

# Integrating nutriepigenomics in Parkinson's disease management: New promising strategy in the omics era

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## ABSTRACT

Parkinson's disease (PD) is the most prevalent brain motor disorder and is frequently regarded as an idiopathic and sporadic disease due to its unclear etiology. Although the pathological mechanisms of PD have already been investigated at various omics levels, no disease-modifying drugs are currently available. At the moment, treatments can only provide symptomatic relief to control or improve motor symptoms. Parkinson's disease is a multifactorial disease, the development and progression of which are influenced by multiple factors, including the genetic markups and the environment. As an indispensable component of our daily life, nutrition is considered one of the most robust environmental factors affecting our health. Consequently, depending on our dietary habits, nutrition can either induce or reduce our susceptibility to PD. Epigenetic mechanisms regulate gene expression through DNA methylation, histone modifications, and non-coding RNAs (ncRNAs) activity. Accumulating evidence from nutriepigenomics studies has reported altered epigenetic mechanisms in clinical and pre-clinical PD models, and the potential role of nutrition in modifying the changes. In addition, through nutrigenetics and nutrigenomics studies, the diet-gene, and gene-diet interactions concerning PD development and progression have been investigated. Herein, current findings on the roles of nutrition in epigenetic mechanisms underpinning PD development and progression are discussed. Recent advancements in the multi-omics approach in PD nutrition research are also underlined. The ability of nutrients to influence epigenetic mechanisms and the availability of multi-omics applications compel the immediate use of personalized nutrition as adjuvant therapy for PD.

## 1. Introduction

Parkinson's disease (PD) is a progressive neurological disorder associated with severe dopaminergic neuron loss in the substantia nigra pars compacta (SNpc). The cardinal motor symptoms of PD resting tremors, bradykinesia, and muscle rigidity are (Kouli et al., 2018). Dopaminergic neurons carry dopamine neurotransmitters from the SNpc to the striatum, where motor tasks are planned and executed. In PD, dopaminergic neurodegeneration in the SNpc results in nigrostriatal denervation, impairing the striatum's ability to coordinate motor processes optimally (Iarkov et al., 2020). Over the last 30 years, the prevalence of PD has surged by 155 %, and there are now more than 10 million PD cases globally. By 2040, it is anticipated that over 12 million

people would have been diagnosed with PD. According to the data from the 2019 Global Burden of Disease study, PD prevalence increased in 164 of 204 countries between 1990 and 2019 (Dorsey et al., 2018; Ou et al., 2021). Increased population growth and ageing, as well as improved diagnostic procedures and health systems, have resulted in a greater number of people being diagnosed with PD and living with it (Rizek et al., 2016). For example, in South-East Asia, PD prevalence has climbed by 170 % over the previous three decades (Ou et al., 2021).

Parkinson's disease is commonly regarded as an idiopathic and sporadic disease due to its mostly unknown etiology and the fact that only about 5–10 % of documented PD cases have a family history of the condition (Kouli et al., 2018). Although the exact cause of PD is unknown, environmental exposure to particular neurotoxic pesticides such

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as paraquat and rotenone, as well as underlying genetic predisposition have all been shown to raise the risk of developing this disease. Additionally, because PD cases are typically sporadic, accumulating research has demonstrated that environmental parameters such as lifestyle, nutrition, and dietary intakes play a role in the development and progression of PD (Angelopoulou et al., 2022). Indeed, these parameters are among the most researched aspects of PD etiology, owing to their modifiable factor.

In the omics era, high-throughput techniques have enabled the investigations of nutritional influence on PD at various molecular levels. It has been discovered that nutrients and bioactive compounds in diets modify the genetic markups via epigenetic modifications, resulting in changes in gene expression and function, without changing the DNA sequence (Tiffon, 2018). Other than that, the widely accepted gut-brain axis hypothesis of PD postulates a link between gastrointestinal (GI) disorders and susceptibility to and progression of the disease. Several GI-related disorders, such as constipation and irritable bowel syndrome (IBS), are often regarded as prodromal signs of PD (Mertsalmi et al., 2021). Though the precise pathophysiological mechanisms are still elusive, it is believed that dysbiosis of the enteric nervous system or changes in the gut microbiota increases the chance of developing PD (Dutta et al., 2019). Dietary consumption has a significant impact on gut microbiota composition and its dynamic ecosystem (Rajoka et al., 2017). Acute dietary interventions have been observed to alter the composition of gut bacteria (Leeming et al., 2019). Given the effects of dietary intakes on health outcomes, increased emphasis should be placed on nutrition and diets, as well as their effects on disease-linked epigenetic and epigenomic mechanisms, including PD.

Nutrigenetics is the study of how different gene variations respond to nutrients and their health consequences, whereas nutrigenomics is the study of how nutrients affect gene expression (Baumler, 2012). Meanwhile, nutriepigenomics is the study of the effect of nutrition on epigenetic regulatory processes like DNA methylation, histone modification, and non-coding RNA activity, all of which affect gene expression and function (Remely et al., 2015). The relationship between dietary intakes and disease development and progression is increasingly being well recognized in PD research (Baumler, 2012). Several studies have been conducted to ascertain the effect of nutritional compounds on the chance of developing PD (Agim and Cannon, 2015; Boulos et al., 2019; Dutta et al., 2019; M. Huang et al., 2021; Y. Huang et al., 2021). On a molecular level, nutrients are capable of activating, repressing, or silencing specific gene expressions associated with PD (Remely et al., 2015). Understanding the epigenetic mechanisms may help close the gap between nutritional intakes and PD development and progression.

Despite extensive research on nutritional status in PD, there are still numerous controversies regarding the influence of various dietary intakes on the risk of developing PD (Boulos et al., 2019). The uncertainty stems from the heterogeneity and complexity of the disease, as well as the influence of other environmental factors such as lifestyle and exercise, especially given the disease's sporadic nature. Nonetheless, the role of nutrition in epigenomics cannot be dismissed. Thus, the ultimate purpose of this review is to discuss current findings regarding the interplay between nutrition and epigenetic mechanisms in the development and progression of PD. Additionally, advancements in genomics, transcriptomics, proteomics, and metabolomics approaches are also discussed, highlighting their contributions to PD nutrition research. Ultimately, this review aims to emphasize the importance of incorporating nutrigenetics and nutrigenomics into the management of PD treatments.

## 2. Nutriepigenomics and Parkinson's disease

The study of how nutrition affects epigenetic changes is known as nutriepigenomics. Integrating nutriepigenomics with nutrigenetics and nutrigenomics can provide insight into nutrient-gene interactions, with the ultimate objective of developing nutrition suited to an individual's

genetic propensity to disease (Fig. 1). Recent evidence reveals that diet can influence epigenetic modifications by altering epigenetic mechanisms, which constitute DNA methylation, histone modifications, and non-coding RNAs (ncRNAs) activity (Remely et al., 2015; Vyas et al., 2018). Consequently, these modifications may either protect against or increase disease susceptibility, without affecting the DNA sequence. Fortunately, alterations in the epigenetic mechanisms are reversible (Damiani and Gabbianelli, 2019). Thus, adopting a healthy diet may represent a critical chance for disease risk reduction. Given the impact of nutrition on epigenetic changes and disease susceptibility, it is unsurprising that it plays a critical role in the pathogenesis and progression of PD.

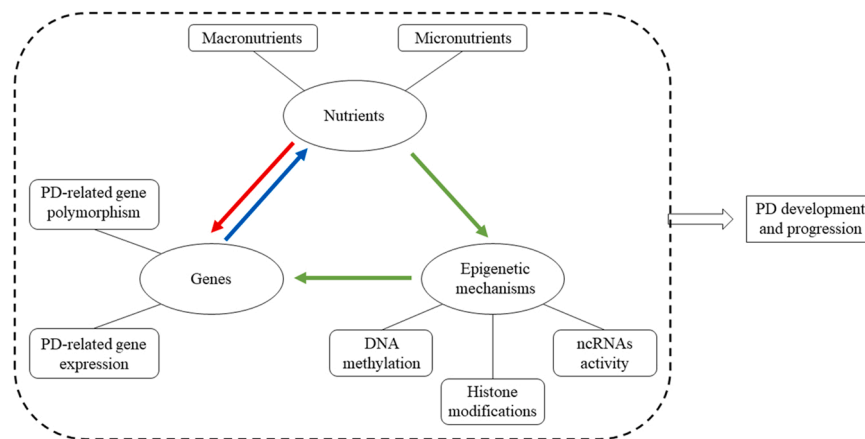
Epigenetic mechanisms are critical regulators of gene expression that serve as links between genetic and environmental influences, including diets. Epigenetic mechanisms, depending on the influences, establish potentially heritable modifications in chromosomes without changing the DNA sequences. The three main epigenetic mechanisms are DNA methylation, histone modification, and non-coding RNA activity. Multiple studies have identified epigenetic modifications as significant modulators of nutrition-PD interactions.

### 2.1. DNA methylation

DNA methylation involves the addition of a methyl group to the DNA strand catalyzed by DNA methyltransferases (DNMTs). Mechanistically, the addition occurs at CpG dinucleotides, mostly on the fifth carbon position of the cytosine ring. In normal physiology, DNA methylation regulates gene expression by recruiting proteins implicated in gene suppression or by preventing the transcription factor from binding to DNA, usually resulting in gene silencing. Demethylated DNA, on the other hand, often results in gene activation (Cheishvili et al., 2015).

Dysregulated DNA methylation process has been identified in PD, such as reduction in methylation capability (Murray & Jadavji, 2019), and hence, altering gene expression, including PD-related genes. Several genes associated with PD pathogenesis are hyper- or hypomethylated in the brains of PD patients (Angelopoulou et al., 2022). A DNA methylation study of cortical tissue from PD patients found 35 hypomethylated and 22 hypermethylated genes when compared to healthy controls (Kaut et al., 2022). Similarly, a methylome and transcriptome study of whole blood from PD patients identified 31 differently methylated CpG sites, with 13 hypermethylated and 18 hypomethylated (Henderson et al., 2021). The  $\alpha$ -synuclein protein is abnormally expressed in the brain of PD patients, and aberrant methylation at CpG sites of the *SNCA* gene is implicated in dysregulation of  $\alpha$ -synuclein expression (Mohd Murshid et al., 2020), suggesting that DNA methylation may, to some extent, underlie synucleinopathy in PD. The *PPARGC1A* gene has been shown to be significantly hypermethylated in PD patients, resulting in decreased expression of the encoded peroxisome proliferator-activated receptor gamma coactivator-1 $\alpha$  (PGC-1 $\alpha$ ) protein (Yang et al., 2020a, 2020b). Notably, PGC-1 $\alpha$  is crucially involved in mitochondrial biogenesis and its downregulation has been implicated with mitochondrial PD pathogenesis (Piccinin et al., 2021). On the contrary, the *CYP2E1* gene was found to be hypomethylated, leading to overexpression of cytochrome P450 2E1 (CYP2E1) protein in PD brains (Kaut et al., 2022). Excessive CYP2E1 protein in the brain is deleterious to dopaminergic neurons since it induces oxidative stress, mitochondrial dysfunction, and eventually, neuronal death (Shah et al., 2021). Other PD-associated genes, such as *MSRA*, *PTPRN2*, and *DAB1*, have also been found to have different DNA methylation levels in PD patients versus healthy controls (Kaut et al., 2022).

Vitamins such as vitamin B6, B9, and B12 are key cofactors in DNA methylation modification (Mohd Murshid et al., 2020). For instance, DNA methylation of dopaminergic neurons is altered in hypovitaminosis B condition, making the neurons more vulnerable and prone to stress (Murray & Jadavji, 2019). Vitamin B12 with folic acid supplementation increased global DNA methylation levels, thereby demonstrating its



**Fig. 1.** The integration of nutriepigenomics, nutrigenetics, and nutrigenomics. A schematic representation illustrating the scope and interplay between nutriepigenomics (green arrows), nutrigenomics (blue arrow), and nutrigenetics (red arrow), and their influence on PD development and progression. PD: Parkinson's disease; ncRNAs: non-coding RNAs. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

significance in modulating DNA methylation (Sae-Lee et al., 2018). Furthermore, it was shown that vitamin C treatment removes DNA methylation and, as a result, upregulates genes related to dopaminergic neuronal development in the midbrain of the rodent PD model (Wulansari et al., 2017). Importantly, vitamin C is a cofactor of TET enzymes, a group of enzymes critically involved in DNA demethylation (Cimmino et al., 2021), implying that vitamin C supplementation might alleviate the hypermethylation issue of PD-related genes. Phytochemicals like flavonoids, carotenoids, and phenolic acids were reported to exert neuroprotective action against the development of synucleinopathy, either directly via transcription factors or indirectly via regulating the epigenetic mechanisms (Surguchov et al., 2021). Aside from that, polyphenols such as flavanols and resveratrol have been demonstrated to influence DNA methylation via blocking DNMT activity (Sae-Lee et al., 2018) and reducing Ten-Eleven Translocation 2 (TET2) protein activity (P. Li et al., 2021; X. Li et al., 2021), respectively. Reportedly, TET2 inactivation was found to reduce inflammation-induced nigral dopaminergic neurodegeneration in mice (Marshall et al., 2020).

## 2.2. Histone modifications

Histone is a nuclear protein that helps package and condense DNA into chromatin. Due to its direct connection with DNA, histone plays a critical role in DNA replication and gene regulation (Henikoff & Smith, 2015). Histone modification is another mechanism of epigenetic changes, that involves post-translational modifications to histone proteins such as methylation, phosphorylation, and acetylation (Ramazi et al., 2020). Consequently, histone modifications alter the interaction between histone and DNA, influencing gene expression levels (Alhamwe et al., 2018).

A genome-wide analysis of histone acetylation revealed histone sites with aberrant acetylation and altered transcriptional regulation in PD brain tissue (Toker et al., 2021). In this study, histone H3 on lysine 27 (H3K27) hyperacetylation was found to be the most prominent among other histones, notably among PD-associated genes like *SNCA*, *PARK7*, *PRKN*, and *MAPT* (Toker et al., 2021). Since H3K27 is well-known as a marker for active enhancers, its hyperacetylation in PD brains predicts enhanced activation of transcription of these genes (Zhang et al., 2020). Another study also highlighted similar H3K27 hyperacetylation in the post-mortem brains of PD patients. Interestingly, given their *ex vivo* and *in vivo* investigations, the study claimed that H3K27 hyperacetylation is induced by mitochondrial dysfunction (Huang et al., 2021), showing a causal relationship between impaired mitochondria and histone modification. Increased histone acetylation is also documented in the midbrain dopaminergic neurons of PD patients. Concomitantly, histone

deacetylases (HDACs) are reduced, as evidenced in the midbrain of PD patients as well as MPTP-treated cells and mice models (Park et al., 2016). In normal physiology, HDACs remove acetyl groups from lysine residues, resulting in the suppression of gene expression. In the case of reduced HDACs, higher levels of genes are transcribed and expressed, causing pathologic overexpression of associated proteins (Wang et al., 2020). Aside from that, tri-methylation of the histone H3 on lysine 4 (H3K4me3) was demonstrated to be elevated in the nigral *SNCA* promoter of PD patients (Guhathakurta et al., 2021). H3K4me3 is a transcription-promoting mark, in which its elevation promotes gene transcription and expression (Chen et al., 2015), suggesting that H3K4 tri-methylation plays a role in triggering nigral  $\alpha$ -synuclein overexpression.

Curcumin and apigenin, two naturally occurring polyphenols, have recently been linked to the histone modification process. Curcumin has been shown to promote HDAC-mediated acetylation-deacetylation balance while apigenin trigger histone H3 on lysine 9 (H3K9) and histone H4 on lysine 12 (H4K12) acetylation (Rodrigues-Costa et al., 2021). Curcumin therapy decreased apoptosis and improved motor impairments in a *PARK7*-knockout rat model of Parkinson's disease by targeting HDACs (Chiu et al., 2013). Apart from that, diet-associated histone modifications have also been found to be mediated by gut microbiota (D'Aquila et al., 2020). Butyrate, a short-chain fatty acid derived from dietary fiber catabolism, can regulate and balance gut microbiota while simultaneously acting as an HDAC inhibitor. Butyrate treatment with trehalose (non-reducing sugar) on  $\alpha$ -synuclein-induced rats significantly elevated dopamine levels and histone H3 acetylation while reducing pro-inflammatory cytokines production (Kakoty et al., 2021). Therefore, butyrate-trehalose treatment could potentially alter dopamine synthesis and inflammatory process through epigenetic histone acetylation. In summary, mounting clinical and pre-clinical evidence highlights dysregulated histone modification in PD and the ability of certain diet/nutrition to influence the changes, implying their involvement in diet-gene interaction.

## 2.3. Non-coding RNAs activity

Non-coding RNA (ncRNAs), as suggested by its name, is an RNA molecule that is not translated into a protein. Previously, this type of RNA molecule was regarded as 'noise' in the transcriptome, however, accumulating evidence has established its significance in a plethora of crucial biological processes, most notably transcriptional and post-transcriptional gene expression regulation (Yang et al., 2020a, 2020b). Besides, ncRNAs are engaged in cellular signalling pathways for disease development and progression, including PD (Kuo et al., 2021). Long

ncRNAs (lncRNAs) and microRNAs (miRNAs) are two functionally important types of ncRNAs that are being widely investigated in relation to PD.

Recent studies have associated lncRNAs dysregulation with PD. Gene microarray analysis identified several differentially expressed lncRNAs and mRNAs in clinical (Fan et al., 2019) and experimental PD subjects (Lin et al., 2018). Suggestively, the HOXA transcript antisense RNA myeloid 1 (HOTAIRM1) and AC131056.3-001 lncRNAs might contribute to PD pathogenesis via involvement in dopaminergic neuronal apoptosis and inflammatory response (MAPK and JAK/STAT-mediated) mechanisms (Fan et al., 2019). Furthermore, the nuclear enriched abundant transcript 1 (NEAT1) lncRNA was documented to be upregulated in the MPTP-induced mice model of PD. In this study, suppression of NEAT1 activity reduced  $\alpha$ -synuclein expression, as well as cell apoptosis activator Bax/Bcl2 ratio and mediator caspase-3 (Liu & Lu, 2018), suggesting the role of NEAT1 in modulating MPTP-induced  $\alpha$ -synuclein and programmed cell death mechanisms, possibly via miR-124/KLF4 axis (Liu et al., 2020). Other than that, serum PD samples and cell models are also found to express elevated levels of rhabdomyosarcoma 2-associated transcript (RMST) lncRNA (Chen et al., 2022). Increased RMST lncRNA abundance has been associated with the upregulation of pro-inflammatory cytokines TNF- $\alpha$  and IL-1 $\beta$  via its target gene miR-150-5p (Chen et al., 2022). In the rats PD model, inhibiting RMST lncRNA activity suppressed the TLR/NF- $\kappa$ B signalling pathway and reduced dopaminergic neuronal damage (Ma et al., 2021).

In addition to lncRNAs, emerging evidence has linked several miRNAs to the development and progression of PD. A study of the differential expression of miRNAs in PD patients indicated that miR-155-5p was upregulated and miR-146a-5p was downregulated (Caggiu et al., 2018). Both miRNAs are implicated in neuroinflammatory response, the former exerts pro-inflammatory action (Mahesh & Biswas, 2019) whereas the latter is anti-inflammatory (Wang et al., 2018), corroborating the increased neuroinflammatory response seen in PD cases. Interestingly, the study found an inverse link between levodopa dosage and miRNA-155-5p levels (Caggiu et al., 2018), implying a possible inhibitory mechanism of miRNA-155-5p by high-dosage levodopa, which deserves further investigation. One study utilizing SHSY-5Y cells reported a protective role of miR-185 in preventing PD pathogenesis. An increase in miR-185 expression downregulated LRRK2 gene expression, thereby reducing rotenone-induced cellular toxicity. Furthermore, lower nigral and striatal miR-185 levels were observed in rotenone-induced rats compared to controls (Rahimmi et al., 2019). Dysregulation of miR-185 level found in this study could explain the increased LRRK2 expression reported in other PD studies (Cook et al., 2017; Wallings et al., 2020). Similarly, miR-150 levels were shown to be downregulated in PD patients and are inversely linked with pro-inflammatory cytokines. Mechanistically, miR-150 suppresses neuroinflammatory response via regulating the AKT3 activity (Li et al., 2020).

A few dietary components have been investigated concerning their influence on ncRNA activity in PD. Coenzyme Q10, a fat-soluble vitamin-like antioxidant, was found to affect miR-149-5p expression levels in 6-OHDA-induced rats (Ghasemloo et al., 2021). Changes in miR-149-5p levels have been associated with BBB damage (Yan et al., 2021). Coenzyme Q10 treatment upregulated miR-149-5p levels while downregulated matrix metalloproteinases 2 and 9 (MMP-2 and MMP-9), which therefore alleviated BBB damage, dopaminergic neuronal death, and motor impairment (Ghasemloo et al., 2021). Hence, coenzyme Q10 may exert its protective role against PD pathologies and PD-induced BBB damage via miR-149-5p/MMPs signalling pathway. Interaction has also been detected between alcohol consumption and ncRNAs. Non-coding RNAs regulate enzymes and neurotransmitters involved in alcohol addiction, particularly dopamine (Zhu et al., 2022). Therefore, ncRNAs are capable of modulating dopamine-related pathways, a pathway majorly affected in PD. Furthermore, in one study investigating the

interaction between manganese and  $\alpha$ -synuclein expression, prolonged manganese exposure to human neuroblastoma SH-SY5Y cells resulted in SNCA and FGF-20 genes upregulation via downregulation of miRNA-7 and miRNA-433 (Tarale et al., 2018). Hence, the effect of manganese on PD risk can be explained by its involvement in  $\alpha$ -synuclein aggregation via specific miRNA-mediated cascades. Besides that, miRNAs have been identified to facilitate the gut-brain axis connection. A high-sugar, high-fat (HSHF) diet given to mice disrupted its gut microbiota, altering a plethora of brain circRNAs (miRNA 'sponges'), perturbing neurotransmitter metabolism, and inducing neuroinflammation (Guo et al., 2021). In another study, mice gut microbiota was found to influence seven hippocampal miRNAs involved in various diseases and biofunctions (Chen et al., 2017). As such, changes in miRNA levels caused by diets may alter the gut microbiota and consequently disrupt signalling between the gut and the brain (Moloney et al., 2019). Interestingly, recent research has demonstrated the potential utility of dietary miRNAs as therapeutic agents in modulating gut microbiota (del Pozo-Acebo et al., 2021; Preethi and Sekar, 2021). Table 1 summarizes the potential modifying effects of several nutrients on epigenetic mechanisms and its influence on PD pathogenesis discussed in this Section.

**Table 1**

Summary of the interplay between nutritional factors, epigenetic mechanisms, and its influence on the pathogenesis of PD.

Nutritional factors	Epigenetic modifications	PD pathogenesis (Protective or detrimental)	References
Vitamin B deficiency	Alters DNA methylation	More vulnerable dopaminergic neurons (detrimental)	Murray & Jdavji (2019)
Vitamin C	Reduces DNA hypermethylation	↑ genes associated to dopaminergic neuronal development (protective)	Wulansari et al. (2017)
Phytochemicals	Epigenetic regulations	Neuroprotective against synucleinopathy (protective)	Surguchov et al. (2021)
Polyphenols	Blocks DNMT and reduces TET2 activities	Prevents nigral dopaminergic neuronal loss (protective)	Marshall et al. (2020) and P. Li et al. (2021), X. Li et al. (2021)
Curcumin, Apigenin	↑ HDAC-mediated acetylation-deacetylation balance, ↑ H3K9 and H4K12 acetylation	↓ apoptosis and improves motor symptoms (curcumin treatment) (protective)	Chiu et al. (2013) and Rodrigues-Costa et al. (2021)
Butyrate	Acts as HDAC inhibitor, ↑ histone H3 acetylation	Regulates gut microbiota, ↑ dopamine levels, ↓ pro-inflammatory cytokines (protective)	Kakoty et al. (2021)
Coenzyme Q10	↑ miR-149-5p, ↓ MMP-2 and MMP-9	↓ BBB damage, ↓ dopaminergic neuronal loss, ↓ motor impairment (protective)	Ghasemloo et al. (2021)
Manganese exposure HSHF diet	↓ miRNA-7 and miRNA-433 Alters circRNAs expression	↑ SNCA and FGF-20 genes (detrimental) Perturbs neurotransmitter metabolism and gut microbiota, ↑ neuroinflammation (detrimental)	Tarale et al. (2018) Guo et al. (2021)

↑: increase; ↓: decrease; DNMT: DNA methyltransferase; HDAC: histone deacetylase; HSHF: high-sugar, high-fat; TET2: Ten-Eleven Translocation 2.

### 3. Omics application in PD nutrigenetics and nutrigenomics

The omics, including genomics, proteomics, transcriptomics, and metabolomics are high throughput analyses that investigate indices of biological activities at various levels. Advancement in omics technology has provided a greater understanding of normal and pathological physiologies of various health conditions. Integration of several omics, such as genomics, proteomics, and metabolomics, reveals the underlying mechanisms relevant to the condition of interest at multiple omics levels (Subramanian et al., 2020). Concerning PD, expanding the multi-omics database has enabled researchers to understand the mechanisms and interactions of underlying disease development and progression (Trifonova et al., 2020). In PD nutrigenetics and nutrigenomics, the emergence of omics technology enables analysis of the relationship between nutrition and gene expression and its consequences on PD.

#### 3.1. Key omics branches in PD research

Genomics studies the entire genetic markups of an individual, including its structural and functional analysis as well as genetic mapping, sequencing, and profiling. Genomic analysis is conducted via sophisticated high-throughput techniques like the Next Generation Sequencing (NGS), fluorescence in situ hybridization (FISH), whole-genome sequencing (WGS), and genome-wide association studies (GWAS) (Gasperskaja & Kučinskas, 2017). Focusing on PD nutrigenetics and nutrigenomics, through these genomic analysis techniques, a plethora of information can be obtained that connects nutrition to PD development and progression. Although obtaining the genomic information of PD patients is not yet being commonly practiced in PD management, accumulating data on sequenced biological samples from numerous PD research has allowed researchers to pinpoint key genetic players of PD pathogenesis.

Transcriptomics is the branch of omics that investigates RNA transcripts, including their sequence, expression, and transcriptional regulation. The two main contemporary approaches in transcriptomics analysis are microarrays and NGS-based RNA-sequencing (RNA-seq) (Lowe et al., 2017). Through the RNA sequencing technique, the expression patterns of genes of interest in a specific biological condition can be investigated. Analysis of the transcriptomes provides insights into differentially expressed genes (DEGs) in PD (Kurvits et al., 2021), allowing for the delineation of critical signalling pathways in PD pathogenesis.

Proteomics refers to the study of proteins in terms of structural and functional identification, quantification, and post-translational modification. Depending on the purpose of the analysis, proteomics techniques can range from the less complicated enzyme-linked immunosorbent assay (ELISA) to the more sophisticated NMR spectroscopy and x-ray crystallography. Comprehensive proteomics analysis also necessitates the use of proteome-related software and databases such as the UniProt (<http://www.pir.uniprot.org/>) and SwissProt (<http://kr.expasy.org/sprot/>) (Aslam et al., 2017). Proteomics analysis enables the discovery of PD-related proteins and the determination of their functional significance in PD development. Besides, evaluating differentially expressed proteins (DEPs) in PD samples allows for the finding of possible protein biomarkers for PD prognosis and diagnosis.

Metabolomics investigates the metabolome, which is the interplay of different metabolites, to study a biological system at its biochemical level. Metabolome analysis is commonly done through nuclear magnetic resonance (NMR) spectroscopy or mass spectrometry (MS) (David and Rostkowski, 2020). Analysis of the metabolome is being intensively employed in PD research to uncover possible metabolic biomarkers of disease development and progression, elucidate molecular mechanisms of PD, and assess treatment outcome and efficacy (Bhinderwala et al., 2019).

Although a single-omics approach might yield significant information, integrating several omics can generate more comprehensive

findings by examining a biological system across different cellular function levels. Genomics, transcriptomics, proteomics, and metabolomics approaches together have proved useful for the discovery of causative genes, proteins, and mechanisms underlying PD (Fig. 2).

#### 3.2. Multi-omics application in PD nutrition research

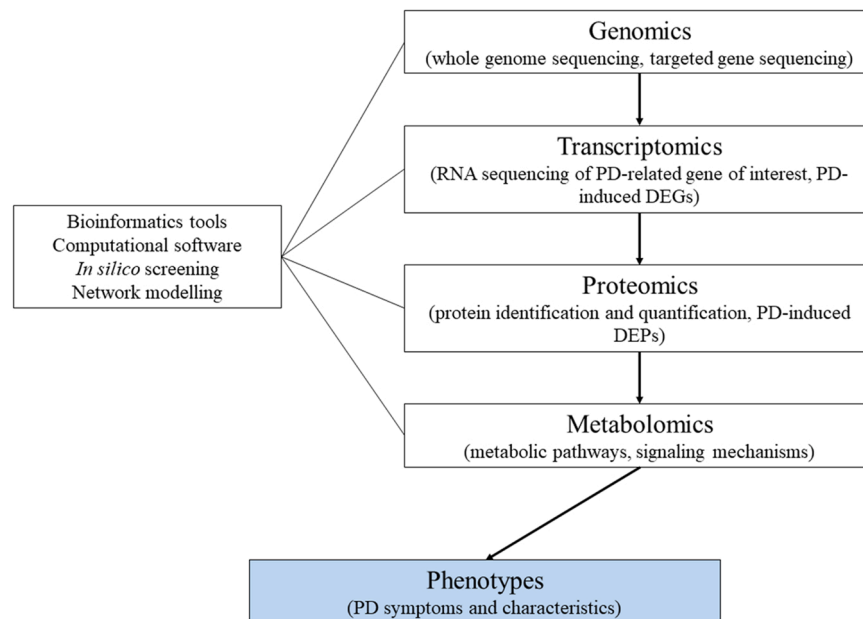
Genes, proteins, and metabolites work together to carry out complex biological processes, and hence, any aberrant processes at any level might trigger harmful repercussions to the host. Parkinson's disease is a complex neurodegenerative disease with multiple pathological mechanisms, such as  $\alpha$ -synuclein aggregation and mitochondrial dysfunction. As previously discussed, diets can either protect or induce PD pathogenesis via modifying epigenetic mechanisms. The central dogma for PD nutrigenetics and nutrigenomics research is thus identifying the genes, proteins, and metabolites implicated in the diet/PD interaction.

Using genomics analysis (NGS), a PD study in Russia analysed mutations in multiple PD-related genes and concluded that *LRRK2* and *GBA* gene mutations were prevalent risk factors for PD in the north-western region of Russia (Emelyanov et al., 2018). Notably, *LRRK2*-mediated neurodegeneration was reported to be associated with high dietary amino acid intake (Chittoor-Vinod et al., 2020), suggesting a possible connection between Russian dietary habits and the prevalence of *LRRK2* mutation. An intervention study performed DNA methylome analysis (Infinium HumanMethylation450 BeadChip array) and revealed that vitamin B12 with folic acid supplementation increased global DNA methylation (Sae-Lee et al., 2018).

Other than that, a proteomics analysis (Q-Exact mass spectrometry) on experimental mice given a high-fat diet identified some differentially expressed proteins (DEPs) with PD-related functional roles. The finding was further validated by transcriptomics analysis (mRNA expression), which demonstrated that the mRNA levels of the DEPs in mice fed with the high-fat diet were differentially expressed compared to the control mice (Pan et al., 2022). Parkinson's disease is associated with the disturbance of plasma lipid metabolism. In a clinical study examining the plasma samples of PD patients, metabolomics analysis (liquid chromatography-mass spectrometry) documented 83 differentially expressed metabolites (DEMs), among which mainly were lipid and lipid-like metabolites. Also, proteomics analysis (tandem MS) revealed 40 DEPs, including apolipoproteins (Hu et al., 2020). Multiple layers of omics analyses from these studies yielded a comprehensive catalogue of lipid-associated genes, proteins, and metabolic markers for PD.

Multi-omics approach has led to a better knowledge of the gut microbiome's influence on PD. Through genomics analysis (shotgun metagenomic sequencing), a database of PD-associated gut microbial genes was successfully established. According to the analysis, 25 gut microbial genes were found to be differentially expressed in PD samples, suggesting their potential as diagnostic biomarkers for PD (Qian et al., 2020). Similarly, metagenomics analysis through NGS and gas-chromatography-mass spectrometry (GC-MS) approach were performed on the intestines of PD patients to evaluate the gut microbiota composition. Intestinal bacteria associated with anti-inflammatory and neuroprotection were drastically diminished in PD samples. Moreover, metabolomics analysis of the same samples revealed DEMs linked with lipid, vitamin, and amino acid metabolisms (Vascellari et al., 2020). Besides that, proteomics (MS) and transcriptomics (RNA sequencing) analyses in the appendix and ileum of PD patients indicated microbial dysbiosis, predominantly affecting cholesterol and lipid metabolisms (P. Li et al., 2021; X. Li et al., 2021).

Taken together, based on the multi-omics approach, various differentially expressed genes, proteins, and metabolites have been linked to changes and alterations in molecular mechanisms of nutrient metabolisms and dysbiosis of the gut microbiota.



**Fig. 2.** Cascade of the omics-based approach in PD research. The key omics analysis begins at genome level (genomics), followed by transcriptome level (transcriptomics), proteome level (proteomics), and metabolome level (metabolomics), with the goal of phenotyping PD. Each level utilizes bioinformatics and computational platforms. DEGs: differentially expressed genes; DEPs: differentially expressed proteins; PD: Parkinson's disease.

#### 4. Discussion and future perspectives

Parkinson's disease is widely recognized as a multifactorial disease, impacted by both genetic and environmental factors. Nutrition is among the most influential environmental factor, influencing an individual since early life. The diet-gene and gene-diet interactions are bridged by epigenetic modifications. In this context, investigating the nutriepigenomics of PD provides greater insight into nutrient-related PD pathogenesis and acts as a platform for the development of personalized nutrition tailored to an individual's genetic markups. Through nutri-genetics and nutrigenomics, comprehensive studies thus far have been able to link diet-gene interaction and PD susceptibility.

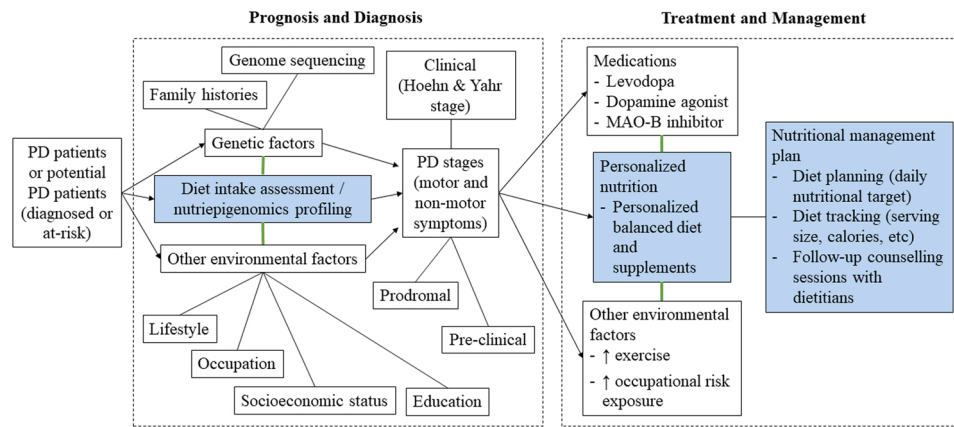
Nevertheless, until now, there is still no comprehensive nutritional strategy for PD. This is due to the complex interaction between genetic variances, cultural diversity, and different lifestyles of PD patients. Despite having the same disease, each patient may require a different nutritional strategy. Other than that, our present understanding of the association between nutrition and PD risk is primarily based upon preliminary/pilot studies that examine the effects of short-term dietary intervention. Additional studies with larger sample sizes and a longer intervention period are needed to arrive at a more definitive conclusion. In this context, readily available online PD databases and consortia such as the Gene4PD (<http://genemed.tech/gene4pd/home>), Parkinson's Progression Markers Initiative (PPMI, <https://www.michaeljfox.org/news/parkinsons-progression-markers-initiative-ppmi>), and LRRK2 Cohort Consortium (<https://www.michaeljfox.org/news/lrrk2-cohort-consortium>) are helpful platforms that allow comparison of genome-wide association study (GWAS), single nucleotide polymorphisms (SNPs), and DEGs analyses from PD patients worldwide. Integrating these data with the omics databases like the Human Metabolome Database (<https://hmdb.ca/>) and the National Omics Data Encyclopedia (NODE, <https://www.biosino.org/node/>) can aid in a comprehensive understanding of the genomics, transcriptomics, proteomics, and metabolomics of PD, such as how gene polymorphisms lead to different degrees of PD susceptibility.

Parallel to the age of personalized medicine, a nutritional intervention that is tailored to a patient's genetic disposition would improve treatment quality and reduce undesirable side effects. Potentially, personalized nutrition can act as adjuvant therapy in PD management.

Since diet profoundly affects the gut microbiota and alteration in the gut is evidenced to affect the brain through the gut-brain axis, optimizing the benefits of diet-gene interaction could undoubtedly enhance treatment efficacy. The integration of nutriepigenomics, nutri-genetics, and nutri-genomics within the omics approach will provide a viable platform for personalized nutrition. By elucidating the interplay between nutrition and PD development and progression, a personalized nutrition strategy with higher benefits and lower side effects could be implemented as adjuvant therapy for PD (Fig. 3), parallel with the 2020–2030 Strategic Plan for NIH Nutrition. Based on the complete genomic information and advanced prediction model, a dietary intervention tailored to each PD patient can be strategized.

There are still several challenges and limitations that need to be considered in personalized nutrition, albeit its benefits for PD treatment. Firstly, the availability of genomic and dietary data of PD patients is still limited since performing genomic sequencing and tracking dietary habits are still uncommon in PD management. Management plans that incorporate genomic sequencing and genetic risk profiling are yet to be practiced in healthcare sectors. Secondly, since patient's genotypic and phenotypic data need to be gathered, personalized nutrition is sophisticated, expensive, and is not as readily available to all healthcare sectors, restricting the benefits of personalized nutrition to only the First World countries (Ordovas et al., 2018). Interestingly, web-based dietary interventions are being increasingly recognized as a way to minimize the cost of personalized nutrition (Al-Awadhi et al., 2021).

Genetic discrimination towards rare mutations as well as race and cultural minorities has been viewed as one of the main challenges of personalized medicine. Besides, existing information on the omics data may be skewed to the dominant population due to higher distribution, thus, discriminating the minorities. In PD, rare mutations of several PD-associated genes have been described (Bandres-Ciga et al., 2020). Moreover, the nutritional paradigm designed specifically for each individual necessitates the sharing of his detailed information, including full genomic sequence and family histories. These concerns underline the major need for ethical considerations and the involvement of legal regulatory bodies. Currently, in the USA, the Genetic Information Nondiscrimination Act of 2008 (GINA) is being enforced, protecting citizens from being discriminated against due to genetic issues (Chapman et al., 2020). In Asian countries, however, such jurisdiction is



**Fig. 3.** Dietary intervention strategy for PD management. Consideration of nutrition or dietary pattern when prognosing and diagnosing Parkinson's disease is a critical step in planning a dietary intervention strategy (blue boxes). Integrating nutritional aspect alongside other factors (green lines) improves the efficiency of PD prognosis and diagnosis and the effectiveness of PD treatment and management. PD: Parkinson's disease; MAO-B: monoamine oxidase-B; †: increase.

still in its infancy with only a few countries enforcing laws and policies regarding genetic discrimination (Kim et al., 2021). That being said, for countries to effectively embrace the benefits of personalized medicine, including personalized nutrition, they must be able to actively engage with the jurisdictions and ethical considerations.

Therefore, how does nutriepigenomics help to overcome present limitations in PD treatments? A multitude of evidence has pointed to epigenetic changes as important components of neurodegeneration in PD. Although no disease-modifying drugs are currently available to treat PD, nutrition is emerging as a viable possibility that, due to its ability to influence epigenetic pathways, may be able to restore epigenomes. Comprehensive knowledge of nutriepigenomics opens the door to the possibility of optimized dietary interventions to achieve disease prevention or modification. This paper comprehensively discusses the significant effects of specific diet or nutrition on DNA methylation, histone modifications, and ncRNAs activity in relation to PD pathogenesis. In Fig. 3, the proposed dietary intervention strategy for PD management focuses on diet intake assessment as a component of prognosis and diagnosis, as well as personalized diet tracking and planning as part of disease treatment and management. The fundamental component of this proposed intervention strategy is based on dietary intake and nutriepigenomics profiling of diagnosed or at-risk PD patients, in addition to other known or possible genetic and environmental risk factors such as family history and occupation. Following the assessment, the information will be utilized to design a personalized nutritional intervention consisting of a balanced diet and supplements. A nutritional management plan, which includes food tracking and planning as well as follow-ups, will also be implemented to assess the compliance with this personalized intervention approach. Due to the ability of nutrition to alter gene expression patterns via epigenetic regulation, a dietary intervention tailored to each PD patient could be a possible disease-modifying approach.

## 5. Conclusion

The development and progression of PD are largely influenced by environmental factors, including dietary habits. Nutrients affect the genetic disposition of an individual by altering the three epigenetic mechanisms - DNA methylation, histone modifications, and ncRNAs activity. Changes in epigenetic mechanisms lead to alteration in gene expression, and subsequently, increase or lessen PD susceptibility. Concurrently, different gene variants respond to nutrients differently, making the gene-diet interaction very diverse for each patient. Multi-omics approach provides high-throughput platforms for PD and nutrition-related genomics, transcriptomics, proteomics, and metabolomics research. Despite its infancy, personalized nutrition is a

promising platform for better management of PD, adapting the treatment to an individual's degree of vulnerability and susceptibility. A deeper understanding of the nutriepigenomics, nutrigenetics, and nutrigenomics underlying PD pathophysiology will potentially lead to more effective treatment strategies.

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## CRediT authorship contribution statement

**Khairiah Razali:** Data curation, Writing – original draft, Writing – review & editing, Visualization. **Khaled Agantri:** Data curation, Writing – original draft. **Su Peng Loh:** Conceptualization, Validation. **Shi-Hui Cheng:** Conceptualization, Validation. **Wael Mohamed:** Conceptualization, Validation, Supervision, Project administration.

## Declaration of interest

None.

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