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A Mechanistic Exploration of Natural Compounds for Neuronal Health

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 Springer

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Natural Compounds as Epigenetic Modulators to Treat Neurodegenerative Disorders

8

Mohammad Rumman and Mohsin Vahid Khan

Abstract

Neurodegenerative disorders largely affect individuals at an advanced age; however, early-onset neurodegenerative diseases have also been reported. Alzheimer's disease (AD) is the most common neurodegenerative disorder that affects millions of people worldwide, along with Huntington's disease, Parkinson's disease (PD), multiple system atrophy, and progressive supranuclear palsy. The etiology and pathological mechanisms of neurodegenerative disorders are diverse; however, dysregulated epigenetic modifications have frequently been observed in these disorders. In AD, DNA methylation is extensively suppressed in the neuronal cells of the affected regions. Similarly, abnormal DNA methylation pattern has been associated with dopaminergic neuron degeneration in PD. Besides, alterations in histone modification patterns have also been reported in the brains of animal models as well individuals with neurodegenerative disorders. Thus, targeting the epigenetic regulators is one of the strategies for managing and treating neurodegenerative diseases. Plant-derived natural compounds hold an immense potential in the field of drug discovery, as these compounds are abundantly available and exhibit minimal to no side effects. The anticancer, anti-diabetic, anti-inflammatory, cardio-protective, hepato-protective, and anti-obesity qualities of these substances have all been thoroughly investigated. Mechanistically, these natural compounds can modulate diverse cellular processes, including transcription, oxidative stress, translation, cellular trafficking, and post-translational modification. A large group of herbal natural compounds are shown to regulate the activity of several epigenetic regulators. By modulating the activity of specific epigenetic regulators, these natural compounds can revert the epigenetic signatures, thereby preventing neurodegenerative disease progres-

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sion. This chapter discusses the possible role of natural compounds as epigenetic modulators in neurodegenerative conditions.

Keywords

Epigenetics · Neurodegeneration · Phytochemicals · Histones · DNA methylation

8.1 Introduction

The goal of the quickly expanding field of epigenetics research is to comprehend how structural variations in nucleotide bases and related proteins, independent of DNA sequence, control gene expression. Traditionally, it was believed that the genetic code that makes us who we are is fixed and unchangeable. However, epigenetics has shown that our genes are not always set in stone and can be affected by external factors, most importantly the environment (Weinhold 2006; Allis and Jenuwein 2016). Whereas genetic changes are irreversible, studies have shown that epigenetic changes are generally reversible. Gene expression can be greatly impacted by epigenetics, which may contribute to the onset of illnesses or have an effect on our physical and mental health (Moosavi and Motevalizadeh Ardekani 2016; Fuggle et al. 2022). Chemical changes to the nitrogenous bases found in DNA, known as histones, are one of the main processes behind epigenetic regulation of gene expression. These modifications can either activate or suppress gene expression, ultimately determining which proteins are produced in our cells. Epigenetic regulation is essential for the proper functioning of our cells, and alterations in epigenetics mechanisms have been observed in several pathological conditions, including cardiovascular diseases, cancer, neurodegenerative diseases, and inflammation, suggesting its potential role in the onset and progression of diseases (Farsetti et al. 2023; Mazzone et al. 2019; Moosavi and Motevalizadeh Ardekani 2016). Environmental influences on our genes have also been clarified by epigenetics. Research indicates that environmental factors, including stress, diet, and exposure to toxins, can result in epigenetic modifications that can be inherited by subsequent generations. This process is known as trans-generational epigenetic inheritance and has been observed in animals and humans. For instance, research has demonstrated that feeding pregnant mice a high-fat diet can alter the offspring's epigenetic makeup, raising the risk of obesity and other metabolic diseases (Harmancıoğlu and Kabaran 2023).

8.2 Epigenetic Modifications

DNA methylation, the most prevalent epigenetic alteration, is the addition of a methyl group to particular DNA bases (Fig. 8.1), typically leading to the silencing of the corresponding gene (Kiselev et al. 2021). DNA methyl transferases (DNMTs) catalyze the addition of methyl groups to specific cytosine residues within the cytosine-guanine sequence in the DNA, commonly known as the CpG island. These