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Review Article

The Epigenetic Impact of Vegetables-Derived Dietary Compounds in Neurodegenerative Conditions: A Review

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ABSTRACT

Dietary compounds from the foods we eat on a daily basis offer several benefits; in particular, they help prevent disease and preserve health. The epigenetic advantages of the vegetables we eat every day are one of the benefits that have not been well-reported. Epigenetic pathways involving histone modification, DNA methylation, and alterations caused by miRNAs, which are extensively engaged in signal transmission, cell development, and death in various disease states, including brain cells. This narrative review is written based on multiple studies available on reputable online databases until March 2022 on the epigenetic advantages of various vegetables' content, such as gallic acid, quercetin, kaempferol, apigenin, luteolin, resveratrol, genistein, sulforaphane, and diallyl disulfide in neurodegenerative conditions. However, in-depth investigations are still required to clarify these epigenetic mechanisms before these compounds are ready for further use in the future, since several studies still provide contradictory results.

INTRODUCTION

Age-related problems continue to raise the community's demand for strategies to prevent, delay, and overcome disabilities (Sarubbo *et al*., 2017). Cells in the human body respond to various signals. The presence of nutrients affects complex signaling pathways, leading to chromatin formation to express multiple genes that are frequently reported to be involved in the aging process (Rangaraju *et al*., 2015). Dietary compounds from everyday food have been shown to have numerous benefits. The bioactive content of nutrients and non-nutrient phytochemicals like polyphenols, carotenoids, glucosinolates, and sulfur from various fruits and vegetables has been reported as epigenome regulators (Molina-Serrano *et al*., 2019). They can either directly inhibit epigenetic enzymes activities like DNA methyltransferase (DNMT), histone deacetylase (HDAC), or histone acetyltransferase (HAT), or can directly alter the substrate availability, and thus affecting enzymatic reactions. This, in turn, alters the expression of critical genes, thereby affecting our overall health and longevity (Choi and Friso, 2010). Among such substances are vegetables-derived secondary metabolites that are only found in certain plants, including garlic (*Allium sativum* L.), onion (*Allium cepa* L.), lettuce (*Lactuca sativa* L.), broccoli (*Brassica olereacea* var. italica), and carrot (*Daucus carota* L.) (Soto *et al*., 2021), which have been adequately investigated as beneficial in treating some age-related diseases, such as cancer, diabetes, and neurodegenerative disease. Several studies have also reported these compounds to influence epigenetic mechanisms, which affect the expression of targeted genes without any changes in DNA sequence (Mastroeni *et al*., 2011). Although there has been much discussion

about the epigenetic mechanisms that influence aging and neurodegenerative disease, there are only few studies that focus solely on the benefits of secondary metabolites from the daily diet, particularly vegetables. As a result, this review aims to give a brief summary of various vegetable-derived dietary compounds' effects on epigenetic mechanisms in neurodegenerative conditions.

METHODS

This literature review focuses on the phytochemical contents of several vegetables listed in the form of secondary metabolites and aims to introduce their efficacy in epigenetic modulation, especially in neurodegenerative conditions. This narrative review provides insights and potential for further research of vegetables as several therapeutic agents such as cancer, neurodegenerative disease, or any other disease involving epigenetic modification. The articles were obtained from reputable online databases, such as PubMed, Scopus, and Google Scholar based on filtering process using some keywords including "*Secondary Metabolites*" AND "*Epigenetic*" AND "*Modulation*" AND "*Neurodegenerative Disease*." All primary researches had to meet inclusion criteria, such as being published by March 2022. Other references were retrieved from the government's official website.

RESULTS

Epigenetic Mechanisms in Neurodegenerative Conditions

Neurodegenerative diseases are still one of the global burdens of disease. One of them is Alzheimer's disease, which involves progressive decline in cognitive function. Diet, age, and epigenetic environment have been widely pointed as the main culprit of the disease. The term epigenetics is used in studies of the alteration in various genes that are characterized by little to no meaningful changes in the DNA sequence (Mastroeni *et al*., 2011). DNA and RNA methylation, histone post-translational modification, and microRNA (miRNAs) are epigenetic changes involved in neurodegenerative conditions and cancer (Shukla *et al*., 2014). This is then supported by the involvement of neurogenesis genes' hypermethylation, histone deacetylation, and miRNA dysfunction that lead to the decline of NSC formation in Alzheimer's disease (Kohyama *et al*., 2008; Li *et al*., 2016). Another study by Desplats *et al*. (2011) revealed an association between hypomethylation in Parkinson's disease (PD) dementia patients with Lewy bodies (DLB).

DNA Methylation

DNA methylation, which has different types of expressions based on the area it presents, is a necessary process that determines learning and memory through modulation of gene expression important in neuronal growth and survival. DNA methylation involves the formation of 5-methylcytosine (5mC) from methyl group addition to the cytosine nucleotide CpG (5'-Cytosine-phosphate-guanosine-3') or the modification of 5mC to 5hmC with the addition of a hydroxymethyl group with the help of Ten-Eleven Translocation (TET) proteins. This methyl group addition is assisted by DNA methyltransferase (DNMT), divided into three families, namely DNMT1, DNMT2, and DNMT3. This process is deemed essential in gene regulation, since DNMT1 is a methylation marker, while DNMT3a and 3b methyltransferases regulate *de novo* methylation of fully unmethylated DNA (Martínez-Iglesias *et al*., 2020). Recent animal studies have revealed a significant decrease of *Dnmt3a* in the hippocampus and cortex of aged mice (Oliveira *et al*., 2012; Sezgin and Dincer, 2014). Another study proposed that *Dnmt*1 levels also decreased in post-mortem samples of patients with PD/DLB, which was then associated with an increase in α-syn due to *Dnmt*1 retention in the cytoplasmic region. This mislocalization causes a raise of global DNA hypomethylation up to 30% (Desplats *et al*., 2011). In addition, in post-mortem brain samples of cases with AD, reduced DNA methylation (5-mC) and DNA hydroxymethylation (5-hmC) in CA1 neurons and CA3 glial cells were also present. Levels of 5-mC and 5-hmC were also inversely related to hippocampal amyloid plaque formation and neurofibrillary tangles (Chouliaras *et al*., 2013).

Histone Modification

Histone modification and chromatin remodeling have been involved in several pathological conditions like cancer and neurodegenerative diseases. This process involves the complex structure of chromatin, namely DNA, histones, and several DNA-binding proteins. The most widely studied histone modifications are histone acetylation and deacetylation.

Table 1. Secondary metabolites activities in neurodegenerative conditions

Phytochemical Group	Phytochemical compound	Vegetable sources	Epigenetic modulation	Targets	Biological Effects	Reference
Flavonoids	*Flavones* Luteolin Apigenin Genistein	Celery, parsley, and spinach. Lupin, soybean, kudzu and psoralea.	Inhibited HAT Inhibited acetylation of H3 and H4 Increased levels of *miR-132* and *miR-212*	*Sox1, Oct4* AChE, GPR30, CREB	Inhibition of embryoid body formation. Enhanced cholinergic function in brain.	Swaminathan *et al.*, 2019 Liu *et al.*, 2018
	Flavonols Quercetin Kaempferol	Onions, asparagus, red leaf lettuce, broccoli, curly peppers, spinach, and turnips.	Inhibits HDAC2 Activate HAT	ERK/CREB, *Bdnf, Syp, Psd-95* MMP-3, NF-κB p65	Prevented cognitive decline. Neuroprotectant in postmenopausal condition. Microglia activation inhibition. Suppression of inflammatory cytokines.	Aggarwal *et al.*, 2020 Li *et al.*, 2019
Phenolic Acids	*Hydroxybenzoic Acid* Gallic acid	Gallnuts, sumac, witch hazel, tea leaves, oak bark.	Inhibits HAT mediated NF-κB activation	COX2, iNOS, IL-6, IL-1β, TNF-α, *Map2*	Proinflammatory cytokines protection, enhanced neuroprotective effect. Elevated neuronal differentiation.	Kim *et al.*, 2011 Maya *et al.*, 2018
Stilbenes	Resveratrol	Grape, peanuts, pistachios	Upregulated *miR-663* to reduce *miR-155* Reduced *miR-124* and *mir-134* levels	BDNF	Improved memory formation and synaptic plasticity.	Zhao *et al.*, 2013
Sulfur-containing compounds	Sulforaphane isothiocyanate Diallyl disulfides (DADS)	Broccoli, cabbage, watercress and brussels sprouts. Onion.	Inhibits HDAC2 Increased H3 and H4 acetylation	BDNF, p-CREB, p-ERK BDNF, MAP2, PSD-5	Increased neuronal survival through neuronal molecule.	Kim *et al.*, 2017 Zhao *et al.*, 2018

Decrease of histone-DNA interactions due to acetyl groups transfer from acetyl-coenzyme A to lysine by histone acetyltransferases (HAT) generates an open chromatin condition causing a series of changes in gene regulation and protein expression. Types of HAT, namely: GCN5 N-acetyltransferase (GNAT), the MOZ/YBF2/SAS2/TIP60 (MYST), and the p300/CBP families (Shukla *et al.*, 2014). Meanwhile, histone deacetylase (HDAC) works the other way around by triggering hypoacetylation. Creating a compressed chromatin structure leads to inhibition of transcription factor interaction to DNA (de Ruijter *et al.*, 2003; Vahid *et al.*, 2015). A study revealed that in Alzheimer's disease, high levels of HDAC2 cause synaptic dysfunction. This is due to the fact that an elevated level of HDAC2

inhibits transcription of synaptic genes like tyrosine kinase c-Abl (Gonzalez-Zuñiga *et al*., 2014). Neuroinflammation and memory impairment were observed in C57BL/6 mice induced by LPS, showing an increased level of HDAC2 in dorsal hippocampal CaMKII^{+} neurons, which resulted in decreased levels of histone acetylation and downstream neurogenic genes such as *Bdnf* and *c-fos* (Sun *et al*., 2019). HDAC inhibitors or structure-alike compounds have been reported to facilitate the repressor complex of DNMT-containing interneurons, resulting in DNA demethylation and histone acetylation, which activate transcription factors at the promoter (Yuniarti *et al*., 2018).

MicroRNAs

MicroRNAs (miRNAs) are regulators of gene expression consisting of 22-nucleotide small non-coding RNA which work in the post-transcriptional region. It works by inhibiting transcription factors and DNA sequence binding, leading to target genes inhibition. Under AD conditions, miRNA upregulation is a marker. For example, loss of miR-137, 181c, and 9 increases the risk of AD in the presence of increased expression of Aβ (Geekiyanage and Chan, 2011). Meanwhile, in senescence-accelerated mice (SAMP8), downregulation of miR-195 and miR-16 is associated with AD development (Liu *et al*., 2012). Likewise, overexpression of miR-132 and miR-212 levels reportedly decreased in CA1 hippocampal neurons isolated from the AD brain (Wong *et al*., 2013).

Phytochemical Compounds of Vegetables and Its Epigenetic Modulation Effects on Neurodegenerative Diseases

Findings based on the research literature are summarized in Table 1, and the details are discussed below.

Flavonoids

Flavonoids are one of the secondary metabolites of plants with pharmacological benefits such as antioxidants, anti-diabetes, and other chronic diseases. Although the flavonoid content may vary depending on where it is grown, as demonstrated by Januarti *et al*. (2020) study that measured the correlation between the flavonoid and total phenolic content of garlic (*Allium sativum* var. solo), its antioxidant activity is directly proportional to its total content. Flavonoids belong to the class of polyphenols with the main structure of 15-carbon (C6-C3-C6) and two benzene rings linked by three carbon chains (Carlos-Reyes *et al*., 2019; Panche *et al*., 2016). Flavonoids have favorable properties in the brain, such as neuroprotection against neurotoxic stress, memory, learning, and cognitive processes (Liu *et al*., 2018). They have been widely studied as cancer therapy and neurodegenerative diseases, including AD. The content of flavonoids commonly found in vegetables can be divided into several groups: flavonols such as quercetin, kaempferol, myricetin, and isorhamnetin. These are found in onions, red lettuce, asparagus, broccoli, curly peppers, spinach, and turnips. Flavones apigenin and luteolin are found in celery, parsley, and spinach. Flavon-3-ols, such as catechins, epicatechins, theaflavins, and thearubigins, are found in onions (Harnly *et al*., 2006; Li *et al*., 2013; USDA (United States Department of Agriculture), 2015).

Flavones

Apigenin and Luteolin

The flavone luteolin exhibited inhibition of early neuronal differentiation in embryonic stem cells as demonstrated in Figure 1 via the inhibition of lysine acetyltransferase p300, which was then supported by fewer mitotic cells in the zebrafish model. Meanwhile, apigenin did not decrease germline marker *Sox1* expression. Histone acetylation inhibition caused by luteolin is directly related to embryonic mortality and poor neural tube development. This impact, however, did not exist in other germlines (Swaminathan *et al*., 2019). In contrast, apigenin improved motor behavior parameters, cognitive function, and spontaneous locomotion D-galactose subcutaneously induced mice (150 mg/kg body weight with eight week-administration). This was due to Keap1-Nrf2 system activation, which promoted the expression of the detoxifying enzymes HO-1 and NQO-1 via Nrf2 nuclear translocation. Aging biomarkers such as Saβ-gal were also reduced, implying that apigenin reversed D-galactose-induced aging (Sang *et al*., 2017).

Genistein

Genistein (4′,5,7-trihydroxyisoflavone), an isoflavone phytoestrogen primarily found in soy products, played a role in post-translational histone changes regarding its high permeability across the blood-brain-barrier (BBB). In mouse astrocytes, genistein could boost the secretion and synthesis of neurotrophic factors, such as BDNF and GDNF (Xu *et al*., 2013). In PC-12 culture, administration of genistein increased neurofilaments by increasing the interaction of cyclic AMP responding element (CRE) with cAMP

response element-binding protein (CREB), leading to increased levels of miR-132 and miR-212. This indicates an increase in neuronal differentiation (Liu *et al*., 2018). Genistein also reportedly alleviated pathological conditions in AD by inhibiting Beta-site APP cleaving enzyme 1 (BACE1) that aided Aβ secretion (Youn *et al*., 2018) and bound directly to the $A\beta_{25-35}$ fragment to reduce its accumulation (Hirohata *et al*., 2012).

Flavonols

Quercetin

Quercetin (3,5,7,3′,4′-pentahydroxyflavone) is a flavonol group from the flavonoid class (Aggarwal *et al*., 2020). It is the major compound in vegetables and fruits, such as onions, red wine, etc. This compound is well-known for its antioxidant, antiapoptotic, and neuro-inflammatory properties (Ishisaka *et al*., 2011) because of its capacity to cross the BBB (Rinwa and Kumar, 2013).

A study in C57BL/6 fed control mice with a quercetin-enriched 2mg/g diet showed that quercetin penetrated the plasma and brain as indicated by an increase of quercetin and isorhamnetin levels after six weeks of administration. However, it was said to not affect AD-related genes (Huebbe *et al*., 2010). Contrary to these results, another study revealed that quercetin reduced paired helical filament (PHF) and β-amyloid (βA) levels by lowering BACE1-mediated cleavage of APP (into CTFβ) on triple transgenic AD mice. Consequently, this improved performance on learning and spatial memory based on the elevated plus maze test (Sabogal-Guáqueta *et al*., 2015). In silico studies with crystal structure analysis of the Sirt6 and Sirt2 complexes, it was reported that quercetin activated Sirt6-dependent deacetylation by binding to the acyl channel Sirt6 (You *et al*., 2019). In addition, supplementation of quercetin given 25 mg/kg body weight in post-ovariectomy female mice was reported to restore HAT/HDAC balance, restore H3 acetylation, and restore neuroplasticity (as measured by neurogenic markers BDNF, SYP, and PSD-95) in the cortex and hippocampus that was disrupted by increased estradiol levels due to ovariectomy (Aggarwal *et al*., 2020). This fact is further presented in Figure 1.

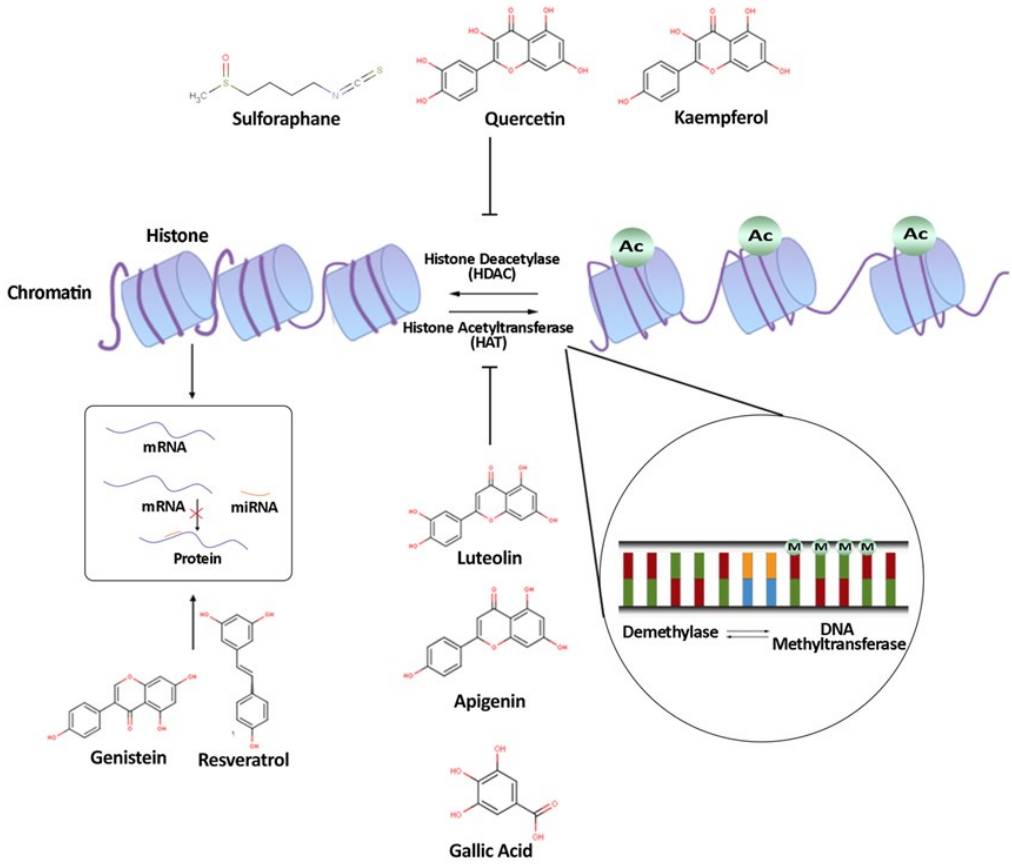

Figure 1. Proposed mechanism of several secondary metabolites in epigenetic activities.

Kaempferol

The flavonoid kaempferol (3,5,7,4-tetrahydroxyflavone) is mainly found in plants and fruits, such as tomatoes, hops, grapefruit, strawberries, and ginkgo biloba extract. It is a naturally occurring polyphenol that has anticancer properties against various types of cancer, including leukemia and colon cancer (Berger *et al*., 2013). In Sprague-Dawley rats, kaempferol of 100 mg/kg body weight administration reduced brain infarct volume and improved neurologic prognosis following ischemia/reperfusion. This was due to the NF-κB pathway suppression by kaempferol following inflammatory cytokines (TNF-α, IL-6, and IL-1β) reduction. Kaempferol also suppressed MMP-3 expression, offering resilience to BBB integrity. (Li *et al*., 2019). Another study has found that kaempferol supplementation protected cells from death via the ERK pathway, elevated the anti-apoptotic molecule Bcl-2, and reduced the pro-apoptotic molecules Bax and caspase-3 in PC-12, in AD in vitro model cells, induced by (Zhang *et al*., 2021).

Phenolic Acids

Hydroxybenzoic acid

Gallic acid (3,4,5-trihydroxy benzoic acid) is a polyphenolic derivative mainly found in gallnuts, sumac, witch hazel, tea leaves, and other plants. It acts as a neuronal cell death inhibitor through lysine residue of NF-κB (RelA) acetylation inhibition that involves HAT enzyme/PCAF. The proposed mechanism is shown in Figure 1. This inhibition led to a reduction of NF-κB acetylation and the production of in vivo cytokines, such as iNOS and COX-2 in the cortex and hippocampus. It was then supported by behavior reversal in mice with cognitive impairment caused by Aβ induction observed from Y-maze and passive avoidance tests after GA administration (Kim *et al*., 2011). In another study, gallic acid extracted from the *Corni fructus* plant protected pheochromocytoma (PC-12) neuronal cells from death by inhibiting intracellular reactive oxygen species (ROS), apoptotic body formation, and caspase-3, a marker of Aβ(25-35) induced apoptosis (Hong *et al*., 2012). This fact was also supported by Maya *et al*. (2018), who reported that the administration of GA 25&50 µg/ml for 2 hours to primary rat cortex neurons (RCNs) induced by glutamate, a neurotoxic agent, resulted in a neuroprotective effect by inhibiting proinflammatory cytokines, maintaining Ca^{2+} balance, and IGF-1 expression.

Stilbenes

Resveratrol

Resveratrol (3,5,4′ -trihydroxystilbene) is a polyphenol primarily found in peanut products with many therapeutic potentials. Its consumption has been linked to several pharmacological activities, and one of which is neuroprotective (Cosín-Tomàs *et al*., 2019). Studies on HSV-1-induced HT22 neuronal culture have shown that resveratrol and quercetin 10 µM exerts a neuroprotective effect by decreasing viral and neurodegenerative markers, such as caspase-3 cleavage of tau protein (TauC3) and tau hyperphosphorylation (p-Tau) via re-activation of AMPK/SIRT1 that are localized in the nucleus and necessary for histone deacetylation (Leyton *et al*., 2015). Resveratrol also upregulates miR-663 to reduce miR-155 levels increased by LPS induction, leading to reduced levels of miR-124, miR-134, and BDNF synthesis, which is modeled in Figure 1 (Zhao *et al*., 2013).

Sulfur-containing Compounds

Sulforaphane

Sulforaphane [1-isothiocyanato-4-(methyl-sulfinyl)] butane is a glucosinolate-isothiocyanate family mainly found in cruciferous vegetables such as broccoli, cabbage, watercress, and brussels sprouts (Dinkova-Kostova and Kostov, 2012). Plants utilize these phytochemicals, which have a distinct odor in harsh environmental conditions, showing beneficial and protective effects (Di Gioia *et al*., 2020). Its cytoprotective benefits were based on an epigenetic modification of the Nrf2 pathway that makes it also epigenetically efficacious against cancer and atherosclerosis (Bai *et al*., 2013; Zhang *et al*., 2013). DNA methylation levels of the Nrf2 promoter were also lowered, leading to an increase of Nrf2 expression levels in cellular model N2a/APPswe cells, making it beneficial in the reduction of $A\beta_{1-40}$ and $A\beta_{1-42}$ synthesis on N2a/APPswe cells by upregulating Nrf2 at low dosage (Zhao *et al*., 2018).

Through a study with a mouse model of Alzheimer's 3x Tg-AD supported by a primary culture of cortical neurons, it was revealed that sulforaphane worked epigenetically by inhibiting HDAC2, increasing histone 3 (H3) and H4 acetylation that is shown in Figure 1, as well as increasing neuronal BDNF expression and neuronal survival as indicated by an increase in neuronal survival through the neuronal molecule and synaptic marker MAP2, synaptophysin and

PSD-5 in both primary cortical neurons and AD mouse model (Kim *et al*., 2017).

Diallyl Disulfides (DADS)

Diallyl disulfide is one of the organosulfur oil-soluble constituents of garlic that has been shown to have in vivo benefits, including attenuating carcinogenesis through modulation of cytochrome P450-dependent monooxygenase, decreasing cell proliferation in G1 and G2/M phases, suppressing apoptosis, modulation of nuclear factor (erythroid-derived 2)-like 2 (Nrf2), phosphoinositide 3-kinase (PI3K) pathway that link onto oncogenes, attenuating antioxidant responsive element, inhibiting histone deacetylase, and so on (Arunkumar *et al*., 2006; Dorrigiv *et al*., 2020). Meanwhile, NPC growth in the dentate gyrus was reduced in DADS-treated C57BL/6 mice. This is related to BDNF downregulation, CREB signaling, and ERKs phosphorylation activities in the hippocampus (Ji *et al*., 2013). DADS (doses of 40 or 80 mg/kg body weight) was also neuroprotective in LPS-induced depression-like behavior in mice compared to the antidepressant imipramine. This was also supported by the reversal of interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and nitric oxide (NO) levels in the hippocampus and prefrontal cortex (Wei *et al*., 2021). However, administration of 20 μM DADS resulted in no significant differences in PC-12 neuronal cells. Still, when the concentration was increased to 50 μM, it was reported that there was an increased risk of cytotoxicity (Koh *et al*., 2005).

CONCLUSIONS

As summarized in Figure 1, the phytochemical content of vegetables works not only molecularly but also epigenetically through various mechanisms. Flavones like luteolin and apigenin primarily affect HAT, whereas quercetin and sulforaphane restore HAT activity while inhibiting HDAC2. Meanwhile, gallic acid and resveratrol have been shown in studies to be more active on microRNA in regulating epigenetic mechanisms in neurodegenerative conditions. These epigenetic changes can be beneficial or detrimental to age-related diseases. As a result, it is necessary to further investigate the vegetables-derived phytochemical compounds' role in increasing appropriate use in age-related diseases. Further investigation is also required to clarify the epigenetic mechanism in-depth, as some compounds produced contradictory results in multiple studies.

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