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Review Article

The use of Nicotinamide in Parkinson's disease; A Possible path to the future

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ABSTRACT

Increasing the prevalence of Parkinson's disease is an alarming sign that needs attention, so focusing on new medications and regimens which play an important role in prevention and treatment becomes a point of concern. Parkinson's disease is the second neurodegenerative disorder caused by the interplay between different mechanisms that are related to genetics, environment, and other factors. One of the potential treatment options under research is nicotinamide which may act as a neuroprotective agent. Although nicotinamide is accepted as a therapeutic agent in many diseases, its action as a Nicotinamide adenine dinucleotide (NAD) precursor against oxidative stress needs to be proved in Parkinson's disease. Here, based on the current literature, we provide a thorough overview of nicotinamide usage in medicine. We summarize chemistry, uses, side effects, different mechanisms, and all available preclinical and clinical data about the activity of nicotinamide. Nicotinamide increases cytoprotection, the release of dopamine, and decreases oxidative stress of mitochondria. As a consequence, we believe that nicotinamide may become a potential drug in the treatment of Parkinson's patients.

Keywords: *Parkinson; Cardinal; genes; Nicotinamide; Drosophila; neuroprotection*.

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1. Introduction

Parkinson's disease is a chronic progressive neurodegenerative disorder with motor and non-motor symptoms. It was described by James Parkinson as an "Essay on the shaking palsy". It has become a very common type of Parkinsonism. It's characterized by cardinal clinical features like rigidity, bradykinesia, tremor, and postural instability **[1]**.

1.1. Epidemiology

The estimated prevalence of Parkinson's disease in developed countries is 3% of the overall population. It affects 1-2% of people whose age is older than 60 years and 3% of people whose age is older than 80 years. Parkinson's disease is unequally distributed among men and women younger than 50 years and it gains its peak between 80-89 years. It is very common for males than females with a ratio of (1.4:1.0). According to the estimates based on healthcare utilization, the annual incidence of people with Parkinson's disease ranges from 5 in 100,000 to more than 35 in 100,000 new cases. From the sixth to the ninth decades of life, the incidence increases by a factor of five to ten.

According to a meta-analysis of four North American populations, the prevalence of Parkinson's disease rises with age. The prevalence has climbed from less than 1% of men and women aged 45 to 54 years to 4% of men and 2% of women aged 85 or older. In the next two decades, the prevalence of Parkinson's disease is predicted to double **[2]**

1.2. Etiology

The Gold standard of risk factors is age, but there are multi factors that lead to Parkinson's disease which combine genetic and environmental etiology. People who are exposed to chemicals, toxins, and pesticides have a higher risk Exposure to environmental factors may influence the genetics involved in Parkinson's disease. Mild to moderate head injury may increase the risk of Parkinson's in most cases. The number of head injuries increases the risk as do genetic susceptibility factors. Exposure to pesticides such as paraquat, rotenone, 2,4-D, and several dithiocarbamates and organochlorines cause parkinsonism in laboratory experiments, chlorinated solvents such as (trichloroethylene, perchloroethylene, carbon tetrachloride) which used during dry cleaning is associated with parkinsonism in animal models [**3**].

Identifiable mutations in certain genes were discovered in 5% to 10% of people who suffer from Parkinson's disease. Certain cause of this disease was unknown but recently, a genetic disposition is identified, as first-degree relative increased the risk of getting Parkinson's by 2-3 folds. Certain genes which encode alpha-synuclein may increase the risk by 2- to 5-fold **[4]**.

Mutant genes associated with Parkinson's disease were rare until the discovery of leucine-rich repeat kinase (LRRK2) mutations which are found in up to 40% of patients. Genetic-associated forms of Parkinson's disease are monogenetic, sporadic, and recessive. While monogenetic differs pathologically and clinically from sporadic, LRRK2 mutation closely resembles sporadic Parkinson's disease in terms of asymmetric onset and frequent tremors. Parkinson’s disease caused by a Synuclein Alpha (SNCA) mutation has an earlier onset, a moderate response to levodopa with a faster progression, pyramidal signs, and psychiatric symptoms. The recessive Parkinson's disease type has early-onset cases with good response to levodopa and early development of dyskinesia **[5]**. Several mechanisms of Parkinson’s disease are elaborated in **Fig. 1**.

1.3. Clinical Presentation

Parkinson's disease is clinically presented by motor and non-motor symptoms. Motor symptoms are represented by four essential symptoms bradykinesia (slowness and progressive small movements), rigidity (stiffness and involuntary resistance to passive movement of joints (limbs and trunk), resting tremors (tremors which fully represent in resting limbs; hands, face, arms, and legs which not related to movements), and finally posture instability (impairment in balance during walking or standing). The latter affects Parkinson’s patients in the late disease progression phase **[6-7]**. Non-motor symptoms include olfactory disorder (hyposmia), sleep disorder, anxiety, depression, psychosis, autonomic disorders (constipation, urinary dysfunction, orthostatic hypotension), and cognitive impairment **[6-7]**.

1.4. Treatment

Treatment options for Parkinson's disease include rehabilitative, restorative, surgery, deep brain stimulation (DBS), and drugs for motor and non-motor symptoms **[8-11]** For motor symptoms, treatment options depend on dopamine based as Levodopa, dopamine agonists (pramipexole and ropinirole), monoamine oxidase B (MAOB) inhibitors (rasagiline and selegiline), catechol-O-methyl transferase

inhibitors (eg, entacapone), and anticholinergic agents for tremor (eg, trihexyphenidyl) **[8]**.

Non-motor symptoms management options in case of constipation (lubiprostone and polyethylene glycol), urinary Incontinence (darifenacin, oxybutynin overactive bladder +/– incontinence solifenacin and tolterodine), anxiety and panic (clonazepam, diazepam, lorazepam in case of depression Selective Serotonin Reuptake Inhibitors (SSRI) as Fluoxetine and Sertraline Serotonin/Norepinephrine Reuptake Inhibitors (SNRI) Duloxetine, Desvenlafaxine, and venlafaxine,) psychosis (clozapine, quetiapine, and Pimavanserin) and orthostatic hypotension (Fludrocortisone, Pyridostigmine, and Droxidopa) **[12-13]**.

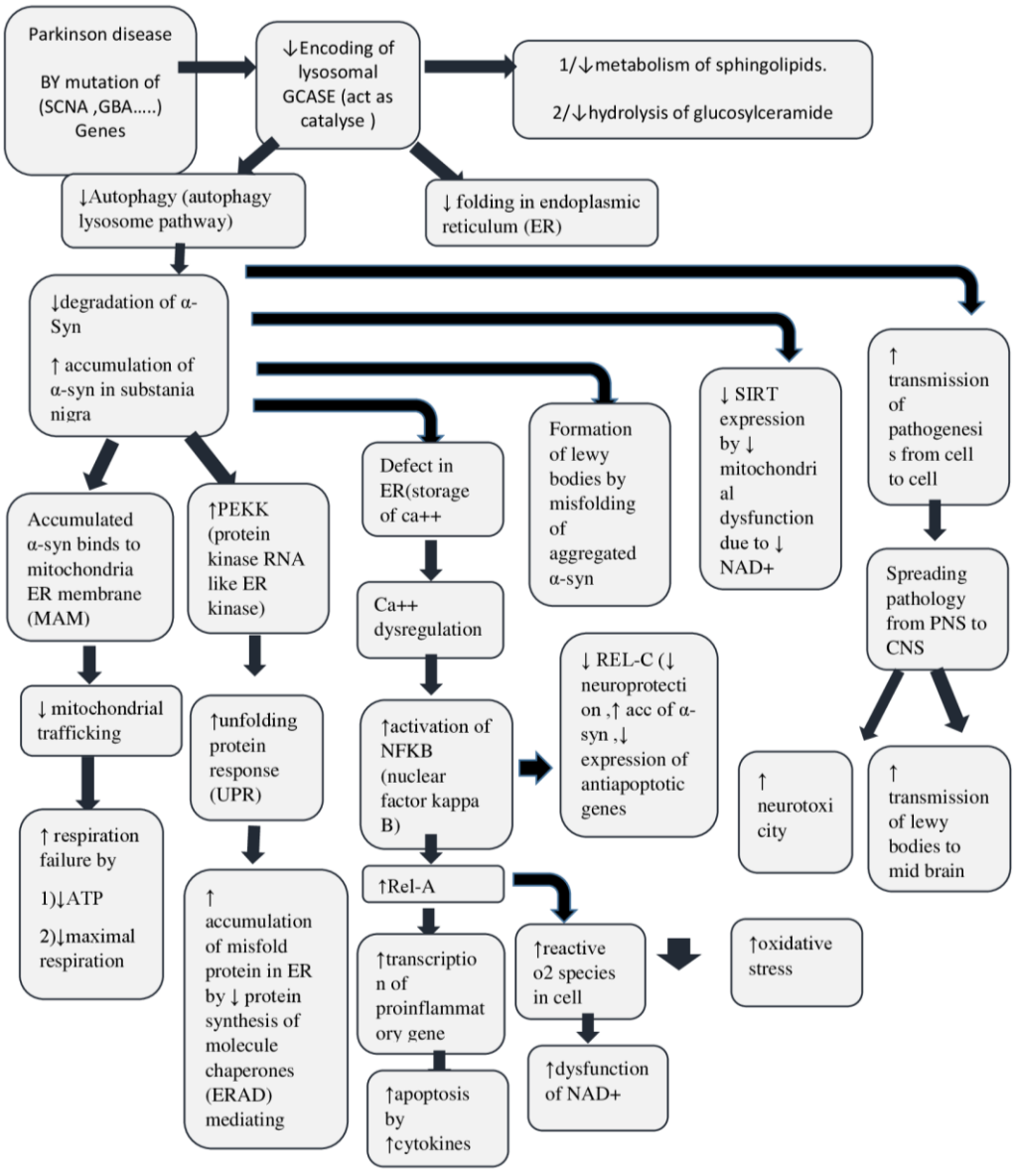

Fig. 1. Mechanisms of Parkinson's disease

1.5. Nicotinamide as a treatment option for PD

Nicotinamide adenine dinucleotide has emerged as a key therapeutic target for neurodegenerative diseases by targeting nicotinamide adenine dinucleotide phosphate oxidase (NADPH) which helps it in reducing microglial activation and stopping increasing oxidative stress **[14]**. NADPH is the main source of reactive oxygen species (ROS), and nicotinamide adenine dinucleotide oxidized form (NAD^+) acts as a substrate for the vital process of DNA repair. Therefore, replacement and supplementation of nicotinamide resources help to increase the lifespan of neurons in neurodegenerative disease as Parkinson's disease. It can be replenished by taking nicotinamide riboside (NR), vitamin B3 and NAD precursors **[14]**.

The dose which was tested to be tolerated is up to 2,000 mg per day, trials that were conducted on healthy individuals with no toxicity and side effects. The NADPARK study showed that Niacin 1000mg daily was well tolerated and led to a significant, increase in cerebral NAD levels and related metabolites in the cerebrospinal fluid which has a role in maintaining mitochondrial integrity and dopaminergic neuron oxidative stress-protective effect **[15]**.

1.5.1. Chemistry

Vitamin B3 is a water-soluble vitamin that includes three forms (Nicotinamide which is known as (Niacinamide), Nicotinic acid which is (also known as Niacin), and Nicotinaribosideuside (NR) **Fig. 2[16]**.

Nicotinic acid is converted into Nicotinamide in the body. Niacin and Nicotinamide are considered identical in their role as vitamins but they have different pharmacological actions **[16]**. Also, nicotinamide and niacin differ in their isomeric forms. Nicotinamide riboside (NR) is a pyridine nucleoside that acts as a precursor to nicotinamide adenine dinucleotide (NAD+). Active forms (NAD+/NADH), Nicotinamide adenine dinucleotide / Nicotinamide adenine dinucleotide hydrogen. The importance of NAD+ as a coenzyme is due to its great need for cellular redox reactions, including most catabolic and anabolic reactions, such as glycolysis, fatty acid oxidation, tricarboxylic acid cycle (TCA), synthesis of fatty acids, cholesterol, and steroid **[17]**. NADP+/NADPH provides electrons of anabolic reactions like a synthesis of fatty acids and steroids and oxidation-reduction reactions. Food sources of Nicotinamide: meat, fish, and wheat are particularly rich sources of Nicotinamide and less present in vegetables. It is worth mentioning that Nicotinamide is classified as a food additive **[18]**.

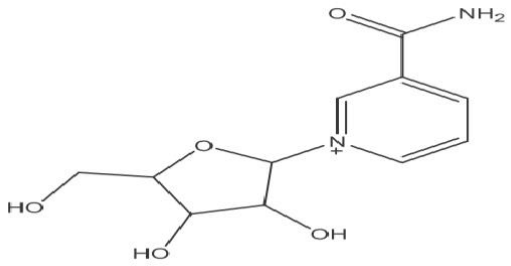

Fig. 2. Structure of nicotinamide riboside

1.5.2. Synthesis

Synthesis occurs through a series of biochemical reactions in the mitochondria. Niacin, nicotinamide, and tryptophan form nicotinamide adenine dinucleotide (NAD) and NAD phosphate (NADP). Biosynthesis of NAD^+ includes several different pathways; In humans, it includes the eight-step de novo pathway from the amino acid, tryptophan precursor, and additional three and two-step pathways from various nicotinoyl precursors such as nicotinic acid (NA) and nicotinamide (NAM), as well as nucleosides, NR, and nicotinic acid riboside (NAR). Metabolism of NAD+ is induced by enzymes (sirtuins, PARPs, CD38/157, SARM1 stress and aging mediators increase the

production of these enzymes by factors such as DNA damage, oxidative stress, and inflammation **[19]**.

A deficiency of niacin would directly lead to pellagra which is a disease that is characterized by erythematous rash, GIT symptoms such as vomiting diarrhea, or constipation, and CNS manifestations such as depression, headache, tiredness, and dementia **[20]**. The causes of these manifestations are due to malnutrition, hartnup diseases which decrease kidney reabsorption of tryptophan, and carcinoid syndrome in which tryptophan is changed into its oxidized forms 5-hydroxytryptophan and serotonin **[20]**. Furthermore, the intake of isoniazid (INH causes a vitamin B6 deficiency diminishing niacin synthesis from tryptophan **[21]**.

1.5.3. Potential Uses of Nicotinamide in different medical disorders

1.5.3.1. Dermatology

Acne vulgaris: since topical nicotinamide has sebo-suppressive, anti-inflammatory, and healing effects, it was found beneficial in the treatment of acne vulgaris, moreover, a noteworthy diminish has been found in the number of papules, pustules, and comedones **[22]**.

Non-melanoma skin cancer: local application of nicotinamide decreased the immunosuppressive aspect of UV radiation which was correlated to non-melanoma skin cancer, as it destroys DNA **[23]**.

Atopic dermatitis and rosacea: nicotinamide showed good results in treating patients with atopic dermatitis and rosacea. Actinic keratosis and basal cell carcinomas in patients with rosacea were found to have decreased greatly **[24]**.

Blistering disorders: the use of nicotinamide in blistering disorders is accredited to its stoppage of pro-inflammatory cytokine pathways **[25]**.

Cosmetic applications: Wrinkles, lentigines, and better elasticity were noted **[26]**.

1.5.3.2. Acute lung injury

Studies in the past conveyed that Nicotinamide (NAM) works by two mechanisms in acute lung injury in mice (which are analogous to that in humans). Firstly, it decreases the secretion of pro-inflammatory mediators in the lung such as TNF-α, IL-1β, and IL-6. Secondly, results revealed that by hindering the MAPK and AKT/NF-κB signaling pathways, acute lung injury has been relieved **[27]**.

1.5.3.3. SARS - COV-2

The SARS-COV-2 virus has shown that it can interfere with the NAD system inside the body by over-expressing the Poly (ADP-ribose) polymerase (PARP) genes and this leads to cellular damage potentiating the complications of pulmonary and cardiac toxicity. As a result, administration of nicotinamide riboside (NR) and nicotinamide mononucleotide (NMN) could be a key factor in Sars-cov-2-associated mortality as they stop the over-expression of PARP genes and give rise to NAD in the body **[8]**. In addition, one of the latest studies revealed that giving NAD+ as a supplement may improve innate immunity to coronaviruses and restrict viral infection **[28]**.

1.5.3.4. Alzheimer’s disease (AD)

Alzheimer’s disease occurs due to a triad of neuroinflammation, mitochondrial dysfunction, and cellular aging, also in Alzheimer’s disease (AD) nerves DNA repair and mitophagy be defective. However, the use of NR diminishes cytoplasmic DNA by increasing mitophagy which also has an important effect in clearing nonfunctional mitochondria in the body. Furthermore, NR diminishes cell aging in HMC3 cells via the Cgas-STING pathway **[29]**.

1.5.3.5. Other uses

In lactating mothers, an augmentation in

production and an increase in the quality of breast milk have been noted **[30]**. It can also aid in the prevention and alleviation of liver cancer **[31]**. It was reported as useful in the following disease: fatty liver disease, aging, aging-related diseases, cardiomyopathy, and noise-induced hearing loss **[32]**.

1.5.4. Niacin Mechanisms of Action in Different Neurological Disorders

The Nicotinamide compound can be synthesized de novo in the human brain, which contains only small amounts of nicotinamide precursors from the KP process **[33]**. The KP enzymes and their functions are discussed in detail in **Table 1**. **Fig. 3 A &B.**

Table 1. The KP enzymes and their functions

Factors	Results		References
Tryptophan 2,3 dioxygenase (TDO)	-	Exists at low levels in fully healthy humans, and contributes to the processes of neurogenesis and anxiety. - In the case of neurodegenerative diseases and cancers; the levels increase.	**[34]**
Indolamine-pyrrole 2,3 dioxygenase (IDO)	-	Levels elevate in cases of depression diseases, age-related disorders, and neuronal inflammation diseases.	**[35]**

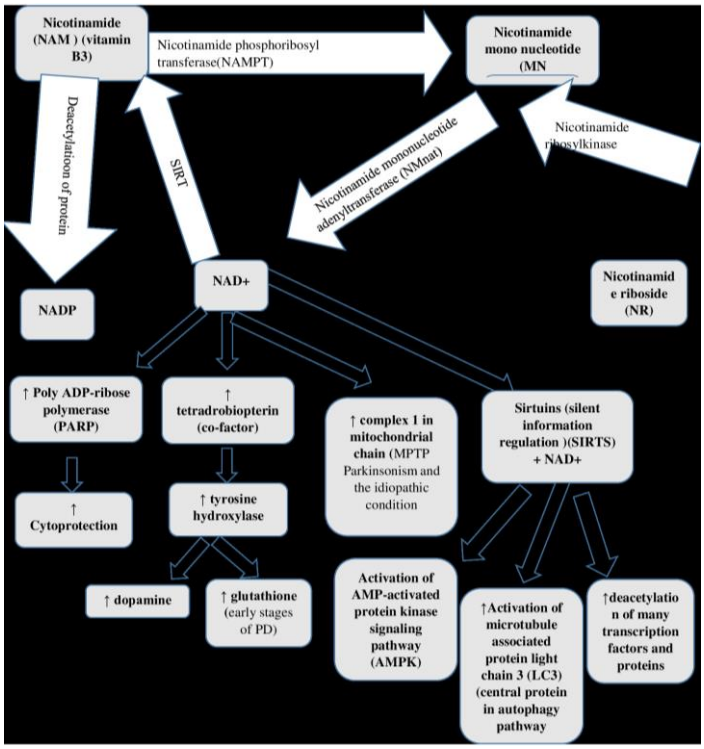

Fig.3 A. Mechanisms of Nicotinamide

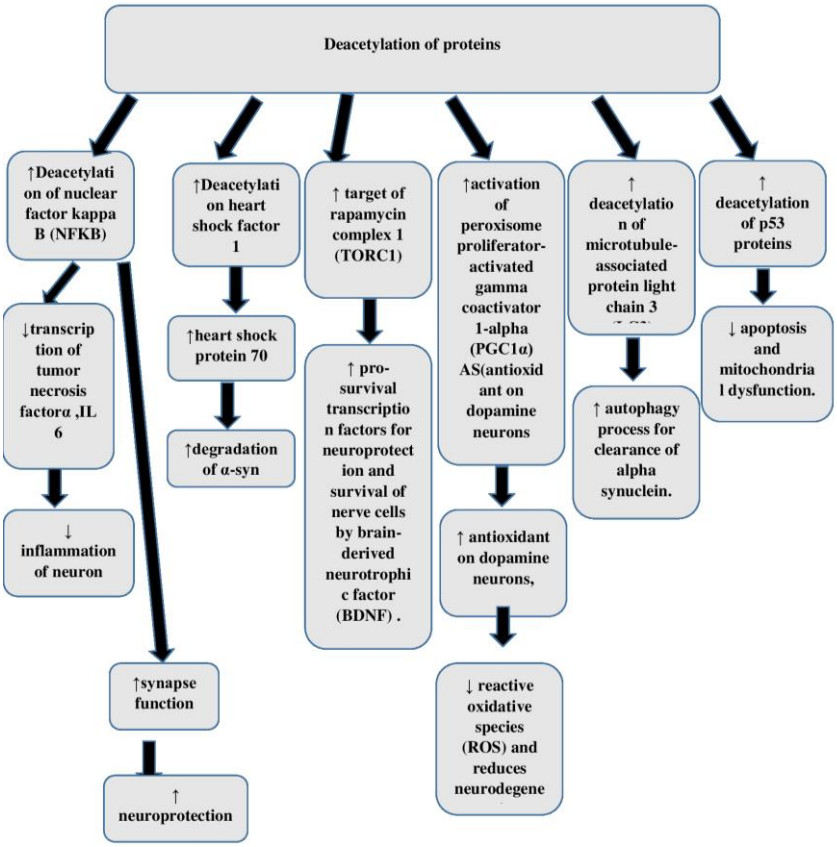

Fig.3 B. Mechanisms of Nicotinamide

Nicotinamide acts on neuronal neurogenesis by increasing stem cell differentiation. In vitro, it was found that niacin promotes cell differentiation into neuronal progenitors, and then further matures into GABA neurons **[36]**. This led to lower amounts of NNMT levels which are needed to maintain stem cell pluripotency activities. As a consequence NNMT substrate levels will accumulate which will promote stem cell differentiation. Nicotinamide also helps in neuron survival in oxidative stress by many mechanisms, such as: inhibiting cytochrome c, caspase-3, and caspase-9 release, preventing caspase-3 degeneration of forkhead transcription factor (FOXO3a) and protein kinase B (Akt) phosphorylation of FOXO3a. Central nervous system vascular integrity is positively associated with NAD levels. For instance, the heterozygous deletion of nicotinamide phosphoribosyl transferase (NAMPT) increases neural death and brain damage caused by ischemic strokes **[37**].

Lastly, Wallerian degeneration occurs in damaged neurons leading to distant axonal degeneration, mainly occurring in aging and chemotherapy peripheral neuropathies **[38]**. This is done through, the SARM1 protein, which increases Ca2+ levels inside the axons; thus accumulating nicotinamide mononucleotide concentration, leading to axonal death [**38**]. However, this action can be reversed by increasing nicotinamide /nicotinic acid mononucleotide adenylyltransferase (NMNAT) 1 – 3 which provides neuronal protection against axonal degeneration by decreasing nicotinamide mononucleotide concentrations or SIRT1 levels **[39] (Table 2 & 3)**.

Table 2. The key findings on niacin's role in neuronal degeneration.

Alzheimer's disorder	Factor	Key findings	References
	Niacin	Dietary niacin consumption is inversely associated with Alzheimer's disease.	**[40]**
	NAD+	Increased levels in the brain restore the functions of the mitochondria and prevent further degeneration in cognition.	**[41]**
	Nam/Nam mononucleotide	Reduce production of APP, PSEN-1, and ROS levels thus protecting from Aβ neuronal toxicity.	**[42]**
	Nam riboside	Protects hippocampal neurons by reducing DNA damage, neuronal inflammation, and cell apoptosis.	**[43]**
	SIRT1	Using the non-amyloid pathway causes decreased neuronal inflammation, oxidative stress, and dysfunction in the mitochondria.	**[44]**
	NMNAT1-3	Reducing nicotinamide mononucleotide and SIRT1 production causing axon protection.	**[45]**
	NMNAT2	Less gene production and activity; resulting in neuronal protection against the tauo pathway	**[46]**
Huntington's Disorder	**NAD**	Lower levels associated with disorder progress	**[47]**
	Nam	- Protects against polyQ protein toxicity - Reserve BDNF proteins, and elevate acetylated PGC-1 α coactivator levels - Improve motor activity by PARP-1 resulting in the prevention of neuron death and oxidative stress	**[48]**
	SIRT1	- Protects against neuronal huntingtin toxicity - Improves the disease's mechanisms depending on the onset	**[49]**

APP, amyloid precursor protein; PSEN-1, presenilin 1 gene; ROS, reactive oxygen species; SIRT1, The silent information regulator sirtuin 1; NMNAT1-3, Nicotinic acid mononucleotide adenylyl transferases 1-3; PARP-1, Poly (ADP-ribose) polymerase; PGC-1, Peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1alpha

Table 3. The key findings of the role of niacin in other neurological disorders.

Injuries related to ischemia and trauma	Factor	Key Findings	Ref.
	Niacin	Reduces behavioral defects in Traumatic brain injury (TBI) and improves the recovery in function.	**[50]**
	Nam	Reduces the neuronal defects, while causing apoptosis in the hippocampal part, including causing injuries in both the axons and microglial leading to activation of the corpus callosum and the oxidative stress; returning NAD (P); limiting the MAPK signaling pathway and caspase 3-cleavage process.	**[51]**
	Nam mononucleotide	Improves hippocampus injury and ameliorates neural results, by diminishing poly-ADP-ribosome proteins and the catabolism of NAD+.	**[52]**
	Nam/PARP-1 blockers	Pre-medication increases ATP stores and the recovery of the neurons throughout the re-oxygenation phase	**[53]**
	Niaspan [Niacin]	Rises the blood flow to the cerebrum; enables angiogenesis process through angpt/Tie2, Akt, and eNOS paths, including angiogenesis process through signaling to both TACE and Notch paths; increases defects in function	**[54]**
	Niacin plus selenium	Reduces cell injuries in the cortex by increasing the phosphorylation of Akt and Nrf2 expression; Reducing oxidative stress	**[55]**
	Nam plus progesterone	Increases functional recovery; reduces the cavitation of the lesions and tissues loss; modifies the expression of inflammatory and immunity genes	**[56]**
	NAMPT	- Lower levels worsen post-ischemic brain damage - Heterozygous gene deletion increases brain damage in photothrombotic-induced focal ischemia - An increased expression of the gene decreases	**[57]**

		infarct mass	
Headaches	**Niacin**	- Reestablishes the metabolism of the mitochondria - Increases blood flow and oxygen supply to the skeletal muscles	**[58]**
	Nicotinic acid	Causes intracranial blood vessel dilation and extracranial blood vessel contraction; proliferates prostaglandin D2 biosynthesis on the skin; increases 9a-prostaglandin and 11b-prostaglandin F2 plasma stores.	**[59]**
Neuropsychiatric diseases	**Niacin**	Reduces dietary consumption in psychiatric disorders.	**[60]**
	Nam	- A positive relationship between niacin levels and schizophrenia disorder - Long-term intake helps maintain bipolar II patients stable and clam	**[61]**
Multiple sclerosis	**NAD+**	- Mitochondrial dysfunction and inflammatory-induced oxidative stress.	**[62]**
	NMAT	Elevated levels of NMAT and SIRT1 showed preventive effects on axons deterioration resulting in neuroprotection	**[63]**
	SIRT1		**[64]**

Nam, Nicotinamide; NMNAT, Nicotinic acid mononucleotide adenylyl transferases; PARP-1, Poly (ADP-ribose) polymerase; PGC-1, Peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1alpha; angpt/Tie2, Angiopiotein/endothelial-specific receptor tyrosine kinase with immunoglobulin-like loops and epidermal growth factor homology domains-2(Tie2); AKt, The serine/threonine kinase; eNOS, Endothelial Nitric Oxide Synthase; NAMPT, nicotinamide phosphoribosyltransferase; NMAT, Nicotinamide/nicotinic acid mononucleotide adenylyltransferase; MAPK, Mitogen-activated protein kinase; Nrf2, Nuclear factor erythroid 2-related factor 2; SIRT1, The silent information regulator sirtuin 1.

1.6. Niacin's adverse effects

Niacin is generally safe and tolerable with minor side effects occurring at doses up to 2 grams. Niacin may cause flushing, pruritus, and a burning feeling commonly on parts of both the facial and the chest areas that lasts for 20-30 minutes. Flushing usually lessens in incidence and degree with time. This side effect usually requires pre-medication with aspirin (maximum 325 mg) 30 min before niacin. In addition, Laropiprant is an effective selective prostaglandin D2 antagonist (PGD) drug that can be used to treat flushing and also optimize therapeutic doses of niacin. In addition, in dyslipidemia, niacin was found to increase the risk of diabetes mellitus when used alone or in combination with laropiprant by 34 percent. Moreover, niacin when used with patients with diabetes was found to elevate the levels of fasting blood glucose. It is recommended to avoid treatment with niacin in a patient with diabetes

mellitus and metabolic syndromes **[65]**.

Other side effects such as gastrointestinal diseases including dyspepsia, nausea and vomiting, hyperuricemia, rashes, hypotension, liver enzymes AST and ALT levels elevations, homocysteine levels elevations, and peripheral paresthesias have been reported as well **[66]**.

Severe adverse effects in large doses include gastrointestinal peptic ulceration, cardiac arrhythmias, generalized anaphylactic reaction, liver necrosis, and edemas **[66]**.

1.7. Niacin contradictions

Presence of active gastrointestinal peptic ulceration, active arterial bleeding, active hepatic disorders, or in the presence of an unexplained increase in liver enzymes AST and ALT. Also, it is contraindicated in patients with hypersensitivity to niacin or any product in the formula **[66]**.

1.8. Niacin monitoring

Monitoring niacin therapy is recommended in patients on chronic use of niacin or using high doses. Frequent monitoring of blood glucose levels is essential in both pre-diabetic and diabetic patients on alogliptin, acarbose, glipizide, or insulin as niacin can cause elevations in the glucose levels. Moreover, niacin increases blood uric acid, which may interact with gout medications such as pegloticase and allopurinol. During niacin intake, blood pressure should be frequently measured. As it may decrease blood pressure especially when used with antihypertensive drugs (such as bisoprolol, diltiazem, amlodipine), opioids medications (tramadol, morphine, oxycodone), antipsychotic medications (risperidone) and phosphodiesterase type 5 inhibitor drugs (tadalafil) causing hypotension **[65]**.

Niacin can increase bleeding risk, by reducing platelet count (11% in 2000mg dose) and increasing prothrombin time (about 4%), especially when used in combination with anticoagulants including warfarin, apixaban, and caplacizumab. Therefore, blood coagulation panels and platelet count should be frequently monitored. When combining niacin with anaplastic lymphoma kinase inhibitor (ALK) ceritinib and blood lowering drug diazoxide cause hyperglycemia. Patients with an elevated risk of hypophosphatemia should monitor phosphate levels as niacin causes a reduction in phosphate levels by 13% in a 2000mg dose. Avoid drugs during nursing as niacin accumulates in breast milk **[65]**.

1.9. Mechanism of Nicotinamide in Parkinson's Disease

Parkinson's disease can be due to:

1.9.1. Mutations in genes responsible for encoding enzymes responsible for degradation of alpha-synuclein as D-glucosyl-N-acylsphingosine glucohydrolase (GCase) called GBA gene or encoding α-synuclein protein itself called SNCA genes **[67]**.

1.9.2. Idiopathic [68].

1.9.3. Aging in healthy old people [68].

GBA gene mutation is the most common gene mutation in Parkinson's disease. It leads to neurotoxicity to dopamine neurons, mitochondrial dysfunction, and aggregation of Lewy bodies (a hallmark of Parkinson's disease by many mechanisms. Heterozygous mutation of the beta-glucocerebrosidase (GBA) gene leads to a deficiency in the lysosomal enzyme D-glucosyl-N-acylsphingosine glucohydrolase (GCase) [69]. The latter catalases the metabolism of sphingolipids as hydrolysis of glucosylceramide (GlcCER) to ceramide and glucose, leading to the alteration of the autophagy-lysosome pathway (ALP), which is responsible for the degradation of alpha-

synuclein so result in accumulation of alpha-synuclein in substantial nigra **[70]**.

1.10. Accumulation of alpha-synuclein is the main reason for Parkinson's disease because its accumulation lead to many pathological mechanisms [71-74].

Formation of Lewy bodies by misfolding of aggregated alpha-synuclein.

Accumulated alpha-synuclein binds to mitochondria endoplasmic reticulum membrane (MAM) leading to reducing mitochondria trafficking, in turn, leads to a reduction of adenine triphosphate (ATP) formation and maximal respiration-caused respiration failure leading to more loss of GCase activity in human dopaminergic neurons

Induction of protein kinase RNA like endoplasmic reticulum kinase (PERK) causes induction of unfolding protein response (UPR) which causes accumulation of misfolded protein in the endoplasmic reticulum by reduction of protein synthesis of molecule chaperones Endoplasmic Reticulum-Associated Degradation (ERAD) mediating apoptotic cell death

Defects in the endoplasmic reticulum leading to Ca^{++} dysregulation activating of nuclear factor kappa B (NFKB) result in **A)** induction of Rel-A mediating transcription of pro-inflammatory gene coding releasing cytokines and the proteolytic enzyme responsible for apoptosis or induction of reactive oxygen species (ROS) result in oxidative stress of mitochondria and NAD+ deficiency **B)** reduction of Rel-C reducing anti-apoptotic gene expression as neuroprotective agent leading to more accumulation of alpha-synuclein

By reduction in NAD^+, mitochondria dysfunction occurs resulting in the deactivation of Selective internal radiation therapy (SIRT).

Induction transmission pathogenesis from cell to cell leads to the spreading of pathology from the peripheral nervous system to the central one so Lewy bodies can be seen in the midbrain and other parts.

So according to these pathological mechanisms of Parkinson's disease, the use of nicotinamide may help in the reduction of its progression, symptoms, and neurodegeneration. Many studies showed the efficacy of nicotinamide as a vitamin B3 agent acting as a precursor for nicotinamide adenine dinucleotide (NAD^+) **[74]**.

Nicotinamide (NAM) and nicotinamide riboside have the same function as the precursors for nicotinamide adenine dinucleotide with the difference in their chemical structure and mechanism. Nicotinamide (NAM) binds to nicotinamide phosphoribosyl transferase enzyme (NAMPT) and converts to nicotinamide mononucleotide (NMN) which produces nicotinamide adenine dinucleotide (NAD^+) by nicotinamide mononucleotide adenylyl transferase enzyme (NMNAT) [219]. While nicotinamide riboside (NR) is phosphorylated by nicotinamide riboside kinase 1 (NRK1) to nicotinamide mononucleotide (NMN) which in turn produces nicotinamide adenine dinucleotide (NAD^+) (219). This pathway is a continuous cycle called the salvage pathway. Salvage pathway used for recycling of nicotinamide adenine dinucleotide (NAD^+) **[75]**.

NAD depletion is considered a critical factor in precipitating cell death during oxidative stress due to compromised energetics. So nicotinamide is responsible for the following **[76-79]**.

Cytoprotection through pathways that involve poly (ADP-ribose) polymerase (PARP)

The formation of tetrahydrobiopterin (a co-factor for tyrosine hydroxylase and therefore important in the production of dopamine and known to be deficient in PD) and reduced glutathione (also known to be deficient in early stages of PD).

The normal function of complex 1 of the mitochondrial chain (known to be defective in MPTP Parkinsonism and the idiopathic condition

With this availability of nicotinamide adenine dinucleotide (NAD^+), sirtuins (silent information regulation, SIRT) are directly regulated by NAD^+, by substrate-dependent activation confirming that NAD^+ acts as a metabolic agent. SIRTS, especially SIRT1, either activates AMP-activated protein kinase signaling pathway (AMPK) which induces autophagy and reduces oxidative stress, endoplasmic stress, and inflammation[or activates microtubule-associated protein light chain 3 (LC3) as central protein in the autophagy pathway in cytoplasm inducing autophagy and clearance of α synuclein or couples directly NAD^+ hydrolysis to the deacetylation of many transcription factors and proteins. Deacetylation of these proteins maintains neuroprotection in many ways **[80-81]**.

1) Deacetylation of nuclear factor kappa B (NFκB) reduces transcription of tumor necrosis factor α and interleukin 6 so reduces inflammation of neurons and activates synapse function so inducing neuroprotection

2) Deacetylation of heat shock factor 1 induces heat shock protein 70 which helps in the degradation of alpha-synuclein.

3) Deacetylation of target-of-rapamycin complex 1 (TORC1) phosphorylates cyclic AMP element binding protein 1 (CREB) inducing pro-survival transcription factors for neuroprotection and survival of nerve cells by a brain-derived neurotrophic factor (BDNF)

4) Activation of peroxisome proliferator-activated gamma coactivator 1-alpha (PGC1α) acting as an antioxidant on dopamine neurons, reduces reactive oxidative species (ROS), and reduces neurodegeneration.

5) Deacetylation of microtubule-associated protein light chain 3 (LC3) as central protein in the autophagy pathway in the nucleus and transfer it to the cytoplasm to induce autophagy process for clearance of alpha-synuclein.

6) Deacetylation of p53 tumor proteins reduces apoptosis and mitochondrial dysfunction

2. Preclinical studies

2.1. Drosophila

Importantly, we found that enhancing the availability of that NAD+ by either diet supplementation or inhibition of NAD+-Dependent enzymes, such as poly (ADP-ribose) polymerase (PARPs), rescues the age-dependent loss of dopamine neurons and improves decline in climbing ability in mutant glucocerebrosidase (GBA)-PD Drosophila model of Parkinson's disease. This is when nicotinamide was used at 15 and 30 mg/100 g diet. High doses decrease oxidative stress and improve mitochondria function **[82]**. It was found in the α-synuclein transgenic Parkinson's disease Drosophila model that treatment with nicotinamide increases climbing ability without extending lifespan. On the other hand, a diet supplemented with Nicotinamide adenine dinucleotide (NAD^+) precursor rescued defective mitochondria in Drosophila models of Parkinson's disease with (phosphatase and TENsin) PTEN- induce kinase 1 (pink1) mutations because they found alterations in nicotinamide adenine dinucleotide salvage metabolism in it **[82]**.

2.2. Rodent

Nicotinamide, the sirtuin histone deacetylase inhibitor (HDACI) (class III), has been shown to act neuro protectively by attenuated striatal dopamine depletion in 6−OHDA Parkinson's disease mouse models and SNc neurons in the 'acute' 1- methyl-4- phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) but not in the 'sub-acute' in a mouse model of Parkinson's disease.

Constantly, it was found that nicotinamide treatment significantly replenishes the levels of NAD+, reduces the level of reactive oxygen species (ROS) in dopamine neurons, increases glutathione (GSH) in the ventral mesencephalon, suppresses the production of tumor necrosis factor (TNF-α), blocks p38 phosphorylation pathway, and finally, reduce inflammation in RAW264 cells in mouse model of Parkinson's disease **[83]**. However, long-term nicotinamide application exacerbated neurodegeneration of dopaminergic neurons, behavioral deficits, and structural brain changes in the lactacystin-lesioned rodent model of Parkinson's disease, by decreasing dopamine levels and downregulation of essential dopamine metabolic genes in both the lesioned and unlesioned side of the substantia nigra **[84]**.

2.3. Cellular

Cell viability by restoring neuronal mitochondrial energy metabolism, promoting cellular proteostasis, and modulating the immune system was rescued by pretreatment with a relatively high concentration of nicotinamide in acute cellular models like in rotenone-treated phaeochromocytoma (PC12) cells. It is a cellular model of Parkinson's disease, pretreated with nicotinamide that has reduced the early- and late-stage apoptosis and the survival rate **[85]**.

Also phaeochromocytoma (PC12) cells treated with increased concentrations of 6hydroxydopamine (6− OHDA) and increased Nicotinamide adenine dinucleotide (NAD+) levels in medium (101 mg/L), may have increased both mitochondrial mass and adenosine triphosphate (ATP) production, and helped maintain mitochondrial membrane **[85]**.

2.4. Elegans

In wild-type worms, Caenorhabditis elegans, NAD^+ supplementation before Methyl mercury treatment may be beneficial for preventing Methyl mercury-induced oxidative stress and cellular damage involved in Parkinson's disease **[86]**. It significantly restored the mitochondrial function and proteostasis in α-synuclein overexpressing models **[85]**.

3. Clinical studies

An experimental test of a double-blinded phase I study was done to compare nicotinamide adenine dinucleotide treatment and nicotinamide riboside oral drug, to know the effect on Parkinson's disease. Thirty cases receive 1000 mg of nicotinamide riboside or a controlled drug for 30 days, the result was nicotinamide riboside may be a neuroprotective agent for Parkinson's disease **[86]**.

Another trial has been done by giving 47 patients with parkinsonism a low dose of niacin (250 mg) for 12 months has led to a reduction of neuro-inflammation, by decreasing GPR 109-A in white blood cells and polarizing the triggered cells of microglial **[87]**.

Nicotinamide has a beneficial benefit in improving neurocognitive functioning. Detection of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) suggests that Parkinson's disease is caused by endogenous toxins that have some mechanisms related to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Higher serum levels of cerebrospinal fluid of N methylated-aza-heterocyclic amines; such as β-carboline and tetrahydroisoquinoline were present in 26 patients with parkinsonism. These patients had taken 100 mg of nicotinamide, versus 20 patients who had taken a placebo, as a control group. The outcome was aldehyde oxidase on the pyridine ring which has led to neurotoxins detoxification **[88]**.

Reactive Oxygen Species are highly present in neurodegenerative diseases such as Parkinson's in which the enzyme NADPH and nitric oxide synthase are involved which in turn leads to damage to dopaminergic neurons in Parkinson's. So, ROS inhibition leads to treat

neurodegeneration in Parkinson's **[88]**. It was found that nicotinamide N-methyltransferase superoxide anion formed via mitochondria, is involved in the etiology of Parkinson's, NAMT converts nicotinamide to NMA which leads to damage to dopaminergic neurons **[89]**. A trial was done in which parental nicotinamide adenine dinucleotide administration with a dose of 10 mg, for seven days, has increased the bioavailability of levodopa in serum fluid by increasing its synthesis **[88]**.

Accumulating data have suggested that activation of GPR109A receptors ameliorates symptoms in these neurological disorders via suppressing pro-inflammatory signaling pathways and the production of pro-inflammatory mediators as well as enhancing anti-inflammatory signaling pathways. The majority of available data on the role of GPR109A in neuroinflammation were derived from experiments where non-specific GPR109 agonists (such as niacin) were used in combination with GPR109A knockout techniques to determine the contribution of GPR109A signaling. Future studies to understand the in-depth biology of GPR109A will open new avenues to identify and develop novel therapeutic targets for the treatment of neuroinflammation-related neurological disease **[89]**. Recently the administration of nutraceuticals such as niacin has been associated with Parkinson's disease severity symptoms **[90]**.

Conclusion

Nicotinamide increases cytoprotection, the release of dopamine, and decreases the oxidative stress of mitochondrial. It is recommended to use it as a treatment option for PD. Further trials on large scales should be conducted to investigate the required dose and duration of niacin. Also, any pharmacogenetic polymorphism studies are needed to reveal if they have any influence on niacin response in PD.

Declarations

Ethics approval and consent to participate

Not applicable

Consent to publish

Not applicable

Availability of data and materials

The data generated or analyzed during this study all are included in the main manuscript.

Competing interests

Authors declare no competing interests

Funding statement

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Authors' contributions

Mona Alshahawey and Sarah Farid contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by Nourhan Mohamed, Nora Gamal, Samar Abdelazim, Nadia Abdelsalam, Heba Abdelrahim, and Reem Hamid. The first draft of the manuscript was written by Nourhan Mohamed, Nora Gamal, Samar Abdelazim, Nadia Abdelsalam, Heba Abdelrahim, Reem Hamid Mona Alshahawey, and Sarah Farid, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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