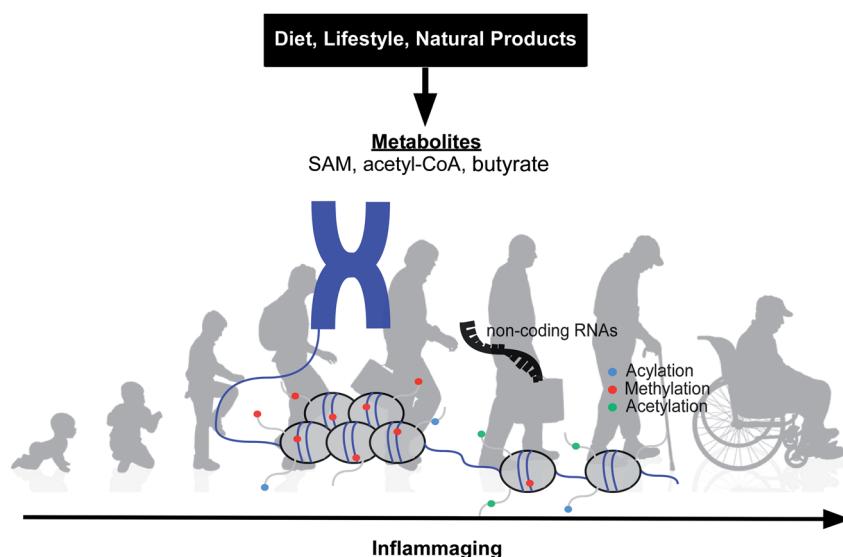
Recent reports link inflammatory dysregulation with epigenetic modifications.<sup>5</sup> Traditionally, epigenetic modifications regulate differential gene expression independently from altering DNA sequences. Well-known epigenetic modifications occur on DNA and histone proteins and include DNA methylation as well as histone methylation, acetylation and acylation. Moreover, there are well-described catalytic enzymes that add/remove these epigenetic modifications, which include: DNA methyltransferases (DNMTs) for DNA methylation; histone methyltransferases for histone methylation; histone demethylases (HDMs) for histone demethylation; histone

acetyltransferases (HATs) for histone acetylation; and histone deacetylases (HDACs) for histone deacetylation. DNMTs, such as DNMT1, promote gene repression by forming hypermethylation-induced heterochromatin (chromatin condensation),<sup>8</sup> inhibiting transcription factors from binding at promoter sites on genomic DNA<sup>9</sup> as well as coupling with other gene repressing proteins such as HDACs.<sup>10</sup> Histone deacetylation is regulated by HDACs, which mediate histone hypoacetylation towards heterochromatin and gene suppression, and HATs, which mediate histone hyperacetylation towards euchromatin and gene upregulation. In contrast to histone acetylation, which primarily occurs on lysine residues, histone methylation can occur on lysine, arginine and several other amino acid residues on histone protein tails, subsequently resulting in either gene expression or suppression.

Understanding epigenetic modifications in human-related diseases is becoming more relevant, and advancements in “-omics” technologies have allowed scientists to gather data regarding epigenetic modification in age-associated diseases. For example, epigenome-wide association studies (EWAS) correlated DNA hypomethylation with increased inflammation and frailty.<sup>11,12</sup> Conversely, delayed hypomethylation was noted in children of centenarians as was better health status when compared to their counterparts.<sup>13,14</sup> Moreover, several inflammatory signaling cascades are regulated in part *via* epigenetic modifications.<sup>15–18</sup> Thus, epigenetic modifications play an integral part in healthy aging and inflammation. Below we will discuss in detail how diet, lifestyle and natural products can alter metabolites that contribute to changes in the epigenome during ‘inflammaging’ (Fig. 1).

### 1.1 Aging-related metabolic dysfunction

As with inflammation, systemic control over metabolic processes decline with age and affect adipose, liver, pancreas



**Fig. 1** Diet, lifestyle and natural product supplementation can alter key metabolites necessary for histone and DNA modifications; these epigenetic adaptations contribute towards the prevention (delay) or promotion of ‘inflammaging’ that ultimately drives age-related chronic diseases (e.g. CVD, diabetes, Alzheimer’s Disease).

and skeletal muscle function. A primary outcome of metabolic dysfunction is insulin resistance, resulting in an impaired ability to regulate blood glucose through critical signaling pathways (*i.e.*, type 2 diabetes (T2D)). Additional outcomes include dysregulated gluconeogenesis in liver; mitochondrial dysfunction in many tissues; lipogenesis that occurs in adipose, liver and skeletal muscle; as well as dyslipidemia and glycogenolysis in liver.<sup>19</sup> Outside of T2D, metabolic dysregulation can result in obesity, non-alcoholic fatty liver disease (NAFLD), cardiovascular disease (CVD) risk and other age-associated diseases including neurodegeneration. NAFLD, often comorbid with obesity and T2D,<sup>20</sup> is associated with increased production of damaging cytokines and chemokines.<sup>21</sup> Several cellular mediators link age-associated metabolic dysfunction to inflammation. For example, the peroxisome proliferator-activated receptors (PPAR; PPAR $\gamma$ , PPAR $\alpha$ , PPAR $\delta$ ) are a family of nuclear receptors that drive transcriptional events involved in fatty acid and glucose metabolism but, importantly, decline with age.<sup>22</sup> Moreover, PPARs play a critical role in combating liver- and adipocyte-derived pro-inflammatory cytokines and chemokines.<sup>23</sup> This is interesting as pro-inflammatory pathways (*e.g.*, NF- $\kappa$ B,<sup>24</sup> JNK<sup>25</sup> and the NOD-like receptor protein 3 (NLRP3) inflammasome<sup>26</sup>) hinder insulin signaling. Therefore, metabolic dysfunction is observed with age and inflammation exacerbates substrate metabolism defects.

Several pathologies outside of obesity and T2D are associated with substrate metabolism dysfunction. For example, while the brain primarily uses glucose as its source for ATP production, metabolic dysregulation of glucose occurs in the brain of patients with age-associated neurodegenerative diseases.<sup>27,28</sup> Conversely, the heart predominantly utilizes fatty acid oxidation (60–90%) for its energy source but shifts to glucose in pathological settings.<sup>29</sup> Metabolic dysregulation of all major substrates (*i.e.*, fatty acids, glucose and protein) is also observed in cancer.<sup>30</sup> Not surprisingly, it has been suggested that influencing differential genomic expression of factors, such as enzymes, involved in metabolic regulation may offer some benefit.<sup>31</sup> Therefore, dietary interventions that modulate such factors *via* epigenetic actions are worth further exploration.

Acetyl Coenzyme A (Acetyl CoA), nicotinamide adenine dinucleotide (NAD $^+$ ) and S-adenosyl methionine (SAM) are metabolites regulated by energy metabolism, yet also function in epigenetic modifications. Availability of these metabolites regulate differential acetylation and methylation status, which impacts gene expression.<sup>32–34</sup> This is interesting because substrate overconsumption (*i.e.* carbohydrates, protein and fat) can initiate metabolic dysfunction, implying that diet-derived DNA and/or histone modification influences obesity, T2D or NAFLD. Indeed, studies have uncovered alterations in epigenetic enzymes and modifications that delineate metabolic abnormalities. For example, the class III, NAD $^+$ -dependent HDAC, sirtuin1 was reduced in obese individuals.<sup>35</sup> The sirtuin family has been well-described in age-associated metabolic dysfunction, partially due to its actions in mitochondria.<sup>36</sup> Another report associated DNA hypomethylation with T2D.<sup>37</sup> From these data, it is clear that ‘inflammaging’ contributes to

epigenetic modifications resulting in metabolic disease; this ultimately can contribute to neuro-impairment and cardiovascular disease.

## 1.2 Aging, inflammation and neurodegeneration

Incidences of neurodegenerative diseases have increased significantly in recent years due to increased life span; these include Parkinson’s Disease (PD) and Alzheimer’s Disease (AD), the latter of which is a leading cause of mortality.<sup>38</sup> Accumulating evidence now demonstrates that inflammation is a pivotal driver of neurodegeneration.<sup>39</sup>

Barriers separate the brain from the circulatory system, namely the blood-brain barrier (BBB) and the blood-cerebrospinal fluid barrier (BCSFB), which ultimately prevent outside offenders, such as mediators of systemic inflammation, from brain intrusion. A tightly controlled system at these brain barriers exists, which includes transport proteins and receptor-mediated signaling to allow an influx and efflux of nutrients, molecules and waste between the brain and the circulatory system. The brain contains a specialized inflammatory response system with similar characteristics and mediators to the immune system found in the periphery. In the brain, astrocytes, microglia and perivascular macrophages and leukocytes engage molecular receptors such as toll-like receptors (TLRs) in response to a pathological assault,<sup>40</sup> which upregulates NF- $\kappa$ B, MAPK and JAK/STAT pathways.<sup>4</sup> T cells further regulate the inflammatory response by mediating cytokine and chemokine production in the brain, and can force macrophage hyperpolarization to a pro-inflammatory state.<sup>41</sup> As with the periphery, microglia macrophages and other mechanisms clear unwanted debris resulting from the insult. These defense systems in the brain can also become dysfunctional over time. Barriers separating the brain from the body become compromised thus allow leakage and pathogenic infiltration.<sup>42</sup> Chronic, low grade inflammation stemming from the circulatory system can stimulate inflammation in the brain,<sup>43</sup> and thus contribute to a pro-inflammatory environment. Brain inflammation contributes to receptor-mediated degradation of myelinated axons and neurons.<sup>44</sup> Unwanted, and oftentimes damaging, proteins aggregate in the brain due to dysfunctional phagosomes, as observed with  $\beta$  (A $\beta$ ) and tau amyloid protein accumulation in neurodegenerative diseases. Such dysfunctions affect cognitive performance and downstream systemic performance such as muscle control; this may even result in death.<sup>45,46</sup>

Several epigenetic modifications are affected in neurodegenerative environments. For example, DNA methylation status of genes involved in neurogenesis were altered in patients with PD.<sup>47,48</sup> In agreement, differential DNA methylation of CpG islands in the genes, reelin and protein phosphatase 1 (PP1), was shown to be important for cognitive performance.<sup>49</sup> In relation to histone acetylation, the repressor element-1 silencing transcription factor (REST) is a corepressor complex that binds and recruits other components, namely HDACs 1 and 2, to transcriptional regions towards gene downregulation.<sup>50</sup> While important during embryogenesis,<sup>51</sup> REST has been implicated in mature neuron cell death within ischemia,<sup>52</sup>

epileptic seizure<sup>53</sup> and Huntington's Disease models.<sup>54</sup> REST suppressed genes associated with neuronal synaptic function and drove neuron cell death in an *in vivo* clinical model of global ischemia, while HDAC inhibitor treatment abated these insults.<sup>50</sup> This is interesting because HDAC inhibitor treatment typically dampens inflammation and the HDAC inhibitor, valproic acid, was the first of its kind to be offered as a prescription for neurological dysfunction.<sup>55</sup> Highlighting the cooperative nature of acetylation and methylation in gene expression regulation, blocking histone hypermethylation *via* methyltransferase-inhibition has also been shown to reduce neuroinflammation.<sup>56,57</sup> Class III HDACs, the sirtuin family, have a more complex role in neurodegeneration. Sirt1 overexpression inhibited NF- $\kappa$ B-mediated inflammation and A $\beta$ -mediated neurodegenerative actions in microglia.<sup>58</sup> Moreover, Sirt6 was depleted in brains of AD patients, while Sirt6 overexpression prevented agonist-induced DNA damage in mouse neurons.<sup>59</sup> In contrast, nicotinamide, a pan sirtuin inhibitor, blocked neurodegeneration and cognitive defects concomitant with increased acetylation of common sirtuin targets in AD mice.<sup>60</sup> Similarly confounding, Sirt6 overexpression in the hippocampal CA1 region was shown to impair cognitive performance.<sup>61</sup> It would seem whether sirtuin-mediated actions are neuroprotective or neurodegenerative is contextual. The cumulative evidence, still, suggests epigenetic regulation of neuro-inflammation and neurodegeneration is promising and worth further exploration.

### 1.3 Aging, inflammation and cardiovascular disease

Cardiovascular diseases (CVD) remain the leading cause of death world-wide and include heart attack, arrhythmias, atherosclerosis and heart failure. Many well-characterized pathogeneses of the heart manifest from inflammation, and pro-inflammatory markers in circulation are used to predict CVD risk.<sup>62</sup> One of the most common of these inflammation-induced heart diseases is atherosclerosis. Chronic, low grade inflammation results in endothelium insult that upregulates the inflammatory response around the affected site.<sup>63</sup> There, macrophages take up oxidized apolipoprotein B (ApoB)-containing lipoproteins that accumulate in the subendothelial space. The macrophages then transform into foam cells, which are primary constituents of atherosclerotic plaques. Intriguingly, rupture or erosion of atherosclerotic plaques initiate myocardial infarction (MI), both of which mediate an ongoing inflammatory response. Following MI, cardiomyocytes suffer ischemic injury or death, which further exacerbates inflammation and cardiac remodeling,<sup>64,65</sup> a common hallmark of heart failure. Cytokines produced from aforementioned cardiac insults activate signaling cascades involved in heart failure pathology, including cardiac hypertrophy, fibrosis and dysfunction.<sup>66,67</sup> These data suggest inflammation drives cardiac pathologies and is a prime target for CVD therapy.

Epigenetic modifications have been characterized in CVD. A recent epigenome-wide association study (EWAS) in myocardial infarct patients associated DNA methylation at several gene promoter regions with CVD risk including associated blood

lipid levels that contribute to atherosclerotic events.<sup>68</sup> Further studies have also linked hypertension and inflammation with methylation status.<sup>69</sup> While these studies focused on methylation, others have reported changes in acetylation. For example, sirtuin levels were reduced in CVD patients, linking changes in acetylation to CVD.<sup>70</sup> Much like in age-associated diseases described in above sections, sirtuin deacetylase activity has been shown to have cardioprotective effects.<sup>71</sup> Consistent with these findings, histone acetyltransferase activity of p300 was shown to be necessary for agonist-induced cardiac hypertrophy.<sup>72</sup> Conversely, HDAC inhibition and histone hyperacetylation have been shown to attenuate cardiac/cardiomyocyte hypertrophy and associated fetal gene re-expression,<sup>73,74</sup> cardiac fibrosis<sup>75</sup> and cardiac dysfunction.<sup>76</sup> Class I HDACs seem to be necessary for the pathological cardiac hypertrophy as well as inflammatory signaling.<sup>18,77</sup> Likewise, recent reports demonstrate an important role for HDACs in age-related diastolic heart failure, where HDAC inhibition improved diastolic function.<sup>78</sup> These data combined, demonstrate an epigenetic role for DNA methylation and histone modification in CVD risk and development, yet further studies are needed to determine the various molecular targets of the HAT and HDAC enzymes that relay different outcomes.

## 2. Phytochemicals in aging-associated inflammation

Phytochemicals are compounds synthesized by plants for protection against pests, pathogens and UV light.<sup>79</sup> Upon human consumption, phytochemicals interact in biological processes such as redox reactions,<sup>80–82</sup> cell signaling<sup>83</sup> and, of interest, inflammation.<sup>82</sup> Indeed, diets rich in phytochemicals have been associated with reduced inflammation and, in doing so, may mitigate inflammation-associated diseases.<sup>84</sup> Indeed, plant based diets have been shown to reduce the risk of developing metabolic dysfunction,<sup>85</sup> neurodegeneration,<sup>86</sup> and cardiovascular disease.<sup>87</sup> An emerging body of evidence suggests that bioactive compounds impart advantageous environments, such as homeostatic inflammation, through differential gene expression.<sup>88,89</sup> This suggests phytochemicals can mitigate deleterious gene expression (e.g., pro-inflammatory genes) and promote beneficial gene expression (e.g., anti-inflammatory genes). Moreover, phytochemicals have been implicated in regulating gene expression through epigenetic modifications. In this section, we will discuss current studies linking phytochemical-mediated epigenetic modifications to age-associated diseases. These and additional compounds are described in Table 1 and basic structures for these compounds discussed are depicted in Fig. 2.

### 2.1 Phytochemicals – DNA methylation and gene expression

**2.1.1 Curcumin and DNA methylation.** Curcumin is a polyphenolic curcuminoid found in the yellow pigmented plant, turmeric, and has been used for centuries as a medicinal herb. Curcumin is one of the more well-studied phytochemicals and has been shown to attenuate metabolic dysfunction.<sup>90,91</sup> Of

Table 1 Natural product regulators of the epigenome, their gene targets and their structures

Epigenetic modification	Natural product	Polyphenolic group	Epigenetic mode of action	Target and effect	References
DNA methylation	Curcumin	Cureuminoid	↓PPAR $\alpha$ promoter region DNA methylation ↓DNMT activity	↑PPAR $\alpha$ expression; ↓DNMT activity, liver steatosis, abdominal fat, LDL cholesterol and triglycerides	92 and 93
Sulforaphane	Isothiocyanate		Reversed pathological DNMT hyperactivity in retina cells	↑Nrf2 expression; ↓neurological inflammation (IL-1 $\beta$ and IL-6) and A $\beta$ accumulation	94
EGCG	Catechin		↓DNA hypermethylation; ↓Ghrl3, Pax3, and Tulp3 CpG island hypermethylation; ↓DNMT3a and 3b expression	↓Ghrl3, Pax3, and Tulp3 expression	109
Quercetin	Flavonol		↓DNA hypermethylation at Pgc-1 $\alpha$ promoter	↓HFD-induced Pgc-1 $\alpha$ expression in rodents	138
Resveratrol	Stilbene		↑DNMT activity; ↑DNMT1, 3a and 3b expression; ↑LINE-1 methylation	Reversed oxidative stress- and inflammation-induced changes in ARPE-19 cells	139
Ascorbic acid	NA; micronutrient		↑TET (DNA demethylase) activity; ↓methylation of Foxp3 CpG enhancer region	↑Foxp3 expression and T <sub>reg</sub> cell differentiation; ↓T <sub>reg</sub> senescence	121, 122, 127 and 128
Emodin	Anthraquinone		↑H3 K27 trimethylation	↑TNF $\alpha$ , IL6, iNOS, IRF4, Arg1 and YM1; ↓IRF5, NF- $\kappa$ Bp65 and STAT1 nuclear activity in M1 macrophages; ↓STAT6 and IRF4 nuclear activity in M2 macrophages	146
Ellagic acid	Hydroxybenzoic acid		↓CARM1 activity and H3 R17 dimethylation	↓PPAR $\gamma$ activity, adipose inflammation and adipose differentiation	158 and 161
Ascorbic acid	NA; micronutrient		↑JMJD3 histone demethylase activity; ↓methylation of H3K9me2, H3K27me2, H3K36me2/3	↓Cell senescence <i>via</i> Ink4/Arf; ↑cell cycle progression	129, 133 and 134
Resveratrol	Stilbene		↑Sirtuin activity	↑Longevity in numerous cell types	167 and 169–176
Histone acetylation			↑Sirtuin activity	↑PPAR $\gamma$ , PGC-1 $\alpha$ , GLUT4 and AMPK/IRS/Akt expression; ↓adipocyte inflammation, triglyceride accumulation and insulin resistance in adipocytes	177–179
Sulforaphane	Isothiocyanate		↑Sirtuin activity; ↓MMP9 promoter region acetylation	↓MAPK, NF- $\kappa$ B and MMP9 signaling; potentially neuro- and metabolically protective	181 and 186–188
Emodin	Anthraquinone		↑Sirtuin activity	↓Oxidative stress in T2D patients	193 and 194
Curcumin	Cureuminoid		↑H3 and H4 acetylation at promoter regions I, II and IV of BDNF	↑BDNF, TrkB and TrkB target expression in cortical neurons and AD-induced mice	196
EGCG	Catechin		↓Class I & II HDAC activity; ↑histone acetylation	Potentially cardioprotective, particularly through NF- $\kappa$ B	205
			↑p300 HAT activity	↑GATA4 signaling, cardio hypertrophic gene expression and cardiac hypertrophy	209–211
			↓HDAC1 activity; ↑TIMP1 promoter region acetylation	↑TIMP1 expression; ↓MMP2, cardiac fibrosis and inflammation	218
				↓Inflammation in endothelial cells	225

Table 1 (Cont'd.)

Epigenetic modification	Natural product	Polyphenolic group	Epigenetic mode of action	Target and effect	References

interest, several studies suggest curcumin is metabolically efficacious by regulating DNA methylation.<sup>92</sup> For example, curcumin was shown to reduce DNA hypermethylation at CpG sites -360, -341, -329, -316 and -307 at the promoter region of peroxisome proliferator-activated receptor-alpha (PPAR $\alpha$ ) in a non-alcoholic fatty liver disease (NAFLD) rat model.<sup>93</sup> These data correlated with increased PPAR $\alpha$  expression and reduced signs of liver cell death.<sup>93</sup> The PPAR $\alpha$ -dependent protective effects of curcumin in rat liver congruently occurred in steatosis-induced liver cells.<sup>93</sup> As reversal of DNA methyl transferase (DNMT)-mediated DNA hypermethylation is associated with gene repression, curcumin likely upregulated PPAR $\alpha$  by inhibiting DNMTs.<sup>94</sup> PPAR $\alpha$  is a transcription factor that predominates in the liver where it regulates expression of genes involved in inflammation and several metabolic processes including gluconeogenesis, cholesterol metabolism and xeno-biotic bioavailability.<sup>95-99</sup> Reduced PPAR $\alpha$  results in increased adiposity and pro-inflammatory adipokines and is correlated with aging.<sup>23,100,101</sup> Moreover, liver steatosis is prevented by PPAR $\alpha$ -dependent fatty acid catabolism.<sup>97,99</sup> Consistent with this, curcumin-induced PPAR $\alpha$  expression resulted in differential expression of several PPAR $\alpha$  targeted genes involved in cholesterol metabolism and insulin sensitivity in NAFLD-induced liver of broiler chickens.<sup>102</sup> These results were linked to reduced abdominal fat, LDL cholesterol and triglycerides, suggesting that the PPAR $\alpha$ -dependent effects of curcumin were observed on a physiological level.<sup>102</sup> Others have also reported that curcumin mediates metabolic protection by regulating DNA methylation.<sup>94</sup> In this report, curcumin attenuated high-glucose-induced DNMT mRNA overexpression, which subsequently reduced DNMT activity in a human cell model of diabetic retinopathy.<sup>94</sup> This is important because diabetic retinopathy is a common complication for inflammaging-associated metabolic dysfunction and is implicated in CVD.<sup>103</sup> These combined data support the postulate that curcumin is metabolically protective by mitigating DNMT activity. Furthermore, as PPAR $\alpha$  is reduced with aging, curcumin may attenuate the deleterious actions associated with age-related depletion of PPAR $\alpha$ , including liver dysfunction and adiposity.

**2.1.2 Sulforaphane and DNA methylation.** Sulforaphane is an isothiocyanate predominantly found in cruciferous vegetables such as broccoli. Sulforaphane has repeatedly been shown to inhibit cancer cell growth as well as attenuate other age-associated diseases; these actions were regulated in part by inhibiting inflammation by changing DNA methylation.<sup>104-108</sup> It is of no surprise, then, that sulforaphane was shown to attenuate DNMT-mediated DNA hypermethylation at the promoter region of NF-E2-related factor 2 (Nrf2), which subsequently reactivated nuclear Nrf2 in a cell model of Alzheimer's Disease (AD).<sup>109</sup> Nrf2 is a transcription factor that regulates reduction-oxidation homeostasis upon nuclear translocation and has been implicated in inflammation and neurodegeneration.<sup>110-114</sup> From the report above, researchers further showed that sulforaphane inhibited pro-inflammatory signaling (IL-1 $\beta$  and IL-6) and  $\beta$  amyloid (A $\beta$ ) protein accumulation as well as oxidative damage.<sup>109</sup> Moreover, the anti-inflammatory actions of sulforaphane diminished upon Nrf2 knockdown, demonstrating that

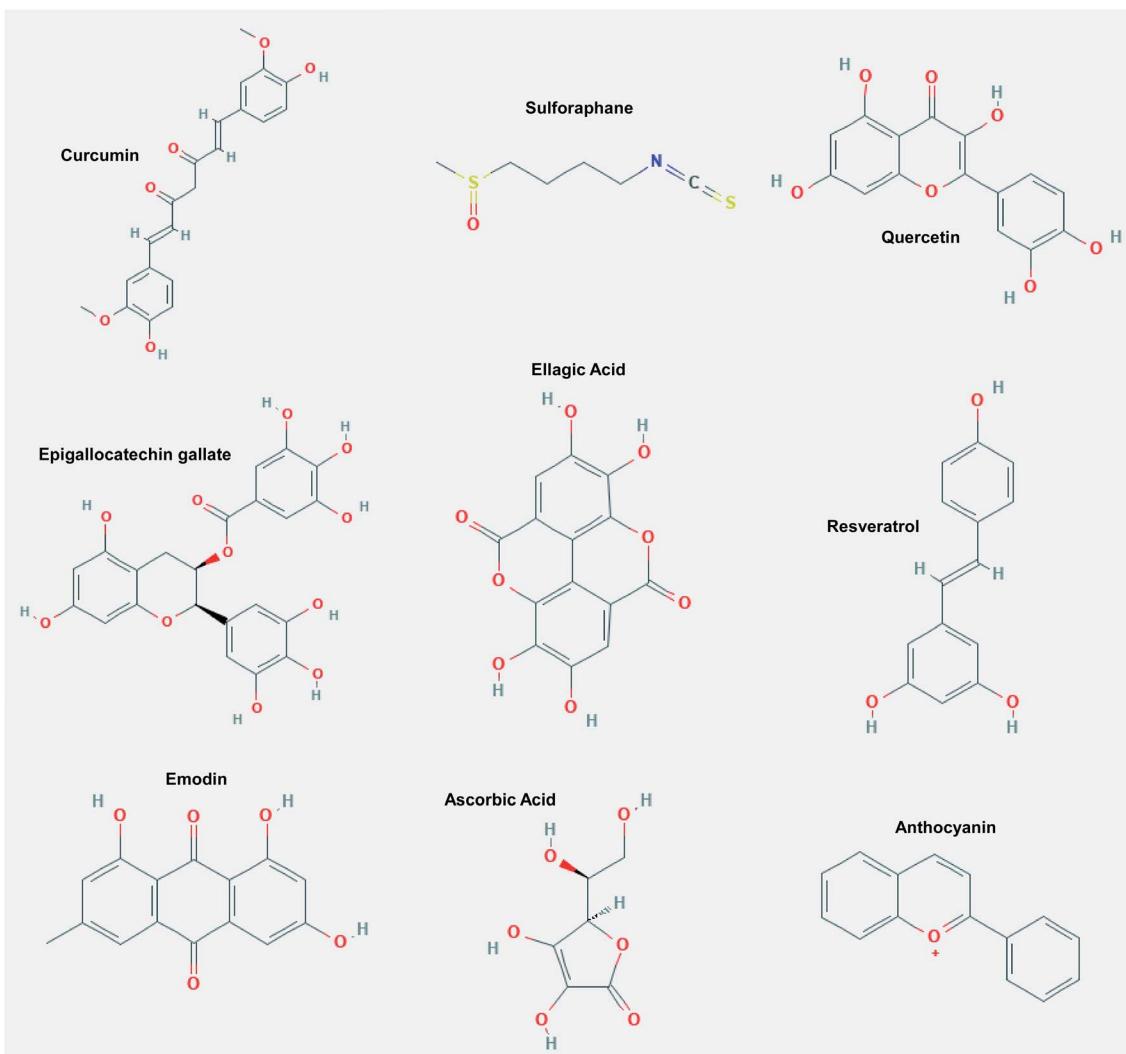


Fig. 2 The basic structure of various phytochemicals and micronutrients important for histone and DNA modifications (epigenetic adaptations) that have been shown to prevent or delay age-related chronic diseases.

DNA hypomethylation of the Nrf2 promoter with sulforaphane treatment was sufficient to inhibit A<sub>β</sub> accumulation.<sup>109</sup> Others have also shown that sulforaphane regulates inflammation *via* Nrf2-dependent changes in gene expression.<sup>115,116</sup> These data suggest that sulforaphane protects from AD-like neurodegeneration by blocking pro-inflammatory signaling through Nrf2-dependent actions and that sulforaphane regulates Nrf2 activity *via* DNA hypomethylation.

**2.1.3 Ascorbic acid and DNA methylation.** Ascorbic acid (*i.e.*, vitamin C) is a micronutrient, which cannot be synthesized by humans due to L-gulono-γ-lactone oxidase dysfunction. Thus, the ascorbic acid deficiency disease, scurvy occurs when ascorbic acid-rich foods (*e.g.*, fruits, vegetables and some animal organs) are underconsumed and ascorbic acid plasma concentrations reach less than 11 μM.<sup>117</sup> Outside of preventing its deficiency disease, ascorbic acid is a potent reducing agent with four hydroxyl groups in its chemical structure. It comes as no surprise, then, that ascorbic acid is a suggested remedy for inflammaging-associated diseases,<sup>118,119</sup> as oxidation is a key

driver of inflammation.<sup>120</sup> However, emerging evidence suggests that ascorbic acid attenuates ‘inflammaging’ independent of anti-oxidation;<sup>121</sup> instead ascorbic acid has been shown to alter the epigenome. For example, ascorbic acid was shown to demethylate CpG-rich conserved noncoding sequence 2 (CNS2) of the transcription factor forkhead box protein 3 (Foxp3) in T regulatory cells (T<sub>reg</sub>).<sup>122</sup> These actions were dependent on the ten-eleven translocation (TET) oxidative demethylation protein, Tet2.<sup>122</sup> CNS2 methylation inversely correlates with Foxp3 expression,<sup>123</sup> which was shown to regulate the physiological function of T<sub>reg</sub> cells.<sup>124</sup> These data are interesting as functional non-senescent T<sub>reg</sub> cells play an important anti-inflammatory role.<sup>125</sup> Moreover, immune senescence and senescence of other cell types, indicative of inflammaging, increases in the aging populace.<sup>126</sup> Thus, ascorbic acid may combat an aging pro-inflammatory state by regulating immune cell function that is dependent on demethylase activation.

Others have also linked inhibited cell senescence and enhanced cell pluripotency and differentiation with DNA or

histone demethylase-dependent ascorbic acid-induced demethylation.<sup>121,127-129</sup> Indeed, hyper di- and/or tri-methylation on histone H3 lysine residues K9, K27 and K36, which increased senescence and inhibited cell pluripotency and differentiation,<sup>130-132</sup> is reversed by ascorbic acid.<sup>129,133,134</sup> Ascorbic acid-induced hypomethylation and differentiation has further been linked to reduced DNA methyltransferase (DNMT) expression in cardiac stem cells.<sup>135</sup> These data suggest that ascorbic acid may not only attenuate inflammaging-associated diseases through DNA and histone demethylation, but may also be a (co-)therapeutic for stem cell rejuvenation of tissues susceptible to age-associated dysfunction.

While this section only focused on two well-studied phytochemicals and one micronutrient, it should be noted that many natural products have been reported to regulate DNA methylation including epigallocatechin gallate (EGCG),<sup>136,137</sup> quercetin<sup>138</sup> and resveratrol.<sup>139</sup> As DNA methylation methodology is commonly used outside of experimental animal models, it would be interesting to examine the effects of individual natural products on DNA methylation and inflammaging-associated cascades in humans.

## 2.2 Phytochemicals – histone methylation and gene expression

**2.2.1 Emodin and histone methylation.** Emodin is an anthraquinone found in plants used in traditional Chinese medicines, such as buckthorn, knotweed, rhubarb and Da Huang, which is a primary ingredient for the decoction, Dahuang Fuzi,<sup>140</sup> as well as other plant-based foods like beans and cabbage.<sup>141,142</sup> As herbal remedies, emodin-rich plants have been used for viral and bacterial insults, kidney disorders and gastrointestinal distress in traditional Chinese medicine. In relation to epigenetics, early reports showed emodin was efficacious in cancer models by regulating DNA methylation.<sup>143-145</sup> However, recent evidence showed that emodin was able to inhibit the removal of histone H3K27 trimethylation in macrophages exposed to inflammatory stress.<sup>146</sup> This was particularly apparent at promoter regions of inflammatory signaling molecules, inducible nitric oxide synthase (iNOS), tumor necrosis factor alpha (TNF $\alpha$ ), interleukin 6 (IL6), interferon regulatory factor 4 (IRF4), arginase 1 (Arg1) and chitinase 3-like protein 3 (Y1M1) in M1 or M2 macrophage phenotypes.<sup>146</sup> Further, emodin inhibited nuclear translocation of interferon regulatory factor 5 (IRF5), nuclear factor kappa B p65 (NF- $\kappa$ Bp65) and signal transducer and activator of transcription 1 (STAT1) in M1 macrophages as well as STAT6 and IRF4 in M2 macrophages.<sup>146</sup> Activation of macrophages by pro-inflammatory signaling molecules is important to the anti-inflammatory response.<sup>147</sup> However, macrophage hyperpolarization into either M1 or M2 phenotypes is deleterious to health.<sup>147,148</sup> The M1 hyperpolarized macrophage is of particular interest in neurodegenerative disease and has been suggested as a target for phytochemicals.<sup>149</sup> Indeed, emodin has been shown to be protective in multiple neurodegenerative disease models, including cerebral ischemic stroke,<sup>150</sup> traumatic brain injury<sup>151</sup> and AD.<sup>152</sup> In the above report, emodin restored the

balance away from M1 and M2 hyperpolarization phenotypes<sup>146</sup> and thus suggests that emodin may provide protection against brain pathologies through epigenetic balancing of macrophage activation *versus* hyperpolarization.

**2.2.2 Ellagic acid and histone methylation.** Ellagic acid is a polyphenolic hydroxybenzoic acid derivative found ubiquitously in many fruits, such as raspberries and strawberries, nuts, such as walnuts and pecans and mushrooms, namely the ox tongue mushroom. Ellagic acid has profound anti-inflammatory effects.<sup>153-156</sup> Of interest, Western diet-induced inflammation and adiposity have been shown to be reversed with ellagic acid treatment.<sup>153,156</sup> Excess accumulation of adipose tissue, or obesity, commonly initiates downstream inflammation and metabolic dysfunction<sup>157</sup> and has become a primary target to resolve metabolic syndrome, T2D and CVD. In relation to epigenetic regulation of metabolic dysfunction, ellagic acid was reported to inhibit coactivator-associated arginine methyltransferase 1 (CARM1) activity,<sup>158</sup> which is an intricate methyltransferase enzyme implicated in both NF- $\kappa$ B-mediated inflammation and inflammation-associated metabolic dysfunction.<sup>159,160</sup> Indeed, ellagic acid has been shown to attenuate NF- $\kappa$ B activity.<sup>155</sup> Consistent with this, ellagic acid was reported to attenuate differentiation-induced hyperdimethylation of histone 3 arginine 17 independent from CARM1 expression in human adipose-derived stem cells.<sup>161</sup> However, PPAR $\gamma$ , a CARM1 target, was also downregulated upon ellagic acid treatment in differentiated adipocytes.<sup>161</sup> PPAR $\gamma$  is an important regulator of adipogenesis and adipocyte function, agonistically targeted for T2D and atherosclerosis treatment and is coactivated in part by CARM1-mediated histone methylation.<sup>162-164</sup> However, PPAR $\gamma$  activation results in increased adiposity,<sup>165</sup> and thus some question the overall efficacy of PPAR $\gamma$  agonists for metabolic dysfunction.<sup>163</sup> Thus, ellagic acid-mediated downregulation of PPAR $\gamma$  may, in fact, be chronically advantageous. On the other hand, others have shown the anti-inflammatory actions of ellagic acid were partially PPAR $\gamma$ -dependent.<sup>166</sup> Further exploration is nevertheless required to fully elucidate the molecular targets of ellagic acid, if its efficacy outweigh the detriments in chronic inflammation/age-associated diseases and how it regulates these actions through epigenetic-mediated mechanisms.

## 2.3 Phytochemicals – histone acetylation and gene expression

**2.3.1 Resveratrol and histone acetylation.** Arguably one of the most well-studied natural dietary products that regulates histone acetylation and health is the stilbene, resveratrol. Resveratrol is found mainly in grapes and wine but also in berries, nuts and cocoa. Resveratrol potently activates sirtuins, which are the nicotinamide adenine dinucleotide (NAD $^{+}$ )-dependent class III HDACs.<sup>167</sup> Sirtuins are ubiquitously expressed and can be found localized to the nucleus, cytoplasm and mitochondria; thus, sirtuins are involved in chromatin remodeling, DNA stability, differential gene expression and metabolic regulation.<sup>168</sup> Studies across numerous models have reported the anti-aging effects of resveratrol-mediated sirtuin

activation.<sup>167,169–176</sup> These studies suggest resveratrol promotes longevity and health in a conserved manner, and does so mostly through Sirt1-dependent mechanisms.<sup>177,178</sup>

Indeed, resveratrol has been shown to reverse age-associated repression of genes that regulate free fatty acid metabolism and  $\beta$ -oxidation (PPAR $\gamma$  and its coactivator, PGC-1 $\alpha$ ) in differentiated adipocytes.<sup>177</sup> These data were linked with reduced triglyceride accumulation upon resveratrol-mediated sirtuin activation.<sup>177</sup> Consistently, resveratrol upregulated genes responsible for glucose sensitivity (AMPK/IRS/Akt signaling, PPAR $\gamma$  and GLUT4), while it inhibited adipokine inflammation within insulin-resistant adipocytes *in vitro* and *in vivo*.<sup>178</sup> Others have also reported that resveratrol-induced sirtuin activation improved glucose sensitivity by upregulating GLUT4 in liver and muscle of metabolically compromised mice.<sup>179</sup> These data suggest resveratrol attenuated age-associated metabolic dysregulation.

In addition to its role in regulating insulin signaling, resveratrol has been shown to inhibit inflammation in part through regulation of the signaling cascades NF- $\kappa$ B and mitogen-activated protein kinases (MAPKs)<sup>180</sup> as well as through regulation of histone deacetylation-dependent gene expression.<sup>181</sup> Specifically, resveratrol was shown to deacetylate the promoter region of matrix metalloproteinase 9 (MMP9) and subsequently downregulate MMP9 expression.<sup>181</sup> Upon Sirt1 knockout, resveratrol no longer attenuated MMP9 expression.<sup>181</sup> MMP9 is an endoproteinase involved in inflammation-induced tissue remodeling that is overly activated in CVD, neurodegeneration and diabetes.<sup>182–184</sup> While no study has linked the cardioprotective benefits of resveratrol and MMP9,<sup>185</sup> several reports suggest that resveratrol-mediated suppression of MMP9 is protective in models of diabetes and neurodegeneration.<sup>186–188</sup> The MAPK, c-Jun N-terminal kinases (JNK), and NF- $\kappa$ B bind the promoter region of, and thus activate, MMP9.<sup>189</sup> As resveratrol has been shown to inhibit JNK and NF- $\kappa$ B,<sup>190,191</sup> the stilbene may further attenuate MMP9 activity independent of its histone deacetylase activity. However, it should be noted that JNK<sup>18</sup> and NF- $\kappa$ B<sup>16,17</sup> have been shown to bind to HDAC complexes and their activity regulated by HDACs or methyltransferases, suggesting that resveratrol may also regulate the activity of these molecules by acting on writer or eraser enzymes (*e.g.* HDACs). Consistent with this, resveratrol has been reported to regulate other epigenetic modifying enzymes, including zinc-dependent HDACs and DNMTs, in age-associated disease models.<sup>139,192</sup>

Despite the positive findings in animal models however, clinical studies using resveratrol have been less exciting. For example, resveratrol supplementation over a six-month period increased sirtuin activation and reduced oxidative stress, yet did not improve markers of metabolic dysfunction in T2D patients.<sup>193,194</sup> One problem in animal models of T2D involves the age of the animal; most are young animals. NAD<sup>+</sup> has been reported to decrease with aging.<sup>195</sup> As sirtuins require NAD<sup>+</sup> for catalytic deacetylase activity, resveratrol treatment may do little in the way of promoting sirtuin activation with declining NAD<sup>+</sup> levels in human subjects.

**2.3.2 Sulforaphane and histone acetylation.** Aside from DNA methylation, sulforaphane has also been reported to

promote brain health by regulating brain-derived natriuretic factor (BDNF) *via* histone acetylation.<sup>196</sup> In primary cortical neurons, sulforaphane increased histone H3 and H4 acetylation at promoter regions I, II and IV of BDNF and subsequently increased BDNF expression.<sup>196</sup> These actions were likely due to reduced HDAC2 expression and HDAC activity upon sulforaphane exposure; HDAC inhibition would be expected to increase histone acetylation and gene expression.<sup>196</sup> Additionally, sulforaphane was shown to upregulate the BDNF receptor, tyrosine kinase receptor B (TrkB), and increase activity of TrkB downstream targets (*i.e.*, cAMP-responsive element-binding protein (CREB), Ca<sup>2+</sup>/calmodulin-dependent protein kinase II (CaMKII), extracellular signal-regulated kinase (ERK) and protein kinase B (Akt)).<sup>196</sup> Consistent with these cell data, sulforaphane also increased BDNF and its downstream targets in a triple-transgenic mouse model of AD.<sup>196</sup> Increased TrkB expression and its activated targets are associated with synaptic plasticity and strength, neurite outgrowth and differentiation, improved cognitive function and neuronal survival in models of neurodegeneration.<sup>197,198</sup> Moreover, HDAC2 has been shown to impair cognitive function by binding, and thus inhibiting, several genes important for memory and synaptic plasticity.<sup>199</sup> Indeed, several studies have shown sulforaphane improves cognitive impairment and attenuates neuronal degradation,<sup>200–202</sup> consistent with its inhibition of HDAC2.<sup>196</sup> In conjunction with all data provided in this review, sulforaphane is a multifaceted regulator of DNA and histone modifications, DNA methylation and histone acetylation in particular, and may protect the brain from age-associated diseases through these epigenetic-mediated actions.

**2.3.3 Emodin and histone acetylation.** Emodin was recently shown to dose-dependently attenuate the NOD-, LRR- and pyrin-domain containing protein 3 (NLRP3) inflammasome pathway in hypoxic-exposed hearts and heart cells.<sup>203</sup> The NLRP3 inflammasome synthesizes pro-inflammatory byproducts and mediates inflammation-induced cell death, or pyroptosis.<sup>204</sup> Indeed, this report showed emodin blocked pro-inflammatory byproduct signaling, namely NF- $\kappa$ B, and pyroptosis concomitantly with reduced scar tissue formation in the heart.<sup>203</sup> As NF- $\kappa$ B activity is regulated by HDACs, emodin may have blocked NF- $\kappa$ B activity through HDAC inhibition. In this regard, our lab recently reported that emodin dose-dependently inhibited cardiac-based HDAC activity and increased histone acetylation in cardiac myoblasts.<sup>205</sup> HDAC inhibition is well-known to prevent and treat cardiac dysfunction in pre-clinical animal models of heart failure, as described above.<sup>73–76</sup> Emodin likely inhibits HDAC activity by chelating zinc ions within HDAC catalytic domains due to its chelating properties.<sup>206</sup> Furthermore, other well-characterized HDAC inhibitors have been shown to block NF- $\kappa$ B signaling,<sup>207</sup> thus, further suggesting emodin is an HDAC inhibitor that regulates pro-inflammatory signaling cascades. Finally, histone acetylation mediates differential gene expression.<sup>73,205,208</sup> This suggests that emodin may reverse stress-induced changes in the transcriptome. Experiments aimed at elucidating the epigenetic-dependent actions of emodin in CVD models are currently underway. Nevertheless, these data collectively suggest emodin inhibits pro-inflammatory signaling and

downstream insults; these actions potentially depend on emodin's role as an HDAC inhibitor.

**2.3.4 Curcumin and histone acetylation.** Curcumin is a pleiotropic compound that has been shown to regulate multiple molecular targets; one such target involves the regulation of histone acetylation. Specifically, curcumin has been shown to inhibit p300 histone acetyltransferase (HAT) activity in experimental models of CVD.<sup>209–211</sup> Curcumin-dependent p300 inhibition was shown to reduce histone acetylation on promoter regions of the GATA binding protein (GATA4) as well as other pro-hypertrophic genes subsequently resulting in decreased expression of cardio-hypertrophic genes.<sup>211</sup> This is in agreement with the canonical role of HATs in catalyzing histone hyperacetylation and gene upregulation. In addition, the GATA4 transcription factor can be acetylated by p300, increasing GATA4 DNA binding to the promoter regions of other cardio hypertrophic genes; this leads to pathological cardiac enlargement.<sup>212</sup> GATA4 can further induce cardiac hypertrophy by promoting the pro-hypertrophic transcription factor, nuclear factor of activated T cells (NFAT).<sup>213</sup> Just as important, GATA4 mediates inflammation and age-associated cell dysregulation, or cell senescence, through NF-κB-dependent mechanisms.<sup>214,215</sup> As such, both NFAT and NF-κB signaling are blocked upon curcumin exposure.<sup>216,217</sup> More so, NF-κB activity is regulated in part *via* p300-dependent actions.<sup>16</sup> It would be interesting to see if curcumin mitigates NFAT or NF-κB signaling pathways through p300/GATA4-dependent regulation.

In addition to its HAT inhibitory actions, curcumin has also been shown to inhibit inflammation-driven cardiac remodeling by inhibiting HDACs.<sup>218</sup> In these studies, curcumin inhibited HDAC1-dependent hypoacetylation at the promoter region of tissue inhibitor of metalloproteinase 1 (TIMP1); this led to increased histone acetylation and subsequent TIMP1 gene expression, as well as attenuation of cardiac fibrosis and inflammation.<sup>218</sup> Consistent with these data, curcumin reduced expression of the TIMP1 inhibitory target, metalloproteinase 2 (MMP2).<sup>218</sup> MMPs contribute to inflammatory signaling,<sup>219</sup> heart remodeling<sup>220</sup> and other diseases detailed within this review.<sup>221,222</sup> Therefore, MMP inhibition may be efficacious in numerous diseased states. In agreement with the data by Hu *et al.*,<sup>218</sup> other reports have shown that curcumin inhibits HDAC activity<sup>223</sup> and protects against inflammaging-associated CVD by regulating TIMP/MMPs.<sup>224</sup> Collectively, these data suggest that curcumin may mitigate pathological molecular imbalances in the heart through several epigenetic modifications, including histone acetylation.

**2.3.5 EGCG and histone acetylation.** Epigallocatechin gallate (EGCG) is a polyphenol found in tea varieties that has been shown to have anti-inflammatory properties. Thus, EGCG is an intriguing therapeutic agent against inflammaging-associated diseases including heart disease. Recent evidence suggests that EGCG can attenuate inflammation by regulating histone acetylation.<sup>225</sup> Specifically, Liu *et al.*<sup>225</sup> showed that EGCG modulated differential binding of p300 and HDACs 1 and 2 at promoter regions of pro-inflammatory genes, including NF-κB subunit p65, which was linked with reversed hyperacetylation and suppressed pro-inflammatory gene expression in stress-induced endothelial cells.<sup>225</sup> Indeed, the pro-

inflammatory activity of NF-κB is, in part, dependent upon p300-, HDAC1- and HDAC2-mediated actions.<sup>15,16</sup> Moreover, endothelial cells are a first line of defense in response to inflammation but will become dysfunctional with over-exposure to inflammation, which can result in fibrogenesis and atherosclerosis.<sup>226,227</sup> This is interesting as EGCG was shown to be efficacious for endothelial dysfunction in patients with coronary artery disease.<sup>228</sup> Therefore, EGCG may prevent inflammation-induced cardiac dysfunction through regulation of histone acetylation at pro-inflammatory gene promoters. In line with this cardioprotective postulate, EGCG reduced acetylation at the promoter region of forkhead box protein O1 (FOXO1) in hyperglycemia-induced cardiomyoblasts.<sup>229</sup> Of particular interest, nuclear FOXO1 acetylation was reduced upon EGCG treatment.<sup>229</sup> This is important because nuclear acetylated FOXO1 induces autophagy in cardiac cells<sup>230,231</sup> and overly active autophagy is linked to cardiac dysmorphology and atherosclerosis.<sup>232</sup> Indeed, EGCG was further shown to block hyperglycemia-induced autophagy in H9C2 heart cells.<sup>229</sup> Finally, EGCG was shown to attenuate age-induced hypoacetylation at the proximal promoter region of cardiac troponin I (cTnI) in aged mice.<sup>233</sup> This is interesting as cTnI is a critical regulator of diastolic function, and EGCG treatment increased cTnI expression and cardiac diastolic function.<sup>233</sup> These data combined suggest EGCG is a natural product that regulates both inflammation homeostasis and cardiac function *via* histone acetylation-dependent mechanisms.

**2.3.6 Anthocyanins and histone acetylation.** Anthocyanins are flavonoids with three phenolic rings and credited for the pigmentation of foods such as berries (e.g., blueberry, raspberry and blackberry), grapes, beans and potatoes. As of late, anthocyanin-rich foods have received attention for their metabolic efficacy in humans<sup>234–236</sup> and have even shown favorable outcomes against fatty liver and inflammation.<sup>237,238</sup> Here, anthocyanins were shown to protect the liver in part *via* changes in histone acetylation. For example, Zhan and colleagues showed that an anthocyanin-rich blueberry extract increased histone H3 acetylation at lysine residues K9, K14 and K18 and reduced liver fibrosis and damage to rats exposed to carbon tetrachloride.<sup>239,240</sup> Acetylation of K9 and K14 was shown to be important for proper liver function; liver dysfunction and fibrosis is increased with aging.<sup>241</sup> Furthermore, histone H3 hyperacetylation results in euchromatin formation and subsequent differential gene expression.<sup>242</sup> These data suggest that anthocyanins improve liver function and block liver fibrosis by regulating gene expression through histone acetylation. In addition to these studies, others have shown that anthocyanins reduce expression of pro-inflammatory transcripts.<sup>243</sup> Unfortunately, Zhan *et al.* did not link anthocyanin-mediated histone acetylation with HDAC or HAT activity.<sup>239,240</sup> However, it should be noted that anthocyanins have been shown to modulate HDAC and HAT activity.<sup>244–246</sup> Intriguingly, H3K9/14 hyperacetylation at transcriptional start sites of TNF $\alpha$  was associated with liver inflammation, a common aggressor of fibrosis, in obesity-induced mice.<sup>247</sup> This was likely due to an increase in HAT activity.<sup>248</sup> Indeed, the hepatoprotective actions of other phytochemicals have been associated with HAT inhibition.<sup>249</sup> As anthocyanins have been shown to concomitantly

reduce HAT activity and pro-inflammatory TNF $\alpha$  signaling outside of liver<sup>244</sup> as well as mitigate pro-inflammatory gene expression and TNF $\alpha$  signaling in liver of aging mice,<sup>243</sup> future research should focus on if anthocyanins block inflammaging-associated liver fibrosis *via* HAT inhibition.

#### 2.4 Phytochemicals – histone acylation and gene expression

To our knowledge, no reports have currently been published examining the role of phytochemicals on histone acylation. A recent report showed that histone crotonylation is increased at transcriptional start sites of neuroglial cell-mediated endocytosis-related genes in a progressive AD cell model.<sup>250</sup> As neuroglial cells clear A $\beta$ , these data suggest that histone hypercrotonylation may serve as a compensatory mechanism to stimulate the expression endocytosis-related genes in order to clear A $\beta$  in AD patients; of course further investigation is warranted to address this question. Of interest, the HAT, p300/CBP regulates crotonyl-CoA-dependent histone crotonylation.<sup>251</sup> Within this report, we described curcumin as a HAT and HDAC inhibitor.<sup>209–211,218</sup> As curcumin has been shown to block inflammation and A $\beta$ -dependent neurodegeneration,<sup>252</sup> curcumin may mediate its neuroprotective effects by regulating histone crotonylation. However, further study is imperative to elucidate how phytochemicals, in particular curcumin, regulate histone acylation and if these actions are efficacious for inflammaging, neurodegeneration and other age-associated diseases.

### 3. Short chain fatty acids (SCFAs) and aging-associated inflammation

Short chain fatty acids (SCFAs) are carboxyl group (COOH) containing chains of 2–6 carbon atoms. SCFAs can be saturated or unsaturated and have a variety of side chain structures. Nomenclature for the SCFA and its corresponding ester/salt are frequently used interchangeably, and will be here, as at physiological pH, the SCFA carboxyl hydrogen is typically lost to form the associated ester. For instance, butyric acid rapidly becomes butyrate in most biological conditions. A number of molecular mechanisms engaged by SCFAs have been described in the literature. These include regulating signaling cascades *via* interaction with G-protein coupled receptors, modulating the activity of epigenetic modifying enzymes, serving as molecular substrates for metabolism, and serving as molecules used in protein post translational modification.

SCFAs are produced endogenously in mammalian systems when cellular glucose levels are low. This can occur in fasting, diabetes, and with some low carbohydrate diets. As oxaloacetate is diverted for gluconeogenesis, the TCA cycle slows and excess acetyl-CoA is processed into 4-carbon SCFA ketones. SCFAs are also produced by a variety of microbes, including in the digestive tracts of animals, where they have been shown to influence host physiology.

Interestingly, in humans, specific circulating SCFAs under fasting conditions are negatively correlated with BMI and positively correlated with insulin sensitivity.<sup>253</sup> Experiments in rodents indicate that with age, the ability to produce ketones in

fasting conditions is diminished or slowed<sup>254</sup> and importantly, a 220 subject human study showed that serum concentrations of total free fatty acid and hydroxybutyrate (unfasted) were decreased with age.<sup>255</sup> These point toward a negative correlation between SCFA concentrations and conditions associated with inflammation, specifically advanced age and obesity/diabetes.

#### 3.1 SCFAs – histone acetylation and gene expression

It has long been known that valproate (C:8 medium chain fatty acid sometimes classified as a branched SCFA) and butyrate function as HDAC inhibitors. In 2012, it was shown that beta-hydroxy butyrate ( $\beta$ -OHB), a SCFA generated by ketogenic diet or caloric restriction/fasting, could inhibit HDAC activity and decrease inflammation, specifically in the kidney.<sup>256</sup> Given that acetylation at specific lysine residues on histone and non-histone proteins is diminished with age,<sup>257–259</sup> acetylation regulating effects of pro-longevity strategies, including SCFA generation from diet manipulation, have become a growing area of research interest. However, a recent report demonstrates that butyrate has a much more dramatic effect on histone acetylation than does  $\beta$ -OHB. In fact  $\beta$ -OHB showed no effect on histone acetylation and increased inflammatory gene expression in cultured endothelial cells.<sup>260</sup> One potential explanation for this discrepancy might be found in regulation of SCFA induced histone modifications by pre-existing modifications,<sup>261</sup> which are likely cell type and culture condition specific.

Ketogenic diet, caloric restriction and intermittent fasting have all been shown to improve recovery in rodents following acute spinal cord injury.<sup>262–265</sup> In each model, the concentration of  $\beta$ -OHB was elevated in the plasma and spinal fluid. These diet manipulations corresponded with increased histone acetylation and oxidative stress resistance factor expression (e.g. Foxo3a, Mt2, catalase, mnSOD), while reducing HDAC activity and lipid peroxidation enzyme expression.  $\beta$ -OHB has been repeatedly shown to increase production of another neuroprotective molecule, brain derived neurotrophic factor (BDNF). It was recently demonstrated that  $\beta$ -OHB induced cAMP/PKA dependent phosphorylation of CREB and activation of the BDNF promoter to increase BDNF expression in hippocampal neurons.<sup>266</sup>

In addition to the common pattern of anti-ROS gene expression seen with SCFA generating diets or direct treatment with SCFAs, these strategies also drive calbindin expression in the brain. This is potentially beneficial *via* buffering of calcium influx, which occurs following exposure to inflammatory cytokines, and excitatory neurotransmitters.<sup>267</sup> There is also evidence that DNA damage repair is governed by histone acetylation and stimulated with HDAC inhibition.<sup>268</sup>  $\beta$ -OHB also demonstrates neuroprotective properties *via* inhibition of the NLRP3 inflammasome.<sup>269</sup> These data sum to indicate that SCFAs are potently anti-inflammatory, including in the brain, through a variety of mechanisms including HDAC/histone acetylation mediated regulation of gene expression.

#### 3.2 SCFAs – histone acylation and gene expression

SCFAs are also used in the production of acyl-CoA molecules important for protein post-translational modifications. Many

short, medium, and even long chain fatty acids have been identified *via* mass spectrometry as modifications on histone and non-histone proteins. Crotonylation of histone lysine residues appears to impact gene expression in a similar manner as does histone lysine acetylation.<sup>270</sup> However, the magnitude of gene expression changes seen in response to histone crotonylation appears to be larger than that for histone acetylation at the select gene loci that have been studied.<sup>251</sup> It is unclear if this pattern will be conserved when chromatin wide studies are conducted. Crotonate is a larger molecule than acetate, with crotonate having two additional carbon atoms, and crotonate also possesses a double bond between the second and third carbon atoms, that is predicted to provide a more rigid structure. This limiting of three dimensional movement of crotonyl-lysine may stabilize protein-protein interactions relative to acetyl-lysine. Surprisingly, class I HDACs can catalyze removal of both acetyl and crotonyl modifications and similarly, P300 can catalyze addition of both to protein lysine residues.<sup>251,271</sup> Several metabolic pathways have been pointed to as potential sources of crotonyl-CoA, including ketogenesis.<sup>272</sup>

Recently, it was shown that  $\beta$ -OHB, once bound to coA, serves as a P300 catalyzed post translational modification. Remarkably, P300 selectively adds hydroxybutyrate to target proteins that do not overlap with other p300 acetyl target proteins.<sup>273</sup> The addition of hydroxyl butyrate to key lysine residues increased the activity of glycolysis pathway enzymes. Clearly, the field is just beginning to uncover the relevance of these and other less traditionally studied acyl modifications, and their impact on cellular functions.

### 3.3 Caloric restriction, SCFAs and aging-associated inflammation

Caloric restriction (CR) has been shown in a variety of species to prolong lifespan and healthspan.<sup>274,275</sup> Anti-oxidative and anti-inflammatory effects of CR have been well documented by many independent groups in many tissues, including the brain and cardiovascular systems.<sup>276-278</sup> CR is also effective at reducing the risks of diabetes, cardiovascular disease, cancer, and neurodegenerative diseases.<sup>279</sup> These effects are often attributed to CR mediated changes to activity of mTOR, HDACs, and other metabolic enzymes. SCFA generation and SCFA molecular targets may help explain shared anti-aging, anti-inflammatory and disease protective effects of caloric restriction, ketogenic diets, exogenous SCFA supplementation, and mTOR and HDAC inhibition.

SCFAs also bind G-protein coupled receptors (GPCRs), specifically Free Fatty Acid Receptors (FFARs) FFAR2 and FFAR3, and the niacin receptor (HCA2). These receptors were previously orphan receptors and are also known as GPCR43, GPCR41, and GPR109A respectively. HCA2 receptors are found in monocytes, macrophages, T cells, and microglia, among others. Binding of HCA2 by butyrate,  $\beta$ -OHB, and niacin, is potently anti-inflammatory and protective effects have been described in a number of neurological and neurodegenerative disease models.<sup>280</sup> Given a plethora of potential mechanisms engaged by these ligands it was important to show that these

benefits were dependent on the HCA2 receptor as was accomplished in stroke and Parkinson's models.<sup>281-283</sup>  $\beta$ -OHB is an inhibitor of FFAR2 and FFAR3, while other SCFAs (e.g. propionate) can act as activators of the receptors, leading to opposite downstream inflammation regulated effects.<sup>284</sup>

Another potential mechanism for SCFA mediated anti-inflammatory effects is *via* use as metabolic substrates. SCFAs relative to lipids are able to bypass multiple  $\beta$ -oxidation cycles before entry to the TCA cycle, which minimizes oxygen consumption and reactive oxidation generation. This is due to avoidance of increased production of FADH2 relative to NADH + H, which occurs during  $\beta$ -oxidation driven metabolism. FADH2 provides electron motive force to complex II of the ETC, which can lead to reverse electron flow through complex I and generation of reactive oxygen species (ROS). ROS accumulation is positively associated with inflammation.<sup>120</sup> Interestingly, propionate and butyrate, which both increased histone acetylation in cultured eosinophils, blocked eosinophil migration and activation and caused mitochondrial depolarization and apoptosis in eosinophils from donors with allergies but not from control donors.<sup>285</sup> This may suggest altered ETC composition or spatial arrangement in the eosinophils from allergic donors.

It is becoming increasingly apparent that cue dependent expansion or differentiation of T regulatory cells ( $T_{reg}$ ) is critical for limiting post inflammation tissue damage.<sup>286,287</sup> Butyrate has been shown to induce expansion of  $T_{reg}$  cells through inhibition of HDAC8 and was beneficial in a model of rheumatoid arthritis.<sup>288</sup> In support of this notion, work from colon cancer cells suggests potential synergy between SCFAs and aryl hydrocarbon receptor (Ahr) activation.<sup>289</sup> Ahr activation is known in other contexts to be anti-inflammatory *via* triggered expansion of  $T_{reg}$  populations.<sup>290,291</sup>

Several other neurologic conditions are also associated with neuro-inflammation. Here also SCFAs or SCFA generating dietary approaches appear to provide benefit. Butyrate, B-OHB, and other SCFA combinations been shown to have anti-depressant and anti-anxiety effects,<sup>292-294</sup> while valproate has proven effective in treating bipolar depression and PTSD.<sup>295,296</sup> HDAC inhibition and exogenous ketone supplementation have also been shown to prevent protein accumulation and memory impairment in mouse models of dementia/AD.<sup>199,297-299</sup> Similarly, a ketogenic diet was shown to increase lifespan and improve memory in aged mice. Again, this corresponded with decreased mTOR activity, increased lysine acetylation and increased antioxidant gene expression.<sup>300</sup>

### 3.4 Pro- and prebiotics, SCFAs and gut-brain axis

SCFAs are synthesized by gut-specific microbiota and have been shown to play a critical role in the gut-brain axis as described above.<sup>301</sup> The gut-brain axis is an intricate communication network between the central nervous system (CNS) in the brain, the autonomic nervous system (ANS), the enteric nervous system (ENS) in the gut and the hypothalamic pituitary adrenal (HPA) axis, within which gut microbiota modulate inflammatory, metabolic and neurological signaling.<sup>301</sup> Indeed, dysbiosis,

an imbalance in microbiota that synthesize SCFAs and promotes pathogenesis, is observed with aging and has been implicated in age-associated diseases including metabolic dysfunction,<sup>302,303</sup> neurological disorders<sup>304</sup> and CVD.<sup>305</sup> Moreover, aging-linked dysbiosis has been shown to increase the pro-inflammatory systemic environment,<sup>306</sup> which may further drive neuro-inflammation and neurodegeneration. While the anti-pathogenic effects of the microbiota are still being elucidated, it has been postulated that the protective effects of gut bacteria are imparted through epigenetic modifications.<sup>307</sup> Consistent with this, dysbiosis is associated with reduced bioavailability of epigenetic modifying SCFAs (see above for SCFAs and histone modification).<sup>308</sup> These data, thus, suggest that creating a balanced microbiota, eubiosis, would deter chronic, low-grade inflammation and its co-morbidities, in part, through epigenetic changes in gene expression. To this end, prebiotics and probiotics have been used to re-establish eubiosis in the gut.

**3.4.1 Prebiotics, SCFAs and aging-linked disease.** Prebiotics are natural products that provide substrates for gut microbiota fermentation; for example, *Bifidobacterium* and *Lactobacillus* produce SCFAs through prebiotic fermentation. Thus, prebiotic bacterial fermentation to SCFAs can promote histone acetylation *via* HDAC inhibition contributing to differential gene expression that imparts neuro-protection.<sup>309-311</sup> Indeed, a recent report linked increased colonic butyric acid, a SCFA HDAC inhibitor, with transcriptome-wide changes in gene expression in aged rats fed the prebiotic fructo-oligosaccharide.<sup>312</sup> Of significance, fructo-oligosaccharide supplementation regulated genes associated with immune function in aged rats, improved cecum pH as well as promoted healthy bacterial growth by increasing the numbers of *Bifidobacterium* and *Lactobacillus*.<sup>312</sup> Colonic pH is critical for the growth of *Bifidobacterium* and *Lactobacillus*, which mainly ferment carbohydrate or prebiotics and thus increase SCFA synthesis.<sup>313</sup> As this study only looked at 12 week prebiotic supplementation,<sup>312</sup> it is unclear if constant prebiotic consumption is required for preventing age-associated dysbiosis long-term. In addition, the researchers in this study did not examine changes in histone modifications linked to SCFAs such as HDAC inhibition or histone hyperacetylation; this makes it difficult to associate the observed differential gene expression with any one epigenetic mark.<sup>312</sup>

In contrast to above, prebiotic supplementation with galacto-oligosaccharide was shown to inhibit HDAC activity in the brains of obese rats;<sup>309</sup> this was linked to increased *Bifidobacterium* microbiota and increased SCFAs that led to improved cognitive function and reduced neuro-inflammation.<sup>314-316</sup> Further studies have reported that prebiotic supplementation contributed to gut eubiosis and subsequently improved cognitive impairment,<sup>317</sup> metabolic function<sup>318</sup> and gut inflammation.<sup>318</sup> Combined, these data suggest that prebiotics confer gut eubiosis that contributes to SCFA synthesis; this subsequently results in HDAC inhibition, changes in histone modifications (e.g., acetylation/acylation) and anti-inflammaging actions in the gut-brain axis. Interestingly, prebiotics have also been suggested to regulate the epigenome independent of SCFA synthesis.<sup>309</sup> For example, while galacto-oligosaccharide

treatment increased the SCFA, acetate, in plasma and inhibited HDAC activity in cortex/hippocampus brain regions, lone acetate treatment was shown to have no such effect in the brain.<sup>309</sup> It may have been other SCFAs that galacto-oligosaccharide synthesized to attenuate neurological HDAC activity, however, no other plasma SCFAs were reported. Given these recent findings, further investigation is needed to elucidate the chromatin remodeling and transcriptomic effects of prebiotics that do not involve butyrate, acetate or propionate.

**3.4.2 Probiotics, SCFAs and inflamaging.** While prebiotics “feed” the gut microbiota, probiotics are living microorganisms that promote microbial growth and deter competing bacterial invasion,<sup>319</sup> thus allowing improved production of SCFAs. Indeed, *Bifidobacterium* supplementation improved microbiota composition in geriatric individuals.<sup>320</sup> Probiotics further promote intestinal barrier function and anti-inflammatory actions.<sup>321</sup> These actions appear, in part, to be epigenetically controlled. For example, *Bifidobacterium* or *Lactobacillus* reduced histone acetylation and increased DNA methylation in LPS-induced epithelial cells.<sup>322</sup> These epigenetic modifications were linked to reduced pro-inflammatory cytokine expression as well as nuclear NF- $\kappa$ B and MAPK signaling.<sup>322</sup> As described throughout this manuscript, NF- $\kappa$ B and MAPK signaling are partially regulated by epigenetic enzymes.<sup>18,323,324</sup> In agreement with these data, histone hypoacetylation and DNA hypermethylation have been associated with gene suppression, suggesting that *Bifidobacterium* or *Lactobacillus* suppress pro-inflammatory genes.<sup>322</sup> Moreover, global histone hyperacetylation and DNA hypomethylation were reversed in *E. coli*-spiked epithelial cells when pre-, co- and post-treated with *Lactobacilli* probiotics.<sup>325</sup> These data suggest probiotic treatment can both prevent and reverse pathological microbiota-mediated epigenetic alterations that are associated with gut and systemic inflammation.

Finally, probiotic treatment has also been shown to attenuate CVD. Here, probiotic treatment reduced myocardial infarct size and pro-inflammatory cytokines TNF $\alpha$  and IL-6 as well as the chemokine monocyte chemoattractant protein-1 (MCP-1) in a mouse model of CVD.<sup>326</sup> In this model, probiotic treatment contributed to T regulatory cell histone hyperacetylation and thus anti-inflammatory function, whereas T regulatory cell depletion attenuated the protective effects of probiotic treatment.<sup>326</sup> T regulatory cells are regulated by the forkhead box P3 (FOXP3), and their acetylation status is critical for immunosuppression during the inflammatory response.<sup>327</sup> Combined, these data suggest that probiotic supplementation increased T regulatory cell hyperacetylation and thus anti-inflammatory function critical for cardioprotection in this model of CVD. Others have reported that probiotic supplementation blocked matrix metalloproteinase-2 (MMP-2) activity and cardiac fibrosis in a mouse model of dysbiosis-induced CVD.<sup>328</sup> While no epigenetic modifications such as histone hyperacetylation were assessed, fecal levels of the SCFA acetate were increased in dysbiotic mice supplemented with probiotics.<sup>328</sup> Acetate is a predominant SCFA in both the gut and systemic circulation that can inhibit HDAC activity<sup>329,330</sup> as well as promote HAT activity.<sup>331</sup> As MMP-2 activity seems to be dependent upon its

acetylation status,<sup>332</sup> this suggests that probiotic treatment regulated acetate-mediated MMP-2 inhibition *via* histone-acetylation-dependent mechanisms.<sup>328</sup> Further investigation is still required to fully elucidate the mechanisms by which probiotics regulate MMP-2 activity and if these mechanisms are, in fact, epigenetically related. However, these and the above data suggest that probiotics can regulate histone modifications and thus play a key role in the regulation of aging, inflammation, neurodegeneration and CVD.

## 4. Conclusion

While the effects of individual products are often examined in a lone experimental environment, phytochemicals and fiber-produced SCFAs are frequently consumed together. Notably, a majority of fiber-rich foods are abundant in several phytochemicals. This brings to question, in what ways do phytochemicals interact with other phytochemicals or SCFAs? Few studies have examined the phytochemical-phytochemical or phytochemical-SCFA interactions, and whether these interactions are competitive, synergistic or compounding in their epigenetic actions. In one report that used colon cancer cells, EGCG and butyrate in combination reduced HDAC activity as well as CpG methylation and were more anti-oncogenic than their individual treatments.<sup>333</sup> While others have also reported the potential for using phytochemical-SCFA combinations in cancer models,<sup>334</sup> no mechanistic study, to our knowledge, has examined it in other inflammaging-associated diseases that were discussed in this review. However, several epigenome-wide association studies (EWAS) have reported that differential methylation of inflammatory and metabolic genes were associated with diets rich in phytochemicals and fiber in peripheral white blood cells isolated from geriatric individuals.<sup>335-337</sup> One EWAS inversely correlated dietary fiber-intake with methylation of lysophosphatidylcholine acyltransferase 1 (LPCAT1) and Ras GTPase-activating protein 3 (RASA3) genes in young African Americans.<sup>338</sup> Furthermore, LPCAT1 methylation was positively associated with visceral adiposity and increased inflammation in the blood.<sup>338</sup> This is important because LPCAT1 mitigates pro-inflammatory signaling cascades associated with metabolic dysfunction<sup>339</sup> and may be regulated by diet-driven epigenetic modifications like DNA methylation. Conversely, another report associated fiber and fruit intake with TNF $\alpha$  hypomethylation in isolated human white blood cells.<sup>340</sup> EWAS studies are often limited to DNA methylation due to many variables including costs of sequencing technologies such as chromatin immunoprecipitation sequencing (ChIP-seq) *vs.* bisulfite sequencing. It should be further noted that epidemiology-based studies like ones described above infer association but not causation. Therefore, future study is required to fully elucidate the epigenomic roles of diet-derived products in regulating inflammation and inflammaging-associated events.

Another consideration is that absorption, distribution, metabolism and excretion of natural products vary.<sup>341,342</sup> This suggests the interaction between compounds that are distributed to the same location and at the same time may only be of interest. Even still, compounds can affect tissues to which they

are not distributed; for example, emodin is not distributed to the heart in considerable amounts<sup>341</sup> yet has been shown to be cardioprotective *in vivo*.<sup>203</sup> Therefore, the metabolites of parent compounds, which enter circulation may be responsible for efficacious actions observed in tissues that have unmeasurable concentrations of their parent compounds. However, a majority of phytochemical metabolites are rendered bio-unavailable upon synthesis.<sup>342,343</sup> While “more is better” comes to mind towards addressing bio-unavailability issues, phytochemicals are also toxic at higher concentrations.<sup>141,344,345</sup> Technologies aimed at increasing bioavailability of natural products at lower concentrations may resolve these dilemmas.<sup>346</sup> Alternatively, cells of the immune system that travel through regions of high compound concentration (*e.g.* mucosa/submucosa of the intestine), may broadcast anti-inflammatory signals as they return to lymph or general circulation, or by secreted signals. Adding further complexity to this diet-epigenome discussion, animal-based foods further contain epigenetic modifying compounds, namely micro RNAs (miRNAs), that may influence health and disease upon consumption.<sup>347</sup> Animal-based compounds may also interact with phytochemicals and/or SCFAs that could alter cellular outcomes, for better or for worse. These are purely speculative but reflect how little is understood about whole food-gene and natural product-gene regulation of health and disease. Nevertheless, researchers and clinicians alike are hopeful that future studies will begin to provide evidence for which foods or natural products are best for optimizing health and deterring inflammaging-associated metabolic dysregulation, neurodegenerative diseases and CVD.

Finally, evidence suggests that dietary interventions may compliment pharmaceutical treatment in ameliorating pathologies, and that the therapeutic actions may be epigenetically-related. For example, vorinostat (SAHA), which is an FDA-approved HDAC inhibitor used for cancer, in combination with curcumin proved more efficacious than their lone treatments for A $\beta$ -dependent neurodegeneration.<sup>252</sup> Moreover, co-treatment of these compounds resulted in differential gene expression,<sup>252</sup> thus hinting that epigenetic-mediated actions were at play. In other studies, using high-fat diet-induced diabetic mice, the anti-diabetic drug, metformin in combination with resveratrol ameliorated inflammation, glucose intolerance and other metabolic insults.<sup>348,349</sup> However, in neither study were DNA methylation or histone modifications reported. Further investigation for common medicine-natural product co-therapies are, therefore, warranted.

In conclusion, there is strong evidence supporting the postulate that foods and natural products influence health and disease through epigenetic modification. While caloric and macronutrient composition govern cofactors involved in non-sequence alterations on DNA and histone proteins, more and more studies suggest (*by*)product composition in food is also important. This report described how phytochemicals and SCFAs regulate DNA methylation and histone modifications (methylation, acetylation and acylation) in experimental models of age-associated diseases. Moreover, observational data has consistently associated foods rich in phytochemicals and SCFA-producing fiber with health and longevity. Nevertheless, few

studies have translated the epigenetic-mediated actions of these food derivatives to human models.

## 5. Conflicts of interest

The authors declare no conflicts of interest.

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