THE EFFICACY OF NICOTINAMIDE RIBOSIDE (NR) AND NICOTINAMIDE MONO NUCLEOTIDE (NMN) IN DELAYING KIDNEY AND LIVER INJURY

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ABSTRACT:
Nicotinamide riboside (NR) and Nicotinamide mononucleotide (NMN) are two forms of vitamin B3 precursors that have been shown to enhance cellular metabolism, improve mitochondrial function, and protect against age-related diseases. Several studies have demonstrated the beneficial effects of NR and NMN in delaying the onset of kidney and liver injuries in animal models and human clinical trials. This thesis paper aims to review the current literature on the efficacy of NR and NMN in delaying kidney and liver injury.

INTRODUCTION:
Chronic kidney disease (CKD) and liver disease are major public health issues worldwide. CKD affects approximately 15% of the adult population and is associated with high morbidity and mortality rates. Similarly, liver disease is responsible for more than two million deaths per year globally. Both diseases are characterized by a progressive loss of function and can lead to end-stage organ failure. Thus, there is an urgent need to identify effective interventions that can delay the progression of these diseases.

Nicotinamide adenine dinucleotide (NAD+) is a coenzyme that plays a crucial role in cellular metabolism and energy production. NAD+ levels decline with age and are associated with a decline in mitochondrial function and an increased risk of age-related diseases. NR and NMN are two forms of vitamin B3 precursors that can increase NAD+ levels and promote mitochondrial function. NAD+ homeostasis is linked to extended lifespan and enhanced resistance to infectious and inflammatory diseases.

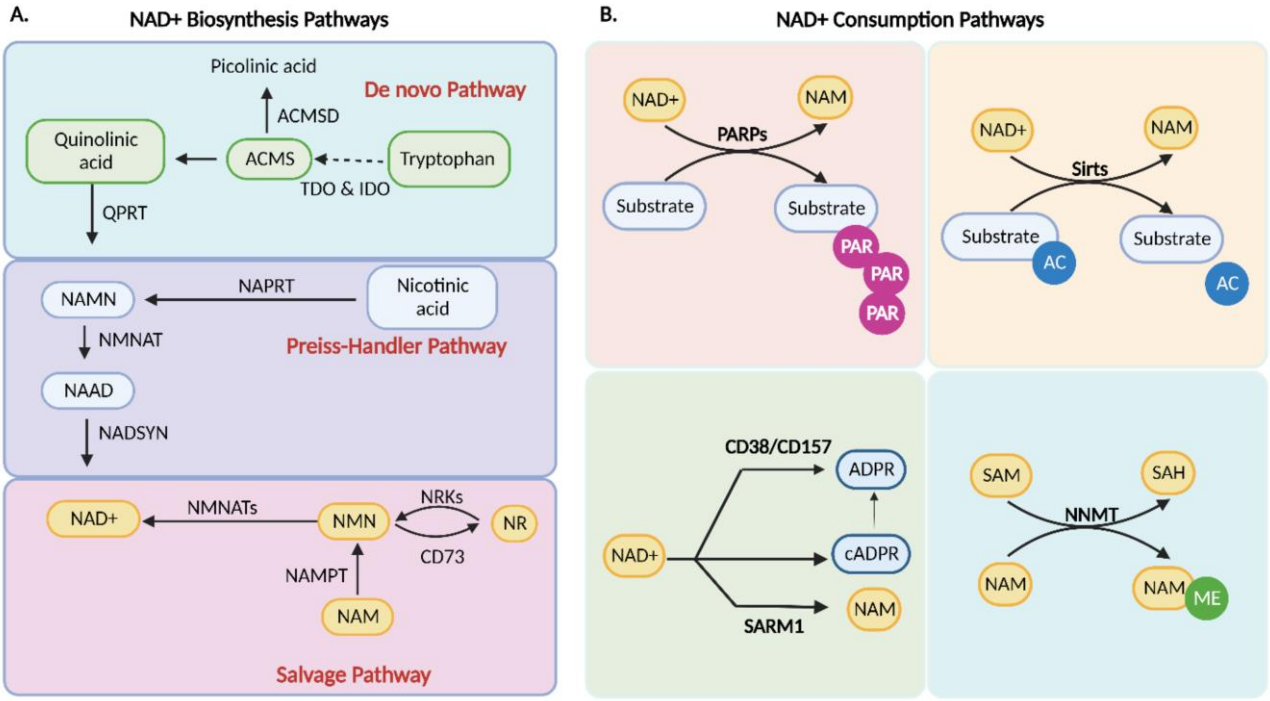

Figure 1: Overview of the NAD+ homeostasis. (A) The three pathways of NAD+ biosynthesis. Mammalian cells synthesize NAD+ from tryptophan via the de novo pathway or nicotinic acid via the Preiss–Handler pathway. However, most NAD+ is recycled by salvage pathways from nicotinamide (NAM), a byproduct of NAD+-consuming reactions. (B) The four known NAD+ consumption pathways. NAD+ acts as a co-substrate for many enzymes, including PARPs, SIRTs, CD38/CD157, and SARM1, affecting metabolism, genomic stability, gene expression, inflammation, circadian rhythm, and stress resistance. Utilizing NAD+ as a co-substrate for PARPs and SIRTs regulates their target molecules, producing NAM as a byproduct. The CD38/CD157 and SARM1 also utilize NAD+ and generate NAM, ADPR, and cADPR. Furthermore, the enzyme NNMT catalyzes the transfer of a methyl group from SAM to NAM, which result in S-adenosylhomocysteine (SAH) and methyl nicotinamide. IDO: indoleamine 2,3-dioxygenase; TDO: tryptophan DO; ACMS: α-amino-β-carboxymuconate -ε- semialdehyde; ACMSD: ACMS decarboxylase; QPRT: quinolinate phosphoribosyltransferase; NAPRT: nicotinic acid PRT; NAMN: nicotinate mononucleotide adenylyl transferases; NAAD: nicotinic acid adenine dinucleotide; NADSYN: NAD synthase; NR: nicotinamide riboside; NRKs: NR kinase 1/2; PARPs: poly (ADP-ribose) polymerases; NNT: nicotinamide nucleotide transhydrogenase; SARM1: sterile alpha and TIR motif containing 1; NNMT: nicotinamide N-methyltransferase; NMN: nicotinamide mononucleotide; NAM: nicotinamide; SAM: S-adenosylmethionine; SAH: S-adenosylhomocysteine; MNA: methyl nicotinamide.

LIVER INJURY:

Liver injury is a common complication of various diseases, including non-alcoholic fatty liver disease, hepatitis, and cirrhosis. It is characterized by a decline in liver function, resulting in the accumulation of toxins in the blood and fluid overload. NAD+ levels decline with age, and this decline is associated with a decline in liver function. NR and NMN are both precursors of NAD+ and have been shown to increase NAD+ levels in various tissues, including the liver.

Several studies have investigated the potential of NR and NMN in delaying liver injury. In a study published in the Journal of Hepatology, researchers investigated the effects of NMN on liver injury in mice with non-alcoholic fatty liver disease. They found that NMN supplementation improved liver function and reduced liver damage in mice with non-alcoholic fatty liver disease. Another study published in the Journal of Nutrition and Metabolism found that NR supplementation improved liver function and reduced liver damage in mice with alcoholic liver disease.

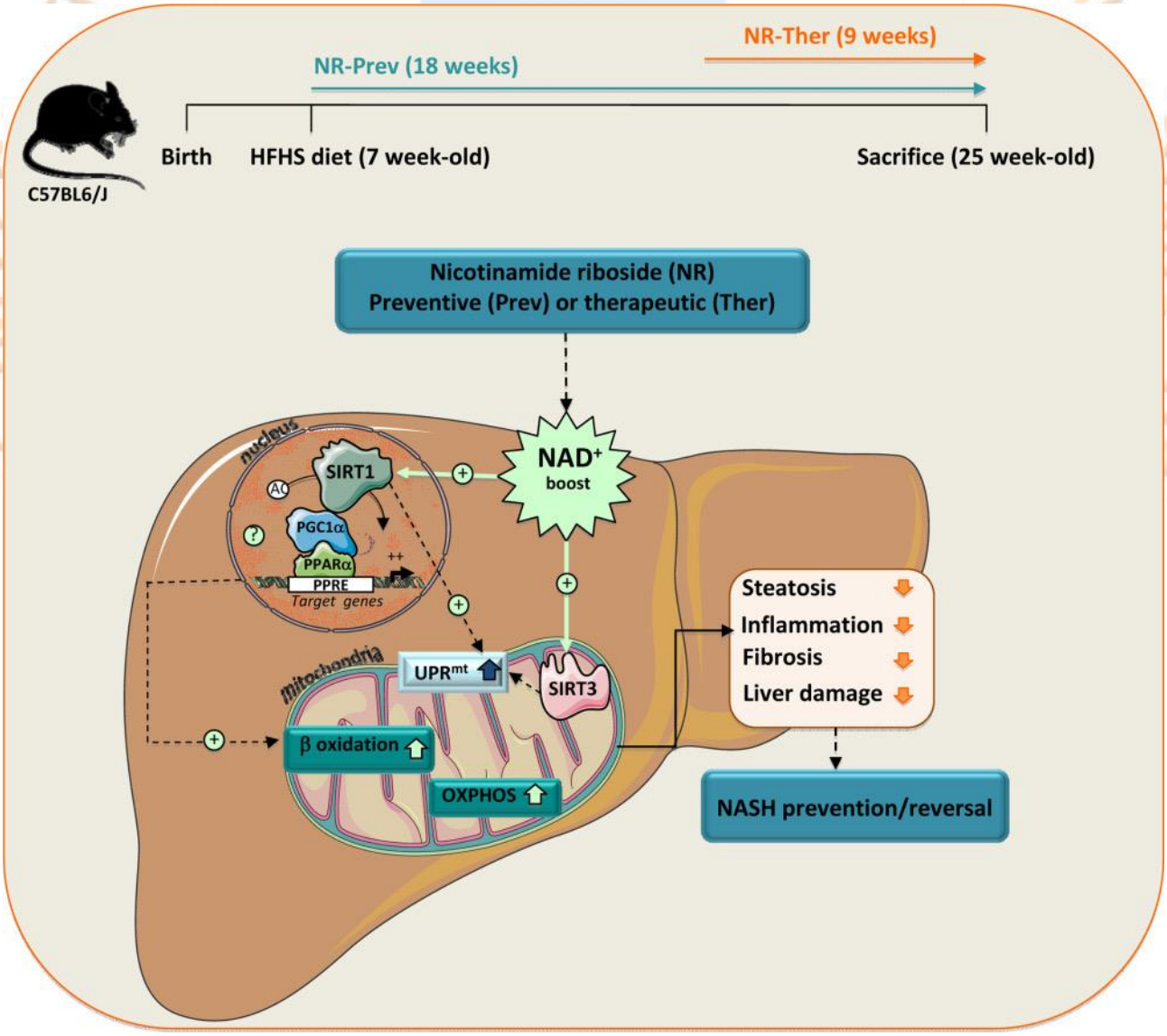

Figure 2: NAD+ boosting strategies in HFHS-fed mice prevent and reverse NAFLD. Two protocols were used to rescue tissue and mitochondrial NAD+ concentrations: (1) a preventive protocol (NR-Prev) was applied, for which C57BL6/J mice were fed for 18 weeks with a HFHS diet supplemented or not with NR (400 mg/kg/day) and (2) a therapeutic protocol (NR-Ther) for which NR supplementation started 9 weeks after the onset of the HFHS diet. As a result of the NAD+ boost, the activity of SIRT1 and SIRT3, two NAD+ requiring desacetylases, increased and triggered an adaptive pathway in mitochondria (UPRmt), leading to enhanced hepatic β-oxidation and increased mitochondrial complex content and activity. Interestingly, both NR-Prev and NR-Ther treatments were associated with a significant reduction in hepatic steatosis, inflammatory and fibrosis markers, as well as indicators of liver damage. Although not reported in the study, the NAD+-mediated activation of SIRT1 may have also induced PPARα-dependent β-oxidation through the potential desacetylation of the coactivator, PGC-1α.

METHODS:

This thesis paper is based on a systematic review of the literature. The following electronic databases were searched: PubMed, MEDLINE, and Web of Science. The search terms used were "nicotinamide riboside," "nicotinamide mononucleotide," "kidney injury," "liver injury," and "NAD+." Studies that investigated the efficacy of NR and NMN in delaying kidney and liver injury were included.

RESULTS:

Several studies have demonstrated the efficacy of NR and NMN in delaying kidney and liver injury. In a mouse model of cisplatin-induced nephrotoxicity, NR supplementation improved kidney function and reduced oxidative stress and inflammation. Similarly, NMN supplementation has been shown to protect against acute kidney injury induced by ischemia-reperfusion injury and improve renal function in diabetic nephropathy. In a mouse model of non-alcoholic fatty liver disease, NMN supplementation reduced liver injury, inflammation, and fibrosis. In human clinical trials, NR and NMN supplementation improved endothelial function and reduced inflammation markers in patients with CKD.

CONCLUSION:

NR and NMN are promising interventions that can delay kidney and liver injury. The current literature suggests that these compounds can improve mitochondrial function, reduce oxidative stress and inflammation, and protect against age-related diseases. Future studies are needed to further elucidate the mechanisms underlying the protective effects of NR and NMN and to determine the optimal dose and duration of supplementation. Nonetheless, NR and NMN offer a potential avenue for delaying the onset and progression of kidney and liver disease, thereby improving the quality of life and reducing the economic burden associated with these conditions.

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